From: "Mielke, Martin" <MielkeM@rki.de>
To: "Rexroth, Ute" <RexrothU@rki.de>
Verteiler-Krisenstab <verteiler-krisenstab@rki.de>
Date: 2/11/2021 10:58:27 AM
Subject: Gerne zu diesem Punkt beilegen AW: Bitten aus dem ÖGD: RKI Empfehlungen allgemein verschärfen

---

Liebe Kolleginnen und Kollegen,
zu dem von Frau Rexroth vorgeschlagenen Punkt könnten für die Diskussion ggf. die folgenden Links hinterlegt werden:

https://www.ecdc.europa.eu/en/publications-data/covid-19-infographic-mutations-current-variants-concern (mit aktuellem RA 21.1.2021)

https://ec.europa.eu/info/sites/info/files/communication-united-front-beat-covid-19_en.pdf

https://ec.europa.eu/commission/presscorner/detail/en/ip_21_195

https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html

Gruß,
Martin Mielke

-----Ursprüngliche Nachricht-----
Von: Rexroth, Ute
Gesendet: Donnerstag, 11. Februar 2021 11:36
An: Verteiler-Krisenstab <verteiler-krisenstab@rki.de>
Betreff: Bitten aus dem ÖGD: RKI Empfehlungen allgemein verschärfen

Liebe Kolleginnen und Kollegen,

wir haben schon mehrfach im Krisenstab darüber diskutiert, ob angesichts der VOC-Verbreitung die Maßnahmen verschärft werden sollten.

Aus verschiedenen Bundesländern (Berlin, Schleswig-Holstein, Rheinland-Pfalz, NRW, Baden-Württemberg, Niedersachsen…) sind diesbezüglich Bitten und Vorschläge an uns herangetragen worden.
(ein Beispiel unten aus Düsseldorf, nebst eindrücklicher Schilderung der Ausbreitung und höheren Übertragbarkeit der UK-Variante).

Die Vorschläge gehen in die Richtung:
- KP 1 großzügiger zu definieren (> 1 min F2F statt > 15 min),
- KP 2 auch stärker einbeziehen, ggf. in Quarantäne nehmen
- keine Ausnahmen zuzulassen
- Quarantäne für alle unabhängig von Variante für 14 Tage, grundsätzlich keine Freitestungen
- Testung während und Abschlusstestung der KP am Ende der Quarantäne

- Testung am Ende der Isolation
- Haushaltsquarantäne für Haushalte der KP 1 (L 1 hatte schon geprüft: keine Rechtsgrundlage)
-...

Diverse Bundesländer gehen derzeit deutlich über die RKI-Empfehlungen hinaus. Es gibt aber Sorgen wegen Einheitlichkeit, Rechtssicherheit und Compliance.

Nun liegen uns ja nur die anekdotischen Berichte und keine harten Daten vor und wir haben das Beispiel von UK, die ihre Empfehlungen nicht angepasst haben.

Vielleicht könnten wir noch einmal im Krisenstab dazu beraten, zumindest darüber, wie wir an die nötigen Daten kommen, damit wir mit einiger Sicherheit sagen können, dass unsere Empfehlungen noch passen, oder aber sie evidenzbasiert anpassen können.

Viele Grüße,

Ute Rexroth

-----Ursprüngliche Nachricht-----
Von: lutz.ehlkes@duesseldorf.de <lutz.ehlkes@duesseldorf.de>
Gesendet: Donnerstag, 11. Februar 2021 10:54
An: an der Heiden, Maria <AnderHeidenMa@rki.de>
Cc: Rexroth, Ute <RexrothU@rki.de>; klaus.goebels@duesseldorf.de; Seidel, Juliane <SeidelJ@rki.de>; pascal.kreuzer@duesseldorf.de
Betreff: Antwort: COVID-19: Wiederaufnahme Empfehlung Flug-KoNa generell bei Flügen prospektiv ab dem 11.02.2021

Liebe Maria,

das ist ein guter Zug. Alles super. Aber wir haben derzeit ca. 20% der lokal erworbenen Fälle mit einem Nachweis von B.1.1.7. Tendenz stark steigend. Vor diesem Hintergrund erscheint die KoNa in Flugzeugen, die nach wie vor extrem zeitintensiv ist, als nicht sehr effizient investierte Zeit. Die PLCs werden ohne System gescannt, bis man sich die zusammengesucht hat ist viel Zeit vergangen und dann sind sie häufig nicht ausgefüllt oder unlesbar.

Unter deren B.1.1.7-Kontaktpersonen der Kategorie 1 liegt die Positivenquote bei uns bei nahezu 100%. In Reihentestungen haben wir festgestellt, dass auch sehr viele KP2 betroffen sind. Wir haben sehr dubiose Konstellationen (doppelt FFP2, Plexiglaswand, offenes Fenster und 2m Abstand), die zu Transmissionen geführt haben.
Alle Gesundheitsämter im Umkreis lösen sich jetzt nach und nach von den RKI-Empfehlungen, weil wir sonst keine Chance mehr sehen, die VoC aufzuhalten. Wir haben aber das Problem, dass eure Empfehlungen als Sachverständigen-Gutachten zählen und daher für uns de facto bindend sind. Sobald jemand Klage einreicht sehen wir alt aus.

Daher die dringende Bitte: Verschärft die Richtlinien für das Kontaktpersonenmanagement!

Anbei unser temporäres Schema, welches für alle Fälle und Kontaktpersonen (ungeachtet etwaiger VoC-Nachweise gilt):

Klassifizierung von Kontaktpersonen der Kategorie 1:

* Kontakt von >5 min unter 1,5m, ohne dass Quellfall und Kontaktpersonen einen medizinischen MNS (chirurgischen MNS, FFP2/3) getragen haben.
* Aufenthalt von >15 min im selben Raum ohne konstante Querlüftung.
* Im Zweifel: Quarantäne!

Management von Infizierten:

* Abschlusstestung dringend empfohlen. Entisolierung möglich mit negativem Ergebnis (PCR-/PoC) oder Ct-Wert > 32 (bzw. < 10^ 6 Virenkopien/ml) an Tag 10.
* Keine Ausnahmeregelungen für medizinisches oder pflegerisches Personal, bzw. KRITIS.

Management von Kontaktpersonen:

* Abschlusstestung dringend empfohlen. Ende der Absonderung mit negativem Ergebnis (PCR-/PoC) an Tag 14 nach Exposition.
* Zwischentestung an Tag 5-7 nach Exposition wird empfohlen.
* Ausnahmeregelungen bei Personalmangel für medizinisches und pflegerisches Personal (Einzelfallentscheidung, wir drängen hier auf Typisierung):
* KP1 von Fällen ohne Nachweis der Virusvariante gilt als Voraussetzung für die Wiederzulassung: Negatives PCR-Ergebnis vor Wiederzulassung ist vorzulegen (Tag 5-7). Früheste Wiederzulassung an Tag 8 nach Exposition.
* Bei KP1 von Virusvarianten-Fällen entfällt die Option der Ausnahmeregelung.

Einige Gesundheitsämter gehen sogar noch über unsere Maßnahmen hinaus (> 1 min Kontakt = KP1). Sobald das RKI eine Verschärfung der Maßnahmen publiziert springen wir und die anderen Kommunen natürlich wieder auf.
Es ist im Sinne aller, einen Flickenteppich zu vermeiden.

Wir können gerne Rücksprache halten.

Mit freundlichen Grüßen
Im Auftrag

Lutz Ehlkes

Sachgebietsleiter Infektionshygiene (53/21) Kommissarischer Abteilungsleiter Gesundheitsschutz (53/2) Landeshauptstadt Düsseldorf Der Oberbürgermeister Gesundheitsamt

Erkrather Straße 385
40231 Düsseldorf

Telefon: 0211 89-26020
E-Mail: lutz.ehlkes@duesseldorf.de

Von: "an der Heiden, Maria" <AnderHeidenMa@rki.de>
An: "Seidel, Juliane" <SeidelJ@rki.de>, "Andrea Jaumann BY" <Andrea.Jaumann@stmgp.bayern.de>, "Anne.Kolenbrander@mags.nrw.de" <Anne.Kolenbrander@mags.nrw.de>, "Antoni Walczok:" <antoni.walczok@stadt-frankfurt.de>, "Astrid Schumann:" <Astrid.Schumann@dahme-spreewald.de>, "Bernd Wicklein:" <Bernd.Wicklein@lgl.bayern.de>, "Bert Schindler" <FB_Gesundheit4@SenGPG.Berlin.de>, "Bianca Garber:" <Bianca.Garber@SenGPG.Berlin.de>, "Christophe Bayer (Ref. -321):" <Christophe.Bayer@bmg.bund.de>, "Claudia Wesner" <Claudia.Wesner@HSM.hessen.de>, "Cornelia.Winten@HSM.hessen.de" <Cornelia.Winten@HSM.hessen.de>, "Corona LZ Hessen" <corona@hsm.hessen.de>, "Detlef Berndt:" <detlef.berndt@masgf.brandenburg.de>, "Elke Jakubowski:" <elke.jakubowski@bgv.hamburg.de>, "Frank Ollroge:" <frank.ollroge@bgv.hamburg.de>, "Gesundheitsamt Dahme-Spreewald" <gesundheitsamt@dahme-spreewald.de>, "Gundel Schirrmeister" <Gundel.Schirrmeister@MSGIV.Brandenburg.de>, "Hannah Höglund-Braun" <hannah.hoeglundbraun@duesseldorf.de>, "Harald.Striegl.extern@bmg.bund.de" <Harald.Striegl.extern@bmg.bund.de>, "Infektionsschutz@stmgp.bayern.de" <Infektionsschutz@stmgp.bayern.de>, "julia.ewers@mags.nrw.de" <julia.ewers@mags.nrw.de>, "Julia.Zeitler@mags.nrw.de" <Julia.Zeitler@mags.nrw.de>, "Justyna Chmielewska" <Justyna.Chmielewska@bmg.bund.de>, "klaus.goebels@duesseldorf.de" <klaus.goebels@duesseldorf.de>, "Knop, Juliane -321 BMG" <Juliane.Knop@bmg.bund.de>, "Lena Ehlers:" <lena.ehlers@hu.hamburg.de>, "Lücking Dr., Gesa -321 BMG" <Gesa.Luecking@bmg.bund.de>, "Lutz Ehlkes" <lutz.ehlkes@duesseldorf.de>, "LZ-Corona-BMG" <LagezentrumCOVID19@bmg.bund.de>, "Manuel.Sieg@bmvi.bund.de" <Manuel.Sieg@bmvi.bund.de>, "Margot Bayer:" <margot.bayer@stmgp.bayern.de>, "Margret Seewald" <Margret.Seewald@MSGIV.Brandenburg.de>, "Marion Scharte:" <Marion.Scharte@Stmgp.bayern.de>, "Markus, Inessa" <MarkusI@rki.de>, "Marlen Suckau-Hagel:" <Marlen.Suckau-Hagel@SenGPG.Berlin.de>, "Martin Dirksen-Fischer:" <martin.dirksen-fischer@hu.hamburg.de>, "Martin Hoch:" <Martin.Hoch@lgl.bayern.de>, "Martina Enke" <Martina.Enke@stmgp.bayern.de>, "martina.pfob@stmgp.bayern.de" <martina.pfob@stmgp.bayern.de>, "Mathias Kalkowski:" <mathias.kalkowski@hu.hamburg.de>, "Matthias Boldt:" <matthias.boldt@hu.hamburg.de>, "Matthias Jeglitza:" <Matthias.Jeglitza@bmvi.bund.de>, "Matthias.Trost@hsm.hessen.de" <Matthias.Trost@hsm.hessen.de>, "Schöll, Meike" <SchoellM@rki.de>, "Merle Böhmer:" <Merle.Boehmer@lgl.bayern.de>, "Monika Theresia Mütter" <monika-theresia.muetter@stmgp.bayern.de>, "nCoV-Lage" <nCoV-Lage@rki.de>, "NRW" <Referat-VB4@mags.nrw.de>, "oeffentlichergesundheitsdienst@bgv.hamburg.de" <oeffentlichergesundheitsdienst@bgv.hamburg.de>, "oegd@stmgp.bayern.de" <oegd@stmgp.bayern.de>, "Pascal Kreuzer" <pascal.kreuzer@duesseldorf.de>, "ref-lf10@bmvi.bund.de" <ref-lf10@bmvi.bund.de>, "Rene Gottschalk:" <Rene.Gottschalk@stadt-frankfurt.de>, "Rexroth, Ute" <RexrothU@rki.de>, "sabine.totsche@hsm.hessen.de"

<sabine.totsche@hsm.hessen.de>, "Sangs, André -321 BMG" <Andre.Sangs@bmg.bund.de>, "Scarlett Kleine-Kampmann" <scarlett.kleine-kampmann@hu.hamburg.de>, "Siegfried Ippisch:" <Siegfried.Ippisch@lgl.bayern.de>, "silja.buehler@hu.hamburg.de" <silja.buehler@hu.hamburg.de>, "Thanheiser, Marc" <ThanheiserM@rki.de>, "Schneider, Timm" <SchneiderT@rki.de>, "Timo Car" <Timo.Car@hsm.hessen.de>, "Udo Goetsch:" <udo.goetsch@stadt-frankfurt.de>, "Ulrich Widders:" <ulrich.widders@masgf.brandenburg.de>, "Wambach, Avila-Victoria -611 BMG" <Avila-Victoria.Wambach@bmg.bund.de>
Datum: 10.02.2021 14:24
Betreff: COVID-19: Wiederaufnahme Empfehlung Flug-KoNa generell bei Flügen prospektiv ab dem 11.02.2021

Liebe Kolleginnen und Kollegen,

wie letzte Woche bei unserer Videokonferenz angekündigt, nehmen wir die Empfehlung für eine Kontaktpersonennachverfolgung nach Exposition im Flugverkehr - unabhängig ob der Flug aus einem Virusvarianten-Gebiet kommt oder nicht - prospektiv ab 11.02.2021 wieder auf.

Die Website ist bereits aktualisiert:
https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Kontaktperson/Management.html;jsessionid=F278F0D98F47E2C462176270C9C01016.internet101?nn=13490888
<https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Kontaktperson/Management.html;jsessionid=F278F0D98F47E2C462176270C9C01016.internet101?nn=13490888>

Viele Grüße
Maria an der Heiden

Dr. Maria an der Heiden
Stellvertretende Leiterin des Fachgebietes Infektionsepidemiologisches Krisenmanagement, Ausbruchsuntersuchungen und Trainingsprogramme, ÖGD Kontaktstelle (Fachgebiet 38) Abteilung für Infektionsepidemiologie Robert Koch-Institut Seestraße 10
13353 Berlin
Tel.: +49 30 18754 3133
Fax.: +49 30 18754 3533
E-Mail: anderheidenma@rki.de
Web: www.rki.de
Twitter: @rki_de

From: "Korr Dr., Gerit Solveig -614 BMG" <GeritSolveig.Korr@bmg.bund.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 2/12/2021 7:37:36 PM
Subject: ID 2823_PCR-Tests ab kommender Woche wieder f ≥r alle mit Symptomen

Liebe Kolleginnen und Kollegen,

das Flussschema ist ja bereits angepasst, aber es gibt zahlreiche andere RKI-Dokumente, die uberarbeitet werden mussen. Ich rege an, diese bis dahin (und sehr zeitnah) von der Internetseite zu nehmen, bis diese uberarbeitet sind, damit vor dem Hintergrund der heutigen Au?erungen von Herrn Minister, siehe unten) keine verwirrenden Botschaften erzeugt werden. Es handelt sich (nach erstem Screening) um folgende Dokumente:

- Testkriterien fur die SARS-CoV-2 Diagnostik bei Patienten mit Verdacht auf COVID-19
- SARS-CoV-2-Testkriterien fur Schulen
- Strategie-Erganzung bei Auftreten von akuten Atemwegserkrankungen im Winterhalbjahr wahrend der COVID-19-Pandemie

Auch (mindestens) die beiden FAQs "Wann sollte ein Arzt eine Laboruntersuchung auf SARS-CoV-2 veranlassen" und "Was sollen Betroffene mit Symptomen tun" mussen uberarbeitet werden.

Diese Dokumente nehmen alle noch Bezug auf die uberlasteten PCR-Kapazitaten im Herbst und befinden sich, soweit ich wei?, bereits bei FG 36 in Bearbeitung.

Gru?
Gerit Korr

-----Ursprungliche Nachricht-----
Von: Spahn, Jens -Minister BMG
Gesendet: Freitag, 12. Februar 2021 12:12
An: 'Wieler, Lothar' <WielerLH@rki.de>
Cc: Holtherm Dr., Hans-Ulrich -AL 6 BMG <Hans-Ulrich.Holtherm@bmg.bund.de>; Wald, Susanne -AL L BMG <Susanne.Wald@bmg.bund.de>; Optendrenk Dr., Sonja -AL 2 BMG <Sonja.Optendrenk@bmg.bund.de>
Betreff: WG: afp: Curevac beginnt rollierendes Zulassungsverfahren fur Corona-Impfstoffkandidaten /PCR-Tests ab kommender Woche wieder fur alle mit Symptomen

Sie passen das Fluss-Schema netsprechend an?

JS

PCR-Tests ab kommender Woche wieder fur alle mit Symptomen - Gesundheitsminister Spahn will uber Sanktionen fur Impfvordrangler diskutieren
Quelle: afpd, vom 12.02.2021 11:52:00

BERLIN (AFP) - Bundesgesundheitsminister Jens Spahn (CDU) will die Empfehlung an die Arzte so uberarbeiten, dass ab kommender Woche wieder jeder mit Corona-Symptomen einen PCR-Test bekommen kann. Angesichts der ausgebliebenen Grippewelle und sinkender Corona-Zahlen gebe es wieder freie Kapazitaten in den Laboren, sagte Spahn am Freitag in Berlin. Er will zudem uber eine mogliche Priorisierung von Grundschullehrkraften sowie von Erzieherinnen und Erziehern bei der Impfung sowie uber Sanktionen fur Impfvordrangler sprechen.

Im November waren die Empfehlungen fur PCR-Tests wegen der stark steigenden Infektionszahlen geandert worden. Seitdem wird nicht mehr jeder mit Symptomen automatisch auf Corona getestet. Diese Empfehlung konne nun geandert werden, sagte Spahn: Arzte sollten bei Symptomen des Patienten wieder einen PCR-Test vornehmen konnen.

Es gebe zudem erste Antrage fur die Zulassung von Schnelltests, die auch Laien anwenden konnten. Ob und wann diese kamen, hange vor allem an ihrer Qualitat. «Wenn sie ausreichend gut sind, ist das ein guter und wichtiger Baustein», so Spahn. In Bereichen der kritischen Infrastruktur wie etwa dem Lebensmittelhandel konnten heute schon zugelassene Schnelltests bezogen und nach einer Schulung genutzt werden.

Zur Bitte von Bund und Landern, eine Priorisierung von Grundschullehrkraften und Erzieherinnen bei der Impfung zu prufen, sagte Spahn, dass er das Gesprach mit der Standigen Impfkommission suchen werde. Die Gruppe mit erster Prioritat musse aber zuerst ein Impfangebot bekommen, weil es dort besonders viele schwere und todliche Verlaufe gebe. Daruber herrsche Konsens. Eine mogliche Impfung fur Mitarbeiter von Grundschulen und Kitas sehe er eher im Fruhling, wenn mehr Impfdosen zur Verfugung stunden.

Spahn au?erte sich in der Pressekonferenz auch zu den Berichten, dass sich mancherorts Politiker, Kirchenleute oder Verwandte von Pflegeheimmitarbeitern bei der Impfung vorgedrangelt hatten. Es sei sehr wichtig, dass alle Impfdosen genutzt wurden, sagte er. Wenn am Ende des Tages noch etwas ubrig ware, das sonst verderben wurde, sollte es Regeln fur die Nutzung geben.

Viele Lander und Impfzentren hatten bereits solche Regeln aufgestellt, so Spahn. Beispielsweise impften sie in solchen Fallen medizinisches Personal einer nahe gelegenen Klinik, Sicherheitspersonal oder Feuerwehrleute. Es sei auch eine Frage von politischer Klugheit, sich nicht vorzudrangeln, betonte der Gesundheitsminister zugleich. «Wenn ich in Verantwortung bin, ist es kein gutes Beispiel fur Solidaritat.»

Er werde noch einmal mit den Landern sprechen, ob das Vorgehen «ein Stuck verbindlicher» zu regeln sei. Auch wolle er prufen, ob

Sanktionen in dem Bereich sinnvoll seien. «Man denkt ja manchmal, man konnte ohne», sagte Spahn. Aber die Diskussion sei angesichts der Vorfalle nachvollziehbar.

From: "Voigt, Sebastian" <VoigtS@rki.de>
To: Verteiler-Krisenstab <verteiler-krisenstab@rki.de>
Date: 2/15/2021 8:21:17 AM
Subject: Isolationszeit Beschlussvorlage für KriSta
Attachments: Isolationszeit_Beschlussvorlage_KriSta.docx

Liebe Kolleg*innen,

im Anhang schicke ich ein Dokument mit der Bitte um Diskussion im Krisenstab.

Grundlage ist die dringliche Bitte des Leiters des Gesundheitsamtes in Friedberg/Hessen um eine fachliche Diskussion hinsichtlich der längeren Präsenz von SARS-CoV-2 auf der Schleimhaut bei älteren Personen, um hieraus für die Praxis erforderliche Anpassungen der Isolationszeiten zu erreichen.

Falls heute aus Termingründen eine Diskussion nicht möglich sein sollte, wäre eine Behandlung des Themas am kommenden Mittwoch wünschenswert.

Mit Dank und freundlichen Grüßen

Sebastian Voigt

Beschlussvorlage für die Krisenstabssitzung am 15.02.2021

E-Mail-Anfrage vom 11.02.2021, hier: Auszüge

Absender:
Dr. Reinhold Merbs
Fachbereichsleitung Gesundheit, Veterinärwesen und Bevölkerungsschutz
Wetteraukreis
Europaplatz
Gebäude B
61169 Friedberg/Hessen

Tel.: 06031 83-2000
Fax: 06031 83-912300
E-Mail: Reinhold.Merbs@wetteraukreis.de

Anliegen:
Bitte um eine fachliche Diskussion hinsichtlich der längeren Präsenz von SARS-CoV-2 auf der Schleimhaut bei älteren Personen, um hieraus für die Praxis erforderliche Anpassungen der Isolationszeiten zu erreichen.

Darstellung des Problems:

1. „Wir haben in einem der ersten Altenheime alle 160 Bewohner getestet, nachdem in einem Zeitraum von 8 Tagen 3 Einzelfälle (**Einweisungen in Krankenhäuser aus unterschiedlichen Gründen, aber mit positivem Virusnachweis bei Aufnahme**) aufgetreten sind. Da wir immer alle zu testenden Personen beim Abstrich durch das Fachpersonal und Ärzten des Gesundheitsamtes untersucht und in Augenschein genommen haben, **hätten wir lediglich 2 Bewohner als krank oder möglicherweise krank eingestuft**. Im Ergebnis waren 117 Bewohner an diesem Tag in der PCR positiv! Im Verlauf der nächsten zwei Wochen sind viele der positiv getesteten Bewohner symptomatisch und krank geworden. In einer zweiten Testung nach 10 Tagen wurden von den bislang negativ gebliebenen nochmal 50 % mit positiver PCR gefunden."

   Einschätzung des RKI:
   Das hier dargestellte Vorgehen des GA entspricht unseren Empfehlungen im Dokument „Hinweise zur Testung von Patienten auf Infektion mit dem neuartigen Coronavirus SARS-CoV-2" sowie der Nationalen Teststrategie und weist nochmal auf die bei alten Menschen oft schwierig zu erkennende Symptomatik hin:

   „Auch im Rahmen der Prävention und des Managements von COVID-19 in Alten- und Pflegeeinrichtungen sowie in Einrichtungen für Menschen mit Beeinträchtigungen und Behinderungen kann es sinnvoll sein, Pflegepersonal und Heimbewohner ohne Beschwerden in Abstimmung mit der lokalen Gesundheitsbehörde periodisch hinsichtlich SARS-CoV-2 zu testen um prä-/asymptomatisch infizierte Personen zu identifizieren und Infektionsketten zu unterbrechen."

   Die Nationale Teststrategie sieht eine PCR-Testung von Personen mit leichten respiratorischen Symptomen wie leichtem Husten vor, wenn sie zu einer Risikogruppe zählen (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Teststrategie/NatTeststrat.html). Bei bestätigter SARS-CoV-2-Infektion sind zur Erkennung von Ausbrüchen PCR-testungen in Alten- und Pflegeheimen durchzuführen. In diesen Einrichtungen ohne COVID-Fall werden für Personal sowie Patienten, Bewohner, Betreute und asymptomatische Besucher Antigenschnelltests eingesetzt. Hierbei kann die Gesundheitsbehörde in Abhängigkeit von der lokalen Inzidenz, der Verfügbarkeit von Antigenschnelltestsystemen sowie der Testkapazität der lokalen Labore die Entscheidung treffen, PCR-Reihentestungen statt Antigenschnelltests einzusetzen. Bei asymptomatischen Besuchern kann auch in Abstimmung mit der Gesundheitsbehörde ein Antigenschnelltest durchgeführt werden.

   Abschnitt 5.2.4 des Dokuments ‚Prävention und Management von COVID-19 in Alten- und Pflegeeinrichtungen und Einrichtungen für Menschen mit Beeinträchtigungen und Behinderungen' (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Alten_Pflegeeinrichtung_Empfehlung.pdf) bezieht sich auf die Indikationsstellung einer SARS-CoV-2-testung und weist auf sehr niederschwellige und sofortige Testungen hin. In Abschnitt 7 (‚Hinweise zur SARS-CoV-2-Testung') desselben Dokuments werden in einer Übersicht zu ‚SARS-CoV-2-Testung in Alten- und Pflegeheimen und Einrichtungen für Menschen mit Beeinträchtigungen und Behinderungen' PCR-Testungen mit Antigenschnelltests gegenübergestellt. Für symptomatische Bewohner*innen/Betreute wird ein PCR-Test empfohlen.

   Die oben beschriebene in Augenscheinnahme folgt dem Musterformblatt ‚Erhebung von Erkältungssymptomen bei Bewohnern/Betreuten'.

   Des Weiteren berücksichtigt diese Vorgehensweise den in der Literatur gut etablierten Sachverhalt, dass insbesondere in Altenpflegeeinrichtungen ein rein symptombasiertes Screening einen Ausbruch nicht zuverlässig unterbinden kann (Arons et al.;https://www.nejm.org/doi/full/10.1056/NEJMoa2008457; Kimball et al. https://www.cdc.gov/mmwr/volumes/69/wr/mm6913e1.htm).

2. „In der Regel haben sich in allen Altenheimen im Ausbruchsgeschehen trotz aller Maßnahmen die Bewohner in 70 bis 100 % im Verlauf infiziert. **Viele Mitarbeiter vom Personal waren jeweils ebenfalls betroffen.** Eine Maßnahme im Wetteraukreis war ein **generelles Besuchsverbot** in Altenheimen von Mitte Dezember 2020 bis zum 31.01.2021. Einerseits um die Einrichtungen zu schützen, andererseits hat es auch einzelne, dokumentierte Infektionen bei Angehörigen durch unkontrollierte Besuche im Altenheim gegeben. FFP2 Maskenpflicht und mit zunehmender Verfügbarkeit (Ende Dezember) auch die Reihentestungen mit Antigenschnelltests."

   Einschätzung des RKI:
   Die vom GA getroffenen Maßnahmen folgen den Empfehlungen, die im Dokument „Prävention und Management von COVID-19 in Alten- und Pflegeeinrichtungen und Einrichtungen für Menschen mit Beeinträchtigungen und Behinderungen' niedergelegt sind, um Infektketten zu unterbrechen (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Alten_Pflegeeinrichtung_Empfehlung.pdf). Dennoch kam es zu ein

Ausbrüchen.
Es wurden Antigenschnelltests eingesetzt, von denen nicht bekannt ist, ob sie die in unseren Hinweisen zur Testung geforderte „akzeptable Sensitivität von ≥80% und eine akzeptable Spezifität von ≥97%“ bzw. eine wünschenswerte „Sensitivität von ≥90% und eine Spezifität von ≥99%“ gewährleisten (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Vorl_Testung_nCoV.html. Unter Abschnitt 5.2.4 (Diagnostische Testung auf SARS-CoV-2) des erstgenannten Dokuments wird ein PCR-Test einem Antigenschnelltest vorgezogen.

3. „Wir hatten in der ersten Welle (April/Mai 2020) einen Ausbruch in einem Altenheim, welches jetzt wieder betroffen war. **Alle Bewohner, die in der ersten Welle positiv getestet waren und jetzt noch gelebt haben, sind in der zweiten Welle in der PCR negativ getestet worden und waren unter vielen Neuinfizierten im direkten Umfeld jetzt quasi immun.“**

Einschätzung des RKI:
Diese Beobachtung passt zu veröffentlichten Daten, die den Verlauf der SARS-CoV-2-Immunität untersuchen (Dan et al.; https://science.sciencemag.org/content/371/6529/eabf4063); jedoch wird in dieser Arbeit nicht nach Altersgruppen unterschieden. **Es existieren keine spezifischen experimentellen Daten zur SARS-CoV-2-Immunität bei älteren Personen.**

4. Aufgrund der in diesen Ausbruchsgeschehen gemachten Beobachtungen ergeben sich folgende Fragen und daraus folgender Handlungsbedarf:

„**Das Krankheitsbild COVID-19 verläuft bei alten Menschen anders**, als wir das von den Einzelfällen in der ersten Welle und in den Monaten vor Dezember (hier waren allerdings auch überwiegend nur junge Menschen bis maximal 50 Jahren betroffen) beobachtet haben. Dies hat meines Erachtens mit dem Lebensalter und dem altersabhängigen Zustand des Immunsystems zu tun.
Die Wenigsten hatten schwere, akute Symptome direkt mit Symptombeginn. In der Regel waren die Verläufe über 3 bis 5 Wochen ab der positiven Testungen. Wir konnten im Prinzip vorhersagen, wenn die kritische Phase für die Mehrzahl der Betroffenen einsetzen würde, was auch eine Versorgung in den Heimen durch Hausärzte, Sauerstoff und Medikamente besser möglich gemacht hat. Gestorben sind die Menschen nicht in einem foudroyanten Krankheitsverlauf sondern eher in einer terminalen Erschöpfung, die palliativ gut zu begleiten war.“

Einschätzung des RKI:
Das RKI stimmt Dr. Merbs Einschätzung zu, dass mit erhöhtem Lebensalter eine Schwächung des Immunsystems (Immunseneszenz; https://pubmed.ncbi.nlm.nih.gov/29242543/) einsetzt und dies bei den gemachten Beobachtungen eine Rolle spielt. Die beobachteten Verläufe gleichen publizierten Arbeiten und sind in den RKI-Hinweisen zur Testung erwähnt:

„Arons et al. berichten über erfolgreiche Virusanzucht bis zu 6 Tage vor Symptombeginn. Einschränkend ist hier hinzuzufügen, dass klare zeitliche Eingrenzung des Symptombeginns nicht immer möglich ist, insbesondere wenn atypische oder paucisymptomatische Verläufe vorliegen (Graham et al., 2020; McMichael et al., 2020“; zitiert aus https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Vorl_Testung_nCoV.html).

Es ist denkbar, dass der Immunstatus und das Lebensalter die Zeitdauer der Ansteckungsfähigkeit beeinflussen. Hohes Alter stellt einen unabhängigen Risikofaktor für die längere Ausscheidung von SARS-CoV-2-RNA dar (Xu et al., 2020; https://academic.oup.com

/cid/article/71/15/799/5818308); Zheng et al., 2020; https://www.bmj.com/content /369/bmj.m1443).

Eine Hypothese zur geschwächten Immunität gegen SARS-CoV-2 im Alter basiert auf Immunseneszenz sowie ein erhöhtes Risiko für eine SARS-CoV-2-induzierte Immunpathologie. Mehrere SARS-CoV-kodierte strukturelle Proteine, die auch bei SARS-CoV-2 vorhanden sind, führen zu einer Unterdrückung der Interferon I-Antwort und einer sich daraus ergebenden geschwächten CD8 T-Zell-Antwort. Dieser altersbedingte schwächere Interferon I-Antwort in Verbindung mit viraler Suppression der zellulären Immunität könnte eine erhöhte Vulnerabilität älterer Menschen hervorrufen (Chen et al.;https://doi.org /10.1016/j.arr.2020.101205).

5. „Wir haben im Sommer und Herbst viele Reihentestungen (>1000 Tests) bei Schülern und Kindergartenkinder gemacht. Hier war in der Regel ein positiver Index und viele Kontaktpersonen. Wir haben nie einen Ausbruch mit Übertragungen nachweisen können. Dennoch wird es die gegeben haben, das zeigen Untersuchungen mit Antikörpernachweisen.

Der Unterschied zu den alten Menschen ist die zeitliche Präsenz des Virus auf der Schleimhaut. Der junge Mensch überwindet die „Infektion“ schnell und saniert seine Schleimhaut. Damit ist die Trefferquote bei einer Reihentestung extrem vom Idealzeitpunkt abhängig. Bei den alten Menschen persistiert das Virus nicht über Tage, sondern über Wochen auf der Schleimhaut und die Nachweisquote im Ausbruchsgeschehen ist entsprechend hoch.
Gleichzeitig wird das Virus auf der Schleimhaut auch in der Umgebung/Kontaktsituation weiter verbreitet. Das Individuum wird nicht wenige Tage ansteckend sein, sondern über Wochen. Dazu **das Mikroklima in Heimen (Kälteempfindliche ältere Herrschaften, wenig Lüftung, gut gewärmte Räume).**
Die Nachweisbarkeit des Virus über Wochen auf der Schleimhaut ist in einer großen Zahl von Einzelfällen unseres Kollektivs belegt, durchaus auch mit CT Werten unter 30 über Wochen. Viele Heimbewohner die Mitte Dezember erstmals positiv auf das Virus getestet waren, sind im Januar dann kritisch krank in Kliniken gekommen und hatten noch entsprechende Virusnachweise. Dies korreliert auch mit den Beobachtungen bei den schwer erkrankten Patienten in der Klinik, die auch über Wochen das Virus nicht eliminiert bekommen und damit wahrscheinlich auch ansteckend sind.“

Einschätzung des RKI:
Möglicherweise befindet sich bei älteren Menschen mehr und/oder über einen längeren Zeitraum Virus im Speichel, da sekretorisches IgA vermindert ist. Es existieren bislang keine Untersuchungen zum IgA-Gehalt im Speichel bei älteren Menschen, die an COVID-19 erkrankt sind. Allerdings ist bekannt, dass der IgA-Gehalt im Serum im Alter abnimmt (Buckley III and Dorsey; https://www.jimmunol.org/content/105/4/964) und dies gilt auch für sekretorisches IgA bei bakteriellen Infektionen (Heaney et al; https://academic.oup.com/biomedgerontology /article/70/12/1578/2605226).

Eine verlängerte Virusausscheidung bei Heimbewohnern wird diskutiert (Smorenberg et al. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7703548/). Nur in wenigen Arbeiten wird die Ausscheidungsdauer von replikationsfähigem Virus longitudinal untersucht (Kim et al., https://www.nejm.org/doi/full/10.1056/NEJMc2027040; Wölfel et al., https://www.nature.com/articles/s41586-020-2196-x sowie The COVID-19 Investigation Team, https://www.nature.com/articles/s41591-020-0877-5). In den letztgenannten zwei Publikationen wurde eine Ausscheidungsdauer replikationsfähiger Viren innerhalb der ersten

10 Tage nach Erkrankungsbeginn beschrieben. Auch basieren die Daten auf kleinen, vorwiegend jüngeren Patientenkollektiven.

Die oben bereits zitierte Arbeit von Arons et al. beschreibt in einem Fall die Virusanzucht 13 Tage nach Symptombeginn bei einer hochbetagten Person. Es handelt sich um eine Querschnittstudie, die nicht darauf abzielte, die Ausscheidungsdauer zu bestimmen. Das heisst, es lässt sich nicht ausschließen, dass unter alten Menschen replikationsfähiges Virus auch >13d ausgeschieden wird. (https://www.nejm.org/doi/suppl/10.1056/NEJMoa2008457/suppl_file/nejmoa2008457_appendix.pdf).

6. **Daraus folgt: Unsere Isolationszeiten nach Virusnachweis mit 14 Tagen sind für diese Altersgruppe viel zu kurz.** Das Schutzziel wird nicht erreicht, wenn die Isolationszeiten zu kurz sind. Gleichzeitig führen die „Empfehlungen" des RKI mittlerweile regelhaft zu Diskussionen, wenn wir die Isolationszeiten länger ansetzen.

7. Wir hatten diese Woche ein Altenheim mit einer Station mit 9 positiv getesteten Bewohnern, die seit dem 16.01.2021 in Isolation waren. Der Heimleiter hat sie mit Antigenschnelltest getestet, alle negativ somit forderte er die Aufhebung der Isolation auf Basis eines Tests, mit dem er auch seine Besucher vor Betreten der Einrichtung kontrolliert. Wir haben am gleichen Tag alle 9 Bewohner per PCR getestet: 8 waren positiv, auch mit CT Werten <30. Auf Basis dieser Tests werden Besuche in Altenheimen möglich gemacht, was ich fachlich für unhaltbar halte. Über die Aussagekraft negativer Schnelltests hatten wir uns ja wiederholt ausgetauscht.

Einschätzung des RKI:
Siehe Kommentar zu Punkt 2: Es wurden Antigenschnelltests eingesetzt, von denen nicht bekannt ist, ob sie die in unseren Hinweisen zur Testung geforderte „akzeptable Sensitivität von ≥80% und eine akzeptable Spezifität von ≥97%" bzw. eine wünschenswerte „Sensitivität von ≥90% und eine Spezifität von ≥99%" gewährleisten (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Vorl_Testung_nCoV.html Unter Abschnitt 5.2.4 (Diagnostische Testung auf SARS-CoV-2) des Dokuments ‚Prävention und Management von COVID-19 in Alten- und Pflegeeinrichtungen und Einrichtungen für Menschen mit Beeinträchtigungen und Behinderungen' (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Alten_Pflegeeinrichtung_Empfehlung.pdf) wird ein PCR-Test einem Antigenschnelltest vorgezogen.

Zusammenfassung:
Ein Gesundheitsamt in Hessen beobachtet vermehrt Ausbrüche in Altenheimen. In den Heimen werden regelmäßig auf Veranlassung der Heimleitung Antigenschnelltest-Untersuchungen auf SARS-CoV-2 bei Bewohnern und Belegschaft durchgeführt.

Das Gesundheitsamt vermutet, dass die Ausbrüche darauf beruhen, dass PCR-positiv getestete Personen nach Entlassung aus zweiwöchiger Isolation andere Mitbewohner im Heim anstecken, da sie auch noch darüber hinaus replikationsfähiges Virus ausscheiden. Es wird vermutet, dass dies mit einem schwächeren Immunsystem bei älteren Personen zusammenhängt und dass ältere Menschen im Gegensatz zu Jüngeren das Virus länger ausscheiden, eventuell, weil die IgA-Spiegel im Speichel bei Älteren geringer sind. Deshalb wird vorgeschlagen, die Isolation zu verlängern.

Daraus ergibt sich Frage 1: Wird eine Verlängerung der Isolation bei Ausbrüchen in Altenheimen oder älteren COVID-19- Erkrankten vom RKI empfohlen?

In einem Altenheim befanden sich seit dem 16.01.2021 9 Bewohner in Isolation, die anschließend mit einem vom Heimleiter eingesetzten Antigenschnelltest negativ getestet wurden. Daraufhin wurde von der Heimleitung die Aufhebung der Isolation gefordert. Mit dem gleichen Antigenschnelltest werden auch Besucher vor Betreten der Einrichtung kontrolliert. Das GA wiederholte die Testung am gleichen Tag mit einer PCR-Untersuchung, bei der 8 Personen positiv teilweise mit CT Werten <30 positiv waren. Auf Basis dieser Tests werden Besuche in Altenheimen ermöglicht.

Daraus ergibt sich Frage 2: Sind Antigenschnelltests bei der Testung von Risikopatienten und Besuchern von Altenheimen ausreichend? Existieren Antigenschnellteste, die den Anforderungen genügen? Welche Teststrategie sollte Anwendung finden?

Beschlussvorschläge

Antwortentwurf zu Frage 1: Wird eine Verlängerung der Isolation bei Ausbrüchen in Altenheimen oder älteren COVID-19-Erkrankten vom RKI empfohlen?

Isolationsdauer – derzeitiger Stand
Die Entlasskriterien aus der häuslichen Isolierung (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Entlassmanagement-Infografik.pdf?__blob=publicationFile) sehen bei jedem Krankheitsverlauf eine Entisolierung frühestens 10 Tage nach Symptombeginn (bei asymptomatischen Verläufen nach Erstnachweis des Erregers) vor. **Darüber hinaus ist bei mildem oder schwerem COVID-19-Verlauf eine 48-stündige Symptomfreiheit gefordert.** Bei schwerem Verlauf ist außerdem ein negatives PCR-Testergebnis oder alternativ ein positives PCR-Ergebnis nur unterhalb eines definierten Schwellenwertes nötig, der eine Aussage über die Anzuchtwahrscheinlichkeit erlaubt (quantitative Bezugsprobe Zellkulturüberstand < 10^6 Kopien/ml).

Abschnitt 3.4 des Dokuments ‚Prävention und Management von COVID-19 in Alten- und Pflegeeinrichtungen und Einrichtungen für Menschen mit Beeinträchtigungen und Behinderungen' (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Alten_Pflegeeinrichtung_Empfehlung.pdf) beschreibt Kriterien zur Aufhebung der Isolierung in Alten- und Pflegeheimen beschrieben. Hierzu zählen Symptomfreiheit für mindestens 48 Stunden, eine mindestens 10-tägige Isolation nach Symptombeginn bzw. Erstnachweis des Erregers bei asymptomatischen Personen sowie eine negative PCR-Untersuchung auf SARS-CoV-2.

Vorschlag zur Diskussion:
Die Isolationsdauer sollte nach Maßgabe des GA verlängert werden können.
In den Entlasskriterien sollte nur ein negatives PCR-Testergebnis als Kriterium zur Entisolierung genannt werden **(oder:** Alternativ wird eine zweimalige positive PCR-Testung an Tag 14 unter Berücksichtigung des Schwellenwertes <10E^5 Kopien/ml akzeptiert.)

Antwortentwurf zu Frage 2: Sind Antigenschnelltests bei der Testung von Risikopatienten und Besuchern von Altenheimen ausreichend? Existieren Antigenschnellteste, die den Anforderungen genügen? Welche Teststrategie sollte Anwendung finden?

Derzeitige Teststrategie:
In Abschnitt 7 'Hinweise zur SARS-CoV-2 Testung des Dokuments ‚Prävention und Management von COVID-19 in Alten- und Pflegeeinrichtungen und Einrichtungen für Menschen mit Beeinträchtigungen und Behinderungen' (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Alten_Pflegeeinrichtung_Empfehlung.pdf) wird eine PCR- oder auch alternativ ein Antigenschnelltest

empfohlen: „Der sogenannte Antigen-Schnelltest kann jedoch auch als Einzeltest vor Ort (Point-of-Care-Test, POCT) d.h. in der Einrichtung eingesetzt werden“ mit dem Hinweis, dass „…aufgrund der geringeren Sensitivität und Spezifität der sachgerechte Einsatz der Antigen-Teste an bestimmte Indikationen und Bedingungen geknüpft“ ist. Diese werden in den ‚**Hinweise zur Testung von Patienten auf Infektion mit dem neuartigen Coronavirus SARS-CoV-2**‘ spezifiziert (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Vorl_Testung_nCoV.htm).
Auf Seite 25 desselben Dokuments werden für Symptomatische Bewohner*innen/Betreute/Mitarbeiter*innen, inklusive jeder ärztlich begründete Verdachtsfall als empfohlenes Testverfahren die PCR genannt. Nur im Ausnahmefall sollten Antigen-Tests angewendet werden, z.B. bei begrenzter PCR-Kapazität oder wenn ein Testergebnis schnell vorliegen muss.

Zahlreiche Antigenschnelltests erfüllen derzeit nicht die minimalen WHO-Kriterien zur Sensitivität und Spezifität. Daher ist ein Großteil der Antigenschnelltests zur frühzeitigen Erkennung kontagiöser Personen nur bedingt geeignet. Es existieren zwei Testsysteme, die den WHO-Anforderungen genügen:
SD Biosensor (https://www.medrxiv.org/content/10.1101/2020.10.01.20203836v1)
Panbio™Covid-19 Ag Rapid Test (https://www.medrxiv.org/content/10.1101/2020.11.20.20235341v1).

Vorschlag zur Diskussion: Für diese Patientengruppe sollen möglichst ausschließlich PCR-Untersuchungen durchgeführt werden. Zur Beendigung der Isolierung sollte 10-14 Tage nach dem ersten positiven PCR-Testergebnis eine zweite PCR-Untersuchung durchgeführt werden. Hierbei sollte die Viruslast der zweiten PCR negativ sein **oder** unter 10^5 Kopien/ml liegen.
Antigenschnellteste, die nicht die WHO Kriterien erfüllen, sollten im hochvulnerablen Bereich der Altenpflege nicht zum Einsatz kommen.
Der Einsatz von Antigenschnelltesten für diese Personengruppe ist zwingend mit dem zuständigen GA abzustimmen. Antigenschnellteste, die die WHO-Kriterien erfüllen, sollen nur im Fall eines Nicht-Ausbruchsgeschehens zur regelmäßigen Testung von Besuchern eingesetzt werden.

Textvorschlag zu Testung vorEntisolierung:

- V.a. für kognitiv eingeschränkte Bewohner ist eine Isolierung schwer umsetzbar. Lange Isolierungsdauer geht mit erheblicher psychischer Belastung einher.
- Daher ist eine testbasierte Strategie zur Beendigung der Isolierung sinnvoll
- Aufgrund des Hochrisikosettings sollte man die Kriterien zur Beendigung der Isolierung möglichst konservativ ansetzen:
    - Mindestens 10 (14?) Tage nach Symptombeginn bzw. 1. positiver PCR
    - Plus mindestens 3 Tage nachhaltige Besserung
    - Plus PCR mit Viruslast $<10^5$ Kopien/ml Ausgangsmaterial in 2 Abstrichen, die zu unterschiedlichen Zeitpunkten entnommen wurden

From: "Ryl, Livia" <RylL@rki.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 2/18/2021 8:31:41 AM
Subject: AW: ID 2769_1 _To do aus dem Krisenstab vom 05.02.2021
Attachments: 210217 Zusammenarbeit mit RKI_Übersicht_COVID_content.docx

---

Liebe Kolleginnen und Kollegen,

bezüglich der Frage zur Aktualisierung von Einträgen zum Thema COVID-19 auf www.gesund.bund.de durch das RKI habe ich am Montag mit Frau Ahmadi im BMG gesprochen (zuständig für Nationale Gesundheitsportal).
Ich habe ihr dargestellt, dass sich die Situation bei uns nicht entspannt hat und eine regelmäßige Überprüfung der Texte im Portal durch uns nicht zu leisten ist. Fr. Ahmadi machte deutlich, dass auf die Expertise (resp. Prüfung) durch das RKI nicht verzichtet werden kann. Die Agentur VALID, die die Seite betreut, beobachtet die Einträge zum Thema auf www.rki.de und nimmt teilweise selbständig Aktualisierungen vor. Fr. Ahmadi betonte aber, dass dies nicht immer durch VALID allein zu gewährleisten ist. Daher die Bitte an uns, die Texte bzw. Aktualisierungen zu prüfen.

Ich bitte um Beachtung der unten aufgeführten Mail von Fr. Ahmadi, die die Arbeitsweise darstellt.

Im Anhang befindet sich ein Dokument, welches die Aktualisierungsbedarfe der vier Texte und eines Videos zum Thema COVID-19 auf gesund.bund.de auflistet.

Mit freundlichen Grüßen
Livia Ryl

_____
Dr. Livia Ryl
Robert Koch-Institut
Abteilung für Epidemiologie und Gesundheitsmonitoring
General Pape-Str. 62-66
12101 Berlin

HomeOffice: 0160 5738701

Journal of Health Monitoring: www.rki.de/journalhealthmonitoring

Homepage: www.rki.de/gesundheitsmonitoring

_____

_____

-----Ursprüngliche Nachricht-----
Von: Ahmadi, Mina -524 BMG <Mina.Ahmadi@bmg.bund.de>
Gesendet: Mittwoch, 17. Februar 2021 14:55
An: Ryl, Livia <RylL@rki.de>
Cc: Schneider, Lisa -524 BMG <Lisa.Schneider@bmg.bund.de>
Betreff: Aktualisierung Inhalte des Nationalen Gesundheitsportals- Prozess der Prüfung

Liebe Frau Ryl,

im Nachgang zu unserem Gespräch am Montag sende ich Ihnen anbei die Übersicht über die Covid -19 relevanten Artikel auf dem Nationalen Gesundheitsportal, die je nach Bedarf mit dem RKI abgestimmt werden.

Die Redaktion bei VALID veranlasst eigenständig kleine Aktualisierungen und scannt die Infos auf der RKI Seite regelmäßig. Ansonsten haben wir VALID gebeten, die Artikel anstatt „geprüft durch“ mit „In Zusammenarbeit mit ..“ zu kennzeichnen. Das wird gerade umgesetzt. Der Irrtum mit dem Datum-Stempel liegt daran, dass die Agentur den Datum der geplanten Veröffentlichung hierfür verwendet hatte. Wir haben das geändert und werden hier immer das „Prüfdatum“ bzw. die Rückmeldung verwenden. Bitte entschuldigen Sie die Verwirrung hierzu.

Sollten Sie Fragen dazu haben, melden Sie sich gerne. Frau Schneider steht auch bei Rückfragen zur Verfügung, die ich in cc gesetzt habe.

Mit besten Grüßen

Im Auftrag

Mina Ahmadi

_____

Referat 524 – Nationales Gesundheitsportal

Bundesministerium für Gesundheit

Johannisstraße 5-6, 10117 Berlin

Postanschrift: 11055 Berlin

Tel. +49 (0)30 18441-1513

Mina.Ahmadi@bmg.bund.de

www.bundesgesundheitsministerium.de <http://www.bundesgesundheitsministerium.de>

www.twitter.com/BMG_Bund <http://www.twitter.com/BMG_Bund>

www.facebook.com/BMG.Bund <http://www.facebook.com/BMG.Bund>

Allgemeinverständliche Informationen zum Coronavirus:

https://www.infektionsschutz.de <https://www.infektionsschutz.de>

Fachinformationen zum Coronavirus:

https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/nCoV.html <https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/nCoV.html>

Hinweis zu externen Links:

Auf Art und Umfang der übertragenen bzw. gespeicherten Daten hat das BMG keinen Einfluss.

Der Schutz Ihrer Daten ist uns wichtig. Nähere Informationen zum Umgang mit personenbezogenen Daten im BMG können Sie der Datenschutzerklärung auf https://www.bundesgesundheitsministerium.de/datenschutz.html <https://www.bundesgesundheitsministerium.de/datenschutz.html> entnehmen.

Zusammenarbeit gesund.bund.de und RKI – Übersicht Inhalte zu COVID-19 und SARS-CoV-2

Artikel

Titel	Inhalt	Letzte Prüfung	Aktualisierung
COVID-19 – die Erkrankung in der Übersicht [https://gesund.bund.de/covid-19]	Krankheitsartikel mit Infos zu Symptomen, Ursachen, Risikofaktoren, Häufigkeit, Verlauf, Vorbeugung, Impfung, Diagnostik, Behandlung	05.02.2021	Erfolgt bei Bedarf; also, wenn gesetzliche Regelungen, neue Erkenntnisse oder andere wesentlichen Neuerungen vorliegen, die eine Aktualisierung erforderlich machen. Über RSS Feeds des RKI werden Entwicklungen regelmäßig (1 bis 2x wöchentlich) beobachtet. Auch die wesentlichen Zahlen im Artikel werden in diesem Zusammenhang geprüft und bei Bedarf angepasst.
COVID-19, Erkältung, Grippe: Kennzeichen im Überblick [https://gesund.bund.de/covid-19-erkaeltung-grippe]	Merkmale COVID, Kennzeichen Grippe, Eigenschaften Erkältung, Pandemie und Grippewelle, Schutzmaßnahmen	27.01.2021	Siehe Basisartikel oben. Aufgrund der Inhalte werden Aktualisierungen hier aber wahrscheinlich deutlich seltener erfolgen müssen.
COVID-19: Alles außer gewöhnlich [https://gesund.bund.de/covid-19-verlauf-folgeerkrankungen]	Informationen zu Besonderheiten bei COVID, Unterschied zu Grippe, Folgeerkrankungen, COVID bei Kindern und Schwangeren, COVID und Krankenhaus, Was tun bei Verdacht	27.01.2021	Siehe Basisartikel oben. Aufgrund der Inhalte werden Aktualisierungen hier aber wahrscheinlich deutlich seltener erfolgen müssen.
COVID-19-Impfung: Antworten auf die wichtigsten Fragen [Artikel noch nicht veröffentlicht]	Informationen zu den Impfstoffen, Wirksamkeit, Sicherheit, Nebenwirkungen, Durchführung Impfungen	04.02.2021	Hier werden sich sicherlich Aktualisierungen ergeben; die Entwicklung muss hier regelmäßig beobachtet werden.

Videos

Titel	Letzte Prüfung	Aktualisierung
COVID-19, Grippe oder Erkältung? [begleitend veröffentlicht in https://gesund.bund.de/covid-19-erkaeltung-grippe]	07.12.2021 (Datum der Freigabe)	Die Inhalte sind so gestaltet, dass im Prinzip kein Änderungsbedarf bestehen sollte. Da die Produktion deutlich aufwändiger ist als bei den Artikeln ist hier keine regelmäßige Aktualisierung vorgesehen. Man könnte aber ggf. einen Zeitpunkt festzulegen, an dem das Video in einen allgemeinen Re-Review geht, um zu entscheiden, ob und welche Änderungen umgesetzt werden können/sollen.
Was ist eine mRNA-Impfung? [in Bearbeitung]	Script noch nicht im Review/Freigabeprozess	s.o.

From: "Dreesman, Johannes" <Johannes.Dreesman@nlga.Niedersachsen.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 2/25/2021 4:27:36 PM
Subject: Situationsbericht Lk Leer wegen britischer VOC

Liebe Kolleginnen und Kollegen am RKI,

das GA des Landkreises Leer hat uns einen Situationsbericht gegeben, den ich gerne weitergeben möchte, aufgrund der Beteiligung der britischen VOC.
Im Lk Leer ist innerhalb von einer Woche die Inzidenz von ca. 60 auf 100 angestiegen.

Der Landkreis beobachtet einen sehr hohen Anteil der britischen Variante.
Bei ca. 40% der laborbestätigten SARS-Cov-2-Fälle wird diese Variante nachgewiesen, hinzu kommen weitere laborbestätigte SARS-Cov-2-Fälle mit epidemiologischem Zusammenhang, bei denen aber keine Variantentestung durchgeführt wurde, so dass der tatsächliche Anteil auf weit über 50 % geschätzt wird.

Die britische Variante wird als weit infektiöser wahrgenommen bzw. weitaus stärker durch Aerosole übertragbar als das Wildvirus. Nach Einschätzung des GA haben sich Personen nachweislich in Situationen angesteckt, wo sie nur als Kontaktpersonen 2 gelten würden, also bei nur sehr kurzem Aufenthalt im selben Raum oder trotz Anwendung von Masken.

Bei den positiv getesteten Fällen sei der Ct-Wert auch deutlich geringer, als man es vom Wildvirus gewohnt sei, bis runter auf einen Ct-Wert von 6 (Bei dem Wildvirus sei man eigentlich nur Wert ab 20 gewohnt).

In manchen Fällen seien positive Nachweise bei Kontaktpersonen sehr schnell aufgetreten, früher als gewohnt, in anderen Fällen erst am Tag 13 nach Kontakt.

Wenn man die Fälle nach 14 Tagen nachgetestet hatte, sei ein sehr großer Anteil immer noch deutlich positiv gewesen (mit Ct-Werten im infektiösen Bereich).

Vor diesem Hintergrund hat der Landkreis Leer entschieden, bereits die initiale Isolierung der Fälle gleich für drei Wochen anzuordnen sowie die Quarantäne für die Haushaltskontaktpersonen ebenfalls.
Hierüber wird auch heute bei uns im NDR berichtet.
Für die übrigen Kontaktpersonen spricht der Lk Leer die Quarantäne weiterhin für zwei Wochen aus.

Für weitere Rückfragen steht vor Ort auch Frau Dr. Schäpker zur Verfügung, unter Tel. 0491 926 1152.

Mit freundlichen Grüßen
Im Auftrag
Johannes Dreesman

Dr. Johannes Dreesman, MSE
Niedersächsisches Landesgesundheitsamt
Roesebeckstr. 4-6; 30449 Hannover
Tel.: 0511/4505-20[redacted]
e-mail: Johannes.Dreesman@nlga.niedersachsen.de

From: "Ulatowski, Jan" <Jan.Ulatowski@BDR.de>
To: "Rottmann-Gro /ner, Heiko -61 BMG" <Heiko.Rottmann-Grossner@bmg.bund.de>
Date: 2/28/2021 7:27:18 PM
Subject: DEA-Meldung: St ≈rung Reisenden-Portal
Attachments: 210228_DEA_Incident.docx

Sehr geehrter Herr Rottmann-Großner,

in der Anlage übersende ich Ihnen die Meldung zur heutigen DEA-Störung, hervorgerufen durch einen Angriff auf die DEA-Systemverfügbarkeit:

- 1. Angriff: 15:46 Uhr bis 16:56 Uhr
- 2. Angriff: 17:38 Uhr bis 18:45 Uhr

Durch die Angriffe gab es Einschränkungen hinsichtlich der Verfügbarkeit des DEA-Dienstes. Die Schutzmechanismen zum Schutz von Vertraulichkeit & Integrität haben funktioniert.
Für etwaige Rückfragen stehen wir Ihnen gern zur Verfügung.

Mit freundlichen Grüßen
Jan Ulatowski
CMS (Credential Management Systems)
Abteilungsleitung PSM (Projekt- und Service-Management)

Bundesdruckerei GmbH
Kommandantenstr. 18 10969 Berlin
T + 49 (0) 30 – 2598 - 2562
jan.ulatowski@bdr.de
www.bundesdruckerei-gmbh.de
Sitz der Gesellschaft: Berlin
Handelsregister: AG Berlin-Charlottenburg HRB 70764 B. USt-IdNr.: DE 812746617
Geschäftsführer: Dr.-Ing. Stefan Hofschen (CEO), Christian Helfrich (stellv. Vorsitzender)

DEA - Incident-Meldeformular Datum: 28.02.2021

Beschreibung / Titel:

Bitte Problembeschreibung in einigen Worten angeben

Einschränkung der Verfügbarkeit DEA Digitale Einreiseanmeldung am 28.02.21 15:46 Uhr bis 18:45 Uhr

Kundenkontakt

Eingabe der Kundenkontaktdaten, für mögliche Rückfragen zur Incident Beschreibung:

Name	Firma	E-Mail	Telefon	Mobiltelefon
Ulatowski	BDr	Jan.ulatowski@bdr.de		[redacted]
Ehreke	BDr	Jens.ehreke@bdr.de		

Auswahl der Komponenten

Komponenten:
[x] Frontend Reisende [] Frontend Gesundheitsämter [] Backend-DB [] Liste Risikogebiete [] CDN [] Infrastrukture [] Entwicklungsumgebung [] Testumgebung [] Produktivumgebung [] …

Auswahl Servicepriorität:

Priorität
[] 3 – minor [] 2 – serious [x] 1 – critical

Fehlerklassen	Definition	Beispiel
Priorität 1 (critical) Nur für Produktivsysteme	Der Geschäftsbetrieb und der Service sind unterbrochen.	Der Incident verursacht z.B. den Ausfall des Reisenden-Frontends.
Priorität 2 (serious)	Das System ist ganz oder teilweise verfügbar. Ein wesentlicher Teil des Systems ist ausgefallen oder nicht verfügbar. Der Incident muss so schnell wie möglich behoben werden.	Ein Incident schränkt den Zugriff auf einen Service ein, z.B. Frontend für die Gesundheitsämter. Es gibt wesentliche Einschränkungen für den Betrieb.
Priorität 3 (minor)	Geringer Einfluss oder Unterbrechung: IT Probleme, andere Services oder Funktionen sind eingeschränkt. Wesentliche Komponenten der Anwendung sind verfügbar.	Ein Incident verursacht eine nicht wesentliche Einschränkung der Anwendung, ohne Einfluss auf die Erreichbarkeit, Funktionsweise oder Layout der Anwendung.

Detaillierte Incident-Beschreibung

Detaillierte Beschreibung des Problems. Einfügen von Screenshot und zusätzlichen Dokumenten

Ablauf:

15:50 Uhr Störung identifiziert: DEA-Dienst nicht verfügbar

15:50 Uhr Störungsmeldung an Entstörungsteam

seit 15:50 Uhr Störungsanalyse

Ursachenanalyse techn. Störung & Maßnahmen

- Angriff auf Systemverfügbarkeit durch DDos-Attacke von unbekannter Seite
    - 1. Angriff: 15:46 Uhr bis 16:56 Uhr
    - 2. Angriff: 17:38 Uhr bis 18:45 Uhr
- dadurch Einschränkung der Verfügbarkeit
- Schutzmechanismen haben hinsichtlich Schutz von Vertraulichkeit & Integrität funktioniert
- eingeleitete Maßnahmen:
    - Black-Holing der Einreiseportal-IP-Adresse um 18:03 Uhr
    - Anpassung des Mechanismus zum Schalten der Störungsseite auch bei Angriffen

Meldekette:

- Informierung BDr-Eskalationshotline um 16.32 Uhr
- nachfolgend telefonische Informierung BMG-Bereitschaftsdienst
- nachfolgend telefonische Informierung RKI-Bereitschaftsdienst durch PL (nicht erfolgreich, da außerhalb der üblichen Dienstzeiten)
- Informierung BMG/RKI per E-Mail um 17:18 Uhr

Störungsseite:

- Umschalten auf Störungsseite war nicht möglich, da von Angriff mit betroffen
- Workaround für Schalten der Störungsseite bei erneutem Angriff implementiert:
    - Umstellung Störungsseite auf AWS

From: "Chmielewska, Justyna -611 BMG" <Justyna.Chmielewska@bmg.bund.de>

To: AGInfektionsschutz <aginfektionsschutz@rki.de>
"Jahn, Klaus \(msagd\)" <Klaus.Jahn@msagd.rlp.de>
"Marcic, Dr., Anne \(Sozialministerium\)" <Anne.Marcic@sozmi.landsh.de>
"Poloschek, Christiane" <C.Poloschek@wm.mv-regierung.de>
R.Iwohn@wm.mv-regierung.de
AGI.MV@wm.mv-regierung.de
m.gebauer@wm.mv-regierung.de
Infektionsschutz@stmgp.bayern.de
Alexandra.Adler@stmgp.bayern.de
Marion.Scharte@stmgp.bayern.de
"Pfob, Martina, Dr. \(StMGP\)" <Martina.Pfob@stmgp.bayern.de>
"Heimsoth-Ranft, Dirk \(Die Senatorin f ≥r Gesundheit, Frauen und Verbraucherschutz\)" <dirk.heimsoth-ranft@GESUNDHEIT.BREMEN.de>
heidrun.boehm@sms.sachsen.de
andrea.shanati@sms.sachsen.de
h.christian@soziales.saarland.de
"Dennebaum, Lisa \(msagd\)" <Lisa.Dennebaum@msagd.rlp.de>
fabian.feil@ms.niedersachsen.de
jan.franke@tmasgff.thueringen.de
beate.handschak@ms.sachsen-anhalt.de
regine.kaemmerer@mags.nrw.de
Anne.Kolenbrander@mags.nrw.de
julia.ewers@mags.nrw.de
Marlen.Suckau-Hagel@SenGPG.Berlin.de
FB_Gesundheit3@SenGPG.Berlin.de
Sylke.Oberwoehrmann@SenGPG.Berlin.de
"Ollroge, Frank Dr." <frank.ollroge@bgv.hamburg.de>
"Bayer, Anita" <anita.bayer@bgv.hamburg.de>
"Jakubowski, Elke Dr." <elke.jakubowski@bgv.hamburg.de>
isolde.piechotowski@sm.bwl.de
cornelius.siewerin@ms.niedersachsen.de
wiebke.sydow@sms.sachsen.de
sabine.totsche@hsm.hessen.de
heidemarie.willer@ms.sachsen-anhalt.de

"H Ƶhne, Anke" <anke.huehne@ms.sachsen-anhalt.de>
"Pitloun, Uta" <Uta.Pitloun@ms.sachsen-anhalt.de>
angela.wirtz@hsm.hessen.de
Matthias.Trost@hsm.hessen.de
"Erkens, Harald Peter -411 BMG" <HaraldPeter.Erkens@bmg.bund.de>
"611 BMG" <611@bmg.bund.de>
"Sangs, Andr ᵛ-611 BMG" <Andre.Sangs@bmg.bund.de>
"Ziegelmann Dr., Antina -RL 614 BMG" <Antina.Ziegelmann@bmg.bund.de>
"614 BMG" <614@bmg.bund.de>
"Taube , Jannis - 315 BMG" <Jannis.Taube@bmg.bund.de>
oegd@stmgp.bayern.de
agi@hsm.hessen.de
"BGV ∃ffentlicher Gesundheitsdienst" <oeffentlichergesundheitsdienst@bgv.hamburg.de>
infektionsschutz@ms.niedersachsen.de
"Infektionsschutz \(Sozialministerium\)" <Infektionsschutz@sozmi.landsh.de>
infektionshygiene@tmasgff.thueringen.de
Oliver.Ommen@bzga.de
linda.seefeld@bzga.de
britta.reckendrees@bzga.de
"Horn Dr., Matthias" <MatthiasHorn@bmvg.bund.de>
Bianca.Garber@SenGPG.Berlin.de
3LZCOVID19 <3LZCOVID19@bmg.bund.de>
"Hell Stefan \(Soziales\)" <S.Hell@soziales.saarland.de>
"Gesch Lftsstelle Nationaler Impfplan \(LGL\)" <NIP-Geschaeftsstelle@lgl.bayern.de>
"Ziehm, Dagmar Dr. \(MS\)" <dagmar.ziehm@ms.niedersachsen.de>
infektionsschutz-corona@stmgp.bayern.de
AL4@gesundheit.bremen.de
martina.enke@stmgp.bayern.de
infektionsschutz-corona@stmgp.bayern.de
Markus.Schaefer@sm.bwl.de
Josefine.Negrassus@sm.bwl.de
Ralf.Wagner@pei.de
Heidi.Meyer@pei.de
Referat-VB4@mags.nrw.de

oegd-corona@mags.nrw.de
G.Koch@wm.mv-regierung.de
sonja.polz@gesundheit.bremen.de
m.binkert@soziales.saarland.de
"113 BMG" <113@bmg.bund.de>
COVID-19-vaccines <COVID-19-vaccines@bmg.bund.de>
"Matysiak-Klose Dr., Dorothea -614 BMG" <Dorothea.Matysiak-Klose@bmg.bund.de>
Ulrich.Widders@MSGIV.Brandenburg.de
Detlef.Berndt@MSGIV.Brandenburg.de
Cornelia.Winten@HSM.hessen.de
Gabriele.Kloeckler@sm.bwl.de
Benno.Schulz@tmasgff.thueringen.de
Frank.Schenker@tmasgff.thueringen.de
Gabriela.Kratzer@tmasgff.thueringen.de
infektionsschutz@sms.sachsen.de
Jens.heimann@sms.sachsen.de
wiebke.sydow@sms.sachsen.de
Fabian.Drebert@msagd.rlp.de
FB_LAGeSo@SenGPG.Berlin.de
alexandra.vonreiswitz@soziales.hamburg.de
"Lange-Bratanova, Elena -611 BMG" <Elena.Lange-Bratanova@bmg.bund.de>
"Wambach, Avila-Victoria -611 BMG" <Avila-Victoria.Wambach@bmg.bund.de>
Bernhard.Stockmeyer@stmgp.bayern.de

Date: 3/1/2021 10:57:39 AM

Subject: St ≈rung des DEA-Systems

Liebe Kolleginnen und Kollegen,

wir mochten Sie informieren, dass es derzeit wegen Cyber-Angriffe massive Storungen beim Zugang zur digitalen Einreiseanmeldung (DEA) gibt. Die Bundesdruckerei arbeitet mit Hochdruck an einer Losung, es kann aber sein, dass das System ca. die nachsten 3 Tage nicht verfugbar sein wird.

Solange die Storung andauert, werden die Einreiseanmeldungen uber die Papier-Ersatzmitteilung (https://www.bundesgesundheitsministerium.de/coronavirus-infos-reisende/merkblatt-dea.html

) abgewickelt und in gescannter Form den zustandigen Behorden zur Verfugung gestellt.

Mit freundlichen Gru?en

Justyna Chmielewska

Referat 611 - Gesundheitssicherheit, Krisenmanagement national
Bundesministerium fur Gesundheit

Unter den Linden 21, 10117 Berlin

Postanschrift: 11055 Berlin
Tel. +49 (0)30 18441-4406
justyna.chmielewska@bmg.bund.de
www.bundesgesundheitsministerium.de

From: "Rottmann-Gro /ner, Heiko -61 BMG" <Heiko.Rottmann-Grossner@bmg.bund.de>
To: Epialert <epialert@rki.de>
nCoV-Lage <nCoV-Lage@rki.de>
DEA-Koordination <DEA-Koordination@rki.de>
"611 BMG" <611@bmg.bund.de>
9.KriSta@bmi.bund.de
"LAGEZENTRUM Lagezentrum, Auswaertiges Amt" <lagezentrum@auswaertiges-amt.de>
Lagezentrum@bmvi.bund.de
Date: 2/28/2021 8:15:58 PM
Subject: z.K. - Erneute Cyber-Angriffe auf DEA

Nochmals „guten Abend“!

Die BDr meldet eine erneute „Angriffswelle“ auf die DEA-Server. Es könnte sein, dass diese Versuche sich die gesamte Nacht über fortsetzen werden.

Die BDr versucht zumind. die Ausweichseite zu stabilisieren.

Freundliche Grüße
Heiko Rottmann
BMG 61; T. 030.18441-3700

Von: Rottmann-Großner, Heiko -61 BMG
Gesendet: Sonntag, 28. Februar 2021 20:30
An: Epialert ; nCoV-Lage ; 'DEA-Koordination@rki.de' ; 611 BMG <611@bmg.bund.de>; '9.KriSta@bmi.bund.de' <9.KriSta@bmi.bund.de>; LAGEZENTRUM Lagezentrum, Auswaertiges Amt ; Lagezentrum@bmvi.bund.de
Cc: 6 BMG <6@bmg.bund.de>; 61 BMG <61@bmg.bund.de>; Gülde, Sebastian -L7 BMG ; Holtherm Dr., Hans-Ulrich -AL 6 BMG ; Chmielewska, Justyna -611 BMG ; Wambach, Avila-Victoria -611 BMG ; Lücking Dr., Gesa -611 BMG ; Sangs, André -611 BMG ; Bayer Dr., Christophe -612 BMG ; 612 BMG <612@bmg.bund.de>; 1LZCOVID19 <1LZCOVID19@bmg.bund.de>
Betreff: Cyber-Angriffe auf DEA
Priorität: Hoch
Vertraulichkeit: Vertraulich

Guten Abend,

wie z.T. heute schon mitgeteilt, gab es heute 2 x massive Störungen beim Zugang zur DEA.

Wie sich inzwischen herausstellte, handelte es sich hierbei um Cyber-Angriffe, bei denen mit einer erheblichen Anzahl von Anfragen die entspr. Server „in die Knie“ gezwungen werden sollten.

Daten sind laut BDr nicht abgeflossen, dennoch war das Angebot zwischenzeitlich gestört oder nicht erreichbar.

Ein schriftl. Bericht der BDr an RKI und BMG folgt in Kürze.

Freundliche Grüße
i.A.
Heiko Rottmann
BMG 61; T. 030.18441-3700

From: "Mielke, Martin" <MielkeM@rki.de>
To: "Korr Dr., Gerit Solveig -614 BMG" <GeritSolveig.Korr@bmg.bund.de>
Date: 2/25/2021 7:49:00 AM
Subject: Im Nachgang zur heutigen AG Testen/ Diagnostik (Länderkoordinatoren , 26.2.2021)
Attachments: Fortgang der Diskussion zu AG-Testen (Bevölkerung).msg
2021-02-22_Nationale Teststrategie_kurz.pptx
RapidTests_Konzeptpapier_Schule_TRACE_v1_0.pdf
s12889-020-10153-1.pdf
nejmp2028209.pdf
PIIS2352464220302509.pdf
2020.10.11.20211011v2.full.pdf
paltiel_2020_oi_200614_1597251392.14363.pdf
covid-19-objectives-school-testing.pdf

Liebe Frau Korr,

die heutige Diskussion mit den Länderkoordinatoren zeigt, wie wichtig es ist, den Einsatz der AG-Tests (professionell versus privat) gut zu kommunizieren. Dazu gehört wohl auch, den bisherigen professionellen Einsatz nicht leichtfertig mit dem geplanten breiten Einsatz von Selbsttests (außerhalb definierter Bereiche) zu vermischen. Das in der AG Testen (BMG) ja sorgfältig besprochene Diagramm berücksichtigt dies ja noch in sachgerechter Weise (s. Anlage; Nationale Teststrategie).

Mit der Testung in Schulen (Bereich Bildung) und Betrieben (Betriebsarzt) in Ergänzung zum Gesundheitsbereich (der ja in der Nationalen Teststrategie seit langem gut verankert ist) könnte ja bereits eine breite Bevölkerung (Familien, Berufstätige, Pflegepersonal, hospitalisierte Bevölkerung) (regelmäßig) erreicht werden.

Die Rolle der "Türöffner-Tests" bleibt schwierig.

SCHULEN:

Zu den Schulen und der Situation in Österreich hatte ja Herr Müller bereits eine Nachricht gesendet.

Ich füge hier noch weitere Literatur sowie Links zum Thema Testung in Schulen bei (s. Anlagen).

Nach meiner Einschätzung könnten z.B. BW , Hessen, Berlin, Brandenburg, SH und MV sehr konstruktiv zur Diskussion beitragen (Erfahrungsberichte):

https://kinderbrauchenkinder-petition.de/wp-content/uploads/2020/11/2020-11_OffBrief_Positionspapier_Schnelltests-Schulen.pdf

https://kultusministerium.hessen.de/presse/pressemitteilung/einsatz-von-antigen-schnelltests

https://www.baden-wuerttemberg.de/de/service/presse/pressemitteilung/pid/erste-eckpunkte-einer-erweiterten-teststrategie-fuer-kitas-und-schulen/

https://km-bw.de/,Lde/startseite/sonderseiten/testen-schule-corona

https://www.baden-wuerttemberg.de/de/service/presse/pressemitteilung/pid/zwei-anlasslose-schnelltests-pro-woche-fuer-schul-und-kitapersonal/

https://www.charite.de/klinikum/themen_klinikum/themenschwerpunkt_coronavirus/teststrategie/

https://www.aerzteblatt.de/nachrichten/113518/Wie-die-Berliner-Teststrategie-fuer-Schulen-und-Kitas-funktioniert

https://www.berlin.de/sen/bjf/corona/tests/

http://www.landtag.ltsh.de/infothek/wahl19/drucks/02100/drucksache-19-02182.pdf

https://www.unfallkasse-mv.de/service/aktuelles/detail/news/kita-beschaeftigte-fuer-wissenschaftliche-testreihe-gesucht.html

https://www.regierung-mv.de/Landesregierung/bm/Blickpunkte/Coronavirus/Coronavirus-%E2%80%93-Informationen-f%C3%BCr-schule/Corona%E2%80%93Teststrategie/

https://kkm.brandenburg.de/kkm/de/presse/pressemitteilungen/detail/~24-11-2020-kabinett-teststrategie-fuer-kitas-und-schulen-verlaengert

Gruß,
Martin Mielke

-----Ursprüngliche Nachricht-----
Von: Mielke, Martin
Gesendet: Donnerstag, 25. Februar 2021 08:56
An: 'Korr Dr., Gerit Solveig -614 BMG' <GeritSolveig.Korr@bmg.bund.de>
Cc: Schuldt Dr., Kathrin -614 BMG (Kathrin.Schuldt@bmg.bund.de) <Kathrin.Schuldt@bmg.bund.de>; Mahanty, Binod -614 BMG (Binod.Mahanty@bmg.bund.de) <Binod.Mahanty@bmg.bund.de>; Semrau Dr., Jutta -324 BMG <Jutta.Semrau@bmg.bund.de>; AL1-Sekretariat <AL1-Sekretariat@rki.de>
Betreff: Unterstützung zu TOP 2/ TOP 4 WG: AG Labor/Testung am Do, 25.02.21, 13:30 Uhr

Liebe Frau Korr,
in Ergänzung und ggf. Vorbereitung/ Unterstützung von TOP 2/ TOP 4 sende ich in der Anlage (Fortgang der Diskussion zu AG-Testen ...) eine aktuelle Synopse (ohne Anspruch auf Vollständigkeit).
Gruß,
Martin Mielke

-----Ursprüngliche Nachricht-----
Von: Korr Dr., Gerit Solveig -614 BMG <GeritSolveig.Korr@bmg.bund.de>
Gesendet: Mittwoch, 24. Februar 2021 18:24
An: AL1-Sekretariat <AL1-Sekretariat@rki.de>; 'Corman' <victor.corman@charite.de>; Jakob, Katharina -123 BMG <Katharina.Jakob@bmg.bund.de>; Kleymann-Hilmes, Janine <Kleymann-HilmesJ@rki.de>; 'Müller' <m.mueller@labor28.de>; 'Nübling' <Micha.Nuebling@pei.de>; 'Stößlein' <ekkehard.stoesslein@bfarm.de>; 'Walger' <walger@vdgh.de>; Mahanty, Binod -614 BMG <Binod.Mahanty@bmg.bund.de>; 'schlaudm@rki.de'; 'mielkem@rki.de'; 'Auch' <DAuch@KBV.DE>; 'seifriedJ@rki.de'; 'abusinM@rki.de'; 123 BMG <123@bmg.bund.de>; Hamouda, Osamah <HamoudaO@rki.de>; Böttcher, Sindy <BoettcherS@rki.de>; Schuldt Dr., Kathrin - 614 BMG <Kathrin.Schuldt@bmg.bund.de>; Nitsche, Andreas <NitscheA@rki.de>; 'Ciesek, Sandra' <Sandra.Ciesek@kgu.de>; 'van Diepen, Laura' <Laura.vanDiepen@bfarm.de>; 'Heinrich.Scheiblauer@pei.de' <Heinrich.Scheiblauer@pei.de>; Semrau Dr., Jutta -324 BMG <Jutta.Semrau@bmg.bund.de>
Cc: 614 BMG <614@bmg.bund.de>; Lange-Bratanova, Elena -611 BMG <Elena.Lange-Bratanova@bmg.bund.de>; Altner, Julia -228 BMG <Julia.Altner@bmg.bund.de>; Danek, Stella -612 BMG <Stella.Danek@bmg.bund.de>
Betreff: AG Labor/Testung am Do, 25.02.21, 13:30 Uhr

Liebe Kolleginnen und Kollegen,

morgen Donnerstag, 13.30 Uhr, findet erneut unser telefonischer Austausch statt.

Einwahldaten: Telefonnummer (0) 069 20009800 Zugangscode 7811937558#

Agenda:

TOP 1 Anzahl Testungen, Positivrate, Testkapazitäten, Lieferengpässe (RKI, ALM)

TOP 2 Informationen zum aktuellen Umsetzungsstand eines breiten und niedrigschwelligen Zugangs zu PoC-Antigentests; anbei aktueller Entwurf der erweiterten Teststrategie (noch nicht frei gegeben)

TOP 3 Erste drei Selbsttests nun zugelassen (siehe BfArM-Seite)
*was für Tests sind es (Material, Qualität, QR-Code?) (BfArM)
*Liefermengen/Vertrieb (123, VDGH?)

TOP 4 Diskussion sinnvoller und nicht sinnvoller Anwendungsbereiche für Selbsttests (für die geplante Kommunikation, nicht für die Strategie) (alle)

TOP 5 Terminmanagement PCR-Bestätigungstestungen nach Selbsttest (alle, KBV)

TOP 6 Entwicklung von Basis-Testkonzepten / Empfehlungen zur Erstellung von Testkonzepten (als Impuls für die Diskussion siehe beiliegendes Konzeptpapier für Schulen) (alle, RKI)

TOP 7 Sind Personen, die mit der Variante B.1.1.7 infiziert sind, zu Beginn der Infektion schon mit geringerer Viruslast infektiös im Vergleich zum Wildtyp? (gern KL, Prof. Ciesek)

TOP 8 Testung von Geimpften und Genesenen (gern RKI)

Herzlichen Dank für Ihre Unterstützung!

Mit freundlichen Grüßen

Im Auftrag

Dr. med. Gerit Solveig Korr, MSc

Referat 614 - "Infektionskrankheiten"

Bundesministerium für Gesundheit

Hausadresse: Lindencorso, Unter den Linden 21, 10117 Berlin

Postanschrift: 11055 Berlin

Tel. 030-18441-3287

GeritSolveig.Korr@bmg.bund.de <mailto:GeritSolveig.Korr@bmg.bund.de>

www.bundesgesundheitsministerium.de <http://www.bundesgesundheitsministerium.de>

www.twitter.com/BMG_Bund <http://www.twitter.com/BMG_Bund>

www.facebook.com/BMG.Bund <http://www.facebook.com/BMG.Bund>

Hinweise zu externen Links.

Auf Art und Umfang der übertragenen bzw. gespeicherten Daten hat das BMG keinen Einfluss.

Der Schutz Ihrer Daten ist uns wichtig. Nähere Informationen zum Umgang mit personenbezogenen Daten im BMG können Sie der Datenschutzerklärung auf https://www.bundesgesundheitsministerium.de/datenschutz.html <https://www.bundesgesundheitsministerium.de/datenschutz.html> entnehmen.

Bundesministerium für Gesundheit

Nationale Teststrategie SARS-CoV-2

Entwurf vom 18.02.2021

Für eine Aufzählung der spezifischen Einrichtungen und Personengruppen ist die Verordnung zum Anspruch auf Testung in Bezug auf einen direkten Erregernachweis des Coronavirus SARS-CoV-2 verbindlich.

Grundsätzlich gilt:
1) Erweiterte Basishygiene

2) Symptom-Monitoring

3) Gemäß Vorschriften Bund/Länder: Abstand halten, Hygieneregeln einhalten, Alltagsmaske tragen, Lüften (AHA+L)

Gesundheitswesen und andere vulnerable [illegible]

				Empfehlung Test-Typ: PCR-Test[2]	Antigentest[3]	Frequenz	Kosten-Regelung	Priorisierung (PCR)
Symptomatische Personen (mit respiratorischen Symptomen jeder Schwere[1])				■	▯ 4	●	K	1
Asymptomatische Personen	Testung nach bekannter Exposition	Kontakt-personen	Personen mit **Kontakt zu bestätigtem COVID-19 Fall** (z.B gleicher Haushalt, 15-minütiger Kontakt, sowie über Corona-[illegible]	■	▯ 4	●	VO	2
		Ausbruch	in Einrichtungen oder Unternehmen nach §§ 23 Abs. 3 und 36 Abs. 1 IfSG, z.B. Arztpraxen, Kitas, Schulen, Asylbewerberheime	■	▯ 5,6	●	VO	3
	Präventive Testungen in Krankenhäuser, Pflegeeinrichtungen, Praxen und weiteren definierten Settings[9]	Patienten, Bewohner, Betreute	bei **(Wieder-)Aufnahme** sowie vor ambulanten Operationen oder vor ambulanter Dialyse	■	▯ 4	●	VO,	3
			Regelmäßig: Reihentests nach Testkonzept der Einrichtung	▯	■ 7,8		K (KHG) VO	4
		Personal	**Anlass-bezogen:** vor Antritt einer neuen Arbeitsstelle	▯	■ 8	●	VO	4
			Regelmäßig: Reihentests nach Testkonzept der Einrichtung	▯ 10	■ 7		VO	4
		Besucher	**Anlass-bezogen**: vor Besuch der Einrichtung	▯	■ 8	●	VO	5

Arbeitsplatz, Bildungseinrichtungen u.a.

Asymptomatische Personen	Präventive Testungen	Personen im Beruf/ Schulen, Kitas	**Regelmäßig und Anlass-bezogen** Wenn Zusammenkünfte mit Menschen oder enger Kontakt am Arbeitsplatz nicht vermeidbar, z.B. Schule, Kita, Sammelunterkünfte; Im Rahmen eines Hygienekonzepts	▯	■ 7,8	●	VO	5

■ Empfohlen
■ Möglich
■ Möglich bei begrenzter Kapazität
▯ Zur Bestätigung von positivem Point-of-Care Antigentest
● Akut (Wiederholung bis zu einmal pro Person)

Mindestens 2x wöchentlich, abhängig von Testkonzept der Einrichtung/Unternehmen

1) Differenzialdiagnostische Aspekte berücksichtigen (z.B. Influenza)
2) Labor-basierte (einschließlich solcher zur Feststellung von Virusvarianten) und Point-of-Care PCR-Tests
3) Bei positivem Antigen-Testergebnis Bestätigung durch PCR
4) Falls schnelles Resultat notwendig
5) Ggf. zur Kohorten-Isolierung
6) Z.B. auch labor-basierte Antigen-Tests zur Entlastung von Kapazitäten
7) Empfehlungen für Reihentestungen: Abstimmung mit der lokalen Gesundheitsbehörde, Einhaltung der Hygienemaßnahmen
8) Nur Point-of-Care Antigentest gemäß VO
9) Umfasst auch Einrichtungen für: Menschen mit Behinderungen, Rehabilitation, Ambulante Operationen, Ambulante Pflege, Ambulante Dialyse, Tageskliniken, Eingliederungshilfe, Hospizdienste, Arztpraxen, Zahnarztpraxen, Rettungsdienste und Praxen anderer humanmedizinischer Heilberufe nach §23 Abs. 3, Satz 1 Nr. 9 IfSG
10) PCR zusätzlich für Reihentests in bestimmten Einrichtungen möglich, Veranlassung durch Öffentlichen Gesundheitsdienst erforderlich

K = Krankenbehandlung; KHG = Krankenhausfinanzierungsgesetz
VO = Verordnung zum Anspruch auf Testung in Bezug auf einen direkten Erregernachweis des Coronavirus SARS-CoV-2

Bundesministerium für Gesundheit

Nationale Teststrategie SARS-CoV-2

Stand 08.02.2021

Für eine Aufzählung der spezifischen Einrichtungen und Personengruppen ist die Verordnung zum Anspruch auf Testung in Bezug auf einen direkten Erregernachweis des Coronavirus SARS-CoV-2 verbindlich.

Grundsätzlich gilt:

1) Erweiterte Basishygiene

2) Symptom-Monitoring

3) Gemäß Vorschriften Bund/Länder: Abstand halten, Hygieneregeln einhalten, Alltagsmaske tragen, Lüften (AHA+L)

				Empfehlung Test-Typ: PCR-Test[2]	Empfehlung Test-Typ: Antigentest[3]	Frequenz	Kosten-Regelung	Priorisierung
Symptomatische Personen[1]				■	□ [4]	●	K	1
Asymptomatische Personen	**Allgemeinbevölkerung (exponiert)**		**Kontaktpersonen**: Personen mit **Kontakt zu bestätigtem COVID-19 Fall** (z.B gleicher Haushalt, 15-minütiger Kontakt, sowie über Corona-Warn-App)	■	□ [4]	●	K VO,	2
			Bei **Ausbruch**: Personen in Einrichtungen oder Unternehmen nach §§ 23 Abs. 3 und 36 Abs. 1 IfSG, z.B. Arztpraxen, Kitas, Schulen, Asylbewerberheime	■	■ [5,6]	●	K VO	3
	Krankenhäuser, Pflegeeinrichtungen, Einrichtungen für -Menschen mit Behinderungen -Rehabilitation -Ambulante Operationen -Ambulante Pflege -Ambulante Dialyse -Hospizdienste	**Patienten, Bewohner, Betreute**	**(Wieder-)Aufnahme** sowie vor ambulanten Operationen oder vor ambulanter Dialyse	■	□ [4]	●	VO,	3
			bei Ausbruch	■	■ [5,6]	●	K (KHG) VO	2
			ohne **COVID-19 Fall**	□	■ [7,9]	●	VO	5
		Personal	**bei Ausbruch**	■	■ [5,6]	●	VO	2
			ohne **COVID-19 Fall**	■ [11]	■ [7]	●	VO	4
		Besucher	vor Besuch der Einrichtung	■	■ [7,9]	●	VO	5
	(Zahn)-, Arztpraxen, weitere Praxen[10], ...	**Personal**	**bei Ausbruch**	■	■ [5,6]	●	VO	2
			ohne **COVID-19 Fall**	□	■ [7]	●	VO	4

■ Empfohlen
■ Möglich
■ Möglich bei begrenzter Kapazität
□ Möglich, Kosten nicht durch VO gedeckt
● Akut (Wiederholung bis zu einmal pro Person)

Regelmäßig, abhängig von Testkonzept der Einrichtung/Unternehmen

1) Differenzialdiagnostische Aspekte berücksichtigen (z.B. Influenza)
2) Labor-basierte (einschließlich solcher zur Feststellung von Virusvarianten) und Point-of-Care PCR-Tests
3) Bei positivem Antigen-Testergebnis Bestätigung durch PCR
4) Falls schnelles Resultat notwendig
5) Ggf. zur Kohorten-Isolierung
6) Z.B. auch labor-basierte Antigen-Tests zur Entlastung von Kapazitäten
7) Empfehlungen für Reihentestungen: Abstimmung mit der lokalen Gesundheitsbehörde, erhöhte 7-Tage-Inzidenz, von z.B. >50/100.000, Einhaltung der Hygienemaßnahmen
8) Empfohlen bei 7-Tage-Inzidenz >50/100.000, Einhaltung der Hygienemaßnahmen
9) Nur Point-of-Care Antigentest gemäß VO
10) Praxen anderer humanmedizinischer Heilberufe nach §23 Abs. 3 Satz 1 Nr. 9 IfSG
11) Veranlassung durch Öffentlichen Gesundheitsdienst erforderlich

K = Krankenbehandlung
KHG = Krankenhausfinanzierungsgesetz
VO = Verordnung zum Anspruch auf Testung in Bezug auf einen direkten Erregernachweis des Coronavirus SARS-CoV-2

Initiative RapidTests
Ansprechpartnerin: Dr. Franziska Briest
Kontakt: mail@rapidtests.de
Webseite: www.rapidtests.de

Version v1.0
23. Februar 2021

Konzeptpapier: Selbsttestungen mit Antigen-Schnelltests an Schulen und Kindertagesstätten mittels “TRACE”

Inhaltsverzeichnis

0. Executive Summary

Antigen-Schnelltests können dazu beitragen, SARS-CoV-2-Eintragungen in **Bildungs- und Betreuungseinrichtungen** (Schulen, Kitas, Kinderhorte etc.) frühzeitig zu erkennen und Ausbrüche zu verhindern. Das **regelmäßige (Inzidenz-abhängige) Testen** des Lehr- und Betreuungspersonals, aber auch der Kinder und Jugendlichen ist dabei unerlässlich. Mit der Zulassung von einfach anwendbaren **Antigen-Schnelltests als Selbsttests für Lai:innen** ist es möglich, genau dies zu tun. Mittlerweile sind unabhängig geprüfte Antigen-Schnelltests erhältlich, welche über einen schmerzfreien Abstrich im vorderen Nasenraum unter Aufsicht sogar von Kindern zuverlässig durchgeführt werden können. In Österreich kommen diese bereits zur Anwendung. Um eine Teststrategie in Schulen und Kitas optimal zu implementieren, haben wir das **TRACE-Modell** entwickelt:

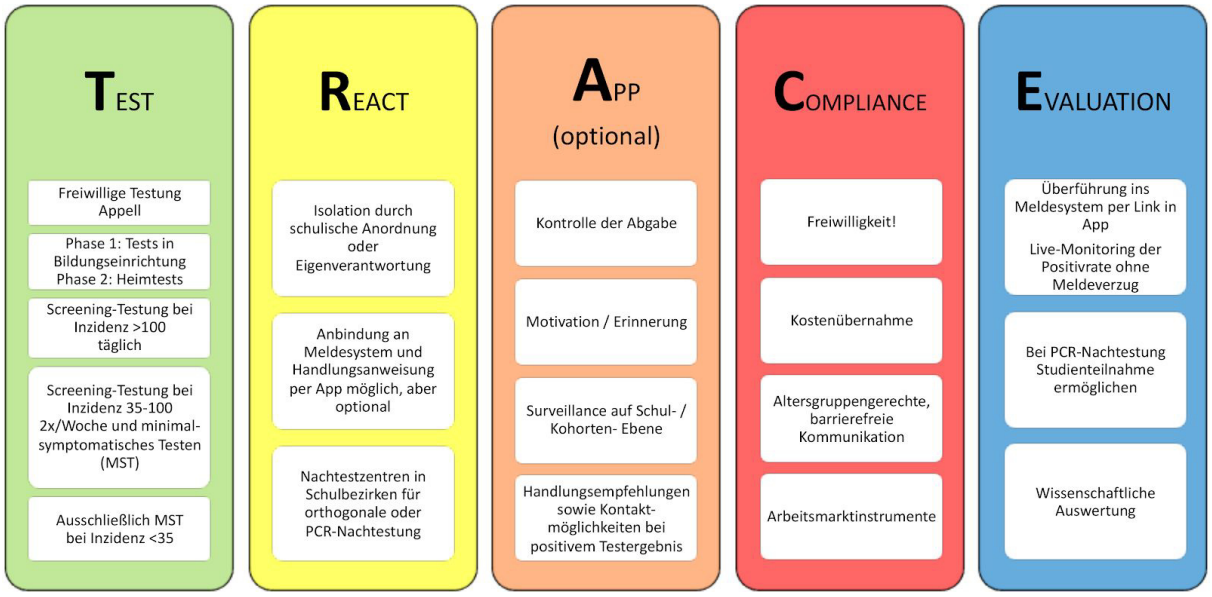


Abbildung 1: Die fünf Säulen der Schnelltest-Strategie in Schulen gemäß Konzeptpapier RapidTests

Testen ist das Kernstück des Modells und beinhaltet folgende Punkte:

1. Wahl eines oder mehrerer geeigneter Antigen-Schnelltests
2. Festlegung, ob die Tests unter Aufsicht in der Einrichtung oder zu Hause durchgeführt werden. Vorteil der Testung zu Hause: Ansteckungen auf dem Schulweg/in der Schule werden vermieden. Vorteil der Testung in der Einrichtung: Höhere Compliance und Kontrolle möglich.
3. **Testhäufigkeit** an **7-Tage-Inzidenz** oder lokalen Ausbruch anpassen:

   a. täglicher Schnelltest bei entdecktem Schulcluster oder 7-Tage-Inzidenz >100
   b. 2x/Woche Schnelltest (zweistufiger Test) bei 7-Tage-Inzidenz von 35-100
   c. ausschließlich minimalsymptomatisches Testen bei 7-Tage-Inzidenz <35
4. Bei Kleinkindern kann die Testung in Form einer „Tandem-Testung“ (regelmäßiges Testen der Eltern, zusätzlich oder anstatt des Kindes) erfolgen.

Weiterhin muss klar sein, welche **Reaktion** ein Antigen-Schnelltest nach sich zieht. Auch bei negativem Antigen-Schnelltest müssen die restlichen Schutzmaßnahmen (AHA+AL + ggf. Klassenteilung oder Wechselunterricht) unbedingt weiter befolgt werden. Ein positiver Antigen-Schnelltest sollte zur Konsequenz haben:

1. Sofortige Isolation
2. Verständigung eines Arztes/einer Ärztin, des Nachtestzentrums oder lokalen Gesundheitsamtes (wünschenswert wäre eine Hotline, ggf. Automatisierung durch App), zur Terminvereinbarung für eine Bestätigungs-PCR.
3. Benachrichtigung von Kontaktpersonen

Um die **Compliance** bei freiwilliger Testung maximal zu fördern, ist eine altersgerechte **Kommunikation** unter Einbindung der Eltern/Erziehungsberechtigten vonnöten. Optimal wäre hierzu die Aufklärung der Schüler:innen im Klassenverband sowie ein virtueller Elternabend, bei dem eine beauftragte Person für Einweisung und Fragen zur Verfügung steht. Zusätzlich sollte leicht verständliches Informationsmaterial an die Sorgeberechtigten ausgegeben werden.

Als **optionales Instrument** könnte eine **App** das Testprogramm noch effizienter machen. Über diese könnten die Ergebnisse eines zu Hause durchgeführten Antigen-Schnelltests mittels Zeitstempel in der Schule kontrolliert werden. Weiterhin könnte diese der Meldung eines positiven Antigen-Schnelltests sowie der Compliancef̈orderung dienen. Zusätzlich könnte sie durch digitale Übermittlung von Testergebnissen zur **Evaluation** des Test- und Infektionsgeschehens sowohl lokal als auch bundesweit, beitragen. Eine Teilnahme an wissenschaftlichen Auswertungen wäre ferner denkbar.

1. Ausgangssituation

Niederschwellige, regelmäßige und einfache Testungen von Erzieher:innen und Lehrer:innen, Kindern und Jugendlichen mittels Schnelltests sollten schnellstmöglich in allen Bundesländern implementiert werden, um die Bildungseinrichtungen, zusätzlich zu den bestehenden Präventionsmaßnahmen, sicherer zu machen und Infektionscluster während des Betriebes zu verhindern [1].

Mehr als 50% der Ansteckungen mit SARS-CoV-2 gehen von Personen aus, die (noch) nichts von ihrer Infektion wissen, da sie (noch) kaum bis keine Symptome verspüren, obwohl sie bereits hochansteckend sind [2–4]. Eine **um proaktive Schnelltests erweiterte Teststrategie** zielt darauf ab, diese frühzeitig zu identifizieren und zu isolieren, um möglichst viele Infektionsketten zu unterbrechen.

Antigen-Schnelltests sind für ein **engmaschiges Screening** optimal geeignet, da sie im Vergleich zu konventionellen PCR-Methoden ein Ergebnis in wenigen Minuten liefern und in weit größeren Mengen produziert und angewendet werden können. Die geringere Sensitivität der Schnelltests im Vergleich zum PCR-Test kann dabei laut Modellrechnungen durch die schnellen Testergebnisse und die regelmäßige Anwendung mehr als ausgeglichen werden [1,5]. Entsprechend können Studien zufolge regelmäßige proaktive Schnelltests (idealerweise 2- bis 3-mal pro Woche) maßgeblich zur früheren Entdeckung ansteckender Personen führen [1,5–8]. Dass Schnelltests eigenständig mit zuverlässigem Ergebnis durchgeführt werden können, wurde bereits gezeigt [9–12]. In einer hessischen Studie wurden einige der über 600 teilnehmenden Lehrer:innen durch regelmäßige Selbsttests zu Hause davon abgehalten, infiziert bzw. infektiös in die Schule zu gehen [9].

Regelmäßiges Testen sowohl von Lehrer:innen und Erzieher:innen als auch von Schüler:innen und Kita-Kindern könnte daher sowohl die Häufigkeit als auch die Stärke von Ausbrüchen in den Einrichtungen entscheidend reduzieren. Mittlerweile sind unabhängig geprüfte Antigen-Schnelltests erhältlich, welche über einen **einfachen und angenehmeren** Abstrich im **vorderen Nasenraum** zuverlässig durchgeführt werden können. Dies erhöht die Akzeptanz in der Bevölkerung, sich regelmäßig selbst zu testen, beträchtlich, was für einen proaktiven Ansatz unerlässlich ist.

Es gibt zwei Möglichkeiten, an welchem Ort die Tests durchgeführt werden können: Zu Hause oder in der Betreuungseinrichtung. Aus infrastrukturellen, Arbeitsschutz- und haftungsrechtlichen Gründen sollten Schnelltests idealerweise als **Selbsttests zu Hause**

durchgeführt werden. Diese Option basiert auf **Freiwilligkeit** und Vertrauen, solange z.B. keine sinnvolle digitale Lösung in Form einer App zur Kontrolle zur Verfügung steht. Das Testen in der Einrichtung könnte zwar mit einer Testpflicht gekoppelt werden, wie es derzeit in Österreich praktiziert wird, geht jedoch mit oben genannter Problematik (z.B. potenzielle Ansteckungen auf dem Schulweg) einher. Es ist daher genau abzuwägen, welche Lösung präferiert wird. Da sich Laien-Selbsttests, von denen jedoch einige prinzipiell heute bereits laientauglich wären, noch im Zulassungsverfahren befinden, aber die Schulen bundesweit bereits schrittweise in den Präsenzbetrieb zurückkehren, schlagen wir **zwei Phasen** zur Implementierung von Schnelltests an Schulen und Kitas vor:

Tabelle 1: Einführungsphasen

	pädagogisches und sonstiges Personal	Schüler:innen	Kita-Kinder
Phase 1 (noch nicht offiziell zugelassener Selbsttest für Lai:innen)	Selbsttest, optimalerweise zu Hause	Test unter Aufsicht vor Schulbeginn, Abstrich Außenbereich, Test-Durchführung Innenbereich	nur Personal
Phase 2 (als Selbsttest für Lai:innen)	Selbsttest zu Hause	Selbsttest zu Hause	Tandemtest zu Hause: Eltern und/oder Kind

2. 5-Säulen-Modell “TRACE"

Die im Folgenden dargestellte Teststrategie stellt eine Empfehlung unter Abwägung der wissenschaftlichen Datenlage zu Antigen-Schnelltests dar und gibt darüber hinaus keine Empfehlungen zu alternativen/weiteren nicht-pharmazeutischen Interventionen, wie z.B. ob und wann Schulen und Kindertagesstätten geschlossen werden sollten oder wieder öffnen können. Eine Einhaltung von gängigen Präventions- und Hygienemaßnahmen im laufenden Betrieb setzen wir jedoch als gegeben voraus. Neben dem Kern einer Teststrategie, der eigentlichen Testung und der damit verbunden Infrastruktur, enthält das hier vorgestellte “**TRACE”-Modell**” vier weitere wichtige Säulen für ein umfassendes Testkonzept an Einrichtungen:

T esten
R eaktion und Maßnahmen
A pp (optional)
C ompliance und Kommunikation
E valuierung und Surveillance

2.1 Testen

Ziel: Maximierung der zeitnahen Identifikation von infektiösen Personen. Minimierung der Anzahl der Personen die in Quarantäne müssen.	
Zentrale Punkte bei der Auswahl der Teststrategie	Bewertungskriterien
• Methode (Antigen-Schnelltest/PCR/Sonstige) • Art des Testes (Selbsttest/Fremdtest) • Testregime (freiwillig/verpflichtend, Häufigkeit, Stufigkeit) • zu testender Personenkreis	• Ressourceneinsatz (Raum, Schutzausrüstung, Testkapazität) • Personalaufwand (Verteilung, Anleitung, Auswertung) • Schnelligkeit • Testgenauigkeit (Sensitivität/Spezifität) • Niedrigschwelligkeit

2.1.1 Methode und Test-Regime: Inzidenz-abhängiges Testen

In Bildungseinrichtungen herrscht eine verhältnismäßig hohe und auch durch Kohortierung nur begrenzt reduzierbare Personen- und Kontaktdichte. Gleichzeitig gibt es Hinweise darauf, dass durch die Altersverteilung ein höherer Anteil asymptomatischer Übertragungen zu erwarten ist als in der Gesamtbevölkerung [4].
Aus beiden Punkten lässt sich die Wichtigkeit der **Schnelligkeit** und der **Regelmäßigkeit** des Testens ableiten. Schon bei einem Verzug der Ergebnisse um einen Tag nimmt die Effektivität eines Screening-Regimes spürbar ab [5] und somit – v.a. bei relativ hoher Personen- und Kontaktdichte – die Anzahl der Personen, die in Isolation und Quarantäne müssen, zu [13].

Durch regelmäßige Tests, die zusätzlich zum sofortigen Testen bei **minimalen Symptomen** erfolgen, werden Personen, die (noch) keine Symptome aufweisen, frühzeitig identifiziert [9]. Antigen-Schnelltests können, unabhängig vom Alter und vom Vorliegen von Symptomen, Personen mit hohen, also ansteckungsrelevanten Viruskonzentrationen in über 90% der Fälle erkennen [14–17]. Durch die Regelmäßigkeit kann sogar eine 100%-ige Erkennungsrate erreicht werden [18] .

Tabelle 2: Test-Regime in Abhängigkeit des lokalen 7-Tage-Inzidenzwertes

7-Tage-Inzidenz pro 100.000 Einwohner:innen[1]	**>100** oder Ausbruch an Schule	**35-100**	**<35**
Nicht-symptomatische Testung (proaktives Screening)	Täglicher Schnelltest Bei Ausbruch: Täglicher Schnelltest über 7 Tage[2]	2x/Woche Schnelltest (zweistufiger Test*) Alternative: 2x/Woche PCR-Pooltestung, soweit Infrastruktur vorhanden und Ergebnis innerhalb von 24h	Bei vorhandener Infrastruktur Sentinel-Testung mittels PCR-Pooling-Verfahren
Minimal-symptomatische Testung	Unverzüglicher Schnelltest beim Auftreten von Minimalsymptomatik**		
Testart	Schule: Selbsttest; Kita: Tandem-Testung		
Anweisung	Empfehlung/Appell	Freiwilliger Screening-Test, Pflichttest bei (minimalen) Symptomen (oder Krankmeldung)	Pflichttest bei (minimalen) Symptomen(oder Krankmeldung)

[1]Je nach Inzidenz alternative/weitere infrage kommende nicht-pharmazeutische Interventionen (z.B. Aussetzung der Präsenzpflicht, Wechselunterricht oder Schulschließung) sind nicht Teil des vorliegenden Papiers; [2]Bei nachgewiesener Übertragung (Quellcluster) kann die tägliche Testung auf die Kohorte begrenzt werden; *Erläuterung zur Zweistufigkeit in Kapitel 2.2.2; **Erläuterungen zur Minimalsymptomatik in Kasten 1.

Unsere Empfehlungen (Tabelle 2) leiten sich v.a. aus Abwägungen zwischen Testaufwand und der erwarteten Anzahl der Personen, die entweder korrekt oder fälschlicherweise als ansteckend erkannt werden, ab (siehe Kasten 2):

- **bei einer 7-Tage-Inzidenz von >100/100.000** empfehlen wir für den Fall, dass die Schulen im Präsenzunterricht offen sind, einen täglichen Test für alle Angehörigen der Bildungseinrichtungen.
- **Für 7-Tage-Inzidenzen von 35-100/100.000** empfehlen wir den regelmäßigen zweistufigen Test (siehe Kasten 2) und ggf. die genauere Beobachtung der Population, in der nicht bestätigte Fälle beim ersten Testen aufgetreten sind.
- **Bei einer 7-Tage-Inzidenz von <35/100.000** sollte die TTI(Test, Trace, Isolate)-Effektivität der Gesundheitsämter gewährleistet sein. Daher sehen wir den erwarteten Anteil an falschen Ergebnissen als nicht mehr angemessen gegenüber einer klassischen TTI-Strategie an und empfehlen in diesem Falle keine regelmäßige, proaktive Durchführung von Antigen-Schnelltests, sondern nur noch das Testen bei Minimalsymptomatik.

- **Bei Minimalsymptomatik immer (unabhängig von aktueller Inzidenz)**: Bei Minimalsymptomatik (Kasten 1) empfehlen wir jederzeit einen sofortigen Schnelltest, da hier die Vortestwahrscheinlichkeit relevant erhöht ist.

  Insbesondere der Symptombeginn einer SARS-CoV-2-Infektion ist unspezifisch und verläuft in den ersten Stunden und Tagen meist mild. Häufig berichten Betroffene von Kopf- und Gliederschmerzen, leichtem Halskratzen oder einer ungewöhnlichen Müdigkeit (Fatigue) [19]. Das Bewusstsein dafür, dass auch leichtes Unwohlsein bereits auf eine Infektion hindeuten kann und ein Antigen-Schnelltest erfolgen sollte, muss durch eine gute Kommunikation geschaffen werden. Davon zu unterscheiden sind spezifische Symptome wie Husten, Geschmacks- oder Geruchsverlust und Fieber. Bei spezifischen Symptomen muss im Einzelfall entschieden werden, ob nicht direkt ein diagnostischer Test (PCR) angebracht ist. Die Grenze zwischen unspezifischen und spezifischen Symptomen ist jedoch fließend, so dass im Zweifel und sofern verfügbar neben der Isolation vorab immer ein Schnelltest sinnvoll ist. Ein zweiter Antigen-Schnelltest am Folgetag nach einem negativen Ergebnis ist hier zudem in jedem Fall ratsam.

Kasten 1: Beispiele für Minimalsymptomatik (**):

Unspezifisch	**Spezifisch**
Kopfschmerzen	Störung des Geruchs- und/oder Geschmackssinns
Rückenschmerzen	Fieber
Gliederschmerzen	Husten
Müdigkeit	Halsschmerzen
“Halskratzen”	Schnupfen mit Fieber >38°C
Bauchschmerzen mit oder ohne Übelkeit und Durchfall	
Muskelschmerzen	

Auch bei Einsatz hochspezifischer Tests (>99,5% Spezifität) wird die Zahl falsch-positiver Ergebnisse rein rechnerisch die Zahl richtig-positiver Ergebnisse unterhalb einer tatsächlichen Prävalenz von etwa 550 infektiösen Personen/100.000 zahlenmäßig übertreffen. Damit verbundene Einbußen an Vertrauen in die Tests können jedoch Schaden anrichten, wenn diese Tatsache nicht vorher proaktiv kommuniziert und damit eine

realistische Erwartungshaltung erzeugt wird. Daher sollten **hochsensitive und spezifische Tests (Sensitivität >90%, Spezifität >99,5%)** eingesetzt werden. Weitere Auswahlkriterien an das Testsystem sind in Tabelle 3 zu finden.

Kasten 2: Abwägung des Test-Regimes (*) - ein Rechenbeispiel:

Bezüglich der Spezifität beruhen unsere Überlegungen auf der Tatsache, dass bei anlasslosem und symptomlosen Testen die Vortestwahrscheinlichkeit in Zeiten mit geringen Fallzahlen eher niedrig ist, und damit der Positive Prädiktive Wert (PPV) ebenfalls eher niedrig sein wird. Der PPV, also der Wert, der aussagt, wie hoch der Anteil der richtig-positiven Ergebnisse an allen positiven Ergebnissen ist, ist vor allem abhängig von der Spezifität der verwendeten Tests und der Vortestwahrscheinlichkeit (PTP: pre-test probability; meist durch die Prävalenz angenähert). Die PTP ist umso höher, je höher der Anteil tatsächlich Positiver in der Testpopulation ist. Die folgende Berechnung basiert auf vereinfachten Annahmen und lässt beispielsweise außer Acht, dass das Verhalten einzelner Personen(-gruppen) ebenfalls einen Einfluss auf die Vortestwahrscheinlichkeit hat. Ein Inzidenzwert der Gesamtpopulation kann daher immer nur einen sehr groben Schätzwert liefern.
Bei den groben Annahmen einer Dunkelziffer von 5x (laut RKI bis 10.12.2020 durchschnittlich 4-6x [20]) und einer durchschnittlichen infektiösen Phase von 7 Tagen [vgl. 18] würde man bei einer 7-Tage-Inzidenz von 100/100.000 (also einem Erwartungswert von 500 infektiösen Personen unter 100.000 Getesteten) mit einem Test mit einer Spezifität von 99,7% [Durchschnittswert laut 21] und einer Sensitivität von 90% (bezogen auf infektiöse Personen [21]) etwa auf einen PPV von 60% kommen, d.h., bei 100.000 Getesteten entdeckte man 450 richtig-positive Fälle (Infektiöse), bekäme aber zusätzlich 300 Falsch-Positive bei 50 Falsch-Negativen (Infektiöse) dazu. Mit einer Anschlusstestung mit einem identisch performenden orthogonalen Test eines anderen Herstellers (der wahrscheinlich ein anderes Epitop erkennt) und bei Annahme, dass keiner der falsch-positiven Fälle eine auch auf den anderen Test zutreffende systematische Ursache hat, könnte man die Aussagekraft der Tests zusätzlich erhöhen. Um nun die Spezifität zu erhöhen, müssten alle widersprüchlichen Testkombinationen (1x positiv plus 1x negativ) als negativ bewertet werden. Dann bekämen 405 von 500 tatsächlich infektiösen Personen ein positives Endergebnis, aber nur 1 der Negativen ein falsch-positives. Daraus ergibt sich eine rechnerische Sensitivität von 81% und Spezifität von 99,9991%. Eine Nachtestung mit einem orthogonalen Schnelltest hätte in diesem Bereich also einen Verlust an Sensitivität zur Folge, würde jedoch Falsch-Positive nahezu ausschließen. Bei einer 7-Tage-Inzidenz von 35/100.000 dagegen (hier nehmen wir konservativ keine Dunkelziffer an, da die TTI-Kapazitäten des ÖGD funktionieren sollten) kämen auf 31 richtig-positive Ergebnisse im einstufigen Testverfahren weiterhin 300 falsch-positive. Im zweistufigen Testverfahren würde man 28 der 35 tatsächlich ansteckenden Personen erkennen, und erhielte wieder nur 1 falsch-positives Ergebnis. Für die Abschätzung des Toleranzbereichs bei Falsch-Negativen ist relevant, dass rund 80% aller Infizierten keine Infektionsketten auslösen [2]. Die Zweistufigkeit lässt also im Bereich 35-100/100.000 keine nennenswerten Änderungen im Zusammenhang mit leicht reduzierter Sensitivität erwarten, da statistisch gesehen von den maximal 95 möglicherweise übersehenen infektiösen Personen bei einem zweistufigen Test im oberen Grenzbereich von 100/100.000 nur etwa 20 überhaupt potenzielle Indexfälle sein würden. Auch aus diesem Grund ist jedoch die weitere Einhaltung der gängigen Präventions- und Hygienemaßnahmen an den Einrichtungen zwingend notwendig.

2.1.2 Durchführung und Auswahl des Testsystems

In der **Übergangszeit (Phase 1)** kann es keine Option sein, an den Schulen nicht zu testen! Da bisher jedoch keine CE-zertifizierten Tests für die Selbsttestung zu Hause in Deutschland erhältlich sind, aber die Abgabe von Point-of-Care-Tests (PoCT) an Angehörige von "Gemeinschaftseinrichtungen" nach § 33 IfSG seit Dezember 2020 erlaubt ist, empfehlen wir für Phase 1 die **Schulung pädagogischen und technischen Personals zur Selbsttestung** und bei **Schüler:innen eine beaufsichtige Selbstentnahme** in Form einer Off-Label-Nutzung (Rechtliche Abwägung: Kasten 3).

Kasten 3: Rechtliche Abwägung

Seit dem 19.11.2020 ist der Arztvorbehalt aus § 24 S. 1 IfSG für In-vitro-Diagnostika, die für Patienten-nahe Schnelltests bei Testung auf SARS-CoV-2 verwendet werden, aufgehoben (§ 24 S. 2 IfSG). Danach können auch Lai:innen, die im Umgang mit entsprechenden Tests geschult sind, diese anwenden. Abgegeben werden durften solche Tests wegen § 3 Abs. 4 S. 1 MPAV zu diesem Zeitpunkt allerdings nur an Ärzt:innen und weitere professionelle Akteur:innen des Gesundheitswesens. Durch die Verordnungen zur Änderung der Medizinprodukte-Abgabeverordnung im Rahmen der epidemischen Lage von nationaler Tragweite wurden allerdings Ausnahmeregelungen geschaffen. Seit dem 3.12.2020 dürfen daher auch Gemeinschaftseinrichtungen i. S. d. § 33 IfSG (u. a. Schulen und Kitas) Antigen-Schnelltests beziehen. Das erklärte Ziel beider rechtlicher Anpassung war es, einen breiteren Einsatz von Schnelltests zur Vermeidung und Unterbrechung von Infektionsketten und Ausbrüchen in diesen Einrichtungen zu erreichen (vgl. für Schulen RefE d. BMG v. 30.11.2020, 5). Erst seit dem 3.2.2021 ist die Abgabe von In-vitro-Diagnostika für die Eigenanwendung, die für den direkten Erregernachweis des Coronavirus SARS-CoV-2 bestimmt sind, an Privatpersonen erlaubt (Anlage 3 MPAV).
Aktuell existieren auf dem Markt keine Schnelltests im letztgenannten Sinne, die das erforderliche Konformitätsbewertungsverfahren vor einer benannten Stelle durchlaufen oder eine entsprechende Sonderzulassung durch das BfArM erhalten haben und daher an Privatpersonen zur Eigenanwendung abgegeben werden dürfen. Es stellt sich daher die Frage, ob die bisher verfügbaren Tests, soweit sie zulässig an Gemeinschaftseinrichtungen wie Schulen und Kitas abgegeben wurden, durch die Testpersonen als Selbsttests eingesetzt werden dürfen. Der Arztvorbehalt des § 24 IfSG steht dem nicht entgegen. Soweit eine entsprechende Einweisung in die Anwendung als Selbsttests stattgefunden hat, ist eine Anwendung als eine Art des sog. Off-Label-Use denkbar. Hier muss insbesondere berücksichtigt werden, dass das BMG keine Bedenken gegen sog. Einsendekits hat, bei denen die Probenentnahme durch die Testperson selbst erfolgt und der PCR-Test anhand des zurückgesendeten Probenmaterials durch geschultes Personal durchgeführt wird [22]. Denn letztlich wird auch in diesen Fällen das Risiko einer falschen Probenentnahme durch Lai:innen hingenommen. Soweit in der medizinrechtlichen Literatur Einwände gegen den Off-Label-Use von Medizinprodukten erhoben werden [23], müssen diese von den politischen Verantwortungsträgern bei ihrer Entscheidung bedacht werden.
Bei Lehrer:innen und anderem Betreuungspersonal von Gemeinschaftseinrichtungen würde ein entsprechender Einsatz in einer Übergangszeit (Phase 1) erfolgen. Tatsächlich hat dies u. a. auch schon in Sachsen-Anhalt oder i. R. v. Pilotprojekten (Hessen) stattgefunden [9,24]. Rechtliche Bedenken gegen diese Vorgehensweise sind bislang nicht geäußert bzw. bekannt geworden. Zur möglichst effektiven Erreichung des auch vom Verordnungsgeber (BMG) und dem Gesetzgeber erstrebten Zwecks, der Vermeidung und Unterbrechung von Infektionsketten und Ausbrüchen in diesen Einrichtungen, wäre der Einsatz dieser Tests allerdings, im Unterschied zur bisher bekannten Vorgehensweise, als Heimtests anzuraten. Auf diesem Wege können potenzielle Virusübertragungen auf dem Weg in die Einrichtungen und vor Ort vermieden werden. Bei Schüler:innen sowie Kindern in anderen Gemeinschaftseinrichtungen ist eine Anwendung als Heimtest allerdings nicht möglich. Die derzeit verfügbaren Tests dürften nur in den Einrichtungen eingesetzt werden. Hier ist es denkbar, nach der Einweisung der Kinder, Selbsttests zu ermöglichen, die unter der Überwachung durch geschultes Personal stattfinden.
Sobald Antigen-Schnelltests auf dem Markt verfügbar sind, die das erforderliche Konformitätsbewertungsverfahren vor einer benannten Stelle durchlaufen bzw. eine entsprechende Sonderzulassung durch das BfArM erhalten haben, können diese an alle Privatpersonen abgegeben werden. Ab diesem Zeitpunkt (Phase 2) sind Selbsttests von Lehrer:innen, Betreuer:innen sowie Schüler:innen und betreuten Kindern in häuslicher Umgebung möglich.

Bei einer niedrigen 7-Tage-Inzidenz von <35/100.000 kann schon bei konsequenter Selbsttestung des Personals bei Minimalsymptomatik oder durch PCR-Pooling-Testungen im Sinne einer Sentinel-Testung Infektionsgeschehen vor Ort aufgedeckt und schnell reagiert werden. Bei vorliegendem Infektionsgeschehen sollte eine Nachtestung positiver Personen und im Bestätigungsfall auch eine Testung der Kohorten in Nachtestzentren (siehe 2.2.3) (oder in kleinen Kommunen bei niedergelassenen Ärzt:innen) z.B. durch PCR durchgeführt werden.

Relevanter ist die Durchführung in Phase 1 jedoch für den Bereich moderater oder erhöhter 7-Tage-Inzidenz (>35/100.000), in dem sich die meisten Kommunen derzeit befinden. Hier kann an geöffneten Bildungseinrichtungen auf eine Testung, auch vor der Einführung von expliziten Selbsttests, nicht verzichtet werden. Eine regelmäßige Screening-Testung muss daher vor Ort an den betroffenen Schulen implementiert werden, um zumindest einen Wechselunterricht mit alternierender Präsenz zu gewährleisten.

Konzeptuell könnte folgende **Infrastruktur** aufgebaut werden:

- Die Einverständniserklärung der Eltern ist einzuholen
- angeleitete Selbstentnahme des Abstrichs/Probenmaterials durch Kinder ab Klasse 5 bzw. bei jüngeren Kindern durch deren Eltern vor Schulbeginn im Außenbereich der Schulen unter Einhaltung der Abstandsregeln (vorderer Nasenabstrich, ggf. Speicheltest)
- Entzerrung durch Staffelung des Unterrichtsbeginns und Staffelung der Testtage
- die Prozessierung der Tests erfolgt im Innenbereich (Turnhalle/Aula) unter Einhaltung der Abstandsregeln und Bereitstellung von Raumlüftern in kohortierten Gruppen durch die Schüler:innen ab Klasse 5 unter Aufsicht einer geschulten Person selbst
- Temperatur der Testkits darf nicht außerhalb der Herstellerangaben fallen, da z.B. zu kalte Reagenzien zu falsch-positiven Ergebnissen führen können [25].
- Alternativ werden die Proben gepoolt und an ein Labor zur PCR-Analyse versendet. Dazu müssen vor Ort die notwendige Infrastruktur für einen schnellen Transport, Rückstellproben etc. vorhanden sein. Dieses Verfahren ist vor allem im niedrigen Inzidenzbereich anzusiedeln, da mit zunehmender Prävalenz der Anteil positiver und damit aufzulösender Pools ansteigt und somit zu ungleich erhöhtem Testaufwand führt.
- Aufsicht bei der Durchführung von Antigen-Schnelltests erfolgt durch speziell geschultes Personal der Schule oder externe Unterstützung (Dienstleister, ÖGD, Bundeswehr)
- in Grundschulen werden die Tests durch speziell geschultes Personal der Schule oder externe Unterstützung prozessiert
- In Phase 2 (Selbsttests) sollte für Schüler:innen eine Möglichkeit (z.B. Raum im Eingangsbereich) geschaffen werden, um diesen bei Versäumnis nachzuholen

Bei positivem Ergebnis erfolgt die **sofortige Information und temporäre Isolation** der positiven Person (und deren Erziehungsberechtigten) und die Weiterleitung an ein **Nachtestzentrum** in dem eine PCR veranlasst wird (alternativ ein orthogonaler Antigen-Schnelltest, siehe Abschnitt Reaktion unter 2.2).

Bei **Vorliegen von Selbsttests (Phase 2)** erfolgt die Abgabe der Tests durch die Schulen oder durch von den Schulen auszugebende Voucher oder QR-Codes mit Anbindung einer App durch die Apotheken. Die Selbsttests werden **morgens vor Besuch der Bildungseinrichtung** im oben definierten Rhythmus durchgeführt. Apotheken können zusätzlich zur Aufklärung und Information beitragen. Bei der Auswahl der Tests können folgende Kriterien herangezogen werden (Tabelle 3):

Tabelle 3: Auswahlkriterien für Antigen-Schnelltests in Phase 1

Kriterium	Erläuterung
Testgenauigkeit	Sehr hohe Spezifität (>99,5%) und hohe Sensitivität (>90%) bei hohen Viruskonzentrationen* gemäß unabhängiger Validierungsstudie (Übersicht) *oder* vorliegende Evaluierung/Validierung durch das PEI oder BAG *oder* gelistet in gemeinsamer EU-Liste.
Leichte Handhabung	Betrifft v.a. Probenentnahme, Zugabe der Pufferlösung, Auftragen auf Testkassette.
Vereinzelbarkeit	Alle benötigten Materialien müssen in die gewünschte Anzahl Testkits aufteilbar sein.
Zulassung	PoC-Schnelltest **muss** für den (vorderen) Nasenabstrich CE-zertifiziert sein

*Sensitivität bei Viruskonzententrationen ≥10^6 RNA-Kopien/ml bzw. Ct≤25. Dafür muss in die Validierungsstudie reingeschaut werden, weil in der Tabelle auf diagnosticsglobalhealth.org die Gesamtsensitivität bei allen (inkl. geringen) Viruskonzentrationen der untersuchten Proben angegeben ist.

2.1.3 Altersgerechtes Testen

Altersgerechte Teststrategien sind zentral zur **Sicherung der Mitwirkungsbereitschaft** bei Kindern und Sorgeberechtigten. Aufgrund der bereits bestehenden Rechtssicherheit bei erwachsenen Angehörigen von “Gemeinschaftseinrichtungen" nach § 33 IfSG fungieren diese prinzipiell als **Sentinel** und sollten daher sofort in einer Teststrategie erfasst werden.

Abgestuft mit dem Alter der Testperson muss auf die Zumutbarkeit der Testmethode Rücksicht genommen werden. Für **Kinder im Schulalter** kann daher ein **anterior-nasaler Abstrich** zum Einsatz kommen. Für **Kinder im Kindergartenalter und jünger** sollte auf

Spuck- oder Lolly-Tests als Alternative zur Verfügung gestellt werden, falls der vordere Nasenabstrich vom Kind nicht angenommen wird. Zur Kompensation daraus resultierender Sensitivitätseinbußen oder bei Nicht-Akzeptanz kann die zusätzliche Testung mittels nasalem Abstrich der Eltern in Form einer **Tandem-Testung** in Erwägung gezogen werden, welche ohnehin die Tests bei ihren Kindern durchführen. Gleichzeitig kann es in einem weniger sensitiven Testsystem notwendig sein, Quarantänemaßnahmen umfassender anzuordnen und ggf. die Quarantänisierung einer kompletten Kohorte vorzusehen.
Zentral bei der Implementierung von Testungen im Elementar- und Kita-Bereich ist zudem eine **altersgerechte Kommunikation** (s. Abschnitt 2.4)

2.2 Reaktion und abgeleitete Maßnahmen

2.2.1 Überblick

Das sofortige Antreten einer Isolation ist essenziell für den eindämmenden Effekt von Schnellteststrategien. Daher bedarf es einer **gesetzlichen Grundlage einer Quarantäne- oder Isolations-Anordnung durch die Schule** oder einer Allgemeinverfügung, die das eigenverantwortliche Antreten einer solchen Maßnahme nach positivem Schnelltest exekutiert. Eine solche ist in den Landesverordnungen zu schaffen.
Ein positiver Schnelltest wird in Phase 1 über die Schulen bzw. spätestens über das Nachtestzentrum gemeldet. Bei einem positiven Selbsttest zu Hause sollte man sich unverzüglich an die Schule und den Hausarzt/die Hausärztin, das Gesundheitsamt oder den kassenärztlichen Bereitschaftsdienst wenden, um das weitere Vorgehen mitgeteilt zu bekommen. Idealerweise kann dies auch durch Meldung des positiven Ergebnisses über eine App erfolgen (siehe 2.3).

2.2.2 Möglichkeiten zur Nachtestung (*Zweistufigkeit)

Je niedriger die Zahl (tatsächlich) Infizierter in der Bevölkerung, umso höher wird der Anteil der falsch-positiven Ergebnisse an allen positiven Ergebnissen sein. Um zu verhindern, dass dadurch ein **Vertrauensverlust** in die Aussagekraft der Tests und somit mangelnde Mitwirkungsbereitschaft entsteht, besteht die Möglichkeit eines **zweistufigen Testregimes**. Dieses führt zur Reduktion von Falsch-Positiven und somit Erhöhung der Spezifität, jedoch unter Verlust eines gewissen Grades an Sensitivität. Folgende Möglichkeiten einer zweiten Testung kommen in Betracht:

- Orthogonale Tests: Verwendung eines zweiten Schnelltests (anderes Fabrikat)
- Erneute Testung mit demselben Schnelltest, entweder sofort oder am Folgetag (und zwischenzeitliche Selbstisolation)
- PCR-Test, der generell für die Bestätigung positiver Schnelltests geeignet ist

Diese Optionen müssen **situationsbedingt abgewogen werden**, da für die Akzeptanz der Maßnahmen der Aufwand einer Nachtestung, die Wartezeit bis zum Ergebnis der Nachtestung und die (gefühlte) Häufigkeit falsch-positiver Ergebnisse sehr relevant sind.

Daraus ergäbe sich folgendes Fließschema (wobei die Option “zu Hause” für Kinder erst ab Phase 2 zur Verfügung steht; Abbildung 2):

Abbildung 2: Fließschema der Teststufen

Die orthogonale Nachtestung schont die PCR-Kapazitäten, da diese nicht durch (zu erwartende) Falsch-Positive belastet werden. Es sollte jedoch auf Wunsch auch **immer die Option einer PCR-Bestätigung** bestehen, um die Akzeptanz der Maßnahmen zu erhalten.

2.2.3 Nachtestzentren

Nachtestzentren sollten in jedem Schulbezirk eingerichtet werden und sowohl orthogonale Nachtestungen (siehe 2.2.2) als auch PCR-Tests zur Bestätigung anbieten. Nachtestzentren werden bei Ausrollen von Screeningtests in die Schüler:innenschaft eine zentrale Rolle spielen und sollten daher zeitnah implementiert werden. Auch die Einrichtung jeweils einer mobilen Testeinheit pro Schulbezirk sollte in Erwägung gezogen werden. Die Zusammenarbeit mit NGOs oder privaten Dienstleistern ist dafür zu prüfen. In kleineren Orten bietet sich ggf. auch die Zusammenarbeit mit Hausarztpraxen an, die bereits PCR-Abstriche durchführen. Vor allem in Phase 2, wenn Menschen orthogonale Tests selbstständig durchführen können, wird der Fokus hier auf der **PCR-Bestätigung positiver**

Schnelltests liegen. Die orthogonale Nachtestung sollte jedoch auch hier eine Option sein, da dadurch PCR-Kapazitäten entlastet werden. In jedem Fall sollte das Ziel des Ausbaus der Testinfrastruktur sein, eine Nachtestung samt Ergebnisübermittlung innerhalb von 24 Stunden zu gewährleisten.
Die infrastrukturelle Organisation der Nachtestzentren sollte am individuellen Bedarf der Kommunen ausgerichtet werden, sollte jedoch folgende Kriterien berücksichtigen:

- Buchung per App/QR/Hotline
- Vergabe per PPP an Dienstleister oder ÖGD/Bundeswehr denkbar
- Ziel: Termin zu orthogonaler Testung **am gleichen Tag**
- Antigen-Schnelltest plus positiver orthogonaler Test gilt als gesichert, auf Wunsch PCR-Bestätigung zur Erhöhung der Compliance möglich

Nach positivem und bestätigtem Antigen-Schnelltest, erfolgt eine Isolation und TTI entsprechend geltender Verordnungen. Bei Vorliegen einer Selbsttestzulassung kann in Abstimmung mit den Behörden vor Ort eine Freitestung durch zwei an Folgetagen erfolgte negative Schnelltests in Erwägung gezogen werden [26]. Darüber hinaus empfehlen wir für Kontaktpersonen 1. Grades, die sich in häuslicher Quarantäne befinden, die tägliche Testung zusätzlich zu den behördlichen Anordnungen, um bei positivem Ergebnis weitere sinnvolle Maßnahmen zu ergreifen (Quarantäne der Haushaltsmitglieder, je nach Alter Isolation innerhalb des Haushaltes).

2.3 App (optional)

Die Koordination von **Zugang, Surveillance und Information** basiert auf einer Schnelltest-App, die zunächst für Bildungseinrichtungen entwickelt wird, aber auch bei bevölkerungsweitem Screening angewendet werden kann (Abbildung 3). Diese basiert auf einem kohortengenau zuordenbaren verschlüsselten **QR-Code**. Apps mit einer solchen Funktionsweise **befinden sich bereits in der Anwendung** und können einen solchen Ablauf **datenschutzkonform** gewährleisten, z.B. Luca-App [27]. Da die Schultestungen jedoch sofort begonnen werden sollen, kann die Einbindung einer App auch optional erfolgen.

Die App funktioniert nach folgendem Prinzip (“digitales Klassenbuch”):

- Kind meldet sich (via Erziehungsberechtigtem) im System an
- Lehrer:innen installieren App und Kinder installieren App optional auf Smartphone oder bekommen verschlüsselten QR-Code von der Schule als Schlüsselanhänger
- In jeder neuen Zusammensetzung einer Klasse scannen Lehrer die QR-Codes aller Schüler:innen
- Meldung eines positiven Schnelltests: “Code gelb” an Schule, Lehrer:innen können alle Schüler:innen aus Kontakt-Kohorten informieren (manuell über App Output und via Smartphone für Kinder mit installierter App): Handlungsanweisung, z.B. Schnelltest bereits am nächsten Morgen zu machen
- bei bestätigtem Positiv-Ergebnis: “Code rot”: automatische Meldung aller fKontaktpersonen an das zuständige Gesundheitsamt und Rückmeldung an alle Nutzer mit installierter App die als Kontaktperson registriert wurden
- Erinnerungsfunktion, den Test zu machen

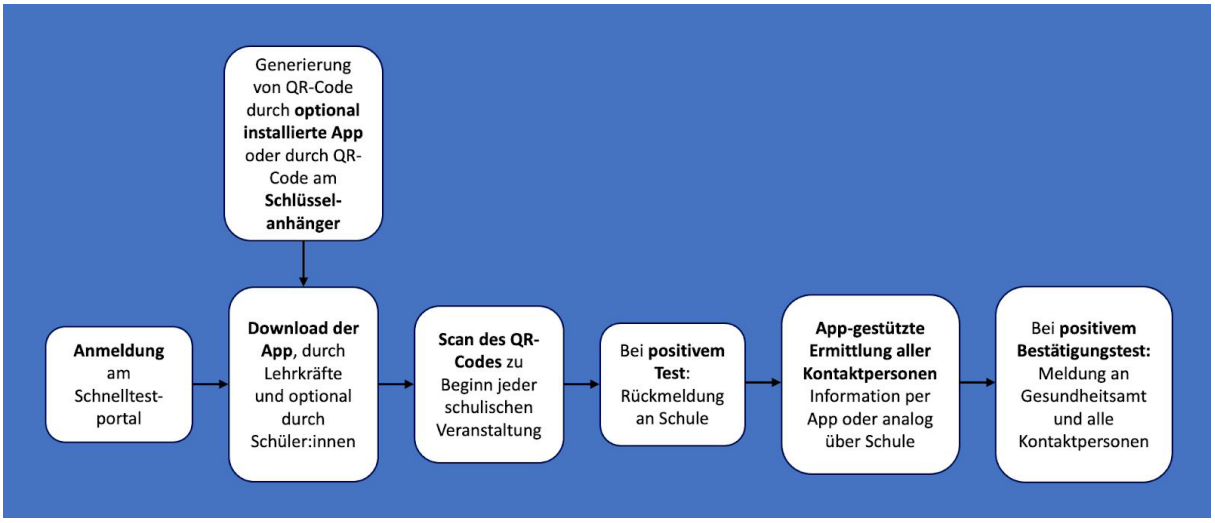


Abbildung 3: Funktionsweise einer geeigneten App

Vorteile der App:

1) Erinnerungsfunktion
2) Monitoring und Schnittstelle zum Meldesystem
3) Schul-/Kohortengenaue Erfassung der Positivrate auch in Phase 2 (Selbsttests)
4) standardisierte Handlungsanweisung bei positivem Test

2.4 Compliance/ Kommunikation

2.4.1. Freiwillige und verpflichtende Teilnahme

Wir schlagen vor, SARS-CoV-2-Testungen an Einrichtungen auf **freiwilliger Basis** durchzuführen, da wir davon ausgehen, dass dies die Compliance gegenüber den Antigen-Schnelltests in der Durchführung und der Bereitschaft, die entsprechenden Maßnahmen bei positivem Testergebnis umzusetzen, steigert. Eine gute Testbereitschaft und Compliance in dieser Kohorte hat Symbolcharakter, da ein Ausrollen der Antigen-Schnelltests auf die gesamte Bevölkerung ein sinnvolles Ziel in der nationalen Teststrategie sein muss.
Selbstverständlich gäbe es auch die in Österreich praktizierte Option, in der eine Testpflicht an die Präsenz gekoppelt ist. Dies würde dann folgendermaßen umgesetzt: Wer die Schule besuchen will, muss sich testen. Für alle anderen gilt Fernunterricht. Bei einer 7-Tage-Inzidenz <35/100.000 wird Testen nur noch bei Symptomatik empfohlen. In diesem Fall entfällt die Testung durch eine Krankmeldung bei gleichzeitiger Reetablierung der Präsenzpflicht. Somit besteht eine Wahl zwischen Präsenzunterricht mit Testpflicht oder Fernunterricht ohne Test. Eine erzwungene Testpflicht in Kombination mit Präsenzpflicht halten wir jedoch für psychologisch ungünstig. Zudem weisen wir darauf hin, dass eine Testpflicht nicht ohne Weiteres mit Selbsttestungen zu Hause zu vereinbaren ist und allein die **Anreise zur Schule**, um dort ggf. einen positiven Test zu erhalten, bereits zu weiteren **Sekundärinfektionen** führen könnte. Ein freiwilliges Selbsttesten zu Hause ist psychologisch **sinnvoller, niedrigschwelliger und risikoärmer.**

2.4.2. Maximierung der Mitwirkungsbereitschaft

Da die Mitwirkungsbereitschaft den größten Einfluss auf den Erfolg der Maßnahmen hat, ist die Kommunikation zur Herstellung der Mitwirkungsbereitschaft sehr wichtig.
Daher benötigt die öffentliche Kommunikation ein **Reframing** von Antigen-Schnelltests: Weg von einem Image, das die Aussagekraft grundsätzlich infrage stellt, hin zur Kommunikation, dass Antigen-Schnelltests (wie Masken oder Abstand) nicht perfekt sind, aber als ergänzende Maßnahme eine **gute, zusätzliche Sicherheit** bieten.

