SARS-CoV-2 viral load dynamics, duration of viral shedding and infectiousness – a living systematic review and meta-analysis

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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.

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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]

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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,
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314 All authors have nothing to disclose.

315 **Table 1: Summary of included studies**

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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.

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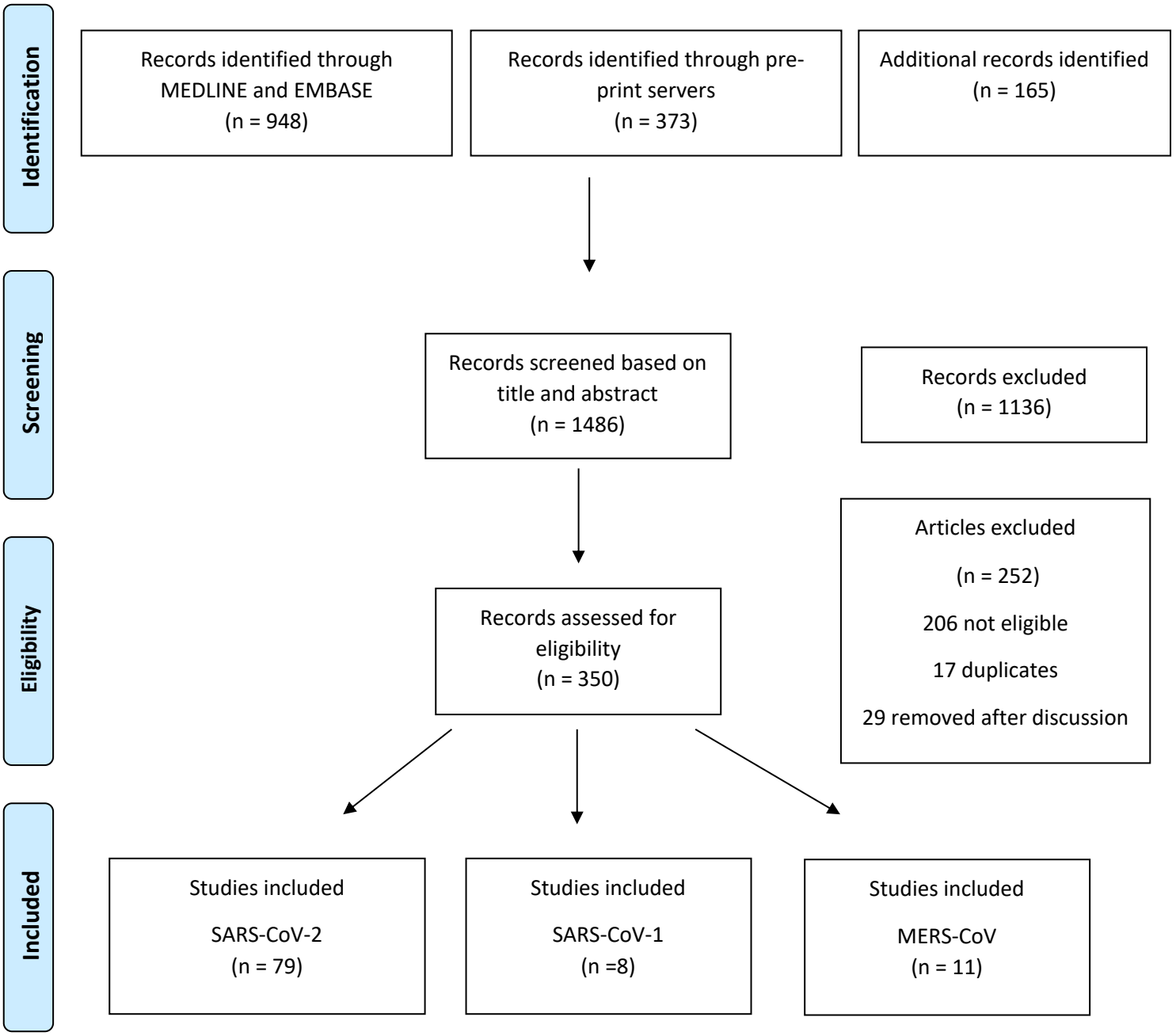
343 **Table 3: SARS-CoV-2 viral dynamics in asymptomatic patients compared to symptomatic**
344 **patients**

