Technical report on the COVID-19 pandemic in the UK

A technical report for future UK Chief Medical Officers, Government Chief Scientific Advisers, National Medical Directors and public health leaders in a pandemic.

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Foreword

COVID-19 has been the most challenging pandemic for the UK since the influenza pandemic of 1918 to 1919, and the most important pandemic globally since HIV. There has been extensive and tragic loss of life and health, and substantial social and economic disruption. This has been the case in all 4 nations of the UK and internationally, and will have many long-term consequences.

This report on COVID-19 has a specific and narrow audience: future UK Chief Medical Officers (CMOs), Government Chief Scientific Advisers (GCSAs), National Medical Directors and UK public health leaders facing a new pandemic or major epidemic. This is not a narrative of the pandemic or an exploration of the decisions made. That will be the subject of extensive public inquiries which, when finished, we anticipate will be the authoritative account. Rather, it covers some technical aspects of interest primarily to our scientific, public health and clinical successors.

We would like to thank the authors and reviewers who wrote and revised sections of this report, in particular Polly Ashmore who brought much of it together.

We pay profound tribute to the many clinical, scientific, and public health professionals who responded again and again as COVID-19 waves hit. Their efforts saved lives, helped to improve understanding of the virus and the disease, and helped to develop the best available responses (both pharmaceutical and non-pharmaceutical). Often this was done at significant personal risk. Some of the scale of this work may be apparent from this report – it was a massive national and international clinical and scientific effort. We are very grateful to international colleagues who have shared their experience and insights throughout the pandemic.

Above all we thank the UK public in all 4 nations who, to protect their fellow citizens, responded collectively over a prolonged period to this major public health challenge, often incurring great difficulties by doing so. Even with this there were many thousands of deaths and people left disabled directly or indirectly due to COVID-19, each one a tragedy. If the public had not responded so altruistically the outcomes would have been significantly worse.

Introduction

The COVID-19 pandemic, which started in China in late 2019 and then spread globally, is the most challenging and widespread pandemic since HIV spread globally in the 1980s. For the UK, this has been the most serious pandemic in terms of mortality and impact on society since the H1N1 influenza pandemic of 1918 to 1919. While pandemics on this scale and severity are rare, major epidemics and near misses are far more common and less severe pandemics occur and still cause significant damage; the H2N2 influenza pandemic of the 1950s and the H3N2 influenza pandemic of the 1960s were both substantial. Epidemics and pandemics since 2000 include the emergence of SARS-CoV-1 (2003), the H1N1 influenza pandemic of 2009 which fortunately resulted in relatively low mortality, MERS-CoV (2012), and major epidemics of Ebola virus (West Africa, 2014 to 2016) and Zika virus (Brazil, 2016). It is therefore not a matter of whether there will be future pandemics or major epidemics affecting the UK but when, and what type, neither of which are predictable.

This report is written for a specific audience: future UK Chief Medical Officers (CMOs), Government Chief Scientific Advisers (GCSAs), National Medical Directors and UK public health leaders facing a new pandemic or major epidemic in the UK. It may be of interest to others, and we make it public for any wider audiences who wish to read it, but it is in places inevitably technical given this specific audience. It is not an attempt to describe policy choices or formation or to analyse operational delivery; in some places operational elements are described but this is for context rather than analysis. Ongoing public inquiries will give the definitive narrative of the COVID-19 pandemic to date, including policy decisions taken and why, and we have therefore restricted this report to technical issues. We have also not attempted to be comprehensive but to concentrate only on things we think our successors may find useful. In addition to this report there is a substantial body of scientific papers in the Scientific Advisory Group in Emergencies (SAGE) repository (https://www.gov.uk/government/collections/scientific-evidence-supporting-the-government-response-to-coronavirus-covid-19) where specific issues are covered in much more detail, which is therefore not repeated here. For future respiratory pandemics or epidemics in particular these will prove useful.

No two pandemics and epidemics, even with the same pathogen, are identical; the H1N1 influenza pandemics in 1918 and 2009 were very different. Different pathogen epidemics using the same route of transmission can be quite distinct – for example COVID-19, influenza, MERS-CoV and SARS-CoV-1 have very important differences including in age structure of mortality and transmission dynamics despite all being viruses transmitted predominantly by the respiratory route. These differences become even more

important when different routes of transmission are involved – so for example public health countermeasures to epidemics of HIV (sexual and bloodborne), Ebola virus (touch), cholera (faeco-oral through water), BSE/nvCJD (food) and Zika virus or malaria (vector), are very different to those for COVID-19.

Independently, science moves on rapidly. In this pandemic we had access even at the start of the pandemic to scientific methods and technologies not available in previous pandemics and more were developed in response to it; our successors will have techniques and scientific insights currently unknown or in the earliest stages of development. Science has, since the 1850s, always provided the exit strategy from the worst of the major pandemics and epidemics and we are confident it will to future ones, but new science takes time and needs to be nurtured in between pandemics. The speed with which effective vaccines against COVID-19 were developed was remarkable, but it cannot be assumed. We still do not have an effective vaccine against HIV/AIDS, and drugs remain the principle medical countermeasure. For cholera and typhoid, the first epidemics a UK CMO had to respond to in the 1850s and 60s, it was drains and clean water that provided the principle countermeasures.

We therefore do not in any way see this as a playbook for a future pandemic or major epidemic, even one caused by a novel respiratory coronavirus. We have however benefitted hugely from experiences from past pandemics, epidemics and outbreaks, both through direct experience (most of the authors have experience of epidemics and pandemics back to HIV in the 1980s and 90s) but even more importantly the reports of others facing past infectious disease challenges in different times and disciplines.

The period of greatest difficulty is early in the pandemic when least is known, the route out via medical countermeasures is not yet clear and public concern is understandably greatest. In the absence of existing medical countermeasures (also called pharmaceutical interventions: drugs and vaccines) the only countermeasures available are likely to be social and societal. In this pandemic in the UK they were collectively called non-pharmaceutical interventions (NPIs). A major aim of medical science is to transition as rapidly as possible from NPIs to drug, vaccine, engineering or diagnostic-driven strategies but this will always take time. The evolution is also generally gradual rather than sudden.

Several questions are central to developing the most efficient and effective countermeasures to any novel pathogen. A lot of this report is about how in this pandemic, at this point in science, the UK built up a picture of the key information needed for pharmaceutical and non-pharmaceutical public health interventions. This key information includes modes of transmission for SARS-CoV-2, common transmission settings, mortality rate in different ages and risk-groups of society, the relative importance of asymptomatic infection, the nature of immunity and reinfection. We then look at technical aspects of several of the interventions. In each section it will be obvious that the picture emerged gradually and from multiple lines of evidence from different disciplines, and the path to creating the picture was neither linear nor

straightforward. Many of the important initial decisions by policymakers in a pandemic have to be taken when many key facts are unknown, or at least uncertain.

In each chapter we draw out points we think may be helpful in the future as we go along, and in several we add some additional reflections for our successors to consider.

Four broad reflections which run through this entire report are however worth highlighting here.

The first is that there were multiple strands of scientific work from different disciplines needed, and these had to be integrated at considerable speed. This is likely to be a repeated theme for any pandemic or major epidemic. The UK started with a strong science and research base and even with this, and swinging most of the medical scientific and research effort over to COVID-19, accumulating evidence for policy was incremental, with initially wide confidence intervals and uncertainty. Evidence will continue to accumulate as time goes on, and new evidence will no doubt come to light after the publication of this report that enables a better understanding of some of the issues we discuss here.

The second is that, unsurprisingly, the UK was relatively effective and rapid in responding in areas in which we already had strengths and substantial capacity, including in biomedicine, which could be adapted and built on. For example, UK strengths in phase 3 clinical trials allowed very rapid progress in assessing clinical effectiveness of pharmaceutical interventions; the relatively small relevant diagnostics industry meant scale up of diagnostic tests was slower and was a significant limitation on the initial response.

The third is that, while we have concentrated on the UK experience because that is the one for which we have first-hand experience, science and medicine are international and pandemics by definition cross borders. Much of what we learned was from scientists, public health experts and clinicians in other countries. The experience of each country in the COVID-19 pandemic, facing the same pathogen, is different, and all had different scientific strengths. It would however have been unwise to have relied entirely on the scientific capacity of others and the UK provided a significant contribution to the global scientific output as well as insights specific to the UK experience.

Finally, the engagement of policymakers and the public in the scientific insights was profound and critical to the response. People rightly wanted to understand why specific interventions, actions or treatments were being recommended and the underlying rationale and evidence for each. Often the most difficult part of medical and scientific communication is explaining uncertainty or evolving science in a transparent way without it leading to paralysis in decision making. Our experience of this was almost entirely positive. Just as people in a one-to-one clinical encounter want to understand the logic, risks, benefits and uncertainties of a course of action, the same was true at national levels in this pandemic.

Chapter 1: understanding the pathogen

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Introduction

Particularly in the early days of the pandemic, there was pressure to develop rapid evidence on SARS-CoV-2 and COVID-19. This was driven by important operational and policy questions at the outset of this public health emergency, such as:

- what were the sensible options for response, and were there public health interventions that could interrupt transmission?
- were there any therapeutics or a vaccine that could be deployed for this pathogen?
- what should the clinical response be – and what would this mean for health system response?
- how extensive did the response need to be – should measures target only cases, or all of society?
- how long would these measures be needed for?
- what strength of evidence would be needed for different responses?
- what could be communicated to the public – what was known about this pathogen and the disease it caused?

Policy decisions were for ministers to take and they involved multiple non-health as well as health-related trade-offs. However, there was a need for clinical and scientific advice on the evidence base about the pathogen and the disease it caused in order to support decision-makers. Of course, there were particular windows for policy decisions and the evidence base did not always give a definitive answer to support one option or another at the time a decision had to be taken. In such cases, there was a need to use basic epidemiological principles and be open and clear about what the evidence base did and did not say, and with what level of certainty any conclusions could be reached. The evidence base evolved throughout the course of the pandemic, and so it was important to keep an open mind and consider all feasible possibilities. It was also important to bring together a range of disciplines and types of evidence to get a fuller, more certain and more nuanced picture.

Some key scientific questions at the outset of this pandemic concerning the pathogen, the disease and its epidemiology are set out below.

The pathogen

1. What was this pathogen?

2. What information could be gathered about the pathogen that could help develop an initial diagnostic test?

3. What information about the pathogen and the disease could support targeting of appropriate repurposed and newly developed pharmaceutical interventions?

4. How could viral evolution be monitored?

The disease

5. How severe was this disease, and were there longer-term sequelae?

6. What was the duration of naturally acquired and vaccine acquired immunity, and the risk of reinfection over time?

Epidemiology

7. What were the case definitions?

8. What were the important routes of transmission?

9. What were the higher risk settings for transmission?

10. What was the proportion of asymptomatic infection and transmission, and could this maintain R over 1?

11. How long were people infectious?

In this chapter, we explore for each question how the evidence base was developed, highlighting important methods that may come into play in a future pandemic.

Our focus is on the UK's experience. However, the science of COVID-19 is a global science and a good part of the evidence base comes from the excellent work of colleagues across the world.

Questions on the pathogen

1. What was this pathogen?

At the onset of the COVID-19 pandemic, when information on SARS-CoV-2 itself was limited, initial risk assessments and hypothesis generation for research drew upon what was already known about similar pathogens. Fortunately, identification and initial characterisation of the causative virus came swiftly. This early virological information fed into risk assessments about the nature of the virus and its risk to the population, when and whether it would be imported into the UK, as well as supporting the development of a diagnostic molecular test. It is likely that future pandemics and significant epidemics will see similarly rapid dissemination of initial information about the pathogen, particularly if they emerge and establish in countries with significant scientific capacity but, even given this, the speed of international information flow from the start of 2020 was impressive.

Early emergence and first sequences

Following the first official reports of pneumonia of unknown origin in Wuhan, China, at the end of December 2019, very early information about the pathogen came from China and other countries that experienced early imported cases. Within days, the causative pathogen was identified as a beta coronavirus, and was subsequently named as SARS-CoV-2. Chinese scientists rapidly performed laboratory-based characterisation (virus culture, electron microscopy) and sequencing (unbiased meta-genomic techniques) of the pathogen from clinical samples.[footnote 1], [footnote 2] The first genomic sequence was generated on 3 January 2020, and publicly released on 10 January 2020. Within weeks, the virus receptor was identified as ACE2, with TMPRSS2 also flagged as important for viral entry.

Early on, phylogenetic analysis of available genomes and epidemiological studies of early cases gave signals that the virus had recently emerged, and consideration was given to the possible origin.[footnote 3], [footnote 4]

Local expertise and access to high-end technology in China enabled rapid identification and characterisation of SARS-CoV-2. Nonetheless, detection of a newly emerged pathogen could take longer if, for example, presence of genomic material was short-lived or difficult to detect, the pathogen was difficult to culture in the laboratory, or if the outbreak had arisen in a region with more limited diagnostic capacity. In the earliest stages, knowledge and expert opinion was reliant on accessible international data. Channels to access this rapidly such as the Global Initiative on Sharing Avian Influenza Data (GISAID) were key.[footnote 5]

Using existing knowledge from similar pathogens

Comparison of genome sequences with other known human pathogens demonstrated that SARS-CoV-1 was the closest related human pathogen, with around 80% genomic similarity to SARS-CoV-2. It was known that SARS-CoV-1 caused severe human infections and used the same ACE2 receptor. Other related human pathogens were also drawn upon for scientific insight, including:

- MERS-CoV, which showed around 50% genomic similarity but did not use ACE2
- NL63, an endemic coronavirus that used ACE2
- other endemic coronaviruses: OC43, 229E and HKU1
- influenza, as a pandemic respiratory virus

As data about SARS-CoV-2 accumulated with time, it became apparent that SARS-CoV-2 was different from SARS-CoV-1 in several aspects, such as in its pre-symptomatic infectiousness, levels of asymptomatic or subclinical infections, and routes of transmission.

In the early stages of the pandemic, before robust data on SARS-CoV-2 itself became available, prior experience and knowledge about these related pathogens guided early understanding and public health actions – for example:

- facilitating prioritisation of potential therapeutics that had already shown in vitro or clinical activity against human and zoonotic coronaviruses
- signalling the potential for reinfections due to prior observations of waning immunity to seasonal coronaviruses

Prior knowledge also fed into early estimates of the incubation period, which was known to be longer for coronaviruses than influenza. Reviewing existing data on the environmental persistence of coronaviruses informed early policy on decontamination.[footnote 6]

In characterising the pathogen from early clinical material, relationships between public health agencies and laboratory networks were key in prioritising distribution of virus isolate (to those with established biocontainment facilities) and planning further investigations. Academic laboratories with technical expertise collaborated with those running approved biocontainment facilities in other organisations to set up and lead work on virus characterisation, such as sequencing, in vitro studies and animal models. This supported assay development and furthered our knowledge of the virus. Clinical studies, in particular use of established protocols via the UK's International Severe Acute Respiratory Infection Consortium (ISARIC) Clinical Characterisation Protocol (https://isaric.net/ccp) and, later, human challenge studies, also delivered important data about the virus and the disease it caused.[footnote 7], [footnote 8]

As the virus reached the UK, early recognition and detection of cases was important in supporting further research into SARS-CoV-2. After the first case was detected in the UK in late January 2020, the virus was cultured and sequenced within days and shared with academic partners, enabling early virological work and feeding into wider research to develop our understanding of the pathogen. This wider research, including into potential pharmaceutical interventions, the duration of protective immunity to this pathogen and likelihood of reinfection, and the nature of severe and long-term disease, is set out in the following sections.

2. What information could be gathered about the pathogen that could help develop an initial diagnostic test?

Testing to identify cases had multiple applications throughout this pandemic, supporting clinical management, infection prevention and control (especially in health and care settings), contact tracing, surveillance, and to understand transmission force, transmission routes and severe disease rates. Testing was especially important because the symptoms of COVID-19 were often non-specific, minimal or absent. It was therefore an early priority – in the UK and globally – to develop diagnostic tests for the SARS-CoV-2 virus. This is likely to be the case for future pandemics and major epidemics.

The early diagnostic test (as is the case for many viruses) was molecular (reverse transcription polymerase chain reaction, or RT-PCR), though development of serological assays was also a major strand from an early stage, and later commercially developed antigen tests were also deployed at scale (for

further detail on test technologies see Chapter 6: testing). Had this been a virus whose genetic material (DNA or RNA) is only briefly detectable (such as dengue virus), serology may have played a greater role for diagnostic purposes. In this pandemic, and in contrast to, for example, HIV, serology was primarily used to monitor seroprevalence and support research (such as understanding rates of asymptomatic infection, the risks of reinfection and vaccine efficacy). Self-performed viral antigen-based tests were implemented for widespread community-based asymptomatic testing and, in the later stages of the pandemic, as a signal for infectiousness to guide isolation timelines.

There was a need for multiple modes and types of testing. The speed of initial development of several different test modalities in this pandemic was impressive, with scale-up being more rate limiting. Scale-up was also hampered by the lack of a significant diagnostics industry capability in the UK (again, this is covered in more detail in Chapter 6: testing).

Evidence informing molecular testing

Sequencing

Typically, with current methods, the development of specific molecular diagnostics for any new emerging viral pathogen requires knowledge of the virus genomic sequence. Once the target sequence is known, sensitivity and specificity of PCR-based or nucleic acid amplification test (NAAT)-based diagnostics is typically greater than 95% and 99%, respectively; this will likely change and improve by the time of the next pandemic. Very early in this pandemic Chinese scientists performed genomic sequencing of SARS-CoV-2 and shared the full sequence globally via a public database.[footnote 1] It was important to have the entire viral sequence for SARS-CoV-2 because different regions of the viral genome could be used for different purposes for diagnostic detection. Within each virus family for RNA and DNA viruses, there tend to be regions of the viral genome which are highly conserved, usually containing family-specific sequences. Such regions of the viral genome have been used to develop family specific diagnostics – for example, pan-coronavirus, influenza A, or herpes virus diagnostics.

Whole genome sequencing also enabled identification of genetic similarity with other coronaviruses, particularly SARS-CoV-1, for which diagnostic expertise and clinical materials existed in several public health laboratories across the world, including the UK. This facilitated rapid development of a diagnostic assay through international collaboration between public health laboratories. SARS-CoV-1 clinical samples were used as control material during the early development of an RT-PCR assay.[footnote 9]

Ongoing sequencing surveillance was important for testing, throughout the pandemic, to highlight mutations within primer sites that could affect test performance.[footnote 10] Multi-target PCR assays helped to reduce this risk – as, for example, when S gene target dropout was observed with the Alpha and Omicron SARS-CoV-2 variants.[footnote 11] Links with industry for rapid development, distribution and validation of laboratory standards to support the monitoring of test performance were essential.

Sampling

Serial clinical sampling from multiple anatomical sites (respiratory and non-respiratory samples) from the first 10 to 20 UK cases that were contained in high consequence infectious disease (HCID) units provided valuable early data on viral shedding.[footnote 12] By mid February 2020 there was growing clarity on which sites the virus was shed from and when, based on sequential sampling studies from small cohorts and case reports.[footnote 13], [footnote 14], [footnote 15] Clinical data and case series began to show that nose and throat swabs were reasonable samples for detection of the virus, and that although faecal shedding occurred there was limited evidence for viraemia. [footnote 11] It is worth noting that there were initial difficulties moving samples around due to their HCID classification, and this is relevant for future pandemics that will likely require rapid moving and investigation into such samples. HCID classification should not be extended beyond the period it is required.

Understanding the kinetics of viral infection in the upper respiratory tract during an acute infection helped to inform the interpretation of PCR test results – in other words, what positive, negative and 'positive at the limit of detection' PCR results imply in terms of infectiousness, at different stages of infection. It was noted that low-level PCR positivity can remain for some time after an acute infection, without infectiousness. Therefore, for example, a single low positive (high cycle threshold value) PCR test result could indicate early infection when the individual is about to become highly infectious, late infection with lower infectiousness, or inadequate sample quality – understanding this nuance was important in interpreting test results for infection control or public health actions. [footnote 16]

As the pandemic progressed and testing was scaled up, the value of easy-to-perform sampling, particularly that which can be performed by the patient themselves at the point of care, became increasingly important. In this pandemic, saliva samples for PCR-based diagnosis, different upper respiratory tract swabbing locations (anterior nares versus nasopharyngeal sampling), oral fluid or dried blood spots versus venous blood sampling for serology were all explored. Longitudinal and cross-sectional sampling studies, collecting novel sample types alongside existing validated sample types, enabled validation of diagnostics.[footnote 17], [footnote 18]

With the ongoing evolution of SARS-CoV-2 and emergence of variants, it has been necessary to repeat and review virological sampling studies to monitor any impact on test performance as pathogen biology changes. We anticipate this will be needed in future epidemics and pandemics.

Virus culture

In general, virus culture work was constrained by requirement for Biosafety Level 3 containment facilities and technical expertise. Distribution of the first live virus isolates required appropriate safety licensing in place at receiving research laboratories, which is a potential rate-limiting step in the event of a pandemic. Virus isolation from clinical material taken from one of the first UK clinical cases had occurred by early February 2020 – this was needed to generate RT-PCR assay control material for diagnostic laboratories. Of note, had the UK not experienced a clinical case of COVID-19 for some time, this material would have

needed to be sourced promptly from an international partner to prevent delays to diagnostic test development and rollout. The same was true for testing new variants where appropriate samples were not available in the UK to use for neutralisation studies. Throughout the pandemic, virus culture, performed ad hoc on clinical samples from cohort studies, provided valuable information about infectiousness timelines (see section 11: How long were people infectious?), which in turn aided interpretation of diagnostic tests results for infection control and public health purposes.[footnote 19]

Evidence informing serological testing

Serological assay development, deployment and interpretation was supported by an understanding of when and which antibodies (IgA/IgM/IgG) develop after infection, to which pathogen antigen (such as SARS-CoV-2 spike, nuclear protein), at which anatomical sites, and for how long. Of course, all serological tests signalled some type of immune response to the virus – however, they had differential sensitivity and specificity depending on the assay and target. It was important to understand potential cross-reactivity with other coronaviruses as well as any differences in the magnitude of the serological response depending on the severity of illness (asymptomatic, mild, severe) or demographics (such as age).

Evaluating test performance requires access to well-characterised positive and negative serum samples. In this pandemic, paired serology was actively collected from persons with suspected COVID-19 in the first months of the pandemic who tested RT-PCR negative. This, in addition to existing banked serum and residual serum from NHS diagnostic laboratories, contributed vital assay control material.[footnote 20] Longitudinal serological sampling studies such as SARS-CoV2 immunity and reinfection evaluation (SIREN) and Enhanced Seroprevalence for COVID-19 Antibodies (ESCAPE) also provided valuable clinical material to help validate assays in development. For example, the ESCAPE study collected oral fluid at the same time as serum to facilitate validation of this sample type. These studies also furthered our understanding of the kinetics of the immune response to infection (such as when people develop detectable antibodies) and of the duration of protective immunity (such as how long antibodies are able to protect us from a further infection). It was then possible, in close collaboration with academic partners, to develop and validate assays for detection of neutralising antibodies, particularly surrogate assays not requiring containment level 3, and to understand their correlation with commercially available serological tests such as enzyme-linked immunosorbent assay (ELISA) tests. Later in the pandemic, having internationally recognised serological standards enabled better comparison between vaccine clinical trials, and specific serological testing was used to differentiate natural from vaccine-derived immunity.

3. What information about the pathogen and the disease could support targeting of appropriate repurposed and newly developed pharmaceutical interventions?

Pharmaceutical interventions (PIs) were an early priority as a means to reduce morbidity and mortality – both directly due to COVID-19 disease and indirectly from healthcare disruption due to high numbers of severe cases.

This section sets out the information required on the pathogen and the host response to guide and support PI development in this pandemic; how this evidence was generated; advice based on this experience. This is set broadly into 2 sections covering the different types of interventions: vaccines and therapeutic agents, including disease modifying host directed therapeutics and antiviral therapeutics. The process of developing and deploying PIs is covered in more detail in Chapter 9.

Early research focused on viral pathophysiology, host susceptibilities and disease course in order to:

- identify targets for preventative, disease modifying and antiviral therapeutics
- shortlist repurposed pharmaceutical candidates
- focus research and development of novel options

Vaccines

The development of vaccines against SARS-CoV-2 was informed by the host immune response to the virus following natural infection and required information on the antigenic target of antibodies that neutralised virus entry into cells. Review of existing data on related human coronavirus structure and host cell binding and vaccine studies for SARS-CoV-1 and MERS-CoV identified the SARS-CoV-2 spike protein as a primary antigenic target for vaccine development and suggested the likely success of vaccines targeting this region of the virus in the first months of the pandemic.[footnote 21], [footnote 22], [footnote 23], [footnote 24], [footnote 25], [footnote 26] Prior knowledge of the mutation rates and duration of immune responses to highly related human coronaviruses also helped to predict the need for repeated vaccinations and regular adaptation of vaccine content. [footnote 27]

By April 2020, spike glycoprotein sequence analysis and structural analysis using cryogenic electron microscopy had confirmed ACE2 as the human host cell receptor.[footnote 28], [footnote 29], [footnote 30] Laboratory studies from early clinical samples enabled a better understanding of the viral lifecycle and identification of the interaction between the SARS-CoV-2 spike protein receptor binding domain (RBD) and ACE2.

The rapid development and validation of neutralisation assays provided methodology for assessing the development of antibodies that could neutralise viral entry into cells and were used to show that antibodies targeting the SARS-CoV-2 spike protein neutralise the virus. This corroborated the use of the spike

protein as a target for vaccine development and identified anti-viral monoclonal antibodies with potential for therapeutic use.[footnote 31]

Neutralisation assays were also used to monitor the immune response following natural infection to examine correlates of protection and duration of immunity, informing protocols for vaccine trials and the need for booster doses.[footnote 32], [footnote 33], [footnote 34]

All of these processes required rapid access to viral specimens to analyse the genetic sequence of the virus and obtain live virus isolates, clinical characterisation of patients with different disease severity, and blood samples to assess antibodies from convalescent patients. This necessitated the early set-up of cohort studies from the outset of the pandemic, with sequential sampling from people across the spectrum of disease, a process that was undertaken first in China and then rapidly across the globe as the pandemic spread.[footnote 35]

A variety of samples (serum, whole blood, peripheral blood mononuclear cell (PBMC), oral fluid) from affected individuals during acute and convalescent phases were obtained. The processing of these samples can be more involved in terms of time and materials than standard diagnostic samples, but these samples were key to understanding the nature and duration of pathogen-specific immune memory and for the identification of further vaccine targets.

Knowledge of the high mutation rate of other human coronaviruses highlighted the need for vigilant monitoring of the genetic evolution of the virus, which was facilitated through the set-up of the COVID-19 Genomics Consortium. This identified new viral variants and guided hypotheses regarding the likely generation of resistance to vaccines and antiviral agents, as well as likelihood of reinfection due to evasion of host immunity.[footnote 36]

By early summer 2020, concurring with earlier studies from China, a cohort study using samples collected from the first infected people in the UK showed that the majority of individuals mounted a detectable antibody response, including neutralising antibodies, following laboratory confirmed infection. This suggested that individuals were likely to respond to vaccination with a protective immune response. The same study also found a higher neutralising antibody associated with more severe disease and highlighted the potential for convalescent plasma as a therapeutic intervention.[footnote 37]

Animal models were an important route to testing hypotheses and delivered early signals on likely host responses to vaccination. In August 2020 non-human primate models indicated protection from re-infection following a primary infection with SARS-CoV-2 or passive immunisation with SARS-CoV-2 specific monoclonal antibodies, supporting the postulation of the likely success of future vaccination programmes in protective immunity, at least in the short term.[footnote 38], [footnote 39], [footnote 40] Simultaneously, SARS-CoV-2 virus-specific B cells were found to be detectable by flow cytometry following mild and severe infection, and for several months following infection, irrespective of waning neutralising antibody titres.[footnote 41], [footnote 42] This demonstrated the presence of a pool of antigen specific immune memory cells primed to respond on re-exposure.

By September 2020, understanding of immune differences between those with mild and severe disease further expanded with T cell enzyme-linked

immunosorbent spot (ELISPOT) on peripheral blood mononuclear cells using synthetic peptides of SARS-CoV-2, finding functional CD4+ and CD8+ memory T cell responses in COVID-19 survivors.[footnote 43] The presence of responses to multiple viral epitopes, including those outside the key spike region of the virus, highlighted novel vaccine targets with the potential to be less susceptible to viral escape mutations within the spike region.

Early detection of neutralising antibodies from patients recovered from SARS-CoV-2 infection were important in the development of monoclonal antibodies blocking the interaction between SARS-CoV-2 and the host cell receptor.[footnote 31] Along the same principles the potential utility of convalescent plasma therapy was considered in the early stages of the pandemic based on historical use in SARS-CoV-1, influenza and other respiratory viral infections.[footnote 44], [footnote 45], [footnote 46] This required sampling from known positive cases and substantial operational input and coordination between public health and blood transfusion services to obtain donations for analysis and therapeutic use. Evaluation in multi-site platform trials subsequently demonstrated this not to have a survival benefit in hospitalised patients, the reasons for which remain unclear, but convalescent plasma may be a useful option to consider in the absence of other therapeutics early in the course of a newly discovered infectious agent.[footnote 47]

In this pandemic, vaccine development was focused on the S protein which was the most obvious and most defined antigenic target. Targeting a wider selection of target proteins, such as the N protein, could potentially be helpful. These targets are less well defined but could be more conserved and offer more durable protection particularly given the possibility of vaccine-escaping new variants. The first targeted antigen for a pandemic organism may not ultimately be the best, so there may need to a broader scientific lens and incentives and support for industry to explore other protein targets. This is important to keep in mind whatever the pathogen.

Therapeutic agents

Therapeutic agents were required for different purposes in different scenarios: in intensive care (ICU) settings the primary aim was to reduce mortality; in hospitalised patients outside of ICU the goal was to reduce escalation to ICU or requirement for oxygen therapy; in the community the aim was preventing hospital admission by treating high risk individuals early or targeting prophylaxis at high-risk individuals who had been exposed. For post-exposure prophylaxis in the community (both vaccines and therapeutics), early studies on the secondary attack rate were helpful in clarifying the incubation period.

Potential therapeutic agents included those acting directly against the virus, immunomodulatory agents directed against the host immune response to infection, and therapeutics directed against other organ system effects of the infection. At the very outset of the pandemic, hypothesis generation and identification of candidate therapeutics for trials relied on existing knowledge of similar pathogens. Knowledge of other human coronaviruses, including SARS-CoV-1 and MERS-CoV, enabled a rapid assessment of potentially viable therapeutic agents, both direct acting antivirals and immunomodulatory agents.

In vitro studies, animal models and human safety data were key in generating early candidates for clinical trials – though caution and expert input were essential when interpreting such evidence in light of SARS-CoV-2.

Virus-directed agents

Initial assessments suggested 2 antiviral candidates to begin trials:

- combination lopinavir/ritonavir, protease inhibitors with activity shown in limited experience with SARS-CoV-1 and in non-human primate models of MERS-CoV
- remdesivir, a nucleoside analogue with activity against MERS-CoV[footnote 48], [footnote 49]

This is covered in Chapter 9: pharmaceutical interventions.

Host-directed therapeutics

Initial selection of host-directed countermeasures for evaluation (such as immunomodulators or anti-thrombotics) depended upon careful clinical characterisation of mild, moderate and severe cases and the mechanisms of pathogenesis, as the efficacy (and safety) of host-directed therapies can depend on the stage and severity of disease. Large-scale cohort studies provided information on the contribution of immune-mediated disease to the pathogenesis of infection and rates of complications, such as thrombosis. They delivered results fast in this pandemic. By March 2020, multi-centre cohort trials with sequential sampling from individuals across the spectrum of disease severity measuring a range of markers highlighted the role of inflammation in pathogenesis of SARS-CoV-2 infection and identified interleukin 6 (IL-6), in particular, as a potential therapeutic target.[footnote 50], [footnote 51] These findings resulted in the inclusion of steroids, tocilizumab, a monoclonal antibody targeting the IL-6 molecule, and sarilumab, a monoclonal antibody inhibiting the IL-6 molecule receptor, in clinical trials in April 2020. This is covered in more detail in Chapter 9: pharmaceutical interventions.

4. How could viral evolution be monitored?

Although whole genome sequencing of viruses during epidemics (for example, during the Ebola outbreak of 2014 and the H1N1 influenza 2009 pandemic) has been employed over the past decade, the SARS-CoV-2 pandemic marked a turning point with many countries, particularly the UK, investing substantially in sequencing large numbers of genomes.[footnote 52] This allowed for fine epidemiological tracking, to understand the introduction of virus and variants into the UK, and rapid detection of novel variants. However, it is important to note that large scale sequencing on its own was not sufficient to understand variant emergence, nor to make meaningful risk assessments to inform policy responses, until it was later coupled with phenotypic analyses including antigenic studies and epidemiologic analyses of clinical severity. It also required robust, large scale epidemiological sampling.

Wastewater sampling helped signal human circulation of SARS-CoV-2 variants of concern and supported tracking lineages of SARS-CoV-2. It could have a potential role in future pandemics, but in this pandemic in the UK there were a number of important caveats to its use, such as the potential to detect viral fragments from past, resolved infections. These are covered in more detail in Chapter 4: situational awareness, analysis and assessment.

Wild type

Large scale sequencing revealed that SARS-CoV-2 arrived in the UK by hundreds of separate introductions carried by travellers returning in large part from Europe after the half-term holidays in February.[footnote 53] This first wave was largely clonal, with the single exception of the early emergence, and rapid worldwide dominance, of the B.1 lineage.[footnote 54] B.1 contained 4 mutations including the D614G substitution in the spike gene. It was not clear until several months later, when detailed phenotypic analyses were performed, that this was something other than a founder effect – in other words, a predominance of a lineage without a clear fitness advantage, largely due to early import and stochastic growth. Subsequent phenotypic work showed the single mutation D614G worked by exposing the part of the spike protein that bound to the ACE2 receptor, and thus increased infectivity.[footnote 55] This analysis was only possible due to a combination of the development of large scale sequencing, which was at the time rapidly scaled up, including by the nascent COVID-19 Genomics UK consortium (COG-UK), coupled with phenotypic characterisation by multidisciplinary collaborators.

Alpha

For several months after summer 2020 there was again relative stasis in SARS-CoV-2 evolution within the UK, with only a few minor and fairly inconsequential mutant lineages emerging. Again, many were carried to UK from mainland Europe by travellers.[footnote 56] Towards late 2020, however, rising case rates in the south-east of the UK were investigated and found to correlate with a negative result for the S gene target, one of the commonly used probe sets for quantitative polymerase chain reaction (qPCR) tests. This variant was later labelled the ‘Alpha’ variant and was relatively easy and fast to track using S gene target failure in qPCR testing.[footnote 57] This underscored the importance of using several different PCR targets in combination for large scale testing of an RNA virus; had this not been done, Alpha infections would have gone undetected until later in the wave. Alpha drove a large wave of cases in the winter of 2020 to 2021, and genome sequencing revealed a constellation of mutations throughout its genome.[footnote 11] Alpha was revealed through later phenotypic testing to have increased transmissibility conferred by changes in receptor binding and also changes in innate immune control.[footnote 58], [footnote 59] With the emergence of Alpha (and, shortly after, Beta detected in Southern Africa), effort was expanded to sequence and rapidly identify and characterise any further variants arising.[footnote 60]

Delta

By spring 2021 signals were seen in India of potential new variants, with a surge in cases reported. These variants were later classified as Delta and Kappa. In the UK, cases of Delta and Kappa were initially predominantly in those travelling from India (see Chapter 8: NPIs, for further epidemiological context on travel restrictions).[footnote 61] Initially, Kappa was assessed to be the larger threat as imports into the UK consisted mostly of Kappa, which contained a mutation at spike position 484 (484Q) that was flagged as a likely antigenic escape mutant due to its similarity to E484K (found in Beta and Gamma). However, Delta began to exhibit a more rapid growth rate and went on to dominate globally in 2021. This was occurring at the same time as the UK was rapidly vaccinating its population and gradually lifting NPIs. Laboratory studies showed that Delta was intrinsically more transmissible than previous variants.[footnote 62] It also showed some modest immune escape properties, potentially allowing it to break through immunity granted by vaccination or prior infection from wild type SARS-CoV-2 with greater efficiency than Alpha.[footnote 63]

Omicron

By November 2021 many countries worldwide, including the UK, were reaching their highest rates of sequencing. Sequencing from Southern Africa and travel-related sequencing from Hong Kong allowed the rapid identification of a novel variant of concern, Omicron, as soon as the first 4 sequences had been uploaded by Southern African researchers to the online sequence database GISAID.[footnote 64] Omicron was characterised by a very large number of mutations, including 35 across the spike gene, many at known antigenic epitopes. The large antigenic distance between Omicron and the wild type spike protein, combined with antibody waning, resulted in poor neutralisation of Omicron by sera from vaccines – and this necessitated rapid implementation of vaccine booster programmes to counter immunological waning associated with the establishment of this variant.[footnote 65]

Discussion

The origin of variants remains an open question. However, immunocompromised hosts have been a hypothetical population for variant emergence prior to the pandemic, and a similar route was implicated in this pandemic by the fact that Alpha and Omicron were phylogenetically similar to much older sequences that circulated 6 to 18 months before their emergence.[footnote 66], [footnote 67]

Whole genome sequencing has been a huge boon to the UK in the pandemic and was probably world-leading in terms of genomic epidemiology, identification of novel variants and understanding the evolution of viruses in real time. This has been a mix of both population-wide surveillance, allowing for high quality epidemiological resolution of new variants, as well as surveillance targeted to hospital populations allowing rapid detection of imported variants or chronic infections in hospitalised patients. It was extremely fortuitous (and very unlikely to be repeated in a future pandemic) that one of the main qPCR toolsets bound to a region of the SARS-CoV-2 genome was not present for some variants, allowing for rapid detection of certain potential variants. Although the UK

deployed qPCR-based targeted genotyping sparingly, this could be very important for future pandemics where a rapid detection method like S gene target failure is unlikely to occur. Furthermore, the UK (like many other countries) invested in associated phenotypic characterisation of variants, allowing rapid risk assessment of emerging variants to feed into public health policy. It has been important to bring together multidisciplinary groups of public health academics including epidemiologists, genomics scientists, bioinformaticians and virologists together to rapidly assess new variants.

Table 1: summary of key SARS-CoV-2 variants and their emergence, 2020 to 2021

Event	Timeline	Description
D614G becomes predominant	Spring 2020	Genomic signal, confirmatory studies
Alpha first found	November 2020	Epidemiological signal from Kent, genotyping signal, genomic signal
Delta takes over	April 2021	Genomics signal from UK and India, travel-related signals
Omicron first found	November 2021	Genomics signal from South Africa, rapid global response

Questions on the disease

5. How severe was this disease, and were there longer-term sequelae?

Gauging the potential impact of COVID-19, and the appropriate response to take, heavily relied on understanding both the severity of acute disease and its possible longer-term sequelae.[footnote 68] The degree of severity and its underlying causes will be central to the management of any future pandemic or epidemic. This section sets out evidence evolved on mortality and morbidity, both acute and chronic, for COVID-19.

Mortality

Mortality rates were difficult to define in the initial stages of this pandemic, as was the case for H1N1 influenza and SARS-CoV-1 – but for slightly different reasons. For SARS-CoV-1 in 2003, initial case fatality rate (CFR) figures underestimated severity due to early estimates missing delayed deaths – though statistical methods were developed to provide a more robust estimate of severity in similar situations which were useful in this pandemic.[footnote 69] For H1N1 influenza in 2009, initial CFR estimates were about 500 times higher than the later agreed infection fatality rate (IFR) of 0.001% to 0.002% due to initially

measuring only symptomatic or confirmed cases and missing milder and asymptomatic ones.[footnote 70], [footnote 71] Later, more accurate estimations of the IFR for H1N1 influenza arose from studies on outbreaks, such as one in a school in New York which included milder cases – though with important caveats on the demographic representativeness of those within specific settings like schools.[footnote 72]

For SARS-CoV-2, too, there were varying estimates of CFRs in the early stages. In the UK, before widespread surveillance was set up, initial estimates of the CFR came from dividing numbers of reported deaths by the estimated number of cases in Wuhan, China at a given time.[footnote 73] These estimates were greatly improved by Chinese Centres for Disease Control (CCDC) data: in mid February 2020, for example, the CCDC weekly bulletin provided a CFR estimate of 2.3% from 72,314 cases identified using either PCR testing (63%) or clinical diagnosis (37%).[footnote 74] Of this group 1.3% were thought asymptomatic. Of the PCR confirmed cases, 81% were classified as mild (which included non-pneumonia or mild pneumonia) and 19% were described as severe or worse (which was classified as dyspnoea, low oxygen saturations and/or greater than 50% lung infiltrates on imaging). The CFR for those with severe disease was high at 49% and increased substantially with age (though the age distribution of this cohort was relatively young compared to the UK, with 68.8% of patients under 60). Another early study incorporated a wider range of cases from PCR testing for international travellers arriving to China, alongside cases and deaths in Wuhan, and reported a CFR of 1.4% for symptomatic COVID-19 cases.[footnote 75] It was initially difficult to interpret such studies for a UK context, in part because denominators and numerators varied and in part because their source populations differed from the UK in several important ways (such as age distribution).

Population-wide surveillance (positive tests, syndromic surveillance) linked to outcomes (hospitalisation, deaths) provided high quality data for the routine calculation of CFRs in particular by providing a robust denominator. In the UK this was initially done using serology, which was difficult to interpret due to waning antibody levels, and after late spring 2020 by large scale surveillance studies such as the Office for National Statistics (ONS) COVID-19 Infection Survey (CIS), Real-time Assessment of Community Transmission (REACT) and Early Assessment of Vaccine and anti-viral Effectiveness 2 (EAVE-2), and in cohorts such as SIREN (healthcare workers) and Vivaldi (care homes). The calculation of an accurate IFR required serological testing of a representative random sample of the population, and establishing a regular serological survey allowed us to estimate the severity of disease on a regular basis. However, this took time to set up and for results to indicate severity more clearly and CFR was available much more quickly. Early establishment of data storage and linkage systems was important for the timely calculation of these statistics. Securely sharing data with academic groups facilitated rapid analysis.

Investigations of large outbreaks of COVID-19, similar to previous experience with H1N1 influenza, also supported CFR and IFR estimates early on, as well as giving signals on the proportion of asymptomatic infections. An outbreak on the cruise ship Diamond Princess in February 2020 provided early data on outcomes for 3,711 passengers and crew, and gave a CFR of 2.6% and an IFR of 1.3%,

likely due to testing across the ship picking up asymptomatic cases.[footnote 76], [footnote 77] Studies of Wuhan residents outlining the likely delay distribution between onset and death were critical in estimating both CFRs and, as testing and surveillance expanded, IFRs.[footnote 78] Other opportunities for screening were passengers on flights from affected areas. However, these figures needed to be interpreted in context, and could not readily be applied to different population groups with different demographic characteristics.

It was not until late spring 2020, when many countries were experiencing high transmission and testing was being ramped up alongside surveillance studies, that a shift from CFR to IFR occurred and estimates converged towards an overall IFR of around 1%.

The presence of asymptomatic cases and asymptomatic transmission for COVID-19 was particularly problematic in early mortality rate estimates, and this had not been the case for the closely related SARS-CoV-1 (for which peak infectiousness matched peak clinical symptoms). Many early studies missed asymptomatic cases in the absence of widespread testing and community surveillance, and in the UK in February to April 2020 a number of cases due to COVID-19 occurred in the community without confirmatory testing. This was likely the reason behind higher early CFR estimates: collated data in England from 31 January to 22 April 2020, for example, recorded 99,137 cases with 16,271 deaths, a crude mortality ratio of 16.4%.[footnote 79] Around the same time, adjusting for age and using serological data alongside case data gave an IFR of 1.6% for the UK.[footnote 80]

As noted above, global comparisons proved difficult as hospitalisation criteria, testing availability and case definitions varied over time and across different health jurisdictions. Mortality itself also varied significantly from country to country, likely due to different age structures of populations as well as differences in a range of other risk factors such as obesity, levels of social deprivation and important comorbidities (see Chapter 2: disparities). A study in Italy, where 37.6% of cases were aged 70 years or older, gave an estimated CFR of 7.3% up to 15 March 2020, compared to a much lower CFR in a Chinese study where just 11.9% of cases were over 70.[footnote 81] Understanding of how these complex and interacting demographic factors influenced severe disease evolved throughout the pandemic and underscored the importance of continual evaluation of variation in severity. Heterogeneity of infection risk and disease severity is covered in more detail in Chapter 2: disparities.

Obesity was also an important driver of mortality rates. A large study of over 13,000 hospital admissions in England found a J-shaped relationship between BMI and death from COVID-19, with a nadir at 23 kg/m^2, and a linear rise with BMI values higher than this.[footnote 82] A BMI of 40 was associated with about a 2-fold increased risk of death. Geography, level of social deprivation and the presence of co-morbidities, often linked to ethnicity, played an important part in understanding rates of severe COVID-19 and disease outcomes overall.[footnote 83], [footnote 84] Gender, too, has been flagged as a risk factor for mortality: in the working-age population, COVID-19 death rates were consistently and markedly

higher for men than women throughout the pandemic.[footnote 85] Early reports during the pandemic were often not able to link and adjust for all relevant variables. This is covered in more detail in Chapter 2: disparities.

In light of these differences, changes in all-cause mortality across different countries was a helpful indicator as it was not sensitive to differences in diagnostic or testing data and encompassed both direct and indirect mortality impacts from the pandemic.[footnote 86] Nevertheless, geographical comparisons even with all-cause mortality needed to be handled very carefully. Future developments in infectious disease modelling may allow more precise determinations of severity earlier in a pandemic.

Morbidity

Mortality was not the only measure of severity; admissions to hospital and ICU with COVID-19 were also important metrics in this pandemic – particularly to help plan healthcare delivery. Understanding delays between infection and severe disease was also crucial in estimating the correct denominator and likely rates of severe disease at any given point. For COVID-19, the mean delay from infection to death was around 4 weeks but with wide variation.