Eine weitere Frage, die im Vorfeld geklärt werden müsste, ist die Frage der **Kostenübernahme**. Auch hier kann die Mitwirkungsbereitschaft durch Übernahme der Kosten durch den Bund/die Länder erhöht werden. Sollten Antigen-Schnelltests in Phase 2 nicht mehr durch die Schulen ausgegeben werden, müssen sie dennoch kostenfrei bleiben. Ein Test, den man vor allem zum Schutz von anderen macht, darf finanziell nicht zur eigenen Belastung werden.
Gleichzeitig muss nicht nur **zur regelmäßigen Testung motiviert** werden, sondern auch zur Mitwirkung an den aus einem positiven Ergebnis abgeleiteten Maßnahmen, insbesondere der Isolation. Grundsätzlich geht einer Testbereitschaft die Bereitschaft zur Umsetzung der Konsequenzen voraus. Hier sollten **Arbeitsmarktinstrumente** verbessert werden, um die Bereitschaft zur Isolation und Quarantänisierung (vor allem in Phase 2) zu erhöhen, z.B. durch einen 100% Lohnausgleich und Kündigungsschutz in Isolation nach positivem Schnelltest. Im Fall von Kindern, die positiv getestet wurden, entsprechend auch für die Sorgeberechtigten. Auch für nachträglich als falsch-positiv erkannten Schnelltest-Ergebnisse braucht es **Rechtssicherheit** bezogen auf die Wartezeit bis zum PCR-Ergebnis.

2.4.3. Informationsmöglichkeiten für Teilnehmende

Zentral ist zudem eine **niedrigschwelle und barrierefreie, mehrsprachige** (inklusive einfache Sprache und Gebärdensprache) **Informationskampagne** in allen verfügbaren Medien. In dieser Informationskampagne müssen auch Apotheken und niedergelassene Ärzt:innen eingebunden werden. Die Beteiligung privater Gesundheitsdienstleister:innen und **Multiplikator:innen** sollte geprüft werden. In allen Schulen ist unbedingt eine **Kick-off-Veranstaltung** in Form eines virtuellen Elternabends vorzusehen, bei der die für die jeweilige Schule benannte Verantwortungsperson für Einweisung und Fragen zur Verfügung steht. In den Kindertagesstätten sollte eine intensive Aufklärung der Eltern durch die Träger erfolgen (z.B. per Videokonferenz) sowie aufsuchende altersangepasste Aufklärung in den Einrichtungen durch den Kinder- und Jugendgesundheitsdienst, Medizinstudierende, Sozialarbeiter:innen etc., z.B. mit Zahnarzt-Bauchrednerpuppen zum Einführen und Erklären. Eine Kommunikationskampagne durch eine professionelle Agentur sollte dazu geprüft werden. Außerdem muss eine bundesweite **Telefonhotline** eingerichtet werden.
Niemand darf mit einem positivem Schnelltestergebnis allein gelassen werden.

Weitere Bausteine einer Kommunikationskampagne können sein:

- Schnelltest-App für Kinder attraktiv machen (durch Belohnungssystem)
- Informationsmaterial als Bilderbuch
- aufsuchende Jugend- und Sozialarbeit für Schulung einbinden, Multiplikator:innen vor Ort einbinden
- Kinder in der Schule schulen (Kinder tragen ihr Wissen in die Familien, das erhöht die Erreichbarkeit bei Familien in Brennpunktbezirken oder mit Sprachbarrieren)
- Informationsveranstaltungen in den Schulen und Kitas anbieten (Videokonferenzen mit Erklärung der Tests)
- Rückmeldung der lokal gemeldeten Fälle in der App zur Motivation und verbesserten Risikoeinschätzung
- Erinnerung zur regelmäßigen Durchführung des Tests (App, Verknüpfung mit Morgenroutine: Aufkleber für Spiegel, Zahnpasta-Tube)

2.5 Evaluation und Surveillance

Zur Sicherstellung der Surveillance werden orthogonale Testungen und PCR-Tests, die in den Nachtestzentren durchgeführt werden, grundsätzlich dokumentiert und dem **Meldewesen** sowie optional **wissenschaftlichen Studien** zugeführt (Patientenaufklärung und -Einwilligung vor Ort). Außerdem werden von den Schulen ausgesprochene Quarantänen/Isolationen an die Behörden weitergeleitet. Aufgrund der QR-basierten Erfassung der ausgegebenen Tests, kann eine Positivrate erfasst, den Schulbezirken zugeordnet und an die App-Nutzer zurückgemeldet werden. Zur Beurteilung und Monitoring des Testprogramms sollte auch die Möglichkeit geschaffen werden negative Testergebnisse zu erfassen.
Zum Monitoring neuer Varianten sollten positive PCR-Ergebnisse bei Clustern über drei Personen zusätzlich sequenziert werden.
Die Schnelltest-App (die den Zugang und die Ergebnisse der Schultestungen in Phase 1 und der Selbsttestungen zu Hause in Phase 2 dokumentiert) sollte eine Schnittstelle zur Corona-Warn-App bekommen. Ebenfalls kann eine Anbindung an SORMAS sinnvoll sein.
Im Optimalfall kann die Schnelltest-App nicht nur manuell eingegebene Testergebnisse erfassen, sondern auch mittels Künstlicher Intelligenz Fotos von Antigen-Schnelltests auswerten oder zur unterstützenden Diagnosestellung an eine zentrale Stelle weiterleiten.

Künftig sollten Antigen-Schnelltests mit einem eindeutigen QR-Code ausgegeben werden. Dies unterstützt die Erfassung von Ergebnissen und gewährleistet auch über das Schulsetting hinaus bei bevölkerungsweitem Screening ein einfaches Monitoring des Infektionsgeschehens. Antigen-Testungen können so auch in das Meldesystem eingebunden werden. Eine Entwicklung dieser App ist somit ressourcentechnisch nicht allein auf das Setting Schule beschränkt. Bei einer dem Datenschutz gerecht werdenden Granularität der ausgegeben Codes lässt sich so auch das räumliche Auftreten von Fällen besser überwachen und Maßnahmen zielgerichteter einsetzten. So könnten beispielsweise QR-Codes einer Schule zuordenbar ausgegeben werden, dann aber zufällig innerhalb der Schule verteilt werden.

3. Praktische Umsetzung vor Ort

Wir bauen derzeit eine Seite mit **Checklisten** und ***Best-Practice* Beispielen** aus Kommunen und Ländern auf, die als Beispiele für die praktische Umsetzung genutzt werden können. Diese finden Sie unter https://rapidtests.de/schule.

Verfasser:innen: Das RapidTests-Team, namentlich

Dr. rer. nat. Franziska Briest (Biochemikerin mit Schwerpunkt Molekulare Medizin)
Nikolaus Kolb (MSc Epidemiology)
Christian Erdmann (Ernährungswissenschaftler)
Alexander Beisenherz (Arzt)
Dr. rer. nat. Aileen Hochhäuser (Arzneimittelwissenschaftlerin und Medizinredakteurin)
Marc Bota (Arzt, Leiter Intensivstation)
Henning Lorenz (M.mel., Jurist)
Dr. rer. nat. Cathleen Pfefferkorn (Virologin)
Dr. rer. nat. Jonas Binding (Biophysiker)
Dr. med. Christine Busch (Ärztin in Weiterbildung Kinder- und Jugendmedizin)

Beratend: Dr. med. Claudia M. Denkinger (Leiterin der Klinischen Tropenmedizin am Universitätsklinikum Heidelberg, FÄ für Innere Medizin und Infektiologie)

Über die Initiative RapidTests

Wir sind ein ehrenamtlicher Thinktank mit naturwissenschaftlich-medizinischem Hintergrund und kooperieren eng mit dem US-amerikanischen RapidTests-Team, dem Harvard-Epidemiologen Dr. Michael Mina sowie verschiedenen deutschen Wissenschaftler:innen. Unser Ziel ist die Pandemieeindämmung. Wir wollen, dass günstige, schnelle, regelmäßig durchführbare, ausreichend zuverlässige SARS-CoV-2-Selbsttests in Deutschland (idealerweise weltweit) möglich bzw. verfügbar gemacht werden, um über ein weiteres Werkzeug zu verfügen, das uns helfen kann, die COVID-19-Pandemie mit möglichst wenig negativen Folgen für Gesundheit, Gesellschaft, Bildung und Wirtschaft zu meistern. Wir haben weder finanzielle Interessen an SARS-CoV-2-Tests, noch fördern wir einzelne Hersteller. Cathleen Pfefferkorn und Jonas Binding arbeiten jeweils in Großkonzernen, die auch SARS-CoV-2-Tests herstellen, jedoch in komplett anderen Geschäftsbereichen (mehr dazu unter rapidtests.de/erweiterte-selbstauskunft).

4. Referenzen

1. Paltiel AD, Zheng A, Walensky RP. Assessment of SARS-CoV-2 Screening Strategies to Permit the Safe Reopening of College Campuses in the United States. JAMA Network Open. 2020;3: e2016818–e2016818.

2. Sun K, Wang W, Gao L, Wang Y, Luo K, Ren L, et al. Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2. Science. 2021;371: eabe2424.

3. Ferretti L, Wymant C, Kendall M, Zhao L, Nurtay A, Abeler-Dörner L, et al. Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. Science. 2020;368: eabb6936.

4. Buitrago-Garcia D, Egli-Gany D, Counotte MJ, Hossmann S, Imeri H, Ipekci AM, et al. Occurrence and transmission potential of asymptomatic and presymptomatic SARS-CoV-2 infections: A living systematic review and meta-analysis. PLoS Med. 2020;17: e1003346.

5. Larremore DB, Wilder B, Lester E, Shehata S, Burke JM, Hay JA, et al. Test sensitivity is secondary to frequency and turnaround time for COVID-19 screening. Sci Adv. 2021;7(1):eabd5393.

6. Lyng GD, Sheils NE, Kennedy CJ, Griffin D, Berke EM. Identifying Optimal COVID-19 Testing Strategies for Schools and Businesses: Balancing Testing Frequency, Individual Test Technology, and Cost. medRxiv. 2020; 2020.10.11.20211011.

7. Tupper P, Colijn C. COVID-19’s unfortunate events in schools: mitigating classroom clusters in the context of variable transmission. medRxiv. 2020; 2020.10.20.20216267.

8. McGee RS, Homburger JR, Williams HE, Bergstrom CT, Zhou AY. Model-driven mitigation measures for reopening schools during the COVID-19 pandemic. medRxiv. 2021; 2021.01.22.21250282.

9. Hoehl S, Schenk B, Rudych O, Göttig S, Foppa I, Kohmer N, et al. At-home self-testing of teachers with a SARS-CoV-2 rapid antigen test to reduce potential transmissions in schools. medRxiv. 2020; 2020.12.04.20243410.

10. Lindner AK, Nikolai O, Rohardt C, Kausch F, Wintel M, Gertler M, et al. SARS-CoV-2 patient self-testing with an antigen-detecting rapid test: a head-to-head comparison with professional testing. medRxiv. 2021; 2021.01.06.20249009.

11. Lindner AK, Nikolai O, Kausch F, Wintel M, Hommes F, Gertler M, et al. Head-to-head comparison of SARS-CoV-2 antigen-detecting rapid test with self-collected anterior nasal swab versus professional-collected nasopharyngeal swab. Eur Respir J. 2020; 2003961.

12. Nikolai O, Rohardt C, Tobian F, Junge A, Corman VM, Jones TC, et al. Anterior nasal versus nasal mid-turbinate sampling for a SARS-CoV-2 antigen-detecting rapid test: does localisation or professional collection matter? medRxiv. 2021; 2021.02.09.21251274.

13. Vortrag von Mina M. Reopening cities, states and schools safely via frequent rapid antigen tests. 2021.

14. Alemany A, Baró B, Ouchi D, Rodó P, Ubals M, Corbacho-Monné M, et al. Analytical and clinical performance of the panbio COVID-19 antigen-detecting rapid diagnostic test. J Infect. 2021;S0163-4453(21)00004-9.

15. Pilarowski G, Marquez C, Rubio L, Peng J, Martinez J, Black D, et al. Field performance and public health response using the BinaxNOW TM Rapid SARS-CoV-2 antigen detection assay during community-based testing. Clin Infect Dis. 2020;ciaa1890.

16. Pollock NR, Jacobs JR, Tran K, Cranston A, Smith S, O’ Kane C, et al. Performance and Implementation Evaluation of the Abbott BinaxNOW Rapid Antigen Test in a High-throughput Drive-through Community Testing Site in Massachusetts. medRxiv. 2021; 2021.01.09.21249499.

17. Pollock NR, Savage TJ, Wardell H, Lee R, Mathew A, Stengelin M, et al. Correlation of SARS-CoV-2 nucleocapsid antigen and RNA concentrations in nasopharyngeal samples from children and adults using an ultrasensitive and quantitative antigen assay. J Clin Microbiol. 2021;JCM.03077-20.

18. Mina M. Noch nicht veröffentlichte Daten. 2021.

19. Liguoro I, Pilotto C, Bonanni M, Ferrari ME, Pusiol A, Nocerino A, et al. SARS-COV-2 infection in children and newborns: a systematic review. Eur J Pediatr. 2020;179: 1029–1046.

20. Pressekonferenz des Robert-Koch-Institutes vom 10.12.2020.

21. Denkinger C. et al. Noch nicht veröffentlichte Metaanalyse. 2021.

22. Apotheker dürfen keine Corona-Tests an Laien abgeben. In: Deutsche Apotheker Zeitung online [Internet]. Available: https://www.deutsche-apotheker-zeitung.de/news/artikel/2020/09/02/apotheker-duerfen-keine-corona-tests-an-laien-abgeben

23. Timke J. Der „Off-Label-Use“ von Medizinprodukten – Medizinprodukterechtliche Bewertung und produkthaftungsrechtliche Divergenzen. 2015. MedR 33:643.

24. Ministerium Für Bildung Des Landes Sachsen-Anhalt. Informationen zur Anwendung

des Antigen- Schnelltests. 2020. Available: https://landesschulamt.sachsen-anhalt.de/fileadmin/Bibliothek/Landesjournal/Bildung_und_Wissenschaft/02_Personalgewinnung/02_01_Lehrkraefte_-_unbefristet/Antigen_Selbsttest.pdf

25. Haage V, Moreira-Soto A, Sacks JA, Corman V, Drosten C, Drexler F. Limited specificity of SARS-CoV-2 antigen-detecting rapid diagnostic tests at low temperatures. medRxiv. 2021; 2021.02.01.21250904.

26. Quilty BJ, Clifford S, Hellewell J, Russell TW, Kucharski AJ, Flasche S, et al. Quarantine and testing strategies in contact tracing for SARS-CoV-2: a modelling study. Lancet Public Health. 2021;S2468-2667(20)30308-X.

27. Persönliche Kommunikation mit Patrick Hennig, neXenio.

Asgary et al. BMC Public Health (2021) 21:125
https://doi.org/10.1186/s12889-020-10153-1

BMC Public Health

RESEARCH ARTICLE Open Access

Simulating preventative testing of SARS-CoV-2 in schools: policy implications

Ali Asgary[1*], Monica Gabriela Cojocaru[2], Mahdi M. Najafabadi[3] and Jianhong Wu[4]

Abstract

Background: School testing for SARS-CoV-2 infection has become an important policy and planning issue as schools were reopened after the summer season and as the COVID-19 pandemic continues. Decisions to test or not to test and, if testing, how many tests, how often and for how long, are complex decisions that need to be taken under uncertainty and conflicting pressures from various stakeholders.

Method: We have developed an agent-based model and simulation tool that can be used to analyze the outcomes and effectiveness of different testing strategies and scenarios in schools with various number of classrooms and class sizes. We have applied a modified version of a standard SEIR disease transmission model that includes symptomatic and asymptomatic infectious populations, and that incorporates feasible public health measures. We also incorporated a pre-symptomatic phase for symptomatic cases. Every day, a random number of students in each class are tested. If they tested positive, they are placed in self-isolation at home when the test results are provided. Last but not least, we have included options to allow for full testing or complete self-isolation of a classroom with a positive case.

Results: We present sample simulation results for parameter values based on schools and disease related information, in the Province of Ontario, Canada. The findings show that testing can be an effective method in controlling the SARS-CoV-2 infection in schools if taken frequently, with expedited test results and self-isolation of infected students at home.

Conclusions: Our findings show that while testing cannot eliminate the risk and has its own challenges, it can significantly control outbreaks when combined with other measures, such as masks and other protective measures.

Keywords: COVID-19, Agent-based Modelling, COVID-19 testing, School testing, Disease modelling

Background

Schools bring together a large number of students with very wide social connections and networks in a closed environment where they share spaces, facilities, and equipment [1]. It is argued and expected that reopening and operations of schools may reinforce the virus spread and thus increase the number of cases both in the schools and in the community. Without testing and gradual relaxation of social distancing, a second wave could occur during the school year [2]. However, given the importance of learning that takes place inside the schools and the inability of working parents to supervise remote learning at home, there are also concerns regarding school closures and full switch to distant learning. To minimize the impact of the pandemic and to create a safe environment for students while continuing school operations, public health agencies have provided schools with reopening guidelines and procedures that mainly focus on social distancing, hygiene practices, screening and

* Correspondence: asgary@yorku.ca
[1]Disaster & Emergency Management, School of Administrative Studies and Advanced Disaster, Emergency and Rapid-response Simulation, York University, Toronto, Canada
Full list of author information is available at the end of the article

monitoring, and reporting in close collaboration with families [3–7].

Testing has been an important element of the COVID-19 pandemic management [8]. Thus, while many schools are currently implementing on-site symptom screening [5], testing may become an additional preventative tool depending on how the pandemic progresses. Testing students prior to and during the school session has become a public health policy and planning issue, as well as a challenge. According to the European Centre for Disease Prevention and Control (ECDC), "*a well-implemented testing strategy in school settings might play an important role in preventing virus transmission within the school setting and to the community*" (p.2) [1]. However, because there is no consensus on school testing, because testing is costly and is perceived as painful or uncomfortable, and because it requires significant preparation and planning, it is vital to analyze and assess the outcome and effectiveness of different testing scenarios in controlling disease outbreaks. Simulation modeling can help with exploring and examining the impacts of different testing scenarios. Although testing capacities are currently limited, as technology enhances, it is argued that systematic testing may help in controlling the outbreaks by identifying pre-symptomatic and asymptomatic individuals, while allowing schools to continue their activities. This is also in line with arguments that challenge the current testing strategies which focus on testing symptomatic individuals [8]. This paper describes and presents sample results of an agent-based simulation tool that is developed to help decisionmakers examine different school testing strategies and scenarios. The simulation results are validated with the help of a theoretical viewpoint on the effective reproduction number of the virus in a school environment, which shows that contact tracing, mask wearing and social distancing within classrooms are helping in decreasing the testing frequency and overall test numbers needed to control outbreaks.

School testing challenges

To test students and staff in elementary and secondary schools, some challenges and issues should be addressed: 1) the need for conducting significant number of tests for finding a small number of infected positive cases; 2) testing, especially frequent swab testing, may cause some pain or discomfort for children-although progress has been made towards less painful tests, such tests are not widely available; 3) almost all currently available tests have significant number of false-negative and false-positive rates [9, 10] that can cause confusion and stress; 4) tests may create a false sense of security among those tested; 5) conducting regular testing in schools is logistically challenging and requires additional resources, planning and operational burdens; 6) large scale testing of students may add more pressures to local public health testing capacities, and in particular, adding school testing may create more issues and increase waiting time for tests and test results; 7) tests are costly and the current PCR tests require specialized machinery and supply-more tests translates into more costs that need to be justified against the benefits that they generate; 8) the time between collecting a sample and receiving the test results is often too long-currently the test results are available after 1 to 6 days depending on the type of test and how many tests are being conducted [9], because the main goal of testing is to identify potential carriers and isolate them and those in close contact with them. As the time between sample collection and test results increases, the effectiveness of tests diminishes (For example, in the Province of Ontario, Canada, test results are returned between 1 to 3 days under normal conditions but this interval can increase to up to a week or even more under busy conditions); 9) public acceptance of mass testing particularly for younger kids in schools is low which may create push back; for example, a study conducted by Statistics Canada found that only 4 in 10 people support mandatory random COVID-19 testing and older adults are more supportive of this idea compared to younger people [11]; 10) privacy issues may arise in school testing-although the tests results can be kept private, subsequent follow up actions such as the temporary exemption from school, may disclose the identity of infected students. A summary of the challenges above is depicted in Table 1.

School testing benefits

According to the ECDC (2020) the objectives of school testing are: "*1) to ensure early identification of cases among students and staff in order to conduct contact tracing and initiate prevention and control measures, thereby reducing further transmission; 2) to identify infection in students and staff at high risk of developing severe disease due to underlying conditions; and 3) to support investigations and studies concerning the role of children in the transmission of COVID-19.*" (ECDC, 2020, p. 1). As such, school testing provides some benefits including: 1) more information about the disease status in the community and its subsystems- in the absence of clinical solutions such as a vaccine or a drug, testing enables early detection of infected students and prevents outbreaks, and thus

Table 1 Summary of School Testing Challenges

1	Significant number of tests should be performed to find a small number of infected positive cases
2	Tests may cause pain or discomfort, especially for children
3	Available tests have significant false-negative and false-positive rates that can cause confusion and stress
4	Tests may create a false sense of security among those tested
5	Regular testing in schools would be logistically challenging and requires additional resources, planning and operational burdens
6	Large-scale testing of students may add more pressures to local public health testing capacities and may increase overall testing waiting times
7	Tests are costly; more tests translate into more costs that need justification over the benefits they generate
8	The delay before test results are available can reduce testing effectiveness because the main goal of testing is to identify and isolate potential viral vectors and those in close contact with them
9	Public acceptance of mass testing particularly for younger kids in schools is low which may create push back
10	Privacy issues may arise in school testing, as subsequent follow up actions may disclose the identity of infected students

is one of the most powerful tools for managing the pandemic as it allows to identify the infected individuals earlier to reduce additional infections; 2) although testing is uncomfortable and may be painful for some people, it is less painful than hospitalization; 3) testing can reduce pressures on different stakeholders, particularly mental pressures on parents and teachers by providing them with some reassurance that schools are being monitored [12]; 4) asymptomatic cases, that are mainly among the younger ages and able to spread the virus, can only be detected through random testing; 5) testing enables schools to continue their operations with lower risks and uncertainty: without testing, schools may have to go to lock down more frequently, most likely because when too many cases are identified by screening, it will be too late to control the outbreak without closing the school. Moreover, if the pandemic continues, closure of schools may not be a long-term solution; 6) without regular testing, co-infection or overlap between influenza and COVID-19 can create more chaos, particularly during the flu season when it will be difficult for parents or those who screen the children for symptoms, to identify most likely COVID-19 symptoms. A summary of the challenges above is depicted in Table 2.

School testing strategies

Public health agencies are undertaking or considering many different strategies with regard to school testing. These include: 1) Random regular testing in which all or a sample of students and schools are tested regularly: For example, the Province of Saskatchewan, Canada has announced that students with parental consent will have the option to participate in random testing [12]. These tests can be integrated into routine in-school childhood vaccinations. Selection of schools to be tested could be based on the surge in communities where schools are located. 2) One-time testing of all students and teachers returning to schools after summer holidays or school closure: This strategy aims to ensure that students come to school uninfected. For example, the Province of Alberta, Canada, aimed to test all students and teachers before reopening the schools [12]. This would need prioritization of testing for students and teachers before school reopening. The Province of Saskatchewan also encourages teachers and education staff to get tested prior to the school year; 3) Testing students and teachers with symptoms: this is in line with the current practice in which suspected students and teachers are requested to be tested. Most of the current guidelines provided by Public Health agencies to schools advise them to recommend students or

Table 2 Summary of School Testing Benefits

1	Allows to identify the infected individuals earlier to reduce additional infections
2	It is less painful than hospitalization for those who would have been infected in the absence of testing
3	It can reduce pressures on different stakeholders, particularly mental pressures on parents and teachers
4	Asymptomatic cases, that are mainly among the younger ages and able to spread the virus, can only be detected through random testing
5	It enables schools to continue their operations with lower risks and uncertainty, which is important because as the pandemic continues, closure of schools may not be a long-term solution
6	without regular testing, co-infection or overlap between influenza and COVID-19 can create more chaos, particularly during the flu season when it will be difficult for parents or those who screen the children for symptoms, to identify most likely COVID-19 symptoms

Table 3 Summary of Pros and Cons of Different School Testing Strategies

Testing Strategy	Major Pros	Major Cons
Random regular testing in which all or a sample of students and schools are tested regularly	Can be integrated into routine in-school childhood vaccinations	Large samples maybe needed to be effective
One-time testing of all students and teachers returning to schools after summer holidays or school closure	Can help reducing the anxiety of reopening among the students, schools' staff and parents	Lsrge number of tests to be processed at a given time and may not prevent contamination after testing.
Testing students and teachers with symptoms	Small number of tests are required.	Detects symptomatic cases only

teachers with COVID-19 symptoms to self-quarantine and get tested. According to this strategy, testing does not have to be done in schools, but provisions can be made to give priority to such tests at designated testing sites. Table 3 summarized these different school testing strategies.

In this paper we focus on the first strategy that is based on the regular random testing in all or some of the schools. This strategy could have several options and scenarios depending on the frequency of testing (daily, weekly), number of days it takes to have test results, test expiry days, and actions taken subsequent to positive test results such as intensified testing or self-isolation of infected classes.

Method

We developed a modeling and simulation tool to assess the outcomes of regular random school testing. We use an agent-based model with two agents of *Student* and *Class*. This model does not include *Teacher* and *Staff*, although the teacher population can be included in the class population adjusting for

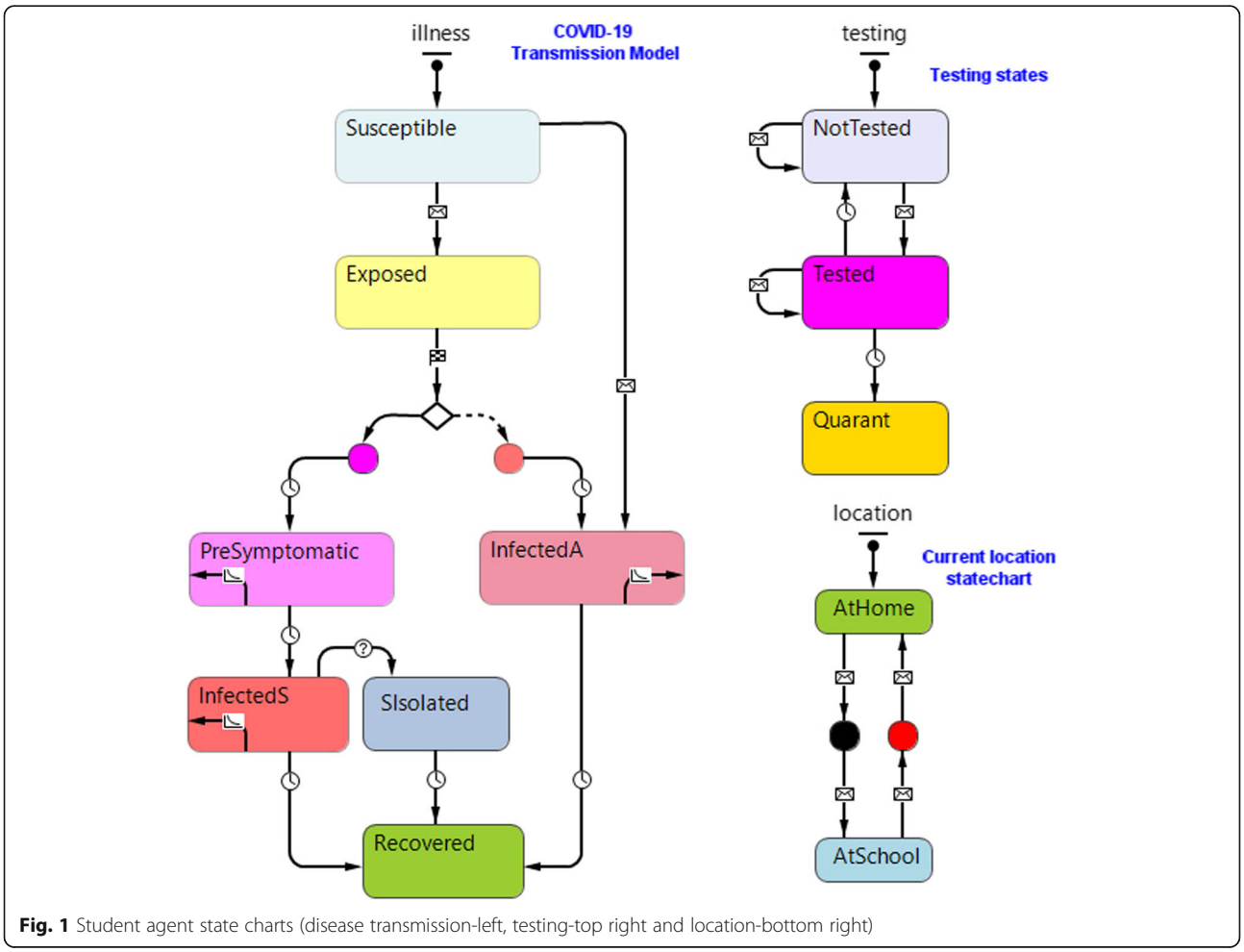


Fig. 1 Student agent state charts (disease transmission-left, testing-top right and location-bottom right)

appropriate contact rates and transmission levels. A modified SEIR model captures the disease transmission (Fig. 1). Students go to their school in the morning of weekdays and return home after the end of the school hours. This movement is captured by the *location* state chart. If a student tested positive, he or she stays home. As shown in the *illness* state chart, each student is at Susceptible state before it is exposed to a random asymptomatic infected classmate. After the exposure, the student may become infectious with different probabilities, either pre-symptomatic or asymptomatic. Transmission rate is defined as a product of *transmission probability* and *number of contacts* when the student resides at school. The model allows for a portion of infected symptomatic cases to be self-isolated. Both asymptomatically and symptomatically infected students recover within a specified number of days. In this model, we have assumed that recovery from the infection would confer lifelong immunity (e.g., within the life span of the modeling), and thus, once an agent is recovered from the infection, it cannot get infected with this virus another time.

The *testing* state chart captures the testing states of student agent. Students are all in NotTested state before being randomly tested. As students are tested their state changes to Tested. They will remain in this state and the school until the test result is provided. If the test result is positive, the student is self-isolated at home (Quarant state), and if not, the student will go back to NotTested state after the test expiry date and the student can be retested. While in Self Isolated state due to symptoms checking (SIsolated) or due to testing (Quarant) states, students stay at home.

The *Class* agent defines the location of students in the school and infectious status of the class. Each class contains its own students throughout the simulation. In other words, students of each class are always together. Once a student in a class becomes infected, it starts infecting others. As testing starts, a subgroup of the class is created to account for tested students.

The transition from Susceptible to InfectedA state is solely for model initialization that allow us to enter one or more infected students at the beginning or at an arbitrary stage of the modeling process. The initial number of infected students can be decides based on the prevalence rate in the community in which the school is operating.

The simulation tool includes a parameter setup page (Fig. 2), a 3D animation window (Fig. 3), a 2D visualization, and a statistics section that presents the simulation results.

Results

The simulation tool allows users to set relevant values for each parameter, and thus examine different

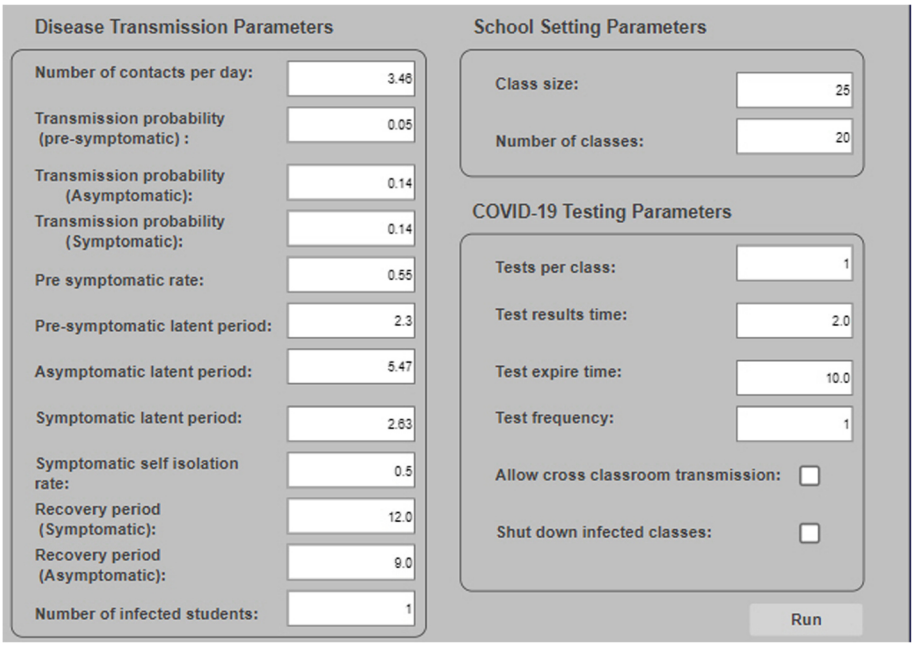


Fig. 2 Parameter setting page of the school testing simulation tool

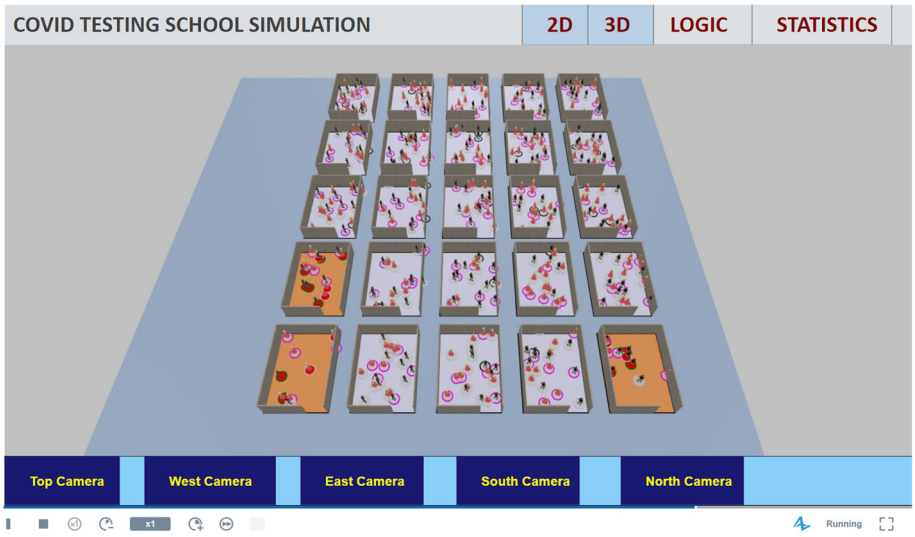


Fig. 3 3D animation page of the simulation

scenarios. We run the model for a baseline parameter setting (Table 4) to demonstrate the simulation results. While parameters can be localized as needed, here we set the parameters based on Ontario information as reported in the existing literature.

We run the base model for a school with 20 classes and 25 students in each class for a total of 500 students. We also assume that the simulation starts with three asymptomatic infected students. Simulation results are presented using Monte Carlo simulations with 500 iterations to capture the stochastic variations and randomness nature of testing. The simulation period is 60 days.

Infections and tests - daily tests

Figure 4 shows the accumulated number of infected students (symptomatic and asymptomatic) under different number of daily tests in each class. As

Table 4 Parameters setting for the base model

Parameter Type	Parameters	Value
Disease related	Number of contacts per school day [13]	3.45
	Transmission probability of pre-symptomatic [14]	0.05
	Transmission probability of symptomatic [15]	0.14
	Transmission probability of asymptomatic [15]	0.14
	Pre-symptomatic rate (portion) [15]	0.45
	Pre-symptomatic latent period day) [14]	2.3
	Asymptomatic latent period (day) [14]	5.47
	Symptomatic latent period (day) [14]	2.63
	Self-isolation rate [14]	0.5
	Symptomatic recovery period (day) [16]	12.0
	Asymptomatic recovery period (day) [16]	9.0
	Number of initially infected students	3
Class related	Class size	25
	Number of classes	20
Test related	Number of tests in each class	1
	Test results time (day)	2
	Test expiry time (day)	10
	Test frequency (day)	10

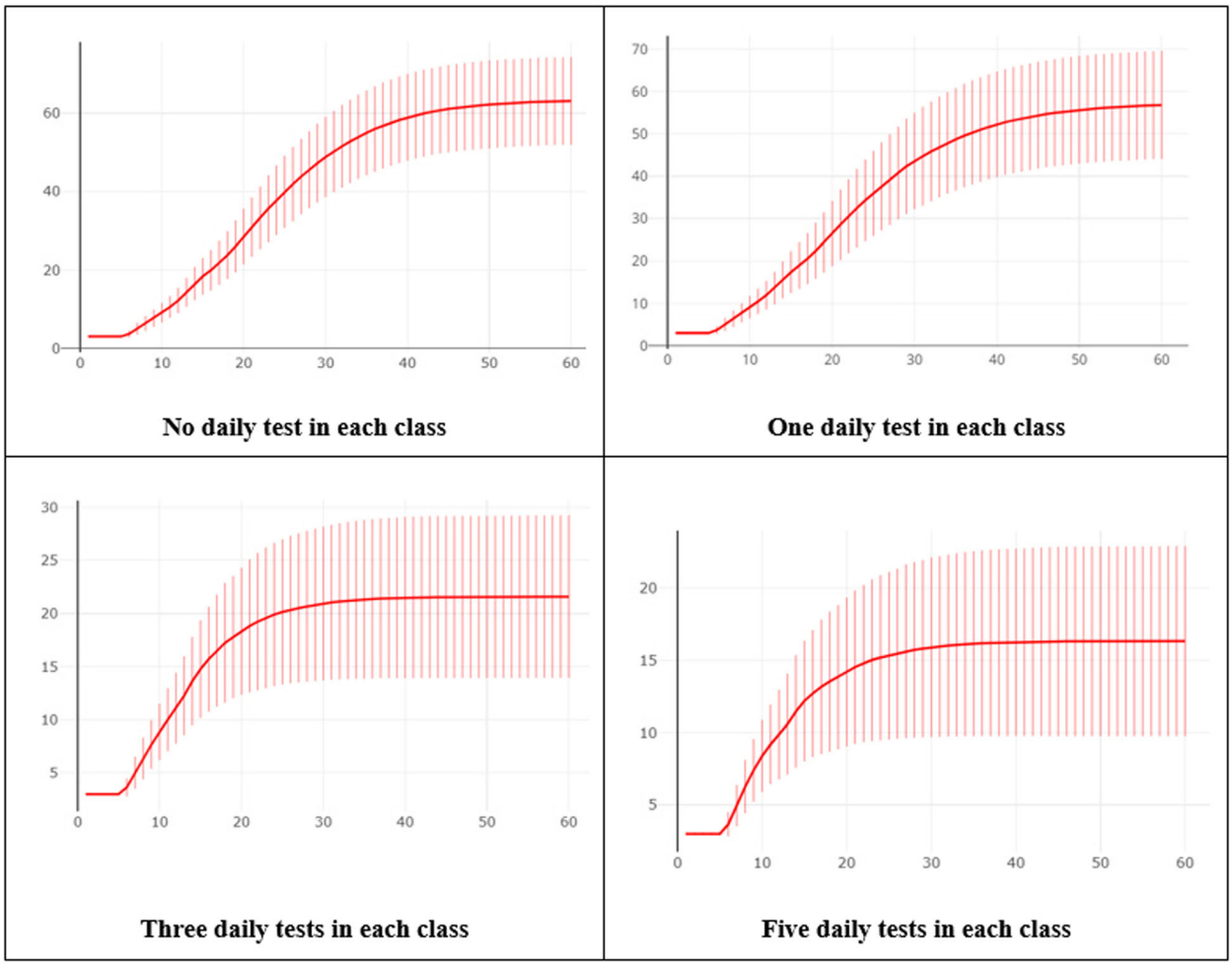


Fig. 4 Number of infected students under different number of daily tests at base parameters setting (Monte Carlo Simulation of the model with 500 iterations)

expected, these results show that increasing the number of tests reduces the number of additional infections. However, interestingly, the results show that increasing the number of daily tests beyond 5 tests per class (as high as 20% percent of the pupils in the class) under the current parameter setting, would not make a significant difference.

Figure 5 Shows the number of tests, number of infected students, and number of students isolated through testing at day 30 and day 60.

Infections and tests - weekly tests

Figure 6 presents the simulation results for the base model considering a weekly test schedule. In this experiment, we compare the accumulated number of infected students based on number of tests per class per week. Although increasing the number of tests in each week can reduce number of cases, it does not seem to be as effective as daily tests for less than the whole class per week.

Figure 7 shows number of tests, number of infected students, and number of students isolated through testing for weekly testing strategy at day 30 and day 60 of the simulation.

Infections and tests - test results days and test expiry days

Figure 8 shows the simulation results for the base model under different waiting days for test results. We compare same day test results with test results provided after 1, 2 and 3 days. As expected, providing the test results on the same day yields a lower number of cases as it expedites the isolation of confirmed positive cases, before they have time to spread the virus further in the school.

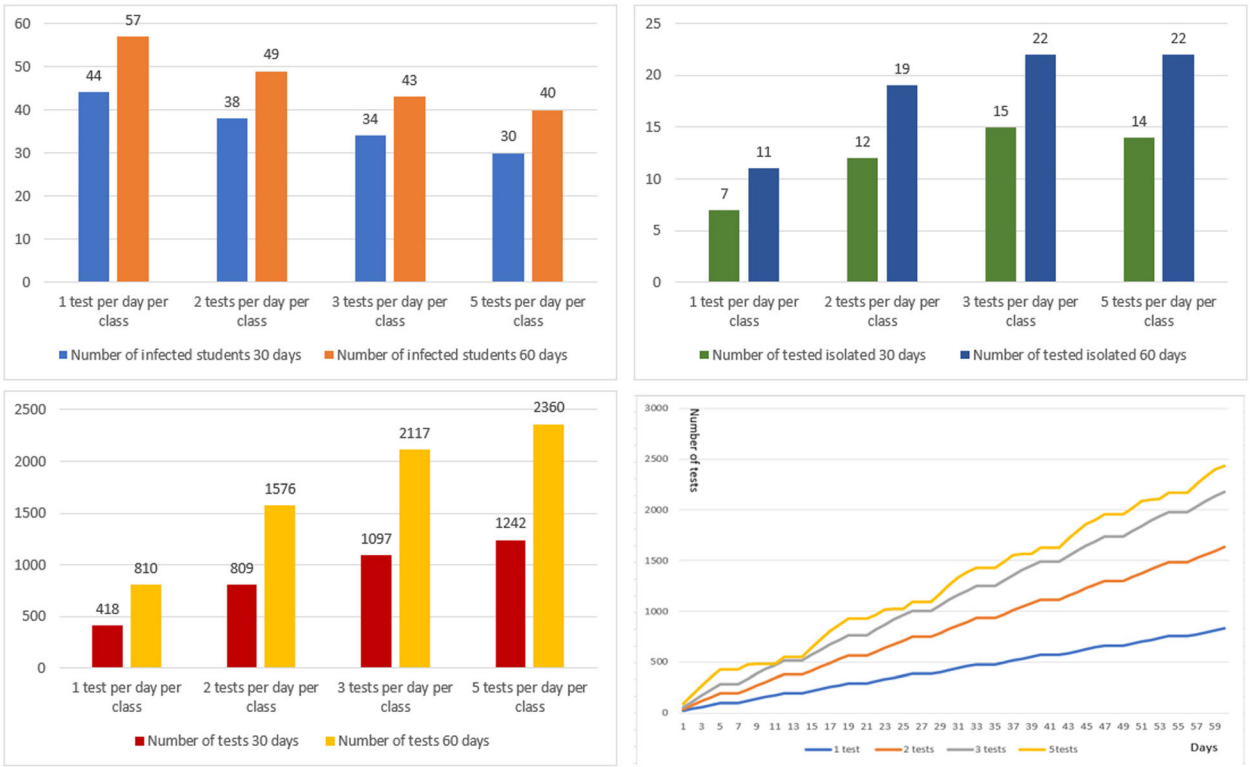


Fig. 5 Number of infected students (top left), number of tested isolated students (top right), tests needed (bottom left), and accumulated number of tests (bottom right)

Test results can be valid for different days before a student needs to be tested again. Test expiry period refers to the days by which a tested student would not be included in the testing. We ran the simulation to understand what the impacts would be setting different test expiry days. Figure 9 present the simulation results for the base model with varying days for test expiry. As expected, earlier expiry of the test reduces the number of detected infected cases, as tested students are added to the tested group, the probability of finding the actual infected students is reduced.

Infections and tests – isolating students in infected classes

One important infection control strategy for the school would be to ask all students from classes with a positive test result to stay home for 14 days. This strategy assumes that in a close classroom the likelihood of infection among the classmates staying together for the school hours and days before the infected student is identified would be very high. Figure 10 and Fig. 11 present the number of students that will be isolated and the total number of infected students under this strategy. According to these results while the total number of isolated students will be similar under different number of tests per day, the total number of infected students decreases as more daily tests are conducted.

Infections and tests -testing all students in infected classes

We also present sample simulation results for a special testing strategy that forces all students in infected classes to be tested after a positive test is found in them. This strategy will allow students to remain in the class if tested negative. Figure 12 and Fig. 13 present the results of these experiments for a sample of tests per day in each class. More daily tests under this strategy allows for significant reduction of infected cases by testing and isolating infected students (Fig. 12).

Figure 13 shows number of tests, number of infected students, and number of students isolated through testing for testing all students in infected classes strategy on day 30 and day 60 of the simulation.

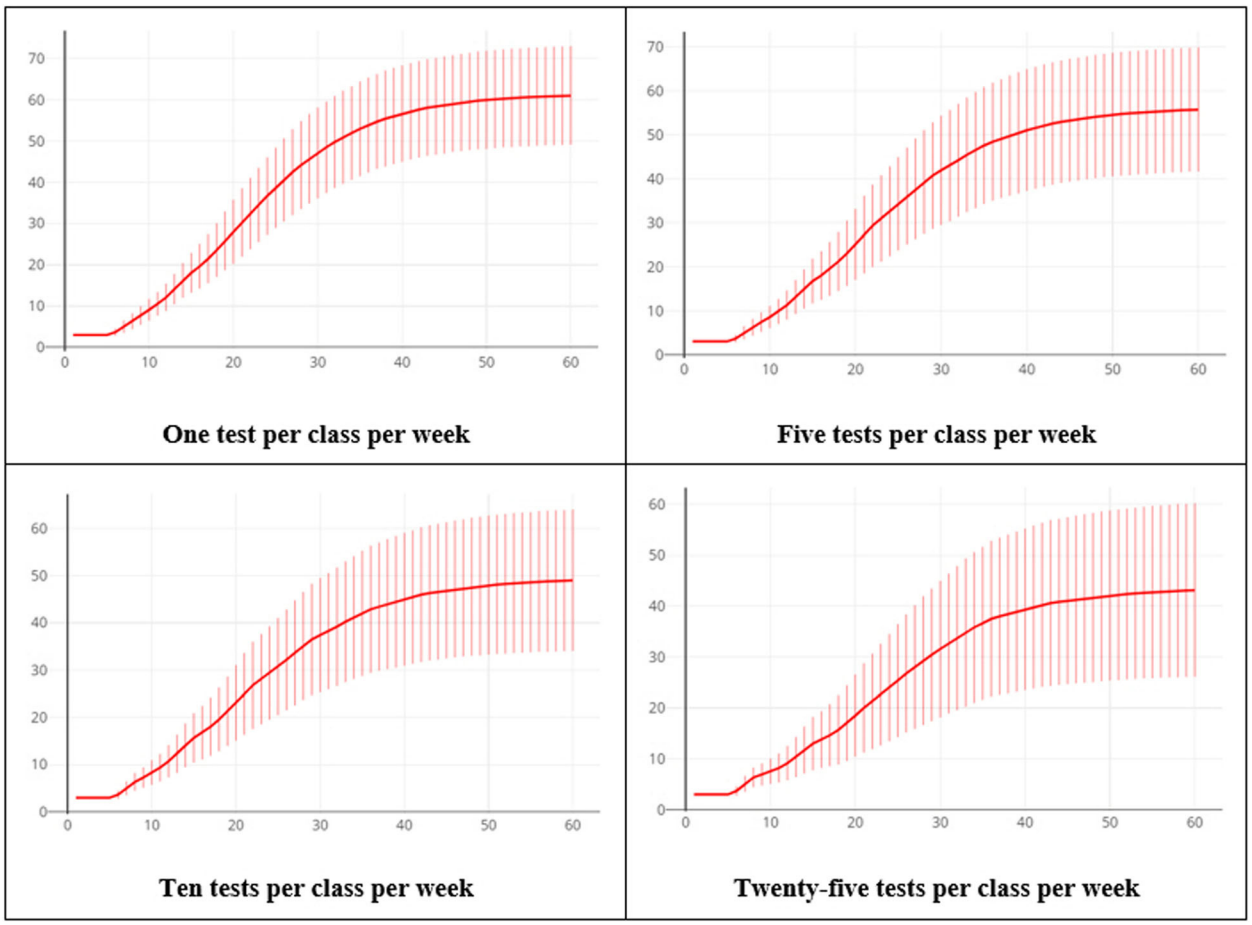


Fig. 6 Accumulated number of infected students under different number of tests per week

Validating the simulation results

Theoretical validity

In this section we present an estimate on the frequency of testing needed to control outbreaks of COVID-19 in Ontario's elementary/secondary schools (ages 5-15 yrs). The testing frequency and number of tests refer to a school's population made up of students & teachers and staff, together. Most importantly, we show that a testing frequency of 3 students per class, per day (as also shown in sections above) is sufficient to keep $R_{eff} \leq 1$ in the school environment, thus preventing outbreaks. In Humphrey et al. [17], a calibrated SEIRL (where L stands for isolated) compartmental model was used to trace the pandemic in various countries. The model gave necessary levels of frequencies for isolating infectious and exposed individuals (via testing and contact tracing) needed to control subsequent waves of the pandemic.

We use here a similar approach but for a school population as follows: We assume a generic elementary/secondary school in Ontario with a population of students (from junior kindergarten to 8-th grade) denoted by N_1 and a population of teachers and staff denoted by N_2. We further denote by subindex-1 the population of students and by subindex-2 the population of teachers & staff. In Prem et al. [13], the authors project average numbers of contacts for 152 countries around the world from the POLYMOD study of Mossong et al. [18] They refer to social contacts that are meaningful in the transmission of influenza and other similar pathogens. The authors give estimates of the average daily number of contacts of children between ages of 5–15 years old in Canada with their peers, during school, to be c_{11} =3.46, while the average contact rate of students with their teachers (which we estimate as adults between the ages of 20–65 who work in elementary and secondary school in

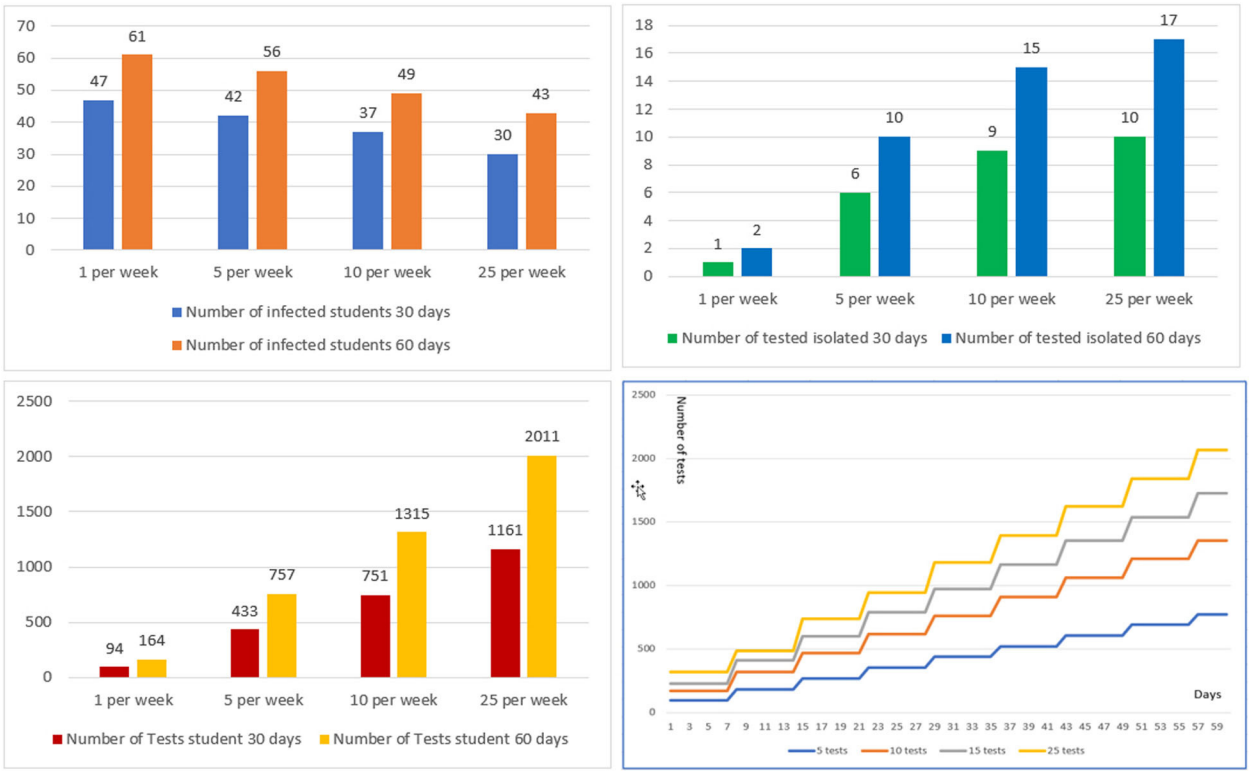


Fig. 7 Number of infected students (top left), number of tested isolated students (top right), tests needed (bottom left), and accumulated number of tests (bottom right)

Ontario) is estimated to be c_{12} =0.39 per day. Using a weighted average mix of 5 yrs. population group sizes in Ontario, we compute the average contact rates of teachers with students to be c_{21} =0.34 and finally the teachers with other teachers rate to be c_{22} =0.31. Since all school contacts take place during school-time (duration 8 h), we obtain the within-school-time contact rate by multiplying the daily number of school contacts by a factor 24 *hrs*/ 8 *hrs* = 3.

To model the transmission in the two subpopulations of the school, during school days, and disregarding for the time being the coupling of students and teachers/staff populations with the community, we consider the following two sets of differential equations ($j \in \{1, 2\}$):

$$\frac{ds_j}{dt} = -\left(\beta_{j1}\, i_1 + \beta_{j2} i_2\right) s_j$$

$$\frac{de_j}{dt} = \left(\beta_{j1}\, i_1 + \beta_{j2} i_2\right) s_j - \sigma\, e_j - {\kappa_1}^j e_j$$

$$\frac{di_j}{dt} = \sigma\, e_j - \left(\gamma + {\kappa_1}^j\right) i_j$$

$$\frac{dl_j}{dt} = \kappa^j\, i_j + {\kappa_1}^j e_j$$

where $\beta_{ji} = c_{ji} prob_{trns}$, $forall\ \ i = \{1, 2\}$ so that c_{j1} is the average contact rate of a person in group j with a child, c_{j2} is the average contact rate of a person in group j with a teacher/staff and where $prob_{trns}$ is the probability of transmission per contact, taken to be, as in previous sections, 0.14 in Ontario. Finally, κ^j and ${\kappa_1}^j$ are isolation rates due to testing and tracing for the subpopulation j. It is understood that the two systems of differential equations describing the subpopulations are to be analyzed together if one wants to extract information on the effective reproductive number *Reff* of the school, as a function of the model parameters.

We assume that the school's disease free equilibrium (DFE) on September 15, 2020 is given by the value $DFE := (s_1^{-} := N_1/N_1 + N_2), 0, 0, 0, s_2^{-} := N_2/(N_1 + N_2), 0, 0, 0)$. An analysis around this DFE describing the two subpopulations [19] can be conducted using the next-

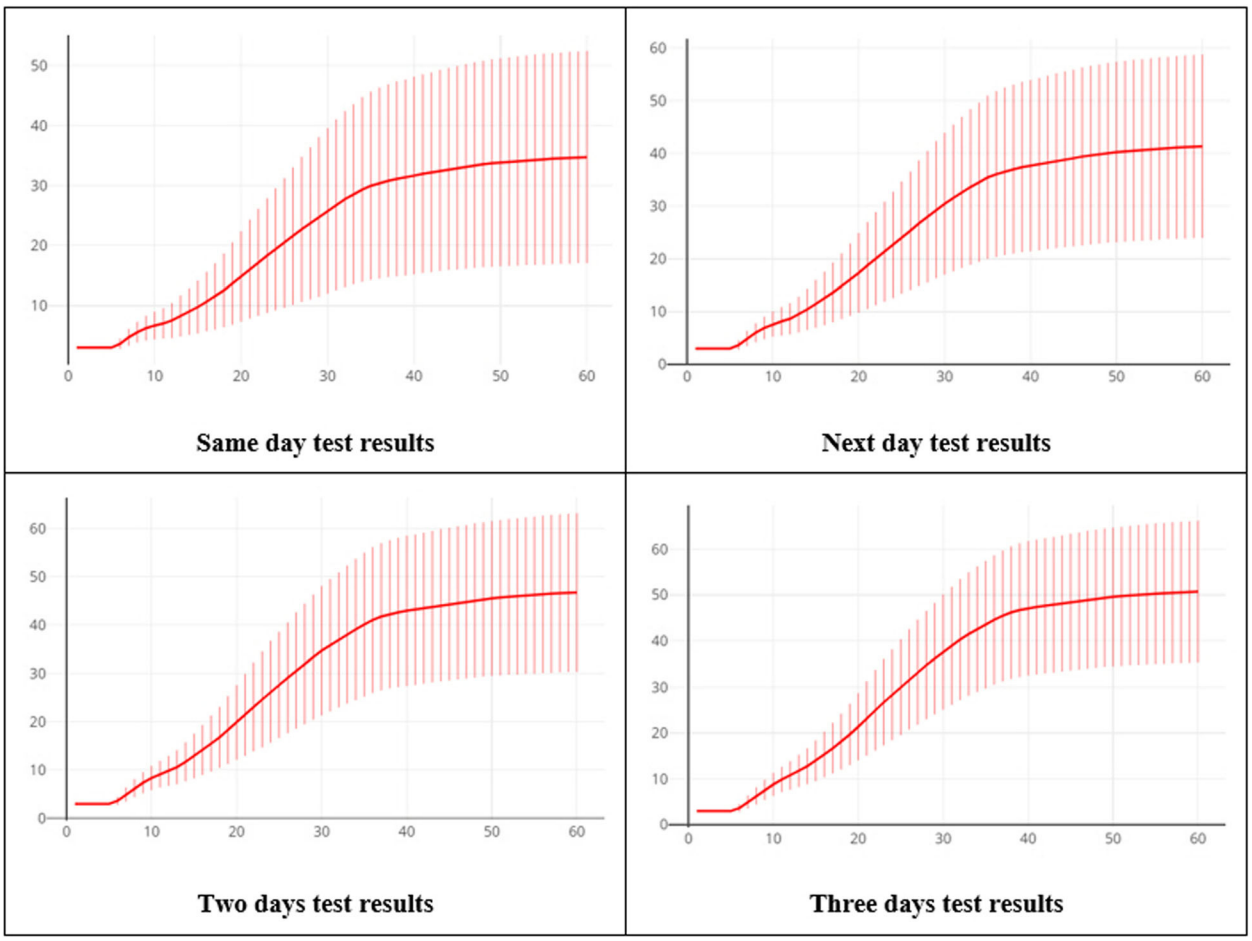


Fig. 8 Simulation results for the base model parameters under different test results waiting times

generation matrix method. With values of contact rates $c_{11} = 10.38$, $c_{12} = 1.17$, $c_{21} = 1.029$, $c_{22} = 0.937$, $\sigma = 1/2.5 = 0.4; \gamma = 0.4, s_2 = 1 - s_1, and\ s_1 = 80\%$ we get that: $R_0 = R_{eff}(t = 0) = 3.03$ in the beginning of the pandemic, in the absence of any mitigation measures. Further, we note that R_{eff} depends primarily on the frequency that the population of students gets tested (κ^1 in the left panel of Fig. 14) but only weakly on the frequency of testing the population of teachers (κ^2 in left panel of Fig. 14).

Therefore we concentrate on getting estimates for the frequency of isolation due to testing (κ^1) and tracing ($\kappa^1{}_1$) in the population of students, in order to keep the effective reproduction number at 1 ($R_{eff} = 1$). To be more conservative, we assume that for every isolated student due to testing positive, one exposed student among its contacts can be isolated on average. Therefore, we consider $\kappa^1 = \kappa^1{}_1$.

Adopting our assumptions of the paper so far, consider a school with 500 students who represent a proportion of 80% of the school, where the teachers and staff population represents 20%. Then we compute that a frequency of testing of $\kappa^1 = 0.999 = > 1/\kappa^1 = 10\ days$ will result in the desired $R_{eff} = 1$. This means that testing every student every 10 days will ensure an effective reproductive number below the threshold value for school outbreaks. Note that keeping $R_{eff} = 1$ is desired when the community transmission and the number of new infections is very low. Otherwise we need to aim for $R_{eff} < 1$.

The effects of facemask and class cohort

Here we show how the theoretical result validates our detailed simulations. In our school of 500 students divided into average class sizes of 25 students, we can, at a minimum, think of testing one student in each class every day. But this is likely not enough to

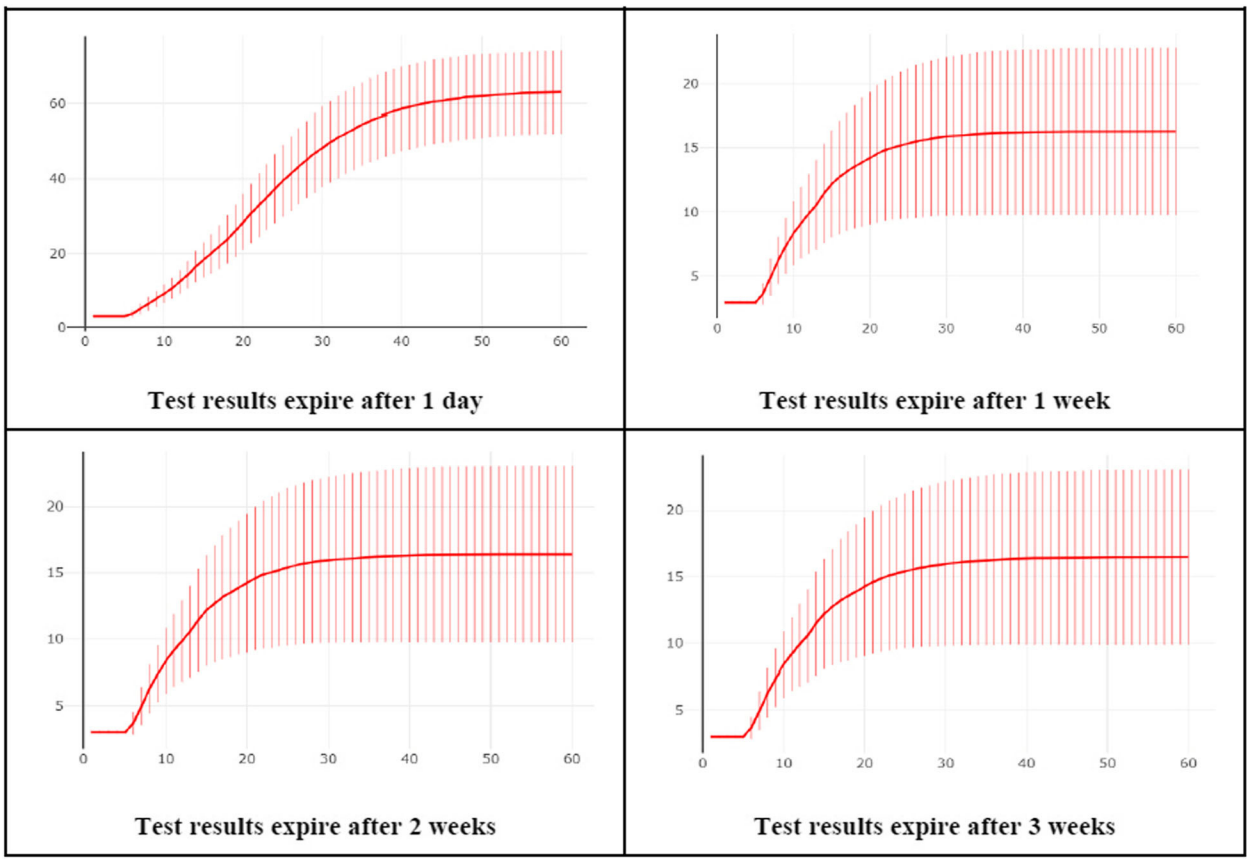


Fig. 9 Simulation results for base parameters under varying test expiry days

prevent outbreaks, as it amounts to testing every student every 25-th day, which is far below our calculated threshold of testing each student on average every 10 days. It turns out that testing 3 students out of every class daily would amount to testing every child every 8.6 days, and leading to $\kappa^1 = 0.1163$ to ensure $R_{eff} < 1$. Specifically, we have $R_{eff} = 0.874$. The number of tests needed per day in the school in the last scenario would be

$$20\ x\ 3 = 60\ tests\ per\ day => 1800\ tests\ per\ month$$

If we consider that pre-symptomatic students may become symptomatic over the weekend and thus self-isolate come Monday morning, then the student isolation rate ${\kappa_1}^1$ can be improved by at least a 2/7 ratio per week, that is to say, a 2/49 ratio per day: ${\kappa_1}^1 = \kappa^1 + 2/49$ which would imply that the frequency of testing to maintain $R_{eff} = 1$ would be $\kappa^1 = 12.45$ *days*. This would mean a decrease to a frequency of 2 tests per class, per day, for a total of

$$20\ x\ 2 = 40\ tests\ per\ day => 1200\ tests\ per\ month.$$

Next, we look at how we can account for mask wearing (and other social-distancing) policies voted into effect by many school boards in Ontario, as well as the policy of class cohorts, i.e. the reduced contacts that individual classes can have with other classes in the school. In general, both of the measures above will affect the effective contact rates, β_{ij}, albeit from two differing angles: mask wearing reduces the per-contact probability of transmission $prob_{trns}$, while class cohorts restrictions reduce the average contacts c_{ij}, $i, j \in \{1, 2\}$. We can incorporate both effects in our estimate by considering the effective contact rates as:

$$\beta_{ij} = (1 - cohort_{red})\ c_{ij}\ (1 - mask_{red})\ prob_{trns}$$

where $cohort_{red}$ and $mask_{red}$ are the notations for the reduction factors described above. The mask wearing reduction factor is taken to be in a range of [0.3, 0.8] [20] where 0.3 effectiveness is the level of a paper mask or 1-layer mask, while 0.8 and higher are surgical masks and N95 masks, which are not typically available to everyday

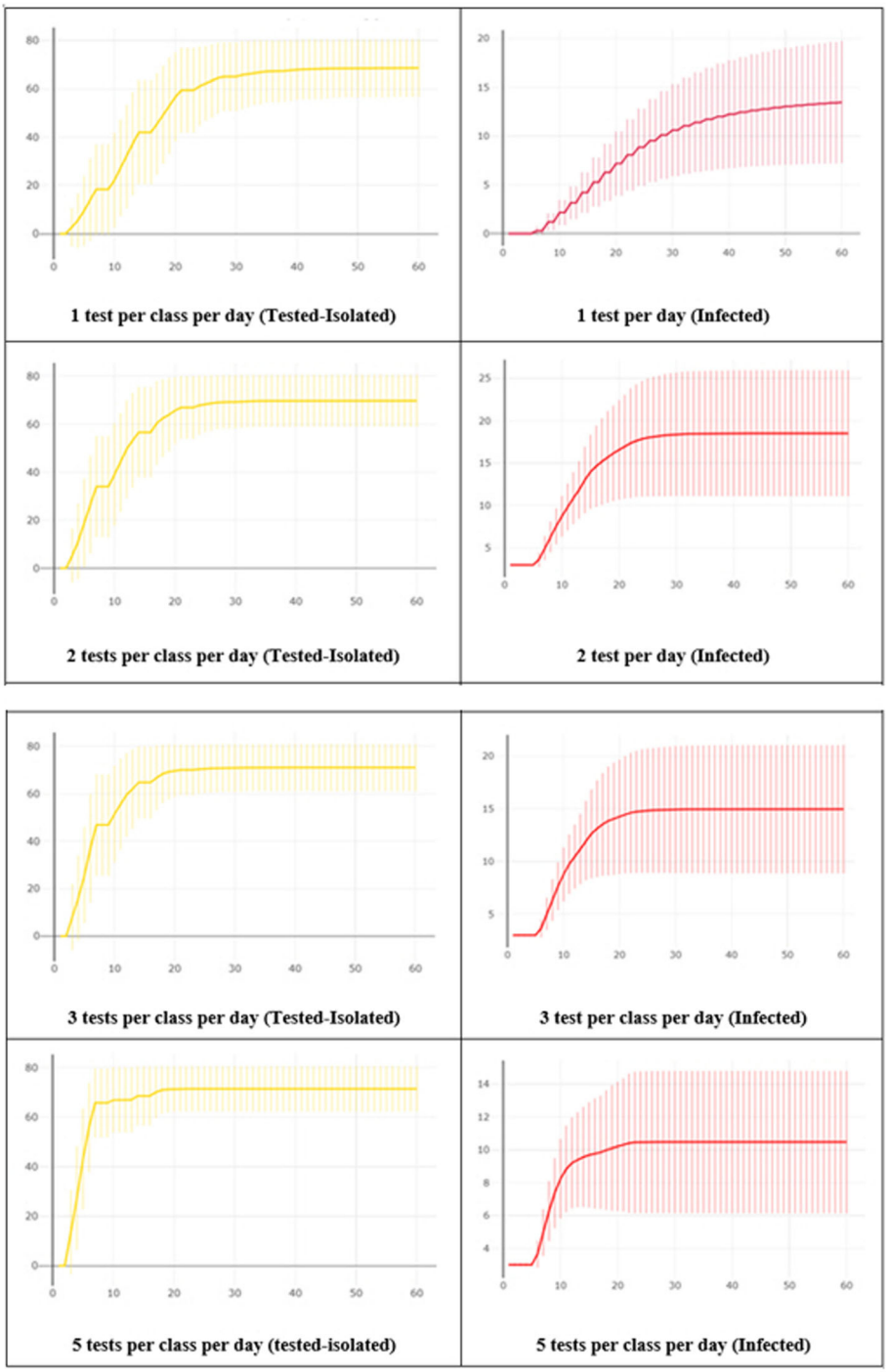


Fig. 10 Number of students isolated (left) and infected (right) under different number of daily tests in each class when all students in infected class are self-isolated at home

students). Specifically, we take it here equal to 0.3. Cohort reduction is taken to be 0.05 for exemplification purposes. Both values are fairly conservative. Under the new assumptions, we compute that the frequency of isolating students due to testing and tracing is to be 17.7 *days* ($\kappa^1 = 0.0565$) for an effective reproductive number of $R_{eff} = 1$. This would amount to roughly 1.5 students needed to be tested per class per day (1 student

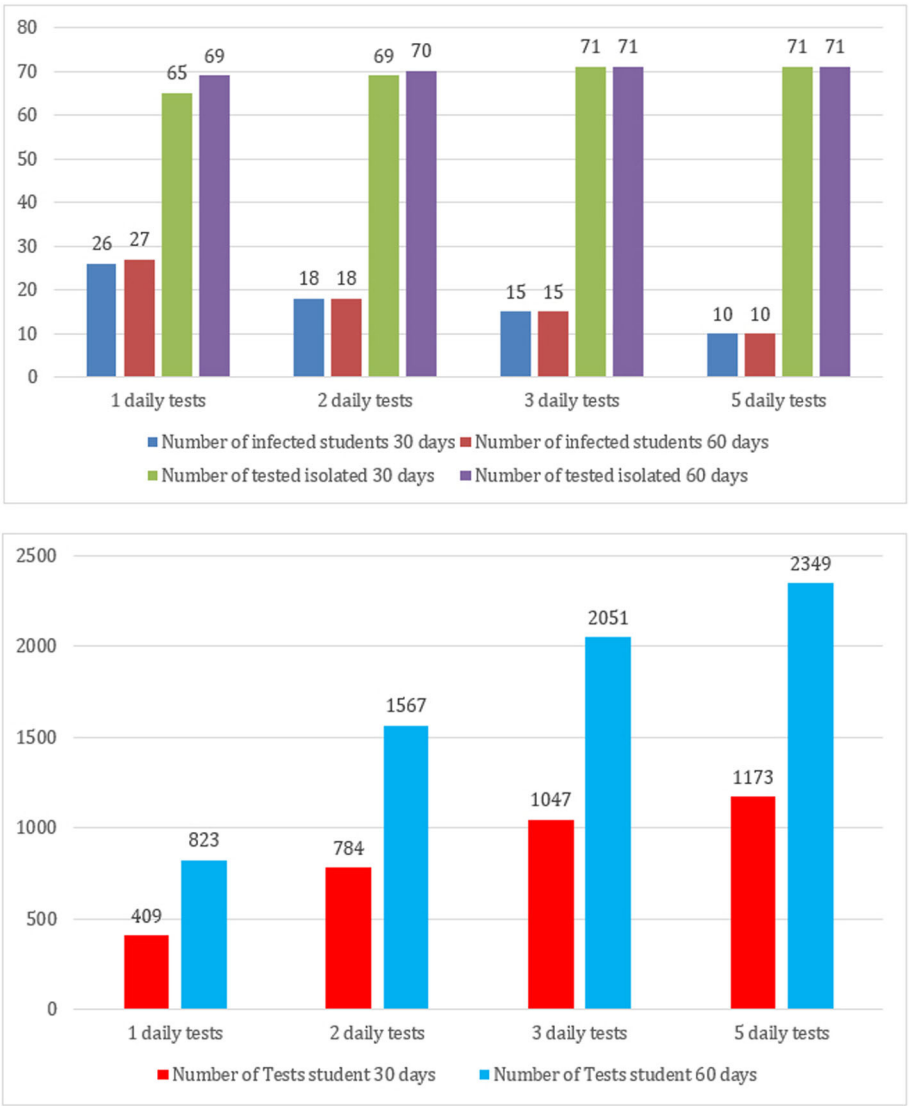


Fig. 11 Total number of tests under different number of daily tests and when all students in infected classes are self-isolated at home

in half the classes, 2 students in the other half per day, then switch the next day). This would mean a decrease to a frequency of 1.5 tests per class, per day, for a total of

$$20\ x\ 1.5 = 30\ tests\ per\ day => 900\ tests\ per\ month.$$

We note that the range of values for the $cohort_{red}$ reduction factor is not yet known. An increase from 0.05 to 0.1 would amount to a further decrease to testing every student every 19.5 days, etc. An increase in $mask_{red}$ to 0.4 (from 0.3) amounts to testing every student every 26 days, which is the equivalent to testing 1 student in every class, per day, for a total of

$20\ tests\ per\ day = > 600\ tests\ a\ month$ for an $R_{eff} = 1$.

All these scenarios are consistent with the results of our simulations in Section 4. In fact, they represent an upper limit on the number of daily tests needed. Our agent-based simulations show a clearer picture of the proposed testing process and take into consideration a much more detailed transmission dynamics.

Discussion

In this simulation we have not included testing accuracy issues that are also very important [10]. Rapid tests that expedite the testing process, if used, may have larger

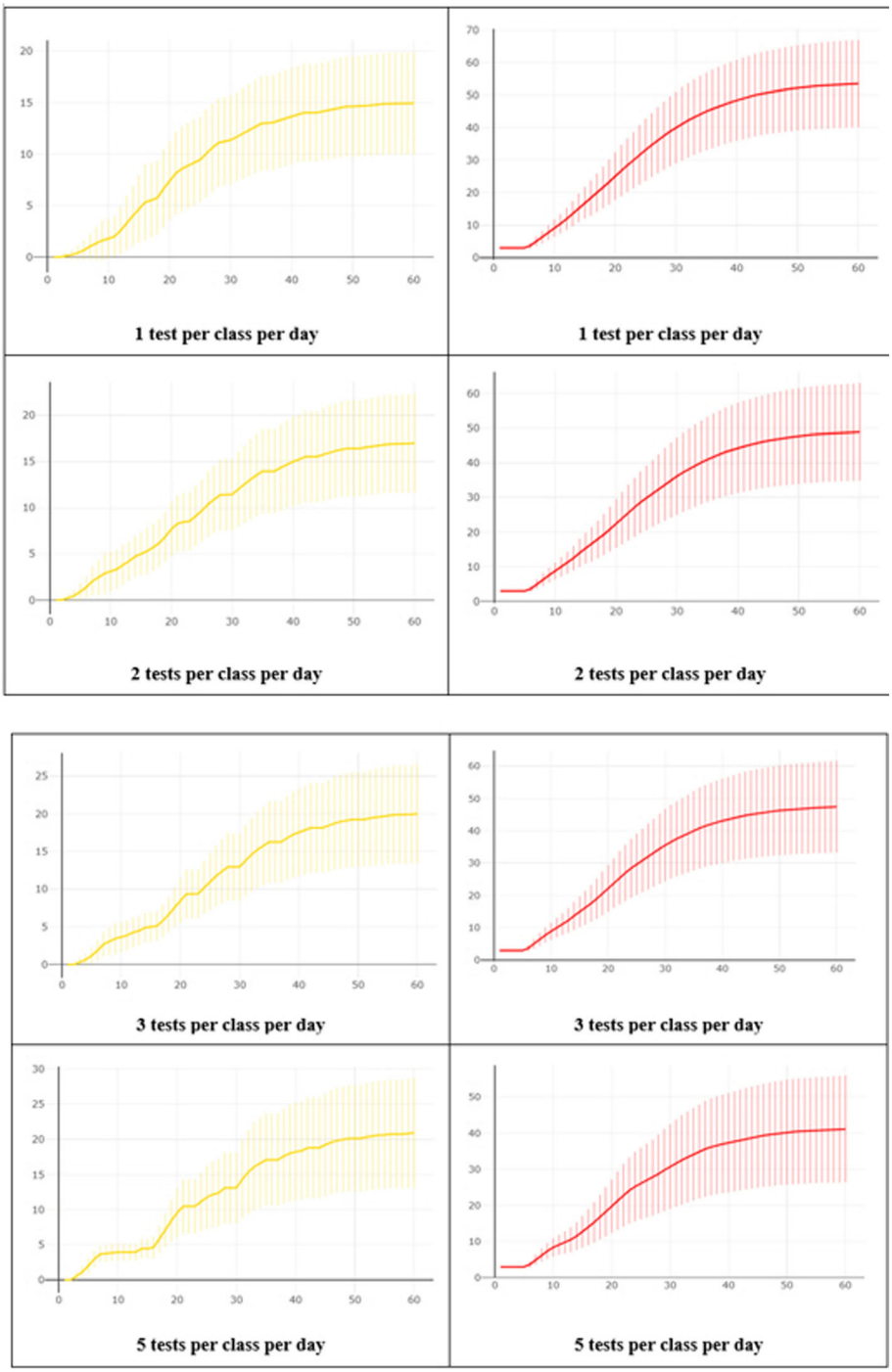


Fig. 12 Number of students isolated (left) and infected (right) under different number of daily tests in each class when all students in infected classes are tested

accuracy issues that need to be considered. The relevant parameter can be added to this simulation tool to account for test accuracy level. Similarly, this simulation in its current form does not factor in contact tracing so that if a student test becomes positive, all students in contact with the infected student are self-isolated which probably means the closure of the whole class. This again can be added to this simulation tool. One possibility would be to design the simulation so that if a

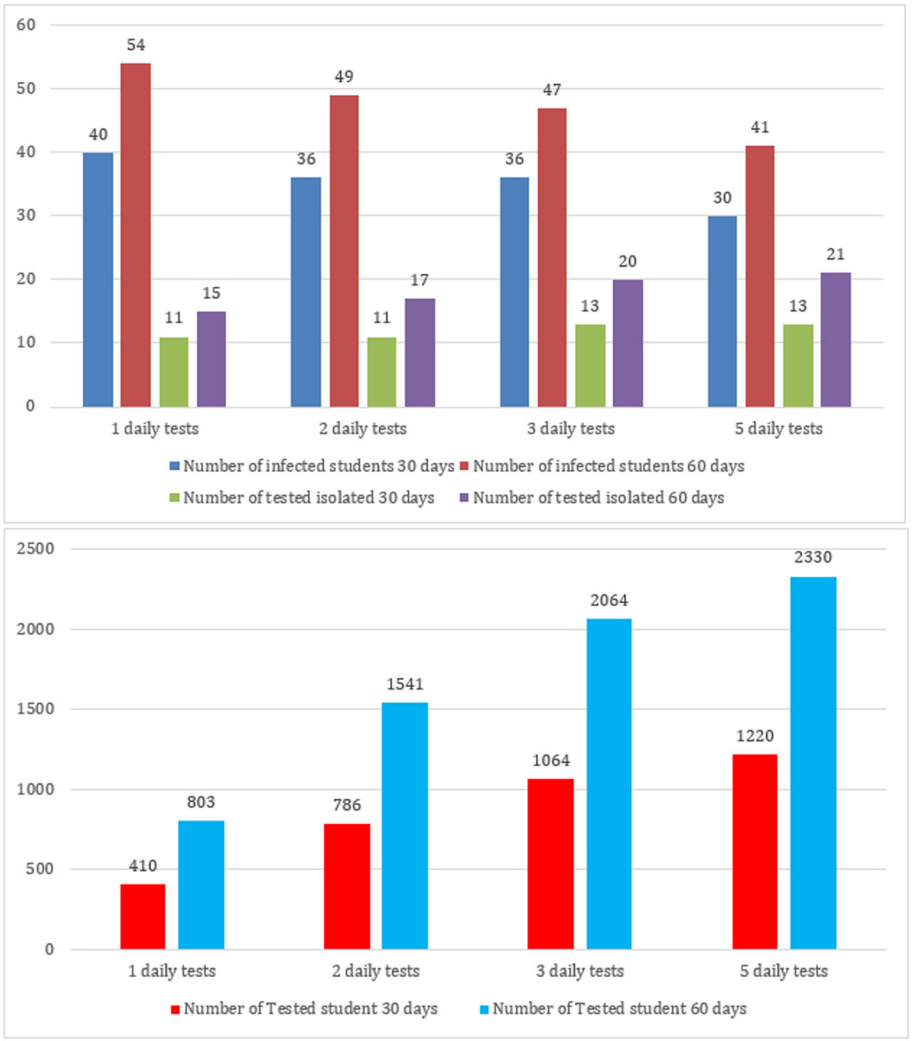


Fig. 13 Total number of tests under different number of daily tests and when all students in infected classed are tested

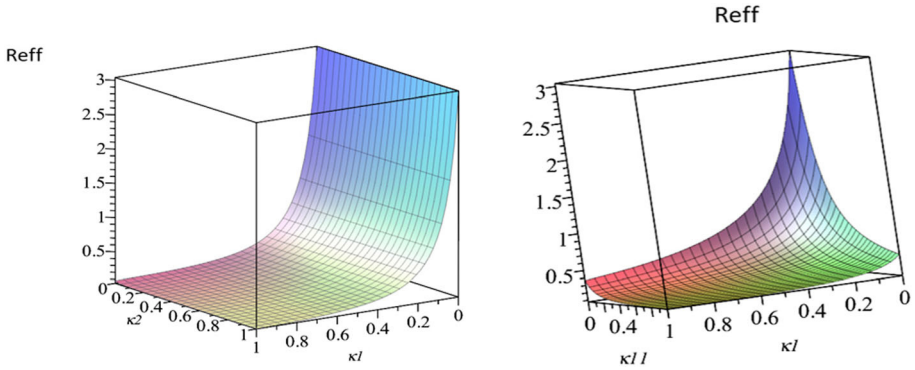


Fig. 14 Left Panel: Testing the teachers & staff population matters less in the evolution of the effective reproductive number in the school. Right Panel: Student population drives the disease spread primarily

student's test in a class becomes positive all students in that class are tested.

If rapid tests are available, the idea of pool testing can also be incorporated in this model. Pool testing adopts this tree-search algorithm to testing specimen aiming to increase the number of people tested using fewer number of tests. In pool testing, several specimens collected from different people are mixed and one test is done to find if that mix of specimens indicates an infection. In that case, the sources of that mix are divided into two groups, mixing the specimens in two or more different groups, to perform the test on the new – drilled-down mixes – to find which subset(s) of the specimen mixes shows an infection. This drill-down process is continued until the infected specimen(s) is (are) identified.

Finally, although this simulation focuses on schools, it can be adapted for similar situations where a number of people stay close to each other in one complex such as universities and workplaces.

Conclusion

In this paper, we presented an agent-based simulation tool for COVID-19 testing at schools. The model allows users to set several parameters and investigate the impacts of different testing approaches for controlling the outbreak in schools. The simulation is flexible in allowing different school sizes (based on number of classes and students in each class) and different parameter settings according to the local disease situation and testing policies.

This simulation is not a means for advocating school testing, rather it aims to help making such decisions. By using this tool, public health decisionmakers and school districts officials can decide whether and to what extent school testing would help them to control the outbreak, while being able to calculate the per capita costs of conducting tests at schools.

Abbreviations

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19: Corona Virus Disease 2019; SEIR: Susceptible, Exposed, Infectious, Recovered; ECDC: European Centre for Disease Prevention and Control (ECDC),

Acknowledgements

None

Authors' contributions

JW, AA and MGC conceived the idea. AA developed the agent-based simulation and MMN made some improvements in the simulation. AA wrote the background, methodology and simulation results. MGC developed the validation model and wrote the validation section. JW, MGC, and MMN reviewed the manuscript and made intellectual input. All authors read and approved the final manuscript.

Funding

Public Health Agency of Canada; Canadian Institute of Health Research, Ontario; Research Funds, National Science and Engineering Research Council of Canada. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Availability of data and materials

The data used in this study are generated by the simulation models developed in this study. The simulation tool is available at: https://cloud.anylogic.com/model/a7c4411e-064e-4283-a93c-b0b27e0430ee

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare no conflict of interest.

Author details

[1]Disaster & Emergency Management, School of Administrative Studies and Advanced Disaster, Emergency and Rapid-response Simulation, York University, Toronto, Canada. [2]Department of Mathematics & Statistics, University of Guelph, Guelph, Ontario, Canada. [3]Advanced Disaster, Emergency and Rapid-response Simulation, York University, Toronto, Canada. [4]Canada Research Chair in Industrial and Applied Mathematics, Laboratory for Industrial and Applied Mathematics (LIAM), York University, Toronto, Ontario, Canada.

Received: 2 October 2020 Accepted: 29 December 2020
Published online: 12 January 2021

References

1. European Centre for Disease Prevention and Control (ECDC). Objectives for COVID-19 testing in school settings. Stockholm: European Centre for Disease Prevention and Control (ECDC); 2020. https://www.ecdc.europa.eu/en/publications-data/objectives-covid-19-testing-school-settings (Accessed 10 2020).
2. Panovska-Griffiths J, Kerr CC, Stuart RM, et al. Determining the optimal strategy for reopening schools, the impact of test and trace interventions, and the risk of occurrence of a second COVID-19 epidemic wave in the UK: a modelling study. Lancet Child Adolesc Health. 2020; published online Aug. https://doi.org/10.1016/S2352-4642(20)30250-9.
3. World Health Organization. Considerations for school-related public health measures in the context of COVID-19: World Health Organization; 2020. https://www.who.int/publications/i/item/considerations-for-school-related-public-health-measures-in-the-context-of-covid-19 (Accessed 10 Sept 2020).
4. Centers for Disease Control and Prevention (CDC). Screening K-12 Students for Symptoms of COVID-19: Limitations and Considerations. United States: Centers for Disease Control and Prevention (CDC); 2020. https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/symptom-screening.html (Accessed 10 Sept 2020).
5. Centers for Disease Control and Prevention (CDC). Cleaning, Disinfection, and Hand Hygiene in Schools – a Toolkit for School Administrators. United States: Centers for Disease Control and Prevention (CDC); 2020. https://www.cdc.gov/coronavirus/2019-ncov/community/schools-childcare/clean-disinfect-hygiene.html (Accessed 10 Sept 2020).
6. Government of Canada. Risk mitigation tool for child and youth settings operating during the COVID-19 pandemic. Ottawa: Government of Canada; 2020. https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/covid-19-risk-mitigation-tool-child-youth-settings-operating-during-pandemic.html (Accessed 10 Sept 2020).
7. Government of Ontario. Archived - approach to reopening schools for the 2020–2021 school year. Ontario: Government of Ontario; 2020. https://www.ontario.ca/page/approach-reopening-schools-2020-2021-school-year (Accessed 10 Sept 2020).
8. Service R. Radical shift in COVID-19 testing needed to reopen schools and businesses, researchers say. Science. 2020; published online Aug 3. https://doi.org/10.1126/science.abe1546.
9. Lazer D, Santillana M, Perlis RH, et al. The State of the Nation: A 50-State COVID-19 Survey Report #8: Failing the Test. Open Sci Framework. 2020. https://doi.org/10.31219/osf.io/gj9x8.

10. Gressman PT, Peck JR. Simulating COVID-19 in a university environment. Math Biosci. 2020;328:108436. https://doi.org/10.1016/j.mbs.2020.108436.
11. Frank K, Arim R. Canadians' willingness to get a COVID-19 vaccine when one becomes available: what role does trust play? 2020 https://www150.statcan.gc.ca/n1/pub/45-28-0001/2020001/article/00043-eng.htm (Accessed 10 Sept 2020).
12. Kirkey S. Should random COVID-19 tests for kids and teachers be part of our back-to-school plans? Natl Post. 2020; published online Aug 20. https://nationalpost.com/news/should-random-covid-19-tests-for-kids-and-teachers-be-part-of-our-back-to-school-plans (Accessed 10 Sept 2020).
13. Prem K, Cook AR, Jit M. Projecting social contact matrices in 152 countries using contact surveys and demographic data. PLoS Comput Biol. 2017;13:e1005697. https://doi.org/10.1371/journal.pcbi.1005697.
14. Abdollahi E, Haworth-Brockman M, Keynan Y, Langley JM, Moghadas SM. Simulating the effect of school closure during COVID-19 outbreaks in Ontario, Canada. BMC Med. 2020;18:230. https://doi.org/10.1186/s12916-020-01705-8.
15. Tang B, Scarabel F, Bragazzi NL, et al. De-escalation by reversing the escalation with a stronger synergistic package of contact tracing, quarantine, isolation and personal protection: feasibility of preventing a COVID-19 rebound in Ontario, Canada, as a case study. Biology. 2020;9:100. https://doi.org/10.3390/biology9050100.
16. Byrne AW, McEvoy D, Collins A, et al. Inferred duration of infectious period of SARS-CoV-2: rapid scoping review and analysis of available evidence for asymptomatic and symptomatic COVID-19 cases. Epidemiology. 2020. https://doi.org/10.1101/2020.04.25.20079889.
17. Humphrey L, Thommes EW, Fields R, Hakim N, Chit A, Cojocaru MG. A path out of COVID-19 quarantine: an analysis of policy scenarios. medRxiv. 2020. https://doi.org/10.1101/2020.04.23.20077503.
18. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med. 2008;5:e74. https://doi.org/10.1371/journal.pmed.0050074.
19. van den Driessche P. Reproduction numbers of infectious disease models. Infect Dis Modelling. 2017;2(3):288–303.
20. Wilson AM, Abney SE, King M-F, et al. COVID-19 and use of non-traditional masks: how do various materials compare in reducing the risk of infection for mask wearers? J Hosp Infect. 2020;105:640–2. https://doi.org/10.1016/j.jhin.2020.05.036.

Publisher's Note

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

DECEMBER 3, 2020

The Missing Piece — SARS-CoV-2 Testing and School Reopening

Yasmin Rafiei, B.Sc., and Michelle M. Mello, J.D., Ph.D.

On August 17, 2020, the Los Angeles Unified School District launched a program to test more than 700,000 students and staff for SARS-CoV-2. The district is paying a private contractor to provide next-day, early-morning results for as many as 40,000 tests daily. As of October 4, a total of 34,833 people had been tested at 42 sites. The program is notable not only because it's ambitious, but also because it's unusual: testing is conspicuously absent from school reopening plans in many other districts. Typically, exhaustive attention has instead focused on physical distancing, face coverings, hygiene, staggering of schedules, and cohorting (dividing students into small, fixed groups). Although the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics, the National Academies of Sciences, Engineering, and Medicine, and state officials have urged schools to prepare for Covid-19 cases, they have offered strikingly little substantive guidance on testing. Immediate attention to improving testing access and response planning is essential to the successful reopening of schools.

Available guidance documents typically instruct schools to gain access to testing by contacting local public health departments, and few schools appear to have solidified a strategy — especially one that extends beyond testing of symptomatic persons. For instance, public schools in Boston and in Miami-Dade County will not conduct screening testing and are placing responsibility on parents for testing symptomatic children. New York State strongly recommends that schools not conduct testing. However, after its teachers union threatened to strike over safety concerns, New York City added monthly random screening testing for 10 to 20% of staff and students, with more frequent testing in hot spots.

Most reopening plans instead focus on screening for Covid-19 symptoms. Yet recent research indicates that symptom screening alone will not enable schools to contain Covid-19 outbreaks.[1] Because an estimated 40% of Covid-19 cases are asymptomatic and 50% of transmissions occur from asymptomatic persons, we believe that screening testing is critical. Nevertheless, until October 13, the CDC recommended against screening testing in schools, citing constraints on testing capacity and the unavailability of real-world studies of its effectiveness. The newer guidance states that schools "might choose" to offer voluntary testing and that their decisions "should be guided

by what is feasible, practical, and acceptable" and should prioritize symptomatic persons and close contacts of persons diagnosed with Covid-19.

SARS-CoV-2 testing presents at least three challenges for schools. The first is access to testing. Disparities in access persist, particularly for people without severe symptoms or known Covid-19 contacts. Whereas many universities can provide testing using their own labs, K–12 schools are reliant on either public health departments or private contracting. They face formidable financial barriers to providing direct access to testing for students given other pandemic-related strains on their budgets, including state requirements to test employees. Costs of individual tests in the community range from $50 to $200,[2] and federal law does not require employers or insurers to pay for SARS-CoV-2 screening tests administered as part of a return-to-work or return-to-school strategy. Congressional funds for testing the uninsured are also limited to tests for "diagnostic" purposes.

A second major challenge is the lag time in receiving test results. The latest available survey data, from August 2020, indicate that only 26% of tested Americans received their results within a day; 35% waited 4 or more days.[3] With limited access to rapid diagnostic tests, screening testing for students and school staff will involve similar wait times. Even outside the high-contact setting of schools, delays in returning results have disturbing consequences: a modeling study showed that same-day results can prevent 80% of new transmissions, whereas a 7-day delay stops only 5%.[4]

Disparities among communities in testing access and lag times exacerbate preexisting socioeconomic and racial inequities among schools. Schools that cannot quickly obtain test results are disproportionately forced to rely on extended quarantines. Given the distinctive difficulties students from low-income households face in distance learning, these disparities are particularly troubling. They also disproportionately burden children with special health needs, who may be at higher risk of Covid-19 infection and may depend on school-based services.

Moreover, schools must ensure timely reporting of test results, which labs cannot legally disclose without authorization. Schools could counsel parents and secure their legal authorization to have their Covid-19 test results released directly to school officials or could ask parents to disclose those results to the school themselves. Alternatively, schools could build a rapid-feedback loop among testing laboratories, the public health department, and potential contacts, in accordance with public health exceptions to privacy laws. There is no indication that these steps are part of schools' plans, however.

Third, implementing recommended responses to positive SARS-CoV-2 test results is logistically daunting. Screening testing involves a potentially large number of both true positive and false positive results, and the best practice is to isolate persons with positive results and quarantine in-school contacts until those persons test negative or the incubation period has elapsed. In schools not using cohorting, quarantines may affect a large number of students and staff. For example, a high school in Cherokee County, Georgia, had to quarantine more than a quarter of its 1800 students and suspend in-person learning after 25 students tested positive. Thus, in addition to arranging quarantines, schools must be able to deliver remote education to confined students on short notice.

Because testing-related challenges pose a serious threat to the viability of school reopening plans, we believe that increasing routine screening using rapid tests in schools should rank among our most urgent national priorities. In September, the federal government purchased 150 million rapid antigen tests for schools, but this effort falls short: one analysis estimated that K–12 schools would deplete this supply in 19 days if most students and staff were tested one to two times per week. Future Covid-19 relief packages should provide appropriations and technical assistance for schools to scale up testing programs, prioritizing districts with the least resources and the highest community risk. Congressional leaders and the White House have reportedly agreed on a "national testing strategy" as part of a proposed economic relief bill, but it is unclear what role, if any, school testing plays in it.

The federal government can also help by continuing to fund development of novel tests, including rapid antigen and saliva-based tests, and by strengthening efforts to ensure swift, broad, and equitable distribution. Investments by the National Institutes of Health and other sponsors have already spurred promising innovations. Several labs have been granted emergency use authorization to test saliva, including one product that has an open-source

protocol and can be implemented using $4 worth of materials per test.

There is a strong rationale for instituting screening testing in schools, in places where adequate testing capacity exists. The CDC's observation that such testing has not been systematically studied will remain true until a program is implemented, but we would argue that modeling studies provide ample evidence for moving forward now and evaluating results. In communities with a low prevalence of Covid-19, pooled testing — in which individual samples are grouped for analysis and, if positive, retested individually — can increase the feasibility of mass testing.[3,5]

State and local governments can assist schools by formulating concrete plans for mass testing and prompt return of results. In districts where schools must rely on testing through private physicians and labs, obtaining patients' authorization for disclosure of results, instituting a strong feedback loop, and emphasizing the need for speed in students' testing are paramount, given the risk of onward transmission.

Some observers have suggested that students from high-risk households (such as those in poorer neighborhoods) be offered more frequent testing than others.[3] Targeted screening yields higher positivity rates, is more cost-effective than universal screening, and may help stem outbreaks in vulnerable communities. However, these benefits must be balanced against the potential for stigmatization. Different communities will weigh these considerations differently.

As schools continue to refine their reopening plans, in addition to strengthening testing, they will have to assume an ongoing need for providing remote education due to quarantines. They should also expect fluctuations in the cohort of students receiving such education. Many K–12 schools have staffed distance-learning programs under the assumption of a constant volume, based on surveys eliciting parents' preferences concerning return to school. In reality, student numbers will be in constant flux. Without planning, this variability could compromise educational continuity.

Finally, return-to-school standards should be linked to Covid-19 community transmission rates. As long as schools are unable to conduct testing at scale, the success of reopening will be heavily determined by rates of disease in the community. Without a comprehensive reopening strategy that incorporates testing as a key pillar, school reopening plans will not make the grade.

Disclosure forms provided by the authors are available at NEJM.org.

From Stanford University School of Medicine (Y.R., M.M.M.) and Stanford Law School (M.M.M.), Stanford, CA.

This article was published on October 21, 2020, at NEJM.org.

1. Paltiel AD, Zheng A, Walensky RP. Assessment of SARS-CoV-2 screening strategies to permit the safe reopening of college campuses in the United States. JAMA Netw Open 2020;3(7):e2016818.
2. Wang CJ, Bair H. Operational considerations on the American Academy of pediatrics guidance for K-12 school reentry. JAMA Pediatr 2020 August 11 (Epub ahead of print).
3. Tirrell M, Wells N, Miller L. Forty percent of U.S. Covid-19 tests come back too late to be clinically meaningful, data show. CNBC. August 15, 2020 (https://www.cnbc.com/2020/08/15/forty-percent-of-us-covid-19-tests-come-back-too-late-to-be-clinically-meaningful-data-show.html).
4. Kretzschmar ME, Rozhnova G, Bootsma MCJ, van Boven M, van de Wijgert JHHM, Bonten MJM. Impact of delays on effectiveness of contact tracing strategies for COVID-19: a modelling study. Lancet Public Health 2020;5(8):e452-e459.
5. Levinson M, Cevik M, Lipsitch M. Reopening primary schools during the pandemic. N Engl J Med 2020;383:981-5.

DOI: 10.1056/NEJMp2028209

Determining the optimal strategy for reopening schools, the impact of test and trace interventions, and the risk of occurrence of a second COVID-19 epidemic wave in the UK: a modelling study

Jasmina Panovska-Griffiths, Cliff C Kerr, Robyn M Stuart, Dina Mistry, Daniel J Klein, Russell M Viner, Chris Bonell**

Summary

Background As lockdown measures to slow the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection begin to ease in the UK, it is important to assess the impact of any changes in policy, including school reopening and broader relaxation of physical distancing measures. We aimed to use an individual-based model to predict the impact of two possible strategies for reopening schools to all students in the UK from September, 2020, in combination with different assumptions about relaxation of physical distancing measures and the scale-up of testing.

Methods In this modelling study, we used Covasim, a stochastic individual-based model for transmission of SARS-CoV-2, calibrated to the UK epidemic. The model describes individuals' contact networks stratified into household, school, workplace, and community layers, and uses demographic and epidemiological data from the UK. We simulated six different scenarios, representing the combination of two school reopening strategies (full time and a part-time rota system with 50% of students attending school on alternate weeks) and three testing scenarios (68% contact tracing with no scale-up in testing, 68% contact tracing with sufficient testing to avoid a second COVID-19 wave, and 40% contact tracing with sufficient testing to avoid a second COVID-19 wave). We estimated the number of new infections, cases, and deaths, as well as the effective reproduction number (R) under different strategies. In a sensitivity analysis to account for uncertainties within the stochastic simulation, we also simulated infectiousness of children and young adults aged younger than 20 years at 50% relative to older ages (20 years and older).

Findings With increased levels of testing (between 59% and 87% of symptomatic people tested at some point during an active SARS-CoV-2 infection, depending on the scenario), and effective contact tracing and isolation, an epidemic rebound might be prevented. Assuming 68% of contacts could be traced, we estimate that 75% of individuals with symptomatic infection would need to be tested and positive cases isolated if schools return full-time in September, or 65% if a part-time rota system were used. If only 40% of contacts could be traced, these figures would increase to 87% and 75%, respectively. However, without these levels of testing and contact tracing, reopening of schools together with gradual relaxing of the lockdown measures are likely to induce a second wave that would peak in December, 2020, if schools open full-time in September, and in February, 2021, if a part-time rota system were adopted. In either case, the second wave would result in R rising above 1 and a resulting second wave of infections 2·0–2·3 times the size of the original COVID-19 wave. When infectiousness of children and young adults was varied from 100% to 50% of that of older ages, we still found that a comprehensive and effective test–trace–isolate strategy would be required to avoid a second COVID-19 wave.

Interpretation To prevent a second COVID-19 wave, relaxation of physical distancing, including reopening of schools, in the UK must be accompanied by large-scale, population-wide testing of symptomatic individuals and effective tracing of their contacts, followed by isolation of diagnosed individuals.

Funding None.

Lancet Child Adolesc Health 2020; 4: 817–27

Published Online August 3, 2020 https://doi.org/10.1016/S2352-4642(20)30250-9

See Comment page 796

*Joint senior authors

Department of Applied Health Research and Institute for Global Health, University College London, London, UK (J Panovska-Griffiths DPhil); **The Queen's College, University of Oxford, Oxford, UK** (J Panovska-Griffiths); **Institute for Disease Modeling, Bellevue, WA, USA** (C C Kerr PhD, D Mistry PhD, D J Klein PhD); **Complex Systems Group, School of Physics, University of Sydney, Sydney, NSW, Australia** (C C Kerr); **Department of Mathematical Sciences, University of Copenhagen, Copenhagen, Denmark** (R M Stuart PhD); **Burnet Institute, Melbourne, VIC, Australia** (R M Stuart); **UCL Great Ormond St Institute of Child Health, London, UK** (R M Viner PhD); **and Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, UK** (C Bonell PhD)

Correspondence to: Dr Jasmina Panovska-Griffiths, Department of Applied Health Research, University College London, London WC1E 6BT, UK **j.panovska-griffiths@ucl.ac.uk**

Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), continues to spread globally.[1] In the UK, since the first two reported cases on Jan 31, 2020, and the first reported COVID-19-related death on March 7, 2020, the number of reported cases and deaths has increased steadily, with 301 455 confirmed cases and more than 45 961 deaths reported up to July 29, 2020.

To slow down spread of the virus, the UK Government imposed strict physical distancing (ie, lockdown) measures on March 23, 2020. Informed by mathematical modelling of the potential spread and mortality of this pandemic,[2] and following the example of the countries affected

For reported **cases and deaths** see https://coronavirus.data.gov.uk

Research in context

Evidence before this study

Since the onset of the COVID-19 pandemic, mathematical modelling has been at the heart of informing decision making, including the implementation of the lockdown in the UK. Although published studies have modelled the epidemic spread across different settings, no studies so far have used modelling to evaluate the impact of reopening schools and society specifically. We searched PubMed for modelling studies that have modelled different schools opening strategies in combination with testing interventions published up to May 10, 2020, using the terms ("SARS-CoV-2" OR "COVID-19") AND ("modelling" OR "model") AND ("testing") AND ("schools"). No language restriction was applied. We did not find any studies that met these criteria. As countries are now starting to ease lockdown measures, it is important to assess the impact of different lockdown exit strategies, including whether and how to reopen schools and relax other physical distancing measures. Reopening of schools represents an early step of reopening society by allowing parents to return to work and hence increased community mixing.

Added value of this study

To our knowledge, our study is the first to provide quantification of the amount of testing and tracing that would be needed to prevent a second wave of COVID-19 in the UK under different school reopening scenarios (accompanied by a society-wide relaxation of lockdown measures) and in the presence of different test–trace–isolate strategies. Reopening of schools and society alongside active testing of the symptomatic population (between 59% and 87% of people with symptomatic SARS-CoV-2 infection across different scenarios), with effective contact tracing and isolation strategies, will prevent a second epidemic wave and avert a large number of COVID-19 cases and deaths. However, in the absence of a large-scale testing, contact tracing, and isolation strategy, having reopened schools partially in June, 2020, and reopening full time or in part-time rotas from September, 2020, alongside reopening society, is likely to induce a second pandemic wave of COVID-19 in the UK.

Implications of all the available evidence

Evidence so far points to the need for additional testing, contact tracing, and isolation of individuals who have been diagnosed with COVID-19 or who are considered to be at high risk of carrying infection because of their contact history or symptoms. Our study supports these conclusions and provides additional quantification of the amount of testing and tracing that would be needed to prevent a second wave of COVID-19 in the UK under different school reopening strategies.

earlier,[3] schools closures have occurred worldwide. On March 19, 2020, the UN Educational, Scientific and Cultural Organisation estimated that 1·6 billion children and young people in more than 180 countries had stopped attending school.[3] In the UK, schools for children and adolescents aged 4–18 years remained open only for the children of key workers and children with defined health, education, or social needs, with up to 2% of school children attending during lockdown.[4]

School closure reduces the number of contacts within the population and hence reduces onward transmission; however, it can also cause considerable harms.[5,6] These harms include hampering health-care and other key workers' ability to go to work;[7] reduced economic productivity;[8] and damage to children and young people's education, development, and physical and mental health[9–11] arising from social isolation,[12] reduced social support, and possible increased exposure to violence at home.[12]

As the rate of increase in the number of COVID-19-related hospital admissions and deaths in the UK has slowed down,[13] lockdown has been eased gradually, with partial reopening of English primary schools (reception, year one, and year six; ages 4–6 and 10–11) from June 1, 2020, and, secondary schools (years 10 and year 12; ages 14–15 and 17–18) from June 15, 2020. These options were based on assumptions of lower transmission among primary school children and on findings from early population testing suggesting very low SARS-CoV-2 infection or asymptomatic carriage rates, particularly in children younger than 10 years.[14]

Under current plans, all primary and secondary school students will return to school in England in September, 2020, but the exact return-to-school policy is undecided. Return in other UK countries is also likely to be in late August or September, 2020. Decisions will be based on an understanding of the likely effect of different policies, but there is still uncertainty about the importance of children and young people in SARS-CoV-2 transmission and the impact of school closures in COVID-19 control.[9–11] Although previous modelling studies have suggested that school closures reduce transmission when implemented alongside other physical distancing interventions,[2] the studies generally assume that transmissibility among children and young people is equivalent to that among adults. Data on susceptibility to and transmission of SARS-CoV-2 among children and adolescents are sparse.[8] A population-based contact tracing study on transmission in schools in Australia identified two likely secondary cases from 18 index cases and 863 contacts.[9] Yet others have suggested that the attack rate (ie, probability that an infected individual will transmit the disease to a susceptible individual) is similar to that in adults,[10] and much of the data on transmission in schools are from periods when schools have been fully or partially closed. A meta-analysis suggested that susceptibility to SARS-CoV-2 among children and adolescents was around half of that among adults,[11] but

symptoms are much less common in children than in adults and the degree of asymptomatic transmission by children is unknown.

Reopening of schools represents the first step of reopening society by allowing parents to return to work and hence increased community mixing. We aimed to use modelling to explore the impact of two possible strategies to reopen all schools from September, 2020, combined with society-wide relaxing of the physical distancing measures in the UK, in combination with three different test–trace–isolate scenarios. The strategies that we have explored have been discussed with members of scientific advisory bodies in the UK.

Methods

Transmission model

We modelled the spread of COVID-19 using Covasim (version 1.4.7), a stochastic agent-based model of SARS-CoV-2 transmission. The model was developed by the Institute for Disease Modeling (Bellevue, WA, USA); further details of the mathematical approach used for Covasim have been published previously as a preprint.[15] Briefly, within the model, individuals are modelled as either susceptible to the virus, exposed to it, infected, recovered, or dead. In addition, infected and infectious individuals are categorised as either asymptomatic or in different symptomatic groups: pre-symptomatic (before viral shedding has begun), or with mild, severe, or critical symptoms (figure 1). For this study, the model was adapted to the UK context.

Covasim's default parameters determine the ways in which people progress through the states depicted in figure 1, including the probabilities associated with onward transmission and disease progression, duration of disease by acuity, and the effects of interventions; these parameters were collated during Covasim's development during May, 2020,[15] and are updated when new evidence becomes available. In addition, Covasim is pre-populated with demographic data on population age structures and household sizes by country, and uses these data to generate population contact networks for the setting. By default, Covasim generates four different contact networks: schools, workplaces, households, and community settings. The per-contact transmission probability (β) that an infectious individual transmits the virus to a susceptible individual is assumed to depend on the contact network. Covasim accounts for testing strategies via parameters that determine the probabilities with which people with different symptoms receive a test each day (appendix p 4).

Data sources and calibration

Publicly available data were collated and used for the analysis. We used Covasim's default settings to generate a population of 100 000 agents who interact over the four networks described previously. This approach is similar to that in the study by Ferguson and colleagues,[2] which

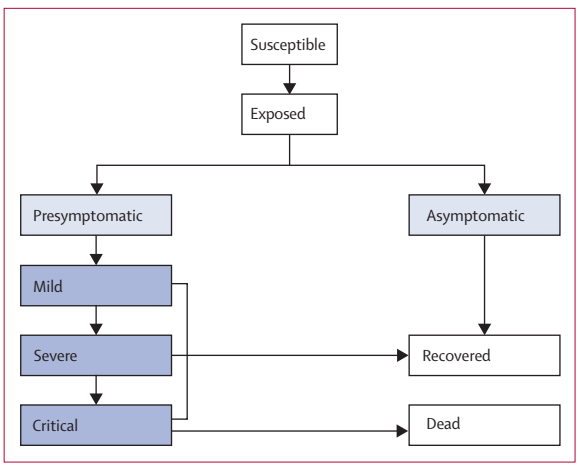


Figure 1: **Modelled disease states**
Blue shading indicates that an individual is infectious and can transmit the disease to other susceptible individuals. States in a darker shade of blue are considered to be symptomatic for the purpose of testing eligibility. This schematic is reproduced from existing work from members of this group.[15]

For more on **Covasim** see http://docs.covasim.org

informed the implementation of lockdown measures in the UK. To fit the model to the UK epidemic, we did an automated search for the optimal values of the number of infected people on Jan 21, 2020, the per-contact layer-dependent transmission probabilities, and the daily testing probabilities for symptomatic individuals (p_s) during May and June that minimised the sum of squared differences between the model's estimates of confirmed cases and deaths, and data on these same two indicators between Jan 21 and June 17, 2020, collated from the UK Government's COVID-19 dashboard. These particular parameters were selected as the most important to estimate because the considerable uncertainties around them—in particular, about whether the per-contact transmission probability is age dependent[16] or differs across asymptomatic and symptomatic cases—translate to uncertainties around the true number of infections in the population and the proportion of those that have been detected. We accounted for the effect of the lockdown by reducing the per-contact transmission probabilities from March 23, 2020, to 2% of their pre-lockdown values within schools, and to 20% of their pre-lockdown values within workplace and community settings.

For the **UK Government's COVID-19 dashboard** see https://coronavirus.data.gov.uk

The calibrated model estimated that between Jan 21 and June 17, 2021, the daily probability of testing people with symptoms was 1·98% corresponding to about 18% of people with symptomatic infection being tested at some point during their illness (assuming an average symptomatic period of about 10 days). In addition, the model assumed that the daily probability of testing people without symptoms was 0·075% corresponding to about 0·75% of people with asymptomatic infection being tested at some point during their illness (assuming an average symptomatic period of about 10 days). In addition, we determined that 1500 people were infected in the UK on

See Online for appendix

	Home contacts	School contacts	Work contacts	Community contacts
Full time				
June 1, 2020	100%	23%*	40%	40%
June 15, 2020	100%	38%†	50%	50%
Sept 1, 2020	100%	90%‡	70%	90%
Part-time rota				
June 1, 2020	100%	23%*	40%	40%
June 15, 2020	100%	38%†	50%	50%
Sept 1, 2020	100%	50%§	70%	70%
Jan 1, 2021	100%	90%‡	70%	90%

Each intervention is simulated by altering the daily transmission probability due to home, school, workplace, and community contact, with details presented in the appendix (pp 5–7). We assume that transmission within schools is proportional to school years going back, which allows parents to go back to work. We thus assume that return to workplaces is proportional to reopening of schools. Furthermore, we assume that 30% of the workforce will remain working from home for the foreseeable future. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. *Representing three of 13 school years returning to school. †Representing five of 13 school years returning to school. ‡Representing all 13 years returning to school full time, with 10% subtracted to account for protective measures assumed to be in place. §All 13 years returning school, but on part-time rota, with half of school years present at one time.

Table: **Scale factors applied to daily SARS-CoV-2 transmission probabilities in households, schools, workplaces, and the community under the scenarios of full-time and part-time rota reopening of schools**

Jan 21, 2020 (appendix p 1), and that the per-contact transmission probability was 0·59% (appendix p 5).

School and society reopening scenarios

The UK Government reopened schools in a phased manner from June 1, 2020, with students in reception (aged 4–5 years), year one (aged 5–6 years), and year six (aged 10–11 years) in English primary schools returning to school on June 1, 2020, followed by secondary school students in years 10 (aged 14–15 years) and 12 (aged 17–18 years) from June 15, 2020. However, although 91% of schools reopened, only 7% of children attended.[17] Under current plans, all school students will return in September, 2020, either full time or part time depending on the state of the epidemic. Therefore, a second plausible scenario is that returning to school in September could include a rota system with students attending school on alternate weeks, with half of the students attending school one week and the other half the following week. We explore these two scenarios of schools returning from September together with phased reopening from June 1 (table).

The phased reopening of schools was implemented by setting the per-contact transmission probabilities within schools to be proportional to the number of school years returning to school, and to 90% of its pre-lockdown value for the full-time reopening scenario (to account for protective measures assumed to be in place; table). In both scenarios, we accounted for holiday periods by assuming no transmission in schools and higher transmission in households (by 29%, based on Google movement data over the lockdown period) over holiday periods.

We also assumed that reopening of schools would correspond to increases in workplace and community transmission probabilities, to account for increased social mixing with reopening of schools and relaxation of the physical distancing restrictions that have applied to work, leisure, and community activities. We assumed that if schools were to reopen full time or in a part-time rota system, the transmission probability in community settings would be respectively 90% or 70% of its pre-lockdown value when schools are in session and 70% during school holiday periods, and workplace transmission would be 70% of its pre-lockdown value during school terms (under the assumption that 30% remain working from home for foreseeable future; personal communication with policy decision makers) and 50% during school holidays. In addition, we assumed that if schools reopen in a part-time rota, this system would be in place for one school term (autumn term, 2020) only and then schools will go back full time from Jan 1, 2021 (table).

Test–trace–isolate strategies

In line with current policy in the UK, we also modelled the implementation of test–trace–isolate strategies to test individuals in the population presenting with COVID-19-like symptoms, isolate those testing positive, and trace their contacts. Since March 23, 2020, the strategy in the UK has been to test people presenting with severe COVID-19 symptoms and ask them to self-isolate, and starting on June 1, 2020, this approach has been complemented by a strategy to trace contacts of those people who test positive for infection. The tracing strategy was simulated in Covasim by introducing two coverage levels of tracing beginning on June 1, 2020. First, to resemble the current scenario of tracing contacts, we assumed that 75%[18] of individuals testing positive are contacted and that 90%[19] of their contacts are traced and asked to isolate, which results in a contact tracing level of 68%. Second, we also simulated a more pessimistic scenario for tracing capability, which could arise if there were problems in scaling up the test–trace–isolate strategy, of a contact tracing level of 40%.

We used the model to derive the testing levels necessary to avoid the second pandemic wave with these two tracing strategies. We assumed 100% sensitivity and specificity of the testing, a delay of 1 day to receive the test result, and that individuals testing positive would immediately be isolated for 14 days. In the model, this isolation reduced their infectiousness by 90%. In addition, with both strategies, symptomatic people were isolated, with their infectiousness reduced by 50%.

Analysis

Overall, we simulated six core scenarios, comprising two different school reopening strategies (students return full time in September *vs* students return

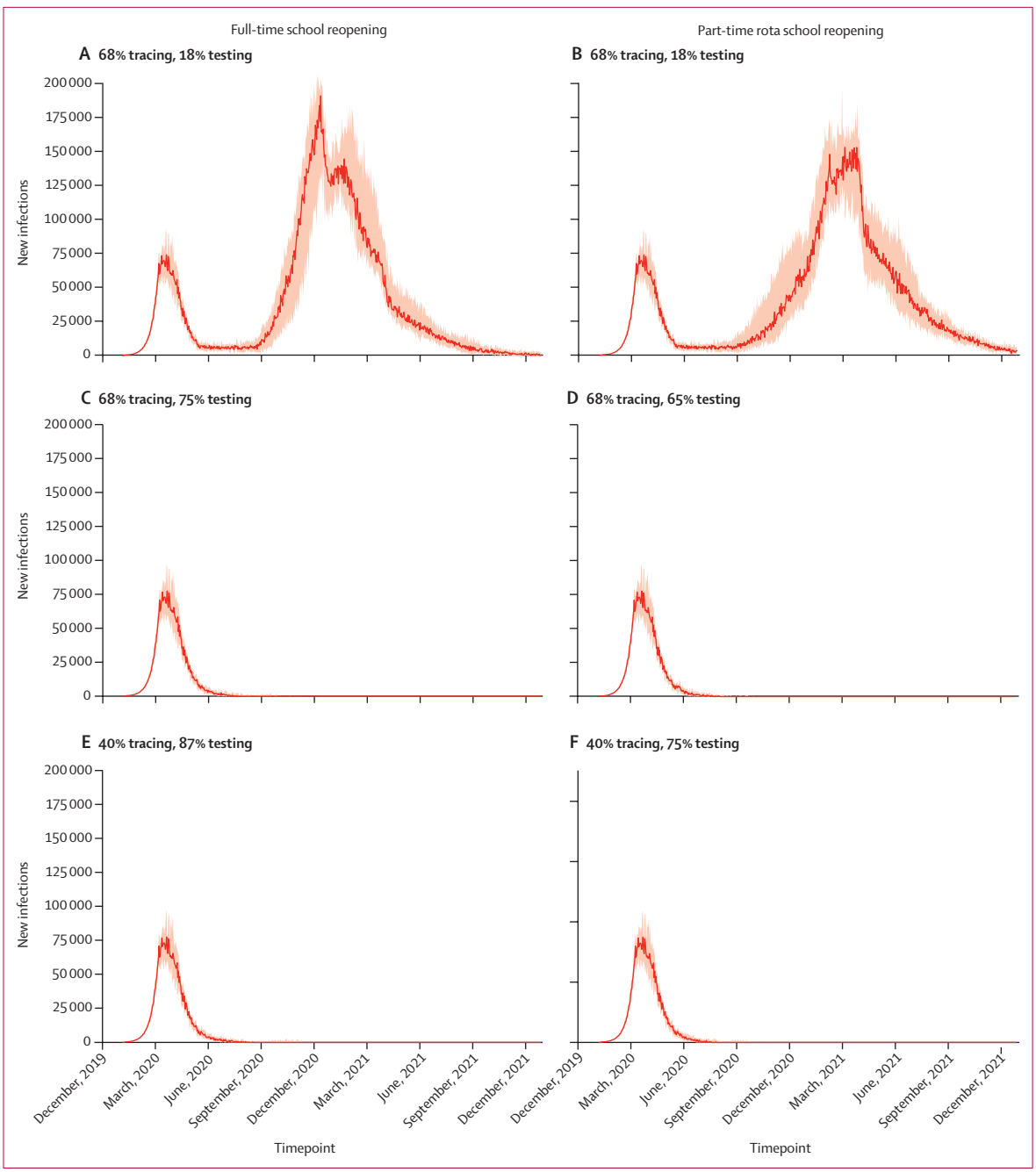


Figure 2: **Model estimates of daily new SARS-CoV-2 infections from Jan 21, 2020, to Dec 31, 2021**
(A) New infections with 68% tracing and 18% testing in the full-time school reopening scenario. (B) New infections with 68% tracing and 18% testing in the part-time rota school reopening scenario. (C) New infections with 68% tracing and 75% testing in the full-time school reopening scenario. (D) New infections with 68% tracing and 65% testing in the part-time rota school reopening scenario. (E) New infections with 40% tracing and 87% testing in the full-time school reopening scenario. (F) New infections with 40% tracing and 75% testing in the part-time rota school reopening scenario. Medians across ten simulations are indicated by solid lines and 10% and 90% quantiles by shading. The results do not change if we run a larger number of simulations, and we tested 1, 3, 6, 8, 10, and 20 simulations. The difference is that the noise in the simulations increases with increased size of simulations; therefore, we chose ten simulations for these figures.
SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

part-time in a rota system in September) and three test–trace–isolate strategies. In the first strategy, 68% of contacts are traced with no scale-up in testing (ie, 18% of people with symptomatic infection and about 0·75% of those with asymptomatic infection are tested). In the second strategy, 68% of contacts are traced and testing is scaled up sufficiently to avoid a second COVID-19 wave. In the third strategy, 40% of contacts are traced

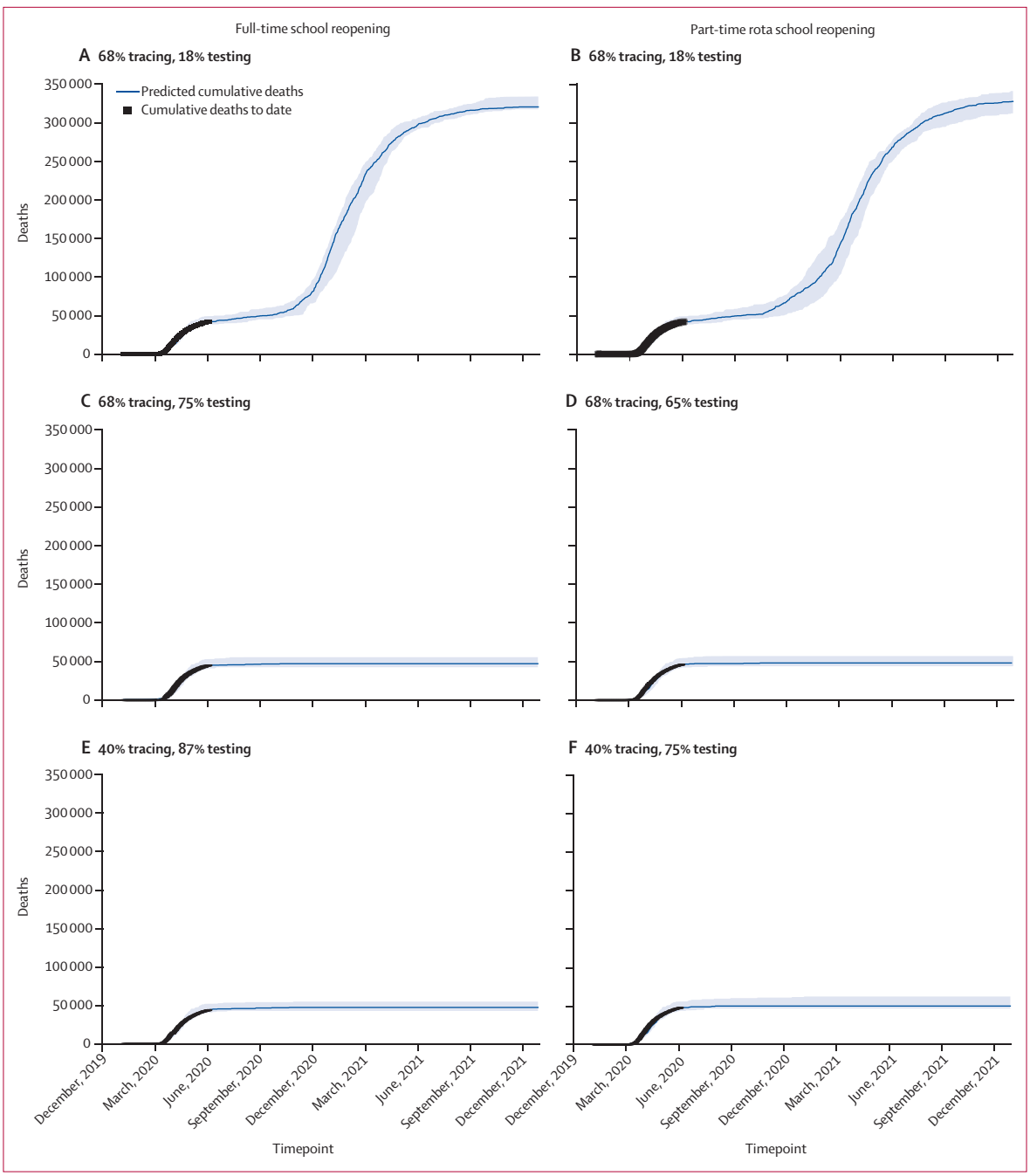


Figure 3: **Model estimates of cumulative COVID-19 deaths from Jan 21, 2020, to Dec 31, 2021**
(A) Deaths with 68% tracing and 18% testing in the full-time school reopening scenario. (B) Deaths with 68% tracing and 18% testing in the part-time rota school reopening scenario. (C) Deaths with 68% tracing and 75% testing in the full-time school reopening scenario. (D) Deaths with 68% tracing and 65% testing in the part-time rota school reopening scenario. (E) Deaths with 40% tracing and 87% testing in the full-time school reopening scenario. (F) Deaths with 40% tracing and 75% testing in the part-time rota school reopening scenario. Medians across ten simulations are indicated by solid lines and the 10% and 90% quantiles by shading.

and symptomatic testing is scaled up sufficiently to avoid a second COVID-19 wave.

For each scenario, we estimated the daily and cumulative numbers of infections and deaths, as well as time series of the effective reproduction number R, until Dec 31, 2021. Since Covasim is stochastic, we simulated each scenario under ten different random number seeds, and we present the median estimates along with ranges corresponding to the upper (90%) and lower (10%) bounds generated by these ten seeds.

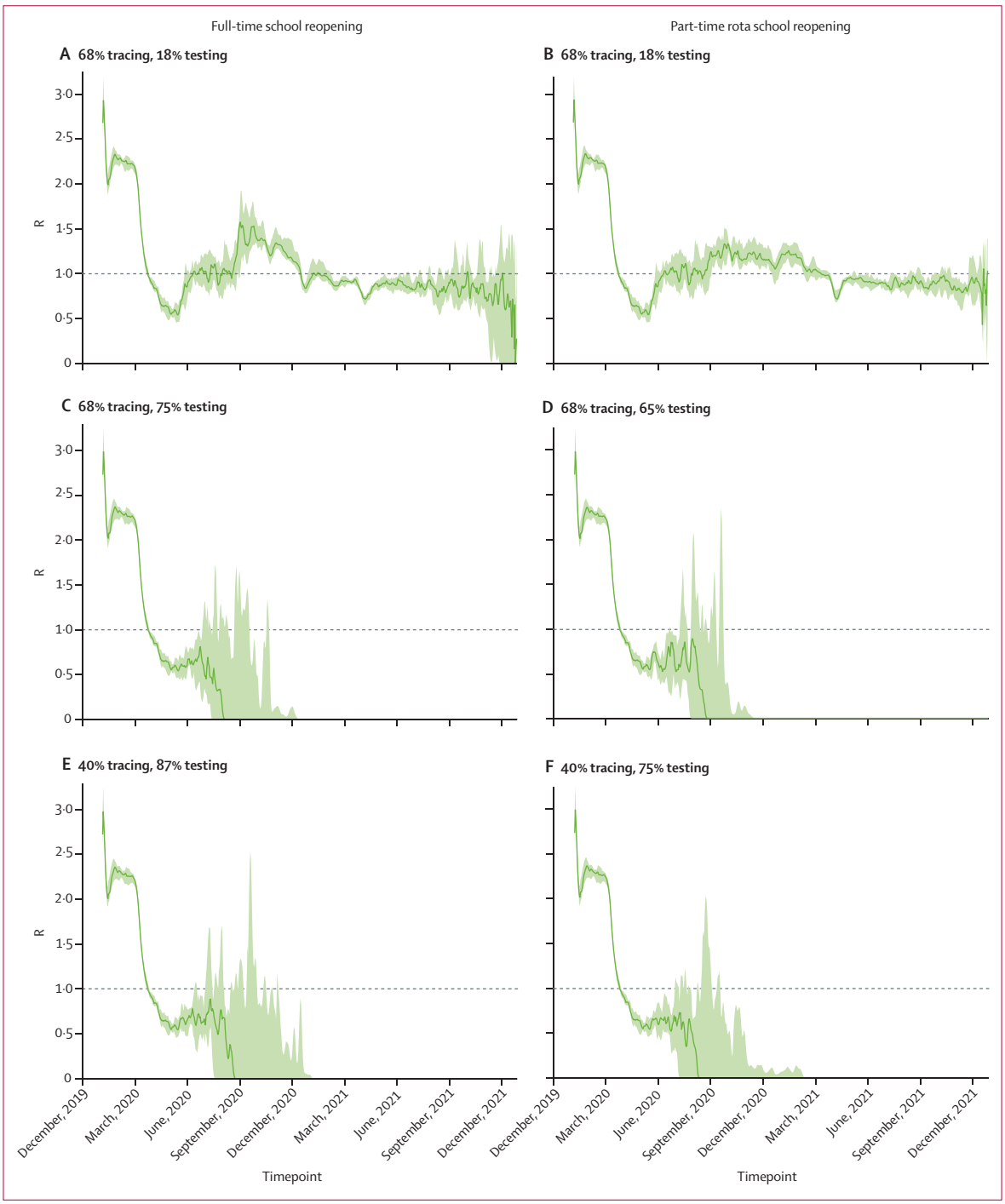


Figure 4: **Model estimates of effective reproduction number R from Jan 21, 2020, to Dec 31, 2021**
(A) Reproductive number R with 68% tracing and 18% testing in the full-time school reopening scenario. (B) Reproductive number R with 68% tracing and 18% testing in the part-time rota school reopening scenario. (C) Reproductive number R with 68% tracing and 75% testing in the full-time school reopening scenario. (D) Reproductive number R with 68% tracing and 65% testing in the part-time rota school reopening scenario. (E) Reproductive number R with 40% tracing and 87% testing in the full-time school reopening scenario. (F) Reproductive number R with 40% tracing and 75% testing in the part-time rota school reopening scenario. Medians across ten simulations are indicated by solid lines and the 10% and 90% quantiles by shading. An R value of less than 1 is necessary for virus suppression.

In view of the uncertainties in the role of different age groups in transmission,[8] we simulated the same scenarios in a sensitivity analysis, in which transmissibility for people aged younger than 20 years was assumed to be half that of people older than 20 years.[20] As part of this analysis, the model was

recalibrated and equivalent analysis to the main one undertaken (appendix pp 5, 7–9).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our model predicts that reopening schools either full time or in a part-time rota system from Sept 1, 2020, alongside relaxation of other social distancing measures will induce a second COVID-19 wave in the absence of a scaled-up testing programme (figures 2A, B, 3A, B, 4A, B). This second wave would peak in December, 2020, if schools open full time in September, and in February, 2021, if a part-time rota system were adopted. In either case, the second wave would be 2·0–2·3 times larger than the first COVID-19 wave in the UK.

Our findings suggest that it might be possible to avoid a second pandemic wave across both school reopening scenarios if enough people with symptomatic infection can be tested, and contacts of those diagnosed can be traced and effectively isolated (figures 2C–F, 3C–F, 4C–F). Assuming 68% of contacts could be traced, we estimate that 75% of those with symptomatic infection would need to be tested and isolated if schools return full time in September, or 65% if a part-time rota system were used. If only 40% of contacts could be traced, these figures would increase to 87% and 75%, respectively.

The temporal profiles of the effective reproduction number R follow the trend of the time series of new infections (comparing respective panels in figures 2 and 4). R evidently increases over the threshold of 1, suggesting an increase in the number of new infections, when a second COVID-19 wave occurs (figures 2A, B, 4A, B). Across both scenarios of school and society reopening and different tracing levels, the test–trace–isolate strategy would need to test a sufficiently large proportion of the population with COVID-19 symptomatic infection and trace their contacts with sufficiently large coverage, for R to diminish below 1 (figures 2C–F, 3C–F). Specifically, our simulations suggest that the timepoint at which R diminishes depends on the degree to which the test–trace–isolate strategy had been implemented and the combination of testing and tracing; the exact association between timing of R diminishment at different levels of testing, tracing, and isolating from June, 2020, will be explored in subsequent analyses.

When we reran the six core scenarios with infectiousness among children and young adults aged younger than 20 years assumed to be 50% of that among older ages (20 years and older), our results remained largely unchanged (appendix pp 8–9). We still found that it is possible to avoid a second COVID-19 wave across all scenarios of school and society reopening and different tracing levels, if the test–trace–isolate strategy tests a sufficiently large proportion of the population with COVID-19 symptomatic infection and traces their contacts with sufficiently large coverage. Assuming that 68% of contacts could be traced, we estimate that 61% of those with symptomatic infection would need to be diagnosed and isolated if schools return full time in September (compared with 75% if children transmit equally to adults), or 59% if a part-time rota system were used (appendix p 8). If only 40% of contacts could be traced, these figures would increase to 78% and 70%, respectively. These results are summarised in the appendix (pp 8–9).

Discussion

Our modelling results suggest that if schools and society reopened full time or in a part-time rota system on Sept 1, 2020, with sufficiently broad coverage of a test–trace–isolate programme, a second COVID-19 wave could be prevented in the UK. Such measures would markedly reduce cumulative numbers of new infections and deaths, and contribute to keeping R below 1. This finding is consistent under both assumptions of infectivity of children and young adults aged younger than 20 years relative to adults (50% and 100%; appendix pp 8–9). We note that depending on the overall population prevalence of COVID-19-like illness, achieving this level of coverage with a test–trace–isolate strategy would probably require testing a large number of people.

However, we also predict that in the absence of sufficiently broad test–trace–isolate coverage, reopening of schools combined with accompanied reopening of society across all scenarios might induce a second COVID-19 wave. For example, our modelling results suggest that full school reopening in September, 2020, without an effective test–trace–isolate strategy would result in R rising above 1 and a resulting second wave of infections that would peak in December, 2020, and be 2·3 times the size of the original COVID-19 wave. Cases would then decline and peak again, with a wave 2·0 times larger than the original wave.

In our modelling, we have assumed that reopening schools is not a binary off–on switch, but instead that reopening schools would be accompanied by broader changes. School reopening would allow parents to go back to work, as reopening a proportion of businesses are anticipated to be an important step in restarting economic activity. Specifically, we simulated increasing not only the transmission in schools, but also increased transmission in workplaces and the community. The exact numbers representing these changes in this analysis are based on modelling assumptions, and the model can be rerun if more reliable numbers are available in future.