	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

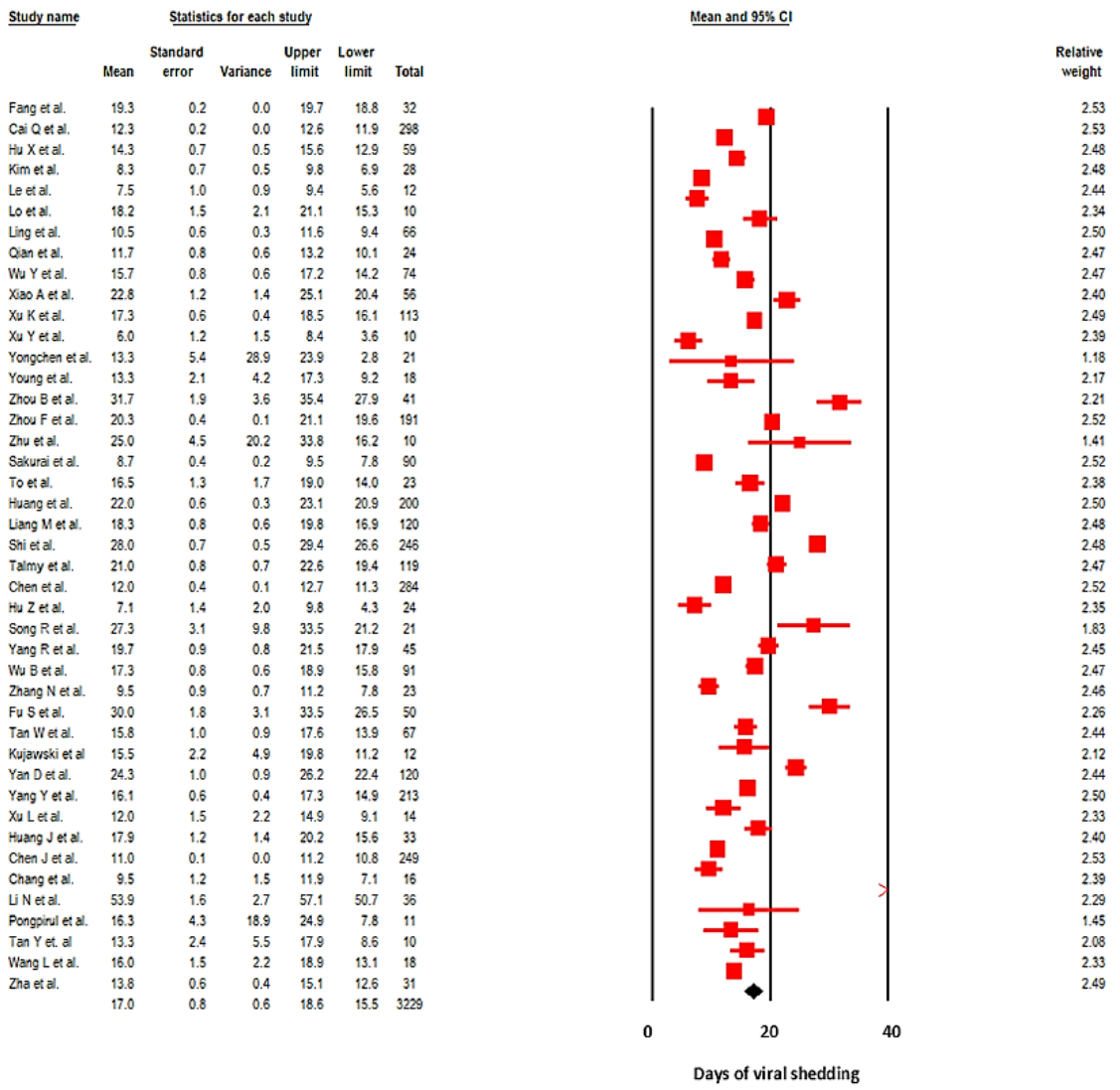
Figure 1. Flowchart describing study selection



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.