Initial clinician impressions from the first cases can give early signals but can be misleading. Many of the early patients seen in the UK with COVID-19 were returning travellers from Europe, the majority of whom were young and fit patients with greater rates of mild disease than the wider population. Within about 2 weeks the disease had spread more widely in the population and hospitals were faced with large numbers of older patients with severe disease and high mortality.

As case rates rose, determining wider population levels of morbidity was complex. Although routine statistics on hospitalisations within the UK were available from early on, a need to prioritise tests during times of limited testing capacity meant that it was difficult to estimate the proportion of cases likely to require hospital admission or ICU care. Early, large-scale testing within the population is of course the best way to gauge severity more accurately, but this is not always feasible, especially when tests need to be developed, or are limited in supply and need to be prioritised to high-risk settings.

Comparisons using other nations' case hospitalisation rates (CHRs), as noted above for CFRs and IFRs, was complicated by differing age structures and hospitalisation criteria and access. It was particularly challenging as some countries hospitalised all cases as an isolation method, while others hospitalised only those with clinical need for hospital care. An early report from Hubei province, China, found that 80% of identified cases were mild (no pneumonia or mild pneumonia) indicating that hospitalisation was unlikely to be required for the majority of cases – though its estimation of cases requiring hospitalisation was undoubtedly too high, most likely because it was restricted to symptomatic patients. Later, widespread testing enabled more accurate estimates which gave significantly lower percentages: a study in Indiana, USA, in early 2020 found an infection hospitalisation rate (IHR) of 2.3%, while a similar analysis in the UK at the end of 2020 (for the wild type strain) gave 3.5%.[footnote 87], [footnote 88]

Estimates of the demand for hospital and ICU beds were challenging. Levels of known risk factors for severe disease, such as population age profiles, were helpful in signalling potential levels of demand. Large scale surveillance, such as via ISARIC, has been important in giving early signals on risk factors.[footnote 89] ICU admission criteria, and indeed the definition of ICU, varied between countries, again making international comparisons complex. There was significant variation in the number of critical care beds in different countries, and population characteristics (such as age) influenced likely need for ICU among COVID-19 cases.[footnote 90] However, criteria for admission and quality of care in ICU were likely similar across comparable health systems, suggested by international comparisons of ICU mortality in early 2020 which showed broadly similar mortality rates of 35% to 40%.[footnote 91] There were, of course, substantial changes in hospital fatality rates (HFRs) over the course of the pandemic: rates in the UK during the first wave had almost halved by summer 2020, but rose again during autumn 2020 and into the 2020 to 2021 Alpha wave as the new variant drove rapidly increasing case rates and hospitals came under significant pressures.

Longer-term consequences of COVID-19

By the summer of 2021, it was becoming apparent that many patients had ongoing symptoms after recovery which persisted for longer than 3 months. One prospective study of 431 individuals testing positive for COVID-19 in Switzerland, published in July 2021, found that 6 to 8 months after infection 55% of the cohort reported ongoing fatigue, 25% had some degree of breathlessness, and 26% fulfilled criteria for depression.[footnote 92] Since that time, the range of chronic symptoms recorded for cases of COVID-19 has expanded greatly.[footnote 93] A diagnostic definition of the condition has been made as post-COVID-19 syndrome by the National Institute for Clinical Excellence (NICE), more commonly referred to as ‘long COVID’ by sufferers and clinicians, although in reality it is likely to represent several overlapping syndromes.[footnote 94]

The exact number who have experienced longer-term symptoms after COVID-19 is likely substantial but remains unclear, as does the aetiology of the syndrome, including whether it was one or (perhaps more likely) a number of different overlapping syndromes. In July 2022 the ONS CIS estimated that 1.4 million people in the UK were experiencing long COVID symptoms that adversely affected their day-to-day activities in the 4 weeks ending 4 June 2022.[footnote 95]

Most children had very minimal medium and long-term health impacts from COVID-19, but rarely some children developed a multisystem inflammatory condition termed paediatric inflammatory multisystem syndrome (PIMS-TS) temporally associated with SARS-CoV-2, or multisystem inflammatory syndrome (in children) (MIS-C).[footnote 96] The true incidence of PIMS-TS was unclear, as many childhood COVID-19 infections went undiagnosed. One study from the US estimated 316 cases per 10^6 COVID-19 infections in persons under 21 years old.[footnote 97] The relationship between the syndrome and COVID-19 infection was shown by about two-thirds of presentations being associated with seroconversion to SARS-CoV-2, and about one-third actually testing positive for SARS-CoV-2 on admission. In some cases, the association was suspected because of close contacts with a confirmed case but without seroconversion or

positive viral PCR. Most cases presented between 2 to 4 weeks after COVID-19 infection was documented. About 70% of cases required ICU admission, though mortality was relatively low at 1.1%.[footnote 98] Some children also experienced long COVID but at a much lower rate than adults.

It is important to note for future pandemic preparedness that there may be longer-term consequences of an infection affecting a large percentage of the population, and that adequate surveillance mechanisms should be in place to capture the epidemiology of the condition accurately to allow adequate planning of healthcare resources in the longer term.

Variants

Over time, new variants arose that led to different clinical outcomes. Detecting these differences was challenging, as it required linking large scale genomic data with hospitalisation and mortality rates. Greater severity was seen with one of the first variants (Alpha), although a subsequent group of variants (Omicron) was found to have had reduced hospitalisations and deaths per case, though due to higher transmissibility and therefore high case rates still resulted in large numbers of hospitalisations. [footnote 99], [footnote 100] Changes in pathogenicity were difficult to measure and it was not possible to assume a shift towards less severe outcomes as the virus evolved. Levels of immunity (both natural and vaccine-derived) were an important confounding factor in determining the intrinsic severity of new variants, as were changing demographic factors (such as the age group predominantly infected) across different waves.

6. What was the duration of naturally acquired and vaccine acquired immunity, and the risk of reinfection over time?

Duration of immunity (natural or vaccine-derived) and risk of reinfection has varied widely in epidemic-potential infections, ranging from lifelong infections such as HIV, infections where a single infection generally confers lifelong protection such as measles, and infections where prior infection provides partial, temporary, or minimal protection from subsequent infection such as influenza and malaria. Cross-protection between different variants of a disease is also highly variable.

As a novel infection, understanding the duration of immunity and risk of reinfection over time for COVID-19 was important to enable individuals, scientists, and policymakers to determine who was protected against infection and for how long, to predict the likely duration of impact of any vaccines, and to inform epidemic modelling. Knowledge of the duration of passive immunity from antibodies was also important for understanding the potential role of antibody drugs.

This information is likely to be important in any new pandemic or major epidemic.

Throughout, there was a need to differentiate between sterilising immunity, which provides protection against both illness and infection, and non-sterilising immunity which provides some, or complete, protection against serious illness but not infection.[footnote 101] Estimating protection against infection required routine systematic testing to detect infections in the presence or absence of symptoms, while symptom-based testing and data on hospitalisations or deaths supported understanding of protection against illness. There was an initial assumption, which had to be tested, that waning of immunity from severe disease would be significantly slower than waning of immunity from infection.

Initial hypotheses

Extrapolation from biologically similar or evolutionarily related pathogens provided the earliest clues to whether reinfection was likely, and after what interval.[footnote 102] Immunity to SARS-CoV-1 and MERS-CoV was thought to wane over time, and there was evidence of confirmed reinfections with seasonal human coronaviruses.[footnote 103], [footnote 104], [footnote 105], [footnote 106], [footnote 107], [footnote 108] This meant that from an early stage there was an assumption that reinfections with SARS-CoV-2 were possible and it was possible to explore the impact of reinfection through mathematical models, monitor early case reports for evidence of proven reinfection and design studies to investigate reinfection rates.[footnote 109] There was also a reasonable assumption that the virus would mutate over time which in turn could impact reinfection risk.

Characterisation of the immune response to infection with SARS-CoV-2 required exploration of both antibody and cell-mediated effects. However, the presence or absence of an antibody or T-cell response was insufficient to confirm protection against infection with SARS-CoV-2.[footnote 110] Measurement of the duration of immunity therefore required establishment of correlates of protection which indicated the presence of an effective immune response.[footnote 102], [footnote 111]

Early data

By early 2020, data emerged indicating that the majority of individuals infected with SARS-CoV-2 displayed an antibody response between 10 to 14 days after symptom onset. [footnote 102] Data showed that in mild cases, antibodies took longer to appear or were low or undetectable during the timescale of completed studies. [footnote 102],[footnote 112], [footnote 113], [footnote 114], [footnote 115], [footnote 116] Much data was gathered through observational studies with serial sampling on small numbers of participants – however, a lack of available validated assays to measure antibody or cell-mediated immunity in early 2020 hampered early attempts to characterise the immune response soon after the emergence of the pathogen. Around this time, data from animal models also signalled that the presence of antibody protected against reinfection when challenged with SARS-CoV-2.[footnote 117], [footnote 118]

Antibodies did not, however, inevitably mean protection from infection (nor did lack of antibodies preclude it due to other immunological mechanisms such as T-cell mediated immunity), so there was a need for further longitudinal studies to examine reinfection risk. The Vivaldi (care homes) and SIREN (healthcare workers) cohort studies were key to developing understanding of infection,

transmission and immunity.[footnote 119], [footnote 120], [footnote 121] These studies were initiated in the first half of 2020 and adapted to provide up-to-date information on issues as they emerged, through adjustment of protocols to include questions on vaccine effectiveness and variant characteristics.[footnote 122] SIREN, for example, recruited its first participant in June 2020, investigated its first reinfection in September 2020, produced an initial reinfection analysis in December 2020, and published its first vaccine effectiveness analysis in January 2021.[footnote 123]

Emerging evidence from the first wave

From early to mid 2020, evidence arose that there was variation in the antibody response produced by different individuals after infection.[footnote 102], [footnote 114], [footnote 124] In May 2020, literature reports emerged of individuals testing positive for SARS-CoV-2 on PCR for 6 to 8 weeks, complicating the differentiation of new infections from ongoing detection.[footnote 55] At this stage, the time to seroconversion and antibody dynamics over the first 3 months following infection were well-characterised for both total antibody and antibody classes.[footnote 125] Mid 2020 also saw the emergence of early observational studies describing the T-cell response to SARS-CoV-2 infection, though there was little data on the T-cell response after the acute phase of infection. Robust evidence characterising the T-cell response to SARS-CoV-2 infection emerged later in the year.[footnote 43]

The first published case reports of SARS-CoV-2 reinfection confirmed by whole genome sequencing also emerged in mid 2020.[footnote 126] Several other reports of reinfection emerged at this time, though many did not have sufficient data to distinguish between persistent primary infection and reinfection.[footnote 127], [footnote 128], [footnote 129], [footnote 130] The corroboration of early reports of reinfections with SARS-CoV-2 was complicated due to restricted access to testing during the time period of primary infections. During the ‘first wave’, the great majority of infected persons did not have access to PCR testing, and viral isolates were not regularly obtained for sequencing.[footnote 131] At this point, reliable information on the proportion of people likely to experience reinfection, the timeline of reinfection, and the characteristics that make reinfection more or less likely was still missing.

Accumulating evidence as time from infection increases

As time since the first infections with SARS-CoV-2 elapsed, the length of time over which the immune response was characterised increased. By the end of 2020, antibodies, in particular neutralising antibodies, were shown to be a useful correlate of protection against SARS-CoV-2, through a combination of animal studies, outbreak studies and cohort studies.[footnote 120], [footnote 132], [footnote 133], [footnote 134], [footnote 135], [footnote 136] Nevertheless, the concentration of antibody that correlated with protection was not yet established. The antibody response following natural infection was shown to persist for at least 3 to 6 months, and the cellular immune response for over 5 months, though seroprevalence studies in the UK showed a decline in the presence of antibody positivity and confirmed reports of reinfection began to emerge, suggesting a waning in protection over time.[footnote 41], [footnote 128], [footnote 129], [footnote 137], [footnote 138] Evidence from

longitudinal observational and cohort studies emerged to suggest that people who had experienced asymptomatic or mild SARS-CoV-2 infection could experience waning immunity over 3 to 5 months.[footnote 33],[footnote 139],[footnote 140]

Data collection in longitudinal cohort studies included the demographic characteristics of participants, routine samples (systematic testing for the identification of the pathogen and its antibodies, with genetic sequencing of the pathogen where applicable), and routine collection of information on symptoms and exposures. Once established, these longitudinal cohort studies were cross-purpose sources of information, providing insight not only into reinfection risk, but also the duration of the protective effect of vaccination following rollout, and the prevalence and incidence of infections in defined populations. Healthcare workers were a useful target population as they were essential for the functioning of the health system, could provide insight into the effectiveness of personal protective equipment and assist in the understanding of nosocomial transmission, and facilitated the establishment of cohort studies at pace.[footnote 121],[footnote 132]

At this time, numerical estimates of the protective effect of baseline antibodies to SARS-CoV-2 against symptomatic reinfection, asymptomatic reinfection, or all infections combined over a period of 3 to 5 months, also became available.[footnote 101], [footnote 132], [footnote 133], [footnote 139] The end of 2020 also brought the first clinical trial data demonstrating that SARS-CoV-2 vaccines could provide a high level of protection against disease – however, the duration of immunity provided remained unknown.

By mid 2021, descriptions of viral loads (as measured by cycle threshold (Ct) values) in reinfected individuals were available.[footnote 120] Cultivable virus had also been isolated from reinfected individuals, demonstrating that reinfections presented a risk of onward transmission.[footnote 141], [footnote 142] Throughout the first half of 2021, understanding of the duration of the immune response to SARS-CoV-2 improved. Antibody was found to be detectable in saliva for at least 8 months following infection, and in blood for at least 9 months. The presence of antibody was shown to be associated with a protective effect against infection over at least 7 to 10 months, with a lower effect in those aged over 65.[footnote 110] The cell-mediated immune response to SARS-CoV-2 was shown to be detectable up to 8 months after infection.[footnote 41], [footnote 110], [footnote 137] Characterisation of neutralising antibody titres over time since either infection or vaccination or both (through longitudinal serological sampling) continued throughout 2022.[footnote 143], [footnote 144]

Variants

The duration of protection against infection and illness with SARS-CoV-2 was driven both by the immune response to either infection or vaccination or both, and the antigenic distance between circulating viruses.[footnote 145] It was recognised that protection would not endure if the variant causing the primary infection (or against which the vaccine is directed) was replaced by a new variant that was antigenically distant from the first.[footnote 146] In late 2020 and early 2021, the emergence of new SARS-CoV-2 variants which were significantly

different to the Wuhan original necessitated exploration of the protection induced by natural infection and vaccines against variants that were antigenically different to the primary infection.[footnote 147], [footnote 148]

In March 2021, early evidence showed that the risk of reinfection with the Alpha variant was comparable to the risk of reinfection with the wild type, though these findings were confounded by the shorter time from primary infection in the case of the alpha variant.[footnote 149], [footnote 150] National surveillance data was used to monitor reinfections, including with newly emerging variants, and showed evidence of increased reinfections at the emergence of the delta and omicron variants.[footnote 151],[footnote 152],[footnote 153]

Epidemiological questions

7. What were the case definitions?

Establishing case definitions is an essential step in any pandemic or major epidemic. As a new disease, the case definitions for COVID-19 evolved over time. During the SARS-CoV-2 pandemic, as with most common infectious diseases, case definitions were used for 3 differentiated but overlapping purposes:

- public health: contact tracing, outbreak investigations, and communication to the public – for example, on when to isolate
- epidemiological: surveillance
- clinical: provision of healthcare

Optimising case definitions to cover different use cases often required trade-offs, especially between sensitivity and specificity. Case definitions used epidemiological, clinical and testing criteria, but the balance of these changed over the course of the pandemic as knowledge of SARS-CoV-2 accumulated and as testing resources expanded to meet demand.

Epidemiological criteria

Initially, UK case definitions placed more emphasis on person and place (such as people who travelled from Wuhan, China) than on testing criteria – which would likely also occur in the initial stages of most future pandemics and major epidemics for which testing is limited.[footnote 154], [footnote 155] Symptoms were included but it was helpful to also include epidemiological information (such as where a person had recently been) due to non-specific symptom profiles for COVID-19 in early 2020.[footnote 154], [footnote 155]

The geographical scope of definitions widened as cases appeared in other countries until such time as it was no longer meaningful and most transmission was domestic.

Clinical criteria

The clinical criteria included in the case definition changed over time as data accumulated. For example, in spring 2020, loss of taste or smell were included in the COVID-19 case definition.[footnote 156]

Robust estimates of the sensitivity and specificity of specific symptoms were not available until later in the pandemic, as much of the early evidence generated was affected by the following limitations:

1. Many studies reported only the frequency of symptoms in persons infected with SARS-CoV-2 and no comparative data on symptomatic people testing negative. This allows assessment of sensitivity but not specificity. Research should include non-infected comparator groups.[footnote 157]
2. Many early symptom reports focused on people who were hospitalised, leaving it unclear whether symptoms would be similar in mild community cases.
3. Data from national testing programmes may be biased as these programmes often specify the symptoms for which they want people to test. This leads to an overestimation of the sensitivity of the symptoms described in the testing criteria.

Throughout the pandemic, there were frequent calls to include a wider range of symptoms in case definitions but there was an ongoing need to balance the need for sensitivity (increased by a broader list of symptoms) with specificity (increased by a narrower list of symptoms).[footnote 158], [footnote 159] Early in the pandemic when the infection was emerging, and the critical objective was to find as high a proportion of all cases as possible and reduce transmission through high impact public health contact tracing, the strategic aim of the case definition was high sensitivity.[footnote 160]

Regular reviews of the sensitivity and specificity of specific symptoms and symptom complexes were undertaken to ensure that a reasonable balance was struck between the ability to correctly identify cases, and the ability to exclude non-cases, in a pragmatic and clinically useful way.[footnote 157], [footnote 161] Algorithmic approaches to case definitions, incorporating both symptoms and epidemiological data, could theoretically have been used to optimise the balance between sensitivity and specificity, but may have been challenging to implement and communicate.

When deliberating the balance between sensitivity and specificity, it was also necessary to consider the impact of changing case definitions. For example, using a highly sensitive case definition would have had a big impact on testing resources, and would have also increased the numbers of individuals who needed to self-isolate, potentially unnecessarily.

Testing criteria

Rapid diagnostic development meant that tests were available early in the pandemic, and testing criteria were included in some early case definitions. However, as the first wave rose in the UK, demand for testing rapidly outstripped capacity, and existing supply had to be prioritised for hospital settings. This impacted the ability to confirm cases in the community so other forms of case definition, such as symptomatic, were prioritised. (See Chapter 6: testing.) Test demand outstripping supply is likely to be the case in a future pandemic; it will be essential to ensure that diagnostic testing is scaled quickly and capacity is created for widespread community testing as early as possible. Understanding of the frequency of certain symptoms over the year (such as influenza-like illnesses in winter) can support preparations for this.[footnote 162]

As testing capacity increased in spring 2020 and became more widely available in the community, testing criteria played a greater role in case definitions. Identifying cases using contact criteria, meanwhile, required effective contact tracing systems, which were under significant pressure during the first wave when community transmission rose rapidly. (See Chapter 6: testing and Chapter 7: contact tracing.) It also required a good understanding of what type of contact constituted a risk of infection, which took time to accumulate.

Evolution of COVID-19 case definitions

The earliest sources of information for the establishment of case definitions were case reports, case series and information shared by national health agencies in East Asia and the WHO.[footnote 15], [footnote 163], [footnote 164] In December 2019, the Wuhan Municipal Health Commission reported a cluster of pneumonia cases in Wuhan, Hubei Province, China.[footnote 165], [footnote 166] By mid January 2020, the WHO had issued a report describing the clinical symptoms and signs associated with the pneumonia cluster.[footnote 165] The first surveillance case definition for human infection with novel coronavirus followed soon afterwards.[footnote 167]

Throughout January, reports describing the clinical signs and symptoms associated with SARS-CoV-2 infection continued to emerge, including the first published case reports and case series. [footnote 15],[footnote 163], [footnote 164], [footnote 168], [footnote 169] By the end of January, the New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG), the Scientific Advisory Group for Emergencies (SAGE), Public Health England (PHE) (later the UK Health Security Agency or UKHSA), and the Department of Health and Social Care (DHSC) had agreed the first epidemiological case definition in the UK, the geographical element of which expanded over the following weeks.[footnote 154], [footnote 155], [footnote 160], [footnote 170], [footnote 171]

In the UK, the First Few Hundred Cases Study (FF100) provided early insight into the symptom profiles of local cases, but these were generally younger and healthier cases.[footnote 172] Existing surveillance studies (such as flu watch) provided useful negative controls against which to compare the symptom profile of positive cases.[footnote 157]

With the passage of time, more sources of data were established. National surveillance data, with symptom surveys linked to test results, provided useful insight into symptom frequency in cases throughout. By mid to late 2020, systematic reviews and meta-analyses with large sample sizes had produced detailed summaries of symptom profiles in different age groups. Non-traditional academic sources, such as healthcare worker symptom reporting, symptom-tracker apps (such as the ZOE app) and social media, also provided information on symptom frequency, though many of these sources were not sampled in a randomised way and were therefore not representative of the population as a whole.

As new variants emerged later in the pandemic, ecological studies were used to compare symptom profiles over time.[footnote 150] Observational studies with large sample sizes also allowed the accumulation of data on symptom profiles.

Population-wide or nationally representative case-control studies and longitudinal studies, and later systematic reviews and meta-analyses, ultimately provided the best insight into symptom profiles and case definitions, though they took time to establish. Studies that tested people regardless of symptoms (such as REACT and those coordinated by ONS) and compared symptom profiles in symptomatic test negative and symptomatic test positive people provided robust estimates of the sensitivity and specificity of specific symptoms, while avoiding the biases often present in national testing data.

Challenges and complexities

Throughout the pandemic, the public nature of case definitions for COVID-19 to direct people to take actions such as self-isolation added complexity. Case definitions for public use (as opposed to use by clinicians) had to be sufficiently simple to be remembered by the general public so that they could take appropriate public health actions, while correctly identifying cases sufficiently frequently for public health action. Evidence suggested that very sensitive case definitions, including many symptoms, could lead to reduced compliance with public health actions (such as testing or self-isolation) especially if they were triggered too frequently.[footnote 173]

There were also important nuances to how symptoms were communicated. For example, many people did not have access to thermometers to measure fever, and so language such as feeling hot or feverish was helpful in addition to a technical definition of fever. It was also important to consider how symptoms were interpreted when transmitted into different languages.

Towards the end of 2020, co-circulation of other influenza-like illnesses threatened to impact the specificity of SARS-CoV-2 public case definitions.[footnote 174] In the event, there was relatively limited co-circulation of SARS-CoV-2 and other influenza-like illnesses in the UK in winter 2020 to 2021 due to widespread implementation of NPIs, though co-circulation has since occurred.

As knowledge of symptom profiles and diagnostic testing capacity accumulated, the strategic objectives of each case definition had to be borne in mind (for example, correctly identifying as many infections as possible) and balanced with a requirement for consistency and public understanding.[footnote 145]

Clinical case definitions were more widely defined throughout the pandemic than the public ones, recognising the wide range of rarer symptoms that people with COVID-19 could present with.

8. What were the important routes of transmission?

Evidence on routes of transmission was important for guiding the pandemic response, especially in the early stages where NPIs were the only interventions that were available.[footnote 175], [footnote 176], [footnote 177]

Evidence of this kind has been important in previous pandemics and recent epidemics, such as HIV (sexual and intravenous), Ebola virus (touch) or Zika virus (vector), and it will be for any future pandemic or major epidemic.

It was established early that the likely principal route of transmission for COVID-19 was respiratory, although secondary routes including faeco-oral were not excluded. From early in the pandemic, 3 components have been considered potentially important for COVID-19: fomite, droplet and aerosol spread. However, global scientific consensus on the relative importance of these different transmission routes, and the potential role of other routes, shifted as new evidence emerged, and evidence has been continually reviewed as new variants of SARS-CoV-2 have become established.[footnote 178]

There were important complexities in understanding transmission routes. First, transmission depends on multiple factors including:

- pathogen dynamics, such as viral load
- environmental factors, such as temperature and ventilation
- host-related factors, such as behavioural adaptation, immunity and contact patterns
- wider contextual factors, such as prevalence of the disease[footnote 175], [footnote 176]

Second, some routes of transmission were easier to measure than others. It was relatively rapidly identified that close contacts were at elevated risk and from that it was inferred that close range droplet transmission was likely to be important. It was less easy to identify the most likely pathway in those with more distant exposure – where respiratory particles will have been diluted by distance – as a contact event was often harder to identify.

Third, there was a need to balance the level of infection risk from a given transmission route with the frequency and likelihood of exposure to this route in day-to-day activities. Aerosol transmission across a room, for example, may present a low risk from any single exposure, but the ability for one infectious person to expose multiple people at the same time means it could present a higher population level risk in some settings than for close direct contact with an infectious person.

Finally, given the challenges inherent in attempting to determine the relative impacts of different routes of transmission, it was important to retain an open mind as understanding evolved over the course of the pandemic. It was also important to ensure that absence of evidence was not interpreted as evidence of absence, and that important transmission routes to which there were potential countermeasures were not ignored.

Expertise in public health, clinical medicine, microbiology, physics, behavioural science, built environment and data science was helpful to interpret a range of evidence on routes of transmission.

Outset: using existing knowledge

Initially, inference was drawn from studies of transmission routes for other respiratory viruses. Phylogenetic studies helped identify similarities to known viruses within the same family, in particular SARS-CoV-1.[footnote 178] In retrospect, this provided mixed early indications – on the one hand, the airborne transmission capabilities of SARS-CoV-2 are similar to SARS-CoV-1; on the other, there are a number of important differences such as in timelines of transmission and the much greater role of asymptomatic transmission seen with SARS-CoV-2 (see section 10).[footnote 177]

As a respiratory virus SARS-CoV-2 carried the potential for transmission via droplets and aerosols, direct physical contact, and indirect (fomite based) physical contact. Existing evidence suggested that close contact with a person with acute respiratory infection carried more risk than a more physically distant contact, implying the importance of close-range droplet and, as now understood, short-range aerosol transmission. Pre-pandemic research into other acute respiratory infections also showed the importance for transmission of exposure in public spaces including public transport, shops, restaurants, parties, theatres and places of worship, suggesting an additional potential role for more distant, primarily aerosol based, transmission.[footnote 179] Existing systematic reviews showed that regular handwashing can reduce incidence of respiratory infections, implying a possible role for direct contact and/or fomite based transmission.[footnote 180] This helped guide early control strategies, but the relative importance of these transmission routes for SARS-CoV-2 was initially unclear and required further investigation.

Early investigations

Early retrospective cohort studies were helpful in generating hypotheses about modes of transmission. In January 2020, for example, a retrospective cohort study of 41 patients in Wuhan, China, provided initial evidence of human transmission. The authors of the study suggested further investigation to exclude major alternate routes of transmission such as faeco-oral and recommended the use of precautions against airborne transmission.[footnote 178]

Outbreaks – especially super-spreading events – also provided valuable opportunities to understand transmission dynamics at the outset of the pandemic, particularly when background prevalence was low. Well-designed outbreak investigations conducted during times of low prevalence could identify

transmission from a single index case and describe the risk of infection according to proximity of contact. For example, early outbreaks in restaurants in China showed the highest risk of infection was for those with closest proximity to the index case. They also showed infections among people at distant tables, implying that some aerosol transmission had occurred – video evidence later discounted the role of fomite transmission.[footnote 181], [footnote 182] Similar findings were seen for outbreaks on coaches and trains.[footnote 183], [footnote 184] An early outbreak investigation in Germany in March 2020, combined with similar studies from China, also suggested the importance of pre-symptomatic transmission as some of those infected had only been exposed to the index case prior to that person becoming symptomatic.[footnote 185], [footnote 186], [footnote 187] Gaining access to outbreak sites to gather samples, however, proved challenging, and at the outset of the pandemic protocols on containment levels hampered efforts to rapidly move samples. Having pre-approved emergency protocols for access and sample transportation, as well as adequate resources to investigate and take samples from outbreaks, will be important in a future pandemic. Adequate resource to undertake reviews of outbreaks occurring internationally is also important.

Systematic studies of contacts of known cases, such as the First Few Hundred approach, provided valuable evidence in the early stages of the pandemic.[footnote 188] In order to describe secondary attack rates according to the nature and setting of exposure, these studies needed carefully to define the nature of the contact in terms of proximity, type of contact, duration and setting, to follow up both close and distant contacts, and to undertake regular testing of contacts regardless of symptoms.

Environmental studies were also important. One environmental study with air and surface sampling, conducted over a period of 2 weeks in a Singaporean hospital with COVID-19 patients, found environmental contamination suggestive of droplet spread, and possible faecal shedding.[footnote 189] However, sampling live virus is difficult and it remained unclear whether shedding in this study indicated transmission risk.

Alongside the above relatively rapid investigations in the early months of the pandemic, there was a need to establish surveillance programmes across multiple settings to provide real-time information and therefore early warning signals on transmission by different routes in household, community, health and social care settings. However, this relied on large scale availability of testing, which was limited in early spring 2020 in the UK as testing capacity struggled to meet rapidly rising demand (for more on this process, see Chapter 6: testing).

The WHO-China Joint Mission analysis in early 2020 triangulated findings from phylogenetic and laboratory studies of COVID-19, outbreak analyses, in-depth analysis of disease progression, and published literature to outline what was known and not known with respect to COVID-19 in order to make recommendations for both China and the international community. This suggested that SARS-CoV-2 was likely to be primarily transmitted through respiratory droplets during close unprotected contact, and also by fomites, an assessment that did not change in their follow-up briefing in March 2020.[footnote 190], [footnote 191]

In recognition of the need to maintain an up-to-date overview of emerging evidence the SAGE Environment and Modelling group (EMG) was established in April 2020 to bring together a range of scientific experts to explore these issues in depth. The group continuously monitored best available evidence on transmission routes, in particular the growing evidence for the significant role of aerosol transmission.[footnote 192], [footnote 193], [footnote 194], [footnote 195]

Throughout the pandemic

Based on a further review of the existing evidence in July 2020, the WHO continued to recommend that direct or close contact with infected people via droplet remained the most likely principal route of transmission, and uncertainty remained about the fomite route. Multiple environmental sampling studies demonstrated presence of viable SARS-CoV-2 virus and/or RNA on surfaces for hours to days – however, there was an absence of case reports or outbreaks robustly demonstrating fomite transmission (most people who came into contact with infectious surfaces had also had close contact with an infectious person). [footnote 196], [footnote 197]

Quantitative microbial risk assessment methods, estimating viral exposure via hand–face touches based on measured environmental contamination, steadily added to the evidence base that fomite transmission risks were low, with one study concluding that each contact with a contaminated surface had less than a 1 in 10,000 chance of causing an infection.[footnote 198] Epidemiological evidence for fomite transmission and the impact of interventions such as surface cleaning and hand hygiene was and remains very limited. There was a notable difference between calls for evidence of the importance of airborne transmission that were not replicated for fomite transmission, which was assumed despite little evidence to support it.

Though SARS-CoV-2 RNA had been detected in some samples of urine and faeces, there remained no published reports by summer 2020 that were able to link transmission to these routes.[footnote 189] Bloodborne transmission was considered low risk due to low viral titres in blood, and there was still no evidence of intrauterine transmission.[footnote 199]

As the evidence base grew, synthesis of evidence from completed studies on viral load across the respiratory tract, fluid dynamic studies examining dispersion of virus from household appliances, environmental air sampling outbreak reports, and studies in animal models all helped enhance understanding of short and long-range airborne transmission risks and the importance of ventilation.[footnote 196], [footnote 200], [footnote 201], [footnote 202], [footnote 203] Despite accumulating evidence, reaching a position of confidence on the full range of transmission routes and their relative importance took longer than expected. A year into the pandemic, the WHO noted that high-quality research was still required to understand routes of transmission, infectious dose and settings in which transmission might be amplified.

As the pandemic progressed the importance of airborne transmission was increasingly recognised.[footnote 204] It was established early on that transmission was far more likely indoors than outdoors, suggesting a role for the environment,

and particularly dilution by air (but also the effects of sunlight), in influencing transmission. The evidence encompassed theory, observation and experiment, and included:[footnote 182], [footnote 205], [footnote 206], [footnote 207], [footnote 208], [footnote 209], [footnote 210],[footnote 211], [footnote 212], [footnote 213]

- outbreak reports relating to choir groups, restaurants and fitness classes
- long-range transmission in quarantine hotels between people who had had no contact with one another
- nosocomial transmission in settings where droplet-based precautions but not aerosol based ones were taken
- animal studies in caged animals which became infected despite only sharing air ducts
- air sampling studies showing infectivity of air for up to 3 hours in rooms occupied by patients with COVID-19
- experimental studies mimicking aerosol dispersion
- a substantial volume of cases arising from pre symptomatic transmission which was most likely to have occurred by the aerosol route

Some transmission events were reported to occur after an infected person had left a setting, indicating likely airborne transmission of the virus.[footnote 205], [footnote 206],[footnote 207]

Although the fact that the respiratory route was dominant was established very early, teasing out the relative contributions of close range and longer distance airborne spread, and of fomites, presented significant challenges. Super-spreading events and rapid epidemiological studies made an important contribution to understanding transmission routes – however, relying solely on these at times led to misleading conclusions about transmission, especially because aerosol and fomite transmission were and remain harder to measure robustly than close range transmission.[footnote 214] Even transmission at close range was subject to prior assumptions, with the belief that the risk was posed by large droplets rather than more concentrated small aerosols, resulting in reduced focus on masks for protection against inhalation for people at close proximity.

This pandemic highlighted the role of controlled laboratory settings in providing evidence on routes of transmission, as well as the importance of rapid investigations into survival of viable virus across different environments (using, for example, quantitative microbial risk assessment). [footnote 198],[footnote 215] Different laboratory detection and sampling methods had differing abilities to detect differences between viable and non-viable virus. It is important to note that the level of viral RNA measured in an environment is not necessarily reflective of its infectivity. As an example, sampling of environments where people have influenza or Monkeypox show far more viral RNA than for SARS-CoV-2, yet the outbreak data indicate that both are much less transmissible. This suggests that a lower viral dose is needed to initiate a SARS-CoV-2 infection than for these other diseases.

There was a need to consider local circumstances when assessing the evidence. For example, early data from China suggested a limited role for healthcare settings in driving transmission, but this was in the context of important differences between these settings in China and the UK, including the imposition of different mitigation measures against aerosol transmission. [footnote 190]

9. What were the higher risk settings for transmission?

In this pandemic it has been important to understand higher risk settings for transmission in order to target mitigation measures at those locations where they would have the greatest impact.

Outset: using existing knowledge

At the outset, in the absence of specific evidence on mechanisms of transmission of SARS-CoV-2, the use of fundamental transmission principles alongside pre-existing research on respiratory-transmitted pathogens helped identify potential high-risk settings for transmission. Fundamental principles suggested that the highest risk of transmission would be in places where people from multiple households could meet, such as hospitality settings, especially if they were physically close and indoors. There were ongoing questions regarding mass events, particularly where these took place predominantly outdoors. Chapter 8 on NPIs covers this in more detail, outlining how greater understanding on this issue was reached, and outlining key epidemiological principles when considering transmission linked to mass events. Pre-existing research on respiratory pathogens supported this approach, with high transmission risks likely in settings including households, schools, hospitals, homeless hostels, prisons and nursing homes.[footnote 216], [footnote 217], [footnote 218], [footnote 219], [footnote 220] There were, however, important caveats to using such evidence. The level of transmission risk within different settings can vary according to the characteristics of different infectious diseases, such as who uses such settings, who is vulnerable to severe disease, and how this might affect their behaviour. There was therefore a need to generate evidence on high-risk settings both in terms of transmission of SARS-CoV-2 and the consequences for those affected, rather than relying on existing evidence alone. It was also important to review findings as new variants became established, vaccines were rolled out, and both guidance and public behaviour changed.

Early investigations

In the first few months of the pandemic, early outbreaks gave an indication of potential high risk contexts including health and care settings, long-term living facilities particularly for older people, prisons and cruise ships.[footnote 190], [footnote 191], [footnote 221] Later in spring 2020, evidence from early outbreaks in choir groups, restaurants and fitness classes was reported.[footnote 182], [footnote 205], [footnote 206], [footnote 207] Formal and informal information channels played a part in reporting possible outbreaks at speed; many apparent outbreaks were reported in the media or on social media long before they were formally described in preprints or journal articles. However, in addition to uncertainties about the reliability of such reports there was an additional important caveat to

this early evidence: the majority of transmission did not take place within recognised large outbreaks, which are more likely to be identified in relatively closed settings than in more open venues such as shops or public transport where tracing of contacts is more difficult and the extent of contact often less clear. In addition, outbreak studies highlighting risks in particular settings had to be balanced with the overall epidemiological importance of that setting in a given population. For example, while shopping may not be inherently high risk, the fact that the majority of people need to shop for essential items means that it makes an important contribution to transmission.[footnote 222] It should also be noted that in the early days testing was very limited, so outbreaks where multiple people were symptomatic or died would have been more likely to be reported.

Early mortality data, alongside outbreak studies, indicated that enclosed settings which housed vulnerable individuals (such as migrants, homeless people and prisoners), and health and care settings (hospitals, care homes, care settings for those with learning disabilities, domiciliary care, long stay mental health institutions) were of particular importance for both mitigation efforts and for research.[footnote 223], [footnote 224]

Differences in mortality by occupation also gave indications of potential higher risk contexts. Data from May 2020 showed that mortality was elevated in occupations with high levels of close contact with others (including health and care contact), and in those with low pay.[footnote 224] Later analyses controlling for key comorbidities with COVID-19 showed that high levels of comorbidities in some occupational groups contributed to these variations, but setting and type of work remained an important factor.[footnote 225] It is also important to note that industrial sectors concentrated in areas with high levels of community prevalence might have given a misleading impression that the type of business posed an elevated risk when this may in fact have primarily been a function of local prevalence or workers living close to one another or sharing social facilities.

Throughout the pandemic

From the early pandemic onwards a number of different scientific approaches were needed to understand high transmission risk settings. In the early stages, outbreak investigations, contact tracing, surveillance studies, environmental sampling, modelling studies and behavioural analysis were the approaches most likely to be able to collect data rapidly. As the pandemic progressed, longer-term methodologies such as case control studies, repeated cross-sectional studies, cohort studies, sequencing and phylogenetic studies, intervention studies and meta-analyses became possible and assumed greater importance.[footnote 176] Implementing such studies required deployment of a variety of robust surveillance programmes and research to gather real-time information on cases in household, community, health and social care settings as well as rapid outbreak analysis.

In prioritising the focus of these studies, it was crucial to understand transmission dynamics and populations at risk from the pathogen as quickly as possible through live surveillance. With H1N1 influenza in 2009, young adults were most at risk, while other infectious disease such as measles generally affect children most.[footnote 226], [footnote 227] With COVID-19, demographics of those at risk

became clear through outbreak and mortality patterns analysed prospectively and retrospectively in cohort studies, with the aid of electronic healthcare data. [footnote 223], [footnote 224], [footnote 228], [footnote 229]

Well-designed epidemiological studies took considerable time to generate statistically robust data. This required the development of reliable methods for testing and sequencing, and the rollout of these at scale. The speed at which this can happen is likely to depend on how similar the pathogen is to existing microorganisms and whether surveillance and sampling approaches for other infections can be easily adapted. It was important to have funding mechanisms, data governance and data sharing agreements in place, and to plan and initiate them as rapidly as possible. They also relied heavily on availability of testing and contact tracing, both of which were running at very limited capacity in the early part of the UK's first wave, and on community surveillance such as the ONS CIS, which went live in April 2020, the same month the UK's first wave peaked nationally.

It was more difficult to generate new evidence on potential high transmission risk settings such as hospitality, some workplaces, or schools during periods of intense restrictions as many such settings were highly restricted or closed down, and thus unable to contribute to generating evidence. Analyses of the Virus Watch cohort submitted to SAGE in December 2021 showed that during restrictions in winter 2020 to 2021 leaving home for work, using public transport, and shopping were all important risk factors for transmission. Following lifting of restrictions all of these activities remained relevant, but other activities which had previously been restricted (such as visiting pubs and restaurants) increased their relative importance as risk factors.[footnote 222]

Analyses that brought together multiple study types were helpful in highlighting consistent signals from particular settings. For example, an analysis of COVID-19 outbreaks in hospitality, retail and leisure facilities in the UK and worldwide, presented to SAGE in January 2021, used multiple analytical approaches to examine transmission risks in these settings including:

- social contacts over time
- case-control studies
- secondary attack rates
- cluster concordance [footnote 230]

It reinforced the initial fundamental principles outlined above that transmission risks were highest in settings that were poorly ventilated and crowded, where mixing was for extended periods of time, and where population turnover was high. Analysis of cases by occupation and sector also highlighted that risk is not necessarily the same across a particular sector or indeed within a setting, with a range of socio-economic factors influencing risks.[footnote 231] For example, food processing is a sector that has been associated with multiple large outbreaks, with analysis suggesting that the likelihood of transmission depends not only on the characteristics of the settings (such as ventilation, social distancing), but also the socio-economic characteristics of the workforce, including shared housing,

lack of sick pay (creating pressure to continue working even if unwell), and use of shared transport.[footnote 232] It was difficult to differentiate beyond fundamental principles to attribute causation to particular properties of these specific settings which increased or reduced risk.[footnote 230]

Understanding transmission risks in different settings was a complex process for a number of reasons, some of which have been outlined above. First, transmission risk in settings was linked to factors that changed throughout the pandemic, across different settings and communities, in response to changing guidance, behaviours and mitigating measures: contact patterns (the type, frequency, proximity and duration of contacts and networks of contacts), levels of immunity, and environmental factors such as ventilation or occupant density.[footnote 176],[footnote 233]

Second, transmission risk may vary depending on factors particular to specific settings (rather than setting types or sectors) such as ventilation or proximity to others in a building. Society-wide guidance for different setting types needed to be accompanied by risk assessments tailored to particular locations, and adaptations that considered the range of activities as well as the environment. Third, background community prevalence and the changing epidemiology of the pandemic needed to be considered. For example, a retrospective study examining outbreaks recorded in educational settings between June and July 2020 when community prevalence was relatively low noted that outbreaks were uncommon; transmission in educational settings was higher later in the pandemic as new variants became established and prevalence rose again.[footnote 234]

Transmission risk in settings was a dynamic factor throughout the pandemic, and this ongoing risk of time-varying and contextual confounding meant that although some settings were indicated as potentially higher risk through epidemiological studies, the level of that risk was complex to assess. Cross-disciplinary expertise across epidemiology, health, microbiology and understanding of specifics behaviours and environments supported interpretation of potential risks.

10. What was the proportion of asymptomatic infection and transmission, and could this maintain R over 1?

Overview

From the outset, asymptomatic infection and transmission were considered possible, but the extent of each was not understood. Existing knowledge of other related human coronaviruses suggested that asymptomatic infection and transmission were possible, but it was difficult to extrapolate directly, and work was needed to clarify:

- the proportion of infections that were asymptomatic
- the role of asymptomatic transmission

These parameters are complex and quantitative, and their estimation required the continual balancing of multiple types of emerging evidence. Continual reassessment of this evidence was also required, as the immunity profile of the population changed due to infection-induced and vaccine-derived immunity, and as new variants emerged. There was conflation of asymptomatic infection and asymptomatic transmission in some public reporting, and it was necessary to highlight that asymptomatic infection does not necessarily lead to asymptomatic transmission (though it was a prerequisite).

Knowing the proportion of infections that were asymptomatic was important for case detection strategies and determining the infection fatality rate. Understanding the role of asymptomatic transmission was important for identifying which public health measures would likely bring R below 1. Transmission of infection from asymptomatic cases can be difficult to control, and the infectious timeline is difficult to establish in the absence of symptoms as a marker of infection or infectiousness, adding complexity to disease control. [footnote 235], [footnote 236]

Asymptomatic cases cannot be detected in the absence of testing, and in the early pandemic the global and UK constraints on test availability significantly slowed the estimation of asymptomatic cases.

Proportion of infections that were asymptomatic

The proportion of SARS-CoV-2 infections that were asymptomatic was defined using 2 different numerators:

- PCR positivity
- antibody positivity

PCR positivity was technically easier to assess but had a shorter duration, which may have resulted in undercounting of infections in some studies. Serology was more labour intensive to collect and analyse, but has a longer duration, providing a more accurate estimate of infection proportions.

There was difficulty in identifying asymptomatic cases as the majority of testing took place in those who were symptomatic, particularly in the early stages of the pandemic when limited tests had to be prioritised.

Simpler study designs (such as cross-sectional studies) were unable to differentiate between asymptomatic and pre-symptomatic infections.[footnote 237] Although these produced estimates of the proportion of asymptomatic infections at pace, they were likely inflated by the inclusion of some pre and post-symptomatic individuals.[footnote 238]

Role of asymptomatic transmission

It was likewise challenging to distinguish between asymptomatic, pauci-symptomatic and pre-symptomatic transmission.[footnote 239] Where studies had designs which did not enable the differentiation of pre and asymptomatic

transmission, there was a tendency to over-report cases resulting from asymptomatic transmission.[footnote 236]

Transmission from one person to another depends on a number of factors including shedding of viable virus and behaviours and contact patterns, noting that asymptomatic people may be more likely to be unaware of infection than symptomatic people.

Methods to understand the proportion and relative infectiousness of asymptomatic infections

1. Case series and cluster investigations provided early signals that asymptomatic infection and transmission were possible while more robust data was being collected.[footnote 240], [footnote 241]
2. Longitudinal designs which collected information on symptoms over time (and thus were able to differentiate between asymptomatic and pre-symptomatic infections) were needed to calculate reliable estimates of the asymptomatic proportion.[footnote 242]
3. Longitudinal studies were also required to understand the potential for transmission from asymptomatic cases. These studies addressed secondary attack rates in households with asymptomatic infections and/or included serial viral culture to indicate the presence of live, infectious virus.[footnote 243]
4. Studies in institutional settings (nursing homes, army barracks) were among the earliest established, and enabled the estimation of asymptomatic proportions and relative infectiousness more quickly.[footnote 244], [footnote 245], [footnote 246] However, their applicability to the general population was potentially limited.[footnote 236]
5. Viral culture was the optimal tool for assessing infectiousness in both symptomatic and asymptomatic cases but was not widely available.