Evidence from countries such as South Korea,[21,22] where large-scale testing and contact tracing have been able to control the spread of COVID-19, points to the need for

additional testing, effective contact tracing, and isolation of individuals who have been diagnosed with COVID-19, or who are considered to be at high risk of carrying infection as a result of their contact history or symptoms, to control the virus spread. Our study supports these conclusions and provides additional quantification of the amount of testing and tracing that would be needed to prevent a second wave of COVID-19 in the UK under different strategies to reopen schools and society from September, 2020.

To our knowledge, this is the first study to give such quantitative modelled measures for the UK. There are differences in policies relating to school reopening across the four UK countries but these findings are likely to be generalisable to each country. We anticipate that re-running the analysis separately for England, Scotland, Wales, and Northern Ireland would highlight the need for a comprehensive test–trace–isolate strategy to avoid second COVID-19 peak, but possibly the minimum testing levels will differ across the four UK countries. Although such analyses were beyond the scope of this paper, we are planning to explore this further in future work.

Our analyses have some limitations. First, although we have made an effort to characterise the pandemic to resemble that of the UK, some of the parameters used are from various sources across different settings.[15] However, the main aspect we have focused on changing to illustrate different scenarios is the transmission probability of social (household, school, workplace, and community) contacts and the primary source for these data was UK based.[23] The changes we have simulated across scenarios reflect our understanding of possible options for school reopening as discussed in the UK. They are, therefore, fit for purpose within this analysis. Second, as with any modelling study, we have made a series of assumptions within the modelling framework. In particular, we made assumptions about the proportion of SARS-CoV-2 infections that are symptomatic, as evidence in the literature is mixed. WHO suggests that 80% of people with infections show mild symptoms[24] and a study from the Italian city of Vo' Euganeo[25] at the epicentre of the European pandemic confirms that a large proportion, 30–50%, of people with infections do not have symptoms; however, other studies suggest that this number is smaller—eg, 10% among children,[26] 18% among passengers on the Diamond Princess cruise ship,[27] and 42% among Japanese people returning from Wuhan.[28] There is currently a high degree of uncertainty around the proportion of asymptomatic infection, with evidence[29] suggesting that asymptomatic incidence ranges from 2% to 57%. We note, however, that many studies do not differentiate between presymptomatic and asymptomatic infection; instead the number reported is the proportion of individuals not exhibiting symptoms at the time of testing positive. Instead, in our model, we have assumed that asymptomatic infections account for 30% of onward-transmitted infections and that development of symptoms is age dependent. The assumption in this study, as in Covasim, is that 70% of infection is symptomatic and, guided by the findings by Davies and colleagues,[20] that the probability of developing clinical symptoms increases from around 20% in individuals aged younger than 20 years to around 69% in people aged older than 70 years. Future analyses will explore how changing the proportion of asymptomatic SARS-CoV-2 infections affects the impact of a test–trace–isolate strategy.

Some of our assumptions about the implementation of a test–trace–isolate strategy are likely to be optimistic in the UK context, so our finding should be interpreted as the minimal amount of testing that would be needed. In particular, we assume a 1-day delay after a test is done before results are communicated, that diagnosed individuals immediately isolate for 14 days with 90% efficacy, and that individuals displaying COVID-19-like symptoms will self-isolate with 50% efficacy until symptoms clear.

Furthermore, in the absence of robust data, we made assumptions (varied in the sensitivity analysis) about the infectiousness among children and young adults aged younger than 20 years. Future analysis might find that infectiousness among children is even lower than 50%, although there are no data suggesting higher transmission than in adults.[8] Finally, we note that in addition to simulating the current test–trace–isolate policy for the UK, we also simulated an additional level of tracing chosen to resemble a more pessimistic tracing level. We have chosen this level to be 40% as a modelling assumption. For both levels of tracing, 40% and 68%, simulated here, we determined the testing level required to avoid a second COVID-19 wave in the UK during 2020 and 2021. We note that we have not swept the entire testing and tracing level parameter space to explore regimes within the phase plane where R is less than 1 at all timepoints and hence a second wave is avoided, as this is beyond the scope of this work. Indeed, follow-up work on this is currently ongoing both for the UK and the USA.

We also have not modelled in this study the behaviour of young people who are not in school and, specifically, we have not assumed increased social mixing outside schools. Inclusion of this parameter is possible within our framework, but it is currently difficult to quantify. We can rerun the model when reliable estimates are available in future.

In summary, our findings suggest that reopening of schools can form part of the next step of gradual relaxing of lockdown if combined with a high-coverage test–trace–isolate strategy. It is currently unclear when the UK test–trace–isolate strategy will achieve sufficient coverage. Such a strategy, to prevent onward transmission, could possibly comprise virus testing for active infection in symptomatic individuals (ie, RT-PCR tests for SARS-CoV-2) and possibly as part of primary care,

followed by contact tracing of individuals within the network of the infected person and isolation of individuals, including those showing symptoms or diagnosed positive for infection. This approach would be an alternative to intermittent lockdown measures, including further school closures while we await an effective vaccine against SARS-CoV-2.

Contributors

JP-G and RMV conceptualised the study. JP-G, CCK, DM, RMS developed the specific modelling framework, based on the Covasim model developed by CCK, RMS, DM, and DJK. JP-G, CCK, RMS, DM, DJK collated data for the parameters used. JP-G ran the modelling analysis with input from CCK, RMS, and DM. JP-G, RMV, and CB defined the different scenarios in the UK context following conversations with the Scientific Pandemic Influenza Modelling Group, which gives expert advice to the UK Department of Health and Social Care and wider UK Government. JP-G wrote the manuscript with input from CCK, RMS, DM, DJK, RMV, and CB. All authors approved the final version.

Declaration of interests

We declare no competing interests.

Data sharing

The model code for Covasim is available from https://github.com/InstituteforDiseaseModeling/covasim. The code used to run all simulations contained in this Article is available from https://github.com/Jasminapg/Covid-19-Analysis.

Acknowledgments

JP-G was supported by the UK National Institute for Health Research (NIHR) Applied Health Research and Care North Thames at Bart's Health National Health Service Trust. CCK, DM, and DJK were supported by the Bill and Melinda Gates Foundation through the Global Good Fund. The views expressed in this Article are those of the authors and not necessarily those of the National Health Service, the NIHR, or the UK Department of Health and Social Care. We acknowledge Graham Medley (London School of Hygiene and Tropical Medicine, London, UK) on helpful discussions around the modelling scenarios, Edwin van Leeuwen (Public Health England, London, UK), Tim Colbourn (University College London, London, UK), and William Waites (University of Edinburgh, Edinburgh, UK) for their helpful conversations about different modelling approaches, and Ruth Gilbert (University College London) for reading an earlier version of the paper.

References

1 WHO. Coronavirus disease (COVID-19). Situation report—156. June 24, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200624-covid-19-sitrep-156.pdf?sfvrsn=af42e480_2 (accessed June 25, 2020).

2 Ferguson NM, Laydon D, Nedjati-Gilani G, et al. Report 9: impact of non-pharmaceutical interventions (NPIs) to reduce COVID-19 mortality and healthcare demand. March 16, 2020. https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf (accessed May 20, 2020).

3 UN Educational, Scientific and Cultural Organisation. COVID-19 educational disruption and response. 2020. https://en.unesco.org/themes/education-emergencies/coronavirus-school-closures (accessed March 19, 2020).

4 Whittaker F. Coronavirus: School attendance around 1%, finds DfE analysis. April 21, 2020. https://schoolsweek.co.uk/coronavirus-school-attendance-around-1-finds-dfe-analysis/ (accessed July 27, 2020).

5 Royal Society DELVE Initiative. Balancing the risks of pupils returning to schools. July 24, 2020. https://rs-delve.github.io/reports/2020/07/24/balancing-the-risk-of-pupils-returning-to-schools.html#1-background (accessed July 31, 2020).

6 Viner RM, Russell SJ, Croker H, et al. School closure and management practices during coronavirus outbreaks including COVID-19: a rapid systematic review. *Lancet Child Adolesc Health* 2020; **4:** 397–404.

7 O'Sullivan TL, Amaratunga C, Phillips KP, et al. If schools are closed, who will watch our kids? Family caregiving and other sources of role conflict among nurses during large-scale outbreaks. *Prehosp Disaster Med* 2009; **24:** 321–25.

8 Brurberg KD. The role of children in the transmission of SARS-CoV-2 (COVID-19), 1st update—a rapid review. Oslo: Norwegian Institute of Public Health, 2020.

9 Macartney K, Quinn HE, Pillsbury AJ, et al. Transmission of SARS-CoV-2 in Australian educational settings: a prospective cohort study. *Lancet Child Adolesc Health* 2020; published online Aug 3. https://doi.org/10.1016/S2352-4642(20)30251-0.

10 Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. *Lancet Infect Dis* 2020; published online April 27. https://doi.org/10.1016/S1473-3099(20)30287-5.

11 Viner RM, Mytton O, Bonell C, et al. Susceptibility to COVID-19 amongst children and adolescents compared with adults: a systematic review and meta-analysis. *medRxiv* 2020; published online May 24. DOI:10.1101/2020.05.20.20108126 (preprint).

12 Abramson A. How COVID-19 may increase domestic violence and child abuse. April 8, 2020. https://www.apa.org/topics/covid-19/domestic-violence-child-abuse (accessed May 20, 2020).

13 UK Government. Coronavirus (COVID-19) in the UK. https://coronavirus.data.gov.uk/?_ga=2.41681382.554770926.1588844302-1722033634.1588620867 (accessed May 6, 2020).

14 Jones TC, Muhlemann B, Veith T, et al. An analysis of SARS-CoV-2 viral load by patient age. *medRxiv* 2020; published online June 9. DOI:10.1101/2020.06.08.20125484 (preprint).

15 Kerr CC, Stuart RM, Mistry D, et al. Covasim: an agent-based model for COVID-9 dynamics and suppression scenarios. *medRxiv* 2020; published online May 15. DOI:10.1101/2020.05.10.20097469 (preprint).

16 Zhang J, Litvinova M, Liang Y, et al. Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China. *Science* 2020; **368:** 1481–86.

17 UK Department for Education. Attendance in education and early years settings during the coronavirus (COVID-19) outbreak – summary of returns to 4 June. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/890949/Attendance_figures_coronavirus_covid_19_4_June_2020.pdf (accessed July 30, 2020).

18 Boseley S. Contact tracers in England get no data from 26% of people with coronavirus. June 18, 2020. https://www.theguardian.com/world/2020/jun/18/contact-tracers-in-england-get-no-data-from-26-of-people-with-coronavirus (accessed May 20, 2020).

19 Triggle N. Coronavirus: One in four infected by virus cannot be reached. June 18, 2020. https://www.bbc.co.uk/news/health-53009775?intlink_from_url=https://www.bbc.co.uk/news/topics/ck2l9qxx17nt/coronavirus-testing&link_location=live-reporting-story (accessed May 20, 2020).

20 Davies NG, Klepac P, Liu Y, et al. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat Med* 2020; published online June 16. DOI:10.1038/s41591-020-0962-9.

21 Shim E, Tariq A, Choi W, Lee Y, Chowell G. Transmission potential and severity of COVID-19 in South Korea. *Int J Infect Dis* 2020; **93:** 339–44.

22 Cohen J, Kupferschmidt K. Countries test tactics in 'war' against COVID-19. *Science* 2020; **367:** 1287–88.

23 Prem K, Cook AR, Jit M. Projecting social contact matrices in 152 countries using contact surveys and demographic data. *PLoS Comput Biol* 2017; **13:** e1005697.

24 WHO. Coronavirus disease 2019 (COVID-19). Situation report—46. March 6, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200306-sitrep-46-covid-19.pdf?sfvrsn=96b04adf_4 (accessed May 20, 2020).

25 Lavezzo E, Franchin E, Ciavarella C, et al. Suppression of COVID-19 outbreak in the municipality of Vo, Italy. *medRxiv* 2020; published online April 18. DOI:10.1101/2020.04.17.20053157 (preprint).

26 Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. *Lancet Infect Dis* 2020; **20:** 689–96.

27 Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Euro Surveill* 2020; **25:** 2000180.

28 Nishiura H, Kobayashi T, Miyama T, et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). *Int J Infect Dis* 2020; **94:** 154–55.

29 Gao Z, Xu Y, Sun C, et al. A systematics review of asymptomatic infections with COVID-19. *J Microbiol Immunol Infect* 2020; published online May 15. DOI:10.1016/j.jmii.2020.05.001.

TITLE: Identifying Optimal COVID-19 Testing Strategies for Schools and Businesses: Balancing Testing Frequency, Individual Test Technology, and Cost

AUTHORS: Gregory D. Lyng, PhD[1], Natalie E. Sheils, PhD[1], Caleb J. Kennedy, PhD[1], Daniel Griffin, MD, PhD[2, 3], Ethan M. Berke, MD, MPH[1]

AFFILIATIONS:

1. UnitedHealth Group, Research and Development, Minnetonka, MN
2. Columbia University, Department of Medicine, Division of Infectious Diseases, New York, NY
3. ProHealth Care, Optum, Lake Success, NY

CORRESPONDING AUTHOR:

Ethan Berke, MD, MPH

Chief Public Health Officer

UnitedHealth Group

5995 Opus Parkway

Minnetonka, MN 55343

T +1 952.219.4025

ethan.berke@uhg.com

ABSTRACT:

Background: COVID-19 test sensitivity and specificity have been widely examined and discussed yet optimal use of these tests will depend on the goals of testing, the population or setting, and the anticipated underlying disease prevalence. We model various combinations of key variables to identify and compare a range of effective and practical surveillance strategies for schools and businesses.

Methods: We coupled a simulated data set incorporating actual community prevalence and test performance characteristics to a susceptible, infectious, removed (SIR) compartmental model, modeling the impact of base and tunable variables including test sensitivity, testing frequency, results lag, sample pooling, disease prevalence, externally-acquired infections, and test cost on outcomes case reduction.

Results: Increasing testing frequency was associated with a non-linear positive effect on cases averted over 100 days. While precise reductions in cumulative number of infections depended on community disease prevalence, testing every 3 days versus every 14 days (even with a lower sensitivity test) reduces the disease burden substantially. Pooling provided cost savings and made a high-frequency approach practical; one high-performing strategy, testing every 3 days, yielded per person per day costs as low as $1.32.

Conclusions: A range of practically viable testing strategies emerged for schools and businesses. Key characteristics of these strategies include high frequency testing with a moderate or high sensitivity test and minimal results delay. Sample pooling allowed for operational efficiency and cost savings with minimal loss of model performance.

INTRODUCTION

As schools and businesses re-open and attempt to stay open, promptly detecting people with infectious COVID-19 is essential, especially as the risk of transmission is expected to increase with colder weather, more time indoors, and closer contact with others.[1, 2] Recommended actions to attenuate spread include symptom checking, monitoring underlying community prevalence, and responsive policy adjustment. In addition to robust public health measures, successful return to normalcy will be accelerated and hopefully sustained by optimal COVID-19 testing strategies. Despite being commonly recommended, little guidance suggests the right approach to testing and how best to balance cost, test selection, results delays, the value of sample pooling, and how changing local disease prevalence should inform strategy adjustments.

Throughout the pandemic the number and variety of tests for detecting active infection have steadily increased.[3] Current tests include nucleic acid amplification tests (NAATs) such as reverse-transcription or reverse transcription polymerase chain reaction (RT-PCR), template mediated amplification (TMA), nicking enzyme amplification reaction (NEAR), loop-mediated isothermal amplification (LAMP), nucleic acid hybridization, viral metagenomic sequencing, and CRISPR-based assays. Most Food and Drug Administration (FDA) - Emergency Use Authorization (EUA) tests are approved for symptomatic patients, but not all are validated in an asymptomatic population. Despite these scientific advancements, there is scant guidance on how to apply a specific technology in the context of the underlying population and the goal of testing, such as diagnosis of an individual versus surveillance of a group. Cost, turnaround time, and convenience in sample collection all play a role in achieving a rate of testing that achieves a goal of detecting and preventing transmission in a cohort. A testing strategy is not feasible if the cost per test at the individual level is too high, or the time to obtain results is too

long, resulting in possible transmission while positive test results are in transit or missing an opportunity to attend work or school if the result is negative. To increase test processing efficiency and reduce cost, pooling of samples is a potential solution provided there is minimal degradation in test performance due to dilution, but a strategy should be devised carefully. Successful pooling strategies rely on a clear understanding of the test's limit of detection (LOD), sensitivity, specificity, and the prevalence of disease in the population being tested.[4]

Testing in large cohort settings such as schools and businesses that require continued surveillance can ensure that facilities remain open safely for the greatest number of people. We model various scenarios of test sensitivity and specificity, testing frequency, cost, and pooling to illustrate the range of practical and sustainable surveillance strategies.

METHODS

To compare the effects of test sensitivity and specificity, test frequency, and the impact of pooling we considered a classical epidemiological susceptible, infectious, removed (SIR) compartmental model for the tested population. To account for the introduction of infections from the surrounding community, we added a time-dependent term which represents the rate (in people/time) of infections from outside interactions continuously in time. With frequent testing, this external forcing drives the behavior of the model (Figure 1). We examine two scenarios for this forcing. The first is a relatively low and more-or-less constant rate of introduced infections, with data from the 7-day rolling average of the case count in Fayette County, Pennsylvania for the 100 days beginning March 26, 2020 as reported in the New York Times.[5] This low-growth profile is reported as panel (a) in Figures 2, 3, and 4. The second scenario used for high-growth external community prevalence is the seven-day rolling average

of daily case counts in Miami-Dade County, Florida for the 100 days beginning June 16, 2020. This profile is shown in panel (b) in Figures 2, 3, and 4. In both profiles, we scaled the cases given by the relative population in our model, which we chose to be 1500. To model pooled testing we solved the SIR model over τ days, with the initial test on day zero. To account for possible delays in receiving test results, we allowed for a delay parameter, d. On day $\tau + d$ we stopped the model and restarted with new "initial conditions" which account for the transfer of people who tested positive and are thus removed from mixing in the model. We adjusted for test sensitivity and applied a linear discount rate for pooling of 0.00323, consistent with minimal sample dilution or degradation in a nasal or nasopharyngeal sample.[6] Other discount rates may be more appropriate in different settings, such as saliva sampling.[7] Our model allows for a varied percent of those that are infected to choose to comply with isolation protocols; in the scenarios presented we set this tunable assumption to be perfect compliance. We assume the basic reproduction number R_0 is 2.5 and the average period of infectiousness is 9 days.[8, 9, 10, 11] The initial conditions are chosen from the average of population-scaled new confirmed cases reported by the New York Times for September 23, 2020 in a sample of counties scaled by average number of infectious days. This results in a starting value of 1.35 infections for a population of size 1500. We take the conservative approach of assuming no one in the population has immunity to the virus based on previous infection. In the tests that follow we vary the testing frequency (τ), delay in the return of results (d), number of samples pooled (m), sensitivity of the test on one sample, and specificity of the test. We computed the cost of each testing strategy at the per person per day level, over 100 days. When pooling ($m > 1$), we assumed a simple 2-stage Dorfman testing process in which each individual in a positive pool is retested individually using a high-sensitivity diagnostic test at $100 per test. We then calculated the expected number of tests required

to complete each round of testing. The complete scientific code is available as a supplementary file. All analysis was done using Julia v1.5.1.[12]

RESULTS

Figure 2 demonstrates scenarios of testing frequency at sensitivities of 98% with a two-day delay in receiving results during which mixing continues (Figure 2c, d), 98% with no delay in receiving results (Figure 2e, f), and 60% with no delay (Figure 2g, h) to simulate testing by various technologies such as PCR with lags between sample collection and centralized laboratory testing, antigen detection, and LAMP. As there are little data on the performance of some tests in asymptomatic people, we used more conservative sensitivity estimates aligning to published LOD for specific devices from the FDA.[13] The sawtooth pattern is the result of removal of infected persons from the population.

Any testing strategy is better than none at all, and as expected, tests with increased sensitivities perform for a given time frequency. At the most lenient frequency considered, every 14 days, the number of infections is reduced approximately 31-98% (Table 1) compared to no testing at all. Each scenario can be explored comparatively. For example, at a test sensitivity of 80%, the effect of testing every day in a population of 1500 compared to testing every 14 days reduced the number of cumulative infections at day 100 by 364 in the low prevalence community and by 958 in the high prevalence community. Increased testing frequency results in a nonlinear decrease in cumulative infections over time, with daily testing resulting in the fewest cumulative infections at 100 days after implementing the testing strategy at any of the sensitivities shown. Importantly, at sensitivities of 98% our models predict that a two-day delay in results (by send-out PCR, for example) will result in a just a 59% reduction in infections experienced at a 14-day testing frequency; however, as the testing

frequency is increased, even with the two-day delay, the number of missed infections goes down rapidly to over a 99% reduction from no testing at all at a daily testing frequency.

Next we looked at testing strategies that incorporate pooling. Figure 3 combines a weekly and every 3 day testing strategy with 98% sensitive tests with varying time delay, and pooling tests in samples of 2, 5, 10, and 30. Pooling potentially reduces the sensitivity of the tests, resulting in more missed infections. This can be overcome by an increase in test frequency, allowed by the cost savings of pooling. Figure 4 weighs cost against testing frequency and pooling size, both with confirmatory and without confirmatory testing of positive pools. Without confirmatory testing, the cost per person decreases dramatically.

DISCUSSION

Our findings demonstrate that it is not only critical to choose the right test in terms of performance in asymptomatic individuals, but to use the test in the defined population at the optimal frequency to reduce the risk of case escalation. Optimization is further enhanced at the population level by understanding of underlying disease prevalence and utilization of pooling to reduce cost and increase efficiency. The "ideal" test strategy must be balanced with the practicalities of cost per person to ensure sustainability. For example, daily testing with a 60% sensitive test attenuates community spread, but at a cost of $30.10 per person per day with confirmatory testing, or $20.00 without, may not be possible. Using a 60% sensitive test less frequently reduces expense but sacrifices significant performance. A 98% sensitive test with no delay in results administered every 3 days with pooling, and no confirmatory test offered by the institution costs less than $1.50 per person per day, with high performance. The model demonstrates that frequency of testing, test sensitivity, turn-around time,

and the external community prevalence are all important factors to consider, and there is often more than one testing strategy to achieve the desired level of performance. The computational code and an is available in the online supplement and an easy-to-use web-based simulator is to test various scenarios at https://calculator.unitedinresearch.com/.

With these scenarios in hand, institutions can make an informed operational choice, devise pods or cohorts to be tested by pooling and potentially isolated if positive, and create clear communication about a surveillance rationale. Acknowledging a dynamic community prevalence, the model can be re-run, and the testing strategy can be optimized to maximize benefit at the lost cost and least amount of disruption.

The frequency of test usage to minimize amplification of infection and allow schools and worksites to remain open is an important factor. Given the cost of high frequency testing, we demonstrate the value of pooling of samples to increase efficiency, particularly in areas with lower population prevalence. As background prevalence increases, the value of pooling diminishes as the likelihood of a positive pool will rise, but even a pool of two to three samples results in a dramatic reduction in the need for individual sample analysis. It is worth noting that with an extremely low prevalence, even in the case of a 99.5% specific test, false positives are much more likely than true positives and confirmatory testing may be necessary. A 90% specificity test would result in a large number of false positives over the course of 100 days. As shown in Figure 4, in order to achieve a minimal cost approach that includes confirmatory testing, one must balance pool size with frequency. Without confirmatory testing, costs drop dramatically (Figure 4g, h). More sophisticated confirmatory testing strategies exist that may lower costs but still reduce the likelihood that uninfected individuals are sent

home, such as sub-pooling of positive pools without individual level testing, each with benefits and disadvantages.[14, 15]

Our work is supported by prior discoveries. Paltiel et al.[16] considered a compartment-based model simulating an abbreviated 80-day semester in a highly-residential college-campus-type setting. Across all scenarios considered, test frequency was more associated with cumulative infection than test sensitivity. That modeling exercise also suggested that symptom-based screening alone is insufficient to contain an outbreak under any of the scenarios considered. Using a model for viral loads in individuals, Larremore et al.[17] studied surveillance effectiveness using an agent-based modeling framework which accounts for test sensitivities, frequency, and sample-to-answer reporting time. The results indicate that frequency of testing and the speed of reporting are the principal contributors to surveillance effectiveness. The results also show that the impact of high sensitivity on surveillance effectiveness is, relatively, small.

Populations housed in long-term care facilities are especially vulnerable to COVID-19; surveillance programs designed for these settings may have different goals and tolerances for infection risk than those designed to maintain functionality for other institutions. Smith and colleagues[6] built a complex modeling framework for long-term care facilities including simulations of the detailed inter-individual contact networks describing patient-staff interactions in such settings. This work showed that symptom-based screening by itself had limited effectiveness. Testing upon admission detected most asymptomatic cases upon entry but missed potential introductions from staff. Random daily testing was determined to be, overall, an inefficient use of resources. This points to the opportunity for

pooled testing as an effective and efficient COVID-19 surveillance strategy for long-term care facilities with limited resources.

Since our work focuses on screening and not performing diagnostic testing, the actual sensitivity of the various available COVID tests for this purpose is not entirely clear. The original testing approaches for COVID-19 focused on the high sensitivity required for diagnosis by clinicians in all stages of the acute period of COVID-19 through detection of SARS-CoV-2 RNA performed on patients with a high pretest probability of disease. This paradigm focused on high sensitivity tests with the performance feature of very low NAAT detectable units/mL (NDU/mL) with a goal of diagnosing patients even if past the contagious period. These tests were not optimized nor validated in terms of sensitivity for the detection of infectious individuals that might spread disease in schools, the workplace or other social situations.

Several studies looking at the ability to culture virus from samples collected from infected individuals have established that RNA copy numbers of 1,000,000 RNA copies/ml or higher are required for any consistent success in viral culture.[18, 19, 20, 21, 22] Based on contact tracing, this defined window of elevated RNA copy numbers starting 2-3 days prior to onset of symptoms and ending 5-9 days after symptom onset corresponds to most if not all cases of transmission. Studies of asymptomatic spreading suggests a very similar window of transmissibility during this period of time when RNA copy numbers are 1,000,000 copies/ml or higher.[11, 23, 24] Given that RT-PCR testing can have a sensitivity or LOD as low as <1,000 RNA copies/mL (1,000 NDU), there should ample performance in testing technology to leverage high-volume, high-frequency pooling, provided samples are not diluted by

storage or buffering media beyond the minimum LOD when employed to detected asymptomatic but infectious individuals.[25]

Our work has a number of limitations. The SIR compartmental model provides a simplified representation of the natural history of the disease. For example, it does not account for the distinction between symptomatic and asymptomatic cases. In addition, the model assumes uniform mixing of the population being tested and a uniform distribution of likelihood of a positive test. The model is formulated at a population level; it does not permit the tracking of individuals. In a low population prevalence, we expect a high number of false positives given assumed specificities of 99.5% and 90%. Individuals who recover from the disease are granted permanent immunity in our model, although the risk of reinfection now appears possible.[26, 27, 28, 29, 30, 31] Our pooling model assumed nasal or naso-pharyngeal swab samples. Because of the nature of saliva, the small sensitivity discount rate assumption in our model may not be valid due to greater sample dilution.[32] Finally, the model does not naturally incorporate phased, pulsed, or partial testing (1st graders on Monday, 2nd graders on Tuesday, etc.).

Despite these limitations, sensitivity, pooling, and frequency modeling can guide institutions on best-fit testing strategies that align to their practical constraints. Organizations can apply this model to determine their best testing strategy given current community prevalence and operational and financial resources that enable sustained testing to stay safely open during the pandemic.

REFERENCES:

1. Service RF. Coronavirus antigen tests: quick and cheap, but too often wrong? Science | AAAS. Published May 22, 2020. Accessed September 23, 2020. https://www.sciencemag.org/news/2020/05/coronavirus-antigen-tests-quick-and-cheap-too-often-wrong

2. Corman VM, Rabenau HF, Adams O, et al. SARS-CoV-2 asymptomatic and symptomatic patients and risk for transfusion transmission. *Transfusion*. 2020;60(6):1119-1122. doi:10.1111/trf.15841

3. FDA. Emergency Use Authorization. *FDA*. Published online September 22, 2020. Accessed September 23, 2020. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization

4. Abdalhamid B, Bilder CR, McCutchen EL, Hinrichs SH, Koepsell SA, Iwen PC. Assessment of Specimen Pooling to Conserve SARS CoV-2 Testing Resources. *Am J Clin Pathol*. Published online April 18, 2020. doi:10.1093/ajcp/aqaa064

5. The New York Times. NYT COVID-19 Data. COVID-19 Data. Published September 23, 2020. Accessed September 23, 2020. https://github.com/nytimes/covid-19-data

6. Smith, David RM, Duval, Audrey, Pouwels, Koen B, et al. Optimizing COVID-19 surveillance in long-term care facilities: a modelling study. Published online August 13, 2020. https://www.medrxiv.org/content/10.1101/2020.04.19.20071639v2

7. Watkins AE, Fenichel EP, Weinberger DM, et al. *Pooling Saliva to Increase SARS-CoV-2 Testing Capacity*. Infectious Diseases (except HIV/AIDS); 2020. doi:10.1101/2020.09.02.20183830

8. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *The Lancet*. 2020;395(10225):689-697. doi:10.1016/S0140-6736(20)30260-9

9. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nature Medicine*. 2020;26(5):672-675. doi:10.1038/s41591-020-0869-5

10. Griffin JM, Collins AB, Hunt K, et al. A rapid review of available evidence on the serial interval and generation time of COVID-19. *medRxiv*. Published online January 1, 2020:2020.05.08.20095075. doi:10.1101/2020.05.08.20095075

11. Ferretti L, Ledda A, Wymant C, et al. The timing of COVID-19 transmission. *medRxiv*. Published online September 16, 2020:2020.09.04.20188516. doi:10.1101/2020.09.04.20188516

12. Bezanson J, Edelman A, Karpinski S, Shah VB. Julia: A Fresh Approach to Numerical Computing. *SIAM Rev*. 2017;59(1):65-98. doi:10.1137/141000671

13. Health C for D and R. SARS-CoV-2 Reference Panel Comparative Data. *FDA*. Published online September 15, 2020. Accessed September 25, 2020. https://www.fda.gov/medical-devices/coronavirus-covid-19-and-medical-devices/sars-cov-2-reference-panel-comparative-data

14. Bilder CR. Group Testing for Identification. In: *Wiley StatsRef: Statistics Reference Online*. American Cancer Society; 2019:1-11. doi:10.1002/9781118445112.stat08227

15. Chan CL, Jaggi S, Saligrama V, Agnihotri S. Non-Adaptive Group Testing: Explicit Bounds and Novel Algorithms. *IEEE Transactions on Information Theory*. 2014;60(5):3019-3035. doi:10.1109/TIT.2014.2310477

16. Paltiel AD, Zheng A, Walensky RP. Assessment of SARS-CoV-2 Screening Strategies to Permit the Safe Reopening of College Campuses in the United States. *JAMA Netw Open*. 2020;3(7):e2016818-e2016818. doi:10.1001/jamanetworkopen.2020.16818

17. Larremore DB, Wilder, Bryan, Lester, Evan, et al. Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance. https://www.medrxiv.org/content/10.1101/2020.06.22.20136309v3

18. Bullard J, Dust K, Funk D, et al. Predicting Infectious Severe Acute Respiratory Syndrome Coronavirus 2 From Diagnostic Samples. *Clin Infect Dis*. doi:10.1093/cid/ciaa638

19. He D, Zhao S, Lin Q, et al. The relative transmissibility of asymptomatic COVID-19 infections among close contacts. *International Journal of Infectious Diseases*. 2020;94:145-147. doi:10.1016/j.ijid.2020.04.034

20. Huang C-G, Lee K-M, Hsiao M-J, et al. Culture-Based Virus Isolation To Evaluate Potential Infectivity of Clinical Specimens Tested for COVID-19. *Journal of Clinical Microbiology*. 2020;58(8). doi:10.1128/JCM.01068-20

21. Perera RAPM, Tso E, Tsang OTY, et al. SARS-CoV-2 Virus Culture and Subgenomic RNA for Respiratory Specimens from Patients with Mild Coronavirus Disease. *Emerging Infectious Diseases*. 26(11). doi:10.3201/eid2611.203219

22. Singanayagam A, Patel M, Charlett A, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. *Eurosurveillance*. 2020;25(32):2001483. doi:10.2807/1560-7917.ES.2020.25.32.2001483

23. Mizumoto K, Kagaya K, Zarebski A, Chowell G. Estimating the asymptomatic proportion of coronavirus disease 2019 (COVID-19) cases on board the Diamond Princess cruise ship, Yokohama, Japan, 2020. *Eurosurveillance*. 2020;25(10):2000180. doi:10.2807/1560-7917.ES.2020.25.10.2000180

24. Savvides, Christina, Siegel, Robert. Asymptomatic and presymptomatic transmission of SARS-CoV-2: A systematic review. https://www.medrxiv.org/content/10.1101/2020.06.11.20129072v2

25. Zhen W, Manji R, Smith E, Berry GJ. Comparison of Four Molecular In Vitro Diagnostic Assays for the Detection of SARS-CoV-2 in Nasopharyngeal Specimens. *Journal of Clinical Microbiology*. 2020;58(8). doi:10.1128/JCM.00743-20

26. Kirkcaldy RD, King BA, Brooks JT. COVID-19 and Postinfection Immunity: Limited Evidence, Many Remaining Questions. *JAMA*. 2020;323(22):2245-2246. doi:10.1001/jama.2020.7869

27. Xing Y, Mo P, Xiao Y, Zhao O, Zhang Y, Wang F. Post-discharge surveillance and positive virus detection in two medical staff recovered from coronavirus disease 2019 (COVID-19), China, January to February 2020. *Eurosurveillance*. 2020;25(10):2000191. doi:10.2807/1560-7917.ES.2020.25.10.2000191

28. Bao L, Deng W, Gao H, et al. Lack of Reinfection in Rhesus Macaques Infected with SARS-CoV-2. *bioRxiv*. Published online May 1, 2020:2020.03.13.990226. doi:10.1101/2020.03.13.990226

29. Xiao AT, Tong YX, Zhang S. False negative of RT-PCR and prolonged nucleic acid conversion in COVID-19: Rather than recurrence. *Journal of Medical Virology*. 2020;92(10):1755-1756. doi:10.1002/jmv.25855

30. Lan L, Xu D, Ye G, et al. Positive RT-PCR Test Results in Patients Recovered From COVID-19. *JAMA*. 2020;323(15):1502-1503. doi:10.1001/jama.2020.2783

31. Wu J, Liu X, Liu J, et al. Coronavirus Disease 2019 Test Results After Clinical Recovery and Hospital Discharge Among Patients in China. *JAMA network open*. 2020;3(5):e209759. doi:10.1001/jamanetworkopen.2020.9759

32. Watkins AE, Fenichel EP, Weinberger DM, et al. Pooling saliva to increase SARS-CoV-2 testing capacity. *medRxiv*. Published online September 3, 2020:2020.09.02.20183830. doi:10.1101/2020.09.02.20183830

Figure 1. Schematic of the model. The model simulates testing for a common group of people who mix continuously in an institution (i.e., in a school or office) and are subject to the introduction of infection from the surrounding unmonitored community. The framework couples regular testing, described by a handful of tunable parameters, to a disease model. The disease model is dynamic in time, and infections may originate both from inside-the-institution mixing and from the surrounding community at varying rates depending on prevalence.

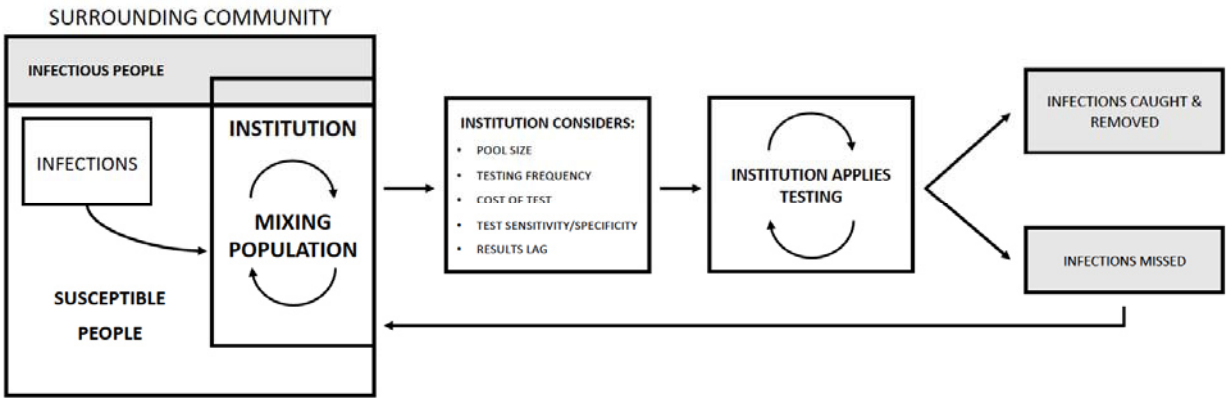
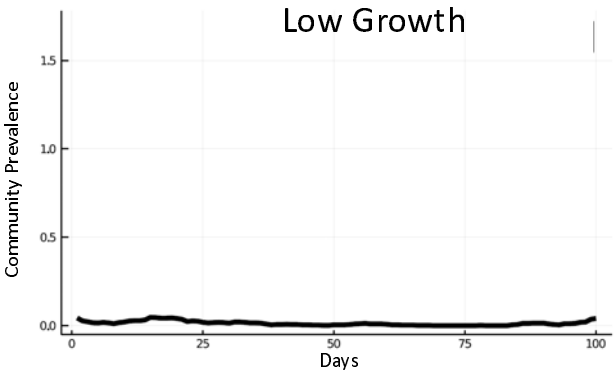
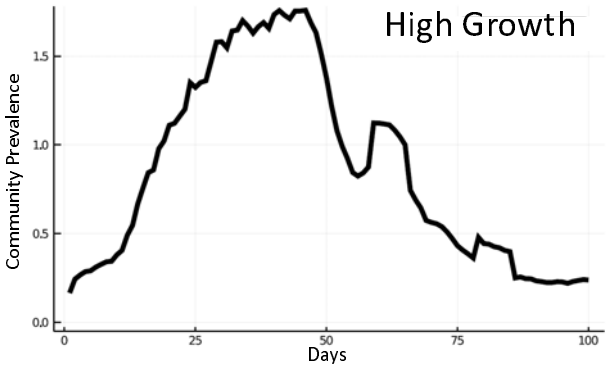


Figure 2. Impact of testing frequency. Two scenarios for community prevalence corresponding, relatively, to low and high rates of imported infections (Panels (a) and (b)). Testing with a test with 98% sensitivity with 0-day resulting delay amidst high and low community prevalence (Panels (c) and (d)). Testing with a test with 98% sensitivity with 2-day resulting delay amidst high and low community prevalence (Panels (e) and (f)). Testing with a test with 60% sensitivity with 0-day resulting delay amidst high and low community prevalence (Panels (g) and (h)). Uncropped figures are available in the supplement. Purple (dash-dot-dot) corresponds to no testing, orange (solid) to testing every two weeks, green for testing every week (dash-dot), blue (dash) for testing every 3 days, and red (dot) for daily testing.

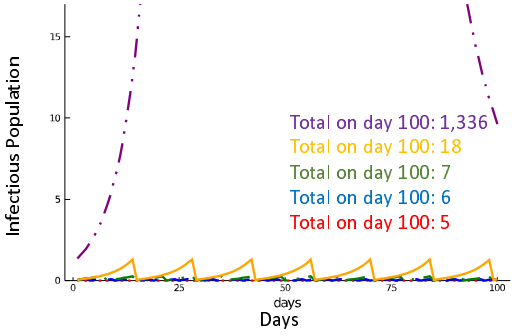


(a)

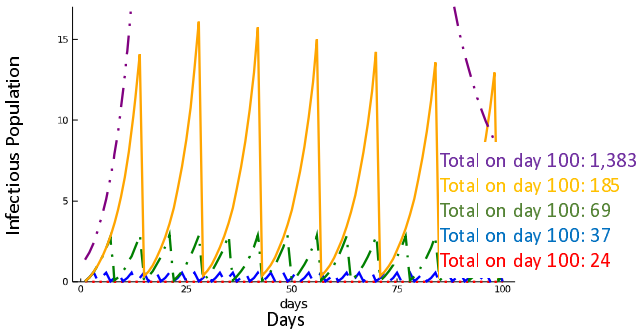


(b)

98% Sensitivity, 0-Day Delay

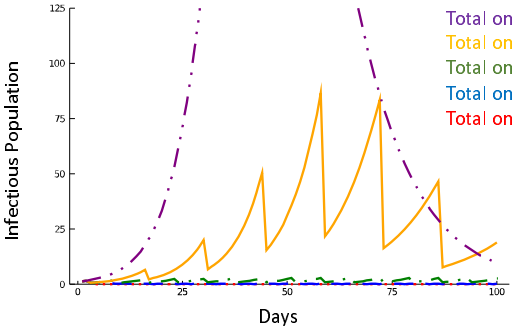


(c)

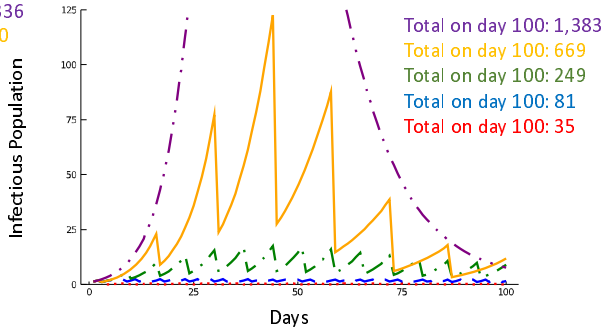


(d)

98% Sensitivity, Two-Day Delay

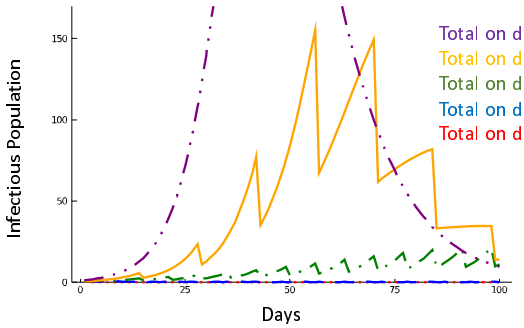


(e)

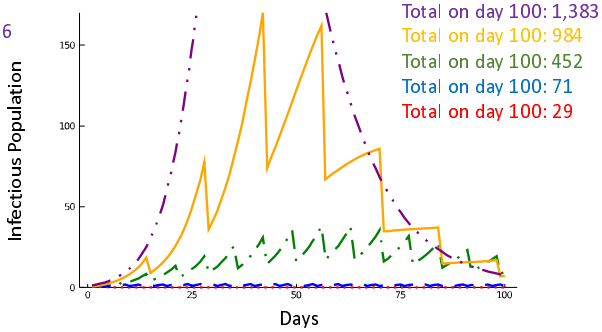


(f)

60% Sensitivity, 0-Day Delay

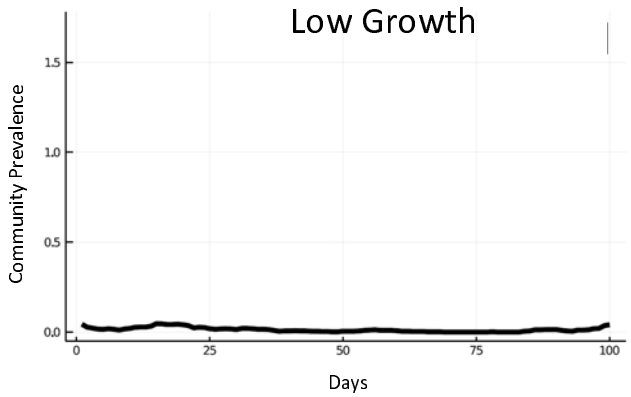


(g)

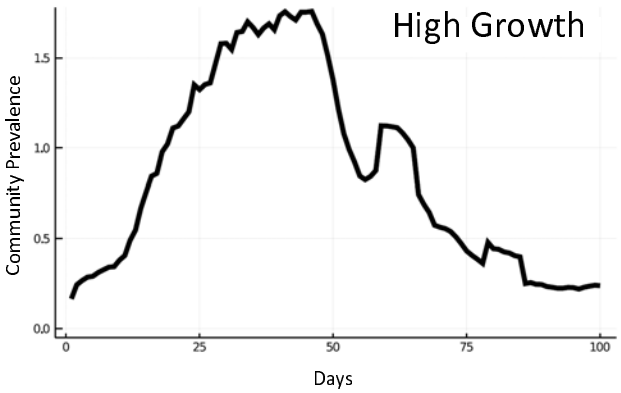


(h)

Figure 3. Effect of pool size. Two scenarios for community prevalence corresponding, relatively, to low and high rates of imported infections (Panels (a) and (b)). Testing weekly with a test with 98% sensitivity with 0-day resulting delay amidst high and low community prevalence (Panels (c) and (d)). Testing weekly with a test with 98% sensitivity with 2-day resulting delay amidst high and low community prevalence (Panels (e) and (f)). Testing ever 3 days with a test with 98% sensitivity with 2-day resulting delay amidst high and low community prevalence (Panels (g) and (h)). Orange lines (solid) correspond to 30 samples pooled, green (dash-dot) to ten samples pooled, blue (dash) to five samples pooled, and red (dot) to 2 samples pooled.

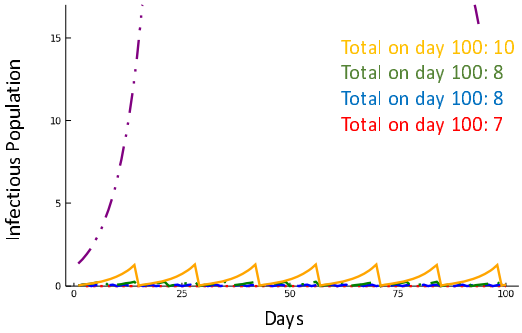


(a)

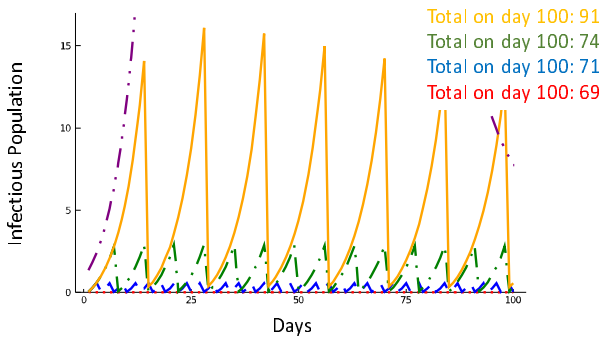


(b)

98% Sensitivity, 0-Day Delay, weekly testing

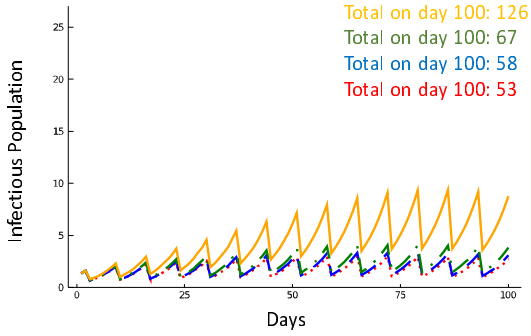


(c)

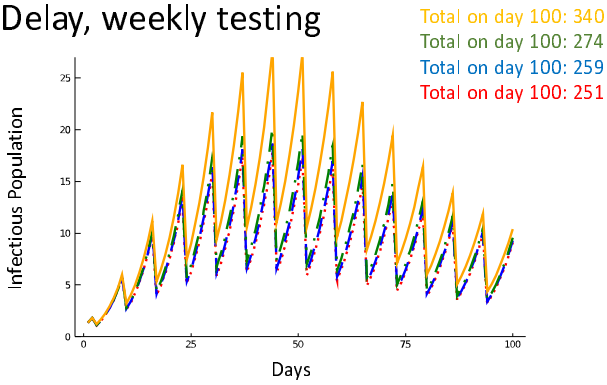


(d)

98% Sensitivity, Two-Day Delay, weekly testing

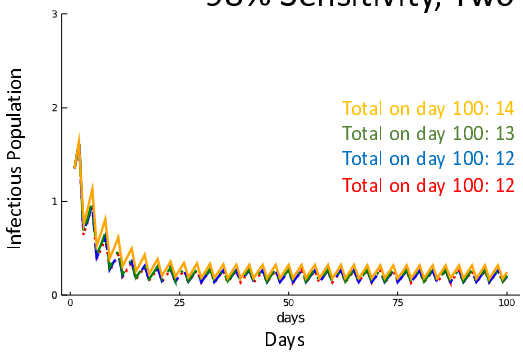


(e)

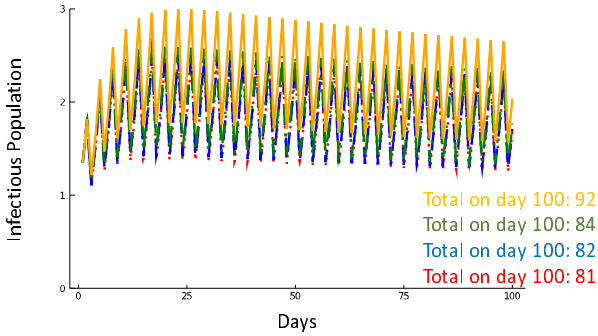


(f)

98% Sensitivity, Two-Day Delay, testing every 3 days



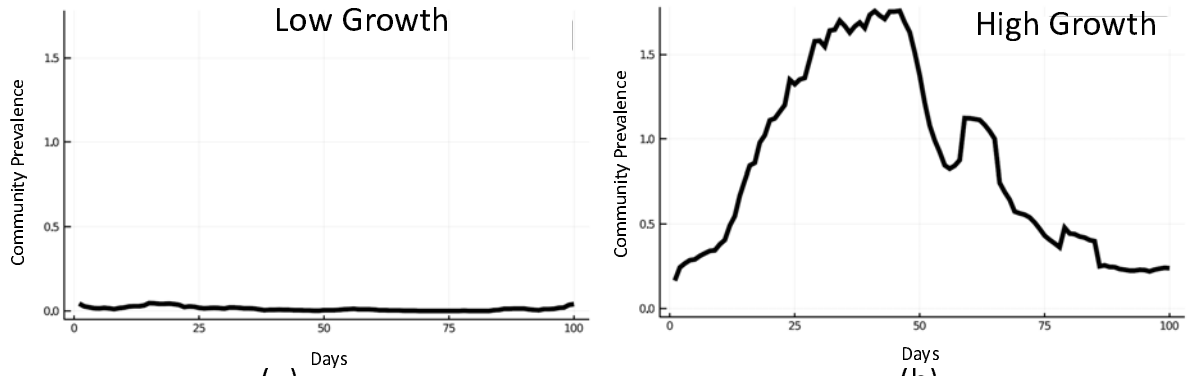
(g)



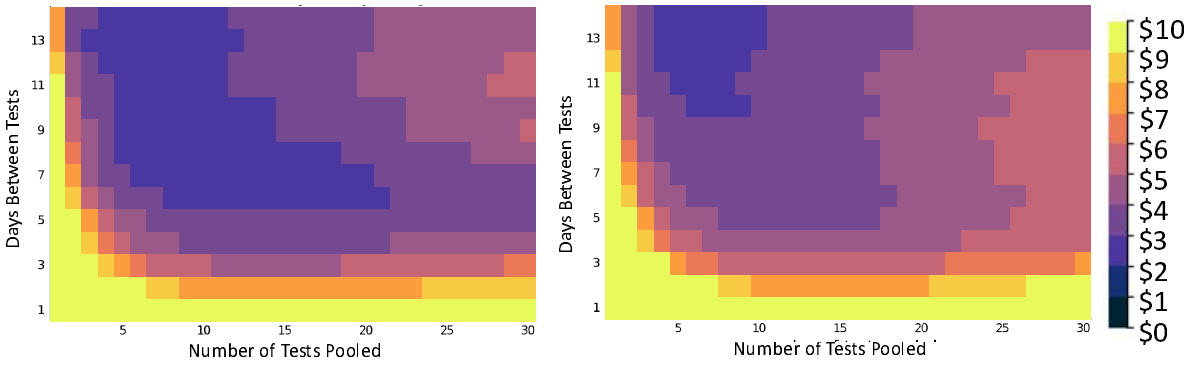
(h)

Figure 4. Cost comparison map for various pooling and frequency scenarios with and without confirmatory testing.*

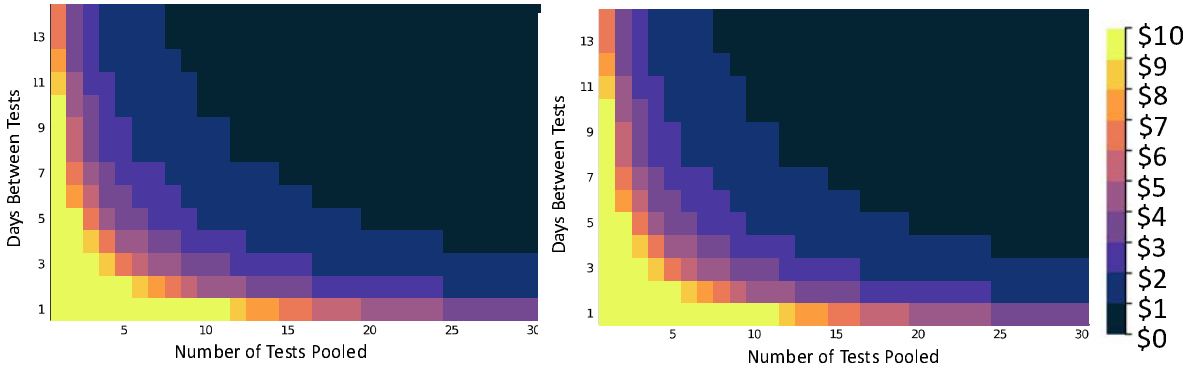
* Use case of a test with 98% sensitivity and 99.5% specificity with a 2-day result delay costing $100 and a 98% sensitive test with 99.5% specificity and a 0 day result delay costing $120. In (c,d, g, h) every person in a positive pool is retested for confirmation and in (e, f) no confirmatory testing is done. We assume all confirmatory tests cost $100. Colors correspond to cost per person per day in dollars.



With Confirmatory Testing, 98% Sensitivity, Two-Day Delay



No Confirmatory Testing, 98% Sensitivity, Two-Day Delay



With Confirmatory Testing, 98% Sensitivity, Zero-Day Delay

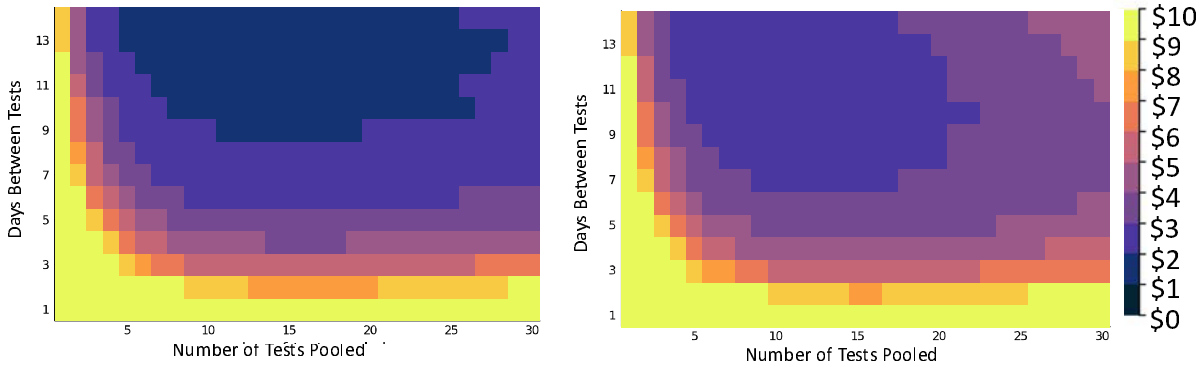


TABLE 1. Selected testing strategies ranked by reduction in cumulative infections, with and without confirmatory testing, for scenarios costing less than $10 per person per day.*

Community Prevalence: Low										
Sensitivity	Specificity	Delay (days)	Frequency (days)	Pool Size	Cumulative Infections experirenced (over 100 days)	Cumulative Infections Caught (over 100 days)	Cumulative False Positives (over 100 days)	Per person, per day cost without confirmatory testing ($)	Per person, Per day cost with confirmatory testing ($)	% Reduction in Cumulative Infections Experienced
0.98	0.995	0	3	5	6	5	262	$ 7.92	$ 8.80	99.58%
0.98	0.995	0	3	10	6	5	262	$ 3.96	$ 5.70	99.57%
0.98	0.995	0	3	30	6	5	262	$ 1.32	$ 6.30	99.54%
0.98	0.995	0	7	2	7	6	120	$ 8.40	$ 8.57	99.44%
0.98	0.995	0	7	5	8	6	120	$ 3.36	$ 3.78	99.43%
0.98	0.995	0	7	10	8	6	120	$ 1.68	$ 2.50	99.39%
0.98	0.995	0	7	30	10	8	120	$ 0.56	$ 2.93	99.23%
0.6	0.9	0	3	1	11	8	5249	$ 6.60	$ 10.10	99.16%
0.98	0.995	2	3	5	12	9	262	$ 6.60	$ 7.50	99.08%
0.98	0.995	2	3	30	14	10	262	$ 1.10	$ 6.16	98.95%
0.8	0.9	0	7	1	16	12	2399	$ 7.00	$ 8.61	98.77%
0.98	0.995	0	14	1	18	14	67	$ 8.40	$ 8.45	98.67%
0.98	0.995	2	7	2	53	35	120	$ 7.00	$ 7.21	96.01%
0.98	0.995	2	7	5	58	38	120	$ 2.80	$ 3.32	95.65%

0.98	0.995	2	7	10	67	44	120	$ 1.40	$ 2.46	94.95%
0.98	0.995	2	7	30	126	80	120	$ 0.47	$ 4.00	90.53%
0.6	0.9	0	7	1	209	124	2379	$ 2.80	$ 4.47	84.38%
0.8	0.9	0	14	1	370	234	1321	$ 3.50	$ 4.54	72.34%
0.98	0.995	2	14	1	550	293	66	$ 7.00	$ 7.24	58.83%
0.6	0.9	0	14	1	915	359	1290	$ 1.40	$ 2.50	31.52%
Community Prevalence: High										
Sensitivity	**Specificity**	**Delay (days)**	**Frequency (days)**	**Pool Size**	**Cumulative Infections experirenced (over 100 days)**	**Cumulative Infections Caught (over 100 days)**	**Cumulative False Positives (over 100 days)**	**Per person, per day cost without confirmatory testing ($)**	**Per person, Per day cost with confirmatory testing ($)**	**% Reduction in Cumulative Infections Experienced**
0.98	0.995	0	3	5	38	34	262	$ 7.92	$ 8.90	97.28%
0.98	0.995	0	3	10	38	34	262	$ 3.96	$ 5.89	97.23%
0.98	0.995	0	3	30	41	36	262	$ 1.32	$ 6.81	97.03%
0.98	0.995	0	7	2	69	56	120	$ 8.40	$ 8.63	95.00%
0.98	0.995	0	7	5	71	57	120	$ 3.36	$ 3.94	94.87%
0.6	0.9	0	3	1	71	53	5241	$ 6.60	$ 10.13	94.86%
0.98	0.995	0	7	10	74	59	120	$ 1.68	$ 2.83	94.64%
0.98	0.995	2	3	5	82	60	262	$ 6.60	$ 7.66	94.06%
0.98	0.995	0	7	30	91	69	120	$ 0.56	$ 3.93	93.41%
0.98	0.995	2	3	30	92	66	262	$ 1.10	$ 7.11	93.33%
0.8	0.9	0	7	1	132	93	2388	$ 7.00	$ 8.65	90.48%

0.98	0.995	0	14	1	185	137	67	$ 8.40	$ 8.54	86.64%
0.98	0.995	2	7	2	251	160	119	$ 7.00	$ 7.37	81.84%
0.98	0.995	2	7	5	259	164	119	$ 2.80	$ 3.72	81.24%
0.98	0.995	2	7	10	274	172	119	$ 1.40	$ 3.23	80.21%
0.98	0.995	2	7	30	340	205	119	$ 0.47	$ 5.75	75.41%
0.6	0.9	0	7	1	452	254	2358	$ 2.80	$ 4.54	67.29%
0.8	0.9	0	14	1	619	336	1308	$ 3.50	$ 4.60	55.22%
0.98	0.995	2	14	1	669	346	66	$ 7.00	$ 7.27	51.60%
0.6	0.9	0	14	1	984	375	1287	$ 1.40	$ 2.51	28.82%

* Cost calculation assumes a test with a 98% sensitivity and 0-day delay in returning results costs $120, a 98% sensitive test with a 2-day delay in results costs $100, an 80% sensitive test costs $50, and a 60% sensitive test costs $20. All (true and false) positive tests are confirmed using a $100 test. The distribution of positive tests among pooled samples is uniform as is consistent with the homogeneous mixing assumptions of the SIR model, and we assume everyone in a pool that is positive will undergo a confirmatory test.

JAMA Network Open

Original Investigation | Public Health

Assessment of SARS-CoV-2 Screening Strategies to Permit the Safe Reopening of College Campuses in the United States

A. David Paltiel, PhD; Amy Zheng, BA; Rochelle P. Walensky, MD, MPH

Abstract

IMPORTANCE The coronavirus disease 2019 (COVID-19) pandemic poses an existential threat to many US residential colleges; either they open their doors to students in September or they risk serious financial consequences.

OBJECTIVE To define severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) screening performance standards that would permit the safe return of students to US residential college campuses for the fall 2020 semester.

DESIGN, SETTING, AND PARTICIPANTS This analytic modeling study included a hypothetical cohort of 4990 students without SARS-CoV-2 infection and 10 with undetected, asymptomatic SARS-CoV-2 infection at the start of the semester. The decision and cost-effectiveness analyses were linked to a compartmental epidemic model to evaluate symptom-based screening and tests of varying frequency (ie, every 1, 2, 3, and 7 days), sensitivity (ie, 70%-99%), specificity (ie, 98%-99.7%), and cost (ie, $10/test-$50/test). Reproductive numbers (R_t) were 1.5, 2.5, and 3.5, defining 3 epidemic scenarios, with additional infections imported via exogenous shocks. The model assumed a symptomatic case fatality risk of 0.05% and a 30% probability that infection would eventually lead to observable COVID-19–defining symptoms in the cohort. Model projections were for an 80-day, abbreviated fall 2020 semester. This study adhered to US government guidance for parameterization data.

MAIN OUTCOMES AND MEASURES Cumulative tests, infections, and costs; daily isolation dormitory census; incremental cost-effectiveness; and budget impact.

RESULTS At the start of the semester, the hypothetical cohort of 5000 students included 4990 (99.8%) with no SARS-CoV-2 infection and 10 (0.2%) with SARS-CoV-2 infection. Assuming an R_t of 2.5 and daily screening with 70% sensitivity, a test with 98% specificity yielded 162 cumulative student infections and a mean isolation dormitory daily census of 116, with 21 students (18%) with true-positive results. Screening every 2 days resulted in 243 cumulative infections and a mean daily isolation census of 76, with 28 students (37%) with true-positive results. Screening every 7 days resulted in 1840 cumulative infections and a mean daily isolation census of 121 students, with 108 students (90%) with true-positive results. Across all scenarios, test frequency was more strongly associated with cumulative infection than test sensitivity. This model did not identify symptom-based screening alone as sufficient to contain an outbreak under any of the scenarios we considered. Cost-effectiveness analysis selected screening with a test with 70% sensitivity every 2, 1, or 7 days as the preferred strategy for an R_t of 2.5, 3.5, or 1.5, respectively, implying screening costs of $470, $910, or $120, respectively, per student per semester.

CONCLUSIONS AND RELEVANCE In this analytic modeling study, screening every 2 days using a rapid, inexpensive, and even poorly sensitive (>70%) test, coupled with strict behavioral

(continued)

Key Points

Question What screening and isolation programs for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) will keep students at US residential colleges safe and permit the reopening of campuses?

Findings This analytic modeling study of a hypothetical cohort of 4990 college-age students without SARS-CoV-2 infection and 10 students with undetected asymptomatic cases of SARS-CoV-2 infection suggested that frequent screening (every 2 days) of all students with a low-sensitivity, high-specificity test might be required to control outbreaks with manageable isolation dormitory utilization at a justifiable cost.

Meaning In this modeling study, symptom-based screening alone was not sufficient to contain an outbreak, and the safe reopening of campuses in fall 2020 may require screening every 2 days, uncompromising vigilance, and continuous attention to good prevention practices.

+ Invited Commentary

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

interventions to keep R_t less than 2.5, is estimated to maintain a controllable number of COVID-19 infections and permit the safe return of students to campus.

JAMA Network Open. 2020;3(7):e2016818.
Corrected on August 18, 2020. doi:10.1001/jamanetworkopen.2020.16818

Introduction

Universities across the United States are struggling with the question of whether and how to reopen for the fall 2020 semester.[1,2] Residential colleges, with communal living arrangements, shared dining spaces, intimate classrooms, and a population of young adults anxious to socialize, pose a particular challenge. In the absence of an effective vaccine, a proven therapy, and/or sufficient herd immunity, the best hope for reopening campuses in the fall is likely to be a robust strategy of behavior-based prevention combined with regular monitoring to rapidly detect, isolate, and contain new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections when they occur.[3]

Evidence on the available monitoring technologies and their performance is limited and rapidly evolving. The US Food and Drug Administration is currently evaluating more than 100 candidate tests that screen for the presence of SARS-CoV-2 infection or antibodies.[4] There are many uncertainties, including the logistics of deployment; the ease and comfort of sample collection; and the accuracy, scalability, turnaround time, and cost of test kits. After a new coronavirus disease 2019 (COVID-19) case is detected, further questions emerge regarding how to conduct subsequent tracing; how to isolate detected cases in the context of congregate housing arrangements; and how to protect other at-risk populations, including faculty, staff, and members of the surrounding community.[5] These uncertainties underscore the pressing need for both a generalized assessment of population-wide screening for SARS-CoV-2 and a comprehensive plan for reopening universities.

For many US colleges, COVID-19 poses an existential threat: either they open their doors to students in September or they suffer severe financial consequences.[6] University administrators struggling with this dilemma must nevertheless keep in mind that their first priority is the safety of the students in their care. We offer specific recommendations on the design of a virologic monitoring program that will keep students safe at an affordable cost. Our specific research objectives were, first, to define the minimum performance attributes of a SARS-CoV-2 monitoring program (eg, frequency, sensitivity, specificity, and cost) that could ensure that college students are kept safe; second, to understand how those minimum performance standards might change under varying assumptions about the severity of the epidemic and the success of behavioral and social distancing interventions; third, to suggest what isolation and treatment capacity would need to be in place; and fourth, to forecast what testing might cost and to help decision-makers understand that information to address the question of a screening and monitoring program's value.

Methods

Study Design

We adapted a simple compartmental epidemic model to capture the essential features of the situation facing university decision-makers that included the epidemiology of SARS-CoV-2; the natural history of COVID-19 illness; and regular mass screening to detect, isolate, and contain the presence of SARS-CoV-2 in a residential college setting (eFigure 1 in the Supplement). A spreadsheet implementation of the model permitted us to vary critical epidemic parameters and to examine how different test performance attributes (ie, frequency, sensitivity, specificity, and cost) would translate to outcomes. Model input data (**Table 1**)[7-19] were obtained from a variety of published sources, adhering whenever possible to the data guidance for modelers recently issued by the US Centers for

Disease Control and Prevention and the Office of the Assistant Secretary for Preparedness and Response. We defined 3 increasingly pessimistic epidemic scenarios and estimated both cumulative outcomes (eg, tests administered, number of true-positive and false-positive results, number of new infections, and person-days requiring isolation) and economic performance (eg, cost, incremental cost-effectiveness, and budget impact) during an abbreviated 80-day semester, running from Labor Day through Thanksgiving.[2] We assumed a medium-sized college setting with a target population of 5000 students, all of them younger than 30 years and nonimmune, living in a congregate setting.[19,20] We seeded this population with 10 undetected, asymptomatic cases of SARS-CoV-2 infection. A publicly accessible version of the model implementation is available online.

This analysis adheres to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline, where applicable. Because this study used only aggregate, published

Table 1. Model Input Parameters and Scenarios

Model parameter	Input	References
Compartments in initial population, No.		
Noninfected, susceptible	4990	US News and World Report,[19] 2020
Infected, asymptomatic	10	Assumption
All other compartments	0	Assumption
Time horizon, d	80	Hubler,[2] 2020
Disease dynamics		
Mean incubation time, θ	3 d	He et al,[8] 2020
Time to recovery, 1/ρ	14 d	Lauer et al,[10] 2020; CDC,[11] 2020
Time to false-positive return, 1/μ	1 d	Assumption
Probability of symptoms given infection, %	30	Day,[12] 2020; Yang et al,[13] 2020; Ing et al,[14] 2020
Symptomatic case fatality ratio, %	0.05	CDC,[7] 2020
Transmission rate, β	Dependent on R_t	NA
Rate of symptom development, σ	Dependent on R_t	NA
Scenarios		
Effective R_t		
Best	1.5	CDC,[7] 2020; Pitzer et al,[15] 2020; Li et al,[16] 2020
Base	2.5	
Worst	3.5	
Test specificity, ie, true-negative rate, %		
Best	99.7	Lieberman et al[17] 2020; Zhen et al,[18] 2020
Base	98.0	
Worst	98.0	
Exogenous infections per wk, No.		
Best	5	Assumption
Base	10	
Worst	25	
Test characteristics		
Sensitivity, ie, true-positive rate, %		
Test I	70	Assumption
Test II	80	
Test III	90	
Cost per test, $		
Test I	10	Assumption
Test II	25	
Test III	50	
Time to test result return, h	8	Assumption
Confirmatory test		
Sensitivity, %	100	Assumption
Cost, $	100	Assumption

Abbreviations: CDC, US Centers for Disease Control and Prevention; NA, not applicable; R_t, reproduction number.

data, the institutional review boards of both the Massachusetts General Hospital and the Yale School of Medicine determined that this research did not involve human participants and did not require their review or approval.

Compartmental Model

To the basic susceptible-exposed-infected-removed compartmental modeling framework, we added the following: the availability of regular, repeated screening with a test of imperfect sensitivity and specificity; the creation of a new compartment for uninfected persons receiving a false-positive test result; separation of the infected compartment to distinguish between asymptomatic patients with undetected infection, asymptomatic patients with detected infection (ie, true-positives), and observed symptomatic patients; and the importation of additional new infections via exogenous shocks (eg, infections transmitted to students by university employees or members of the surrounding community or during superspreader events, such as parties).

We defined 3 epidemic severity scenarios: a base case with a reproduction number (R_t) of 2.5, test specificity of 98%, and the exogenous introduction of 10 new, undetected infections to the susceptible population each week; a worst case with an R_t of 3.5, test specificity of 98%, and 25 exogenous new infections every week; and a best case with an R_t of 1.5, test specificity of 99.7%, and 5 exogenous new infections each week.

Isolation

We assumed that after a lag of 8 hours, individuals receiving a positive test result (true or false) and those exhibiting COVID-19 symptoms would be moved from the general population to an isolation dormitory, where their infection would be confirmed, where they would receive supportive care, and from which no further transmissions would occur. The lag reflected both test turnaround delays and the time required to locate and isolate identified cases. Students with confirmed (ie, true-positive) results would remain in the isolation dormitory a mean of 14 days to ensure they were not infectious before proceeding to a recovered or immune state.[10,11] Students with false-positive results would remain isolated for 24 hours, reflecting our assumption that a highly specific confirmatory test could overturn the original diagnosis, permitting them to return to the campus population.

We assumed a mean time from exposure to both infectiousness and screening detectability of 3 days, a symptomatic case fatality risk of 0.05%, and a 30% probability that infection would eventually lead to observable COVID-19–defining symptoms in this young cohort.[7-9,12-14]

Screening

We sought to evaluate both existing SARS-CoV-2 detection methods and newer technologies that could plausibly be available in the near future. Accordingly, we considered a range of different test sensitivities (ie, 70%-99%), specificities (ie, 98%-99.7%),[17,18] and per-test costs (ie, $10-$50). For each combination of these test characteristics, we considered both symptom-based screening and routine testing every 1, 2, 3, and 7 days. We assumed that a confirmatory test with 100% specificity could distinguish false-positive from true-positive results at a cost of $100.

Cost-effectiveness

Next, we estimated incremental cost-effectiveness ratios, denominated in screening costs per infection averted. This measure of return on investment in screening was compared with a crude benchmark of value estimated using the following 4 terms: (1) COVID-related mortality (0.05% in persons of college age; 0.4% overall)[7]; (2) survival loss of 60 years per college-age fatality; 20 years overall[21]; (3) societal willingness-to-pay (WTP) threshold of $100 000 per year of life gained[22]; and (4) R_t + 1, assuming that each infection averted prevents half the R_t secondary infections among college-age students and half among other adult members of the campus community.[7,15,16] This method yielded a maximum WTP to avert 1 infection of $5500 in the best case, $8500 in the base case, and $11 600 in the worst case.

Cost-effectiveness analysis identified a preferred screening strategy from among 13 possibilities—3 test sensitivities (70%, 80%, and 90%) and 4 frequencies (1, 2, 3, and 7 times per week) in addition to symptom-based screening—under each epidemic scenario (base, worst, and best cases) already described. We also considered the more restricted case, in which the only available test cost $25 and had a sensitivity of 80%. Finally, to help decision-makers understand the fiscal consequences of pursuing these preferred strategies, we conducted a budget impact assessment, reporting the cumulative costs for the semester on a per-student basis.

Statistical Analysis

The model was implemented as a spreadsheet. All analyses were conducted in Microsoft Excel. Because no statistical tests were run, no prespecified level of statistical significance was set.

Results

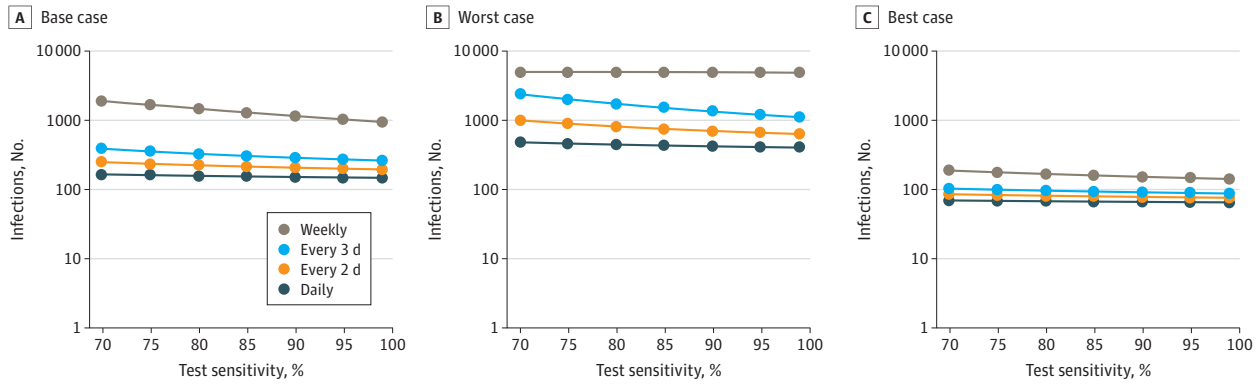
Test Frequency and Sensitivity

At the start of the semester, the hypothetical cohort of 5000 students included 4990 (99.8%) with no SARS-CoV-2 infection and 10 (0.2%) with SARS-CoV-2 infection. During an 80-day semester in the base case (ie, R_t of 2.5 and 10 exogenous infections each week), screening every 1, 2, 3, or 7 days with a 70% sensitive, 98% specific test resulted in 162, 243, 379, and 1840 cumulative infections, respectively. Symptom-based screening yielded 4970 infections. Raising the sensitivity of the test from 70% to 90% reduced total infections (eg, from 162 to 149 for daily screening and from 1840 to 1118 for weekly screening). **Figure 1** shows cumulative infections as a function of test sensitivity and test frequency for the 3 epidemic severity scenarios.

Isolation Dormitory Occupancy

In the base case, daily screening with a 70% sensitive, 98% specific test resulted in a mean isolation dormitory census of 116 occupants, of whom 21 (18%) had true-positive results (**Figure 2**A). With screening every 2 days, mean daily census was reduced to 76, as fewer tests were performed and fewer false-positive results were obtained; however, less frequent testing was also associated with greater transmission of infection and a higher mean proportion of students with true-positive results in isolation (28 students [37%]) (Figure 2B). Weekly and symptom-based screening were associated with large increases in the infected occupancy of the isolation dormitory (Figure 2C and Figure 2D). For example, screening every 7 days resulted in a mean daily isolation census of 121 students, with

Figure 1. Cumulative Infections as a Function of Test Sensitivity and Frequency



During an 80-day horizon, for the base case (R_t of 2.5, test specificity of 98%, and 10 exogenous infections per week) (A), worst case (R_t of 3.5, test specificity of 98%, and 25 exogenous infections per week) (B), and best case (R_t of 1.5, test specificity of 99.7%, and 5 exogenous infections per week) (C), these panels report cumulative infections for tests with sensitivity ranging from 70% to 99%.

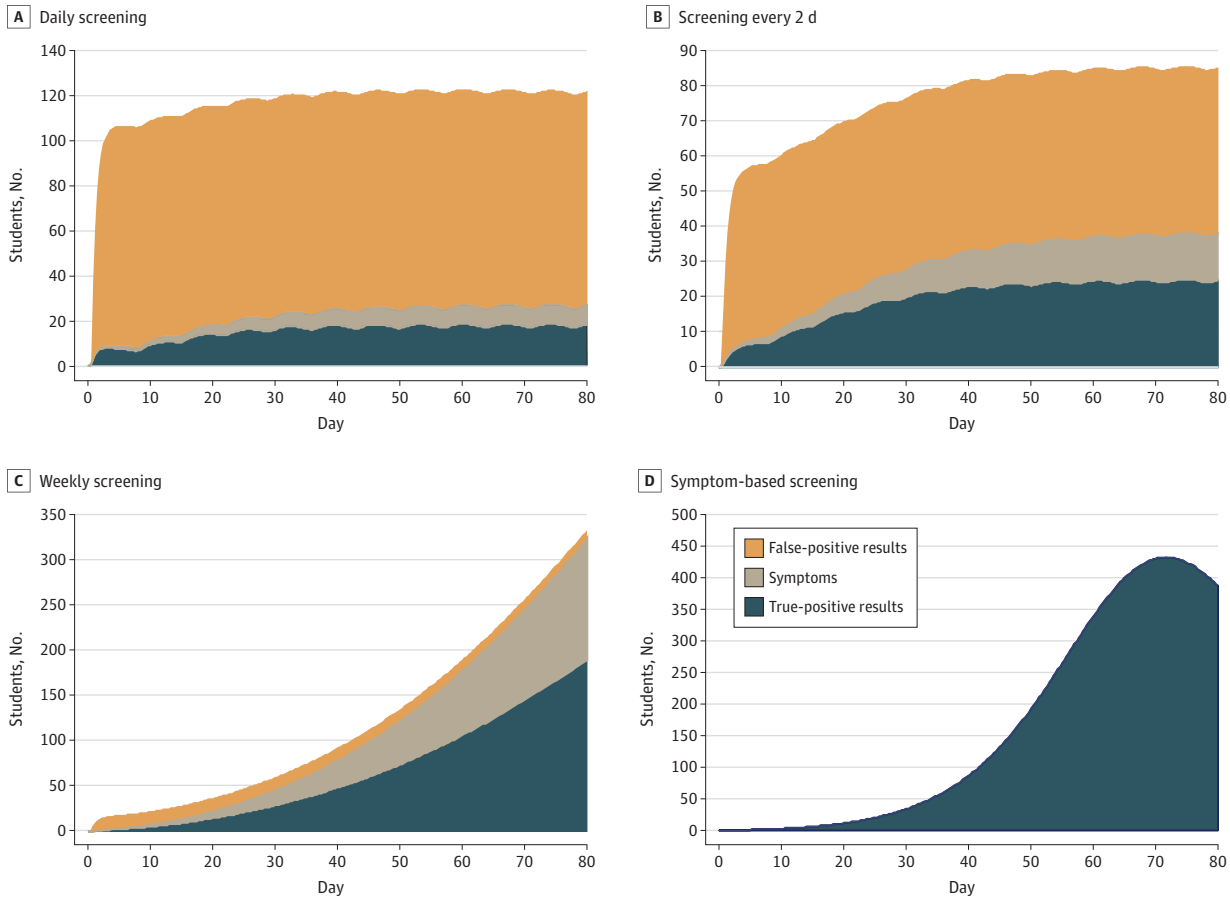
108 (90%) with true-positive results. Sensitivity analysis revealed that the trends evident in Figure 2 extended beyond the 80-day planning horizon (data not shown). Varying the initial number of asymptomatic infections between 0 and 100 did not materially change our findings.

The number of students with false-positive results and the isolation capacity required to accommodate them were reduced in the presence of a more specific test. For example, with daily screening in the base case, increasing the test specificity from 98% to 99.7% was associated with a decrease in the mean daily census of students with false-positive results in isolation from 95 to 15.

Under worst-case assumptions (ie, R_t of 3.5 with 25 exogenous infections every week), daily screening yielded mean isolation dormitory census of 152 students, of whom 60 (39%) had true infections (eFigure 2A in the Supplement). Screening every 2 days produced similar census (151) but a higher proportion (106 [70%]) of true infections (eFigure 2B in the Supplement). With weekly screening or symptom-based screening, nearly the entire student population would be infected before the conclusion of the 80-day semester (eFigure 2C and eFigure 2D in the Supplement).

In the best case (ie, R_t of 1.5 with 5 exogenous shocks each week and a test with 99.7% specificity), mean occupancy of the isolation dormitory was 18 (16 with infection; 2 with false-positive results) with weekly screening and 24 (all true infections) with symptom-based screening (eFigure 3 in the Supplement).

Figure 2. Projecting the Required Size of the Isolation Dormitory



An isolation dormitory needs to be large enough to house students with false-positive results, students with symptoms, and students without symptoms who have received true-positive results. During the 80-day horizon, these panels depict the number of students in the isolation dormitory using a 70% sensitive, 98% specific test under the base case scenario (ie, R_t of 2.5). The effect of exogenous shocks (10 per week) is visible in the scalloped borders with daily screening and screening every 2 days (A, B); this is less evident with less frequent testing and symptom-based screening (C, D), in which the number of true-positive cases masks the comparatively small effect of exogenous shocks.

Cost-effectiveness and Budget Impact Assessment

In the base case, screening with a less expensive, less sensitive test dominated screening with more expensive, more accurate tests (ie, it cost less and averted greater numbers of infection) for all plausible WTP values. At the benchmark maximum WTP ($8500 per infection averted), screening every 2 days with a 70% sensitive test was the preferred strategy. For WTP exceeding $28 400 per infection averted, daily screening with this same test was optimal (**Table 2**). Under worst-case assumptions, daily screening strategies were the only undominated choices for WTP values

Table 2. Results of the Incremental Cost-effectiveness Analysis in the Base-Case, Worst-Case, and Best-Case Scenarios

Frequency	Test sensitivity, %	Cost, $	Total infections	Incremental cost-effectiveness ratio, $/infection averted[a]
Base-case scenario[b]				
Symptom-based screening	NA	NA	4970	NA
Weekly	70	696 000	1840	200
Weekly	80	1 490 700	1422	Dominated
Every 3 d	70	1 564 500	379	600
Every 2 d	70	2 340 600	243	5700
Weekly	90	2 837 500	1118	Dominated
Every 3 d	80	3 501 800	319	Dominated
Daily	70	4 642 700	162	28 400
Every 2 d	80	5 254 900	219	Dominated
Every 3 d	90	6 740 400	280	Dominated
Every 2 d	90	10 118 700	202	Dominated
Daily	80	10 440 000	154	752 600
Daily	90	20 106 900	149	1 692 900
Worst-case scenario[c]				
Symptom-based screening	NA	NA	4991	NA
Weekly	70	673 600	4991	Dominated
Weekly	80	1 274 200	4988	Dominated
Every 3 d	70	1 509 300	2373	Dominated
Every 2 d	70	2 266 400	998	600
Weekly	90	2 310 000	4951	Dominated
Every 3 d	80	3 292 800	1731	Dominated
Daily	70	4 543 900	481	4400
Every 2 d	80	5 063 200	814	Dominated
Every 3 d	90	6 347 900	1335	Dominated
Every 2 d	90	9 764 100	701	Dominated
Daily	80	10 207 500	445	159 700
Daily	90	19 666 200	420	377 500
Best-case scenario[d]				
Symptom-based screening	NA	NA	1067	NA
Weekly	70	587 800	188	700
Every 3 d	70	1 364 600	103	9100
Weekly	80	1 432 700	168	Dominated
Every 2 d	70	2 044 500	85	38 800
Weekly	90	2 842 200	152	Dominated
Every 3 d	80	3 343 100	96	Dominated
Daily	70	4 080 900	69	128 100
Every 2 d	80	5 013 900	81	Dominated
Every 3 d	90	6 642 100	91	Dominated
Every 2 d	90	9 964 200	78	Dominated
Daily	80	10 016 800	68	3 156 700
Daily	90	19 911 200	66	6 833 800

Abbreviations: NA, not applicable.

[a] Strategies that cost more and result in more infections than some combination of other strategies are labeled *dominated*.

[b] Base-case scenario had a reproduction number of 2.5, 10 exogenous shock infections each week, and a maximum willingness-to-pay threshold of $8500 per infection averted.

[c] Worst-case scenario had a reproduction number of 3.5, 25 exogenous shock infections each week, and a maximum willingness-to-pay threshold of $11 600 per infection averted.

[d] Best-case scenario had a reproduction number of 1.5, 5 exogenous shock infections each week, a test with 99.7% specificity, and a maximum willingness-to-pay threshold of $5500 per infection averted.

exceeding $4400 per infection averted; at the benchmark maximum WTP ($11 600 per infection averted), daily screening with the least sensitive (ie, 70%) test was the preferred choice. Under best-case assumptions (with a WTP maximum of $5500 per infection averted), weekly screening with a 70% sensitive test was optimal. If the only available test cost $25 and had a sensitivity of 80%, the optimal frequency of screening would be every 7, 3, and 2 days in the best, base, and worst case scenarios, respectively (eAppendix and eTable 1 in the Supplement). If the probability of progressing from infection to symptoms rose from 30% to 65%, screening every day would be optimal in the base case scenario (eTable 2 in the Supplement). During the 80-day semester, the per-student costs of implementing the preferred screening strategy were $120, $470, and $910 in the best, base, and worst case scenarios, respectively (**Table 3**).

Discussion

The safe return of students to residential colleges demands an effective SARS-CoV-2 monitoring strategy. Results from this modelling study suggest that a highly specific screening test that can easily be administered to each student every 1 to 7 days—and that reports results quickly enough to permit newly detected cases to be isolated within hours—would be required to blunt the further transmission of infection and to control outbreaks at a justifiable cost. We identified no circumstance in this modelling study under which symptom-based screening alone would be sufficient to contain an outbreak.

Of the many uncertain variables driving our assessment of the required frequency of screening, we highlight R_t. This uncertain measure of the transmission potential of infection will depend in part on factors that are within the control of students and university administrators. Strict adherence to handwashing, mandated indoor masking, elimination of buffet dining, limited bathroom sharing with frequent cleaning, dedensifying campuses and classrooms, and other best practices could reduce R_t to best-case levels, rendering containment possible with weekly testing. However, any relaxation of these measures in the residential college setting could easily increase R_t to worst-case levels, requiring daily screening. All members of the university community must understand the fragility of the situation and the ease with which inattention to behavior may propagate infections and precipitate the need once again to shut down campus.

Much depends on the judicious management of positive test results, both true and false. Rapid detection, confirmation, isolation, and treatment of true-positive cases is, of course, essential. We found that frequent screening with a test of modest sensitivity and a turnaround time of 8 hours would be required for this purpose. The greater difficulty lies in managing the overwhelming number of false-positives that will inevitably result from repeated screening for low-prevalence conditions. False-positive results threaten to overwhelm isolation housing capacity, a danger whose gravity increases with screening frequency. The specificity of the initial test will matter far more than its sensitivity. Many current virologic tests report a 99.8% to 100% specificity in the context of use to date for symptomatic testing[23]; we examined a value of 99.7% in the best case but used a lower value of 98% in the base-case and worst-case scenarios, given that most virologic tests have yet to be used for the kind of large-scale surveillance described in this model.

Even with a 98% specific screening test, false-positive results will present a challenge. Until a confirmatory test result is obtained, anyone receiving a positive test result will be presumed to be

Table 3. Per-Student Costs for Optimal Policies During an 80-Day Horizon Under Base-Case, Worst-Case, and Best-Case Scenarios

Scenario	Optimal policy	Cost per student, $
Base case, ie, R_t of 2.5	Screening every 2 d, 70% sensitivity	470
Worst case, ie, R_t of 3.5	Daily screening, 70% sensitivity	910
Best case, ie, R_t of 1.5	Weekly screening, 70% sensitivity	120

Abbreviation: R_t, reproduction number.

infectious and need to be separated from other students. Setting aside the logistic challenges and financial costs, administrators must anticipate the anxiety such separations may provoke among both students and their families. Excessive numbers of false-positive results may fuel panic and undermine confidence in the reliability of the monitoring program. It may be possible to work with test manufacturers to tune test kits under development for use in this setting, sacrificing some small measure of sensitivity in favor of higher specificity.

Obtaining an adequate supply of testing equipment will be a challenge. On a college campus with 5000 enrollees, screening students alone every 2 days will require more than 195 000 test kits during the abbreviated semester. Our analysis assumed per-test costs (including equipment and associated personnel costs) ranging from $10 to $50. Lower-cost, self-administered testing modalities may soon be available and could make screening more affordable. Pooling could also facilitate more efficient, higher-volume screening.[24] However, pooling introduces its own logistic challenges and could increase the time to definitively identifying and isolating a positive case, resulting in further transmission and provoking anxiety among the many uninfected students notified that they are among the members of an initially positive pool.

We have tried to help decision-makers make sense of the value question by conducting a cost-effectiveness analysis and by comparing our findings with a rough estimate of the societal WTP per infection averted.[25] While we have adhered to the broad outlines of recommended practice for the conduct of economic evaluations,[25] we urge readers to interpret our results with caution. Most of our assumptions are conservative, ie, they understate the value of more frequent testing. For example, we ignored the clinical harms and attributable costs of COVID-19–related morbidity and treatment. We also ignored the value of infections averted beyond the student population. However, a few assumptions (eg, our failure to account for the economic and quality-of-life effects of false-positive results) may pull in the direction of less testing.

Reopening college campuses imposes risks that extend beyond students to the faculty who teach them, the many university employees (administrative and facilities staff) who come into close daily contact with them, and the countless other members of the surrounding community with whom students come into contact. University presidents have a duty to consider the downstream effect of their reopening decisions on these constituencies. However, their first responsibility is to the safety of the students in their care. While we certainly do not intend to minimize the broader effects of the reopening decision, we have quite deliberately excluded from consideration any transmissions exported off campus.

Limitations

The simple model underlying this analysis has notable limitations. We assumed homogenous mixing without age-dependent transmission. We did not explicitly include the effect of screening on faculty and staff, although these and other nonstudent members of the college community include a higher proportion of older, more medically vulnerable individuals. We assumed that no students arrive on campus with immunity to COVID-19. We excluded the effects of contact tracing. Given its implementation challenges, this is a noteworthy omission. However, our results suggest that with frequent enough screening, contact tracing would not be necessary for epidemic control. While this analysis offers guidance on the frequency of screening, it does not speak to the logistic challenges of deploying testing strategies on large college campuses. Such challenges include the acquisition of supplies; the orchestration of screening at scale; the monitoring of adherence; the development of a strategy for rapid result return, contact, and isolation; and the availability and maintenance of an isolation dormitory with all single rooms and bathrooms.

Conclusions

We believe that there is a safe way for students to return to college in fall 2020. In this study, screening every 2 days using a rapid, inexpensive, and even poorly sensitive (>70%) test, coupled

with strict interventions that keep R_t less than 2.5, was estimated to yield a modest number of containable infections and to be cost-effective. This sets a very high bar—logistically, financially, and behaviorally—that may be beyond the reach of many university administrators and the students in their care.

ARTICLE INFORMATION

Accepted for Publication: July 2, 2020.

Published: July 31, 2020. doi:10.1001/jamanetworkopen.2020.16818

Correction: This article was corrected on August 18, 2020, to fix a broken link in the eAppendix of the Supplement.

Corresponding Author: A. David Paltiel, PhD, Public Health Modeling Unit, Yale School of Public Health, 60 College St, New Haven, CT 06510 (david.paltiel@yale.edu).

Author Affiliations: Public Health Modeling Unit, Yale School of Public Health, New Haven, Connecticut (Paltiel); Harvard Medical School, Boston, Massachusetts (Zheng, Walensky); Medical Practice Evaluation Center, Division of Infectious Diseases, Massachusetts General Hospital, Boston (Walensky).

Author Contributions: Drs Paltiel and Walensky had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Critical revision of the manuscript for important intellectual content: Paltiel, Walensky.

Statistical analysis: Walensky.

Obtained funding: Paltiel, Walensky.

Administrative, technical, or material support: All authors.

Supervision: Paltiel.

Conflict of Interest Disclosures: None reported.

Funding/Support: Dr Paltiel was supported by grant R37 DA015612 from the National Institute on Drug Abuse of the National Institutes of Health. Dr Walensky was supported by the Steve and Deborah Gorlin Research Scholars Award from the Massachusetts General Hospital Executive Committee on Research.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Massachusetts General Hospital Executive Committee on Research.

Additional Contributions: The authors thank the Massachusetts university presidents of the COVID-19 Testing Group for motivating this research. Helpful conversations with these and other college presidents shaped and refined our analysis, strategies, and assumptions.

REFERENCES

1. Centers for Disease Control and Prevention. Interim guidance for administrators of US institutions of higher education: plan, prepare, and respond to coronavirus disease 2019. Updated March 18, 2020. Accessed July 7, 2020. https://www.cdc.gov/coronavirus/2019-ncov/community/guidance-ihe-response.html

2. Hubler, S. College calendars in the pandemic: no fall break and home by Thanksgiving. *New York Times*. Published May 19, 2020. Accessed July 7, 2020. https://www.nytimes.com/2020/05/19/us/coronavirus-college-fall-semester.html

3. National Governors Association. Memorandum: reopening institutions of higher education. Published May 27, 2020. Accessed July 7, 2020. http://www.nga.org/wp-content/uploads/2020/05/State-Higher-Ed-reopening-final.pdf

4. US Food and Drug Administration. Coronavirus (COVID-19) update: daily roundup May 21, 2020. Published May 21, 2020. Accessed July 7, 2020. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-may-21-2020

5. Walensky RP, Del Rio C. From mitigation to containment of the COVID-19 pandemic: putting the SARS-CoV-2 genie back in the bottle. *JAMA*. 2020;323(19):1889-1890. doi:10.1001/jama.2020.6572

6. McLaughlin, K. The coronavirus could force smaller liberal arts and state colleges to close forever. *Insider*. Published April 26, 2020. Accessed July 7, 2020. https://www.insider.com/smaller-colleges-may-never-reopen-because-of-the-coronavirus-2020-4

7. US Centers for Disease Control and Prevention. COVID-19 pandemic planning scenarios. Updated May 20, 2020. Accessed July 7, 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html

8. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med*. 2020;26(5):672-675. doi:10.1038/s41591-020-0869-5

9. Davies NG, Klepac P, Liu Y, Prem K, Jit M, Eggo RM; CMMID COVID-19 working group. Age-dependent effects in the transmission and control of COVID-19 epidemics. *Nat Med*. 2020. doi:10.1038/s41591-020-0962-9

10. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Ann Intern Med*. 2020;172(9):577-582. doi:10.7326/M20-0504

11. US Centers for Disease Control and Prevention. Quarantine if you might be sick. Updated July 3, 2020. Accessed July 7, 2020. https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine-isolation.html

12. Day M. COVID-19: four-fifths of cases are asymptomatic, China figures indicate. *BMJ*. 2020;369:m1375. doi:10.1136/bmj.m1375

13. Yang R, Gui X, Xiong Y. Comparison of clinical characteristics of patients with asymptomatic vs symptomatic coronavirus disease 2019 in Wuhan, China. *JAMA Netw Open*. 2020;3(5):e2010182. doi:10.1001/jamanetworkopen.2020.10182

14. Ing AJ, Cocks C, Green JP. COVID-19: in the footsteps of Ernest Shackleton. *Thorax*. Published online May 27, 2020;thoraxjnl-2020-215091. doi:10.1136/thoraxjnl-2020-215091

15. Pitzer VE, Chitwood M, Havumaki J, et al. The impact of changes in diagnostic testing practices on estimates of COVID-19 transmission in the United States. medRxiv. Preprint posted online April 24, 2020. doi:10.1101/2020.04.20.20073338

16. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. *N Engl J Med*. 2020;382(13):1199-1207. doi:10.1056/NEJMoa2001316

17. Lieberman JA, Pepper G, Naccache SN, Huang ML, Jerome KR, Greninger AL. Comparison of commercially available and laboratory developed assays for in vitro detection of SARS-CoV-2 in clinical laboratories. *J Clin Microbiol*. 2020;JCM.00821-20. doi:10.1128/JCM.00821-20

18. Zhen W, Manji R, Smith E, Berry GJ. Comparison of four molecular in vitro diagnostic assays for the detection of SARS-CoV-2 in nasopharyngeal specimens. *J Clin Microbiol*. 2020;JCM.00743-20. doi:10.1128/JCM.00743-20

19. US News and World Report. 10 colleges with the most undergraduates. Published October 1, 2019. Accessed July 7, 2020. https://www.usnews.com/education/best-colleges/the-short-list-college/articles/colleges-with-the-most-undergraduates

20. National Center for Education Statistics. Characteristics of postsecondary students. Updated April 2020. Accessed July 7, 2020. https://nces.ed.gov/programs/coe/indicator_csb.asp

21. US Department of Health and Human Services. United States Life Tables, 2016. Published May 7, 2019. Accessed July 7, 2020. https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_04-508.pdf

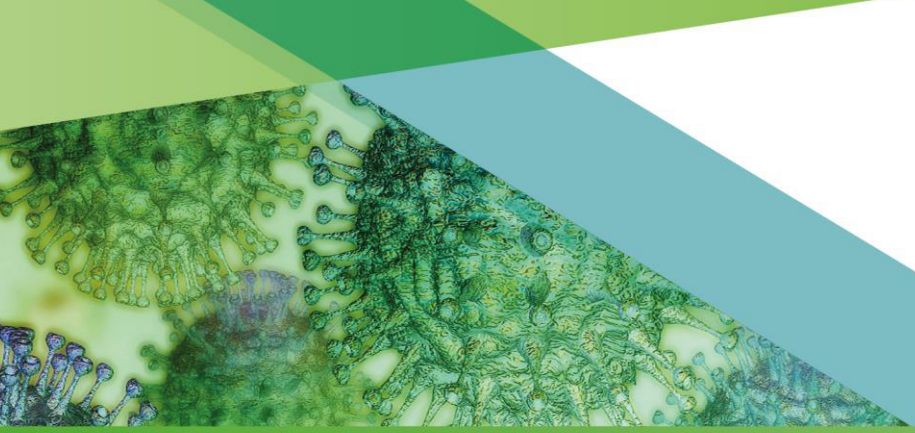
22. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med*. 2014;371(9):796-797. doi:10.1056/NEJMp1405158

23. US Food and Drug Administration. EUAs for coronavirus disease 2019 (COVID-19). Updated July 1, 2020. Accessed July 7, 2020. https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations#coronavirus2019

24. Hogan CA, Sahoo MK, Pinsky BA. Sample pooling as a strategy to detect community transmission of SARS-CoV-2. *JAMA*. 2020;323(19):1967-1969. doi:10.1001/jama.2020.5445

25. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 2016;316(10):1093-1103. doi:10.1001/jama.2016.12195

SUPPLEMENT.



Objectives for COVID-19 testing in school settings – first update

21 August 2020

Objectives for testing in school settings

- To ensure early identification of cases among students and staff in order to conduct contact tracing and initiate prevention and control measures, thereby reducing further transmission.
- To identify infection in students and staff at high risk of developing severe disease due to underlying conditions.
- To support investigations and studies concerning the role of children in the transmission of COVID-19.

Scope of this document

This document provides an overview of major aspects of testing, contact tracing, contact identification and contact follow-up in school settings within the EU/EEA countries and the United Kingdom (UK).

Target audience

The target audience for this technical report is public health experts working in school settings and public health authorities in EU/EEA countries and the UK.

Glossary

The school structures within the EU/EEA Member States and UK are heterogeneous, with children entering and moving through educational establishments at different ages [1]. Given this variation, it is not possible to define the age of attendance in EU education establishments with full consistency. Therefore, for the purposes of this document, the following classification has been used:

Schools	The generic term used to define all educational establishments within the scope of the document.
Staff	Includes teachers, administrators and management, school nurses, janitors, cleaning and kitchen personnel and other adults working in childcare and educational settings.

Background

School settings bring children and young adults of different age groups together at close quarters. They share teaching rooms, and sports and other community facilities. It has been shown that children have a higher number of social contacts than adults, which is also related to school settings [2]. Similarly, school staff have a large number of contacts with pupils as well as other staff. These contacts may result in transmission of infectious diseases. Many countries have closed schools and kindergartens to reduce transmission and mitigate the impact of the COVID-19 pandemic. However, even if there is increasing evidence of the low impact of COVID-19 in children

Suggested citation: Objectives for COVID-19 testing in school settings – first update, 21 August 2020. Stockholm: ECDC; 2020.

[3], the overall role that children play in transmission and spread of SARS-CoV-2 remains unclear [4]. Furthermore, a recent study suggests that the viral load in children under five years with mild to moderate COVID-19 symptoms is higher than in older children and adults [5]. Although schools and educational settings do not seem to play an important role in transmission of COVID-19 in general, virus transmission by asymptomatic and pre-symptomatic children is possible. Therefore, a well-implemented testing strategy in school settings might play an important role in preventing virus transmission within the school setting and to the community.

Objective of testing in schools

The current document proposes guidelines for testing for SARS-CoV-2 in schools based on the ECDC surveillance strategy objectives for COVID-19 [4,6,7] and ECDC's publication 'COVID-19 in children and the role of school settings in COVID-19 transmission' [4]. The following objectives could be considered relevant for testing in school settings:

- to ensure early identification of cases among students and staff in order to conduct contact tracing and initiate prevention and control measures, thereby reducing further transmission;
- to identify infection in students and staff at high risk of developing severe disease due to underlying conditions;
- to support investigations and studies concerning the role of children in the transmission of COVID-19.

A protocol for the investigation of COVID-19 transmission in schools and other educational institutions is available as part of the World Health Organization's Unity studies [8].

Testing guidance

All students and staff showing symptoms compatible with COVID-19 should be tested for SARS-CoV-2 in accordance with ECDC's testing strategy [6] and current laboratory testing guidance [9]. The symptoms include acute respiratory tract infection (sudden onset of at least one of the following: cough, fever, shortness of breath) or sudden onset of anosmia, ageusia or dysgeusia.

Contact tracing should be initiated promptly following identification of a confirmed case and should include contacts in the school (students, teachers and other staff), household and other settings as relevant, in accordance with ECDC or national guidance [10].

Asymptomatic persons identified as high-risk exposure (close) contacts of cases (Table 1) during contact tracing could be considered for SARS-CoV-2 testing. This allows for prompt isolation of new potential cases and early contact tracing of the contacts of these new cases.

If testing capacity is limited, the following groups should be prioritised for testing:

- symptomatic students and staff that are at high risk of developing severe disease due to age or pre-existing conditions (e.g. such as lung disease, cancer, heart failure, cerebrovascular disease, renal disease, liver disease, hypertension, diabetes, and immunocompromising conditions) [9];
- symptomatic students and staff in regular contact with people who are at high risk of developing severe disease due to age, living in long-term care facilities or having the aforementioned pre-existing conditions [6].

In a situation where a nasopharyngeal or other upper respiratory specimen is not acceptable and/or to increase the acceptance of children being tested, saliva could be considered as an alternative specimen [11,12].

Contact tracing

Contact tracing [10,13] is a public health measure aiming to rapidly identify people who have been in contact with a case. The purpose of identifying and managing the contacts of probable or confirmed COVID-19 cases is to rapidly identify secondary cases, which may arise after transmission from the primary known cases, in order to intervene and interrupt further onward transmission. This is achieved by:

- promptly identifying contacts of a confirmed case of COVID-19;
- providing contacts with information on self-quarantine, proper hand hygiene and respiratory etiquette measures, and advising them on what to do if they develop symptoms;
- ensuring timely laboratory testing for SARS-CoV-2 detection among all contacts with symptoms and asymptomatic high-risk exposure (close) contacts.

Please see ECDC's guidance on contact tracing [10] for the definition of a contact person in terms of length of exposure to the infected case.

The associated risk of infection depends on the level of exposure (Table 1), which will in turn determine the type of management and monitoring.

Table 1. Classification of a contact based on level of exposure [10]

High-risk exposure (close contact)	Low-risk exposure
A person: • having had face-to-face contact with a COVID-19 case within two metres for more than 15 minutes; • having had physical contact with a COVID-19 case; • having had unprotected direct contact with the infectious secretions of a COVID-19 case (e.g. being coughed on); • who was in a closed environment (e.g. household, classroom, meeting room, hospital waiting room, etc.) with a COVID-19 case for more than 15 minutes; • travelling together (less than 2 metres proximity) with a COVID-19 case in any mode of transport for more than 15 minutes.	A person: • having had face-to-face contact with a COVID-19 case within two metres for less than 15 minutes; • who was in a closed environment with a COVID-19 case for less than 15 minutes; • travelling together (less than 2 metres proximity) with a COVID-19 case in any mode of transport for less than 15 minutes.

Longer duration of contact is assumed to increase the risk of transmission; the 15-minute limit is arbitrarily selected for practical purposes. Public health authorities may consider some persons who have had a shorter duration of contact with the case as having had high-risk exposure, based on individual risk assessments.

In the context of school settings, high-risk exposure (close) contacts are defined as follows:

- Students and staff who have shared a classroom with the confirmed case and during the same time period.
- Other students and staff with whom the confirmed case has spent time, according to the definition in Table 1 'High risk exposure' (e.g. students with whom the confirmed case have been in close proximity during breaks or sport activities, in the cafeteria, gym or school playground).
- Students and staff in boarding schools/residential schools - also those sleeping in the same room or sharing a common kitchen, social space and/or bathroom.

Low-risk exposure contacts are defined as follows:

- Other students and staff with whom the confirmed case had contact, according to the definition in Table 1 'Low-risk exposure'.
- Public health authorities may consider some children with a low-risk exposure to a case as having had high-risk exposure, based on individual risk assessments.

Public health authorities should define contacts in these circumstances in conjunction with the school authorities and ensure that any decisions are clearly translated and understood by staff, students and guardians.

Contact identification and follow up

Contact tracing should begin immediately after a confirmed case has been identified to avoid any delays in reducing transmission through public health action, regardless of whether the confirmed case is a child, teacher or other member of school staff. Contact tracing should be carried out by local public health authorities, who may need to work closely with school authorities when the contact tracing involves a school. Contacts should be managed based on their exposure category, as outlined in the ECDC guidance on contact tracing, and this includes quarantine for high-risk exposure contacts [10]. Information should be given to parents about the symptoms to look out for in children, as well as where to access testing and medical advice. If symptoms occur in contacts they should immediately be isolated and provided with medical attention and promptly tested.

Children should quarantine and not attend school for 14 days if they live in a household with someone who has been confirmed to have COVID-19.

For further details on quarantine recommendations, see ECDC's guidance on contact tracing [10].

Consulted experts (in alphabetical order)

Cornelia Adlhoch, Eeva Broberg, Stefania De Angelis, Joana Gomes Dias, Erika Duffell, Maria Keramarou, Pete Kinross, Csaba Ködmön, Katrin Leitmeyer, Hanna Merk, Angeliki Melidou, Lina Nerlander, Pasi Penttinen, Emmanuel Robesyn, Gianfranco Spiteri, Ivo Van Walle.

References

1. European Commission/EACEA/Eurydice. The Structure of the European Education Systems 2018/19: Schematic Diagrams [Internet]. Luxembourg: Publications Office of the European Union; 2018. Available from: https://eacea.ec.europa.eu/national-policies/eurydice/sites/eurydice/files/the_structure_of_the_european_education_systems_2018_19.pdf.
2. Mossong J, Hens N, Jit M, Beutels P, Auranen K, Mikolajczyk R, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Med. 2008 Mar 25;5(3):e74.
3. Posfay-Barbe KM, Wagner N, Gauthey M, Moussaoui D, Loevy N, Diana A, et al. COVID-19 in Children and the Dynamics of Infection in Families. Pediatrics. 2020 May 26.
4. European Centre for Disease Prevention and Control (ECDC). COVID-19 in children and the role of school settings in COVID-19 transmission: ECDC; 2020. Available from: https://www.ecdc.europa.eu/en/covid-19-pandemic.
5. Heald-Sargent T, Muller WJ, Zheng X, Rippe J, Patel AB, Kociolek LK. Age-Related Differences in Nasopharyngeal Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Levels in Patients With Mild to Moderate Coronavirus Disease 2019 (COVID-19). JAMA Pediatrics. 2020.
6. European Centre for Disease Prevention and Control (ECDC). Strategies for the surveillance of COVID-19 2020. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/COVID-19-surveillance-strategy-9-Apr-2020.pdf.
7. European Centre for Disease Prevention and Control (ECDC). Coronavirus disease 2019 (COVID-19) in the EU/EEA and the UK– ninth update 2020. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-rapid-risk-assessment-coronavirus-disease-2019-ninth-update-23-april-2020.pdf.
8. Lavezzo E, Franchin E, Ciavarella C, Cuomo-Dannenburg G, Barzon L, Del Vecchio C, et al. Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. Nature. 2020 Jun 30.
9. European Centre for Disease Prevention and Control (ECDC). Testing strategies 2020. Available from: https://www.ecdc.europa.eu/en/covid-19/surveillance/testing-strategies.
10. European Centre for Disease Prevention and Control (ECDC). Contact tracing: public health management of persons, including healthcare workers, having had contact with COVID-19 cases in the European Union – second update 2020. Available from: https://www.ecdc.europa.eu/en/covid-19-contact-tracing-public-health-management.
11. Wyllie AL, Fournier J, Casanovas-Massana A, Campbell M, Tokuyama M, Vijayakumar P, et al. Saliva is more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs. medRxiv. 2020:2020.04.16.20067835.
12. Czumbel LM, Kiss S, Farkas N, Mandel I, Hegyi AE, Nagy AK, et al. Saliva as a Candidate for COVID-19 Diagnostic Testing: A Meta-Analysis. medRxiv. 2020:2020.05.26.20112565.
13. European Centre for Disease Prevention and Control (ECDC). Contact tracing for COVID-19: current evidence, options for scale-up and an assessment of resources needed 2020. Available from: https://www.ecdc.europa.eu/en/publications-data/contact-tracing-covid-19-evidence-scale-up-assessment-resources.
14. European Centre for Disease Prevention and Control (ECDC). Guidance for discharge and ending isolation in the context of widespread community transmission of COVID-19 – first update 2020. Available from: https://www.ecdc.europa.eu/en/publications-data/covid-19-guidance-discharge-and-ending-isolation.

From: "Mielke, Martin" <MielkeM@rki.de>
To: "Mielke, Martin" <MielkeM@rki.de>
Date: 2/25/2021 7:49:00 AM
Subject: Fortgang der Diskussion zu AG-Testen (Bev lkerung)
Attachments: 20210222_Ruckkehr vo~uern und Gasten.pdf
23.02.2021_Flussdiagramm SARS-CoV-2 direkter Erregernachweis.pptx

---

Liebe Kolleginnen und Kollegen,

In Fortführung der Überlegungen zum Thema - AG-Tests für alle - sende ich 2 Grafiken in der Anlage (Flussdiagramm) und Links zu aktuell relevanten Dokumenten.

EpiBull 8/2021 : https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2021/Ausgaben/08_21-Selbsttests.pdf?__blob=publicationFile

Testkriterien: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Teststrategie/Testkriterien_Herbst_Winter.html;jsessionidÌ6F316D91528CE9B0740F9A016422F8.internet072?nn#86228

Hinweise zur Testung: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Vorl_Testung_nCoV.html;jsessionidÌ6F316D91528CE9B0740F9A016422F8.internet072?nn#86228

Nationale Teststrategie: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Teststrategie/Nat-Teststrat.html;jsessionidÌ6F316D91528CE9B0740F9A016422F8.internet072?nn#86228

Schulen: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Teststrategie/Testkriterien-Schulen.pdf?__blob=publicationFile

Ich denke es ist gut, folgende Lebensbereiche in diesem Zusammenhang im Blick zu haben, sowie den jeweils zu erzielenden Zusatznutzen:

1) Gesundheitstssektor (s. Nationale Teststrategie)
2) Kitas/ Schulen (indirekt damit Familien; s. Aktualsierung der Nationalen Teststrategie)
3) Betriebliche Konzepte (Betriebsarzt/ Hygienekonzept; " " HACCP-Konzept " " ; s. Aktualisierung der Nationalen Teststrategie)

4) Privater Bereich/ Öffnung (Reiseveranstalter, Konzert, Theater, Kino, Sport, Chor, etc.; s. Anlage " " Rückkehr ..... " " Punkt 3.4 ; Teststrategie; Nachweis von Genesung/ Impfung).

Zitat aus der Anlage " " Rückkehr .... " " :
Punkt 3.4: " " Ein negativer Antigentest kann eine Infektion nie zu 100% ausschließen. Das Risiko eines Ereignisses mit massenhaften Ansteckungen (?Superspreading?) wird ? insbesondere in Kombination mit der Maskenpflicht ? hierdurch jedoch auf ein Minimum reduziert. Um die höchstmöglichste Sicherheit zu gewährleisten, behält das Testergebnis nur für den Tag seiner Durchführung Gültigkeit. Ein negativer Antigentest kann somit niemals für mehrere Tage einen Zugang zu einer Veranstaltung ermöglichen. " "
Die grundlegende hier geschilderte Vorgehensweise entspricht beispielsweise auch der Empfehlung der Bundesregierung bei Zugang zu einem Pflegeheim: Schutz der Risikogruppen durch Antigentest bei den Besuchern (und ggf. Mitarbeitern). Ähnliche Vorgehensweisen mit einem Testkonzept sind auch
bei anderen Veranstaltungsformaten ? beispielsweise ohne feste Sitzplatzzuordnung ? möglich und umsetzbar. " "

Wissenschaftliche Begleitung

B-FAST: Ich habe Kontakt zu B-FAST. Dort ist ggf. die Region Kinzigtal eine geeignete Modellregion.

https://www.b-fast-umm.de/arbeitsumfeld/

QUALITÄT DER TESTE: Die Qualität der AG-Tests ist noch sehr unterschiedlich. Im März wird es einen Ringversuch von INSTAND e.V. geben.

SURVEILLANCE-SYSTEME: Ferner ist die Kenntnis der Untererfassung in unseren Surveillance-Systemen von Bedeutung. Wer infiziert sich aktuell wo mit welcher Variante ? Wieviele Fälle bleiben unerkannt ?

Bericht der AG Testkapazität (Juli 2020)
https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Laborkapazitaeten.html;jsessionidC6F316D91528CE9B0740F9A016422F8.internet072?nn#86228
Auszüge:
Die zuverlässige Identifizierung Infizierter durch entsprechende Tests ist weltweit die Basis für ein genaues Lagebild und Maßnahmen zur Eindämmung der Pandemie. Die Tests sind außerdem Grundlage für die adäquate Diagnose und Behandlung von Betroffenen, das Meldewesen, die Surveillance sowie für Screeningmaßnahmen in definierten Populationen. Das koordinierte Zusammenwirken aus der niederschwelligen Testung Krankheitsverdächtiger, der konsequenten Nachverfolgung von Ansteckungsverdächtigen und der Aufmerksamkeit für Risikopopulationen z.B. in Heimen und Krankenhäusern stellt Basis und tragende Säulen einer Teststrategie dar. Diese wird flankiert durch Studien, wie etwa seroepidemiologische Erhebungen in bestimmten Kontexten und Regionen.

Das Zusammenspiel sollte im Hinblick auf effiziente Abläufe transparent und optimiert sein.
Die Steuerung von Maßnahmen zur Eindämmung der Pandemie (wie z.B. Hygienemaßnahmen, Abstandsregeln, Kontaktbeschränkungen, Quarantäne) beruht auf einer Lagebewertung mittels:-Testungen zur Erkennung akuter Infektionsfälle, gefolgt von Meldung und Kontaktnachverfolgung durch den öffentlichen Gesundheitsdienst sowie-Studien (Erhebungen),bei denen es nicht um individuelle Diagnosen, sondern um die Gewinnung von Erkenntnissen zum Infektionsgeschehen in einer Region oder Gruppe von Menschengeht. Ein bevölkerungsweites Screening kann zunächst attraktiv erscheinen, findet seine Begrenzung jedoch an den Testkapazitäten sowie dem daraus ableitbaren Erkenntnisgewinn und den Leistungsparametern der jeweils verwendeten Tests. So geht bei niedriger Prävalenz, wie sie aktuell vorliegt und auch nur geringgradig eingeschränkter Spezifität ein ungezieltes Testen mit einer relevanten Zahl von falsch-positiven Befunden einher. Die Herausforderung besteht somit in einer Optimierung des Einsatzes der Teste unter Berücksichtigung der erforderlichen Datenbasis, der epidemiologischen Situation und den zur Verfügung stehenden Testkapazitäten.

Die Identifizierung von mit SARS-CoV-2 akut infizierten Menschenergänzt die generellen Vorsichtsmaßnahmen (Abstand, MNS, Händehygiene) zur Verminderung der Krankheitslast durch COVID-19. Diese Erkennung basiert auf der Aufmerksamkeit für Krankheitssymptome(Symptommonitoring) sowie auf dem laborbasierten Nachweis einer (akuten) Infektion, insbesondere in Bereichen, in denen Risikopatientenbehandelt oder gepflegt werden (z.B. Krankenhäuser sowie Alten-oder Pflegeheime).Ein positives Testergebnis hat Bedeutung für die medizinische Beurteilung sowie für ggf. durch den ÖGD einzuleitende infektionspräventive Maßnahmen.

Ein einzelnes negatives Testergebnis schließt eine Infektion nicht sicher aus und bedarf entsprechend der Empfehlungen zum anlassbezogenen Testen gegebenenfalls einer Überprüfung. Untersuchungen symptomfreier Personen zur Früherkennung einer Infektion (beispielsweise bei Mitarbeiterinnen/ Mitarbeitern im Gesundheitswesen) ersetzen nicht die Einhaltung präventiver Maßnahmen einschließlich erweiterter Basishygiene in Einrichtungen des Gesundheitswesens. Diese Früherkennungsuntersuchungen sind immer nur eine (rückblickende) Momentaufnahme.

Gruß,
Martin Mielke

PS:
The effectiveness of population-wide, rapid antigen test based screening in reducing SARS-CoV-2 infection prevalence in Slovakia

https://www.medrxiv.org/content/10.1101/2020.12.02.20240648v1?rss

Paper von Larremore modelliert frequent testing:

These results demonstrate that effective surveillance, including time to first detection and outbreak control, depends largely on frequency of testing and the speed of reporting, and is only marginally improved by high test sensitivity. We therefore conclude that surveillance should prioritize accessibility, frequency, and sample-to-answer time; analytical limits of detection should be secondary

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7325181.2/

Schrittweise Rückkehr von Zuschauern und Gästen:

Ein integrierter Ansatz für Kultur und Sport

Stand: 22.02.2021

Die nachfolgende Konzeption wurde interdisziplinär entworfen, um für die Kultur- und Sportbranche einen **risikominimierenden Weg zur Rückkehr von Gästen und Zuschauern** aufzuzeigen. Dabei wird ein mehrstufiges Konzept skizziert, welches in der Breite für jede Kultur- und Sportstätte funktionieren kann und gleichzeitig die Anpassung an individuelle Situationen ermöglicht. Der Leitfaden entstand unter Mitwirkung von Experten aus der **Hygiene- und Umweltmedizin**, **Mikrobiologie und Virologie**, **Infektiologie**, dem **Crowdmanagement**, der **Sportmedizin** und den **Kultur-** und **Rechtswissenschaften** sowie der **Raumlufttechnik** und **Gesundheitsökonomie**.

Mitwirkende (in alphabetischer Reihenfolge)

Marcel Altenburg, MSc MA (Lehrstuhl Crowd Science, Manchester Metropolitan University)

Prof. Dr. Roland Eils (BIH-Zentrum Digitale Gesundheit , Charité – Universitätsmedizin Berlin)

Prof. Dr. Lutz Fritsche (Facharzt für Innere Medizin, Vorstand Johannesstift Diakonie, Berlin)

Prof. Dr. Barbara Gärtner (Fachärztin für Mikrobiologie und Infektionsepidemiologie, Universitätsklinikum des Saarlandes)

Prof. Dr. Petra Gastmeier (Fachärztin für Hygiene und Umweltmedizin, Charité – Universitätsmedizin Berlin)

Dr. Oliver Harzer MBA (Facharzt für Laboratoriumsmedizin, Gesundheitsökonom, Ingelheim)

Prof. Dr. Frank Heppner (Facharzt für Neuropathologie, Charité – Universitätsmedizin Berlin)

Dr. Florian Kainzinger (Gesundheitsökonom, Berlin; *Koordinator*)

Prof. Dr. Martin Kriegel (Hermann-Rietschel-Institut, Technische Universität Berlin)

Priv.-Doz. Dr. Matthias Krüll (Facharzt für Innere Medizin, Pneumologie und Infektiologie, Berlin)

Christoph Lassahn, MD (Facharzt für Hygiene und Umweltmedizin, Hannover)

Prof. Dr. Tim Meyer (Institut für Sport und Präventivmedizin, Universität des Saarlandes)

Dr. Heinz-Jörn Moriske (Geschäftsführung Innenraumlufthygiene-Kommission am Umweltbundesamt, Dessau-Roßlau)

Prof. Dr. Peter Raue (Rechtsanwalt, Berlin)

Prof. Dr. Wolfgang Schade (Fraunhofer Heinrich-Hertz-Institut, Goslar)

Prof. Dr. Wolfgang Spoerr (Rechtsanwalt, Berlin)

Katja Wilhelm, MD (Ärztin, München)

Dr. Katharina Wodarz (Rechtsanwältin, Berlin)

Prof. Dr. Bernd Wolfarth (Sportmedizin, Charité – Universitätsmedizin Berlin)

Dr. Georg-Christian Zinn (Facharzt für Hygiene und Umweltmedizin, Ingelheim)

I. Einleitung

Seit dem Frühjahr 2020 ist die Welt den Einflüssen der COVID-19-Pandemie ausgesetzt. Infektionsrisiken mit dem SARS-CoV-2-Erreger haben fast in allen Ländern dazu geführt, dass der Kulturbetrieb, Breiten- und Amateursport sowie Profiligen ihren Betrieb zwischenzeitlich oder gänzlich einstellen mussten und auch bei einer Wiederaufnahme des Betriebs noch immer ohne Gäste bzw. Zuschauer auskommen müssen.

Viele Sportligen haben ab Mai/Juni 2020 auf der Grundlage von mit den jeweiligen Behörden abgestimmten Hygienekonzepten den Betrieb wieder aufgenommen und konnten teilweise im Sommer 2020 wieder vor einer begrenzten Zuschauerzahl spielen. Der Kulturbereich durfte ebenfalls unter Einschränkungen in manchen Bundesländern wieder Veranstaltungen durchführen. Viele Darbietungsformate waren jedoch im ganzen Jahr 2020 nicht mehr möglich (u.a. Konzerte, Clubveranstaltungen).

Infolge des zweiten „Lockdowns“ im November 2020 wurden Kulturveranstaltungen unabhängig von bestehenden Hygienekonzepten deutschlandweit wieder eingestellt, Profisportligen mussten zum ausschließlichen „Geisterspielbetrieb“ unter Ausschluss von Zuschauern zurückkehren.

Durch die erneuten starken Einschränkungen im öffentlichen Leben konnte der Anstieg der Infektionszahlen Ende 2020 gebremst werden. Seit Dezember 2020 sind europaweit Impfstoffe gegen eine COVID-19-Erkrankung verfügbar, die schrittweise der Bevölkerung zur Verfügung gestellt werden.

Für den organisierten Profisport, den Breitensport sowie für die gesamte Kulturbranche war das Jahr 2020 mit erheblichen Einschränkungen und Verlusten verbunden – nicht nur wirtschaftlicher Natur, sondern auch auf emotionaler Ebene. Denn durch die Einstellung des Spielbetriebs oder die Durchführung von nur medial übertragenen Ereignissen droht ein großer emotionaler und kultureller Verlust der Bindung zwischen Besuchern, Zuschauern und Aktiven.

Durch den Beginn der Impfungen ist gleichzeitig der Einstieg in die vermutlich letzte Phase der Pandemie gelungen. Unzweifelhaft wird sich der gesamte Prozess bis zu einem ausreichenden Impfschutz der Risikogruppen und gesamten Bevölkerung viele Monate hinziehen (voraussichtlich bis Spätsommer 2021).

Da nicht mit einem stichtagsbezogenen, abrupten Ende der Pandemie zu rechnen ist, müssen jetzt geeignete Konzepte mit ausreichendem Vorlauf entworfen werden, um allen Kultur- und Sportsparten mit Zuschauerpartizipation den sicheren, schrittweise erfolgenden und nachhaltigen Weg zurück in eine Normalität zu ermöglichen. Eine Normalität, die die jeweilige epidemische Lage in

Abstimmung mit den politisch Verantwortlichen und den Gesundheitsbehörden berücksichtigt. Es geht also darum eine ausbalancierte Situation herzustellen, die Aspekte des Gesundheitsschutzes und insbesondere die Lage in den Kliniken berücksichtigt, andererseits verantwortungsbewusste Veranstaltungen mit Zuschauern zu ermöglichen. Wegen der ständig neuen Erkenntnisse der Wissenschaft und Entwicklungen (z.B. von Impfstoffen), aber auch dem Auftreten und der Verbreitung neuer Varianten des SARS-CoV-2-Virus (*variants of concern*, VOCs) mit modifizierten Eigenschaften, sprechen wir hier von einem *dynamischen Konzept*, das engmaschig weiterentwickelt wird. Die VOCs haben grundsätzlich denselben Übertragungsweg und sind daher auch denselben Präventionsmaßnahmen zugänglich.

Die hier vorliegende Konzeption spannt einen Bogen von der Organisation allgemeiner Breitenveranstaltungen (einfach und praktikabel umzusetzen bei insgesamt geringen Kosten) bis hin zu aufwändigen Spezialkonzepten für individuelle Veranstaltungen, um so dem gesamten Spektrum der mannigfaltigen Ansprüche gerecht zu werden bzw. diese angemessen abzudecken. Sämtliche Annahmen wurden unter Einbeziehung verschiedener hierfür notwendiger Expertisen entwickelt, darunter die Infektionsmedizin, die Raumlufttechnik, die Veranstaltungsorganisation sowie das Kultur- und Sportmanagement. Die Ergebnisse bereits bestehender wissenschaftlicher Untersuchungen - wie beispielsweise der RESTART-19 Studie der Universitätsmedizin Halle (Saale) oder des Fraunhofer Heinrich-Hertz-Instituts am Konzerthaus Dortmund - untermauern die hier getroffenen Empfehlungen (u.a. *Schade et al. 2020, Moritz et al. 2020*). Weitere Vertreter der Veranstaltungs- und Eventbranche haben in den vergangenen Wochen eigene Konzeptionen auf den Weg gebracht, die in einer Gesamtwürdigung durch die Politik und Entscheidungsträger einfließen sollten (vgl. *https://forumveranstaltungswirtschaft.org*).

Den Autoren ist bewusst, dass durch die Umsetzung der hier beschriebenen Maßnahmen Infektionen jeglicher Art nicht zu 100% ausgeschlossen werden können. Dies entspricht jedoch der Realität in nahezu allen Bereichen des täglichen Lebens. Es gilt jedoch, eine Abwägung verschiedener Risikobereiche vorzunehmen und durch verantwortungsbewusste Entscheidungen einmalige Kultur- und/oder Sportbereiche bzw. -veranstaltungen und die damit verbundenen Arbeitsplätze zu schützen. Zudem gilt es, den emotionalen, soziokulturellen und wirtschaftlichen Totalverlust durch das Fehlen von Vorort-Zuschauern und den damit verbundenen Konsequenzen soweit wie möglich zu vermeiden.

II. Grundlagen

2.1 Grundlagen von Übertragungswegen

Der Hauptübertragungsweg für SARS-CoV-2 von Mensch zu Mensch ist die respiratorische Aufnahme virushaltiger Partikel, die beim Atmen, Husten, Sprechen, Singen und Niesen entstehen. Je nach Partikelgröße wird zwischen den größeren Tröpfchen und kleineren Aerosolen unterschieden, wobei der Übergang zwischen beiden Formen fließend ist.

Größere respiratorische Partikel in Form von Tröpfchen entstehen hauptsächlich beim Husten und Niesen und sinken aufgrund ihrer physikalischen Eigenschaften schnell zu Boden. Klassische Aerosole werden beim Atmen und Sprechen sowie verstärkt beim Schreien und Singen freigesetzt. Im Gegensatz zu Tröpfchen können Aerosole auch über längere Zeit in der Luft schweben und sich in geschlossenen und schlecht durchlüfteten Räumen verteilen.

Grundsätzlich ist die Wahrscheinlichkeit einer Exposition gegenüber infektiösen Partikeln jeglicher Größe und deren Aufnahme über die Schleimhäute von Mund und Nase oder Augen im Umkreis von 2 bis 3 Metern um eine infizierte Person herum erhöht. Bei längerem Aufenthalt kann eine Übertragung in kleinen, schlecht gelüfteten Räumen stattfinden – jedoch nach aktuellen wissenschaftlichen Erkenntnissen ebenso in Räumen mit guter Belüftung. Neben verschiedenen anderen Kriterien ist insbesondere die Menge der im Raum übertragenen Aerosole für die Wahrscheinlichkeit einer Infektion entscheidend. Durch die Anreicherung und Verteilung der Aerosole im Raum ist das Einhalten des Mindestabstandes zur Infektionsprävention ggf. nicht mehr ausreichend. Dagegen kann durch einen effektiven Luftaustausch die Aerosolkonzentration in einem Raum vermindert werden. Insbesondere scheinen hier eine vertikale Frischluftzufuhr (Zufuhr von Frischluft am Boden und Abzug flächig in der Decke verteilt) sowie eine Luftaustauschrate (*air exchange rate per hour*, ACH) von ACH>=3 sehr effizient zu sein (*Schade et al. 2020*).

Im Außenbereich kommen Übertragungen aufgrund der Luftbewegung und des Verdünnungseffektes insgesamt wesentlich seltener vor. Bei Wahrung des Mindestabstandes ist die Übertragungswahrscheinlichkeit im Außenbereich sehr gering.

Da vermehrungsfähige SARS-CoV-2-Viren unter Laborbedingungen auf Flächen einige Zeit infektiös bleiben können, ist auch die Möglichkeit einer Übertragung durch kontaminierte Oberflächen in Betracht zu ziehen, wenngleich diese im Vergleich zur respiratorischen Aufnahme virushaltiger Partikel eine deutlich untergeordnete Rolle spielt. Dabei wird nicht unterschieden, um welchen SARS-CoV-2-Stamm es sich handelt, da die entsprechende Prävention und die vorbeugenden Maßnahmen bei allen

bekannten SARS-CoV-2 Stämmen – auch den neueren, wohl infektiöseren – gleichermaßen wirksam sind.

2.2 Hygieneschutzmaßnahmen

Durch zahlreiche wissenschaftliche Studien und Untersuchungen wurden im Laufe des Jahres 2020 Erkenntnisse zum effektiven Schutz (Risikoreduktion) vor Infektionen mit dem COVID-19-Erreger gesammelt. Die wesentlichen Ergebnisse haben die meisten Regierungen, Behörden und Institute inzwischen in allgemeingültige Regeln und Handlungsempfehlungen umgesetzt:

- **Abstand halten**, um Infektionen durch große Tröpfchen im Nahfeld (<1,5 m) zu vermeiden.
- Umfangreiche **Hygiene** durch Händewaschen, Händedesinfektion und Nies-Etikette, um manuelle Übertragungen zu unterbinden.
- **Mund-Nasen-Schutz**, um das Risiko der Übertragung durch Partikel jeglicher Größe im unmittelbaren Umfeld um eine infizierte Person zu reduzieren.
- **Effektiver Luftaustausch**, um die Aerosolkonzentration in (insbesondere geschlossenen) Räumen zu vermindern und das Risiko einer Übertragung über größere Distanzen zu reduzieren.
- **Kontakte verfolgen**, um im Ansteckungsfall Betroffene zu informieren (z.B. durch Apps) und Infektionsketten schnell aufklären und unterbrechen zu können.

Andere Maßnahmen gelten inzwischen als wenig zielgerichtet bzw. haben die wissenschaftliche Evidenz für einen Schutz nicht erreichen können (u.a. Fiebermessen, Handschuhe im allgemeinen Breiteneinsatz, Desinfektionsmaßnahmen von Oberflächen).

Im Rahmen der Konzeption von Veranstaltungsformaten mit Zuschauern und Gästen müssen die verfügbaren Hygieneschutzmaßnahmen sinnvoll eingesetzt und adaptiert werden. Die nachfolgend entworfene Struktur skizziert dies in mehreren Komplexitätsstufen – von einfach umsetzbaren Allgemeinmaßnahmen bis zu spezifischen Anwendungen in den jeweiligen Veranstaltungsstätten.

2.3 Annahmen zur Impfung

Um die Corona-Pandemie langfristig zu kontrollieren, bedarf es einer sicheren Immunität gegen SARS-CoV-2 für einen Großteil der Bevölkerung. Diese entsteht durch natürliche Infektion mit SARS-CoV-2 oder SARS-CoV-2-spezifische Impfung. Da versucht wird, natürliche Infektionen einzudämmen, kann nur durch eine flächendeckende und effektive SARS-CoV-2-Impfung in einem akzeptablen Zeitrahmen eine ausreichende Immunität erreicht werden.

Aktuell existieren in der Europäischen Union drei zugelassene Impfstoffe und zahlreiche weitere Impfstoffkandidaten befinden sich in der Entwicklung, Prüfung oder Zulassung. Es werden größte Anstrengungen unternommen, die Produktionskapazitäten der existierenden Impfstoffe auszuweiten und die gerechte Verteilung und Anwendung im Sinne der nationalen Impfstrategie umzusetzen. Die erste Zulassung erfolgte am 21.12.2020 und der Impfstart wurde in Deutschland auf den 27.12.2020 datiert. Aufgrund der derzeit noch begrenzten Impfstoffverfügbarkeit wurde unter Einschluss der Empfehlungen der Ständigen Impfkommission (STIKO) eine Priorisierung für die Impfung festgelegt (und ab 08.02.2021 auf Basis der Zulassung des dritten Impfstoffes aktualisiert). Diese sieht vor, dass vulnerable Personengruppen mit besonders erhöhtem Risiko für schwere oder tödliche Verläufe einer COVID-19-Erkrankung (Bewohner von Senioren- und Altenpflegeheimen, Personen über 80 Jahre), Personal mit besonders hohem Expositionsrisiko in medizinischen Einrichtungen und Personal mit besonders engem Kontakt zu vulnerablen Personengruppen prioritär geimpft werden. Allein diese erste Gruppe mit der „höchsten“ Priorität umfasst ca. 8,6 Millionen Menschen in Deutschland. Für diese ist der Impfzeitraum vom Januar bis ca. April 2021 vorgesehen. Darauf sollen ab ca. Mai 2021 12,7 Millionen Menschen der Gruppe 2 (Priorität hoch) folgen und anschließend die Menschen der Gruppe 3 (Priorität erhöht).

In der Realität konnten bis zum 20.02.2021 kumulativ 3.179.290 Personen in Deutschland mit mindestens der Erstdosis geimpft werden, darunter >760.000 Bewohner von Alten- und Pflegeheimen. Allein die letztgenannte Gruppe macht ca. ein Drittel der bisherigen Todesfälle in Verbindung mit SARS-CoV-2 in deutschen Krankenhäusern aus. Somit sind aktuell bereits >95% der ca. 800.000 Bewohner in deutschen Pflegeheimen geimpft (min. Erstdosis).

Generell können aktuell nur schwer Prognosen zum Impfverlauf und der relevanten Abdeckung der Bevölkerung aufgestellt werden (es ist nicht davon auszugehen, dass die Impfbereitschaft 100% der Bevölkerung umfasst). Mit Zulassung weiterer Impfstoffe, einer ausgeweiteten Produktion zugelassener Impfstoffe, einer Steigerung des Durchsatzes in den Impfzentren und einer veränderten Impfstrategie (z.B. durch das Hinauszögern der zweiten Impfung) ist jedoch davon auszugehen, dass zumindest bis Ende April ein Großteil der Risikogruppe 1 geimpft sein wird (Stand 20.02.2021: ca. 25%).

In Zusammenschau der genannten Aspekte ist davon auszugehen, dass trotz Impfstoffs kein zeitnahes Ende der Erregerverbreitung in Sicht ist. Hochrisikogruppen und Risikogruppen werden jedoch zunehmend geschützt sein und damit ist davon auszugehen, dass die Krankheitslast (insbesondere in Krankenhäusern und auf Intensivstationen) signifikant sinkt. Ca. 69% der bis dato in Deutschland aufgetretenen Todesfälle stammen aus der Altersgruppe >80 Jahre, die mit der ersten Priorität bis Frühjahr 2021 ein Impfangebot erhält und damit geschützt sein soll (*Quelle: RKI*).