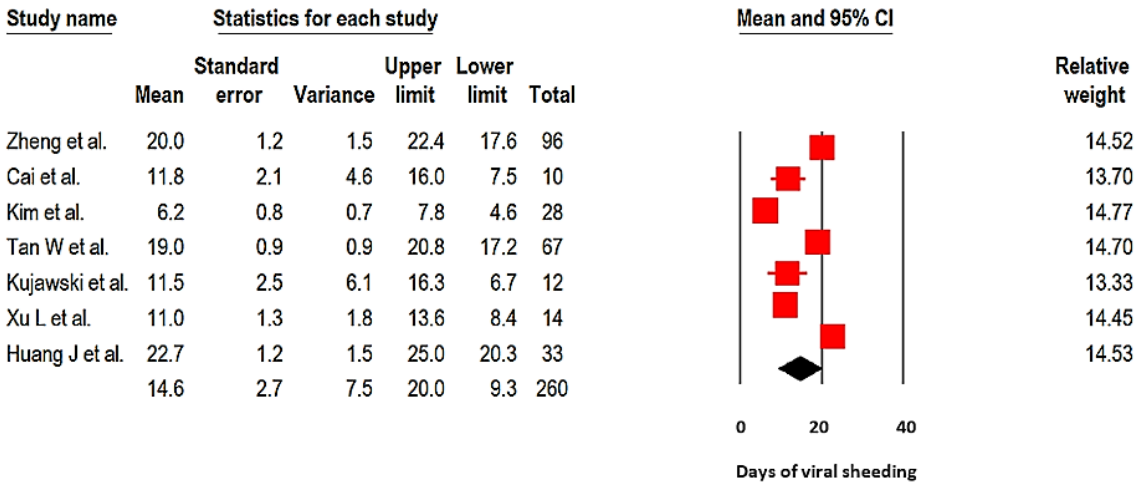
Figure 2: Pooled mean duration (days) of SARS-CoV-2 shedding from the upper respiratory tract (random-effects model).



Note: the overall effect is plotted as a black square.

Test for heterogeneity: Q-value = 4076,08, df(Q) = 42, $p < 0.001$, $I^2 = 99\%$.

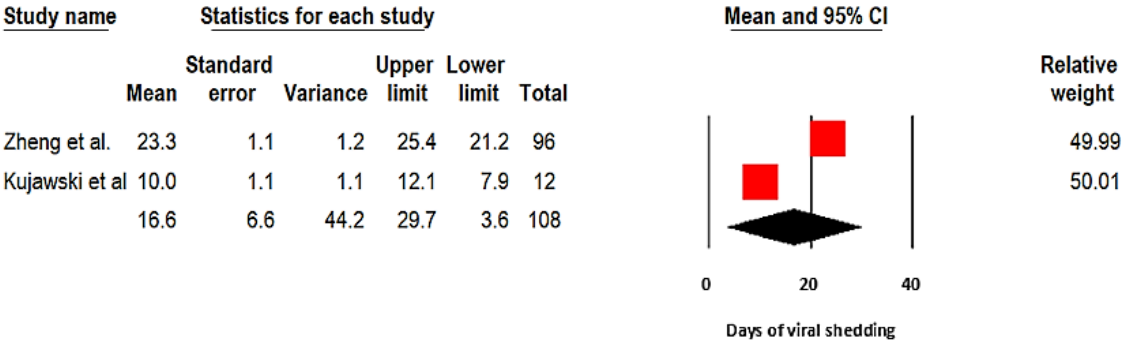
Figure 3: Pooled mean duration (days) of SARS-CoV-2 shedding from the lower respiratory tract (random-effects model).



Note: the overall effect is plotted as a black square.

Test for heterogeneity: Q-value = 203.3, df(Q) = 6, $p < 0.001$, $I^2 = 97\%$.