Summary of the types of evidence available, and broad timelines

For SARS-Cov-2, the asymptomatic proportion and the relative infectiousness of asymptomatic individuals varied substantially depending on the setting and characteristics of the individuals involved. In addition, they changed over time as the population gained protection from prior infection or vaccination and viral variants with different biological properties emerged.[footnote 238]

Early case and cluster reports raised the possibility of asymptomatic infection and transmission but often with poor differentiation between asymptomatic and pre-symptomatic transmission.[footnote 240], [footnote 247], [footnote 248] At this stage, robust data on asymptomatic infections and whether they may be infectious to others was lacking, and estimates of the asymptomatic proportion varied widely.[footnote 249]

After a few months, outbreak studies in closed or institutional environments provided early estimates of the asymptomatic proportion of PCR-confirmed cases, but may have included pre-symptomatic cases. Descriptive reports of transmission chains and clusters described apparently asymptomatic transmission.[footnote 241], [footnote 250]

Over time, evidence of positive tests in asymptomatic individuals mounted, and more robust data on asymptomatic transmission emerged. Estimates of the asymptomatic proportion were high. Cross-sectional studies were conducted which were unable to differentiate between pre and asymptomatic transmission.

By mid 2020, further estimates of the asymptomatic proportion in closed and/or institutional settings had been published, and the first evidence that infectious virus could be recovered from asymptomatic individuals emerged.[footnote 244], [footnote 245], [footnote 246], [footnote 251], [footnote 252], [footnote 253] Early systematic reviews and meta analyses of asymptomatic proportions followed, with wide variation in the estimates of the asymptomatic proportion, and lower estimates from studies that were better able to differentiate between pre and asymptomatic cases.[footnote 238], [footnote 242] Around this time, early data comparing cycle threshold (Ct) values between asymptomatic and symptomatic individuals became available, though the link between Ct values and infectiousness was not firmly established.[footnote 245], [footnote 254], [footnote 255], [footnote 256]

Eventually, large random-sample swabbing studies, such as REACT and those led by the ONS, were established and provided robust estimates of the asymptomatic proportion on a regular basis. By mid to late 2020, studies of household transmission had been established that were able to robustly identify asymptomatic infections and transmission, and the viral load dynamics in asymptomatic individuals had been characterised.[footnote 243], [footnote 254], [footnote 257]

Establishing that asymptomatic transmission occurred was well in advance of establishing what proportion of transmission was from asymptomatic people, and whether, if all symptomatic transmission ceased (for example, due to case isolation) asymptomatic transmission alone was capable of sustaining the reproduction number (R) above 1.

11. How long were people infectious?

Understanding duration of infectiousness is central to infection prevention and control and will be for any future pandemic or epidemic. Infections vary widely in their duration of infectiousness from a few days to lifelong (the last major new pandemic, HIV, was lifelong when untreated). It was important to understand the duration of the infectious period of SARS-CoV-2 in order to make informed decisions on the duration of isolation and contact tracing windows, to optimise prevention of transmission in health and care settings, and to be able to understand and model the dynamics of the pandemic.

For SARS-CoV-2, epidemiological and virological methods were primarily used to develop this understanding.

Detecting the presence of SARS-CoV-2 virus

The presence of SARS-CoV-2 virus was an essential piece of information for determining timelines of infectiousness. Presence of SARS-CoV-2 virus can be detected in several ways:

- RT-PCR testing (see Chapter 6: testing): detects the presence of virus genetic material but does not reliably indicate viable infectious viral particles. It provides Ct values, which allow estimation of the amount of virus present in a sample. Ct values correlate with, but are not a predictor for, infectiousness[footnote 258]
- virus culture: detects the presence of live infectious virus, thus can be used as a proxy for infectiousness[footnote 19]
- rapid antigen: detects the presence of viral antigen in a clinical sample

RT-PCR testing was used to detect infection, and measurement of Ct values on RT-PCR allowed quantification of the amount of virus present in a sample. Serial Ct values, obtained using the same type of assay, were used to show the variation in viral load in an individual over time.[footnote 259], [footnote 260] Ct values were also used as a proxy for infectiousness. A reasonably firm correlation between cycle threshold values and the presence of live, infectious virus was established approximately 6 months into the COVID-19 pandemic through studies with serial sampling, RT-PCR testing and viral culture.[footnote 261], [footnote 262]

Early in the SARS-CoV-2 pandemic, clinical sampling was of variable quality and there was wide variation in diagnostic targets and sensitivity.[footnote 263] Clinical samples were obtained on relatively small numbers of individuals, often after symptom onset and without systematic follow up. Estimates of trends in viral load throughout the entire course of illness, as measured by RT-PCR, were available but low certainty until 6 to 8 months into the pandemic.[footnote 261], [footnote 262], [footnote 264]

Viral culture was used to infer infectiousness. Results were not available in the UK until 3 to 4 months into the pandemic, and at this time, studies assessing the presence of infectious virus through viral culture were few and based on small numbers of persons and datapoints.[footnote 265] The most timely datasets came from both international sources and PHE's laboratories, which shared results with expert groups at 6 months.[footnote 261]

Ultimately, longitudinal studies with serial sampling of cases, quantitative RT-PCR and viral culture allowed the most direct measures of the kinetics of infectiousness.[footnote 19],[footnote 259] As would be expected, SARS-CoV-2 viral load dynamics and kinetics of infectiousness were found to vary between individuals depending on symptom severity, immune response, prior infection and vaccination status.[footnote 259], [footnote 260], [footnote 266]

Timeline of discovery

Initially, knowledge of other coronaviruses (SARS-CoV-1 and MERS-CoV) was used to develop broad estimates of the expected kinetics of viral shedding of SARS-Cov-2, but this needed to be supplemented with pathogen-specific evidence.[footnote 267], [footnote 268], [footnote 269], [footnote 270]

Epidemiological studies of transmission chains provided the earliest estimates of infectious periods. Studies of clusters and chains of transmission, and early models of transmission dynamics, were used to infer the infectious period.

After 3 to 4 months, initial estimates of the infectious period, informed by longitudinal data on viral shedding, were available.[footnote 14], [footnote 50], [footnote 271], [footnote 272] The first viral culture results from the UK became available in April 2020.[footnote 265], [footnote 273] At this time, absolute numbers of data points and persons investigated remained small.

By mid 2020, accumulating data on viral dynamics (as measured by RT-PCR) had demonstrated a peak in viral load at the onset of symptoms, followed by a gradual decline in viral load.[footnote 263] Viral culture data suggested that cultivable virus levels were correlated with PCR values and time after symptom onset, and that viable virus could be isolated from pre-symptomatic cases, providing support for infectiousness of pre-symptomatic cases.[footnote 261], [footnote 262], [footnote 274] Longitudinal or cross-sectional sampling and culture showed that beyond 14 days the majority of infected people shed virus at amounts lower than could be cultured, suggesting they were no longer infectious.[footnote 261], [footnote 275], [footnote 276]

By the end of 2020 there was a robust understanding of viral dynamics over time. Further data emerged to suggest a strong relationship between Ct values and ability to recover viable virus.[footnote 19], [footnote 264], [footnote 277] Throughout 2021, comparisons of viral kinetics across people infected with different variants were undertaken, as well as across vaccinated and unvaccinated individuals.[footnote 259], [footnote 260], [footnote 278], [footnote 279]

Later in the pandemic, human challenge studies in controlled environments with systematic daily sampling allowed complete characterisation of the viral dynamics of infection, though these were often limited to young, healthy volunteers.[footnote 8]

Reflections and advice for a future CMO or GCSA

Most of the reflections are in the body of the text above, but in addition we would highlight the following.

Point 1

Scientific and medical advice will often need to be formulated on the basis of limited data.

This was the case for SARS-CoV-2 in early 2020 with respect to several areas, including, for example, asymptomatic transmission or spread via aerosols.

This cannot be avoided but it is critical therefore to explain in the advice the strength of the evidence and the degree of uncertainty about the conclusions, and to prepare the ground for the advice to change as evidence accumulates.

Point 2

> Understanding the pathogen and the disease was a global effort, particularly at the outset, and sharing data and expertise from the beginning was key.

Reports from China and Italy were critical in this respect. Personal and professional networks of CMOs, the GCSA, public health leaders and SAGE participants were invaluable. In some cases, rapid identification of counterparts in other countries was difficult and establishing clear points of contact in preparation for future emergencies would be helpful.

Point 3

> Gaining a clear understanding of the pathogen and the disease required an array of cross-disciplinary studies to be initiated quickly.

Many study types and disciplines were needed but some study designs set up early in the pandemic delivered useful evidence across multiple areas. These included:

- longitudinal cohort studies with relevant baseline measures and systematic symptom review
- linked or shared surveillance data with demographic details
- clinical studies of patients with severe disease

Point 4

> Building on and adapting existing research systems and networks was usually much faster than setting up new systems, but strong leadership, direction and coordination are required.

‘Peacetime’ processes were adapted, bringing together funders, researchers, CMOs, the GCSA and PHE (later UKHSA) to mobilise sufficient resources and stand up research rapidly.

Point 5

> Viral variants, population behaviours and population immunity changed significantly over time requiring continuation of studies.

In contrast to some infectious agents, pathogenesis and disease characteristics of COVID-19 continually changed over the first 2 years. This needed continual review and re-validation of tools, for example:

- revalidating assays for testing
- revalidating vaccine efficacy
- adapting models

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Chapter 2: disparities

Contents

Introduction

Infectious disease epidemics and pandemics usually expose and exacerbate existing disparities in society, such as those associated with deprivation, ethnicity, sex, age and sexuality.[footnote 1], [footnote 2], [footnote 3] The COVID-19 pandemic had some predictable and some less predictable disparities in health outcomes such as the striking age gradient in risk, and the risk of severe disease for people living with obesity.[footnote 4]

Some health impacts are distinct to certain infections – for example, the heightened risk of HIV for men having sex with men in the 1980s, or the risk of severe disease among young adults as well as the very young and the elderly during the 1918 to 1919 influenza pandemic.[footnote 5] Others appear repeatedly across different pandemics, such as more socio-economically deprived groups consistently experiencing greater risk of exposure to infection and worse health outcomes. [footnote 6], [footnote 7], [footnote 8], [footnote 9]

Some disparities observed in the COVID-19 pandemic would be expected to arise from an airborne respiratory pathogen – such as increased spread among people living in crowded households or individuals working in face-to-face settings with inadequate ventilation or protective equipment and relative sparing of rural areas.[footnote 10]

In addition to the direct health impacts, certain interventions put in place to control COVID-19 can themselves give rise to disparities – though the extent of the impact of COVID-19 control measures may never be fully understood due to lack of a clear counterfactual. For example, more deprived communities and younger people were disproportionately impacted by public health control measures in the short term, including closures to school and the hospitality sector. It is however difficult to say the size of the relative impact of not instigating these measures (and seeing potentially sustained high levels of community transmission) on these groups.[footnote 11]

This chapter sets out how we understood what the key disparities were, and briefly sets out some efforts in response to this evidence – though this is by no means exhaustive and work to reduce disparities continues.

What knowledge was needed and why it was important

Evidence from previous pandemics indicated that it was important to understand differences in infection risk, disease severity and outcomes between groups. These may be linked, or separate; for example, the need to

go to work may increase risk of acquiring disease but not severity, while living with obesity may increase risk of severe disease once acquired, but not of being infected.

Alongside this, it was also important to understand the differential impact among population groups of interventions introduced to try and control disease spread. For example, are the right communications getting to the right people, do people needing to isolate have the social, economic and practical support they need, and can everyone get adequate access to the necessary testing and clinical support? It was also essential to understand how different population groups responded to different communication channels, styles and languages, so that interventions could be adapted appropriately.

Disparities arising from the infection and the subsequent policy response will not always be immediately apparent and will instead emerge as the pandemic unfolds, and this was true for COVID-19.

How we found out the information

Our understanding of disparities related to SARS-CoV-2 exposure and COVID-19 outcomes rapidly evolved as the epidemic progressed across the UK. This was a result of the virus reaching increasing numbers of people and communities, and as research programmes, routine statistics and community engagement evolved to better capture the necessary data.

First wave

Early case reports and epidemiological studies on outbreaks provided some important early signals about potential disparities. As early as January 2020, reports from China indicated that COVID-19 led to worse outcomes among older patients and men.[footnote 12] Over the next 2 to 3 months, additional data emerged, primarily from China and Italy, suggesting that people with certain underlying health conditions and immunosuppression were at increased risk of disease and death.[footnote 13], [footnote 14] Early data from China also suggested low skilled workers were at increased risk of progression to severe disease.[footnote 15]

As cases began to appear in the UK, the First Few Hundred (FF100) enhanced surveillance protocol was commissioned, following World Health Organization (WHO) protocols and in line with previous pandemic response for MERS-CoV and H7N9 influenza.[footnote 16], [footnote 17] This provided basic demographic data and enhanced surveillance of clinical presentation on the first few hundred cases of SARS-CoV-2 infection, allowing for an initial detailed description of people affected.[footnote 18] Early indications of key populations most affected were highlighted – for example, the increased clinical risk in people with underlying health conditions. However, it is worth

noting that FF100 investigations are prone to biases (for example, where the first few hundred cases may be returning travellers with similar socio-economic status or health status). This is also covered in Chapter 1: understanding the pathogen.

Several surveillance systems and routine data sets were in place before the pandemic, such as the Second Generation Surveillance System (SGSS) laboratory monitoring and the Office for National Statistics (ONS) death certification. These systems indicated early on that exposure and infection risk were disproportionately high for those working in frontline care or other in-person service occupations, such as transport and cleaning. Although the systems were unable to provide detailed reasons for this, they were likely to be multifactorial and possibly include some non-work risk factors in addition to occupational ones.[footnote 19] Some bespoke surveillance systems were also designed from scratch – for example, to count COVID-19 deaths in hospitals and COVID-19 attendances and admissions to NHS hospitals.

Hospital admission data then rapidly began to produce signals on potential disparities: by February 2020 there was evidence of increased risk of hospital admission for older adults, men and those with certain underlying health conditions.[footnote 20] The regular publication of intensive care data also supported a rapidly growing understanding of ethnic disparities in the UK: in the first wave, statistics highlighted high rates of hospitalisations among patients of black and Asian ethnic groups compared to white ethnic groups.[footnote 21] However, ethnic disparities were often confounded by deprivation and living in areas with high prevalence. As the pandemic went on, patterns of risk for both infection and severe disease changed as the epicentre shifted to areas with different ethnic makeup and as vaccines were rolled out with differing levels of uptake across different communities.

Testing data also supported understanding of disparities: in England, COVID-19 laboratory reporting forms included age and sex from the outset, and ethnicity information was then added by linking laboratory surveillance data with Hospital Episode Statistics data sets.

In order to properly monitor and report on characteristics linked to health disparities (such as ethnicity), there was a need to rapidly link data and enhance routine data sources with clinical and demographic information. This was achievable following rapid issuing of a Control of Patient Information (COPI) notice (for more details see Chapter 4: situational awareness, analysis and assessment). This expedited rapid data sharing between government organisations without requiring unduly long paperwork and approval processes which previously could have taken years.

There was also a need for in-depth reviews alongside these data sets, such as the report ‘Disparities in the risk and outcomes of COVID-19’, published in June 2020 by Public Health England (PHE).[footnote 22] This report was largely undertaken on cases presenting to hospital with a clinical need where testing was concentrated. It highlighted important disparities by age, ethnic group,

sex and occupation, likely to reflect disparities in both infection risk and clinical severity. It was not exhaustive and was unable at the time to adjust for some relevant factors in all analyses, such as underlying health conditions, which may affect some groups more than others. It highlighted however some important areas for further investigation, prompting a series of actions to address and mitigate this issue which were documented in reports published by the Equality Hub and Race Disparities Unit.[footnote 23]

Public engagement exercises were used throughout the pandemic to understand the experiences and drivers of observed disparities in COVID-19 health outcomes. For example, an in-depth public engagement exercise with representatives of key affected groups alongside a rapid literature review and qualitative analysis culminated in the publication of another report 'Understanding the Impact of COVID-19 on Black and Minority Ethnic (BAME) Communities', which produced a series of recommendations on how to better understand and mitigate the impact of the pandemic on ethnic minority groups.[footnote 24] This included a clear ask for improved data collection on ethnicity, occupation and faith in all routine clinical data and death certification. Alongside this, weekly calls between the CMO's office and directors of public health helped highlight emerging issues in their communities.

Finally, several studies established in the early phases of the COVID-19 response provided an invaluable contribution to the understanding of COVID-19 disparities. These included the ONS COVID-19 Infection Survey, which provided weekly estimates of infection and immunity, and enabled detailed analyses of disparities such as occupation, ethnicity and deprivation.[footnote 25] The Vivaldi study, meanwhile, collected qualitative and quantitative data on care homes to understand working conditions and the spread of infection and immunity in care home populations.[footnote 26] Its findings have been used to inform the ongoing policy response, including vaccine recommendations. Other studies on specific groups and settings, such as for children and adults with learning disabilities, homeless shelters and prison populations, were helpful in exploring the impact of the pandemic on these groups.[footnote 27]

The QCovid® tool, using population health data to predict outcomes from COVID-19 for different groups, also helped inform the response – for example, vaccination prioritisation. Although designed originally around likely clinical risk factors, it was one of the few tools to include socio-economic deprivation as a component of risk alongside clinical risk as data were refined. It was used slightly differently across the UK – this is explored in more detail in Chapter 8: non-pharmaceutical interventions.

Ongoing response

The regular and transparent publication of disparities data was helpful in maintaining a public and professional focus on disparities as they emerged and changed. Although some disparities data, such as hospital admissions by age and sex, were published from the outset of the pandemic, there was a need to expand and update both data collection and data publication. By the second wave the PHE weekly COVID-19 surveillance report had been expanded to include a wider range of disparities data, and other analyses and research also expanded to examine disparities. The publication of the PHE COVID-19 Health Disparities Monitoring for England (CHIME) tool from May 2021 onwards ensured regular reporting of COVID-19 disparities for a number of determinants and outcomes and is publicly available for use by a range of stakeholders.[footnote 28] In common with most other surveillance systems during the pandemic, CHIME did not have access to data on underlying conditions so this limited the extent to which it could adjust for comorbidities in assessing disparities. Alongside these regular publications, the Scientific Advisory Group for Emergencies (SAGE) regularly reviewed evidence and data on disparities and published its minutes to support public discussion and response to these issues.[footnote 29]

The surveillance landscape was regularly assessed and mapped to identify gaps in disparities data. As a general principle, healthcare and disease surveillance systems need to be designed at the outset with reporting forms that included information on key protected characteristics.[footnote 30] This is to ensure that disparities linked to any of these characteristics could be assessed at the earliest stages of the pandemic. There was also an ongoing need to secure public trust in data gathering and usage, ensuring usage of data was transparently communicated.

Important factors in the COVID-19 pandemic

Infection risk

Certain occupational groups such as factory workers, healthcare workers, emergency service workers, social care workers and high contact professions, such as taxi drivers or security professionals, were shown to carry a heightened risk of exposure to infection. Living in urban and more deprived areas was an additional risk. In major cities, infection rates were initially higher than in rural settings, and more people reported participation in essential daily activities such as using public transport and attending work or education.[footnote 31] Although to some extent this trend has persisted throughout the pandemic, urban areas benefitted from a great deal of national attention and consequent mitigation measures. Rural areas, which had largely been spared in earlier waves, came to experience high incidence

in later waves due to lower immunity levels after most national public health control measures had lifted.

Crowded and multi-generational housing is a further risk factor commonly linked to infectious disease spread.[footnote 32] Overcrowded housing is linked to socio-economic status and in the UK is more common in Bangladeshi, Pakistani and black African groups compared to white British.[footnote 33] Importantly too, shared accommodation settings such as those for people experiencing homelessness and rough sleeping presented a significant risk of transmission for an already highly vulnerable population experiencing multiple existing socio-economic pressures and health needs.[footnote 34] The 'Everyone In' initiative, launched in March 2020, aimed to provide safe accommodation for people experiencing homelessness and rough sleeping and was widely credited with saving lives during the pandemic.[footnote 35]

Severe disease and mortality

Since the start of the pandemic, age has been the strongest risk factor for COVID-19 hospital admission and mortality,[footnote 36] with older adults at high risk and children and young people at very low risk of severe outcomes.[footnote 37] Mortality rates from COVID-19 in the most deprived areas of the country were more than double that found in the least deprived areas, with differences remaining after adjustment for age, sex, region and ethnicity. As a single group, ethnic minorities experienced higher all-cause death rates and death rates from COVID-19 compared to those of white British ethnicity, with relative differences varying throughout the pandemic and across different ethnic groups.[footnote 38] In the working-age population, COVID-19 death rates were consistently and markedly higher for men than women throughout the pandemic.[footnote 39]

Another group at particularly high risk for severe disease and premature mortality were those with a disability. In the first wave, 6 out of 10 deaths in England were among people who reported having a disability.[footnote 40] Research based on the learning disability register found a persistent, marked increased risk in COVID-19 hospitalisation and mortality for people with a learning disability – though it is important to note that there are major limitations with the learning disability register as a robust assessment tool, with wider coding for learning disability, and that not all analyses adjusted for underlying health conditions.[footnote 41]

Co-morbidities such as diabetes, severe asthma and obesity were identified as risk factors for poor outcomes, and were more prevalent in more deprived and in some ethnic minority groups. Linked primary care records of over 17 million adults with over 10,000 deaths between February and December 2020 found that while comorbidity did explain some of the different death rates by ethnicity, people from black and South Asian ethnic groups were both more likely to test positive and more likely to die from COVID-19 during the first wave compared with people from white ethnic groups after adjustment for deprivation, age, sex and comorbidity.[footnote 42] Analysis of

the second wave found that while differences in testing positive and higher death rates among South Asian ethnic groups remained, they were far less stark for black ethnic groups.

Disentangling the principal drivers was often complex because of the overlapping nature of many of the risk factors. For example, some South Asian populations might have higher probability of being in contact professions such as taxi driving or care work, higher rates of diabetes, more multigenerational households and being in an area of enduring transmission such as in the north-west of England. Some populations may use care and testing differently or face barriers in their access. Working out which was a risk factor and which was a confounding factor was inevitably complex and some residual confounding was likely.

Impact of public health measures

High case rates during the pandemic led to pressures on health and care services which in turn impacted different population groups in need of health and care support. Measures put in place to mitigate transmission, too, impacted interactions with health and care services for many – for example, visiting restrictions. This is covered in more detail in Chapter 10: improvements in care. Non-COVID-19 clinical harms were worse for some groups. For example, there was a greater reduction in routine elective admissions for care home residents compared to the general population, and routine referrals to hospital care fell 90% for children and young people in the first wave.[footnote 43], [footnote 44]

Many people saw a deterioration in mental health during the pandemic; the impact was particularly felt in some groups, such as women who reported worse mental health during the pandemic than men.[footnote 45] Disparities in mental health outcomes in unemployed people and those experiencing financial insecurity widened during the pandemic.[footnote 46] The public health response to the pandemic had wider impacts on the economy, wellbeing and education. Children and young people missed significant amounts of face-to-face education with impacts including lost learning, poor mental health and a reduction in the number of safeguarding referrals.[footnote 47]

Widespread closures in sectors such as hospitality, leisure and tourism had significant economic impacts for individuals employed in these sectors, a greater proportion of whom were women. People in ethnic minorities were also more likely to work in insecure and casual forms of employment which were impacted by pandemic control measures. While the Coronavirus Job Retention Scheme (‘furlough’) provided some protection against unemployment, individuals on furlough experienced a 20% reduction in wages and this was more common for people on low-income wages and part-time workers.[footnote 48] Rural and coastal areas were disproportionately impacted by some of the public health measures used to control spread, with these areas experiencing:

- an increased impact on hospital waiting times
- a reliance on the tourism and hospitality sector
- high levels of digital exclusion and an ageing population [footnote 49]

Areas of enduring transmission, such as Leicester and the north-west of England, were also disproportionately impacted by both continual transmission and long-running measures to bring this down – for example, in disruption to education.

The reasons for these disparities are complex and involve a range of social, economic, behavioural and biological risks.[footnote 50] Disparities were the result of a complex interaction between existing disparities, the progression of the epidemic across the country (for example, which areas saw early seeding of infection), and the measures taken to control disease spread. For some communities, a relative lack of trust in government or the health service resulted in mistrust of national communications, which was compounded by disparities exposed by the pandemic. At times responses and communications were not appropriately tailored to different communities. This was sometimes exacerbated by interventions directly aimed at certain higher risk groups, leading to actual or potential stigmatisation by implying certain groups were more vulnerable to COVID-19 or more likely to transmit the virus. Tailoring messages for the highest risk groups without increasing stigma can be a very difficult balance to navigate in epidemics and pandemics, and was particularly important in the earlier stages (for example, for the Chinese community). It was seen previously – for example, in HIV and more recently in Monkeypox.

What was done in response

This sets out some elements of the response but is by no means exhaustive. Efforts to minimise disparities sat across a number of organisations and individuals and continue to evolve today.

Following publication of the PHE report on COVID-19 disparities in risks and outcomes, the Cabinet Office Race Disparity Unit was tasked to lead cross-government work to address the report findings, with the activities undertaken summarised in a series of reports.[footnote 51]

Actions to address disparities initially focused on reducing the risk of infection, for example, the government published guidance on how to make workplaces more secure for individuals unable to work from home, including specific practical guidance for occupations at higher risk of exposure such as taxi drivers. Guidance and infographics for the public were translated into the most commonly spoken languages, and communications campaigns worked closely with the third sector to ensure local dissemination into communities.

Throughout the pandemic, different testing programmes were implemented to address certain disparities. This included mass asymptomatic testing programmes in care homes, the NHS and across the education sector as well as targeted community testing in areas of high or enduring transmission. Targeted community testing programmes were delivered through local authorities to benefit from in-depth knowledge of local community needs, trusted voices and detailed local data.[footnote 52]

Other efforts to tackle COVID-19 disparities were focused on building vaccine confidence and promoting vaccine uptake among those groups that were more hesitant about vaccination. This required detailed discussions to unpick where the issues were. Delivery of the mass vaccination programme and targeted work with specific communities has been a result of a partnership approach between national and local government, health agencies, and the voluntary and community sector. One key component of this response was the Community Champions scheme launched in January 2021 which enabled councils and voluntary organisations to develop local networks of trusted local champions to provide advice about COVID-19 and the vaccine programme.[footnote 53]

Discussion

Disparities in COVID-19 arose because of differences in infection risk, risk of severe disease or mortality, non-COVID-19 clinical harms and the wider impacts of public health measures to control the pandemic. The pattern of disparities highlighted the need to consider, as much as possible, disparities according to the following determinants:

1. Protected characteristics: as defined by the Equality Act (2010):

- age
- disability
- gender reassignment
- marriage and civil partnership
- pregnancy and maternity
- race, religion or belief
- sex and sexual orientation

2. Socio-economic circumstances such as:

- deprivation
- occupation (particularly key workers)
- geographical region

3. Inclusion health groups: those who have been socially excluded typically experience multiple overlapping risk factors for poor health (such as poverty, violence and complex trauma), experience stigma and discrimination, and are not consistently accounted for in routine data sets. In the UK, the concept of inclusion health has typically encompassed people experiencing homelessness, Gypsy, Roma and Traveller communities, vulnerable migrants and sex workers, among others.[footnote 54]

It was essential to gather data and information about the existence and drivers of disparities in this pandemic – both quantitative and qualitative – and this required multiple different methodologies. Key informant interviews and focus group discussions, and more generally early engagement with communities, were vital to effectively tailoring interventions and anticipating future challenges in implementing any large-scale intervention. It was a resource-intensive method but has held great value. Access to major data sets (for example, via 'OpenSafely') has also enabled continuous surveillance and research on clinical and health outcomes from COVID-19, though there were occasional issues with sharing, linkage and timeliness of data (this is covered in more detail in Chapter 4: situational awareness, analysis and assessment). In the future, this could be better supported by joint working with and between local government, the health service (in particular data and digital teams), central government and academia.

A routine approach to evaluation and research on the direct and indirect benefits and harms of the public health response on local population groups and communities was also important from the start of the pandemic. This could help identify disparities more rapidly and facilitate the rapid adaptation of interventions to better meet the needs of specific population groups and minimise harms.

The data and information needed to understand disparities was often sensitive and was being asked of communities with relatively low trust in government organisations and understandable concerns about privacy and the use of their data. It has therefore been important, as it will continue to be beyond this pandemic, to engage closely with communities and to work with trusted organisations to understand disparities and avoid extractive methods of research in favour of close engagement and coproduction. This is likely to be true of any future pandemic or epidemic.

It was also important to empower and adequately resource local areas to adapt and respond to the specific needs of their communities, designing and implementing approaches with the communities most impacted. The long-term impacts of these disparities are yet to be fully felt, and an inclusive pandemic recovery programme will be key to ensuring that the same populations disproportionately impacted during the pandemic will not suffer ongoing disparities throughout the subsequent socio-economic recovery.[footnote 55], [footnote 56]

Our response to future pandemics will be strengthened by understanding these long-term effects and by improving our understanding of the key drivers of health and inequalities, and of the different needs of different communities. This will enable local and national policymakers to improve community resilience between pandemics to better mitigate harms in the future.

The findings of this pandemic have led to a renewed effort to address pervasive inequalities in health in some areas – for example, in the work of the NHS in recovery including equity audits of waiting lists and the Duty to Reduce Inequalities on the emerging integrated care boards in England. The pandemic has reinforced the message seen in many previous pandemics that those already marginalised, socio-economically disadvantaged and suffering poorer health outcomes are likely to be at increased risk during a pandemic. Routine data sets (particularly for health and care), surveillance systems, research and planning exercises therefore need to involve these groups while keeping flexible to evolving evidence on the specific risk factors for any new pathogen in the future.

Reflections and advice for a future CMO or GCSA

Point 1

> This pandemic, in common with many others, reflected and in many cases exacerbated existing inequalities.

Understanding how the combination of existing inequalities and pathogen-specific vulnerabilities affect individuals across the population was essential to inform the policy and public health responses.

Point 2

> Research on where the disparities were, what their causes were and how best to reduce them needed to begin from the outset of the pandemic.

Some signals only come when the epidemic reaches a particular stage or hits a particular area. Some disparities also changed with the changing epidemic (for example, as waves hit different areas of the country).

Point 3

A wide range of qualitative and quantitative research methods were needed to understand disparities.

These included:

- population-level surveillance
- research directly with affected groups
- surveys and in-depth reviews alongside routine data sets

Properly completed demographic and other fields in a range of data sets, and linkage of data, were particularly important in understanding disparities – and this can be strengthened in ‘peacetime’.

Point 4

Continual dialogue with local communities was important in understanding risks and vulnerabilities, and to co-design effective responses at a hyper-local level that may not be picked up in larger, national data sets or research.

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Chapter 3: research

Contents

Research and scientific advice are cross-cutting themes that are relevant to much of this report, and so we set out a summary here of the structures and practices that have been important in this pandemic for both research and scientific advice, alongside our reflections.

Introduction

In all pandemics and major epidemics the initial response depends on sparse information, and in the case of a new pandemic such as COVID-19 there will often be no proven medical countermeasures. The key purpose of research is:

- to understand the disease itself
- to improve information for policy and clinical decision-making
- to optimise existing clinical treatment
- to provide the tools to move from social to medical countermeasures

The central role of research in supporting the response is sometimes underestimated by non-medical planners and policymakers. Since the mid-nineteenth century science has always been, and will almost always be, the exit strategy from pandemics and epidemics. Throughout the COVID-19 pandemic research has been important in informing the response.

CMOs and GCSAs had a central role in making the case to prioritise science from the earliest stages, supporting the direction and co-ordination of research as well as interpreting its outputs to policymakers and the public. This is likely to be true in future pandemics and large epidemics. Science and technical meetings in January 2020 considered research funding needs and coordination between funding agencies and across different disciplines including the social sciences. In the initial coronavirus action plan laid out in early March 2020 the government priorities were ‘contain, delay, research, mitigate’. Many policymakers were surprised that research was given this priority at that stage, but it was in our view essential from the start to undertake the research to lay the groundwork for any realistic exit from the pandemic.

The ultimate success of scientific endeavours throughout this pandemic has however relied on the collective efforts of thousands of researchers, clinical professionals and the public in undertaking research. We have been struck by the selflessness of the public in taking part in trials and observational studies in great numbers; over a million took part in the UK alone. Their efforts enabled us collectively to test and then deploy life-saving interventions throughout this pandemic at an unprecedented speed. The extraordinary efforts of scientists, and of clinicians who undertook clinical research while treating a major influx of severely ill patients was remarkable.

Unsurprisingly, in many aspects of the pandemic the response was best in those areas where the UK already had strengths pre-pandemic. Pre-pandemic research preparation was also important in enabling rapid initiation of various studies and was stronger in some areas than others.

At the outset of the pandemic the UK had:

- a strong and established clinical, public health and biomedical research sector
- broadly based but reasonably centralised processes to fund and manage publicly funded research
- a relatively large and highly skilled research-focused workforce and research infrastructure
- expertise across a range of relevant disciplines – particularly in clinical sciences

A strong industrial research and development base was also present in some areas, with a skilled and experienced workforce. Public sector research establishments such as the Office for National Statistics (ONS), the Health and Safety Executive and Public Health England (PHE, latterly the UK Health Security Agency (UKHSA)) were also important in enabling rapid commissioning and execution of research. It was also important to have a rigorous and experienced regulator for therapeutics and vaccines in the Medicines and Healthcare products Regulatory Agency (MHRA), and for research ethics in the Health Research Authority (HRA). The UK also had in the NHS and devolved equivalents a workforce with a long tradition of basing clinical decisions on trial data, and undertaking trials and observational studies.

On the other hand, there were areas where the UK was not as strong as other countries, and these are equally important to reflect upon. The UK's diagnostics industry, for example, was not as large as some other high-income countries that were able to more rapidly step up large-scale testing operations.

In any emergency there are 4 key considerations for scientific research:

1. What are the most important questions to answer at a given point in time – and what will be the future ones research needs to start for now?
2. How can these be answered most effectively and efficiently with the tools available and involving the right people? This often required a degree of pragmatism.
3. How can the outputs of research be shared, interpreted and translated into scientific advice at speed to support practical decision-making, but without

losing rigour?

4. What are the practical applications of science that will be needed and how will this be achieved?

Under normal circumstances assessing the relative priority of different disease areas and mobilising funds takes much of the time before research can be conducted. The clear international priority of combatting COVID-19 made this much faster. Similarly, many processes which normally are time consuming, including data sharing and scientific and ethical review, were made extremely rapid – often taking days rather than months. Regulators including the HRA and the MHRA turned things around at remarkable speeds, without losing rigour. This was however at the expense of a lot of otherwise excellent non-COVID-19 research which was deprioritised or stopped altogether and has proved slow to restart.

There is always some degree of tension between speed and strength of scientific methodology, but this is much more acute during a medical emergency. Methodologically weak research is potentially dangerous because it gives a false sense of certainty and can mislead. At several points in this pandemic there was pressure to agree widespread deployment of treatments before trials or other research had been undertaken and analysed based on weak (or absent) evidence. Helping to make the case for proper studies and then waiting for evidence was a key role of senior medical and scientific leaders in the system. NHS staff were extremely disciplined in randomising new treatments to trials rather than just giving them based on theory and this paid dividends in rapid results with convincing answers, whether positive (such as dexamethasone, various vaccines) or negative (such as chloroquine, HIV drugs, ivermectin). For example, even at the peak of the first wave some hospitals recruited 60% of eligible patients into the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial.[footnote 1]

This chapter does not go into the details of the hundreds of studies undertaken, or even the major ones, some of which are covered in subsequent chapters. It simply aims to identify some common themes that may prove useful in subsequent pandemics and epidemics.

How the most important questions changed over time

The relative importance of different kinds of research for policy and practice changed as the pandemic evolved. In part this was due to the urgency of the decisions being taken, but largely because different study designs were inevitably going to report along different timelines. They all needed to be running from as soon as possible after COVID-19 was clearly likely to be a global threat. Many of the major studies were approved and launched within a few weeks of the first cases of COVID-19 being reported outside China,

although it was accepted that some of them, especially clinical trials, would take many months to years to provide definitive results. The sections below set out some broad areas of enquiry, some of which are covered in more detail in other chapters of this report.

Understanding the virus and the disease

(For more detail on this see Chapter 1: understanding the pathogen.)

In the first 3 months as COVID-19 moved from being a localised disease in China to a pandemic, basic epidemiological and clinical data were urgently needed to inform public health and clinical advice. Key variables included:

- mortality by age and other characteristics
- the basic reproduction number (R0) and doubling time
- probable routes of transmission and their relative importance

Much of this was initially from Chinese scientists and clinicians, and then replicated in other countries, especially Italy with a more similar age structure and health service to the UK. Having the genotype publicly available early on due to the work of the Chinese and other scientists was essential to the development of polymerase chain reaction (PCR) tests and the initial work on possible vaccine candidates, including in the UK. The global sharing of genotype information has been a critical part of the response to COVID-19 throughout the pandemic to date. We consider these are likely to be common to the majority of future epidemics. The rapid establishment of COVID-19 Genomics UK consortium (COG-UK) supported viral genotyping at scale which enabled an understanding of viral spread and evolution.

Modelling data were important in helping to refine the key epidemiological variables and helped inform advice on early policy and public health decisions. In the initial phase of the response, modelling research played a critical role. Modelling is covered in Chapter 5 in more detail.

Studies on virology and immunology were important to inform an understanding of the clinical picture and potential interventions. Early establishment of sample collections was important.

Understanding the impact of the pandemic and of different interventions

Observational clinical studies were also needed both to inform early policy and clinical practice. The First Few Hundred (FF100) study was specifically designed to answer clinical questions early and something similar needs to be undertaken for any pandemic or epidemic. These have the advantage of producing early data when there are none, and the disadvantage that early

cases tend to be atypical. Recognising this, several important clinical and cohort studies were conceived or launched in these early months. These included:

- the International Severe Acute Respiratory and emerging Infection Consortium's (ISARIC) COVID-19 Clinical Information Network (CO-CIN) study of patients from across the UK with severe disease
- the SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) study of healthcare workers
- the Easter study in care homes
- the Vivaldi study

ONS data and data on disparities in outcome including by ethnicity and geography from PHE (subsequently UKHSA) became very accurate (for more details see Chapter 2: disparities). Observational data from combined studies were increasingly granular and influential as the first wave progressed and going into the second wave, meaning that the epidemiological and clinical understanding of the disease was substantially better in late 2020 than in March 2020. This also allowed for more accurate modelling. The combined effect was that the scientific advice to inform policy could be much more certain from the start of the second wave onwards. Routine data flows and interoperability improved and became an important resource for research.

Observational data helped change the scientific consensus on several key variables over this time. Important examples for public health measures included:

- the relative contribution of asymptomatic transmission
- the relative contribution of aerosols compared to droplets
- the risks for people from different ethnicities, for children and for those living with obesity

Examples for clinical practice included the clinical course of severe disease, the role of thrombosis and anticoagulation, and mechanical ventilation.

COVID-19 led to significant experimentation with different ways of deploying mass testing of different forms to try to improve clinical outcomes, reduce transmission and provide practical isolation advice. Some of this was conducted with formal scientific methodology. Mass testing was most central to thinking during the second wave, after reliable rapid tests usable by the public had been developed but before a vaccine had been deployed at scale. The development of tests and their deployment are covered in Chapter 6: testing.

Building knowledge of medical countermeasures

In the case of a variant of a known pathogen such as influenza, the normal early research would be to determine whether existing medical countermeasures to that pathogen (drugs, vaccines) work or can be adapted. In the case of COVID-19 there were no coronavirus-specific human medical countermeasures. An assessment from first principles was undertaken, which informed early drug trial candidates (most of which did not work). A decision was therefore taken to trial existing drugs with some theoretical reason they might work, largely undertaken in the public sector, while accelerating development of coronavirus-specific treatments in the pharmaceutical industry with some public sector support. The trials of existing drugs were expected to take months, and development of new drugs years. The first readouts from clinical trials of existing drugs occurred before the second wave peaked, with the most important ones being those which altered the immune reaction to COVID-19 (steroids and other rheumatology drugs) rather than antivirals. Drugs specifically for COVID-19 inevitably took longer. The development and testing of therapeutics and vaccines is covered in more detail in Chapter 9: pharmaceutical interventions.

Studies to develop a vaccine for COVID-19 started within weeks of the genotype being published. It was supported by clinical trial data within 9 months and available from midway through the second wave in the UK. The one general point it is worth making here is that the extraordinary speed of development and effectiveness of viral vector and RNA vaccines was a surprise to almost all scientists. On the positive side this demonstrates how fast a vaccine could be developed for the next pandemic, if it is achievable. There is a danger this falsely reassures some policymakers that a vaccine can be produced at this speed for the next pandemic. The last major pandemic was HIV where there is still no effective vaccine, despite decades of serious investment and scientific effort.

Mechanisms to get research studies prioritised and underway

From the start of the pandemic there were several concurrent risks which are likely to remain a theme in future pandemics including:

- the risk that research would not be undertaken because of the urgent need to act. This can lead to research being perceived as a luxury or getting in the way of action, in turn leading to an endless cycle of unevidenced intervention and the science for an exit not being undertaken. This risk is exacerbated where clinical research staff have to be reassigned to provide clinical care

- multiple studies launching together competing for resources so that none of them had sufficient statistical power to get a definitive answer in a realistic timeframe. This was seen in many countries around the world
- research would only be undertaken in the teaching hospitals, slowing its completion and raising equity and generalisability concerns
- novel interventions (such as new drugs) would be prioritised over the more easily scalable testing of existing interventions (such as steroids)
- the risk of not translating research findings into practical deliverable products – there is a tendency to underestimate the needs of development and deployment science leading to delays in the pull through and implementation

At all stages, but particularly in the earliest months, there were hundreds of potential questions to answer about the pathogen, the disease, their impacts and possible effective interventions – and these therefore required careful but rapid prioritisation. Doing so involved multidisciplinary panels and committees drawing on a range of scientific expertise – for example, in the 'Urgent Public Health' (UPH) badging panel which was activated in January 2020 to determine the most important COVID-19 research for priority funding and resource. This is covered more fully in Chapter 9: pharmaceutical interventions. The National Institute for Health and Care Research (NIHR), the Medical Research Council (MRC) and NHS England in particular used this mechanism in England to prioritise their resources, and this was supported by the CMOs and national clinical directors. These panels directed resources to a limited set of studies considered of national importance, at the expense of others. National panels could take account of international panel views of priorities such as those convened by the World Health Organization (WHO). Later, the 7 strands of the National Core Studies programme brought together senior experts to identify research projects, integrated teams and infrastructure needed to answer essential policy and operational questions ranging from transmission risk in specific setting or groups through to immunity and long COVID. This coordination, cross disciplinary working and focus on implementation was important. With a limited ability to test treatments, the COVID-19 Therapeutic Advisory Panel collated expert views on which drugs to bring into major trials to get answers on the most promising.

Not every observer will agree with every decision taken by these prioritisation panels, especially knowing with hindsight which studies and interventions worked. The alternative, which was potentially multiple uncompleted, underpowered or slow-to-report studies, would however almost certainly have been worse, and the relative contribution of UK science to the global stock of knowledge about COVID-19 in the first 2 years supports the overall approach. Large studies on the few most important practical questions

enabled us to get results fast, though this approach does not work for all potential research interventions and so a range of approaches will be needed. The UK approach was successful for phase 3 and 4 trials but less effective for phase 1 and 2.

In addition to sifting proposals from researchers, interdisciplinary expert groups helped to review current evidence and flag gaps in the evidence base to highlight further questions that might have been missed. They were supported by a number of evidence review teams. Throughout the pandemic, ongoing collaboration between scientific experts (including the Scientific Advisory Group for Emergencies (SAGE)) and policy and operational teams, helped determine which questions were most needed to inform the response as well as what science could reasonably deliver to answer them in a given timeframe.

Close working between government experts and academics was important in targeting resource to high priority research in both directions. There were routine updates – for example, between the National Immunisation Schedule Evaluation Consortium (NISEC) and UKHSA, the Joint Committee on Vaccination and Immunisation (JCVI), the Deputy CMO (DCMO) and the Vaccine Task Force to keep NISEC's clinical research relevant to the UK Immunisation Programme. The New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) also worked closely with the UK's major platform trial for repurposed therapeutics, RECOVERY. It was also helpful to communicate regularly across all 4 nations of the UK, and joint UK GCSA and CMO forums supported this.

Conducting research swiftly and efficiently

Early coordination, rapid funding mechanisms from UK Research and Innovation (UKRI), MRC, NIHR and the joint CMO and GCSA fund enabled a fast start.

For clinical research, once broad prioritisation had happened, swift ethical review and regulatory review by HRA and MHRA was key.

A UK CMO letter to clinicians (1 April 2020) supported the UPH badging process for clinical studies by asking the NHS to prioritise recruitment to UPH trials, and to desist from prescribing off-licence drugs outside of trials.[footnote 2] UK CMOs also supported recruitment for priority trials in the NHS by writing to doctors to encourage enrolment and by mobilising the NIHR and equivalent workforce in devolved nations in April and May 2020.[footnote 2], [footnote 3] Central direction helped clarify research priorities, and academics worked at speed and with innovative approaches to complex issues to make the prioritised questions researchable.

Sleeping protocols and contracts designed pre-pandemic for emergencies helped stand up research rapidly – for example, CO-CIN, which built on the inFLUenza Clinical Information Network (FLU-CIN) established during the 2009 to 2010 H1N1 influenza pandemic. From the outset of the pandemic, there was a need for management protocols, data collection protocols and ethics approvals to collect samples and data rapidly, as well as plans and a repository to enable data sharing and linkage. Further examples are given in Chapters 9: pharmaceutical interventions, and Chapter 10: improvements in care.