Sobald dieses Ziel (Reduktion der Krankenhausbelastung) erreicht ist, sind Einschränkungen des öffentlichen Lebens und der Freiheitsrechte nicht mehr ohne Weiteres zu rechtfertigen. Um in der Saison 2021 für den Kultur- und Sportbereich einem weiteren ideellen und ökonomischen Ausfall entgegenzuwirken und Veranstaltungen im Rahmen des Möglichen mit einem Höchstmaß an Sicherheit stattfinden zu lassen, ist es daher unerlässlich, adäquate Konzepte zu erstellen, welche suffizienten Infektionsschutz und Diagnostik umfassen und damit verschiedene Interessenslagen in Einklang miteinander bringen.

III. Konzeption einer schrittweise erfolgenden Rückkehr von Zuschauern und Gästen zu Kultur- und Sportveranstaltungen

Das vorliegende Konzept versucht, einen Bogen über unterschiedlichste Veranstaltungsformen zu spannen, will dabei Veranstaltungen in geschlossenen oder offenen Räumen und solche mit geringen bis großen Teilnehmerzahlen einbeziehen. Dies geschieht unter Berücksichtigung verschiedener Budgetmöglichkeiten.

3.1 Ausschluss von Zuschauern bei Überlastung des Gesundheitswesens

In der Vergangenheit wurde – insbesondere unter Verweis auf die begrenzten Kapazitäten und Ressourcen im Gesundheitswesen – an vielen Stellen in der Pandemiebekämpfung das Erreichen eines Zielwerts i.H.v. maximal 50 Neuerkrankungen pro 100.000 Einwohner in 7 Tagen als höchste Priorität und politische Richtschnur ausgegeben (inzwischen teilweise 35 Neuerkrankungen). Auch der Sport sowie die Kultur haben sich in diese Struktur eingefügt und in eigenen Konzepten entsprechende Beschränkungen bei steigender Inzidenz eingefügt.

Aus Sicht der Autoren dieses Konzepts müssen die genannten Zielwerte mit einem Fortschreiten der Erkenntnisse sowie insbesondere dem kontinuierlich steigenden Impfschutz, vor allem der Risikogruppen, angepasst oder abgeschafft werden. Alternative Ziele, wie beispielsweise die Auslastung der Krankenhäuser oder die Inzidenz in speziellen Altersgruppen, müssen vermehrt in den Blick genommen werden. Dies ist besonders notwendig, weil mit der Impfung von Risikogruppen, sich die Infektionszahlen nicht mehr parallel zur Belastung des Gesundheitswesen bewegen werden. Wesentliche Grundlage für die Einschränkung von Freiheitsrechten soll die Krankheitslast auf Intensivstationen und in Krankenhäusern sein. Dafür sind geeignete Messgrößen zu entwickeln, die bei der Überschreitung von Maximalwerten auch den Ausschluss von Zuschauern und Gästen bei Veranstaltungen bedeuten können. Die Corona-Ampel in Berlin kann hierfür ein gutes Vorbild sein – beispielsweise unter Anpassung der Inzidenzbetrachtung auf die Altersgruppen von 60 bis 79 Jahren und die Altersgruppe 80+. Risikogruppen in jüngeren Jahrgängen werden über die Messgrößen der Belastung des Gesundheitssystems adäquat integriert.

3.2 Konzeption ohne spezielle unterstützende Maßnahmen (Basiskonzept)

Der vorliegende Leitfaden sieht ein Basiskonzept zur Rückkehr von Zuschauern und Gästen vor, welches insbesondere auch bei Veranstaltungen mit begrenzten finanziellen Ressourcen zur Anwendung kommen kann. Es wird hierbei zwischen Veranstaltungen in geschlossenen Räumen und Freiluftveranstaltungen mit Sitzplatzvergabe unterschieden. Eine Differenzierung nach Impfstatus oder Inzidenzlevel erfolgt an dieser Stelle nicht.

a.) Veranstaltungen in geschlossenen Räumen (Indoor)

Zu Veranstaltungen in geschlossenen Räumen zählen beispielsweise Kulturveranstaltungen in Konzerthäusern, Theatern und Opern oder Sportevents in Hallen bzw. Arenen. Auch ein Übertrag auf andere Veranstaltungen in geschlossenen Räumlichkeiten, beispielsweise Kongresse oder Gottesdienste, kann hier vorgenommen werden. Für ein Allgemeinkonzept, das nicht auf die Spezifika der jeweiligen Lokalität eingeht, muss – um einen möglichst hohen Infektionsschutz zu erreichen – ein hoher Mindeststandard auf Basis der im einleitenden Kapitel definierten Hygieneschutzmaßnahmen etabliert werden.

Im Spätsommer 2020 war den Ausrichtern von Profisportveranstaltungen bereits die Rückkehr von bis zu 20% der maximalen Zuschauerkapazität gestattet – auch in Kultureinrichtungen wurden Gäste bei stark reduzierter Sitzzahl wieder zugelassen. Gemeinsam fanden in der Basketball Bundesliga (BBL) und der Handball Bundesliga (HBL) sowie den dazugehörigen internationalen Wettbewerben insgesamt 61 Spiele vor Zuschauern mit einer vorhandenen Datenbasis statt. Diese Spiele wurden von insgesamt 57.934 Zuschauern besucht. Zu keinem der Spiele ist den Ausrichtern bzw. Ligen ein Infektionsfall mit Übertragungsgeschehen bekannt – in keinem Fall kam es zu Kontaktnachverfolgungen durch die Gesundheitsbehörden bzw. Anfragen zu Ticket- und Platzdaten. Bei allen Veranstaltungen wurden umfangreiche Hygienekonzepte etabliert, Abstandsregeln eingeführt und überwacht sowie eine weitgehende Maskenpflicht umgesetzt. Auf Basis der vorhandenen Erkenntnisse sind keine daraus resultierenden Ausbruchsereignisse oder „Superspreading-Events“ bekannt.

Bei voranschreitender Impfung der Risikogruppen sowie auf Basis der wissenschaftlichen Daten zu Hygieneschutzmaßnahmen, Indoor-Aerosolverteilungen (*Bazant 2021*) und der Grundlage der

Erfahrungen aus dem Spätsommer 2020 können folgende Eckpunkte für Veranstaltungen in geschlossenen Räumen formuliert werden:

- Erstellung eines Hygiene-, Lüftungs- und Infektionsschutzkonzeptes für den Veranstaltungsort.
- Maximal 25-30% der Gesamtauslastung durch Zuschauer bei Anwendung des nachfolgend geschilderten „Empfehlungsmodells“ (**so dass die allgemeinen Abstandsregeln weitgehend eingehalten werden können**) – eine Steigerung über die bisher zugelassenen 20% im Spätsommer 2020 kann über den steigenden Schutz der Risikogruppen und die nach wie vor vorhandene Einhaltung von Abstandsregeln begründet werden.
- Tickets werden ausschließlich personalisiert vergeben, um eine Kontaktverfolgung zu ermöglichen (inkl. Abgleich mit dem Personalausweis beim Zugang zur Veranstaltung).
- Personen eines Haushalts können ohne Mindestabstand zusammensitzen (zwei Haushalte, wenn die jeweilige Landesverordnung den Kontakt zweier Haushalte zulässt).
- Einsatzmöglichkeit von Sitz- und Stehplätzen – Stehplätze jedoch ausschließlich in nummerierten und markierten Zonen (analog zu Sitzplätzen) und mit zusätzlichem Ordnungspersonal.
- Durchgehende Maskenpflicht unter Nutzung von mindestens OP-Schutzstandard (Mund-Nasen-Schutz).
- Kein Konsum von Speisen und Getränken im Arenabereich (Sitzbereich) bzw. Theatersaal, um eine hohe Compliance der Maskenpflicht sicherzustellen.
- Zusätzliches Ordnungspersonal zur Überwachung der Maskenpflicht und Abstände.
- Angabe von Maximalpersonenzahlen je Toiletten- und Sanitärbereich und Abstandsgebote.
- Kein Ausschank von alkoholischen Getränken bei Veranstaltungen > 1.000 Besucher.
- Ergänzende Konzepte zum Ein- und Auslass, der Pause/Halbzeit sowie der An- und Abreise.
- Einführung einer „Bagatelluntergrenze“ für Veranstaltungen im Amateur- und Breitensport: Bei Veranstaltungen mit ausreichend Flächen sollte es eine Sonderregelung mit folgenden Inhalten geben: Verpflichtendes Tragen eines MNS während der gesamten Veranstaltung, Einhaltung eines erweiterten Mindestabstands (z.B. 2,0 m), Nachweis und Nachverfolgung von Infektionsketten der Anwesenden durch z.B. eine App-Lösung, aber keine konkrete notwendige Zuordnung mit personalisierten Tickets und individueller Platzzuweisung.

Nachfolgendes Sitzplatzschema wird als genereller Standard für Veranstaltungen in geschlossenen Räumlichkeiten empfohlen.[1] Es kann von einer durchschnittlichen Sitzbreite von 50 cm ausgegangen werden, so dass bei einer entsprechenden Zahl an freien Plätzen Mindestabstände eingehalten werden.

[1] In historischen oder modernen Kulturveranstaltungsräumen bzw. Theatersälen kann es im Unterschied zu Arenen zu anderen Sitzplatzanforderungen kommen.

Benachbarte Plätze werden ausschließlich einheitlich verkauft und an Personen aus einem Haushalt vergeben (Haushaltsgruppen) bzw. an Personen aus maximal zwei Haushalten (falls ein gemeinsamer Aufenthalt bzw. ein Zusammentreffen aus zwei Haushalten im jeweiligen Bundesland gestattet ist). Zwei freie Reihen ermöglichen einen vertikalen Abstand von ca. 1,50 m.

Die Empfehlung geht ausschließlich von 4er und 2er Haushaltsgruppen aus. Sollten auch Plätze an beispielsweise 3er Haushalte oder Einzelpersonen vergeben werden, sinkt die Auslastungsmöglichkeit entsprechend. Bei Schulvorstellungen ist es möglich, Schüler wie in der Schule im Klassenverband sitzen zu lassen. Ein Sicherheitsabstand von 2,0 m sollte zur nächsten Klasse gewährleistet sein.

Das Empfehlungsmodell realisiert fast durchgehend 1,50 m Abstand zwischen Haushalten (mit geringen Einschränkungen in der Diagonale, die jedoch bei einem durchschnittlichen Neigungswinkel von 33 Grad auf Tribünen sowie einer einheitlichen Blickrichtung als wenig kritisch eingeschätzt werden kann) und ermöglicht eine theoretische Auslastung von ca. 30 % der Gesamtkapazität. Es kann ohne zusätzliche Investition in Lüftungsgutachten oder Teststrategien implementiert werden.

Empfehlungsmodell Sitzplätze Indoor

x	x	x	x					x	x	x	x
					x	x					
x	x	x	x					x	x	x	x
					x	x					
x	x	x	x					x	x	x	x
					x	x					
x	x	x	x					x	x	x	x

Das beschriebene „Basismodell“ sieht keine Unterscheidung zwischen geimpften und nicht geimpften Personen („Immunitätsnachweis“) vor. Ebenso ist eine Differenzierung nach Personen, die bereits eine COVID-19 Erkrankung durchgemacht haben und damit potenziell eine Immunität besitzen, nicht von Nöten. **Es ist somit ein allgemein anwendbares Modell zur Risikoreduktion (Abstand, Maske) bei Indoor-Veranstaltungen in einer Zeitperiode mit vertretbarer Inzidenz und steigendem Impfschutz**

der Risikobevölkerung. Zur weiteren Verfeinerung und Präzisierung sowie Risikoabschätzung können Online-Tools aus wissenschaftlichen Einrichtungen verwendet werden, um ein Infektionsrisiko in geschlossenen Räumlichkeiten abzuschätzen (z.B. https://indoor-covid-safety.herokuapp.com) oder um maximale Personenzahlen zu berechnen (vgl. z.B. Modell der TU Berlin). Weiter können zur individuellen Risikoabschätzung gezielte Untersuchungen zu Aerosolverteilungen in Abhängigkeit der jeweils installierten Belüftungsanlagen in Veranstaltungssälen durchgeführt werden (Angebot des Fraunhofer HHI).

b.) Veranstaltungen im Freiluftbereich (Outdoor)

Kultur- und Sportveranstaltungen im Freiluftbereich haben grundsätzlich eine günstigere Lüftungssituation als Veranstaltungen in geschlossenen Räumlichkeiten. Die Situation der Umluft und Luftbewegung ist ein wesentliches Kriterium, um das Ansteckungsrisiko im direkten Umfeld zu bewerten (vgl. RKI-Kriterien zum Kontaktpersonenmanagement). Analog zu Indoor-Sportveranstaltungen wurden im Spätsommer und Herbst 2020 auch beispielsweise Fußballspiele wieder ausgetragen. Insgesamt fanden 72 Spiele mit einer für diesen Zweck auswertbaren Datenbasis der Bundesliga und 2. Bundesliga statt. Diese Spiele wurden von insgesamt 250.570 Zuschauern besucht. Auch bei den hier ausgewerteten Outdoor-Veranstaltungen, die unter einem strengen Hygienemanagement stattfanden, sind keine Infektionsübertragungen oder Ausbruchsereignisse bekannt. Im Rahmen der Spiele kam es insgesamt zu drei Anfragen der zuständigen Gesundheitsämter, da zum Zeitpunkt des Spiels (nachträglich identifizierte) positiv getestete Personen das Stadion besucht hatten. In diesem Zusammenhang wurden 47 Personendatensätze an die Behörden übergeben. Zu 8 von 47 Personen liegt ein Rücklauf der Gesundheitsämter vor, dass keine Infektionen/Ansteckungen festgestellt werden konnten. Bei den weiteren 39 Personen gibt es keine Rückmeldung seitens der Behörden. Da von weiteren Behördenkontakten im Falle einer festgestellten Übertragung ausgegangen werden kann, gehen die Bundesligavereine von keinen Folgeinfektionen aus.

In Anlehnung an die Indoor-Veranstaltungen soll an dieser Stelle ein Rahmen für Kultur- und Sportevents im Freiluftbereich geschaffen werden, welcher einen allgemeingültigen Standard für beliebige Outdoor-Austragungsorte auf einem hohen Schutzniveau sicherstellt:

- Erstellung eines Hygiene- und Infektionsschutzkonzeptes für den Veranstaltungsort.
- Maximal 35-40% der Gesamtauslastung durch Zuschauer (zur Einhaltung von Abstandsregeln) – eine Steigerung über die bisher zugelassenen 20% im Spätsommer 2020 kann über den

steigenden Schutz der Risikogruppen und die nach wie vor vorhandene Einhaltung von Abstandsregeln begründet werden.

- Tickets werden ausschließlich personalisiert vergeben, um eine Kontaktverfolgung zu ermöglichen.
- Personen eines Haushalts können ohne Mindestabstand zusammensitzen (zwei Haushalte dann, wenn die jeweilige Landesverordnung den Kontakt zweier Haushalte zulässt).
- Einsatzmöglichkeit von Sitz- und Stehplätzen – Stehplätze jedoch ausschließlich in nummerierten und markierten Zonen (analog zu Sitzplätzen) und mit zusätzlichem Ordnungspersonal.
- Maskenpflicht in allen Bereichen bis zum zugeteilten Sitzplatz (Mund-Nasen-Bedeckung) oder auch durchgängig während der Veranstaltung.
- Zusätzliches Sicherheitspersonal zur Überwachung der Maskenpflicht und Abstände.
- Angabe von Maximalpersonenzahlen je Toiletten- und Sanitärbereich.
- Kein Ausschank von alkoholischen Getränken bei Veranstaltungen > 1.000 Besucher.
- Ergänzende Konzepte zum Ein- und Auslass, der Pause/Halbzeit sowie der An- und Abreise.
- Einführung einer „Bagatelluntergrenze“ für Veranstaltungen im Amateur- und Breitensport: Bei Veranstaltungen mit ausreichend Außenflächen sollte es eine Sonderregelung mit folgenden Inhalten geben: Verpflichtendes Tragen eines MNS während der gesamten Veranstaltung, Einhaltung eines erweiterten Mindestabstands (z.B. 2,0 m), Nachweis und Nachverfolgung von Infektionsketten der Anwesenden durch z.B. eine App-Lösung, aber keine konkrete notwendige Zuordnung mit personalisierten Tickets und individueller Stehplatzzuweisung.

Die vorgenannten Eckpunkte gelten ausschließlich für Veranstaltungen mit fester Platzzuordnung (z.B. Fußballspiele, Stadion-Leichtathletikveranstaltungen, Konzerte mit Sitzplätzen). Bei Durchführung von Veranstaltungen mit freier Bewegung der Zuschauer während des jeweiligen Events (z.B. Laufveranstaltungen/Marathon oder Veranstaltungen mit unbestuhlten Arenabereichen) werden adaptierte Konzepte unter Anwendung weiterer Maßnahmen gestaltet (z.B. Festlegung von Maximalpersonen je Veranstaltungsfläche, Maskenpflicht, Testkonzepte).

Das nachfolgende Sitzplatzschema wird als genereller Standard für Veranstaltungen im Freiluftbereich empfohlen. Es kann von einer durchschnittlichen Sitzbreite von 50 cm ausgegangen werden, so dass bei einer entsprechenden Zahl an freien Plätzen Mindestabstände eingehalten werden. Benachbarte Plätze werden ausschließlich an Personen aus einem Haushalt vergeben (Haushaltsgruppen). Im vertikalen Sitzbereich ermöglicht eine freie Reihe einen Abstand zwischen zwei Personen i.H.v. ca. 1,00

m. Dies wird aufgrund der Freiluftsituation und vor allem der einheitlichen Ausrichtung der Blickrichtung der Personen (kein längerer Face-to-Face-Kontakt) als vertretbar angesehen.

Die Empfehlung geht ausschließlich von 4er und 2er Haushaltsgruppen aus. Sollten auch Plätze an beispielsweise 3er Haushalte oder Einzelpersonen vergeben werden, sinkt die Auslastungsmöglichkeit entsprechend.

Das Empfehlungsmodell ermöglicht eine theoretische Auslastung von ca. 40% der Gesamtkapazität. Es kann ohne zusätzliche Investition in Lüftungsgutachten oder Teststrategien implementiert werden.

Empfehlungsmodell Sitzplätze Outdoor

x	x	x	x					x	x	x	x
					x	x					
x	x	x	x					x	x	x	x
					x	x					
x	x	x	x					x	x	x	x
					x	x					
x	x	x	x					x	x	x	x
					x	x					
x	x	x	x					x	x	x	x
					x	x					

Das beschriebene „Basismodell“ sieht keine grundsätzliche Unterscheidung zwischen Personen mit und ohne Immunitätsnachweis vor (Gewährung Zugang etc.). **Es ist somit ein allgemein anwendbares Modell zur Risikoreduktion (Abstand, Maske) bei Outdoor-Veranstaltungen in einer Zeitperiode mit vertretbarer Inzidenz und gleichzeitig schrittweise steigendem Impfschutz der Risikobevölkerung**.

3.3 Fachärztliche Konzeption mit zusätzlichem Lüftungsgutachten

Die beschriebenen Basismodelle für eine kontrollierte Rückholung von Gästen und Zuschauern zu Kultur- und Sportveranstaltungen ermöglichen die Auslastung von Spielstätten mit 25-30 bzw. 35-40% der üblicherweise vorhandenen Kapazität – unter Anwendung von strengen Hygiene- und

Infektionsschutzmaßnahmen. Es handelt sich hierbei um eine Allgemeinstruktur, die mit vertretbarem Aufwand von jeder Spielstätte bei Entwicklung eines Hygienekonzeptes umgesetzt werden kann.

Aus zahlreichen wissenschaftlichen Untersuchungen und Modellierungen ist bekannt, dass die individuelle Raumsituation (gilt für indoor und outdoor) einen erheblichen Einfluss auf die Luftbewegung und Lüftung sowie auf das damit verbundene Infektionsrisiko mit dem SARS-CoV-2-Erreger hat.

In geeigneten, zumeist modernen Veranstaltungsorten mit neuer Lüftungstechnik wird es oftmals möglich sein, über die Standards des beschriebenen Basismodells hinauszugehen und eine höhere Zuschauerzahl bei Veranstaltungen zuzulassen. Dies gilt insbesondere für große Veranstaltungsarenen mit hohen Raumvolumina und mehrfachem aktivem Luftwechsel. Ebenso können spezifische Lüftungssituationen im Freiluftbereich (beispielsweise Stadien mit starken Zugeffekten) eine überlegene Infektionsschutzsituation bieten.

Diese Kriterien müssen immer **individuell für die jeweilige Lokalität** geprüft und ausgewertet werden. Hierbei spielt nicht nur der Arenabereich eine Rolle – bei insgesamt steigender Auslastung sind auch die allgemeinen Wegesituationen / Flure, die Sanitärbereiche, die An- und Abreise sowie mögliche VIP- und Hospitalitybereiche sowie die Speisenversorgung neu zu bewerten.

Eine **verantwortungsbewusste Steigerung** der Kapazität über die Auslastungswerte des Basismodells hinaus erfordert daher ein **Spezialkonzept**, welches mit zusätzlichen Aufwendungen verbunden ist und damit nicht für jeden Veranstaltungsort als praktikabel umsetzbar angesehen wird. Um einen einheitlichen Standard sicherzustellen und eine neutrale Prüfinstanz zu involvieren, wird empfohlen, ein **fachärztliches Hygienekonzept** als Voraussetzung für die Steigerung der Auslastung über die Basiswerte hinaus zu definieren (erstellt durch beispielsweise eine/n Fachärztin/Facharzt für Hygiene und Umweltmedizin, eine/n Fachärztin/Facharzt für Mikrobiologie oder einen Infektiologen). Dieses Konzept muss nicht nur Ausführungen zu jedem der vorgenannten „neuralgischen“ Bereiche enthalten, es soll auch eine **Einschätzung** auf Basis von erhobenen Messwerten zur vorhandenen Raumlufttechnik und Lüftungssituation beinhalten.

Die hier beschriebene Vorgehensweise setzt bewusst einen **hohen (medizinischen) Standard**, um einen unkontrollierten „Wildwuchs“ von Hygienekonzepten zu unterbinden. Die Überschreitung eines allgemein umsetzbaren Basismodells (25-30/40% Auslastung) ist somit nur auf Basis individueller Konzeptionen unter Einbindung von Expertise und Datenerhebungen möglich.

3.4 Konzeption mit unterstützender Teststrategie

Neben dem Basismodell und der individuellen Steigerungsmöglichkeit der Auslastung auf Basis von medizinischen Fachkonzepten ist auch ein **„Maximalmodell" auf Basis einer Teststrategie** für die Durchführung von Veranstaltungen denkbar.

Noch im Sommer 2020 hat die Veranstaltungs- und Sportbranche mehrheitlich die Durchführung von Massentests als Zugangskriterium zu Veranstaltungen abgelehnt. Dies begründete sich vor allem darin, dass zum damaligen Zeitpunkt nur die PCR-Technologie zur Detektion akuter Infektionen zur Verfügung stand. Nicht nur, dass die PCR in der Durchführung zeitaufwändig und teuer ist, insbesondere stellt die Diagnostik auf Basis dieser molekularbiologischen Methode eine knappe Ressource dar, die aus Sicht der Veranstaltungsbranche nicht massenhaft für Besucher bei Kultur- oder Sportevents verbraucht werden sollte (gemäß auch den Empfehlungen des RKI, von massenhaften PCR-Tests bei asymptomatischen Personen ohne Begründung durch den ausgeübten Beruf abzusehen).

Durch die Etablierung von zugelassenen Antigen-Testsystemen hat sich jedoch die Diagnostiklandschaft im Herbst 2020 weiterentwickelt. Antigenteste sind weniger sensitiv als die PCR und detektieren eine Infektion erst ab einer höheren Viruslast. Die Detektionsschwelle von Antigentests korreliert jedoch nach bisherigen (indirekten und abgeleiteten) wissenschaftlichen Erkenntnissen mit der Infektiosität einer infizierten Person (*Jefferson et al., 2020*). Zudem sind Antigentests in weit größeren Mengen verfügbar, als dies bei PCR-Reagenzien der Fall ist, und mit geringerem Zeitaufwand sowie kostengünstiger und v.a. dezentral, d.h. am Veranstaltungsort, durchführbar. Zur genauen Interpretation von Antigentestergebnissen wird es jedoch erst in den kommenden Monaten weitere Forschungsergebnisse geben, die sorgfältig beachtet werden müssen (vgl. zur Einschränkung in der Sensitivität auch *Möckel et al., 2021*).

Auf Basis dieser neuen Diagnostikmöglichkeiten soll die Erweiterung der Zugangsmöglichkeit zu Veranstaltungen umgesetzt werden – bis hin zu einer möglichen Vollauslastung von Opern, Konzerten und Sportereignissen. Folgende Eckpunkte sollen dabei verbindlich umgesetzt werden:

- Kultur- und Sporteinrichtungen fördern gemeinsam **digitale Portale zur Unterstützung des Kontaktmanagements** sowie des erleichterten administrativen Zugangs zu einer Vielzahl von Veranstaltungen (unter Beachtung des Datenschutzes).
- Besucher erhalten einen Antigentest bei Ankunft am Veranstaltungsort (oder an dezentralen Teststellen am Tag der Veranstaltung) – ausschließlich auf Basis von CE-zugelassenen Tests, die auch in weiteren wissenschaftlichen Auswertungen positiv abgeschnitten haben (z.B. *Corman et al., 2020*). Die Probenentnahme und Auswertung erfolgt ausschließlich durch

geschultes Personal (kein Selbsttest zur Manipulationssicherheit) – hierfür ist ausreichend Zeit und räumliches Platzangebot – inkl. Einhaltung der Mindestabstände – einzuplanen. Andernfalls ist eine Umsetzung dieses Konzeptansatzes nicht möglich.

- Positive Antigentestergebnisse werden gemäß den gesetzlichen Vorgaben gemeldet. Bei größeren Veranstaltungen ist eine direkte Verifizierung auf Basis sensitiverer Methoden bzw. mobiler PCR-Strukturen möglich. Personen mit einem positiven Antigentestergebnis sowie alle gemeinsam angereisten (und in einer Haushaltsgruppe gebuchten) Tickets erhalten keinen Zugang zur Veranstaltung.
- Besucher können **freiwillig einen Impfnachweis oder eine durchgemachte und PCR-bestätigte COVID-19-Erkrankung digital verifizieren** lassen („Immunitätsnachweis“) – dies hat ausschließlich zur Folge, dass ein Test vor Ort nicht durchgeführt werden muss und damit die Testkapazitäten entlastet werden (vorausgesetzt, zum Zeitpunkt der Etablierung dieses Konzepts ist der Nachweis erbracht, dass geimpfte Personen selbst nicht mehr Überträger der Infektion sein können; vgl. *Levine-Tiefenbrun et al.*). Eine Diskriminierung von Personen ohne Immunitätsnachweis ist damit nicht verbunden, im Gegenteil – alle Besucher profitieren bei steigender (verifizierter) Impfquote von kürzeren Wartezeiten. Ein Immunitätsnachweis wird nur für eine bestimmte, noch zu definierende Zeitperiode bestehen (z.B. keine unbegrenzte Immunität aufgrund einer durchgemachten Infektion).
- Für die Prozesse der Verifizierung (beispielsweise der Impfbestätigung) wird ein Ablauf auf höchstem medizinischen Standard sichergestellt, um Missbrauch und Fälschungen zu verhindern. Ggf. wird dies auch mit einem persönlich wahrzunehmenden Termin in einer medizinischen Ambulanz kombiniert werden. **Digitale Portale** ermöglichen eine weitreichende Nutzungsmöglichkeit einer erfolgten Verifizierung bei vielen Veranstaltungen (für die jeweils gültigen Zeiträume). Mögliche Umsetzungsbeispiele wurden innerhalb von Workshops bereits beispielhaft erarbeitet.
- Weitere Maßnahmen des Hygienemanagements (siehe Basiskonzept oben) bleiben in Kraft und werden als zusätzlicher Schutz umgesetzt.

Ein negativer Antigentest kann eine Infektion nie zu 100% ausschließen. Das Risiko eines Ereignisses mit massenhaften Ansteckungen („Superspreading“) wird – insbesondere in Kombination mit der Maskenpflicht – hierdurch jedoch auf ein Minimum reduziert. Um die höchstmöglichste Sicherheit zu gewährleisten, behält das Testergebnis nur für den Tag seiner Durchführung Gültigkeit. Ein negativer Antigentest kann somit niemals für mehrere Tage einen Zugang zu einer Veranstaltung ermöglichen. Die grundlegende hier geschilderte Vorgehensweise entspricht beispielsweise auch der Empfehlung der Bundesregierung bei Zugang zu einem Pflegeheim: Schutz der Risikogruppen durch Antigentest bei den Besuchern (und ggf. Mitarbeitern). Ähnliche Vorgehensweisen mit einem Testkonzept sind auch

bei anderen Veranstaltungsformaten – beispielsweise ohne feste Sitzplatzzuordnung – möglich und umsetzbar. Diese Schutzmaßnahme kann beispielsweise auch ein Teilnehmerfeld einer großen Sportveranstaltung (z.B. Marathon) sicher zusammenkommen lassen und in Kombination mit anderen Hygieneregeln die Durchführung dieser Events wieder ermöglichen („mass gathering events“). Bei Schulvorstellungen in Theatern ist es möglich, zur vollen Auslastung des Veranstaltungsraumes zurückzukehren, wenn es für Schüler und Lehrende eine regelmäßige und lückenlose Teststrategie gibt.

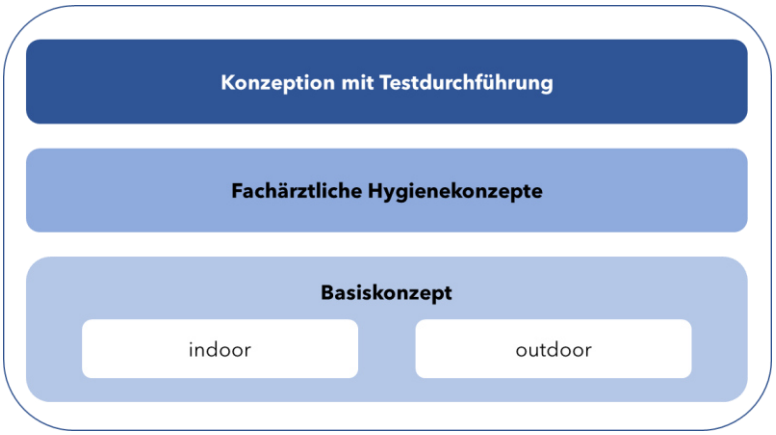
Unternehmen der Veranstaltungsbranche haben in den vergangenen Monaten intensiv an der praktikablen Umsetzbarkeit von kleinen, mittleren und großen Teststationen auf Basis von Antigendiagnostik gearbeitet sowie Prototypen getestet.

IV. Schlussplädoyer / Zusammenfassung

Alle Gesellschaftsgruppen haben in Deutschland in den vergangenen Monaten in einer gemeinsamen solidarischen Kraftanstrengung einen Beitrag zur Bekämpfung der SARS-CoV-2-Pandemie geleistet. Insbesondere die Mitarbeiterinnen und Mitarbeiter im Gesundheitswesen sowie in den Behörden und Gesundheitsämtern haben dabei weit oberhalb der eigentlichen Zeit- und Kapazitätsgrenzen gearbeitet. Die Kultur- und Veranstaltungsbranche hat den Betrieb weitgehend eingestellt und damit einen Beitrag zur Verhinderung der Infektionsausbreitung geleistet – der professionelle Spitzensport hat seine Ereignisse seit Mai 2020 fast ausschließlich unter Ausschluss von Zuschauern ausgetragen.

Gleichzeitig haben in Deutschland jedoch auch viele Gruppen, Institutionen und Unternehmen einen Beitrag zur globalen Innovationsentwicklung rund um die Pandemie geleistet. Der erste weltweit eingesetzte mRNA-Impfstoff wurde wesentlich in Mainz entwickelt, mehrere Startups haben relevante Diagnostik-Tools auf den Markt gebracht und die zuerst in Deutschland etablierte Teststrategie von Profisportlern ist inzwischen zum weltweiten Standard geworden.

In der nächsten – und hoffentlich abschließenden – Phase der Pandemie geht es nun darum einen intelligenten, schrittweise erfolgenden und auch innovativen Weg zurück zur Normalität zu finden. Der in diesem Konzeptpapier beschriebene Ansatz ermöglicht es, Breitenveranstaltungen mit vertretbarem Aufwand und Risiko sowie Spitzenveranstaltungen unter relevanten Zusatzinvestitionen wieder zu den Zuschauern und Gästen zu transportieren. Entsprechende Innovationen können wissenschaftlich begleitet werden und bieten das Potenzial zur globalen Weitergabe. Darüber hinaus werden Arbeitsplätze im Event- und Kulturbereich gesichert und Künstlern und Sportlern wieder die Grundlagen ihres Schaffens zurückgegeben sowie ein gesellschaftlicher Beitrag zur Rückkehr in eine Normalität geleistet. Das Basishygienekonzept und die speziellen Hygienekonzepte dienen dem kollektiven Infektionsschutz, aber auch dem berechtigten individuellen Anspruch der Besucher und Teilnehmenden auf eine sichere Veranstaltung in Zeiten der Corona-Pandemie.



V. Literatur

Bazant MZ, Bush JWM (2021). Beyond Six Feet: A Guideline to Limit Indoor Airborne Transmission of COVID-19. medRxiv 2020.08.26.20182824; doi: https://doi.org/10.1101/2020.08.26.20182824.

Corman VM, Haage VC, Bleicker T, Schmidt ML, Mühlemann B, Zuchowski M, Jó Lei WK, Tscheak P, Möncke-Buchner E, Müller MA, Krumbholz A, Drexler JF, Drosten C (2020). Comparison of seven commercial SARS-CoV-2 rapid Point-of-Care Antigen tests. medRxiv 2020.11.12.20230292; doi: https://doi.org/10.1101/2020.11.12.20230292.

Jefferson, T., Spencer, E., Brassey, J., and Heneghan, C. (2020). Viral cultures for COVID-19 infectivity assessment. Systematic review. medRxiv, 2020.2008.2004.20167932.

Levine-Tiefenbrun M, Yelin I, Katz R, Herzel E, Golan Z, Schreiber L, Wolf T, Nadler V, Ben-Tov A, Kuint J, Gazit S, Patalon T, Chodick G, Kishony R (2021). Decreased SARS-CoV-2 viral load following vaccination. medRxiv 2021.02.06.21251283; doi: https://doi.org/10.1101/2021.02.06.21251283.

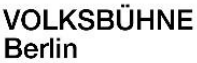
Möckel M, Corman VM, Stegemann MS, Hofmann J, Stein A, Jones TC, Gastmeier P, Seybold J, Offermann R, Bachmann U, Lindner T, Bauer W, Drosten C, Rosen A, Somasundaram R (2021). SARS-CoV-2 Antigen Rapid Immunoassay for Diagnosis of COVID-19 in the Emergency Department, Biomarkers, DOI: 10.1080/1354750X.2021.1876769.

Moritz S, Gottschick C, Horn J, Popp M, Langer S, Klee B, Purschke O, Gekle M, Ihling A, Mikolajczyk R (2020). The Risk of Indoor Sports and Culture Events for the Transmission of COVID-19 (Restart-19). medRxiv 2020.10.28.20221580; doi: https://doi.org/10.1101/2020.10.28.20221580

Paul G, Plecko T, Sethi S, Schilling T, Wienand O, Jürgensen J S, Menzel C U (2020): Klinische Performance eines neuen SARS-CoV-2-Antigen-Tests in der Notaufnahme eines Maximalversorgers. Epid Bull 2021;3:13 -18 | DOI 10.25646/7732.2

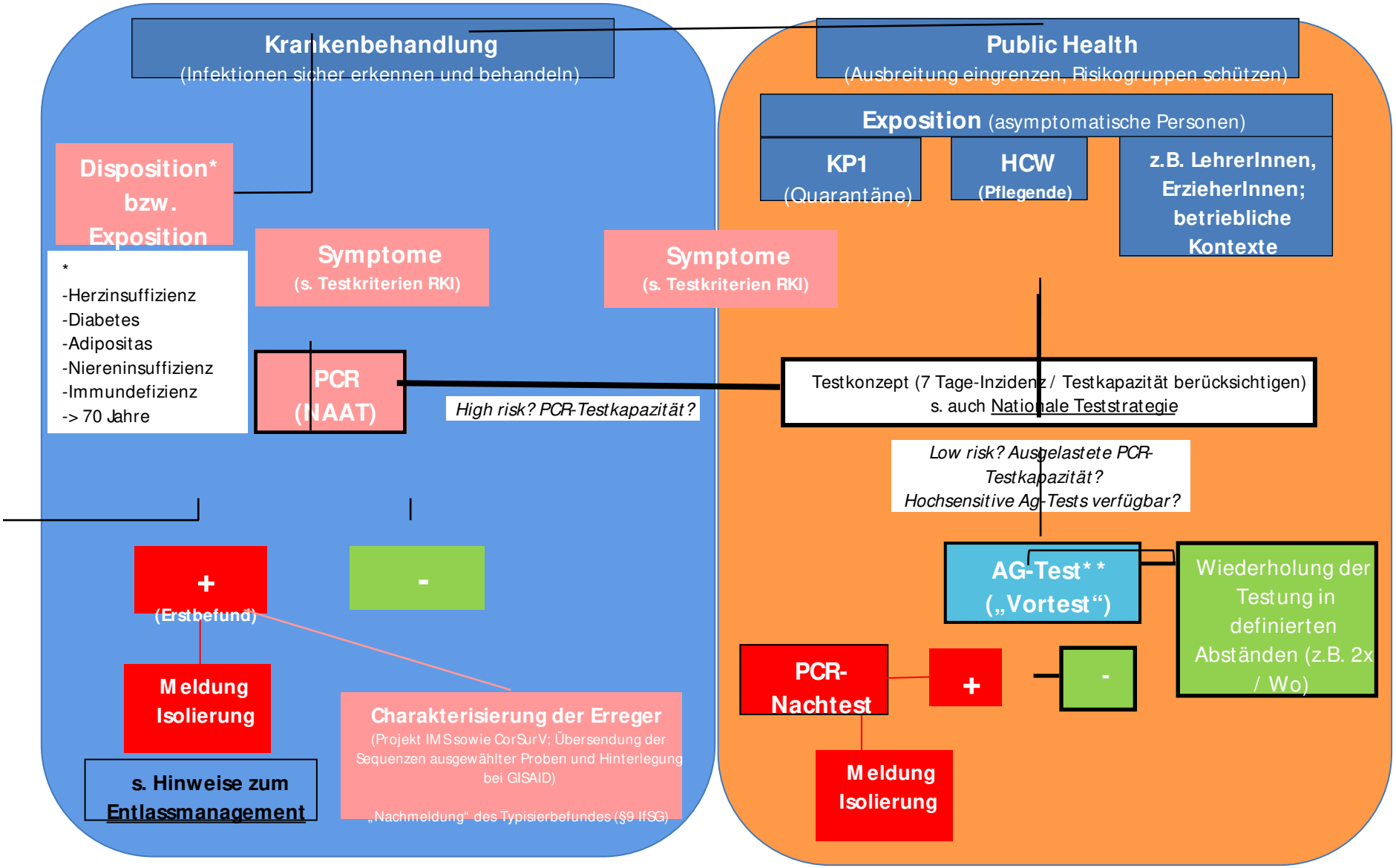
Schade W, Reimer V, Seipenbusch M, Willer U, Hübner EG (2021). Viral aerosol transmission of COVID-19 from simulated human emission in a concert hall, Int. J. Infect. Dis. 2021, submitted.

Unterstützende Organisationen und Institutionen:



SARS-CoV-2 Nachweis (direkter Erregernachweis)

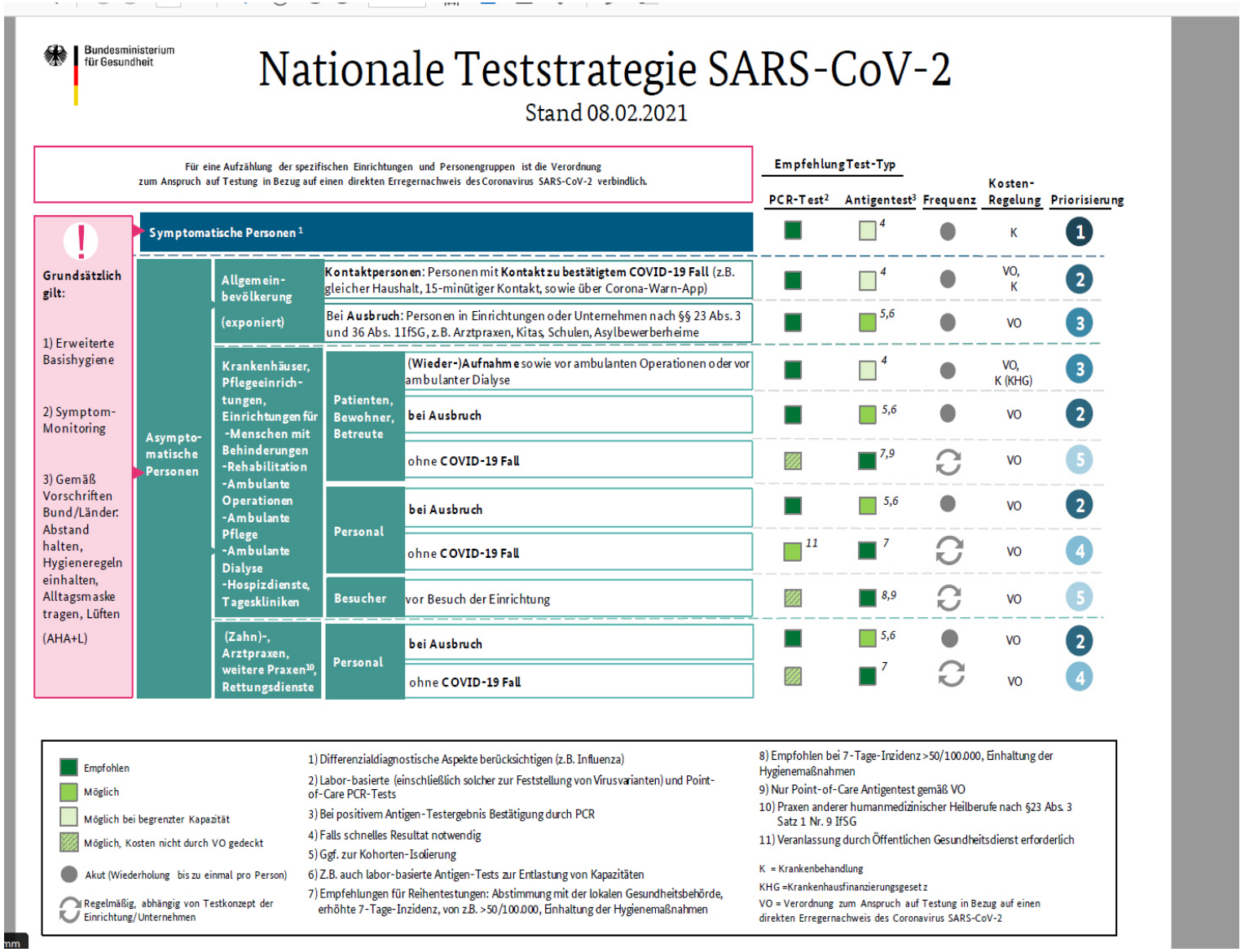
Hinweise zur Testung https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Vorl_Testung_nCoV.html



** s. Mindestanforderungen (PEI/ RKI; BfArM)

Vorschlag Mielke RKI
Ergänzung Müller

Nationale Teststrategie



Bundesministerium für Gesundheit

Nationale Teststrategie SARS-CoV-2

Stand 08.02.2021

Für eine Aufzählung der spezifischen Einrichtungen und Personengruppen ist die Verordnung zum Anspruch auf Testung in Bezug auf einen direkten Erregernachweis des Coronavirus SARS-CoV-2 verbindlich.

Grundsätzlich gilt:

1) Erweiterte Basishygiene

2) Symptom-Monitoring

3) Gemäß Vorschriften Bund/Länder: Abstand halten, Hygieneregeln einhalten, Alltagsmaske tragen, Lüften (AHA+L)

				Empfehlung Test-Typ: PCR-Test[2]	Antigentest[3]	Frequenz	Kosten-Regelung	Priorisierung
Symptomatische Personen[1]				■	□ 4	●	K	1
Asymptomatische Personen	Allgemeinbevölkerung (exponiert)		**Kontaktpersonen**: Personen mit **Kontakt zu bestätigtem COVID-19 Fall** (z.B. gleicher Haushalt, 15-minütiger Kontakt, sowie über Corona-Warn-App)	■	□ 4	●	VO, K	2
			Bei **Ausbruch**: Personen in Einrichtungen oder Unternehmen nach §§ 23 Abs. 3 und 36 Abs. 1 IfSG, z.B. Arztpraxen, Kitas, Schulen, Asylbewerberheime	■	■ 5,6	●	VO	3
	Krankenhäuser, Pflegeeinrichtungen, Einrichtungen für -Menschen mit Behinderungen -Rehabilitation -Ambulante Operationen -Ambulante Pflege -Ambulante Dialyse -Hospizdienste, Tageskliniken	Patienten, Bewohner, Betreute	**(Wieder-)Aufnahme** sowie vor ambulanten Operationen oder vor ambulanter Dialyse	■	□ 4	●	VO, K (KHG)	3
			bei Ausbruch	■	■ 5,6	●	VO	2
			ohne **COVID-19 Fall**	▨	■ 7,9	⟳	VO	5
		Personal	**bei Ausbruch**	■	■ 5,6	●	VO	2
			ohne **COVID-19 Fall**	■ 11	■ 7	⟳	VO	4
		Besucher	vor Besuch der Einrichtung	▨	■ 8,9	⟳	VO	5
	(Zahn)-, Arztpraxen, weitere Praxen[10], Rettungsdienste	Personal	**bei Ausbruch**	■	■ 5,6	●	VO	2
			ohne **COVID-19 Fall**	▨	■ 7	⟳	VO	4

■ Empfohlen
■ Möglich
□ Möglich bei begrenzter Kapazität
▨ Möglich, Kosten nicht durch VO gedeckt
● Akut (Wiederholung bis zu einmal pro Person)
⟳ Regelmäßig, abhängig von Testkonzept der Einrichtung/Unternehmen

1) Differenzialdiagnostische Aspekte berücksichtigen (z.B. Influenza)
2) Labor-basierte (einschließlich solcher zur Feststellung von Virusvarianten) und Point-of-Care PCR-Tests
3) Bei positivem Antigen-Testergebnis Bestätigung durch PCR
4) Falls schnelles Resultat notwendig
5) Ggf. zur Kohorten-Isolierung
6) Z.B. auch labor-basierte Antigen-Tests zur Entlastung von Kapazitäten
7) Empfehlungen für Reihentestungen: Abstimmung mit der lokalen Gesundheitsbehörde, erhöhte 7-Tage-Inzidenz, von z.B. >50/100.000, Einhaltung der Hygienemaßnahmen
8) Empfohlen bei 7-Tage-Inzidenz >50/100.000, Einhaltung der Hygienemaßnahmen
9) Nur Point-of-Care Antigentest gemäß VO
10) Praxen anderer humanmedizinischer Heilberufe nach §23 Abs. 3 Satz 1 Nr. 9 IfSG
11) Veranlassung durch Öffentlichen Gesundheitsdienst erforderlich

K = Krankenbehandlung
KHG = Krankenhausfinanzierungsgesetz
VO = Verordnung zum Anspruch auf Testung in Bezug auf einen direkten Erregernachweis des Coronavirus SARS-CoV-2

From: "Buda, Silke" <BudaS@rki.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 3/15/2021 9:17:01 AM
Subject: AW: Erlass: Hochwertige Datensätze pandemierelevanter Daten

---

Liebes LZ, können wir das bitte im Krisenstab heute besprechen? Ich sehe mich für FG36 nicht in der Lage, eine sinnvolle Antwort zu geben, ohne mindestens eine umfassende Beratung durch L1 zu bekommen, welche Daten wie nach der im Anhang erklärten Gesetzeslage das betrifft (braucht schon die Erhebung eine gesetzliche Grundlage, was ist mit wissenschaftlichen Daten, die das RKI selbst auswerten und publizieren will, gibt man die Rechte an den Daten ab, wie das beim ECDC der Fall ist, kommt Deutschland schon dieser Verpflichtung nach, indem pandemierelevante Daten ans ECDC übermittelt werden und damit der Öffentlichkeit zur Verfügung stehen, wer prüft bei pseudonymisierten Daten, ob sich durch mögliche externe Verlinkung von Informationen datenschutzrechtliche Probleme ergeben?).
VG, Silke

-----Ursprüngliche Nachricht-----
Von: Schmidt, Franziska Im Auftrag von Leitung_RKI
Gesendet: Montag, 15. März 2021 09:57
An: nCoV-Lage <nCoV-Lage@rki.de>
Cc: Haas, Walter <HaasW@rki.de>; Buda, Silke <BudaS@rki.de>; Diercke, Michaela <DierckeM@rki.de>; Streib, Viktoria <StreibV@rki.de>
Betreff: WG: Erlass: Hochwertige Datensätze pandemierelevanter Daten
Priorität: Hoch

Liebe Kolleginnen und Kollegen,

i. A. VPräs übersende ich Ihnen vorab einen Erlass des BMG - GG: bitte über LZ als Aufgabe vergeben lassen an FG 36, Beteiligung FG 32. DMS folgt.

Ich entschuldige mich für die kurze Frist.

Viele Grüße
Franziska Schmidt

****
(V)Präs-Sek
Tel.: -2620
Fax: -2602

-----Ursprüngliche Nachricht-----
Von: 61 BMG <61@bmg.bund.de>
Gesendet: Freitag, 12. März 2021 14:18
An: Leitung_RKI <Leitung@rki.de>
Cc: 61 BMG <61@bmg.bund.de>; 611 BMG <611@bmg.bund.de>
Betreff: Erlass: Hochwertige Datensätze pandemierelevanter Daten

Priorität: Hoch

Sehr geehrte Damen und Herren,

anbei übersende ich Ihnen einen Erlass nebst Anlage mit der Bitte um Beachtung. Achtung! Frist ist am Montag, 15. März 2021, DS.

Wir entschuldigen uns für die kurze Frist.

Mit freundlichen Grüßen
Im Auftrag

Sandra Piller

Büro Abteilungsleiter 6
GSA Dr. Hans-Ulrich Holtherm

Bundesministerium für Gesundheit

Unter den Linden 21, 10117 Berlin

Postanschrift: 11055 Berlin
Tel. +49 (0)30 18441-4801
Sandra.Piller@bmg.bund.de
www.bundesgesundheitsministerium.de
www.twitter.com/BMG_Bund
www.facebook.com/BMG.Bund
www.instagram.com/bundesgesundheitsministerium/
www.zusammengegencorona.de

From: "Schlosser, Frank" <SchlosserF@rki.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 4/1/2021 10:12:33 AM
Subject: Mobilität und Ausgangssperren
Attachments: 2020-03-31_P4_mobility_ausgangssperre_impact.pdf

Liebe Kolleg:innen,

anbei sende ich unsere Präsentation von P4 zu möglichen Auswirkungen von Ausgangssperren auf die Mobilität, die ich gestern im Krisenstab vorgestellt habe.

Wir haben dazu mittlerweile auch einen Blog-Beitrag online gestellt:
https://www.covid-19-mobility.org/reports/mobility-curfew/

Kurz zusammengefasst: Direkt von einer Ausgangssperre betroffen ist nur ein geringer Anteil der Mobilität (~7-12%). Vermutlich wird auch nicht 100% dieser Mobilität durch eine Ausgangssperre unterdrückt, und Teile der Mobilität werden möglicherweise durch Ausweicheffekte nur verschoben (Besorgungen werden früher erledigt).

Wir werden weiter untersuchen wie sich die Mobilität verändert in Regionen in denen Ausgangssperren aktiv sind oder waren, und hoffen hier nächste Woche Antworten zu haben.

Viele Grüße und frohe Ostern,
Frank Schlosser

Mögliche Auswirkung einer Ausgangssperre auf die Mobilität in Deutschland

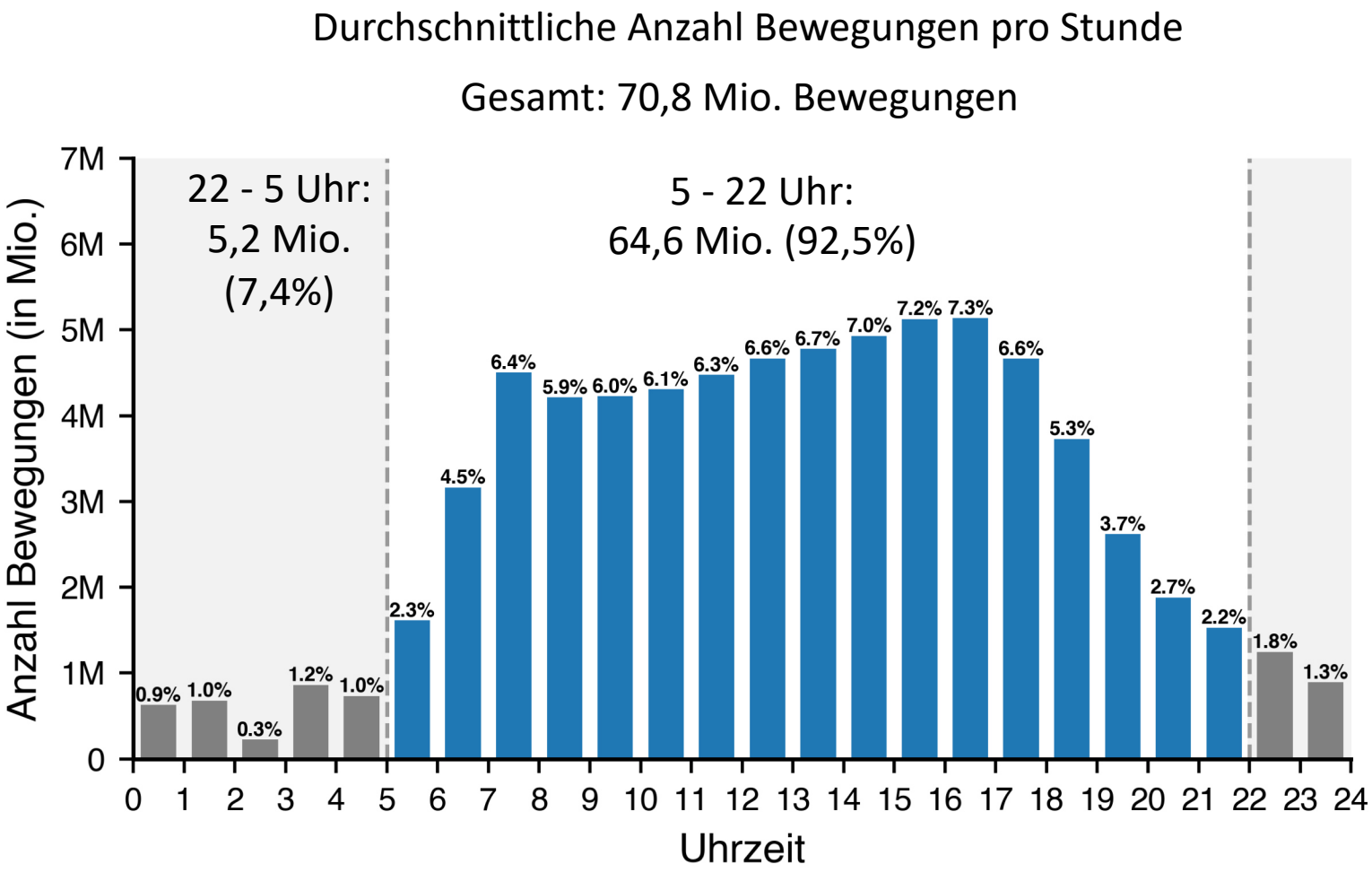
Frank Schlosser

Covid-19 Mobility Project

Complex Systems Lab, HU Berlin / RKI (Prof. Dirk Brockmann)

31. März 2021

Deutschlandweite Mobilität im Tagesverlauf



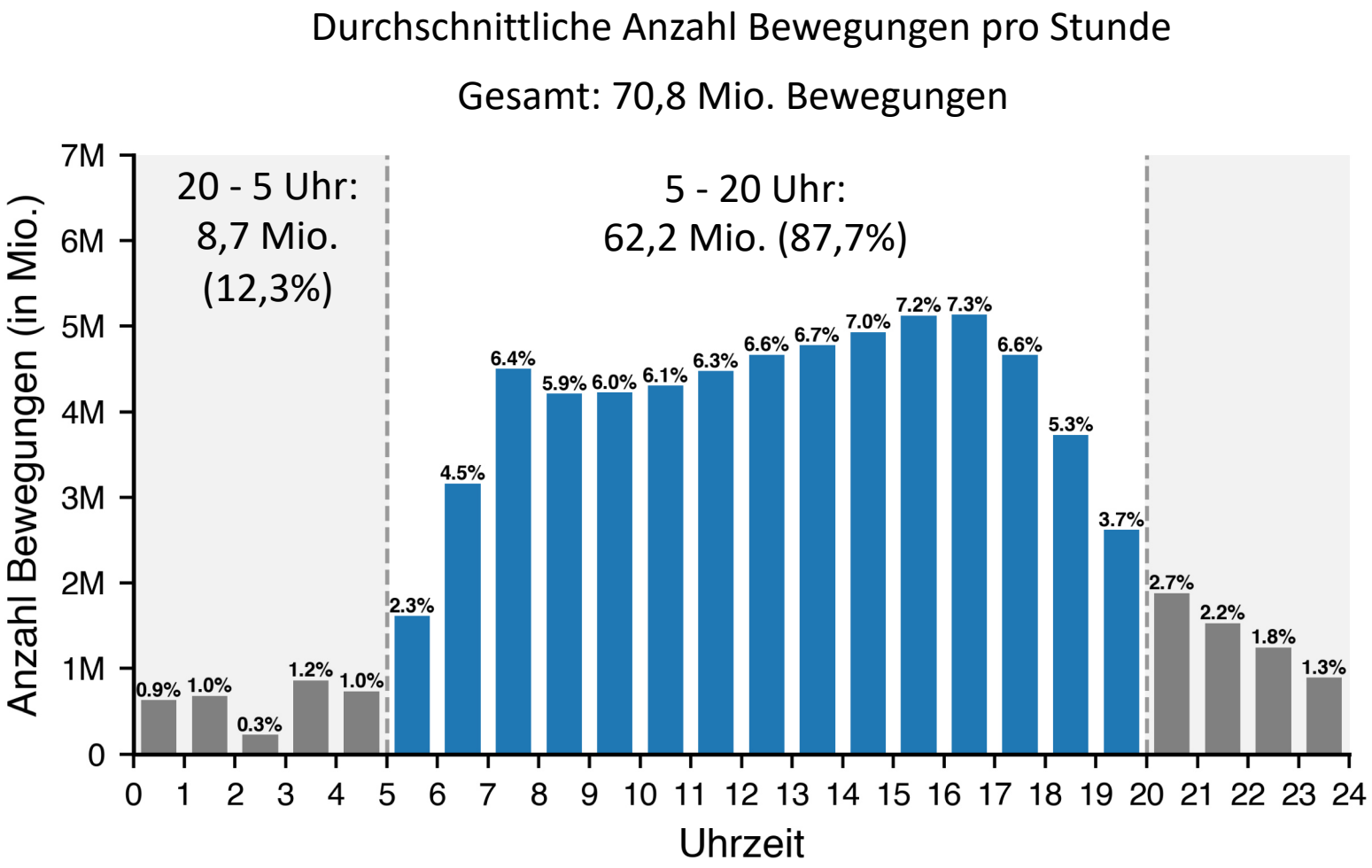
Datengrundlage:
Erfasst sind alle Bewegungen **innerhalb von Landkreisen** in Deutschland (lokale Mobilität), mit der Uhrzeit in der die Bewegung begann, gemittelt über die ersten drei März-Wochen (1.3.- 21.3.2021).

Szenario 1:
Ausgangssperre 22-5 Uhr

Der Großteil der Mobilität findet während des Tages statt.

Etwa **7,4% aller Bewegungen finden Nachts im Zeitraum zwischen 22 und 5 Uhr statt**.

Deutschlandweite Mobilität im Tagesverlauf

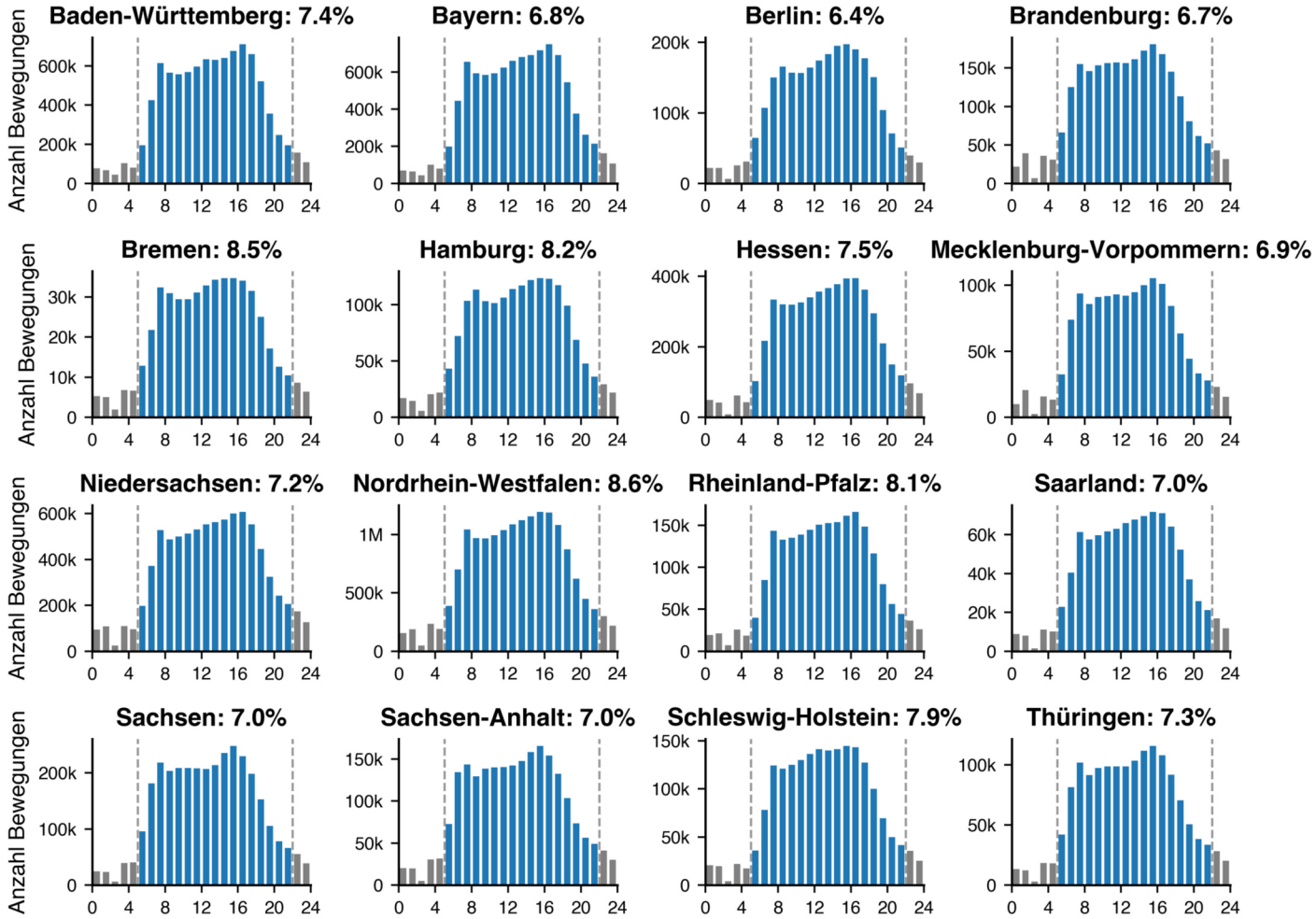


Szenario 1:
Ausgangssperre 20-5 Uhr

Etwa **12,3%** aller Bewegungen finden Nachts im Zeitraum **zwischen 20 und 5 Uhr statt** (verglichen mit 7,4% im Zeitraum 22-5 Uhr).

Mobilität in Bundesländern

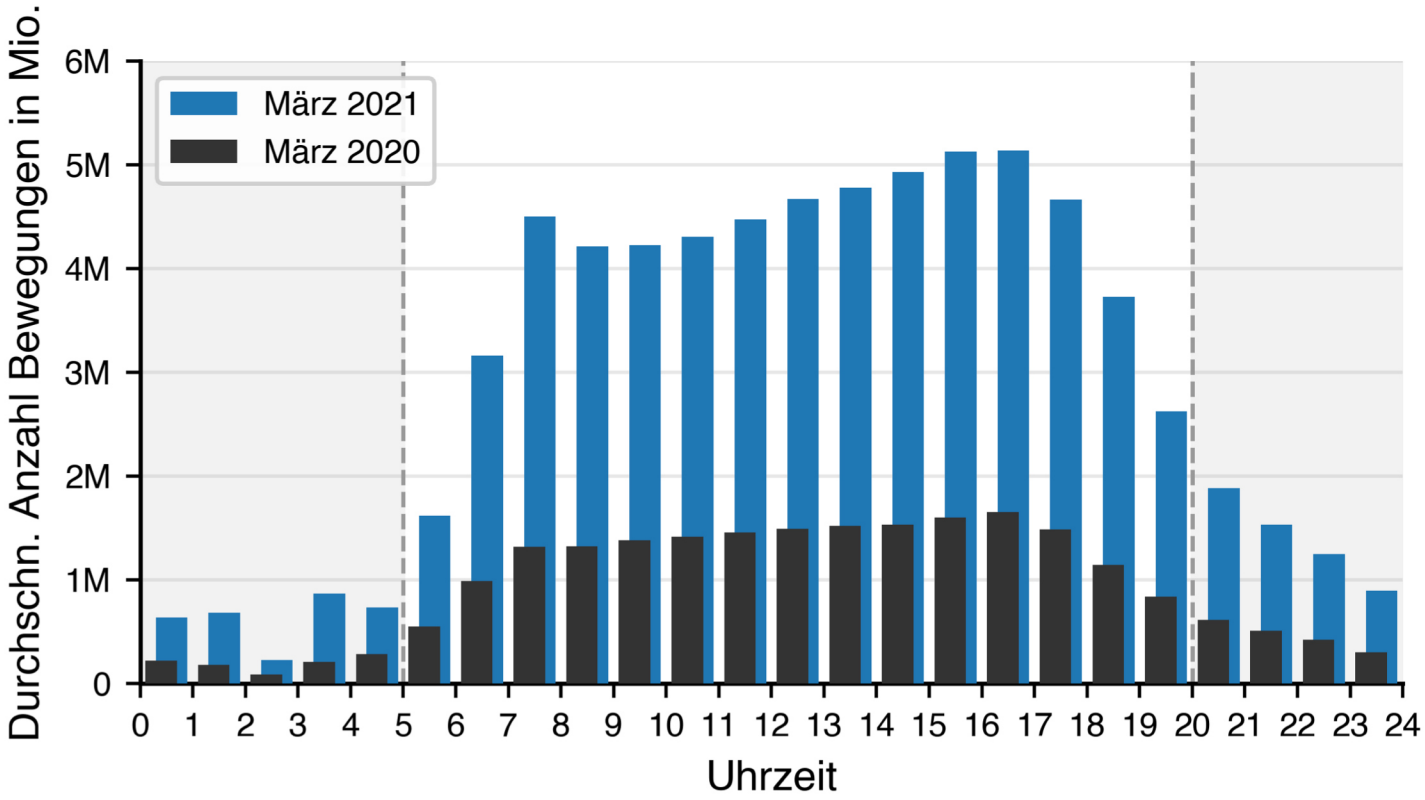
Anzahl Bewegungen und Prozentsatz an Bewegungen zwischen 22-5 Uhr (graue Balken)



Auf Bundesländer aufgeschlüsselt sehen wir **keine starken Abweichungen** vom deutschlandweiten Durchschnitt.

Den geringsten Anteil an nächtlicher Mobilität hat Berlin (6.4%), den größten Anteil Bremen (8,5%).

Vergleich mit dem erstem Lockdown



Verglichen ist die durchschnittliche Anzahl an Bewegungen im **März 2021** (Zeitraum 1.3.-21.3.) mit der Anzahl im **März 2020**, zum Höhepunkt des ersten Lockdowns (23.3.-29.3.2020).

Die Mobilität war im März 2020 deutlich geringer:

März 2021:
70.8 Mio. Bewegungen pro Tag

März 2020:
22.5 Mio. Bewegungen pro Tag

From: nCoV-Lage <nCoV-Lage@rki.de>
To: Verteiler-Krisenstab <verteiler-krisenstab@rki.de>
Date: 4/10/2021 1:05:09 PM
Subject: f ≥r Krisenstab // WG: Frist 13.04. DS: Genesenenzertifikat

Liebe Kolleginnen und Kollegen,

aus dem BMG erreichte uns eine Anfrage zum "Genesenenzertifikat" und dessen praktischen Umsetzung. Wir mochten dies auf die Tagesordnung fur die Krisenstabsitzung am Montag setzen und Ihnen allen die Anfrage vorab zur Information zukommen lassen.
Vielen Dank!
Susi Schink fur Lagezentrum/Sichtung

-----Ursprungliche Nachricht-----
Von: Korr Dr., Gerit Solveig -614 BMG <GeritSolveig.Korr@bmg.bund.de>
Gesendet: Freitag, 9. April 2021 19:02
An: nCoV-Lage <nCoV-Lage@rki.de>
Cc: 614 BMG <614@bmg.bund.de>; Kramer, Niklas -521 BMG <Niklas.Kramer@bmg.bund.de>; Lucking Dr., Gesa -611 BMG <Gesa.Luecking@bmg.bund.de>; Semrau Dr., Jutta -324 BMG <Jutta.Semrau@bmg.bund.de>; Heinrich Dr., Sven -226 BMG <Sven.Heinrich@bmg.bund.de>; 612 BMG <612@bmg.bund.de>; 611 BMG <611@bmg.bund.de>
Betreff: Frist 13.04. DS: Genesenenzertifikat

Liebe Kolleginnen und Kollegen,

Deutschland wird aller Voraussicht nach seitens EU verpflichtet werden, Genesenenzertifikate auszustellen. In diesem Zusammenhang finden derzeit zahlreiche Austausche statt. Parallel erreichen uns – vor dem Hintergrund der hohen Infektionszahlen derzeit – vermehrt Anfragen von Burgern, denen bei noch positivem PCR-Test nach kurzlich durchgemachter Erkrankung (aber abgeschlossener Isolation) die Einreise verwehrt ist.

In diesem Zusammenhang erbitten wir bis Dienstag (13.04., DS) um Stellungnahme zu folgenden Fragen:

- Kann ein positiver PCR-Laborbefund nach Einschatzung des RKI als Genesenenbescheinigung dienen und unter welchen Bedingungen (Zeitpunkt des Befundes in der Vergangenheit; ggf. auch aktuelles positives PCR-Ergebnis nach erfolgter Isolation, so lange sich dieses unterhalb eines definierten Schwellenwertes, der eine Aussage uber die Anzuchtwahrscheinlichkeit erlaubt, befindet (in Analogie zu den „Entlassungskriterien aus der Isolierung“)?

- Denkbare weitere Konstellationen fur Genesenenbescheinigung (stationare Behandlung etc.)

- Denkbare Aussteller

Vielen herzlichen Dank!

Gru?

Gerit Korr

Dr. Gerit Solveig Korr, MSc

Referat 614 - "Infektionskrankheiten"

Bundesministerium fur Gesundheit

Hausadresse: Lindencorso, Unter den Linden 21, 10117 Berlin

Postanschrift: 11055 Berlin

Tel. 030-18441-3287

GeritSolveig.Korr@bmg.bund.de <mailto:GeritSolveig.Korr@bmg.bund.de>

www.bundesgesundheitsministerium.de <http://www.bundesgesundheitsministerium.de/>

www.twitter.com/BMG_Bund <http://www.twitter.com/BMG_Bund>

www.facebook.com/BMG.Bund <http://www.facebook.com/BMG.Bund>

Hinweise zu externen Links.

Auf Art und Umfang der ubertragenen bzw. gespeicherten Daten hat das BMG keinen Einfluss.

Der Schutz Ihrer Daten ist uns wichtig. Nahere Informationen zum Umgang mit personenbezogenen Daten im BMG konnen Sie der Datenschutzerklarung auf https://www.bundesgesundheitsministerium.de/datenschutz.html <https://www.bundesgesundheitsministerium.de/datenschutz.html> entnehmen.

From: "Wieler, Lothar" <WielerLH@rki.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 4/16/2021 6:26:42 AM
Subject: Krisenstab heute

Liebe Alle,

ich werde nur partiell an der Sitzung teilnehmen konnen, daher zwei Punkte die ich bitte zu diskutieren - muss ja nicht heute sein, mussen wir aber eine Position zu finden bald

1) Mogliche vierte Welle im Herbst/Winter 2021
Warum sehe ich diese Moglichkeit? Hier funf Grunde
Hallo Lothar - ohne Springerpresse war es besser (.
1.1) saisonaler Effekt (wahrscheinlich klein, aber trotzdem)
1.2) Kinder alle ungeimpft
1.3) wer wei? wie lange der Impfschutz halt (meines Wissens sind iGa-Antikorper, in den URT-Sekreten, die die Ubertragung verhindern, nur ca. 2 Monate vorhanden. Das hei?t, dass danach die Ubertragung trotz Impfung wieder zunimmt (bei weiterem Schutz gegen klinische Verlaufe). Die klinischen Studien, die jetzt Viruslastverringerung und PCR-Pravalenz-Erniedrigung nach Impfung gesehen haben, haben die Patienten jeweils innerhalb der ersten 2 Monate nach Zweitimpfung ausgewertet. Darum ist in den Studien die Ubertragungsschutz-Wirkung wahrscheinlich uberschatzt.
1.4) wer wei? wie viele Menschen sich dann wirklich haben impfen lassen,
1.5) das Virus ist ja weltweit weiterhin ordentlich unterwegs mit der Option zur Entstehung von Escape-Varianten, also Infektionen wird es ja weiterhin geben.

Also ich ware froh wenn wir da modellieren, entweder FG33, Brockmann oder externe oder alle gemeinsam. Wir mussen hier sprachfahig sein

2) gezielte Unterdruckung gefahrliche VOCS - also Immune escape VOCs
Wie konnen wir da etwas unternehmen zusammen mit anderen Playern? Ideen? (sind hier die Gesundheitsamter geeignet?)

Mit freundlichen Gru?en

Prof. Dr. Lothar H. Wieler
Robert Koch Institute
13353 Berlin, Germany
e-mail: president@rki.de
phone: +49(0)30 18754-2000

From: "Wieler, Lothar" <WielerLH@rki.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 4/16/2021 8:20:34 AM
Subject: AW: Krisenstab heute

Im Nachgang: wie ware der Gedanke unsere Ausbruchseinsatzteams ganz spezifisch auf Ausbruche mit neu erkannten Varianten zu konzentrieren? Hier musste eng mit der Bioinformatik + Virologie zusammengearbeitet werden die rasch Signale geben muss auf problematische Varianten, also fur mich stehen hier immune escape varianten im Fokus

Mit freundlichen Gru?en

Prof. Dr. Lothar H. Wieler
Robert Koch Institute
13353 Berlin, Germany
e-mail: president@rki.de
phone: +49(0)30 18754-2000

-----Ursprungliche Nachricht-----
Von: Wieler, Lothar
Gesendet: Freitag, 16. April 2021 08:27
An: nCoV-Lage <nCoV-Lage@rki.de>
Betreff: Krisenstab heute

Liebe Alle,

ich werde nur partiell an der Sitzung teilnehmen konnen, daher zwei Punkte die ich bitte zu diskutieren - muss ja nicht heute sein, mussen wir aber eine Position zu finden bald

1) Mogliche vierte Welle im Herbst/Winter 2021 Warum sehe ich diese Moglichkeit? Hier funf Grunde Hallo Lothar - ohne Springerpresse war es besser (.
1.1) saisonaler Effekt (wahrscheinlich klein, aber trotzdem)
1.2) Kinder alle ungeimpft
1.3) wer wei? wie lange der Impfschutz halt (meines Wissens sind iGa-Antikorper, in den URT-Sekreten, die die Ubertragung verhindern, nur ca. 2 Monate vorhanden. Das hei?t, dass danach die Ubertragung trotz Impfung wieder zunimmt (bei weiterem Schutz gegen klinische Verlaufe). Die klinischen Studien, die jetzt Viruslastverringerung und PCR-Pravalenz-Erniedrigung nach Impfung gesehen haben, haben die Patienten jeweils innerhalb der ersten 2 Monate nach Zweitimpfung ausgewertet. Darum ist in den Studien die Ubertragungsschutz-Wirkung wahrscheinlich uberschatzt.
1.4) wer wei? wie viele Menschen sich dann wirklich haben impfen lassen,
1.5) das Virus ist ja weltweit weiterhin ordentlich unterwegs mit der Option zur Entstehung von Escape-Varianten, also Infektionen wird es ja weiterhin geben.

Also ich ware froh wenn wir da modellieren, entweder FG33, Brockmann oder externe oder alle gemeinsam. Wir mussen hier sprachfahig sein

2) gezielte Unterdruckung gefahrliche VOCS - also Immune escape VOCs Wie konnen wir da etwas unternehmen zusammen mit anderen Playern? Ideen? (sind hier die Gesundheitsamter geeignet?)

Mit freundlichen Gru?en

Prof. Dr. Lothar H. Wieler
Robert Koch Institute
13353 Berlin, Germany
e-mail: president@rki.de
phone: +49(0)30 18754-2000

From: "Wessel Dr., Theda -313 BMG" <Theda.Wessel@bmg.bund.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 4/22/2021 3:26:24 PM
Subject: [ID 3455] Definitionen Geimpfte, Genesene, Getestete

Liebe Kolleginnen und Kollegen,

im Rahmen von Gesetzgebungsverfahren/Verordnungen werden zunehmend einheitliche und aktuelle Definitionen für Geimpfte, Genesene und Getestete notwendig sein.
Ich bitte um Einrichtung einer gut auffindbaren Seite auf der Website des RKI, wo diese Definitionen hinterlegt sind und auf dem neuesten Stand gehalten werden. Im Hinblick auf Geimpfte sollte der vollständige Impfstatus nach STIKO möglichst knapp und übersichtlich zusammengefasst sein. Im Hinblick auf Getestete kann bei der Art der zu verwendenden Antigentests dann ja auf die entsprechende Seite des BfArM verwiesen werden.

Ich bitte – wenn möglich – um Umsetzung bis zum 28. April.

Für Rückfragen stehe ich gern zur Verfügung
Vielen Dank und mit freundlichen Grüßen
Theda Wessel

Dr. Theda Wessel
Referat 614 - Infektionskrankheiten
Referat 313 - Molekulare Medizin, Fortpflanzungsmedizin, Bioethik
Tel.: 030-18441-4627
[redacted]

From: "Wessel Dr., Theda -313 BMG" <Theda.Wessel@bmg.bund.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 4/22/2021 3:26:24 PM
Subject: [ID 3455] Definitionen Geimpfte, Genesene, Getestete

Liebe Kolleginnen und Kollegen,

im Rahmen von Gesetzgebungsverfahren/Verordnungen werden zunehmend einheitliche und aktuelle Definitionen für Geimpfte, Genesene und Getestete notwendig sein.
Ich bitte um Einrichtung einer gut auffindbaren Seite auf der Website des RKI, wo diese Definitionen hinterlegt sind und auf dem neuesten Stand gehalten werden. Im Hinblick auf Geimpfte sollte der vollständige Impfstatus nach STIKO möglichst knapp und übersichtlich zusammengefasst sein. Im Hinblick auf Getestete kann bei der Art der zu verwendenden Antigentests dann ja auf die entsprechende Seite des BfArM verwiesen werden.

Ich bitte – wenn möglich – um Umsetzung bis zum 28. April.

Für Rückfragen stehe ich gern zur Verfügung
Vielen Dank und mit freundlichen Grüßen
Theda Wessel

Dr. Theda Wessel
Referat 614 - Infektionskrankheiten
Referat 313 - Molekulare Medizin, Fortpflanzungsmedizin, Bioethik
Tel.: 030-18441-4627
[redacted]

From: "Brunke, Melanie" <BrunkeM@rki.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
"Arvand, Mardjan" <ArvandM@rki.de>
"Thanheiser, Marc" <ThanheiserM@rki.de>
Date: 4/22/2021 4:24:12 AM
Subject: KS-Sitzung am 23.04.2020 / KRINKO-Sitzung FG14

Liebes Lagezentrum,

aufgrund der KRINKO-Sitzung am 23.04.2021 wird FG14 an diesem Tag leider an der Teilnahme am Krisenstab verhindert sein. Am Montag, dem 26.04.2021, werden wir wieder wie gewohnt teilnehmen.

Freundliche Gru?e aus FG14
Melanie Brunke

From: "Denkel, Luisa" <DenkelL@rki.de>
To: "Rexroth, Ute" <RexrothU@rki.de>
"Diercke, Michaela" <DierckeM@rki.de>
Date: 5/8/2021 9:22:17 AM
Subject: AW: Internationale Lage in der kommenden Woche

Liebe Ute,

vielen herzlichen Dank fur die Info und dass du uns so rechtzeitig Bescheid gibst. Das hilft sehr bei der Planung. Dann gebe ich am Mittwoch gern einen kurzen Uberblick zur COVID-19-Situation weltweit. Am Freitag wird ggf. Andreas fur die ZIG1 am "Mini-Krisenstab" teilnehmen, sollte es relevantes im Bereich "Internationales" geben. Ich hoffe, dass alle, die ein paar Tage frei haben, ihre Akkus wieder ein bisschen aufladen konnen.

Viele Gru?e und ein schones Wochenende,
Luisa

Dr. rer. nat. Luisa Denkel, MSc (Epidemiologie)
Teamleitung Public Health Intelligence
Informationsstelle fur Internationalen Gesundheitsschutz (INIG)
Liaison fur Impfpravention (Fachgebiet 33)

Tel. +49 30 18754 3392
[redacted]
E-Mail: DenkelL@rki.de

-----Ursprungliche Nachricht-----
Von: Rexroth, Ute
Gesendet: Freitag, 7. Mai 2021 21:29
An: Denkel, Luisa <DenkelL@rki.de>; Diercke, Michaela <DierckeM@rki.de>
Cc: nCoV-Lage <nCoV-Lage@rki.de>
Betreff: AW: Internationale Lage in der kommenden Woche

Liebe Luisa, liebe Michaela,

Hr. Schaade erwartet keinen Vortrag von der ZIG am nachsten Freitag. Wenn Ihr gerne vorstellen mochtet, wurde ich Euch lieber Mittwoch vorschlagen, denn am Freitag wird es nur ein Mini-Krisenstab, ohne Protokoll, bei dem aktuelle Aufgaben diskutiert werden.

Schones Wochenende!

Ute

-----Ursprungliche Nachricht-----
Von: Denkel, Luisa
Gesendet: Mittwoch, 5. Mai 2021 13:22
An: Rexroth, Ute <RexrothU@rki.de>
Betreff: Internationale Lage in der kommenden Woche

Liebe Ute,

findet in der kommenden Woche der Krisenstab am Freitag (14.05.) statt? Falls nicht, wurde ich die internationale Lage am Mittwoch prasentieren.

Vielen herzlichen Dank im Voraus und viele Gru?e, Luisa

Dr. rer. nat. Luisa Denkel, MSc (Epidemiologie) Team lead Public Health Intelligence Informationsstelle fur Internationalen Gesundheitsschutz (INIG) Liaison fur Impfpravention (Fachgebiet 33)

Tel. +49 30 18754 3392
Mobil [redacted]
E-Mail: DenkelL@rki.de

-----Ursprungliche Nachricht-----
Von: an der Heiden, Maria
Gesendet: Mittwoch, 5. Mai 2021 13:04
An: Denkel, Luisa <DenkelL@rki.de>; Christophe Bayer (Christophe.Bayer@bmg.bund.de) <Christophe.Bayer@bmg.bund.de>
Cc: Rexroth, Ute <RexrothU@rki.de>; Scholl, Meike <SchoellM@rki.de>; Seidel, Juliane <SeidelJ@rki.de>; nCoV-Lage <nCoV-Lage@rki.de>; Espelage, Werner <EspelageW@rki.de>
Betreff: AW: Einladung WHO EURO - Consultation on coordinated decision-making on international travel measures, 12 May 2021

Liebe Luisa,

vielen Dank, dass Du mich auf den Wochentag-Verdreher aufmerksam machst, das erleichtert meinen eigenen Wochenplan nachste Woche. Ja, Mittwoch ist korrekt!

Schon Werner, dass Du dabei bist!

Viele Gru?e
Maria

-----Ursprungliche Nachricht-----
Von: Denkel, Luisa
Gesendet: Mittwoch, 5. Mai 2021 12:53
An: an der Heiden, Maria <AnderHeidenMa@rki.de>; Christophe Bayer

(Christophe.Bayer@bmg.bund.de) <Christophe.Bayer@bmg.bund.de>
Cc: Rexroth, Ute <RexrothU@rki.de>; Scholl, Meike <SchoellM@rki.de>; Seidel, Juliane <SeidelJ@rki.de>; nCoV-Lage <nCoV-Lage@rki.de>; Espelage, Werner <EspelageW@rki.de>
Betreff: AW: Einladung WHO EURO - Consultation on coordinated decision-making on international travel measures, 12 May 2021

Liebe Maria,

vielen herzlichen Dank fur deine Nachricht und die Koordination des Treffens. Nur um Missverstandnissen vorzubeugen: Das Treffen findet am kommenden Mittwoch (12.5.) 10 - 12 Uhr statt, oder? Von der PHI wird Werner Espelage teilnehmen. Ich bin leider zur selben Zeit im RKI-KS.
Viele Gru?e,
Luisa

Dr. rer. nat. Luisa Denkel, MSc (Epidemiologie) Team lead Public Health Intelligence Informationsstelle fur Internationalen Gesundheitsschutz (INIG) Liaison fur Impfpravention (Fachgebiet 33)

Tel. +49 30 18754 3392
Mobil[redacted]
E-Mail: DenkelL@rki.de

-----Ursprungliche Nachricht-----
Von: an der Heiden, Maria
Gesendet: Montag, 3. Mai 2021 16:52
An: Christophe Bayer (Christophe.Bayer@bmg.bund.de) <Christophe.Bayer@bmg.bund.de>; Denkel, Luisa <DenkelL@rki.de>
Cc: Rexroth, Ute <RexrothU@rki.de>; Scholl, Meike <SchoellM@rki.de>; Seidel, Juliane <SeidelJ@rki.de>; nCoV-Lage <nCoV-Lage@rki.de>
Betreff: WG: Einladung WHO EURO - Consultation on coordinated decision-making on international travel measures, 12 May 2021
Prioritat: Hoch

Lieber Christophe, liebe Luisa,

kommenden Montag findet von 10-12 Uhr eine WHO Euro Konsultation mit Thema "Consultation on coordinated decision-making on international travel measures" statt. FG38 wird sich zur Teilnahme anmelden, aus unserer Sicht ware es aber auch gut, wenn jemand vom BMG sowie Public Health Intelligence Team vertreten ware.

Anmeldung erfolgt uber das Monitoring and Evaluation Team der WHO Euro. Fur das RKI wurden wir in FG38 die Teilnehmenden bundeln und an das Team der WHO Euro zurucksenden, eine Ruckmeldung dazu ware bis Mittwoch DS prima, dann senden wir am Donnerstag,

viele Gru?e
Maria

-----Ursprungliche Nachricht-----
Von: Baum, Jonathan Im Auftrag von nCoV-Lage
Gesendet: Donnerstag, 29. April 2021 22:49
An: an der Heiden, Maria <AnderHeidenMa@rki.de>; Rexroth, Ute <RexrothU@rki.de>
Cc: Scholl, Meike <SchoellM@rki.de>; Seidel, Juliane <SeidelJ@rki.de>; Markus, Inessa <MarkusI@rki.de>; Schneider, Timm <SchneiderT@rki.de>; nCoV-Lage <nCoV-Lage@rki.de>
Betreff: Einladung WHO EURO - Consultation on coordinated decision-making on international travel measures, 12 May 2021
Prioritat: Hoch

Liebe Kolleginnen und Kollegen,

WHO EURO ladt am 12. Mai 2021 von 10:00-12:00 (CEST) zu einem Zoom Meeting zu Reisebeschrankungen im Kontext der COVID-19-Pandemie.
Die Teilnahme seitens RKI bzw. BMG ware sicherlich sinnvoll, Anmeldung via eurocme@who.int ist erforderlich.
Nahere Informationen entnehmen Sie bitte dem Anhang.

Beste Gru?e
Jonathan Baum
Lagezentrum COVID-19

-----Ursprungliche Nachricht-----
Von: GMLZ (BBK I.5) <GMLZ@bbk.bund.de>
Gesendet: Donnerstag, 29. April 2021 19:51
An: Epialert <epialert@rki.de>
Cc: gesundheitssicherstellung@bmg.bund.de; seuchenhygiene@bmg.bund.de
Betreff: IGV WHO/NCP - [EXTERN]Consultation on coordinated decision-making on international travel measures, 12 May 2021
Prioritat: Hoch

Gemeinsames Melde- und Lagezentrum von Bund und Landern (GMLZ) German Joint Information and Situation Centre

BITTE SOFORT VORLEGEN

An
- RKI (E-Mail)

Nachrichtlich
- BMG (E-Mail)

IGV – IHR / WHO IGV-Mitteilung/ -Anfrage: IGV WHO/NCP - [EXTERN]Consultation on coordinated decision-making on international travel measures, 12 May 2021

Sehr geehrte Damen und Herren,

vereinbarungsgema? ubermitteln wir Ihnen die unten beigefugte Mitteilung des WHO EURO IHR.

Mit freundlichen Gru?en
GMLZ Dauerdienst

-----Ursprungliche Nachricht-----
Von: EURO IHR [mailto:euroihr@who.int]
Gesendet: Donnerstag, 29. April 2021 19:46
An: EURO IHR
Cc: SCHMIDT, Tanja; GATINA, Regina; ADDO, Jennifer; PEREHINETS, Ihor
Betreff: [EXTERN]Consultation on coordinated decision-making on international travel measures, 12 May 2021 || ⇶∯ ∬:~∪≥:✶≈^≪.∳ ∝∳ .∵.∳ :~ :∩∳∳ ∵∟^∬^.∳ ∝✶∭∯ ∝∳ .∵.∳ ≈∠: :✶.∵∵^∬≪:^≪∵∠≒∠∬^∨∳ ∫ ∠∵✶≅ ∝∳ :∭ ≒∠∬^^∫ ∠| ∟~∬✶.∳ ∟∬≤≅ .∳ ∠|∟∳ ∩,12 ∫ ✶≪2021
Wichtigkeit: Hoch

(⇰✶∪∠∠ :∪∠∟~∠:::∠∩:::∬✶∵~::∩∳∫ ⋖| ≤∩∠/ this message follows in Russian)

Dear National IHR Focal Points,

Dear colleagues,

We kindly invite you to participate in the upcoming consultation on “Coordinated decision-making on international travel measures in the context of COVID-19 in the WHO European Region” organised by the WHO Regional Office for Europe on May 12, 2021, 10-12 CET.

The overall objective of the consultation is to strengthen national decision-making and communication in relation to international travel measures to ensure better coordination throughout the next phase of the COVID-19 pandemic. More detailed information can be found in Scope and Purpose attached.

Please confirm if you will participate by sending an email to eurocme@who.int

Connection details, final agenda and background documents will be shared later on.

For queries specific to the meeting, please email: eurocme@who.int <mailto:eurocme@who.int>

Best regards,

WHO Health Emergencies Programme

WHO Regional Office for Europe

⇷⋈∝⋇∣ ⋇∠∫ ≤∠⇹⇶.∴∲ ⇸⇸⇷⇻!

⇷⋈∝⋇∣ ⋇∠∫ ≤∠∩∲ ⋃⋃∠∞∖!

⇻∵∧∞⋃⋇≒ ⋇∠∫ ∝⋇∶ ∴∵∧∬≪≥ ~≌⋇∷∧∠∝ ∴∵∠∟∷∲≪ ∠∨∩∲ ∬∶~⋃≥⋇≈∧∧ ∬⋇∶∠∫ ~«⇷∩∲∲ ∵∟∧∬∧∵∲ ∝⋇∬∬≤∨ ∴∵∲ ≈∠∶∶∴∵∧∬≪∧≪∵∠≒∠∬∧∨∲ ∫ ∠∵⋇≡ ∝∲∶∬∲ ≒∠∬∧∧∫ ∠∣ ∟~∬⋇.∲ ∟∬≤≡ .∵∲ ∠∣∟∲ ∩∝∩∲ ∬∶∠∩∷∠COVID -19 ∝⇱∝.∲ .∵∠∨∶∩∲∫ ∵∠∞∧∲ ∬∠⇮⇻⇳, ∲ ∵∞⋇∬∧∣ ~∠∫ ∲ ∨⇱∝.∲ .∵∠∨∶∩∧∫ ∵∠∞∧∲ ∬⋇⋃≥∬≤∫ √≧∵∲ ⇮⇻⇳ ⇶∲ ∬∶~⋃≥⋇≈∧≪√~∟∠∶∴∵∲≡∲ ∟∧∶≥12 ∫ ⋇≪2021 ∻ ∶10:00 ∟∲ 12:00 .∵∲ ≈∠∬∶∴⋇⋃≥∬∲ ∠∝.∲ .∵∠∨∶∩∲∫ ~∝∵∠∫ ∠∬∧

⇹√≠ ⋇≪≈∠⋃≥ ∲ ∝∠≠ ⋇∬∧≪∲ ∷∲ ∧∶∶∝ ~∩∵∠∵⋃∠∬∧∧ ∬⋇≈∧∲ ∬⋇⋃≥∬∲∞∲ ∴∵∲ ≈∠∶∶⋇∴∵∧∬≪∧≪∵∠≒∠∬∧∨ ∧∞∣⋇∧∫ ∲∟∠∨∷∝∧≪∝∲ √⋃⋇∷∧ ∵∠⋇⋃∧∣⋇≈∧∧∫ ∠∵; ∩⋇∶⋇≧≠ ∧≡∶≪∫ ∠∣ ∟~∬⋇.∲ ∟∬≤≡ .∵∲ ∠∣∟∲ ∩, ∶≈∠⋃≥≧ ∲ √∠∵∠≌∠∬∧≪⋃~≌≒ ∠∨∩∲∲ ∵∟∧∬⋇≈∧∧ ∬⋇ ∶⋃∠∟~≧≠ ∠∫ ≦⋇∵∠∴⋇∬∟∠∫ ∧∧COVID-19. ⇯∲ ⋃∠∠.∵∲ ∟∵∲ √∬⋇≪ ∧∬∾∲ ∵∫ ⋇≈∧≪∴∵∠∟∷⋇∝⋃∠∬⋇∝∟∲ ∩~∫ ∠∬∶∠« ∃∠⋃∧ ∧∥⋇∟⋇≌∧», ∴∵∧⋃⋇∞⋇∠∫ ∲∫ ∩∟⋇∬∬∲∫ ~∴∧∶≥∫ ~

⇻∵∲ ∶≥√⋇.∵∲ ∟∶∝∠∵∟∧∶≥ ∶∞∲ ∠~≌⋇∷∧∠,∲ ∶∴∵⋇∝∧∝∴∧∶≥∫ ∲ .∵∲ ⋇∟∵∠∶~eurocme@who.int.

⇴∬∾∲ ∵∫ ⋇≈∧≪∲ .∵∲ ∟∩⋃≧ ≌∠∬∧∧, ∲ ∩∲ ∬≌⋇∠⋃≥∬⋇≪.∵∲ ∝∠∷∩⋇∟∬≪∧ ∶∴∵⋇∞∲ ≌∬≤∠∟∲ ∩~∫ ∠∬∶≤ √~∟~∶∶ ∴∵∠∟∷⋇∝⋃∠∬≤ .∵∲∥∣ ∠

⇹∳ ∝:∠∫ ∞∳ .∴.∳ :∺∫ , ∩★:★≧≠ ∧∫ :≪ :∳ ∝∠≠ ★∫∫∧≪ .∴.∳ :∧∫ ∳ √·:·≠ ★: ≥:≪.:∳ ≦∪∠∩ :.∳ ∫∫∫∭ ∨ .:∳ ≦: ∠
eurocme@who.int.

⇐ ~∝∺ ∠∫∫∧∠∫ ,

⇹·.∳ ∞.·∺∫ ∫ ★ ⇮⇹⇳ .:∳ ≦·.·∠╢ ∝≤≦★∨∫∫≤∫ :∧: :~★≈∧≪∜ ∝∳ √∪★:: :∧ ‖ ∟:.·★∞∳∳≅·.·★∫∫∠∫∫∧≪

⇱∝·.∳ .∴∠∨ :∩∳ ∠ ·.·∠∞∳ ∫∫★∪≥∫∭ ∠ √≧ ·.∳ ⇮⇹⇳

From: "Kramer, Niklas -521 BMG" <Niklas.Kramer@bmg.bund.de>
To: "Lücking Dr., Gesa -611 BMG" <Gesa.Luecking@bmg.bund.de>
"Korr Dr., Gerit Solveig -614 BMG" <GeritSolveig.Korr@bmg.bund.de>
"Rexroth, Ute" <RexrothU@rki.de>
Date: 4/14/2021 9:24:50 AM
Subject: AW: Genesenenzertifikate
Attachments: st07552.en21.pdf
citizen_recovery-interoperable-certificates_en.pdf

Liebe Kollegen/innen,

Danke fur die Hinweise, die ich an das IBM Projekt weitergeben werde.
Anbei der aktuelle Stand der VO und des Datensatzes.

Ich bitte um Berucksichtigung und nochmalige Prufung des Erwagungsgrundes 32 und Art. 7.

Die Hinweise von Frau Rexroth erscheinen mir doch, korrigieren Sie mich bitte, hypothetischer Natur zu sein, ich vermute, dass Intensivpatienten in einem Krankenwagen gerade keine Genesenen-Zertifikate erhalten, auch wenn der EU-Rahmen die Berucksichtigung der Symptomatik ggf. nicht explizit macht (letzteres konnen wir im Ubrigen auch noch einbringen).

Ich lese es so, dass die Datenelemente Gultigkeit grundsatzlich von den Mitgliedstaaten bestimmt werden, grundsatzlich werden aber Mindestvorgaben gemacht (Mindestens 11 Tage und maximal 180 Tage, also 6 Monate).
Zudem hat die EU-KOM die Moglichkeit uber delegierte Rechtsakte Anderung der Lange der Gultigkeit der Zertifikate zu bestimmen sowie ggf. die zugrundeliegenden Tests auszuweiten basierend auf Beratungen im HSC und durch das ECDC. Die MS verbleiben frei, daruber zu entscheiden, ob sie diese zur Lockerung von Reisebeschrankungen anerkennen, sie mussen diese jedoch grundsatzlich ihren Burger/innen anbieten.

Erwagungsgrund 32
A certificate of recovery should be issued at the earliest from the eleventh day after the first positive test and should be valid for not more than 180 days. According to ECDC, recent evidence shows that despite shedding of viable SARS-CoV-2 between ten and twenty days from the onset of symptoms, convincing epidemiological studies have failed to show onward transmission of disease after day ten. According to ECDC, recent evidence shows that despite shedding of viable SARS-CoV-2 between ten and twenty days from the onset of symptoms, convincing epidemiological studies have failed to show onward transmission of disease after day ten. The Commission should be empowered to change this period on the basis of guidance from the Health Security Committee or from ECDC, which is closely studying the evidence base for the duration of acquired immunity after recovery."

Article 7 Certificate of recovery
1. Each Member State shall issue, upon request, certificates of recovery as referred to in Article 3(1)(c) at the earliest from the eleventh day after a person has received his or her first positive test for SARS-CoV-2 infection.
The Commission is empowered to adopt delegated acts in accordance with Article 11 to amend the number of days as of which a certificate of recovery may be issued, based on guidance received from the Health Security Committee in accordance with Article 3(6) or on scientific evidence reviewed by

ECDC.
The certificate of recovery shall contain the following categories of personal data:
(a) identification of the holder;
(b) information about past SARS-CoV-2 infection following a positive test;
(c) certificate metadata, such as the certificate issuer or a unique certificate identifier.
The personal data shall be included in the certificate of recovery in accordance with the specific data fields set out in point 3 of the Annex.
The Commission is empowered to adopt delegated acts in accordance with Article 11 to amend point 3 of the Annex by adding, modifying or removing data fields on the categories of personal data mentioned in this paragraph, including until when a certificate of recovery shall be valid, where such amendment is necessary to confirm or verify the authenticity, validity and integrity of the certificate, in case of scientific progress in containing the COVID-19 pandemic or to ensure interoperability with international standards.
3. The certificate of recovery shall be issued in a secure and interoperable format as provided for in Article 3(2).
3a Based on guidance received pursuant to Article 3(6), the Commission is empowered to adopt delegated acts in accordance with Article 11 to amend the provisions in Article 3(1)(c) and Article 7(1) to allow for the issuance of the certificate of recovery also based on a positive rapid antigen test, serological testing for antibodies against SARS-CoV-2 or any other scientifically validated method. Any such delegated act shall add, modify or remove the data fields on the categories of data included in the certificate. The issuance and acceptance of the certificate of recovery based on the tests and methods mentioned in this paragraph shall be optional.
4. Where, in the case of newly emerging scientific evidence or to ensure interoperability with international standards and technological systems, imperative grounds of urgency so require, the procedure provided for in Article 12 shall apply to delegated acts adopted pursuant to this Article.
5. Where Member States accept proof of recovery from SARS-CoV-2 infection as a basis for waiving restrictions to free movement put in place, in compliance with Union law, to limit the spread of COVID-19, they shall accept, under the same conditions, valid certificates of recovery issued by other Member States in compliance with this Regulation.

Mit freundlichen Gru?en
Im Auftrag

Niklas Kramer
Referent

Referat 521 - Grundsatzfragen der gematik, Telematikinfrastruktur und eHealth
Bundesministerium fur Gesundheit
Friedrichstra?e 108, 10117 Berlin
Postanschrift: 11055 Berlin
Tel. +49 (0)30 18441-4384
Niklas.Kramer@bmg.bund.de
www.bundesgesundheitsministerium.de
www.twitter.com/BMG_Bund
www.facebook.com/BMG.Bund
www.instagram.com/bundesgesundheitsministerium/
www.zusammengegencorona.de

-----Ursprungliche Nachricht-----
Von: Lucking Dr., Gesa -611 BMG
Gesendet: Mittwoch, 14. April 2021 08:45
An: Korr Dr., Gerit Solveig -614 BMG <GeritSolveig.Korr@bmg.bund.de>; 'Rexroth, Ute' <RexrothU@rki.de>
Cc: Bartels Dr., Cornelius - 614 BMG <Cornelius.Bartels@bmg.bund.de>; Kramer, Niklas -521 BMG <Niklas.Kramer@bmg.bund.de>; Ramirez Dr., Michaela -611 BMG <Michaela.Ramirez@bmg.bund.de>
Betreff: AW: Genesenenzertifikate

Liebe Gerit, liebe Ute,

das Zertifikat soll "fruhestens" nach dem 11 Tag ausgestellt werden. Da wir fur die Rechtsfolgen verantwortlich sind - d.h. was darf man mit dem Zertifikat in DEU - konnen wir festlegen, dass dieses ungultig ist fur Patienten, die nach DEU med. aufgrund COVID-19 evakuiert werden.

Viele Gru?e,
Gesa

-----Ursprungliche Nachricht-----
Von: Korr Dr., Gerit Solveig -614 BMG <GeritSolveig.Korr@bmg.bund.de>
Gesendet: Mittwoch, 14. April 2021 08:18
An: 'Rexroth, Ute' <RexrothU@rki.de>
Cc: Lucking Dr., Gesa -611 BMG <Gesa.Luecking@bmg.bund.de>; Bartels Dr., Cornelius - 614 BMG <Cornelius.Bartels@bmg.bund.de>; Kramer, Niklas -521 BMG <Niklas.Kramer@bmg.bund.de>
Betreff: Genesenenzertifikate

Liebe Ute,

guter Punkt, wir nehmen das mit in die Diskussionen auf. Ich setze die Kollegen, die damit ebenfalls befasst sind, cc.

Herr Kramer, konnen Sie mir bitte einmal den aktuellen Stand (aktueller Entwurf) schicken?

Vielen Dank
Gerit Korr

-----Ursprungliche Nachricht-----
Von: Rexroth, Ute <RexrothU@rki.de>

Gesendet: Dienstag, 13. April 2021 22:51
An: Korr Dr., Gerit Solveig -614 BMG <GeritSolveig.Korr@bmg.bund.de>
Betreff: pauschale Genesenenzertifikate?

Liebe Gerit,

Wegen des Genesenenzertifikats ist mir noch aufgefallen: Wenn Frankreich oder die EU diese pauschale 2-Wochen Regel nach PCR ohne Berucksichtigung der Symptomatik einfach umsetzt, und Deutschland das akzeptiert, dann kommen kunftig alle die medizinisch evakuierten COVID-19-Falle, die aus dem Ausland fur ihre Intensivtherapie nach Deutschland gebracht werden, mit gultigem Genesenenzertifikat rein und mussen folglich weder wahrend des Transport noch auf der Intensivstation isoliert werden. Man wird sich allerdings die Frage stellen lassen mussen, warum diese Personen uberhaupt Behandlung brauchen, wo sie doch amtlich genesen sind. Konnte in den Medien etwas schrag ruber kommen.
Habt Ihr Euch das uberlegt?

Viele Gru?e,
Ute Rexroth

Dr. med. Ute Rexroth, MPH MSc

Robert Koch-Institut
Abteilung fur Infektionsepidemiologie
Leiterin des Fachgebiets fur infektionsepidemiologisches Krisenmanagement, Ausbruchsuntersuchungen und Trainingsprogramme

Seestr. 10
13353 Berlin

E-Mail: rexrothu@rki.de
Tel.: 030 18 754-3259
FAX: 030 18 754-3533

Council of the European Union

Brussels, 13 April 2021
(OR. en)

7552/21

Interinstitutional Files:
2021/0068(COD)
2021/0071(COD)

LIMITE

COVID-19 122	**COCON 21**
JAI 357	**COMIX 185**
FRONT 120	**CODEC 479**
FREMP 79	**SCHENGEN 23**
IPCR 40	**AVIATION 61**
VISA 67	**PHARM 57**
MI 224	**RELEX 265**
SAN 190	**TOUR 16**
TRANS 191	**POLGEN 47**

NOTE

From:	General Secretariat of the Council
To:	Permanent Representatives Committee
No. Cion doc.:	7128/21 7129/21
Subject:	Digital Green Certificate - Proposal for a Regulation of the European Parliament and of the Council on a framework for the issuance, verification and acceptance of interoperable certificates on vaccination, testing and recovery to facilitate free movement during the COVID-19 pandemic - Proposal for a Regulation of the European Parliament and of the Council on a framework for the issuance, verification and acceptance of interoperable vaccination, testing and recovery certificates for third country nationals legally residing in the Schengen area to facilitate free movement during the COVID-19 pandemic = Mandate for negotiations with the European Parliament

INTRODUCTION

1. On 17 March 2021, the Commission submitted the following proposals:

   – Regulation on a framework for the issuance, verification and acceptance of interoperable certificates on vaccination, testing and recovery to facilitate free movement during the COVID-19 pandemic ("main regulation")[1];

[1] 7128/21

– Regulation on a framework for the issuance, verification and acceptance of interoperable certificates on vaccination, testing and recovery to third-country nationals legally staying or legally residing in the territories of Member States during the COVID-19 pandemic ("twin regulation")[2].

Both proposals are subject to the ordinary legislative procedure.

2. On 19 March 2021, Coreper approved the establishment and mandate of the Ad hoc Working Party on the proposals for a Digital Green Certificate (AWP DGC) [3] to examine and negotiate the abovementioned proposals.

3. On 19 and 30 March 2021, Coreper examined the proposals.

4. On 31 March 2021, the European Data Protection Board and the European Data Protection Supervisor issued a joint opinion[4].

5. On 8 and 12 April 2021, the AWP DGC discussed the text of the proposals. The latest version of the proposals can be found in Annexes I and II to this document[5].

STATE OF PLAY

6. Delegations welcomed the proposals which aim to provide a framework for the issuance, verification and acceptance of interoperable certificates on vaccination, testing and recovery to facilitate free movement during the COVID-19 pandemic.

7. Delegations underlined their commitment to have the framework ready by the summer of 2021. In this context, work would need to advance expeditiously in two parallel tracks: Reaching full agreement on the legislative texts by the beginning of May at the latest and ensuring that the necessary technological solutions are in place in the Member States by the time of the start of operations whilst ensuring coherence with international standards.

---

2 7129/21
3 6802/21
4 7307/21
5 Changes compared to the Commission proposal are marked in **bold/underline** for additions and in ~~bold/strikethrough~~ for deletions. New changes compared to the previous version are also grey shaded.

8. As regards the legislative texts, the main amendments which were introduced during the discussions could be summarized as follows:

– In order to stress the principle of non-discrimination, in particular towards non vaccinated persons, the operative part of the main regulation explicitly states that possession of a Digital Green Certificate is no precondition to exercise free movement rights. (Article 3(3a))

– In order to cope with scientific uncertainties, the option has been created for Member States to issue and accept certificates of recovery based on rapid antigen tests, serological testing for antibodies against SARS-CoV-2 or any other scientifically validated method on the basis of future scientific guidance confirming that these tests or methods constitute a reliable proof of recovery. (Article 7(3a) of the main regulation)

– The main regulation includes a justification for the differentiated treatment in the acceptance of vaccination certificates depending on the type of market authorization of the vaccine. (recital 25a and 25b, Article 5(5) and Article 15 (2))

– The text of the main regulation includes a new Article 7a to provide more clarity on the international dimension of the Digital Green Certificate. It clarifies the treatment to be given to certificates issued to Union citizens and their family members as well as legally-staying/residing third-country nationals vaccinated in third countries, both before and after the adequacy finding referred to in paragraph 2 of that article.

– The data protection provisions have been strengthened throughout the text of the main regulation, in particular on the basis of the joint opinion of the European Data Protection Supervisor and the European Data Protection Board (recitals 20a and 47 and Article 9 of the main regulation, recital 18 of the twin regulation)

– The procedure foreseen in Article 10 of the main regulation has been reworded to focus on a timely information exchange between the Member States and the Commission as well as information to the public. As regards the timeline, the same wording as in Recommendation 2020/1475 has been used.

– The Commission proposal made the suspension of the main regulation and the report on its application dependent on non-EU actors. It also provided for the suspension of the main regulation and its possible new application by delegated act. The amended text provides for a 12-month application period, a report by the Commission at the latest 3 months before the end of the application of the main regulation and a possible suspension/extension through the ordinary legislative procedure. (Article 15)

– The text of the main regulation includes a transitional provision to ensure that Member States can continue using the systems that they have currently in place during a short period of six weeks after the entry into force of the main regulation and until the Digital Green Certificate framework is fully operational on their territory (Article 14).

– The text of the main regulation contains amendments in order to limit the scope of the delegated acts aimed at modifying the certificates' data to what is strictly necessary, i.e. scientific progress and interoperability with international standards (Articles 5(2), 6(2) and 7(2)).

– The text of the twin regulation contains a provision enabling Ireland and the other Member States to mutually accept certificates issued to third country nationals based on reciprocity (recital 13 and Article 1a). Furthermore, in this context, small changes were introduced in Article 2 (1) and Article 7a (1) of the main regulation.

CONCLUSION

9. Coreper is invited to examine the text of the two regulations and, on that basis, agree on a mandate for negotiations with the European Parliament.

ANNEX I

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on a framework for the issuance, verification and acceptance of interoperable certificates on vaccination, testing and recovery to facilitate free movement during the COVID-19 pandemic (Digital Green Certificate)

(Text with EEA relevance)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 21(2) thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Acting in accordance with the ordinary legislative procedure,

Whereas:

(1) Every citizen of the Union has the **fundamental** right to move and reside freely within the territory of the Member States, subject to the limitations and conditions laid down in the Treaties and by the measures adopted to give effect to them. Directive 2004/38/EC of the European Parliament and of the Council[6] lays down detailed rules as regards the exercise of that right.

(2) On 30 January 2020, the Director-General of the World Health Organization ('WHO') declared a public health emergency of international concern over the global outbreak of severe acute respiratory syndrome coronavirus 2 (*SARS-CoV-2*), which causes coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO made the assessment that COVID-19 can be characterized as a pandemic.

---

[6] Directive 2004/38/EC of the European Parliament and of the Council of 29 April 2004 on the right of citizens of the Union and their family members to move and reside freely within the territory of the Member States amending Regulation (EEC) No 1612/68 and repealing Directives 64/221/EEC, 68/360/EEC, 72/194/EEC, 73/148/EEC, 75/34/EEC, 75/35/EEC, 90/364/EEC, 90/365/EEC and 93/96/EEC (OJ L 158, 30.4.2004, p. 77).

(3) To limit the spread of the virus, the Member States have adopted various measures, some of which have had an impact on citizens' right to move and reside freely within the territory of the Member States, such as restrictions on entry or requirements for cross-border travellers to undergo quarantine/self-isolation or a test for SARS-CoV-2 infection.

(4) On 13 October 2020, the Council adopted Council Recommendation (EU) 2020/1475 on a coordinated approach to the restriction of free movement in response to the COVID-19 pandemic[7]. That Recommendation establishes a coordinated approach on the following key points: the application of common criteria and thresholds when deciding whether to introduce restrictions to free movement, a mapping of the risk of COVID-19 transmission based on an agreed colour code, and a coordinated approach as to the measures, if any, which may appropriately be applied to persons moving between areas, depending on the level of risk of transmission in those areas. In view of their specific situation, the Recommendation also emphasises that essential travellers, as listed in its point 19, and cross-border commuters, whose lives are particularly affected by such restrictions, in particular those exercising critical functions or essential for critical infrastructure, should in principle be exempted from travel restrictions linked to COVID-19.

(5) Using the criteria and thresholds established in Recommendation (EU) 2020/1475, the European Centre for Disease Prevention and Control ('ECDC') has been publishing, once a week, a map of Member States, broken down by regions, in order to support Member States' decision-making[8].

(6) ~~As emphasised by Recommendation (EU) 2020/1475 any,~~ **Member States may limit the fundamental right of free movement for public health reasons. Any** restrictions to the free movement of persons within the Union put in place to limit the spread of COVID-19 should be based on specific and limited public interest grounds, namely the protection of public health **as emphasised by Recommendation (EU) 2020/1475**. It is necessary for such limitations to be applied in compliance with the general principles of Union law, in particular proportionality and non-discrimination. Any measures taken should thus not extend beyond what is strictly necessary to safeguard public health. Furthermore, they should be consistent with measures taken by the Union to ensure seamless free movement of goods and essential services across the Single Market, including those of medical supplies and personnel through the so-called "Green Lane" border crossings referred to in the Commission Communication on the implementation of the Green Lanes under the Guidelines for border management measures to protect health and ensure the availability of goods and essential services[9].

(7) The free movement of persons who do not pose a risk to public health, for example because they are immune to and cannot transmit SARS-CoV-2, should not be restricted, as such restrictions would not be necessary to achieve the objective pursued.

---

7 OJ L 337, 14.10.2020, p. 3.

8 Available at: https://www.ecdc.europa.eu/en/covid-19/situation-updates/weekly-maps-coordinated-restriction-free-movement

9 OJ C 96I, 24.3.2020, p. 1.

(8) Many Member States have launched or plan to launch initiatives to issue vaccination certificates. However, for these to be used effectively in a cross-border context when citizens exercise their free movement rights, such certificates need to be fully interoperable, secure and verifiable. A commonly agreed approach is required among Member States on the content, format, principles and technical standards of such certificates.

(9) Unilateral measures in this area have the potential to cause significant disruptions to the exercise of free movement rights, as national authorities and passenger transport services, such as airlines, trains, coaches or ferries, are confronted with a wide array of diverging document formats, not only regarding a person's vaccination status but also on tests and possible recovery from COVID-19.

(10) To facilitate the exercise of the right to move and reside freely within the territory of the Member States, a common framework for the issuance, verification and acceptance of interoperable certificates on COVID-19 vaccination, testing and recovery, entitled "Digital Green Certificate" should be established.

(11) This Regulation should not be understood as facilitating or encouraging the adoption of restrictions to free movement, or other fundamental rights, in response to the pandemic. In particular, the exemptions to the restriction of free movement in response to the COVID-19 pandemic referred to in Recommendation (EU) 2020/1475 should continue to apply **and the specific situation of cross border communities should be taken into account.** At the same time, the "Digital Green Certificate" framework will ensure that interoperable certificates are also available to essential travellers.

(11a) This Regulation should not cover Member States' decisions to impose or waive restrictions to free movement put in place, in compliance with Union law, to limit the spread of COVID-19. The use of the Digital Green Certificate in view of lifting restrictions should remain the responsibilty of the Member States.

(12) The foundation of a common approach for the issuance, verification and acceptance of such interoperable certificates hinges upon trust. False COVID-19 certificates may pose a significant risk to public health. Authorities in one Member State need assurance that the information included in a certificate issued in another Member State is trustworthy, that it has not been forged, that it belongs to the person presenting it, and that anyone verifying this information only has access to the minimum amount of information necessary.

(13) The risk posed by false COVID-19 certificates is real. On 1 February 2021, Europol issued an Early Warning Notification on the illicit sales of false negative COVID-19 test certificates[10]. Given the available and easily accessible technological means, such as high-resolution printers and various graphics editor software, fraudsters are able to produce high-quality forged, faked or counterfeit certificates. Cases of illicit sales of fraudulent test certificates have been reported, involving more organised forgery rings and individual opportunistic scammers selling false certificates offline and online.

---

10 https://www.europol.europa.eu/early-warning-notification-illicit-sales-of-false-negative-covid-19-test-certificates

(14) To ensure interoperability and equal access, **including for persons with disabilities**, Member States should issue the certificates making up the Digital Green Certificate in a digital or paper-based format, or both, **depending on the choice of the prospective holder**. This should allow the prospective holder to request and receive a paper copy of the certificate or to store and display the certificate on a mobile device. The certificates should contain an interoperable, digitally readable barcode containing the relevant data relating to the certificates. Member States should guarantee the authenticity, validity and integrity of the certificates by electronic seals or similar means. The information on the certificate should also be included in human-readable format, either printed or displayed as plain text. The layout of the certificates should be easy to understand and ensure simplicity and user-friendliness. To avoid obstacles to free movement, **and although there may be a charge for related services, such as for tests**, the certificates **themselves** should be issued free of charge, and citizens should have a right to have them issued. Member States should issue the certificates making up the Digital Green Certificate automatically or upon request, ensuring that they can be obtained easily and providing, where needed, the necessary support to allow for equal access by all citizens.

(15) The security, authenticity, integrity and validity of the certificates making up the Digital Green Certificate and their compliance with Union data protection legislation are key to their acceptance in all Member States. It is therefore necessary to establish a trust framework laying out the rules on and infrastructure for the reliable and secure issuance and verification of certificates. The outline on the interoperability of health certificates[11] adopted, on 12 March 2021, by the eHealth Network set up under Article 14 of Directive 2011/24/EU[12] should form the basis for the trust framework.

(16) Pursuant to this Regulation, the certificates making up the Digital Green Certificate should be issued to beneficiaries as referred to in Article 3 of Directive 2004/38/EC, that is, Union citizens and their family members, by the Member State of vaccination or test, or where the recovered person is located. **Where reference is made to issuance by Member States, this should be understood as also covering issuance by designated bodies on behalf of Member States, including when they are issued in Overseas Countries and Territories or the Faroe Islands on behalf of a Member State.** Where relevant or appropriate, the certificates should be issued on behalf of the vaccinated, tested or recovered person, for example on behalf of legally incapacitated persons or to parents on behalf of their children. The certificates should not require legalisation or other similar formalities.

(17) The certificates making up the Digital Green Certificate could also be issued to nationals or residents of Andorra, Monaco, San Marino and the Vatican/Holy See. ~~in particular where they are vaccinated by a Member State.~~

---

[11] Available at: https://ec.europa.eu/health/sites/health/files/ehealth/docs/trust-framework_interoperability_certificates_en.pdf

[12] Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare (OJ L 88, 4.4.2011, p. 45).

(18) It is necessary to take into account that the agreements on free movement of persons concluded by the Union and its Member States, of the one part, and certain third countries, of the other part, provide for the possibility to restrict free movement for public health reasons. Where such an agreement does not contain a mechanism of incorporation of European Union acts, certificates issued to beneficiaries of such agreements should be accepted under the conditions laid down in this Regulation. This should be conditional on an implementing act to be adopted by the Commission establishing that such a third country issues certificates in accordance with this Regulation and has provided formal assurances that it would accept certificates issued by the Member States.

(19) Regulation (EU) 2021/XXXX applies to third-country nationals who do not fall within the scope of this Regulation and who reside or stay legally in the territory of a State to which that Regulation applies and who are entitled to travel to other States in accordance with Union law.

(20) The framework to be established for the purpose of this Regulation should seek to ensure coherence with global initiatives, in particular involving the WHO **and the International Civil Aviation Organisation (ICAO)**. This should include, where possible, interoperability between technological systems established at global level and the systems established for the purpose of this Regulation to facilitate free movement within the Union, including through the participation in a public key infrastructure or the bilateral exchange of public keys. To facilitate the free movement rights of Union citizens vaccinated **or tested** by third countries **or by Overseas Countries or Territories referred to in Article 355 (2) TFEU or listed in its annex II or the Faroe Islands**, this Regulation should provide for the acceptance of certificates issued by third countries **or by Overseas Countries or Territories or the Faroe Islands** to Union citizens and their family members where the Commission finds that these certificates are issued according to standards equivalent to those established pursuant to this Regulation.

(20a) If the technical solution chosen for verification requires a Member State to transfer personal data to a recipient in a third country to confirm and verify the vaccination, testing or recovery status of the holder of a certificate issued by a third country, such transfer should be limited to the data necessary for the verification of the authenticity, validity and integrity of the certificate and may only be carried out in compliance with the conditions set out in Chapter V of Regulation (EU) 2016/679.

(21) To facilitate free movement, and to ensure that restrictions of free movement currently in place during the COVID-19 pandemic can be lifted in a coordinated manner based on the latest scientific evidence available, an interoperable vaccination certificate should be established. This vaccination certificate should serve to confirm that the holder has received a COVID-19 vaccine in a Member State. The certificate should contain only the necessary information to clearly identify the holder as well as the COVID-19 vaccine, number, date and place of vaccination. Member States should issue vaccination certificates **to** ~~for~~ persons receiving vaccines that have been granted marketing authorisation pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council[13], ~~for~~ vaccines that have been granted marketing authorisation pursuant to Directive 2001/83/EC of the European Parliament and of the Council[14], or vaccines whose distribution has been temporarily authorised pursuant to Article 5(2) of Directive 2001/83/EC.

(22) Persons who have been vaccinated before the date of application of this Regulation, including as part of a clinical trial, should also have the **right** ~~possibility~~ to obtain a certificate on COVID-19 vaccination that complies with this Regulation **given that the Digital Green Certificate provides the mutually accepted framework to facilitate free movement**. **Where Union citizens or their family members are not in possession of a certificate that complies with the requirements of this Regulation, in particular because they have been vaccinated before the entry into force of this Regulation, they should be given every reasonable opportunity to corroborate or prove by other means that they should benefit from the waiving of relevant restrictions to free movement afforded by a Member State. This should not be understood as affecting the obligation of Member States to issue certificates that comply with the requirements of this Regulation nor the right of Union citizens or their family members to receive, from Member States, certificates that comply with the requirements of this Regulation.** At the same time, Member States should remain free to issue proofs of vaccination in other formats for other purposes, in particular for medical purposes.

(23) Member States **may** also issue **upon request** such vaccination certificates to Union citizens and their family members who have been vaccinated in a third country and provide **all necessary information, including** reliable proof to that effect. **This is of particular importance to allow the persons concerned to make use of an interoperable and accepted vaccination certificate when exercising their right of free movement within the Union. There is no requirement for Member States to issue such vaccination certificates at consular posts.**

---

13 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1).

14 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p.67).

(24) On 27 January 2021, the eHealth Network adopted guidelines on proof of vaccination for medical purposes, which it updated on 12 March 2021[15]. These guidelines, in particular the preferred code standards, should form the basis for the technical specifications adopted for the purpose of this Regulation.

(25) Already now, several Member States exempt vaccinated persons from certain restrictions to free movement within the Union. Where Member States accept proof of vaccination in order to waive restrictions to free movement put in place, in compliance with Union law, to limit the spread of COVID-19, such as requirements to undergo quarantine/self-isolation or be tested for SARS-CoV-2 infection, they should be required to accept, under the same conditions, valid vaccination certificates issued by other Member States in compliance with this Regulation. This acceptance should take place under the same conditions, meaning that, for example, where a Member State considers sufficient a single dose of a vaccine administered, it should do so also for holders of a vaccination certificate indicating a single dose of the same vaccine. ~~On grounds of public health, this obligation should be limited to persons having received COVID-19 vaccines having been granted marketing authorisation pursuant to Regulation (EC) No 726/2004. This should not prevent Member States from deciding to accept vaccination certificates issued for other COVID-19 vaccines, such as vaccines having been granted marketing authorisation by the competent authority of a Member State pursuant to Directive 2001/83/EC, vaccines whose distribution has been temporarily authorised based on Article 5(2) of Directive 2001/83/EC, or vaccines having received a WHO Emergency Use Listing.~~

[15] Available at : https://ec.europa.eu/health/sites/health/files/ehealth/docs/vaccination-proof_interoperability-guidelines_en.pdf

(25a) Regulation (EC) No 726/2004 puts in place harmonised procedures, involving all Member States, for the authorisation and surveillance of medicinal products at Union level, ensuring that only high quality medicinal products are placed on the market and administered to persons throughout the Union. As a result, the marketing authorisations granted by the Union pursuant to Regulation (EC) No 726/2004, including the underlying evaluation of the medicinal product concerned in terms of quality, safety and efficacy, are valid in all Member States. In addition, efficacy follow-up and supervision procedures of medicinal products authorised pursuant to Regulation (EC) No 726/2004 are carried out centrally for all Member States. The assessment and approval of vaccines via the centralised procedure follows shared standards and is done in a consistent way on behalf of all Member States. Member States' participation in the review and endorsement of the assessment is ensured through various committees and groups, which also benefits from the expertise from the EU Medicines Regulatory Network. The authorisation via the centralised procedure provides the confidence that all Member States can rely on the authorisation and data on efficacy as well as safety and on the consistency of the batches being used for vaccination of citizens. The obligation to accept, under the same conditions, valid vaccination certificates issued by other Member States should therefore cover COVID-19 vaccines having been granted marketing authorisation pursuant to Regulation (EC) No 726/2004. In order to support the work of WHO and to strive for better global interoperability, Member States are in particular encouraged to accept vaccination certificates issued for other COVID-19 vaccines having received a WHO Emergency Use Listing.

(25b) This should not prevent Member States from deciding to accept vaccination certificates issued for other COVID-19 vaccines, such as vaccines having been granted marketing authorisation by the competent authority of a Member State pursuant to Directive 2001/83/EC, vaccines whose distribution has been temporarily authorised based on Article 5(2) of Directive 2001/83/EC, or vaccines having received a WHO Emergency Use Listing. Where one of these COVID-19 vaccines is subsequently granted marketing authorisation pursuant to Regulation (EC) No 726/2004, the obligation to accept, under the same conditions, would also cover valid vaccination certificates issued by a Member States for that COVID-19 vaccine, regardless whether the certificates were issued before or after the authorisation via the centralised procedure.

(26) It is necessary to prevent discrimination against persons who are not vaccinated, for example because of medical reasons, because they are not part of the target group for which the vaccine is currently recommended **or allowed, such as children**, or because they have not yet had the opportunity or chose not to be vaccinated. Therefore, possession of a vaccination certificate, or the possession of a vaccination certificate indicating a specific vaccine medicinal product, should not be a pre-condition to exercise free movement rights, in particular where those persons are, by other means, able to show compliance with lawful, public-health-related requirements, and cannot be a pre-condition to use cross-border passenger transport services such as airlines, trains, coaches or ferries.

(27) Many Member States have been requiring persons travelling to their territory to undergo a test for SARS-CoV-2 infection before or after arrival. At the beginning of the COVID-19 pandemic, Member States typically relied on reverse transcription polymerase chain reaction (RT-PCR), which is a nucleic acid amplification test (NAAT) for COVID-19 diagnostics considered by the WHO and ECDC as the 'gold standard', that is, the most reliable methodology for testing of cases and contacts[16]. As the pandemic has progressed, a new generation of faster and cheaper tests has become available on the European market, the so-called rapid antigen tests, which detect the presence of viral proteins (antigens) to detect an ongoing infection. On 18 November 2020, the Commission adopted Commission Recommendation (EU) 2020/1743 on the use of rapid antigen tests for the diagnosis of SARS-CoV-2 infection[17].

(28) On 22 January 2021, the Council adopted Council Recommendation 2021/C 24/01 on a common framework for the use and validation of rapid antigen tests and the mutual recognition of COVID-19 test results in the EU[18], which provides for the development of a common list of COVID-19 rapid antigen tests. On this basis, the Health Security Committee agreed, on 18 February 2021, on a common list of COVID-19 rapid antigen tests, a selection of rapid antigen tests for which Member States will mutually recognise their results, and a common standardised set of data to be included in COVID-19 test result certificates[19].

(29) Despite these common efforts, Union citizens and their family members exercising their free movement right still face problems when trying to use a test result obtained in one Member State in another. These problems are often linked to the language in which the test result is issued, or to lack of trust in the authenticity of the document shown. **Such problems are compounded for persons who cannot be vaccinated yet, in particular children, for whom test results may be the only way to travel in case restrictions are in place.**

(30) To improve the acceptance of test results carried out in another Member State when presenting such results for the purposes of exercising free movement, an interoperable test certificate should be established, containing the necessary information to clearly identify the holder as well as the type, date and result of the test for SARS-CoV-2 infection. To ensure the reliability of the test result, only the results of NAAT tests and rapid antigen tests featured in the list established on the basis of Council Recommendation 2021/C 24/01 should be eligible for a test certificate issued on the basis of this Regulation. The common standardised set of data to be included in COVID-19 test result certificates agreed by the Health Security Committee on the basis of Council Recommendation 2021/C 24/01, in particular the preferred code standards, should form the basis for the technical specifications adopted for the purpose of this Regulation.

---

16 https://www.ecdc.europa.eu/sites/default/files/documents/TestingStrategy_Objective-Sept-2020.pdf

17 OJ L 392, 23.11.2020, p. 63.

18 OJ C 24, 22.1.2021, p. 1.

19 https://ec.europa.eu/health/sites/health/files/preparedness_response/docs/covid-19_rat_common-list_en.pdf

(31) Test certificates issued by Member States in compliance with this Regulation should be accepted by Member States requiring proof of a test for SARS-CoV-2 infection in the context of the restrictions to free movement put in place to limit the spread of COVID-19.

(32) According to existing evidence, persons who have recovered from COVID-19 can continue to test positive for SARS-CoV-2 for a certain period after symptom onset[20]. Where such persons are required to undergo a test when seeking to exercise free movement, they may thus be effectively prevented from travelling despite no longer being infectious. To facilitate free movement, and to ensure that restrictions of free movement currently in place during the COVID-19 pandemic can be lifted in a coordinated manner based on the latest scientific evidence available, an interoperable certificate of recovery should be established, containing the necessary information to clearly identify the person concerned and the date of a previous positive test for SARS-CoV-2 infection. A certificate of recovery should be issued at the earliest from the eleventh day after the first positive test and should be valid for not more than 180 days. According to ECDC, recent evidence shows that despite shedding of viable SARS-CoV-2 between ten and twenty days from the onset of symptoms, convincing epidemiological studies have failed to show onward transmission of disease after day ten. The Commission should be empowered to change this period on the basis of guidance from the Health Security Committee or from ECDC, which is closely studying the evidence base for the duration of acquired immunity after recovery.

(33) Already now, several Member States exempt recovered persons from certain restrictions to free movement within the Union. Where Member States accept proof of recovery in order to waive restrictions to free movement put in place, in compliance with Union law, to limit the spread of SARS-CoV-2, such as requirements to undergo quarantine/self-isolation or be tested for SARS-CoV-2 infection, they should be required to accept, under the same conditions, valid certificates of recovery issued by other Member States in compliance with this Regulation. The eHealth Network, in collaboration with Health Security Committee, is also working on guidelines on recovery certificates and respective datasets.

(33a) Taking into account the latest scientific and technological developments, the Commission should be empowered to adapt the provisions on the certificate of recovery by providing for its issuance on the basis of a positive rapid antigen test, serological testing for antibodies against SARS-CoV-2 or any other scientifically reliable method by means of a delegated act. This delegated act should include the necessary data fields on the categories of data to be included in the certificate. It should also contain specific provisions on the maximum validity period as it might depend on the type of the test carried out. The issuance and acceptance of the certificate of recovery based on the tests and methods mentioned above should be optional.

[20] https://www.ecdc.europa.eu/sites/default/files/documents/Guidance-for-discharge-and-ending-of-isolation-of-people-with-COVID-19.pdf

(34) To be able to obtain a common position quickly, the Commission should be able to ask the Health Security Committee established by Article 17 of Decision No 1082/2013/EU of the European Parliament and of the Council[21] to issue guidance about the available scientific evidence concerning the effects of medical events documented in the certificates established in accordance with this Regulation, including the effectiveness and duration of the immunity conferred by COVID-19 vaccines, whether vaccines prevent asymptomatic infection and transmission of the virus, the situation of people having recovered from the virus, and the impacts of the new SARS-CoV-2 variants on people having been vaccinated or already contaminated.

(35) In order to ensure uniform conditions for the implementation of the trust framework certificates established by this Regulation, implementing powers should be conferred on the Commission. Those powers should be *exercised* in accordance with Regulation (EU) No 182/2011 of the European Parliament and of the Council[22].

(36) The Commission should adopt immediately applicable implementing acts where, in duly justified cases relating to the technical specifications necessary to establish interoperable certificates*,* imperative grounds of urgency so require or when new scientific evidence becomes available.

(37) Regulation (EU) 2016/679 of the European Parliament and of the Council[23] applies to the processing of personal data carried out when implementing this Regulation. This Regulation establishes the legal ground for the processing of personal data, within the meaning of Articles 6(1)(c) and 9(2)(g) of Regulation (EU) 2016/679, necessary for the issuance and verification of the interoperable certificates provided for in this Regulation. It ~~also~~ does not regulate the processing of personal data related to the documentation of a vaccination, test or recovery event for other purposes, such as for the purposes of pharmacovigilance or for the maintenance of individual personal health records. **Member States may process such data for other purposes, if** ~~T~~the legal basis for processing **of such data** for other purposes, **including the related retention periods,** is ~~to be~~ provided for in national law, which must comply with Union data protection legislation.

(38) In line with the principle of minimisation of personal data, the certificates should only contain the personal data necessary for the purpose of facilitating the exercise of the right to free movement within the Union during the COVID-19 pandemic. The specific categories of personal data and data fields to be included in the certificates should be set out in this Regulation.

---

21 Decision No 1082/2013/EU of the European Parliament and of the Council of 22 October 2013 on serious cross-border threats to health and repealing Decision No 2119/98/EC (OJ L 293, 5.11.2013, p. 1).

22 OJ L 55, 28.2.2011, p. 13.

23 Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (OJ L 119, 4.5.2016, p. 1).

(39) For the purposes of this Regulation, personal data may be transmitted/exchanged across borders with the sole purpose of obtaining the information necessary to confirm and verify the holder's vaccination, testing or recovery status. In particular, it should allow for the verification of the authenticity of the certificate.

(40) This Regulation does not create a legal basis for retaining personal data obtained from the certificate by the Member State of destination or by the cross-border passenger transport services operators required by national law to implement certain public health measures during the COVID-19 pandemic.

(41) To ensure coordination, the Member States and the Commission should be informed when a Member State requires holders of certificates to undergo, after entry into its territory, quarantine/self-isolation or a test for SARS-CoV-2 infection, or if it **imposes other restrictions on holders of such certificates** ~~denies entry to such persons~~.

(41a) Clear, comprehensive and timely communication to the public on the issuance and acceptance of each type of certificate making up the Digital Green Certificate is crucial to ensure predictability for travel and legal certainty. The Commission should support the Member States' efforts in this regard, for example by making available the information provided by Member States on the 'Re-open EU' web platform.