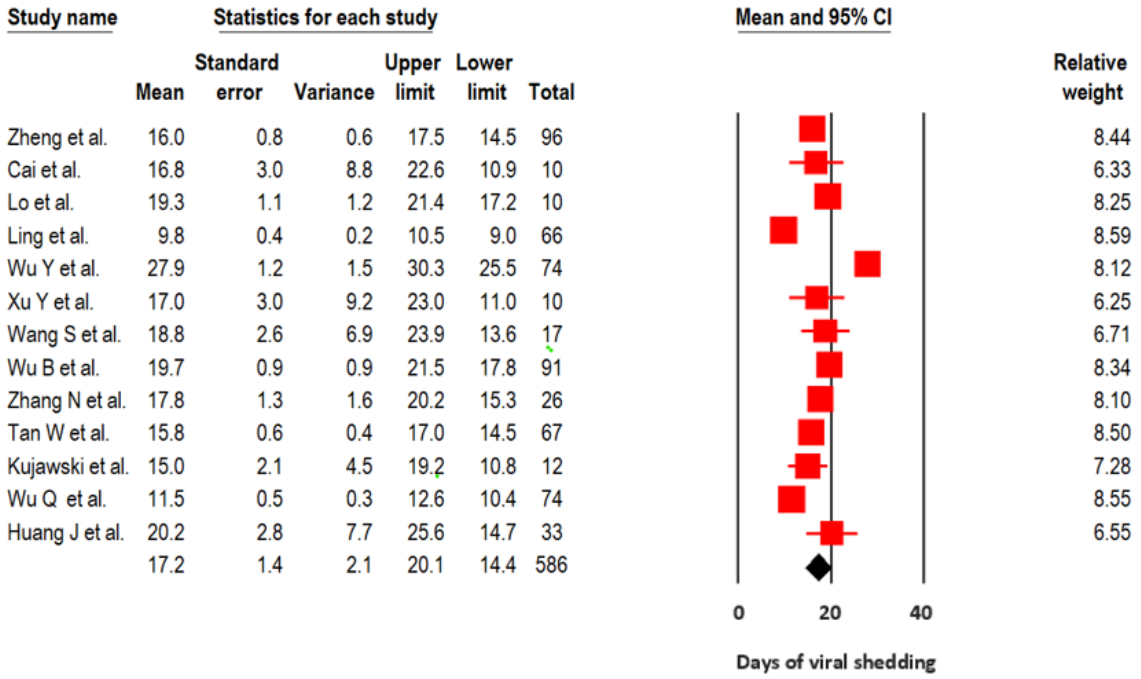
Figure 4. Pooled mean duration (days) of SARS-CoV-2 shedding in the blood (random-effects model).



Note: the overall effect is plotted as a black square.

Test for heterogeneity: Q-value = 77,6, df(Q) = 1, $p < 0.001$, $I^2 = 99\%$.

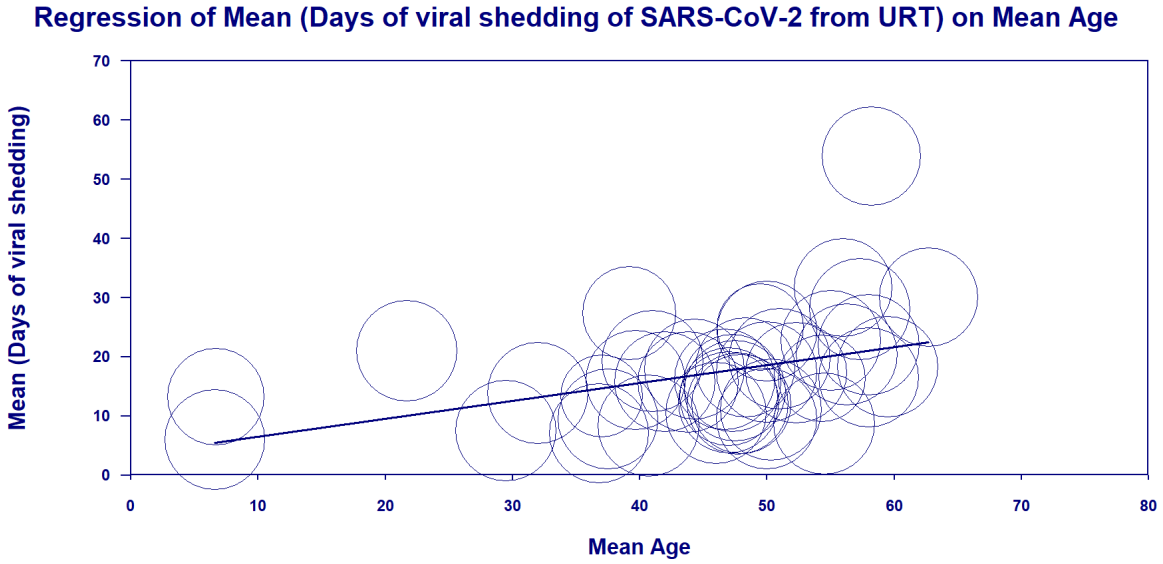
Figure 5. Pooled mean duration (days) of SARS-CoV-2 shedding from the stool (random-effects model).



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.

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