Wider practical coordination across government, the private sector, the NHS and academia was also needed – for example, to ensure sufficient tests were made available to support vaccine trials and key observational studies at a time when testing capacity was under pressure. These relationships and processes helped keep researchers apprised of policy and operational challenges so that their work adapted as necessary throughout the pandemic, and kept government clear on what research could realistically deliver, when, and where the blocks to doing this might lie.

It was, as is usual in emergencies, most efficient to adapt existing infrastructure and processes where possible to rapidly commission and undertake research once priorities were set. This included using the NIHR's clinical research staff to support trials, engaging Health Protection Research Units (HPRUs) or using existing research consortia such as NISEC. Setting up new systems invariably takes longer.

There was a need to use multiple approaches to funding or commissioning new research in order to move things along swiftly. Broadly, these approaches in the UK were:

- open calls for research through funders. This included rapid calls for research that were set up in the first months of the pandemic, longer term research calls, and targeted calls for research on particular topics such as an NIHR and UKRI call in early summer 2020 for research to explain and mitigate the disproportionate death rate from COVID-19 among people from black, Asian and minority ethnic (BAME) backgrounds, including BAME health and social care workers
- direct funding for urgent research, which drew on existing funding release mechanisms – such as the Fighting Fund which distributed NIHR funding for research following joint agreement from both CMO (England) and GCSA. Work funded through this route included the Oxford vaccine, CO-CIN and COG-UK
- support for commercial studies – for example, by mobilising clinical research networks to support Novavax vaccine trials

A wide range of disciplines have been important in supporting the pandemic research response including biological, medical and pharmaceutical sciences, social sciences (including behavioural science), data sciences, epidemiology, immunology and engineering among others.

It should be acknowledged that not every intervention was easy to test. Established methods for testing drugs, vaccines and diagnostics, augmented by platform trials, allowed rapid progress. The established science of advanced manufacturing then enabled production of vaccines and therapeutics at speed. Testing social interventions or indeed the effects of face coverings was much harder.

Sharing, interpreting and translating research outputs into scientific advice at speed

During this pandemic there was a global shift in research practices, with open access and pre-prints widely available from early on and experts able to review evidence as soon as it was available. In March 2020, chief science advisers from 12 countries wrote an open letter to journals outlining their support for open access practices, building on experience of previous epidemics on sharing data.[footnote 4], [footnote 5] There is no doubt these practices were beneficial to pandemic response and should be supported in a future pandemic. The rapid review processes did, however, present some difficulties in some cases in interpreting the evidence, especially when rigorous peer review processes were bypassed and there was a pressing need for expert review of research evidence. Review is important not only to translate research outputs for decision-makers, but also to examine their methods and implications in depth.

The public and general media engaged with research to a degree not seen before, debating its outputs and methods in public forums and often with unprecedented levels of discussion between the media and scientific experts. Organisations such as the Science Media Centre also helped explore diverse expert views and summarise latest evidence at speed.

SAGE had a central role in interpreting the latest research evidence and its relevance to UK policy, determining confidence in research outputs, summarising where consensus views were clearest, and highlighting further questions that needed research focus. The breadth of disciplines present at various SAGE meetings where new research was considered is notable; a list of participants is publicly available.[footnote 6] Alongside existing sub-groups of SAGE such as the Scientific Pandemic Influenza Group on Modelling Operations (SPI-M-O), further groups were set up to provide regular specialist advice on key topics such as:

- children and young people
- care settings
- environmental modelling

Scotland and Wales also set up national groups of experts to consider the latest evidence for their local contexts, the COVID-19 Advisory Board and the Technical Advisory Cell respectively. After a short delay SAGE minutes and papers were made publicly available from early in the pandemic and provide summaries of emerging evidence with confidence statements alongside to aid decision-makers and the public in interpreting research outputs.[footnote_7]

Clinical research was generally assessed by clinical panels, existing expert groups and individual clinicians reviewing evidence relevant to their clinical practice, though the speed and volume of review needed could make this challenging. Research for vaccine scaling, high-tech manufacturing and production required industrial as well as academic scientists.

Reflections and advice for a future CMO or GCSA

Point 1

> Research will always be one of the most important parts of any response.

It is fundamental to turning a response to any new pandemic or major epidemic from a very broad-based societal response to a much more focused (and therefore less potentially harmful) medical one, as well as improving clinical management.

Point 2

> The main reason that a research response was possible at scale was pre-existing strengths.

These strengths included:

- the excellence and broad base of UK academic and industrial science
- the strong culture of evidence-based medicine in the NHS
- co-ordinated funding
- above all a remarkable spirit of volunteering by the public

Point 3

> Pre-planning before the pandemic where possible, and adapting existing structures rather than building new ones, allowed a much faster response than would have been possible otherwise.

It was also important to prioritise key areas for an accelerated response. [footnote 8]

Point 4

> Rapid prioritisation and review was essential, along with a commitment to test clinical interventions rather than just deploy them.

CMOs and GCSA had to take a visible role in this along with the collective clinical and scientific leadership of the UK, as the temptation just to deploy untested clinical interventions in the face of a rising wave or to launch multiple underpowered studies was very strong.

Point 5

> Several methods and processes came to the fore in this pandemic including:
>
> - platform trials
> - preprints and open access
> - very rapid review

They were essential for the emergency phase, but short-cutting peer review comes with some disadvantages. Which of them should be retained for non-emergency times needs debating. Disadvantages included a potential loss of rigour in peer review and potential for early or minimally evidenced findings to be misinterpreted in the public arena.

Point 6

> Multidisciplinary research increased in importance and strong cross-disciplinary teams emerged.

This was a feature of several aspects of the response and is likely to be important for any future pandemic. Funding mechanisms and coordination across disciplines, and between industry and academia were needed.

Point 7

> The testing of social interventions and policies was difficult.

More work in this area would be beneficial.

Point 8

> It is important to plan not only for stepping up pandemic-related research, but also reinstating other (non-pandemic) research as soon as possible.

It was possible to stop non-COVID-19 and less urgent research very rapidly due to the work of many teams of researchers and their sponsors. It has been difficult and slow to stand up this research again after the initial emergency phase. This is a concern.

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Chapter 4: situational awareness, analysis and assessment

Contents

Introduction

An accurate assessment of the pandemic was critical to the response to COVID-19. This necessitated data, which had to be created, collected, managed, appropriately accessed, shared, linked prior to analyses using a range of methodologies and synthesised for assessment. Data visualisation was central to this and provided a usable way for decision-makers to see trends, outliers and geographical or other groupings.

In the initial months data were sparse and there were considerable challenges gaining access to even the most basic data to understand the situation. Sharing and linking data across organisational and sectoral boundaries were among the hardest and most often recurring challenges of the pandemic response, and are covered in more detail later in this chapter.

Alongside this, there were issues collecting sufficient and appropriate data initially – for example, with limited testing early in the pandemic. As testing expanded, allowing for much richer data from multiple sources, and as data sharing was set up and processes automated, an effective suite of charts, maps and other visualisations were available to underpin decisions.

Enabling integration of data from different parts of the health and public health system and different UK nations and regions is an important learning and legacy of the pandemic – and was not always easy. We anticipate future pandemics will have the same challenges of initially sparse data, and probably of data linkage and automation.

To enable full assessment, data streams from clinical testing, health and care and community settings, genomics, death records and non-health sources were needed. Serological data was also helpful in assessing early cumulative attack rates, and for a range of studies to understand immunity and reinfection, severe disease and transmission dynamics (see Chapter 1: understanding the pathogen), as well as tracking seroprevalence at a population level (for more on serological testing see Chapter 6: testing).

Tables 1 to 5 summarise these data streams, giving a brief description of each type and setting out their strengths and limitations. These data streams included core data on cases, people admitted to hospital, and deaths, as well as demographic data about people in each of these groups (age, sex, ethnicity, occupation, deprivation) and their location (geographically and by setting).

Data on underlying health needs were also key, though this remained challenging throughout the pandemic. Underlying all of these was an accurate test properly recorded to say whether a person did or did not have COVID-19 and until that was available the data streams had limited usable

information. Data on outbreaks in specific settings, such as care homes or prisons, and in hospitals, including by different levels of care up to intensive care, were important.

The effects of non-pharmaceutical interventions (NPIs) were also important to assess, requiring data on mobility, contact patterns and behaviour. Over the course of the pandemic, as new SARS-CoV-2 variants emerged and population immunity developed (both natural and vaccine-induced) the ability to link core data to disease outcome, vaccination status, past infection and SARS CoV-2 variant became essential. This continued to be challenging to do properly – for example, linking to past infection required an individual to have been tested and provide identical details for linkage.

Each data set has its own story in terms of what had to be done to get what was needed to those who needed it.[footnote 1] Some data streams were well established, such as data on cause of death from death certificates, held by the Office for National Statistics (ONS). Some data sets existed but were not accessible, shareable or linked. Some data sets had to be created in response to the pandemic.

A range of organisations, therefore, created and/or held relevant data – for example, each of the national public health organisations (Public Health England (PHE, latterly the UK Health Security Agency, UKHSA), Public Health Wales, Public Health Scotland and the Public Health Agency in Northern Ireland) as well as the National Health Services for each of the UK nations (both hospital data and general practitioner (GP) records). Alongside this were other government agencies, consortia such as the COVID-19 Genomics UK consortium (COG-UK), private companies, and academic organisations across the UK nations undertaking relevant studies – for example, Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) in Scotland.[footnote 2], [footnote 3] All these organisations had their own platforms for data, adding to operational challenges of sharing data even where data sharing agreements were in place.

The users of data were also varied: as well as data use across the UK government, data were needed by the National Health Services and public health organisations of the 4 nations as well as academia – for example, the academic groups providing expert advice within the Scientific Pandemic Influenza Group on Modelling Operations (SPI-M-O).[footnote 4] In addition, there was high public interest in relevant data and, over time, data were made increasingly publicly available – for example, through the COVID-19 dashboard or, for genomic sequence data, through the Global Initiative on Sharing Avian Influenza Data (GISAID) platform.[footnote 5]

There have been important lessons about the data and information needed at different stages of the pandemic. The processes required to bring these data together, analyse and assess them have evolved through the pandemic. This section covers:

- what data were needed, what data we used and where data were sourced
- important processes for data and analysis with a case study on the UK COVID-19 Dashboard
- how analyses were assessed to inform policy, with case studies on Prime Minister and other senior ministers' briefings and bronze, silver and gold situation reports
- reflections on data, analysis and assessment

What data were needed, and where data were sourced

Testing data from clinical pathways and surveillance studies

From the outset of the pandemic, there was a requirement for estimates of incidence and prevalence of SARS CoV-2 at a national and regional level, along with details of the case composition and demographics.

Data on cases initially came from early studies using the First Few Hundred (FF100) protocol to investigate the clinical and epidemiological characteristics of at least the first few hundred confirmed COVID-19 cases. This provided important data to inform case definitions and early situational awareness, [footnote 6] and was essential for quantifying the delays from infection to clinical outcome, and therefore the lag time between any policy interventions and observable impact on the healthcare system. The rapid growth of the outbreak led to many variables being incomplete, delaying many analyses.

Hospital admissions (from clinical testing) provided an early signal for increases in incidence. Due to limitations in testing capacity, tests were initially prioritised towards clinical presentations of COVID-19 within hospitals. Once diagnostic testing was available at scale, detailed description of case rates by demographics and at lower-level geographies helped to inform policy decision-making. Routine asymptomatic testing across institutions and sections of the population (such as school children and healthcare workers) gave more complete data from late 2020 onwards. This helped to highlight socio-economic disparities in the burden of disease (see Chapter 2: disparities). However, diagnostic testing data were always going to be biased to some degree by testing capacity and access and variation in uptake across socio-economic groups.

In addition to testing data, 4 primary surveillance approaches were also utilised to help better understand population level incidence:

- sentinel
- syndromic
- prevalence studies
- wastewater

All had their pros and cons – triangulation was key.

Sentinel

Sentinel data were provided through the repurposing of influenza surveillance infrastructure. This included the COVID-19 Hospitalisation in England Surveillance System (CHESS), adapted from the UK Severe Influenza Surveillance System and severe acute respiratory infection (SARI) data. These data were primarily used by external academic partners.

Syndromic

The main sources of syndromic surveillance data included:

- the ZOE COVID symptom study
- the NHS COVID-19 app
- NHS Pathways data (111)
- online COVID-19 symptom searching behaviour

The ZOE COVID symptom study was initiated in March 2020 and provided data from those who joined through an online app and self-reported their presence or absence of symptoms a subset of which were confirmed through diagnostic tests.[footnote 7] The ZOE study is an interesting example of crowdsourced data from this pandemic that shows both its strengths (such as the speed of signals) and limitations (such as selection biases and poor comparability of data over time). The NHS COVID-19 app was launched across England and Wales on 24 September 2020 and allowed us to identify contacts of those who have tested positive for COVID-19. NHS Pathways data (111) and online COVID-19 symptom searching behaviour both provided early indicators for potential increases in symptomatic prevalence, including at smaller geographies. All of these studies can give an early indication of the epidemic trajectory and change points. However, they are likely to be limited in their ability to estimate true population prevalence or incidence.

Prevalence studies

To understand prevalence in the population the ONS Coronavirus (COVID-19) Infection Survey (ONS CIS) and the REal-time Assessment of Community Transmission (REACT) study (in England, table 2) were established.[footnote 8], [footnote 9] The CIS was a new endeavour for the ONS,

which engaged an external supplier to support the rapid setting up of this large-scale survey. These studies were developed to sample the population and provide more representative data on infections in the community.

The ONS CIS was a prospective cohort study, initiated in April 2020 and was UK-wide. The initial sample was created through an amalgamation of pre-existing surveys (around 4,000 participants per fortnightly round in April 2020) and was scaled up by autumn 2020, including the use of financial incentives (around 116,000 participants per fortnightly round by October 2020).

The REACT study was a separate population surveillance study undertaken in England to examine prevalence from May 2020. It was helpful to have 2 similar studies to triangulate results. Additional studies were used to investigate infections in key settings, such as the SARS-CoV2 immunity and reinfection evaluation study (SIREN) studying case rates and reinfection in healthcare workers across the UK, and Vivaldi studying case rates in care homes in England.[footnote 10], [footnote 11]

These types of studies are considered the ‘gold standard’ but take time and considerable resource to set up and obtain sufficiently large and representative samples. Their weekly data summaries were central to analysis of the epidemiology, but were not available as quickly as mass testing data (which was produced daily) and provided a lagged estimate of population prevalence. Epidemiological analysis therefore continually triangulated the more representative (but lagged) surveillance studies with the more timely (but often biased) testing case data. It is important to ensure line-level data is available from separate studies to support comparisons of different analyses across studies.

Wastewater

Wastewater testing was used to measure SARS-CoV-2 viral ribonucleic acid (RNA) concentrations at various sites and geographic levels (institution, community, city or town, regional and national) across the UK. In England, the Environmental Monitoring for Health Protection wastewater monitoring programme started in June 2020 at 44 sewage treatment works and was scaled up to cover 74% of the population at its peak by early 2022.[footnote 12]

Generally, wastewater monitoring can provide an indication of presence or absence of detectable pathogens shed into wastewater systems (such as SARS-CoV-2) and is helpful within closed institutional settings such as prisons to give early indication of an outbreak within the monitored population. In this pandemic it also signalled circulation of SARS-CoV-2 variants of concern and supported tracking lineages of SARS-CoV-2.

However, in England it has not been possible to consistently standardise comparable samples between and within locations and so wastewater monitoring was not relied upon for prevalence estimates. This was in part due

to differing biases across sites and over time such as:

- temperature
- rain
- flow of wastewater
- sampling consistency
- cross contamination
- obstructions in the system
- efficiency of the sequencing methods
- time of year
- time of day

It is also not possible to link wastewater analysis with infection timelines for individual cases and therefore monitor incidence. This is because polymerase chain reaction (PCR) testing conducted on samples can detect viral fragments from long-resolved infections, and therefore it is difficult to judge whether samples reflect active or past infections. It has, however, been reviewed alongside testing and surveillance data to triangulate signals. Although wastewater monitoring has not typically been a leading indicator for prevalence or incidence, it can help corroborate other indicators and in particular provide early signals on new variant presence in a particular area. In Scotland, for example, wastewater monitoring was used to corroborate findings from testing data.

Case data and genomic information

Internationally, case data were generally accessible but cross-country comparisons were unreliable because of biases such as differences in testing capacity, access, uptake and technologies deployed impacting data. On the other hand, in some cases close sharing of data and international comparison was helpful in understanding the rapidly changing epidemiology – for example, between Northern Ireland and the Republic of Ireland, where the epidemiological picture often looked similar. Case data were complemented by contact tracing data, including data from mobile apps informing individuals of exposure to confirmed COVID-19 cases (for more detail on these apps across the UK's 4 nations see Chapter 7: contact tracing and isolation).[footnote 13]

As new variants emerged and established, there was a need to bring detailed genomic information alongside case data in order to understand the evolving epidemiology of the pandemic. In doing this, whole genome sequencing (WGS) was key in confirming variants and enabling more detailed virological analyses. WGS processes used samples from surveillance studies, case

data and wastewater samples, though genomic surveillance of wastewater samples would have benefited from standardised methods and analysis to support comparison of data across the UK nations.

WGS was also used to track imported variant cases from mandatory testing of international passengers from February 2021 to March 2022. This was important not only to inform interventions for variant cases once in the UK, but also to give some information on likely circulation of variants in other countries where their own WGS capacity was limited. The UK joined many countries worldwide in sharing WGS data on open platforms such as GISAID, making a substantial contribution to global genomic data.

WGS was key in tracking the course of genetic evolution of the virus and tracking variants, but its (sometimes multi-week) lag to results meant it was not ideal to enable timely analysis or inform rapid interventions. It could, however, be triangulated with case data as a retrospective tool to spot the establishment of variants with a growth rate advantage, and besides this it was helpful to get genomic surveillance data from other countries experiencing variant establishment ahead of the UK in order to pre-empt possible response needs should a similar establishment be seen here.

Other, more timely, methods were therefore used. As noted in Chapter 1: understanding the pathogen, by chance some variants did or did not carry one of the genetic targets of PCR testing, the S gene – and therefore many PCR testing labs were able to signal potential variants by tracking ‘S gene dropout’ during testing. These diagnostic test (S gene) data were much timelier (and more readily linked to other data sets) than the data subsequently available from WGS, though not all labs used the same gene targets and so population coverage of this marker was incomplete. Later in the pandemic, genotyping for specific variants provided timelier data than WGS and more specific data than the use of the S gene as a proxy.

Healthcare data

Healthcare data were needed to understand disease severity across different demographic groups and also pressure on the healthcare system.

General acute hospital admissions and admissions to intensive care for COVID-19 were important in understanding rates of severe disease from the outset. Early in the pandemic in England, the first data set that provided insight into hospitalisations was CHESS (later, renamed SARI). This was an aggregate and line list data set, providing detail on general admissions and high dependency unit (HDU) or intensive care unit (ICU) admissions. It was sourced from sentinel sites and other participating trusts.[footnote 14] The sentinel trusts were not a representative sample of hospital admissions within England and therefore inferences that were drawn had limitations. These data were biased towards critical care admissions, which made it

unrepresentative of clinical pathways and severity. However, it was a valuable tool for modelling patient length of stay and the required bed days for patients with COVID-19.

To better understand pressure on the healthcare system, COVID-19 situational reports were set up to collect key management information across the 4 nations. These situational reports provided aggregate data on COVID-19 hospital admissions and bed occupancy, and these data became available in near real-time across the 4 nations.[footnote 15] In the early days there were data consistency issues across NHS trusts. These were smoothed out as the pandemic progressed, but no retrospective corrections were made to the historical data. As the pandemic evolved, the range of management information collected was expanded to include:

- beds occupied by adults with COVID-19
- beds occupied by adults without COVID-19
- available beds:
  - general
  - acute
  - ICU beds

This was done to better reflect capacity, as hospital bed types were not interchangeable. Challenges remain regarding the sharing of this data between the 4 nations. Staff absences from COVID-19 and CRITCON data (NHS trust declared assessments of ICU capacity) also became helpful metrics for measuring healthcare pressure.

It was also important to link data streams – for example, linking testing data or vaccine status with hospital admission data (see section below on data linkage). In England, the Secondary Users Service is a comprehensive repository of healthcare data, including Admitted Patient Care and Emergency Care Data Set. These data sets allow for linkage at an individual level to vaccination or infection history, variant, clinical characteristics and demographics.[footnote 16], [footnote 17] Clinical characteristics included a flag for ‘clinically extremely vulnerable’ status or ‘COVID-19 at risk’. However, this did not allow us to differentiate between underlying health conditions.

In addition, data fields on diagnosis were only completed at patient discharge and were also combined with reporting delays of up to 30 days post-discharge. As a result these data lagged admissions by weeks or even months, depending on length of stay. This problem was mitigated by using data on individual admissions to hospital through emergency departments, a subset of individual hospital-level data available for national linkage and analysis, which was only subject to reporting delays rather than length of

stay. These data were then linked to information on variants and vaccine status, supporting studies on the severity of disease associated with new variants of concern such as Delta in June 2021.[footnote 18]

Vaccine data

With vaccination rollout from December 2020, quantitative and qualitative data streams on vaccine uptake and attitudes towards vaccines were set up to understand the extent of vaccine uptake across different communities and demographic groups, guide vaccination campaigns and support subsequent studies on vaccine effectiveness.[footnote 19], [footnote 20]

However, analysis of vaccine uptake was challenging because the size of the denominator was uncertain. In England, the National Immunisation Management Service (NIMS) used a denominator based on NHS England's Primary Care Registration Management service database, as for many other vaccine programmes. This register relied on registration with primary care and so could underestimate some populations not routinely engaged with primary care, and overestimate others where people had moved and not de-registered from their GP.

The alternative was using mid-census estimates updated annually based on the last UK national census in 2011, but this was similarly uncertain and in some calculations underestimated population size to such an extent that vaccine coverage exceeded 100%. Therefore ONS population estimates were not used in the analysis of vaccine uptake. It was also particularly important to ensure that government departments and analytical teams used the same denominator in vaccine analysis and presented consistent figures to seniors and ministers to avoid confusion.

Death data

Data on deaths from COVID-19 were the subject of intense scrutiny globally from the outset of the pandemic, and were important in situational awareness, particularly where testing was more limited, and in understanding the severity of disease in different groups. The definition of a mortality from COVID-19 is multifaceted and evolved across the pandemic.

Early in the pandemic there was a need for consistency in public reporting of deaths. ONS produced weekly summaries of deaths with COVID-19 mentioned on the death certificate, but these data were lagged. Initially, daily figures for hospital deaths were published. In April 2020 this was updated to include deaths of those with lab-confirmed COVID-19 whatever the setting, including those in the community and care homes.[footnote 21]

In August 2020 it was agreed that deaths within 28 days of a positive COVID-19 test would be reported through official channels.[footnote 22] However, this definition still had limitations and other definitions included:

- death within 60 days of a positive test (for example, in the PHE and Cambridge real-time model in late March 2020)
- COVID-19 as the primary cause on the death certificate
- COVID-19 mentioned on the death certificate[footnote 23]

As changes in treatment and the management of patients with COVID-19 improved and the pathogenesis of the virus evolved, the average time from an infection to a mortality increased and it became more difficult to understand how many of these deaths were with COVID-19 rather than from COVID-19. Therefore, while each definition had limitations, alternative definitions for a COVID-19 death were used to inform a more complete picture of the burden of disease.

As the pandemic progressed it was important to track changes in mortality rates overall as a result of the pandemic – not just directly from COVID-19 but also due to healthcare disruption, the impact of interventions to limit transmission and the wider social and economic impacts.[footnote 24] For this, all-cause excess mortality aided in our understanding. This analysis was produced by academic institutions and the ONS from 2020.[footnote 25] The importance of excess mortality in national data is that it captured the indirect impact of COVID-19. These included the effects of highly stretched healthcare and changed healthcare seeking, the impact of lockdown and other indirect effects.

Further to this, PHE (latterly, UKHSA) provided excess mortality estimates, and later the World Health Organization (WHO) produced global excess mortality estimates for 2020 and 2021.[footnote 26], [footnote 27] Such analyses enabled both an understanding of the full impacts of the pandemic, and also enabled more international comparisons which until that point had been difficult due to different methods of recording and reporting COVID-19 deaths globally. Given the very different ways nations detected and recorded COVID-19 cases, age-adjusted all-cause excess mortality was in the view of the CMOs the most appropriate way to compare international data. Even this, however, is not easy as the ‘expected’ mortality can be calculated in many ways.

As with other data sets outlined above, it remained important throughout to link deaths data with, for example, data sets on clinically extremely vulnerable or COVID-19 at-risk status, variants, vaccination status and demographic variables. This enabled us to understand which groups COVID-19 was impacting most severely as the viris evolved and new medical countermeasures became available. In due course we managed to link deaths data to key variables of interest which facilitated vaccine effectiveness and waning immunity modelling. However, it remained the case that the data lacked the granularity to be able to analyse in detail the clinical impact of different comorbidities.

Other non-health data

Non-health data were also important in understanding the trajectory of the epidemic and responses to interventions. Transport operators, educational establishments, search engines and telecommunications operators provided anonymised, aggregate data. This provided insight into mobility, behaviour and social interactions, to facilitate assessment of the impact of non-pharmaceutical interventions. Types of data used varied across the UK nations due to differences in data collection, storage, reporting and access. [footnote 28], [footnote 29]

Behavioural and attitudinal data – for example, from surveys and/or polling – helped interpret quantitative data and understand interpretations of and adherence to NPIs. In Wales for example, the Public Health Wales 'How are we doing in Wales' survey provided updates on public attitudes to, interpretations of and adherence to NPIs. Studies of contact patterns in population samples – for example, the UK-wide CoMix study and the COVID-19 Scottish Contact Survey – also highlighted changing behaviours throughout the pandemic. This was important in informing policies and communications.[footnote 30], [footnote 31]

Figure 1: timeline of daily deaths across the UK with COVID-19 on the death certificate

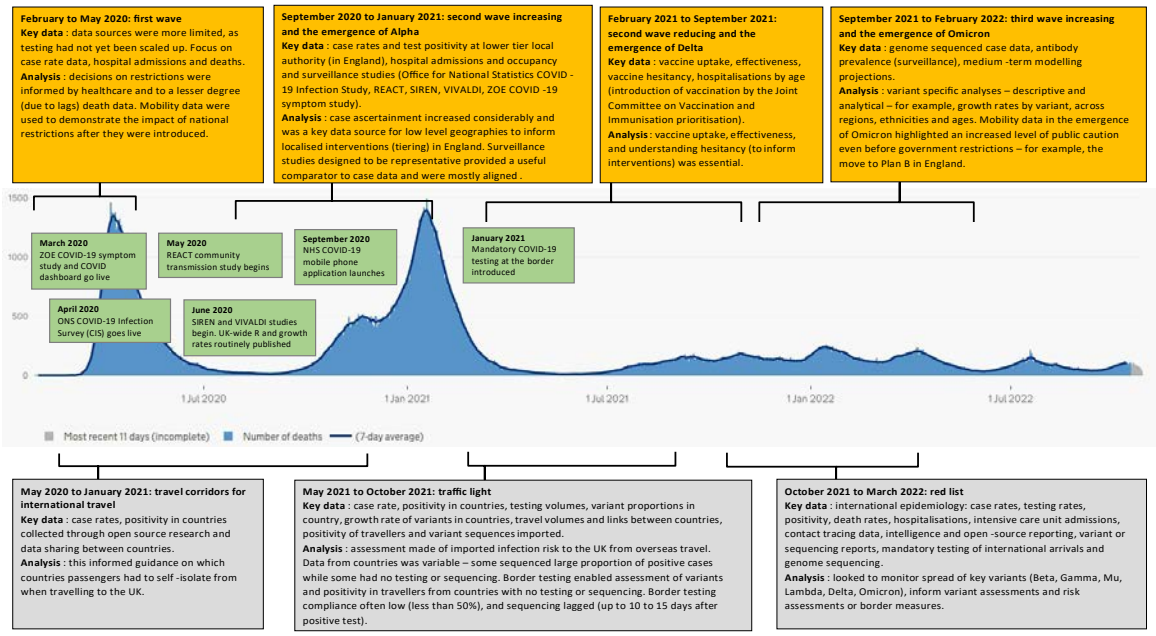


Table 1: testing data types, sub-types, strengths and limitations for COVID-19 in the UK (2020 to 2022)

Type of testing data and source	Description or subsets	Strengths	Limitations
Clinical nose or throat swab testing[fn 33]: UKHSA and NHS laboratories	Data sets on clinical testing providing data on cases were developed across the 4 UK nations, with data updated daily (at the height of the pandemic). For example, in England, ‘pillar 1’ clinical swab testing in UKHSA laboratories and NHS hospitals was undertaken for those with a clinical need.	Small data lag, included those with most severe illness.	Included a mixture of key workers as well as those admitted to hospital.

Type of testing data and source	Description or subsets	Strengths	Limitations
Clinical nose or throat swab testing: NHS Test and Trace	Data sets on clinical testing providing data on cases identified in the community were developed across the 4 UK nations, with data updated daily (at the height of the pandemic). For example, in England ‘pillar 2’ clinical swab testing was initially for key workers, then widened to testing in the community for those symptomatic or identified as a contact. Later lateral flow device (LFD) tests were provided for home use.	Increasingly, data at scale, giving high power for analysis, including by age, ethnicity, lower-level geographies Allowed more detailed analyses of variant through PCR target data and the presence or absence of the S gene where testing was in specific laboratories (see below).	Case ascertainment affected by: - behaviours and attitudes to testing - policy changes in testing eligibility - sensitivity and specificity of tests used (PCR vs LFD). [fn 34]

Type of testing data and source	Description or subsets	Strengths	Limitations
PCR gene-target data (presence or absence of S gene)	Data sets provided details of the cycle thresholds for detection of specific gene targets in positive clinical tests (and surveillance studies) for SARS-CoV-2. Data were updated daily (at the height of the pandemic). Four main 'Lighthouse laboratories' used a TaqPath assay including S, ORF and N gene targets for a subset of community testing, which provided data on the S gene, which was important for identifying changes in variant.[fn 35]	The gene targets allowed differentiation between the presence and absence of the S gene, which aided differentiation between variants, as its presence alternated between wild type, Alpha, Delta and the first wave of Omicron.	The presence and absence of the S gene which alternated in replacing variants (wild type, Alpha, Delta, Omicron) was fortuitous.
Genotyping	Reflex assays on positive tests to assess genotypes in a subset of positive clinical tests, following initial PCR testing. [fn 36]	Rapid assessment of known variants, available later in the epidemic.	Only types specific (known) variants can be tested for with these assays.

Type of testing data and source	Description or subsets	Strengths	Limitations
Whole genome sequencing (WGS) data: COG-UK and Test and Trace[fn 37]	Data set of the genetic code for SARS-CoV-2 viruses detected through testing. WGS was undertaken on a subset of SARS-CoV-2 viruses detected in the 4 nations through clinical testing, and from surveillance studies – ONS CIS and REACT (REACT in England only), and for investigation, in wastewater.	WGS data provided detailed data on strains of viruses circulating and supported identification of variants under investigation or of concern.	WGS data are lagged, and while undertaken at scale the proportion of those sequenced decreased at times of high prevalence.
Contact tracing data: NHS Test and Trace and NHS COVID-19 app[fn 38]	Data sets of the contacts of cases identified through active case follow-up, including with setting of exposure – for example, household contact. Data sets of contacts per case from digital app.	Indicates how COVID-19 is spreading between contacts and allowed analysis of, for example, secondary attack rates in households. Automatically generated data from digital app on exposure.	Only contacts identified by cases were captured. For app data, this only included those that had installed the app and self-reported a case. It did not provide detail on location of cases and was influenced by individuals' willingness to report cases, when it had consequences for self-isolation.

Table 2: surveillance data types, sub-types, strengths and limitations for COVID-19 in the UK (2020 to 2022)

Type of surveillance data and source	Description or subsets	Strengths	Limitations
COVID-19 Infection Survey[fn39]: ONS and Oxford University (also, a National Core Study, see below)	Longitudinal household cohort study provided data sets on positivity from a well-described sample of individuals across the 4 nations, allowing headline estimates and multiple sub studies – for example, on reinfections and waning of immunity. Included data on PCR gene targets and WGS to analyse variants.	Consistent positivity ascertainment with longitudinal design. More representative of community infections than clinical testing data, although still subject to some recruitment bias. Assessment of immunity through antibody tests. [fn 40] Detailed studies of reinfection by variant as well as cycle threshold (Ct), symptoms, contact analyses and predictors of positivity.	Sample size limited precision and power for analyses – for example, those at smaller geographies, particularly at times of low positivity and/or with the first emergence of new variants of concern. Study does not include people living in institutional settings such as prisons and care homes.

Type of surveillance data and source	Description or subsets	Strengths	Limitations
REal-time Assessment of Community Transmission (REACT)[fn 41]: Imperial College London	Repeated cross-sectional study provided data sets with positivity on random samples of individuals included in England. Detailed data on participants allows multiple sub studies – for example, on risk factors for infection.	Consistent positivity ascertainment with cross-sectional design. More representative of community infections than clinical testing data, although still subject to some recruitment bias. Sharing of data supported timely ad hoc analyses to inform policy, such as modelling prevalence at small spatial scales. Detailed sub-studies – for example, on socio-economic risk factors for infection.	Sample size limited precision and power for analyses – for example, those at smaller geographies, particularly at times of low positivity and/or with the first emergence of new variants of concern. The repeat cross-sectional rounds, rather than continuous sampling, meant there were gaps in data availability.

Type of surveillance data and source	Description or subsets	Strengths	Limitations
ZOE COVID Symptom study[fn 42]: Kings College London	Data sets includes participants who have downloaded a digital app and use this to self-report symptoms (approximately over 4 million users during pandemic) and other relevant data – for example, the results of any testing undertaken.	Prevalence estimated from self-reported symptomatic people. High participation and app enabled flexibility to ask new questions for policy insights. Trends tracked ONS CIS and REACT at the height of the pandemic. Rapid data, not reliant on testing and the cost associated with this.	Reliant on individuals using the app and self-reporting symptoms. Participants were less representative of the community than other studies (though outputs were modelled). Did not detect asymptomatic of pre-symptomatic individuals who would test positive for SARS-CoV-2.

Type of surveillance data and source	Description or subsets	Strengths	Limitations
Wastewater testing data for the Environmental Monitoring for Health Protection programme[fn 43]: NHS Test and Trace	Data set on the quantity of viral fragments that entered sewage systems, with testing from sewage flowing into wastewater treatment plants and key locations across the sewer network.[fn 44]	Can provide data when other data streams (for example, clinical test data) are not routinely in use in the community. Unobtrusive data collection. Used, with other data sources, in modelling the pandemic.[fn 45]	Difficult to determine accurate location of infections. Without combined tracking of faecal shedding, surveillance was limited to detection and identification of known and cryptic lineages circulating.

Table 3: healthcare data types, sub-types, strengths and limitations for COVID-19 in the UK (2020 to 2022)

Type of healthcare data and source	Description or subsets	Strengths	Limitations
Aggregated COVID-19 hospital admissions and bed occupancy: NHS in each nation (for example, England) [fn 46]	Data sets on hospital bed occupancy for COVID-19 (general and acute) available for each of the 4 UK nations, updated daily (at the height of the pandemic). Later data streams specific to bed	Direct measures of healthcare pressure from COVID-19 in the most seriously ill. Healthcare pressures further illustrated when data streams specific to	Hospital occupancy with COVID-19 was influenced by length of stay, with some changes, for example, due to age of those admitted, over the course of the pandemic. The data must be interpreted in

Type of healthcare data and source	Description or subsets	Strengths	Limitations
	type were used to describe COVID-19 occupancy, non-COVID-19 occupancy, and available beds. Data sets on hospital mechanical ventilation bed occupancy for COVID-19 available for each of the 4 UK nations, updated daily (at the height of the pandemic). Data streams specific to bed type were used to describe COVID-19 occupancy in HDU or ICU, non-COVID-19 occupancy in HDU or ICU, and available beds in HDU or ICU.	bed type were used to describe COVID-19 occupancy, non-COVID-19 occupancy and available beds.	the operational context – for example, beds not able to be used due to isolation requirements should be ‘void’ rather than ‘unoccupied’. Hospital data do not reflect pressures in the primary care system, including pressures on transport (ambulance) services.

Type of healthcare data and source	Description or subsets	Strengths	Limitations
Aggregated staff absence in hospitals	Data sets on overall hospital staff absence (later COVID-19-related absence specifically as well as overall absence).	Reflects ill-health in the population. Reflects healthcare pressure directly, but also healthcare pressures causing contributing to ill health in staff.	Measure of healthcare pressure in hospitals, may not be specialist specific and thus key pressures (for example, limited respiratory care or ICU specialised staff) may not be identified.
Healthcare – individual level: NHS Digital	Data set with individual level data on hospital admissions – for example, in England, the Secondary Users Service provides a comprehensive repository for healthcare data. Updated weekly to monthly.[fn 47]	Data were linkable to testing data types (including variants) and vaccination status. Information on co-morbidities was available, to assess risk factors. Linkage was done earlier in some UK nations, notably Scotland, providing important information for the 4 nations.	Data on admissions were lagged as they were completed at discharge. The emergency care data set (from emergency department admission) was a proportion of admissions and timelier. Data sharing took time and was only linked in real time late in 2020.

Type of healthcare data and source	Description or subsets	Strengths	Limitations
Healthcare demand: NHS	Data set with NHS 111 calls and online COVID-19 search activity, updated weekly.	Provided early markers of healthcare demand and allowed triangulation with other healthcare metrics, as well as use in more complex modelling.	Impacted by overall government communications and strategy.
Vaccination administration[fn 48]: NHS	Data set on the number of vaccinations administered by age and location, updated daily.	Provided an indication of vaccine coverage by the major risk factor – age – which was used to prioritise vaccination rollout.[fn 49]	Choice of population denominator (NIMS or ONS) was difficult as both had limitations, with NIMS using data from primary care registries and ONS estimating based on the last census. [fn 50], [fn 51]

Type of healthcare data and source	Description or subsets	Strengths	Limitations
Primary care health data	Data set of sample of primary care (GP) health records in England.	Open-source software platform (for instance, OpenSafely) for analysis of electronic health records data. [fn 52] Allows for more in-depth analysis of the comparative impact of comorbidities. Enables analysis of community administered anti-viral drugs and neutralising monoclonal antibodies.	Sample of GP practices in England with geographical variation in coverage. Data reporting lag can be considerable for real-time assessment. Challenge linking to other data sets such as hospital admissions and infection history.
SIREN immunity study[fn 53]	Data set on results of testing for immunity in healthcare workers following vaccination and/or (re)infection over 2 years, across the UK.	Provided data on immunity following SARS-CoV-2 infection and vaccination in healthcare workers, allowing analysis of vaccine effectiveness.	Not representative of the population.

Table 4: deaths data types, sub-types, strengths and limitations for COVID-19 in the UK (2020 to 2022)

Type of deaths data and source	Description or subsets	Strengths	Limitations
Mortality – individual level: ONS	Data set of deaths, with causes of death as recorded on death certificate.	Assessment of specific mortality contribution of COVID-19.	Lagged data, and deaths within 28 days of positive test were used as a timelier indicator.
Mortality – individual level: NHS	Data set of deaths within 28 days of a positive test[fn 54]	Timely assessment of deaths with COVID-19.	May have some incompleteness in comparison to diagnoses on death certifications. In high-prevalence, low-severity settings (later in the epidemic) deaths became more apparent as being 'with' COVID-19 as opposed to 'from' COVID-19.
Excess mortality[fn 55]: ONS	Data set of excess mortality.	Includes indirect deaths due to the pandemic as well as direct deaths, and deaths due to a changing context (for example, healthcare pressure).	Data were too lagged to be interpreted during the pandemic.

Table 5: other data types, sub-types, strengths and limitations for COVID-19 in the UK (2020 to 2022)

Type of data and source	Description or subsets	Strengths	Limitations
COVID-19 national core studies[fn56], [fn 57]	Data sets from a number of studies across epidemiology and surveillance (such as ONS CIS), transmission, clinical trials infrastructure, immunity (such as SIREN), longitudinal health and wellbeing, data and connectivity.	Bespoke studies providing data to answer key areas where the UK needed to increase its research scale or infrastructure to respond to key near-term strategic, policy and operational questions regarding COVID-19.	Initiated early in the pandemic, which was important due to the time required to set up the studies needed.
Mobility: Google and telecom providers	Data sets on mobility by sector. Data sets of mobile phone network logs of cell connections. To note: these data were not linked to health or patient data, and were only used in aggregate form to signal population-level changes in activity types.	Non-health data source adding context – for example, adherence to NPIs (reflected in reduced mobility).	Require careful baseline comparison. Aggregated at source to ensure privacy.

Type of data and source	Description or subsets	Strengths	Limitations
Social contact studies: London School of Hygiene and Tropical Medicine, and Scottish Government	Social contact studies – for example, the CoMix social contact study in England and Scottish Contact Survey – provided data on the number of contacts people had over the course of the pandemic.[fn58], [fn59]	Important context to understand mixing and interpret cases, incidence, positivity across different demographics and inform modelling and public health interventions.	Participants may not fully reflect the population.
Behavioural science: YouGov (polling) and public health organisations	Data on attitudes, and other aspects influencing behaviour – for example, in relation to interventions, both NPIs and vaccines – were undertaken regularly through YouGov polling. [fn 60] In addition, specific behavioural science studies from academia and public health organisations across the 4 nations provided data – for example, the Public Health Wales 'How are we doing in Wales' survey.[fn 61]	Important to understand challenges to NPIs, adherence and vaccine uptake.	Participants may not fully reflect the population. Studies at scale (for example, through polling) may lack nuance compared with methodologies using interviews, but these are not feasible at scale.

Important processes for data and analysis

It was helpful to have a central body bringing together, linking and analysing data with the right skills to get analytical outputs at speed for decision-makers in an easy-to-interpret format. In England, the Joint Biosecurity Centre (JBC) was established in May 2020, bringing together data science, intelligence assessment, academia and public health expertise to provide insight on the status of the COVID-19 epidemic in the UK.[footnote 62] It was important to have a wide range of expertise (for example, geospatial, coding, modelling and data visualisation) working in a single team and with access to a range of data at speed.

The following processes were key for effective data analysis and assessment.

Data acquisition and sharing

Data acquisition and sharing between different organisations was essential to understand a range of data available across the health and social care systems.

Early in the pandemic, however, there was a proliferation of separate data summaries from different organisations, shared in different formats – for example, through slides – rather than sharing data sets that could easily be analysed alongside one another.

Data acquisition at speed was extremely challenging, and this was due to:

- a lack of understanding about exactly what data sat where across multiple organisations
- a lack of routine relationships across some organisations
- a lack of formal agreements and data governance processes in place at the outset of the pandemic
- a need for an appropriate platform and sufficient data engineering capacity to onboard data swiftly

In response, the JBC set up a dedicated team for data acquisition to map what data sat where, form relationships with organisations to agree access and unblock barriers to access as they arose. Over time, understanding of data available, relationships across organisations and relevant formal agreements improved – for example, on 17 March 2020, a Control of Patient Information (COPI) notice was served to NHS Digital requesting that it

securely share patient confidential data (with appropriate safeguards in place) to support situational analysis and assessment for pandemic response.[footnote 63]

However, this was slow and hampered speedy understanding of the situation that was key to the response. In some cases analytical teams used direct agreements for data sharing with a selection of NHS trusts in order to get more timely signals. Other organisations also made efforts to support swifter data sharing – for example, the Secure Research Service within the ONS offered a secure environment for the analysis of ONS data. This was fundamental to understand prevalence and severity, though the platform was originally designed for academic research and not operational response.

These efforts went a long way to facilitating swift data sharing, but they had to be done while responding to the pandemic. In the future, this risk can be mitigated by:

- mapping data locations so analytical teams know what data sits where
- forming strong working relationships across data product owners and analytical teams across organisations likely to be involved in emergency response
- preparing formal data sharing agreements and governance processes in advance
- having access to the right skills at speed, including:
  - data engineers to onboard data
  - legal teams to amend formal agreements as needed
  - link teams to involve end users throughout
  - dedicated data acquisition teams to unblock barriers

Data sharing improved over the course of the pandemic, particularly between national health services and public health organisations, but work is ongoing on this.

Data linkage

Linkage of data was also critically important and was similarly problematic in the early stages of the pandemic. Data linkage platforms and agreements were not in place and there needed to be expedited processes to review and enable data linkage at speed in an emergency.

Data linkage requires line list data and a secure research environment where multiple data sets can be linked securely. This can be facilitated through pseudo-identifiers for wider dissemination allowing for greater academic engagement.

Linkage across some data sets was possible in 2020 but the process of bringing all the necessary data sets together (including vaccination data) was not complete until late 2021. However, once established, data linkage enabled a number of important analyses such as on vaccine effectiveness and hospital admissions by variant and vaccination status.[footnote 64]

In the future, this process could be speeded up through:

- routine cooperation between organisations holding and analysing data
- creation of suitable environments for sharing data
- having data engineers in receiving organisations to onboard the data swiftly
- having legal agreements in place for sharing data
- a broader visibility of data sources and what types of data are stored where across relevant health and public health agencies likely to be involved in emergency response

Data analytics

Automated production of analytics, which was often based on open-source analytical software such as R and Python, enabled rapid analysis.

At the outset of the pandemic, some teams and organisations had labour-intensive manual compilation of data in place, but this was rapidly adapted to automated processes.

In the future, automated processes should (and most likely will) be in place from the outset.[footnote 65], [footnote 66]

Transparency

Transparency in terms of data was supported through tools such as public dashboards, which are explored in more detail below (case study 1).

Transparency for analysis and interpretation was supported through publication of the Scientific Advisory Group for Emergencies (SAGE) papers and other advisory bodies, such as SPI-M-O and the Scientific Pandemic Insights Group on Behaviours (SPI-B).

There was a strong emphasis on explanation of the limitations of the data and analysis, alongside any internally produced products or published outputs. The 4 UK nations had their own advisory structures for seeking and adapting advice specific to their circumstances. The Scottish Government's COVID-19 Advisory Group, for example, reported particular benefit in the

reciprocity agreement it had with SAGE. There was an ongoing challenge in the discrepancy of operational outputs and public health surveillance that could be misinterpreted by the public.