(42) In accordance with Recommendation (EU) 2020/1475, any restrictions to the free movement of persons within the Union put in place to limit the spread of SARS-CoV-2 should be lifted as soon as the epidemiological situation allows. This also applies to obligations to present documents other than those required by Union law, in particular Directive 2004/38/EC, such as the certificates covered by this Regulation. ~~Therefore, the Regulation's provisions on the "Digital Green Certificate" framework for the issuance, verification and acceptance of interoperable certificates on COVID-19 vaccination, testing and recovery should be suspended once the Director-General of the WHO has declared, in accordance with the International Health Regulations, that the public health emergency of international concern caused by SARS-CoV-2 has ended. At the same time, their application should resume if the Director-General of the WHO declares another public health emergency of international concern due to an outbreak of SARS-CoV-2, a variant thereof, or similar infectious diseases with epidemic potential. Where this is the case, the provisions concerned should again be suspended once that public health emergency of international concern has ended.~~**This Regulation should apply for 12 months from the date of its entry into force.** ~~(43)~~ **At the latest 3 months before the end of the application of this Regulation, taking into account the evolution of the epidemiological situation on the pandemic,** the Commission should publish a report on the lessons learned from the application of this Regulation, including on its impact on the facilitation of free movement and data protection. ~~one year after the Director-General of the WHO has declared that the public health emergency of international concern caused by SARS-CoV-2 has ended~~.

(42a) A transitional period should be provided to give Member States the possibility to continue issuing certificates which are not yet in compliance with this Regulation. During the transitional period, such certificates as well as certificates issued before the entry into force of this Regulation should be accepted by Member States provided they contain the necessary data.

(44) In order to take into account the epidemiological situation and the progress in containing the COVID-19 pandemic and to ensure interoperability with international standards, the power to adopt acts in accordance with Article 290 of the Treaty on the Functioning of the European Union should be delegated to the Commission in respect of the application of certain Articles of this Regulation as well as the list of personal data to be included in the certificates covered by this Regulation. It is of particular importance that the Commission carry out appropriate consultations during its preparatory work, including at expert level, and that those consultations be conducted in accordance with the principles laid down in the Interinstitutional Agreement on Better Law-Making of 13 April 2016[24]. In particular, to ensure equal participation in the preparation of delegated acts, the European Parliament and the Council receive all documents at the same time as Member States' experts, and their experts systematically have access to meetings of Commission expert groups dealing with the preparation of delegated acts.

(45) Since the objectives of this Regulation, namely to facilitate the free movement within the Union during the COVID-19 pandemic by establishing interoperable certificates on the holder's vaccination, testing and recovery status, cannot be sufficiently achieved by the Member States but can rather, by reason of the scale and effects of the action, be better achieved at Union level, the Union may adopt measures, in accordance with the principle of subsidiarity as set out in Article 5 of the Treaty on European Union. In accordance with the principle of proportionality, as set out in that Article, this Regulation does not go beyond what is necessary in order to achieve those objectives.

(46) This Regulation respects the fundamental rights and observes the principles recognised in particular by the Charter of Fundamental Rights ('Charter'), including the right to respect for private life and family life, the right to the protection of personal data, the right to equality before the law and non-discrimination, the right to free movement and the right to an effective remedy. Member States should comply with the Charter when implementing this Regulation.

(47) The European Data Protection Supervisor **and the European Data Protection Board have** ~~has~~ been consulted ~~pursuant to~~ in accordance with Article 42~~(1)~~ of Regulation (EU) 2018/1725[25] **and delivered a joint opinion on 31 March 2021**,

---

[24] OJ L 123, 12.5.2016, p. 1.

[25] Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC (OJ L 295, 21.11.2018, p. 39).

HAVE ADOPTED THIS REGULATION:

Article 1
Subject matter

This Regulation lays down a framework for the issuance, verification and acceptance of interoperable certificates on COVID-19 vaccination, testing and recovery. **It shall** ~~in order to~~ facilitate the holders' exercise of their right to free movement during the COVID-19 pandemic ("Digital Green Certificate").

It provides for the legal ground to process personal data necessary to issue such certificates and to process the information necessary to confirm and verify the authenticity and validity of such certificates.

Article 2
Definitions

For the purposes of this Regulation, the following definitions apply:

(1) "holder" means the **person** ~~Union citizen or their family members~~ to whom an interoperable certificate containing information about his or her vaccination, testing and/or recovery status has been issued in accordance with this Regulation.

(2) "Digital Green Certificate" means interoperable certificates containing information about the vaccination, testing and/or recovery status of the holder issued in the context of the COVID-19 pandemic;

(3) "COVID-19 vaccine" means an immunological medicinal product indicated for active immunisation to prevent COVID-19;

(4) "NAAT test" means a molecular nucleic acid amplification test (NAAT), such as reverse transcription polymerase chain reaction (RT-PCR), loop-mediated isothermal amplification (LAMP) and transcription-mediated amplification (TMA) techniques, used to detect the presence of the SARS-CoV-2 ribonucleic acid (RNA);

(5) "rapid antigen test" means a testing method that relies on detection of viral proteins (antigens) using a lateral flow immunoassay that gives results in less than 30 minutes;

(6) "interoperability" means the capability of verifying systems in a Member State to use data encoded by another Member State;

(7) "barcode" means a method of storing and representing data in a visual, machine-readable format;

(8) "electronic seal" means data in electronic form, which is attached to or logically associated with other data in electronic form to ensure the latter's origin and integrity;

(9) "unique certificate identifier" means a unique identifier given, in accordance with a common structure, to each certificate issued in accordance with this Regulation;

(10) "trust framework" means the rules, policies, specifications, protocols, data formats and digital infrastructure regulating and allowing for the reliable and secure issuance and verification of certificates to guarantee the certificates' trustworthiness by confirming their authenticity, validity and integrity, including by the possible use of electronic seals.

Article 3
Digital Green Certificate

1. The interoperable Digital Green Certificate **framework** shall allow for the issuance and cross-border verification and acceptance of any of the following certificates:

   (a) a certificate confirming that the holder has received a COVID-19 vaccine in the Member State issuing the certificate ('vaccination certificate');

   (b) a certificate indicating the holder's result**, type** and date of a NAAT test or a rapid antigen test listed in the common and updated list of COVID-19 rapid antigen tests established on the basis of Council Recommendation 2021/C 24/01[26] **carried out by health professionals in the Member State issuing the certificate** ('test certificate');

   (c) a certificate confirming that the holder has recovered from a SARS-CoV-2 infection following a positive NAAT test ~~or a positive rapid antigen test listed in the common and updated list of COVID-19 rapid antigen tests established on the basis of Recommendation 2021/C 24/01~~ ('certificate of recovery').

   The Commission shall publish the list of COVID-19 rapid antigen tests established on the basis of Council Recommendation 2021/C 24/01, including any updates.

2. Member States, **or designated bodies acting on behalf of Member States,** shall issue the certificates referred to in paragraph 1 in a digital or paper-based format, or both. The certificates issued by Member States shall contain an interoperable barcode allowing for the verification of the authenticity, validity and integrity of the certificate. The barcode shall comply with the technical specifications established in accordance with Article 8. The information contained in the certificates shall also be shown in human-readable form and shall be, at least, in the official language or languages of the issuing Member State and English.

[26] Council Recommendation on a common framework for the use and validation of rapid antigen tests and the mutual recognition of COVID-19 test results in the EU (2021/C 24/01) (OJ C 24, 22.1.2021, p. 1).

3. The certificates referred to in paragraph 1 shall be issued free of charge. The holder shall be entitled to request the issuance of a new certificate if the personal data contained in the certificate is not or no longer accurate or up to date, or the certificate is no longer available to the holder. **Appropriate fees may be charged in case of repeated loss.**

3a **The certificate shall include the following text:**

"This certificate is not a travel document. The scientific evidence on COVID-19 vaccination, testing and recovery continues to evolve, also in view of new variants of concern of the virus. Before traveling, please check the applicable public health measures and related restrictions applied at the point of destination."

3b **Possession of a Digital Green Certificate shall not be a precondition to exercise free movement rights.**

4. Issuance of the certificates referred to in paragraph 1 shall not affect the validity of other proofs of vaccination, test or recovery issued before the entry into application of this Regulation or for other purposes, in particular for medical purposes.

5. Where the Commission has adopted an implementing act pursuant to the second sub-paragraph, certificates **equivalent to those** issued in accordance with this Regulation by a third country with which the European Union and its Member States have concluded an agreement on free movement of persons allowing the contracting parties to restrict such free movement on grounds of public health in a non-discriminatory manner and which does not contain a mechanism of incorporation of European Union acts shall be accepted under the conditions referred to in Articles 5(5), **6(5) and 7(5)**.

The Commission shall assess whether such a third country issues certificates **equivalent to those issued** in accordance with this Regulation and has provided formal assurances that it will accept certificates issued by the Member States. In that case, it shall adopt an implementing act in accordance with the examination procedure referred to in Article 13(2).

6. **Where necessary,** the Commission **shall** ask the Health Security Committee established by Article 17 of Decision No 1082/2013/EU**, the European Center for Disease Prevention and Control or the European Medicines Agency** to issue guidance on the available scientific evidence on the effects of medical events documented in the certificates referred to in paragraph 1, **in particular in view of newly emerging SARS-CoV-2 variants of concern**.

Article 4
Digital Green Certificate trust framework

1. The Commission and the Member States shall set up and maintain a trust framework digital infrastructure allowing for the secure issuance and verification of the certificates referred to in Article 3.

2. The trust framework shall **seek to** ensure~~, where possible,~~ interoperability with technological systems established at international level.

~~3. Where the Commission has adopted an implementing act pursuant to the second sub-paragraph, certificates issued by third countries to Union citizens and their family members according to an international standard and technological system that are interoperable with the trust framework established on the basis of this Regulation and that allows for the verification of the authenticity, validity and integrity of the certificate, and which contain the data set out in the Annex shall be treated like certificates issued by Member States in accordance with this Regulation, for the purpose of facilitating the holders' exercise of their right to free movement within the European Union. For the purposes of this sub-paragraph, the acceptance, by the Member States, of vaccination certificates issued by third countries shall take place under the conditions referred to in Article 5(5).~~

~~The Commission shall assess whether certificates issued by a third country fulfil the conditions set out in this paragraph. In that case, it shall adopt an implementing act in accordance with the examination procedure referred to in Article 13(2).~~

Article 5
Vaccination certificate

1. Each Member State shall issue vaccination certificates as referred to in Article 3(1)(a) to a person to whom a COVID-19 vaccine has been administered, either automatically or upon request by that person.

2. The vaccination certificate shall contain the following categories of ~~personal~~ data:

   (a) identification of the holder;

   (b) information about the vaccine medicinal product administered;

   (c) certificate metadata, such as the certificate issuer or a unique certificate identifier.

   The ~~personal~~ data shall be included in the vaccination certificate in accordance with the specific data fields set out in point 1 of the Annex.

The Commission is empowered to adopt delegated acts in accordance with Article 11 to amend point 1 of the Annex by adding, modifying or removing data fields, ~~on the categories of personal data mentioned in this paragraph~~ **where such amendment is necessary to confirm or verify the authenticity, validity and integrity of the certificate, in case of scientific progress in containing the COVID-19 pandemic or to ensure interoperability with international standards.**

3. The vaccination certificate shall be issued in a secure and interoperable format as provided for in Article 3(2) **after the administration of each dose** and shall clearly indicate whether or not the vaccination course has been completed.

4. Where, in the case of newly emerging scientific evidence or to ensure interoperability with international standards and technological systems, imperative grounds of urgency so require, the procedure provided for in Article 12 shall apply to delegated acts adopted pursuant to this Article.

5. Where Member States accept proof of vaccination in order to waive restrictions to free movement put in place, in compliance with Union law, to limit the spread of COVID-19, they shall also accept, under the same conditions, valid vaccination certificates issued by other Member States in compliance with this Regulation for a COVID-19 vaccine having been granted marketing authorisation pursuant to Regulation (EC) No 726/2004.

Member States may also accept, for the same purpose, valid vaccination certificates issued by other Member States in compliance with this Regulation for a COVID-19 vaccine having been granted marketing authorisation by the competent authority of a Member State pursuant to Directive 2001/83/EC, a COVID-19 vaccine whose distribution has been temporarily authorised based on Article 5(2) of Directive 2001/83/EC, or a COVID-19 vaccine having received a WHO Emergency Use Listing. **Where Member States accept valid vaccination certificates issued in compliance with this Regulation for a COVID-19 vaccine having been granted marketing authorisation by the competent authority of a Member State pursuant to Directive 2001/83/EC, a COVID-19 vaccine whose distribution has been temporarily authorised based on Article 5(2) of Directive 2001/83/EC, or a COVID-19 vaccine having received a WHO Emergency Use Listing they shall also accept, under the same conditions, valid vaccination certificates issued by other Member States.**

~~6. Where a Union citizen or a family member of a Union citizen has been vaccinated in a third country with one of the types of COVID-19 vaccines referred to in paragraph 5 of this Article, and where the authorities of a Member State have been provided with all necessary information, including reliable proof of vaccination, they shall issue a vaccination certificate as referred to in Article 3(1)(a) to the person concerned.~~

Article 6
Test certificate

1. Each Member State shall issue test certificates as referred to in Article 3(1)(b) to persons tested for COVID-19, either automatically or upon request by that person.

2. The test certificate shall contain the following categories of ~~personal~~ data:

   (a) identification of the holder;

   (b) information about the test carried out;

   (c) certificate metadata, such as the certificate issuer or a unique certificate identifier.

   The ~~personal~~ data shall be included in the test certificate in accordance with the specific data fields set out in point 2 of the Annex.

   The Commission is empowered to adopt delegated acts in accordance with Article 11 to amend point 2 of the Annex by adding, modifying or removing data fields ~~on the categories of personal data mentioned in this paragraph~~ **where such amendment is necessary to confirm or verify the authenticity, validity and integrity of the certificate, in case of scientific progress in containing the COVID-19 pandemic or to ensure interoperability with international standards.**

3. The test certificate shall be issued in a secure and interoperable format as provided for in Article 3(2).

4. Where, in the case of newly emerging scientific evidence or to ensure interoperability with international standards and technological systems, imperative grounds of urgency so require, the procedure provided for in Article 12 shall apply to delegated acts adopted pursuant to this Article.

5. Where Member States require proof of a test for SARS-CoV-2 infection as part of the restrictions to free movement put in place, in compliance with Union law **and taking into account the specific situation of cross-border communities**, to limit the spread of COVID-19, they shall also accept**, under the same conditions,** valid test certificates issued by other Member States in compliance with this Regulation.

Article 7
Certificate of recovery

1. Each Member State shall issue, upon request, certificates of recovery as referred to in Article 3(1)(c) at the earliest from the eleventh day after a person has received his or her first positive test for SARS-CoV-2 infection.

   The Commission is empowered to adopt delegated acts in accordance with Article 11 to amend the number of days as of which a certificate of recovery may be issued, based on guidance received from the Health Security Committee in accordance with Article 3(6) or on scientific evidence reviewed by ECDC.

2. The certificate of recovery shall contain the following categories of ~~personal~~ data:

(a) identification of the holder;

(b) information about past SARS-CoV-2 infection **following a positive test**;

(c) certificate metadata, such as the certificate issuer or a unique certificate identifier.

The ~~personal~~ data shall be included in the certificate of recovery in accordance with the specific data fields set out in point 3 of the Annex.

The Commission is empowered to adopt delegated acts in accordance with Article 11 to amend point 3 of the Annex by adding, modifying or removing data fields ~~on the categories of personal data mentioned in this paragraph~~, including until when a certificate of recovery shall be valid, **where such amendment is necessary to confirm or verify the authenticity, validity and integrity of the certificate, in case of scientific progress in containing the COVID-19 pandemic or to ensure interoperability with international standards.**

3. The certificate of recovery shall be issued in a secure and interoperable format as provided for in Article 3(2).

3a Based on guidance received pursuant to Article 3(6), the Commission is empowered to adopt delegated acts in accordance with Article 11 to amend the provisions in Article 3(1)(c) and Article 7(1) to allow for the issuance of the certificate of recovery also based on a positive rapid antigen test, serological testing for antibodies against SARS-CoV-2 or any other scientifically validated method. Any such delegated act shall add, modify or remove the data fields on the categories of data included in the certificate. The issuance and acceptance of the certificate of recovery based on the tests and methods mentioned in this paragraph shall be optional.

4. Where, in the case of newly emerging scientific evidence or to ensure interoperability with international standards and technological systems, imperative grounds of urgency so require, the procedure provided for in Article 12 shall apply to delegated acts adopted pursuant to this Article.

5. Where Member States accept proof of recovery from SARS-CoV-2 infection as a basis for waiving restrictions to free movement put in place, in compliance with Union law, to limit the spread of COVID-19, they shall accept, under the same conditions, valid certificates of recovery issued by other Member States in compliance with this Regulation.

New Article 7a

COVID-19 certificates and other documentation issued by a third country

1. **Where a vaccination certificate has been issued in a third country for a vaccine medicinal product that corresponds to one of the COVID-19 vaccines referred to Article 5(5) and where the authorities in a Member State have been provided with all necessary information, including reliable proof of vaccination, they may, upon request, issue a vaccination certificate as referred to in Article 3(1)(a) to the person concerned. A Member State shall not be required to issue a certificate for a vaccine not authorised for use on its territory.**

2. **Where the Commission has adopted an implementing act pursuant to the second sub-paragraph, certificates referred to in Article 3 issued by third countries according to a standard and technological system that are interoperable with the trust framework established on the basis of this Regulation that allow for the verification of the authenticity, validity and integrity of the certificate, and which contain the data set out in the Annex shall be treated like certificates issued by Member States in accordance with this Regulation, for the purpose of facilitating the holders' exercise of their right to free movement within the European Union.**

The Commission shall assess whether certificates issued by a third country fulfil the conditions set out in this paragraph. In that case, it shall adopt an implementing act in accordance with the examination procedure referred to in Article 13(2).

3. **For the purposes of this article, the acceptance by the Member States of certificates issued pursuant to this Article, shall take place under the conditions referred to in Articles 5(5), 6(5) and 7(5).**

4. **If a Member State accepts a certificate for a COVID-19 vaccine referred to in Article 5(5) second subparagraph issued pursuant to this Article, it shall also accept certificates for the same COVID-19 vaccine issued by a Member State.**

4a. **This Article shall also apply to COVID-19 certificates and other documentation issued by Overseas Countries and Territories referred to in Article 355(2) TFEU and listed in its Annex II, and by the Faroe Islands. It shall not apply to COVID-19 certificates and other documentation issued in Overseas Countries and Territories referred to in Article 355(2) TFEU and listed in its Annex II, and in the Faroe Islands, issued on behalf of a Member State.**

Article 8
Technical specifications

To ensure uniform conditions for implementation of the trust framework established by this Regulation, the Commission shall adopt implementing acts containing the technical specifications and rules to:

(a) securely issue and verify the certificates referred to Article 3;

(b) ensure the security of the personal data, taking into account the nature of the data;

(c) populate the certificates referred to Article 3, including the coding system and any other relevant elements;

(d) lay down the common structure of the unique certificate identifier;

(e) issue a valid, secure and interoperable barcode;

(f) ensure**, where possible,** interoperability with international standards and/or technological systems;

(g) allocate responsibilities amongst controllers and as regards processors, **in accordance with Article 28(3) of Regulation 2016/679**.

Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 13(2).

On duly justified imperative grounds of urgency, in particular to ensure a timely implementation of the trust framework, the Commission shall adopt immediately applicable implementing acts in accordance with the procedure referred to in Article 13(3).

Article 9
Protection of personal data

0. **Regulation (EU) 2016/679 shall apply to the processing of personal data carried out when implementing this Regulation.**

1. The personal data contained in the certificates issued in accordance with this Regulation shall be processed **only** for the purpose of accessing and verifying the information included in the certificate in order to facilitate the exercise of the right of free movement within the Union during the COVID-19 pandemic.

2. The personal data included in the certificates referred to in Article 3 shall be processed by the competent authorities of the Member State of destination **or transit**, or by the cross-border passenger transport services operators required by national law to implement certain public health measures during the COVID-19 pandemic, to confirm and verify the holder's vaccination, testing or recovery status. For this purpose, the personal data shall be limited to what is strictly necessary. The personal data accessed pursuant to this paragraph shall not be retained.

3. The personal data processed for the purpose of issuing the certificates referred to in Article 3, including the issuance of a new certificate, shall not be retained longer than is necessary for its purpose and in no case longer than the period for which the certificates may be used to exercise the right to free movement.

4. The authorities **or other designated bodies** responsible for issuing the certificates referred to in Article 3 shall be considered as controllers referred to in Article 4(7) of Regulation (EU) 2016/679.

4a. The natural or legal person, public authority, agency or other body that has administered the vaccine or carried out the test for which a certificate is to be issued shall transmit to the authorities or other designated bodies responsible for issuing the certificates the categories of data referred to in Articles 5(2), 6(2) and 7(2) necessary to complete the data fields set out in the Annex.

Article 10

Information exchange ~~*Notification procedure*~~

1. Member States shall **inform other** ~~notify~~ Member States and the Commission on the **issuance and** acceptance of the certificates referred to in Article 3 and the conditions thereof, **including which vaccines they accept pursuant to Article 5(5) second subparagraph**.

2. Where a Member State requires holders of certificates referred to in Article 3 to undergo, after entry into its territory, quarantine, self-isolation or a test for SARS-CoV-2 infection, or if it **imposes other restrictions on holders of such certificates** ~~denies entry to such persons~~, it shall **inform,** ~~notify~~ the other Member States and the Commission **thereof, if possible 48 hours in advance of the introduction of new measures.** ~~before the planned introduction of such restrictions.~~ To that end, the Member State shall supply the following information:

   (a) the reasons for such restrictions ~~including all relevant epidemiological data supporting such restrictions~~;

   (b) the scope of such restrictions, specifying **the holders of which certificates** ~~which travellers~~ are subject to or exempt from such restrictions;

   (c) the date and duration of the restrictions.

   ~~Where necessary, the Commission may request additional information from the Member State concerned.~~

2a Member States shall provide the public with clear, comprehensive and timely information on the topics covered by paragraphs 1 and 2. As a general rule, this information should be published 24 hours before the measures come into effect, taking into account that some flexibility is required for epidemiological emergences. The information provided by the Member States may also be made publicly available by the Commission in a centralised manner.

Article 11
Exercise of the delegation

1. The power to adopt delegated acts is conferred on the Commission subject to the conditions laid down in this Article.

2. The power to adopt delegated acts referred to in Articles 5(2), 6(2), 7(1) **and** ~~,~~ 7(2) ~~and 15~~ shall be conferred on the Commission for an indeterminate period of time from [date of entry into force].

3. The delegation of power referred to in Articles 5(2), 6(2), 7(1) **and** ~~,~~ 7(2) ~~and 15~~ may be revoked at any time by the European Parliament or by the Council. A decision to revoke shall put an end to the delegation of the power specified in that decision. It shall take effect the day following the publication of the decision in the *Official Journal of the European Union* or at a later date specified therein. It shall not affect the validity of any delegated acts already in force.

4. Before adopting a delegated act, the Commission shall consult experts designated by each Member State in accordance with the principles laid down in the Interinstitutional Agreement on Better Law-Making of 13 April 2016.

5. As soon as it adopts a delegated act, the Commission shall notify it simultaneously to the European Parliament and to the Council.

6. A delegated act adopted pursuant to Articles 5(2), 6(2), 7(1) **and** ~~,~~ 7(2) ~~and 15~~ shall enter into force only if no objection has been expressed either by the European Parliament or by the Council within a period of two months of notification of that act to the European Parliament and the Council or if, before the expiry of that period, the European Parliament and the Council have both informed the Commission that they will not object. That period shall be extended by two months at the initiative of the European Parliament or of the Council.

Article 12
Urgency procedure

1. Delegated acts adopted under this Article shall enter into force without delay and shall apply as long as no objection is expressed in accordance with paragraph 2. The notification of a delegated act to the European Parliament and to the Council shall state the reasons for the use of the urgency procedure.

2. Either the European Parliament or the Council may object to a delegated act in accordance with the procedure referred to in Article 11(6). In such a case, the Commission shall repeal the act immediately following the notification of the decision to object by the European Parliament or by the Council.

Article 13
Committee procedure

1. The Commission shall be assisted by a committee. That committee shall be a committee within the meaning of Regulation (EU) No 182/2011.

2. Where reference is made to this paragraph, Article 5 of Regulation (EU) No 182/2011 shall apply.

3. Where reference is made to this paragraph, Article 8 of Regulation (EU) No 182/2011, in conjunction with Article 5 thereof, shall apply.

Article 14
Transitional provision

Member States may issue the certificates referred to in Article 3 in a format which does not comply with the requirements of this Regulation until 6 weeks after the entry into force of this Regulation. During this period, certificates issued in accordance with this Article as well as certificates issued before the entry of force of this Regulation shall be accepted by the Member States in accordance with Articles 5(5), 6(5) and 7(5) where they contain the data fields set out in the Annex.

~~*Reporting*~~

~~One year after the Director-General of the World Health Organization has declared, in accordance with the International Health Regulations, that the public health emergency of international concern caused by SARS-CoV-2 has ended, the Commission shall present a report to the European Parliament and the Council on the application of this Regulation.~~

~~The report shall contain, in particular, an assessment of the impact of this Regulation on the facilitation of free movement of Union citizens and their family members as well as on the protection of personal data during the COVID-19 pandemic.~~

Article 15
*Entry into force, applicability **and reporting***

1. This Regulation shall enter into force on**, and apply from,** the ~~third~~ day ~~following that~~ of its publication in the *Official Journal of the European Union*.

2. **The Regulation shall apply for 12 months from the date of its entry into force.**

At the latest 3 months before the end of the application of this Regulation, the Commission shall present a report to the European Parliament and the Council on the application of this Regulation.

The report shall contain, in particular, an assessment of the impact of this Regulation on the facilitation of free movement, including the acceptance of the different types of vaccines, as well as on the protection of personal data during the COVID-19 pandemic.

This report may be accompanied with legislative proposals, in particular to extend the date of application of this Regulation, taking into account the evolution of the epidemiological situation on the pandemic.

~~2. The Commission shall adopt a delegated act in accordance with Article 11 specifying the date from which the application of Articles 3, 4, 5, 6, 7 and 10 is to be suspended once the Director-General of the World Health Organization has declared, in accordance with the International Health Regulations, that the public health emergency of international concern caused by SARS-CoV-2 has ended.~~

~~*3.* The Commission is empowered to adopt a delegated act in accordance with Article 11 specifying the date from which Articles 3, 4, 5, 6, 7 and 10 are to apply again if, after the suspension referred to in paragraph 2 of this Article, the Director-General of the World Health Organization declares a public health emergency of international concern in relation to *SARS-CoV-2, a variant thereof, or similar* infectious diseases with epidemic potential. *Following the adoption of such a delegated act, paragraph 2 of this Article shall apply.*~~

~~4. Where, in the case of developments regarding public health emergencies of international concern, imperative grounds of urgency so require, the procedure provided for in Article 12 shall apply to delegated acts adopted pursuant to this Article.~~

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels,

For the European Parliament	*For the Council*
The President	*The President*

ANNEX
Certificate datasets

Data fields to be included in the vaccination certificate:

(a) name: surname(s) and forename(s), in that order;

(b) date of birth;

(c) disease or agent targeted: **COVID-19**;

(d) vaccine/prophylaxis;

(e) vaccine medicinal product;

(f) vaccine marketing authorization holder or manufacturer;

(g) number in a series of vaccinations/doses **and the overall number of doses in the series**;

(h) date of vaccination, indicating the date of the latest dose received;

(i) Member State of vaccination;

(j) certificate issuer;

(k) a unique certificate identifier.

Data fields to be included in the test certificate:

(a) name: surname(s) and forename(s), in that order;

(b) date of birth;

(c) disease or agent targeted: **COVID-19**;

(d) the type of test;

(e) test name (optional for NAAT test);

(f) test manufacturer (optional for NAAT test);

(g) date and time of the test sample collection;

(h) date and time of the test result production (optional for rapid antigen test);

(i) result of the test;

(j) testing centre or facility;

(k) Member State of test;

(l) certificate issuer;

(m) a unique certificate identifier.

Data fields to be included in the certificate of recovery:

(a) name: surname(s) and forename(s), in that order;

(b) date of birth;

(c) disease or agent the citizen has recovered from: **COVID-19**;

(d) date of first positive test result;

(e) Member State of test;

(f) certificate issuer;

(g) certificate valid from;

(h) certificate valid until (not more than 180 days after the date of first positive test result);

(i) a unique certificate identifier.

ANNEX II

Proposal for a

REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

on a framework for the issuance, verification and acceptance of interoperable certificates on vaccination, testing and recovery to third-country nationals legally staying or legally residing in the territories of Member States during the COVID-19 pandemic (Digital Green Certificate)

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty on the Functioning of the European Union, and in particular Article 77(2)(c)thereof,

Having regard to the proposal from the European Commission,

After transmission of the draft legislative act to the national parliaments,

Acting in accordance with the ordinary legislative procedure,

Whereas:

(1) Under the Schengen acquis, third country nationals lawfully residing in the Union and third country nationals who have legally entered the territory of a Member State may move freely within the territories of all other Member States during a period of 90 days in any 180-day period.

(2) On 30 January 2020, the Director-General of the World Health Organization ('WHO') declared a public health emergency of international concern over the global outbreak of severe acute respiratory syndrome coronavirus 2 (*SARS-CoV-2*), which causes coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO made the assessment that COVID-19 can be characterized as a pandemic.

(3) To limit the spread of the virus, the Member States have adopted various measures, some of which have had an impact on travel to and within the territory of the Member States, such as restrictions on entry or requirements for cross-border travellers to undergo quarantine.

(4) On 13 October 2020, the Council adopted Council Recommendation (EU) 2020/1475 on a coordinated approach to the restriction of free movement in response to the COVID-19 pandemic[1].

(5) On 30 October 2020, the Council adopted Council Recommendation (EU) 2020/1632[2] on a coordinated approach to the restriction of free movement in response to the COVID-19 pandemic in the Schengen area, in which it recommended Member States that are bound by the Schengen *acquis* to apply the principles, common criteria, common thresholds and common framework of measures, set out in Council Recommendation (EU) 2020/1475.

(6) Many Member States have launched or plan to launch initiatives to issue vaccination certificates. However, for these to be used effectively in connection with cross-border travel within the Union, such certificates need to be fully interoperable, secure and verifiable. A commonly agreed approach is required among Member States on the content, format, principles and technical standards of such certificates.

(7) Already now, several Member States exempt vaccinated persons from certain travel restrictions. Where Member States accept proof of vaccination in order to waive travel restrictions put in place in compliance with Union law to limit the spread of COVID-19, such as requirements to undergo quarantine/self-isolation or be tested for SARS-CoV-2 infection, they should be required to accept, under the same conditions, valid vaccination certificates issued by other Member States in compliance with the proposal for a Regulation on a Digital Green Certificate (COM(2021)/xxx). This acceptance should take place under the same conditions, meaning that, for example, where a Member State considers a single dose of an administered vaccine to be sufficient, it should do so also for holders of a vaccination certificate indicating a single dose of the same vaccine. On grounds of public health, this obligation should be limited to persons having received COVID-19 vaccines having been granted marketing authorisation pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council[3]. This should not prevent Member States from deciding to accept vaccination certificates issued for other COVID-19 vaccines, such as vaccines having been granted marketing authorisation by the competent authority of a Member State pursuant to Directive 2001/83/EC of the European Parliament and the Council[4], vaccines whose distribution has been temporarily authorised based on Article 5(2) of that Directive 2001/83/EC, or vaccines having received a WHO Emergency Use Listing. Regulation (EU) No 2021/xxxx of xx xx 2021 lays down a framework for the issuance, verification and acceptance of interoperable certificates on COVID-19 vaccination, testing and recovery to facilitate free movement during the COVID-19 pandemic. It applies to Union citizens and third-country nationals who are family members of Union citizens.

---

1 OJ L 337, 14.10.2020, p. 3.

2 Council Recommendation (EU) 2020/1632 of 30 October 2020 on a coordinated approach to the restriction of free movement in response to the COVID-19 pandemic in the Schengen area (OJ L 366, 4.11.2020, p. 25).

3 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p.1).

4 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67).

(8) In accordance with Articles 19, 20 and 21 of the Convention implementing the Schengen Agreement, the third-country nationals covered by these provisions may travel freely within the territories of the other Member States.

(9) To facilitate travel within the territories of the Member States by third country nationals who have the right to such travel, the framework for the issuance, verification and acceptance of interoperable certificates on COVID-19 vaccination, testing and recovery established by Regulation (EU) No 2021/xxxx should also apply to third-country nationals who are not already covered by that Regulation, provided that they are legally staying or legally residing in the territory of a Member State and are entitled to travel to other Member States in accordance with Union law.

(10) For certificates to be used effectively in connection with cross-border travel, such certificates need to be fully interoperable.

(11) This Regulation should not be understood as facilitating or encouraging the adoption of travel restrictions to free movement, or other fundamental rights, in response to the pandemic. In addition, any need for verification of certificates established by Regulation (EU) 2021/xxx cannot as such justify the temporary reintroduction of border controls at internal borders. Checks at internal borders should remain a measure of last resort, subject to specific rules set out in Regulation (EU) 2016/399 (Schengen Borders Code)[5].

(11a) Since this Regulation applies to third country nationals already legally staying or residing in the territories of the Member States, it should not be understood as granting third country nationals wishing to travel to a Member State the right to request a Digital Green Certificate from that Member State before arrival on its territory.

(11b) On 30 June 2020, the Council adopted Recommendation (EU) 2020/912 on the temporary restriction on non-essential travel into the EU and the possible lifting of such restriction. This Regulation does not cover the temporary restrictions on non-essential travel into the Union.

(12) In accordance with Articles 1 and 2 of Protocol No 22 on the position of Denmark annexed to the Treaty on European Union and to the TFEU, Denmark is not taking part in the adoption of this Regulation and is not bound by it or subject to its application. Given that this Regulation builds upon the Schengen acquis, Denmark shall, in accordance with Article 4 of the said Protocol, decide within a period of six months after the Council has decided on this Regulation whether it will implement it.

---

[5] Regulation (EU) 2016/399 of the European Parliament and of the Council of 9 March 2016 on a Union Code on the rules governing the movement of persons across borders (OJ L 77, 23.3.2016 p.1).

(13) This Regulation constitutes a development of the provisions of the Schengen acquis in which Ireland does not take part, in accordance with Council Decision 2002/192/EC[6]; Ireland is therefore not taking part in its adoption and is not bound by it or subject to its application. **In order to allow Member States to accept, under the conditions of the Regulation (EU) 2021/XXXX [Regulation on a Digital Green Certificate], certificates issued by Ireland to third country nationals legally residing or legally staying in its territory for the purposes of facilitating travel within the Union, Ireland should issue these third-country nationals with certificates that comply with the requirements of the Digital Green Certificate trust framework.** ~~Although Ireland is not subject to this Regulation, for the purposes of facilitating travel within the Union, Ireland could also issue certificates, which comply with the same requirements as those applicable to the Digital Green Certificate, to third-country nationals legally residing or legally staying in its territory. and Member States could accept such certificates. Ireland could also accept certificates issued by Member States to third-country nationals legally residing or legally staying in their territories.~~ **Ireland and the other Member States should mutually accept certificates issued to third country nationals covered by this Regulation based on reciprocity**.

(14) As regards Bulgaria, Croatia, Cyprus and Romania, this Regulation constitutes a development of the Schengen acquis within, respectively, the meaning of Article 3(1) of the 2003 Act of Accession, Article 4(1) of the 2005 Act of Accession and Article 4(1) of the 2011 Act of Accession.

(15) As regards Iceland and Norway, this Regulation constitutes a development of the provisions of the Schengen acquis within the meaning of the Agreement concluded by the Council of the European Union and the Republic of Iceland and the Kingdom of Norway concerning the latter's association with the implementation, application and development of the Schengen acquis which fall within the area referred to in Article 1, point C, of Council Decision 1999/437/EC[7].

(16) As regards Switzerland, this Regulation constitutes a development of the provisions of the Schengen acquis within the meaning of the Agreement between the European Union, the European Community and the Swiss Confederation on the Swiss Confederation's association with the implementation, application and development of the Schengen acquis which fall within the area referred to in Article 1, point C, of Decision 1999/437/EC read in conjunction with Article 3 of Council Decision 2008/146/EC[8].

---

6 Council Decision of 28 February 2002 concerning Ireland's request to take part in some of the provisions of the Schengen acquis (OJ L 64, 7.3.2002, p. 20).

7 Council Decision of 17 May 1999 on certain arrangements for the application of the Agreement concluded by the Council of the European Union and the Republic of Iceland and the Kingdom of Norway concerning the association of those two States with the implementation, application and development of the Schengen acquis (OJ L 176, 10.7.1999, p. 31).

8 Council Decision of 28 January 2008 on the conclusion, on behalf of the European Community, of the Agreement between the European Union, the European Community and the Swiss Confederation on the Swiss Confederation's association with the implementation, application and development of the Schengen acquis (OJ L 53, 27.2.2008, p. 1).

(17) As regards Liechtenstein, this Regulation constitutes a development of provisions of the Schengen acquis within the meaning of the Protocol between the European Union, the European Community, the Swiss Confederation and the Principality of Liechtenstein on the accession of the Principality of Liechtenstein to the Agreement between the European Union, the European Community and the Swiss Confederation on the Swiss Confederation's association with the implementation, application and development of the Schengen acquis which fall within the area referred to in Article 1 point C, of Decision 1999/437/EC read in conjunction with Article 3 of Decision 2011/350/EU[9].

(18) The European Data Protection Supervisor and the European Data Protection Board have been consulted in accordance with Article 42 of Regulation (EU) 2018/1725 of the European Parliament and of the Council[10] and delivered a~~n~~ **joint** opinion on **31 March 2021**,

HAVE ADOPTED THIS REGULATION:

Article 1

Member States shall apply the rules laid down in Regulation (EU) 2021/XXXX [Regulation on a Digital Green Certificate] to those third country nationals who do not fall within the scope of that Regulation but who reside or stay legally in their territory and are entitled to travel to other Member States in accordance with Union law.

---

9 Council Decision of 7 March 2011 on the conclusion, on behalf of the European Union, of the Protocol between the European Union, the European Community, the Swiss Confederation and the Principality of Liechtenstein on the accession of the Principality of Liechtenstein to the Agreement between the European Union, the European Community and the Swiss Confederation on the Swiss Confederation's association with the implementation, application and development of the Schengen acquis, relating to the abolition of checks at internal borders and movement of persons (OJ L 160, 18.6.2011, p. 19).

10 Regulation (EU) 2018/1725 of the European Parliament and of the Council of 23 October 2018 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data, and repealing Regulation (EC) No 45/2001 and Decision No 1247/2002/EC (OJ L 295, 21.11.2018, p. 39).

Article 1a

Provided that Ireland has notified the Council and the Commission that it accepts certificates issued by Member States to persons covered by this Regulation, Member States shall accept, under the conditions of Regulation (EU) 2021/XXXX [Regulation on a Digital Green Certificate], certificates making up the Digital Green Certificate issued by Ireland to third country nationals who may travel freely within the territory of the Member States.

Article 2

This Regulation shall enter into force on**, and apply from,** the ~~third~~ day ~~following that~~ of its publication in the *Official Journal of the European Union*.

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at Brussels,

For the European Parliament	*For the Council*
The President	*The President*

eHealth Network

Guidelines on

COVID-19 citizen recovery interoperable certificates - minimum dataset

Release 1

2021-03-15

The eHealth Network is a voluntary network, set up under article 14 of Directive 2011/24/EU. It provides a platform of Member States' competent authorities dealing with eHealth.

Adopted by the eHealth Network, 15 March 2021

The periods of infectiousness and protection mentioned in this guideline follow the ECDC Guidance and might undergo changes as new scientific evidence arises.

Table of Contents

1 Introduction

To date, the results of COVID-19 testing have been the principal factor to decide on implementation of measures, e.g. isolation/quarantine, cross-border movement, etc. Despite efforts for a common approach on free movement across the EU/EEA, citizens are still facing problems when trying to present test certificates issued by one Member States in another (issues include language used or lack of trust in the authenticity of the document). To facilitate free movement within EU/EEA Member States, a common certificate for COVID-19 testing is needed. With the rollout of the first COVID-19 vaccines on the EU market, there is also a desire from some Member States to introduce vaccination certificates for the purposes of free movement across borders. Under the proposal for a Digital Green Certificate, a framework for interoperable certificates on COVID-19 vaccination, testing and recovery should be established.

The guideline follow epidemiological guidance[1] and the specific values will be provided in due time by relevant institutions.

2 Use case – COVID-19 citizen recovery

According to the current evidence, individuals who recover from COVID-19 can continue to test positive for SARS-CoV-2 for some time after no longer being infectious. In those cases, the virus being shed is no longer viable and there is therefore limited risk of transmission to others. However, for the purposes of free movement, those individuals are unable to present a negative test result, and would thus be prevented from crossing borders. However, despite some uncertainties (described in the following chapter), on balance the evidence suggests that those who have recovered from COVID-19 have a reduced risk of infection.

[1] https://www.ecdc.europa.eu/en/publications-data/covid-19-guidance-discharge-and-ending-isolation

2.1 Scientific unknowns

Some scientific unknowns remain regarding the infectiousness of a person infected with COVID-19. The following aspects are of particular relevance:

- there is insufficient information on levels of immunity conferred by previous infection. It is widely accepted that previous infection provides in general some reduced risk of subsequent infection, but there is a lack of consensus on how much reduced risk of infection, the length of the protection and the extent of variation between individuals.

- although relatively uncommon, reinfection in persons recently recovered from COVID-19 has been documented. It has been reported that up to 9% of PCR positive cases do not mount an antibody response and may be susceptible for reinfection and further transmitting disease. More recently, possible reinfections with emerging variant strains such as B.1.351 and P.1 are of special concern.

- the exact duration of the protection conferred by a previous infection, in particular in view of the increased transmission in EU/EA MSs of the new variants of concern, should be revised as new evidence is collected.

Due to the current unknowns, the validity of certificates might undergo changes according to new scientific evidence. Considering the emergence of SARS-CoV-2 variants, this epidemiological evidence may change and ECDC, the Commission and Member States should take all the measures to update all the relevant guidance, legal acts and IT systems.

3 Minimum dataset

A minimum dataset, including a unique identifier, enables minimum information to be generated according to a common agreed structure, facilitating cross-border sharing and use.

Table 1 – COVID-19 citizen recovery minimum dataset

Section	Data element	Description	Preferred Code System
Person identification	Person name	The legal name of the person recovered from the infection surname(s) and forename(s) in that order	
	Person date of birth	Recovered person's date of birth.	Complete date, without time, following the ISO 8601.

	Person identifier (optional)	The type of identifier and identifier of the person, according to the policies applicable in each country. Examples: citizen ID and/or document number (ID-card/passport)	
Information about past infection	Disease or agent	Disease or agent the citizen has recovered from	ICD-10, SNOMED CT GPS
	Date of first positive test result	Date when the sample for the test was collected that led to positive test obtained through a procedure established by a public health authority in the MS [specific rules to be determined later]	Complete date, without time, following the ISO 8601.
	Country of test	Country in which the first positive test was performed	ISO 3166 Country Codes
Certificate metadata	Certificate issuer	Entity that has issued the certificate (allowing to check the certificate)	
	Certificate Identifier	Unique identifier of the certificate to be printed into the certificate; the way of defining it should be similar to the vaccination guidelines[2]	
	Certificate valid from	Certificate valid from [specific rules to be determined later] *Subject to change as new evidence arises*	ISO 8601 or other international stated format

[2] https://ec.europa.eu/health/sites/health/files/ehealth/docs/vaccination-proof_interoperability-guidelines_en.pdf

	Certificate valid until	Certificate valid until [specific rules to be determined later] *Subject to change as new evidence arises*	ISO 8601 or other international stated format

All fields that contain non-enumeration/numeric data should be encoded in UTF-8 must be fully canonicalised and normalised according to http://unicode.org/reports/tr15/

4 Further steps towards cross-border interoperability

The guidelines on *COVID-19 Citizen Recovery interoperable certificates - minimum dataset* will be followed by further steps towards cross-border interoperability of COVID-19 certificates.

In close cooperation with ECDC and WHO and supported by the European Commission, the eHealth Network and the Health Security Committee will continue working towards the design and implementation of interoperable solutions that work across borders and world regions.

In addition, the European Commission is invited to support the development of toolboxes and trust frameworks to facilitate the deployment of interoperable solutions.

From: "Kröger, Stefan" <KroegerS@rki.de>
To: "Rexroth, Ute" <RexrothU@rki.de>
"Glasmacher, Susanne" <GlasmacherS@rki.de>
RKI-Pressestelle <Presse@rki.de>
Date: 5/10/2021 7:05:57 AM
Subject: AW: [ID 3581] Re: AW: Quarantäne "besorgniserregende" Variante B 1.1.7

Liebe Ute,
finde den Vorschlag sehr gut und sehe aktuell keine bessere Lösung. Bei Nachfragen würden wir auf die hohe Prävalenz (oder das BMG?) verweisen.

Einzig, es könnte mittelfristig zu Problemen mit anderen Varianten die eine ähnliche Charakteristik aufweisen, führen. Ich schlage vor, wir diskutieren das kurz im Krisenstab und können es bei Zustimmung noch heute online stellen.

VG
Stefan

Am 10. Mai 2021 um 08:51:00 MESZ schrieb Rexroth, Ute :

> Lieber Stefan, liebe Pressestelle,
>
> ich glaube, wir müssen das schnell klären.
> Was hältst Du/Sie davon, wenn wir in dem Abschnitt unter B.1.1.7 einfach einen Satz ergänzen:
> https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Virusvariante.html
>
> **"B.1.1.7 (20I/501Y.V1):**Im Dezember 2020 berichteten britische Behörden von dieser neuen SARS-CoV-2-Virusvariante, die sich seit September 2020 in Großbritannien ausbreitet. Sie ist noch leichter von Mensch zu Mensch übertragbar als die zuvor zirkulierenden Varianten und weist eine höhere Reproduktionszahl auf, so dass ihre Ausbreitung schwerer einzudämmen ist. Es gibt Hinweise darauf, dass sie mit einer erhöhten Fallsterblichkeit in allen Altersgruppen einhergeht. Hinweise auf eine substantiell verringerte Wirksamkeit der Impfstoffe gibt es bislang nicht. Bei B.1.1.7 E484K handelt es sich um eine Sonderform der Variante, die mehrfach in Großbritannien nachgewiesen wurde, derzeit aber noch als selten gilt. Sie weist im S-Protein eine zusätzliche Mutation auf (E484K), die auch in den Varianten B.1.351 und P.1 auftritt (siehe unten) und das Virus unempfindlicher gegen bereits gebildete neutralisierende Antikörper macht. Deswegen wird vermutet, dass die derzeit erhältlichen Impfstoffe gegen diese Variante eine geringere Wirksamkeit aufweisen könnten.**Die Variante B.1.1.7 (20I/501Y.V1)gilt nicht als "besorgniserregend" im Sinne des §10 Abs.2 Satz 1 der Verordnung zur Regelung von Erleichterungen und Ausnahmen von Schutzmaßnahmen zur Verhinderung der Verbreitung von COVID-19 (COVID-19-Schutzmaßnahmen-Ausnahmenverordnung – SchAusnahmV). "**
>
> Viele Grüße,
>
> Ute Rexroth
>
> -----Ursprüngliche Nachricht-----
> Von: Neuperdt, Laura Im Auftrag von nCoV-Lage
> Gesendet: Sonntag, 9. Mai 2021 14:50
> An: Kröger, Stefan
> Cc: Rexroth, Ute ; nCoV-Lage ; Hamouda, Osamah ; Haas, Walter ; Mehlitz, Joachim-Martin ; Wichmann, Ole ; RKI-Pressestelle ; Glasmacher, Susanne ; Sievers, Claudia ; Schaade, Lars ; Diercke, Michaela ; Verteiler-FG36-

Teamleitung
Betreff: WG: [ID 3581] Re: AW: Quarantäne "besorgniserregende" Variante B 1.1.7

Sehr geehrter Herr Kröger,

wir vergeben die unten stehende Aufgabe mit der ID 3581. Wir haben dazu die Frist auf den 12.05.2021 (DS) gesetzt.

Aufgabe ID 3581
Federführende RKI-Organisationseinheit: FG 36 Weitere RKI-Organisationseinheit/en: FG 32
Bearbeitende/r: Hr. Kröger (FG 36), Fr. Sievers (FG 32)
Thema: Quarantäne "besorgniserregende" Variante B 1.1.7
Beschreibung: Ausweisung der VOC gemäß Paragraph 28c IfSG mit Hinweis auf der Website des RKI
Frist: 12.05.2021 (DS)
Bei Erledigung: bitte E-Mail an nCoV-Lage@rki.de Im Betreff bitte die Aufgaben ID angeben.
Anmerkung: falls Sie den Eindruck haben, dass die Aufgabe falsch zugewiesen wurde oder der Auftrag nicht verständlich ist, bitten wir um Rückmeldung!

Vielen Dank für Ihre Unterstützung.

Mit freundlichen Grüßen,

i.A. Laura Neuperdt

Lagezentrum COVID-19
Robert Koch-Institut
Seestr. 10
13353 Berlin

Tel.: 030 18754 3063
E-Mail: nCoV-Lage@rki.de
Internet: www.rki.de
Twitter: @rki_de
Das Robert Koch-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministeriums für Gesundheit

-----Ursprüngliche Nachricht-----
Von: Schaade, Lars
Gesendet: Samstag, 8. Mai 2021 11:30
An: Rexroth, Ute
Cc: nCoV-Lage ; Hamouda, Osamah ; Haas, Walter ; Mehlitz, Joachim-Martin ; Kröger, Stefan ; Wichmann, Ole ; RKI-Pressestelle ; Glasmacher, Susanne
Betreff: [ID 3581] Re: AW: Quarantäne "besorgniserregende" Variante B 1.1.7

Ich denke, wenn BMG da abgesegnet hat, müssen wir das nicht nochmal rechtlich prüfen.

Aber ist es nicht besser, hier die Ausnahmen aufzuführen, also nicht VOC im Sinne der RVO ist B1.1.7.? So hatten wir es BMG ja auch vorgeschlagen.

Sonst müssen wir hier ständig aktualisieren, denn es werden ja mehr VOC werden, Ausnahmen werden sie aber erst dann, wenn sie sich durchgesetzt haben. Die VOC positiv im Sinne der RVO aufzulisten hätte allerdings den Vorteil, dass keine Unklarheiten aufkommen, wenn UK bereits aus einer VOI eine VOC macht - wir, WHO und ECDC aber noch nicht.

Hat BMG da eine Präferenz?

Gruß
LS

Am 8. Mai 2021 um 11:17:58 MESZ schrieb Rexroth, Ute :

Lieber Herr Schaade,

Sollen wir also versuchen, eine Klarstellung auf die Internetseite zu stellen, oder muss das noch durch unser Rechtsreferat geprüft werden, ob wir die Verordnung in dem Sinne präzisieren dürfen?

Ich schlage vor, auf der Internetseite:https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Virusvariante.html
Noch vor „Übersicht“ eine Aufzählung voranzukommen stellen:
Z.B. so:
„Folgende Varianten gelten nach Einschätzung des RKI als „besorgniserregend“ im Sinne der

Rechtsverordnung RVO gemäß Paragraph 28c IfSG:

B.1.351
P.1
„

Man könnte noch klarstellen, warum zw. Dass B1.1.7 nicht mehr erwähnt ist.
B 1.617 müssten wir vermutlich auch erwähnen, da Einreisende aus Indien ja in Quarantäne sollen, oder ?

Viele Grüße,

Ute Rexroth

Am 8. Mai 2021 um 09:46:26 MESZ schrieb Rottmann-Großner, Heiko -61 BMG:

Guten Morgen!

Ich unterstütze diese Lösung ausdrücklich!

Herzlichen Dank dafür!

Heiko Rottmann

Gesendet von meinem BlackBerry 10-Smartphone.
Originalnachricht

Von: Sangs, André -611 BMG
Gesendet: Freitag, 7. Mai 2021 23:37
An: Rexroth, Ute; Rottmann-Großner, Heiko -61 BMG
Cc: Lars Schaade; nCoV-Lage; Hamouda, Osamah; Haas, Walter; Mehlitz, Joachim-Martin; Kröger, Stefan; Wichmann, Ole; RKI-Pressestelle
Betreff: AW: Quarantäne "besorgniserregende" Variante B.1.1.6

Liebe Frau Dr. Rexroth,

ein wichtiger Punkt, den ich unterstützen würde. Ich hatte im Verfahren versucht nur solche Varianten zu erfassen, die das RKI speziell für die VO nach 28c definiert, bin damit aber nicht mehr durchgedrungen. Deshalb könnte man, wenn Herr Rottmann zustimmt, mE nach Ihrem Vorschlag verfahren.

Mit freundlichen Grüßen
Im Auftrag

André Sangs
Stellv. Referatsleiter

Referat 611 Gesundheitssicherheit, Krisenmanagement national
Bundesministerium für Gesundheit
Friedrichstr. 108
10117 Berlin
Tel.: 030 18441 4576
Fax : 030 18441 3222
Originalnachricht
Von: Rexroth, Ute
Gesendet: Freitag, 7. Mai 2021 22:55
An: Rottmann-Großner, Heiko -61 BMG; Sangs, André -611 BMG
Cc: Lars Schaade; nCoV-Lage; Hamouda, Osamah; Haas, Walter; Mehlitz, Joachim-Martin; Kröger, Stefan; Wichmann, Ole; RKI-Pressestelle
Betreff: WG: AW: Quarantäne "besorgniserregende" Variante B.1.1.6

Lieber Herr Rottmann, lieber Herr Sangs,

anlässlich einer (u.g.) Presseanfrage, die uns heute erreichte, sind wir auf eine Unklarheit im Zusammenhang mit der Rechtsverordnung gestoßen:
Im Gesetz heißt es: "Quarantäne für Geimpfte, die Kontaktperson zu einer infizierten Person sind, entfällt. Es sei denn, es handelt sich um eine Virusmutation, die vom RKI als „besorgniserregend“ eingestuft wird." Nun ist die bei uns vorherrschende Variante B 1.1.7. ja nach internationalem Verständnis auch "besorgniserregend". Das RKI orientiert sich an der internationalen Bezeichnung und bezeichnet sie in allen Dokumenten und auf seiner Internetseite als Solche (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Virusvariante.html).
In unserem Kontaktpersonenmanagementpapier nehmen wir B.1.1.7. aber von den anderen "VOC" aus: " Bei Verdacht auf eine Infektion des laborbestätigten Quellfalls mit einer der besorgniserregenden SARS-CoV-2-Varianten, außer der Variante B.1.1.7, ist eine erneute Quarantäne der vollständig geimpften bzw. genesenen Kontaktperson grundsätzlich immer empfohlen."
Damit steht die Empfehlung Kontaktpersonenmanagementpapier scheinbar im Widerspruch zur Verordnung. Das ist aber natürlich nicht gewollt. Wir könnten versuchen, auf der Website klarzustellen, welche VOC KEINE VOC im Sinne der RVO gemäß 28c sind. Das ist kommunikativ sicher nicht ganz einfach und müsste sicherlich auch rechtlich geprüft werden.

Oder ist diese Frage bei Ihnen diskutiert worden und Sie haben bereits eine Lösung?

Viele Grüße,

Ute Rexroth

****

Von: Wittmann, Stefan

Gesendet: Freitag, 7. Mai 2021 08:46

An: RKI-Pressestelle

Betreff: Rückfrage Quarantäne "besorgniserregende" Variante

Sehr geehrte Frau Glasmacher,

ich erreiche Sie telefonisch noch nicht und habe eine inhaltliche Frage, die mir offen ist:

Im Bundesrat wird heute über die Rückgabe von Rechten an Geimpfte und Genesene abgestimmt. Im Gesetz heißt es: Quarantäne für Geimpfte, die Kontaktperson zu einer infizierten Person sind, entfällt. Es sei denn, es handelt sich um eine Virusmutation, die vom RKI als „besorgniserregend“ eingestuft wird.

Jetzt gilt laut RKI ja die britische Mutante als „besorgniserregend“. Die macht mittlerweile ja mehr als 90% der Infektionen aus. Also gilt in der Praxis weiterhin Quarantäne für Geimpfte? Oder handelt es sich bei einer „besorgniserregenden“ Einstufung in diesem Fall um mögliche neue Mutanten, bei denen absehbar sein wird, dass der Impfstoff eventuell weniger wirksam ist?

Ich freue mich auch eine schnelle, kurze Rückmeldung – gerne auch per Telefon. Diese Frage würde ich unseren Zuschauern gerne konkret beantworten können.

Freundliche Grüße

Stefan Wittmann | Redakteur/Reporter WELT

Telefon: +49 30 2591 5 2498

Mob [redacted]

Email: stefan.wittmann@welt.de <mailto:stefan.wittmann@welt.de>

Postanschrift: Axel-Springer-Straße 65 | 10888 Berlin

Besucheradresse: Marlene-Dietrich-Platz 5 | 10785 Berlin

WeltN24 GmbH | Sitz: Berlin | Amtsgericht Charlottenburg | HRB 115398 B

Geschäftsführer: Frank Hoffmann | Christian Nienhaus | Dr. Ulf Poschardt (Sprecher)

Steuer-Nr.: 29/010/60362 | FA Kö III Berlin

USt-ID: DE295295623

From: "Klaus, Ina -RL -Stab Lageführung COVID-19 BMG" <Ina.Klaus@bmg.bund.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 11/5/2021 8:05:22 AM
Subject: Sitzung des Krisenstabes BMI-BMG am 9.11.2021_16 Uhr
Attachments: 211104_externe TO 96. Krista-Sitzung.docx

Liebe Kolleginnen und Kollegen,

in der kommenden Sitzung des Krisenstabes haben wir einen TOP zu „nicht-pharmazeutische Corona-Schutzmaßnahmen (AHA+L)“ aufgenommen. Gerade mit Blick auf die kalte Jahreszeit ein wichtiger Punkt. Das BMI bittet zudem um eine kurze Einschätzung zur erwarteten Situation im Herbst/Winter. Hier hat das RKI ja die Risikoeinschätzung aktuell angepasst. Wir würden uns daher freuen, wenn das RKI in der Sitzung dazu kurz berichtet. Bitte geben Sie uns Bescheid, wer vom RKI diesen Part übernehmen wird.

Einwahldaten und die finale Tagesordnung sende ich Ihnen zu, soweit sie mir vorliegen.

Danke und beste Grüße
Ina Klaus

Bundesministerium für Gesundheit

Bundesministerium des Innern, für Bau und Heimat

Presse- und Informationsamt der Bundesregierung

VS - NUR FÜR DEN DIENSTGEBRAUCH

Tagesordnung
der als Videokonferenz durchgeführten 96. Sitzung des Krisenstabes
am Dienstag, 9.11.2021,
von 16:00–17:00 Uhr

TOP	Thema
1	**Begrüßung und Abfrage der Teilnehmenden** **Beschluss der Tagesordnung** **Genehmigung des Protokolls der 95. Sitzung** **Moderation:** BMI
2	**Bericht zur aktuellen Lage** • Infektionsgeschehen **Vortragender:** BMG **Anmelder:** BMG
3	**Nicht-pharmazeutische Corona-Schutzmaßnahmen (AHA+L)** **Situation im Herbst/Winter 2021/2022** **Neue Erkenntnisse zu Aerosolen in Innenräumen** **Vortragende:** RKI,Prof. Dr.-Ing. Martin Kriegel, Leiter des Hermann-Rietschel-Instituts der TU Berlin **Anmelder:** BMG
4	**Impfen gegen SARS-CoV-2** • Aktuelle Zahlen und Fortschritt der Impfkampagne **Vortragender:** BMG **Anmelder:** BMG
5	**Festlegung von Risikogebieten und Einreiseregime/ Besorgniserregende Virusvarianten („Variants of Concern")** • Verbreitung von VoCsnational/international (BMG) Vortragender: BMG Anmelder: BMG
6	**Verschiedenes**

From: "Wieler, Lothar" <WielerLH@rki.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 6/7/2021 7:44:55 AM
Subject: WG: CO2 Messungen zur Infektionspr Lvention

Liebe Alle,

diese Mail sollten wir im Krisenstab besprechen. Unterstutzen wir diesen Gedanken?

Mit freundlichen Gru?en

Prof. Dr. Dr. h.c. Lothar H. Wieler
Robert Koch Institute
13353 Berlin, Germany
e-mail: president@rki.de
phone: +49(0)30 18754-2000

-----Ursprungliche Nachricht-----
Von: Prof. Dr.-Ing. Martin Kriegel <m.kriegel@tu-berlin.de>
Gesendet: Donnerstag, 3. Juni 2021 13:40
An: Jens.Spahn@bmg.bund.de; Wieler, Lothar <WielerLH@rki.de>
Betreff: CO2 Messungen zur Infektionspravention

?Lieber Herr Spahn, lieber Herr Wieler,

auf diesem Wege mochte ich noch einmal eindringlich dafur werben, dass flachendeckend CO2 Messungen in Raumen stattfinden sollten, insbesondere zur Vorbereitung fur kommenden Herbst /Winter.

Der CO2 Gehalt in Innenraumen korreliert mit dem Infektionsrisiko. Eine Erhohung der Luftqualitat reduziert evidenzbasiert Infektionszahlen. Es gibt mittlerweile auch epidemiologische Studien dazu.

CO2 Messung ist eine sehr einfache, preiswerte Moglichkeit ein Permanent-Monitoring durchzufuhren und basierend darauf Ma?nahmen zu ergreifen. Insbesondere fur uber Fenster geluftete Raume, sollte das zum Standard gehoren.

Es ist die EINZIGE preiswerte und schnell umsetzbare Moglichkeit, indirekt das Infektionsrisiko zu „messen“.

Luft ist unser wichtigstes Lebensmittel. Im Vergleich zu Wasser: Wir atmen 15-25 kg Luft pro Tag und brauchen 3 kg Wasser.

Die Luft im Innenraum wird uberhaupt nicht kontrolliert, im Gegensatz zu Trinkwasser.

Was auch ohne Corona schon unhaltbar ist (Nichteinhaltung der Arbeitsstattenrichtlinie ASR 3.6 in der Praxis), sollte doch zumindest jetzt von hoher Wichtigkeit sein.

Mit Luftungsregeln alleine ist es nicht getan und jeder hat ein anderes Verstandnis von "moglichst oft Luften".

In der BPK im letzten Herbst habe ich gesagt, dass in gut gelufteten Raumen keine Superspreader-Events stattfinden werden. Mit den neuen Mutanten hat sich die Situation aber verscharft, so dass diese Aussage nicht mehr stehenbleiben kann.

Die Bundesregierung konnte analog zu Tests/Masken, etc. CO2 Messgerate/Ampeln und dazugehorige Bedienungs- und Handlungsanweisungen fur kritisch anzusehende Bereiche kostenlos zur Verfugung stellen. Diese hatten auch nach der Pandemie noch einen erheblichen Nutzen.

Bei den Geraten sollten die Grenzwerte in jedem Fall programmierbar sein.

Fur Ruckfragen stehe ich Ihnen jederzeit zur Verfugung.

Mit freundlichen Gru?en,

M. Kriegel

--

Prof. Dr.-Ing. Martin Kriegel

Head of Hermann-Rietschel-Institut

Technische Universitat Berlin

Hermann-Rietschel-Institut

Chair of Energy, Comfort & Health in Buildings

Marchstr. 4, 10587 Berlin

GERMANY

Tel: +49 (0)30 314-24170

Fax: +49 (0)30 314-21141

m.kriegel@tu-berlin.de

www.tu-berlin.de

www.hri.tu-berlin.de

From: nCoV-Lage
To: "Mylius , Maren - 614 BMG" <Maren.Mylius@bmg.bund.de>
RKI-Fach-Erlasswesen <RKI-Fach-Erlasswesen@bmg.bund.de>
Date: 6/14/2021 2:56:01 PM
Subject: AW: EILT: Frist HEUTE DS; Bitte um Stellungnahme: Maskenpflicht in öffentlichen Verkehrsmitteln

---

Liebe Frau Mylius,

das RKI hat sich zum Tragen von Masken in der Öffentlichkeit u. a. in den FAQhttps://www.rki.de/SharedDocs/FAQ/NCOV2019/gesamt.html;jsessionid=E0F98A0098673F228EAB19C4BA3493C2.internet062?nn=2386228 auf den Internetseiten geäußert, siehe zB "Was ist beim Tragen einer Mund-Nasen-Bedeckung bzw. eines Mund-Nasen-Schutzes ("OP-Maske") in der Öffentlichkeit zu beachten?" und "Welche Funktion bzw. Einsatzbereiche haben FFP2-Masken außerhalb des Arbeitsschutzes?"
Hier finden sich u.a. folgenden Hinweise "Das RKI empfiehlt das generelle Tragen das generelle Tragen einer Mund-Nasen-Bedeckung (Alltagsmaske) bzw. eines Mund-Nasen-Schutzes (MNS, "OP-Maske") in bestimmten Situationen im öffentlichen Raum als einen weiteren Baustein, um den Infektionsdruck und damit die Ausbreitungsgeschwindigkeit von COVID-19 in der Bevölkerung zu reduzieren und somit Risikogruppen zu schützen."
" Was muss im Zusammenhang mit der Anwendung von FFP2-Masken durch Laien zusätzlich berücksichtigt werden? Bisher wurden keine wissenschaftlichen Untersuchungen über den möglichen Effekt einer solchen Maßnahme gemacht. Bei der Anwendung durch Laien ist ein Eigenschutz über den Effekt eines korrekt getragenen Mund-Nasen-Schutzes hinaus daher nicht zwangsläufig gegeben. Im Kontext der allgemeinen Infektionsschutzmaßnahmen stellt das Tragen von Masken eine wichtige Einzelmaßnahme da, die alleine weniger effektiv ist als in der Kombination mit weiteren Maßnahmen. Deshalb sollte das Tragen von Masken keinesfalls dazu führen, dass andere Komponenten der AHA+L-Regeln vernachlässigt werden oder Risiken sogar bewusst in Kauf genommen werden. Risiken wie z.B. die Erhöhung der Personendichte in geschlossenen Räumen mit schlechter Belüftung, oder die Wahrnehmung nicht zwingend erforderlicher persönlicher Kontakte sollten nicht aufgrund der Maske in Kauf genommen werden."

Des Weiteren möchten wir auf folgenden Passus aus dem aktuellen Lagebericht verweisen
"Es ist weiterhin ein kontinuierlicher Rückgang der 7-Tage-Inzidenz zu beobachten, der Trend hat sich leicht abgeflacht. Der 7-Tage-R- Wert liegt unter 1. In den letzten Wochen sank die 7-Tage-Inzidenz in allen Altersgruppen. ...Um diese positive Entwicklung nicht zu gefährden, ist es weiterhin erforderlich, dass alle Menschen ihr Infektionsrisiko entsprechend der Empfehlungen des RKI (AHA + L) minimieren und bei Zeichen einer Erkrankung eine Testung vornehmen lassen und zuhause bleiben. Es wird außerdem empfohlen, Angebote für eine Impfung gegen COVID-19 wahrzunehmen. Die Rücknahme von Maßnahmen sollte aus epidemiologischer Sicht unbedingt schrittweise und nicht zu schnell erfolgen (vgl. ControlCOVID - Optionen und Perspektiven für die stufenweise Rücknahme von Maßnahmen bis Anfang September 2021 im Kontext der Impfkampagne)." Sowohl die Deutsche Bahn als auch die BVG haben in Zusammenarbeit mit der Charité bzw der TU Berlin Studien zum Infektionsrisiko bei Nutzung öffentlicher Verkehrsmittel unter Einhaltung von Schutzkonzepten durchgeführt, siehe bspw.https://www.deutschebahn.com/de/presse/pressestart_zentrales_uebersicht/Abschluss-Charit%C3%A9-Langzeitstudie-Kein-erhoehtes-Corona-Risiko-im-Fernverkehr-6189116?contentId=1204030; https://www.besserweiter.de/pendler-coronastudie-der-charite.html; https://www.bvg.de/de/Aktuell/Newsmeldung?newsid=4309).

Aus Sicht des RKI wird das Tragen eines Mund-Nasen-Schutzes in öffentlichen Verkehrsmitteln des Nah- und Fernverkehrs weiterhin empfohlen, insbesondere unter anderem auch da in den öffentlichen Verkehrsmitteln der Abstand nicht immer sicher eingehalten und eine ausreichende Lüftung nicht durchgehend gewährleistet werden kann.

Freundliche Grüße

i.A.

Muna ABU SIN

Lagezentrum COVID-19

Robert Koch-Institut
Seestr. 10
13353 Berlin

Tel.: 030 18754 3063
E-Mail: nCoV-Lage@rki.de
Internet: www.rki.de
Twitter: @rki_de

-----Ursprüngliche Nachricht-----
Von: Mylius , Maren - 614 BMG <Maren.Mylius@bmg.bund.de>
Gesendet: Montag, 14. Juni 2021 14:23
An: nCoV-Lage <nCoV-Lage@rki.de>
Cc: Rottmann-Großner, Heiko -61 BMG <Heiko.Rottmann-Grossner@bmg.bund.de>; 614 BMG <614@bmg.bund.de>; Ziegelmann Dr., Antina -RL 614 BMG <Antina.Ziegelmann@bmg.bund.de>; RKI-Fach-Erlasswesen <RKI-Fach-Erlasswesen@bmg.bund.de>
Betreff: WG: EILT: Frist HEUTE DS; Bitte um Stellungnahme: Maskenpflicht in öffentlichen Verkehrsmitteln
Priorität: Hoch

Liebe Kolleginnen und Kollegen am RKI,

wir haben u.s. Mitteilung des BMVI erhalten und bitten Sie um eine fachliche Stellungnahme zur Bewertung einer bundeseinheitlich vollständigen Aufhebung der Maskenpflicht, der Beibehaltung des Tragens von FFP2-Masken oder einer Pflicht zum Tragen von Alltags- oder OP-Masken in öffentlichen Verkehrsmitteln nach Auslaufen der bundeseinheitlichen Regelungen zu Ende Juni 2021.

Die Frist ist mit Blick auf die Verkehrsministerkonferenz am Mittwoch leider sehr kurz bis heute, 14.06.2021 DS, gesetzt. Wir bitten bis dahin um Ihre Rückmeldung.

Vielen Dank.
Mit freundlichen Grüßen
Maren Mylius

Dr. Maren Mylius
Bundesministerium für Gesundheit
Referat 614 - Infektionskrankheiten
Tel 030-18441-2785

-----Ursprüngliche Nachricht-----
Von: StabKM <StabKM@bmvi.bund.de>
Gesendet: Montag, 14. Juni 2021 11:23
An: 611 BMG <611@bmg.bund.de>; 9.KriSta@bmi.bund.de; '11.KriSta@bmi.bund.de' <11.KriSta@bmi.bund.de>
Cc: StabKM <StabKM@bmvi.bund.de>; Schmalen, Dominik <Dominik.Schmalen@bmvi.bund.de>
Betreff: EILT: Bitte um Stellungnahme: Maskenpflicht in öffentlichen Verkehrsmitteln

Liebe Kolleginnen und Kollegen,

unsere Hausleitung hat uns gebeten, die Haltung Ihrer Häuser zum Thema Maskenpflicht im ÖPNV (und Fernverkehr) abzustimmen.

Angesichts sinkender Inzidenzen sowie des Auslaufens der Bundesnotbremse zum Ende dieses Monats entfällt die bundeseinheitliche Regelung zur Maskenpflicht in öffentlichen Verkehrsmitteln (Tragen von FFP2 Masken für Fahrgäste) und es gelten hier wieder die einzelnen Regelungen der Länder. Mit der positiven Entwicklung der bundesweiten Inzidenz werden zudem erste Debatten um eine mögliche Aufhebung bzw. Lockerung der Maskenpflicht geführt, erste Länder passen ihre Verordnungen bereits für einige Bereiche an.

BMVI schlägt vor, mit Blick auf den Sommer und den beginnenden Lockerungen den Ländern vorzuschlagen, die Maskenpflicht in öffentlichen Verkehrsmitteln weiterhin einheitlich zu regeln, um ein Regelungswirrwar aus unterschiedlichen Landesverordnungen zu vermeiden. Eine vollständige Aufhebung der Maskenpflicht wird aus hiesiger Sicht noch nicht als zielführend betrachtet, aber es käme eine Anpassung der zu tragenden Maskenkategorie in Betracht. BMVI würde daher den Ländern daher vorschlagen, dass diese angesichts der beginnenden Lockerungen/Öffnungen für öffentliche Verkehrsmittel einheitlich eine Pflicht zum Tragen von Alltags- oder OP-Masken festschreiben.

Wir bitten Sie um eine Stellungnahme aus Ihren Häusern, ob Sie den Vorschlag des BMVI unterstützen können. Da am Mittwoch bereits eine Verkehrsministerkonferenz stattfindet, auf der das Thema behandelt wird, bitten wir um Ihre Rückmeldung bis heute, 14.06.2021, DS. Die kurze Frist bitten wir zu entschuldigen.

Herzlichen Dank für Ihre Unterstützung und beste Grüße i.A.

Stefanie Gutzat

From: "Glasmacher, Susanne" <GlasmacherS@rki.de>
To: Verteiler-Krisenstab <verteiler-krisenstab@rki.de>
Date: 6/30/2021 7:47:35 AM
Subject: AW: Vorbereitung auf den Herbst/Winter 2021/22

Liebe Kollegen,
von mir eine Anmerkung zum folgenden Abschnitt in der Einleitung:

Das Ziel der infektionspräventiven Maßnahmen ist weiterhin die Minimierung schwerer Erkrankungen durch SARS-CoV-2 unter Berücksichtigung der Gesamtsituation der Öffentlichen Gesundheit (Minimierung der Krankheitslast, Verfügbarkeit von ausreichend medizinischen Kapazitäten zur Versorgung der Bevölkerung, Reduktion der langfristigen durch LongCOVID verursachten Folgen sowie non-COVID-19 Effekte). Hierfür ist wichtig, die Infektionszahlen nachhaltig niedrig zu halten.

Bei "Hierfür ist wichtig, die Infektionszahlen nachhaltig niedrig zu halten" fehlt mir ein Hinweis, dass die Infektionszahlen an Aussagekraft verlieren, weil durch die Impfung der vulnerablen Gruppen die Korrelation von Inzidenz und ITS-Belastung zunehmend lockerer wird. Weiter hinten werden auch die anderen Indikatoren erwähnt, aber eine kurze Einordnung des Parameters Fallzahlen habe ich nicht so ausdrücklich gefunden, und gerade in der Einleitung, die viele noch lesen dürften, fände ich es bedeutsam. Ganz weglassen kann man den Satz "Hierfür ist wichtig ..." wohl nicht.

Gruß, Glasmacher

-----Ursprüngliche Nachricht-----
Von: Mankertz, Annette
Gesendet: Mittwoch, 30. Juni 2021 09:40
An: Arvand, Mardjan <ArvandM@rki.de>; Schulze, Kai <SchulzeK@rki.de>; Verteiler-Krisenstab <verteiler-krisenstab@rki.de>
Cc: Streib, Viktoria <StreibV@rki.de>
Betreff: AW: Vorbereitung auf den Herbst/Winter 2021/22

Liebe Kolleginnen und Kollegen,

anbei das Dokument mit in der Hauptsache sprachlichen und wenigen inhaltlichen Änderungsvorschlägen.

Gruß
AM

-----Ursprüngliche Nachricht-----
Von: Arvand, Mardjan
Gesendet: Dienstag, 29. Juni 2021 10:45
An: Schulze, Kai <SchulzeK@rki.de>; Verteiler-Krisenstab <verteiler-krisenstab@rki.de>
Cc: Streib, Viktoria <StreibV@rki.de>
Betreff: AW: Vorbereitung auf den Herbst/Winter 2021/22

Lieber Herr Schulze,

Liebe Alle,
vielen Dank. Auch wenn das Dok "final" heißt möchte ich trotzdem noch einen letzten Vorschlag zum Punkt Maßnahmen in Gesundheitseinrichtungen machen (Anhang). M.E. wäre es gut, hier die prioritären Punkte zuerst zu nennen. Gerade in GE z.B. Krankenhaus oder Arztpraxis ist die Luftübertragung nicht unbedingt die wichtigste Übertragungsart und dies sollten wir m.E. entsprechend gewichten.
Viele Grüße
M. Arvand

-----Ursprüngliche Nachricht-----
Von: Schulze, Kai
Gesendet: Montag, 28. Juni 2021 18:33
An: Verteiler-Krisenstab <verteiler-krisenstab@rki.de>
Cc: Streib, Viktoria <StreibV@rki.de>
Betreff: AW: Vorbereitung auf den Herbst/Winter 2021/22

Liebe Kolleg:innen,

bitte finden Sie im Anhang die finale Version zum Herbstdokument (Stand letzten Donnerstag).

VG
KS

__
Kai Schulze, PhD Mphil
Abteilung für Infektionsepidemiologie
Robert Koch-Institut
Seestraße 10
13353 Berlin
Tel.: +49 30 18754 3276
Mobil[redacted]
Email: schulzek@rki.de

-----Ursprüngliche Nachricht-----
Von: Schulze, Kai
Gesendet: Dienstag, 22. Juni 2021 16:25
An: Verteiler-Krisenstab <Verteiler-Krisenstab@rki.de>
Cc: Streib, Viktoria <StreibV@rki.de>
Betreff: Vorbereitung auf den Herbst/Winter 2021/22

Liebe Kolleg:innen,

im Anhang finden Sie die aktuelle Version der Empfehlungen und Modellierungen zur Vorbereitung auf den Herbst und Winter 2021/22, mit Bitte zur Kenntnisnahme und / oder Kommentierung bis morgen früh 10 Uhr.

Wir werden das Dokument dann auch morgen im Krisenstab vorstellen.

VG

KS

—

Kai Schulze, PhD Mphil
Abteilung für Infektionsepidemiologie
Robert Koch-Institut
Seestraße 10
13353 Berlin
Tel.: +49 30 18754 3276
Mobi[redacted]
Email: schulzek@rki.de

From: "Haas, Walter" <HaasW@rki.de>
To: "an der Heiden, Maria" <AnderHeidenMa@rki.de>
Date: 7/12/2021 6:14:49 PM
Subject: AW: Nachtrag: Formulierungen in der aktualisierten Risikobewertung

---

Liebe Maria,

vielen Dank, wir konnen das gerne am Mittwoch im Krisenstab besprechen.

Viele Gru?e
Walter

-----Ursprungliche Nachricht-----
Von: an der Heiden, Maria
Gesendet: Montag, 12. Juli 2021 19:24
An: Haas, Walter <HaasW@rki.de>
Cc: nCoV-Lage <nCoV-Lage@rki.de>; Hamouda, Osamah <HamoudaO@rki.de>
Betreff: WG: Nachtrag: Formulierungen in der aktualisierten Risikobewertung

Lieber Walter,

ich leite Dir hier die Kommunikation bzgl. der Risikobewertung zwischen Lagezentrum, Osamah und Herrn Wieler weiter.

Auch wenn die Formulierungen sicherlich noch gescharft werden konnen, hatte ich mit Bettina vorhin am Telefon ausgemacht, dass wir - da es eine Abstimmung am Freitag im Krisenstab gab - eher nun nicht noch weiter daran schrauben. BMG hat ja Freigabe gegeben.

Ggf. sind aber noch Formulierungsuberarbeitungen notig.

Das konnen wir ja dann ggf. am Mittwoch im Krisenstab besprechen.

VG Maria

-----Ursprungliche Nachricht-----
Von: Rosner, Bettina Im Auftrag von nCoV-Lage
Gesendet: Montag, 12. Juli 2021 19:18
An: an der Heiden, Maria <AnderHeidenMa@rki.de>
Cc: nCoV-Lage <nCoV-Lage@rki.de>
Betreff: Nachtrag: Formulierungen in der aktualisierten Risikobewertung

Liebe Maria,

bei dem Versuch, Teile der aktuellen Risikobewertung in den heutigen Lagebericht zu ubernehmen, sind folgende beiden Satze als nicht gut verstandlich angesehen worden (von Osamah bzw. Herrn Wieler). Vielleicht muss sich da jemand nochmal Gedanken machen, ob man die Inhalte in der

aktualisierten Risikobewertung nicht klarer und leicht verstandlicher formulieren konnte.

1.) "Eine leicht verringerte Schutzwirkung bei B1.617.2 (Delta) im Vergleich zu B.1.1.7 (Alpha) zeigte sich in den bisher vorliegenden Daten hauptsachlich nach Erhalt der ersten Impfstoffdosis und in Bezug auf milde Krankheitsverlaufe."

Wurde nach Rucksprache mit Osamah und Walter Haas fur den Lagebericht umformuliert zu:
"Die bisher vorliegenden Daten zeigen, dass nach Erhalt von nur einer von zwei Impfstoffdosen die Schutzwirkung gegenuber der Delta-Variante (B1.617.2) im Vergleich zur Alpha-Variante (B.1.1.7) leicht verringert ist."

Der Teil mit den milden Verlaufen wurde im Lagebericht weggelassen, weil es in der Kurze der Zeit nicht gelungen ist, dies korrekt und trotzdem gut verstandlich zu formulieren.

2.) Herr Wieler fand folgenden Satz nicht besonders gut gelungen (die Verknupfung mit "wobei"). Den Satz hatte ich vorhin mit Dir ja bereits besprochen, weil ich den Satz auch nicht gut verstandlich finde:
"Fur vollstandig Geimpfte wird die Gefahrdung als moderat eingeschatzt, wobei Menschen mit chronischen Erkrankungen und vulnerable Bevolkerungsgruppen besonders betroffen sind."

Der Satz konnte dann trotzdem auch in den Lagebericht ubernommen werden, nachdem ich Herrn Wieler erklart habe, was Du mir vorhin erklart hast. Damit zeigt sich aber, dass der Satz nicht selbsterklarend ist...Vielleicht ist auch das Wort "betroffen" an dieser Stelle nicht so gut.

Viele Gru?e,
Bettina

Lagezentrum COVID-19
Robert Koch-Institut
Seestr. 10
13353 Berlin

Tel.: 030 18754 3063
E-Mail: nCoV-Lage@rki.de
Internet: www.rki.de
Twitter: @rki_de

From: "Wieler, Lothar" <WielerLH@rki.de>
To: "Haas, Walter" <HaasW@rki.de>
"Mielke, Martin" <MielkeM@rki.de>
"Rexroth, Ute" <RexrothU@rki.de>
Date: 7/29/2021 2:34:30 PM
Subject: AW: Anmerkungen zum aktuellen Dokument: Einladung Telko heute 17:00Uhr/Bund-Länder Papier_Eindämmung von COVID-19_Herbst2021_ohne Änd.docx

---

Das müssen wir im KS noch besprechen. Das leuchtet mir tatsächlich nicht vollständig ein, denn der Anteil der Vulnerablen hat ja durch die Impfung stark abgenommen. Hat FG33 denn die Verläufe der IST, Toten etc. denn auch in Abhängigkeit verschiedener Inzidenzen berechnet?

-----Ursprüngliche Nachricht-----
Von: Haas, Walter
Gesendet: Donnerstag, 29. Juli 2021 16:29
An: Wieler, Lothar <WielerLH@rki.de>; Mielke, Martin <MielkeM@rki.de>; Rexroth, Ute <RexrothU@rki.de>
Cc: Buda, Silke <BudaS@rki.de>; Schaade, Lars <SchaadeL@rki.de>; Abu Sin, Muna <Abu-SinM@rki.de>; nCoV-Lage <nCoV-Lage@rki.de>; Hamouda, Osamah <HamoudaO@rki.de>; AL1-Sekretariat <AL1-Sekretariat@rki.de>; Buchholz, Udo <BuchholzU@rki.de>
Betreff: AW: Anmerkungen zum aktuellen Dokument: Einladung Telko heute 17:00Uhr/Bund-Länder Papier_Eindämmung von COVID-19_Herbst2021_ohne Änd.docx

Lieber Herr Wieler,

ausgehend von den Modellierungen von FG33 denke ich, dass sich höhere Inzidenzen bei den derzeit erreichten Impfquoten, sich sehr rasch in einen steileren und höheren Verlauf der 4. Welle übersetzen. Außerdem glaube ich, dass fixe Trigger genau diese Dynamik nicht gut abbilden können, abgesehen von den lokal/regional unterschiedlichen Settings.

Daher bin ich bez. der (anhand des Verlaufs während der 1. und 2. Welle auf Basis einer ungeimpften Bevölkerung gewählten) Grenzen aus dem Stufenplan sehr konservativ und denke der Zeitpunkt, diese deutlich anzuheben, ist bei den aktuellen Impfquoten und der bereits erfolgten Zunahme infektionsrelevanter Kontakte in der Bevölkerung ungünstig.

Viele Grüße
Walter

-----Ursprüngliche Nachricht-----
Von: Wieler, Lothar
Gesendet: Donnerstag, 29. Juli 2021 13:31
An: Mielke, Martin <MielkeM@rki.de>; Haas, Walter <HaasW@rki.de>; Rexroth, Ute <RexrothU@rki.de>
Cc: Buda, Silke <BudaS@rki.de>; Schaade, Lars <SchaadeL@rki.de>; Abu Sin, Muna <Abu-SinM@rki.de>; nCoV-Lage <nCoV-Lage@rki.de>; Hamouda, Osamah <HamoudaO@rki.de>; AL1-Sekretariat <AL1-Sekretariat@rki.de>; Buchholz, Udo <BuchholzU@rki.de>
Betreff: AW: Anmerkungen zum aktuellen Dokument: Einladung Telko heute 17:00Uhr/Bund-Länder

Papier_Eindämmung von COVID-19_Herbst2021_ohne Änd.docx

Aber die Schwellenwerte der Inzidenz - die sollten schon nach oben verschoben werden…

-----Ursprüngliche Nachricht-----
Von: Mielke, Martin
Gesendet: Donnerstag, 29. Juli 2021 13:28
An: Haas, Walter <HaasW@rki.de>; Wieler, Lothar <WielerLH@rki.de>; Rexroth, Ute <RexrothU@rki.de>
Cc: Buda, Silke <BudaS@rki.de>; Schaade, Lars <SchaadeL@rki.de>; Abu Sin, Muna <Abu-SinM@rki.de>; nCoV-Lage <nCoV-Lage@rki.de>; Hamouda, Osamah <HamoudaO@rki.de>; AL1-Sekretariat <AL1-Sekretariat@rki.de>; Buchholz, Udo <BuchholzU@rki.de>
Betreff: AW: Anmerkungen zum aktuellen Dokument: Einladung Telko heute 17:00Uhr/Bund-Länder Papier_Eindämmung von COVID-19_Herbst2021_ohne Änd.docx

Lieber Herr Haas,
vielen Dank! Ich kann Ihrer Argumentation gut folgen.

Gruß und Dank für den Gedankenaustausch, Martin Mielke

-----Ursprüngliche Nachricht-----
Von: Haas, Walter
Gesendet: Donnerstag, 29. Juli 2021 12:48
An: Wieler, Lothar <WielerLH@rki.de>; Mielke, Martin <MielkeM@rki.de>; Rexroth, Ute <RexrothU@rki.de>
Cc: Buda, Silke <BudaS@rki.de>; Schaade, Lars <SchaadeL@rki.de>; Abu Sin, Muna <Abu-SinM@rki.de>; nCoV-Lage <nCoV-Lage@rki.de>; Hamouda, Osamah <HamoudaO@rki.de>; AL1-Sekretariat <AL1-Sekretariat@rki.de>; Buchholz, Udo <BuchholzU@rki.de>
Betreff: AW: Anmerkungen zum aktuellen Dokument: Einladung Telko heute 17:00Uhr/Bund-Länder Papier_Eindämmung von COVID-19_Herbst2021_ohne Änd.docx

Lieber Herr Mielke,

bezüglich Ihres Vorschlags zur internen Diskussion unter Punkt 3 einer Einrechnung der Impfquote in die Inzidenz als Quotient - die Wirksamkeit der Impfung in der Verhinderung bildet sich bereits in der Inzidenz ab, da diese auch effektiv Infektionen verhindert. Das bedeutet, die gleich hohe Inzidenz in einer in Teilen geimpften Bevölkerung entspricht einer deutlich stärkeren Ausbreitung bzw. einem höheren (!) Infektionsdruck. Der Einfluss der Impfung findet sich in der Verringerung der individuellen klinischen Schwere der Erkrankungen, welche in der Hospitalisierungsinzidenz erfasst werden sollte sowie in einer geringeren Belastung des Gesundheitssystems bei gleicher Inzidenz.

Aufgrund der sekundären Effekte eines hohen Infektionsdrucks, insbesondere auf Kinder und Jugendliche in den Bereichen Schule/KiTa sowie die ältere, pflegebedürftige Bevölkerung (wie im Herbstpapier beschrieben), bleibt die Verringerung der Ausbreitung, insbesondere durch die Basismaßnahmen und gezielte Maßnahmen hinsichtlich Großveranstaltungen und der Situation in Innenräumen (Arbeitsplatz, Feiern etc.) m. E. weiter relevant.

Die Inzidenzen proportional zur Impfquote nach oben zu korrigieren halte ich persönlich aus den

oben genannten Gründen daher nicht für einen geeigneten Ansatz.

Viele Grüße
Walter Haas

-----Ursprüngliche Nachricht-----
Von: Wieler, Lothar
Gesendet: Donnerstag, 29. Juli 2021 10:22
An: Mielke, Martin <MielkeM@rki.de>; Rexroth, Ute <RexrothU@rki.de>
Cc: Haas, Walter <HaasW@rki.de>; Buda, Silke <BudaS@rki.de>; Schaade, Lars <SchaadeL@rki.de>; Abu Sin, Muna <Abu-SinM@rki.de>; nCoV-Lage <nCoV-Lage@rki.de>; Hamouda, Osamah <HamoudaO@rki.de>; AL1-Sekretariat <AL1-Sekretariat@rki.de>
Betreff: AW: Anmerkungen zum aktuellen Dokument: Einladung Telko heute 17:00Uhr/Bund-Länder Papier_Eindämmung von COVID-19_Herbst2021_ohne Änd.docx

Liebe Alle,

ich stimme Herrn Mielke zu, wir sollten diese Aspekte benennen und müssen ja auch unser ControlCOVID entsprechend überarbeiten, die dort genannten Grenzwerte zu Inzidenzen sind ja so nicht mehr haltbar wegen der steigenden Impfrate.

Ich bin morgen im Urlaub, bitte entscheiden sie im KS morgen wie sie weiter vorgehen. Nächste Woche sind sowohl Herr Schaade als auch ich vor Ort.

Beste Grüße

LHW

-----Ursprüngliche Nachricht-----
Von: Mielke, Martin
Gesendet: Donnerstag, 29. Juli 2021 09:08
An: Rexroth, Ute <RexrothU@rki.de>
Cc: Haas, Walter <HaasW@rki.de>; Buda, Silke <BudaS@rki.de>; Mielke, Martin <MielkeM@rki.de>; Wieler, Lothar <WielerLH@rki.de>; Schaade, Lars <SchaadeL@rki.de>; Abu Sin, Muna <Abu-SinM@rki.de>; nCoV-Lage <nCoV-Lage@rki.de>; Hamouda, Osamah <HamoudaO@rki.de>; AL1-Sekretariat <AL1-Sekretariat@rki.de>
Betreff: Anmerkungen zum aktuellen Dokument: Einladung Telko heute 17:00Uhr/Bund-Länder Papier_Eindämmung von COVID-19_Herbst2021_ohne Änd.docx
Priorität: Hoch

Liebe Frau Rexroth, liebe Kolleginnen und Kollegen,

Bezug nehmend auf die gestrige Diskussion im Krisenstab und das beiliegende Dokument übersende ich hier noch folgende Gedanken:

1) Bitte finden Sie einige Ergänzungen von meiner Seite direkt im Text (s. Anlage).

2) Aus meiner Sicht kommt gegenwärtig in dem Dokument noch nicht so ganz klar zum Ausdruck,

dass die Überlegungen durch die (vermeintlich) geänderte Situation bei Berücksichtigung der Impfquote/ des Impfschutzes vulnerabler Populationen ausgelöst wurden (Was hat sich gegenüber dem Herbst 2020 verändert ?). Herr Prof. Watzl sprach heute im DLF von einem "Korrekturfaktor" für die Bewertung der 7 Tage-Inzidenz im Hinblick auf die zu ergreifenden Maßnahmen. Anders ausgedrückt: Welche Indikatoren sind in Anbetracht der durch die Impfung veränderten Situation nun wegweisend ? Welche Freiheiten können trotz einer ggf. höheren 7 Tage-Inzidenz (anders als bisher) gewährt werden ? Aktuell soll diese "Korrektur" durch Berücksichtigung mindestens eines weiteren Faktors (Hospitalisierung/ ITS-Belastung) erreicht werden.
Frau Buda hatte den MMWR-Artikel des CDC (July27, 2021) herumgeschickt. Dort wird auch die Positivquote zur besseren Einschätzung der 7 Tage-Inzidenz aufgeführt.

3) Nur für die interne Diskussion:
a) ggf. wäre auch über einen (regionalen) "Index" aus 7 Tage-Inzidenz x 7 Tage-Hosp-Inzidenz / Impfquote nachzudenken.
b) Welche Gefährdung Geimpfter (> 75 Jahre; z.B. im Pflegebereich) geht von SARS-CoV-2 Infizierten aus ?
c) Wie verändert sich die Situation bei Auftreten einer Immunescape-Variante ?

Soweit zunächst, Gruß,
Martin Mielke

Personen, die geimpft werden könnten, d.h. bei denen keine medizinischen Gründe gegen eine Impfung sprechen, aber alternativ eine anlassbezogene Testung vorzie-hen (z.B. für die Teilnahme an Veranstaltungen oder im Innenbereich der Gastrono-mie) (3G), sollten selbst für die Testung aufkommen müssen

-----Ursprüngliche Nachricht-----
Von: Rexroth, Ute
Gesendet: Mittwoch, 28. Juli 2021 17:33
An: Haas, Walter <HaasW@rki.de>; Buda, Silke <BudaS@rki.de>; Mielke, Martin <MielkeM@rki.de>; Wieler, Lothar <WielerLH@rki.de>; Schaade, Lars <SchaadeL@rki.de>; Abu Sin, Muna <Abu-SinM@rki.de>
Cc: nCoV-Lage <nCoV-Lage@rki.de>; Hamouda, Osamah <HamoudaO@rki.de>
Betreff: WG: Einladung Telko heute 17:00Uhr/Bund-Länder Papier_Eindämmung von COVID -19_Herbst2021_ohne Änd.docx
Priorität: Hoch

Liebe Kolleginnen und Kollegen,

zur Information:
Wir haben das Dokument gerade bekommen. Es wird nun weiter diskutiert.
Wir haben schon klar gemacht, dass wir als RKI nicht als Autoren, sondern nur als beratende

Einrichtung genannt werden. Dies ist von der Gruppe gut aufgenommen worden und wird so umgesetzt.

Das ist umso wichtiger, weil die Diskussion nun doch in die Richtung geht, Maßnahmen abzuleiten. Allerdings in Anlehnung an unser Stufenplan.

Viele Grüße,

Ute Rexroth

-----Ursprüngliche Nachricht-----
Von: Jahn, Klaus (MWG) <Klaus.Jahn@mwg.rlp.de>
Gesendet: Mittwoch, 28. Juli 2021 16:36
An: BW Dr. Isolde Piechotwoski <Isolde.Piechotowski@sm.bwl.de>; BY Elzbieta Voigtländer <lage-Corona@stmgp.bayern.de>; BY Martina Enke <Martina.Enke@stmgp.bayern.de>; HE Dr. Sabine Totsche <Sabine.Totsche@hsm.hessen.de>; HH Dr. Alexandra von Reiswitz <alexandra.vonreiswitz@soziales.hamburg.de>; HH Elke Jakubowski <elke.jakubowski@bgv.hamburg.de>; Höflich, Cornelia (MWG) <Cornelia.Hoeflich@mwg.rlp.de>; Jahn, Klaus (MWG) <Klaus.Jahn@mwg.rlp.de>; Kolb, Julia (MWG) <Julia.Kolb@mwg.rlp.de>; MV Dr. Gero Koch <G.Koch@wm.mv-regierung.de>; NI Claudia Schröder <claudia.Schroeder@ms.niedersachsen.de>; NI Dr. Karin Reinelt <karin.reinelt@ms.niedersachsen.de>; NRW Sandra Dybowski <Sandra.Dybowski@mags.nrw.de>; Hamouda, Osamah <HamoudaO@rki.de>; Rexroth, Ute <RexrothU@rki.de>; SH Annicka Reuss <annicka.reuss@sozmi.landsh.de>; SH Dr.Anne Marcic <Anne.Marcic@sozmi.landsh.de>; SN Andrea Shanati <andrea.shanati@sms.sachsen.de>; SN Dr. Michael Kurth <Michael.Kurth@sms.sachsen.de>; SN Fr. Dr. Attiya Khan <Attiya.Khan@sms.sachsen.de>; TH Dr. Jan Franke <jan.franke@tmasgff.thueringen.de>
Cc: Höflich, Cornelia (MWG) <Cornelia.Hoeflich@mwg.rlp.de>; Kolb, Julia (MWG) <Julia.Kolb@mwg.rlp.de>
Betreff: Einladung Telko heute 17:00Uhr/Bund-Länder Papier_Eindämmung von COVID -19_Herbst2021_ohne Änd.docx
Priorität: Hoch

Liebe Kolleginnen und Kollegen,

anbei die neue Version auf der Basis der gestrigen Diskussion.

Im Hinblick auf etwaige justiziable Maßnahmen habe ich auf Grundlage des RKI-Papiers den einzelnen Warnstufen Beispielmaßnahmen zugeordnet.

Sollte ich etwas vergessen haben, bitte melden Sie sich.

Zur weiteren Abstimmung lade Sie ganz herzlich zur 3. UAG-Sitzung der AGI, heute, 28.07.2021, 17:00 Uhr ein.

Ziel ist es das Papier heute zu finalisieren – wenigsten inhaltlich!!

Im Folgenden die Einwahldaten:

https://meetsozminrlp.de/b/jul-ygr-gc8-3rk

Passwort: 388643

Ich freue mich auch die weitere Diskussion mit Ihnen.

Besten Gruß

Klaus Jahn

--
i.A.

Dr. Klaus Jahn

Leiter Referat Infektionsschutz, Öffentlicher Gesundheitsdienst

MINISTERIUM FÜR WISSENSCHAFT UND GESUNDHEIT

Mittlere Bleiche 61

55116 Mainz

Telefon +49 6131 16 2307

klaus.jahn@mwg.rlp.de <mailto:klaus.jahn@mwg.rlp.de>

www.mwg.rlp.de <http://www.mwg.rlp.de>

-----Ursprüngliche Nachricht-----

From: ZBS7-Lage <ZBS7-Lage@rki.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 8/12/2021 3:57:56 PM
Subject: AW: [Aufgabe ID 4089] Daten zu verlLngerter Virusausscheidung bei Delta Variante
Attachments: Shedding Infectiousness s41467-020-20568-4.pdf
SARS-CoV-2 viral loaddynamics, duration of viral sheddingand infectiousness 2020.07.25.20162107v1.full.pdf
Shedding Review fpubh-09-652842.pdf
Shedding journal.pbio.3001333.pdf
shedding eabi5273.full.pdf
Shedding Delta 2021.07.28.21261295v1.full.pdf

Liebes Lagezentrum,

in Rucksprache mit ZBS1 und in Absprache mit Abt. 1 hatten wir folgende Antwort fur die diskutierte Frage:

Die Kinetik der Virusausscheidung folgt auch bei der Delta-Variante dem von SARS-CoV-2 bekannten Muster (Cevik et al 2020; Yan et al 2021; Jones et al 2021; Kissler et al 2021; sowie unsere Hinweise zur Testung auf SARS-CoV-2). Es gibt jedoch Hinweise auf eine initial hohere Viruslast. Der weitere Verlauf der Infektion scheint in den meisten Fallen analog den bisher bekannten Verlaufen zu erfolgen. Allerdings sind Falle protrahierter Ausscheidung auch uber den Tag 14 hinaus beschrieben (Chia et al 2021). Dies gilt allerdings auch fur die initiale Variante (van Kampen et al 2021).

Durch die bereits im Februar 2021 beim Entlassmanagement erfolgten Anpassungen auf mind. 14 Tage mit abschlie?endem Antigentest zur Detektion von hohen Viruslasten zu diesem Zeitpunkt ist zunachst eine weitere Beobachtung der Datenlage gerechtfertigt. Wir schlagen Wiedervorlage der Fragestellung Ende September 2021 zur Berucksichtigung der zwischenzeitlich verfugbar werdenden Literatur vor. (Literatur in der Anlage)"

Zur Frage der ggf. gebotenen Anpassung von Quarantanezeiten im Zusammenhang mit der Delta-Variante (Inkubationszeit) befasst sich aktuell FG36 (siehe Protokoll KS vom 11.08.21)

Gerne kann dieser Punkt auch im Krisenstab nochmal diskutiert werden.

Vielen Dank und viele Gru?e,
Michaela Niebank

-----Ursprungliche Nachricht-----
Von: Schmid, Bernhard Im Auftrag von nCoV-Lage
Gesendet: Donnerstag, 12. August 2021 13:37

An: Lang, Katharina <LangK@rki.de>; Nitsche, Andreas <NitscheA@rki.de>; Michel, Janine <MichelJ@rki.de>
Cc: nCoV-Lage <nCoV-Lage@rki.de>; ZBS1-Diagnostik <ZBS1-Diagnostik@rki.de>; ZBS7-Lage <ZBS7-Lage@rki.de>
Betreff: WG: [Aufgabe ID 4089] Daten zu verlangerter Virusausscheidung bei Delta Variante

Liebe Kolleginnen und Kollegen,

wir mochten uns hiermit nach dem Stand der Bearbeitung der Aufgabe ID 4089, Frist morgen DS, erkundigen.

Vielen Dank und viele Gru?e,
Bernhard Schmid, LZ Aufgaben

-----Ursprungliche Nachricht-----
Von: Stern, Daniel Im Auftrag von nCoV-Lage
Gesendet: Donnerstag, 5. August 2021 16:14
An: Lang, Katharina <LangK@rki.de>; Nitsche, Andreas <NitscheA@rki.de>; Michel, Janine <MichelJ@rki.de>
Cc: nCoV-Lage <nCoV-Lage@rki.de>; ZBS7-Lage <ZBS7-Lage@rki.de>; ZBS1-Diagnostik <ZBS1-Diagnostik@rki.de>
Betreff: [Aufgabe ID 4089] Daten zu verlangerter Virusausscheidung bei Delta Variante

Lieber Katharina, Lieber Andi, Liebe Janine,

Aus dem Protokoll der Krisenstabssitzung hat sich eine Aufgabe mit der Bitte um Ubernahme ergeben:

* Gibt es Daten zu einer langeren Virusausscheidung bei Delta?

ToDo: Fr. Lang nimmt Frage mit ins Fachgebiet.

ToDo: Evtl. konnte sich ZBS1 das ansehen. Klarung, ob eine retrospektive Betrachtung aus klinischen Proben moglich ist.

Bei der Erledigung von Erlassen: Beantwortung sollte immer durch das Lagezentrum erfolgen!

Aufgabe ID 4089

Federfuhrende RKI-Organisationseinheit: ZBS7

Weitere RKI-Organisationseinheit/en: ZBS1

Bearbeitende/r: Lang, Nitsche, Michel

Thema: Daten zu verlangerter Virusausscheiden bei Delta

Beschreibung:

Dokumentenordner:

Frist: 13.08.2021 DS

Bei Erledigung: bitte E-Mail an nCoV-Lage@rki.de <mailto:nCoV-Lage@rki.de>

Im Betreff bitte die Aufgaben ID angeben.

Anmerkung: falls Sie den Eindruck haben, dass die Aufgabe falsch zugewiesen wurde oder der Auftrag nicht verstandlich ist, bitten wir um Ruckmeldung!

Vielen Dank und viele Gru?e,

Daniel

i.A. Daniel Stern

Lagezentrum COVID-19

Robert Koch-Institut

Seestr. 10

13353 Berlin

Tel.: 030 18754 3063

E-Mail: nCoV-Lage@rki.de

Internet: www.rki.de

Twitter: @rki_de

Das Robert Koch-Institut ist ein Bundesinstitut im Geschaftsbereich des Bundesministeriums fur Gesundheit

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-20568-4 OPEN

Duration and key determinants of infectious virus shedding in hospitalized patients with coronavirus disease-2019 (COVID-19)

Jeroen J. A. van Kampen[1]✉, David A. M. C. van de Vijver[1], Pieter L. A. Fraaij[1,2], Bart L. Haagmans[1], Mart M. Lamers[1], Nisreen Okba[1], Johannes P. C. van den Akker[3], Henrik Endeman[3], Diederik A. M. P. J. Gommers[3], Jan J. Cornelissen[4], Rogier A. S. Hoek[5,6], Menno M. van der Eerden[5], Dennis A. Hesselink[6,7], Herold J. Metselaar[6,8], Annelies Verbon[9], Jurriaan E. M. de Steenwinkel[9], Georgina I. Aron[1], Eric C. M. van Gorp[1], Sander van Boheemen[1], Jolanda C. Voermans[1], Charles A. B. Boucher[1], Richard Molenkamp[1], Marion P. G. Koopmans[1,10], Corine Geurtsvankessel[1,10] & Annemiek A. van der Eijk[1,10]

Key questions in COVID-19 are the duration and determinants of infectious virus shedding. Here, we report that infectious virus shedding is detected by virus cultures in 23 of the 129 patients (17.8%) hospitalized with COVID-19. The median duration of shedding infectious virus is 8 days post onset of symptoms (IQR 5–11) and drops below 5% after 15.2 days post onset of symptoms (95% confidence interval (CI) 13.4–17.2). Multivariate analyses identify viral loads above 7 $\log_{10}$ RNA copies/mL (odds ratio [OR] of 14.7 (CI 3.57-58.1; $p < 0.001$) as independently associated with isolation of infectious SARS-CoV-2 from the respiratory tract. A serum neutralizing antibody titre of at least 1:20 (OR of 0.01 (CI 0.003-0.08; $p < 0.001$) is independently associated with non-infectious SARS-CoV-2. We conclude that quantitative viral RNA load assays and serological assays could be used in test-based strategies to discontinue or de-escalate infection prevention and control precautions.

[1] Department of Viroscience, Erasmus MC, Rotterdam, The Netherlands. [2] Department of Pediatrics, Subdivision Infectious Diseases and Immunology, Erasmus MC - Sophia, Rotterdam, The Netherlands. [3] Department of Intensive Care, Erasmus MC, Rotterdam, The Netherlands. [4] Department of Hematology, Erasmus MC, Rotterdam, The Netherlands. [5] Department of Pulmonary Medicine, Erasmus MC, Rotterdam, The Netherlands. [6] Erasmus MC Transplant Institute, Rotterdam, The Netherlands. [7] Department of Internal Medicine, Division of Nephrology and Transplantation, Erasmus MC, Rotterdam, The Netherlands. [8] Department of Gastroenterology and Hepatology, Erasmus MC, Rotterdam, The Netherlands. [9] Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands. [10] These authors contributed equally: Marion P. G. Koopmans, Corine Geurtsvankessel, Annemiek A. van der Eijk. ✉email: j.vankampen@erasmusmc.nl

Coronavirus disease-2019 (COVID-19) is a new clinical entity caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1,2]. In particular, persons with underlying diseases, such as diabetes mellitus, hypertension, cardiovascular disease, and respiratory disease, are at increased risk for severe COVID-19, and case fatality rates increase steeply with age[3].

Understanding the kinetics of infectious virus shedding in relation to potential for transmission is crucial to guide infection prevention and control strategies[4]. Long-term shedding of viral RNA has been reported in COVID-19 patients, even after full recovery, putting serious constraints on timely discharge from the hospital or de-escalation of infection prevention and control practices[5–7]. Detection of viral RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) is the gold standard for COVID-19 diagnosis and this technique is used in test-based strategies to discontinue or de-escalate infection prevention and control precautions[8–10]. However, there is no clear correlation between detection of viral RNA and detection of infectious virus using cell culture[5,11,12]. Detection of infectious virus, also called live virus or replication-competent virus, by demonstration of in vitro infectiousness on cell lines is regarded as a more informative surrogate of viral transmission than detection of viral RNA[8–10]. In a COVID-19 hamster model, the window of transmission correlated well with the detection of infectious virus using cell culture but not with viral RNA[13]. Key questions in COVID-19, like in any other infectious disease, are how long a person sheds infectious virus and what the determinants are of infectious virus shedding[5,11,12,14,15].

Two studies reported that infectious virus could not be detected in respiratory tract samples obtained more than 8 days after onset of symptoms despite continued detection of high levels of viral RNA[5,12]. For one patient, infectious virus shedding up to 18 days after onset of symptoms was reported[11]. Shedding of infectious SARS-CoV-2 has not been studied in larger groups of patients nor in patients with severe or critical COVID-19. Here, we show that patients with critical COVID-19 may shed infectious virus for longer periods of time compared to what has been reported for in patients with mild COVID-19. In addition, we show that infectious virus shedding drops to undetectable levels below a viral RNA load threshold and once serum neutralizing antibodies are present, which suggests that quantitative viral RNA load assays and serological assays could be used in test-based strategies to discontinue or de-escalate infection prevention and control precautions.

Results

We included 129 hospitalized individuals that had been diagnosed with COVID-19 by RT-PCR and for whom at least one virus culture from a respiratory tract sample was available (Table 1). Of these, 89 patients (69.0%) had been admitted to the intensive care and the remaining 40 patients (31.0%) were admitted to the medium care. Mechanical ventilation was only performed at the intensive care (81 or 91.0% of patients). Supplemental oxygen was given to 8 (9.0%) of the intensive care patients and to 35 (87.5%) medium care patients. Thirty patients were immunosuppressed (23%) of whom 19 (14.7%) were nonseverely immunocompromised and 11 (8.5%) were severely immunocompromised.

We tested 690 respiratory samples from the 129 patients for the presence of infectious virus using cell culture and determined the viral RNA load with RT-qPCR (Fig. 1). Infectious SARS-CoV-2 was isolated from 62 respiratory tract samples (9.0%) of 23 patients (17.8%). The median time of infectious virus shedding was 8 days post onset of symptoms (IQR 5–11, range 0–20) and probit analysis showed a probability of ≤5% for isolating infectious SARS-CoV-2 when the duration of symptoms was 15.2 days (95% CI 13.4–17.2) or more (Fig. 2A). The median viral load was significantly higher in culture positive samples than in culture negative samples (8.14 versus 5.88 Log_{10} RNA copies/mL, $p < 0.0001$) and the probability of isolating infectious SARS-CoV-2 was less than 5% when the viral load was below 6.63 Log_{10} RNA copies/mL (95% CI 6.24–6.91) (Fig. 2B).

For 27 patients, neutralizing antibody titers from 112 serum samples that were obtained on the same day as a respiratory tract sample were available in our diagnostic database (Table 2). The probability of isolating infectious virus was less than 5% when the neutralizing antibody titer was 1:80 or higher (Fig. 2C). In addition to these neutralizing antibody measurements, we performed RT-PCRs to detect SARS-CoV-2 subgenomic messenger RNA in the 112 corresponding respiratory tract samples. Detection of the subgenomic RNAs outlasted the detection of infectious virus (Supplementary Figs. 1 and 2), and predicted poorly if virus cultures were positive (positive predictive value of 37.5%). In addition, quantitative assessment of subgenomic RNA using cycle threshold (CT) values had no added value over measuring viral genomic RNA loads or serological response to predict infectious virus shedding (Supplementary Fig. 3).

Finally, the key parameters were compared using multivariate generalized estimating equations (Table 3). For this, timepoints for which all three data types (RT-qPCR, virus culture and serum neutralizing antibody titer) were available were included ($n = 112$). A viral load exceeding 7 Log_{10} RNA copies/mL, less than 7 days of symptoms, absence of serum neutralizing antibodies and being immunocompromised were all associated with a positive virus culture in univariate analysis. After submitting all these variables into a multivariate analysis, we found that only a viral load above 7 Log_{10} RNA copies/mL and absence of serum neutralizing antibodies were independently associated with isolation of infectious SARS-CoV-2 from the respiratory tract.

Discussion

In this study we assessed the duration and key determinants of infectious SARS-CoV-2 shedding in patients with severe and critical COVID-19. Such information is critical to design test-based and symptom-based strategies to discontinue infection prevention and control precautions. Both strategies only allow for discontinuation of infection prevention and control precautions after partial resolution of symptoms. Symptom-based strategies use as additional criterion that a certain time interval should have passed since onset of symptoms, while test-based strategies use negative SARS-CoV-2 RT-PCR results as main additional criterion.

The duration of infectious virus shedding found in this study was longer than has been reported previously[5,11,12]. Wölfel and colleagues showed for patients with mild COVID-19 that infectious virus could not be detected after more than eight days since onset of symptoms[5]. Bullard and colleagues obtained similar results, but disease severity was not reported[12]. Shedding of infectious virus up to 18 days after onset of symptoms has been reported for a single case of mild COVID-19[11]. The patients in this study had severe or critical COVID-19 and detection of infectious virus was common after eight days or more since onset of symptoms. For a single patient, infectious virus was detected up to 20 days after onset of symptoms. Higher viral loads have been reported for severe COVID-19 cases compared to mild cases, which may in part explain the longer duration of shedding found in this study[16–20]. Our findings imply that symptom-based strategies to discontinue infection prevention and control precautions should take diseases severity into account. For example, the CDC currently use a minimum disease duration of 10 days in their symptom-based strategy as the statistically estimated likelihood of recovering replication-competent virus approaches zero after ten days of symptoms[8,21]. Based on our findings, a longer disease duration could be considered for severely-ill patients.

High viral RNA loads were independently associated with shedding of infectious virus, but, upon seroconversion, shedding of

Table 1 Patient characteristics.

Characteristic	All	Intensive care	Ward	p value (ICU vs ward)
Number[a]	129	89 (69.0%)	40 (31.0%)	
Male	86 (66.7%)	65 (73.0%)	21 (52.5%)	0.04
Age (median—IQR)	65 (57–72)	66 (57–72)	63 (57–74)	0.90
Immunocompromised[b]				
Moderate	19 (14.7%)	10 (11.2%)	9 (22.5%)	0.04
Severe	11 (8.5%)	5 (5.6%)	6 (15.0%)	
Clinical parameters				
Mechanical ventilation	81 (62.8%)	81 (91.0%)	0	
Supplemental oxygen	43 (33.3%)	8 (9.0%)	35 (87.5%)	
Died	14 (10.9%)	11 (12.3%)	3 (7.5%)	
Duration of illness[c]				
Median (IQR)	18 (13–21)	18 (13–22)	15 (12–18)	0.009
Tests per patient, total (mean per person)				
Culture	690 (5.3)	601 (6.8)	89 (2.2)	
PRNT	112 (0.9)	82 (0.9)	30 (0.8)	
PCR	688 (5.3)	599 (6.7)	89 (2.2)	

[a]Disease severity classification according to NIH criteria (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/): 81/129 (62.5%) critical disease, 43/129 (33.3%) severe disease, 5/129 (3.9%) moderate disease.
[b]Immunocompromised level was scored as described previously[25]. Patients with severe immunosuppression ($n = 11$): Lung transplantation, or other solid organ transplantation and treatment for rejection within the last 3 months ($n = 3$); Underlying disease treated with daily corticosteroid dosages (based on prednisone) >30 mg for >14 days and/or immunomodulating biologicals ($n = 4$); Allogeneic hematopoietic stem cell transplantation within the last 12 months, or allogeneic hematopoietic stem cell transplantation with with graft-versus-host-disease treated with immunosuppressive drugs, or acute leukemia ($n = 4$). Patients with nonsevere immunosuppression ($n = 19$): Untreated auto-immune disease or underlying disease treated with immunosuppressive drugs (excluding treatment with daily corticosteroid dosages (based on prednisone) >30 mg for >14 days and/or treatment with immunomodulating biologicals) ($n = 10$); At least 1 year after solid organ transplantation (excluding lung transplantation) and no rejection ($n = 3$); Hematological malignancies (excluding acute leukemia and leukemia treated with induction therapy or chemotherapy resulting in neutropenia for >7 days) ($n = 4$); Other nonsevere immunodeficiencies ($n = 2$).
[c]As of April 17th 2020. PRNT = plaque-reduction neutralization titer. Respiratory tract samples for virus culture and PCR were obtained from the lower respiratory tract (sputum) on the intensive care unit (538/690 samples, 78%) and from the upper respiratory tract (swabs) on the intensive care unit as well as on the medium care unit (152/690 samples, 22%). A total of 127 out of the 690 respiratory tract samples that were submitted for virus culture (18.4%) were obtained from immunocompromised patients. For categorical variables a two-sided Chi-square test was used and for continuous variables a two-sided student's *t*-test was used. No adjustments were made for multiple comparisons.

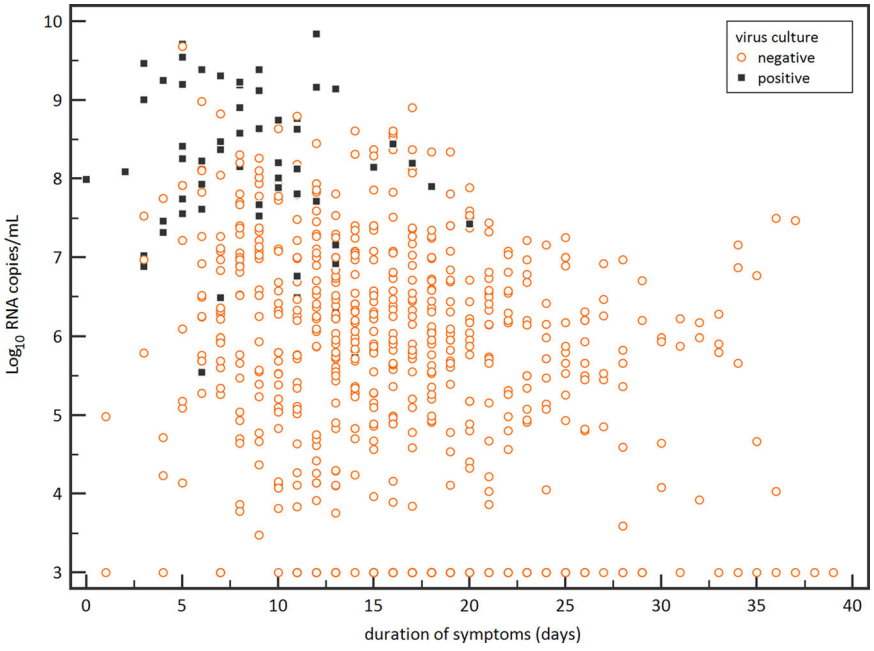


Fig. 1 Viral loads and duration of symptoms for infectious virus shedding. Viral RNA loads (Log_{10} RNA copies/mL) in the respiratory samples versus the duration of symptoms (days). Black boxes represent virus culture positive samples and open red circles represent the virus culture negative samples.

infectious virus dropped rapidly to undetectable levels. Infectious virus could not be isolated from respiratory tract samples once patients had a serum neutralizing antibody titer of at least 1:80. These results warrant the use of quantitative viral RNA load assays and serological assays in test-based strategies to discontinue or de-escalate infection prevention and control precautions. The probability of isolating infectious virus was less than 5% when viral RNA load was below 6.63 Log10 RNA copies/mL, which is strikingly similar compared to the cutoff of 6.51 Log10 RNA copies/mL reported by Wölfel et al.[5]. In addition, Bullard and colleagues used cycle threshold (ct) values as quantitative measure for viral RNA load and reported that infectious virus could not be isolated from diagnostic samples when ct values were above 24[12]. Together, these results indicate that viral RNA load cutoffs could be used in test-based strategies to discontinue infection prevention and control precautions. In addition, we report here a very strong association between neutralizing antibody response and shedding of infectious virus with an odds ratio of 0.01 for isolating infectious virus after seroconversion. Antibody responses were measured with a plaque-reduction neutralization test (PRNT)[22]. Neutralization assays, which are the gold standard in coronavirus serology, are labor-intensive and require a biosafety level 3 laboratory. We have recently cross-validated various commercial immunoassays using our PRNT50% as gold standard. Some commercial assays showed good agreement with our PRNT50%: For example, the

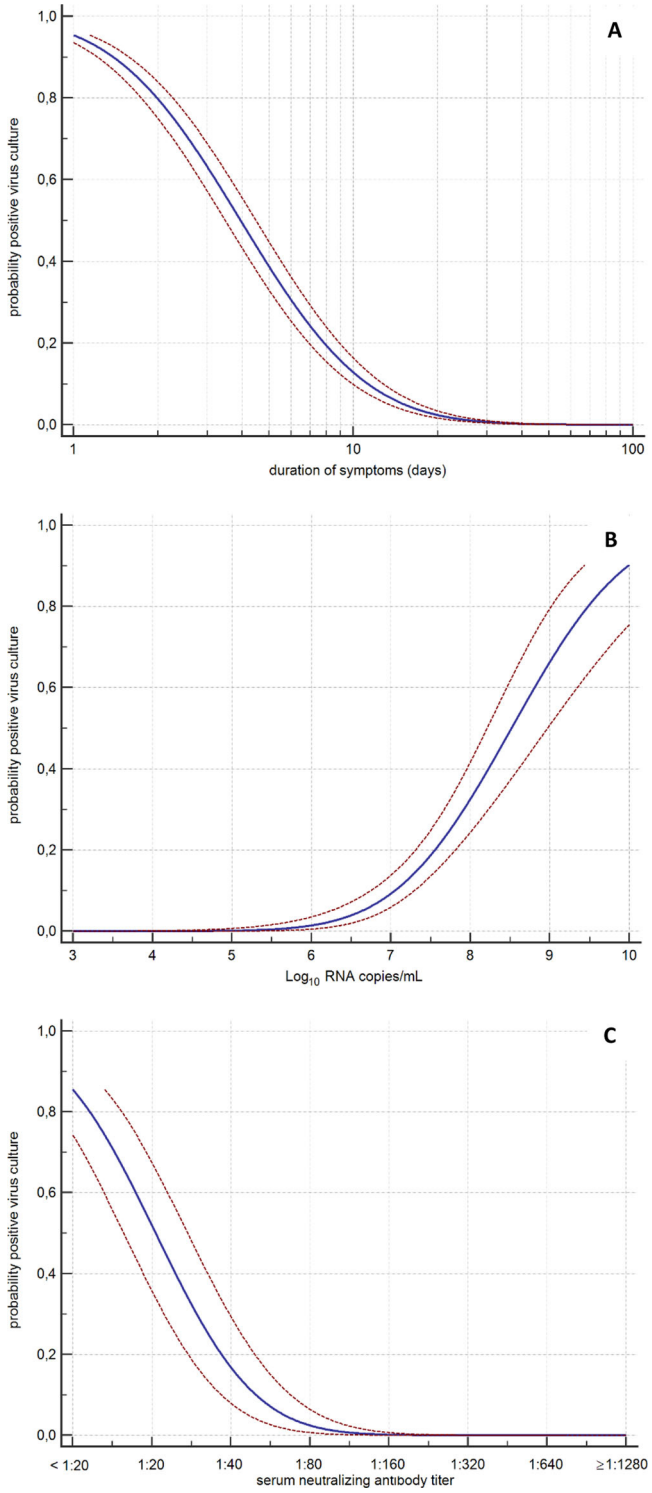


Fig. 2 Probabilities of infectious virus shedding. Probit analyses of the detection of infectious virus in respiratory samples with cell culture for duration of symptoms in days (**A**) ($n = 690$ samples), viral RNA load in Log10 copies per mL (**B**) ($n = 688$ samples), and serum neutralizing antibody titer (**C**) ($n = 112$ samples). Blue line represent the probit curve and the dotted red lines represent the 95% confidence interval. Serum neutralizing antibody titers are expressed as plaque-reduction neutralization titers 50% as described previously[27].

Table 2 Serum neutralizing antibody titers and isolation of infectious virus from the respiratory tract.

Serum neutralizing antibody titer	Total number samples	Number culture positive samples (%)	Number culture negative samples (%)
<1:20	31	27 (87%)	4 (13%)
1:20	10	4 (40%)	6 (60%)
1:40	7	2 (29%)	5 (71%)
1:80	2	0 (0%)	2 (100%)
1:160	4	0 (0%)	4 (100%)
1:320	11	0 (0%)	11 (100%)
1:640	9	0 (0%)	9 (100%)
1:1280	14	0 (0%)	14 (100%)
1:2560	16	0 (0%)	16 (100%)

Serum neutralizing antibody titers against SARS-CoV-2 were determined using a plaque-reduction neutralization assay[17]. Neutralizing antibodies (titers of 1:20 or higher) were detected in 72.3% (81/112) of the serum samples. For six patients, infectious SARS-CoV-2 was isolated from the respiratory tract despite the presence of neutralizing SARS-CoV-2 antibodies in the serum sample pairs. In four of these six patients, infectious virus was not isolated in the consecutive respiratory tract samples obtained after a virus culture positive sample (sampled from day +1, +1, +4, and +4 in respect to virus culture positive sample). For one patient, infectious virus was not isolated in the respiratory tract sample obtained one day after the virus culture positive respiratory tract sample, while the respiratory tract sample obtained 2 days after the virus culture positive respiratory tract sample was positive for infectious SARS-CoV-2. All respiratory tract samples obtained thereafter tested negative for infectious virus. For one patient, no follow-up respiratory tract samples were available.

Wantai SARS-CoV-2 Ig total ELISA has a sensitivity of 99% (95% CI 97–100%) and a specificity of 99% (95% CI 96–100%)[23]. These commercial immunoassays require less stringent biosafety measures and are amenable to high throughput use resulting in a broad application of our results to guide infection prevention strategies and discharge management for clinical cases being hospitalized.

Detection of viral subgenomic RNA correlated poorly with shedding of infectious virus. These RNAs are produced only in actively infected cells and are not packaged into virions. Subgenomic RNAs were still detected when virus cultures turned negative. This could indicate that active replication continues in severely-ill symptomatic COVID-19 patients after seroconversion and after shedding of infectious virus has stopped. Possibly, infectious virions are produced but are directly neutralized by antibodies in the respiratory tract. On the other hand, the half-life of viral subgenomic RNAs is not known in COVID-19 and these RNAs may still be detected once replication has stopped.

Our study has some limitations. Firstly, virological data were obtained from diagnostic samples only and samples were not prospectively collected at predefined timepoints. However, as many aspects of COVID-19 were still unclear, a sampling-rich diagnostic approach was applied in our institution with regular virological monitoring of confirmed COVID-19 patients. This approach resulted in a large high quality dataset from a considerable number of patients including patients with a immunocompromised status. The strikingly similar viral RNA load cutoff for a 5% probability of a positive virus culture found by us and by Wölfel et al. underpins the validity of the results[5]. Secondly, we used in vitro cell cultures as a surrogate marker for infectious virus shedding. The success of SARS-CoV-2 isolation is dependent on which cell lines is used[24]. Vero cells are currently regarded as the gold standard to detect infectious SAR-CoV-2, but the true limit of detection is unknown. Notwithstanding the above, experimental evidence from a COVID-19 hamster model showed that transmission of SARS-CoV-2 correlated well with detection of infectious SARS-CoV-2 from respiratory tract samples using in vitro Vero cell cultures while detection of viral RNA did not[13]. More data from experimental models, and epidemiological and modeling

Table 3 Univariate and multivariate analysis of key determinants for infectious virus shedding.

Variable	Positive virus culture ($n = 33$)	Negative virus culture ($n = 79$)	Univariate odds ratio (95% CI)	Multivariate odds ratio (95% CI)
Viral RNA load				
>10^7 RNA copies/mL	29 (87.9%)	22 (27.8%)	18.8 (5.5–64.2), $p < 0.001$	14.7 (3.7–58.1), $p < 0.001$
Duration of symptoms				
<7 days	20 (60.6%)	17 (21.5%)	5.6 (1.7–18.1), $p = 0.004$	2.1 (0.4–11.7), $p = 0.31$
Serum neutralizing antibody titer				
1:20 or higher	6 (18.2%)	75 (94.9%)	0.01 (0.003–0.05), $p < 0.001$	0.01 (0.002–0.08), $p < 0.001$
Immunocompromised				
Yes	10 (30.3%)	10 (12.7%)	3.00 (0.8–11.0), $p = 0.098$	2.0 (0.7–5.3), $p = 0.22$

Results of the univariate and multivariate generalized estimating equation analysis. The analyses were limited to the samples for which a viral RNA load and a serum neutralizing antibody titer were available from samples taken at the same day.

studies on transmission, which take viral RNA load and antibody response into account, are needed for further validation of this approach. It should be noted that, besides the infectious viral load, additional factors determine virus transmissibility. Finally, our study only included hospitalized symptomatic adults with severe or critical COVID-19 and important differences were noted in our study compared to what has been reported for in mild COVID-19. Thus, further studies are needed on the determinants and duration of infectious virus shedding in specific patient groups.

In conclusion, infection prevention and control guidelines should take into account that patients with severe or critical COVID-19 may shed infectious virus for longer periods of time compared to what has been reported for in patients with mild COVID-19. Infectious virus shedding drops to undetectable levels when viral RNA load is low and serum neutralizing antibodies are present, which warrants the use of quantitative viral RNA load assays and serological assays in test-based strategies to discontinue or de-escalate infection prevention and control precautions.

Methods

Samples and patients. Between March 8, 2020 and April 8, 2020, diagnostic respiratory samples of COVID-19 patients from the Erasmus MC that were send to our laboratory for SARS-CoV-2 PCR were also submitted for virus culture. From these patients, results from SARS-CoV-2 PCRs on diagnostic respiratory samples and results from SARS-CoV-2 neutralizing antibody measurements on serum samples were extracted from our diagnostic laboratory information management system (LabTrain version 3, bodegro, the Netherlands). The following information was extracted from the electronic patient files (HiX version 6.1, ChipSoft, the Netherlands): date of onset of symptoms, disease severity (hospitalized on ICU with mechanical ventilation, hospitalized on ICU with oxygen therapy, hospitalized to ward with oxygen therapy, hospitalized to ward without oxygen therapy), information to classify patients as immunocompetent, nonseverely immunocompromised (excluding diabetes mellitus), or severely immunocompromised as described previously[25], disease severity score according to the NIH classification (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/), and whether the patients were still alive or not as of April 17, 2020. Excel 2016 (Microsoft Corp, USA) was used as data collection software.

Sample processing and analysis. Swabs from the upper respiratory tract were collected in tubes containing 4 mL virus transport medium (Dulbecco's modified eagle's medium (DMEM, Lonza) supplemented with 40% FBS, 20 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), NaCO3, 10 µg/ml amphotericin B, 1000 U/mL penicillin, 1000 µg/mL streptomycin). Supernatant was passed through a 45-µm filter and used for PCR analysis and virus culture. For sputum samples, 6 mL sample processing medium (DMEM supplemented with 17 mM HEPES, $NaCO_3$, 1000 U/mL penicillin, 1000 µg/mL streptomycin, 12.5 µg/ml amphotericin B) was added until the final volume was 6 mL. Subsequently, samples were vortexed, centrifugated, passed through a 45-µm filter, and 1 part FBS was added to 1.5 parts supernatant. Subsequently, processed samples were used for PCR analysis and virus culture.

Real-time RT-PCR detection of SARS-CoV-2 was performed using an in-house assay[26] or using the SARS-CoV-2 test on a cobas® 6800 system (Roche Diagnostics). Subsequently, cycle threshold (ct) values were converted to Log_{10} RNA copies/mL using calibration curves based on quantified E-gene in vitro RNA transcripts[5]. SARS-CoV-2 subgenomic RNAs were detected with RT-PCR[5].

Respiratory samples were cultured on Vero cells, clone 118, using 24-wells plates with glass coverslips[27]. Cells were inoculated with 200 µL sample per well and centrifugated for 15 min at 3500 × *g*. After centrifugation, inoculum was discarded, virus culture medium (Iscove's modified Dulbecco's medium (IMDM; Lonza) supplemented with 2 mM L-glutamine (Lonza), 100 U/mL penicillin (Lonza), 100 µg/mL streptomycin (Lonza), 2.5 µg/mL amphotericin B (department of hospital pharmacy, Erasmus MC), and 1% heat-inactivated fetal bovine serum (Sigma)) was added, and samples were cultured at 37 °C and 5% CO_2 for 7 days. Each sample was cultured in triplicate: Two replicates were fixed with ice-cold acetone after 24 and 48 h, respectively irrespective if cytopathic effect (CPE) was visible. The fixed samples were further analyzed with immunofluorescence (see below). The remaining replicate was scored for CPE on a daily basis for 7 days. When CPE was visible, the sample was fixed with ice-cold acetone and further analyzed with immunofluorescence (see below). Virus cultures were regarded as negative if no CPE was visible during 7 days. For immunofluorescence read-out, the fixed cells were washed with phosphate buffer saline (PBS), and incubated for 30 min at 37 °C with 25 µL 1000-fold diluted polyclonal rabbit SARS-CoV anti-nucleoprotein antibodies (Sino Biological, catalogue number 40143-T62). After incubation, samples were washed with three times with PBS and once with deionized water. Subsequently, cells were incubated for 30 min at 37 °C with 25 µL 2000-fold diluted Alexa Fluor 488-labeled polyclonal goat anti-rabbit IgG (Invitrogen, catalogue number A-11070). Subsequently, cells were washed three times with PBS. Finally, cells were incubated for 1 min with 25 µL Evan's Blue (counterstain), washed twice with deionized water, air dried and analyzed with a fluorescence microscope.

Serum neutralizing antibodies titers against SARS-CoV-2 (German isolate; GISAID ID EPI_ISL 406862; European Virus Archive Global #026V-03883) were determined using a plaque-reduction neutralization test[22]. A plaque-reduction neutralization titer 50% (PRNT50%) of 1:20 or more was considered to be positive and a PRNT50% below 1:20 negative.

Medical ethical approval. All patient samples and data used in this study were collected in the context of routine clinical patient care. Additional analyses were performed only on surplus of patient material collected in the context of routine clinical patient care. The institutional review board of the Erasmus MC (Rotterdam, The Netherlands) approved the use of these data and samples (METC-2015-306). METC-2015-306 is a generic protocol to study viral diseases. Informed consent for COVID-19 research was waived by the privacy knowledge office of the Erasmus MC (Rotterdam, The Netherlands). Instead, patients had the right to opt-out against the use of their surplus patient material and their medical data for research. The opt-out system of the Erasmus MC was checked for all patients included in this study, and none of the patients included in this study opted-out against the use of their surplus patient material and their medical data for research.

Statistical analysis. Categorical and continuous variables were compared using the Chi-square test the student's *t*-test, respectively. Generalized estimating equations were used to identify factors that are associated with a virus culture positive respiratory tract sample. The continuous data in the generalized estimating equations were dichotomized using various cutoff values. In the main paper we present the results of the best fitting generalized estimating equations using the levels of dichotomizing that had the best fit according to the quasi-likelihood under the independence criterion (QIC)[28]. Sensitivity analysis is shown in Supplementary Table 1 and Supplementary Table 2. All variables having a p value < 0.1 in univariate analysis were submitted into a multivariate general estimating equation to account for repeated measurements obtained from the same patient during hospitalization[29]. For this analysis we used the geepack package version 1.3-1 and R version 4.0.0[29]. Probit analyses were performed with MedCalc version 19.2.3 (MedCalc Software Ltd).

Role of the funding source. This work partially was funded through EU COVID-19 grant RECOVER 101003589. The study sponsors were involved neither in the study design, the collection, analysis and interpretation of the data, writing of the report, nor in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Reporting summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

All relevant data are available from the authors upon request. Source data are provided with this paper.

Received: 30 June 2020; Accepted: 1 December 2020;
Published online: 11 January 2021

References

1. Huang, C. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **395**, 497–506 (2020).
2. Zhu, N. et al. China Novel Coronavirus Investigating and Research Team. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N. Engl. J. Med.* **382**, 727–733 (2020).
3. Docherty, A. B. et al. ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* **369**, m1985 (2020).
4. Anderson, R. M. et al. Epidemiology, transmission dynamics and control of SARS: the 2002–2003 epidemic. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* **359**, 1091–1105 (2004).
5. Wölfel, R. et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* https://doi.org/10.1038/s41586-020-2196-x (2020).
6. Ling, Y. et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chin. Med. J. (Engl.).* **133**, 1039–1043 (2020).
7. Lan, L. et al. Positive RT-PCR test results in patients recovered from COVID-19. *JAMA* https://doi.org/10.1001/jama.2020.2783 (2020).
8. CDC. *Discontinuation of Transmission-Based Precautions and Disposition of Patients with COVID-19 in Healthcare Settings (Interim Guidance).* https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html (2020).
9. ECDC. *Guidance for discharge and ending isolation in the context of widespread community transmission of COVID-19—first update 8 April 2020.* https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-guidance-discharge-and-ending-isolation-first%20update.pdf (2020)
10. WHO. *Clinical management of COVID-19*. WHO Reference Number: WHO/2019-nCoV/clinical/2020.5. https://www.who.int/publications/i/item/clinical-management-of-covid-19 (2020).
11. Liu, W. D. et al. Prolonged virus shedding even after seroconversion in a patient with COVID-19. *J. Infect.* **S0163-4453**, 30190–30190 (2020).
12. Bullard, J. et al. Predicting infectious SARS-CoV-2 from diagnostic samples. *Clin. Infect. Dis.* **71**, 2663–2666 (2020).
13. Sia, S. F. et al. Pathogenesis and transmission of SARS-CoV-2 in golden hamsters. *Nature* https://doi.org/10.1038/s41586-020-2342-5 (2020).
14. Munster, V. J., Koopmans, M., van Doremalen, N., van Riel, D. & de Wit, E. A novel coronavirus emerging in China—key questions for impact assessment. *N. Engl. J. Med.* **382**-, 692–694 (2020).
15. Wang, W. et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA* https://doi.org/10.1001/jama.2020.3786 (2020).
16. Liu, Y. et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect. Dis.* **20**, 656–657 (2020).
17. Zheng, S. et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. *BMJ* **369**, m1443 (2020).
18. Lui, G. et al. Viral dynamics of SARS-CoV-2 across a spectrum of disease severity in COVID-19. *J. Infect.* **81**, 324–327 (2020).
19. He, X. et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat. Med.* **26**, 672–675 (2020).
20. Xu, T. et al. Clinical features and dynamics of viral load in imported and non-imported patients with COVID-19. *Int. J. Infect. Dis.* **94**, 68–71 (2020).
21. CDC. *Symptom-Based Strategy to Discontinue Isolation for Persons with COVID-19—Decision Memo.* https://www.cdc.gov/coronavirus/2019-ncov/community/strategy-discontinue-isolation.html (2020).
22. Okba, N. M. A. et al. Severe acute respiratory syndrome coronavirus 2-specific antibody responses in coronavirus disease 2019 patients. *Emerg. Infect. Dis.* **26**, 1478–1488 (2020).
23. GeurtsvanKessel, C. H. et al. An evaluation of COVID-19 serological assays informs future diagnostics and exposure assessment. *Nat. Commun.* **3436**, 1–5 (2020).
24. Hoffmann, M. et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* **181**, 271–280.e8 (2020).
25. Fraaij, P. L. et al. Viral shedding and susceptibility to oseltamivir in hospitalized immunocompromised patients with influenza in the Influenza Resistance Information Study (IRIS). *Antivir. Ther.* **20**, 633–642 (2015).
26. Corman, V. M. et al. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Euro. Surveill.* **25**, 23–30 (2020).
27. Kuiken, T. et al. Experimental human metapneumovirus infection of cynomolgus macaques (Macaca fascicularis) results in virus replication in ciliated epithelial cells and pneumocytes with associated lesions throughout the respiratory tract. *Am. J. Pathol.* **164**, 1893–1900 (2004).
28. Hanley, J. A., Negassa, A., Edwardes, M. D. D. & Forrester, J. E. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am. J. Epidemiol.* **157**, 364–375 (2003).
29. Højsgaard, S., Halekoh, U. & Yan, J. The R package geepack for generalized estimating equations. *J. Stat. Softw.* **15**, 11 (2005).

Acknowledgements

We gratefully acknowledge EVA-g and Christian Drosten for provision of the quantified E-gene transcript. Bibi Slingerland, Ga-Lai Chong, Rose Willemze, Jordy Dekker, George Sips, Stephanie Popping, Daphne Mulders, Alex de Ries, and Jeroen Ijpelaar gratefully acknowledged for their technical and analytical contributions. John T. Brooks (CDC) is acknowledged for his helpful discussions on COVID-19 disease severity classification. This work was partially funded through EU COVID-19 grant RECOVER 101003589.

Author contributions

J.J.A.v.K. conceived and designed the study, supervised the study, wrote the first draft of the manuscript. D.A.M.C.v.d.V., P.L.A.F., C.G., A.E., M.K., R.M., and C.B. contributed to the conception and design of the study. G.I.A. performed the virus cultures. C.G. and J.J.A.v.K. supervised the virus culture experiments. B.H. and M.M.L. provided intellectual input for virus culture experiments and analyses. N.O. performed the virus neutralization tests. B.L. and C.G. supervised virus neutralization tests. R.M., S.v.B., and J.C.V. supervised and interpreted the molecular analyses. D.A.M.C.v.d.V. performed the statistical analyses. P.L.A.F. and J.J.A.v.K. supervised the clinical data analyses. J.P.C.v.d.A., H.E., D.A.M.P.J.G., J.J.C., R.A.S.H., M.M.v.d.E., D.A.H., H.J.M., A.V., J.E.M.d.S., and E.C.M.v.G. were involved in COVID-19 patient care, data, and specimen collection. All authors discussed the results and implications and commented on the manuscript at all stages.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information is available for this paper at https://doi.org/10.1038/s41467-020-20568-4.

Correspondence and requests for materials should be addressed to J.J.A.v.K.

Peer review information *Nature Communications* thanks Joshua Schiffer and Clemens-Martin Wendtner for their contribution to the peer review of this work. Peer reviewer reports are available.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

SARS-CoV-2 viral load dynamics, duration of viral shedding and infectiousness – a living systematic review and meta-analysis

Author: Muge Cevik[1,2], Matthew Tate[3], Ollie Lloyd[2,4], Alberto Enrico Maraolo[5], Jenna Schafers[2], Antonia Ho[6]

Affiliations:

1. Division of Infection and Global Health Research, School of Medicine, University of St Andrews, UK
2. NHS Lothian Infection Service, Regional Infectious Diseases Unit, Western General Hospital, Edinburgh, U.K.
3. Respiratory Medicine, University Hospital Wishaw, Wishaw, UK
4. Edinburgh Medical School, College of Medicine & Veterinary Medicine, University of Edinburgh, UK
5. First Division of Infectious Diseases, Cotugno Hospital, AORN dei Colli, Naples, Italy.
6. MRC-University of Glasgow Centre for Virus Research, University of Glasgow, Glasgow, UK

Corresponding author:

Dr Muge Cevik
Division of Infection and Global Health Research,
School of Medicine, University of St Andrews, Fife, KY16 9TF
Telephone number: +447732800814
Email address: mc349@st-andrews.ac.uk

Keywords: SARS-CoV-2, COVID-19, viral shedding, viral dynamics, infectiousness

ABSTRACT

Background Viral load kinetics and the duration of viral shedding are important determinants for disease transmission. We aim i) to characterise viral load dynamics, duration of viral RNA, and viable virus shedding of SARS-CoV-2 in various body fluids and ii) to compare SARS-CoV-2 viral dynamics with SARS-CoV-1 and MERS-CoV.

Methods: Medline, EMBASE, Europe PMC, preprint servers and grey literature were searched to retrieve all articles reporting viral dynamics and duration of SARS-CoV-2, SARS-CoV-1 and MERS-CoV shedding. We excluded case reports and case series with < 5 patients, or studies that did not report shedding duration from symptom onset. PROSPERO registration: CRD42020181914.

Findings: Seventy-nine studies on SARS-CoV-2, 8 on SARS-CoV-1, and 11 on MERS-CoV were included. Mean SARS-CoV-2 RNA shedding duration in upper respiratory tract, lower respiratory tract, stool and serum were 17.0, 14.6, 17.2 and 16.6 days, respectively. Maximum duration of SARS-CoV-2 RNA shedding reported in URT, LRT, stool and serum was 83, 59, 35 and 60 days, respectively. Pooled mean duration of SARS-CoV-2 RNA shedding was positively associated with age (p=0.002), but not gender (p = 0.277). No study to date has detected live virus beyond day nine of illness despite persistently high viral loads. SARS-CoV-2 viral load in the upper respiratory tract appears to peak in the first week of illness, while SARS-CoV-1 and MERS-CoV peak later.

Conclusion: Although SARS-CoV-2 RNA shedding in respiratory and stool can be prolonged, duration of viable virus is relatively short-lived. Thus, detection of viral RNA cannot be used to infer infectiousness. High SARS-CoV-2 titres are detectable in the first week of illness with an early peak observed at symptom onset to day 5 of illness. This review underscores the importance of early case finding and isolation, as well as public education on the spectrum of illness. However, given potential delays in the isolation of patients, effective containment of SARS-CoV-2 may be challenging even with an early detection and isolation strategy.

Funding: No funding was received.

INTRODUCTION

Viral load kinetics and the duration of viral shedding are important determinants for disease transmission. They determine the duration of infectiousness which is a critical parameter to inform effective control measures and disease modelling. While a number of studies have evaluated SARS-CoV-2 shedding, viral load dynamics and duration of viral shedding reported across studies so far have been heterogenous.[1] In several case series with serial respiratory sampling, peak viral load was observed just before, or at the time of symptom onset.[2-4] Viral ribonucleic acid (RNA) shedding was reported to be persistent in the upper respiratory tract and in faeces, for over one month after illness onset.[1] However, the duration of SARS-CoV-2 RNA detection has not been well characterised. A comprehensive understanding of viral load dynamics, length of viral shedding, and how these relate to other factors, such as age and disease severity is lacking.

The aim of this systematic review and meta-analysis was to i) characterise the viral load dynamics of SARS-CoV-2, duration of viral RNA shedding by reverse transcriptase polymerase chain reaction (RT-PCR) and viable virus shedding in various body fluids and ii) compare SARS-CoV-2 viral dynamics with that of SARS-CoV-1 and MERS-CoV.

METHODS

Search Strategy

We retrieved all articles reporting viral dynamics and/or the duration of shedding of SARS-CoV-2, SARS-CoV-1 or MERS-CoV in various specimens through systematic searches of major databases including Medline, EMBASE, Europe PMC, pre-print databases (MedRxiv, BioRxiv) and the grey literature from 1 January 2003 to 6th June 2020 using Medical Subject Headings (MeSH) terms (Supplementary Material). We also manually screened the references of included original studies to obtain additional studies. Studies prior to 2003 were excluded since the first recognised case of SARS-CoV-1 was identified in March 2003.

This systematic review was registered in PROSPERO on 29th April 2020 (CRD42020181914) and will be updated in three monthly intervals as a living systematic review.

Study Selection

Studies were eligible if they met the following inclusion criteria: (1) report on SARS-CoV-2, SARS-CoV-1 or MERS-CoV infection and (2) report viral load kinetics, duration of viral shedding or viable virus. We excluded: (1) review papers; (2) animal studies; (3) studies on environmental sampling; (4) case reports and case series with < 5 participants, due to likely reporting bias; (5) papers where the starting point of viral shedding was not clear or reported from post-discharge and (6) modelling studies with no original data.

Data Extraction

Two authors (MT and OL) screened and retrieved articles according to the eligibility criteria. Four reviewers (MT, OL, JS, MC) performed full text review and final article selection. From each study, the following variables were extracted as a minimum: name of first author, year of publication, city and country, sample size, median age, sex ratio, time from symptom onset to viral clearance detected by RT-PCR and culture in different specimens, and longest reported time to viral clearance. If these data were not reported, we also contacted the authors to request the data. If available, we extracted data on peak viral load, clinical outcome, and reported factors associated with duration of viral shedding.

Risk of bias in included studies

Two authors (OL and JS) independently assessed study quality and risk of bias using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist tools,[5] which comprise standardised checklists, for the different study designs included in this review. Any disagreements regarding grading of quality were resolved through discussion with a third author (MC).

Meta-Analysis

For every study included, mean duration of viral shedding and 95% confidence interval (CI) were calculated. The random-effects model (DerSimonian or Laird) was applied to estimate a pooled effect size. Forest plots illustrated the detailed representation of all studies based on the effect size and 95% CI. If not reported, means and standard deviations were derived from sample size, median, interquartile range (IQR), minimum and maximum values.[6] Heterogeneity between studies were quantified by the I^2 index and Cochran's Q test. Publication bias was not assessed as usual

appraisal methods are uninformative when meta-analysed studies do not include a test of significance. A weighted meta-regression using an unrestricted maximum likelihood model was performed to assess the impact of potential moderators on the pooled effect size (P-values <0.05 were considered significant). All statistical analyses were performed using Comprehensive Meta-Analysis (CMA) version 3 software (Biostat, Englewood, mNJ).

RESULTS

The systematic search identified 1486 potentially relevant articles. Three hundred and fifty articles were retrieved for full text review. After reviewing the eligibility criteria, a total of 79 studies on SARS-CoV-2, eight on SARS-CoV-1, and 11 on MERS-CoV were included (Figure 1).

Summary of SARS-CoV-2 studies

Of the 79 papers included, 58 studies were conducted in China (Table 1). Six studies included outpatient or community cases, the remainder comprised hospitalised patients only. Six studies reported viral load dynamics exclusively in children.[7-12] Two additional studies included children, but data on viral load dynamics were presented in aggregate with adults.[13,14] One study reported findings in renal transplant patients.[15]

Median duration of viral shedding

In total, 61 studies reported median or maximum viral RNA shedding in at least one body fluid and six studies provided duration of shedding stratified by illness severity only. Of those, 43 (3229 individuals) reported duration of shedding in upper respiratory tract (URT), seven (260 individuals) in lower respiratory tract (LRT), 13 (586 individuals) in stool, and 2 studies (108 individuals) in serum samples were eligible for quantitative analysis. Means viral shedding durations were 17.0 days (95% CI, 15.5-18.6), 14.6 days (95% CI, 9.3-20.0), 17.2 days (95% CI, 14.4-20.1) and 16.6 days (95% CI, 3.6-29.7), respectively (Figures 2 to 5). Maximum duration of RNA shedding reported in URT, LRT, stool and serum was 83, 59, 35 and 60 days, respectively.

Studies reporting duration of viral shedding in URT and stool samples were eligible for meta-regression analysis. Pooled mean viral shedding duration was positively associated with age

(slope: +0.304; 95% CI, +0.115 to +0.493; p = 0.002 Fig 6), but not gender (p = 0.277, Supplementary Fig 3). When adjusted for the proportion of male subjects in a multivariable analysis, mean age was positively associated with the mean duration of viral shedding in URT specimens (p = 0.003). There was a positive but non-significant association between mean age and duration of shedding in stool (p=0.37) (Supplementary Fig 4).

Peak viral load

The majority of studies evaluating SARS-CoV-2 viral load in serial URT samples demonstrated peak viral loads within the first week of symptom onset. [2,4,8,16-24] The highest viral loads were reported either soon after or at the time of symptom onset[2,8,16,23,24] or at day 3-5 of illness[4,18,20,22] followed by a consistent decline.

Five studies that evaluated viral load dynamics in LRT samples observed a peak viral load in the second week of illness.[4,18,20,23,25] In contrast, the dynamics of SARS-CoV-2 shedding in stool is more erratic, with highest viral loads reported on day 7,[18] 2-3 weeks,[24,25] and up to 5-6 weeks after symptom onset.[23] While several studies reported significantly higher viral titres in stool compared to respiratory samples,[8,25] Huang *et al.* reported lower viral load in stool than in both LRT and URT samples early in the disease course.[23]

Severity and association with duration of viral shedding

In total, 20 studies evaluated duration of viral RNA shedding based on disease severity. The majority (n=13) reported longer duration of viral shedding in patients with severe illness than those with non-severe illness, [18,25-36] while five studies reported similar shedding durations according to disease severity in URT samples [17,19,37-39] and one study in stool samples. [40] Only one study reported shorter viral shedding in moderate to severe illness compared to mild to moderate illness.[41] Six studies have performed comparative analysis based on severity of illness;[18,25,27,28,38,39] the majority (n=5) demonstrated significantly longer duration of shedding among the severe illness group compared to the non-severe patients and only one study observed no difference.[39] (Table 2).

Other factors associated with prolonged shedding

All but one study[42] (n=10) that examined the impact of age on SARS-CoV-2 shedding identified an association between older age and prolonged viral RNA shedding.[25,26,28,33,37-39,43-45] Three studies identified age as an independent risk factor for delayed viral clearance.[25,26,38] Male sex was also associated with prolonged shedding,[25,38,46] and the association remained significant even when patients were stratified based on illness severity.[25,38] Corticosteroid treatment was associated with delayed viral clearance in four studies,[33,38,47,48] and one study that recruited 120 critically ill patients, found no difference between corticosteroid and control groups.[49]

In a phase 2 open-label study evaluating interferon beta-1b, lopinavir–ritonavir, and ribavirin a shorter duration of viral shedding was seen with combination treatment compared to the control.[50] None of the antiviral regimens (chloroquine, oseltamivir, arbidol, and lopinavir/ritonavir) independently improved viral RNA clearance.[28,51] In a retrospective study of 284 patients, lopinavir/ritonavir use was associated with delayed viral clearance even after adjusting for confounders.[28]

Asymptomatic SARS-CoV-2 shedding

Twelve studies reported on viral load dynamics and/or duration of viral shedding among patients with asymptomatic SARS-CoV-2 infection (Table 3); two demonstrated lower viral loads among asymptomatic patients compared to symptomatic patients,[8,52] while four studies found similar initial viral loads. [13,14,53,54] However, Chau *et al* reported significantly lower viral load in asymptomatic patients during the follow up compared to symptomatic patients.[53] Faster viral clearance was observed in asymptomatic individuals in five out of six studies.[13,28,53,55,56] The exception Yongchen *et al*., found longer shedding duration among asymptomatic cases, but the difference was not significant.[36]

Live virus detection

We identified 11 studies that attempted to isolate live virus. All eight studies that attempted virus isolation in respiratory samples successfully cultured viable virus within the first week of illness, [9,17,20,54,57-60] No live virus was isolated from any respiratory samples taken after day 8 of symptoms

in three studies,[20,57,58] or beyond day 9 in two studies[17,54] despite persistently high viral RNA loads. One study demonstrated the highest probability of positive culture on day 3 of symptoms.[57] Arons *et al*. cultured viable virus 6 days before typical symptom onset, however onset of symptom was unclear.[54]

The success of viral isolation correlated with viral load quantified by RT-PCR. No successful viral culture was obtained from samples with a viral load below 10^6 copies/ml, [20] Ct values >24,[57] or >34,[54,58] with culture positivity declining with increasing Ct values.[58] Several other studies cultured live virus from RT-PCR positive specimens; however, they did not correlate these results with viral load titres.[9,59,60]

Only one study reported the duration of viable virus shedding in respiratory samples; the median time to clearance from URT and LRT samples was 3.5 and 6 days, respectively.[20] Arons *et al*. cultured viable virus in one out of three asymptomatic cases from the respiratory tract.[54]

Of 3 studies attempting to isolate viable virus from stool,[20,61] culture was successful in two of three RNA-positive patients in one study, but the time points from symptom onset were not reported.[62] Andersson *et al.* failed to culture virus from 27 RT-PCR positive serum samples.[63]

Summary of SARS-CoV-1 and MERS studies

Eight studies on SARS-CoV-1 were included; the majority of studies did not report mean or median duration of viral shedding thus, were not eligible for quantitative analysis. The maximum duration of viral shedding reported was 8 weeks in URT,[64,65] 52 days in LRT,[61,64] 6-7 weeks in serum,[66] and 126 days in stool samples.[61,64,67-69] Dialysis patients had longer viral shedding in stool compared to non-dialysis patients.[68] Studies that have evaluated SARS-CoV-1 kinetics found low viral load in the initial days of illness, increasing after the first week of illness in URT samples, peaking at day 10,[70] or day 12-14,[67] and declining after week 3-4.[65] High viral loads correlated with severity of illness[65] and poor survival.[65] While Chen *et al.* identified an association between younger age and lower viral titers, [65] Leong *et al*. found no difference.[69] Viable SARS-CoV-1 was isolated from stool and respiratory samples up to 4 weeks, and urine specimens up to day 36.[64,66] All attempts to isolate virus from RT-PCR–positive stool specimens collected >6weeks after

disease onset failed.[61] The isolation probability for stool samples was approximately 5 to 10 times lower compared to respiratory specimens.[64]

We identified 11 studies on MERS-CoV. Three studies (324 subjects) reporting MERS-CoV shedding in URT and four studies (93 subjects) in LRT were included in the quantitative analysis. The mean shedding duration was 15.3 days (95% CI, 11.6 – 19.0) and 16.6 days (95% CI, 14.8 – 18.4), respectively (Supplementary Figures 1 and 2). Only one study reported duration of viral shedding in serum with a median of 14 days and max of 38 days.[71] In a small study, mortality rates were higher in patients with viraemia.[72] In URT and LRT specimens, prolonged shedding was associated with illness severity[73,74] and survival[75] with the shortest duration observed in asymptomatic patients.[73] Peak viral loads were observed between days 7 to 10 and higher viral loads was observed among patients with severe illness and fatal outcome.[71,73,74,76,77] Differences in viral loads between survivors and fatal cases was more pronounced in the second week of illness (P< .0006).[77] The proportion of successful viable culture was 6% in respiratory samples with a viral load values below 10^7copies/ml.[78]

Qualitative analysis

All but 11 studies (6 cohort studies, 2 cross-sectional studies, and 1 RCT on SARS-CoV-2 and 2 cohort studies on MERS-CoV) were case series, the majority of which recruited non-consecutive patients and therefore prone to possible selection bias. (Supplementary Table 1)

DISCUSSION

This systematic review and meta-analysis provide comprehensive data on the viral dynamics of SARS-CoV-2 including the duration of RNA shedding and viable virus isolation. Our findings suggest that while patients with SARS-CoV-2 may have prolonged RNA shedding, median time to live virus clearance from upper and lower respiratory tract samples were 3.5 days and 6 days respectively. No live virus isolated beyond day nine of symptoms despite persistently high viral RNA loads, thus emphasising that the infectious period cannot be inferred from the duration of viral RNA detection. This finding is supported by several studies demonstrating a relationship

between viral load and viability of virus, with no successful culture from samples below a certain viral load threshold.

SARS-CoV-2 viral load appears to peak in the URT within the first week of illness, and later in the LRT. In contrast, peaks in SARS-CoV-1 and MERS-CoV viral loads in the URT occurred at days 10-14 and 7-10 days of illness, respectively. Combined with viable isolation in respiratory samples within the first week of illness, patients with SARS-CoV-2 infection are likely to be most infectious in the first week of illness. Several studies report viral load peaks during the prodromal phase of illness or at the time of symptom onset, [2,4,8,16-23] providing a rationale for the efficient spread of SARS-CoV-2. This is supported by the observation in contact tracing studies that the highest risk of transmission occurs during the prodromal phase or early in the disease course.[79,80] No secondary cases were identified beyond 5 days after the symptom onset.[81] Although modelling studies estimated potential viral load peak before symptom onset, we did not identify any study that confirms pre-symptomatic viral load peak.[16]

Emerging evidence suggests a correlation between virus persistence and disease severity and outcome. [18,25,27-29,38] This is consistent with the viral load dynamics of influenza, MERS-CoV, and SARS-CoV-1 whereby severity of illness was also associated with prolonged viral shedding.[73,74,82] However, more studies are needed to understand the duration of viable virus in patients with severe illness.

Similar to SARS-CoV-1, SARS-CoV-2 can be detected in stool for prolonged periods, with high viral loads detected even after 3 weeks of illness. A clear difference between SARS-CoV and MERS-CoV is the detection of viral RNA in stool. In SARS-CoV-1, RNA prevalence in stool samples was high, with almost all studies reporting shedding in stool. Although viable SARS-CoV-1 was isolated up to 4 weeks of illness, faecal-oral transmission was not considered to be a primary driver of infection. Whereas in MERS-CoV, none of the studies reported duration of viral shedding in stool and RNA detection was low.[77,83] To date, only a few studies demonstrated viable SARS-CoV-2 in stool.[62,84] Thus, the role of faecal shedding in viral transmission remains unclear.

Although viral loads at the start of infection appear to be comparable between asymptomatic and symptomatic patients infected with SARS-CoV-2, most studies demonstrate faster viral clearance

among asymptomatic individuals. This suggests similar transmission potential among both groups at the onset of infection, but a shorter period of infectiousness in asymptomatic patients. This is in keeping with viral kinetics observed with other respiratory viruses such as influenza and MERS-CoV, in which people with asymptomatic infection have a shorter duration of viral shedding than symptomatic individuals. [73,85] However, there are limited data on the shedding of infectious virus in asymptomatic individuals to quantify their transmission potential.

We identified a systematic review of SARS CoV-2 viral load kinetics that included studies published up until 12 May 2020.[86] This review included many studies that did not meet our eligibility criteria, including 26 case reports and 13 case series involving <5 individuals; these are prone to significant selection bias, reporting atypical cases with prolonged viral shedding. Additionally, the review included studies that reported viral shedding duration from the time of hospital admission or initial PCR positivity, rather than symptom onset. Furthermore, no meta-analysis of the duration of viral shedding was performed.

This is the first study that has comprehensively examined and compared SARS-CoV-2, SARS-CoV-1 and MERS-CoV viral dynamics and performed a meta-analysis of viral shedding duration. Our study has limitations. First, some patients in the included studies received a range of treatments, including steroids and antivirals, which may have modified the shedding dynamics. Second, most of the included studies are case series, which are particularly vulnerable to selection bias. Third, our meta-analysis identified substantial study heterogeneity, likely due to differences in study population, follow up and management approaches. Further, shedding duration is reported as median ± IQR for most studies, but meta-analysis necessitates conversion to mean ± SD.[6] The validity of this conversion is based on the assumption that duration of viral shedding is normally distributed, which may not apply to some studies.

In conclusion, although SARS-CoV-2 RNA shedding can be prolonged in respiratory and stool samples, the duration of viable virus is short-lived, with culture success associated with viral load levels. No study has reported live SARS-CoV-2 beyond day nine. Most studies detected the SARS-CoV-2 viral load peak within the first week of illness. These findings highlight that isolation practices should be commenced with the start of first symptoms including mild and atypical

298 symptoms that precede more typical COVID-19 symptoms. This systematic review underscores
299 the importance of early case finding and isolation, as well as public education on the spectrum of
300 illness. However, given potential delays in the isolation of patients, effective containment of
301 SARS-CoV-2 may be challenging even with an early detection and isolation strategy.[87]

302

303 **Authors contributions:**

304 M. Cevik: conceptualisation, methodology, investigation, data curation, writing – original draft. M.
305 Tate: investigation, data curation, writing – original draft; O Lloyd: investigation, data curation,
306 writing – review and editing; A. E. Maraolo: formal analysis, writing – original draft; J. Schafers:
307 investigation, data curation, writing – review and editing; A Ho: conceptualisation, methodology,
308 data curation, writing – original draft, supervision.

309

310 **Financial support and sponsorship**

311 No financial support received

312

313 **Conflicts of interest**

314 All authors have nothing to disclose.

315 **Table 1: Summary of included studies**

316

Study	Geographical location	Study setting	Study design	Number of patients	Age Median (IQR)	Male sex N (%)	Specimen types
SARS-CoV-2							
Andersson et al. [63]	Oxford, UK	Hospital	Case series	167	56 (46-76)	89 (53)	Serum
Arons et al.[54]	King's County, USA	Care home	Cross-sectional	46	78.6 ± 9.5*	NR	URT
Bullard et al.[57]	Manitoba, Canada	Hospital	Case series	90	45 (30-59)	44 (49)	Respiratory samples (not specified)
Cai et al.[7]	Shanghai/ Hefei/ Qingdao, China	Hospital	Case series	10	6	4 (40)	LRT, blood, stool, urine
Cai et al.[26]	Shenzhen, China	Hospital	Case series	298	47 (33-61)	149 (50)	URT
Chang et al.[88]	Bejing, China	Hospital	Case series	16	35.5 (24-53)	11 (69)	URT
Chau et al.[53]	Ho Chi Minh City, Vietnam	Hospital	Case series	30	29 (16-60)	15 (50)	URT
Chen et al.[27]	Shanghai, China	Hospital	Case series	249	51 (36-64)	126 (51)	URT
Chen et al. [89]	Wuhan, China	Hospital	Case series	25	51.4 ±16.6*	11 (44)	URT
Chen et al.[28]	Guangzhou, China	Hospital	Case series	284	48 (33-62)	131 (46)	URT
Chen et al. [29]	Wuhan, China	Hospital	Case series	42	51	15 (36)	URT, stool, urine
Corman et al.[90]	Germany	Hospital	Case series	18	NR	12 (67)	Blood
Fan et al.[30]	Shenyang, China	Hospital	Case series	55	46.8	30 (55)	URT, sputum
Fang et al.[31]	Xiangtan, China	Hospital	Case series	32	41	16 (50)	URT, stool, blood
Fu et al.[91]	Huazhong, China	Hospital	Case series	50	64 (37-87)	27 (54)	URT
Han et al.[8]	Chongqing, South Korea	Hospital	Case series	12	6.5 (0.007-16)	5 (42)	URT, stool
He et al.[16]	Guangzhou, China	Hospital	Case series	94	46	47 (50)	URT
Hu et al.[37]	Qingdao, China	Hospital	Case series	59	46 (33-57)	28 (47)	URT
Hu et al.[55]	Nanjing, China	Hospital	Case series	24	32.5 (21-57)	8 (33)	URT
Huang et al.[51]	Guangzhou, China	Hospital	Case series	27	NR	12 (44)	URT

Huang et al.[23]	Wenzhou, China	Hospital	Case series	33	47 (range 2-84)	17 (52)	URT, LRT, stool
Huang et al.[92]	Wuhan, China	Hospital	Retrospective cohort	200	58± 17*	115 (48)	URT
Hung et al.[50]	Hong Kong	Hospital	RCT	127	52 (32-62)	68 (54)	URT, stool
Kim et al.[4]	Soeul/ Incheon/ Seongna, South Korea	Hospital	Case series	28	40 (28-54)	15 (54)	URT, LRT
Kujawski et al.[17]	6 states, USA	Hospital /Outpatient	Case series	12	53 (range 21-68)	8 (75)	URT, LRT, stool, blood, urine
L'Huillier et al.[9]	Geneva, Switzerland	Hospital	Case series	23	12 (3.8-14.5)	NR	URT
La Scola et al.[58]	France	Hospital	Case series	155	NR	NR	URT, LRT
Lavezzo et al.[14]	Vo', Italy	Community	Cross-sectional	Only sample # reported	Mixed	Mixed	URT
Le et al.[59]	Hanoi, Vietnam	Hospital	Case series	12	29.5*	3 (25)	URT
Li et al.[93]	Wuhan China	Hospital	Case series	36	57.5 (52-65)	23 (64)	URT
Liang et al.[49]	Wuhan, China	Hospital	Case series	120	61.5 (47-70)	68 (57)	URT
Ling et al.[47]	Shanghai, China	Hospital	Case series	66	44 (16-778)	38 (58)	URT, stool, blood, urine
Liu et al. [94]	Wuhan, China	Hospital	Case series	238	55 (38.3-65)	138 (58)	URT
Liu et al.[32]	Nanchang, China	Hospital	Case series	76	48.3	48 (63)	URT
Lo et al.[95]	Macau, China	Hospital	Case series	10	54 (27-64)	3 (30)	URT, LRT, stool, urine
Lou B et al.[96]	Zhejiang, China	Hospital	Case series	80	55 (45-64)	50 (69)	LRT
Pongpirul et al.[97]	Bangkok, Thailand	Hospital	Case series	11	61 (28-74)	6 (55)	URT
Qian et al.[98]	Ningbo, China	Hospital	Case series	24	NR	NR	URT
Quan et al.[99]	Wuhan/Shenzhen/ Xiangyang, China	Hospital	Case series	23	60.3 ±15.3*	23 (100)	Prostatic secretions all negative (URT)

Sakurai et al.[43]	Aichi, Japan	Hospital	Case series	90	59.5 (36-68)	53 (59)	URT
Seah et al.[100]	Singapore	Hospital	Case series	17	NR	NR	Tears
Shastri et al.[46]	Mumbai, India	Reference lab	Case series	68	37 (range 3-75)	48 (71)	URT
Shi et al.[33]	Wuhan, China	Hospital	Case series	246	58 (47-67)	126 (51)	URT
Song et al.[101]	Nanjing, China	Hospital	Case series	13	22 – 67 (range only)	13 (100)	URT, semen, testicular sample
Song et al. [102]	Beijing, China	Hospital/Outpatient	Case series	21	37 (21-59.5)	8 (38)	URT
Talmy et al.[44]	Ramat Gan, Israel	Outpatient	Case series	119	21 (19-25)	84 (71)	URT
Tan et al. [34]	Chongqing, China	Hospital	Case series	142	NR	NR	URT
Tan et al.[18]	Chongqing, China	Hospital	Case series	67	49 (10-77)	35 (52)	URT, LRT, stool, blood, urine
Tan et al.[10]	Changsha, China	Hospital	Case series	10	7 (1-12)	3 (30)	URT, stool
Tian et al. [41]	Beijing, China	Hospital/Outpatient	Case series	75	41.5 (range 0.8 – 88)*	42 (56)	Respiratory tract sample (not specified further)
To et al.[19]	Hong Kong, China	Hospital	Case series	23	62 (37-75)	13 (57)	URT, stool, blood, urine
To et al. [60]	Hong Kong, China	Hospital	Prospective Cohort	12	62.5 (37-75)	7 (58)	URT (saliva)
Tu et al. [103]	Anhui, China	Hospital	Case series	40	Viral shedding <10 days: 40.86 ± 8.26 Viral shedding ≥10 days: 45.5 ± 14.60	21 (53)	URT
Wang et al.[104]	Henan, China	Hospital	Case series	18	39 (29-55)	10 (56)	URT
Wang et al.[105]	Jinhua, China	Hospital	Case series	17	42 ±17*	10 (59)	URT, stool
Wölfel et al.[20]	Munich, Germany	Hospital	Case series	9	NR	NR	URT, blood, urine
Wu et al.[106]	Hainan, China	Hospital	Case series	91	50 (range 21-83)*	52 (57)	URT, stool

Wu et al.[11]	Qingdao, China	Hospital	Case series	74	6 (0.1-15.08 range)	44 (59)	Stool
Wu et al.[40]	Zhuhai, China	Hospital	Case series	74	43.8*	35 (47)	Stool
Wyllie et al.[21]	New Haven, USA	Hospital	Case series	44	61 (23-92 range)*	23 (52)	URT (saliva)
Xiao et al. [45]	Wuhan, China	Hospital	Case series	56	55 (42-68)	34 (61)	URT
Xiao et al.[62]	Guangzhou, China	Hospital	Case series	28			Stool
Xu et al. [38]	Shenzhen/ Zheijang, China	Hospital	Retrospective Cohort	113	52 (42-63)	66 (58)	URT
Xu et al.[107]	Shenyang, China	Hospital	Case series	14	48 ± 13.4*	7 (50)	URT, LRT, serum, conjunctiva
Xu et al. [12]	Guangzhou, China	Hospital	Case series	10	6.6	6 (60)	URT, rectal swab
Yan et al.[39]	Hubei, China	Hospital	Case series	120	52 (35-63)	54 (45)	URT
Yang et al.[56]	Wuhan, China	Hospital	Case series	78 (45 symptomatic)	Symptomatic: 56 (34-63) Asymptomatic: 37 (26-45)	Symptomatic:31 (40) Asymptomatic: 11 (33)	URT
Yang et al.[108]	Shenzhen, China	Hospital	Case series	213	52 (range 2-86)	108 (51)	URT, LRT
Yongchen et al.[36]	Nanjing, Xuzhou, China	Hospital	Case series	21	37	13 (62)	URT, stool
Young et al.[22]	Singapore	Hospital	Case series	18	47	9 (50)	URT, stool, blood, urine
Zha et al.[48]	Wuhu, China	Hospital	Case series	31	39 (32-54)	20 (65)	URT
Zhang et al.[24]	Beijing, China	Hospital	Case series	23	48 (40-62)	12 (52)	URT, stool, blood, urine
Zhang et al. [13]	Shenzhen, China	Hospital	Case series	56	Mixed	Mixed	URT, stool
Zheng et al.[25]	Zhejiang, China	Hospital	Retrospective Cohort	96	53 (33.4-64.8)	NR	LRT, stool, blood, urine
Zhou et al.[42]	Wuhan, China	Hospital	Case series	41	58 (48-62)	22 (54)	URT
Zhou et al. [35]	Wuhan, China	Hospital	Case series	191	56 (46-67)	119 (62)	URT
Zhou et al.[52]	Guangzhou, China	Hospital	Case series	31	45 (33-60) 37 (28-57)	4 (44) 6 (27)	URT
Zhu et al. [15]	Wuhan, China	Hospital	Case series	10	49.5	8 (80)	URT

Zou et al.[2]	Zhuhai, China	Hospital/outpatient	Case series	18	59 (range 26-76)	9 (50)	URT
SARS-CoV-1							
Chan et al.[64]	Hong Kong, China	Hospital	Case series	415	11.3 ± 4.1* 37.1 ± 11.2*	132 (33)	URT, LRT, stool, urine
Chen et al.[65]	Taiwan	Hospital	Case series	108	Stratified	95	URT
Cheng et al.[67]	Hong Kong, China	Hospital	Case series	1041	NR	NR	URT, LRT, stool, urine
Kwan et al.[68]	Hong Kong, China	Hospital	Case series	12 dialysis 33 controls	Dialysis: 58 (range 34-74);* Controls: 57 (range 34-75)	6 (50)	URT, stools, urine
Liu et al.[61]	Beijing, China	Hospital	Case series	56	31 (male) 34 (female)	31 (55)	LRT, stool
Leong et al.[69]	Singapore	Hospital	Case series	64	35.2 (17-63 range)*	16 (25)	URT, stool, blood, urine
Peiris et al. [70]	Hong Kong, China	Hospital	Case series	75	39.8 (SD 12.2)	0.92	URT
Xu et al.[109]	Beijing, China	Hospital	Case series	54	NR	NR	LRT, blood, urine
MERS-CoV							
Al Hosani et al.[73]	Abu Dhabi, UAE	Hospital/community	Case series	65	20 -59	43 (66)	LRT
Al-Jasser et al.[110]	Riyadh, Saudi Arabia	Hospital	Case series	167	46.71*	142 (57)	URT
Alkendi et al.[111]	Tawam/Al Ain, UAE	Hospital	Case series	58	43.5	41 (71)	URT
Arabi et al.[75]	Saudi Arabia	Hospital	Cohort	330	58 (44-69)	225 (68)	URT
Corman et al.[77]	Riyadh, Saudi Arabia	Hospital	Case series	37	69 (24–90)*	27 (39)	URT, LRT, stool, blood, urine
Hong et al.[76]	Seoul, South Korea	Hospital	Case series	30	49*	19 (63)	Blood
Min et al.[71]	Seoul/others, South Korea	Hospital	Case series	14	62	6 (35)	LRT, serum
Muth et al.[78]	Riyadh, Saudi Arabia	Hospital	Case series	32	66 (24-90)	24 (75)	LRT
Oh et al.[74]	Seoul, South Korea	Hospital	Case series	17	NR	NR	URT, LRT, serum
Park et al.[112]	Seoul, South Korea	Hospital	Case series	17	NR	NR	URT, LRT

Shalhoub et al.[72]	Jeddah, Saudi Arabia	Hospital	Retrospective cohort	32	65	14 (44)	LRT, serum

Abbreviations: UK, United Kingdom, USA; United States of America; UAE, United Arab Emirates; RCT, randomised controlled trial; URT, upper respiratory tract; LRT, lower respiratory tract; NR, not reported.

* Mean ± standard deviation (or range if stated).

333 **Table 2: Severity of illness and viral dynamics**

Study	Classification of severity	Median duration - days (IQR)	Viral dynamics in severe patients compared to non-severe patients	P-value
Chen *et al.*[27]	ICU vs. non-ICU patients	11	Median time to viral clearance significantly longer in ICU vs. non-ICU patients (HR=3.17, 95% CI, 2.29-4.37)	Only HR provided
Chen *et al* [28]	China CDC guideline (version 7)	12 (8-16)	Shedding duration varies by severity: asymptomatic 6 days; mild 10 days; moderate 12 days; serious 14 days; critical 32 days	<0.0001
Tan *et al.*[18]	China CDC guideline (version 6)	NP: 12 Any sample: 22	Viral shedding significantly longer in severe patients: any sample 23 vs. 20 days (note NP: 14 vs. 11 days – non-significant)	p=0.023 (any sample)
Xu *et al.*[38]	WHO criteria	17 (13-32)	Higher proportion of severe patients had shedding >21 days (34.2% vs.16.2%)	0.49
Yan *et al.* [39]	China CDC guideline (version 6)	23 (18-32)	No difference in shedding duration (general 23 days vs. severe 26 days vs. critical 28 days)	0.51
Zheng *et al.*[25]	China CDC guideline (version 6)	Resp: 18 (13-29)	Shedding duration significantly longer in severe patients (21 vs 14 days) in respiratory samples. No difference in shedding duration in stool/serum	p=0.04

334 Abbreviations: IQR, interquartile range; ICU, intensive care unit; HR, hazard ratio; CDC, Centers

335 for Disease Control and Prevention; WHO, World Health Organization.

336

337

338

339

340

341

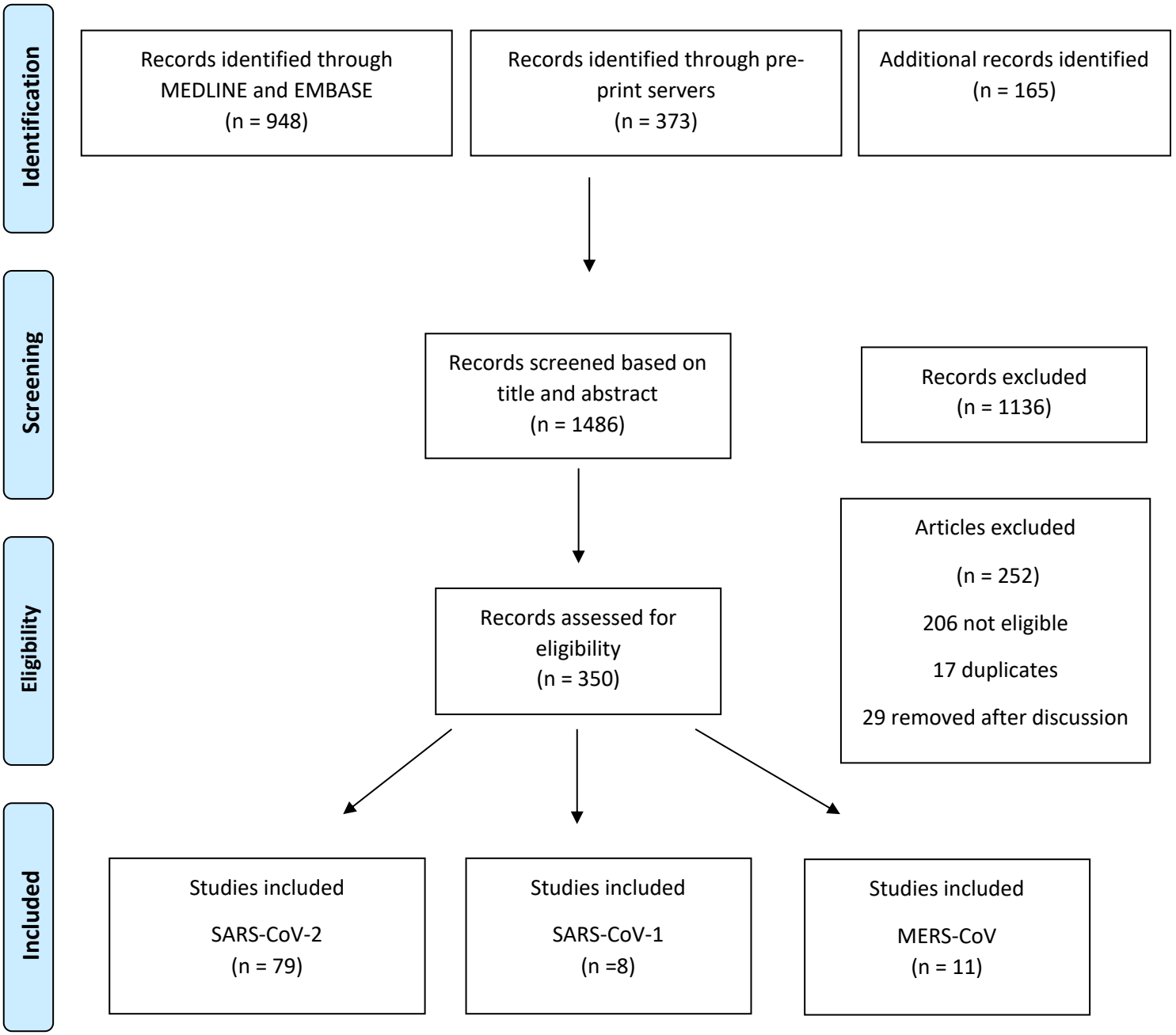
342

343 **Table 3: SARS-CoV-2 viral dynamics in asymptomatic patients compared to symptomatic**
344 **patients**

	Median duration – days (IQR)	Viral dynamics in asymptomatic patients compared to symptomatic patients	P-value
Arons *et al.* [54]	NR	No difference in viral load	NS
Chau *et al.* [53]	NR	Initial viral load similar. Asymptomatic patients had significantly lower viral load during the follow up compared to symptomatic patients and faster viral clearance in asymptomatic, compared to symptomatic individuals	0.027
Chen *et al.* [28]	6 (3.5-10)	Significantly shorter duration of viral shedding among asymptomatic cases (median 6 days, IQR 3.5-10), with increasing shedding duration associated with increasing illness severity	<0.0001
Han *et al.* [8]	NR	Symptomatic children had higher initial RNA load in nasopharyngeal swab specimens than asymptomatic children (9.01 vs. 6.32 $\log_{10}$ copies/mL; p = 0.048).	0.048
Hu *et al.* [55]	6 (2-12)	Asymptomatic patients had shorter duration of viral shedding compared to pre-symptomatic patients (median duration of SARS-CoV-2 positivity was 6.0 (2.0 - 12.0) compared to 12.0 (12.0 - 14.0))	NR
Lavezzo *et al.* [14]	NR	No difference in viral load	NS
Le *et al.* [59]	9	NR	N/A
Sakurai *et al.* [43]	9 (6-11)	NR	N/A
Yang et al. [56]	8 (3-12)	Significantly shorter duration of viral shedding from nasopharynx swabs was observed among asymptomatic compared to symptomatic patients	P= .001
Yongchen *et al.* [36]	18 (5-28)	Longer shedding duration among asymptomatic cases (median 18 days, range 5-28), compared to non-severe (10 days, range 2-21) and severe (14 days, range 9-33) cases	NS
Zhang *et al.* [13]	9.63	Initial viral load similar, viral clearance occurred earlier in the asymptomatic (9.6 days) and symptomatic individuals (9.7 days, compared to pre-symptomatic group (13.6 days)	
Zhou *et al.* [52]	NR	Significantly higher viral load in symptomatic (n=22) compared to asymptomatic (n=9) patients (median cycle threshold (Ct) value 34.5 vs. 39.0, respectively) but duration of shedding was similar	

345 Abbreviations: IQR, interquartile range; RNA, ribonucleic acid; NR, not reported; NS, non-
346 significant; N/A, not applicable

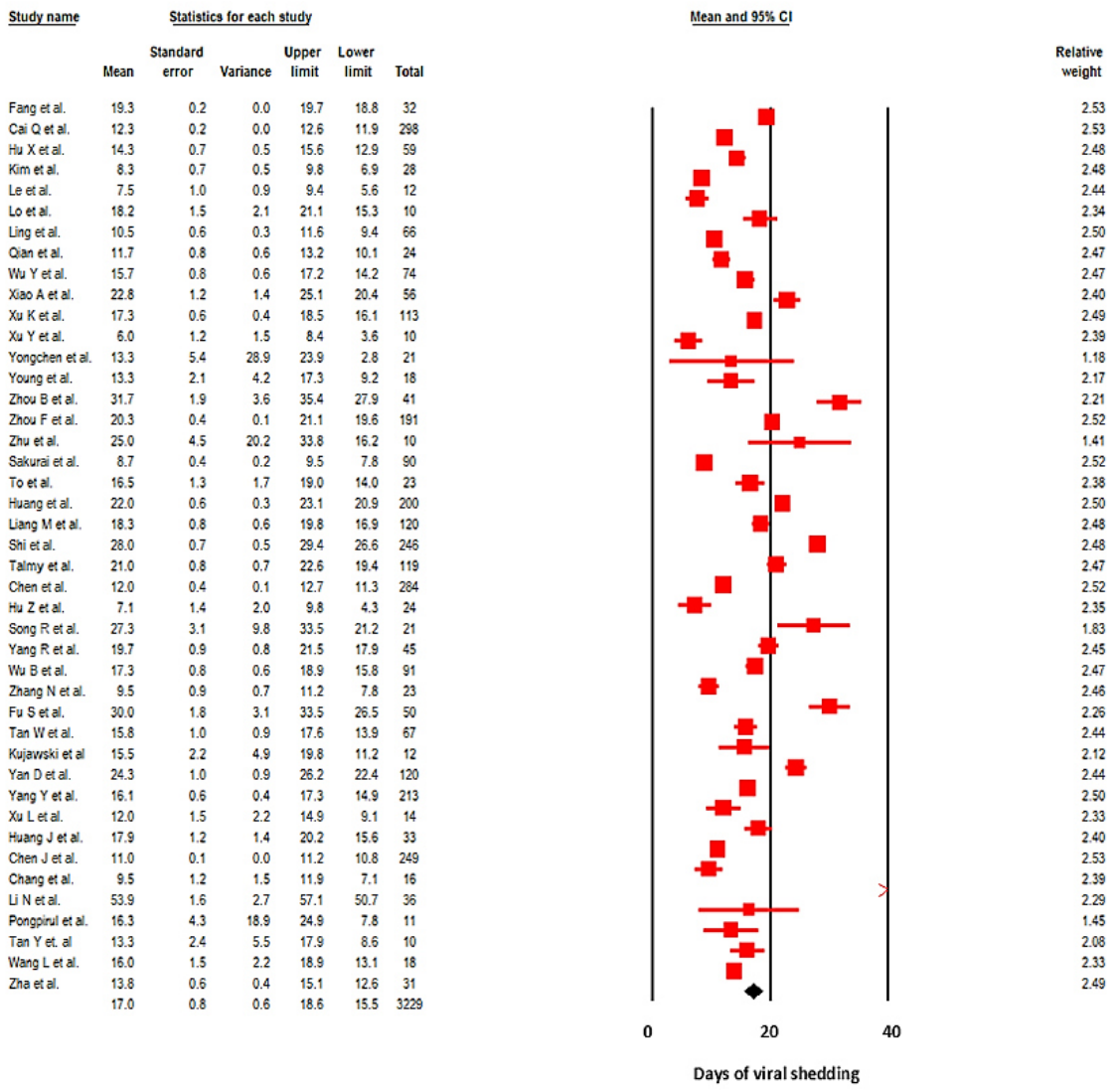
Figure 1. Flowchart describing study selection



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

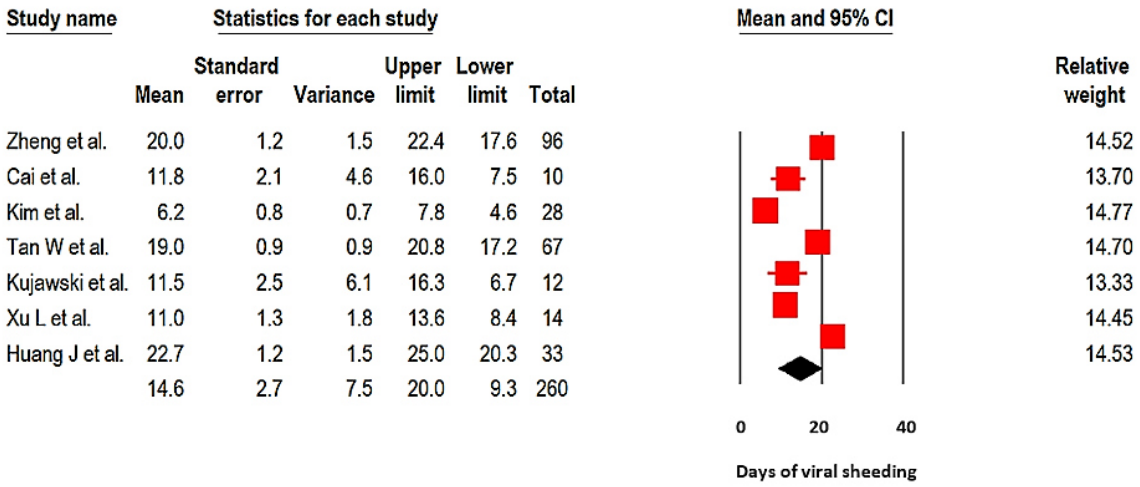
Figure 2: Pooled mean duration (days) of SARS-CoV-2 shedding from the upper respiratory tract (random-effects model).



Note: the overall effect is plotted as a black square.

Test for heterogeneity: Q-value = 4076,08, df(Q) = 42, $p < 0.001$, $I^2 = 99\%$.

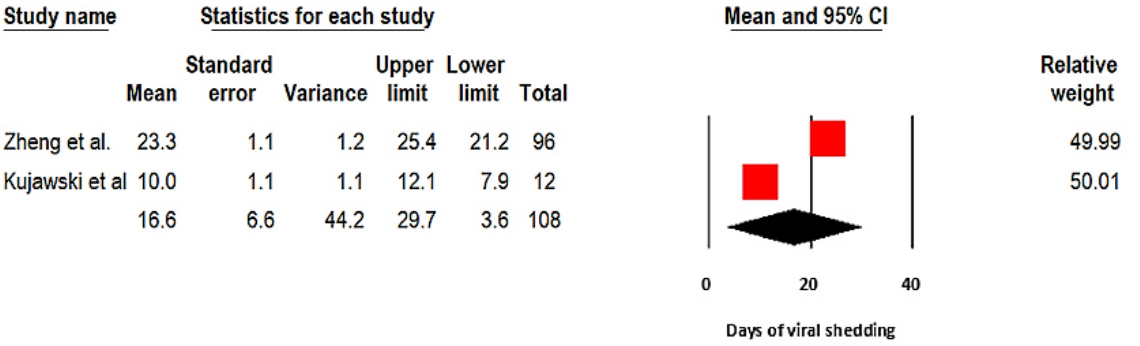
Figure 3: Pooled mean duration (days) of SARS-CoV-2 shedding from the lower respiratory tract (random-effects model).



Note: the overall effect is plotted as a black square.

Test for heterogeneity: Q-value = 203.3, df(Q) = 6, $p < 0.001$, $I^2 = 97\%$.

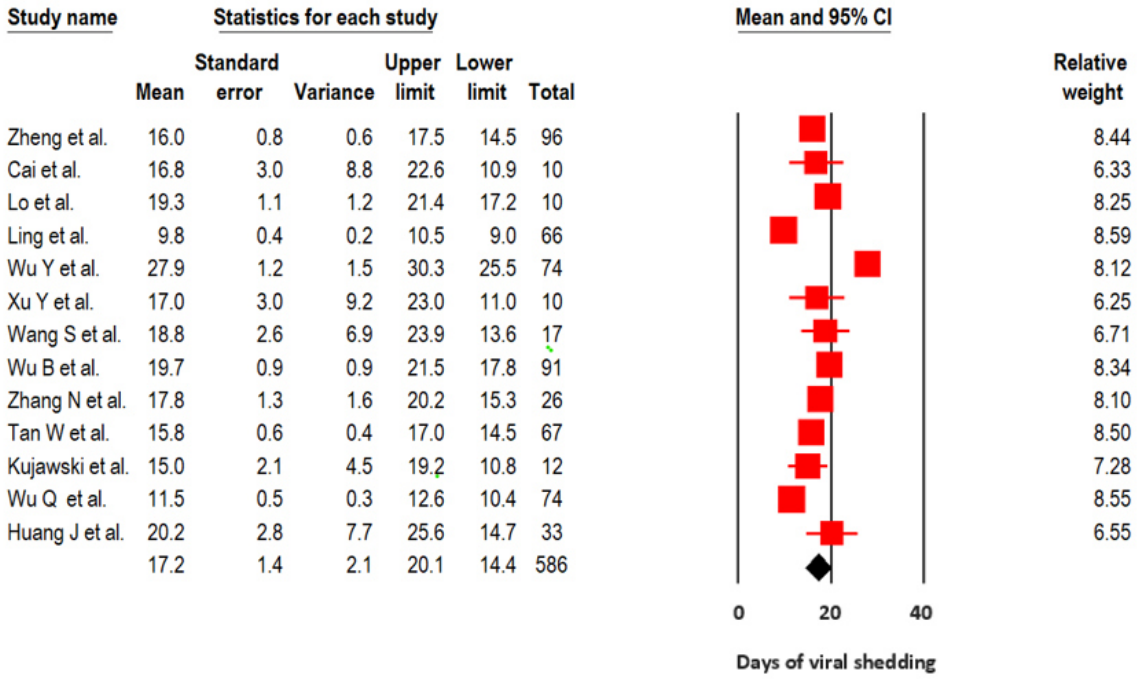
Figure 4. Pooled mean duration (days) of SARS-CoV-2 shedding in the blood (random-effects model).



Note: the overall effect is plotted as a black square.

Test for heterogeneity: Q-value = 77,6, df(Q) = 1, $p < 0.001$, $I^2 = 99\%$.

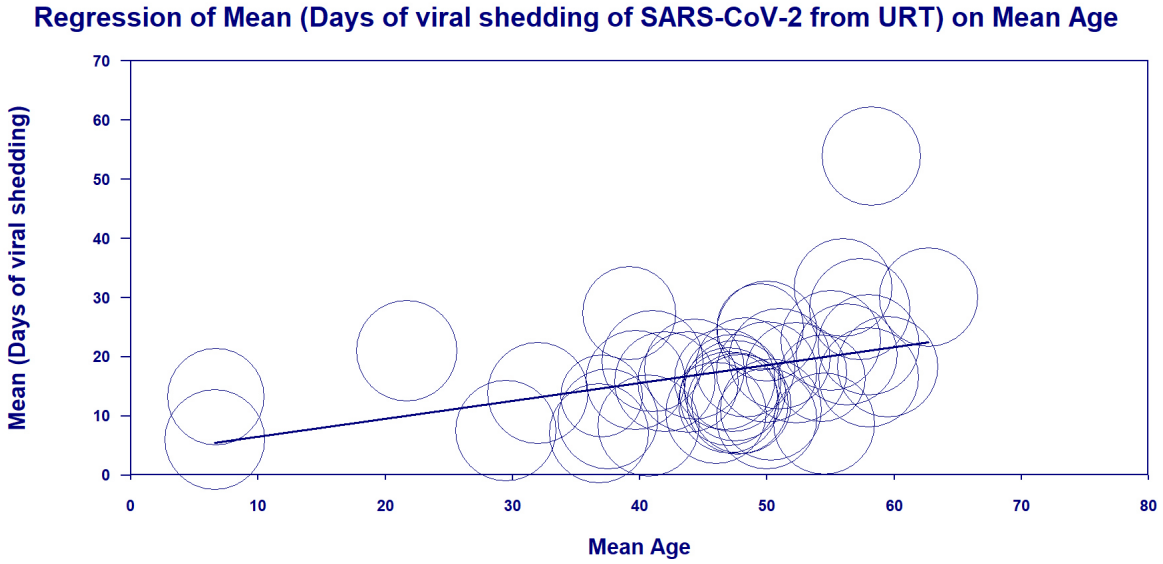
Figure 5. Pooled mean duration (days) of SARS-CoV-2 shedding from the stool (random-effects model).



Note: the overall effect is plotted as a black square.

Test for heterogeneity: Q-value = 356.0, df(Q) = 12, $p < 0.001$, $I2 = 96.6\%$.

Figure 6. Meta-regression bubble plot of the impact of age on mean SARS-CoV-2 shedding from the upper respiratory tract



URT: upper respiratory tract.

Note: the plot was built upon 41 studies (no data on mean age from the study of Qian et al.[98]). A random-effects model was used.

References:

1. Cevik M, Bamford CGG, Ho A. COVID-19 pandemic-a focused review for clinicians. *Clin Microbiol Infect* 2020; **26**(7): 842-7.
2. Zou L, Ruan F, Huang M, et al. SARS-CoV-2 Viral Load in Upper Respiratory Specimens of Infected Patients. *New England Journal of Medicine* 2020; **382**(12): 1177-9.
3. Wolfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020.
4. Kim ES, Chin BS, Kang CK, et al. Clinical Course and Outcomes of Patients with Severe Acute Respiratory Syndrome Coronavirus 2 Infection: a Preliminary Report of the First 28 Patients from the Korean Cohort Study on COVID-19. *J Korean Med Sci* 2020; **35**(13): e142.
5. Institute TJB. The Joanna Briggs Institute Critical Appraisal tools for use in JBI systematic reviews–checklist for case series. , 2017.
6. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology* 2014; **14**(1): 135.
7. Cai J, Xu J, Lin D, et al. A Case Series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clinical Infectious Diseases* 2020; **28**: 28.
8. Han MS, Seong M-W, Kim N, et al. Early Release - Viral RNA Load in Mildly Symptomatic and Asymptomatic Children with COVID-19, Seoul - Volume 26, Number 10—October 2020 - Emerging Infectious Diseases journal - CDC.
9. L'Huillier A, Torriani G, Pigny F, Kaiser L, Eckerle I. Shedding of infectious SARS-CoV-2 in symptomatic neonates, children and adolescents. 2020.
10. Tan Y-p, Tan B-y, Pan J, Wu J, Zeng S-z, Wei H-y. Epidemiologic and clinical characteristics of 10 children with coronavirus disease 2019 in Changsha, China. *Journal of Clinical Virology* 2020; **127**: 104353.
11. Wu Q, Xing Y, Shi L, et al. Epidemiological and Clinical Characteristics of Children with Coronavirus Disease 2019. 2020.
12. Xu Y, Li X, Zhu B, et al. Characteristics of pediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding. *Nature Medicine* 2020; **26**(4): 502-5.
13. Zhang Z, Xiao T, Wang Y, et al. Early viral clearance and antibody kinetics of COVID-19 among asymptomatic carriers. *medRxiv* 2020: 2020.04.28.20083139.
14. Lavezzo E, Franchin E, Ciavarella C, et al. Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. *Nature* 2020: 1-.
15. Zhu L, Gong N, Liu B, et al. Coronavirus Disease 2019 Pneumonia in Immunosuppressed Renal Transplant Recipients: A Summary of 10 Confirmed Cases in Wuhan, China. *Eur Urol* 2020; **18**: 18.
16. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nature Medicine*; **26**(5): 672-5.
17. Kujawski SA, Wong KK, Collins JP, et al. Clinical and virologic characteristics of the first 12 patients with coronavirus disease 2019 (COVID-19) in the United States. *Nature Medicine* 2020; **26**(6): 861-8.
18. Tan W, Lu Y, Zhang J, et al. Viral Kinetics and Antibody Responses in Patients with COVID-19. 2020.
19. To KK-W, Tsang OT-Y, Leung W-S, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *The Lancet Infectious Diseases* 2020; **20**(5): 565-74.
20. Wolfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature* 2020; **581**(7809): 465-9.
21. Wyllie AL, Fournier J, Casanovas-Massana A, et al. Saliva is more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs.

22. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA* 2020; **03**: 03.
23. Huang J, Mao T, Li S, et al. Long period dynamics of viral load and antibodies for SARS-CoV-2 infection: an observational cohort study. *medRxiv* 2020: 2020.04.22.20071258.
24. Zhang N, Gong Y, Meng F, Bi Y, Yang P, Wang F. Virus shedding patterns in nasopharyngeal and fecal specimens of COVID-19 patients. 2020.
25. Zheng S, Fan J, Yu F, et al. Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. *BMJ* 2020; **369**.
26. Cai Q, Huang D, Ou P, et al. COVID-19 in a designated infectious diseases hospital outside Hubei Province, China. *Allergy* 2020; **n/a**(n/a).
27. Chen J, Qi T, Liu L, et al. Clinical progression of patients with COVID-19 in Shanghai, China. *Journal of Infection* 2020; **80**(5): e1-e6.
28. Chen X, Zhang Y, Zhu B, et al. Associations of clinical characteristics and antiviral drugs with viral RNA clearance in patients with COVID-19 in Guangzhou, China: a retrospective cohort study.
29. Chen Y, Chen L, Deng Q, et al. The presence of SARS-CoV-2 RNA in the feces of COVID-19 patients. *Journal of Medical Virology* 2020; **03**: 03.
30. Fan L, Liu C, Li N, et al. Medical treatment of 55 patients with COVID-19 from seven cities in northeast China who fully recovered: a single-center, retrospective, observational study.
31. Fang Z, Zhang Y, Hang C, Ai J, Li S, Zhang W. Comparisons of viral shedding time of SARS-CoV-2 of different samples in ICU and non-ICU patients. *Journal of Infection* 2020; **21**: 21.
32. Liu Y, Yan L-M, Wan L, et al. Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect Dis* 2020; **20**(6): 656-7.
33. Shi J, Cheng C, Yu M, et al. Systemic Inflammatory Cytokines Associate With SARS-COV-2 Viral Shedding Time in Covid-19 Inpatients. *ResearchSquare* 2020.
34. Tan L, Kang X, Ji X, et al. Validation of Predictors of Disease Severity and Outcomes in COVID-19 Patients: A Descriptive and Retrospective Study. *Med* 2020.
35. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**(10229): 1054-62.
36. Yongchen Z, Shen H, Wang X, et al. Different longitudinal patterns of nucleic acid and serology testing results based on disease severity of COVID-19 patients. *Emerg* 2020; **9**(1): 833-6.
37. Hu X, Xing Y, Jia J, et al. Factors associated with negative conversion of viral RNA in patients hospitalized with COVID-19. *Science of the Total Environment* 2020; **728 (no pagination)**.
38. Xu K, Chen Y, Yuan J, et al. Factors associated with prolonged viral RNA shedding in patients with COVID-19. *Clinical Infectious Diseases* 2020; **09**: 09.
39. Yan D, Liu X-y, Zhu Y-n, et al. Factors associated with prolonged viral shedding and impact of Lopinavir/Ritonavir treatment in patients with SARS-CoV-2 infection.
40. Wu Y, Guo C, Tang L, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol* 2020; **5**(5): 434-5.
41. Tian D, Wang L, Wang X, et al. Clinical research and factors associated with prolonged duration of viral shedding in patients with COVID-19. *ResearchSquare* 2020.
42. Zhou B, She J, Wang Y, Ma X. The duration of viral shedding of discharged patients with severe COVID-19. *Clinical Infectious Diseases* 2020; **17**: 17.
43. Sakurai A, Sasaki T, Kato S, et al. Natural History of Asymptomatic SARS-CoV-2 Infection. *New England Journal of Medicine* 2020.
44. Talmy T, Tsur A, Shabtay O. Duration of Viral Clearance in IDF Soldiers with Mild COVID-19. *medRxiv*.
45. Xiao AT, Tong YX, Zhang S. Profile of RT-PCR for SARS-CoV-2: a preliminary study from 56 COVID-19 patients. *Clinical Infectious Diseases* 2020; **19**: 19.

46. Shastri A, Wheat J, Agrawal S, et al. Delayed clearance of SARS-CoV2 in male compared to female patients: High ACE2 expression in testes suggests possible existence of gender-specific viral reservoirs.
47. Ling Y, Xu S-B, Lin Y-X, et al. Persistence and clearance of viral RNA in 2019 novel coronavirus disease rehabilitation patients. *Chinese Medical Journal* 2020; **133**(9).
48. Zha L, Li S, Pan L, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). *Medical Journal of Australia* 2020; **212**(9): 416-20.
49. Liang M, Chen P, He M, et al. Corticosteroid Treatment in Critically Ill Patients with COVID-19: A Retrospective Cohort Study. *ResearchSquare* 2020.
50. Hung IFN, Lung KC, Tso EYK, et al. Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *The Lancet* 2020; **395**(10238): 1695-704.
51. Huang H, Guan L, Yang Y, et al. Chloroquine, arbidol (umifenovir) or lopinavir/ritonavir as the antiviral monotherapy for COVID-19 patients: a retrospective cohort study. 2020.
52. Zhou R, Li F, Chen F, et al. Viral dynamics in asymptomatic patients with COVID-19. *International Journal of Infectious Diseases* 2020; **96**: 288-90.
53. Chau NVV, Thanh Lam V, Thanh Dung N, et al. The natural history and transmission potential of asymptomatic SARS-CoV-2 infection. *Clinical Infectious Diseases* 2020.
54. Arons MM, Hatfield KM, Reddy SC, et al. Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. *New England Journal of Medicine* 2020; **382**(22): 2081-90.
55. Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. *Science China Life Sciences* 2020; **63**(5): 706-11.
56. Yang R, Gui X, Xiong Y. Comparison of Clinical Characteristics of Patients with Asymptomatic vs Symptomatic Coronavirus Disease 2019 in Wuhan, China. *JAMA Netw Open* 2020; **3**(5).
57. Bullard J, Dust K, Funk D, et al. Predicting infectious SARS-CoV-2 from diagnostic samples. *Clinical Infectious Diseases*.
58. La Scola B, Le Bideau M, Andreani J, et al. Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. *Eur J Clin Microbiol Infect Dis* 2020: 1-3.
59. Le TQM, Takemura T, Moi ML, et al. Severe Acute Respiratory Syndrome Coronavirus 2 Shedding by Travelers, Vietnam, 2020. *Emerg Infect Dis* 2020; **26**(7): 02.
60. To KK-W, Tsang OT-Y, Yip CC-Y, et al. Consistent Detection of 2019 Novel Coronavirus in Saliva. *Clinical Infectious Diseases* 2020; (ciaa149).
61. Liu W, Tang F, Fontanet A, et al. Long-term SARS coronavirus excretion from patient cohort, China. *Emerg Infect Dis* 2004; **10**(10): 1841-3.
62. Xiao F, Sun J, Xu Y, et al. Infectious SARS-CoV-2 in Feces of Patient with Severe COVID-19. *Emerging Infectious Disease journal* 2020; **26**(8).
63. Andersson M, Arancibia - Carcamo CV, Auckland K, et al. SARS-CoV-2 RNA detected in blood samples from patients with COVID-19 is not associated with infectious virus. *medRxiv*.
64. Chan PK, To WK, Ng KC, et al. Laboratory diagnosis of SARS. *Emerg Infect Dis* 2004; **10**(5): 825-31.
65. Chen WJ, Yang JY, Lin JH, et al. Nasopharyngeal shedding of severe acute respiratory syndrome-associated coronavirus is associated with genetic polymorphisms. *Clinical Infectious Diseases* 2006; **42**(11): 1561-9.
66. Xu D, Zhang Z, Jin L, et al. Persistent shedding of viable SARS-CoV in urine and stool of SARS patients during the convalescent phase. *European Journal of Clinical Microbiology and Infectious Diseases* 2005; **24**(3): 165-71.
67. Cheng PK, Wong DA, Tong LK, et al. Viral shedding patterns of coronavirus in patients with probable severe acute respiratory syndrome. *Lancet* 2004; **363**(9422): 1699-700.
68. Kwan BC, Leung CB, Szeto CC, et al. Severe acute respiratory syndrome in dialysis patients. *J Am Soc Nephrol* 2004; **15**(7): 1883-8.

69. Leong HN, Chan KP, Khan AS, et al. Virus-specific RNA and antibody from convalescent-phase SARS patients discharged from hospital. *Emerg Infect Dis* 2004; **10**(10): 1745-50.
70. Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *The Lancet* 2003; **361**(9371): 1767-72.
71. Min CK, Cheon S, Ha NY, et al. Comparative and kinetic analysis of viral shedding and immunological responses in MERS patients representing a broad spectrum of disease severity. *Sci* 2016; **6**: 25359.
72. Shalhoub S, Farahat F, Al-Jiffri A, et al. IFN-alpha2a or IFN-beta1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother* 2015; **70**(7): 2129-32.
73. Al Hosani FI, Pringle K, Al Mulla M, et al. Response to Emergence of Middle East Respiratory Syndrome Coronavirus, Abu Dhabi, United Arab Emirates, 2013-2014. *Emerg Infect Dis* 2016; **22**(7): 1162-8.
74. Oh MD, Park WB, Choe PG, et al. Viral load kinetics of MERS coronavirus infection. *New England Journal of Medicine* 2016; **375**(13): 1303-5.
75. Arabi YM, Al-Omari A, Mandourah Y, et al. Critically Ill Patients With the Middle East Respiratory Syndrome: A Multicenter Retrospective Cohort Study. *Crit Care Med* 2017; **45**(10): 1683-95.
76. Hong KH, Choi JP, Hong SH, et al. Predictors of mortality in Middle East respiratory syndrome (MERS). *Thorax* 2018; **73**(3): 286-9.
77. Corman VM, Albarrak AM, Omrani AS, et al. Viral Shedding and Antibody Response in 37 Patients With Middle East Respiratory Syndrome Coronavirus Infection. *Clinical Infectious Diseases* 2016; **62**(4): 477-83.
78. Muth D, Corman VM, Meyer B, et al. Infectious middle east respiratory syndrome coronavirus excretion and serotype variability based on live virus isolates from patients in Saudi Arabia. *Journal of Clinical Microbiology* 2015; **53**(9): 2951-5.
79. Wang Y, Tian H, Zhang L, et al. Reduction of secondary transmission of SARS-CoV-2 in households by face mask use, disinfection and social distancing: a cohort study in Beijing, China. *BMJ Global Health* 2020; **5**(5): e002794.
80. Böhmer MM, Buchholz U, Corman VM, et al. Investigation of a COVID-19 outbreak in Germany resulting from a single travel-associated primary case: a case series. *The Lancet Infectious Diseases*.
81. Cheng H-Y, Jian S-W, Liu D-P, et al. Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods Before and After Symptom Onset. *JAMA Internal Medicine* 2020.
82. Wang Y, Guo Q, Yan Z, et al. Factors Associated With Prolonged Viral Shedding in Patients With Avian Influenza A(H7N9) Virus Infection. *J Infect Dis* 2018; **217**(11): 1708-17.
83. Memish A. Viral shedding and antibody response in MERS. *Vox Sanguinis* 2016; **111 (Supplement 1)**: 48-9.
84. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA* 2020; **323**(18): 1843-4.
85. Ip DKM, Lau LLH, Leung NHL, et al. Viral Shedding and Transmission Potential of Asymptomatic and Paucisymptomatic Influenza Virus Infections in the Community. *Clin Infect Dis* 2017; **64**(6): 736-42.
86. Walsh KA, Jordan K, Clyne B, et al. SARS-CoV-2 detection, viral load and infectivity over the course of an infection. *Journal of Infection*.
87. Kretzschmar ME, Rozhnova G, Bootsma MCJ, van Boven M, van de Wijgert JHHM, Bonten MJM. Impact of delays on effectiveness of contact tracing strategies for COVID-19: a modelling study. *The Lancet Public Health*.

88. Chang D, Mo G, Yuan X, et al. Time Kinetics of Viral Clearance and Resolution of Symptoms in Novel Coronavirus Infection. *Am J Respir Crit Care Med* 2020; **201**(9): 1150-2.
89. Chen X, Ling J, Mo P, et al. Restoration of leukomonocyte counts is associated with viral clearance in COVID-19 hospitalized patients. *medRxiv* 2020: 2020.03.03.20030437.
90. Corman VM, Rabenau HF, Adams O, et al. SARS-CoV-2 asymptomatic and symptomatic patients and risk for transfusion transmission. *Transfusion* 2020; **60**(6): 1119-22.
91. Fu S, Fu X, Song Y, et al. Virologic and clinical characteristics for prognosis of severe COVID-19: a retrospective observational study in Wuhan, China. 2020.
92. Huang L, Chen Z, Ni L, et al. Impact of Angiotensin-converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Inflammatory Responses and Viral Clearance in COVID-19 Patients: A Multicenter Retrospective Cohort Study. *ResearchSquare* 2020.
93. Li N, Wang X, Lv T. Prolonged SARS-CoV-2 RNA shedding: Not a rare phenomenon. *Journal of Medical Virology*; **n/a**(n/a).
94. Liu L, Liu W, Zheng Y, et al. A preliminary study on serological assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 238 admitted hospital patients. *Microbes and Infection* 2020; **22**(4): 206-11.
95. Lo IL, Lio CF, Cheong HH, et al. Evaluation of SARS-CoV-2 RNA shedding in clinical specimens and clinical characteristics of 10 patients with COVID-19 in Macau. *Int J Biol Sci* 2020; **16**(10): 1698-707.
96. Lou B, Li T, Zheng S, et al. Serology characteristics of SARS-CoV-2 infection since the exposure and post symptoms onset.
97. Pongpirul WA, Mott JA, Woodring JV, et al. Clinical Characteristics of Patients Hospitalized with Coronavirus Disease, Thailand - Volume 26, Number 7—July 2020 - Emerging Infectious Diseases journal - CDC.
98. Qian GQ, Chen XQ, Lv DF, et al. Duration of SARS-CoV-2 viral shedding during COVID-19 infection. *Infect Dis (Lond)* 2020: 1-2.
99. quan w, zheng q, tian j, et al. No SARS-CoV-2 in expressed prostatic secretion of patients with coronavirus disease 2019: a descriptive multicentre study in China.
100. Seah IYJ, Anderson DE, Kang AEZ, et al. Assessing Viral Shedding and Infectivity of Tears in Coronavirus Disease 2019 (COVID-19) Patients. *Ophthalmology* 2020; **24**: 24.
101. Song C, Wang Y, Li W, et al. Detection of 2019 novel coronavirus in semen and testicular biopsy specimen of COVID-19 patients.
102. Song R, Han B, Song M, et al. Clinical and epidemiological features of COVID-19 family clusters in Beijing, China. *Journal of Infection* 2020.
103. Tu Y-H, Wei Y-Y, Zhang D-W, Chen C-S, Hu X-W, Fei G. Analysis of factors affected the SARS-CoV-2 viral shedding time of COVID-19 patients in Anhui, China: a retrospective study. 2020.
104. Wang L, Gao Y-h, Lou L-L, Zhang G-J. The clinical dynamics of 18 cases of COVID-19 outside of Wuhan, China. *European Respiratory Journal* 2020.
105. Wang S, Tu J, Sheng Y. Clinical characteristics and fecal-oral transmission potential of patients with COVID-19. *medRxiv*.
106. Wu B, Lei Z-Y, Wu K-L, et al. Epidemiological and clinical features of imported and local patients with coronavirus disease 2019 (COVID-19) in Hainan, China. *ResearchSquare* 2020.
107. Xu l, Zhang X, Song W, et al. Conjunctival polymerase chain reaction-tests of 2019 novel coronavirus in patients in Shenyang,China.
108. Yang Y, Yang M, Shen C, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. 2020.
109. Xu D, Zhang Z, Jin L, et al. Persistent shedding of viable SARS-CoV in urine and stool of SARS patients during the convalescent phase. *Eur J Clin Microbiol Infect Dis* 2005; **24**(3): 165-71.
110. Al-Jasser FS, Nouh RM, Youssef RM. Epidemiology and predictors of survival of MERS-CoV infections in Riyadh region, 2014-2015. *J Infect Public Health* 2019; **12**(2): 171-7.

111. Alkendi F, Nair SC, Hashmey R. Descriptive Epidemiology, Clinical Characteristics and Outcomes for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Infected Patients in AlAin - Abu Dhabi Emirate. *J Infect Public Health* 2019; **12 (1)**: 137.

112. Park WB, Poon LLM, Choi SJ, et al. Replicative virus shedding in the respiratory tract of patients with Middle East respiratory syndrome coronavirus infection. *International Journal of Infectious Diseases* 2018; **72**: 8-10.

frontiers in Public Health

SYSTEMATIC REVIEW
published: 19 March 2021
doi: 10.3389/fpubh.2021.652842

Characteristics of Viral Shedding Time in SARS-CoV-2 Infections: A Systematic Review and Meta-Analysis

Danying Yan†, Xiaobao Zhang†, Can Chen, Daixi Jiang, Xiaoxiao Liu, Yuqing Zhou, Chenyang Huang, Yiyi Zhou, Zhou Guan, Cheng Ding, Lu Chen, Lei Lan, Xiaofang Fu, Jie Wu, Lanjuan Li* and Shigui Yang**

State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, College of Medicine, The First Affiliated Hospital, Zhejiang University, Hangzhou, China

OPEN ACCESS

Edited by:
Walid Alali,
Kuwait University, Kuwait

Reviewed by:
Rami H. Al-Rifai,
United Arab Emirates University, United Arab Emirates
Abhilash Perisetti,
University of Arkansas for Medical Sciences, United States

***Correspondence:**
Shigui Yang
yangshigui@zju.edu.cn
Lanjuan Li
ljli@zju.edu.cn
Jie Wu
15955118479@163.com

†These authors have contributed equally to this work and share first authorship

Specialty section:
This article was submitted to Infectious Diseases - Surveillance, Prevention and Treatment, a section of the journal Frontiers in Public Health

Received: *13 January 2021*
Accepted: *22 February 2021*
Published: *19 March 2021*

Citation:
Yan D, Zhang X, Chen C, Jiang D, Liu X, Zhou Y, Huang C, Zhou Y, Guan Z, Ding C, Chen L, Lan L, Fu X, Wu J, Li L and Yang S (2021) Characteristics of Viral Shedding Time in SARS-CoV-2 Infections: A Systematic Review and Meta-Analysis. Front. Public Health 9:652842. doi: 10.3389/fpubh.2021.652842

Background: The viral shedding time (VST) of SARS-CoV-2 mainly determines its transmission and duration of infectiousness. However, it was heterogeneous in the existing studies. Here, we performed a meta-analysis to comprehensively summarize the VST of SARS-CoV-2.

Methods: We searched PubMed, Web of Science, MedRxiv, BioRxiv, CNKI, CSTJ, and Wanfang up to October 25, 2020, for studies that reported VSTs of SARS-CoV-2. Pooled estimates and 95% CIs for the VSTs were calculated using log-transformed data. The VSTs in SARS-CoV-2 infections based on different demographic and clinical characteristics, treatments and specimens were stratified by subgroup analysis.

Results: A total of 35 studies involving 3,385 participants met the inclusion criteria. The pooled mean VST was 16.8 days (95% CI: 14.8–19.4, $I^2 = 99.56\%$) in SARS-CoV-2 infections. The VST was significantly longer in symptomatic infections (19.7 days, 95% CI: 17.2–22.7, $I^2 = 99.34\%$) than in asymptomatic infections (10.9 days, 95% CI: 8.3–14.3, $I^2 = 98.89\%$) ($P < 0.05$). The VST was 23.2 days (95% CI: 19.0–28.4, $I^2 = 99.24\%$) in adults, which was significantly longer than that in children (9.9 days, 95% CI: 8.1–12.2, $I^2 = 85.74\%$) ($P < 0.05$). The VST was significantly longer in persons with chronic diseases (24.2 days, 95% CI: 19.2–30.2, $I^2 = 84.07\%$) than in those without chronic diseases (11.5 days, 95% CI: 5.3–25.0, $I^2 = 82.11\%$) ($P < 0.05$). Persons receiving corticosteroid treatment (28.3 days, 95% CI: 25.6–31.2, $I^2 = 0.00\%$) had a longer VST than those without corticosteroid treatment (16.2 days, 95% CI: 11.5–22.5, $I^2 = 92.27\%$) ($P = 0.06$). The VST was significantly longer in stool specimens (30.3 days, 95% CI: 23.1–39.2, $I^2 = 92.09\%$) than in respiratory tract specimens (17.5 days, 95% CI: 14.9–20.6, $I^2 = 99.67\%$) ($P < 0.05$).

Conclusions: A longer VST was found in symptomatic infections, infected adults, persons with chronic diseases, and stool specimens.

Keywords: viral shedding time, SARS- CoV-2, COVID-19, systematic review, meta-analysis

INTRODUCTION

Coronaviruses (CoVs), belonging to Nidovirales order, have caused three global outbreaks in the past 20 years. The first epidemic was Severe Acute Respiratory Syndrome (SARS) caused by SARS-CoV-1 in 2003, the second outbreak was Middle East Respiratory Syndrome (MERS) caused by MERS-CoV in 2012, and the third and most recent pandemic was Coronavirus Disease 2019 (COVID-19) caused by SARS-CoV-2 (1, 2). As of February 4, 2021, more than 104 million cases of COVID-19 have been reported with over 2.2 million deaths globally (3). Pulmonary clinical manifestations are the most common clinical presentations of COVID-19, such as fever, cough, shortness of breath, sputum production, respiratory failure and even acute respiratory distress syndrome (ARDS). Diarrhea, loss of smell or taste, and other extra-pulmonary clinical manifestations can also be found in some patients (4–7).

Persons infected with SARS-CoV-2 with long viral shedding times (VSTs) have drawn considerable concern, which put greater challenges and difficulties on epidemic prevention and control (8–11). The VST is an important parameter for judging hospital discharge, discontinuation of quarantine and the effect of antiviral treatment for infectious diseases, which mainly determines disease transmission and the duration of infectiousness (12). However, the characteristics of the VST in SARS-CoV-2 infections have not been well-clarified. Although there have been many studies on the VSTs of SARS-CoV-2, the results across studies so far have been heterogeneous (13, 14). A meta-analysis performed by Muge Cevik found that the mean VST of SARS-CoV-2 in the upper respiratory tract, lower respiratory tract, stool and serum was 17.0, 14.6, 17.2, and 16.6 days, respectively (15). However, a comprehensive summary of VSTs in SARS-CoV-2 infections with different demographic and clinical features is still lacking. Therefore, we performed a meta-analysis to estimate the mean VST in SARS-CoV-2 infections and explore the characteristics of VSTs in SARS-CoV-2 infections based on different demographic features, clinical characteristics, treatments and specimens.

MATERIALS AND METHODS

Our meta-analysis was strictly conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines (16).

The Definition of the VST

The definition of the VST varied among the studies, so a unified definition was made. We defined the VST as the time from illness onset to viral shedding cessation. Illness onset was defined as the first appearance of the symptoms for symptomatic infections and the first positive RT-PCR results for asymptomatic infections. Viral shedding cessation referred to the occurrence of the last positive RT-PCR results or negative RT-PCR results.

Search Strategy and Selection Criteria

We searched PubMed, Web of Science, MedRxiv, BioRxiv, the China National Knowledge Infrastructure Database (CNKI), the China Science and Technology Journal Database (CSTJ), and the Wanfang Database up to October 25, 2020, for studies that reported VSTs of SARS-CoV-2. The details of the search strategy are shown in **Supplementary Table 1**.

In this systematic review with no study design limit, studies meeting the following inclusion criteria were eligible: (i) SARS-CoV-2 infections were based on positive RT-PCR results; (ii) the VSTs of SARS-CoV-2 infections including sample size, mean and standard deviation (SD) could be obtained directly from the original studies or by calculation; and (iii) the definition of the VST in the original studies was consistent with our definition.

We excluded (i) duplicated data; (ii) case reports and case series with <5 participants due to reporting bias; and (iii) studies without original data (e.g., modeling studies and reviews). Studies presenting VSTs with medians and interquartile ranges (IQRs) or ranges were excluded to reduce the errors caused by data conversion.

Screening, Data Extraction, and Quality Assessment

After removing duplicates, two reviewers (DY and XZ) independently performed the initial screening of titles and abstracts to exclude studies that clearly contained no data for VST of SARS-CoV-2. All retained full-text articles were scrutinized against the eligibility criteria by two independent reviewers (DY and XZ). Nine investigators (DY, XZ, CC, DJ, XL, YZ, CH, YZ, and ZG) participated in the data extraction. And data extraction from each study was performed by three independent investigators. Disagreements and uncertainties were consulted by SY to reach a consensus. The following data were extracted: basic information of the studies (first author, publication time, journal name, sample size), VSTs in SARS-CoV-2 infections based on sex, age (adult and child), infection status (symptomatic infection and asymptomatic infection), disease severity (severe infection and non-severe infection), treatments (corticosteroid treatment and antiviral therapy) and specimens (respiratory tract specimens (RTS), upper respiratory tract specimens (URTS), lower respiratory tract specimens (LRTS), stool and serum). The cutoff point for classifying adults and children was 18 years old. Asymptomatic infections referred to the absence of any clinical symptoms throughout the disease course. Non-severe infections included mild and moderate infections, and severe infections included severe and critical infections. Antiviral drugs included interferon, lopinavir/ritonavir, abidor, ribavirin, chloroquine and hydroxychloroquine. URTS included nasopharyngeal, oropharyngeal and oronasopharyngeal swabs, and LRTS included sputum and bronchoalveolar lavage fluid.

The overall VST of the total participants was extracted to estimate the overall pooled VST. If studies did not report the overall VST of the total participants, the stratified VSTs were extracted to estimate the overall pooled VST. If a study included more than one independent study population, each population was extracted as a separate dataset in the meta-analysis. When the same study reported the VSTs of multiple specimens, the VSTs of the URTS were extracted to estimate the overall pooled VST, and the VSTs of other specimens were

displayed in the subgroup analysis. In subgroup analysis, only studies having clear population characteristics were included in the corresponding subgroup, and studies having no clear information or mixed population group were included in the unclassified group.

The scale recommended by the Agency for Healthcare Research and Quality was used to assess the quality of the included studies (17). The scale consists of 11 items, and 1 point is given to each item when the conditions are met. It mainly focuses on information source, inclusion and exclusion criteria, study period, selection of participants, evaluation of subjective outcomes/components, quality assurance, possible confounding variables, handling of missing data, participants' response rates and completeness of data collection. According to the total score, the studies were divided into low-(0–3), medium-(4–7) and high-quality (8–11) groups. EndNote (version X9) was used to manage the articles and citations.

Statistical Analysis

We first extracted the individual VSTs from the published articles and found that the distribution type of the VST was approximately in accordance with the log-normal distribution by using P-P plots (**Supplementary Figure 1**). Then, we used the method developed by McAloon C (18) to transform the original VST data to make the data obey a normal distribution. We used random-effects model to perform the meta-analysis due to the high heterogeneity. Finally, we used the method developed by McAloon C (18) to back-transform the point estimates and their 95% confidence intervals (CIs). The *I*-squared (I^2) statistic was used to evaluate the heterogeneity among the studies. Meta-regression was used to quantify the sources of heterogeneity and to explore the level of significance between subgroup comparisons. We did not assess publication bias because usual appraisal methods are uninformative when studies in the meta-analysis do not include a test of significance. The data cleaning and analysis were performed using the Microsoft Excel 2016 and R version 3.2.3.

RESULTS

A total of 17,284 records were retrieved through a database search. The titles and abstracts of 11,911 records were screened after deleting duplicates, and then 526 records were selected for full-text review. Finally, 35 full texts met the inclusion criteria (**Figure 1**). This study included 35 observational studies and involved 3,385 individuals infected with SARS-CoV-2, of which 2,955 were symptomatic infections and 338 were asymptomatic infections (**Table 1**). According to the scale, 32 studies were of high quality, 3 studies were of medium quality and none were of low quality (**Table 1** and **Supplementary Table 2**).

VSTs in SARS-CoV-2 Infections and Subgroup Results Based on Clinical Characteristics

The initial pooled estimate of the log-transformed VST in SARS-CoV-2 infections was 2.82 (95% CI: 2.69–2.96) (**Figure 2**). The pooled mean VST was 16.8 days (95% CI: 14.8–19.4) in SARS-CoV-2 infections. The mean VST of symptomatic infections was 19.7 days (95% CI: 17.2–22.7), which was significantly longer than that of asymptomatic infections (10.9 days, 95% CI: 8.3–14.3) ($P < 0.05$). The mean VST was 24.3 days (95% CI: 18.9–31.1) in severe patients and 22.8 days (95% CI: 16.4–32.0) in non-severe patients (**Figure 3**).

VSTs in SARS-CoV-2 Infections Subgrouped by Demographic Features

The mean VST was 19.4 days (95% CI: 9.5–39.4) in females and 11.9 days (95% CI: 8.4–16.9) in males. The VST was significantly shorter in the infected children (9.9 days, 95% CI: 8.1–12.2) than in the infected adults (23.2 days, 95% CI: 19.0–28.4) ($P < 0.05$). The VST of persons with chronic diseases was 24.2 days (95% CI: 19.2–30.2), which was significantly longer than that of persons without chronic diseases (11.5 days, 95% CI: 5.3–25.0) ($P < 0.05$) (**Figure 3**).

VSTs in SARS-CoV-2 Infections Subgrouped by Treatments

In persons receiving corticosteroid treatment, the VST was 28.3 days (95% CI: 25.6–31.2), which was longer than that in those without corticosteroid treatment (16.2 days, 95% CI: 11.5–22.5). However, there was no statistically significant difference between them ($P = 0.06$). The VST was 17.6 days (95% CI: 13.4–22.2) in persons receiving antiviral therapy, 21.2 days (95% CI: 15.3–29.2) in persons receiving mono-antiviral therapy and 20.3 days (95% CI: 13.7–30.3) in persons receiving multi-antiviral therapy (**Figure 3**). Only one study reported the VSTs of 5 patients without antiviral therapy, and the result was 11.2 ± 5.2 days (33).

VSTs in SARS-CoV-2 Infections Subgrouped by Different Specimens

Most studies (63%) reported the VSTs in the URTS. Among the different specimens, the mean VST was 17.5 days (95% CI: 14.9–20.6) in the RTS and 17.5 days (95% CI: 14.6–21.0) in the URTS. Compared with the RTS, a longer VST was found in the stool specimens (30.3 days, 95% CI: 23.1–39.2) ($P < 0.05$) (**Figure 4**). No included study reported VSTs in LRTS or serum specimens.

Meta-Regression for Heterogeneity

The univariate meta-regression model indicated that the mean age ($R^2 = 35.28\%$, $P < 0.05$) and the proportion of the asymptomatic cases ($R^2 = 22.64\%$, $P < 0.05$) could partly explain the overall heterogeneity. By introducing these two variables into the multivariate meta-regression model, nearly half of

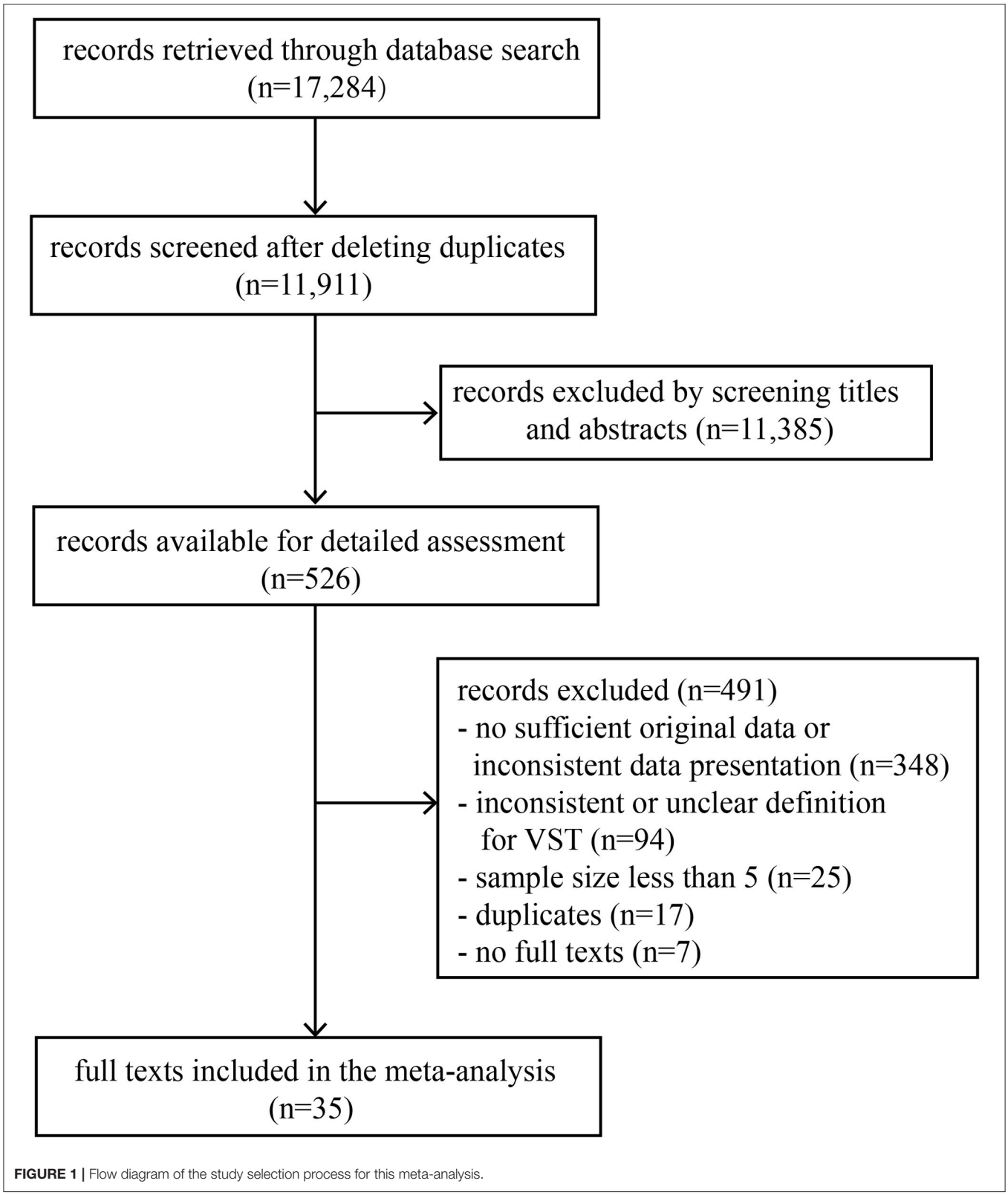


FIGURE 1 | Flow diagram of the study selection process for this meta-analysis.

TABLE 1 | Characteristics of included studies.

References	Country	Study design	Sample size, n	Age, years*	Female, n (%)	Infection status	Asymptomatic case#, n (%)	Specimen types	Study quality
Jiehao et al. (19)	China	Case series	10	6.5	6 (60)	sym	0 (0)	URTS	8 (High)
Xiong et al. (20)	China	Cohort study	51	/	21 (41)	asym	51 (100)	URTS	8 (High)
Yang et al. (21)	China	Case series	5	49	2 (40)	sym, asym	2 (40)	URTS	8 (High)
Noh et al. (22)	Korea	Cohort study	53	/	/	asym	53 (100)	/	8 (High)
Zheng et al. (23)	China	Cohort study	1,320	50	741 (56)	sym	0 (0)	URTS	8 (High)
Lee et al. (24)	Korea	Cohort study	89	22	55 (62)	asym	89 (100)	RTS	8 (High)
Song et al. (25)	China	Case series	16	8.5	6 (38)	sym, asym	8 (50)	URTS	8 (High)
Jun et al. (26)	China	Cross-sectional study	242	/	/	sym	0 (0)	URTS	8 (High)
Zhu et al. (27)	China	Case series	20	/	/	sym	0 (0)	URTS	8 (High)
Han et al. (28)	China	Cohort study	206	62.5	115 (56)	sym	0 (0)	URTS	8 (High)
Yan et al. (29)	China	Cross-sectional study	24	/	/	asym	24 (100)	RTS	8 (High)
Gong et al. (30)	China	Cohort study	34	/	12 (35)	sym	0 (0)	URTS	8 (High)
Warabi et al. (31)	Japan	Cross-sectional study	8	14	6 (75)	sym	0 (0)	URTS	8 (High)
Pan et al. (32)	China	Cross-sectional study	26	29.5	10 (38)	asym	26 (100)	RTS	7 (Medium)
Hua et al. (33)	China	Cross-sectional study	43	/	/	/	/	URTS	8 (High)
Cano et al. (34)	Switzerland	Cohort study	251	53	103 (41)	sym	0 (0)	URTS	7 (Medium)
Wu et al. (35)	China	Cross-sectional study	74	/	/	sym	0 (0)	URTS, stool	8 (High)
Otsubo et al. (36)	/	Case series	5	74	2 (40)	sym	0 (0)	URTS	7 (Medium)
Tan et al. (37)	China	Case series	12	34.5	3 (25)	asym	12 (100)	URTS	8 (High)
Xiao et al. (38)	China	Cohort study	63	/	/	sym, asym	19 (30)	/	8 (High)
Yao et al. (39)	China	Case series	5	47	3 (60)	sym, asym	1 (20)	URTS	8 (High)
Liu et al. (40)	China	Cohort study	53	8	19 (36)	asym	53 (100)	URTS	8 (High)
Shi et al. (41)	China	Cross-sectional study	33	41	14 (42)	sym	0 (0)	URTS	8 (High)
Li et al. (42)	China	Cohort study	46	45.6	25 (54)	sym	0 (0)	/	8 (High)
Jiang et al. (43)	China	Cross-sectional study	24	37	10 (42)	sym	0 (0)	/	8 (High)
Gong et al. (44)	China	Cross-sectional study	179	57.4	90 (50)	sym	0 (0)	URTS	8 (High)
Zhao et al. (45)	China	Cohort study	63	/	32 (51)	sym	0 (0)	/	8 (High)
Zhang et al. (46)	China	Cross-sectional study	30	/	/	sym	0 (0)	RTS, stool	8 (High)
Xu et al. (47)	China	Cohort study	59	49.3	31 (53)	sym	0 (0)	URTS	8 (High)
Xie et al. (48)	China	Cross-sectional study	49	49.4	24 (49)	/	/	/	8 (High)
Sun et al. (49)	China	Cross-sectional study	46	/	/	sym	0 (0)	RTS	8 (High)
Ren et al. (50)	China	Cross-sectional study	89	/	/	sym	0 (0)	RTS	8 (High)
Ran et al. (51)	China	Cross-sectional study	28	59.4	9 (32)	sym	0 (0)	RTS	8 (High)
Liu et al. (53)	China	Cross-sectional study	41	68	21 (51)	sym	0 (0)	URTS	8 (High)
Li et al. (54)	China	Cohort study	88	46	34 (39)	sym	0 (0)	URTS	8 (High)

sym, symptomatic infection; asym, asymptomatic infection; RTS, respiratory tract specimen; URTS, upper respiratory tract specimen.
**: Median or mean; #: Asymptomatic cases with VST of SARS-CoV-2; /: Unreported or unclassified or incalculable.*

the heterogeneity could be explained (R^2= 44.18%, $P < 0.05$) (**Supplementary Table 3**).

DISCUSSION

We performed a meta-analysis to clarify the characteristics of VSTs in SARS-CoV-2 infections, which was important for determining hospital discharge, discontinuation of quarantine and the effect of antiviral treatment for COVID-19. Compared with the meta-analysis conducted by Muge Cevik (15), our study not only estimated the VSTs in different specimens but also summarized the VSTs in SARS-CoV-2 infections based on different demographic features, clinical characteristics and treatments.

Previous studies have shown that the basic reproduction number (R0) of SARS-CoV-2 is between 2 and 6.7, which indicates that SARS-CoV-2 is more infectious than SARS-CoV-1 and MERS-CoV (55–57). In our study, we found that the mean VST of SARS-CoV-2 was 16.8 days (95% CI: 14.8–19.4), which was between that of SARS-CoV-1 (21.0 days) and MERS-CoV (13.2 days) (58, 59). In addition to the VST, the viral load released is also important to evaluate the transmissibility. Some studies

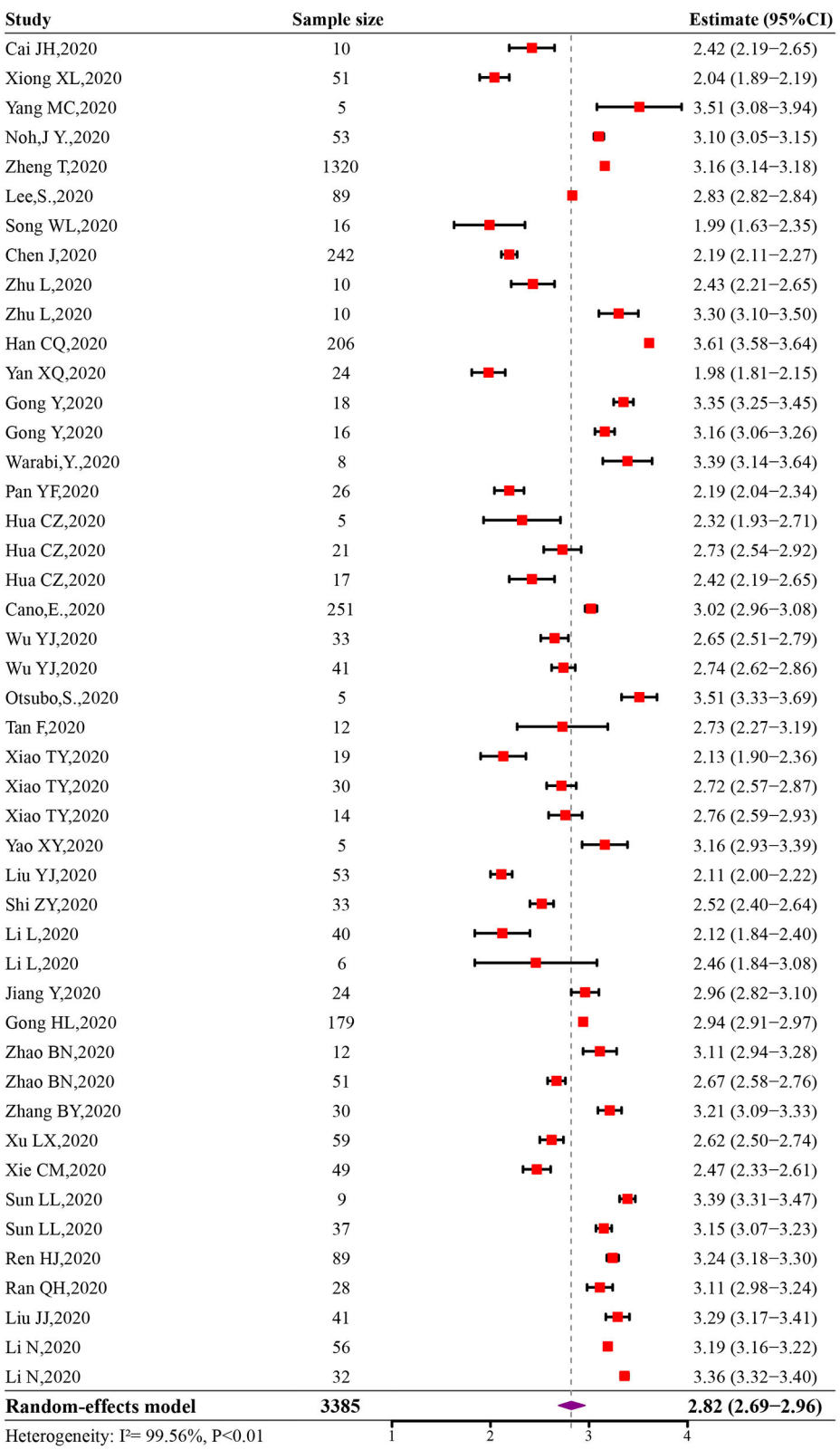


FIGURE 2 | Forest plot of meta-analysis of log-transformed VST in SARS-CoV-2 infections.

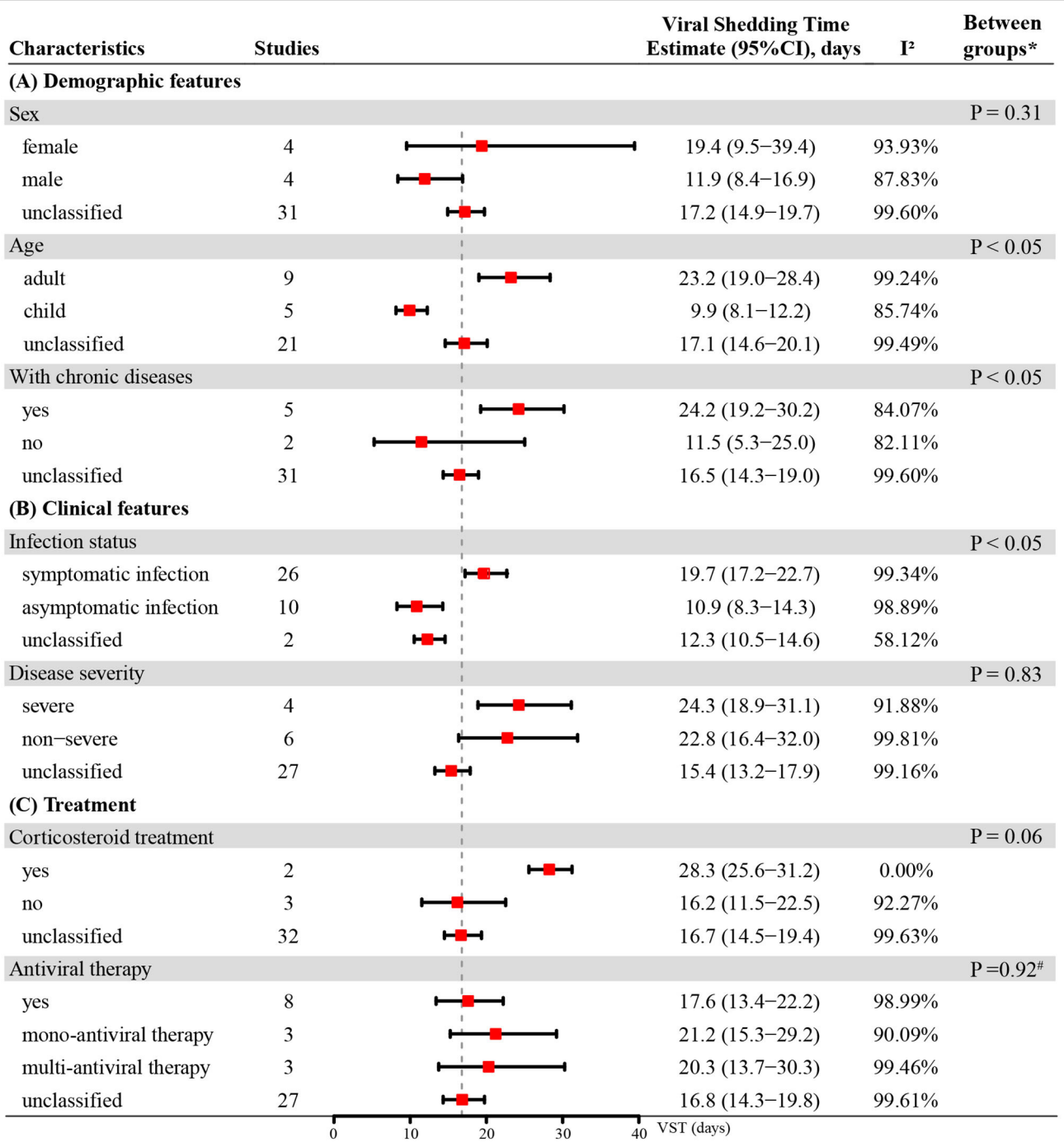


FIGURE 3 | The VST in SARS-CoV-2 infections based on different demographic features, clinical features and treatments. * Unclassified groups were not included in the *P*-values calculation for the subgroup comparisons. #*P*-value for comparison between group with antiviral mono-therapy and group with antiviral muti-therapy.

have found that the viral load of SARS-CoV-2 is highest during the 1st week after symptom onset and subsequently declines with time (60–62). Based on the above analysis, from the perspective of epidemic prevention and control, strict precautions should be taken throughout the disease course, especially within 1 week after the onset of the disease.

The duration of viral shedding is mainly related to the host immune status (63). Persons with chronic diseases always have relatively low immunity, which might lead to longer viral shedding. In our study, we found that the VST of symptomatic infections was longer than that of asymptomatic infections. One reason is that virus clearance in asymptomatic individuals is

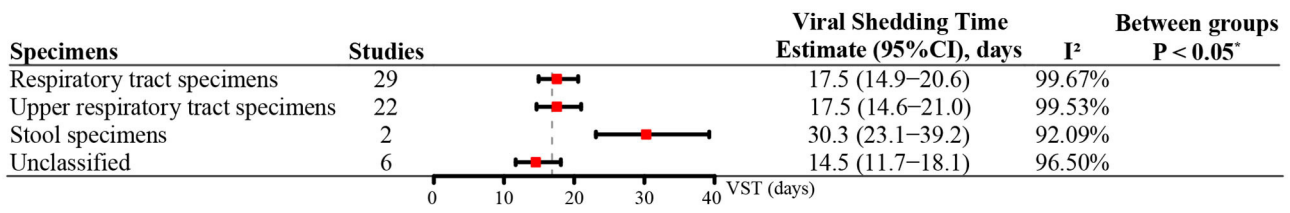


FIGURE 4 | The VST in SARS-CoV-2 infections based on different specimens. **P*-value for comparison between respiratory tract specimens and stool specimens.

indeed faster than that in symptomatic cases (38, 52). Another reason was that the VST for asymptomatic infections was calculated from the first positive PCR results and depended mainly on close contact tracking investigations. These individuals might have begun viral shedding before the first positive PCR results, and were ignored due to the absence of clinical features. A higher proportion of asymptomatic infections and milder clinical symptoms were found in infected children compared with infected adults (64, 65), which might explain the shorter VST of children.

The VST is an important parameter for evaluating the effect of antiviral treatment for infectious diseases. Until now, there have been no specific antiviral drugs for COVID-19, and inhibiting the cytokine storm has been an important treatment for patients with severe COVID-19. Corticosteroids are used because of their rapid, powerful anti-inflammatory effects. In our study, we found that the patients who received corticosteroid treatment had longer VSTs, although no statistically significant difference was found. This phenomenon was also found in severe SARS and MERS, where high-dose corticosteroids could cause prolonged viral clearance, secondary infection and long-term complications (66). Although corticosteroids can inhibit lung inflammation and alleviate possible immune-mediated pulmonary damage, it can also inhibit the systemic immune response dominated by T cell response, resulting in the delayed virus clearance (67). This finding alerted us that high-dose corticosteroids might prolong VSTs in SARS-CoV-2 infections and that appropriate doses of corticosteroids should be used after weighing the advantages and disadvantages according to the patients' condition.

The VST is also an important parameter for determining hospital discharge and discontinuation of quarantine. Two consecutive negative PCR results of RTS are one of the current criteria for hospital discharge or discontinuation of quarantine in China (68). The overexpression of ACE-2 in the gastrointestinal (GI) epithelial cells suggested the replication and shedding of SARS-CoV-2 in GI tract (69). Similar to SARS-CoV-1 (59), the VST of SARS-CoV-2 in stool specimens was longer than that in RTS. One study suggested that the VST in stool specimens could be prolonged by 5 weeks after SARS-CoV-2 had turned negative in RTS (35). Given that, the negative PCR results in RTS might not guarantee that patients no longer shed virus. Recently, several incidents of cold chain food polluted by SARS-CoV-2 have caused widespread concern by indicating that the virus could indeed infect individuals by polluting the environment. Considering the potential risk of oral-fecal transmission (70) and the long VST in stool specimens, more comprehensive protective measures should be taken for high-risk groups of oral-fecal transmission, such as GI endoscopy staff (2, 71), and stool or anal swabs collection and testing staff.

Our results might provide scientific support for the formulation of antiviral treatment and criteria for hospital discharge and discontinuation of quarantine for COVID-19, and help identify which patients need more attention and more effective preventive measures. Based on the mean VST of SARS-CoV-2 infections, hospitals could estimate the number of individuals with COVID-19 who can be admitted in a period of time, and reasonably allocate medical resources, such as the number of beds and medical staff.

This study has several limitations. The mean age, disease severity, treatment regimens, underlying diseases and infection status of individuals infected with SARS-CoV-2 varied in the included studies, which might cause high statistical heterogeneity. In the multivariate meta-regression model, nearly half of the heterogeneity could be explained by mean age and the proportion of the asymptomatic cases ($R^2 = 44.18\%$, $P < 0.05$). In some subgroup analyses, the number of included studies was small and most were case series with limited sample sizes, which might make the effect size of some outcomes insufficient. For example, the pooled mean VST in the stool specimens was based on estimates obtained in only two studies. More studies on the VST of SARS-CoV-2 are needed to provide further evidence. It would be better to incorporate as many studies as possible to obtain sufficient subgroup data and to ensure the homogeneity of the studies. Furthermore, the day of symptom onset for symptomatic infections depended on subjective memories and the day of the first positive RT-PCR results for asymptomatic infections relied mainly on close contact tracking investigations. If the individuals' recall was incorrect or close contact tracking investigations were not timely, these would cause the obtained VSTs to deviate from the real values.

CONCLUSIONS

This study provided a comprehensive overview of VSTs in SARS-CoV-2 infections, which was important for determining hospital discharge, discontinuation of quarantine and the effect of antiviral treatment for COVID-19. The pooled mean VST was 16.8 days (95% CI: 14.8–19.4) in SARS-CoV-2 infections. Due to the high infectivity of SARS-CoV-2, strict precautions should be taken to reduce the risk of disease transmission,

especially for adults, persons with chronic diseases, symptomatic infections and persons with positive RT-PCR results in stool specimens, in whom longer VSTs were found. Given that high-dose corticosteroids could alleviate possible immune-mediated pulmonary damage but might prolong VSTs in SARS-CoV-2 infections, corticosteroids should be used with caution after analyzing the risk of prolonged VST with reducing the disease severity.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

SY, LJL, and JW designed the study and revised the manuscript. DY and XZ independently performed the literature identification and uncertainties were consulted by SY to reach a consensus. DY, XZ, CC, DJ, XL, YZ, CH, YZ, and ZG extracted data. CD, LC, LL, and XF rechecked the data. DY carried out the data analysis. DY and XZ interpreted data and wrote the manuscript. All authors have read and approved the final version of the manuscript for submission.

FUNDING

This study was supported by grants from the National Natural Science Foundation of China (Grant Nos: 81672005, U1611264, and 81001271), the Mega-Project of National Science and Technology for the 12th and 13th Five-Year Plan of China (Grant Nos: 2018ZX10715-014-002 and 2014ZX10004008).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.652842/full#supplementary-material

REFERENCES

1. Mann R, Perisetti A, Gajendran M, Gandhi Z, Umapathy C, Goyal H. Clinical characteristics, diagnosis, and treatment of major coronavirus outbreaks. *Front Med.* (2020) 7:766. doi: 10.3389/fmed.2020.581521
2. Perisetti A, Gajendran M, Boregowda U, Bansal P, Goyal H. COVID-19 and gastrointestinal endoscopies: current insights and emergent strategies. *Dig Endosc.* (2020) 32:715–22. doi: 10.1111/den.13693
3. World Coronavirus Death. *Coronavirus Death Toll and Trends –Worldometer*. (2020). Available online at: https://www.worldometers.info/coronavirus (accessed February 4, 2021).
4. Perisetti A, Gajendran M, Mann R, Elhanafi S, Goyal H. COVID-19 extrapulmonary illness - special gastrointestinal and hepatic considerations. *Dis Mon.* (2020) 66:101064. doi: 10.1016/j.disamonth.2020.101064
5. Johnson KD, Harris C, Cain JK, Hummer C, Goyal H, Perisetti A. Pulmonary and extra-pulmonary clinical manifestations of COVID-19. *Front Med.* (2020) 7:526. doi: 10.3389/fmed.2020.00526
6. Aziz M, Goyal H, Haghbin H, Lee-Smith WM, Gajendran M, Perisetti A. The association of "loss of smell" to COVID-19: a systematic review and meta-analysis. *Am J Med Sci.* (2020) 361:216–25. doi: 10.1016/j.amjms.2020.09.017
7. Goyal H, Sachdeva S, Perisetti A, Mann R, Inamdar S, Tharian B. Hyperlipasemia and potential pancreatic injury patterns in COVID-19: a marker of severity or innocent bystander? *Gastroenterology.* (2020) 160:946–8.e2. doi: 10.1053/j.gastro.2020.10.037
8. Tan L, Kang X, Zhang B, Zheng S, Liu B, Yu T, et al. A special case of COVID-19 with long duration of viral shedding for 49 days. *medRxiv.* (2020). doi: 10.1101/2020.03.22.20040071
9. Yang JR, Deng DT, Wu N, Yang B, Li HJ, Pan XB. Persistent viral RNA positivity during the recovery period of a patient with SARS-CoV-2 infection. *J Med Virol.* (2020) 92:1681–3. doi: 10.1002/jmv.25940
10. Li Q, Zheng XS, Shen XR, Si HR, Wang X, Wang Q, et al. Prolonged shedding of severe acute respiratory syndrome coronavirus 2 in patients with COVID-19. *Emerg Microbes Infect.* (2020) 9:2571–7. doi: 10.1080/22221751.2020.1852058
11. Xing YH, Ni W, Wu Q, Li WJ, Li GJ, Wang WD, et al. Prolonged viral shedding in feces of pediatric patients with coronavirus disease 2019. *J Microbiol Immunol Infect.* (2020) 53:473–80. doi: 10.1016/j.jmii.2020.03.021
12. de Sousa R, Reusken C, Koopmans M. MERS coronavirus: data gaps for laboratory preparedness. *J Clin Virol.* (2014) 59:4–11. doi: 10.1016/j.jcv.2013.10.030
13. Shi D, Wu W, Wang Q, Xu K, Xie J, Wu J, et al. Clinical characteristics and factors associated with long-term viral excretion in patients with severe acute respiratory syndrome coronavirus 2 infection: a single-center 28-day study. *J Infect Dis.* (2020) 222:910–8. doi: 10.1093/infdis/jiaa388
14. Shen Y, Zheng F, Sun D, Ling Y, Chen J, Li F, et al. Epidemiology and clinical course of COVID-19 in Shanghai, China. *Emerg Microbes Infect.* (2020) 9:1537–45. doi: 10.1080/22221751.2020.1787103
15. Cevik M, Tate M, Lloyd O, Maraolo AE, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. *Lancet Microbe.* (2020) 2:e13–22. doi: 10.1016/S2666-5247(20)30172-5
16. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med.* (2015) 162:777–84. doi: 10.7326/m14-2385
17. Meyers D. Introduction from the agency for healthcare research and quality. *J Am Board Fam Med.* (2012) 25(Suppl 1): S1. doi: 10.3122/jabfm.2012.02.120023
18. McAloon C, Collins Á, Hunt K, Barber A, Byrne AW, Butler F, et al. Incubation period of COVID-19: a rapid systematic review and meta-analysis of observational research. *BMJ Open.* (2020) 10:e039652. doi: 10.1136/bmjopen-2020-039652
19. Jiehao C, Jin X, Daojiong L, Zhi Y, Lei X, Zhenghai Q, et al. A case series of children with 2019 novel coronavirus infection: clinical and epidemiological features. *Clin infect Dis.* (2020) 71:1547–51. doi: 10.1093/cid/ciaa198
20. Xiong X, Chua GT, Chi S, Kwan MYW, Sang Wong WH, Zhou A, et al. A comparison between Chinese children infected with coronavirus disease-2019 and with severe acute respiratory syndrome 2003. *J Pediatr.* (2020) 224:30–6. doi: 10.1016/j.jpeds.2020.06.041
21. Yang MC, Hung PP, Wu YK, Peng MY, Chao YC, Su WL. A three-generation family cluster with COVID-19 infection: should quarantine be prolonged? *Public Health.* (2020) 185:31–3. doi: 10.1016/j.puhe.2020.05.043
22. Noh JY, Yoon JG, Seong H, Choi WS, Sohn JW, Cheong HJ, et al. Asymptomatic infection and atypical manifestations of COVID-19: Comparison of viral shedding duration. *J Infect.* (2020) 81:816–46. doi: 10.1016/j.jinf.2020.05.035
23. Zheng T, Yang C, Wang H-Y, Chen X, Yu L, Wu Z-L, et al. Clinical characteristics and outcomes of COVID-19 patients with gastrointestinal symptoms admitted to Jianghan Fangcang Shelter Hospital in Wuhan, China. *J Med Virol.* (2020) 92:2735–41. doi: 10.1002/jmv.26146

24. Lee S, Kim T, Lee E, Lee C, Kim H, Rhee H, et al. Clinical course and molecular viral shedding among asymptomatic and symptomatic patients with SARS-CoV-2 infection in a community treatment center in the Republic of Korea. *JAMA Inter Med.* (2020) 180:1–6. doi: 10.1001/jamainternmed.2020.3862
25. Song W, Li J, Zou N, Guan W, Pan J, Xu W. Clinical features of pediatric patients with coronavirus disease (COVID-19). *J Clin Virol.* (2020) 127:104377. doi: 10.1016/j.jcv.2020.104377
26. Jun C, Tangkai Q, Li L, Yun L, Zhiping Q, Tao L, et al. Clinical progression of patients with COVID-19 in Shanghai, China. *J Infect.* (2020) 80:e1–6. doi: 10.1016/j.jinf.2020.03.004
27. Zhu L, Gong N, Liu B, Lu X, Chen D, Chen S, et al. Coronavirus disease 2019 pneumonia in immunosuppressed renal transplant recipients: a summary of 10 confirmed cases in Wuhan, China. *Euro Urol.* (2020) 77:748–54. doi: 10.1016/j.eururo.2020.03.039
28. Han C, Duan C, Zhang S, Spiegel B, Shi H, Wang W, et al. Digestive symptoms in COVID-19 patients with mild disease severity: clinical presentation, stool viral RNA testing, and outcomes. *Am J Gastroenterol.* (2020) 115:916–23. doi: 10.14309/ajg.0000000000000664
29. Yan X, Han X, Fan Y, Fang Z, Long D, Zhu Y. Duration of SARS-CoV-2 viral RNA in asymptomatic carriers. *Crit Care.* (2020) 24:245. doi: 10.1186/s13054-020-02952-0
30. Gong Y, Guan L, Jin Z, Chen S, Xiang G, Gao B. Effects of methylprednisolone use on viral genomic nucleic acid negative conversion and CT imaging lesion absorption in COVID-19 patients under 50 years old. *J Med Virol.* (2020) 92:2551–5. doi: 10.1002/jmv.26052
31. Warabi Y, Tobisawa S, Kawazoe T, Murayama A, Norioka R, Morishima R, et al. Effects of oral care on prolonged viral shedding in coronavirus disease 2019 (COVID-19). *Special Care Dentistr.* (2020) 40:470–4. doi: 10.1111/scd.12498
32. Pan Y, Yu X, Du X, Li Q, Li X, Qin T, et al. Epidemiological and clinical characteristics of 26 asymptomatic severe acute respiratory syndrome coronavirus 2 carriers. *J Infect Dis.* (2020) 221:1940–7. doi: 10.1093/infdis/jiaa205
33. Hua CZ, Miao ZP, Zheng JS, Huang Q, Sun QF, Lu HP, et al. Epidemiological features and viral shedding in children with SARS-CoV-2 infection. *J Med Virol.* (2020) 92:2804–12. doi: 10.1002/jmv.26180
34. Cano E, Corsini Campioli C, O'Horo JC. Nasopharyngeal SARS-CoV-2 viral RNA shedding in patients with diabetes mellitus. *Endocrine.* (2020) 71:26–7. doi: 10.1007/s12020-020-02516-w
35. Wu Y, Guo C, Tang L, Hong Z, Zhou J, Dong X, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *Lancet Gastroenterol Hepatol.* (2020) 5:434–5. doi: 10.1016/s2468-1253(20)30083-2
36. Otsubo S, Aoyama Y, Kinoshita K, Goto T, Otsubo Y, Kamano D, et al. Prolonged shedding of SARS-CoV-2 in COVID-19 infected hemodialysis patients. *Therap Apher Dial.* (2020). doi: 10.1111/1744-9987.13566
37. Tan F, Wang K, Liu J, Liu D, Luo J, Zhou R. Viral transmission and clinical features in asymptomatic carriers of SARS-CoV-2 in Wuhan, China. *Front Med.* (2020) 7:547. doi: 10.3389/fmed.2020.00547
38. Xiao T, Wang Y, Yuan J, Ye H, Wei L, Liao X, et al. Early viral clearance and antibody kinetics of COVID-19 among asymptomatic carriers. *medRxiv.* (2020) 2020.04.28.20083139. doi: 10.1101/2020.04.28.20083139
39. Yao X, Zhao X, Wang M, Xu W, Bai H, Ai X. Familial clustering infection caused by asymptomatic COVID-19 (in Chinese). *Int J Respi.* (2020) 40:982–7. doi: 10.3760/cma.j.cn131368-20200318-00175
40. Liu YJ, Chen P, Liu ZS, Li Y, Du H, Xu JL. Clinical features of asymptomatic or subclinical COVID-19 in children (in Chinese). *Zhongguo Dang dai er ke za zhi.* (2020) 22:578–82. doi: 10.7499/j.issn.1008-8830.2004088
41. Shi Z, He Y, Yang M, Duan M, Wang Y, Lai M, et al. Influencing factors of negative conversion time of viral nucleic acid of nasopharyngeal swabs in patients with novel coronavirus infected pneumonia (in Chinese). *Pract J Clin Med.* (2020) 17:45–8. Available online at: http://www.wanfangdata.com.cn/details/detail.do?_type=perio&id=syyylczz202002015
42. Li l, Yang H, Gou C, Wang X, Luo X, Zhang J, et al. Traditional Chinese medicine characteristics of 46 patients with COVID-19 (in Chinese). *J Capital Med Univ.* (2020) 41:155–60. doi: 10.3969/j.issn.1006-7795.2020.02.002
43. Jiang Y, Wang H, Si G, Deng L, Ou C, Rong X. Clinical ananlysis of corona virus disease 2019: a report of 24 cases (in Chinese). *J Chongqing Med Univ.* (2020) 45:968–70. doi: 10.13406/j.cnki.cyxb.002453
44. Gong H, Huang H, Zhou X, Luo S, Zhang Z, Zhang S, et al. Related factors of the conversion time of virus nucleic acid turning negative in patients with coronavirus disease 2019 and its effect on prognosis (in Chinese). *Herald Med.* (2020) 39:811–4. doi: 10.3870/j.issn.1004-0781.2020.06.015
45. Zhao B, Liu D, Liu Y, Lan L, Du Q, Chen H, et al. Differences in laboratory indicators and prognosis between COVID-19 patients with or without diabetes mellitus (in Chinese). *Sichuan Med J.* (2020) 41:913–7. doi: 10.16252/j.cnki.issn1004-0501-2020.09.005
46. Zhang B, Zhang Z, Li Z, Chi Q, Zheng J, Dai X. Retrospective analysis of viral nucleic acid test results of 116 fecal samples from COVID-19 patients (in Chinese). *Jinagsu Med J.* (2020) 46:571–2. doi: 10.19460/j.cnki.0253-3685.2020.06.009
47. Xu L, Peng P, Li S, Wu P, Han J, Mo X. Clinical characteristics of 59 cases of COVID-19 in Guangzhou (in Chinese). *China Trop Med.* (2020) 20:871–4. doi: 10.13604/j.cnki.46-1064/r.2020.09.17
48. Xie C, Qin P, Zeng X, Deng H, Cheng S, Xie Y. Dynamic changes of IgM and IgG in confirmed COVID-19 cases: detection results analysis (in Chinese). *Chin J Publ Heal.* (2020) 36:1396–8. doi: 10.11847/zgggws1130146
49. Sun L, Li X, Li S, Niu C, Pan S, Wang Q, et al. Nucleic acid detection analysis of 71 cases of COVID-19 with biological samples of diferent disease course(in Chinese). *China Trop Med.* (2020) 20:763–6. doi: 10.13604/j.cnki.46-1064/r.2020.08.16
50. Ren H, Lei H, Sun G, Li H, Bai J, Tang L. Clinical characteristics of 2019 novel coronavirus pneumonia in a mobile cabin hospital in Wuhan: analysis of 94 cases (in Chinese). *Chinese J Hygiene Rescue.* (2020) 6:209–13. doi: 10.3877/cma.j.issn.2095-9133.2020.04.003
51. Ran Q, Chen H, Zhang L, Zhong Y. Analysis of Factors influencing viral shedding time in severe and critical COVID-19 patients (in Chinese). *Adv Clin Med.* (2020) 10:1717–24. doi: 10.12677/acm.2020.108258
52. Lu Y, Li Y, Deng W, Liu M, He Y, Huang L, et al. Symptomatic infection is associated with prolonged duration of viral shedding in mild coronavirus disease 2019: a retrospective study of 110 children in Wuhan. *Pediatr Infect Dis J.* (2020) 39:e95–9. doi: 10.1097/inf.0000000000002729
53. Liu J, Liu X, Yang M, Xiao X, Cen C. Influencing factors for positive duration of viral nucleic acid in patients with severe coronavirus disease 2019 (in Chinese). *Acad J Second Military Med Univ.* (2020) 41:966–9. doi: 10.16781/j.0258-879x.2020.09.0966
54. Li N, Xie T, Wei X, Yi S, Cao Y, Jiang S, et al. Chloroquine phosphate accelerates the conversion of nucleic acid to negative in 88 common COVID?19 patients (in Chinese). *J Pract Med.* (2020) 36:2759–62. doi: 10.3969/j.issn.1006-5725.2020.20.003
55. Tang B, Wang X, Li Q, Bragazzi NL, Tang S, Xiao Y, et al. Estimation of the transmission risk of the 2019-nCoV and its implication for public health interventions. *J Clin Med.* (2020) 9:462. doi: 10.3390/jcm9020462
56. Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *Lancet.* (2020) 395:689–97. doi: 10.1016/s0140-6736(20)30260-9
57. Zhao S, Lin Q, Ran J, Musa SS, Yang G, Wang W, et al. Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: a data-driven analysis in the early phase of the outbreak. *Int J Infect Dis.* (2020) 92:214–7. doi: 10.1016/j.ijid.2020.01.050
58. Al-Jasser FS, Nouh RM, Youssef RM. Epidemiology and predictors of survival of MERS-CoV infections in Riyadh region, 2014-2015. *J Infect Public Health.* (2019) 12:171–7. doi: 10.1016/j.jiph.2018.09.008
59. Liu W, Tang F, Fontanet A, Zhan L, Zhao QM, Zhang PH, et al. Long-term SARS coronavirus excretion from patient cohort, China. *Emerg Infect Dis.* (2004) 10:1841–3. doi: 10.3201/eid1010.040297
60. He X, Lau EHY, Wu P, Deng X, Wang J, Hao X, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med.* (2020) 26:672–5. doi: 10.1038/s41591-020-0869-5
61. To KK, Tsang OT, Leung WS, Tam AR, Wu TC, Lung DC, et al. Temporal profiles of viral load in posterior oropharyngeal saliva

samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis.* (2020) 20:565–74. doi: 10.1016/s1473-3099(20)30196-1
62. Wölfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Müller MA, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature.* (2020) 581:465–9. doi: 10.1038/s41586-020-2196-x
63. Hao S, Lian J, Lu Y, Jia H, Hu J, Yu G, et al. Decreased B cells on admission associated with prolonged Viral RNA shedding from the respiratory tract in coronavirus disease 2019: a case-control study. *J Infect Dis.* (2020) 222:367–71. doi: 10.1093/infdis/jiaa311
64. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the chinese center for disease control and prevention. *JAMA*. (2020) 323:1239–42. doi: 10.1001/jama.2020.2648
65. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, et al. SARS-CoV-2 infection in children. *N Engl J Med.* (2020) 382:1663–5. doi: 10.1056/NEJMc2005073
66. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. (2020) 395:473–5. doi: 10.1016/s0140-6736(20)30317-2
67. Lee N, Allen Chan KC, Hui DS, Ng EK, Wu A, Chiu RW, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. *J Clin Virol.* (2004) 31:304–9. doi: 10.1016/j.jcv.2004.07.006
68. National Health Commission of the People's Republic of China. *Diagnosis and Treatment for COVID-19 (Trial Version 8).* (2020). Available online at: http://www.nhc.gov.cn (accessed November 16, 2020).
69. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS Coronavirus. *J Virol.* (2020) 94:e00127-20. doi: 10.1128/jvi.00127-20
70. Islam MS, Rahman KM, Sun Y, Qureshi MO, Abdi I, Chughtai AA, et al. Current knowledge of COVID-19 and infection prevention and control strategies in healthcare settings: a global analysis. *Infect Control Hosp Epidemiol.* (2020) 41:1196–206. doi: 10.1017/ice.2020.237
71. Perisetti A, Goyal H, Sharma N. Gastrointestinal endoscopy in the Era of COVID-19. *Front Med.* (2020) 7:587602. doi: 10.3389/fmed.2020.587602

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

PLOS BIOLOGY

RESEARCH ARTICLE

Viral dynamics of acute SARS-CoV-2 infection and applications to diagnostic and public health strategies

Stephen M. Kissler[1☯], Joseph R. Fauver[2☯], Christina Mack[3,4☯], Scott W. Olesen[1], Caroline Tai[3], Kristin Y. Shiue[3,4], Chaney C. Kalinich[2], Sarah Jednak[5], Isabel M. Ott[2], Chantal B. F. Vogels[2], Jay Wohlgemuth[6], James Weisberger[7], John DiFiori[8,9], Deverick J. Anderson[10], Jimmie Mancell[11], David D. Ho[12], Nathan D. Grubaugh[2‡], Yonatan H. Grad[1‡*]

1 Department of Immunology and Infectious Diseases, Harvard T.H. Chan School of Public Health, Boston, Massachusetts, United States of America, **2** Department of Epidemiology of Microbial Diseases, Yale School of Public Health, New Haven, Connecticut, United States of America, **3** Real World Solutions, IQVIA, Durham, North Carolina, United States of America, **4** Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, United States of America, **5** Department of Health Management and Policy, University of Michigan School of Public Health, Ann Arbor, Michigan, United States of America, **6** Quest Diagnostics, San Juan Capistrano, California, United States of America, **7** Bioreference Laboratories, Elmwood Park, New Jersey, United States of America, **8** Hospital for Special Surgery, New York, New York, United States of America, **9** National Basketball Association, New York, New York, United States of America, **10** Duke Center for Antimicrobial Stewardship and Infection Prevention, Durham, North Carolina, United States of America, **11** Department of Medicine, University of Tennessee Health Science Center, Memphis, Tennessee, United States of America, **12** Aaron Diamond AIDS Research Center, Columbia University Vagelos College of Physicians and Surgeons, New York, New York, United States of America

☯ These authors contributed equally to this work.
‡ These authors are joint senior authors on this work.
* ygrad@hsph.harvard.edu

Citation: Kissler SM, Fauver JR, Mack C, Olesen SW, Tai C, Shiue KY, et al. (2021) Viral dynamics of acute SARS-CoV-2 infection and applications to diagnostic and public health strategies. PLoS Biol 19(7): e3001333. https://doi.org/10.1371/journal.pbio.3001333

Academic Editor: Steven Riley, Imperial College London, UNITED KINGDOM

Received: January 14, 2021

Accepted: June 21, 2021

Published: July 12, 2021

Data Availability Statement: Data are available at https://github.com/gradlab/CtTrajectories.

Funding: This study was funded by the NWO Rubicon 019.181EN.004 (CBFV), a clinical research agreement with the NBA and NBPA (NDG), the Huffman Family Donor Advised Fund (NDG), Fast Grant funding support from the Emergent Ventures at the Mercatus Center, George Mason University (NDG), and the Morris-Singer Fund for the Center for Communicable Disease Dynamics at the Harvard T.H. Chan School of Public Health (YHG).