Embedding personnel

Embedding people across partner organisations and throughout the 4 nations supported close joint working across a number of disciplines.

For example, personnel from organisations across the 4 UK nations were embedded within UKHSA and had access to its data and analysis, supporting data sharing and analytical collaboration across the UK.

Case study 1: the UK COVID-19 Dashboard

The Coronavirus (COVID-19) in the UK Dashboard (https://coronavirus.data.gov.uk/) supported transparency through provision of near real-time data to the public and the research community.

By providing timely, open data, the dashboard supported not only formal research initiatives but also ‘citizen science’. Many amateur analysts or analysts from different fields (such as actuaries) conducted analyses with important insights – these of course needed rapid review by experts to ensure findings were accurate and complemented larger research initiatives that were more regularly used in the response.

Individual UK nations had additional dashboards to focus on relevant data for their nation, such as Northern Ireland’s COVID-19 Dashboard, Scotland’s COVID-19 Dashboard, and Public Health Wales’s COVID-19 dashboard.[footnote 67], [footnote 68], [footnote 69]

The UK dashboard supported strategic decision-making, informed the pandemic response and updated the public and the media, reporting near real-time data on testing, cases, deaths, vaccinations and healthcare. [footnote 70]

In addition, metadata gave context to data sets. There was guidance for developers to set up automated data feeds and a customisable downloads page. There were multiple application programming interfaces (APIs) to make the data as open and reusable as possible.

How the dashboard developed

The dashboard was set up on a platform supplied by the NHS in England and managed by a small, multidisciplinary team of data scientists, information specialists, user researchers and development staff based in UKHSA. It was overseen by a multi-agency steering group, and work focused across 3 equally important areas:

- statistics
- engineering
- the digital user journey

Data were collated from numerous sources across all 4 nations of the UK at national and neighbourhood level, and the 4 nations worked jointly to improve cross-UK data available on the dashboard throughout.

As the pandemic progressed and evolved, so too did the dashboard. In its first iteration, the dashboard simply presented a map and a limited number of charts reporting key metrics on cases and deaths. Following updates in response to user research, the dashboard had the following updates:

- accessibility and user experience improvements, including different visualisations (https://coronavirus.data.gov.uk/details/interactive-map/cases) – such as graphs of different time frames, waffle charts and heatmaps, data tables, simple summary documents and interactive maps
- a postcode search facility, to allow people to view their local information and tell them what local alert level they were in – this allowed users to understand more clearly the epidemiological data informing some of the decisions on tiering
- addition of the vaccination topic page, including data on uptake by demographics and interactive map to allow comparison of percentage of uptake by dose
- a new metrics documentation page that lists all current and historic metrics searchable by name, category, type or availability by area type (by May 2022 the dashboard presented over 200 metrics)
- What's new (https://coronavirus.data.gov.uk/details/whats-new) pages detailing the latest updates, changes and any data issues
- one of the bigger changes in early 2022 was the move to a new-episode based definition, with metrics showing first episodes and possible reinfections by specimen date.[footnote 71]

Most data were updated daily throughout much of the pandemic – for example, cases presented by specimen date and deaths reported by date of death. However, by early 2022, due to falling mortality data, these no longer needed to be updated with such frequency. Weekend reporting in England ended, and front-page charts were changed to show 7 days of data rather than daily changes, in line with the government's Living with

COVID-19 strategy.[footnote 72] Reporting cadence reduced to weekly from early July 2022, with contingency plans in place should a return to increased reporting frequency be required.

The dashboard has been a prominent public resource, both through media reports and through direct access by the public. At its peak, there were around one million unique users per day and up to 70 million daily hits. Public use of the dashboard further increased when local data were added and provided more personally relevant data to individuals.

Reflections on the public-facing dashboard

Challenges developing the dashboard included:

- data volume: data came from over 26 separate sources, providing in excess of 700 million raw figures to handle each day
- daily surge in demand: at 4pm each day, demand surged for updated data, with dashboard usage reaching 250,000 to 300,000 per minute on data release – this required constant monitoring and activity to prevent service failure. Actions included increasing database capacity, optimising code, and implementing multiple layers of caching
- creating UK data: the 4 nations collaborated to provide a single UK figure for as many metrics as possible – this brought challenges with different nations working to different timescales and collecting data in different formats

Lessons learned from developing the COVID-19 Dashboard

1. The value of feedback: feedback was received from user surveys, user testing and emails and informed improvements to user research session design, standard operating procedures, quality assurance processes and overall design and ‘user experience’.

2. Open format data: this allowed access, building trust and rapid identification of errors. Downsides included:

- room for misinterpretation: for example, media reporting incorrect information requiring urgent correction
- pressure to publish: daily publishing to such high demand and over a prolonged period was difficult to sustain for a small team
- no room for delays: once expectation was set, it was hard to change. People relied on the information – for example, in planning activities

3. The need for reproducible analytical pipelines (RAPs): RAPs were essential for handling large volumes of data rapidly. The data pipeline began on NHS Foundry and iteratively expanded over time to several hundred transforms covering billions of data points, from numerous different disparate sources.

Some key lessons:

- consider changes carefully: once a flow was set up, altering one part could have unintended consequences later
- timescales and planning: RAPs can both decrease and increase turnaround times for changes to outputs – incorporating fundamental changes or new reporting requests takes time, so planning was essential

How analyses were assessed to inform policy

It was important to have clear processes to collate various data streams and analyses to assess the current situation throughout the pandemic – including how and who should communicate data and insights to decision-makers.

A technical board with representation from all 4 UK nations oversaw an overall assessment of the risk that COVID-19 presented at any time. This board oversaw and agreed the methodology for the UK COVID-19 alert level, which provided public communications on risk across the 4 nations by using 5 levels to describe the epidemic.[footnote 73] The technical board also agreed a consistent framework for monitoring COVID-19 internationally, with analysis of a range of indicators for each country, territory, or island group, to inform risk assessment and the need for intervention.[footnote 74]

Each of the UK nations also set up its own assessments to support decision-making.

In Wales, for example, an internal dashboard within the Welsh Government was developed and used to populate reports, such as the COVID-19 situational report.[footnote 75]

In England, a cadence of bronze, silver and gold local action committee meetings was established and undertaken each week to assess latest data alongside input from local directors of public health and regional teams (see case study 3 below). The bronze meeting used early warning indicators to identify areas and key issues of concern, ensuring local insight and professional judgement from public health leads was considered alongside quantitative data (for example, on cases and admissions to hospital). Key

situational awareness updates and associated policy recommendations were then escalated up through the silver meeting chaired by the CMO for England with input from public health regional directors) and the gold meeting (chaired by the Secretary of State for Health and Social Care).

Data, analysis and assessment from these meetings for England were shared across government, including through the Cabinet Office Dashboard, with frequent meetings including the Prime Minister (see case study 2, below). At key times the data, analysis and assessment were brought to national decision-making committees, together with assessment from other agencies to inform decision-making. COVID-O was a ministerial committee convened to handle the COVID-19 emergency and the decision-making body in England.

Alongside this, other forums conducted assessments of specific or technical questions, such as the Variant Technical Group which brought together interdisciplinary technical expertise to risk-assess new variants, or the Data Debrief Group which compared data from different surveillance studies across the 4 nations.[footnote 76] Finally, daily situational awareness calls were used to share information across public health communities.

The outputs of such assessments were important to government departments, operational agencies and SAGE and its sub-groups.

Case study 2: the Prime Minister's and other senior ministers' daily data brief

Over the course of the pandemic, and particularly in the run-up to major decisions, the Prime Minister held regular data briefings alongside discussion and review with the CMO for England and the GCSA.

These briefings were supported by presentation of data visualisations and analysis, prepared by the COVID-19 Taskforce at the Cabinet Office and generally known as 'the Cabinet Office Dashboard'.

The frequency of briefings varied over time, up to daily. Separate data briefings were also given to the First Ministers and leaders of the 4 UK nations, ministers, and senior officials. The Cabinet Office dashboard presented a broad range of data from different departments, much of which was manually assembled overnight each day, providing an overview of the pandemic and its impacts on society and the economy.

Reflections

The main challenge to assembling the Cabinet Office dashboard was inconsistent data formatting. Most government departments did not have the data engineering expertise required to set up APIs to facilitate data

exchange and this meant that data sets often had to be assembled by hand which was time consuming and a potential source of error.

By Autumn 2020, key testing and health data sets were available via API from PHE (latterly UKHSA) and the NHS, but other data continued to be shared by other mechanisms (for example, email) throughout the pandemic.

Machine-readable data and the development of reproducible analytical pipelines (RAPs) were critical to the data briefings, as noted above for the UK COVID-19 Dashboard. The RAPs allowed millions of individual data points to be ingested and transformed and a suite of several hundred charts and visualisations to be generated in a timely and robust fashion. The RAPs allowed more analytical resource to be devoted to refining the end product to ensure that it met the needs of the Prime Minister and other decision-makers.

Case study 3: bronze, silver and gold situation reports

In England, the bronze, silver and gold local action committees were informed by comprehensive national and regional situation reports which were developed using the latest data visualisations and analysis.

How the situation reports developed

The content of situation reports evolved to reflect the changing landscape of the pandemic and to support decision-makers with relevant data to inform upcoming policy decisions. In October 2020, decision-making was focused on the implementation of local COVID-19 restrictions (tiering and local COVID-19 alert levels). A range of epidemiological data were presented alongside healthcare metrics (pressure on the NHS – people admitted to hospital and occupancy of hospital beds) regionally and locally to inform interventions.[footnote 77]

In March 2021 when the government was preparing to lift national NPIs, the reports were updated and re-structured to give senior decision-makers an update on progress made against the 4 key tests for exiting lockdown, with key data on variants or vaccine uptake.[footnote 78]

The creation of these reports involved a considerable resource initially, with staff manually adding charts from a range of data sources and other products (including outputs from PHE, latterly UKHSA, Department of Health and Social Care (DHSC) and the NHS). As data were increasingly shared directly across organisations it was possible to automate this.

The situation reports also increasingly incorporated relevant data from Northern Ireland, Scotland and Wales to understand the progression of the pandemic across the UK, as well as relevant international comparators which were helpful for understanding emerging variants in spite of variations in case ascertainment and genomic surveillance.

Finally, the situation reports were refined weekly in response to continual feedback – for example, refining how data were visualised to aid interpretation. For example, heatmaps (see Figure 2) were useful to visualise large and complex data while further detail was provided in reports.[footnote 79]

Value

The reports brought together a range of health and non-health data, as well as local insights on this data, and provided an assessment of the important messages arising from both the data and local intelligence for decision-makers. This supported decision-makers as well as those involved in the pandemic response, including those who did not have a public health background.

Cross-departmental collaboration in the production of the reports helped ensure data consistency and avoided decision-makers being presented apparently conflicting data due to presentational differences.

The reports provided the basis for a range of other situational awareness products and briefings which used their data visualisations and analysis, but this brought the risk that nuances were lost in the process. Abridged versions were used for briefing MPs, the WHO, the Prime Minister, and senior leaders across government, as well as in COVID-O meetings, discussions involving international liaison and for media communications.

The automation of the reports required support and collaboration from across government but was important in saving resource and allowing teams to work on more complex analyses.

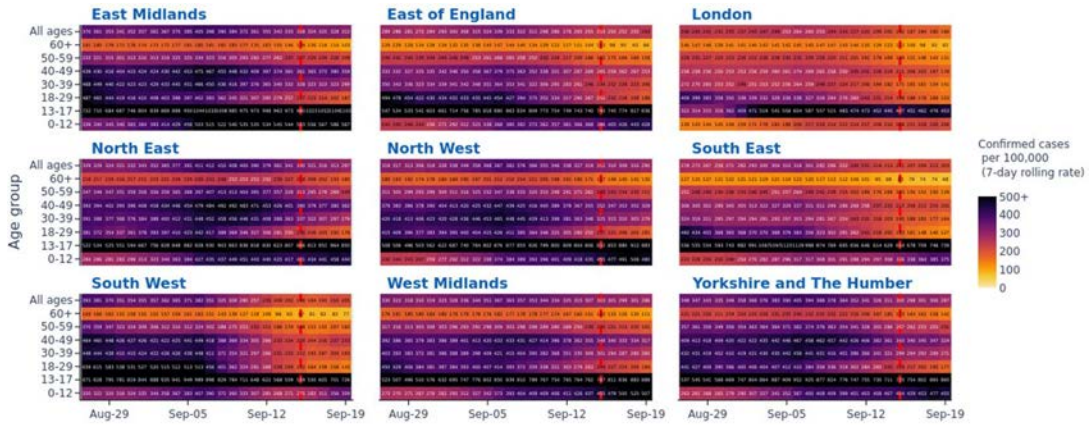
Reflections

The initial reports were very large (with around 400 slides at times) providing a range of different graphs and data visualisations with different data types often detailed by demographics and geographies. These provided a comprehensive assessment and were important especially at a time when different measures were in force in different geographical locations but were challenging to produce, quality assure, distribute and navigate in meetings.

The shift to shorter, more focused presentations enabled clearer narratives but required more iteration. It was essential that key stakeholders saw situation reports in advance of local action committee

meetings.

Figure 2: heatmap of COVID-19 case rates, by age group and region for England in 2021[footnote 80]



Reflections and advice for a future CMO or GCSA

Point 1

Good data are essential for an effective pandemic response – otherwise decision-makers, service providers and researchers are flying blind.

Lack of even basic data was particularly acute in the early stages of the pandemic but difficulties with accessing, sharing and linking data persisted for much longer, although the situation improved significantly thanks to the efforts of those involved.

Point 2

Data sharing and linkage is essential from the outset.

In any health emergency, data from hospitals, primary care, health protection agencies and academic research will need to be shared rapidly between a range of government departments, public sector organisations and academic researchers. This requires data governance processes and interoperable data platforms to support data sharing and interorganisational collaboration.

The following 4 areas are important to understand:

- which data are required, with consideration of who ‘owns’ the data and how data will be accessed
- which disparate data sets need to be linked to enable necessary analyses, and how will this be done
- who will analyse the data to provide insight and inform assessment
- which data sets will need to be newly created

Point 3

Data curation and analysis required considerable resource.

This was only fully effective once automation allowed multiple data streams to be integrated very rapidly.

Point 4

Surveillance studies, in particular the ONS CIS and REACT, were important to provide consistent, representative data on positivity in the community and in particular settings, and to include those who were asymptomatic.

Point 5

Analyses had to be continually adapted to understand the evolving epidemic.

For example, later in the epidemic with high levels of immunity, a less severe variant of concern (Omicron) and high prevalence of infection (from January 2022) meant it was increasingly apparent people were being admitted to hospital ‘with’ COVID-19, rather than ‘for’ COVID-19, based on symptoms and reported diagnoses. This was important for risk assessment and the distinction needs to be adequately captured in data.

Point 6

Data lags limited analyses.

Some are unavoidable (for example, the natural lag between infection and hospitalisation). Others reflected operational processes – for example,

individual data on diagnoses were completed at discharge, affecting the linkage of individual-level hospital data to case data to allow analysis of hospital admissions for specific variants.

Point 7

> Transparency of data helped engage the public with public health interventions.

The COVID-19 dashboard was central to this. Data visualisations are important for the public but also help tell the story to and for decision-makers.

Point 8

> Rapid collation of data, analysis and assessment of the situation required multidisciplinary working.

This included epidemiologists, clinicians, analysts, statisticians and data scientists (including data visualisation experts). Cross-organisational working, including across geographies and within and beyond government (for example, with academia) was also key.

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Chapter 5: modelling

Contents

What epidemiological modelling was used for in this pandemic

Overview

Epidemiological modelling has been an important tool throughout the pandemic to interpret data to support understanding the situation, and to provide scenarios to develop awareness of the potential impacts of different options for policy choices.

At the outset of the pandemic data were limited, and modelling pulled together sparse, messy evidence to consider what impact COVID-19 might have when it reached the UK. Modelling has been able to support wide-ranging policy decisions in the past years, from influencing the development of the roadmap out of lockdown (https://www.gov.uk/government/publications/covid-19-response-spring-2021) in spring 2021 through to supporting individual government departments with their own strategic (and operational) responses.

Over the course of the pandemic, modelling evolved, moving from a handful of models providing individual estimates that were subject to challenge from other experts to a concerted consensus effort across an entire community, including devising new methodologies for statistically combined estimates of key parameters and projections. This move to a combined consensus estimate using a range of models was an important progression; consensus positions offered greater confidence than individual models could.

Understanding of what modelling can and cannot provide (and communication of this) and what principles and insights can be concluded has also developed markedly, as have the logistics of managing such analyses.

How epidemiological modelling has been used in the COVID-19 pandemic

Early in the pandemic when little was known about COVID-19 in the UK as a disease, modelling relied on working from first principles to estimate the severity and transmissibility of the virus using initial data, including from China, and providing high-level insights such as the extent to which reducing peoples' contacts could break chains of transmission and thus delay the spread of a UK epidemic, and that earlier intervention is more effective than later intervention.[footnote 1], [footnote 2], [footnote 3]

As more was understood about COVID-19, models could become tailored to reflect COVID-19's particular characteristics and modelling assumptions were updated accordingly and continuously.

Throughout COVID-19, a wide range of such modelling techniques have been used. These include but are not limited to the following:

1. Supporting the interpretation of limited, unclear, and sparse data to give early estimates of key parameters, such as the basic reproduction number (R0), and understand how an infectious agent is moving through a population

Epidemiological modelling was able to use data, for example, from the Diamond Princess cruise ship in February 2020, to estimate infection hospitalisation, infection fatality, and hospitalisation fatality ratios.[footnote 4], [footnote 5], [footnote 6], [footnote 7], [footnote 8] These were then applied to a UK context to infer what impact COVID-19 might have here.

As new variants of SARS-CoV-2 have emerged, both in the UK and abroad, it has also been possible to use modelling to understand how infection levels might translate into future hospital admissions and deaths.[footnote 9], [footnote 10] As individuals have been vaccinated and repeatedly exposed to the virus, severity estimates in modelling have also been updated to reflect the changing understanding of COVID-19 at a particular time.

There are, however, limitations to such extrapolation. For example, as the Omicron variant emerged in South Africa in November 2021, it was impossible to tell whether its early apparent decreased severity would be replicated in the UK. South Africa is very different from the UK, both at the time in epidemiological terms (COVID-19 epidemic timing and variant composition to date have been different, vaccination types and programmes have been different, as well as other factors) but also demographically, with quite different population structures.[footnote 11]

2. A method to combine multiple parameters, such as the rate of transmission or contact rates among the population, into individual metrics that can be used to monitor the ongoing situation, such as estimating the effective reproduction number (R), growth rate, or incidence

Early in the pandemic, groups estimated such nowcasts in an informal manner, and their agreed consensus position was reported through the Scientific Pandemic Influenza Group on Modelling Operations (SPI-M-O) consensus statement for that week. From around May 2020, SPI-M-O began to combine these nowcasts using a statistical approach across a minimum of 3, but often more than 10, models to provide a consensus range.

Over time, these sorts of estimates expanded to different nations of the UK and geographical regions of England. These were produced weekly from 29 May 2020 until 1 April 2022 (with transfer of ownership from SPI-M-O to the UK Health Security Agency (UKHSA) on 23 July 2021).[footnote 12]

These nowcasts have their own specific limitations; they are average measures that cover different geographies, variants of the virus, different groups or settings, and so on, that make it more difficult to interpret than, say, case rates or hospitalisation data. They are also lagged indicators that reflect transmission from 2 to 3 weeks earlier. Once a methodology was agreed by SPI-M-O, the process of producing such metrics became simpler. However, such methodologies need constant review as the situation and requirements for monitoring change. For example, all models have been weighted equally when estimating R, but other methods of statistical combination might be more appropriate in the future.

3. Providing a structured way to test and challenge assumptions about, for example, the properties of the pathogen or the disease itself, how population mixing affects transmission, or how infections translate into the need for healthcare

These results and changes to assumptions were then used to update and improve representativeness of models over time, as knowledge about the disease increased. For example, early in the pandemic, the frameworks of some models for COVID-19 were initially adapted from previous influenza models – these were significantly changed and adapted as the various early inherent unknowns about SARS-CoV-2 became clear, and continue to be so as more and more is understood.

4. Using models to provide insight into what future epidemic patterns might look like

This allowed a potential infinite range to be narrowed to support policymakers understand the “decision space” they were within. Modelled trajectories showed which variables were critical, how uncertainty could be resolved, over what time period, and with which data. Over the COVID-19 pandemic, different methods for such trajectories have included the following:

1. Projections were used to extrapolate trends into the short to medium term (a few weeks) to show how current rates of growth or decay would change trajectories of key metrics such as hospital admissions and deaths, assuming no policy or behavioural changes affected the trends observed at the time. These considered the inherent delays between infection, developing symptoms and requiring healthcare, and extrapolated one or two generations of transmission. They were sensitive to initial growth rates and differences in data streams, and so using a statistical combination of different models during the pandemic, as for nowcast estimation, has restricted the influences of different biases. These projections, however,

are especially volatile at times of change (for example, when a wave is turning over) and they cannot predict precise timings or scale of peaks. During COVID-19, these sorts of projections were particularly useful as hospitalisations increased substantially in autumn 2020. SPI-M-O's combined projections showed that, without policy or behaviour change, the number of daily hospital admissions in England could match or surpass those seen in spring 2020.[footnote 13], [footnote 14] They were less useful during times when policies changed frequently.

2. Medium-term scenarios are a variant of these projections that were developed to understand potential futures when a policy was changed. The scale of any potential change on, say hospitalisations or deaths, is unknown until it is observed in the data and so, to investigate this, multiple different R values were stipulated from a given date and modelled forward for a given length of time. These were combined from different models (at least 3). The resulting combinations then provided a possible envelope for future trajectories that could support discussions about how big a change in transmission might be 'manageable'. These were particularly useful during the roadmap out of lockdown in spring 2021.[footnote 15], [footnote 16], [footnote 17], [footnote 18] As each step of the roadmap was taken, it was possible to see in advance what range of outcomes that step might lead to but also, as data accumulated after the step was implemented, which broad trajectory the change may actually have led to.
3. Scenarios were generated from transmission dynamic models that range from simple to large and complex. These analyses consider how the future could turn out under different sets of assumptions, extending out over several weeks and even months. These scenarios are often misunderstood as predictions but cannot be due to the number of assumptions that need to be taken, both in terms of model parameters, biological assumptions (for example, how effective vaccines would be), what policy decisions may be taken in future, and how people may behave. These last 2 heavily influence one another and, while behaviour can be incorporated into modelling, calibrating this can be incredibly difficult and it changes over time. Some assumptions were provided to modellers by policy officials – for example, assumptions on the speed of rollout of vaccinations – while others were left to modellers' expert judgement – for example, vaccine effectiveness before real-world data were available. Different model outputs were not combined, but rather insights drawn from differences between scenario runs.

These models were most useful when used to determine which variables the trajectories were most sensitive to (and therefore where the pandemic response should be focused) and the broad order of magnitude of future changes that might be expected. They are highly complex analyses that require interpretation by specialists who can distil the key high-level principles relevant for policy and decision-makers. This sort of modelling particularly influenced both the development of and the decisions taken during the roadmap out of lockdown. For example, such analyses showed that:

- effective widespread population immunity was almost certainly unachievable through vaccination alone
- therefore a large wave of infections was highly likely at some point as restrictions were lifted (an exit wave)
- extremely high vaccination coverage in older age groups was needed before all restrictions were removed
- while at the time it was impossible to know either how effective vaccines would be against transmission and severe disease, or how people's behaviour would change as restrictions were lifted, modelling showed that both were key to the future of the epidemic. These could only be known after there had been enough time for data to accrue and therefore these insights led to a key recommendation that the release of measures should be based on the data rather than particular dates[footnote 19], [footnote 20], [footnote 21]

Each of these findings was borne out in practice.

Models do not and cannot predict what is going to happen. They can only illustrate potential futures. Modelling can extrapolate trends based on input data and assumptions, but it is extremely difficult for them to call precisely when growth may turn into decline, and vice versa, as is estimating exactly how high or low that peak or trough might be. There has been substantial pressure, throughout the pandemic, to 'predict' what might happen next and so communication that this is not the purpose of modelling has been vital.

General limitations of epidemiological modelling

For models to provide the best insights, good data are required. If data entering models are of poor quality, then the models' results will be too. There needs to be a diverse range of data, collected from different sources, using different methodologies, that is available to all modellers. When data have been lacking, assumptions were required to fill the gaps – these unknowns may be biological, sociological, or related to policy.

Data will always be lacking in the early phases of an epidemic or wave with a new variant, and this in particular was a major limitation for epidemiological modelling early in the pandemic. Robust modelling was not possible until reliable data were available. Speed of access to data is also important, as lagged data mean that models will be out of date when they are produced.

As more and more factors and/or heterogeneities have been included, models have become more complicated and data hungry. Population mixing and disease risk are very heavily age and space-related, making age and geography important data variables for many models.

For example, as immunity builds up, it significantly affects transmission, so vaccination status and previous infection status needed to be included. With each additional dimension included, the models' data needs increase exponentially as a power of the models' complexity, as does computing resource requirement and the potential for coding errors. Such complexity is partly determined by the epidemiology but also by the questions asked of modelling. For example, as the pandemic progressed, some SPI-M-O participants began modelling at very granular scale geographies using the index of multiple deprivation (IMD). With access to the right data, future modelling could consider more socio-economic factors and the resulting impact on outcomes.

Flexibility is crucial as it will not be possible to preempt all the data that will be needed in advance. For example, at the very start of the COVID-19 pandemic, it was not anticipated that mobility data, vaccine rollout plans and testing data would become such central data sources. Fast-tracking access to new data streams as their importance becomes obvious is crucial and requires significant cross-organisational working to identify such data and implement the necessary logistics for access.

Infectious disease modelling is also not a tool that can balance direct disease burden with other harms, such as the economic and social impacts of policy decisions or interventions. It cannot and should not replace other disciplines or the interrogation of data.

How epidemiological modelling was managed in this pandemic

The way modelling was used, and its limitations, during this pandemic is illustrative of options in future pandemics and epidemics. From the second meeting of the Scientific Advisory Group for Emergencies (SAGE) that considered COVID-19, the Scientific Pandemic Influenza group on Modelling was put on an operational footing, as a subgroup (SPI-M-O) reporting exclusively through SAGE. This allowed for an expansion in the number of academics providing support to the government response and increased the diversity (of models, modelling approaches, data and assumptions used, experience, academic institutions) of the group, and for a wider range of observers from government departments and the devolved administrations to attend and understand the principles and evidence derived from modelling.

SPI-M-O acted to draw together results and insights across the various individual models and the significant expertise and experience of its participants to provide a consensus position. This scientific evidence was then used to inform SAGE advice, which was then used to inform policy.

Generally, SPI-M-O (and SAGE) took a UK-wide approach to COVID-19. As policy development considered different spatial scales and as the epidemic spread at different speeds across the UK, models that considered different nations, regions or even smaller geographical areas became more and more useful. For example, in Northern Ireland case rates and variant spread often more closely matched the Republic of Ireland – as when it experienced a wave of the BA.2 variant ahead of the other 3 UK nations in early 2022. As the pandemic progressed, all 4 nations of the UK adapted their modelling approaches to take account of differing epidemiology and policy questions:

- in Wales, modelling from 2 Welsh universities contributed to their response – this was commissioned by the Technical Advisory Cell and the outputs reviewed by the Technical Advisory Group[footnote 22]
- modellers from both Scottish Government and a range of universities across the UK and further afield developed models for use in Scotland. Estimates and projections from these were used throughout the pandemic using Scottish-specific data and parameters. These were used to inform the Scottish response and fed into SPI-M-O cross-UK estimates. Cross-UK estimates in turn informed weekly updates modelling the epidemic in Scotland.[footnote 23] Scottish modelling groups worked with SPI-M-O participants to develop specific modelling tools for Scotland – for example, on establishing local authority projections
- in Northern Ireland, a modelling group was established by the Department of Health and a lead modeller was brought into the Public Health Agency to produce modelling estimates using more locally relevant parameters at pace. These were supported by academics and public health specialists. These were compared with SPI-M-O modelling to refine them and see where differences were arising, and were published as weekly summaries for the public in their R Paper[footnote 24]

Dialogue between UK-wide and devolved administration modelling efforts continued throughout the pandemic, with SPI-M-O's individual academics or academic groups sitting on the above advisory groups, and providing what became standard products (nowcasts, short-term forecasts and medium-term projections) for the 4 UK nations where possible.

Modelling is considerably more robust when more than one model (ideally a minimum of 3) is considered and a consensus is built and agreed across a broad community. If the models give the same message, there is greater faith in the results. If they give different results, it is an opportunity to understand why and emphasises the uncertainty.

The consensus approach also acts as quality assurance, lowering the risk of spurious results due to coding errors or biases within an individual model. The modelling evidence provided as a consensus reduces the profile of the quantitative results and emphasises the qualitative insights.

A variety of different approaches and sensitivity analyses also allows for consideration of a problem from several different perspectives – for example, large complex transmission dynamic models may allow for a level of detail that is not possible from simpler models, or different structures might allow trends at, say, lower tier local authority level to be investigated. Generating a consensus does take more time but leads to significantly more robust results.

Alongside consensus, diversity of inputs and approaches has enabled challenge which has been an important part of the process. This has come from within the committee itself in a rapid review process, from within government (while maintaining academic independence), and from external sources as analyses were released into the public domain and externally peer reviewed.

During the pandemic, some countries such as Denmark, the Netherlands and Australia have drafted technical modelling expertise into governments, whereas the UK has been almost unique with modelling conducted externally, yet publicly available and informing government policies. In particular, the strength in depth of the UK's academic community has been and is a huge asset. COVID-19 has demonstrated the importance of:

1. Effective policy-modelling dialogue: early in the pandemic, requests for modelling to SPI-M-O were framed in ways that focused on 'predicting the future' rather than considering what high-level insights and principles that modelling could provide. There was a risk that policymakers wanted and expected greater certainty than is possible from modelling, especially of future events. As the pandemic progressed, understanding grew of what infectious disease modelling can and cannot do. Combining this with an analytical coordination hub at the centre of government led to commissions becoming more appropriate (both in terms of content and timelines), with the roadmap out of lockdown being an excellent example of where appropriately tailored modelling requests led to invaluable evidence to support decision-making. A government co-chair of SPI-M-O with extensive understanding of academic modelling, as well as the government's strategic questions, also facilitated this open dialogue.
2. Diverse range of models and modelling groups: at the start of COVID-19, the larger SPI-M-O modelling groups were able to quickly flex resources to the pandemic, while smaller groups could not at the same pace. This made building consensus difficult as individual groups' results could not be subject to the same breadth of quality assurance from multiple contributors that became the norm later in the pandemic. As the pandemic progressed, smaller groups became more able to contribute, improving the resilience of the modelling community as well as the consensus process and diversifying the models available, and thus the insights available to government.

3. Focusing academic expertise appropriately: as COVID-19 emerged in the UK, many modelling groups were extensively involved in monitoring the epidemic, as well as modelling potential futures. As government started developing its extended capabilities in summer to autumn 2020, divisions of responsibility could become much clearer and allowed for better management of SPI-M-O's extensive expertise and for prioritising their time accordingly.

Communication of epidemiological modelling

Modelling is a complex process that requires careful interpretation and explanation of highly technical outputs to both decision-makers and the public. It is likely that senior clinical and scientific advisers will need to clearly communicate modelling outputs for future pandemics and epidemics. Experiences during COVID-19 have reinforced some important principles:

1. The craving for certainty of what is to come, particularly in the early stages of a pandemic, may mean that model outputs are seen as 'the answer', which they can never be. Policy decisions, however, should be based on several considerations, and infectious disease modelling outputs are only one source of scientific evidence.
2. Clarity about the uncertainties, both from models' outputs and the wider strategic and evidence context, helps decision-makers and the public understand the key principles and insights that can and cannot be drawn from modelling. This needs consistent communication of the limitations of epidemiological modelling, the dependence on assumptions, and when it is best used, in collaboration with modelling experts. Policymakers are often comforted by being able to see a line on a graph purporting to show what will happen under a given policy, but modelling will never be able to precisely predict the future.
3. Setting out the assumptions underpinning models and summarising what may happen if or when these change helps to demonstrate how modelling outputs may also change. Managing these uncertainties alongside the pressure to present results simply and concisely has been a delicate balance during the pandemic. The sometimes large differences between individual models were due mainly to differences in assumptions.
4. All SPI-M-O modelling that fed into policymaking through SAGE was made publicly available. As well as the benefits to the public of this transparency, this greatly improved the modelling itself. However, the public mostly experienced this work through filters such as the press or social media, which invariably focus on the most extreme results, even when a range is reported and appropriately caveated. For example, in autumn 2020 SPI-M-O modelling groups conducted preparatory work to support planning for winter and development of a new reasonable worst-case scenario iteration. Four modelling groups' scenarios were considered.[footnote 25] However, the

most pessimistic trajectory of the 4 was focused on by many outlets. Proactive engagement through appropriate experts and relevant sector press is important to avoid unintentional misinterpretation of outputs.

Reflections and advice for a future CMO or GCSA

Point 1

Modelling is just one tool of many that can be used to understand the situation and be taken into account in decision-making.

A wide range of data and evidence must be used, alongside modelling. Complete data is ultimately more helpful than models.

Point 2

A range of types of modelling and analysis may be needed in the future.

During the COVID-19 pandemic, SPI-M-O focused on epidemiological modelling to help assess the potential direct health impacts of the virus. Others were responsible for different aspects of evidence, such as economic and societal analysis, and assessing indirect health impacts. Future decision-makers in local and national government may need to use a combination of such tools to balance decisions about future policy choices and the associated opportunity costs.

Point 3

Modelling is not forecasting.

It proved difficult to communicate this important distinction to decision-makers, the press and the public.

Point 4

Epidemiological modelling is most useful for looking at ‘what if…’ questions in the form of scenarios.

For example, what if the number of contacts people have were to halve, or vaccines were to reduce the chance of infected individuals requiring hospitalisation by two-thirds? This sort of modelling is good at identifying which factors will have the biggest impact on the course of the pandemic, but is also the most intensive and complex to run.

Point 5

> The SPI-M-O secretariat played a vital role in bridging the gap between expert modellers and policymakers.

Secretariat staff:

- had experience in both policy analysis and epidemiology
- were empowered to shape the modellers' programme of work (ensuring outputs were the most relevant for policy teams while maintaining a sustainable modeller workload)
- helped interpretation of modelling results to policymakers, scientific advisers and the wider public

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Chapter 6: testing

Contents

Introduction

In pandemics and major epidemics, the development of a test or tests and their scaling up is often a rate-limiting step to:

- optimising clinical care
- deploying control measures
- developing a clear epidemiological picture
- assessing community-based countermeasures

This was true with HIV and Ebola virus, for example. Testing technology evolves, but the centrality of developing and scaling tests will remain. This is particularly true where an infection has non-specific symptoms, or can be asymptomatic, both of which were the case for SARS-CoV-2. In COVID-19, tests were developed rapidly, but the time taken to scale up limited the response in the early phases. COVID-19 was over time notable for widespread use of self-testing for an acute infection. As with all tests accurate, rapid reporting systems and clear use cases were as important as the test technology.

This chapter explores the test technologies needed, the testing strategies deployed and the scale and speed of the systems required to deliver those strategies in this pandemic. It sets out some of the most important innovations and approaches in testing from this pandemic, including mass population symptomatic and asymptomatic testing with the use of lateral flow devices (LFDs) which helped people manage risk in day-to-day activities, the widespread use of self-testing and the unprecedented scale of testing operations reaching across the UK.

It also explores the challenges in scaling up testing – a particular issue in the initial stages of the pandemic – evaluating and assessing new technologies and formulating appropriate testing strategies for different stages of the pandemic.

Broadly, testing types and the use cases they supported in this pandemic were as follows:

1. Diagnostic testing, including in the general population, helped guide clinical care and infection prevention and control in high-risk settings. It also enabled targeted isolation guidance and contact tracing to flag linked cases, supporting cluster and outbreak identification.
2. Asymptomatic testing enabled case-finding for outbreak management and routine detection of asymptomatic or pre-symptomatic cases for higher-risk settings, for those at higher risk of severe outcomes and for some critical infrastructure roles such as health and social care staff. It also supported

risk management for a number of day-to-day activities across the population (such as for international travel or attending events), and data from asymptomatic testing supported surveillance – for example, at borders. Scientific consensus on the effectiveness of asymptomatic testing evolved in the early stages of the pandemic. Initially, it wasn't clear if asymptomatic people had a lower viral load and how this might impact sensitivity and specificity – but this question was resolved scientifically quite early.

3. Large-scale diagnostic testing across the population enabled monitoring of prevalence and spread of infections at an unprecedented level. Surveying the virus genome from affected patients helped inform the clinical and public health measures needed to minimise severe disease.
4. Wastewater testing provided signals on the presence or absence of cases and variants in an area or setting. This was most useful when case, variant or testing rates were very low – for example, where a variant was newly detected in an area or to assess whether local community infections had ended. Results were also relatively fast, so offered a good chance to triangulate signals with other sources in advance of surveillance programmes such as the Office for National Statistics (ONS) Coronavirus (COVID-19) Infection Survey (CIS).
5. Testing for research enabled us to track outcomes within a range of studies – for example, on vaccine effectiveness in preventing severe disease or on rates of reinfection. Linked data from mass community testing was also key to research – for example, supporting calculation of the infection fatality rate – which in turn supported projections of potential case hospitalisation and fatality rates.

Of course, testing strategies had a number of broader aims beyond this, for example keeping sectors of the economy open or building trust with parents when schools reopened to enable them to manage potential risks. Political leaders had to consider these wider aims when taking decisions.

To support such aims, there was a need throughout the pandemic for:

- accurate and reliable tests (the technology) to determine both current and previous infection (though testing for current infection made up the bulk of demand) – there was a continual balance in selecting technologies between sensitivity and specificity, and turnaround times from sample to result
- a testing network to deliver those tests at scale and speed, analyse them, process and return results to individuals and/or professionals as needed
- scaled-up genomic sequencing to monitor new and emerging variants of concern (VOCs)

- summary data from testing to inform clinical and wider health system management, outbreak management and public health response at a local and national level, and policy decisions
- ongoing review of testing systems and strategies to continually adapt processes, strategies, communications and technologies. In practice, evaluations often focused on acceptability, uptake and outputs of testing (such as number of cases identified). It was difficult to formally assess the public health impact of testing in the rapidly changing context of a multi-wave pandemic, though there is little doubt that testing was an important part of pandemic response that provided surveillance, enabled interventions like isolation of cases, supported research and helped guide pandemic control strategies

Some of these elements were less developed at the outset of the pandemic – most notably the ability to rapidly scale systems to support widespread community testing. For COVID-19 the initial development and validation of molecular tests was very rapid by historical standards, but there were delays scaling up to mass community testing at the outset of the pandemic and this was of critical importance.

Timeline of testing

Throughout the pandemic, the capacity and effectiveness of laboratory processing, delivery and distribution routes and global demand and supply of materials continually changed. Testing strategies were continually adapted in response, and as the epidemiology changed and wider pandemic strategies also adjusted (for example, where routine testing enabled strategies supporting the labour market).[footnote 1] Testing strategies also evolved as new technologies became available and as evidence emerged on the potential needs, use cases and population responses to different testing options – such as self-testing, as opposed to that undertaken by a health professional or in clinical settings only, or accessibility of public testing centres. Testing evaluation initiatives were important throughout in understanding this and helped shape government policy.

Early 2020: targeted testing

As the first few hundred cases reached the UK, testing of symptomatic patients was central to refining the clinical case definition, confirming clinical diagnoses, and conducting epidemiological studies to understand the speed and extent of the transmission to inform public health control measures. Diagnostic polymerase chain reaction (PCR) tests, processed by existing lab infrastructure, were primarily used in hospitals for case finding and early

outbreak management, to prevent incursions of SARS-CoV-2 into healthcare settings, and for infection prevention and control in clinical settings. Some genomic sequencing was available from an early stage and, following the research funding provided to the COVID-19 Genomics UK consortium (COG-UK), enabled retrospective analysis of incursions into the UK.[footnote 2]

In these early weeks, when we had a relatively small number of imported cases to test, existing capacity using the rapidly developed reverse transcription PCR (RT-PCR) test in existing lab arrangements was sufficient for diagnostics for those meeting early clinical and epidemiological case definition in the community. At this early stage, rapid expansion of local testing in clinical settings would have been helpful in identifying whether any further high-risk patients had COVID-19 as well as giving early signals on the possible proportion of asymptomatic infection and transmission, though this relied on local testing capacity and available resources.

The early days of the pandemic brought much academic, practitioner and media attention about the reliability and performance characteristics of new diagnostics. It was essential to have robust validation and verification data to support the mass deployment of new tests. This was both to ensure clinical and public confidence in the use and reliability of any test but also to minimise the necessity for further development work, lest the test prove to be insufficiently robust when field tested.

Spring 2020: widespread community transmission and testing scale-up

Once community transmission rose steeply in the UK in early spring 2020, community cases soon outstripped the supply of tests and existing systems were not capable of the rapid scale needed to meet demand. We anticipate this may well be a repeated problem in future pandemics and epidemics.

There was a need for rapid scaling up of capacity and wider infrastructure to enable high throughput of (particularly diagnostic) tests. Eventually this was achieved but there was a period in which testing supply did not meet demand and this was a rate-limiting factor for a number of interventions.[footnote 3] This difficulty scaling existing systems was for several reasons, including:

- the limited size of the pre-existing diagnostic industry (which was not the case in all comparable countries, some of which were able to scale more quickly)
- the fact that pre-existing testing systems used multiple small labs with multiple platforms and space constraints

Although they had an expert workforce, many smaller labs also faced difficulties rapidly expanding the workforce.

At the same time, global testing supplies (particularly swabs and reagents) were significantly impacted by both increasing demand and reduced production in spring 2020 as the epidemic spread more widely, including to regions producing test materials. This was exacerbated by the fact that testing platforms were previously only validated for certain swab types, so it was difficult to flex to alternative supply routes when existing supplies were disrupted. Rising demand also put extreme pressure on existing testing systems in many countries, particularly where these were not set up in a resilient way enabling rapid scale-up. This should be anticipated in any future pandemic.

These pressures meant that early in the first wave, testing capacity was limited, and there was a need to prioritise testing. In the UK this prioritisation focused on:

- clinical care
- key workers
- vulnerable settings such as hospitals
- outbreaks in care homes, prisons and immigration and detention centres
- selected key studies to inform policy or clinical practice (such as the 'Easter 6' study on care homes in early April 2020)

Testing strategy was to support infection prevention and control in settings with vulnerable groups and to ensure essential services kept running by reducing ingress of COVID-19 while allowing those with COVID-19 symptoms to confirm if they needed to self-isolate. There were of course many further uses that were not implemented at this stage of limited testing capacity.

There were simultaneously major efforts to expand systems and infrastructure to provide community testing at scale in spring 2020. Many offers were made by individual sequencing facilities or staff in laboratories. There was considerable expertise, existing workforce and technology across multiple smaller labs in universities, research institutes and the NHS, and many of these labs came forward to offer help. However, without a full and integrated system of testing and reporting and quality control mechanisms, using many such smaller facilities did not easily provide a solution to delivering rapidly scaled and integrated mass testing. It was also important to protect the resources and workforce in NHS and Public Health England (PHE) labs so that testing in clinical settings and other necessary ongoing testing was not impacted by expansion of community testing. Therefore a cross-UK, centrally funded testing network was established for mass community testing alongside a shared testing operations function.

By late April 2020 the COVID-19 Testing Delivery Programme had been stood up to provide mass community testing across the UK with a single shared IT system and end-to-end processes to manage the delivery and processing of tests and results at an unprecedented scale. Large 'lighthouse' laboratories

were set up with the support of private sector and academic partners in the diagnostics industry and existing laboratory staff and experts to provide high throughput test processing at speed. Regional and mobile testing sites were set up for community testing and a digital infrastructure was created to track and locate tests and communicate results (which were linked to existing NHS records). It was important – and will likely remain so in the future – to link national infrastructure back to local teams. For example, regional and mobile testing sites needed to be set up in a way that gave access to testing for all communities and did not exacerbate inequalities in public health and healthcare use.

On 23 March 2020, testing in the community and study-based testing (often referred to as pillar 2, under the COVID-19 Testing Delivery Programme) tested 23 samples per day. By late April, testing capacity exceeded 100,000 tests a day and continued to expand throughout the pandemic. In the month of December 2021 alone the UK laboratory network processed over 13 million samples.[footnote 4]

This was a major undertaking, particularly bearing in mind the processes, networks and skills to set this up were not already in place and so needed to be brought together at pace. The COVID-19 Testing Delivery Programme operated in a unique position across the UK as a service provider, service commissioner, product procurer and, while not the actual manufacturer, the legal device manufacturer for some products.

The following core capabilities were needed to deliver effective testing at scale across the UK:

- product development: progressing concepts from idea generation through to market entry at pace
- product management: ability to manage and launch products following an iterative approach with defined release dates, and ability to add and remove products from a system seamlessly
- technical validation and evaluation of testing technologies
- high throughput lab capacity to deliver low-cost testing, which end point PCR helped achieve – it is helpful to have this lab capacity sufficiently flexible to change application to new pathogens or use new assays and equipment
- a digital platform for ordering and reporting tests – this needed to be rapidly designed and coordinated with digital partners, ensuring platforms remain up to date for latest policy requirements

- access to a national distribution network to move sensitive tests or samples around the country (including from homes and hospitals) and across the UK labs network
- supply chain and logistics expertise about both international and national inbound and outbound supplies, including supply chain planning, business operations and manufacturing – industry leaders brought valuable expertise here
- ability to operationalise policy at pace, leveraging public or private partnerships where beneficial

As a result of this scaling up in testing, from May 2020 onwards symptomatic diagnostic testing was widened from clinical and keyworker testing to the general public, though there were points at which peaks in demand and operational issues resulted in delays processing tests. As PCR capacity expanded, testing strategies were adapted – for example:

- widening criteria for diagnostic testing to anyone in the community with key symptoms
- regular asymptomatic testing in high-risk settings, such as for staff in care homes and healthcare settings

Although efforts to scale up testing were unprecedented and constituted a major achievement, there were critical months in which testing capacity did not meet demand and in which testing capacity limited options for a number of strategies and interventions – and this bears consideration for future preparedness in being able to rapidly scale up testing systems if needed and appropriate.

Alongside cross-UK community testing at scale in the cross-UK laboratory network, each nation also maintained its own testing capacity, which was predominantly in NHS labs but flexibly used for both clinical and non-clinical settings as needed. In Scotland, for example, the 3 NHS Scotland regional hub laboratories were established to provide resilience during rapid spikes in demand. There was also some variation in testing deployment and the detail and timing of testing policies – for example, workplace testing continued for longer in Wales, Scotland and Northern Ireland than in England.

Other testing methods, including reverse-transcription loop-mediated isothermal amplification (RT LAMP) and other testing functions, notably antibody testing, were also explored. Technologies (and why some were used over others) are explored in more detail below.

Later 2020 to 2022: expansion of asymptomatic testing

Although PCR had been used for asymptomatic testing during 2020, turnaround times, the need for laboratory processing, relatively high costs and high resource needs to conduct PCR testing at routine mass population scale, and the fact that PCR testing was sensitive to viral fragments long after infection had resolved, all meant that it was not realistic for routine, mass asymptomatic and pre-symptomatic testing. The arrival of LFDs to the market in later 2020 and 2021, which produced results for self-testing within 15 minutes on average, enabled increasingly widespread self-testing across the population during this period, and testing strategies adapted accordingly.

Initially, there were few LFD products available on the market, and the quality of initial products was very variable with some showing low sensitivity and/or specificity. Manufacturer claims about the performance of individual tests were often not matched when tests were analysed against criteria for quality and reliability. A national scheme was set up to address this and evaluate test quality and reliability. This process is set out in more detail below under 'Quality evaluation, improvement and validation of testing technologies'.

Of course, LFDs generally have lower sensitivity and specificity than PCR (see 'Technologies' below), but once LFDs of sufficient quality became available at scale they were sufficiently reliable and accurate to enable mass routine asymptomatic testing. This supported individuals to assess their likelihood of infectiousness on a day-to-day basis, and was important for key settings such as schools, hospitals and care homes. The asymptomatic testing programmes operated in 4 main testing groups:

- group 1: repeated testing to detect positive cases among asymptomatic individuals (and remove them from circulation) – for example, testing regimes for staff working in high-risk settings such as the NHS, social care, homeless shelters and prisons
- group 2: testing prior to an activity to reduce risk (this may be one or more tests)
- group 3: asymptomatic testing where there was a signal of a potential outbreak (or where there had been an outbreak) to control infections, or where there was perceived to be a higher risk
- group 4: daily testing of contacts to identify positive cases early

As evidence emerged during 2021 on the potential use of LFDs at a population level to highlight potential infectiousness and as a rapid diagnostic tool, further use cases evolved:

- to guide antiviral prescription for those eligible

- for those isolating and contacts to assess their infectiousness (and exit isolation where tests on 2 subsequent days from day 5 onwards were negative)

In 2021 and 2022, more transmissible variants established and many population-wide non-pharmaceutical interventions (NPIs) were eased as both natural and vaccine-derived immunity rose and weakened the link between infections and severe disease. This led to much higher case rates – and testing demand – than that seen in 2020. As a result, LFDs became increasingly central in testing strategies as a way to rapidly test millions of (symptomatic and asymptomatic) people on a weekly basis without needing to further expand laboratory capacity. In under 5 months, the number of LFD tests reported using the existing UK National Testing Programme digital infrastructure had risen from 73 in the week commencing 22 October 2020 to more than 7.6 million in the week commencing 11 March 2021.[footnote 5]

Throughout this period, groups, nations and regions in the UK innovated ways in which testing could be used, with initiatives such as the Events Research Programme which examined the risk of COVID-19 transmission from attendance at events and interventions to reduce that risk, and the commissioning of school and general population trials of daily testing for contacts versus self-isolation.[footnote 6], [footnote 7], [footnote 8]

The city-wide Liverpool voluntary COVID-19 rapid antigen testing pilot provided community open-access LFD testing for those with or without symptoms to understand the possible role of mass LFD testing in various pandemic control strategies.[footnote 9] More than half the population took up asymptomatic testing, and the evaluation found that LFDs identified most COVID-19 cases with high viral load and that the pilot led to an estimated 21% reduction in cases during its first 6 weeks. It also found that test uptake was lower and infection rates were higher in deprived areas, in areas with fewer digital resources or lower digital literacy, and among non-white ethnic groups. Fear of income loss from self-isolation was a key barrier to testing. These were important findings informing not only the possible role of LFDs in pandemic control strategies but also considerations in their deployment. LFD testing differed slightly across the UK nations, predominantly in its deployment timing, but overall strategic aims were similar.

Throughout the pandemic

Testing supported research and clinical trials throughout the pandemic, but no systematic process existed to link people engaging in testing to trials or research studies. Approaches by individual trials to different parts of the testing infrastructure enabled some level of linking, for example with testing supporting trials for the AstraZeneca vaccine, followed by Valneva phase 1 and phase 2, and Novavax phase 3. Testing was also made available to key studies such as SIREN and also the ZOE app study. Systems were put in

place to enable this, such as text alerts referring eligible people to National Institute for Health and Care Research (NIHR) trials or processes to enable access to testing infrastructure for research. However, in the future an established process to proactively identify eligible people for trials in advance of a pandemic and through the routine testing infrastructure would be helpful.

Throughout the pandemic, sequencing enabled baseline surveillance for emerging variants and changes in existing variants. This was used in conjunction with more timely case data to assess the potential impacts of new variants and adapt strategies accordingly. There was also a continuous need to evaluate the effectiveness of assays for new variants. Viral neutralising assay studies informed, for example, our understanding of potential vaccine escape. This process is outlined below under ‘Quality evaluation, improvement and validation of testing technologies’.

There were some differences across the UK in variant testing – for example, ‘surge’ testing following identification of variant cases in the first half of 2021 was predominantly conducted in England. At the time of writing there is not yet conclusive evidence on the effectiveness of surge testing to slow or stop the spread of variants, though it was also implemented to gather data supporting early assessment of the characteristics and dynamics of a given variant. This highlights the need for ongoing evaluations during pandemic response to be embedded in all areas.

Technologies

To expand capacity, reduce risk of supply failure and to service anticipated use cases, a wide selection of diagnostic technologies were supported into development and evaluation in this pandemic. At the inception of testing, a number of technologies were explored as it was unclear how effective, scalable or reliable each was. Broadly, there were 3 methods:

- molecular, to detect viral ribonucleic acid (RNA)
- antigen, to detect viral proteins
- serology, to detect host antibodies

What was available and what tests were used for changed over the course of the pandemic, and we anticipate this will be true also of future pandemics and epidemics. It was important to establish the sensitivity and specificity under specific conditions (for example, depending on viral load) and at which points after infection testing was most effective. The training and equipment needed was also important, as was acceptability of different testing methods and sample sites. It was important to engage operational and industry experts early on to understand, alongside the technological capabilities of a given test, what would be feasible in practical terms for its widespread use.

Alternatives to improve accessibility were continually reviewed, such as saliva sampling. However:

- LFDs with saliva sampling methods did not pass UK Health Security Agency (UKHSA) performance tests until relatively late on in the pandemic
- PCR with saliva sampling would have required changes to lab and logistics infrastructure (or parallel lab and logistics infrastructure) which would be costly, while the benefits in increased uptake were not compelling in evaluations
- LAMP testing using saliva samples did exist, but it was challenging to deploy LAMP testing at scale

Nasal and throat swabs were predominantly used, later switching to nasal only. We anticipate testing technologies will continue to evolve, and the next pandemic may well have technologies not currently available, but the broad principles of lab-based or point-of-use testing for acute infection, and serology or similar for prior infection, will remain.

Table 1: advantages and disadvantages of different methods

Method type	**Advantages**	**Disadvantages**
Molecular (PCR)	- High clinical and analytical sensitivity and specificity - Samples can easily be moved off-site and sent to labs far away -Can use self-collected samples - Possible to conduct at scale - Can indicate some variants in advance of genomic testing	Turnaround time longer than LFD (this varied depending on a number of factors – see main text) - Cannot easily distinguish between whole virus and viral fragments, so can continue to show positive after active infection has subsided
Molecular (RT-LAMP)	- Rapid results (less than 20 minutes) - Performed well in pre-infectious and infectious phase - Comparable performance to RT-quantitative PCR (qRT-PCR)	- RT-LAMP machines usually need to be on-site with regular quality checks - Staff training requirements to use

Method type	Advantages	Disadvantages
Antigen (LFD)	- Rapid results (10 to 30 minutes) - Results at point of testing (convenient) - Does not require laboratory process or specialist knowledge to interpret results and can use self-collected samples, decentralising testing - Possible to conduct at very large scale - Lower cost than RT-LAMP (for example, for asymptomatic testing) - Can indicate infectiousness	- Lower clinical and analytical sensitivity and specificity than PCR - Results can be misinterpreted by inexperienced users
Serology	- Enables retrospective analyses of outbreaks (for example, highlighting asymptomatic disease) - Enables surveillance of seroprevalence	- Results only available when antibodies detectable, which may be outside window for informing intervention

Molecular tests

RT-PCR tests for SARS-CoV-2 were developed early in the pandemic in the UK, with tests available in small numbers from January 2020. The workup of a new PCR diagnostic test for SARS-CoV-2 took between 3 and 6 weeks as it was dependent on:

- knowledge of exact viral sequence and viral diversity in target area (see chapter 1, question 2: ‘What information could be gathered about the pathogen that could help develop an initial diagnostic test?’)
- ability to source key reagents (primers and probes)
- ability to source appropriate clinical material for assay validation purposes (establishing analytical sensitivity and specificity)
- ability to source control material (known template)
- ability to deploy the new test against relevant clinical material acquired from cases of new virus infection (which may be difficult to acquire)

RT-PCR tests did not easily distinguish between whole viable virus and viral fragments, and so repeat PCR tests were not advised within 90 days of infection. Initial PCR turnaround was slow because of limited supply and number of testing sites. Over the course of 2020 turnaround times reduced but this varied significantly during 2020 to 2022 according to:

- the level of demand
- wider testing processes and infrastructure
- whether the testing was performed in 4 nations' NHS and public health laboratories (often referred to as pillar 1) or in the cross-UK laboratory network of pillar 2

The samples were initially taken by healthcare professionals, then by trained individuals operating in the established test sites for the collection of community samples, and finally, with guidance and communications, by the general population in self-collected samples. There was an option to self-test at home using posted tests (though delivery of tests to individuals extended the turnaround time), or to self-test at testing centres.

The analytical sensitivity (ability within the lab to detect a SARS-CoV-2 positive sample of RT-PCR) was very high, and as is typical for PCR specificity for virus was also high. Clinical sensitivity, taking into account not just the accuracy within the lab but also all other factors in collecting a relevant sample and processing it, was also high. The long tail of positive tests after infection, however, had an impact on clinical specificity as well as on individuals needing to comply with restrictions for those testing positive, as PCR could be detecting viral fragments from a previous infection in an individual who was no longer infectious. Clinical sensitivity and specificity, as well as positive and negative predictive values, can be impacted by many different factors such as the anatomical location of viral replication, which clinical sample was taken for diagnosis or, in the case of positive and negative predictive values, background prevalence.

It was important to have more than one diagnostic target to provide assurance of accuracy, and in the very early days of the expansion of testing for COVID-19 it was important to have a detection and confirmation strategy as separate steps. A confirmation strategy involved the use of a second viral target or a partial genome sequence to give confidence in accuracy.

There was a need to adjust test design or critical reagents during the early stages of this pandemic, as a result of emerging knowledge about optimum clinical sample or information about viral diversity.

Modest re-configurations of the same underlying test technology as PCR testing, and of a technology used in agriculture settings, led to development of high throughput endpoint PCR (ePCR) testing for SARs-CoV-2. This

offered an efficient means to expand test capacity in the community-based testing programme.[footnote 10] The technology incorporated high throughput sample handling into a large-batch-size, continuous manufacturing process.

RT-PCR was a core technology in the UK's testing system and has provided the vast majority of molecular symptomatic diagnostic testing to date. It was also used for asymptomatic testing with weekly PCR tests supplemented by further LFD testing as part of the care home staff testing regime until March 2022. As the pandemic progressed and more variants circulated, the national testing programme (in conjunction with the regulator) requested that manufacturers reported the ability of the PCR technology to detect the circulating variants at the time, in order to ensure that viral identification was maintained.

It was important to recognise that the testing system needed to involve more than the ability to detect the virus in a laboratory and it needed to link to an end-to-end informatics system from individual through to clinical care and public health needs.

Loop-mediated isothermal amplification

RT-LAMP is a rapid nucleic acid (molecular) amplification technique that takes less than 20 minutes to provide a result. Two assay formats were developed and deployed to detect SARS CoV-2: first, using extracted RNA, and second, direct using saliva samples. RT-LAMP assays amplify larger genomic regions than RT-qPCR, and therefore performed well during the pre-infectious and infectious phase when there is freshly produced RNA. RNA RT-LAMP has comparable performance (sensitivity and specificity) to RT-qPCR on swabs and can detect virus in a wide clinical window. The first multicentre pilot deploying a LAMP CE-marked assay to detect SARS CoV-2 began in August 2020, and the assay was validated by the Technical Validation Group in December 2020.[footnote 11]

For COVID-19 detection the direct RT-LAMP assay was predominantly deployed for asymptomatic testing in the NHS in staff members, with smaller use cases in school and social care. Twenty-nine mobile processing units making use of RNA RT-LAMP were also deployed, which were able to respond to outbreak areas in care homes, hospitals, schools, prisons and town centres as well as providing testing at events such as the G7 Summit, and could use the same swabs as the PCR infrastructure.

Direct RT-LAMP testing was not widely used in this pandemic, because the machines to process tests were large and needed space to sit and required regular maintenance. They were also a relatively new technology that had not been used at scale for other pathogens and so required staff training for use. For these reasons they were not as easy to scale and manage in a national end-to-end pathway as PCR. Similarly, for widespread deployment of

asymptomatic testing, another testing technology (LFDs) provided a lower cost option that did not require healthcare professionals, maintenance of machinery or dedicated areas to store machines.

Antigen tests

LFDs enabled rapid point-of-care or self-test for current infection and when people are likely most infectious, with results appearing on the device in 10 to 30 minutes.[footnote 12] LFDs did not require sophisticated laboratory infrastructure or skilled personnel and therefore provided decentralised testing. A digital process was set up to enable ordering and distribution of LFDs and reporting of the outcome by individuals.

LFDs were increasingly used by individuals as the pandemic progressed to conduct routine asymptomatic testing and manage their own risk (for example, by testing before high-risk activities or contact with a clinically vulnerable person, daily contact testing or case testing for infectiousness to determine appropriate end date for isolation). They were also used in research – for example, in the SARS-CoV2 immunity and reinfection evaluation (SIREN) study, which was an important source of evidence on duration of immunity. By the spring of 2022, they also took an increasingly central role in assessing infectiousness to guide isolation timelines (with 2 negative tests on sequential days after day 5 enabling confirmed COVID-19 cases to end isolation).

LFDs are less sensitive than molecular tests. However, they have been shown to be effective in indicating high viral load, and so were used as an indication of likely infectiousness.[footnote 13] COVID-19 Testing Delivery Programme data indicates that the LFDs in use detect between 83.0% (95% confidence interval 82.8% to 83.1%) and 89.5% (95% confidence interval 89.4% to 89.6%) of cases.[footnote 14] Their ease of use and speed of results therefore had to be balanced with careful interpretation of results, and public messaging stressing this – for example, recommending repeat testing on sequential days to increase sensitivity.

LFD quality was initially highly variable and this is an area that required strong regulatory processes (see ‘Quality evaluation, improvement and validation of testing technologies’ below). In order to identify those LFDs that displayed high specificity and high sensitivity against viral loads associated with infectiousness, in August 2020 ministers commissioned the UKHSA laboratories at Porton Down to evaluate LFDs, with UKHSA and Oxford University setting evaluation protocols and providing oversight and UK government labs used to rapidly evaluate the tests.[footnote 15] Importantly, there was a need to monitor real-world data alongside these lab evaluations to understand true effectiveness in use.

Finally, for highly accurate data collation from testing modalities, data from LFDs relied on people self-reporting their results and this could not always be relied upon, particularly where there might be little incentive to do so.

However, by giving individuals information on their likely infection status, the tests still supported early access to treatments for those most at risk of severe outcomes and changes in behaviour to reduce transmission following a positive test.

In 2021, UKHSA refined the types of LFD it evaluated, focusing on more usable devices that had regulatory approval for self-testing and used less invasive nasal swabs.

There were other important antigen tests besides LFDs, such as microfluidic immunofluorescence assay point-of-care antigen tests using nasal and nasopharyngeal swab samples which were used for rapid admissions testing in clinical settings.

Serology tests

Antibody tests were available from February 2020 and were initially considered to guide interventions on an individual level (for example, to enable those with previous infection to return to work). Many healthcare workers were offered antibody testing to judge potential immunity status, particularly in the first wave when there were no known effective medical countermeasures and risk to staff and patients was potentially at its highest. However, using antibody testing to guide individual interventions requires extensive understanding of reinfection and immunity across different individuals. Therefore potential use cases for antibody tests – such as prioritising antivirals for those with immunosuppression – needed to be treated with care.

Antibody testing has been an important tool for research throughout the pandemic to date – for example, in the SIREN study on healthcare staff reinfection rates.[footnote 16] It has also been key in understanding population seroprevalence – for example, through the ONS CIS, Public Health Scotland's seroprevalence survey or the Real-time Assessment of Community Transmission 2 (REACT-2) study.[footnote 17], [footnote 18], [footnote 19] In COVID-19 it was possible to differentiate between antibodies due to prior infection and to vaccination; this is not always possible.

Genomic sequencing and genotyping

In the UK, the first COVID-19 sequence was generated by UKHSA laboratories. Joint work across these laboratories, the public health services of the UK, the Wellcome Trust Institute and a network of NHS clinical laboratories and universities through the COG-UK consortia enabled the collective establishment of a national sequencing and analysis capability that tracked several VOCs. COG-UK was instrumental in getting genomic sequencing established and scaled in the UK. It was also successful in integrating the skills and expertise of academic experts with public health

specialists to understand the genomic variation within the virus, how this was evolving and which mutations might be responsible for severe disease or increased transmission.

Rapid and scalable whole genome sequencing capacity was needed to underpin efforts to control transmission. Genomic sequencing was transitioned from research into a sustained service linking genomic sequencing with serological and biological analysis to understand the impact of the emergence of variants on the trajectory of the pandemic.

In March 2021, the UK provided close to 50% of the world's registered output in genomic sequencing. By September 2022, over 2.8 million cases had been sequenced in the UK with the Wellcome Sanger Institute leading the sequencing of community cases. The institute also provided an important early interpretation signal throughout the pandemic for genomic surveillance of viral evolution and for VOCs once these were identified. UKHSA laboratories in 2021 expanded sequencing capacity to 25,000 genomes per week and since then led the sequencing of the virus from hospitalised patients across the NHS.

New variants made it an imperative to build an integrated capability to rapidly test, diagnose and sequence samples, and to continue to undertake baseline surveillance for emerging variants. To speed the detection of known VOCs, genotyping was introduced alongside PCR testing into both hospital and community testing laboratory networks in order to test for specific mutations in known variants. This enabled an early warning system (usually within 24 hours of a positive PCR result) ahead of definite results from whole genome sequencing.

Genomic surveillance has supported research on vaccine and therapeutic effectiveness for new variants by tracking the growth and distribution of variants in circulation alongside changes in rates of hospital admissions and severe disease. It also enabled monitoring of the virus for genetic mutations which could cause it to be more easily transmitted or to escape vaccines, and for the public health response to be guided accordingly. Sequencing has also supported timely assessment of the efficacy of diagnostic tests for different variants. An early warning system was introduced for laboratories performing genotyping to report and refer concerns in assay performance, and to identify assays that did not work for particular variants at earliest opportunity. This was linked with a Medicines and Healthcare products Regulatory Agency (MHRA) regulatory requirement for manufacturers to report ongoing evaluation of deployed technologies in relation to variants.

The ability to track variants and monitor emergence of variants also supported international collaboration and planning, both directly with other countries and with the World Health Organization (WHO). When border testing was introduced, the COVID-19 Testing Delivery Programme set the standards for private sector providers to widen the performance of whole genome sequencing on positive samples and track the introduction of new

variants into the UK. Across many countries during this pandemic, genomic surveillance was expanded and results were shared early with other nations. This was important to track variants and highlight potential risks early.

Further technical innovations

Testing without a way to create information for the individual and for the pandemic monitoring process is of limited use. Information technology was vital to:

- delivering tests
- processing tests
- reporting, storing and sharing the data
- communicating the results and action to be taken

It was also key to bringing results together at scale for rapid analysis and assessment of the situation, with testing data supporting policymakers, public health professionals (nationally, regionally and locally), health and care professionals, academics and the public to understand the course of the epidemic. Localised testing data also supported people to take informed decisions on day-to-day activities in their local area. For the first time within a national system, testing results were returned into individuals' healthcare records, giving them a permanent healthcare record of their test result. This included self-reported LFDs, though there were questions around the robustness of these results as there were limited incentives for individuals to upload results, and in some instances incentives to falsely upload negative results – for example, to enter venues or events where certification was in place, or to attend work.

Electronic contact tracing also generated real-time data on the rate of transmission and the geographical distribution of cases and enabled us to track the effectiveness of control strategies over time.

Digital readers for LFD results improved the accuracy of the tests while making reporting of results easier. Digital readers had to go through a full development process including regulatory steps, and this took time. Once regulatory approval was in place, an initial pilot and evaluation was undertaken followed by wider rollout of the technology.[footnote 20] Other innovations included quick response (QR) codes – for example, to identify individual LFDs, the development of mobile laboratories for use in outbreaks and specific settings, and improvements in accessibility across a number of areas (for example, apps providing visual support for home PCR test sample collection and self-test LFDs).[footnote 21]

Table 2: summary of testing technology uses

Strategy	Use	Deployed testing technologies
Symptomatic Testing	- Diagnostic testing for clinical care - Diagnostic testing for public health purposed to stop onward transmission - Confirmatory testing - Surge/outbreak testing - Directing therapies eg AV - Testing to determine infectiousness (and therefore guide isolation timelines) following infection	- qRT-PCR - ePCR - Viral sequencing - RNA LAMP - Point of Care (PoC) - Genotyping – reflex assay - LFDs (at a later stage of the pandemic)
Asymptomatic testing	- Universal offer - School/university testing - Daily contact testing - Regular testing of staff members in high-risk workplaces - Borders testing - Certification/COVID-pass to access events - One-off testing for closed environments such as elective care testing, testing of visitors to care homes - Discharge/transfer testing - Outbreak testing - Testing for outbound international travel (which private suppliers provided) - Testing to determine infectiousness (and therefore guide isolation timelines) following infection	- LFDs - Direct LAMP – saliva - PoC tests - qRT-PCR/ ePCR (in limited situations)
Surveillance	- Detection of existing VOCs - Detection of new VOCs - Pandemic trajectory - Research studies - Borders testing for surveillance	- qRT-PCR - Viral sequencing - Antibodies - Genotyping – reflex assay - Wastewater sequencing

Quality evaluation, improvement and validation of testing technologies

Throughout the pandemic there was a pressing need to:

- act swiftly
- review a wide range of technologies across the testing pathway
- encourage and enable innovation, in particular from the private sector

At the same time, technologies needed to be high quality and effective, and entry to the market needed to be properly managed by a regulator at a time of high demand and rapid innovation. The United Kingdom Accreditation Service (UKAS) was of course in place, but there was considerable pressure on the organisation due to a rapid increase in inspection demands during the pandemic. This need for rapidly scaled-up and independent accreditation is an important lesson from this pandemic, and we set out here the steps taken to set this up at speed.

An evaluation process for diagnostic technologies was established in the national testing programme in mid-2020 to support procurement strategies, including performance testing in real-world settings. Early engagement and support from the MHRA facilitated entry into the regulatory system and entry to market for effective technologies. In lab-based testing technologies this included the full pathway, from validation of sample collection methods to quality assurance in laboratories and behavioural insight review of results messages. In LFDs this included pre and post-deployment evaluation to ensure technologies continued to perform as expected once deployed.

To evaluate and improve quality, product and laboratory validation oversight was set up alongside assurance of regulatory compliance both pre and post-deployment in the market. A number of frameworks and processes supported this, including:

- measurement of key performance indicators against service standards
- compliance with relevant standards and regulatory requirements across all organisation functions
- continuous quality improvement
- review and monitoring of any risks associated with the delivery of products and services

Public health agencies, alongside the UKAS and regulators including the MHRA, worked jointly to manage these processes, but the pandemic exposed a gap in the regulatory process for diagnostic testing both in the UK

and globally. For example, data packs provided for self-certification were variable and often limited so it was difficult to judge real-world performance from these.

There was also a need for validation processes to confirm manufacturers' performance claims. Initially, manufacturers of SARS-CoV-2 detection devices could self-declare compliance to obtain their CE marking and there were no set processes or minimum evidence levels for test performance required when making this declaration. This allowed manufacturers to maximise performance claims, and validation for Department of Health and Social Care (DHSC) procurement of tests flagged that a significant number of these devices were failing to replicate their claimed performance when assessed in a technical lab validation.

For example, 75% of lateral flow test devices that applied for DHSC procurement and went through the validation process failed the validation standard. However, these devices remained available for sale on the UK market for anyone to buy, including NHS trusts and commercial providers of testing services. It is unclear what harm this may have caused. Without an independent validation process it was extremely difficult to know whether these test devices performed as claimed for a particular use case. As the private testing market grew, the issue of these poorly performing tests continuing to be available became more acute, both for testing processes and testing kit (such as swabs) both of which required quality assurance.

To address this issue, legislation came into force on 28 July 2021 requiring all antigen and molecular detection tests for COVID-19 to be validated. From 1 November 2021, it was unlawful to supply an unvalidated SARS-CoV-2 test (subject to limited exceptions).

As universal testing offers came to an end in different nations of the UK, the general public have been able to purchase tests from online and high street retailers. The Coronavirus Test Device Approvals regime has helped to drive up performance standards and should give greater confidence to UK consumers in the accuracy and performance of the tests they purchase.

Collaboration

A cross-UK approach to setting up community testing at scale meant that surge capacity could be offered more efficiently and to areas needing it most, and built resilience into the system (for example, if one lab was suddenly out of operation, samples could easily be diverted). This was particularly helpful to smaller nations but not exclusively: in 2021, for example, Public Health Wales supported surge testing for variants in Bristol by processing samples in its genomic sequencing facilities. It was also particularly important at points in the pandemic where there was a very sudden and acute need to ramp up capacity, encourage the population to test (symptomatic and asymptomatic), or change public health guidance on isolation. Although some elements of

delivery and policies varied across the UK, approaches to testing were underpinned by the same evidence base and testing principles and a major lesson from this pandemic is the value of joint working across the 4 nations.

Data systems and health systems differ across the 4 nations, and there was a need to consider the full range of circumstances when designing a shared testing system. Testing policy and delivery is complex, with multiple interacting systems and needs, and so governance structures need to bring in and work collectively with colleagues from across the UK while remaining simple and understood across the relevant sectors or organisations involved, and while enabling appropriate governance within each nation for operational deliveries and devolved responsibilities. For future preparedness, early consideration, delineation and resource allocation to any necessary regulatory and assurance bodies should also be seen as necessary for rapid but robust innovative diagnostic provision.

Collaboration was essential to testing delivery – between government, the NHS, public health agencies, industry and academia, through the exchange of staff, equipment, knowledge, skills, data sharing and interoperable systems. It was a significant challenge, particularly during the first wave when multiple organisations were having to act outside their usual remit, an unprecedented volume of samples and data had to be gathered, stored and shared, and there were multiple competing demands on resources. There was widespread sharing of staff between universities and the cross-UK laboratory network, but interoperability has not yet been achieved – the UKHSA Rosalyn Franklin laboratory, for example, is not interoperable with NHS testing laboratories, and sample tracking and results sharing has had to be retrofitted rather than done using shared interoperable systems across laboratories. Having agreements and sleeping protocols for sharing information, equipment, samples and staff across the sector (including with private sector suppliers) is an important step to avoid this in the future, but realistically the move to scale up any testing system in such a short time will likely meet similar challenges in the future.

Information sharing across testing systems was important across the 4 nations – for example, when people travelled from one nation to another. It was also important globally, with global sharing of sequence and variant data informing the global response as well as allowing evaluation of the performance of diagnostic tools as the virus's properties emerged.

The changing nature of the pathogen impacted testing strategies and operations. The ability to track variants and monitor emergence of variants informed and strengthened the ongoing response to the pandemic and informed the government response, especially at the borders and when working with governments in other countries and international agencies. Genomic surveillance enabled monitoring the virus for genetic mutations which could cause it to be more easily transmitted or to escape vaccines, and for the public health response to be guided accordingly.

Reflections and advice for a future CMO or GCSA

Point 1

There were 2 important questions at the outset:

1. What do we need?
2. How should we prioritise what we have while we build up to what we need?

Limitations in testing capacity and an end-to-end system to effectively use the output of testing were initially a major constraint. The magnitude and speed of scale-up required in the testing system for COVID-19 was unprecedented. The major efforts required to expand testing capacity highlighted the importance of building testing systems that maintain some form of contingency response, or at least retain some expertise on how to surge in the event of a new variant or an entirely new pandemic. The diagnostics industry should be included in planning as they may be a key partner (for example, in providing rapid surge capacity).

Point 2

It was important – and the UK did not always get this right – to align testing aims, use cases, technologies, data flows and communications in coherent testing strategies.

This can be challenging in the context of new systems and processes, new testing technologies and use cases, and inter-organisational working. An agreed plan for prioritising usage was also required – for example, targeted at high-risk settings (staff and patients in hospital and in care homes) and for outbreak management.

Point 3

Testing was deployed for a wide range of use cases in this pandemic, some of which may be required in future pandemics.

Some use cases were very similar to normal use of tests in infectious disease outbreaks, including for clinical diagnosis, infection control in hospitals, case finding, surveillance and research. Others, such as repeated testing using self-read and self-reported testing, were new at this scale.

Once reliable lateral flow tests were available it significantly improved people's ability to manage their own risks and the risks for those they were meeting, as well as supporting surveillance at scale.

Point 4

> Testing innovations came at speed and required a rapid, independent quality assurance and validation process.

Quality in the market was very variable and the regulatory approach globally was variable.

Point 5

> Communication of the rationale and practical requirements of testing strategies and changes to testing policy was important, whether with the public or professionals.

Although better communications were developed throughout the pandemic, there are some specific interventions – such as translating testing instructions and advice from the very outset, and engaging through trusted community leaders – which could be delivered better in future responses.

Some elements of testing were, and will remain in a future pandemic, complex to communicate – such as the link between the positive or negative predictive value of a test and prevalence. Pilots were helpful in understanding how new strategies or policies might operate and how people might respond to them.

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Chapter 7: contact tracing and isolation

Contents

Introduction

Contact tracing is a recognised public health activity used to identify and break chains of transmission to help reduce the spread of infectious diseases. It has been used for many decades in the response to infectious disease outbreaks and epidemics, usually alongside other public health activities and control measures. Its purpose, to identify people with an infection or potentially infected and isolate them before they infect others, is widely accepted and works in many, but not all, infectious diseases to a greater or lesser degree. It is routine practice in managing many sexually transmitted infections in the UK, and was used effectively, including by UK public health personnel in support of the Government of Sierra Lerone during the 2014 Ebola virus epidemic in West Africa.

However, the scale of contact tracing needed in COVID-19 was unprecedented in the UK. Contact tracing was used during the H1N1 influenza pandemic of 2009, to guide post-exposure prophylaxis – but this was only implemented for 3 months, with far lower case numbers, and even with those lower case numbers pressures on existing systems rapidly became unsustainable. The experience of implementing contact tracing at such scale during this pandemic, and the operational challenges in doing this, are therefore important to reflect on. Although, as now, it is unlikely that future CMOs and GCSA will have operational responsibility for contact tracing, some of the experience from this pandemic may be useful background for them and we have added some of the experience from the 4 nations in brief below.

In the UK, a key part of the pandemic response included the tracing of contacts of COVID-19 cases and timely provision of self-isolation and other public health advice. SARS-CoV-2 is highly transmissible, and COVID-19 often presents with non-specific or no symptoms, which introduced 2 issues.

First, without timely and adequate testing provision, infected people might not be rapidly identified and contact tracing initiated. As contact tracing was dependant on timely confirmation of cases through laboratory testing, this proved to be a limiting factor when testing capacity did not meet demand.

Second, the high transmissibility of SARS-CoV-2 meant that a high percentage of contacts need to be reached for each case within a short timeframe if contact tracing was to identify sufficient contacts in time to stop infection spreading further. This was in contrast with some previous epidemics such as SARS-CoV-1 or MERS-CoV, which showed an epidemic trajectory characterised by less rapid increase in case numbers and therefore less need for large-scale contact tracing from an early stage.

Contact tracing and self-isolation certainly played a useful role in helping reduce transmission and reducing reliance on other non-pharmaceutical interventions (NPIs). The Welsh Government Technical Advisory Group

undertook 2 modelling studies on the impact of the Test, Trace, Protect (TTP) system in Wales in 2021, both of which indicated that the TTP programme had significantly reduced the effective reproduction (R) number.[footnote 1], [footnote 2] However, it is not yet clear what the impact of contact tracing has been in different contexts, and evidence on its impact on the pandemic is still emerging.

There has been important learning from this pandemic on effective ways to deploy contact tracing at scale for an extended period. These include technical issues such as:

- the use of combined digital and telephone approaches and when to switch between them
- the potential uses of apps for automated and anonymised contact tracing

Operational issues included:

- the role of national and local teams
- ways to communicate effectively across different communities
- the importance of supportive packages alongside self-isolation
- the infrastructural requirements to run contact tracing at scale

It has also been a chance to test new approaches and technologies, such as web-based self-serve contact tracing and mobile phone alerts warning people when they had been within 2 metres of a case.

This chapter explores these issues in brief, first setting out the evolution of contact tracing approaches during this pandemic and what this meant for operations, and then bringing together our reflections on contact tracing.

Evolution of contact tracing during this pandemic

In the early ‘contain’ phase of January to March 2020, there were relatively small numbers of cases, and the aim of contact tracing was to identify and manage all contacts using existing structures and testing capacity available at that stage. Contact tracing and self-isolation focused on delaying the establishment of community transmission of COVID-19 in the UK.

At this point, when case numbers were small, tracing of cases could potentially have significant impact on the course of the epidemic and indeed a realistic chance of delaying community transmission. Contact tracing produced important evidence at this stage – for example, on the risk of transmission on flights, in settings such as schools and workplaces, and in population groups with the highest risk of infection.[footnote 3] At this point,

contact tracing was conducted within existing public health structures and systems and it followed existing guidance and protocols for managing high consequence infectious diseases and undertaking large-scale contact tracing.

As community transmission picked up following widespread incursions in February 2020 from multiple countries, 2 linked issues arose. First, testing capacity was insufficient to flag all cases needing contact tracing.[footnote 4] Available tests had to be prioritised for clinical care and in settings with vulnerable people such as hospitals and care homes. This of course impacted contact tracing, as only a limited proportion of true cases in the community were being picked up through testing. Second, the existing contact tracing workforce, resources and systems were not able to handle such a large spike in demand.

As the first wave grew, the relative impact of contact tracing to pandemic control reduced as lockdown was implemented (see Chapter 8: non-pharmaceutical interventions (NPIs) for more on lockdown). There remained, however, an important role for contact tracing to:

- promptly identify as many contacts of confirmed COVID-19 cases as possible to prevent or reduce onwards transmission from secondary cases
- offer advice to cases including signposting to clinical support (for example, where cases may have deteriorated while in the home)
- inform national and local surveillance
- support ongoing research into the epidemiology of the disease and transmission dynamics
- gather information on outbreaks to support rapid local response, including in hospitals
- identify sources and settings of transmission by including the pre-symptomatic period in the contact tracing journey (‘backwards contact tracing’). This was important as a small number of cases in particular settings (such as those with crowding or enclosed space) could account for a disproportionately large number of transmission and secondary cases. It helped identify settings with a high or higher risk of transmission so appropriate policy and public health measures could be implemented, though it can be resource-intensive[footnote 5], [footnote 6], [footnote 7]

Fulfilling the above aims required rapid completion of key steps by contact tracing teams that included:

- contacting cases
- gathering relevant information

- giving public health advice
- signposting to further support where needed
- sharing this data with surveillance teams so that potential clusters, outbreaks and sources of transmission can be identified

The scale of the task was underpinned by a recommendation by the Scientific Advisory Group for Emergencies (SAGE) in May 2020 that at least 80% of contacts for an index case needed tracing for the system to be maximally effective.[footnote 8] Undertaking these steps using existing resources and systems during a rapidly growing epidemic proved to be challenging, and so all 4 nations of the UK established large-scale testing and contact tracing systems. This required significant funding, technology and staffing and was not fully scaled up until summer 2020.

These large-scale contact tracing systems continually adapted as subsequent waves led to further surges in contact tracing demand. The arrival of new and more transmissible variants and changes in the epidemiology necessitated continual reviews and updates to the protocols. For contact tracing to be effective, the public needed to have:

- up-to-date knowledge and understanding of the symptoms of COVID-19
- ways to access testing
- the advice to self-isolate
- available support services

For cases and contacts who were advised to self-isolate, provision of support – both financial and practical – was an important consideration to improve adherence, although there is not yet clear evidence on what types of support were most effective in achieving higher adherence rates. Contact tracing approaches and communications adapted to changing policies such as testing and self-isolation support policies.

There were several shared challenges across the 4 nations:

- a need to rapidly develop and continually improve digital infrastructure to support contact tracing
- a large and flexible workforce of adequately trained professionals to deliver contact tracing
- ongoing review and adaptation of scripts and protocols to communicate effectively and incorporate parallel policy changes (such as support payments for self-isolation)

There were also similar technological needs:

- online self-serve options for the public
- call handler-facilitated contact tracing systems
- apps to alert mobile phone users when they had been within 2 metres of a case

Apps were particularly helpful in tracing without exposing sensitive information where a case may have unknown contacts (for example, from public spaces). App development can often be complex, particularly when personal data is involved and it is taking place at scale, and there were challenges in setting this up. Industrial expertise can be useful here, as can an overall principle of building on existing infrastructure and expertise.

While the underlying principles for contact tracing were the same, operations differed slightly across the 4 nations of the UK. These are set out below.

Cross-UK operational differences and similarities

Key differences

Contact tracing set-up and model

There were differences across the 4 UK nations' approach to contact tracing in terms of local, regional and national responsibilities and utilisation of new versus existing systems. Broadly, England set up a new national system whereas Scotland, Wales and Northern Ireland adapted existing structures for large-scale contact tracing. The strengths of national, regional and local approaches are considered below under 'Reflections'.

England

In England, a new national large-scale contact tracing system, NHS Test and Trace, was set up in May 2020, without a local delivery arm at that time, while existing Public Health England (PHE, subsequently the UK Health Security Agency (UKHSA)) health protection teams continued to manage complex or high-risk settings and outbreaks.

By summer 2020, however, feedback from local authorities and the public indicated that the centralised, national contact tracing model did not always make best use of local expertise, and the focus of national tracing teams might have constrained the timely identification and management of local clusters and outbreaks. The national contact tracing service therefore partnered with local authorities from summer 2020 onwards, bringing local authority public health teams into tracing 'hard to reach' cases and, from spring 2021, enabling them also to manage local outbreaks.

An early evaluation of the local tracing partnerships showed that the introduction of local authority teams had a small positive impact but the effectiveness and timeliness of local contact tracing varied.[footnote 9] Case studies from some local authority areas showed that local contact tracing was more acceptable and helped to trace 'hard to engage' cases and provide locally relevant information and services to cases and contacts, but again it is not known whether this was a consistent outcome for all local areas.[footnote 10] Educational establishments, healthcare settings and elite sports had separate contact tracing arrangements that were supported by the national trace service and PHE (subsequently UKHSA) health protection teams and national specialist professionals.[footnote 11], [footnote 12]

Wales

In Wales, the population-wide contact tracing service used existing public sector structures and had a focus on joint local–regional–national working across:

- the Welsh Government
- Public Health Wales
- all 7 health boards and 22 local authorities
- NHS Wales Informatics Service (subsequently Digital Health and Care Wales)

The Welsh Government provided national oversight, Public Health Wales provided technical expertise and experience (for example, writing an operating framework for regional teams and writing scripts), and health boards and local authorities delivered the contact tracing service using their local intelligence and knowledge.

Scotland

In Scotland, the overall approach was to use existing organisations and partnerships and pivot rather than set up new services. Test and Protect, a Scottish Government-led partnership between the 14 territorial NHS health boards, Public Health Scotland and NHS Scotland, was established in May 2020. This allowed work to begin rapidly as a solid understanding of ways of working was already in place and there was limited need for new financial or contractual arrangements. The operational delivery was through a local–national partnership: each local health board was resourced to recruit a contact tracing team, and a large-scale national contact centre was set up in partnership between Public Health Scotland and National Services Scotland.

Northern Ireland

In Northern Ireland, the contact tracing service was established and delivered by the Public Health Agency (PHA) working closely with the Department of Health. The service operated initially as a short pilot project involving

contacting a sample of people who had a confirmed positive test result before a full operational contact tracing service was implemented from May 2020.

An evolved contact tracing model was introduced in November 2020 involving an increased focus on digital solutions to deliver early messages to contacts and cases, while at the same time enabling professional staff to risk assess and deal with the more complex cases and clusters and outbreaks.

PHA also worked with partner organisations such as the Department for Communities to ensure that citizens were able to access financial and practical support when required.

Staffing and prioritisation during surges in demand

There were differences in staffing models across the UK nations (outlined below), but all nations:

- applied risk stratification to prioritise high-risk cases and complex outbreaks during times of surging demand
- offered digital self-serve to manage demands on contact tracing capacity
- needed to recruit further contact tracers (though they took different routes to do this)
- operated some form of mutual aid

There were earlier publicly stated aims to call every case, but across the UK all contact tracing systems faced the challenge of delivering this in times of extremely high demand and had to adapt accordingly. There were 2 important lessons from this:

- first, rather than switching between these modes of operation, a ‘steady state’ should be sought that sets realistic expectations of the system
- second, as far as possible, digital self-tracing should be the norm, with human resource focused on complex situations or outbreaks (or situations where digital self-trace is not possible)

A focus on local–national partnership also enabled local teams to flex their approach according to their assessments of risk and need.

England

In England, the online contact tracing approach was complemented with a phone-based service, to facilitate contact tracing of citizens who do not use digital services, and improve and accelerate citizen compliance. A national call centre service was set up, commissioned through external suppliers, and a data feed was developed between the contact tracing web platform and a third-party telephony system.

The national call centre was staffed by 2 main types of workforce:

1. Call handlers contracted via third party suppliers. These staff were trained to undertake contact tracing phone calls using scripted guidance and bespoke FAQs.
2. NHS Professionals (NHSP), a private sector staffing provider who provides staff from across the NHS in England. NHSP staff provided clinical expertise across the call centre service with numbers of agents highest in 2020, eventually reduced to only a small number of specialist clinicians retained for escalations and the quality assurance function.

The national call centre was enhanced by a local phone-based tracing workforce when the contact tracing service partnered with local authorities.

The efficiency of the online self-serve versus call handler-facilitated contact tracing approach varied as the pandemic evolved and the demand rapidly changed. There were periods when the national call centre was responsible for approximately 40% of all successful trace attempts, with the remainder being picked up by the digital self-serve or local channels. However, at the highest peaks of the pandemic the phone-based service became saturated, and the use of digital self-serve was expanded.

Given the scale of contact tracing and the number of unknown variables in the pandemic response – such as lockdown and other control measures, new variants and transmission variability of SARS-CoV-2 – the phone-based service had to:

- be simplistic in nature to follow (both for call handlers and citizens)
- be scalable (ramp up or ramp down) at short notice
- interact and integrate with existing systems and structures where possible
- be able to flex and respond to changes in policy and guidance

Wales

In Wales, during the first wave, staff from within health boards and local authorities were redeployed to contact tracing teams from other services that were on pause due to various closures during lockdown. However, by late summer 2020 it had become clear that contact tracing capacity would have to be significantly and rapidly expanded in order to cope with demand. Health boards and local authorities thus recruited additional staff, particularly during the autumn of 2020.

In common with other UK nations, local teams operated ‘mutual aid’ to share cases between regions if one region was experiencing pressures. In addition, the Welsh Government set up an all-Wales national team in November 2020

to help regions with daily surges in case numbers, introduced e-forms in early 2021 and, at times of overwhelming demand such as at the start of the Omicron wave, introduced a prioritisation framework.

Scotland

In Scotland, a system of mutual aid was established so the national contact centre and boards could support each other as demand varied over time. As case numbers grew rapidly in June, August and December 2021, 'higher risk' cases (such as care home workers) were identified (either from testing data or self-identification) and were prioritised for phone calls, while others were sent SMS self-completion forms only.

Northern Ireland

In Northern Ireland, the service was mostly staffed by healthcare professionals such as nurses. As case numbers rose in spring 2020, staff from other backgrounds were recruited and existing PHA staff were redeployed and trained as contact tracers.

High-risk settings and large outbreaks were risk assessed by the clinical team and overseeing public health consultant, with more complex situations managed by the core health protection service. Separate teams within PHA supported care homes, schools, early years and some other settings, working with the contact tracing service as required. This approach of stratified responsibilities and rapid surge training enabled contact tracing during the peaks in demand, though this had to be balanced with demands from other work under the PHA's remit. It will be important to maintain core skills in case of possible future surges (for COVID-19 or another disease).