Abstract

SARS-CoV-2 infections are characterized by viral proliferation and clearance phases and can be followed by low-level persistent viral RNA shedding. The dynamics of viral RNA concentration, particularly in the early stages of infection, can inform clinical measures and interventions such as test-based screening. We used prospective longitudinal quantitative reverse transcription PCR testing to measure the viral RNA trajectories for 68 individuals during the resumption of the 2019–2020 National Basketball Association season. For 46 individuals with acute infections, we inferred the peak viral concentration and the duration of the viral proliferation and clearance phases. According to our mathematical model, we found that viral RNA concentrations peaked an average of 3.3 days (95% credible interval [CI] 2.5, 4.2) after first possible detectability at a cycle threshold value of 22.3 (95% CI 20.5, 23.9). The viral clearance phase lasted longer for symptomatic individuals (10.9 days [95% CI 7.9, 14.4]) than for asymptomatic individuals (7.8 days [95% CI 6.1, 9.7]). A second test within 2 days after an initial positive PCR test substantially improves certainty about a patient's infection stage. The effective sensitivity of a test intended to identify infectious individuals declines substantially with test turnaround time. These findings indicate that SARS-CoV-2 viral concentrations peak rapidly regardless of symptoms. Sequential tests can help

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: I have read the journal's policy and the authors of this manuscript have the following competing interests: JW is an employee of Quest Diagnostics. JW is an employee of Bioreference Laboratories. NDG has a consulting agreement for Tempus and receives financial support from Tempus to develop SARS-CoV-2 diagnostic tests. SMK, SWO, and YHG have a consulting agreement with the NBA.

Abbreviations: CI, credible interval; Ct, cycle threshold; NBA, National Basketball Association; RT-qPCR, quantitative reverse transcription polymerase chain reaction.

reveal a patient's progress through infection stages. Frequent, rapid-turnaround testing is needed to effectively screen individuals before they become infectious.

Introduction

A critical strategy to curb the spread of SARS-CoV-2 is to rapidly identify and isolate infectious individuals. Because symptoms are an unreliable indicator of infectiousness and infections are frequently asymptomatic [1], testing is key to determining whether a person is infected and may be contagious. Real-time quantitative reverse transcription polymerase chain reaction (RT-qPCR) tests are the gold standard for detecting SARS-CoV-2 infection. Normally, these tests yield a binary positive/negative diagnosis based on detection of viral RNA. However, they can also quantify the viral titer via the cycle threshold (Ct). The Ct is the number of thermal cycles needed to amplify sampled viral RNA to a detectable level: the higher the sampled viral RNA concentration, the lower the Ct. This inverse correlation between Ct and viral concentration makes RT-qPCR tests far more valuable than a binary diagnostic, as they can be used to reveal a person's progress through key stages of infection [2], with the potential to assist clinical and public health decision-making. However, the dynamics of the Ct during the earliest stages of infection, when contagiousness is rapidly increasing, have been unclear, because diagnostic testing is usually performed after the onset of symptoms, when viral RNA concentration has peaked and already begun to decline, and is performed only once [3,4]. Without a clear picture of the course of SARS-CoV-2 viral concentrations across the full duration of acute infection, it has been impossible to specify key elements of testing algorithms such as the frequency of rapid at-home testing [5] that would be needed to reliably screen infectious individuals before they transmit infection. Here, we fill this gap by analyzing the prospective longitudinal SARS-CoV-2 RT-qPCR testing performed for players, staff, and vendors during the resumption of the 2019–2020 National Basketball Association (NBA) season.

Methods

Data collection

The study period began in teams' local cities from June 23 through July 9, 2020, and testing continued for all teams as they transitioned to Orlando, Florida, through September 7, 2020. A total of 68 individuals (90% male) were tested at least 5 times during the study period and recorded at least 1 positive test with Ct value < 40. Most consecutive tests (85%) were recorded within 1 day of each other, and fewer than 3% of the intervals between consecutive tests exceeded 4 days (S1 Fig). Many individuals were being tested daily as part of Orlando campus monitoring. Due to a lack of new infections among players and team staff after clearing quarantine in Orlando, all players and team staff included in the results predate the Orlando phase of the restarted season. A diagnosis of "acute" or "persistent" infection was abstracted from physician records. "Acute" denoted a likely new infection. "Persistent" indicated the presence of virus in a clinically recovered individual, likely due to infection that developed prior to the onset of the study. There were 46 acute infections; the remaining 22 individuals were assumed to be persistently shedding SARS-CoV-2 RNA due to a known infection that occurred prior to the study period [6]. This persistent RNA shedding can last for weeks after an acute infection and likely represents noninfectious viral RNA [7]. Of the individuals included in the study, 27 of the 46 with acute infections and 40 of the 68 overall were staff and vendors. The Ct values for all tests for the 68 individuals included in the analysis, with their designations of acute or

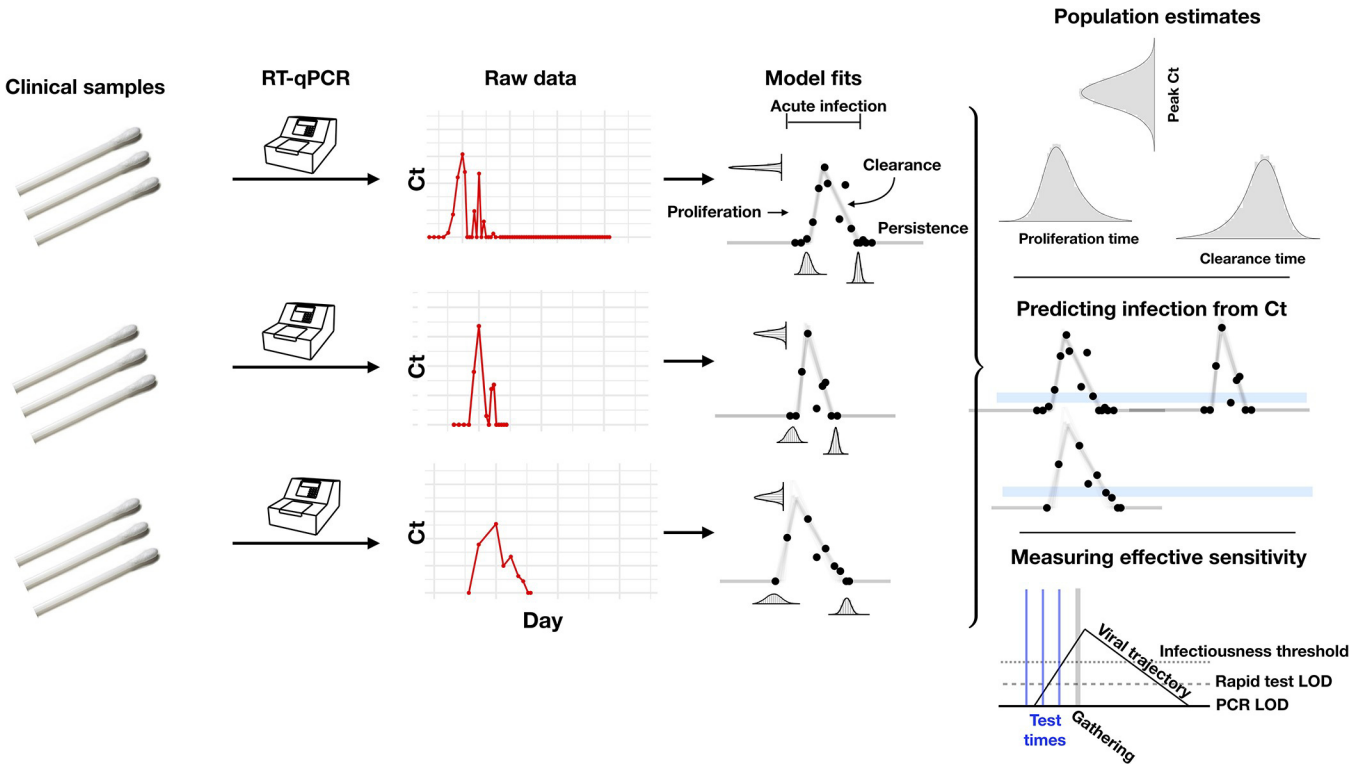


Fig 1. Illustration of the analysis pipeline. Combined anterior nares and oropharyngeal swabs were tested using a RT-qPCR assay to generate longitudinal Ct values ("Raw data"; red points) for each person. Using a statistical model (see S6 Fig for a schematic of the model), we estimated Ct trajectories consistent with the data, represented by the thin lines under the "Model fits" heading. These produced posterior probability distributions for the peak Ct value, the duration of the proliferation phase (first potential detectability of infection to peak Ct), and the duration of the clearance phase (peak Ct to resolution of acute infection) for each person. We estimated population means for these quantities (under the heading "Population estimates"). The model fits also allowed us to determine how frequently a given Ct value or pair of Ct values within a 5-unit window (blue bars, under the heading "Predicting infection from Ct") was associated with the proliferation phase, the clearance phase, or a persistent infection. Finally, the model fits allowed us to measure the "effective sensitivity" of a test for predicting future infectiousness. The schematic illustration titled "Measuring effective sensitivity" depicts the relationship between testing lags and the ability to detect infectious individuals at a gathering. The illustrated viral trajectory surpasses the infectiousness threshold (dotted line) at the time of the gathering (vertical grey bar), so unless this individual is screened by a pre-gathering test, he or she would attend the event while infectious. One day prior to the gathering, the individual's infection could be detected by either a rapid test or a PCR test. Two days prior to the event, the individual's infection could be detected by a PCR test but not by a rapid test. Three days prior to the event, neither test would detect the individual's infection. Ct, cycle threshold; LOD, limit of detection; RT-qPCR, quantitative reverse transcription polymerase chain reaction.

https://doi.org/10.1371/journal.pbio.3001333.g001

persistent infection, are depicted in S2–S5 Figs. A schematic diagram of the data collection and analysis pipeline is given in Fig 1.

Ethics

Residual de-identified viral transport media from anterior nares and oropharyngeal swabs collected from NBA players, staff, and vendors were obtained from Quest Diagnostics or BioReference Laboratories. In accordance with the guidelines of the Yale Human Investigation Committee, this work with de-identified samples was approved for research not involving human subjects by the Yale Institutional Review Board (HIC protocol #2000028599). This project was designated exempt by the Harvard Institutional Review Board (IRB20-1407).

Statistical analysis

Due to imperfect sampling, persistent viral shedding, and test uncertainty near the limit of detection, a straightforward analysis of the data would be insufficient to reveal the duration

and peak magnitude of the viral trajectory. Imperfect sampling would bias estimates of the peak viral concentration towards lower concentrations/higher Ct values since the moment of peak viral concentration is unlikely to be captured. Persistent shedding and test uncertainty would bias estimates of the trajectory duration towards longer durations of infection. To address these problems, we used a Bayesian statistical model to infer the peak Ct value and the durations of the proliferation and clearance stages for the 46 acute infections (Fig 1; S1 Text). We assumed that the viral concentration trajectories consisted of a proliferation phase, with exponential growth in viral RNA concentration, followed by a clearance phase, characterized by exponential decay in viral RNA concentration [8]. Since Ct values are roughly proportional to the negative logarithm of viral concentration [2], this corresponds to a linear decrease in Ct followed by a linear increase. We therefore constructed a piecewise linear regression model to estimate the peak Ct value, the time from infection onset to peak (i.e., the duration of the proliferation stage), and the time from peak to infection resolution (i.e., the duration of the clearance stage). This allowed us to separate the viral trajectories into the 3 distinct phases: proliferation (from the onset of detectability to the peak viral concentration, or t_o to t_p in S6 Fig), clearance (from the peak viral concentration to the resolution of acute infection, or t_p to t_r in S6 Fig), and persistence (lasting indefinitely after the resolution of acute infection, or after t_r in S6 Fig; see also Fig 1). Note that for the 46 individuals with acute infections, the persistence phase is identified using the viral trajectory model, whereas for the 22 other infections, the entire series of observations was classified as "persistent" due to clinical evidence of a probable infection prior to the start of the study period. We estimated the parameters of the regression model by fitting to the available data using a Hamiltonian Monte Carlo algorithm [9] yielding simulated draws from the Bayesian posterior distribution for each parameter. Full details on the fitting procedure are given in S1 Text. Code is available at https://github.com/gradlab/CtTrajectories [10].

Inferring stage of infection

Next, we determined whether individual or paired Ct values can reveal whether an individual is in the proliferation, clearance, or persistent stage of infection. To assess the predictive value of a single Ct value, we extracted all observed Ct values within a 5-unit window (e.g., between 30.0 and 34.9 Ct) and measured how frequently these values sat within the proliferation stage, the clearance stage, or the persistent stage. We measured these frequencies across 10,000 posterior parameter draws to account for the fact that Ct values near stage transitions (e.g., near the end of the clearance stage) could be assigned to different infection stages depending on the parameter values (see Fig 1, bottom right). We did this for 23 windows with midpoint spanning from Ct = 37.5 to Ct = 15.5 in increments of 1 Ct.

To calculate the probability that a Ct value sitting within a 5-unit window corresponded to an acute infection (i.e., either the proliferation or the clearance stage), we summed the proliferation and clearance frequencies for all samples within that window and divided by the total number of samples in the window. We similarly calculated the probability that a Ct sitting within the 5-unit window corresponded to just the proliferation phase.

To assess the information gained by conducting a second test within 2 days of an initial positive test, we restricted our attention to all samples that had a subsequent sample taken within 2 days. We repeated the above calculations for (a) consecutive tests with decreasing Ct and (b) consecutive tests with increasing Ct. That is, we measured the frequency with which a given Ct value sitting within a 5-unit window, followed by a second test with either a lower or a higher Ct, sat within with the proliferation, clearance, or persistence stages.

Measuring the effective sensitivity of screening tests

The sensitivity of a test is defined as the probability that the test correctly identifies an individual who is positive for some criterion of interest. For clinical diagnostic SARS-CoV-2 tests, the criterion of interest is current infection with SARS-CoV-2. Alternatively, a common goal is to predict infectiousness at some point in the future, as in the context of test-based screening prior to a social gathering. The "effective sensitivity" of a test in this context (i.e., its ability to predict future infectiousness) may differ substantially from its clinical sensitivity (i.e., its ability to detect current infection). A test's effective sensitivity depends on its inherent characteristics, such as its limit of detection and sampling error rate, as well as the viral dynamics of infected individuals.

To illustrate this, we estimated the effective sensitivity of (a) a test with a limit of detection of 40 Ct and a 1% sampling error probability (akin to RT-qPCR) and (b) a test with a limit of detection of 35 Ct and a 5% sampling error probability (akin to some rapid antigen tests). We measured the frequency with which such tests would successfully identify an individual who would be infectious at the time of a gathering when the test was administered between 0 and 3 days prior to the gathering, given viral trajectories informed by the longitudinal testing data (see schematic in Fig 1). To accomplish this, we drew 1,000 individual-level viral concentration trajectories from the fitted model, restricting to trajectories with peak viral concentration above a given infectiousness threshold (any samples with peak viral concentration below the infectiousness threshold would never be infectious and so would not factor into the sensitivity calculation). For the main analysis, we assumed that the infectiousness threshold was at 30 Ct [11]. In a supplemental analysis, we also assessed infectiousness thresholds of 35 and 20 Ct. We drew onset-of-detectability times (i.e., the onset of the proliferation stage) according to a random uniform distribution so that each person would have a Ct value exceeding the infectiousness threshold at the time of the gathering. Then, we calculated the fraction of trajectories that would be successfully identified using a test with (a) a limit of detection of 40 Ct and (b) a limit of detection of 35 Ct, administered between 0 and 3 days prior to the gathering. Full details are given in S1 Text and S7A Fig.

Next, we shifted attention from the individual to the gathering. We estimated the number of individuals who would be expected to arrive at a 1,000-person gathering while infectious given each testing strategy (40-Ct limit of detection with 1% false negative rate; 35-Ct limit of detection with 5% false negative rate) assuming a 2% prevalence of PCR-detectable infection in the population. To do so, we again drew 1,000 individual-level viral concentration trajectories from the fitted model and drew onset-of-detectability times according to a random uniform distribution from the range of possible times that would allow for the person to have detectable virus ($Ct < 40$) during the gathering. We counted the number of people who would have been infectious at the gathering (a) in the absence of testing and (b) given a test administered between 0 and 3 days prior to the gathering. As before, we assumed that the infectiousness threshold corresponded to a Ct value of 30 for the main analysis and considered infectiousness thresholds of 35 Ct and 20 Ct in a supplemental analysis. Full details are given in S1 Text and S7B Fig. To facilitate the exploration of different scenarios, we have generated an online tool (https://stephenkissler.shinyapps.io/shiny/) where users can input test and population characteristics and calculate the effective sensitivity and expected number of infectious individuals at a gathering.

Results

Of the 46 individuals with acute infections, 13 reported symptoms at the time of diagnosis; the timing of the onset of symptoms was not recorded. The median number of positive tests for

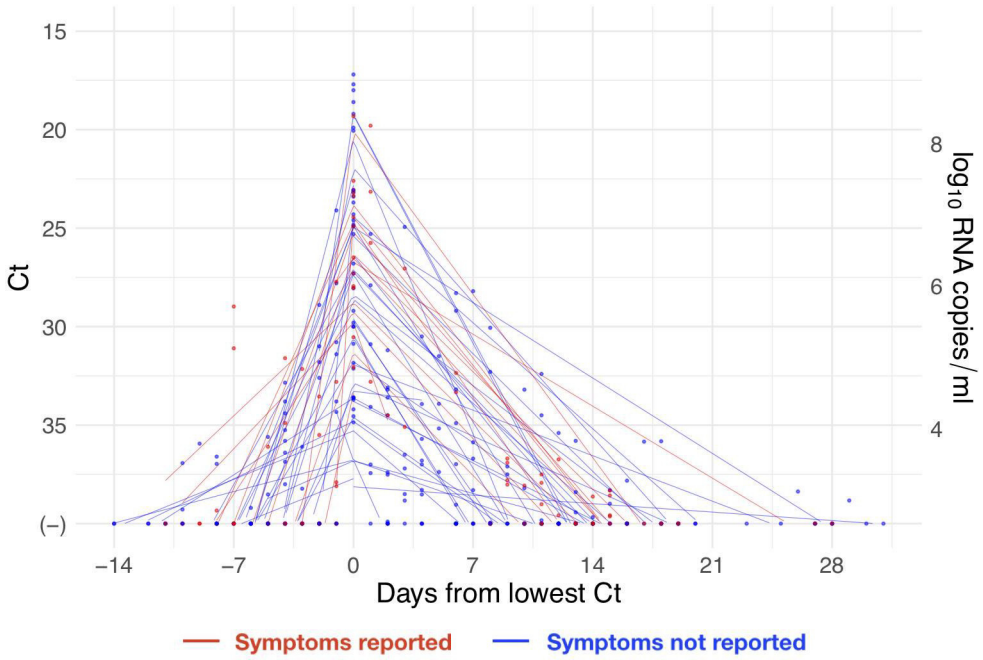


Fig 2. Reported cycle threshold (Ct) values with individual-level piecewise linear fits. Ct values (points) for the 46 acute infections aligned by the date when the minimum Ct was recorded for each individual. Lines depict the best-fit piecewise linear regression lines for each individual with breakpoint at day 0. Red points/lines represent individuals who reported symptoms, and blue points/lines represent individuals who did not report symptoms. Five positive tests were omitted that occurred >20 days prior to the individual's minimum Ct value, all of which had Ct > 35. The vertical axis on the right-hand side gives the conversion from Ct values to RNA concentration. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/figure_data/Fig2 [10].

https://doi.org/10.1371/journal.pbio.3001333.g002

the 46 individuals was 3 (IQR 2, 5). The minimum recorded Ct value across the 46 individuals had mean 26.4 (IQR 23.2, 30.4). The recorded Ct values for the acute infections with individual-level piecewise linear regressions are depicted in Fig 2.

Based on the viral trajectory model, the mean peak Ct value for symptomatic individuals was 22.3 (95% credible interval [CI] 19.3, 25.3), the mean duration of the proliferation phase was 3.4 days (95% CI 2.0, 4.8), and the mean duration of clearance was 10.9 days (95% CI 7.9, 14.4) (Fig 3). This compares with 22.3 Ct (95% CI 20.0, 24.4), 3.5 days (95% CI 2.5, 4.5), and 7.8 days (95% CI 6.1, 9.7), respectively, for individuals who did not report symptoms at the time of diagnosis (Fig 3). This yielded a slightly longer overall duration of acute infection for individuals who reported symptoms (14.3 days [95% CI 11.0, 17.7]) versus those who did not (11.2 days [95% CI 9.4, 13.4]). For all individuals, regardless of symptoms, the mean peak Ct value, proliferation duration, clearance duration, and duration of acute shedding were 22.3 Ct (95% CI 20.5, 23.9), 3.3 days (95% CI 2.5, 4.2), 8.5 days (95% CI 6.9, 10.1), and 11.7 days (95% CI 10.1, 13.6) (S8 Fig). A full list of the model-inferred viral trajectory parameters is reported in Table 1. There was a substantial amount of individual-level variation in the peak Ct value and the proliferation and clearance stage durations (S9–S14 Figs).

Using the full dataset of 68 individuals, we estimated the frequency with which a given Ct value was associated with an acute infection (i.e., the proliferation or clearance phase, but not the persistence phase) and, if so, the probability that it was associated with the proliferation stage alone. The probability of an acute infection increased rapidly with decreasing Ct (increasing viral load), with Ct < 30 virtually guaranteeing an acute infection in this dataset (Fig 4A). However, a single Ct value provided little information about whether an acute infection was in

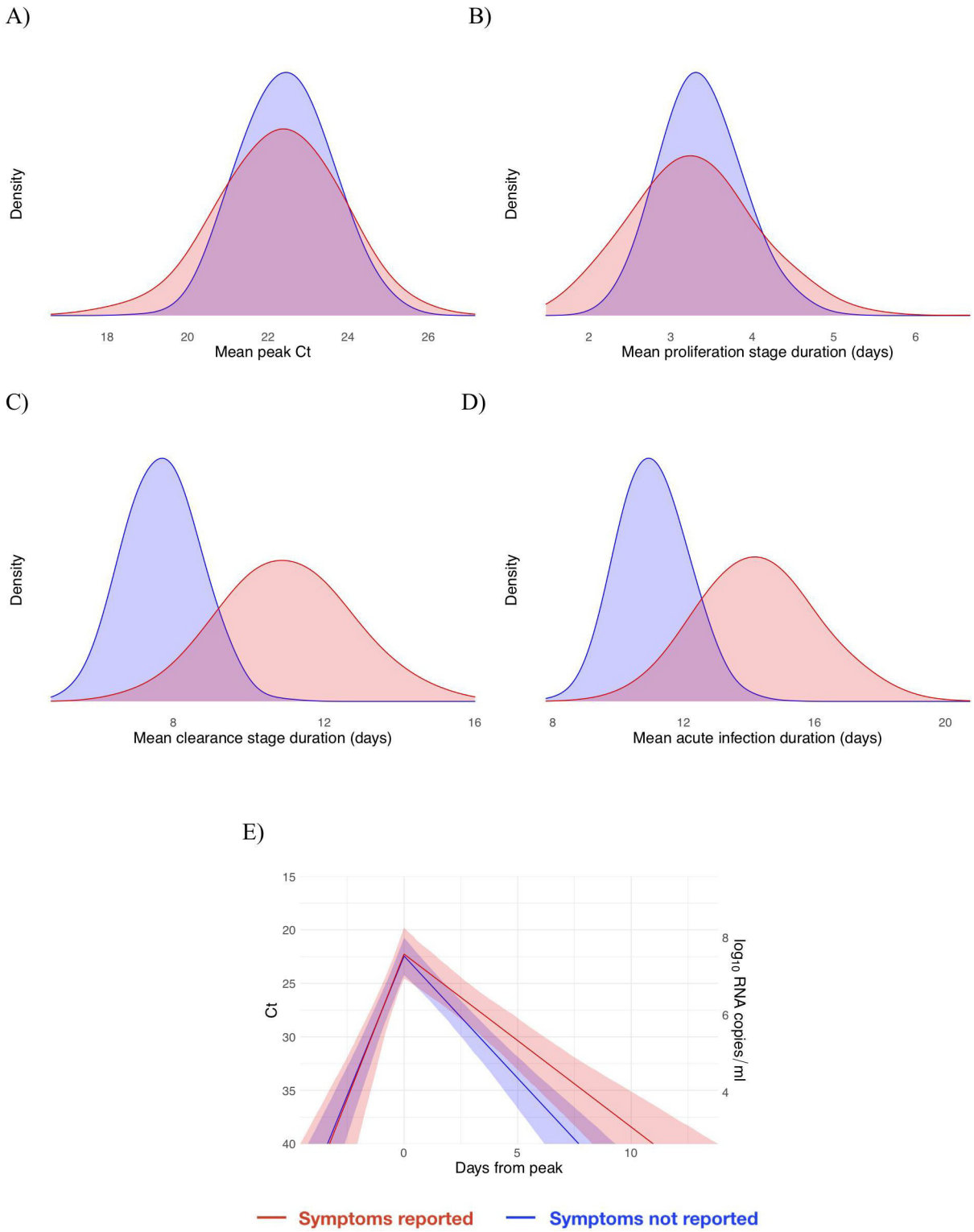


Fig 3. Peak cycle threshold (Ct) value and infection stage duration distributions according to symptoms reported at time of diagnosis. Posterior distributions obtained from 2,000 simulated draws from the posterior distributions for mean peak Ct value (A), mean duration of the proliferation stage (first potential infection detectability to peak Ct) (B), mean duration of the clearance stage (peak Ct to resolution of acute RNA shedding) (C), and total duration of acute shedding (D) across the 46 individuals with an acute infection. The distributions are separated according to whether the person reported symptoms (red, 13 individuals) or did not report symptoms (blue, 33 individuals). The mean Ct trajectory corresponding to the mean values for peak Ct, proliferation duration, and clearance duration for symptomatic versus asymptomatic

individuals is depicted in (E) (solid lines), where shading depicts the 90% credible intervals. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/output/params_df_split.csv [10].

https://doi.org/10.1371/journal.pbio.3001333.g003

the proliferation or the clearance stage (Fig 4B). This is unsurprising since the viral trajectory must pass through any given value during both the proliferation and the clearance stage. With roughly uniform sampling over time, a given Ct value is more likely to correspond to the clearance stage simply because the clearance stage is longer.

We assessed whether a second test within 2 days of the first could improve these predictions. A positive test followed by a second test with lower Ct (higher viral RNA concentration) was slightly more likely to be associated with an active infection than a positive test alone (Fig 4C), and was much more likely to be associated with the proliferation phase than with the clearance phase (Fig 4D).

We next estimated how the effective sensitivity of a pre-event screening test declines with increasing time to the event. For a test with a limit of detection of 40 Ct and a 1% chance of sampling error, the effective sensitivity declines from 99% when the test coincides with the start of the event to 76% when the test is administered 2 days prior to the event (Fig 5A), assuming a threshold of infectiousness at 30 Ct [11]. This 2-day-ahead sensitivity is slightly lower than the effective sensitivity of a test with a limit of detection at 35 Ct and a 5% sampling error administered 1 day before the event (82%), demonstrating that limitations in testing technology can be compensated for by reducing turnaround time. Using these effective sensitivities, we estimated the number of infectious individuals who would be expected to arrive at a gathering with 1,000 people given a pre-gathering screening test and a 2% prevalence of infectiousness in the population. Just as the effective sensitivity declines with time to the gathering, the predicted number of infectious individuals rises with time to the gathering (Fig 5B) since longer delays between the screening test and the gathering make it more likely that an individual's infection will be undetectable at the time of testing but the individual will be infectious at the time of the event. Changing the infectiousness threshold modulates the magnitude of the decline in effective sensitivity associated with longer testing delays; however, the overall pattern is consistent (S18 Fig).

Discussion

We provide to our knowledge the first comprehensive data on the early-infection RT-qPCR Ct dynamics associated with SARS-CoV-2 infection. We found that viral titers peak quickly,

Table 1. Viral dynamic parameters, overall and separated by reported symptoms.

Parameter	Mean (95% CI)		
	Symptoms*	No symptoms*	Overall
Peak Ct	22.2 (19.1, 25)	22.4 (20.2, 24.5)	22.4 (20.7, 24)
Peak viral concentration (log RNA copies/ml/day)	7.6 (6.8, 8.4)	7.5 (7, 8.1)	7.5 (7.1, 8)
Proliferation duration (days)	3.3 (1.9, 5.1)	3.4 (2.5, 4.5)	3.2 (2.4, 4.2)
Proliferation rate (Ct/day)	5.6 (3.4, 9.3)	5.2 (3.8, 7.1)	5.6 (4.2, 7.3)
Proliferation rate (log RNA copies/ml/day)	1.6 (0.9, 2.6)	1.5 (1.0, 2.0)	1.5 (1.2, 2)
Clearance duration (days)	10.9 (7.8, 14.2)	7.8 (6.1, 9.7)	8.5 (6.8, 10.2)
Clearance rate (Ct/day)	1.7 (1.2, 2.4)	2.3 (1.7, 3)	2.1 (1.7, 2.6)
Clearance rate (log RNA copies/ml/day)	0.5 (0.3, 0.7)	0.6 (0.5, 0.8)	0.6 (0.5, 0.7)
Infection duration (days)	14.3 (11, 17.8)	11.2 (9.4, 13.3)	11.7 (9.9, 13.5)

CI, credible interval; Ct, cycle threshold. Population sizes for each category are as follows: symptoms, $N = 13$; no symptoms, $N = 33$; overall, $N = 46$.

*Symptom reporting was imperfect as follow-up during the course of the disease was not systematic for all individuals.

https://doi.org/10.1371/journal.pbio.3001333.t001

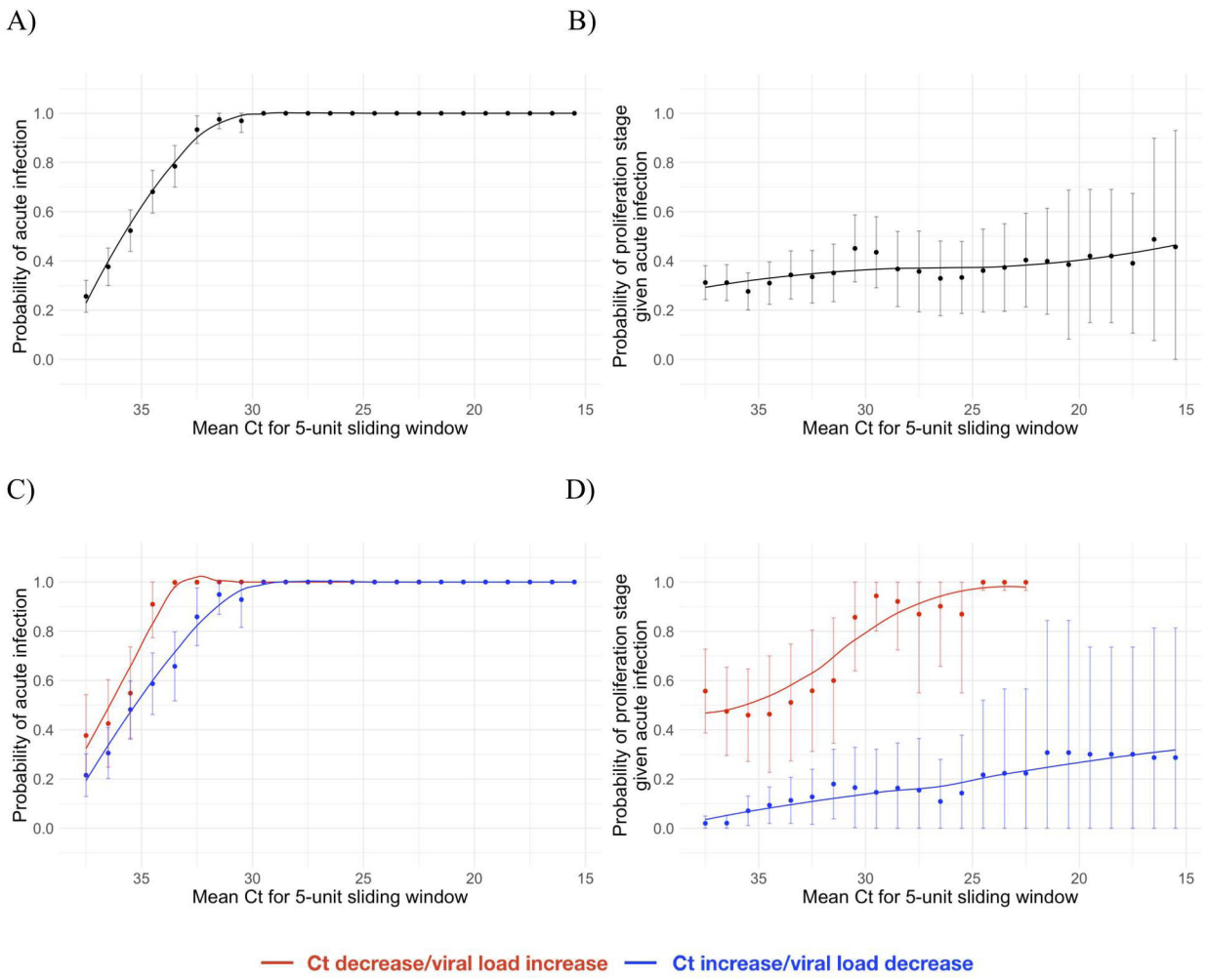


Fig 4. Relationship between single/paired cycle threshold (Ct) values and infection stage. Probability that a given Ct value lying within a 5-unit window (horizontal axis) corresponds to an acute infection (A and C) or to the proliferation phase of infection assuming an acute infection (B and D). (A) and (B) depict the predictive probabilities for a single Ct value, while (C) and (D) depict the predictive probabilities for a positive test paired with a subsequent test with either lower (red) or higher (blue) Ct. The curves are locally estimated scatterplot smoothing (LOESS) curves to better visualize the patterns. Error bars represent the 90% Wald confidence interval. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/figure_data/Fig4 [10].

https://doi.org/10.1371/journal.pbio.3001333.g004

normally within 3 days of the first possible RT-qPCR detection, regardless of symptoms. Our findings highlight that repeated PCR tests can be used to infer the stage of a patient's infection. While a single test can inform on whether a patient is in the acute or persistent viral RNA shedding stage, a subsequent test can help identify whether viral RNA concentrations are increasing or decreasing, thus informing clinical care. For example, patients near the beginning of their infection may need to be isolated for different amounts of time than patients near the end of their infection. For patients at risk for complications, closer monitoring and more proactive treatment may be preferred for patients near the start of infection than for those who are already nearing its resolution. We also show that the effective sensitivity of pre-event screening tests declines rapidly with test turnaround time due to the rapid progression from detectability to peak viral titers. Due to the transmission risk posed by large gatherings [12], the trade-off between test speed and sensitivity must be weighed carefully. Our data offer to our knowledge the first direct measurements capable of informing such decisions.

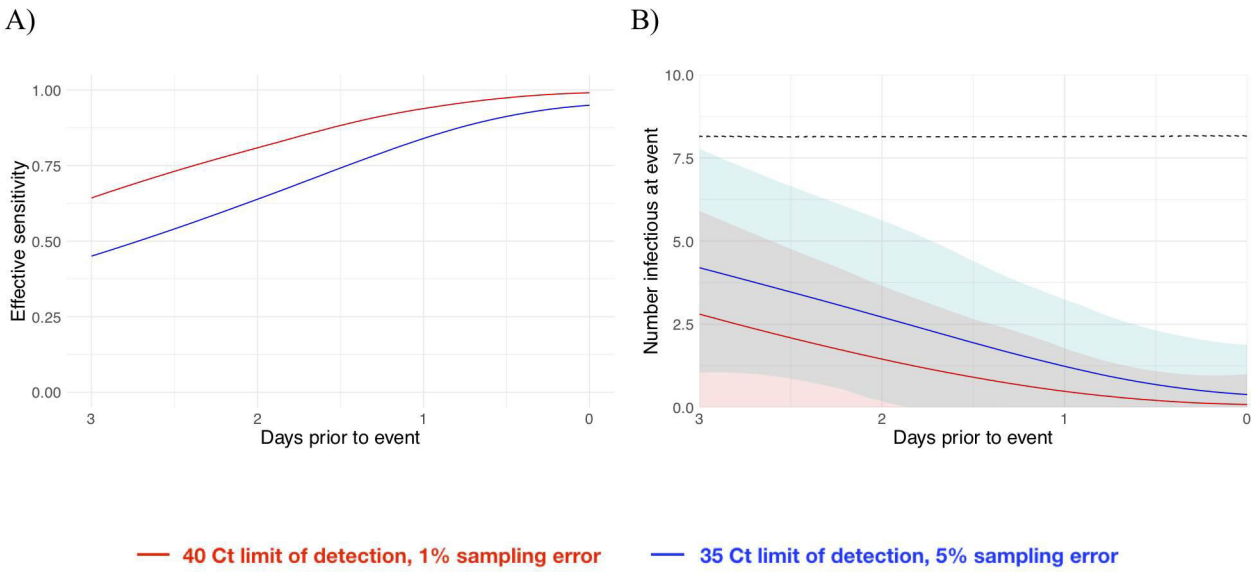


Fig 5. Effective sensitivity and expected number of infectious attendees at an event, for tests with varying sensitivity. (A) Effective sensitivity for a test with limit of detection of 40 Ct and 1% sampling error probability (red) and limit of detection of 35 Ct and 5% sampling error probability (blue). (B) Number of infectious individuals expected to attend an event of size 1,000 assuming a population prevalence of 2% infectious individuals for a test with limit of detection of 40 Ct and 1% sampling error probability (red) and limit of detection of 35 Ct and 5% sampling error probability (blue). Shaded bands represent 90% prediction intervals generated from the quantiles of 1,000 simulated events and capture uncertainty both in the number of infectious individuals who would arrive at the event in the absence of testing and in the probability that the test successfully identifies infectious individuals. The dashed line depicts the expected number of infectious individuals who would attend the gathering in the absence of testing. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/figure_data/Fig5 [10].

https://doi.org/10.1371/journal.pbio.3001333.g005

Our findings on the duration of SARS-CoV-2 viral RNA shedding expand on and agree with previous studies [13–15] and with observations that peak Ct does not differ substantially between symptomatic and asymptomatic individuals [3]. While previous studies have largely relied on serial sampling of admitted hospital patients, our study used prospective sampling of ambulatory infected individuals to characterize complete viral dynamics for the presymptomatic stage and for individuals who did not report symptoms. This allowed us to assess differences between the viral RNA proliferation and clearance stages for individuals with and without reported symptoms. The similarity in the early-infection viral RNA dynamics for symptomatic and asymptomatic individuals underscores the need for SARS-CoV-2 screening regardless of symptoms. The progression from a negative test to a peak Ct value 2–4 days later aligns with modeling assumptions made in various studies [5,16] to evaluate the potential effectiveness of frequent rapid testing programs, strengthening the empirical bases for their findings. Taken together, the dynamics of viral RNA shedding substantiate the need for frequent population-level SARS-CoV-2 screening and a greater availability of diagnostic tests.

The statistical model we developed to infer the viral trajectory parameters is phenomenological: It assumes an exponential increase in viral RNA concentration followed by an exponential decay but does not explicitly encode a biological mechanism leading to these exponential rates and the transition between them. Similar phenomenological models have been used to study the viral dynamics of HIV [17]. More biologically explicit mechanistic models have been used to study SARS-CoV-2 [18,19], but these remain in the early stages of development due to the limited amount of data available to inform such models. Since our primary interest is in the public health implications of SARS-CoV-2 viral trajectories with different magnitudes and durations, a phenomenological model is suitable and has the advantage of being straightforward to implement. The data presented here could be used to parameterize

detailed mechanistic models as well, from which further biological insights about SARS-CoV-2 might be gained.

Our findings are limited for several reasons. The sample size is small, especially with respect to symptomatic acutely infected individuals. The cohort does not constitute a representative sample from the population, as it was a predominantly male, healthy, young population inclusive of professional athletes. Viral trajectories may differ for individuals who have been vaccinated or who have been infected with different SARS-CoV-2 variants, which we were unable to assess due to the time frame of our study. Some of the trajectories were sparsely sampled, limiting the precision of our posterior estimates. Symptom reporting was imperfect, particularly after initial evaluation, as follow-up during the course of the disease was not systematic for all individuals. As with all predictive tests, the probabilities that link Ct values with infection stages (Fig 4) pertain to the population from which they were calibrated and do not necessarily generalize to other populations for which the prevalence of infection and testing protocols may differ. Still, we anticipate that the central patterns will hold across populations: first, that low Ct values (<30) strongly predict acute infection and, second, that a follow-up test collected within 2 days of an initial positive test can substantially help to discern whether a patients are closer to the beginning or the end of their infection. Our study did not test for the presence of infectious virus, though previous studies have documented a close inverse correlation between Ct values and culturable virus [11]. Our assessment of pre-event testing assumed that individuals become infectious immediately upon passing a threshold and that this threshold is the same for the proliferation and for the clearance phase. In reality, the threshold for infectiousness is unlikely to be at a fixed viral concentration for all individuals and may be at a higher Ct/lower viral concentration during the proliferation stage than during the clearance stage. Further studies that measure culturable virus during the various stages of infection and that infer infectiousness based on contact tracing combined with prospective longitudinal testing will help to clarify the relationship between viral concentration and infectiousness.

To manage the spread of SARS-CoV-2, we must develop novel technologies and find new ways to extract more value from the tools that are already available. Our results suggest that integrating the quantitative viral RNA trajectory into algorithms for clinical management could offer benefits. The ability to chart patients' progress through their infection underpins our ability to provide appropriate clinical care and to institute effective measures to reduce the risk of onward transmission. Marginally more sophisticated diagnostic and screening algorithms may greatly enhance our ability to manage the spread of SARS-CoV-2 using tests that are already available.

Supporting information

S1 Fig. Distribution of intervals between consecutive tests. Histogram of the proportion of consecutive tests that are within n days of one another up to $n = 12$ days. Only 12 of 2,343 intervals (0.05%) exceeded 12 days. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/figure_data/FigS1.
(PDF)

S2 Fig. Observed Ct values from the study participants (1/4). Points depict observed Ct values, which are connected with lines to better visualize patterns. Individuals with presumed acute infections are in red. All others are in black. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/data.
(PDF)

S3 Fig. Observed Ct values from the study participants (2/4). Points depict observed Ct values, which are connected with lines to better visualize patterns. Individuals with presumed acute infections are in red. All others are in black. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/data.
(PDF)

S4 Fig. Observed Ct values from the study participants (3/4). Points depict observed Ct values, which are connected with lines to better visualize patterns. Individuals with presumed acute infections are in red. All others are in black. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/data.
(PDF)

S5 Fig. Observed Ct values from the study participants (4/4). Points depict observed Ct values, which are connected with lines to better visualize patterns. Individuals with presumed acute infections are in red. All others are in black. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/data.
(PDF)

S6 Fig. A theoretical Ct trajectory. E[Ct] is the expected Ct value on a given day. The Ct begins at the limit of detection, then declines from the time of infection (t_o) to the peak at χ cycles below the limit of detection at time t_p. The Ct then rises again to the limit of detection after t_r days. The model incorporating these parameter values used to generate this piecewise curve is given in the equation for E[Ct(t)] in S1 Text (Supplemental Methods, under the heading "Model fitting").
(PDF)

S7 Fig. Schematics illustrating calculations for effective sensitivity for the expected number of infectious attendees at a gathering, given a pre-gathering test. (A) To calculate the effective sensitivity of a test intended to screen infectious individuals before a gathering, we first drew 1,000 viral trajectories as defined by the peak Ct, proliferation time, and clearance time from the fitted model (step 1, with 3 draws illustrated in red, green, and blue). We restricted to only individuals with viral concentrations above the infectiousness threshold (here the threshold is at Ct = 30, requiring us to omit the fourth entry). Then, we assigned detectability onset times—i.e., the times at which the trajectories could first be detected by PCR with limit of detection at 40 Ct—according to a standard uniform distribution, ensuring that the trajectories surpassed the infectiousness threshold at some point during the gathering (step 2). The onset times are depicted as colored dots. Finally, for a test administered some span of time prior to the event, we calculated the fraction of these infections the test would detect—this is the effective sensitivity (step 3). For a test administered at the time marked by the vertical black bar, the green trajectory would be detected by both PCR and a rapid test, the red trajectory would be detected by PCR but not a rapid test, and the blue trajectory would not be detected by either test. (B) To calculate the number of people who would arrive at a gathering while infectious, we performed a similar procedure. First, given a gathering size N and prevalence of PCR-detectable individuals p, we drew η trajectories from the fitted model where $\eta \sim \text{Binomial}(N, p)$. Three such draws are depicted in step 1; note that, here, the only requirement was that the individuals were detectable (not necessarily infectious) at the time of the gathering, and so the previously omitted value could now be chosen. Then, as before, detectability onset times (colored dots) were drawn from a uniform distribution ensuring that the individuals were PCR-detectable at the time of the gathering (2). Finally, in step 3, the number of infectious individuals who would attend the gathering in the absence of a pre-gathering test were counted (in this case just the blue trajectory) as well as the number of

individuals who would attend the event given a pre-gathering test. Here, the blue trajectory would be detected by a PCR test but not a rapid test at the test time depicted by the vertical black bar. The purple trajectory would be detected by both a rapid test and a PCR test, yet it would not have been infectious at the gathering (in fact, this trajectory never surpasses the infectiousness threshold depicted here). The green trajectory would not be detected by either test but also would not have arrived at the gathering while infectious since it has a relatively late onset time. Repeating this procedure for many simulated gatherings gives an estimate of the expected number of infectious people who would arrive at a gathering given a pre-gathering testing protocol.
(PDF)

S8 Fig. Mean peak Ct value and distributions of the proliferation stage, clearance stage, and acute infection duration for individuals with acute infections. Posterior distributions obtained from 10,000 posterior draws from the distributions for peak Ct value (A), duration of the proliferation stage (infection detection to peak Ct) (B), duration of the clearance stage (peak Ct to resolution of acute RNA shedding) (C), and total duration of acute shedding (D) across the 46 individuals with a verified infection. The mean Ct trajectory corresponding to the mean values for peak Ct, proliferation duration, and clearance duration is depicted in (E) (solid lines), where shading depicts the 90% credible interval. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/output/params_df_combined.csv.
(PDF)

S9 Fig. Posterior peak Ct value distributions for the 46 individuals with acute infections. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/output/params_df_split.csv.
(PDF)

S10 Fig. Posterior distributions for the duration of the proliferation stage for 46 individuals with acute infections. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/output/params_df_split.csv.
(PDF)

S11 Fig. Posterior distributions for the clearance stage duration for 46 individuals with acute infections. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/output/params_df_split.csv.
(PDF)

S12 Fig. Best-fit Ct trajectories for the 46 individuals with acute infections. Thin grey lines depict 500 sampled trajectories. Points represent the observed data, with symptomatic individuals represented in red and asymptomatic individuals in blue. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/output/params_df_split.csv (lines) and https://github.com/gradlab/CtTrajectories/tree/main/data (points).
(PDF)

S13 Fig. Individual-level peak Ct value and distribution of the proliferation stage, clearance stage, and acute infection duration. Histograms (grey bars) of 10,000 posterior draws from the distributions for peak Ct value (A), time from onset to peak (B), time from peak to recovery (C), and total duration of infection (D) across the 46 individuals with an acute infection. Grey curves are kernel density estimators to more clearly exhibit the shape of the histogram. Black curves represent the best-fit normal (A) or gamma (B–D) distributions to the histograms. The duration of infection is the sum of the time from onset to peak and the time from peak to recovery. The best-fit normal distribution to the posterior peak Ct value

distribution had mean 22.3 and standard deviation 4.2. The best-fit gamma distribution to the proliferation stage duration had shape parameter 2.3 and inverse scale parameter 0.7. The best-fit gamma distribution to the clearance stage duration had shape parameter 2.4 and inverse scale parameter 0.3. The best-fit gamma distribution to the total duration of infection had shape parameter 4.3 and inverse scale parameter 0.4. Alternatively, the proliferation, clearance, and total duration of infection distributions can be summarized as log-normal distributions. The best-fit log-normal distribution to the proliferation stage duration had location parameter $\mu = 0.93$ and scale parameter $\sigma = 0.82$. The best-fit log-normal distribution to the clearance stage duration had location parameter $\mu = 1.9$ and scale parameter $\sigma = 0.83$. The best-fit log-normal distribution to the total duration of infection had location parameter $\mu = 2.3$ and scale parameter $\sigma = 0.53$. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/output/params_df_split.csv.
(PDF)

S14 Fig. Peak viral concentration and overall posterior viral concentration trajectories in terms of genome equivalents per milliliter. Posterior peak viral concentration distribution for symptomatic (red) and asymptomatic (blue) individuals (A) and for all individuals combined (B). Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/output/params_df_split.csv (A) and https://github.com/gradlab/CtTrajectories/tree/main/output/params_df_combined.csv (B).
(PDF)

S15 Fig. Ct values from the Yale and Florida labs. Points depict the Ct values for SARS-CoV-2 nasal swab samples that were tested in both the Florida and Yale labs. Ct values from Florida represent Target 1 (ORF1ab) on the Roche cobas system, and Ct values from Yale represent N1 in the Yale multiplex assay. The solid black line depicts the best-fit linear regression (intercept = −6.25, slope = 1.34, $R^2 = 0.86$). The dashed black line marks the 1–1 line where the points would be expected to fall if the 2 labs produced identical results. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/figure_data/FigS15.
(PDF)

S16 Fig. Residuals from the Yale/Florida Ct regression. Points depict the residual after removing the best-fit linear trend in the relationship between the Yale and Florida Ct values. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/figure_data/FigS16.
(PDF)

S17 Fig. Quantile–quantile plot of the residuals from the Yale/Florida Ct regression. The residuals were standardized (by subtracting the mean of all residuals from each residual and then dividing each residual by the standard deviation of all residuals) before being compared with the theoretical quantiles of a normal distribution with mean 0 and standard deviation 1. The points depict the empirical quantiles of the data points, and the line depicts where the points would be expected to fall if they were drawn from a standard normal distribution. Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/figure_data/FigS17.
(PDF)

S18 Fig. Effective sensitivity and expected number of infectious attendees at a gathering, given a pre-gathering test and varying infectiousness thresholds. (A and C) Effective sensitivity and (B and D) number of infectious individuals expected to attend a gathering of size 1,000 assuming a population prevalence of 2% infectious individuals and a test with limit of

detection of 40 Ct and 1% sampling error probability (red) and a test with limit of detection of 35 Ct and 5% sampling error probability (blue) administered between 0 and 3 days before the gathering. For (A) and (B) individuals are assumed to be infectious when their Ct value is below 35. For (C) and (D) individuals are assumed to be infectious when their Ct value is below 20. Shaded bands represent 90% prediction intervals generated from the quantiles of 1,000 simulated events and capture uncertainty both in the number of infectious individuals who would arrive at the event in the absence of testing and in the probability that the test successfully identifies infectious individuals. The dashed lines in (B) and (D) depict the expected number of infectious individuals who would attend the gathering in the absence of testing. Setting the infectiousness threshold at higher viral concentration (20 Ct versus 35 Ct) makes it less likely that an individual will become infectious at all during the course of their acute infection, leading to the lower expected number of infectious individuals at the gathering in (D) versus (B). Underlying data are available at https://github.com/gradlab/CtTrajectories/tree/main/figure_data/FigS18.
(PDF)

S19 Fig. Illustration of why effective sensitivity declines more sharply with testing delays for high versus low infectiousness thresholds. For a given viral trajectory conditioned on infectiousness during a gathering, there is a wider range of possible proliferation onset times when the infectiousness threshold is low (blue) versus when the infectiousness threshold is high (red). Additionally, the range of possible onset times for the low infectiousness threshold versus the high infectiousness threshold is skewed to the left since the clearance time is longer than the proliferation time. Because of this, a low infectiousness threshold makes it easier for a pre-gathering test to pick up a trajectory that would be infectious at the time of the gathering. Conversely, a high infectiousness threshold shortens the window of possible onset times that guarantee infectiousness during the gathering, making it more difficult for a pre-gathering test to detect the trajectory. This is reflected in the steeper decline in the effective sensitivity for a high infectiousness threshold (Ct = 20) than for a low infectiousness threshold (Ct = 35) (see S18A and S18C Fig).
(PDF)

S1 Table. Standard curve relationship between genome equivalents and Ct values. Synthetic T7 RNA transcripts corresponding to a 1,363-base-pair segment of the SARS-CoV-2 nucleocapsid gene were serially diluted from 10^6 to 10^0 and evaluated in duplicate with RT-qPCR. The best-fit linear regression of the average Ct on the log10-transformed standard values had slope −3.60971 and intercept 40.93733 ($R^2 = 0.99$).
(PDF)

S2 Table. Viral dynamic parameters for sensitivity analysis 1, omitting person 3047.
(PDF)

S3 Table. Viral dynamic parameters for sensitivity analysis 2, assuming 95% PCR sensitivity or a 5% probability of false negative.
(PDF)

S4 Table. Viral dynamic parameters for sensitivity analysis 3, removing the upper bounds for the proliferation and clearance times.
(PDF)

S5 Table. Viral dynamic parameters for sensitivity analysis 4, using "low" priors for the proliferation and clearance times (mean 3.5 and 7.5 days, respectively).
(PDF)

S6 Table. Viral dynamic parameters for sensitivity analysis 5, using "high" priors for the proliferation and clearance times (mean 10.5 days and 22.5 days, respectively).
(PDF)

S1 Text. Supplemental methods.
(PDF)

Acknowledgments

We thank the NBA, the National Basketball Players Association (NBPA), and all of the study participants who are committed to applying what they learned from sports towards enhancing public health. In particular, we thank D. Weiss of the NBA for his continuous support and leadership. We are appreciative of the discussions from the COVID-19 Sports and Society Working Group. We also thank D. Larremore for comments on the manuscript, J. Hay and R. Niehus for suggestions on the statistical approach, and P. Jack and S. Taylor for laboratory support.

Author Contributions

Conceptualization: Stephen M. Kissler, Joseph R. Fauver, Christina Mack, Scott W. Olesen, Caroline Tai, John DiFiori, Nathan D. Grubaugh, Yonatan H. Grad.

Data curation: Joseph R. Fauver, Christina Mack, Caroline Tai, Kristin Y. Shiue, Chaney C. Kalinich, Sarah Jednak, Isabel M. Ott, Jay Wohlgemuth, James Weisberger, John DiFiori, Deverick J. Anderson, Jimmie Mancell, David D. Ho, Nathan D. Grubaugh.

Formal analysis: Stephen M. Kissler, Joseph R. Fauver, Scott W. Olesen, Nathan D. Grubaugh.

Funding acquisition: Nathan D. Grubaugh, Yonatan H. Grad.

Investigation: Stephen M. Kissler, Joseph R. Fauver, Christina Mack, Caroline Tai, Chaney C. Kalinich, Sarah Jednak, Nathan D. Grubaugh, Yonatan H. Grad.

Methodology: Stephen M. Kissler, Joseph R. Fauver, Scott W. Olesen, Caroline Tai, Kristin Y. Shiue, Isabel M. Ott, Chantal B. F. Vogels, Jay Wohlgemuth, James Weisberger, John DiFiori, Deverick J. Anderson, Jimmie Mancell, David D. Ho, Nathan D. Grubaugh, Yonatan H. Grad.

Project administration: Nathan D. Grubaugh, Yonatan H. Grad.

Resources: Nathan D. Grubaugh, Yonatan H. Grad.

Software: Stephen M. Kissler, Scott W. Olesen.

Supervision: Nathan D. Grubaugh, Yonatan H. Grad.

Validation: Stephen M. Kissler.

Visualization: Scott W. Olesen.

Writing – original draft: Stephen M. Kissler, Joseph R. Fauver, Christina Mack, Caroline Tai, John DiFiori, Nathan D. Grubaugh, Yonatan H. Grad.

Writing – review & editing: Stephen M. Kissler, Joseph R. Fauver, Christina Mack, Caroline Tai, Kristin Y. Shiue, Chaney C. Kalinich, Sarah Jednak, Isabel M. Ott, Chantal B. F. Vogels, Jay Wohlgemuth, James Weisberger, John DiFiori, Deverick J. Anderson, Jimmie Mancell, David D. Ho, Nathan D. Grubaugh, Yonatan H. Grad.

References

1. Furukawa NW, Brooks JT, Sobel J. Evidence supporting transmission of severe acute respiratory syndrome coronavirus 2 while presymptomatic or asymptomatic. Emerg Infect Dis. 2020; 26(7):e201595. https://doi.org/10.3201/eid2607.201595 PMID: 32364890
2. Tom MR, Mina MJ. To interpret the SARS-CoV-2 test, consider the cycle threshold value. Clin Infect Dis. 2020; 71(16):2252–4. https://doi.org/10.1093/cid/ciaa619 PMID: 32435816
3. Walsh KA, Jordan K, Clyne B, Rohde D, Drummond L, Byrne P, et al. SARS-CoV-2 detection, viral load and infectivity over the course of an infection. J Infect. 2020; 81(3):357–71. https://doi.org/10.1016/j.jinf.2020.06.067 PMID: 32615199
4. Wyllie AL, Fournier J, Casanovas-Massana A, Campbell M, Tokuyama M, Vijayakumar P, et al. Saliva or nasopharyngeal swab specimens for detection of SARS-CoV-2. N Engl J Med. 2020; 383(13):1283–6. https://doi.org/10.1056/NEJMc2016359 PMID: 32857487
5. Larremore DB, Wilder B, Lester E, Shehata S, Burke JM, Hay JA, et al. Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance. Sci Adv. 2021; 7(1):eabd5393. https://doi.org/10.1126/sciadv.abd5393 PMID: 33219112
6. Mack CD, DiFiori J, Tai CG, Shiue KY, Grad YH, Anderson DJ, et al. SARS-CoV-2 transmission risk among National Basketball Association players, staff, and vendors exposed to individuals with positive test results after COVID-19 recovery during the 2020 regular and postseason. JAMA Intern Med. 2021 Apr 22. https://doi.org/10.1001/jamainternmed.2021.2114 PMID: 33885715
7. Xiao AT, Tong YX, Zhang S. Profile of RT-PCR for SARS-CoV-2: a preliminary study from 56 COVID-19 patients. Clin Infect Dis. 2020; 71(16):2249–51. https://doi.org/10.1093/cid/ciaa460 PMID: 32306036
8. Cleary B, Hay JA, Blumenstiel B, Harden M, Cipicchio M, Bezney J, et al. Using viral load and epidemic dynamics to optimize pooled testing in resource-constrained settings. Science Translational Medicine. 2021 apr 14. https://doi.org/10.1126/scitranslmed.abf1568 PMID: 32511487
9. Carpenter B, Gelman A, Hoffman MD, Lee D, Goodrich B, Betancourt M, et al. Stan: a probabilistic programming language. J Stat Softw. 2017; 76(1). https://doi.org/10.18637/jss.v076.i01
10. Kissler S. gradlab/CtTrajectories. Zenodo. 2021 Jun 17. https://doi.org/10.5281/zenodo.4977246
11. Singanayagam A, Patel M, Charlett A, Lopez Bernal J, Saliba V, Ellis J, et al. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro Surveill. 2020; 25(32):2001483. https://doi.org/10.2807/1560-7917.ES.2020.25.32.2001483 PMID: 32794447
12. Cevik M, Marcus J, Buckee C, Smith T. SARS-CoV-2 transmission dynamics should inform policy. SSRN Electron J. 2020 Sep 21. https://doi.org/10.1093/cid/ciaa1442 PMID: 32964919
13. Cevik M, Tate M, Lloyd O, Enrico Maraolo A, Schafers J, Ho A. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. The Lancet Microbe. 2020 19 Nov. https://doi.org/10.1016/S2666-5247(20)30172-5 PMID: 33521734
14. Houlihan C, Vora N, Byrne T, Lewer D, Heaney J, Moore DA, et al. SARS-CoV-2 virus and antibodies in front-line Health Care Workers in an acute hospital in London: preliminary results from a longitudinal study. medRxiv. 2020 Jun 9. https://doi.org/10.1101/2020.06.08.20120584
15. Lee S, Kim T, Lee E, Lee C, Kim H, Rhee H, et al. Clinical course and molecular viral shedding among asymptomatic and symptomatic patients with SARS-CoV-2 infection in a community treatment center in the Republic of Korea. JAMA Intern Med. 2020; 180(11):1447–52. https://doi.org/10.1001/jamainternmed.2020.3862 PMID: 32780793
16. Paltiel AD, Zheng A, Walensky RP. Assessment of SARS-CoV-2 screening strategies to permit the safe reopening of college campuses in the United States. JAMA Netw Open. 2020; 3(7):e2016818. https://doi.org/10.1001/jamanetworkopen.2020.16818 PMID: 32735339
17. Huang Y, Dagne GA, Zhou S, Wang Z. Piecewise mixed-effects models with skew distributions for evaluating viral load changes: a Bayesian approach. Stat Methods Med Res. 2015; 24(6):730–46. https://doi.org/10.1177/0962280211426184 PMID: 22045781
18. Ke R, Zitzmann C, Ribeiro RM, Perelson AS. Kinetics of SARS-CoV-2 infection in the human upper and lower respiratory tracts and their relationship with infectiousness. medRxiv. 2020 Sep 27. https://doi.org/10.1101/2020.09.25.20201772
19. Goyal A, Reeves DB, Cardozo-Ojeda EF, Schiffer JT, Mayer BT. Viral load and contact heterogeneity predict SARS-CoV-2 transmission and super-spreading events. eLife. 2021 Feb 23. https://doi.org/10.7554/eLife.63537 PMID: 33620317

RESEARCH ARTICLE SUMMARY

CORONAVIRUS

Estimating infectiousness throughout SARS-CoV-2 infection course

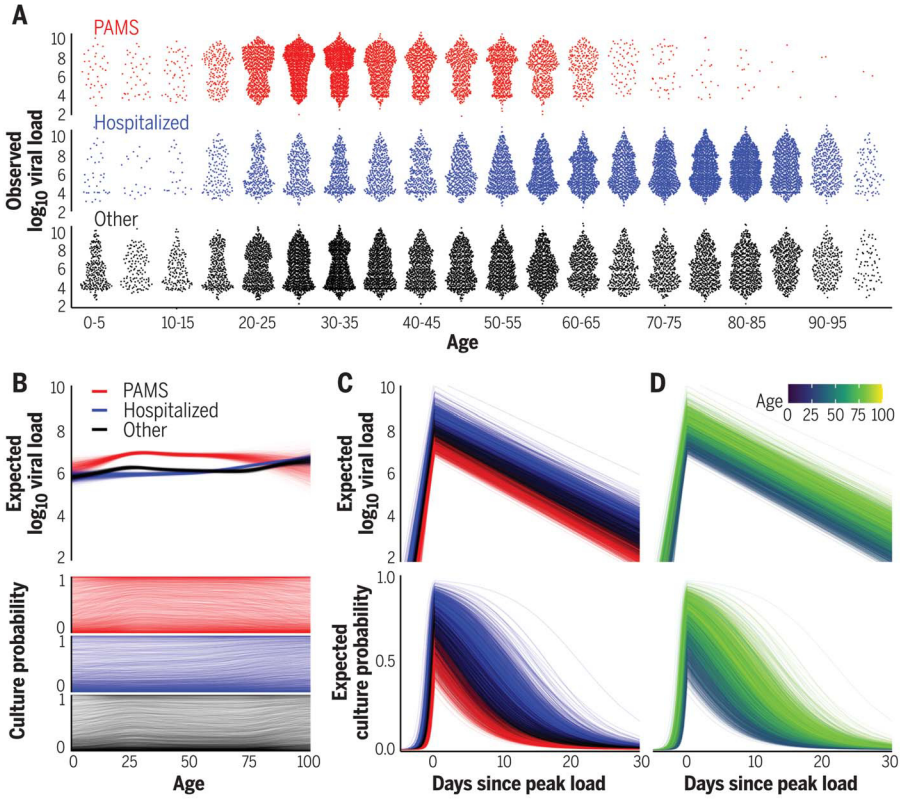
Terry C. Jones[1,2,3]†, Guido Biele[4,5]†, Barbara Mühlemann[1,2], Talitha Veith[1,2], Julia Schneider[1,2], Jörn Beheim-Schwarzbach[1], Tobias Bleicker[1], Julia Tesch,[1] Marie Luisa Schmidt[1], Leif Erik Sander[6], Florian Kurth[6,7], Peter Menzel[8], Rolf Schwarzer[8], Marta Zuchowski[8], Jörg Hofmann[8], Andi Krumbholz[9,10], Angela Stein[8], Anke Edelmann[8], Victor Max Corman[1,2], Christian Drosten[1,2]*

INTRODUCTION: Although post facto studies have revealed the importance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission from presymptomatic, asymptomatic, and mildly symptomatic (PAMS) cases, the virological basis of their infectiousness remains largely unquantified. The reasons for the rapid spread of variant lineages of concern, such as B.1.1.7, have yet to be fully determined.

RATIONALE: Viral load (viral RNA concentration) in patient samples and the rate of isolation success of virus from clinical specimens in cell culture are the clinical parameters most directly relevant to infectiousness and hence to transmission. To increase our understanding of the infectiousness of SARS-CoV-2, especially in PAMS cases and those infected with the B.1.1.7 variant, we analyzed viral load data from 25,381 German cases, including 9519 hospitalized patients, 6110 PAMS cases from walk-in test centers, 1533 B.1.1.7 variant infections, and the viral load time series of 4434 (mainly hospitalized) patients. Viral load results were then combined with estimated cell culture isolation probabilities, producing a clinical proxy estimate of infectiousness.

RESULTS: PAMS subjects had, at the first positive test, viral loads and estimated infectiousness only slightly less than hospitalized patients. Similarly, children were found to have mean viral loads only slightly lower (0.5 $\log_{10}$ units or less) than those of adults and ~78% of the adult peak cell culture isolation probability. Eight percent of first-positive viral loads were 10^9 copies per swab or higher, across a wide age range (mean 37.6 years, standard deviation 13.4 years), representing a likely highly infectious minority, one-third of whom were PAMS. Relative to non-B.1.1.7 cases, patients with the B.1.1.7 variant had viral loads that were higher by a factor of 10 and estimated cell culture infectivity that was higher by a factor of 2.6. Similar ranges of viral loads from B.1.1.7 and B.1.177 samples were shown to be capable of causing infection in Caco-2 cell culture. A time-course analysis estimates that a peak viral load of $10^{8.1}$ copies per swab is reached 4.3 days after onset of shedding and shows that, across the course of infection, hospitalized patients have slightly higher viral loads than nonhospitalized cases, who in turn have viral loads slightly higher than PAMS cases. Higher viral loads are observed in first-positive tests of PAMS subjects, likely as a result of systematic earlier testing. Mean culture isolation probability declines to 0.5 at 5 days after peak viral load and to 0.3 at 10 days after peak viral load. We estimate a rate of viral load decline of 0.17 $\log_{10}$ units per day, which, combined with reported estimates of incubation time and time to loss of successful cell culture isolation, suggests that viral load peaks 1 to 3 days before onset of symptoms (in symptomatic cases).

CONCLUSION: PAMS subjects who test positive at walk-in test centers can be expected to be approximately as infectious as hospitalized patients. The level of expected infectious viral shedding of PAMS people is of high importance because they are circulating in the community at the time of detection of infection. Although viral load and cell culture infectivity cannot be translated directly to transmission probability, it is likely that the rapid spread of the B.1.1.7 variant is partly attributable to higher viral load in these cases. Easily measured virological parameters can be used, for example, to estimate transmission risk from different groups (by age, gender, clinical status, etc.), to quantify variance, to show differences in virus variants, to highlight and quantify overdispersion, and to inform quarantine, containment, and elimination strategies. ■



Viral load and cell culture infectivity in 25,381 SARS-CoV-2 infections. (**A**) Viral loads in presymptomatic, asymptomatic, and mildly symptomatic cases (PAMS; red), hospitalized patients (blue), and other subjects (black). (**B**) Expected first-positive viral load and cell culture isolation probability, colored as in (A). (**C**) Temporal estimation with lines representing patients, colored as in (A). (**D**) As in (C), but colored by age.

The list of author affiliations is available in the full article online.
*Corresponding author. Email: christian.drosten@charite.de
†These authors contributed equally to this work.

Cite this article as T. C. Jones *et al.*, *Science* **373**, eabi5273 (2021). DOI: 10.1126/science.abi5273

READ THE FULL ARTICLE AT
https://doi.org/10.1126/science.abi5273

RESEARCH ARTICLE

CORONAVIRUS

Estimating infectiousness throughout SARS-CoV-2 infection course

Terry C. Jones[1,2,3]†, Guido Biele[4,5]†, Barbara Mühlemann[1,2], Talitha Veith[1,2], Julia Schneider[1,2], Jörn Beheim-Schwarzbach[1], Tobias Bleicker[1], Julia Tesch[1], Marie Luisa Schmidt[1], Leif Erik Sander[6], Florian Kurth[6,7], Peter Menzel[8], Rolf Schwarzer[8], Marta Zuchowski[8], Jörg Hofmann[8], Andi Krumbholz[9,10], Angela Stein[8], Anke Edelmann[8], Victor Max Corman[1,2], Christian Drosten[1,2]*

Two elementary parameters for quantifying viral infection and shedding are viral load and whether samples yield a replicating virus isolate in cell culture. We examined 25,381 cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Germany, including 6110 from test centers attended by presymptomatic, asymptomatic, and mildly symptomatic (PAMS) subjects, 9519 who were hospitalized, and 1533 B.1.1.7 lineage infections. The viral load of the youngest subjects was lower than that of the older subjects by 0.5 (or fewer) $\log_{10}$ units, and they displayed an estimated ~78% of the peak cell culture replication probability; in part this was due to smaller swab sizes and unlikely to be clinically relevant. Viral loads above 10^9 copies per swab were found in 8% of subjects, one-third of whom were PAMS, with a mean age of 37.6 years. We estimate 4.3 days from onset of shedding to peak viral load ($10^{8.1}$ RNA copies per swab) and peak cell culture isolation probability (0.75). B.1.1.7 subjects had mean $\log_{10}$ viral load 1.05 higher than that of non-B.1.1.7 subjects, and the estimated cell culture replication probability of B.1.1.7 subjects was higher by a factor of 2.6.

Respiratory disease transmission is highly context-dependent and difficult to quantify or predict at the individual level. This is especially the case when transmission from presymptomatic, asymptomatic, and mildly symptomatic (PAMS) subjects is frequent, as with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (*1*–*8*). Transmission is therefore typically inferred from population-level information and summarized as a single overall average, known as the basic reproductive number, R_0. Although R_0 is an essential and critical parameter for understanding and managing population-level disease dynamics, it is a resultant, downstream characterization of transmission. With regard to SARS-CoV-2, many finer-grained upstream questions regarding infectiousness remain unresolved or unaddressed. Three categories of uncertainty are (i) differences in infectiousness among individuals or groups such as PAMS subjects, according to age, gender, vaccination status, etc.; (ii) timing and degree of peak infectiousness, timing of loss of infectiousness, rates of infectiousness increase and decrease, and how these relate to onset of symptoms (when present); and (iii) differences in infectiousness due to inherent properties of virus variants.

These interrelated issues can all be addressed through the combined study of two clinical virological parameters: the viral load (viral RNA concentration) in patient samples, and virus isolation success in cell culture trials. Viral load and cell culture infectivity cannot be translated directly to in vivo infectiousness, and the impact of social context and behavior on transmission is very high; nonetheless, these quantifiable parameters can generally be expected to be those most closely associated with transmission likelihood. A strong relationship between SARS-CoV-2 viral load and transmission has been reported (*9*), comparing favorably with the situation with influenza virus, where the association is less clear (*10*, *11*).

The emergence of more transmissible SARS-CoV-2 variants, such as the B.1.1.7 lineage (UK Variant of Concern 202012/01), emphasizes the importance of correlates of shedding and transmission. The scarcity of viral load data in people with recent variants, and in PAMS subjects of all ages (*12*), is a blind spot of key importance because many outbreaks have clearly been triggered and fueled by these subjects (*2*, *13*–*17*). Viral load data from PAMS cases are rarely available, greatly reducing the number of studies with information from both symptomatic and PAMS subjects and that span the course of infections (*12*, *18*). Making matters worse, it is not possible to place positive reverse transcription polymerase chain reaction (RT-PCR) results from asymptomatic subjects in time relative to a nonexistent day of symptom onset, so these cases cannot be included in studies focused on incubation period. Additionally, viral load time courses relative to the day of symptom onset rely on patient recall, a suboptimal measure that is subject to human error and that overlooks infections from presymptomatic or asymptomatic contacts (*12*). An alternative and more fundamental parameter, the day of peak viral load, can be estimated from dated viral load time-series data, drawn from the entire period of viral load rise and fall and the full range of symptomatic statuses.

To better understand SARS-CoV-2 infectiousness, we analyzed viral load, cell culture isolation, and genome sequencing data from a diagnostic laboratory in Berlin (Charité–Universitätsmedizin Berlin Institute of Virology and Labor Berlin). We first address a set of questions regarding infectiousness at the moment of disease detection, especially in PAMS subjects whose infections were detected at walk-in community test centers. Because these people are circulating in the general community before their infections are detected, and are healthy enough to present themselves at such centers, their prevalence and shedding are of key importance to the understanding and prevention of transmission. In addition to PAMS subjects, we consider the infectiousness suggested by first-positive tests from hospitalized patients, including differences according to age, virus variant, and gender. A further set of temporal questions are then addressed by studying how infectiousness changes during the infection course. Using viral load measurements from patients with at least three RT-PCR tests, we estimate the onset of infectious viral shedding, peak viral load, and the rates of viral load increase and decline. Knowledge of these parameters enables fundamental comparisons between groups of subjects and between virus strains, and highlights the misleading impression created by viral loads from first-positive RT-PCR tests if the time of testing in the infection course is not considered.

Study composition

We examined 936,423 SARS-CoV-2 routine diagnostic RT-PCR results from 415,935 subjects aged 0 to 100 years from 24 February 2020 to 2 April 2021. Samples were collected at test centers and medical practices mostly in and around Berlin, Germany, and analyzed with LightCycler 480 and cobas 6800/8800 systems from Roche. Of all tested subjects, 25,381 (6.1%)

[1]Institute of Virology, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, 10117 Berlin, Germany. [2]German Centre for Infection Research (DZIF), partner site Charité, 10117 Berlin, Germany. [3]Centre for Pathogen Evolution, Department of Zoology, University of Cambridge, Cambridge CB2 3EJ, U.K. [4]Norwegian Institute of Public Health, 0473 Oslo, Norway. [5]University of Oslo, 0315 Oslo, Norway. [6]Department of Infectious Diseases and Respiratory Medicine, Charité–Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, 10117 Berlin, Germany. [7]Department of Tropical Medicine, Bernhard Nocht Institute for Tropical Medicine, and Department of Medicine I, University Medical Centre Hamburg-Eppendorf, 20359 Hamburg, Germany. [8]Labor Berlin–Charité Vivantes GmbH, Sylter Straße 2, 13353 Berlin, Germany. [9]Institute for Infection Medicine, Christian-Albrechts-Universität zu Kiel and University Medical Center Schleswig-Holstein, Campus Kiel, 24105 Kiel, Germany. [10]Labor Dr. Krause und Kollegen MVZ GmbH, 24106 Kiel, Germany.
*Corresponding author. Email: christian.drosten@charite.de
†These authors contributed equally to this work.

Table 1. Age stratification of first-positive RT-PCR tests and viral load for 25,381 positive cases.
N, number of subjects with a positive test result; Pos. %, percentage of positive subjects; Load (SD), mean $\log_{10}$(viral load) and standard deviation; ≥3 tests, number of subjects with at least three RT-PCR test results, as used in the viral load time course analysis. Age ranges (in years) are open-closed intervals.

	All cases				PAMS cases			Hospitalized cases		
Age	*N*	Pos. %	Load (SD)	≥3 tests	*N*	Pos. %	Load (SD)	*N*	Pos. %	Load (SD)
0–5	330	1.8	5.9 (1.84)	16	36	5.1	6.6 (1.87)	32	0.9	5.6 (2.22)
5–10	185	1.8	6.0 (1.73)	12	39	6.2	6.1 (1.83)	18	1.4	5.8 (1.97)
10–15	227	2.2	6.0 (1.76)	8	51	6.9	6.4 (1.92)	22	1.4	6.0 (2.02)
15–20	643	3.0	6.3 (1.87)	39	192	5.1	6.7 (1.77)	121	2.5	6.1 (1.95)
20–25	1637	3.2	6.5 (1.89)	110	696	4.0	6.9 (1.86)	246	2.7	5.9 (1.92)
25–35	4452	3.0	6.6 (1.90)	320	1988	3.9	7.0 (1.83)	614	2.2	6.0 (1.88)
35–45	3393	2.7	6.4 (1.84)	323	1277	3.5	6.9 (1.79)	576	2.0	6.0 (1.90)
45–55	3341	3.1	6.4 (1.81)	401	1012	3.4	6.9 (1.83)	733	2.3	5.9 (1.77)
55–65	3322	2.7	6.3 (1.78)	623	674	3.0	6.8 (1.82)	1039	2.1	5.9 (1.80)
>65	7851	3.0	6.4 (1.79)	2492	145	5.8	6.8 (1.87)	3434	2.3	6.2 (1.86)

had at least one positive RT-PCR test (Table 1). Positive subjects had a mean age of 51.7 years with high standard deviation (SD) of 22.7 years, and a mean of 4.5 RT-PCR tests (SD 5.7), of which 1.7 (SD 1.4) were positive. Of the positive subjects, 4344 had tests on at least 3 days (with at least two tests positive) and were included in a time-series analysis.

We divided the 25,381 positive subjects into three groups (Fig. 1). The Hospitalized group (9519 subjects, 37.5%) included all those who tested positive in an in-patient hospitalized context at any point in their infection. The PAMS group (6110 subjects, 24.1%) included people whose first positive sample was obtained in any of 24 Berlin COVID-19 walk-in community test centers, provided they were not in the Hospitalized category. The Other group (9752 subjects, 38.4%) included everyone not in the first two categories (table S1). As Fig. 1 shows, there were relatively low numbers of young subjects in all three groups, and very few elderly PAMS subjects. The validity of the PAMS classification is supported by the fact that of the overall 6159 infections detected at walk-in test centers, only 49 subjects (0.8%) were later hospitalized. Subjects testing positive at these centers are almost certainly receiving their first positive test because they are instructed to immediately self-isolate, and our data confirm that such subjects are rarely retested: Only 4.6% of people with at least three test results had their first test at a walk-in test center. Of the 9519 subjects who were ever hospitalized, 6835 were already in hospital at the time of their first positive test. PAMS subjects had a mean age of 38.0 years (SD 13.7), typically younger than Other subjects (mean 49.1 years, SD 23.5), with Hospitalized the oldest group (mean 63.2 years, SD 20.7). Typing RT-PCR indicated that 1533 subjects were infected with a strain belonging to the B.1.1.7 lineage, as confirmed by full genomes from next-generation sequencing (see materials and methods).

First-positive viral load

Across all subjects, the mean viral load [given as $\log_{10}$(RNA copies per swab)] in the first positive-testing sample was 6.39 (SD 1.83). The PAMS subjects had viral loads higher than those of the Hospitalized subjects for ages up to 70 years, as exemplified by a 6.9 mean for PAMS compared to a 6.0 mean in Hospitalized adult subjects of 20 to 65 years. Crude comparisons of viral loads in age groups showed no substantial difference in first-positive viral load between groups of people older than 20 years (Table 1). Children and adolescents had mean first-positive viral load differences ranging between −0.49 (−0.69, −0.29) and −0.16 (−0.31, −0.01) relative to adults aged 20 to 65 (Table 2). Here and below, parameter differences between age groups show the younger value minus the older, so a negative difference indicates a lower value in the younger group. Ranges given in parentheses are 90% credible intervals.

We used a Bayesian thin-plate spline regression to estimate the relationship among age, clinical status, and viral load from the first positive RT-PCR of each subject, adjusting for gender, type of test center, and PCR system used. The Bayesian model well represents the observed data (Fig. 1B, Table 2, and fig. S1). The raw data and the Bayesian estimation (Fig. 2A) suggest consideration of subjects in three age categories: young (ages 0 to 20 years, grouped into 5-year brackets), adult (20 to 65 years), and elderly (over 65 years). We estimated an average first-positive viral load of 6.40 (6.37, 6.42) for adults and a similar mean of 6.35 (6.32, 6.39) for the elderly (Fig. 2A). Younger age groups had lower mean viral loads than adults, with the difference falling steadily from −0.50 (−0.62, −0.37) for the very youngest (0 to 5 years) to −0.18 (−0.23, −0.12) for older adolescents (15 to 20 years) (Table 2). Young age groups of PAMS subjects had lower estimated viral loads than older PAMS subjects, with differences ranging from −0.18 (−0.29, −0.07) to −0.63 (−0.96, −0.32). Among Hospitalized subjects these differences were smaller, ranging from −0.18 (−0.45, 0.07) to −0.11 (−0.22, 0.01) (Table 2 and Fig. 2B). Viral loads of subjects younger than 65 years were ~0.75 higher for PAMS subjects than for Hospitalized subjects (Fig. 2A), likely because of a systematic difference in RT-PCR test timing, discussed below.

Associating viral load with cell culture infectivity

We estimated the association between viral load and successful cell culture isolation probability (hereafter "culture probability") by combining the viral load estimated from the Bayesian regression with cell culture isolation data from our own laboratory (*19*) and from Perera *et al.* (*20*) (Fig. 2C). Across all ages, the average estimated culture probability at the time of first positive RT-PCR was 0.35 (0.01, 0.94). The mean culture probability for PAMS cases, 0.44 (0.01, 0.98), was higher than for Hospitalized cases, 0.32 (0.00, 0.92) (Fig. 2D). Comparing PAMS cases, we found differences, in particular for children aged 0 to 5 compared to adults aged 20 to 65, with average culture probabilities of 0.329 (0.003, 0.950) and 0.441 (0.008, 0.981) respectively, and a difference of −0.112 (−0.279, −0.003). Age group differences in Hospitalized cases ranged from −0.028 (−0.104, 0.009) to −0.018 (−0.055, 0) (Table 2).

First-positive viral loads are weakly bimodally distributed (Figs. 1A and 2A), which is not reflected in age-specific means. The resultant distribution includes a majority of subjects with relatively low culture probability and a minority with very high culture probability (Fig. 2E and fig. S2). The highly infectious subset includes 2228 of 25,381 positive subjects (8.78%) with a first-positive viral load of at least 9.0, corresponding to an estimated culture probability of ~0.92 to 1.0. Of these 2228 subjects, 804 (36.09%) were PAMS at the time of testing, with a mean (median) age of 37.6 (34.0) and SD of 13.4 years. PAMS subjects are overrepresented in this highly infectious group among people aged 20 to 80 years, and Hospitalized subjects are overrepresented in people aged 80 to 100 years (fig. S3).

Estimating B.1.1.7 infectiousness at first-positive test

The 1533 subjects infected with a B.1.1.7 virus in our dataset had an observed mean first-positive viral load of 7.38 (SD 1.54), which is 1.05 higher (0.97, 1.13) than non-B.1.1.7 subjects in the full dataset. To increase specificity, we compared 1453 B.1.1.7 cases with

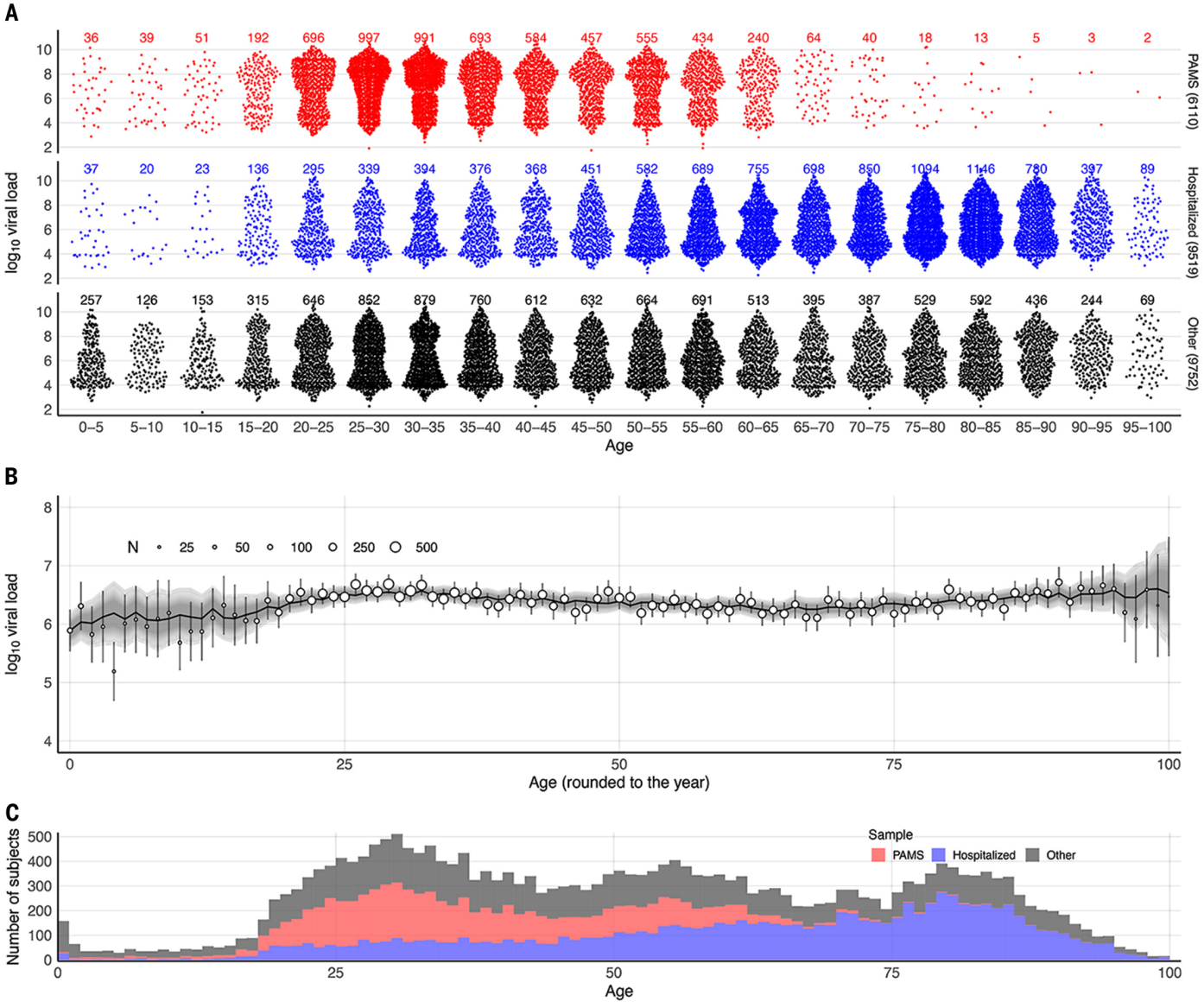


Fig. 1. Distribution of age and first-positive viral load in PAMS, Hospitalized, and Other subjects. (**A**) Distribution of observed first-positive viral loads for 25,381 subjects according to clinical status (6110 PAMS, 9519 Hospitalized, 9752 Other) and age group. (**B**) Age–viral load association. Observed viral loads are shown as circles (circle size indicates subject count) with vertical lines denoting confidence intervals; model-predicted viral loads are shown as a black, roughly horizontal line, with gray shading denoting credible intervals. (**C**) Stacked age histograms according to subject clinical status. Because inclusion in the study required a positive RT-PCR test result, and because testing is in many cases symptom-dependent, the study may have a proportion of PAMS cases that differs from the proportion in the general population.

977 non-B.1.1.7 cases using viral loads only from centers with B.1.1.7 and non-B.1.1.7 cases, and only from the same day or 1 day before or after the B.1.1.7 sample was taken. This analysis adjusted for clinical status, gender, RT-PCR system, and subject age, and also modeled random test center effects. The results show that B.1.1.7 cases are associated with a 1.0 (0.9, 1.1) higher viral load (Fig. 3 and table S2). This results in a mean estimated B.1.1.7 subject culture probability of 0.50 (0.03, 0.97), considerably higher than the overall figure of 0.31 (0.00, 0.94) for the non-B.1.1.7 subjects in the comparison, corresponding to a median factor of 2.6 (50% credible interval: 1.4, 5.1) higher culture probability for samples from B.1.1.7 cases. To investigate whether there might be a difference in cell culture infectivity due to a factor other than viral load, we isolated virus from 105 samples (22 B.1.1.7, 83 B.1.177) in Caco-2 cells from a collection of 223 samples with matched viral loads. Although no statistical difference was seen in the distribution of viral loads that resulted in successful isolation (fig. S4), uncertainty attributable to the routine diagnostic laboratory context—including uncontrolled preanalytical parameters such as transportation time and temperature, together with the small isolation-positive sample sizes—are insufficient to support a conclusion that the distributions do not differ (see materials and methods).

Estimating infectiousness over time

To investigate viral load over the course of the infection, we estimated the slopes of a model of linear increase and then decline of $\log_{10}$ viral load using a Bayesian hierarchical model. The analysis used the time series of the 4344 subjects who had RT-PCR results on at least 3 days (with at least two tests being positive). The number of subjects with multiple test

Table 2. Pairwise age comparisons of first-positive RT-PCR viral load and estimated culture probability calculated from spline regression or raw data. Only the spline-based regression adjusts for effects of the test center and RT-PCR system. Differences are mean differences, with 90% credible intervals or confidence intervals from null-hypothesis significance testing given in parentheses. *P* values are from Mann-Whitney *U* tests (*96*).

		Spline-based regression (adjusted)		Raw data (unadjusted)	
Sample	**Comparison**	**Culture probability difference**	**log_{10}(load difference)**	**log_{10}(load difference)**	***P***
All	0–5 vs. 20–65	−0.067 (−0.167, −0.002)	−0.50 (−0.62, −0.37)	−0.49 (−0.69, −0.29)	<0.001
All	5–10 vs. 20–65	−0.054 (−0.132, −0.002)	−0.40 (−0.50, −0.30)	−0.38 (−0.64, −0.13)	0.004
All	10–15 vs. 20–65	−0.045 (−0.111, −0.002)	−0.30 (−0.39, −0.22)	−0.42 (−0.65, −0.18)	<0.001
All	15–20 vs. 20–65	−0.033 (−0.076, −0.001)	−0.18 (−0.23, −0.12)	−0.16 (−0.31, −0.01)	0.033
PAMS	0–5 vs. 20–65	−0.067 (−0.167, −0.002)	−0.50 (−0.62, −0.37)	−0.49 (−0.69, −0.29)	<0.001
PAMS	5–10 vs. 20–65	−0.112 (−0.279, −0.003)	−0.63 (−0.96, −0.32)	−0.37 (−1.00, 0.26)	0.213
PAMS	10–15 vs. 20–65	−0.092 (−0.228, −0.003)	−0.51 (−0.77, −0.26)	−0.86 (−1.46, −0.26)	0.004
PAMS	15–20 vs. 20–65	−0.064 (−0.162, −0.002)	−0.35 (−0.54, −0.17)	−0.56 (−1.10, −0.02)	0.034
Hospitalized	0–5 vs. 20–65	−0.033 (−0.087, −0.001)	−0.18 (−0.29, −0.07)	−0.26 (−0.52, −0.01)	0.046
Hospitalized	5–10 vs. 20–65	−0.028 (−0.104, 0.009)	−0.18 (−0.45, 0.07)	−0.36 (−1.10, 0.37)	0.115
Hospitalized	10–15 vs. 20–65	−0.025 (−0.084, 0.003)	−0.16 (−0.36, 0.03)	−0.48 (−1.38, 0.43)	0.172
Hospitalized	15–20 vs. 20–65	−0.022 (−0.071, 0.001)	−0.14 (−0.29, 0.02)	−0.11 (−0.97, 0.74)	0.625
Other	0–5 vs. 20–65	−0.018 (−0.055, 0.000)	−0.11 (−0.22, 0.01)	0.00 (−0.33, 0.33)	0.845
Other	5–10 vs. 20–65	−0.058 (−0.148, −0.001)	−0.36 (−0.51, −0.20)	−0.33 (−0.55, −0.10)	0.004
Other	10–15 vs. 20–65	−0.044 (−0.110, −0.001)	−0.27 (−0.39, −0.15)	−0.10 (−0.40, 0.20)	0.586
Other	15–20 vs. 20–65	−0.026 (−0.072, −0.001)	−0.16 (−0.27, −0.06)	−0.31 (−0.58, −0.04)	0.045

results skews heavily toward older subjects, with very few below the age of 20 meeting the criterion (Fig. 4A). We estimated time from onset of shedding to peak viral load of 4.31 (4.04, 4.60) days, mean peak viral load of 8.1 (8.0, 8.3), and mean decreasing viral load slope of −0.168 (−0.171, −0.165) per day (fig. S5). Figure S6 shows that while Hospitalized patients are estimated to be uniformly highly infectious at peak viral load, the infectiousness of PAMS subjects at peak load is more variable.

The temporal placement of the full 18,136 RT-PCR results from these 4344 subjects (80% of whom were hospitalized with COVID-19 at some point in their infections) is shown in fig. S7. Per-subject trajectories can differ considerably from that described by the mean parameters (Fig. 4B and fig. S8). Across all subjects, PAMS cases were on average detected 5.1 (4.5, 5.7) days after peak load, 2.4 (1.7, 3.0) days before non-PAMS cases, which were on average detected 7.4 (7.2, 7.6) days after peak load. We estimate that 962 (914, 1010) of the 4344 subjects [22.14% (21.04, 23.25)] had a first positive test before the time of their peak viral load, with a mean of 1.4 (1.3, 1.5) days before reaching peak viral load. Among the infections detected after peak viral load, the timing of the first positive RT-PCR test is estimated at 9.8 (9.6, 10.0) days after peak viral load, with SD of 6.9 (6.8, 7.0) days, reflecting a broad time range of infection detection. Estimated peak viral loads were higher in Hospitalized subjects than in Other subjects, and higher in Other subjects than in PAMS subjects, with differences of 0.68 (0.83, 0.52) and 0.96 (0.33, 1.53) respectively (fig. S9 and table S3). No differences according to gender were seen. Viral load time courses were similar across age groups, although younger subjects had lower peak viral load than adults aged 45 to 55 (Fig. 5, A and C, fig. S10, and table S4). Model parameters suggest a slightly longer time to peak, a higher peak, and a more rapid decline in viral load when the analysis is restricted to subjects with successively higher numbers of RT-PCR results (fig. S11 and table S5), with an increasing percentage of hospitalized subjects. Differences in model parameters according to the number of tests in subjects may reflect increased parameter accuracy due to additional data, although other factors associated with being tested more frequently may be responsible. The Bayesian estimation of the model agrees well with a separate second implementation based on simulated annealing (fig. S12, table S5, and supplementary text).

We estimate that the rise from near-zero to peak culture probability takes 1.8 (1.3, 2.6) days, with a mean peak culture probability of 0.74 (0.61, 0.85). Mean culture probability then declines to 0.52 (0.40, 0.64) at 5 days and to 0.29 (0.19, 0.40) at 10 days after peak viral load. Subject-level time courses can deviate substantially from these mean estimates (Fig. 4C). Peak culture probabilities for age groups range from a low of 0.54 (0.39, 0.71) for 0- to 5-year-olds to 0.80 (0.67, 0.90) for subjects more than 65 years old. The least infectious youngest children have 78% (61, 94) of the peak culture probability of adults aged 45 to 55 (Fig. 5, B and D, and table S4). An insufficient amount of data precludes a reliable B.1.1.7 viral load time-series analysis at this point.

Discussion

Limitations

Our analysis attempted to account for the effects of gender, PCR system, and test center type. Although we could not incorporate inter-run variability or the variability in the sample preanalytic (such as type of swab or initial sample volume) in our conversion of RT-PCR cycle threshold values to log_{10}(viral load) values, these variabilities apply to all age groups and do not affect the interpretation of data for the purpose of our study. If the proportion of subjects with a certain clinical status differs between age groups in the study sample, this could lead to over- or underestimation of differences in viral load between age groups. However, as our study compares viral load between age groups stratified by clinical status, it appears unlikely that differential testing biases our results.

Interpreting first-positive viral loads

Viral loads and their differences are not easy to interpret without knowledge of when in the disease course the samples were taken, and of the correspondence between viral load and shedding. The higher first-positive viral loads in PAMS subjects than in Hospitalized subjects are likely due to time of detection. This is suggested in the first place by the estimated difference of 2.4 (1.7, 3.0) days in test timing, which would produce a viral load difference of ~0.4 using the −0.168 daily viral load decline gradient from the (mainly hospitalized) time-series subjects. Additionally, from the time series of PAMS, Other, and Hospitalized subjects, we can estimate that throughout the infection

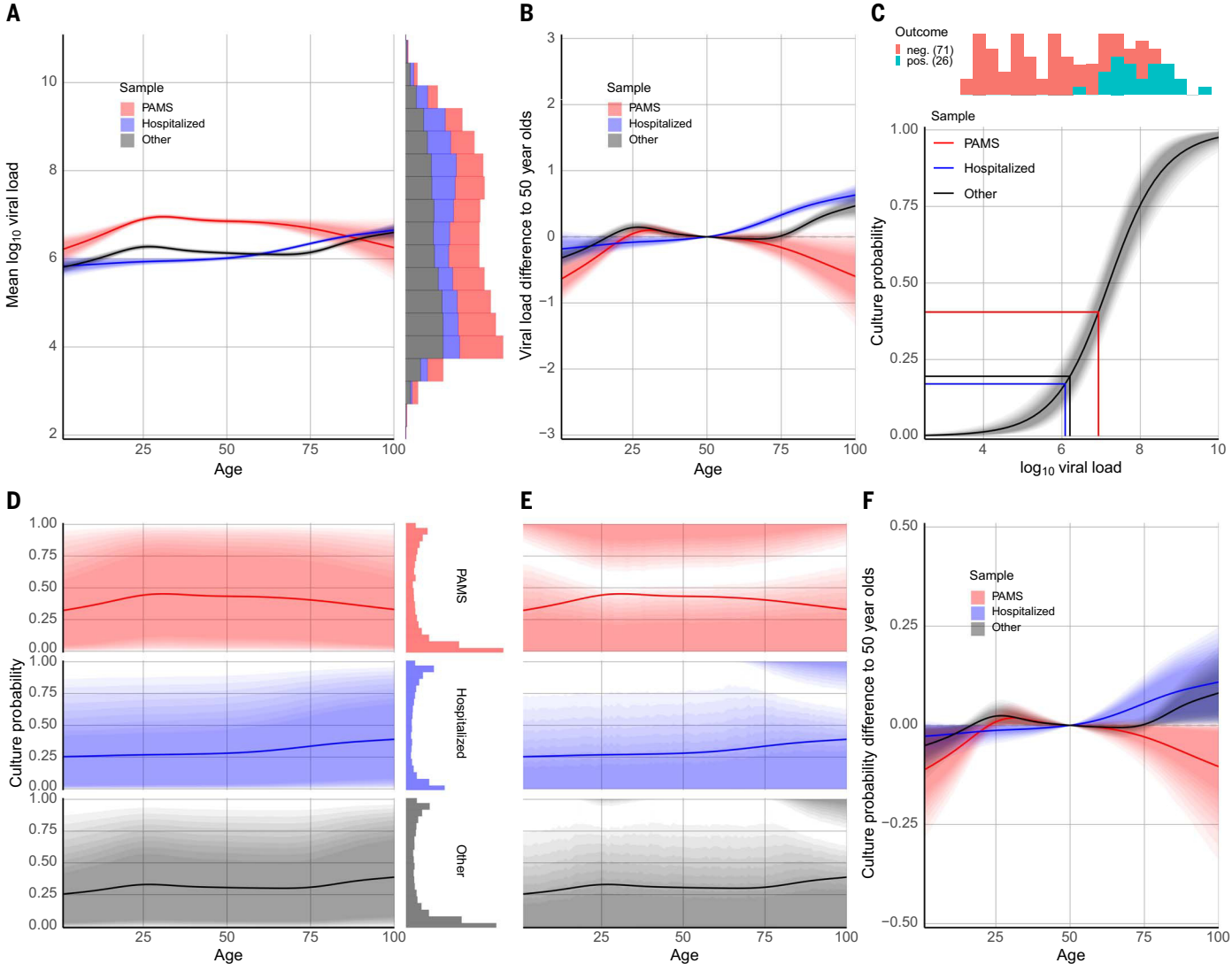


Fig. 2. Estimated viral load and culture probability at time of first positive RT-PCR test. Shaded regions denote 90% credible intervals in all panels. To indicate change within each 90% region, shading decreases in intensity from a narrow 50% credibility interval level to the full 90%. (**A**) Estimated mean viral load in first-positive RT-PCR tests according to age and status. The stacked histogram (right) shows the observed viral load distribution. Because the shaded region shows the 90% credible interval for the mean, it does not include the higher values shown in the histogram on the right. (**B**) Differences in estimated first-positive viral load according to age and status. Each colored line is specific to a particular subset of subjects (PAMS, Hospitalized, Other). Each line shows how viral load differs by age for subjects of the corresponding status from that of 50-year-old (rounded age) subjects of the same status. The comparison against 50-year-olds avoids comparing any subset of the subjects against a value (such as the overall mean) that is computed in part on the basis of that subset, thereby partially comparing data to the same data. The mean first-positive viral loads for 50-year-old PAMS and Hospitalized subjects are 7.2 and 6.2, respectively, allowing relative *y*-axis differences to be translated to approximate viral loads. (**C**) Estimation of the association between viral load and cell culture isolation success rate based on data from our own laboratory (*19*) and Perera *et al*. (*20*). Viral load differences in the $\log_{10}$ range ~6 to ~9 have a large impact on culture probability, whereas the impact is negligible for differences outside that range. The vertical lines indicate the observed mean first-positive viral loads for different subject groups; the horizontal lines show the corresponding expected probabilities of a positive culture. (**D**) Estimated culture probability at time of first-positive RT-PCR according to age and status, obtained by combining the results in (A) and (C). Culture probability is calculated from posterior predictions [i.e., the posterior means shown in (A) plus error variance]. The histogram at right shows that mean culture probabilities calculated from observed viral loads are not well matched by credible intervals, which do not include the most probable estimated culture probabilities. (**E**) Culture probability with highest–posterior density regions, which do include the most probable estimated culture probabilities and match the histograms in (D) well. The *y* axis is the same as in (D). (**F**) Differences of estimated expected culture probability at time of first-positive RT-PCR for age groups, with plot elements as described for (B).

course, the Hospitalized group has higher viral loads than the Other group, whose viral loads are in turn higher than those of the PAMS group (fig. S9 and table S3). This relationship holds across age groups (fig. S13) and also in a fine-grained split of test centers by clinical severity (fig. S14). Similarly, the lower first-positive viral loads in elderly PAMS subjects may be due to these subjects being less likely to be tested as early because they are more likely to be house-bound, less likely to be employed, less mobile, more cautious (therefore disinclined to get tested with only mild symptoms), etc. The impact on infectiousness of differences in viral load must be informed by

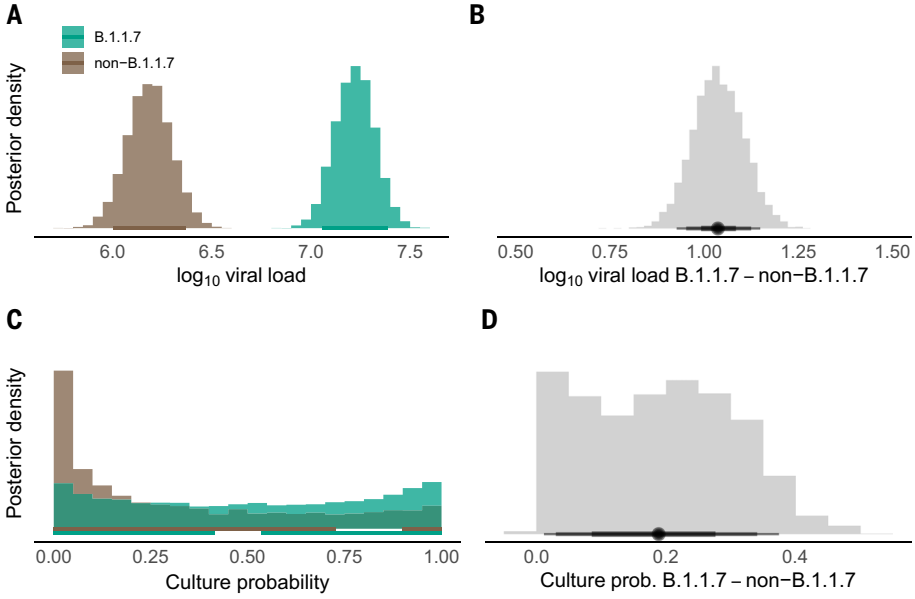


Fig. 3. Posterior distributions of estimated viral loads and culture probabilities for B.1.1.7 and non-B.1.1.7 subjects, and their differences. Viral loads and estimated culture probabilities of 1387 B.1.1.7 subjects and 977 non-B.1.1.7 subjects are represented. To select a comparable subset of non-B.1.1.7 viral loads for the comparison, we included only non-B.1.1.7 subjects from test centers that had detected a B.1.1.7 variant as well as at least one non-B.1.1.7 subject, and only if the non-B.1.1.7 infection was detected on the same day as a B.1.1.7 infection was detected, plus or minus 1 day. Similar differences exist when viral loads from larger, less restrictive, subsets of non-B.1.1.7 subjects are used in the comparison (table S2; see materials and methods). (**A**) Posterior distribution of viral load. (**B**) Posterior distribution of difference of average viral load between B.1.1.7 and non-B.1.1.7 cases. (**C**) Posterior distribution of the estimated culture probability. See also fig. S2. (**D**) Difference of mean culture probability between B.1.1.7 and non-B.1.1.7 cases. Horizontal lines indicate 90% credible intervals in (A), (B), and (D) and the highest posterior density intervals in (C).

where the viral loads fall on the viral load–culture probability curve. In our data, the viral loads involved in the difference between means in children and adults and the difference between means in B.1.1.7 and non-B.1.1.7 subjects result in quite different corresponding culture probabilities (see below).

A highly infectious minority and overdispersion

The bimodal distribution of culture probabilities (Fig. 2, D and E) shows a small group of 8.78% of highly infectious subjects. This qualitatively agrees with a model (*21*) and a study (*22*) concluding that 10% and 15% of index cases, respectively, may be responsible for 80% of transmission. Other studies reported that 8 to 9% of individuals harbored 90% of total viral load (*23*), and that in cases from India (*24*) and Hong Kong (*6*) ~70% of index cases had no secondary cases. PAMS subjects can be construed to pose a risk for several reasons: 36.1% of the highly infectious subjects in our study were PAMS at the time of the detection of their infection, their mean age was 37.6 years with a high standard deviation of 13.4 years (figs. S2 and S3), and we estimate that infectiousness peaks 1 to 3 days before onset of symptoms (if any).

Comparison with influenza virus

Without direct knowledge from a large number of SARS-CoV-2 transmission events, we could try to draw conclusions regarding infectiousness from studies of other respiratory viruses, such

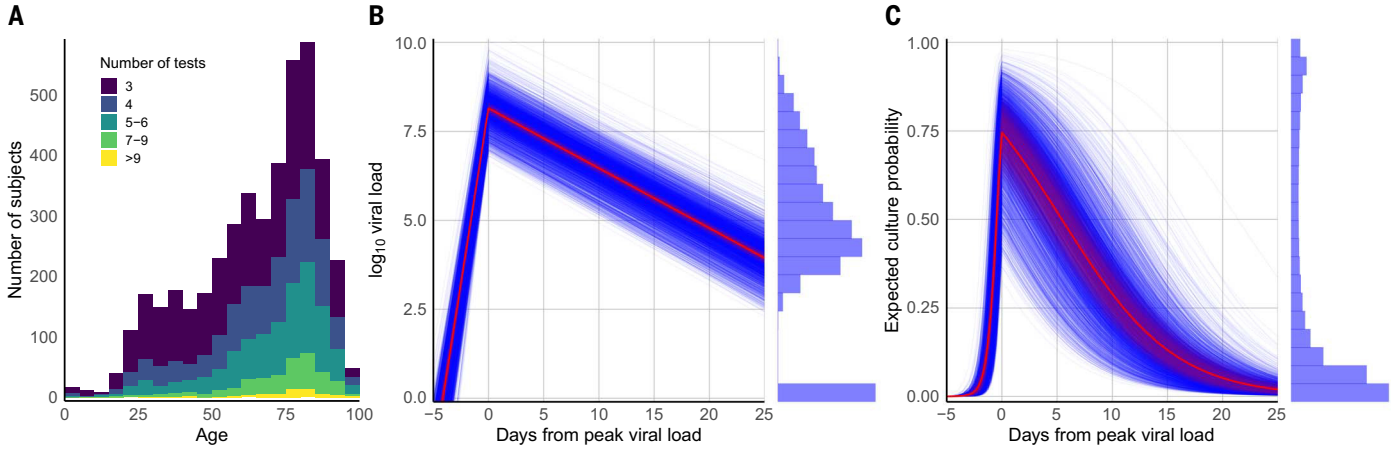


Fig. 4. Viral load and estimated infectious virus shedding time series. Of 25,381 positive subjects, 4344 had three or more RT-PCR test results available, and these were used in a viral load time-series analysis. Subjects with only one result cannot be placed in time because of inherent ambiguity (given that the model has both an increasing and a decreasing phase), and those with only two test results are excluded from the time-series analysis because of insufficient data for temporal placement (their number of data points is less than the number of model parameters being estimated). (**A**) Number of subjects with three or more RT-PCR test results available, at least two of which were positive, according to age. (**B**) Estimated time course of viral load for 18,136 RT-PCR results from the 4344 subjects with at least three RT-PCR results. Blue lines are expected complete time courses for individual cases. The sample mean is shown in red, with its 90% credible interval as a shaded area. The histogram at right shows the distribution of all observed viral loads. The histogram values at zero correspond to the initial and trailing negative tests in subject timelines. Figure S8 shows raw viral load time series, per subject and split by number of RT-PCR tests. (**C**) Estimated time course of positive cell culture probability, calculated by applying the results shown in Fig. 2C to the estimated viral load time courses in (B). Blue lines are expected time courses for individual subjects. The sample average is shown in red, with its 90% credible interval as a shaded area. The histogram at right shows the distribution of culture probabilities in the sample and was obtained by applying the curve in Fig. 2C to the data in the histogram in (B).

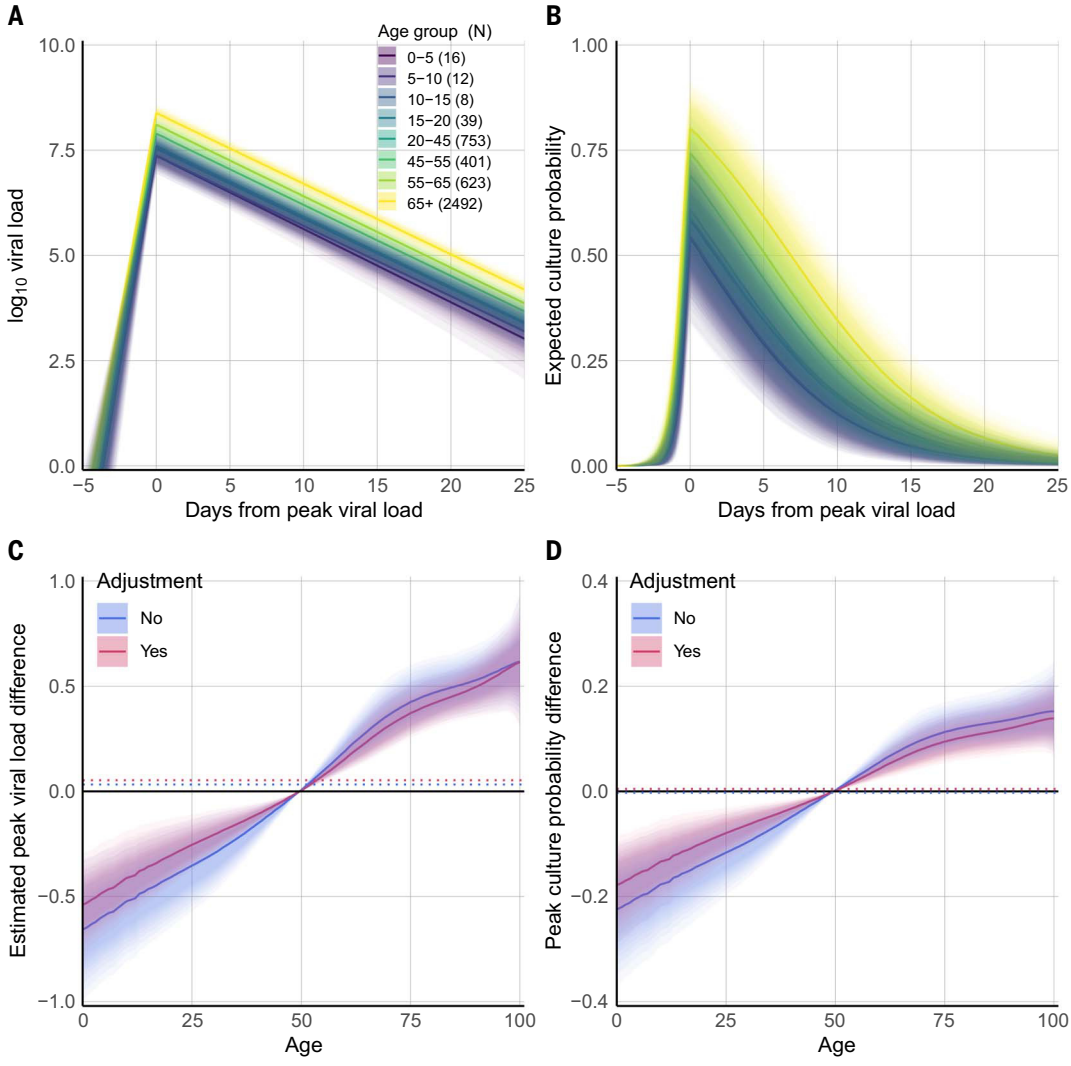


Fig. 5. Estimated expected viral load and culture probability for age groups by time. (**A**) Change in estimated viral load over time according to age group for 4344 subjects with at least three RT-PCR tests, at least two of which were positive. Shading indicates the 90% credible interval of the mean. (**B**) Change in estimated culture probability over time according to age. Age groups, coloring, and shading are as in (A). (**C**) Estimated age group differences in mean peak viral load, corresponding to the values at day zero in (A). (**D**) Estimated age group differences in mean peak culture probability, corresponding to the values at day zero in (B). In (C) and (D), adjusted differences account for variations by age in clinical status and gender. Dotted lines indicate grand means for the 4344 subjects.

as influenza. However, it has become clear that there are important differences and uncertainties that would cast doubt on such a comparison. Influenza may have later onset of viral shedding; shedding finishes earlier; there may be a lower secondary attack rate; viral loads are much lower; there is variation between virus subtypes; the role of asymptomatic subjects in transmission is uncertain or thought to be reduced; and the frequency of asymptomatic infections is uncertain, especially in children (*10*, *11*, *25*–*29*). Age-specific behavioral differences do, however, make a large contribution to the established higher shedding of children relative to adults in influenza. This should be an important consideration for SARS-CoV-2, as shown by studies indicating higher transmission between children of similar ages (*6*, *24*) and high transmission heterogeneity (*22*). Despite many decades of close study of influenza virus, the relationship between viral load and transmission is unclear (*10*, *11*). The situation with respiratory syncytial virus is even less clear (*30*). Understanding SARS-CoV-2 transmission will likely be at least as challenging, given the high frequency of transmission from PAMS subjects (*1*–*8*). This suggests an important role for clinical parameters, given the apparently strong association between viral load and transmission, independent of symptoms (*9*).

Estimated infectiousness in the young

The differences we observe in first-positive RT-PCR viral load between groups based on age are minor, as in other studies (*31*–*35*), and the viral loads in question—in the range of 5.9 to 6.6 (Table 1)—are in a region of the viral load–culture probability association where changes in viral load have relatively little impact on estimated culture probability (Fig. 2C). Comparisons between adult viral loads and those of children, and the relative infectious risks they pose, are impeded by the likely influence of nonviral factors. Nasopharyngeal swab samples, which often carry higher viral loads, are rarely taken from young children because they can be painful, and the sample volume carried by smaller pediatric swab devices is lower than in larger swabs used for adults (*36*). Infections in mildly symptomatic children may be initially missed and only detected later (*37*), resulting in lower first-positive viral loads. Our results of similar viral load trajectories for children and adults (Fig. 5), and the numeric range of the viral load values in question (Fig. 2C), suggest that viral load differences between children and adults are too small to be solely responsible for large differences in infectiousness. The impact on transmission of general age-related physiological differences, such as different innate immune responses (*38*), may be small relative to the impact of large differences in frequency of close contacts and transmission opportunities.

Timing of estimated peak infectiousness relative to onset of symptoms

We estimated the time from onset of shedding to peak viral load at 4.3 days. Previous studies

and reviews of COVID-19 report mean incubation times of 4.8 to 6.7 days (*4*, *39*–*44*), which suggests that, on average, a period of high infectivity can start several days before the onset of symptoms. Viral load rise may vary between individuals, and limitations of the available data suggest that our analysis may underestimate interindividual variation in viral load increase. The failure to isolate virus in cell culture beyond 10 days from symptom onset (*19*, *20*, *35*, *45*, *46*), together with our estimated slope of viral load decline, also suggest that peak viral load occurs 1 to 3 days before symptom onset (supplementary text). Data from 171 hospitalized patients from a Charité-Universitätsmedizin cohort suggest a figure of 4.3 days (fig. S15 and supplementary text).

Estimated infectiousness of the B.1.1.7 variant

We found that people infected with a B.1.1.7 virus had a first-positive viral load that was ~1 higher than in people infected with a wild-type virus. The scale of the viral load difference, and its presence in the comparison between B.1.1.7-infected and non–B.1.1.7-infected subjects drawn from the same test centers at the same times, argue that the difference is not due to a systematic difference in time of sampling. The higher B.1.1.7 viral load can be compared to the findings of two large and closely controlled UK studies, a mortality study (*47*) and a vaccine trial (*48*), which imply higher B.1.1.7 viral loads by a factor of 5 to 10 (based on RT-PCR cycle threshold differences of 2.3 and ~3, respectively). Several other studies also appear to point to a higher B.1.1.7 viral load (*49*–*52*) (supplementary text).

The mean B.1.1.7 viral load value in our study falls in a region of the viral load–culture probability curve with a steep gradient (Fig. 2C), resulting in an estimated culture probability considerably higher than for non-B.1.1.7 subjects. Although a strong correlation has been observed between SARS-CoV-2 viral load and transmission (*9*), here we are estimating infectivity probability from cell culture trials. Any impact of a change in viral load on transmission will be highly dependent on context, so the large difference in estimated culture probability in our data is only a proxy indication of potentially higher transmissibility of the B.1.1.7 strain. We estimate that B.1.1.7-infected subjects' mean culture probability is higher than that of non–B.1.1.7-infected subjects by a factor of 2.6. This can be compared to a UK study that found a factor of 1.3 relative increase in secondary attack rates for B.1.1.7 index cases in ~60,000 household contacts (*53*), a UK study estimating a factor of 1.7 to 1.8 increase in transmission (*54*), and an estimate of a 43% to 90% higher reproductive number (*55*).

Summary

Our results indicate that PAMS subjects in apparently healthy groups can be expected to be as infectious as hospitalized patients at the time of detection. The relative levels of expected infectious virus shedding of PAMS subjects (including children) is of high importance because these people are circulating in the community and it is clear that they can trigger and fuel outbreaks (*56*). The results from our time-series analysis, and their generally good agreement with results from studies based on other metrics (often epidemiological), show that accurate estimations can be directly obtained from two easily measured virological parameters, viral load and sample cell culture infectivity. Such results can be put to many uses: to estimate transmission risk from different groups (by age, gender, clinical status, etc.), to quantify variance, to show differences in virus variants, to highlight and quantify overdispersion, and to inform quarantine, containment, and elimination strategies. Our understanding of the timing and magnitude of change in viral load and infectiousness, including the impact of influencing factors, will continue to improve as data from large studies accumulate and are analyzed. A major ongoing challenge is to connect what we learn about estimated infectiousness from these clinical parameters to highly context-dependent in vivo transmission. On the basis of our estimates of infectiousness of PAMS subjects and the higher viral load found in subjects infected with the B.1.1.7 variant, we can safely assume that nonpharmaceutical interventions such as social distancing and mask wearing have been key in preventing many additional outbreaks. Such measures should be used in all social settings and across all age groups wherever the virus is present.

Materials and methods

Age ranges

Age categories for the analysis of the first-positive test results mentioned in the text indicate mathematically open-closed ranges of years (e.g., 0-5 signifies (0-5] years). We group subjects up to 20 years old into age categories spanning 5 years, subjects from 20 to 65 years into an adult group, and elderly subjects into a 65+ category. This categorization is motivated by the observed data and the Bayesian estimation of viral load differences between children of different ages and adults. The age groupings used in the viral load time-series analysis are broader in the younger categories to increase the cardinality of those groups, because few young people have at least three RT-PCR tests (Fig. 4A).

Viral loads

Viral load is semiquantitative, estimating RNA copies per entire swab sample, whereas only a fraction of the volume can reach the test tube. The quantification is based on a standard preparation tested in multiple diluted replicates to generate a standard curve and derive a formula in which RT-PCR cycle threshold values are converted to viral loads. This approach does not reflect inter-run variability or the variability in the sample preanalytic, such as type of swab or initial sample volume (varying between 2.0 and 4.3 ml). However, these variabilities apply to all age groups and do not affect the interpretation of data for the purpose of the present study.

Viral load figures are given as the logarithm base 10. Viral load is estimated from the cycle threshold (Ct) value using the empirical formulae $14.159 - (Ct \times 0.297)$ for the Roche Light Cycler 480 system and $15.043 - (Ct \times 0.296)$ for the Roche cobas 6800/8800 systems. The formulae are derived from testing standard curves and cannot be transferred to calculate viral load in other laboratory settings. Calibration of the systems and chemistries in actual use is required.

B.1.1.7 viral load analysis

No analysis regarding symptomatic status was made for B.1.1.7 subjects because of uncertainties regarding exact operational protocols at outbreak hospitals. B.1.1.7 assignment to samples was initially made according to typing RT-PCR tests that detect the N501Y and 69/70 deletion in the amino acid sequence of the virus spike protein. Examination of the complete viral genome of 49 samples confirmed that the subjects were in fact infected with the B.1.1.7 variant, with all variant-defining substitutions and deletions (*57*) found in all cases. No consistent additional mutations or deletions/insertions were found in the sequences.

Sequencing read mapping was performed with Bowtie, with alignment using MAFFT and visual inspection using Geneious Prime (all version numbers given below). For the statistical comparison of B.1.1.7 and non-B.1.1.7 subjects, we identified test centers (hospital departments or wards, or organizations outside hospitals) that reported B.1.1.7 cases, and chose as comparison groups non-B.1.1.7 cases that were detected in these test centers on the same day or 1 day earlier or later. By modeling random effects for test centers, we estimate the expected viral load difference as the average of the within-test center differences. The consistent effect of B.1.1.7 throughout a range of comparison scenarios is shown in table S2.

Sample type

An estimated 3% of our samples were from the lower respiratory tract. These were not removed from the dataset because of their low frequency and the fact that the first samples for patients are almost universally swab samples. Samples from the lower respiratory tract are generally taken from patients only after intubation, by which point viral loads have typically fallen.

PAMS status

Metadata needed to discriminate patients into subcohorts on the basis of underlying diseases,

outcome, or indications for diagnostic test application, including symptomatic status, were not always available. In the absence of subject-level data, we inferred PAMS status using the type of submitting test center as an indicator, classifying subjects as PAMS at the time of testing if their first-positive sample was taken from a walk-in COVID-19 test center and the subject had no later RT-PCR test done in a hospitalized context (e.g., in a ward or an intensive care unit). The correspondence between viral load and PAMS status derived herein may therefore be less accurate than in studies with subject-level symptom data. However, we make no formal claims regarding symptomatic status, and instead emphasize the fact that these PAMS subjects were healthy enough to be presenting at walk-in COVID-19 test centers, and were therefore capable to some extent, at that time, of circulating in the general community.

Bayesian analysis of age–viral load associations

We estimated associations of viral load and age with a thin-plate spline regression using the brms package (*58*, *59*) in R (*60*). Spline coefficients were allowed to vary between groups determined by the clinical status (PAMS, Hospitalized, or Other), and random intercepts captured effects of test centers. To reduce the impact of outliers, we used Student *t*–distributed error terms. The analysis additionally accounted for baseline differences between subject groups, B.1.1.7 status, gender, and for the effect of the RT-PCR system. We also estimated the association between viral load and culture probability in order to calculate the expected culture probability at different age levels. This analysis used weakly informative priors and was estimated using four chains with 1000 warm-up samples and 2000 post–warm-up samples. Convergence of MCMC chains was examined by checking that potential scale reduction factors (R-hat) values were below 1.1. All calculations of age averages and group differences are based on posterior predictions generated from estimated model parameters. Expected probabilities of positive cultures (and their differences) were calculated by applying the posterior distribution of model parameters from the culture probability model to posterior predictions from the age association model.

Combining culture probability data

To estimate the association between viral load and culture probability, we used data previously described by Wölfel (*19*) and Perera (*20*). Four other datasets could not be included because Ct values were not converted to viral loads (*35*, *46*, *61*, *62*). The data from the study by van Kampen *et al.* (*63*) were not included because they differed (by viral load of ~1.0) from the data used for the current analysis (*97*); this is likely due to a combination of factors including many patients who were in critical or immunocompromised condition, a high proportion of samples obtained from the lower respiratory tract (including late in the infectious course), and likely differences in cell culture trials. It is unsurprising that these data result in a shifted viral load/culture probability curve, and we excluded them because our focus was largely on first positive RT-PCR results from the upper respiratory tract, including from many subjects who were PAMS. [See (*97*) for a figure comparing the plot of the van Kampen dataset to the two we used.] To calculate the expected culture probability, by age (as in Fig. 2D) or by day from peak viral load (as in Fig. 4C), we combined the estimated viral loads (Figs. 2A and 4B) with the results of the regression of culture probability shown in Fig. 2C. We used posterior predictions from the age regression model, which reflect the variation of viral load within age groups, to estimate culture probabilities by age. For instance, to obtain the culture probability for a specific age and group, we look up the estimated (expected) viral load for that group, add an error term according to the estimated error variance, and, using the association shown in Fig. 2C, determine the expected culture probability. We used expected time courses (i.e., the model's best guess for a time course) to estimate culture probability time courses.

B.1.1.7 isolation data

The Institute of Virology at Charité–Universitätsmedizin Berlin routinely receives SARS-CoV-2–positive samples for confirmatory testing and sequencing. For this study we used anonymized remainder samples from a large laboratory in northern Germany, which were all stored in phosphate-buffered saline (PBS) and therefore suitable for cell culture isolation trials. Sample transport to the originating lab and later to Berlin was unrefrigerated, via road. As part of the routine testing, these samples were classified by typing RT-PCR and complete genome sequencing (*64*); 113 B.1.1.7 lineage samples and 110 B.1.177 lineage samples were selected, with approximately matched (pre-inoculation) SARS-CoV-2 RNA concentrations. Caco-2 (human colon carcinoma) cell cultures (*65*) were inoculated twice from each sample, once with undiluted material and once with a 1:10 dilution. The diluted inoculant was used to reduce the probability of culturing failure due to the possible presence of host immune factors (antibodies, cytokines, etc.) that might have a negative impact on isolation success, and to reduce the possibility of other unrelated agents (bacteria, fungi, etc.) resulting in cytopathic effect in the culture system. For cell culture isolation trials, 1.6×10^5 cells were seeded per well in a 24-well plate. Cells were inoculated with swab suspensions for 1 hour at 37°C, subsequently rinsed with PBS, and fed with 1 ml of fresh Dulbecco's modified Eagle's minimum essential medium (DMEM; ThermoFisher Scientific) supplemented with 2% fetal bovine serum (FBS; Gibco), penicillin and streptomycin (P/S; 100 U/ml and 100 μg/ml, respectively; ThermoFisher Scientific), and amphotericin B (2.5 μg/ml; Biomol), then incubated for 5 days before harvesting supernatant for RT-PCR testing. Positive cell culture isolation was defined by a minimum 10× higher SARS-CoV-2 RNA load in the supernatant compared to the inoculant and signs of a typical SARS-CoV-2 cytopathic effect. Culture isolation was successful for 22 B.1.1.7 and 61 B.1.177 samples. Because of uncertainty regarding sample handling before arrival at the originating diagnostic laboratory and the unrefrigerated transport, it was not possible to determine whether isolation failures were due to samples containing no infectious particles (due to sample degradation) or for other reasons. Such reasons could include systematic handling differences according to variant type or a difference in virion stability and durability regarding environmental factors such as temperature. Therefore, samples with negative isolation outcome were excluded from analysis. The strong likelihood of many cases of complete sample degradation is evident from the isolation failure of many samples with high pre-inoculation viral load, with the viral load in these cases merely indicating the presence of noninfectious SARS-CoV-2 RNA (fig. S4). Given this context, we were reduced to questioning whether there might be a difference in the range of viral loads that were able to result in isolation between B.1.1.7 and non-B.1.1.7 variants. Such a difference could result from a difference in the ratio of viral RNA to infectious particles produced by the variants, or from a difference other than viral load in the variants. We examined the distribution of pre-inoculation viral loads from isolation-positive samples from both variants for a difference. No statistically significant difference was found, but in the converse, the isolation-positive sample sizes are too low to support the assertion that the distributions do not differ.

Estimating viral load time course

Each RT-PCR test in our dataset has a date, but no information regarding the suspected date of subject infection or onset of symptoms (if any). Although determining the day of peak viral load for a single person based on a series of dated RT-PCR results would not in general be feasible because of individual variation, data from a large enough set of people would enable the inference of a clear and consistent model of viral load change over time with very few assumptions.

We included a single leading and/or trailing negative RT-PCR result, if dated within 7 days of the closest positive RT-PCR. To produce a model of typical viral load decline on a reasonable single-infection time scale, we excluded

subjects whose full time series contains positive RT-PCRs spread over a period exceeding 30 days. Such time series may be attributable to contamination, to later swabbing that picks up residual RNA fragments in tonsillar tissue (*66*), or to re-infection (*67*–*69*), or they may represent atypical infection courses (such as in immunocompromised or severely ill elderly patients) (*70*). We excluded data from subjects with an infection delimited by both an initial and a trailing negative test when there was only a single positive RT-PCR result between them.

We estimated the slopes for a model of linear increase and then decline of $\log_{10}$(viral load). To compensate for the absence of information regarding time of infection, we also estimated the number of days from infection to the first positive test for each participant, so as to position the observed time series relative to the day of peak viral load. The analysis was implemented in two ways. Initially, simulated annealing was used to find an optimized fit of the parameters, minimizing a least-squares error function. Second, a Bayesian hierarchical model estimated subject-specific time courses, imputed the viral load assigned to each initial or trailing negative test, and captured effects of age, gender, clinical status, and RT-PCR system with model parameters. We tested both methods on data subsets ranging from subjects with at least three to at least nine RT-PCR results. The two methods produced results that were in generally good agreement (table S5). The finer-grained Bayesian approach appears more sensitive than the simulated annealing; its results, for subjects with at least three RT-PCR results, are those described in the main text.

Simulated annealing approach: A simulated annealing optimization algorithm (*71*) was used to adjust the time series for each subject slightly earlier or later in time, by amounts drawn from a normal distribution with mean 0.0 and standard deviation 0.1 days. The error function was the sum of squares of distances of each viral load from a viral load decline line whose slope was also adjusted as part of the annealing process. In the error calculation, negative test results were assigned a viral load of 2.0, in accordance with our SARS-CoV-2 assay limit of detection and sample dilution (*19*). The initial slope of the decline line was set to –2.0 and was varied using $N(0, 0.01)$. A second, optional, increase line initialized with a slope of 2.0, adjusted using an $N(0, 0.01)$ random variable, was included in the error computation if the day of a RT-PCR test was moved earlier than day zero (the modeled day of peak viral load). The height of the intercept (i.e., the estimated peak viral load) between the increase line (if any) and the decline line was also allowed to vary randomly [starting value 10.0, varied using $N(0, 0.1)$]. The full time series for each subject was initialized with the first positive result positioned at day 2 + $N(0.0, 0.5)$ after peak viral load. The random-move step of the simulated annealing modified either of the two slopes or the intercept, each with probability 0.01, otherwise (with probability 0.97) one subject's time series was randomly chosen to be adjusted earlier or later in time. After the simulated annealing stage, each time series was adjusted to an improved fit (when possible) based on the optimized increase and decline lines. Linear regression lines were then fitted through the results occurring before and after the peak viral load ($x = 0$) and compared to the lines with slopes optimized by the simulated annealing alone. This final step helped to fine-tune the simulated annealing, in particular sometimes placing a time series much earlier or much later in time after it had stochastically moved initially in a direction that later (when the increase and decline line slopes had converged) proved to be suboptimal. The slopes of the lines fitted via linear regression after this final step were in all cases very similar (generally ±0.1) to those produced by the initial simulated annealing step. The final adjustments can be regarded as a last step in the optimization, using a steepest-descent movement operator instead of an uninformed random one. A representative optimization run for subjects with at least three RT-PCR results is shown in fig. S12.

Bayesian approach: The Bayesian analysis of viral load time course implements the same basic model, and additionally estimates associations of model parameters with covariates age, gender, B.1.1.7 status, and clinical status, estimates subject-level parameters (slope of $\log_{10}$ viral load increase, peak viral load, slope of $\log_{10}$ viral load decrease) as random effects, and accounts for effects of PCR system and test center types with random effects. To estimate the number of days from infection to the first test (henceforth "shift"), we constrained the possible shift values from –10 to 20 days and used a uniform prior on the support. In contrast to the other subject-level parameters, we estimated subject-level shifts independently (i.e., without a hierarchical structure). Figure S7 shows the placement in time of individual viral loads after shifting for subjects with RT-PCR results from at least 3 days. Model parameters changed gradually when subsets of subjects with an increasing minimum number of RT-PCR results, from three to nine, were examined (fig. S11 and table S5). The viral load assigned to negative test results (which may include viral loads below the level of detection) is estimated with a uniform prior on the support from –Inf to 3 (see also the caption of fig. S7). Using prior predictive simulations, we specified (weakly) informative priors for this analysis. This analysis was implemented in Stan (*72*), as described in (*97*).

Checking convergence of the model parameters showed that although 99.3% of all parameters converged with an R-hat value below 1.1, some subject-level parameters of 118 subjects (among 4344 subjects with at least three RT-PCR results) showed R-hat values between 1.1 and 1.74. Inspection of these parameters showed that these convergence difficulties were due to observed time courses that could arguably be placed equally well at the beginning or a later stage of the infection. Figure S16 shows a set of 81 randomly selected posterior predictions, to give an impression of time-series placement; fig. S17 shows the 49 participants with the parameters with the highest R-hat values. Although the high R-hat values could be removed by using a mixture approach to model shift for these participants, in light of their low frequency we retained the simpler model to avoid additional complexity. Alternatively, constraining the shift parameter to negative numbers would also improve R-hat values for these subjects, at the cost of the additional assumption that infections are generally not detected weeks after infection.

Sensitivity analysis: In addition to examining the viral load time series of subjects with RT-PCR results on at least 3 days, we tested both approaches on data from subjects with results from a minimum of 4 to 9 days. Given the degree of temporal viral load variation seen in other studies (*18*–*20*, *35*, *41*, *46*, *63*, *73*, *74*) and in our own data, our expectation was that a relatively high minimum number of results might be required before reliable parameter estimates with small variance would be obtained, but this proved not to be the case. The simulated annealing approach was tested with a wide range of initial slopes and intercept heights as well as seven different methods for the initial placement of time series. In general, maximum viral load and decline slopes were robust to data subset and initial time-series location, although there was variation in the length of the time to peak viral load, depending on how early in time the time series were initially positioned, the initial slopes of the increase and decrease lines and height of the maximum viral load. This is as expected, as the settings of these parameters can be used to bias the probability that a time series is initially positioned early or late in time and how difficult it is for it to subsequently move to the other side of the peak viral load at day zero. Table S5 shows parameter values for both approaches on the various data subsets.

Onset of shedding: We define the onset of shedding as the time point at which the increasing viral load crosses zero of the $\log_{10}$ y axis—that is, when just one viral particle was estimated to be present. Because the estimated time of infection depends on the estimated peak viral load and the slope with which viral load increases, the data should optimally include multiple pre-peak viral load test results for each individual. If, as in the

current dataset, only a subset of subjects have test results from pre-peak viral load, a hierarchical modeling approach still allows calculating subject-level estimates. Intuitively, this approach uses data from all subjects to calculate an average slope parameter for increasing viral load. In addition, it models subject-level parameters as varying around the group-level parameter. To further refine the estimation of slope parameters, the model also uses the age (see fig. S10), gender, and clinical status as covariates. Because negative test results could be false negatives, viral loads for these tests are imputed (with an upper bound of 3). Subject-level peak viral load and declining slope are modeled with the same approach. More generally, using a hierarchical model and shrinkage priors for the effects of covariates results in more accurate predictions in terms of expected squared error (*75*) compared to analyzing each subject in isolation, but the overall improvement introduces a slight bias toward the group mean, resulting in an underestimation of the true variability of subject-level parameters. This is especially the case if, as in the current dataset, subject-level data are sparse.