Another approach to manage high case numbers was to promote the digital self-trace platform to the public which, once details were completed, sent automated SMS messages with public health advice to cases and contacts. Other contingency measures deployed during periods of peak case numbers included:

- reducing the number of attempts to contact positive cases
- redeployment of existing PHA staff
- pausing enhanced contact tracing

Use of private sector contractors to manage some elements of contact tracing

In England, NHS Test and Trace contracted commercial providers to run the call centre and provide the call handler-facilitated contact tracing service, to call or visit cases and contacts linked to international travel, to improve compliance with self-isolation and reduce the risk of transmission of imported SARS-CoV-2 variants of concern. While the web-based contact tracing tool was initially developed in-house by PHE (latterly UKHSA), a commercial company was contracted to maintain and further develop the platform.

In the rest of the UK, public sector providers were used to deliver the core contact tracing service, and in Scotland private support for operational delivery was only for surge flexibility when needed.

Legal enforcement

In both England and Wales, cases and their contacts had a legal duty to self-isolate and breaching their self-isolation could result in fines. This was changed to guidance in spring 2022.

In Scotland and Northern Ireland there was not a legal duty to self-isolate for domestic cases and contacts, though isolation after international travel was legally required in Northern Ireland and Scotland. There were existing powers to restrict or exclude under public health legislation, but these were not used for COVID-19 cases.

It is difficult to assess the impact of legal enforcement (as opposed to guidance) on isolation compliance, in part because social norms around isolation evolved throughout the pandemic and in response to changing epidemiology. There is a study noting self-reported isolation compliance in Scotland to be similar to that recorded in England, but this is not conclusive evidence that either approach is preferable. It is also complicated by possible 'cross-contamination' across nations where the public may not be fully aware whether legal enforcement was in force or not due to media reporting across the UK.[footnote 13] Besides its epidemiological impact, the decision to legally enforce isolation also has a number of legal and practical considerations that will no doubt be important in a future pandemic and may look different across the UK's 4 nations.

Similarities

Isolation support

In all UK nations there was some form of financial support for isolation, although the routes to access this and eligibility varied across the UK. All nations required a person to have tested positive for COVID-19 or been advised to isolate by relevant services in order to access financial support for isolation, though other eligibility criteria also applied (such as being on a low income in England).

Case and contact information management systems with regular data summaries

England

In England, a bespoke contact tracing and advisory tool was developed as a web-based application to facilitate large-scale contact tracing in England. The application received data on positive COVID-19 cases from the existing English laboratory surveillance system and the newly developed COVID-19

Real Time Testing Service. The application was used by the citizens to self-complete contact tracing online, and by both national and local contact tracers to collect and record contact tracing information from cases and their close contacts, and advise on self-isolation and support.

The platform was adopted as the main contact tracing database which was used to regularly extract contact tracing data, undertake analyses and report on contact tracing performance and metrics. The tool has become fundamental to the whole contact tracing infrastructure and was interlinked with other systems deployed during the pandemic response.

Alongside the bespoke contact tracing tool, PHE (subsequently UKHSA) health protection teams continued to use the existing case management system to manage complex cases and outbreaks. However, this system was not designed to record contact tracing information in a consistent way. There were challenges with using 2 separate systems: on the one hand it was not possible for health protection teams to move away from their case management system, and on the other hand it was resource intense to operate 2 systems that were not integrated.

Wales

In Wales, a national case information management system was built and deployed in 6 weeks and linked to the Welsh laboratory information system, enabling regional teams to share details of those who needed support to self-isolate with local authority teams, who linked with third sector support. Management information and performance metrics were extracted to report contact tracing performance to ministers on a weekly basis. Performance information was also published on a weekly basis.

Scotland

In Scotland, there was a single digital case management system logging case, contact and cluster information for use by contact tracers and health protection teams. This single digital case management system was the first unified national health protection database in Scotland that allowed full national access to the data.

Allowing local health protection teams access to all data, including cases outside their own local area, enabled them to agree with national contact centre and each other how they would divide up work. Variation in contact tracing practice between areas was acceptable to fit the local epidemiology (such as capacity to trace contacts in school classrooms), but this caused some public confusion and operational challenge.

Overall, the benefits of local flexibility within a national guidance framework were felt to outweigh the disadvantages.

Northern Ireland

In Northern Ireland, the contact tracing service used an existing digital platform which also supported epidemiological investigation as well as management of cases and contacts. This integrated approach was an important strength of the system, allowing early identification of clusters and outbreaks as well as monitoring spread across Northern Ireland.

Separately, an existing health protection case management software was used for outbreaks and complex cases managed by the health protection team. Use of multiple systems could be challenging at times. The PHA published weekly contact tracing data from these systems including on cases, clusters and outbreaks.

Sharing information

Regular data summaries were used to share information across the UK, as well as with World Health Organization (WHO) member states to support global monitoring and surveillance. Weekly summaries of contact tracing activity were published and daily and/or weekly summaries of key contact tracing indicators were also shared with key stakeholders.

Digital self-trace options

All nations introduced a digital self-trace option for cases to self-complete a contact tracing questionnaire online, complementing the telephone-based approach, and an SMS text follow-up was available to provide information to contacts. Phone lines were available to assist people who were unable or did not wish to use the digital platforms, and provided information, guidance and support for people to check symptoms, book tests or find advice on self-isolating.

Generally, take-up of digital self-trace was between 30% to 50% and the quality of data supplied was low.

Check-in and automated tracing apps

In England and Wales, from September 2020, there was an NHS COVID-19 app (separate to the NHS app which supported vaccine recording, among other things). This enabled automated digital tracing using Bluetooth processing algorithms to log nearby app users and alert those who were likely to have been exposed to SARS-CoV-2. It was downloaded on 21 million unique mobile devices and used by at least 16.5 million citizens at its peak in late 2020. To date, there have been over 30 million downloads registered.

The app uptake was variable, with increased app use associated with more rural areas and less poverty. The use also changed over time and across geographies.

The app also allowed users to ‘check in’ to venues, record their symptoms

and test results, and count down periods of self-isolation. Modelled analyses of its effectiveness found that approximately one COVID-19 case was averted for each case consenting to notification of their contacts, with one estimate that for every percentage point increase in app uptake, the number of cases could be reduced by 0.8% (using modelling) or 2.3% (using statistical analysis).[footnote 14]

In addition, particular venues were required to support contact tracing by either collecting information directly on attendees (with relevant data security processes) or by using a check-in NHS quick response (QR) code which linked to the COVID-19 app.

In Scotland, NHS partners developed bespoke tools during this pandemic, including a proximity app and a separate check-in app. An independent proximity app, Protect Scotland, was developed and launched in Scotland in September 2020 following privacy concerns over the England NHS COVID-19 app (outlined above), due to the centralised nature of its data collection. Protect Scotland was based on a decentralised model. The app became interoperable with English and Welsh apps in November 2020 with notification possible when an England app user was in contact with a Scottish app user. Development of separate apps would ideally be avoided in future pandemics with a single UK application with decentralised data the preferred model.

Check In Scotland was Scotland's location check-in digital intervention, using QR codes to log attendance at venues to allow alerts to be sent where a person was at an event or venue at the same time as a case. This was widely used by the public to check in, but poorly used by health protection teams who sent a very small number of alerts. The additional 'call to action' following an alert was minimal once asymptomatic self-testing was recommended for everyone twice weekly.

In Northern Ireland, the StopCOVID NI proximity app sent anonymous alerts to people via Bluetooth when they had been in close contact with a case. There were approximately 685,000 downloads of the app at its peak, but there is not (as yet) a comprehensive evaluation of its effectiveness. The app was interoperable with other UK regions and Ireland. The app did not have a 'check in' functionality for attendance at venues.

In Northern Ireland, similar to the other UK nations, venues also gathered relevant information on staff and attendees in order to support contact tracing. However, QR codes were less routinely used in Northern Ireland to support contact tracing than other UK nations.

In Wales, the NHS COVID-19 app developed by England was adopted. Users were asked to enter their postcode district area and select their local authority after downloading so that all information and user journeys were accurate for Wales and in line with Welsh policy. A contact tracing app interoperability group met weekly at its peak to discuss and agree actions on critical interoperability issues between Wales, England, Scotland, Northern Ireland,

Jersey and Gibraltar. The app was not available in Welsh at the outset but a fully bilingual version was available by November 2020.

In Wales, too, venues were required to collect information supporting contact tracing. The use of a QR code to support this was optional. QR code information did not link directly to Test, Trace and Protect systems, though it did enable ‘push notifications’ to those who had scanned the QR code if, for example, they may have come into contact with a positive case at a given venue.

Backwards contact tracing

In summer and autumn 2020, all nations set up ‘backwards’ or ‘enhanced’ contact tracing (outlined above) to provide intelligence and alerts to local authorities and health protection teams on suspected clusters and outbreaks, though this was resource-intensive and increasingly difficult when case numbers were high.[footnote 15], [footnote 16]

Piloting and proof of concept

Piloting and proof of concept was used to test all nations’ contact tracing systems:

- in England there was a proof of concept prior to the first lockdown for web-based and phone-based contact tracing and a digital management platform
- in Northern Ireland contact tracing systems were also piloted before implementation
- in Wales, contact tracing pilots were run in 4 local authority areas for 2 weeks in May 2020 to test many of the key aspects of contact tracing, including:
  - likely volumes, workforce roles and training requirements
  - data capture and information flow
  - potential legal issues
  - scenario planning
  - high-risk contact requirements
- in Scotland there were phased introductions of contact tracing but there was limited time for pilots with formal evaluations

In all UK nations, learning and development could have been more routinely built into contact tracing systems. Ways to achieve this include:

- better feedback mechanisms from both the public and professionals involved in contact tracing

- more translational research (for example, though partnerships with academics)
- dedicated improvement roles in contact tracing teams
- routine publication of data on contact tracing performance to support third-party analysis

Scale of operations

In all nations, the scale of contact tracing operations was unprecedented: from inception to winding down in 2022, respective contact tracing systems traced:

- 15.8 million cases and 31.3 million contacts in England
- 1.04 million cases and 1.68 million contacts in Wales
- 2.07 million cases and 3.22 million contacts in Scotland
- 0.6 million cases and 0.95 million contacts in Northern Ireland

Reflections and advice for a future CMO or GCSA

Point 1

> It is important, but not always easy, to be clear with decision-makers and the public about what contact tracing and self-isolation can and cannot achieve in different circumstances.

The role and impact will vary depending on:

- the pathogen and disease being managed
- the stage of the pandemic response, prevalence and incidence
- wider pandemic control strategies

Point 2

> Pre-symptomatic and asymptomatic transmission, in the absence of routine mass asymptomatic testing, are a huge challenge for even a highly effective contact tracing system and place a premium on short turnaround times.

Contact tracing is an effective public health tool particularly in situations where case numbers are relatively low, or the focus is on rapid detection of clusters and outbreaks. Backward contact tracing can be effective to identify sources or risk factors in clusters and outbreaks.

Point 3

> The scientific and public health principles of contact tracing and self-isolation are well established, and most of the challenges in this pandemic were operational, and not directly within the remit of CMOs or GCSA.

However, if contact tracing at this scale is needed again, operational planning and experience on scaling up across the 4 nations will be helpful.

Point 4

> Large-scale contact tracing should wherever possible build on existing systems and expertise.

Local teams may have important intelligence about their communities that can guide the response to ensure it meets local needs. They may also be effective in building rapport and tailoring support for individual cases and contacts.

Regional teams can bring together epidemiological signals from across their patch and can also support pooling of resource to adapt operations to a fast-moving epidemic.

National teams have an important role in:

- pooling resource
- rapidly scaling up unified systems such as digital platforms and data sharing systems
- providing scientific advice
- producing guidance to support local and regional contact tracing teams

Point 5

> Preparedness plans should include the need for large-scale digital platforms.

Early development and use of a digital platform enabling contact management, rapid epidemiological data reporting, and management information was needed but took time to design and implement.

Developing disease-agnostic case and contact management platforms ahead of another pandemic should enable a faster response to deliver a large-scale contact tracing service.

Digital self-service platforms for cases to enter contacts' details were also an important innovation that helped manage the demands on the telephone-based contact tracing service.

Point 6

> The rapid design and execution of pilots and research studies was needed to support dynamic evaluation of contact tracing and to address evidence gaps.

Gaps in the evidence base included effective methods and approaches to contact tracing in different settings, different stages of the response and in different population sub-groups. Other gaps were addressed through rapid research; for example, a randomised control trial of daily contact testing as an alternative to self-isolation for contacts showed that daily contact testing was non-inferior to self-isolation.[footnote 17]

Point 7

> The health equity dimension to contact tracing is important but was not always fully addressed.

Digital-first approaches can exclude, for example, people with visual, hearing, and other disabilities – and so it was important to provide phone and other support alongside this. Some people were not closely engaged with formal information sources and were disengaged from systems delivering elements of the pandemic response.

Long-term engagement with all communities is important in reducing the risk that people become disengaged or misinformed. Digital and other technological solutions deployed to support the delivery of contact tracing should proactively address accessibility and other health equity gaps identified from impact assessments and by local partners.

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Chapter 8: non-pharmaceutical interventions

Contents

Introduction

Non-pharmaceutical interventions (NPIs), also known as ‘public health and social measures’, referred in COVID-19 to the measures to reduce transmission that did not depend on drugs, vaccines or other specific medical countermeasures. The aim throughout this pandemic, as with previous pandemics and major epidemics, is through science to get to medical countermeasures as soon as possible. Inevitably there was a period at the start of the pandemic when medical countermeasures were not available and almost all of the actions to blunt the effect of the pandemic had to be NPIs. This is hardly new – NPIs of some form have been used in almost all pandemics, from case isolation and contact quarantine during plagues in medieval Europe to public advice on safe sex in the HIV pandemic. NPIs had also been a standard part of pandemic planning since 2004, but they were not needed at scale in the 2009 H1N1 influenza pandemic. This pandemic was the first time in living memory that NPIs were used so extensively and at such scale in the UK. As medical countermeasures came on stream the relative contribution of NPIs decreased, but this was a gradual process.

Many NPIs, including hygiene measures, isolation and quarantine, can be a part of routine control of infectious disease outbreaks. A wide variety of measures sit under the term ‘NPIs’, and these can be grouped into:

- measures for individual protection from acquiring the infection from someone who unwittingly is infectious, including:
  - social (physical) distancing
  - surface cleaning
  - face coverings
  - encouraging meeting outdoors (for droplet or aerosol spread)
  - handwashing (for fomite spread)
- measures by an individual to reduce the probability that if they are unwittingly infectious they pass it on to someone else, including:
  - face coverings and masks
  - social (physical) distancing
  - handwashing
  - cough etiquette
- measures to identify (or self-identify) people who are infectious and get them to isolate until they are minimally infectious – the introduction of widespread testing was important in achieving this (see Chapter 6:

testing), as was contact tracing (see Chapter 7: contact tracing and isolation)

- measures to limit the number of households that come into contact, and thereby reduce the chains of transmission. These include closing or limiting places where large numbers of people from different households come together in one place, especially if those places are crowded indoors or with poor ventilation. Examples in this pandemic have included restrictions on the hospitality sector, schools and public transport, and working from home. Full lockdown was the most extensive end of this but there was a spectrum
- measures to provide additional protection to the most vulnerable – which in this pandemic was initially termed ‘shielding’ – so that they are at lower risk of acquiring COVID-19 than the general population
- measures to reduce transmission in high-risk environments
- travel restrictions to prevent or slow the importation of cases, particularly in the early stages of the pandemic, and then to slow the importation of concerning new variants

These each varied in their effectiveness, difficulty, evidence base and negative social, public health and economic consequences. At all times in the pandemic to date, medical and science advice, as well as political decision-making, had to recognise the balance between the harms of not undertaking measures and the potential harms caused by these measures.

A central point that needed to be made repeatedly was that, in having to rely on NPIs in whole or part for the first 2 years of the pandemic, it was always a matter of the least bad option, not a ‘good’ one. In contrast to medical countermeasures where there are long-standing structures and processes to measure the benefits (protection from or treatment of disease) and risks (side effects) using clinical trials, many of the disbenefits of NPIs were in broader social, societal, educational or economic terms that were often harder to measure and required wider technical advice beyond the remit of the Scientific Advisory Group for Emergencies (SAGE) or the CMOs.

It was always the likelihood that medical countermeasures, the products of science, would increasingly come to bear, so NPIs were used to hold the line until that point. It was however very unclear at the start of the pandemic which medical countermeasures might be gained (vaccines, for example, had no role in controlling HIV – drugs did) or how long they would take. Conveying to policymakers and the public that reliance on NPIs was not

indefinite, but that it was not possible to put a time on how long medical countermeasures would take to be deployed, was a challenge in the early stages of the pandemic.

The need for extensive use of NPIs was greatest early in this pandemic, when the population was all immunologically naïve (first wave) or mainly immunologically naïve (second wave), much was unknown about the virus, spread was rapid and mortality and morbidity were both high. The relative importance of NPIs in controlling the pandemic decreased as the availability of effective drugs and vaccines, alongside steadily increasing hybrid immunity from vaccination and infection, reduced both transmission and severe disease for the majority of people. We would expect a broadly similar pattern in a future pandemic, though delays in drugs or vaccines being available, or the emergence of a variant with greater transmissibility, vaccine escape or leading to more severe disease, could result in longer deployment of NPIs.

The next section sets out some of the key NPIs used in this pandemic, some considerations in their implementation and emerging evidence arising from their use – though that evidence has a number of limitations. The list of NPIs set out here is not exhaustive, nor are the references to emerging evidence. SAGE documents hold much greater detail on many of these NPIs, and further academic studies in the coming years will continue to increase our understanding of the effects of NPIs, both in controlling COVID-19 and their wider consequences – so we do not consider this the final point of knowledge.[footnote 1]

There were some differences in the timing, extent and delivery of NPIs across the UK. However, here we offer a cross-UK view for clarity. There were also many further examples of NPIs used in other countries during this pandemic which will be of interest to future CMOs and GCSAs. The science of COVID-19 was a global science, and on many of these NPIs the scientific consensus shifted globally over the course of the pandemic as the epidemiology of the pandemic (such as seroprevalence or variants), its impact and responses to it varied across different countries over time. While changes to scientific consensus demonstrated growing scientific understanding of the pandemic, they could pose challenges in public communications when messages changed over time.

Finally, we should acknowledge in this section the remarkable response of society to the advice to use NPIs. The success of NPIs depended on people from all parts of society acting together to protect the most vulnerable, often at significant disadvantage to themselves. The fact they did, near universally, over prolonged periods – particularly in areas of enduring transmission – is one of the most important lessons of this pandemic, and an extraordinary tribute to a widespread sense of community across society.

Important considerations in deploying NPIs

A number of factors influenced choice of NPIs in this pandemic, including the predominant respiratory route of transmission, the mortality rate, and the distribution of mortality and morbidity across the population with the greatest risks in the elderly but much lower in children. The same NPIs used in other recent epidemics and pandemics, most obviously HIV (sexually transmitted), but also Ebola virus (touch transmitted) or Zika virus (vector transmitted) would have been largely ineffective.

In the early part of the pandemic, the force of transmission was such that extensive use of multiple NPIs used together was needed to get the reproduction number (R) below 1. In reviewing different combinations of NPIs to achieve this, there were some important considerations.

First, the ratio of harms and benefits looked different for individual NPIs. For example:

- hand washing has few downsides but was unlikely to be sufficient to bring community transmission of COVID-19 down significantly
- mass closure of settings may contribute substantially to bringing down community transmission but at a significant societal cost

Second, the appropriateness of NPIs was different for different groups – for example, ‘shielding’ advice for those with high clinical vulnerability. Similarly, differing local circumstances as well as varying levels of population movement across different areas were important when considering localised interventions – this is covered in more detail below under ‘Local tiers or levels’.

Third, the blend of NPIs chosen was important as different interventions can mitigate the risk of exposure via different routes (such as close-range droplet versus longer range aerosol transmission). Although modelling was used to help determine appropriate bundles of interventions, this was complicated by the fact that individual NPIs were not additive but interacting. For example:

- widespread working from home also impacted travel patterns, social contacts and hospitality use
- school closures reduced mixing of children, but also of parents

Some NPI packages may also have had impacts beyond the sum of their parts. Many NPIs used in this pandemic were also not mutually exclusive, such as regulations or guidance to work from home and closure of settings (most of which were workplaces). This had implications for communication and implementation of NPIs, public interpretation and acceptance, and also

for generating and analysing evidence on the impacts of individual NPIs or NPI packages. Attempts to separate the effectiveness of individual NPIs were therefore both difficult and potentially misleading, as NPIs will likely always be implemented in packages and in a particular epidemiological context.

There were also wider considerations in the deployment of NPIs. First, there is always a need for societal consent for NPIs, especially the most potentially damaging ones. There is also a major potential for NPIs to create or exacerbate inequalities and have widespread impacts across society in health, economic and social terms. Decisions on whether and how to implement such wide-ranging interventions go well beyond health and rightly sit with elected ministers on behalf of society. Evidence from observation and behavioural sciences shows that major interventions like NPIs must be felt by the public to be fair, and suspicions that some and not others were following rules was damaging to adherence. It was also important to work closely with local areas and with different communities to ensure NPIs were feasible and appropriately communicated, to understand how they were being interpreted in practice and to understand any barriers to adherence. This was not always in place at the outset of the pandemic and is an important consideration for future pandemics.

Different types of harms were considered from early in the pandemic by scientific advisers and CMOs and they were discussed publicly early in the pandemic.[footnote 2] CMO advice from March 2020 was that excess mortality would come from a number of causes:

1. The most obvious is direct mortality from people dying of the virus despite best medical care.
2. A second major indirect cause of mortality is from the NHS emergency services being overwhelmed and therefore providing significantly less effective care both for those with coronavirus and for those with other medical emergencies.
3. A third cause of mortality and more commonly increased ill health will be the postponement of important but non-urgent medical care and public health programs such as screening while the NHS is diverting resources to manage the epidemic.
4. There is a strong correlation between economic disadvantage and ill health and in the long term any prolonged increase in poverty due to our countermeasures will feed through to poor physical and mental health outcomes.

Alongside this, the impact of the pandemic on disparities was an important concern. The Welsh Technical Advisory Cell for COVID-19 added this formally as a ‘fifth harm’.[footnote 3] (For more detail see Chapter 2: disparities.)

A joint report by the Department of Health and Social Care (DHSC), the Office for National Statistics (ONS), Government Actuary's Department and Home Office, commissioned for SAGE, has a more detailed working-through of COVID-19 direct and indirect impacts on excess deaths and morbidity. [footnote 4] Political decision-makers had to consider all types of harm, including non-health harms and those that were harder to measure or assess.

Considerations when interpreting the evidence

In this chapter, we reference some emerging evidence on the effectiveness and wider impacts of NPIs in this pandemic, but there are several important caveats to this evidence that we would like to highlight here. There are also gaps in the evidence base on NPIs, which we expect will continue to evolve in the coming years.

As noted above, NPIs were implemented in packages and have complex combined effects, which complicates interpretation of the evidence base. It is not a simple additive calculation to understand their combined impact on transmission or indeed their wider impacts. It may never be possible fully to disentangle some of the effects of individual NPIs in this pandemic as many were used together.

Comparisons of NPI impacts over time and across the world were complicated by varying applications of NPIs, varying definitions, varying populations and changing epidemiology and immunity. The effectiveness of NPIs in reducing transmission was influenced by how interventions were implemented, communicated and interpreted, when and where they were used, how (and how far) they were adhered to, and changes in transmission dynamics due to pathogen or behavioural changes – all of which varied across populations and over time. Comparisons across studies is challenging due to this. It was important to have careful critical analysis of systematic reviews bringing together different studies, to interpret these with caution, and to have diverse scientific and professional experts reviewing the literature.

It was often not feasible to unpick the impacts of NPI policies from wider behavioural changes, and this demonstrates the importance of embedding behavioural studies when planning, implementing and evaluating NPIs. NPIs were usually introduced in response to escalating risk, and in this pandemic behaviours also changed in response to escalating risk and often prior to the formal implementation of the NPIs. For example, in a sample of UK adults on 17 to 18 March 2020, 45% reported they had stopped attending bars, pubs and restaurants, 27% had reported stopping seeing family and 30% stopping

seeing friends entirely – all in advance of formal measures to limit such activities.[footnote 5] This made measurement of the independent impact of government measures on transmission difficult to delineate.

For all NPIs there were potential gaps between the theoretical maximum reduction in transmission and that observed in practice due to, for example:

- the design and implementation of NPIs
- the effectiveness of communication around NPIs
- whether and how measures were enforced
- the level of support for behaviour change particularly for those with fewer physical and financial resources to adhere to NPIs

These factors can contribute to incomplete adherence, imperfect adherence (such as incorrect face covering wearing), and lower levels of people continuing to follow public health guidance even when not directed by government. Again, this underlines the importance of embedding behavioural and social sciences to inform modelling on the impacts of different NPI packages, which became more sophisticated as the pandemic moved on (for example, with the 2021 roadmap (https://www.gov.uk/government/publications/covid-19-response-spring-2021/covid-19-response-spring-2021-summary)), as well as informing delivery of services. [footnote 6]

Related to this, it was important to be clear where evidence and advice was about individual-level or societal-level NPI effects on transmission, and to consider the difficulties reading across from one level to the other. For example, although face coverings may have modest impact on risk of transmission for a given individual, at a societal level (and particularly with a highly transmissible pathogen) the benefits may be considerably greater. [footnote 7]

Many research methods were not feasible for population-wide NPIs in an emergency – for example, randomised controlled trials. It was considered neither ethical nor feasible to, for example, randomise shielding and associated social support to only a selection of those deemed clinically vulnerable. It is noteworthy than even for face coverings, which may be the easiest NPI to assess, studies have not been done in a way that provides as clear an answer as medical countermeasures.

Observational studies on NPIs were often complicated by several potential confounders, such as changes in the availability and accessibility of testing alongside changes in behaviours and NPI implementation. Many NPIs were introduced and removed contemporaneously and alongside changes such as:

- variants influencing the force of transmission

- population immunity (vaccine-derived, through infection and hybrid) rising and waning
- methods for implementation and communication around NPIs adjusting
- individuals' perception of risk and approach to risk management changing

This makes it extremely challenging to attribute causal impact to individual NPIs.

Some NPIs had a 'critical mass' of usage below which their impact on transmission may have been negligible but above which they could be an important tool in reducing transmission. The extent to which mobile phone contact tracing apps could alert potential contacts of cases, for example, was contingent on the proportion of the population downloading and using the app, testing, and reporting their result. Determining this critical mass was more straightforward for some NPIs than others.

When considering the impacts of NPIs, it was important continually to bear in mind the possible counterfactual they enabled us to avoid. For example, closure of certain settings had important economic, societal and indeed health impacts – but unmitigated transmission, too, would likely have had major significant harmful impacts across these domains.

Finally, the full effect of many NPIs cannot yet be investigated, because impacts may take many years to become apparent or because they have affected behaviour which has not yet returned to pre-pandemic levels (such as working from home patterns).

Summary of NPIs used in the pandemic with some emerging evidence and key principles

Many of the NPIs used in this pandemic were already well known to the general public when managing the spread of respiratory infections:

- hand washing
- covering coughs and sneezes
- cleaning surfaces

Others were deployed as a regular part of infection control and prevention practice (in health and social care settings in particular) but were perhaps less universally used by the UK public, such as face masks and physical distancing. Others were used for the first time at scale in the UK in living memory during this pandemic:

- limits on group sizes and activities to reduce contacts
- working from home orders
- closure of selected settings and events
- domestic and international travel restrictions
- shielding of the most clinically vulnerable
- lockdowns – perhaps the term that will come to be most associated with this pandemic

Some of these were centuries-old tools to manage epidemics and pandemics across the world, though in this pandemic there were adaptations to these based on the technology available – such as using a mobile phone app to alert individuals when they had been within 2 metres of a case.

In the UK the definition of a ‘contact’ was based on the combination of time and proximity that was judged to be highest risk for exposure and whether the contact was indoors or outdoors, and this was reviewed as the evidence base developed (for example, on transmission dynamics). The risk associated with contacts in the community changed as case rates rose and fell, population immunity increased, new variants arose and medical countermeasures became available.

NPIs in care homes, educational settings and healthcare settings are addressed in chapters 8.1 on educational settings, 8.2 on care homes and 10 on improvements in care respectively. For more details on testing see Chapter 6 and on contract tracing see Chapter 7.

Measures to reduce risk within interactions

Hand and environmental cleaning

Guidance on the frequency, duration and technique of hand and environmental cleaning to reduce fomite transmission was available in the UK from early in the pandemic using existing infection prevention and control guidance.[footnote 8] As the pandemic progressed, and in particular as public settings reopened after the first lockdown, there were further measures to widen access to cleaning facilities such as hand sanitiser in public spaces and sprays to clean common touch surfaces.

Scientific consensus on the relative importance of hand and environmental hygiene shifted throughout the pandemic as evidence developed indicating more limited viability of virus in the environment than initially suspected, and strengthening evidence for the proportionately more significant role of airborne as opposed to droplet transmission.[footnote 9], [footnote 10], [footnote 11] Of course, the likelihood of transfer is greatest the shortest amount of time since a surface has been touched, and so hand cleaning was generally more

important than environmental cleaning. Hand and environmental cleaning no doubt played a role in reducing transmission risk across a range of settings, but it is important to remember that transmission in these settings also depended on proximity, types of contact and other mitigating measures (such as ventilation).

Nevertheless, hand and environmental hygiene advice has remained in place, not least because it has had the additional benefit of reducing transmission for some other infectious agents and, besides, is part of routine advice to many settings. Importantly, this measure also had almost no downsides except the impact of regular cleaning on operations (for example, in schools and businesses), some costs (such as installing basins or buying sanitiser), and on people for whom regular hand washing aggravated skin conditions. It was also a relatively straightforward intervention to implement, though the capacity to make facilities available for cleaning varied across different settings, areas and communities.

Social (physical) distancing

Physical distancing was identified as an important tool to reduce transmission early in the pandemic, and there is now substantial evidence in favour of its use to support control of SARS-CoV-2 transmission.[footnote 12], [footnote 13] The relative importance attributed to physical distancing shifted as evidence strengthened on the role of airborne as opposed to fomite transmission. However, widespread reduction in physical proximity of community contacts was important in interrupting both routes and in fact physical distancing had its greatest impact on reducing respiratory droplet transmission.

There was some global variation in who was advised to distance, when, where and to what degree. In the UK physical distancing was to 2 metres (or one metre with additional measures). Targeting of physical distancing to different groups or settings also adjusted throughout the pandemic as control strategies were updated in response to the changing situation. When the risk of severe disease from infection was higher (before vaccine and naturally derived immunity reached high levels) and there was an urgent need to reduce overall community transmission, physical distancing was deployed as a society-wide measure with all non-household physical encounters requiring distancing. When the aim was to manage risk in the community in a more targeted way as vaccines reduced the risk of severe disease from infection, physical distancing was focused on higher risk settings, situations and individuals, and became advisory.

There were some wider considerations when deploying physical distancing as an NPI that our experience in this pandemic has underlined:

- the variable feasibility of distancing in different settings and situations – for example, in personal care services, and its economic impacts

- the variable impacts of physical distancing – for example, on young children in childcare for whom physical distancing may have an important developmental impact or on those with dementia
- the potential need for widespread detailed guidance and support to implement distancing – for example, in workspaces using one-way routes or in hospitality with adjustments to seating
- the importance of environment and surrounding behaviours in the effectiveness and role of physical distancing – for example, whether contact is indoor or outdoor, in a crowded setting or taking place for a long time
- the interactions between distancing and other NPIs[footnote 14]

Face coverings in the community

This section refers to cloth masks as 'face coverings' to distinguish them from medical grade face masks. Personal protective equipment (PPE) in health and social care is covered in more detail in Chapter 10: improvements in care of COVID-19.

Although some countries, especially in East Asia, promoted widespread use of face coverings or masks from an early stage, the global and UK scientific consensus on the appropriateness of face coverings or masks for preventing transmission evolved during the early stages of the pandemic. In April 2020 SAGE advised that on balance there were benefits in widespread use of face coverings, though as the country was under a national lockdown at the time this was unlikely to be instrumental in reducing community transmission.[footnote 15] In the same month, interim World Health Organization (WHO) guidance advised against the use of face masks for healthy (uninfected) people in community settings. However, as evidence on the routes of transmission and the effectiveness of face masks evolved, this was updated in June 2020 to recommend their use in the community.[footnote 16], [footnote 17] In late July 2020, as the national lockdown in the UK gradually lifted, face coverings became mandatory in a range of public settings across the UK, such as on public transport or in shops (though this differed slightly across the UK nations).[footnote 18] There was variation in enforcement across the UK's 4 nations and across different settings that needed to adapt rapidly to a number of new requirements.

Evolving recommendations on face covering or mask use in the community – from the WHO, the UK government and other governments worldwide – were at times difficult to communicate. They were, however, a reflection of a developing evidence base and also of operational realities at different stages of the pandemic and the need to continually balance multiple risks. At the outset of the pandemic, for example, demand for face masks globally was

extremely high and there was concern that widespread use of medical-grade face masks in settings where they were thought to have marginal or no effect would impact supply lines for health and social care professionals who were in close contact with infectious and vulnerable people.[footnote 19]

The type of face covering was not mandated in the UK outside healthcare settings, and there was widespread use of cloth face coverings by the public. There was some evidence outlining differences in effectiveness across different types of face covering (which we do not cover here). Alongside this, face covering quality and correct wearing were both important. However, in the context of high case rates and a proportion of asymptomatic and pre-symptomatic transmission, logic follows that it is more important to have more people wearing some form of effective face covering correctly rather than fewer wearing high-grade respirators. Feasibility of implementation was important – face coverings were relatively cheap and widely available (once global shortages had cleared) and relatively straightforward to implement with public guidance.

In general, face coverings were advised or mandated in the UK during periods and areas of high transmission and in higher risk settings or situations where distancing and sufficient ventilation were not feasible. In contrast to some countries, they were never recommended outdoors except in very crowded environments. Their purpose has primarily been as source control, with some protection to uninfected wearers – however, in reality adherence varies across different settings, situations and individuals, and studies still give widely varying estimates of their impact on transmission. [footnote 20] Widespread face covering use had some potential impacts on social and educational interactions, such as for younger children, those with dementia and those who rely on facial expression or lip reading for communication. Some groups were exempted from guidance to use face coverings.[footnote 21] There were strong, and opposing, views on the best approach to face coverings in public alongside scientific discourse on the topic.

Ventilation

As evidence accumulated on the importance of airborne transmission for SARS-CoV-2 (see Chapter 1: understanding the pathogen), ventilation was increasingly advised as an important measure to reduce risk of transmission. [footnote 22] In the UK, ventilation was encouraged with guidance for people to go outside or open windows, which was relatively simple and lower cost than many other interventions, although it was not feasible in all situations (for example, in large buildings without individual control over ventilation). This was clearly harder to adhere to in the winter months. The primary purpose was to dilute any airborne viable SARS-CoV-2, and by doing so effectively reduce the range of potential transmission from a given individual, so types of activities within settings also had to be considered.[footnote 23]

More extensive interventions were also deployed, such as funding to put ventilating measures like high efficiency particulate air filters or carbon dioxide monitors in place. Buildings can also be fitted with passive ventilation systems, but this requires expert input, quality standards and training as well as capital investment which would be considerable if implementing across society. There was also a need to balance ventilation needs with energy efficiency and heat retention in buildings and the impact of noise, air pollution and security on ventilation behaviours were important.[footnote 24]

Measures to restrict personal contacts

Case isolation

As is the case for many infectious diseases, case isolation was one of the first and most important tools for controlling SARS-CoV-2 transmission and was implemented in the UK from the beginning of the pandemic when only a handful of cases were in the UK and in advance of population-wide NPIs. It has remained in place throughout, with varying levels of enforcement and guidance.

The effectiveness of case isolation is reliant on the speed and completeness of case identification, the speed and effectiveness of guidance to cases instructing isolation, and finally the extent of adherence to isolation by cases. The speed, accuracy and completeness of case identification in this pandemic was reliant on available testing, due to the relatively generic symptoms of COVID-19 and the existence of asymptomatic and pauci-symptomatic infection (see Chapter 6: testing). It was also reliant on contact tracing to identify further potential cases (see Chapter 7: contact tracing). Case identification was less complete at points when testing demand outstripped supply or when contact tracing was not performed swiftly enough to identify further cases before they began to transmit SARS-CoV-2 to others. It was important throughout to have accurate case identification so that only true cases and contacts were asked to isolate to avoid unnecessary disruption, and for the public to trust that this was the case.

Levels of adherence to isolation no doubt varied across individuals and over time, though it was difficult to read clear signals from surveys of the public on this issue due to obvious social pressures to answer positively and resulting possible response biases. Ability to isolate also varied across individuals, and so financial and practical support for isolation was provided during this pandemic. In some countries, accommodation away from the home was also provided for cases to isolate, but in the UK the scale of case numbers in the community from early spring 2020 onwards rendered this challenging to implement for all case isolation. Accommodation was however provided for quarantining inbound travellers early in the pandemic, and for homeless people – in the ‘Everybody In’ initiative – an unprecedented and important measure to protect this highly vulnerable population.

Timely and complete adherence to case isolation can go some way to avoiding or delaying the need for population-wide measures like lockdown, but realistically adherence will never be 100%. There may come a point in any pandemic where case rates have reached such a level that population-wide measures to limit contacts are needed to reduce community transmission. Some of those used in this pandemic are outlined below.

Working from home, closure of specific settings and closure of public events

These 3 interventions are addressed together here because they overlapped considerably: events and settings were also workplaces, and events often took place within settings. Transmission within households was a considerable risk that was difficult to mitigate, and therefore limiting out-of-household contacts through these measures was important not only for the individual taking part in an activity, but also in protecting their household contacts. In addition, restrictions on these activities reduced a series of related contacts, such as travelling to settings or events, or social contacts linked to these activities (such as visiting a restaurant before an event). Closure of outdoor events, for example, was probably more important for restricting associated activities such as travel or congregating in indoor hospitality venues than for limiting outdoor contacts within the event itself.

The impacts of large parts of society working from home can be considerable, reducing the number of contacts not only within the workplace but also in other public settings such as public transport and hospitality. In late 2020 SAGE noted that around a third of contacts were linked to work and its associated activities, and in late 2021 it assessed that reintroduction of working from home guidance may have the largest impact on transmission out of proposed measures (such as certification and face coverings).[footnote 25], [footnote 26] One global systematic review of NPI studies found that workplace closure was associated with a reduction in transmission in 12 out of 14 studies – though it was difficult to distinguish within these studies (and generally when reviewing evidence on this measure) where working from home was distinct from settings closures.[footnote 27]

Working from home measures differed slightly across the UK over the course of the pandemic, and there were changes over time in whether working from home was mandated or advised. For large parts of the pandemic, guidance for employers and individuals was that those able to work from home should do so – and this had implications for disparities.

First, because patterns of workplace attendance varied across the country and also linked to existing disparities. Analysis of the DHSC tracker survey between January and February 2021 found that non-essential workplace attendance was significantly independently associated with a range of socio-demographic variables and personal circumstances. Financial hardship,

lower socio-economic status, having a dependent child at home and working in certain key sectors were associated with higher likelihood of workplace attendance.[footnote 28]

The second reason was that only around half of the working population were likely to be able to work from home at any given point.[footnote 29] Those unable to work from home continued to face risk of infection when attending work, though the measure itself acted to reduce overall transmission so there remained overall benefit to this group from the intervention in terms of SARS-CoV-2 transmission. Those working from home for extended periods, meanwhile, may have faced mental and physical health impacts such as musculoskeletal issues from altered working patterns. It was, however, challenging to assess the impacts of working from home as many have not returned to pre-pandemic working patterns and there were several potential confounders to observational approaches, such as differing practices across different workforce groups or demographic differences across different professions (for example, the hospitality sector tending to have a relatively young workforce).[footnote 30]

Closure of specific settings (such as hospitality, non-essential retail, personal care, leisure settings or places of worship) was also implemented slightly differently across the UK throughout the pandemic. Some of this was a national question and some differed by locality (see: 'Local tiers or levels' below); regardless, local complexities in communication and implementation needed to be considered. The combined impact of settings closures has been easier to determine than the contribution of individual setting types: a SAGE paper in September 2020 concluded that the closure of bars, pubs, cafés and restaurants together had a moderate impact on COVID-19 transmission overall (medium confidence), while closure of close-contact personal services (such as hairdressing) may have had a lower impact on transmission (low confidence).[footnote 31] The effects of all the closures on transmission was, however, cumulative and it made logical sense to start with settings where large numbers of households met together indoors, often with limited ventilation in close proximity. The relative impact of settings closures on transmission also depended on mitigations in place while open (such as ventilation and distancing). Essential shops and schools were likely to become more important relatively as sites for transmission as other places where households mixed indoors closed. It was important to consider a range of factors in determining risks associated with different settings including the layout of the setting and physical features (such as ventilation), activities taking place within settings, who would be mixing within settings, at what proximity and how often (see Chapter 1, section 9: What were higher risk settings of transmission for SARS-CoV-2?).

The evidence base was complicated, however, by changes in behaviours throughout the pandemic in response to changing policies and restrictions, and to wider factors such as seasons and holidays. There was therefore a need to consider these NPIs as complex behavioural interventions with many barriers and enablers. A range of studies and information was needed to

unpick this, such as qualitative studies to understand the drivers of changing behaviours, local intelligence on likely higher risk settings to manage individual outbreaks, and monitoring of contact patterns – for example, through the CoMix and COVID-19 Rapid Survey of Adherence to Interventions and Responses (CORSAIR) studies.[footnote 32], [footnote 33]

As with working from home, there were important considerations for disparities associated with settings closures. Some groups had relied on particular settings for social or economic support more than others and settings closures and their associated loss of work can disproportionately impact those in insecure work, with little financial security, or working in sectors more directly impacted such as hospitality or retail. Again, continual monitoring of impacts alongside links to local communities helped signal where some disparities were arising.

Finally, there were limits on the numbers and settings for gatherings and public events across the UK to reduce mixing in the community and drive down transmission. There was some variation in this across the 4 nations throughout the pandemic, though importantly some related policies such as business support were set by the UK government. Greater understanding of the range and modes of transmission and the dispersion parameter, alongside epidemiological studies on outbreaks, has supported a growing understanding of the potential role of gatherings and events in outbreaks of SARS-CoV-2.[footnote 34], [footnote 35] In June 2020, for example, SAGE noted the strong evidence for super-spreader events, and in August 2020 the SAGE Environmental Modelling Group and Public Health England (PHE, subsequently the UK Health Security Agency (UKHSA)) produced a joint review of evidence that singing and shouting were associated with transmission of SARS-CoV-2. [footnote 36], [footnote 37] This type of evidence generation gave greater clarity on some potential risks for activity types, settings and participant numbers. However, transmission dynamics vary by event, setting, attendees and their relationships, behaviours within an event or setting and background epidemiology (such as dominant variants and community case rates), and so assessing the risk of given events, settings or activities is highly complex. Proximity of relationship with other attendees at an event, for example, may be as important as setting or size of the event – one meta-analysis found that contacts at social events with family and friends were higher than those for casual contacts.[footnote 38]

The type and setting of gatherings and events were important factors in the extent to which they enabled transmission, as well as possible mitigations in place such as testing before and after events, ventilation and face coverings. The UK Events Research Programme, which examined the risk of COVID-19 transmission from attendance at events and interventions to reduce that risk, pointed out the importance of these measures to limit transmission. Low testing adherence following its pilot events, however, limited its ability to reach firm conclusions on how far particular mitigations at events impacted transmission.[footnote 39]

There was a particular concern about the impact of limiting social mixing at one-off life events where the timing was not movable, in particular end-of-life meetings and funerals. The family and social importance of these is considerable but they also often involved elderly or medically vulnerable people mixing. Getting the balance right here was extremely difficult for policymakers.

Lockdown

This was the most intensive measure taken to reduce spread of COVID-19 and was highly effective even in the face of more transmissible variants. This pandemic was the first time in living memory that lockdowns were implemented across so many countries worldwide, so extensively and for such a long period of time. Variations of them were, however, well documented throughout history, and the principles behind lockdowns follow the same epidemiological logic as settings or events closures, working from home and limits to contacts. Definitions and implementation varied worldwide and throughout the pandemic, but broadly lockdowns consisted of:

- travel restrictions
- closure of all non-essential settings
- stay-at-home orders

Lockdowns were highly effective in reducing transmission of SARS-CoV-2. SAGE concluded that the lockdown introduced in March 2020 was associated with a reduction in the reproduction number (R) from an estimated range of 2.5 to 3.0 to an estimated range of 0.5 to 0.7 – though with an initial period of continued high case rates due to ongoing household transmission. [footnote 40] This was due to high adherence and significant sacrifices by the public who went to great efforts to follow guidance and protect one another from exposure. [footnote 41]

There was a range of possible wider impacts arising from lockdown, such as on mental health, levels of physical activity and levels of domestic abuse and safeguarding concerns. These are explored below, but this overview is neither complete nor exhaustive, nor is it possible to say whether these associations were certainly with lockdown as opposed to with the wider conditions of the pandemic. There will also be further impacts that were not measured or have not yet been fully realised.

On mental health, an analysis of the UK Households Longitudinal Study during the first lockdown found that general psychological distress increased substantially from 19% (95% confidence interval 18% to 20%) to 30% (95% confidence interval 29% to 32%). This could be partly the influence of the pandemic itself. However, the most significant decline was in ‘enjoyment of day-to-day activities’. Symptoms of poor concentration, poor sleep and loss of purpose were also cited, and loneliness in young people in particular increased during the first lockdown. [footnote 42]

On physical activity, there were likely variable effects, with some forms of activity (such as walking and cycling) potentially increasing while team sports and activities taking place at (closed) venues reduced sharply during lockdowns. Official road traffic statistics, for example, show a marked increase in cycling in 2020 compared to 2019.[footnote 43] A PHE study showed a decrease in the average duration of strength and balance activity for older people from 126 to 77 minutes per week in March to May 2020 compared to the corresponding period in 2019.[footnote 44] This may have been a result of lockdown, shielding or voluntary precautionary behaviour. Reductions in activity will have had a number of associated health impacts, particularly for those with existing health needs such as musculoskeletal conditions.[footnote 45] Importantly, physical activity outdoors was permitted during the UK's lockdowns, which was not the case in many comparable countries (in which a lockdown meant staying indoors without leaving the home at all).