Onset of symptoms: The 317 onset-of-symptoms dates for hospitalized patients were collected as part of the Pa-COVID-19 study, a prospective observational cohort study at Charité–Universitätsmedizin Berlin (*76*, *77*), approved by the local ethics committee (EA2/066/20), conducted according to the Declaration of Helsinki and Good Clinical Practice principles (ICH 1996), and registered in the German and WHO international clinical trials registry (DRKS00021688).

Software

The following Python (version 3.8.2) software packages were used in the data analysis and in the production of figures: Scipy (version 1.4.1) (*78*), pandas (version 1.0.3) (*79*), statsmodels (version 0.11.1) (*80*), matplotlib (version 3.2.1) (*81*), numpy (1.18.3) (*82*), seaborn_sinaplot (*83*), simanneal (version 0.5.0) (*71*), and seaborn (version 0.10.1) (*84*). Sequence analysis used Bowtie2 (2.4.1) (*85*), bcftools and samtools (1.9) (*86*, *87*), Geneious Prime (2021.0.3) (*88*), ivar (1.2.2) (*89*), and MAFFT (4.475) (*90*). Analyses in R (4.0.2) (*60*) were conducted using the following main packages: brms (2.13.9) (*58*, *59*), rstanarm (2.21.1) (*91*), rstan (2.21.2) (*92*), data.table (1.13.3) (*93*), and ggplot2 (3.3.2) (*94*). Bayesian analysis in R was based on Stan (2.25) (*72*). Parallel execution was performed with GNU Parallel [20201122 ('Biden') (*95*)].

Data curation and anonymization

Research clearance for the use of routine data from anonymized subjects is provided under paragraph 25 of the Berlin *Landeskrankenhausgesetz*. All data are anonymized before processing to ensure that it is not possible to infer patient identity from any processing result. All patient information is securely combined into a token that is then replaced with a value from a strong one-way hash function prior to the distribution of data for analysis. Viral loads are calculated from RT-PCR cycle threshold values that have only one decimal place of precision.

REFERENCES AND NOTES

1. S. Lee *et al*., Clinical Course and Molecular Viral Shedding Among Asymptomatic and Symptomatic Patients With SARS-CoV-2 Infection in a Community Treatment Center in the Republic of Korea. *JAMA Intern. Med.* **180**, 1447–1452 (2020). doi: 10.1001/jamainternmed.2020.3862; pmid: 32780793
2. C. M. Szablewski *et al*., SARS-CoV-2 Transmission and Infection Among Attendees of an Overnight Camp - Georgia, June 2020. *MMWR Morb. Mortal. Wkly. Rep.* **69**, 1023–1025 (2020). doi: 10.15585/mmwr.mm6931e1; pmid: 32759921
3. Q.-X. Long *et al*., Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections. *Nat. Med.* **26**, 1200–1204 (2020). doi: 10.1038/s41591-020-0965-6; pmid: 32555424
4. Q. Bi *et al*., Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: A retrospective cohort study. *Lancet Infect. Dis.* **20**, 911–919 (2020). doi: 10.1016/S1473-3099(20)30287-5; pmid: 32353347
5. T. Waterfield *et al*., Seroprevalence of SARS-CoV-2 antibodies in children: A prospective multicentre cohort study. *Arch. Dis. Child.* 10.1136/archdischild-2020-320558 (2020). doi: 10.1136/archdischild-2020-320558; pmid: 33172887
6. D. C. Adam *et al*., Clustering and superspreading potential of SARS-CoV-2 infections in Hong Kong. *Nat. Med.* **26**, 1714–1719 (2020). pmid: 32943787
7. M. Hippich *et al*., A public health antibody screening indicates a six-fold higher SARS-CoV-2 exposure rate than reported cases in children. *Med* **2**, 149–163.e4 (2020). doi: 10.1038/s41586-020-2488-1; pmid: 32604404
8. E. Lavezzo *et al*., Suppression of a SARS-CoV-2 outbreak in the Italian municipality of Vo'. *Nature* **584**, 425–429 (2020). doi: 10.1038/s41586-020-2488-1; pmid: 32604404
9. M. Marks *et al*., Transmission of COVID-19 in 282 clusters in Catalonia, Spain: A cohort study. *Lancet Infect. Dis.* **21**, 629–636 (2021). doi: 10.1016/S1473-3099(20)30985-3; pmid: 33545090
10. L. L. H. Lau *et al*., Viral shedding and clinical illness in naturally acquired influenza virus infections. *J. Infect. Dis.* **201**, 1509–1516 (2010). doi: 10.1086/652241; pmid: 20377412
11. T. K. Tsang *et al*., Individual Correlates of Infectivity of Influenza A Virus Infections in Households. *PLOS ONE* **11**, e0154418 (2016). doi: 10.1371/journal.pone.0154418; pmid: 27153194
12. E. A. Meyerowitz, A. Richterman, I. I. Bogoch, N. Low, M. Cevik, Towards an accurate and systematic characterisation of persistently asymptomatic infection with SARS-CoV-2. *Lancet Infect. Dis.* S1473-3099(20)30837-9 (2020). doi: 10.1016/S1473-3099(20)30837-9; pmid: 33301725
13. A. Fontanet *et al*., SARS-CoV-2 infection in schools in a northern French city: A retrospective serological cohort study in an area of high transmission, France, January to April 2020. *Euro Surveill.* **26**, 2001695 (2021). doi: 10.2807/1560-7917.ES.2021.26.15.2001695
14. C. Stein-Zamir *et al*., A large COVID-19 outbreak in a high school 10 days after schools' reopening, Israel, May 2020. *Euro Surveill.* **25**, (2020). doi: 10.2807/1560-7917.ES.2020.25.29.2001352; pmid: 32720636
15. I. W. Pray *et al*., COVID-19 Outbreak at an Overnight Summer School Retreat - Wisconsin, July-August 2020. *MMWR Morb. Mortal. Wkly. Rep.* **69**, 1600–1604 (2020). doi: 10.15585/mmwr.mm6943a4; pmid: 33119558
16. J. P. Torres *et al*., SARS-CoV-2 antibody prevalence in blood in a large school community subject to a Covid-19 outbreak: A cross-sectional study. *Clin. Infect. Dis.* ciaa955 (2020). doi: 10.1093/cid/ciaa955; pmid: 32649743
17. M. H. Ebell, C. Chupp, M. Bentivegna, A high proportion of SARS-CoV-2-infected university students are asymptomatic. *J. Fam. Pract.* **69**, 428–429 (2020). pmid: 33176345
18. S. M. Kissler *et al*., Viral dynamics of SARS-CoV-2 infection and the predictive value of repeat testing. medRxiv 20217042 [preprint]. 23 October 2020. pmid: 20217042
19. R. Wölfel *et al*., Virological assessment of hospitalized patients with COVID-2019. *Nature* **581**, 465–469 (2020). doi: 10.1038/s41586-020-2196-x; pmid: 32235945
20. R. A. P. M. Perera *et al*., SARS-CoV-2 Virus Culture and Subgenomic RNA for Respiratory Specimens from Patients with Mild Coronavirus Disease. *Emerg. Infect. Dis.* **26**, 2701–2704 (2020). doi: 10.3201/eid2611.203219; pmid: 32749957
21. A. Endo, S. Abbott, A. J. Kucharski, S. Funk, Centre for the Mathematical Modelling of Infectious Diseases COVID-19 Working Group, Estimating the overdispersion in COVID-19 transmission using outbreak sizes outside China. *Wellcome Open Res.* **5**, 67 (2020). doi: 10.12688/wellcomeopenres.15842.3; pmid: 32685698
22. K. Sun *et al*., Transmission heterogeneities, kinetics, and controllability of SARS-CoV-2. *Science* **371**, eabe2424 (2021). pmid: 33234698
23. N. J. Lennon *et al*., Comparison of viral levels in individuals with or without symptoms at time of COVID-19 testing among 32,480 residents and staff of nursing homes and assisted living facilities in Massachusetts. *Open Forum Infect. Dis.* **7** (suppl. 1), 848–849 (2020). doi: 10.1093/ofid/ofaa515.1908
24. R. Laxminarayan *et al*., Epidemiology and transmission dynamics of COVID-19 in two Indian states. *Science* **370**, 691–697 (2020). doi: 10.1126/science.abd7672; pmid: 33154136
25. T. Suess *et al*., Comparison of shedding characteristics of seasonal influenza virus (sub)types and influenza A(H1N1)pdm09; Germany, 2007-2011. *PLOS ONE* **7**, e51653 (2012). doi: 10.1371/journal.pone.0051653; pmid: 23240050
26. M. Loeb *et al*., Longitudinal study of influenza molecular viral shedding in Hutterite communities. *J. Infect. Dis.* **206**, 1078–1084 (2012). doi: 10.1093/infdis/jis450; pmid: 22837493
27. B. J. Cowling *et al*., Comparative epidemiology of pandemic and seasonal influenza A in households. *N. Engl. J. Med.* **362**, 2175–2184 (2010). doi: 10.1056/NEJMoa0911530; pmid: 20558368
28. D. K. M. Ip *et al*., Viral Shedding and Transmission Potential of Asymptomatic and Paucisymptomatic Influenza Virus Infections in the Community. *Clin. Infect. Dis.* **64**, 736–742 (2017). pmid: 28011603
29. N. H. L. Leung, C. Xu, D. K. M. Ip, B. J. Cowling, The Fraction of Influenza Virus Infections That Are Asymptomatic: A Systematic Review and Meta-analysis. *Epidemiology* **26**, 862–872 (2015). doi: 10.1097/EDE.0000000000000340; pmid: 26133025
30. L. P. Moreira *et al*., Respiratory syncytial virus evaluation among asymptomatic and symptomatic subjects in a university hospital in Sao Paulo, Brazil, in the period of 2009-2013. *Influenza Other Respir. Viruses* **12**, 326–330 (2018). doi: 10.1111/irv.12518; pmid: 29078028
31. D. Jacot, G. Greub, K. Jaton, O. Opota, Viral load of SARS-CoV-2 across patients and compared to other respiratory viruses. *Microbes Infect.* **22**, 617–621 (2020). doi: 10.1016/j.micinf.2020.08.004; pmid: 32911086
32. T. Heald-Sargent *et al*., Age-Related Differences in Nasopharyngeal Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Levels in Patients With Mild to Moderate Coronavirus Disease 2019 (COVID-19). *JAMA Pediatr.* **174**, 902–903 (2020). doi: 10.1001/jamapediatrics.2020.3651; pmid: 32745201
33. L. M. Yonker *et al*., Pediatric SARS-CoV-2: Clinical Presentation, Infectivity, and Immune Responses. *J. Pediatr.* **227**, 45–52.e5 (2020). doi: 10.1016/j.jpeds.2020.08.037; pmid: 32827525
34. S. Baggio *et al*., SARS-CoV-2 viral load in the upper respiratory tract of children and adults with early acute COVID-19. *Clin. Infect. Dis.* ciaa1157 (2020). doi: 10.1093/cid/ciaa1157; pmid: 32761228
35. A. Singanayagam *et al*., Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. *Euro Surveill.* **25**, (2020). doi: 10.2807/1560-7917.ES.2020.25.32.2001483; pmid: 32794447
36. V. M. Corman *et al*., Comparison of seven commercial SARS-CoV-2 rapid point-of-care antigen tests: a single-centre

laboratory evaluation study. *Lancet Microbe* 10.1016/S2666-5247(21)00056-2 (2021). doi: 10.1001/jamapediatrics.2020.3988; pmid: 32857112
37. M. S. Han *et al*., Clinical Characteristics and Viral RNA Detection in Children With Coronavirus Disease, 2019 in the Republic of Korea. *JAMA Pediatr.* **175**, 73–80 (2021). doi: 10.1001/jamapediatrics.2020.3988; pmid: 32857112
38. C. A. Pierce *et al*., Natural mucosal barriers and COVID-19 in children. *JCI Insight* **6**, e148694 (2021). doi: 10.1172/jci.insight.148694; pmid: 33822777
39. Q. Li *et al*., Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N. Engl. J. Med.* **382**, 1199–1207 (2020). doi: 10.1056/NEJMoa2001316; pmid: 31995857
40. L. Ferretti *et al*., The timing of COVID-19 transmission. medRxiv [preprint]. 7 September 2020. pmid: 20188516
41. X. He *et al*., Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat. Med.* **26**, 672–675 (2020). doi: 10.1038/s41591-020-0869-5; pmid: 32296168
42. C. McAloon *et al*., Incubation period of COVID-19: A rapid systematic review and meta-analysis of observational research. *BMJ Open* **10**, e039652 (2020). doi: 10.1136/bmjopen-2020-039652; pmid: 32801208
43. P. Banka, C. Comiskey, The incubation period of COVID-19: A scoping review and meta-analysis to aid modelling and planning. MedRxiv 20216143 [preprint]. 3 November 2020.
44. B. Rai, A. Shukla, L. K. Dwivedi, Incubation period for COVID-19: A systematic review and meta-analysis. *J. Public Health* 10.1007/s10389-021-01478-1 (2021). doi: 10.1007/s10389-021-01478-1; pmid: 33643779
45. J. Bullard *et al*., Predicting infectious SARS-CoV-2 from diagnostic samples. *Clin. Infect. Dis.* **71**, 2663–2666 (2020). doi: 10.1093/cid/ciaa638
46. M. M. Arons *et al*., Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility. *N. Engl. J. Med.* **382**, 2081–2090 (2020). doi: 10.1056/NEJMoa2008457; pmid: 32329971
47. R. Challen *et al*., Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: Matched cohort study. *BMJ* **372**, n579 (2021). pmid: 33687922
48. K. R. W. Emary, T. Golubchik, Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 VOC 202012/01 (B.1.1.7). SSRN [preprint]. 4 February 2021; https://ssrn.com/abstract=3779160.
49. M. D. Parker *et al*., Altered subgenomic RNA expression in SARS-CoV-2 B.1.1.7 infections. bioRxiv 433156 [preprint]. 4 March 2021. pmid: 433156
50. M. Kidd *et al*., S-variant SARS-CoV-2 lineage B1.1.7 is associated with significantly higher viral loads in samples tested by TaqPath Polymerase Chain Reaction. *J. Infect. Dis.* jiab082 (2021). doi: 10.1093/infdis/jiab082; pmid: 33580259
51. T. Golubchik *et al*., COVID-19 Genomics UK (COG-UK) Consortium, Early analysis of a potential link between viral load and the N501Y mutation in the SARS-COV-2 spike protein. medRxiv 20249080 [preprint]. 15 January 2021. pmid: 20249080
52. S. Kissler *et al*., "Densely sampled viral trajectories suggest longer duration of acute infection with B.1.1.7 variant relative to non-B.1.1.7 SARS-CoV-2" (Harvard T. H. Chan School of Public Health, 2021); https://dash.harvard.edu/handle/1/37366884.
53. Public Health England, "Investigation of novel SARS-CoV-2 Variant of Concern 202012/01: Technical briefing 5" (2021).
54. K. Leung, M. H. Shum, G. M. Leung, T. T. Lam, J. T. Wu, Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. *Euro Surveill.* **26**, (2021). doi: 10.2807/1560-7917.ES.2020.26.1.2002106; pmid: 33413740
55. N. G. Davies *et al*., Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England. *Science* **372**, eabg3055 (2021). doi: 10.1126/science.abg3055; pmid: 33658326
56. R. Li *et al*., Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). *Science* **368**, 489–493 (2020). doi: 10.1126/science.abb3221; pmid: 32179701
57. Public Health England, "Investigation of novel SARS-CoV-2 Variant of Concern 202012/01: Technical briefing 1" (2020).
58. P.-C. Bürkner, brms: An R Package for Bayesian Multilevel Models Using Stan. *J. Stat. Softw.* **80**, (2017). doi: 10.18637/jss.v080.i01
59. P.-C. Bürkner, Advanced Bayesian Multilevel Modeling with the R Package brms. *R J.* **10**, 395 (2018). doi: 10.32614/RJ-2018-017
60. R Core Team, *R: A Language and Environment for Statistical Computing* (R Foundation for Statistical Computing, 2020); www.R-project.org/.
61. K. Basile *et al*., Cell-based culture of SARS-CoV-2 informs infectivity and safe de-isolation assessments during COVID-19. *Clin. Infect. Dis.* ciaa1579 (2020). doi: 10.1093/cid/ciaa1579; pmid: 33098412
62. B. La Scola *et al*., Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. *Eur. J. Clin. Microbiol. Infect. Dis.* **39**, 1059–1061 (2020). doi: 10.1007/s10096-020-03913-9; pmid: 32342252
63. J. J. A. van Kampen *et al*., Duration and key determinants of infectious virus shedding in hospitalized patients with coronavirus disease-2019 (COVID-19). *Nat. Commun.* **12**, 267 (2021). doi: 10.1038/s41467-020-20568-4; pmid: 33431879
64. M. Widera *et al*., Surveillance of SARS-CoV-2 in Frankfurt am Main from October to December 2020 Reveals High Viral Diversity Including Spike Mutation N501Y in B.1.1.70 and B.1.1.7. *Microorganisms* **9**, 748 (2021). doi: 10.3390/microorganisms9040748; pmid: 33918332
65. T. Toptan *et al*., Evaluation of a SARS-CoV-2 rapid antigen test: Potential to help reduce community spread? *J. Clin. Virol.* **135**, 104713 (2021). doi: 10.1016/j.jcv.2020.104713; pmid: 33352470
66. S. Herberhold, A.-M. Eis-Hübinger, M. Panning, Frequent detection of respiratory viruses by real-time PCR in adenoid samples from asymptomatic children. *J. Clin. Microbiol.* **47**, 2682–2683 (2009). doi: 10.1128/JCM.00899-09; pmid: 19494063
67. F. M. Liotti *et al*., Assessment of SARS-CoV-2 RNA Test Results Among Patients Who Recovered From COVID-19 With Prior Negative Results. *JAMA Intern. Med.* **181**, 702–704 (2021). doi: 10.1001/jamainternmed.2020.7570; pmid: 33180119
68. R. L. Tillett *et al*., Genomic evidence for reinfection with SARS-CoV-2: A case study. *Lancet Infect. Dis.* **21**, 52–58 (2021). doi: 10.1016/S1473-3099(20)30764-7; pmid: 33058797
69. K. K.-W. To *et al*., Coronavirus Disease 2019 (COVID-19) Re-infection by a Phylogenetically Distinct Severe Acute Respiratory Syndrome Coronavirus 2 Strain Confirmed by Whole Genome Sequencing. *Clin. Infect. Dis.* **9**, 1664 (2020).
70. P. Simmonds, S. Williams, H. Harvala, Understanding the outcomes of COVID-19 – does the current model of an acute respiratory infection really fit? *J. Gen. Virol.* **102**, 10.1099/jgv.0.001545 (2020). doi: 10.1099/jgv.0.001545; pmid: 33331810
71. M. Perry, simanneal: A Python Module for Simulated Annealing Optimization; https://github.com/perrygeo/simanneal.
72. Stan Development Team, Stan Modeling Language Users Guide and Reference Manual (version 2.25); https://mc-stan.org.
73. Y. Liu *et al*., Viral dynamics in mild and severe cases of COVID-19. *Lancet Infect. Dis.* **20**, 656–657 (2020). doi: 10.1016/S1473-3099(20)30232-2; pmid: 32199493
74. K. K.-W. To *et al*., Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: An observational cohort study. *Lancet Infect. Dis.* **20**, 565–574 (2020). doi: 10.1016/S1473-3099(20)30196-1; pmid: 32213337
75. S. Greenland, Principles of multilevel modelling. *Int. J. Epidemiol.* **29**, 158–167 (2000). doi: 10.1093/ije/29.1.158; pmid: 10750618
76. F. Kurth *et al*., Studying the pathophysiology of coronavirus disease 2019: A protocol for the Berlin prospective COVID-19 patient cohort (Pa-COVID-19). *Infection* **48**, 619–626 (2020). doi: 10.1007/s15010-020-01464-x; pmid: 32535877
77. C. Thibeault *et al*., Clinical and virological characteristics of hospitalised COVID-19 patients in a German tertiary care centre during the first wave of the SARS-CoV-2 pandemic: A prospective observational study. *Infection* 10.1007/s15010-021-01594-w (2021). doi: 10.1007/s15010-021-01594-w; pmid: 33890243
78. P. Virtanen *et al*., SciPy 1.0: Fundamental algorithms for scientific computing in Python. *Nat. Methods* **17**, 261–272 (2020). doi: 10.1038/s41592-019-0686-2; pmid: 32015543
79. W. McKinney, Data Structures for Statistical Computing in Python. In *Proceedings of the 9th Python in Science Conference* (2010). doi: 10.25080/majora-92bf1922-00a
80. S. Seabold, J. Perktold, Statsmodels: Econometric and Statistical Modeling with Python. In *Proceedings of the 9th Python in Science Conference* (2010). doi: 10.25080/majora-92bf1922-011
81. J. D. Hunter, Matplotlib: A 2D Graphics Environment. *Comput. Sci. Eng.* **9**, 90–95 (2007). doi: 10.1109/MCSE.2007.55
82. T. Oliphant, *Guide to NumPy* (CreateSpace, ed. 2, 2015).
83. M. Parker, seaborn_sinaplot; https://github.com/mparker2/seaborn_sinaplot.
84. M. Waskom *et al*., seaborn: v0.5.0 (2014); DOI: 10.5281/zenodo.12710.
85. B. Langmead, S. L. Salzberg, Fast gapped-read alignment with Bowtie 2. *Nat. Methods* **9**, 357–359 (2012). doi: 10.1038/nmeth.1923; pmid: 22388286
86. P. Danecek *et al*., Twelve years of SAMtools and BCFtools. *Gigascience* **10**, giab008 (2021). doi: 10.1093/gigascience/giab008; pmid: 33590861
87. J. K. Bonfield *et al*., HTSlib: C library for reading/writing high-throughput sequencing data. *Gigascience* **10**, giab007 (2021). doi: 10.1093/gigascience/giab007; pmid: 33594436
88. G. Dick, *Genomic Approaches in Earth and Environmental Sciences* (Wiley, 2018).
89. N. D. Grubaugh *et al*., An amplicon-based sequencing framework for accurately measuring intrahost virus diversity using PrimalSeq and iVar. *Genome Biol.* **20**, 8 (2019). doi: 10.1186/s13059-018-1618-7; pmid: 30621750
90. K. Katoh, D. M. Standley, MAFFT multiple sequence alignment software version 7: Improvements in performance and usability. *Mol. Biol. Evol.* **30**, 772–780 (2013). doi: 10.1093/molbev/mst010; pmid: 23329690
91. B. Goodrich, J. Gabry, I. Ali, S. Brilleman, rstanarm: Bayesian applied regression modeling via Stan (2020); https://mc-stan.org/rstanarm.
92. B. Carpenter *et al*., Stan: A Probabilistic Programming Language. *J. Stat. Softw.* **76**, (2017). doi: 10.18637/jss.v076.i01
93. M. Dowle, A. Srinivasan, data.table: Extension of 'data.frame' (2020).
94. H. Wickham, *ggplot2: Elegant Graphics for Data Analysis* (Springer, 2016).
95. O. Tange, GNU Parallel 20201122 ('Biden') (2020); www.gnu.org/software/parallel/.
96. H. B. Mann, D. R. Whitney, On a Test of Whether One of Two Random Variables is Stochastically Larger than the Other. *Ann. Math. Stat.* **18**, 50–60 (1947). doi: 10.1214/aoms/1177730491
97. Additional statistical information and the R code and data to reproduce the results, figures, and tables are available at https://doi.org/10.5281/zenodo.4774226.

ACKNOWLEDGMENTS

Computation was performed on the HPC for Research/Clinic cluster of the Berlin Institute of Health, supported by D. Beule, M. Holtgrewe, and O. Stolpe. We thank U. Gieraths and L. Meiners for careful commentary on the manuscript, T. D. Best for compiling cell culture isolation data, the Charité–Universitätsmedizin Pa-COVID-19 collaborative study group for providing additional onset of symptoms data, and S. Kissler for providing additional details regarding their NBA study. The conditions allowing the work to be done with no need for consent are given at https://gesetze.berlin.de/bsbe/document/jlr-KHGBE2011V4P25. **Funding:** Work at Charité–Universitätsmedizin Institute of Virology is funded by European Commission via project ReCoVer, German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung) through projects DZIF (301-4-7-01.703) to C.D.; VARIPath (01KI2021) to V.M.C.; PROVID (FKZ 01KI20160C) to C.D., V.M.C., and L.E.S.; and NaFoUniMedCovid19 (NUM)–COVIM (FKZ 01KX2021) to C.D., V.M.C., and L.E.S. The Pa-COVID 19 Study is supported by grants from the Berlin Institute of Health. This study was supported in part by the German Ministry of Health (Konsiliarlabor für Coronaviren and SeCoV) to C.D. and V.M.C. T.C.J. is in part funded through NIAID-NIH CEIRS contract HHSN272201400008C. **Author contributions:** T.C.J., G.B., B.M.: bioinformatic processing, statistical analysis, interpretation of results, writing of original draft and final text; T.V.: statistical analysis, interpretation of results, writing of original draft and final text, next-generation sequencing; J.S., J.B.-S., T.B., J.T., M.L.S.: sample preparation, virus isolation and culturing, RT-PCR, next-generation sequencing; L.E.S., F.K.: collection of symptom onset data; P.M., R.S., M.Z., J.H., A.K., A.S., A.E.: diagnostic work and collection of raw data; V.M.C.: diagnostic data collection, viral load calibration, supervision of laboratory work, interpretation of results; C.D.: project concept, interpretation of results, writing of original draft and final text. **Competing interests:** The authors declare that they have no

competing interests. **Data and materials availability:** Additional statistical information and the R code and data to reproduce the results, figures, and tables are available (*97*).

SUPPLEMENTARY MATERIALS

science.sciencemag.org/content/373/6551/eabi5273/suppl/DC1
Supplementary Text
Figs. S1 to S17
Tables S1 to S5
References (*98*–*102*)
MDAR Reproducibility Checklist

15 March 2021; accepted 21 May 2021
Published online 25 May 2021
10.1126/science.abi5273

Science

Estimating infectiousness throughout SARS-CoV-2 infection course

Terry C. Jones, Guido Biele, Barbara Mühlemann, Talitha Veith, Julia Schneider, Jörn Beheim-Schwarzbach, Tobias Bleicker, Julia Tesch, Marie Luisa Schmidt, Leif Erik Sander, Florian Kurth, Peter Menzel, Rolf Schwarzer, Marta Zuchowski, Jörg Hofmann, Andi Krumbholz, Angela Stein, Anke Edelmann, Victor Max Corman and Christian Drosten

Science **373** (6551), eabi5273.
DOI: 10.1126/science.abi5273originally published online May 25, 2021

Correlates of infectiousness

The role that individuals with asymptomatic or mildly symptomatic severe acute respiratory syndrome coronavirus 2 have in transmission of the virus is not well understood. Jones *et al.* investigated viral load in patients, comparing those showing few, if any, symptoms with hospitalized cases. Approximately 400,000 individuals, mostly from Berlin, were tested from February 2020 to March 2021 and about 6% tested positive. Of the 25,381 positive subjects, about 8% showed very high viral loads. People became infectious within 2 days of infection, and in hospitalized individuals, about 4 days elapsed from the start of virus shedding to the time of peak viral load, which occurred 1 to 3 days before the onset of symptoms. Overall, viral load was highly variable, but was about 10-fold higher in persons infected with the B.1.1.7 variant. Children had slightly lower viral loads than adults, although this difference may not be clinically significant.

Science, abi5273, this issue p. eabi5273

Science (print ISSN 0036-8075; online ISSN 1095-9203) is published by the American Association for the Advancement of Science, 1200 New York Avenue NW, Washington, DC 20005. The title *Science* is a registered trademark of AAAS.

Virological and serological kinetics of SARS-CoV-2 Delta variant vaccine-breakthrough infections: a multi-center cohort study

Po Ying Chia, MBBS[1,2,4]; Sean Wei Xiang Ong, MBBS[1,2]; Calvin J Chiew, MPH[1,3]; Li Wei Ang, MSc[1]; Jean-Marc Chavatte PhD[1]; Tze-Minn Mak, PhD[1]; Lin Cui, PhD[1]; Shirin Kalimuddin, MPH[5,6]; Wan Ni Chia, PhD[6]; Chee Wah Tan, PhD[6]; Louis Yi Ann Chai, PhD[7,8]; Seow Yen Tan, MBBS[9]; Shuwei Zheng, MBBS[10]; Raymond Tzer Pin Lin, MBBS[1]; Linfa Wang, PhD[6], Yee-Sin Leo, MPH[1,2,4,8]; Vernon J Lee, PhD[3]; David Chien Lye, MBBS[1,2,4,8]; Barnaby Edward Young, MB BChir[1,2,4]

[1] National Centre for Infectious Diseases, Singapore
[2] Tan Tock Seng Hospital, Singapore
[3] Ministry of Health, Singapore
[4] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[5] Singapore General Hospital, Singapore
[6] Duke-NUS Medical School, National University of Singapore, Singapore
[7] National University Health System, Singapore
[8] Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[9] Changi General Hospital, Singapore
[10] Sengkang General Hospital, Singapore

Running title: Delta VOC: Viral Kinetics for Vaccinated

Corresponding Author:

Barnaby Young, National Centre for Infectious Diseases, 16 Jln Tan Tock Seng, Singapore 308442

E-mail: Barnaby_young@ncid.sg; Telephone: (+65) 6256 6011

Keywords: COVID-19; SARS-CoV-2; breakthrough infection; delta; variants of concern; vaccine breakthrough; vaccination

Objectives

Highly effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed but variants of concerns (VOCs) with mutations in the spike protein are worrisome, especially B.1.617.2 (Delta) which has rapidly spread across the world. We aim to study if vaccination alters virological and serological kinetics in breakthrough infections.

Methods

We conducted a multi-centre retrospective cohort study of patients in Singapore who had received a licensed mRNA vaccine and been admitted to hospital with B.1.617.2 SARS-CoV-2 infection. We compared the clinical features, virological and serological kinetics (anti-nucleocapsid, anti-spike and surrogate virus neutralization titres) between fully vaccinated and unvaccinated individuals.

Results

Of 218 individuals with B.1.617.2 infection, 84 had received a mRNA vaccine of which 71 were fully vaccinated, 130 were unvaccinated and 4 received a non-mRNA. Despite significantly older age in the vaccine breakthrough group, the odds of severe COVID-19 requiring oxygen supplementation was significantly lower following vaccination (adjusted odds ratio 0.07 95%CI: 0.015-0.335, p=0.001). PCR cycle threshold (Ct) values were similar between both vaccinated and unvaccinated groups at diagnosis, but viral loads decreased faster in vaccinated individuals. Early, robust boosting of anti-spike protein antibodies was observed in vaccinated patients, however, these titers were significantly lower against B.1.617.2 as compared with the wildtype vaccine strain.

Conclusion

The mRNA vaccines are highly effective at preventing symptomatic and severe COVID-19 associated with B.1.617.2 infection. Vaccination is associated with faster decline in viral RNA load and a robust serological response. Vaccination remains a key strategy for control of COVID-19 pandemic.

Background

Availability of effective vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) within one year of the first report of coronavirus disease 2019 (COVID-19) is remarkable. Phase 3 clinical trials of messenger RNA (mRNA) vaccines have demonstrated 92-95% efficacy in preventing symptomatic infection and severe disease [1-4] and intensive vaccination programs have reduced infection and mortality rates in multiple settings [5-7].

Emerging variants of concern (VOCs), such as B.1.1.7 (Alpha in the World Health Organization classification), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) exhibit varied sequence changes and alteration of amino acid sequences of the spike protein. This has led to concerns of viral immune evasion and decreased vaccine effectiveness. Furthermore, these VOCs have been shown to be more transmissible [8-10], and B.1.1.7 and B.1.617.2 has been associated with increased disease severity and hospitalization [11, 12]. B.1.617.2 has rapidly spread outside India, becoming the most frequently sequenced lineage worldwide by end of June 2021 [13]. Case series of vaccine-breakthrough infections have reported an over-representation by these VOCs [14, 15].

Understanding vaccine effectiveness in the context of VOCs requires granular data: which vaccines were administered, at what time point prior to infection, number of doses, and particularly which VOC has caused the infection. Important VOC-specific vaccination outcomes include severity of infection and vaccine effects on transmission.

The COVID-19 vaccination program was initiated in Singapore on 30 December 2020, with free vaccinations provided to all Singapore residents in phases, beginning with the elderly and those in high-risk occupations such as healthcare workers. Vaccines used are mRNA vaccines, Pfizer/BioNTech BNT162b2 and Moderna mRNA-1273. As of 19 July 2021, 6,837,200 vaccine doses had been administered and ~2,792,430 individuals (47% of the total population) had completed the vaccination course [16]. In May 2021, B.1.617.2 became the dominant circulating variant based on local sequencing data.

In this multi-center cohort study, we characterize the clinical features, virological and serological kinetics of patients with vaccine-breakthrough PCR-confirmed B.1.617.2 infection and compared them with unvaccinated patients.

Methods

Patient Recruitment

Adults aged ≥18 years with COVID-19 confirmed by positive SARS-CoV-2 PCR and admitted to any of the five study sites from 1 April to 14 June 2021 were screened. Patients with B.1.617.2 infection (identification methods delineated below) were included in this analysis. Vaccine-breakthrough infection was defined as PCR-confirmed COVID-19 with symptom onset or first positive PCR (whichever was earlier) ≥14 days following a second dose of BNT162b2 or mRNA-1273 vaccine. Incomplete vaccination was defined as receipt of one dose of these vaccines ≥14 days prior to symptom onset or first positive PCR. Patients who received non-mRNA vaccines or developed infection within 14 days after the first dose were excluded from this analysis. B.1.617.2 vaccine-breakthrough infections were compared with a retrospective cohort of unvaccinated patients with B.1.617.2 infection admitted to one study site.

Data Collection

Clinical and laboratory data were collected from electronic medical records using a standardized data-collection form [17]. Laboratory data including cycle threshold (Ct) values from SARS-CoV-2 RT-PCR assays and serological results from Elecsys® (Roche, Basel, Switzerland) Anti-SARS-CoV-2 chemiluminescent immunoassays [anti-nucleocapsid (anti-N) and anti-spike protein (anti-S)] and surrogate virologic neutralization test (sVNT) cPass™ (Genscript, NJ, USA) were recorded. cPass™ detects total neutralizing antibodies targeting the viral spike protein receptor-binding domain [18]. These tests were performed as part of routine clinical care.

Additional Serologic testing

Serum samples from a subset of vaccine-breakthrough patients who had separately consented for specimen collection were additionally tested with a newly developed multiplex-sVNT assay using the Luminex platform. Further details can be found in the supplementary information.

Viral RNA sequencing and VOC determination

SARS-CoV-2 PCR was performed using various commercially available assays in different clinical laboratories. As part of active genomic surveillance, whole genome sequencing (WGS) by National Public Health Laboratory is performed for all patients in Singapore with SARS-CoV-2 detected by RT-PCR with a Ct value less than 30. Pangolin COVID-19 Lineage Assigner and CoVsurver were used to assign lineage to each sequence. For individuals with PCR confirmed infection without available sequencing results, lineage was inferred based on epidemiological investigations by the Singapore Ministry of Health (MOH), and likely B.1.617.2 infections were included (i.e., clear epidemiologic link with patients with sequencing confirmed B.1.617.2 infection).

Clinical Management

All individuals with confirmed COVID-19 (including asymptomatic cases) in Singapore are admitted to hospital for inpatient evaluation and isolation. Individuals with pneumonia requiring supplemental oxygen are treated with intravenous remdesivir, while dexamethasone and other agents were reserved for progressive infections per national guidelines [19]. Disease severity was stratified into asymptomatic, mild (no pneumonia on chest radiography), moderate (presence of pneumonia on chest radiography), severe (requiring supplemental oxygen), or critical (requiring intensive care unit [ICU] admission or mechanical ventilation). Collection of clinical data was censored on discharge from hospital.

Statistical Analysis

For descriptive analysis, data were presented as median (interquartile range (IQR)) for continuous parameters and frequency (percentage) for categorical variables. Chi-square and Fisher's exact tests

were used to compared categorical variables, while for continuous variables, t-test was used for normal data and Mann-Whitney U test for non-normal data. For asymptomatic patients, the day of confirmatory COVID-19 diagnosis was denoted as day one of illness. For symptomatic patients, the day of symptom onset or the day of confirmatory COVID-19 diagnosis, whichever earlier, was denoted as day one of illness.

Previously reported risk factors for disease severity [20] were evaluated and included in a multivariate logistic regression model [21]. For serial Ct values, we fitted a generalized additive mixed model (GAMM) with a random intercept by patient. To investigate the effect of vaccination status on rate of increase of Ct value, we included fixed factors of vaccination status and day of illness with smoothing terms and interaction between these two fixed factors. We plotted Ct values with marginal effect of day of illness by vaccination status and 95% confidence intervals (CI) from the GAMM.

For analysis of cPass™ and anti-S titres we fitted a GAMM to serial titres with random intercept by patient in addition to fixed factor of day of illness with smoothing terms, separately for vaccine-breakthrough and unvaccinated patients infected with Delta variant. We plotted cPass™/anti-S titres with marginal effect of day of illness and 95%CI from GAMM for each group of vaccine-breakthrough and unvaccinated patients.

P-values less than 0.05 were considered statistically significant, and all tests were 2-tailed. Data analyses were performed using Stata Release 15 (StataCorp, College Station, TX) and R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

Written informed consent was obtained from study participants of the multi-centre study approved by National Healthcare Group Domain Specific Review Board (NHG-DSRB) (Study Reference

2012/00917). Informed consent for retrospective data collection at National Centre for Infectious Diseases (NCID) was waived (NHG-DSRB reference number 2020/01122).

Results

218 B.1.617.2 infections were identified across the five study sites (Supplementary Figure S1). Of these, 71 met the definition for vaccine-breakthrough. An additional 13 only received one dose ≥14 days prior to disease onset or received both doses but within 14 days of disease onset, while four had received a non-mRNA vaccine overseas. Majority of participants meeting study definition for vaccine-breakthrough had received two doses of BNT162b2 (n=66, 93%).

Clinical Features

In line with Singapore's national vaccination strategy wherein older adults were prioritized for vaccination, our vaccine-breakthrough cohort was of significantly older age; median age of 56 years (IQR:39-64) versus 39.5 (IQR:30-58) ($p<0.001$) (Table 1). Other baseline demographics were similar.

Vaccine-breakthrough patients were significantly more likely to be asymptomatic (28.2% versus 9.2%, $p<0.001$); and if symptomatic, had fewer number of symptoms (Table 1). Unvaccinated individuals had worse levels of known biomarkers associated with increased COVID-19 severity including lymphocyte count, C-reactive protein [CRP], lactate dehydrogenase [LDH] and alanine transferase [ALT]. Correspondingly, a higher proportion of the unvaccinated cohort had pneumonia, required supplementary oxygen and ICU admission compared with the vaccinated cohort. A broader analysis comparing unvaccinated versus those who had received at least one dose of vaccine (i.e. both vaccine-breakthrough and incomplete vaccination) demonstrated similar findings (Supplementary Table T1).

Multivariate logistic regression analysis for development of severe COVID-19 (defined by supplementary oxygen requirement) demonstrated that vaccination was protective with an adjusted odds ratio (aOR) of 0.073 (95% confidence interval [CI]):0.016-0.343) ($p=0.001$) (Table 2). Analysis

comparing unvaccinated versus those who had received at least one dose of vaccine demonstrated similar findings (Supplementary Table T2). Multivariate logistic regression analysis for development of moderately severe COVID-19 (defined by development of pneumonia) also demonstrated that vaccination was protective with aOR of 0.069 (95%CI:0.027-0.180) (p<0.001) (Supplementary Table T3).

Virologic kinetics

Serial Ct values of individuals were analyzed as a surrogate marker for the viral load. The initial median initial Ct value did not differ between unvaccinated and fully vaccinated patients (unvaccinated median Ct 18.8 (14.9-22.7), vaccinated 19.2 (15.2-22.2), p=0.929). However, fully vaccinated patients had a faster rate of increase in Ct value over time compared with unvaccinated individuals, suggesting faster viral load decline (coefficient estimates for interaction terms ranged from 9.12 (standard error 3.75) to 12.06 (standard error 3.03); p-value <0.05 for each interaction terms) (Figure 1).

Serologic data

69 fully vaccinated individuals and 45 unvaccinated had serologic data available on record. 66/66 (100%) of vaccinated individuals had detectable S antibodies in week 1 of illness, while 7/45 (16%) of unvaccinated individuals did (Supplementary Figure S2). There was no difference in the proportion of individuals who seroconverted with the anti-N assay in week 1 (vaccinated 7/68 (10%) vs unvaccinated 11/107 (10%)) or week 2 (vaccinated 2/11 (18%), unvaccinated 4/20 (20%).

Analysis of sVNT with cPass indicated very high inhibition among vaccinated individuals in week 1 of illness (median 98.3% (IQR:91.0-99.4%)) which increased to 99.6% (IQR 99.3-99.9%) in week 2 (Figure 2A, 2B). Among unvaccinated individuals, median inhibition was below the 20% threshold at both week 1 and week 2. Among the 37 vaccinated individuals with a serum sample available for

193 testing by the multiplex sVNT assay, titres were significantly higher against wildtype virus compared
194 with B.1.617.2 and other VOCs (Figure 3). sVNT titres were lowest against B.1.617.2 and P.1 VOCs.

195 **Discussion**

196 In this study, we found that fully vaccinated patients had significantly lower odds of moderate or
197 severe outcomes following infection by the SARS-CoV-2 VOC B.1.617.2. Vaccination was associated
198 with lower peak measures of systemic inflammation, fewer symptoms, including more asymptomatic
199 infection, and better clinical outcomes. Notably, in contrast to existing studies that showed lower
200 viral load in vaccinated patients [22], initial viral load indicated by PCR Ct values was similar between
201 vaccinated and unvaccinated patients with B.1.617.2. However, vaccinated patients appeared to
202 clear viral load at a faster rate. Our serologic data suggest an early rapid rise in neutralizing and
203 binding antibodies indicated by C-Pass and Roche anti-S antibodies, which may be evidence of
204 memory immunity to COVID-19 vaccination on challenge with a breakthrough infection with
205 B.1.617.2.

206 As part of active case finding and surveillance in Singapore, all patients with fever or respiratory
207 symptoms, close contacts of confirmed cases, and newly arrived travelers are screened for COVID-19
208 using PCR. Additionally, high-risk individuals in frontline occupations or congregate settings are
209 tested as part of routine surveillance. All confirmed COVID-19 cases are reported to MOH and
210 admitted to a hospital for initial evaluation. As such, our hospitalized cohort uniquely captures the
211 entire spectrum of disease severity of COVID-19 infection and provides granular data even for mild
212 and asymptomatic vaccine-breakthrough infections, giving us the opportunity to analyze virologic
213 and serologic kinetics of these patients.

214 The finding of diminished severity with B.1.617.2 infection in vaccinated individuals is reassuring and
215 corroborates emerging data from the United Kingdom which have found that mRNA vaccination
216 remains protective against symptomatic and severe disease[12, 23]. An observational cohort study
217 conducted in Scotland suggested that ≥14 days after the second dose, BNT162b2 vaccine offered

92% vaccine effectiveness against presumptive non-B.1.617.2 infection and 79% protection against presumptive B.1.617.2 [24]. Protection associated with the ChAdOx1 nCoV-19 vaccine was 73% and 60% respectively. Although vaccine-breakthrough infections are increasingly reported, with the largest series to date in the United States reporting 10,262 breakthrough infections, a majority of these were mild (27% asymptomatic, 10% hospitalization, 2% mortality)[25]. Vaccine-breakthrough infections will continue to be observed, especially with genetic drift and selection pressures resulting in emergence of newer VOCs; however, it is likely that there will be a shift toward milder disease spectrum with more widespread implementation of vaccination programs.

To our knowledge, we provide the first data characterizing impact of vaccination on virologic kinetics by the B.1.617.2 variant. While initial Ct values were similar; the effect of vaccination with a more rapid decline in viral load (and hence shorter duration of viral shedding) has implications on transmissibility and infection control policy. A shorter duration of infectivity may allow a shorter duration of isolation for vaccinated individuals. Based on our data, it seems likely that vaccination reduces secondary transmission, though this needs to be further studied in larger community surveillance studies. Other studies found similar impact of vaccination on other variants. Pritchard and colleagues found that vaccinated individuals had higher Ct values compared with unvaccinated individuals in B.1.1.7 infections [7], while Levine-Tiefenbaum and colleagues similarly found a reduction in viral loads after BNT162b2 vaccine, though no data was provided on variant type [26].

There are several limitations to our study. Firstly, we only compared vaccine-breakthrough infections with unvaccinated COVID-19 patients. We did not study vaccinated individuals who had similar exposure risk but did not develop COVID-19 infection. We thus could not evaluate vaccine efficacy against asymptomatic infection. We also did not have detailed epidemiologic data to study the effect of vaccination on preventing secondary transmission.

Secondly, we could only obtain serologic tests after infection since patients were recruited after confirmation of infection. While active contact tracing and case finding in Singapore resulted in early

identification of most COVID-19 cases, the first available serologic result was at a median of 2 (IQR:1-3) days of illness and antibody levels are likely to already have been boosted by natural infection. We thus could not evaluate the underlying immunologic mechanisms behind vaccine-breakthrough infection, e.g., diminished neutralizing antibody level or impaired cellular immunity. Further study should compare similarly exposed vaccinated individuals who develop breakthrough infection with those who do not, to elucidate the underlying drivers of susceptibility, which may enlighten us on how to optimize protection (e.g., through enhanced/boosted dosing schedules).

Thirdly, PCR testing was not standardized in a centralized laboratory, and instead conducted at each centre using different validated commercial assays. Ct values are only a surrogate measure of viral load and shedding. We did not evaluate viability of shed virus via viral culture. In addition, we only evaluated participants with mRNA vaccination, and thus our findings are restricted to mRNA vaccines and not all COVID-19 vaccines.

Conclusion

mRNA vaccines against COVID-19 are protective against symptomatic infection and severe disease by the B.1.617.2 variant. Vaccinated individuals had a more rapid decline in viral load, which has implications on secondary transmission and public health policy. Rapid and widespread implementation of vaccination programs remains a key strategy for control of COVID-19 pandemic. Further studies should elucidate immunologic features driving vaccine-breakthrough infection to improve vaccine-induced protection.

Conflict of Interest Disclosures

BEY reports personal fees from Roche and Sanofi, outside the submitted work. All other authors declare no competing interests.

Acknowledgments

We thank all clinical and nursing staff who provided care for the patients and staff in the Infectious Disease Research and Training Office of the National Centre for Infectious Diseases who assisted with data collection. We will also like to thank Jeremy Cutter at the National Public Health and Epidemiology Unit of National Centre for Infectious Diseases who assisted with data management on Ct values.

Funding

This study was funded by grants from the Singapore National Medical Research Council (COVID19RF-001, COVID19RF-008). The funders had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication.

287

288

	Unvaccinated n = 130	Vaccinated n = 71	*p*-value
Median age (IQR), years	39.5 (30-58)	56 (39-64)	<0.001
Male (%)	67 (51.5)	27 (38)	0.067
Median Charlson Comorbidity Index (IQR)	0 (0-1)	0 (0-0)	0.125
Diabetes mellitus (%)	28 (21.5)	5 (7.0)	0.008
Hypertension (%)	28 (21.5)	14 (19.7)	0.762
Hyperlipidaemia (%)	32 (24.6)	18 (25.4)	0.908
Median Ct value on diagnosis (IQR)*	18.8 (14.9-22.7)	19.2 (15.2-22.2)	0.929
Asymptomatic	12 (9.2)	20 (28.2)	<0.001
Symptom onset after Diagnosis (%)	11 (9.3)	11 (21.6)	0.030
Median day of illness symptoms start (IQR)	2 (2-3)	3 (2-3)	0.715
Median Ct values for Symptom Onset After (IQR)	21.87 (18.8-31.2)	19.2 (16.6-21.5)	0.279
Median Sum of Symptoms Reported (IQR)	2 (1-3)	1 (0-2)	<0.001
Fever (%)	96 (73.9)	29 (40.9)	<0.001
Cough (%)	79 (60.8)	27 (38)	0.002
Shortness of Breath (%)	17 (13.1)	1 (1.4)	0.004
Runny Nose (%)	31 (23.9)	27 (38)	0.034
Sore Throat (%)	43 (33.1)	18 (25.4)	0.255
Diarrhoea (%)	8 (6.2)	0	0.052
Median highest Neutrophil (IQR) $\times 10^9$/L	4.50 (3.07-5.92)	4.33 (3.52-5.43)	0.117
Median lowest Lymphocyte (IQR) $\times 10^9$/L	0.95 (0.65-1.50)	1.36 (1.02-1.87)	<0.001
Median highest C-Reactive Protein (IQR), mg/L	24.7 (6.9-84.8)	12.6 (6.5-22.5)	<0.001
Median highest Lactate Dehydrogenase (IQR), U/L	486 (365-672)	373 (314-421)	0.062
Median highest Alanine Transferase (IQR), U/L	35	19	<0.001

	(18-74)	(13-34)	
Disease Outcome			
Pneumonia (%)	69 (53.1)	9 (21.7)	<0.001
Supplementary O2 required (%)	27 (20.8)	2 (2.8)	<0.001
ICU admission required (%)	7 (5.4)	0	0.053
Median days of ICU admission required (IQR)	4 (3-9)	-	-
Intubation (%)	2 (1.5)	0	0.541
Median days of Intubation (IQR)	7 (3-11)	-	-
COVID-19 specific treatment (%)	39 (30)	5 (7)	<0.001
Mortality	2 (1.54)	0	0.541

289

290 Table 1: Baseline characteristics and disease outcome between unvaccinated and completed mRNA

291 vaccination COVID-19 B1.617.2 infected patients

292

	Univariable model		Multivariable model	
	Crude OR (95% CI)	***p*-value**	**Adjusted OR (95% CI)**	***p*-value**
Vaccinated	0.111 (0.025-0.480)	0.003	0.073 (0.016-0.343)	0.001
Age group				
<45 years old	1	-	1	-
45-64 years old	6.19 (1.90-20.2)	0.003	8.29 (2.29-30.0)	0.001
>64 years old	13 (3.90-42.9)	<0.001	13.5 (2.66-68.8)	0.002
Male	0.913 (0.414-2.01)	0.821	1.09 (0.418-2.85)	0.857
Diabetes	6.18 (2.59-14.7)	<0.001	2.24 (0.785-6.41)	0.132
Hypertension	4.8 (2.09-11.0)	<0.001	1.62 (0.509-5.18)	0.413
Presence of other comorbidities, if any	3.96 (1.66-9.44)	0.002	0.897 (0.262-3.07)	0.862

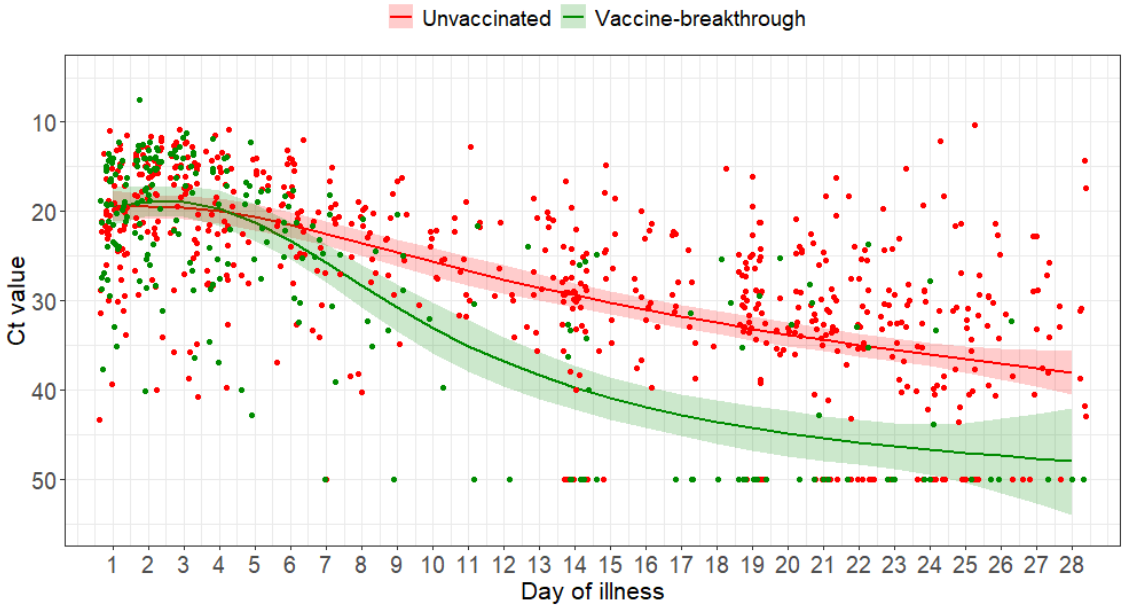
293

294 **Table 2:** Odds ratio of candidate risk factors for development of severe COVID-19 for completed

295 mRNA vaccination COVID-19 B1.617.2 infected patients. CI, confidence interval; OR, odds ratio

296

297



298

299 **Figure 1:** Scatterplot of Ct values and marginal effect of day of illness of COVID-19 B1.617.2 infected

300 patients with 95% confidence intervals from generalized additive mixed model with interaction term

301 between vaccination status and day of illness

302

303

304

305

306

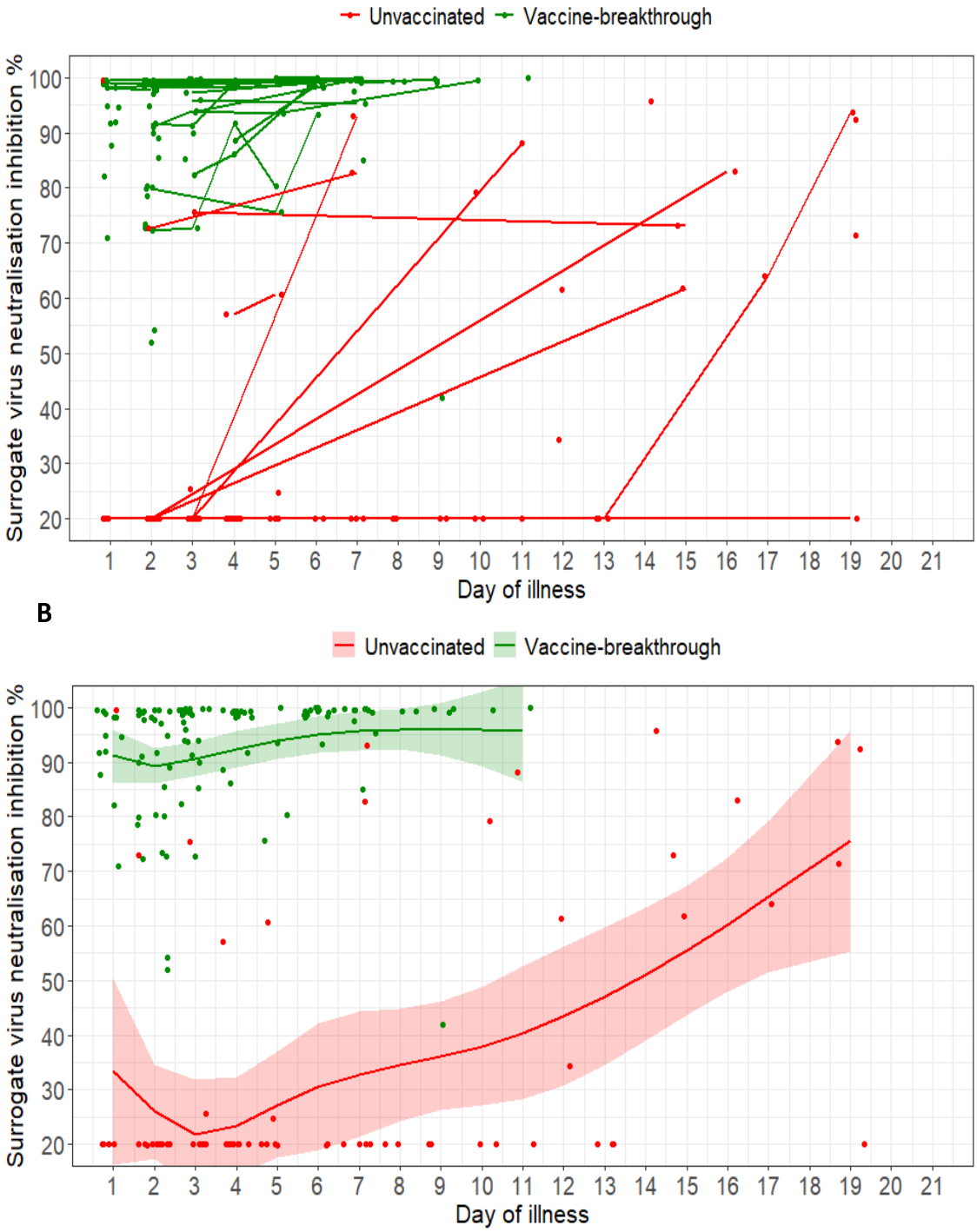


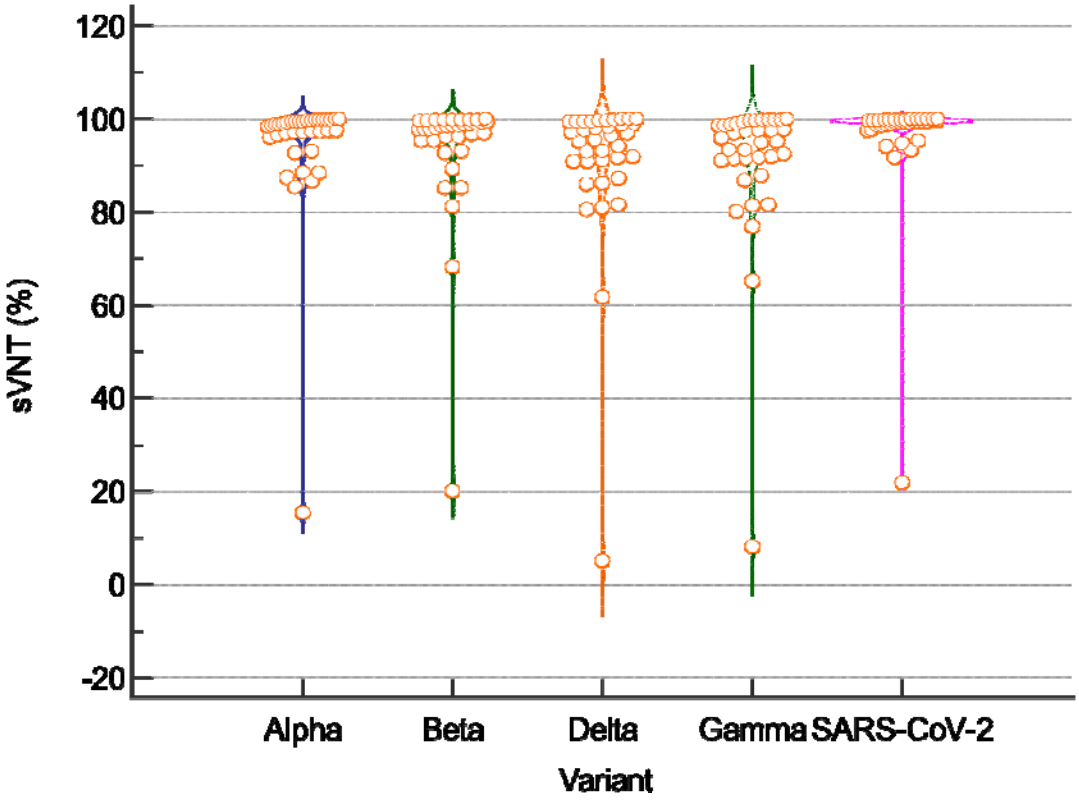
Figure 2: (A) Spaghetti plot of surrogate virus neutralisation (sVNT) inhibition % as measured by cPass; (B) Scatterplot of sVNT inhibition % and marginal effect of day of illness by vaccine-breakthrough and unvaccinated groups of COVID-19 B1.617.2 infected patients with 95% confidence

313 intervals from generalized additive mixed models. For both plots, n=127; vaccine-breakthrough = 67,

314 unvaccinated = 60

315

316



317

318 **Figure 3:** Violin plots of of surrogate virus neutralisation (sVNT) inhibition % against wildtype SARS-

319 CoV-2 and the B.1.617.2 variant for 36 patients with vaccine-breakthrough infection (median day of

320 sample collection from infection onset 6 days (inter-quartile range (IQR) 3-7). Titres against the four

321 variants were significantly lower than against wildtype SARS-CoV-2 [median sVNT, B.1.1.7 98.5%

322 (IQR: 96.3-99.5); B.1.351 98.2% (IQR: 95.3-99.5); B.1.617.2 96.0% (IQR: 90.9-99.3); P.1 95.5% (IQR:

323 91.3-98.9); Wildtype 99.4% (IQR: 98.5-99.7), Kruskal-Walis p-value = 0.00055, Post-hoc pairwise

324 comparison (Conover) Wildtype versus each variant $p<0.05$]

References

[1] F.P. Polack, S.J. Thomas, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J.L. Perez, G. Perez Marc, E.D. Moreira, C. Zerbini, R. Bailey, K.A. Swanson, S. Roychoudhury, K. Koury, P. Li, W.V. Kalina, D. Cooper, R.W. Frenck, Jr., L.L. Hammitt, O. Tureci, H. Nell, A. Schaefer, S. Unal, D.B. Tresnan, S. Mather, P.R. Dormitzer, U. Sahin, K.U. Jansen, W.C. Gruber, C.C.T. Group, Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine, N Engl J Med 383(27) (2020) 2603-2615.

[2] N. Dagan, N. Barda, E. Kepten, O. Miron, S. Perchik, M.A. Katz, M.A. Hernan, M. Lipsitch, B. Reis, R.D. Balicer, BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting, N Engl J Med 384(15) (2021) 1412-1423.

[3] Y. Angel, A. Spitzer, O. Henig, E. Saiag, E. Sprecher, H. Padova, R. Ben-Ami, Association Between Vaccination With BNT162b2 and Incidence of Symptomatic and Asymptomatic SARS-CoV-2 Infections Among Health Care Workers, JAMA (2021).

[4] L.R. Baden, H.M. El Sahly, B. Essink, K. Kotloff, S. Frey, R. Novak, D. Diemert, S.A. Spector, N. Rouphael, C.B. Creech, J. McGettigan, S. Khetan, N. Segall, J. Solis, A. Brosz, C. Fierro, H. Schwartz, K. Neuzil, L. Corey, P. Gilbert, H. Janes, D. Follmann, M. Marovich, J. Mascola, L. Polakowski, J. Ledgerwood, B.S. Graham, H. Bennett, R. Pajon, C. Knightly, B. Leav, W. Deng, H. Zhou, S. Han, M. Ivarsson, J. Miller, T. Zaks, C.S. Group, Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine, N Engl J Med 384(5) (2021) 403-416.

[5] E.J. Haas, F.J. Angulo, J.M. McLaughlin, E. Anis, S.R. Singer, F. Khan, N. Brooks, M. Smaja, G. Mircus, K. Pan, J. Southern, D.L. Swerdlow, L. Jodar, Y. Levy, S. Alroy-Preis, Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data, Lancet 397(10287) (2021) 1819-1829.

[6] E. Vasileiou, C.R. Simpson, T. Shi, S. Kerr, U. Agrawal, A. Akbari, S. Bedston, J. Beggs, D. Bradley, A. Chuter, S. de Lusignan, A.B. Docherty, D. Ford, F.R. Hobbs, M. Joy, S.V. Katikireddi, J. Marple, C. McCowan, D. McGagh, J. McMenamin, E. Moore, J.L. Murray, J. Pan, L. Ritchie, S.A. Shah, S. Stock, F. Torabi, R.S. Tsang, R. Wood, M. Woolhouse, C. Robertson, A. Sheikh, Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study, Lancet 397(10285) (2021) 1646-1657.

[7] E. Pritchard, P.C. Matthews, N. Stoesser, D.W. Eyre, O. Gethings, K.D. Vihta, J. Jones, T. House, H. VanSteenHouse, I. Bell, J.I. Bell, J.N. Newton, J. Farrar, I. Diamond, E. Rourke, R. Studley, D. Crook, T.E.A. Peto, A.S. Walker, K.B. Pouwels, Impact of vaccination on new SARS-CoV-2 infections in the United Kingdom, Nat Med (2021).

[8] N.G. Davies, S. Abbott, R.C. Barnard, C.I. Jarvis, A.J. Kucharski, J.D. Munday, C.A.B. Pearson, T.W. Russell, D.C. Tully, A.D. Washburne, T. Wenseleers, A. Gimma, W. Waites, K.L.M. Wong, K. van Zandvoort, J.D. Silverman, C.C.-W. Group, C.-G.U. Consortium, K. Diaz-Ordaz, R. Keogh, R.M. Eggo, S. Funk, M. Jit, K.E. Atkins, W.J. Edmunds, Estimated transmissibility and impact of SARS-CoV-2 lineage B.1.1.7 in England, Science (2021).

[9] H. Tegally, E. Wilkinson, M. Giovanetti, A. Iranzadeh, V. Fonseca, J. Giandhari, D. Doolabh, S. Pillay, E.J. San, N. Msomi, K. Mlisana, A. von Gottberg, S. Walaza, M. Allam, A. Ismail, T. Mohale, A.J. Glass, S. Engelbrecht, G. Van Zyl, W. Preiser, F. Petruccione, A. Sigal, D. Hardie, G. Marais, N.Y. Hsiao, S. Korsman, M.A. Davies, L. Tyers, I. Mudau, D. York, C. Maslo, D. Goedhals, S. Abrahams, O. Laguda-Akingba, A. Alisoltani-Dehkordi, A. Godzik, C.K. Wibmer, B.T. Sewell, J. Lourenco, L.C.J. Alcantara, S.L. Kosakovsky Pond, S. Weaver, D. Martin, R.J. Lessells, J.N. Bhiman, C. Williamson, T. de Oliveira, Detection of a SARS-CoV-2 variant of concern in South Africa, Nature 592(7854) (2021) 438-443.

[10] R. Pung, T.M. Mak, A.J. Kucharski, V.J. Lee, Serial intervals observed in SARS-CoV-2 B.1.617.2 variant cases, medRxiv (2021) 2021.06.04.21258205.

[11] N.G. Davies, C.I. Jarvis, C.C.-W. Group, W.J. Edmunds, N.P. Jewell, K. Diaz-Ordaz, R.H. Keogh, Increased mortality in community-tested cases of SARS-CoV-2 lineage B.1.1.7, Nature (2021).

[12] A. Sheikh, J. McMenamin, B. Taylor, C. Robertson, SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness, Lancet 397(10293) (2021) 2461-2462.
[13] Á. O'Toole, Hill, V., and Rambaut Group, PANGO lineages International Lineage Report B.1.617.2 Report <https://cov-lineages.org/global_report_B.1.617.2.html>, (accessed 8 July 2021.).
[14] T. Kustin, N. Harel, U. Finkel, S. Perchik, S. Harari, M. Tahor, I. Caspi, R. Levy, M. Leshchinsky, S. Ken Dror, G. Bergerzon, H. Gadban, F. Gadban, E. Eliassian, O. Shimron, L. Saleh, H. Ben-Zvi, E. Keren Taraday, D. Amichay, A. Ben-Dor, D. Sagas, M. Strauss, Y. Shemer Avni, A. Huppert, E. Kepten, R.D. Balicer, D. Netzer, S. Ben-Shachar, A. Stern, Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2-mRNA-vaccinated individuals, Nat Med (2021).
[15] A.E. McEwen, S. Cohen, C. Bryson-Cahn, C. Liu, S.A. Pergam, J. Lynch, A. Schippers, K. Strand, E. Whimbey, N.S. Mani, A.J. Zelikoff, V.A. Makarewicz, E.R. Brown, S.A.M. Bakhash, N.R. Baker, J. Castor, R.J. Livingston, M.L. Huang, K.R. Jerome, A.L. Greninger, P. Roychoudhury, Variants of concern are overrepresented among post-vaccination breakthrough infections of SARS-CoV-2 in Washington State, Clin Infect Dis (2021).
[16] Updates on COVID-19 (Coronavirus Disease 2019) Local Situation. <https://www.moh.gov.sg/covid-19>, 2021 (accessed June 10 2021.).
[17] COVID-19 therapies and vaccine landscape, Nat Mater 19(8) (2020) 809.
[18] C.W. Tan, W.N. Chia, X. Qin, P. Liu, M.I. Chen, C. Tiu, Z. Hu, V.C. Chen, B.E. Young, W.R. Sia, Y.J. Tan, R. Foo, Y. Yi, D.C. Lye, D.E. Anderson, L.F. Wang, A SARS-CoV-2 surrogate virus neutralization test based on antibody-mediated blockage of ACE2-spike protein-protein interaction, Nat Biotechnol 38(9) (2020) 1073-1078.
[19] Treatment Guidelines for COVID-19. <https://www.ncid.sg/Health-Professionals/Diseases-and-Conditions/Pages/COVID-19.aspx>, 2021 (accessed 1 June 2021.).
[20] J.J.Y. Zhang, K.S. Lee, L.W. Ang, Y.S. Leo, B.E. Young, Risk Factors for Severe Disease and Efficacy of Treatment in Patients Infected With COVID-19: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis, Clin Infect Dis 71(16) (2020) 2199-2206.
[21] J. Coveney, FIRTHLOGIT: Stata module to calculate bias reduction in logistic regression. Statistical Software Components S456948, Boston College Department of Economics, revised 25 Apr 2021., (2008).
[22] M.G. Thompson, J.L. Burgess, A.L. Naleway, H. Tyner, S.K. Yoon, J. Meece, L.E.W. Olsho, A.J. Caban-Martinez, A.L. Fowlkes, K. Lutrick, H.C. Groom, K. Dunnigan, M.J. Odean, K. Hegmann, E. Stefanski, L.J. Edwards, N. Schaefer-Solle, L. Grant, K. Ellingson, J.L. Kuntz, T. Zunie, M.S. Thiese, L. Ivacic, M.G. Wesley, J. Mayo Lamberte, X. Sun, M.E. Smith, A.L. Phillips, K.D. Groover, Y.M. Yoo, J. Gerald, R.T. Brown, M.K. Herring, G. Joseph, S. Beitel, T.C. Morrill, J. Mak, P. Rivers, B.P. Poe, B. Lynch, Y. Zhou, J. Zhang, A. Kelleher, Y. Li, M. Dickerson, E. Hanson, K. Guenther, S. Tong, A. Bateman, E. Reisdorf, J. Barnes, E. Azziz-Baumgartner, D.R. Hunt, M.L. Arvay, P. Kutty, A.M. Fry, M. Gaglani, Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines, New England Journal of Medicine (2021).
[23] J.L. Bernal, N. Andrews, C. Gower, E. Gallagher, R. Simmons, S. Thelwall, J. Stowe, E. Tessier, N. Groves, G. Dabrera, R. Myers, C. Campbell, G. Amirthalingam, M. Edmunds, M. Zambon, K. Brown, S. Hopkins, M. Chand, M. Ramsay, Effectiveness of COVID-19 vaccines against the B.1.617.2 variant, medRxiv (2021) 2021.05.22.21257658.
[24] A. Sheikh, J. McMenamin, B. Taylor, C. Robertson, SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness, The Lancet 397(10293) (2021) 2461-2462.
[25] CDC COVID-19 Vaccine Breakthrough Case Investigations Team. COVID-19 Vaccine Breakthrough Infections Reported to CDC — United States, January 1–April 30, 2021. MMWR Morb Mortal Wkly Rep 2021;70:792–793. .

423 [26] M. Levine-Tiefenbrun, I. Yelin, R. Katz, E. Herzel, Z. Golan, L. Schreiber, T. Wolf, V. Nadler, A.
424 Ben-Tov, J. Kuint, S. Gazit, T. Patalon, G. Chodick, R. Kishony, Initial report of decreased SARS-CoV-2
425 viral load after inoculation with the BNT162b2 vaccine, Nat Med 27(5) (2021) 790-792.

426
427

From: "Gottwald, Susanne" <GottwaldS@rki.de>
To: nCoV-Lage <nCoV-Lage@rki.de>
Date: 8/24/2021 1:44:42 PM
Subject: AW: P4 Beitrag f ≥r Krisenstab 25.8.

Liebe Frau Houareau,

nein, wir können das gerne auch am Freitag präsentieren. P4 war sonst immer am Montag dran, daher war ich mir nicht sicher, welcher Tag nun vorgesehen ist.

Ich gebe dem Kollegen Bescheid.

Vielen Dank und viele Grüße,
Susi Gottwald

Susi Gottwald | Project Management | Robert Koch Institute | Nordufer 20 | 13353 Berlin | +49 172 1835638
www.rki.de | Project Group P4 | Head: Prof. Dr. Dirk Brockmann
All research projects on our updated website: https://rocs.hu-berlin.de呉

Von: Houareau, Claudia im Auftrag von nCoV-Lage
Gesendet: Dienstag, 24. August 2021 12:38
An: Gottwald, Susanne; nCoV-Lage
Cc: Buda, Silke
Betreff: AW: P4 Beitrag für Krisenstab 25.8.

Liebe Frau Gottwald,

vielen Dank für Ihren Themenvorschlag für die morgige KS-Sitzung. Eigentlich sind Themen zur Modellierung für die freitags Sitzungen eingeplant. Handelt es sich um ein dringendes Thema, dass auf jeden Fall morgen besprochen werden sollte?

Mit vielen freundlichen Grüßen

i.A.
Claudia Houareau

Lagezentrum COVID-19
Robert Koch-Institut
Seestr. 10
13353 Berlin

Tel.: 030 18754 3063

E-Mail: nCoV-Lage@rki.de
Internet: www.rki.de
Twitter: @rki_de
Das Robert Koch-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministeriums für Gesundheit

---

Von: Gottwald, Susanne
Gesendet: Dienstag, 24. August 2021 11:54
An: nCoV-Lage
Betreff: P4 Beitrag für Krisenstab 25.8.

Liebe Mitarbeiter:innen vom Lagezentrum,
bei einer der letzten Sitzungen hatte Frau Buda eine Frage bzgl. einer Modellierung von Kontakten zwischen Fremden oder Bekannten.
Ich habe diese Frage in unser Team weiter gegeben und wir würden gerne eine Analyse des Kontaktindex zeigen. Wir können zwar nicht direkt die oben genannte Frage beantworten, da es sich um GPS Daten handelt, die keinen Aufschluss über den Status von Kontakten geben.
Aber der Kontaktindex (CX - Contact IndeX) ist eine alternative Methode zur Berechnung von R und in den letzten Wochen steigt dieser wieder steil an.
Das würde Dr. Klamser gerne morgen zeigen, falls das von Interesse ist und ein Zeitslot frei wäre.
Daneben würden wir dieses oder das nächste Mal auch gerne ein Update der Datenspende geben. Wir haben anhand historischer Inzidenzen und aktueller Fieberdetektionen ein Nowcast entwickelt, das sehr präzise die aktuellen Inzidenzen voraussagen kann: https://corona-datenspende.de/science/monitor/
Viele Grüße,
Susi Gottwald

Susi Gottwald | Project Management | Robert Koch Institute | Nordufer 20 | 13353 Berlin | +49 172 1835638
www.rki.de | Project Group P4 | Head: Prof. Dr. Dirk Brockmann
All research projects on our updated website: https://rocs.hu-berlin.de

---

From: AL1-Sekretariat <AL1-Sekretariat@rki.de>
To: "Mielke, Martin" <MielkeM@rki.de>
Date: 12/13/2021 9:33:08 AM
Subject: Ausgang BMG_WG: Erneuter Erlass zu [ID 4609_1] // Gültigkeitsdauer von Impfnachweisen und von Genesenen-Nachweisen
Attachments: Antwortentwurf ID 4609_1.docx
ErlassAntwort_editsInclTabelle_MvK_dyo_v2.pptx

-----Ursprüngliche Nachricht-----
Von: Bannert, Norbert Im Auftrag von nCoV-Lage
Gesendet: Mittwoch, 1. Dezember 2021 13:35
An: Rottmann-Großner, Heiko -61 BMG <Heiko.Rottmann-Grossner@bmg.bund.de>; nCoV-Lage <nCoV-Lage@rki.de>; Leitung_RKI <Leitung@rki.de>
Cc: 614 BMG <614@bmg.bund.de>; Friedrich Dr., Lena -614 BMG <Lena.Friedrich@bmg.bund.de>; 611 BMG <611@bmg.bund.de>; Sangs, André -RL -611 BMG <Andre.Sangs@bmg.bund.de>; RKI-Fach-Erlasswesen <RKI-Fach-Erlasswesen@bmg.bund.de>; Ziegelmann Dr., Antina -RL 614 BMG <Antina.Ziegelmann@bmg.bund.de>; Holtherm Dr., Hans-Ulrich -AL 6 BMG <Hans-Ulrich.Holtherm@bmg.bund.de>; Schaade, Lars <SchaadeL@rki.de>
Betreff: AW: Erneuter Erlass zu [ID 4609_1] // Gültigkeitsdauer von Impfnachweisen und von Genesenen-Nachweisen

Sehr geehrter Herr Rottmann-Großner,

bitte finden Sie im Anhang die Beantwortung Ihrer Anfrage vom 26. November 2021.

Mit den besten Grüßen,

i.A.

Norbert Bannert

Lagezentrum COVID-19

Robert Koch-Institut

Seestr. 10

13353 Berlin

Tel.: 030 18754 3063

E-Mail: nCoV-Lage@rki.de

Internet: www.rki.de

Twitter: @rki.de

Das Robert Koch-Institut ist ein Bundesinstitut im Geschäftsbereich des Bundesministeriums für Gesundheit

Relevanter Auszug aus dem ERLASS:

"Aus dem Parlament wird nunmehr die Frage gestellt, mit

-----Ursprüngliche Nachricht-----
Von: Rottmann-Großner, Heiko -61 BMG
Gesendet: Freitag, 26. November 2021 22:55
An: nCoV-Lage ; Leitung_RKI
Cc: 614 BMG <614@bmg.bund.de>; Friedrich Dr., Lena -614 BMG ; 611 BMG <611@bmg.bund.de>; Sangs, André -RL -611 BMG ; RKI-Fach-Erlasswesen ; Ziegelmann Dr., Antina -RL 614 BMG ; Holtherm Dr., Hans-Ulrich -AL 6 BMG ; Schaade, Lars
Betreff: Erneuter Erlass zu [ID 4609] // Gültigkeitsdauer von Impfnachweisen und von Genesenen-Nachweisen
Priorität: Hoch

Liebes RKI-Team,

herzlichen Dank für den beigefügten Bericht, der sehr hilfreich war.

Mit Blick auf die weiteren parlamentarischen Beratungen zur erneuten Änderung des Infektionsschutzgesetzes (IfSG) muss ich dennoch erneut um Einschätzungen zu weiteren Fragestellungen in diesem Zusammenhang bitten.

Das IfSG sieht in seinem aktuellen § 28 b (Abs. 2) u.a. Testvorschriften für Gesundheits- und Pflegeeinrichtungen bzgl. des neuartigen Coronavirus SARS-CoV2 vor.

Aus dem Parlament wird nunmehr die Frage gestellt, mit welchen Risikoeinschätzungen die Testfrequenzen, die Testart und der zu testende Personenkreis verändert werden könnten.

Für die Antwort(en) bitte ich dabei nach folgenden Merkmalen/Kriterien zu unterscheiden:

Zu testende Personen:

a) 3-fach Geimpfte

b) 2-fach Geimpfte

c) Nicht- bzw. "nichtvollständig"- Geimpfte

Settings/Einrichtungen:

d) Alten- und Pflegeheime

e) Krankenhäuser (in der Akutversorgung)

f) Arztpraxen

g) Zahnarzt-Praxen

Testarten:

h) Antigen-Schnelltests

i) PCR-Tests

Hinterfragt werden soll, ob in den o.g. Settings für bestimmte Gruppen bspw. eine (arbeits-)wöchentliche 2- oder 3-fach-Testung mit Antigen-Tests zur Risikominimierung in Bezug auf eine potenzielle Virusübertragung auf zu schützende Personen "ausreichend" sein könnte, oder welche anderen Frequenzen mit Blick auf die genannten Settings und Impfniveaus "empfehlenswert" wären.

Mir ist sehr bewusst, dass hierzu vermutlich keine "absoluten" Aussagen möglich sein werden (es sei denn, man ginge erneut von einer täglichen Testung aus). Insofern wird um eine abgestufte (ggf. "bezifferbare") Risikoeinschätzung gebeten.

Dabei ist zu bedenken, dass dies präjudizierend auf andere Bereiche (Einreisekriterien, Ausnahmen von Schutzmaßnahmen) wirken könnte.

Trotz dieser Komplexität wird um einen zeitnahen Bericht gebeten, da die Beratungen mit den Abgeordneten und Ressorts in der kommenden Woche fortgesetzt werden sollen.

Ich bitte diese E-Mail (auch ohne Briefkopfbogen) als Erlass zu betrachten.

Herzlichen Dank!

Freundliche Grüße

i.A.

Heiko Rottmann-Großner

===

Bundesministerium für Gesundheit

Leiter der Unterabteilung 61

- Gesundheitssicherheit -

Besuchsadresse:

Unter den Linden 21 (3. OG)

10117 Berlin

Postanschrift:

11055 Berlin

Tel.: +49 (0)30/18441-3700

Fax: +49 (0)30/18441-3222

E-Mail: heiko.rottmann@bmg.bund.de

Aktuelle Informationen zum Coronavirus:

https://www.bundesgesundheitsministerium.de/coronavirus.html

https://www.zusammengegencorona.de/

https://impfdashboard.de/

www.bundesgesundheitsministerium.de

www.twitter.com/BMG_Bund

www.facebook.com/BMG.Bund

Hinweis zu externen Links.

Auf Art und Umfang der übertragenen bzw. gespeicherten Daten hat das BMG keinen Einfluss.

Der Schutz Ihrer Daten ist uns wichtig. Nähere Informationen zum Umgang mit personenbezogenen Daten im BMG können Sie der Datenschutzerklärung auf
https://www.bundesgesundheitsministerium.de/datenschutz.html

entnehmen.

-----Ursprüngliche Nachricht-----

Von: Rosner, Bettina [mailto:RosnerB@rki.de] Im Auftrag von nCoV-Lage

Gesendet: Donnerstag, 25. November 2021 16:41

An: Ziegelmann Dr., Antina -RL 614 BMG

Cc: 614 BMG <614@bmg.bund.de>; Friedrich Dr., Lena -614 BMG ; 611 BMG <611@bmg.bund.de>; Sangs, André -RL -611 BMG ; Rottmann-Großner, Heiko -61 BMG ; nCoV-Lage ; RKI-Fach-Erlasswesen ; Leitung_RKI

Betreff: AW: [ID 4609] WG: Gültigkeitsdauer von Impfnachweisen und von Genesenen-Nachweisen

Liebe Frau Ziegelmann,

anbei die Erlassantwort des RKI.

Mit freundlichen Grüßen,

i.A.

Bettina Rosner

Lagezentrum COVID-19

Robert Koch-Institut

Seestr. 10

13353 Berlin

Tel.: 030 18754 3063

E-Mail: nCoV-Lage@rki.de

Internet: www.rki.de

Twitter: @rki_de

-----Ursprüngliche Nachricht-----

Von: Ziegelmann Dr., Antina -RL 614 BMG

Gesendet: Mittwoch, 24. November 2021 12:54

An: nCoV-Lage

Cc: 614 BMG <614@bmg.bund.de>; Friedrich Dr., Lena -614 BMG ; 611 BMG <611@bmg.bund.de>; Sangs, André -RL -611 BMG ; Rottmann-Großner, Heiko -61 BMG

Betreff: [ID 4609] WG: Gültigkeitsdauer von Impfnachweisen und von Genesenen-Nachweisen

Priorität: Hoch

Liebe Kolleginnen und Kollegen,

die Ampel-Partner haben das BMG gebeten zu prüfen, ob es für die Gültigkeitsdauer von Impfnachweisen und von Genesenen-Nachweisen mit Blick auf Impfdurchbrüche und notwendige Booster-Impfungen einer Anpassung der SchAusnahmV und der CoronaEinreiseV bedarf.

§ 2 Nr. 3 b SchutzAusnahmV sowie § 2 Nr. 10 Corona-EinreiseV definieren den Impfnachweis gleichlautend bisher wie folgt:

* Ein Impfnachweis ist ein Nachweis hinsichtlich des Vorliegens einer vollständigen Schutzimpfung gegen das Coronavirus SARS-CoV-2 in deutscher, englischer, französischer, italienischer oder spanischer Sprache in verkörperter oder digitaler Form, wenn die zugrundeliegende Schutzimpfung mit einem oder mehreren vom Paul-Ehrlich-Institut im Internet unter der Adresse www.pei.de /impfstoffe/covid-19 genannten Impfstoffen erfolgt ist, und

a) entweder aus einer vom Paul-Ehrlich-Institut im Internet unter der Adresse www.pei.de/impfstoffe /covid-19 veröffentlichten Anzahl von Impfstoffdosen, die für eine vollständige Schutzimpfung erforderlich ist, besteht und seit der letzten erforderlichen Einzelimpfung mindestens 14 Tage vergangen sind oder

b) bei einer genesenen Person aus einer verabreichten Impfstoffdosis besteht.

Vor diesem Hintergrund bitten wir Sie um eine wissenschaftliche Einschätzung zur Dauer des Impfschutzes bei Impfung mit einem in der EU-zugelassenen oder damit äquivalenten Impfstoff, sofern möglich nach folgender Differenzierung:

* Grundimmunisierung mit einem 2-Dosen-Impfstoff bzw. bei Kreuzimpfung

* Impfschutzes nach einer Janssen-Impfung

* Impfschutzes nach einer Genesenenimpfung

* Impfschutzes nach einer Auffrischimpfung

* Schutz nach Genesung

Als Grundlage für Verhandlungen auf EU-Ebene bitten wir auch um die Bewertung, welche Zeiträume der Gültigkeit insbesondere im Hinblick auf den bestehenden Impfschutz akzeptabel sein können. Im Hinblick darauf, dass eine Änderung der Gültigkeitsdauer oder eine nachträgliche Anhebung der Voraussetzungen für den Fortbestand des Impfschutzes eine Grundrechtsrelevanz aufweist, wäre es wünschenswert, ein möglichst einheitliches Schutzniveau definieren zu können, von dem der Fortbestand des Impfzertifikats für die Zwecke der Coronavirus-Einreiseverordnung oder der COVID -19-Schutzmaßnahmen-Ausnahmeverordnung abhängig gemacht werden kann.

Ich bitte um Ihren Bericht bis morgen, 25.11.2021 um 15 Uhr.

Viele Grüße, Antina Ziegelmann

Dr. Antina Ziegelmann

Federal Ministry of Health

Head of Division "Infectious Diseases"

Unter den Linden 21

10117 Berlin - Germany

Telefon + 49 30 18441 3257

Telefax + 49 30 18441 4862

E-Mail antina.ziegelmann@bmg.bund.de

Mit welchen Risikoeinschätzungen können die Testfrequenzen, die Testart und der zu testende Personenkreis verändert werden?

- *Stand: 01.12.2021*

AUSGANGSLAGE:

Mit E-Mail (Erlass) vom Freitag, 26. November 2021 22:55

geben Sie eine Frage aus dem Parlament an uns zur Beantwortung weiter:

Relevanter Auszug aus dem ERLASS:
"Aus dem Parlament wird nunmehr die Frage gestellt, mit welchen Risikoeinschätzungen die Testfrequenzen, die Testart und der zu testende Personenkreis verändert werden könnten.

Für die Antwort(en) bitten Sie dabei folgende Merkmale/Kriterien zu unterscheiden:

Zu testende Personen:
a) 3-fach Geimpfte
b) 2-fach Geimpfte
c) Nicht- bzw. "nichtvollständig"- Geimpfte

Settings/Einrichtungen:
d) Alten- und Pflegeheime
e) Krankenhäuser (in der Akutversorgung)
f) Arztpraxen
g) Zahnarzt-Praxen

Testarten:
h) Antigen-Schnelltests
i) PCR-Tests

Hinterfragt werden soll, ob in den o.g. Settings für bestimmte Gruppen bspw. eine (arbeits-) wöchentliche 2- oder 3-fach-Testung mit Antigen-Tests zur Risikominimierung in Bezug auf eine potenzielle Virusübertragung auf zu schützende Personen "ausreichend" sein könnte, oder welche anderen Frequenzen mit Blick auf die genannten Settings und Impfniveaus "empfehlenswert" wären.

Es wird um eine abgestufte (ggf. "bezifferbare") Risikoeinschätzung gebeten“.

ANTWORT:

In der Sache geht es um die **Prävention nosokomialer Übertragungen von SARS-CoV-2 von Pflegenden auf Patienten bzw. Bewohner von Pflegeheimen.**
Diese beruht auf einem Multibarrierensystem aus

- Impfung
- MNS/Atemschutz und Basishygienemaßnahmen

sowie
- Ergänzenden SARS-CoV-2 Tests.

Tests auf SARS-CoV-2 vermindern das Übertragungsrisiko (insbesondere in Zeiten hoher 7-Tage-Inzidenzen), da auch Geimpfte das Virus nach entsprechendem Kontakt und anschließender Infektion ausscheiden können. Die durch die ergänzenden Tests zu erzielende Risikoreduktion ist abhängig von

- Der 7-Tage-Inzidenz
- Der Tragfähigkeit des Impfschutzes
- Der Exposition (z.B. in der Familie)
- Der Testfrequenz und
- Der Sensitivität der verwendeten Tests.

Eine tägliche Testung aller MitarbeiterInnen wurde von Fachgesellschaften (etwa DGI bzw. BÄK) als nicht praktikabel angesehen.

Im Hinblick auf die Praxisnähe sind folgende Settings zu unterscheiden

A) stationäres Setting
a) Alten- und Pflegeheime
b) Krankenhäuser (in der Akutversorgung)

B) ambulantes Setting
c) Arztpraxen
d) Zahnarzt-Praxen

In diesen beiden Settings unterscheiden sich Zahl und Art von Kontakten zwischen Personal und Patienten bzw. zu Pflegenden.

Auch möchten wir aus Gründen der Praktikabilität vorschlagen, nur zwischen i) **vollständig Geimpften** (letzte Impfung < 6 Monate zurückliegend) und ii) **Ungeimpften** zu unterscheiden.

Die entsprechenden Berechnungen finden sich in der Anlage. Mithilfe der dort dargelegten Formel lässt sich die Risikominimierung in Abhängigkeit von den entsprechenden Variablen berechnen (auf Folie 11 findet sich auch eine orientierende Tabelle). Beispielhaft ist bei 2G und dem Tragen von Masken eine mindestens 2x-wöchentliche Testung im Bereich der Alten- und Pflegeheime ein plausibler Ansatz. Ungeimpfte müssten häufiger getestet werden (s. Anlage).

FAZIT:

Zum Schutz vulnerabler Gruppen in Zeiten hoher Viruszirkulation kann im Rahmen eines Multibarrierensystems (Impfung, MNS/ Basishygiene, Tests) ein 2G+ Konzept mit 2x wöchentlicher Testung als Orientierungsmaßstab für pflegendes Personal gelten. (s. auch die Tabelle auf Folie 11).

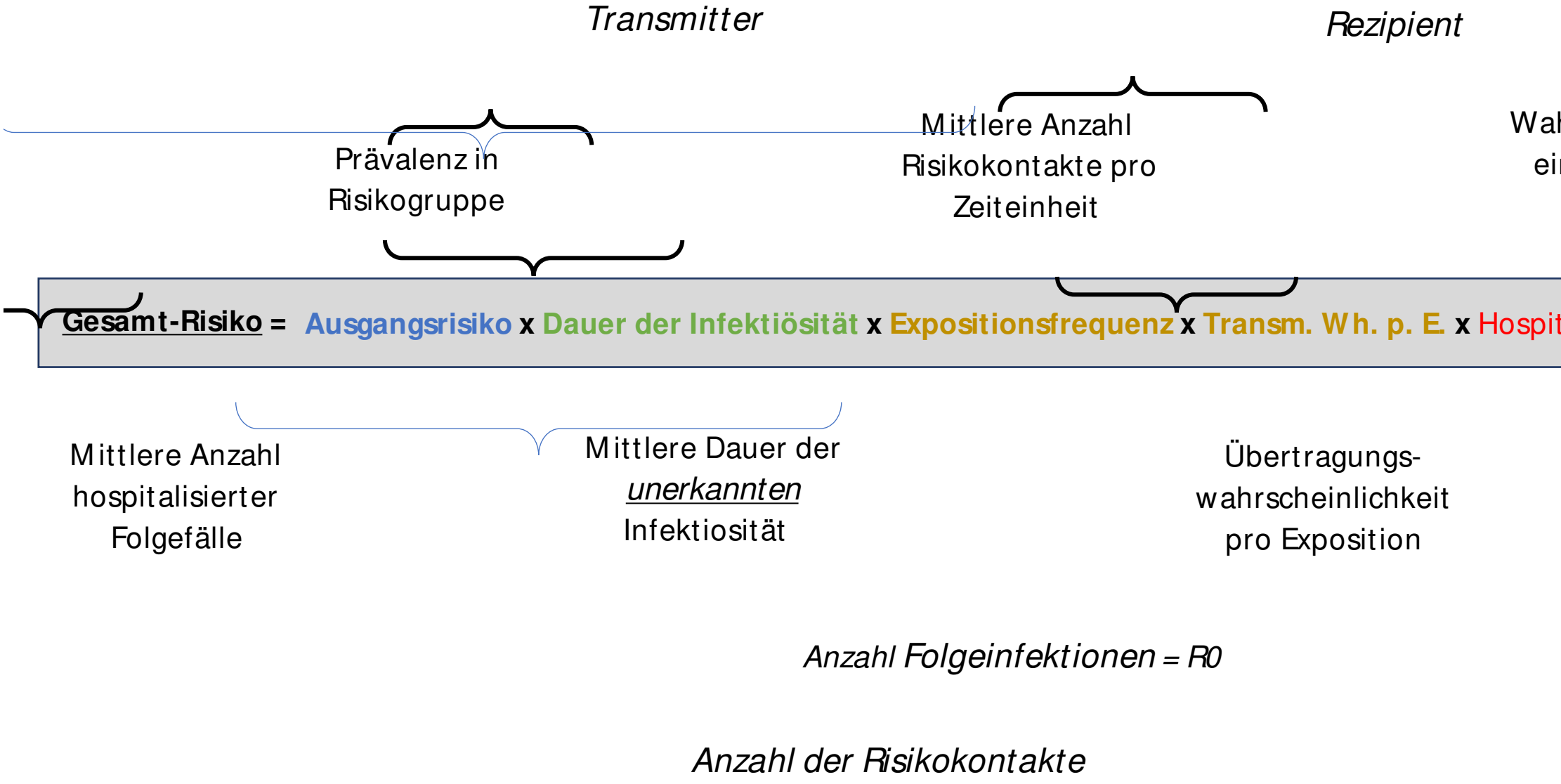
Ungeimpfte sollten häufiger getestet werden. Das Restrisiko ist aber dennoch höher als bei zweifach getesteten Geimpften.
Für MitarbeiterInnen ohne Patientenkontakt ist eine 3G- oder 2G- Regelung ausreichend (s. hierzu auch https://www.dgi-net.de/unzumutbare-belastung-des-unter-hochdruck-stehenden-gesundheitssystems-dgi-fordert-umgehende-anpassung-der-testpflicht/).

Eine zu starke Differenzierung geht häufig mit Einschränkungen der Compliance einher.

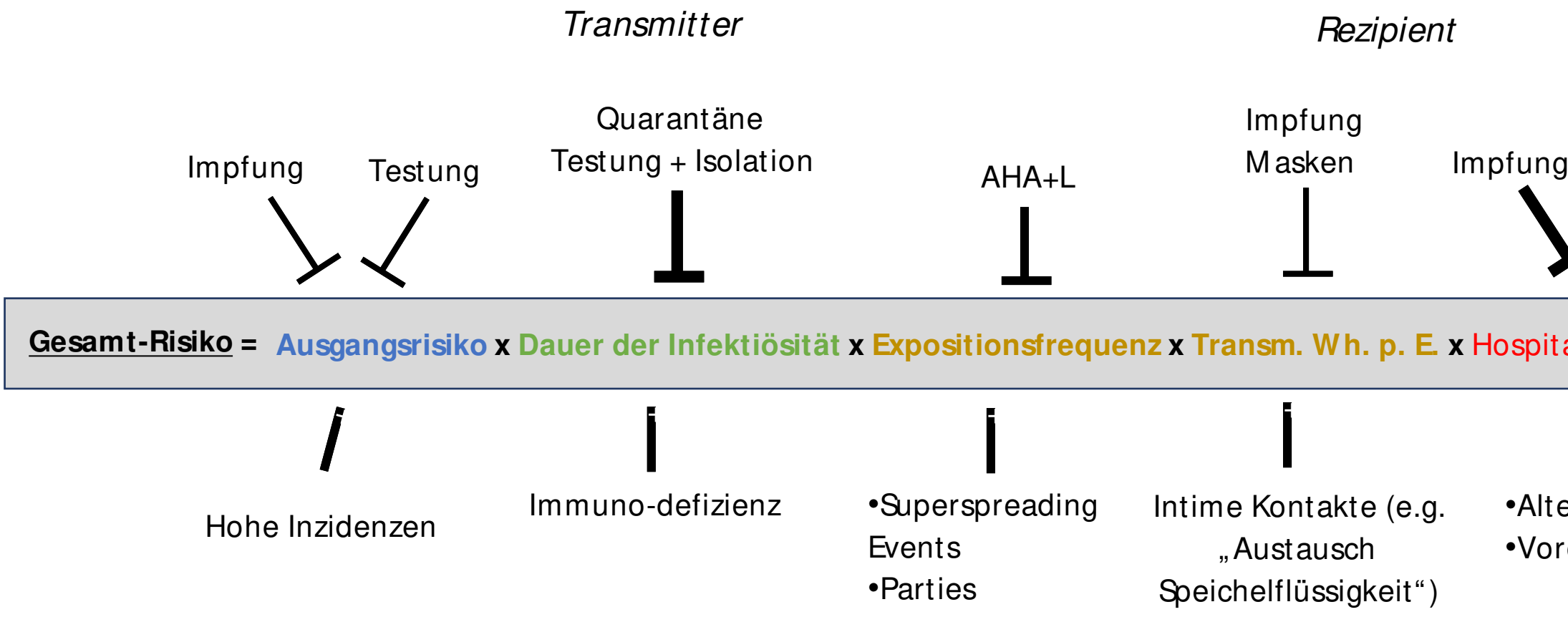
Kontextueller "Zusatznutzen" von Testung und Impfung für den Fremdschutz

Projektgruppe 5 im Auftrag AG Diagnostik @RKI

Überblick: Faktoren, die zur Hospitalisierungsdynamik beitragen



Maßnahmen im Kontext



Risikoeinschätzung

Mit welchen Risikoeinschätzungen werden
Testfrequenz & Test-Art und
Personenkreis
bei der Teststrategie berücksichtigt?

Aufschlüsselung

-

3.Testfrequenz und Test-Art

4.Die **Dauer der Infektiosität** kann mittels mittels Testung und Isolation reduziert werden (Annahme: positiver Test führt zur augenblicklichen Selbstisolation). Berechnung mit Hilfe des im ‚COVIDStrategyCalculators' implementierten Modells.

Van der Toorn et al (2021), 10.1016/j.patter.2021.100262

6.

7.Personenkreis

Relevante Variablen:

9.Potentielle Transmitter → **Ausgangsrisiko** der Infektion (‚Prävalenz')

Beispiel: bei einer Impfeffektivität gegen Infektion von 90% ist die Wahrscheinlichkeit, dass ein Geimpfter infiziert ist 0.1 relativ zu der Wahrs bei einem Ungeimpften.

11.Exponierte Personen → **Hospitalisierungsrisiko** pro Infektion

Beispiel: Eine Person gehobenen Alters hat z.B. ein 10-fach höheres Risiko der Hospitalisierung im Vergleich zu einer jungen Person, ohne Vo Eine geimpfte Person hat ein geringeres Hospitalisierungsrisiko als eineungeimpfte Person (?*je nach Dauer der letzten Impfung*?)

14.Art der Exposition

15.Übertragungswahrscheinlichkeit pro Exposition (**Transm. Wh. p. E**)

Die **Transm. Wh. p. E** hängt mit der Art der Exposition zusammen. Beispiel: Bei einer x-fach höheren Virusexposition ist das Infektionsrisiko u

Gesamt-Risiko = **Ausgangsrisiko** x **Dauer der Infektiösität** x **Expositionsfrequenz** x **Transm. Wh. p. E.** x Hospita

Ad 1a) Reduktion der **Dauer der Infektiosität** **(Risikoreduktion)**

Annahmen

Intra-patienten virus-dynamik Modell

Van der Toorn et al. (2021), 10.1016/j.patter.2021.100262

Viruskinetiken bei Geimpften und Ungeimpften sind nahezu identisch

Sofort-Isolierung bei positivem Test ODER beim Auftreten von Symptomen

Test-Art

PCR-Tests mit maximaler Sensitivität von 80%

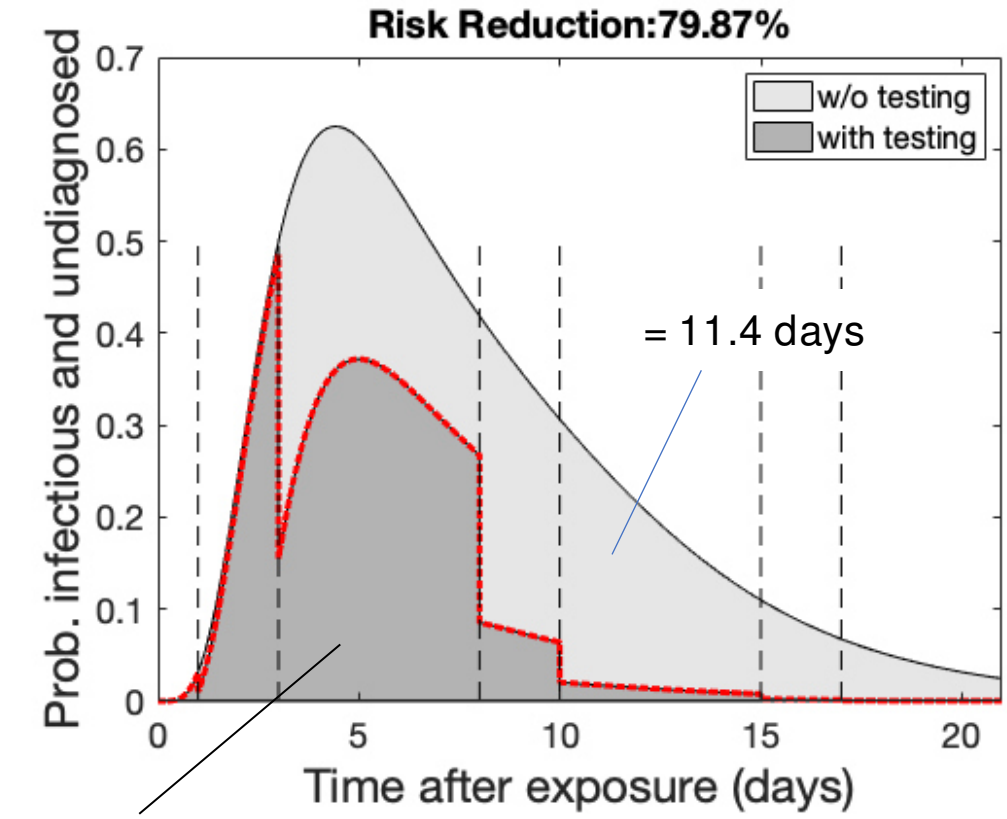
Antigen-Tests mit maximaler Sensitivität von 68% (gute Tests)

Antigen-Tests mit maximaler Sensitivität von 40% (schlechte Tests)

Anteil asymptomatischer Infektionen: 20%

* FYI: Alle Parameter können bei Bedarf angepasst werden.

Erläuterungen: Berechnung Risikoreduktio



•Das Transmissionspotential ist durch die Fläc
der Kurve gegeben. I.e.: die mittlere **Da**
unerkannten **Infektiosität**

•

•

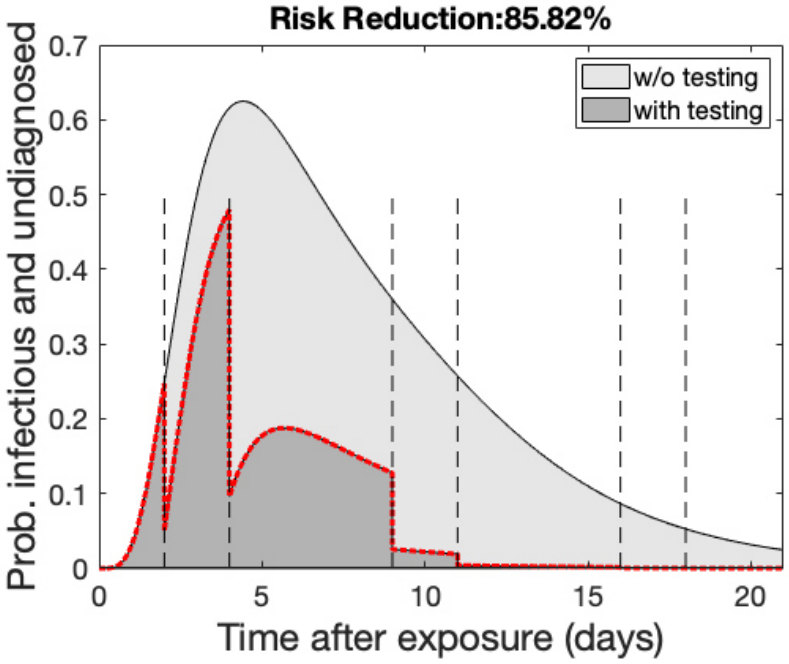
•Die Effektivität der Maßnahme (= Risikore
beschreibt das Verhältnis der beiden Flächen
dem Beispiel links (Infektion an einem Sonnta
wöchentliches Testen mit gutem Ag-Test, Be
Montag) wird die Fläche um 79.87% verringer

Vertical dashed lines: ti

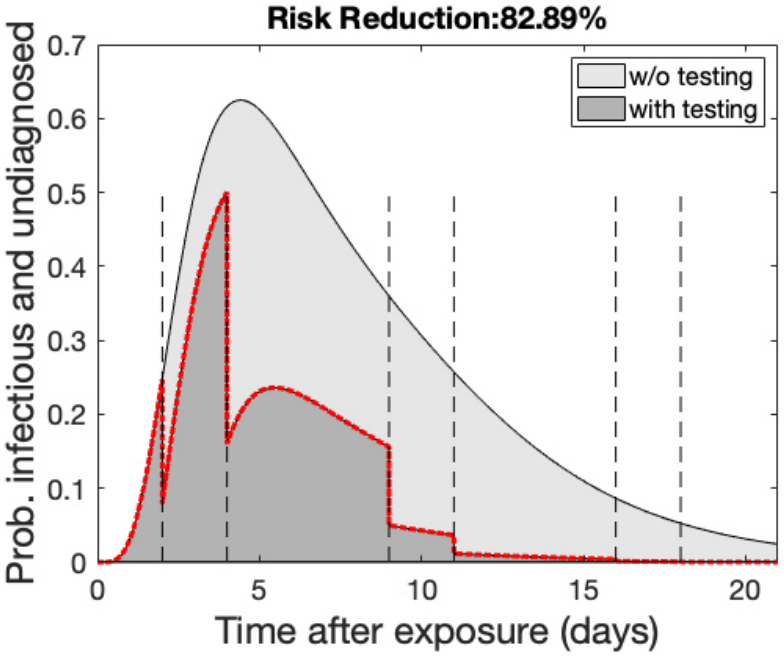
Zweimal pro Woche

(Infektion am Samstag, erster Test am Montag)

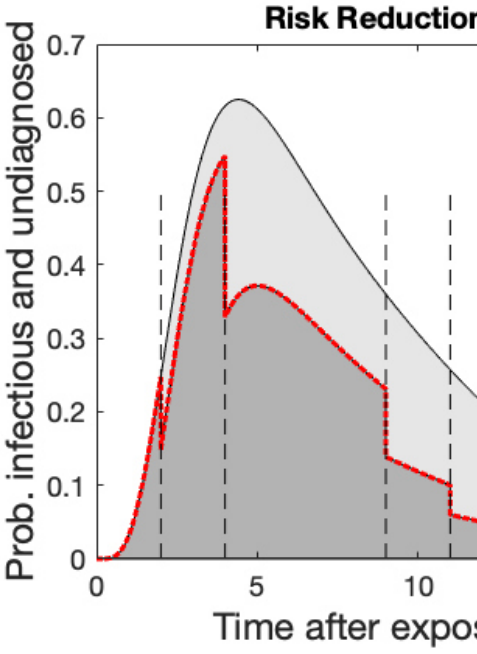
PCR



guter Ag-Test



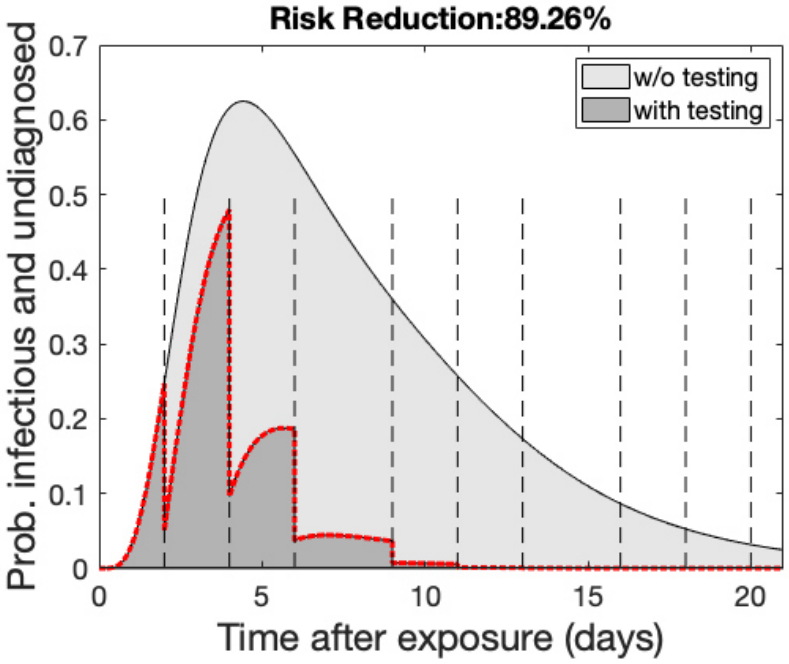
schlechter



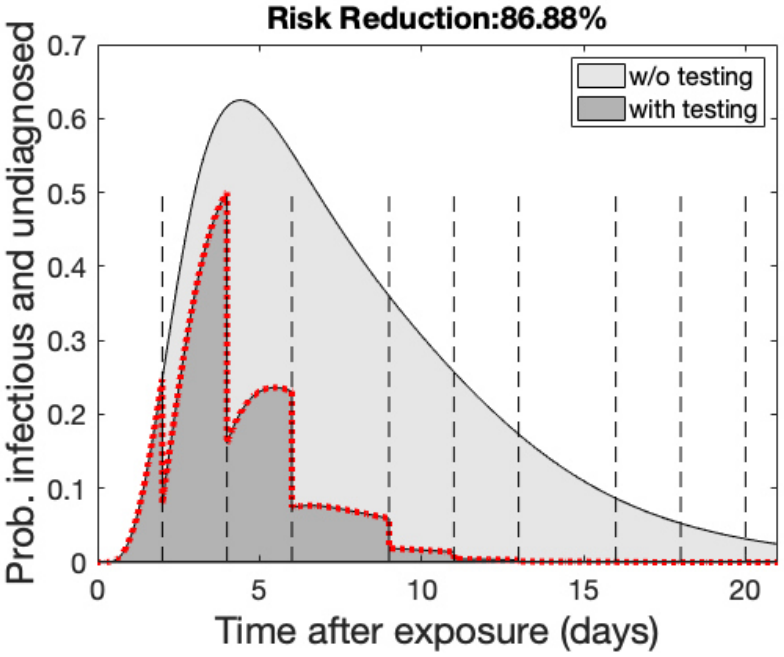
Dreimal pro Woche

(Infektion am Samstag, erster Test am Montag)

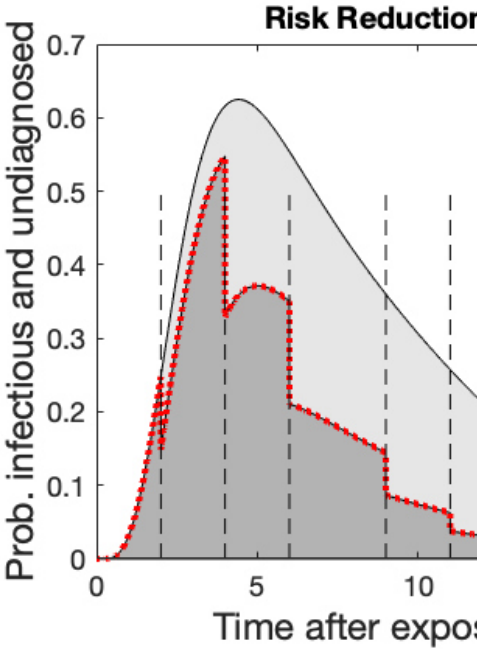
PCR



guter Ag-Test



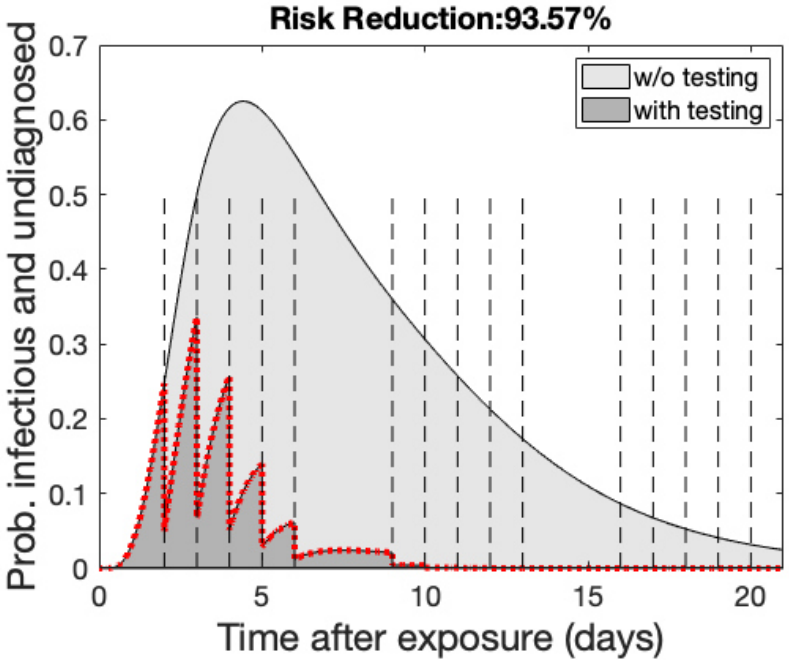
schlechter



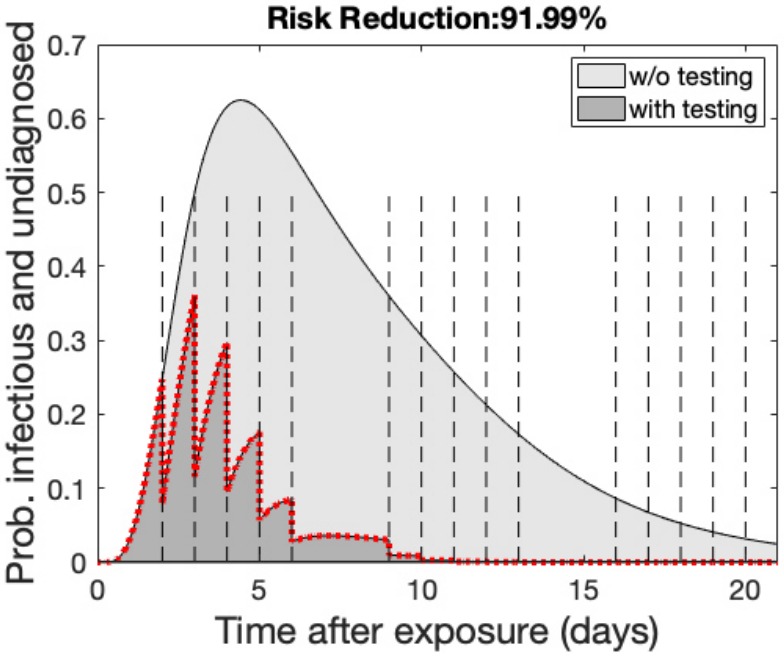
Fünfmal pro Woche(„täglich“)

(Infektion am Samstag, erster Test am Montag)

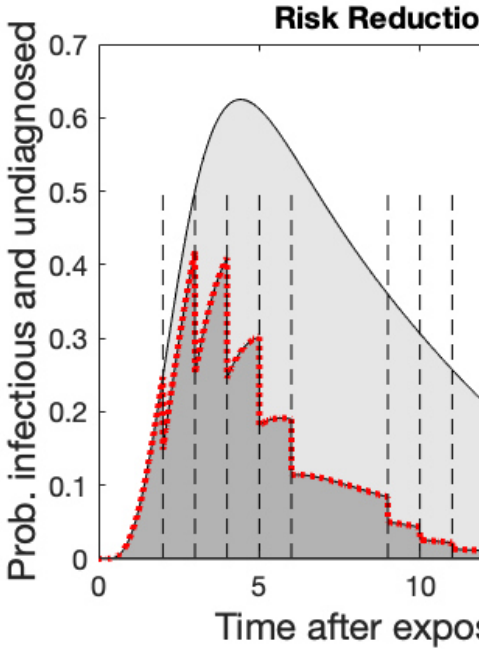
PCR



guter Ag-Test



schlechter



Risikoreduktion bei unterschiedlichen Teststrateg

	PCR	„guter“ Antigentest	„schlechter“ Antigentest
2 x pro Woche	85.82%	82.89%	73.94%
3 x pro Woche	89.26%	86.88%	78.66%
5 x pro Woche	93.57%	91.99%	85.6%

Ad 2a) **Ausgangsrisiko**

Die Impfeffektivität (gegen Infektion) VE beschreibt das Verhältnis der Infektionsrisiken (bei typischer Exposition) zwischen geimpften und ungeimpften Personen

-> Wahrscheinlichkeit dass sich eine Person infiziert, die vor *t* Tagen geimpft wurde

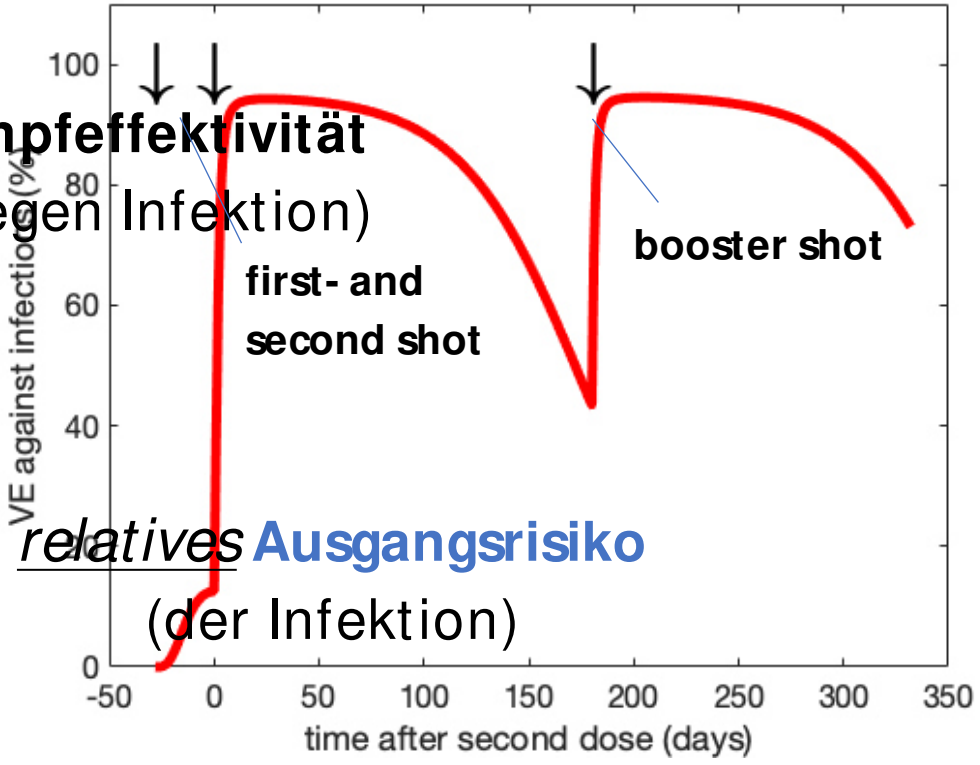
-> Wahrscheinlichkeit, dass sich eine ungeimpfte Person infiziert

Daraus lässt sich das das *relative* **Ausgangsrisiko** bestimmen (relativ zur ungeimpften Person):

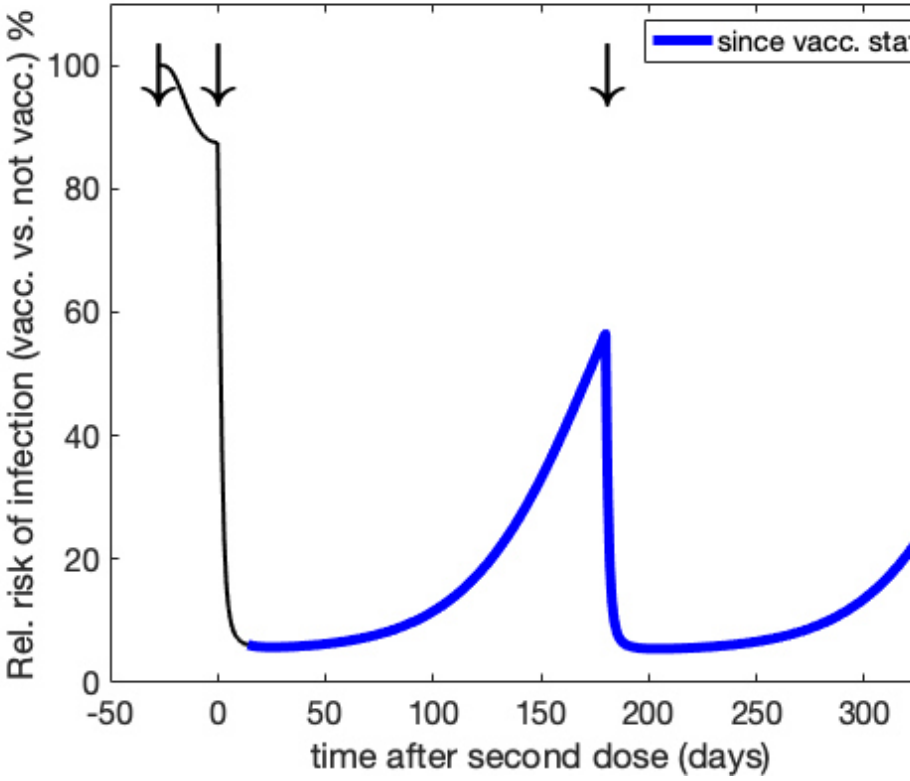
Impfeffektivität & Ausgangsrisiko

Disclaimer: die hier gezeigte
dienen der *Veranschaulichu*
D.h.: Sie sind noch nicht an l
angeglichen, unterliegen int
Schwankungen und sind var
Der grobe Trend sollte allerd

Impfeffektivität
(gegen Infektion)



relatives **Ausgangsrisiko**
(der Infektion)



| time of vaccine shot

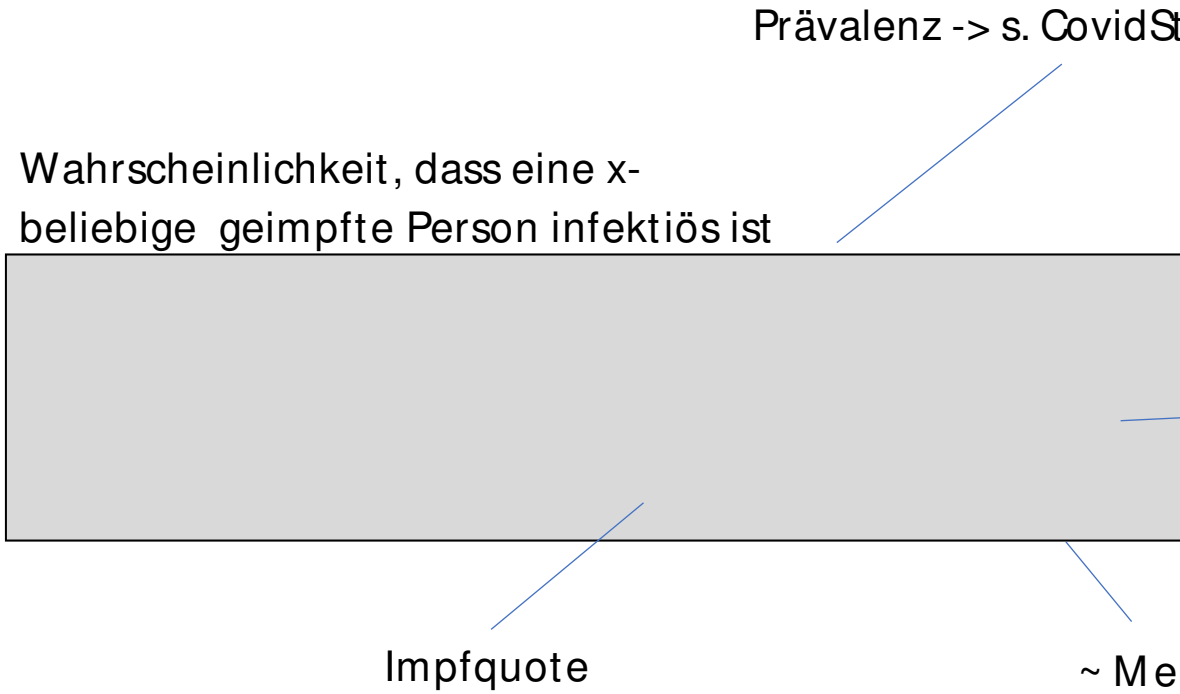
Ad 2a) **Ausgangsrisiko**

*https://www.rki.de/DE/Con
/Neuartiges_Coronavirus/Da
/Impfeffektivitaet.html

- *relatives* **Ausgangsrisiko**
-

absolutes **Ausgangsrisiko:**

Prävalenz an *Infektiösen*+



Wahrscheinlichkeit, dass eine x-beliebige ungeimpfte Person inf

+CovidStrategyCalculator
https://covidstrategycalculator.github.io

Beispielrechnung

absolutes **Ausgangsrisiko:**

rävalenz nach Impfstatus

Wahrscheinlichkeit, dass eine x-beliebige geimpfte Person infektiös ist

Wahrscheinlichkeit, dass eine x-beliebige ungeimpfte Person infektiös ist

Prävalenz an *Infektiösen*

VE = 67%
P(vacc) = 70%

Recap

Gesamt-Risiko = **Ausgangsrisiko** x **Dauer der Infektiösität** x **Expositionsfrequenz** x **Transm. Wh. p. E.** x Hospit

1.Effektivität der Teststrategie (=Risikoreduktion)

Zwischen 74-93% je nach Teststrategie; I.e. die **Dauer der Infektiosität** und Anzahl Folgeinfektionen w
Faktor 4 bis 14 reduziert. (Faktor = 100/(100-Risikoreduktion))

 Folie 8-10

4. *relatives* **Ausgangsrisiko**

Nicht-geimpfte: 100% | ge-impfte: 5-80%, je nach Dauer der letzten Impfung*

Folie 11-14

absolutes **Ausgangsrisiko** = , bzw.

Settings:

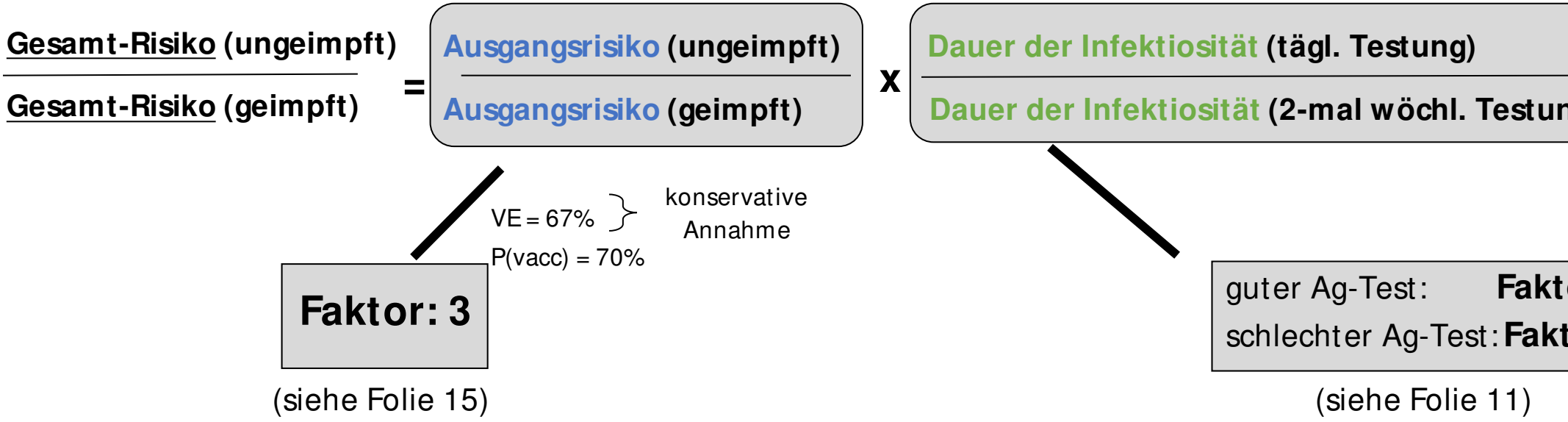
Alten & Pflegeheime erhöhtes Hospitalisierungsrisiko

Arztpraxen erhöhte **Expositionsfrequenz**?

Zahnarztpraxen erhöhtes **Transmissionsrisiko pro Exposition** aufgrund der Art der Exposition?

Rechnung Ungeimpft vs. Geimpft

Kann häufige Testung das von einem Ungeimpften ausgehende Transmissionsrisiko
senken, dass es dem eines seltener getesteten Geimpften entspricht?

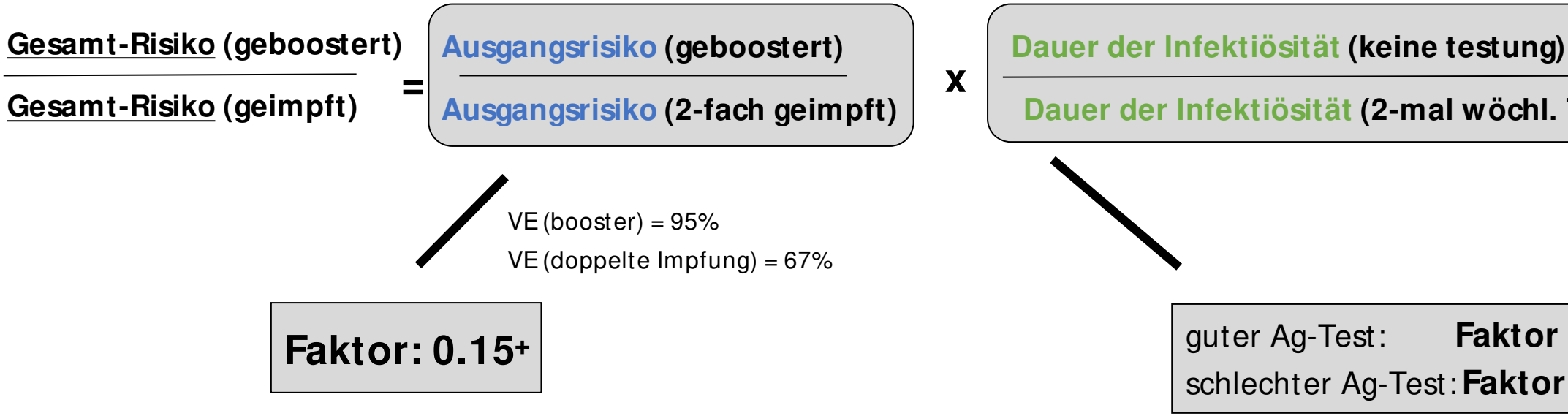


-

- Das von einem Ungeimpften ausgehende Infektionsrisiko kann durch erhöhte Testfreq
unterhalb das von einem 2-mal wöchentlich getesteten Geimpften ausgehende Infektio

Rechnung (frisch) geboostert vs. vor wenigen Monaten geimpft

- Muss eine frisch geboosterte Person getestet werden?



-

- Rechnerisch geht von frisch geboosterten, nicht getesteten Personen ein leicht geringer Infektionsrisiko aus als von (vor längerer Zeit) doppelt-geimpften, die sich 2-mal wöchentl lassen
- **Achtung**: Hängt alles von der Dauer der Zeit seit der letzten Impfung ab. Wenn solche R entworfen werden, dann müssen sie ständig angepasst werden.

+ Rechnung (Folie 17): Faktor
+ Rechnung: Faktor = (1-VE(b)

From: "Schaade, Lars" <SchaadeL@rki.de>
To: Verteiler-Krisenstab <verteiler-krisenstab@rki.de>
Date: 12/13/2021 9:18:44 AM
Subject: WG: Entwurf Beschlussvorlage Aufhebung Testpflicht
Attachments: GMK-Beschlussentwurf_Aufhebung der Testpflicht nach Auffrischimpfung.docx

---

Fur die Diskussion nachher im Krisenstab - bitte vertraulich halten.

Gru?

LS

-----Ursprungliche Nachricht-----
Von: Rottmann-Gro?ner, Heiko -61 BMG <Heiko.Rottmann-Grossner@bmg.bund.de>
Gesendet: Montag, 13. Dezember 2021 10:09
An: Schaade, Lars <SchaadeL@rki.de>
Betreff: WG: Entwurf Beschlussvorlage Aufhebung Testpflicht
Prioritat: Hoch

Hallo!

Das hier ist der Entwurfstext, wie er am Freitag aussah...

Dank und Gru?, -hrg-

94. Gesundheitsministerkonferenz

Beschluss vom XX.12.2021

Aufhebung der Testpflicht nach Auffrischimpfung

Beschluss (Entwurf):

Einzelne Länder haben Personen, die bereits eine Auffrischungsimpfung erhalten haben, von der Testpflicht im Rahmen der 2G-Plus-Regelung befreit. Wissenschaftliche Erkenntnisse zeigen, dass die Auffrischungsimpfung sowohl die Gefahr einer Infektion als auch das Risiko einer weiteren Übertragung deutlich reduziert. Zudem können durch die Aufhebung der Testpflicht die stark beanspruchten Testkapazitäten entlastet werden.

Vor diesem Hintergrund fassen die Ministerinnen und Minister, Senatorinnen und Senatoren für Gesundheit der Länder im Einvernehmen mit dem Bundesminister für Gesundheit folgenden Beschluss:

1. Bund und Länder sind sich einig, dass Personen mit erhaltener Auffrischungsimpfung von der Testpflicht im Rahmen der 2G-Plus-Regelung zu befreien sind.

2. Der Bund wird zeitnah die entsprechende COVID-19-Schutzmaßnahmen-Ausnahmenverordnung in diesem Sinne anpassen.

3. Die Länder werden diese Änderungen in ihren Corona-Verordnungen nachvollziehen, um bundeseinheitliche Regelungen sicherzustellen.

4. Für den Zutritt in Einrichtungen mit besonders vulnerablen Personengruppen kann weiterhin auch von Personen mit einer Auffrischimpfung ein negatives Testergebnis verlangt werden.

Votum:

From: "Schaade, Lars" <SchaadeL@rki.de>
To: Verteiler-Krisenstab <verteiler-krisenstab@rki.de>
Date: 12/28/2021 10:51:39 AM
Subject: Telefonat mit Herr Rottmann-Grossner zur Quarantäne

Liebe Kolleginnen und Kollegen,

Habe um 11:00 Uhr ein Telefonat mit Herr Rottmann gehabt, kurz:

1) Es gibt Überlegungen zur Arbeitsquarantäne in Ergänzung zur KRTIS-Empfehlung, Frage an RKI nach unserer Einschätzung dazu.

2) Die Schutzmaßnahmen-Ausnahmeverodnung soll geändert werden, Entwurf soll bereits am 5.1. ins Kabinett. Favorisiert werden im BMG gleitende Regelungen in Paragraph 2 und 10. Das wäre auch unsere bevorzugte Lösung; das BMJ ist da aber wohl noch kritisch.

3) Wir werden um einen Entwurf zum Kontaktpersonen-Management zu Omikron gebeten. Ich habe auf die unterschiedlichen Phasen/Ziele für Containment und Funktion der Kritis hingewiesen. Wir sollten das aber alles nochmals diskutieren, ob hier Verkürzung denkbar und Ausnahmen von der Quarantäne für frisch Geimpfte/ Geboosterte auch für Omikron. Das ganze soll spätestens am 7.1. zur MPK fertig sein.

4) Schule: Sind unsere Quarantäne-Empfehlungen bei Omikron noch richtig oder bedeutet die höhere Übertragbarkeit nicht vielleicht doch, das grundsätzlich eine Kohorten-Quarantäne gemacht werden muss, möchte BMG wissen. Ich habe gesagt, dass die Bedeutung von Omikron im Schulsettung noch nicht klar ist und wir insofern hier erst abwartend wären.

Herr Rottmann-Grossner wird dazu noch einen Erlass formulieren.

Ich bitte aber in jedem Fall das LZ, diese Punkte morgen auf die TO des KriSta zu nehmen.

Danke, Gruß

LS