On domestic abuse and children's safeguarding, concerning increases were seen in presentations after the first lockdown, such as suspected abusive head trauma in children, which may suggest delayed reporting of concerns due to settings closures and confinement to the home.[footnote 46] Authors of several studies have cautioned, however, that attaining comparable data and attributing causes for changes in domestic violence patterns is highly complex.[footnote 47]

The health and wellbeing impacts of economic changes during lockdown also bear consideration, and the literature linking health to macroeconomic changes is well established.[footnote 48] However, it was difficult to unpick these from the wider impacts of the pandemic itself, or indeed to say whether these impacts would have been similar or worse had unmitigated spread taken place and people had proactively adjusted behaviours. There was evidence that people changed their behaviour in response to the pandemic even when not legally required to do so, as outlined above under 'Considerations when interpreting the evidence'.

These impacts – whether from the pandemic or lockdown itself – were not evenly felt across society, and it is particularly difficult to quantify this due to variable data capture of key demographic characteristics such as ethnicity (see Chapter 2: disparities). Lockdown requirements were adapted to lessen these impacts as evidence on routes of transmission and relative risks of different activities evolved and as the introduction of vaccines reduced the risk of both transmission and severe disease. One example was a 'bubbling' policy which allowed contact between 2 households in specific circumstances. Another was loosening restrictions on access to green spaces and playgrounds to enable lower-risk social contact and encourage physical activity – an important protective factor for physical and mental health.[footnote 49] There is a much wider discussion of these in SAGE minutes and papers.[footnote 50]

It is important to note that we are using the term ‘lockdown’ to mean extensive social and economic closure across society, by law, usually including some degree of stay-at-home orders. In the later part of the pandemic there was some use in the media and elsewhere of the term ‘lockdown’ to mean a more limited set of NPIs.

Local ‘tiers’ or ‘levels’

Any NPI (from face covering guidance to lockdown) can theoretically be implemented at any geographical level. Graded NPI packages (known in England as ‘tiers’ and in Scotland as ‘levels’) were implemented at local or regional (rather than national) level during this pandemic, to adapt control measures to local circumstances.

It was difficult to quantify the impacts of local tiers or levels, both on transmission and beyond this on health and wellbeing, in part due to significant confounding where areas with similar populations and epidemiology entered the same level or tier at the same time, and in part due to difficulties in pinpointing the effects of localised NPIs where neighbouring areas with extensive travel links were in different tiers or levels. A scientific pandemic influenza modelling group (SPI-M) analysis on the impact of a 3-tier locally specified set of interventions in England, presented to SAGE in late 2020, found that:

- local authorities in the lowest tier continued to see epidemics growing
- some local authorities in the middle tier saw a reduction in their epidemics
- all local authorities in the highest tier saw decreased growth rates after introduction[footnote 51]

There was, however, significant heterogeneity at this point, both across UK nations and between local authorities implementing measures – SAGE noted that most areas in the highest tier in England had additional restrictions above the minimum set for that tier.

There was an ongoing balance between minimising wider disruption by implementing targeted local policies, being effective enough to be meaningful, and avoiding ‘border’ problems between local tiers. Localisation of measures was complex, particularly where there was extensive travel between localities. Although routine local travel and contact patterns across different areas were recognised in public health advice on local tiers or levels, it was generally not possible to ‘lock down’ an area outside a pre-existing administrative boundary such as a county or district border so it was often difficult to specify tiers or levels to be relevant to local travel or contact patterns. Localised interventions may be pragmatic where there is considerable variation across local areas and minimal travel between them, but once transmission is widespread regional and national policies are often preferable.

There was also a need for decision-makers to consider political issues such as public perceptions of fairness when highly localised policies were implemented, and this influenced policies around tiers and levels. Some people in areas under heavier restrictions may have felt the impact on local economies was unfair, for example, while some of those under lighter restrictions may have felt they were not being properly protected. Of course, public and political support for any measure is an important element of its success or failure, and this can be particularly difficult at smaller geographies where people moved regularly between different tiers and changing rules and communications could rapidly become confusing. The introduction of multiple different levels or tiers nationally also meant increased demands for clarification and advice for local areas and stakeholders. These issues were important – but they also had to be balanced with epidemiological need. In some cases local concerns about increasing tiers or levels delayed decisions to such a point that the intervention was less effective by the time it was enacted.

Finally, there was a risk of widening disparities across different areas by localising restrictions. For example, areas with high levels of low-income manual employment were more likely to see people having to attend the workplace and therefore see higher case rates, which in turn triggered restrictions that further impacted the local economy. Of course, these considerations of fairness and disparities were equally important in deciding on national policies, particularly at times when prevalence in different areas varied widely.

Other measures

Travel restrictions

International travel restrictions were also introduced during this pandemic, and they included bans on travel to and from certain places, testing requirements (including the type of test required and timing of tests relative to travel) and quarantine (both directly supervised and advisory). There was some variation in travel restrictions across the UK, but as a broad summary:

- in January and February 2020, travel restrictions focused on specific countries (initially East Asian) judged to be high risk for case importations, with advice against travel for UK nationals and quarantine of arrivals from these countries[footnote 52]
- in March 2020, as the UK entered a national lockdown, this shifted to advice against all non-essential travel worldwide as well as domestically
- as lockdowns lifted across the UK in summer 2020 and tests were available, advice adjusted to enable international travel in specified circumstances, and testing requirements were introduced for international

travel, whether pre-departure or on arrival

- restrictions were updated throughout the pandemic (both across the UK and globally) as variants of concern were detected in different areas

Border issues combine epidemiological information with wider travel, trade and geopolitical considerations, which are rightly the preserve of elected political leaders. Here we focus on the epidemiology. The important epidemiological principles underlying advice on travel restrictions were:

- imported cases generally matter most when there is a very low level of domestic infection but higher rates elsewhere – for example, in delaying establishment at the very outset of the pandemic, which gives time to assess potential further countermeasures. Importantly, the extent of this delay is often days or at most weeks, rather than months
- when domestic transmission was very high, imported cases were such a small proportion of total infection burden that they made little significant difference to the epidemic
- when local incidence and prevalence reduced and imported cases were a higher proportion of total cases, preventing imported cases became more important again. This question was reconsidered for variants of concern, where the risk associated with importing an individual case changed according to which variant it was. The changing ratios of domestic to imported cases (including of variants) was a gradual process and there was not a set threshold below or above which travel restrictions were or were not important

Judging the appropriateness of travel restrictions in supporting pandemic control depended on the respective rates of infection (including for specific variants) across different territories. There were also considerations beyond the remit of CMO or GCSA advice, such as wider public confidence in the government's response, or the impact of restrictions on travel and trade. In epidemiological terms, the following 2 considerations were important.

First, there was significant global variation in the quality of data informing risk assessments for travel to different areas. In the initial stages of the pandemic, the combination of limited testing, pre-symptomatic and pauci-symptomatic spread and syndromic surveillance relying on non-specific symptoms meant that the extent of transmission in a country was often not visible until hospitalisations began to rise. Data sharing globally was also challenging, with a lack of data on risks for many areas. Retrospective genomic analysis showed that in February 2020 the UK saw several hundred incursions from countries not known to be a high transmission risk at the time, mostly in

Europe.[footnote 53] This improved during the pandemic with the expansion of genomic and other surveillance and with early sharing of data which was critical in judging potential risks, though it remained an ongoing challenge worldwide with many countries unable to provide timely, accurate and representational data.

Second, as with all other NPIs, travel restrictions were not implemented in a policy or epidemiological fixed state and their impact on transmission depended on a number of factors including adherence to measures and behaviours surrounding travel. One international study on border policies, for example, noted that the impact of quarantine on imported cases depended on adherence and other factors such as testing policies in different countries. [footnote 54]

Interpretation of testing data from travel-related testing required careful review and caveats – for example, to flag that positive test rates for those quarantining from a certain country did not translate to case rates in that country. Besides this, in some cases those travelling internationally may have particular behavioural patterns or health profiles that are not representative of the wider population.

Shielding

There were 3 potential approaches to supporting those with heightened risk of severe disease during this pandemic:

1. To identify those at higher risk (who in this pandemic at the outset were thought to number in the millions) and inform them so they would be able to better manage their own risk.

2. To put a programme in place with guidance on managing risk, and support to do so, alongside a wider package of NPIs to reduce transmission in the community.

3. To put measures in place only for those at higher risk, without a wider package of NPIs to reduce community transmission.

In this pandemic, the first 2 options were adopted, and are described here alongside our reflections. Some people (most well known as part of the Great Barrington Declaration) promoted targeting NPIs to the vulnerable group alone or implementing only shielding as a viable option to reduce overall severe disease and deaths, allowing the infection to spread in all others. There were serious questions about the practicalities, ethics and indeed effectiveness of such an approach. For a highly transmissible infection with often minimal symptoms it was extremely difficult to target specific people or groups successfully. Identifying the vulnerable is also an inexact science and the level of vulnerability and associated numbers of those affected changed through the pandemic. Ultimately the most effective way to reduce risk for the vulnerable was to reduce overall community transmission. Many of those shielding lived in households or settings with others who could be at risk of

introducing infection when community rates were high, and those requiring care and support services also had regular contacts from outside the home. [footnote 55]

A core element of the programme to support those at higher risk was advice not to leave their home unless essential ('shielding'), while a wider package of NPIs sought to reduce community transmission.[footnote 56] This advice was accompanied by supportive measures such as eligibility for free food and medicines delivery, differential GP follow-up, access to virtual services, statutory sick pay, and various other forms of support which local authorities and the voluntary and community sector played a major part in delivering. The programme was paused after the first wave but continued in some areas with high transmission (such as Leicester). It formally ended in September 2021 with a letter to those remaining on the clinically vulnerable list.[footnote 57]

The first iteration of a list of clinically vulnerable people across the country was supported by expert panel review of current epidemiological and clinical data, alongside routine data sets (a particular strength of the UK NHS) which were used to identify those considered most vulnerable.[footnote 58] This was updated throughout the pandemic in order to establish and maintain as accurate a 'Shielded Patient List' as possible given current knowledge, which was then flagged in GP records and used to support shielding policy and associated initiatives across the system as well as direct communication with patients. GPs themselves also supported this process by flagging which of their patients had specified health conditions (though people could also opt out of being on the list by contacting their GP – shielding was not compulsory).

This list evolved as understanding of the disease and data on vulnerabilities grew, and in October 2020 a risk prediction model called QCovid® was released that estimated a person's combined risk of catching coronavirus and being admitted to hospital, as well as their combined risk of catching coronavirus and dying (see also Chapter 2: disparities; Chapter 1: understanding the pathogen; Chapter 1, section 5: How severe was this disease, and were there longer-term sequelae?).[footnote 59], [footnote 60] Using the anonymised health records of more than 8 million people from GP records, hospital records and mortality data during the first wave, the tool supported population risk assessment, clinical support, vaccine rollout prioritisation and patients themselves in understanding potential vulnerabilities to severe COVID-19. Importantly, QCovid® also included a measure of socio-economic deprivation.

The approach to development of a list varied slightly across the UK. Scotland, for example, did not apply QCovid® to population records, though findings in England from use of QCovid® such as the identification of vulnerability in adults with Downs Syndrome and people with chronic kidney disease stage 5 resulted in these groups being added to Scotland's clinically vulnerable list. Scotland did not use QCovid® for clinical decision-making, for clinically vulnerable group vaccine prioritisation in January 2021 (when

Scotland's Shielding List itself was used as a proxy), or for the Shielding List update in February 2021. This was partly due to QCovid® not being compatible with Scottish data structures (such as CancerCare records, or measures of deprivation), and the requirement for separate validation of the model for the Scottish population. It was also partly due to data gaps in earlier iterations of the QCovid® model (which are explored below), with early data used to develop the model not accounting for protection from vaccination or for newly established variants.

The tool adapted to new evidence as it became available and did not initially incorporate background infection rates, seropositivity (whether through vaccine or previous infection), the possible mitigating impacts of other interventions (such as lockdowns) or behaviours that could heighten or reduce risk. It was continually validated by a 4-nations panel with expert support, particularly clinical, and was updated accordingly:

- 1.5 million people were added to the list in February 2021 after further evidence emerged through the pandemic on relative risk for either both single or multiple conditions, around 800,000 of whom were then prioritised for vaccine rollout
- children and young people were removed in August 2021

It is currently difficult to quantify the impact of shielding on either SARS-CoV-2 transmission, COVID-19 outcomes or wider impacts, because its early and universal application for relevant groups left no control groups – nor would it have been considered ethical to do so. However, in summer 2021 QCovid® was validated to be performing well in predicting COVID-19 mortality.[footnote 61]

The quality, breadth and completeness of data and evidence available on clinical vulnerabilities impacted the accuracy of the list, and these improved throughout the pandemic. This was partly why the UK was able to enact a formalised shielding policy, with existing datasets alongside local and GP intelligence enabling targeted support to those advised to shield. The evolution of more accurate risk predictions was in part a consequence of amassing further data from the pandemic itself, and in part a result of major efforts to lift barriers in data access, coding read-across between datasets, record linkage and of course bringing together the technical skills to analyse that data.

There are some important principles that bear consideration for similar interventions in the future:

- shielding should normally be an addition to rather than an alternative to other NPIs to reduce community transmission, for the reasons outlined above

- at the outset of a pandemic in an immunologically naïve population with potentially high-risk comorbidities for a novel disease, it was thought important to act swiftly and advise people on their potential risk based on the understanding of the disease at the time. An iterative approach was then needed when forming a list of clinically vulnerable, particularly in the early stages of the pandemic when the disease was moving through populations with different health profiles to the UK's
- communication about clinical vulnerability is complex and can have long-term impacts. Early messages on clinical vulnerability may 'stick' even as the evidence base evolves or may become confused with other vulnerability issues such as economic vulnerability – and often they overlap. There can therefore be a wider group of people who are not formally clinically vulnerable but may be particularly concerned for their health, and they may as a consequence follow shielding advice. In addition, some groups previously thought to be high risk were then found to no longer be deemed 'clinically vulnerable'. Early interventions to protect the vulnerable, regardless of whether they are formally lifted, may effectively stay in place for many over a much longer period due to ongoing concerns about risks. Communication about the intervention itself therefore needed to be clear as to who was vulnerable and why this was changing, as well as what was being asked and why. Communications also needed to be accessible to different groups – accessible versions of shielding letters were in time hosted online, with translations into 13 different languages, easy read and audio described versions – but this took time. Resource is needed from early on to make it happen more speedily in the future
- shielding had a major impact on many people's lives – ONS data describing a self-delineated group of those at higher risk (not necessarily the same as those advised to shield for clinical vulnerability reasons) highlighted that shielding was likely to have saved lives but with considerable associated psychological morbidity in some[footnote 62]
- the risk of experiencing these negative wider impacts was high for clinically vulnerable populations, and for some this was compounded by having limited space at home to exercise or by a lack of digital tools or skills. ONS surveys of those considered to be 'clinically extremely vulnerable' (though noting this list changed throughout the pandemic) have been run to help to

understand, among other things, behaviours, mental and physical health and support requirements during the pandemic.[footnote 62] These have helped to inform guidance and communications, as well as council funding allocations in relation to shielding

- there can also be wider impacts on services, such as GPs and clinicians needing to offer advice on clinical vulnerability, and this needed to be incorporated into plans
- having a tool in the public domain to understand risk in the community has been helpful (in this pandemic QCovid®), and existing data sets have enabled coordination to support those advised to stay at home such as food or medicine delivery

Reflections and advice for a future CMO or GCSA

Point 1

> In the absence of pharmaceutical interventions, NPIs are the only option for pandemic control.

Adherence was generally very high across a range of NPIs in all 4 nations of the UK and in all groups with the public proving willing to take extraordinary measures in order to protect one another in a public health emergency. This included, for example, the efforts made by young people even though they correctly perceived limited personal risk.

Point 2

> NPIs have complex impacts and involved balancing multiple known, potential and unknown harms and benefits.

On several issues evidence and scientific consensus in the UK and globally evolved over this pandemic, such as on the relative contribution of asymptomatic and aerosol transmission, and this had to be continually reviewed and clearly communicated to decision-makers and the public.

There were challenges developing the evidence base on the impact and effectiveness of individual NPIs, especially in real-world settings. We initially lacked off-the-shelf study designs, evaluation protocols, protocols for funders'

rapid review and prioritisation and a pre-agreed framework for NPIs.

Point 3

> The effectiveness of NPIs depends largely on how far individuals are able and willing to adhere.

It was therefore important to understand behavioural responses to changing policies (including enforcement and supportive measures), changing social norms around adherence and changing risk perceptions as natural and vaccine-acquired immunity increased. Behaviours may not always match intention, and understanding the gap between the two was important. Local authorities managing outbreaks fed back that this gap between intention and practice was linked to:

- financial considerations (such as reimbursement for time off work)
- practical considerations (such as support with getting shopping or caring responsibilities)
- information needs (such as providing clear detail on why individuals should isolate and how they can do this practically and safely)
- emotional and mental health support

The effectiveness and impacts of NPIs were difficult to predict and could vary significantly between groups, locations and stages of the epidemic.

Point 4

> Trust was important in public communications around NPIs so that people knew what to do and, as importantly, why.

Using the right communicators, different voices, and the best methods of communication to build trust and communicate clearly and consistently to a range of people throughout the pandemic was a difficult judgement call.

In this pandemic, a range of professional voices played a part, as did community champions and other local and community leaders. Volunteering initiatives and co-production can also develop relationships and support dialogue between service providers and communities that do not start with a high level of trust in authorities.

Local directors of public health amplified and clarified national messaging, which was the main source of information for a large proportion of the population, as well as giving local messages and providing leadership.

Point 5

> The risks of entrenching or exacerbating inequalities in the deployment of NPIs needs to be considered.

Those living in the most deprived areas were:

- least likely to be able to work from home
- more likely to use family or neighbour care-givers
- more likely to use public transport
- more likely to live in high-density accommodation
- more likely to have insecure employment and minimal or no financial resilience

All of these increased the risk of exposure in a population which was also more likely to have the co-morbidities which increased the chance of hospitalisation or death. Although support packages such as self-isolation payments can be designed, there still remain important epidemiological issues such as living in high-density multi-generation homes when isolating, or work conditions that involve living together, so it is important to understand local circumstances and community support networks when designing and implementing NPIs.

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Chapter 8.1: NPIs in education settings

Contents

Introduction

Education is very important for multiple reasons. It is one of the best ways to:

- reduce disparities
- improve life chances
- identify and respond to the most vulnerable
- intervene in mental illness

For this reason education has important public-health positive effects including on physical and mental health in the short and long term. Schools provide a setting in which households mix, both directly through children and young people mixing in class and play, and indirectly including through parents meeting at school gates, travel and being able to return to work with additional associated social and workplace transmission risks. During this pandemic, the fundamental aims were to simultaneously reduce transmission as far as possible, both within educational settings and in the wider community, and also to continue to deliver education and support for the millions of children and young people relying on educational settings. These aims were in tension and are likely to be in tension in any future pandemic or epidemic where transmission in, or around, schools is a significant factor – for example, with respiratory pathogens, or where the risk of harm to children and young people is high. COVID-19 was a pandemic where the risks to children of the disease, while far from trivial, were found to be much smaller than for many other infections, including influenza, relative to older adults.

There was a need to strike a balance between no interventions on the one hand, which risked widespread transmission and resulting impacts on provision of education and health, and on the other hand intensive interventions that could impact education delivery and in turn social development and life chances for many children. Educational settings also provide important safeguarding functions which needed to be considered in the event of closures or restrictions in attendance. The balance shifted between these 2 broad aims at different points in the first 2 years of the pandemic.

In general, the quality of the evidence on the role of non-pharmaceutical interventions (NPIs) collected from education and childcare studies has not been strong and has largely been observational in design or based on modelling.[footnote 1] Where there is evidence, it has tended to focus on the impact on transmission or healthcare utilisation, and there remains a lack of real-world evidence on the wider consequences of control measures, including the implementation challenge and opportunity cost within the sector. All education settings including early years, schools, colleges and higher education institutions, and settings supporting children and young people

with special educational needs and disabilities, have been impacted significantly by this pandemic and appropriate interventions needed to be considered for each. There is a short section below on higher and further education but, because schools tended to receive more central direction during this pandemic than many other educational settings, much of this chapter focuses on schools.

There were important differences in the pandemic experience for different types of schools. For example, special educational needs and disabilities (SEND) schools generally have higher numbers of children with clinical vulnerabilities, and experienced greater challenges implementing NPIs such as face coverings or regular testing due to the additional needs of the children and young people.

Considerations for public health advice for educational settings

As education and health are devolved responsibilities, public health measures and policies in educational settings and school attendance restrictions have varied across the UK. The clinical and scientific advice around implementing such interventions has however been continually jointly reviewed with reference to 5 main considerations:

1. The transmission dynamics of SARS-CoV-2 within educational settings and impact on transmission of the virus across the population.
2. The short and longer-term clinical impact of the pathogen on those within educational settings, including students, teachers and other staff, families and communities in relation to age and other protected characteristics.
3. The public health (clinical, social, educational, wellbeing) impacts of both unmitigated transmission and of the public health interventions themselves.
4. The evidence on the efficacy of different mitigating actions, including evidence of effect against transmission as well as any disbenefits (such as impacts on education and childhood development) or logistical challenges.
5. Rising immunity of the population, obtained through vaccinations and prior infection, which varied by age and some other factors.

Balancing these considerations was complex, not least because the education sector is large and heterogenous. There are 14.9 million 0 to 18 year olds in the UK, accounting for 22.2% of the total population, with a wide range of settings included under the banner of education and childcare. The

heterogeneity of these settings adds to the difficulty of understanding or generalising the impacts of any public health measures implemented, as does the way existing data have been collected.

On the first consideration (understanding transmission dynamics in educational settings), it is important to remember that transmission to and from children, young people and families can occur in household, community and educational settings. The infection risk from behaviours and contacts within schools is also difficult to separate from the wider 'end to end' behaviours and contacts taking place outside of the setting. We found in this pandemic that the majority of transmission was from children to other children, staff to staff, and within families. Several UK-based surveillance studies have provided evidence – for example, demonstrating the impact of school holidays on reducing transmission, and the relatively low transmission within schools in the early phases (wave 1, first part of wave 2). [footnote 2], [footnote 3], [footnote 4] Better links between school-based surveillance and community-based surveys would have allowed for further identification of routes of transmission between settings and communities. There is also some evidence that adolescents and older children have similar patterns of onward transmission to adults given their higher level of social mixing, and some (weaker) evidence that younger children may transmit SARS-CoV-2 less effectively.[footnote 5], [footnote 6] The contribution of asymptomatic infection in children and young people to transmission is not fully understood.

On the second consideration (the short and long-term clinical impacts of COVID-19), early research indicated a different phenotype of COVID-19 in children and young people compared to adults, with most experiencing a mild or asymptomatic form of disease.[footnote 7], [footnote 8] As the pandemic has progressed, the evidence has accumulated to show a very low risk of hospitalisation, severe disease and death from COVID-19 in this group, even for those with chronic conditions.[footnote 9], [footnote 10] A small number of children and young people report experiencing symptoms in the post-acute phase, though robust immune responses to vaccination and natural infection are seen in children and there are now high levels of immunity in this population.[footnote 11], [footnote 12], [footnote 13], [footnote 14] There is also a need to consider the particular symptom profile for children and young people. Despite reports of differing presentations, the symptom profile of COVID-19 for children and young people was generally described in the same way as for adults.[footnote 15]

A paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) was first identified in April 2020, with 216 cases observed between March and June 2020. However, rates of PIMS-TS relative to COVID-19 infection were shown to reduce over time and with the Delta and Omicron waves.[footnote 16], [footnote 17] There are conflicting estimates on the prevalence of persistent COVID-19 symptoms in children and young people, partly due to confusion over the definition and clinical phenotype. Most studies that have utilised a control group indicate a similar level of self-reported persistent symptoms between SARS-CoV-2 positive cases and

controls.[footnote 18] The Office for National Statistics (ONS) estimated 1.8% of primary pupils and 4.8% of secondary pupils reported symptoms compatible with the definition for long COVID beyond 12 weeks post-infection.[footnote 19], [footnote 20] Nonetheless the impact of PIMS-TS and long COVID needed to be considered in the risk–benefit of public health advice.

The clinical risks of COVID-19 to teachers and other education staff were an important consideration, with over 1.5 million adults employed in the sector across the UK. Over time, evidence was collated to suggest that although staff working within the education sector may be at increased risk of transmission, the risk of poor outcomes, including hospitalisation and mortality were not significantly different from the general population.[footnote 21] Subsequent data showed that after adjusting for differences across occupations, the reported ability to socially distance in the workplace and work from home, there was no statistical evidence of a difference in the likelihood of testing for COVID-19 between occupations.[footnote 22] Self-reported data suggests the proportion of the population reporting symptoms compatible with long COVID may be higher in people working in social care, teaching and education or healthcare, compared to other occupational groups.[footnote 23] However, it is not possible to infer from this analysis whether the self-reported symptoms are caused by coronavirus infection.

The consideration, on the (clinical, social, educational, wellbeing) impacts of both unmitigated transmission and of public health interventions themselves, is perhaps the most complex. Case rates of COVID-19 in educational settings tended to mirror community transmission, and high community transmission rates cause disruption to educational settings through pupil and staff absence. Staff illness and absence closely correlated with community transmission and hit a peak in spring 2022, affecting the ability of education settings to deliver teaching and learning.[footnote 24]

In future pandemics, there may therefore be a benefit in restricting attendance in educational settings to priority groups in order to manage unmitigated transmission – not only to the broader population but also to children and younger people themselves who would experience health impacts and educational disruption from extremely widespread transmission.

This must be heavily caveated with the health and wellbeing impacts of limiting attendance in educational settings to priority groups – which are substantial.[footnote 25] They include:

- missed learning
- a reduction in non-COVID-19-related healthcare utilisation
- exacerbation of existing inequality for both children and parents

Globally, full and partial school closures and restrictions on attendance have lasted an average of 224 days and affected more than 1.6 billion learners.[footnote 26]

Data in the UK has emerged on the mental health impacts of pandemic restrictions, including an observed 81% increase in the number of referrals to child and adolescent mental health services (CAMHS) and a 4-fold increase in demand for eating disorder treatment in the period April to September 2021 compared to the same period in 2019.[footnote 27] There is also evidence that pandemic restrictions impacted the behaviours of children and young people with evidence of poor and disrupted sleep, increases in screen time and reductions in physical activity. Additionally, the National Child Measurement Programme interim data collection in 2021 identified a substantial increase from 2020 in the prevalence of obesity in primary-aged pupils in England.[footnote 28] Survey data found a greater proportion of higher education students reporting dissatisfaction with their academic experience and limited opportunities for social or recreational activity.[footnote 29] For many children and young people, attendance at education and childcare is not only vital for learning but also for access to food and nutrition, physical activity opportunity, and health and therapy services. Restrictions on school attendance also gave rise to additional childcare and home-schooling responsibilities for parents and carers, leaving less time for work and leisure activities and impacting parental mental health. The long-term effects for children and families are not yet known.[footnote 30]

On the fourth consideration on the efficacy of mitigations, the evidence base has changed over time. Early decisions around the use of NPIs in education were largely based on modelling data or evidence from adult populations. With time, the challenges and opportunities of applying public health measures to a largely paediatric population became more apparent. Many of the NPIs that are effective in adult populations, such as social distancing and face coverings, are more difficult to implement in younger age groups and have differential impacts – for example, on social interactions.

Finally, rising immunity of the population through vaccines and prior infection has weakened the link between infection and severe disease. In March 2022, an estimated 99% of secondary school pupils and 82% of primary school pupils had SARS-CoV-2 antibody levels above the limit of detection.[footnote 31]

Summary of key measures taken in educational settings during this pandemic

In this pandemic, widespread attendance restrictions were implemented in the UK, and around the world, to reduce transmission of SARS-CoV-2. A number of other measures were also introduced including:

- distancing
- segmenting staff and students into ‘bubbles’

- regular asymptomatic testing
- wearing of face coverings
- contact tracing and isolation
- outbreak management and ventilation

Throughout the pandemic, schools stayed open for children of essential workers and for vulnerable children, enabled in no small part by the efforts of the teaching profession and other school staff, whose work meant that both remote and in-person education could take place. In many cases, and preceding formal restrictions on attendance in schools, parents removed their children from school settings in a response to potential transmission risks. [footnote 32] It was important throughout that parents were confident that measures in schools were both safe and proportionate. This is entirely understandable and will likely be the case in a future pandemic.

Initial response and limiting education setting attendance

Children and young people were initially assumed potentially to be effective transmitters of respiratory infections in general. Pandemic flu models, utilised to inform early advice during COVID-19, considered education and childcare settings as key contributors to spread.[footnote 33], [footnote 34] There was, however, significant debate about whether school closures or attendance restrictions would be needed for the initial wave in addition to other NPIs. Early discussions on the relative contribution of school closures to community transmission in the Scientific Advisory Group for Emergencies (SAGE) highlighted uncertainties around their impact and flagged that due to a relatively long serial interval for COVID-19, any closures would need to be longer than for previous epidemics to achieve the same impact on delaying the first wave or peak, with models suggesting closures of 8 to 12 weeks being required for maximum reduction of peak incidence.[footnote 35], [footnote 36] Debate centred on the role of schools in linking households, recognising that children and young people also mixed in other settings, and that the response of parents to any closures or attendance restrictions were a significant factor in their effectiveness. Early attention was given to the societal costs in terms of parental absenteeism and missed education.

In March 2020, the consensus SAGE view was that while school closures constituted one of the less effective single measures to reduce the epidemic peak, they may be necessary to manage NHS capacity.[footnote 37] The first attendance restrictions were initiated on 20 March 2020, just prior to national stay at home orders. Schools remained open for face-to-face learning for vulnerable children and the children of essential workers. At this time, the overall attendance of students who normally attend school in England was around 3% to 4% for primary school and 1% for secondary school children. [footnote 38]

The subsequent early signals from China were indicative of a mild clinical phenotype of COVID-19 in children and young people, with higher levels of less symptomatic infection. There was uncertainty regarding their role in transmission and the subsequent impact this may have on families, staff and communities. It was initially hoped that it would be possible to achieve a reproduction number (R) below 1 without school closures, but the speed of the initial wave and relatively high R0 made this uncertain with modelling implying it was unlikely that control would be achieved without school closures or attendance restrictions. Widespread attendance restrictions were therefore implemented during the first wave of COVID-19 in spring 2020, with face-to-face provision retained for vulnerable children and the children of essential workers throughout. Attendance restrictions in education occurred alongside widespread restrictions across wider society including a stay-at-home directive as part of a package. These measures were preceded by a level of behaviour change in the population that had already impacted on attendance and the ability of education settings to maintain staffing.

As the pandemic progressed, UK paediatric surveillance studies helped to monitor the course, progression and outcomes of COVID-19 in educational settings. Initial findings were suggestive of a low prevalence rate of COVID-19 infection in schools with the risk of outbreaks increasing as community incidence increased and limited transmission from child to teacher or vice versa, a lower secondary attack rate observed in schools compared to households, and low infection rates in school-based close contacts.[footnote 39], [footnote 40], [footnote 41], [footnote 42] Over time, the evidence strengthened to support a mild clinical phenotype for children and young people; however, PIMS-TS was seen in a small number of children requiring specialist care.[footnote 43] The long-term impacts of post-acute infection were poorly understood and there remains at the time of writing some uncertainty about the prevalence of long COVID in paediatric populations, though high-quality studies suggest this to be low.

Evidence of the likely wider impacts of widespread attendance restrictions were not immediately apparent, but in the first wave evidence also started to emerge of the harms associated with widespread attendance restrictions with lost learning, inequalities in the ability of children and young people to learn from home and a marked reduction in the number of child protection referrals being made.[footnote 44], [footnote 45], [footnote 46], [footnote 47]

Reopening with further measures

In August 2020, the 4 UK CMOs published a consensus statement which summarised the current evidence of risks and benefits to health from schools and childcare settings reopening.[footnote 48] The statement concluded it to be likely that opening schools to all would put some upward pressure on transmission more widely but that there was high confidence that schools were much less important in the transmission of COVID-19 than for influenza or some other respiratory infections.

All attendance restrictions were removed for educational settings in September 2020 with several public health measures in place to reduce contacts including social distancing, segmentation ('bubbles'), and contact tracing and isolation.

Initially, close contacts in education were described in the same way as for adults and contact tracing conducted within settings. This led to high numbers of close contacts being identified for a single case in the early phases, and many staff and students experienced repeat bouts of isolation, impacting parents and carers' ability to work with low-income families vulnerable to job losses.[footnote 49] As further evidence emerged on the relatively low attack rate within education settings, changes were made to contact tracing policy, including a shift of responsibility to NHS Test and Trace (England), use of 'high and low risk contacts' (Scotland, Wales and Northern Ireland), and a removal of the self-isolation recommendation for contacts under 18 years of age.[footnote 50] Education and childcare settings also segmented staff and students into smaller, consistent groups, or 'bubbles', to reduce transmission and aid in limiting the number of close contacts per case. There were also anecdotal reports of benefits to segmentation by reducing inter-year bullying, though we have not seen a formal measurement of this. Overall, the effective identification and isolation of cases and close contacts has been shown in this pandemic to be effective for reducing transmission in school and other settings – though with a need to adjust its application for educational settings.[footnote 51]

Settings were also advised to implement 'social' (physical) distancing measures such as spacing of desks within classrooms, closure of communal areas – for example, staff rooms – and one-way systems in corridors to reduce the number of contacts. Modelling studies have shown that reducing the number of contacts between students led to a reduction in the number of cases, with the magnitude of the effect dependent on the level of community transmission and susceptibility of individuals to infection.[footnote 52] School-based surveillance studies while segmentation was in place demonstrated a lower secondary attack rate observed in schools compared to households, and low infection rates in school-based close contacts.[footnote 53], [footnote 54] However, these measures were very difficult to implement and impacted the ability of the setting to deliver a full curriculum. Head teachers reported having to balance advice on social distancing and reducing close contacts with the ability for children to learn, especially in primary schools where reducing contact is more difficult.[footnote 55]

Building on strong existing local relationships, many local authorities provided intensive support to education settings throughout the pandemic for interpretation of guidance and outbreak management. In England a helpline was established by Public Health England and the Department for Education to provide public health advice, though local feedback highlighted that this did not always work in parallel with local systems.

Attendance restrictions during the second wave, mass asymptomatic testing and face coverings

In January 2021, attendance restrictions were once again implemented following the emergence of the Alpha variant which, ahead of widespread vaccine rollout, threatened high hospitalisation and death rates for adults. This was again accompanied by wider social restrictions including work from home directives and hospitality closures. Children were a higher proportion of those infected in this wave than the first wave.

At this time, it was well documented that children and young people were much less susceptible to severe clinical disease than older people.[footnote 56] In addition, there was clear evidence of the negative impacts of attendance restrictions for schools, including impacts on educational outcomes, mental health and physical health. It was acknowledged that measures with similar stringency and adherence to what had been in place in England in November 2020 (where schools were open) would be highly unlikely to be sufficient to maintain R below 1.[footnote 57] SAGE advice consistently highlighted that while the opening and closing of schools to the majority of pupils was likely to have an impact on transmission, policy decisions needed to balance the observed risks and harms.

Education settings were prioritised for re-opening in March 2021 and accompanied by mass testing policies. Routine lateral flow device (LFD) testing programmes for all staff and students of secondary age and above were implemented in all 4 nations in early 2021 (see Chapter 6: testing). The testing was a combination of onsite testing following return from a period of absence and regular home-based testing using LFDs to identify cases earlier on in the infectious period or that may not otherwise present.

Modelling studies have demonstrated the potential impact of mass testing and isolation on transmission in education settings – however, there is limited real-world data on their effectiveness, and uptake appeared to wane with time.[footnote 58], [footnote 59] The models suggest the impact is highest when testing coverage and the number of contacts identified is high.[footnote 60] Some barriers to uptake of the testing programme included concerns regarding the accuracy of the tests and perceived discomfort of undertaking the test.[footnote 61]

A school-based randomised controlled trial in summer 2021 showed serial testing of close contacts as non-inferior to isolation for transmission. Serial testing was later introduced as national policy to reduce disruption.[footnote 62]

Face coverings were first recommended in education settings on return in March 2021 following evidence supporting their use in community settings to reduce COVID-19 through source control, wearer protection and universal masking.[footnote 63] Policies have varied with time and included use in communal areas, classrooms and on school transport. They have primarily

focused on all staff and students of secondary age and above, and face coverings for under 11s have not been proactively recommended, nor face covering type mandated.

An association between face covering use and decreased COVID-19 incidence in children is shown in 10 studies, and the World Health Organization (WHO) conclude that evidence from adults and community settings can also be extrapolated to children and young people. However, the evidence is generally of poor quality. Other, quasi-experimental studies have demonstrated null effects, with age-dependency being a higher risk factor for COVID transmission risk.[footnote 64] Experimental analyses from the Department for Education suggested a reduction in COVID-19-related absence in secondary schools that introduced a face covering recommendation compared to those that did not. The difference was statistically significant, however the study made a number of assumptions and causality cannot be determined.[footnote 65] Therefore findings should be interpreted with caution.

The use of face coverings in education settings has had to balance the potential impact on transmission with impacts on communication and learning. Survey data from Scotland reported concerns with understanding when face coverings were worn and a survey of teachers and secondary school leaders in England found 94% think wearing face coverings had made communication between teachers and students more difficult.[footnote 66], [footnote 67] There are also likely greater impacts on children with special educational needs and disabilities, existing speech, language and communication issues or those who have hearing loss or auditory problems. [footnote 68] Overall, panel surveys indicate that it was the cumulative impact of COVID-19 mitigations, including face coverings, that had an impact on pupil wellbeing, and many staff found strategies to minimise disruption.[footnote 69]

Reopening, continued mass asymptomatic testing, outbreak management and ventilation

By late 2021, the availability of vaccines and effective therapeutics reduced the link between cases and hospitalisations and deaths in more vulnerable groups, and this reduced the need for such intensive measures to manage transmission to be taken. In summer 2021 many of the more restrictive public health measures such as social distancing were removed from education, in line with wider society and the UK government roadmap.[footnote 70] Education policy therefore focused on asymptomatic testing, outbreak management (including face coverings) and ventilation. Attendance restrictions for education were ultimately considered a last resort.

Improving ventilation is an important factor in mitigating against risk of airborne transmission of COVID-19, with greater benefit seen in occupied spaces with poor ventilation.[footnote 71] Education and childcare settings have been encouraged to ensure good ventilation as a baseline infection

prevention and control measure and the 4 nations introduced different policies to provide carbon dioxide monitors to the education sector to support the detection of areas of poor ventilation. In England, a survey suggested that only 12% of education settings using carbon dioxide monitors reported identification of spaces with sustained high carbon dioxide readings, and of these only 3% were unable to remedy through quick fixes or remedial building works.[footnote 72]

High efficiency particulate air (HEPA) filter devices are a type of air cleaning device designed to filter pollutants or contaminants out of the air that passes through them, and although not a substitute for good ventilation, may be of benefit in areas of poor ventilation where it is not possible for ventilation to be improved through other means such as opening windows. Evidence of the effectiveness of air cleaning devices in school settings is still being collated but, so far, the observed reduction in risk is modest compared to other interventions.[footnote 73] A widely reported study from Italy suggested ventilation could reduce the transmission of COVID-19 in schools by more than 80%. However, the paper has not yet undergone peer review.[footnote 74] A randomised control trial is underway in Bradford to help answer questions around feasibility and impact of air filtration devices in primary schools.[footnote 75] There is also differing evidence on the impact of good ventilation on other health measures such as cognitive performance.[footnote 76], [footnote 77] To be effective, many classrooms would require more than one air filtration device and they can be noisy.[footnote 78]

Asymptomatic testing was continued, though the balance of benefit in detecting asymptomatic cases to reduce transmission and harm (in taking repeat tests and in missing school by isolating asymptomatic cases) changed throughout the pandemic as vaccines and therapeutics became available.[footnote 79] Children and young people attending education have been one of the most heavily tested groups throughout the pandemic despite the low risk of clinical harm. Testing can be unpleasant for some and not well tolerated by some groups with additional needs. Alternatives to swab-based testing such as saliva-based approaches were explored but not universally implemented. In autumn 2021, the emergence of more transmissible variants led to a surge in cases and onward household transmission in the school-aged population, suggesting that asymptomatic testing alone was not sufficient to control transmission.[footnote 80] Asymptomatic test policies had been removed from the majority of education settings by Easter 2022.

Vaccination

There was considerable debate on the place of vaccination in children and its relative importance to reduce educational disruption in addition to health benefits. The UK CMOs were asked to advise on the universal vaccination programme for children and young people aged 12 to 15 years, and to avoid duplication a link to their published advice is in Appendix A: some key UK

CMO joint statements during COVID-19. We therefore do not replicate it here. It is worth reiterating here, however, that decisions were made on the basis of risks and benefits in children, and did not take account of any impact on wider society.

Further and higher education

The further and higher education sectors in the UK are very varied, providing a range of educational opportunities to all ages, including adults, and offering varying learning types that include online approaches, apprenticeships and courses requiring face-to-face learning such as medicine or nursing. The sectors also cover settings of different sizes and in different locations: from large universities in large cities catering for over 40,000 students to smaller further education colleges in smaller towns. Most, but not all, of the sectors offer residential accommodation and ordinarily students in higher education travel from around the world to attend.

In March 2020 university and college campuses were closed and teaching moved online, reopening for face-to-face provision in autumn 2020. The risk of this reopening amplifying local and national transmission was highlighted in SAGE meetings in September 2020, with guidance provided to the sector on how to mitigate this risk.[footnote 81] There was a rapid rise in cases of COVID-19 in 17 to 21 year olds following the start of the academic year. However, the trend was not uniform across universities or local areas. In the early phase of the pandemic, several settings undertook studies of transmission dynamics and were able to demonstrate that at the time the bulk of transmission that occurred between students was taking place within residential spaces, with minimal evidence of transmission within learning environments or to the wider community.[footnote 82]

Key interventions utilised in the higher education sector were contact tracing and isolation, cluster identification and outbreak management, wider quarantine across settings, and use of other NPIs such as face coverings. Mass testing was implemented for higher education students returning home for Christmas in December 2020 to reduce household transmission risks as they returned to their households. The bulk of teaching returned online for the second period of national lockdown in winter 2020 to 2021, with face-to-face education reopening for most settings in May 2021 with mass testing programmes and other NPIs in place. Some universities chose to implement their own policies such as requiring negative test results for access to social events.[footnote 83]

While there remain a small number of settings that have not yet returned to face-to-face teaching, higher and further education students and staff went to great efforts to mitigate the risk of transmission into the wider community, enduring prolonged isolation and quarantine rules – for many students this was during their first experience of being away from home. Several studies

have since highlighted the impact of these experiences on mental health with more than half of students reporting their wellbeing and mental health had worsened as a result of the pandemic.[footnote 84]

Reflections and advice for a future CMO or GCSA

Point 1

> NPIs in educational settings have the potential to have lasting effects on children's education, developmental and life chances.

To strike the right balance between health and educational impacts, it is important therefore with any new pathogen to understand as soon as possible the clinical risk to younger age groups (as well as staff and families) and the role that educational settings play in transmission. The latter proved particularly difficult and contentious with COVID-19.

Point 2

> Educational settings should not be seen in isolation.

Transmission of COVID-19 in education and childcare settings, for example, was strongly correlated with transmission in the wider community, and public health interventions that reduce community levels of transmission will help minimise ingress into these settings.

Point 3

> NPIs in education can exacerbate problems of inequality and deprivation.

Education and childcare settings in more deprived areas were often in areas of enduring transmission and were also more likely to struggle to implement NPIs due to resource or capacity limits. Similarly, effective home education was influenced by access to digital resources such as computers and wifi, and parents' ability to work from home.

Point 4

> The education and childcare sector and the educational estate should not be seen as a single block.

Early years settings or support for those with special educational needs have faced additional challenges implementing public health interventions like distancing. No two schools are the same in terms of how best to implement, for example, ventilation and air filtration. These are important considerations for the provision of guidance to the sector.

Point 5

> The difficulties of real-world evaluation of NPIs in educational settings should be anticipated.

Children and young people do not behave or respond in the same way as adults and while there can be valuable extrapolation, it is important that research takes account of these differences.

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Chapter 8.2: care homes

Contents

Introduction

The COVID-19 pandemic had significant impacts on residents, staff and carers across care homes.[footnote 1], [footnote 2], [footnote 3] In this pandemic, care homes were a substantially higher risk setting for COVID-19 as so much of the risk was in older people, in particular the most vulnerable older people, and spread occurred most readily in indoor environments. This was not always the case in previous pandemics and epidemics, and could look different in a future pandemic. Experience from COVID-19 will be most relevant in pandemics where the elderly are particularly at risk, and where respiratory infection and close contact are important routes of transmission.

In addition, COVID-19 (in common with many other infectious diseases) often presented atypically in the older population, and so there needed to be increased vigilance and a lower threshold for investigation. One of the single biggest reasons for needing long-term care is dementia which is also an important risk factor both for SARS-CoV-2 transmission and poor outcomes. There was a need to reduce risk of transmission among this clinically vulnerable cohort, while continuing to support residents physically and mentally and deliver care services over a prolonged period.

In the UK, the adult social care sector covers multiple types of setting, but here we focus on residential and nursing homes (care homes) as this is the adult social care sector most significantly impacted in this pandemic. The vulnerability of the care home sector to COVID-19 was similar in most high-income countries with large populations of older people. This was flagged as a risk early on in the pandemic, though many countries struggled with the best way to respond and it took longer than anybody would have wished to respond effectively. In the UK, as in many comparable countries, the care sector is complex, large, varied, fragmented and in places was fragile even before the pandemic. The care homes sector alone currently has 7,500 separate providers with 15,500 homes of varying sizes (1 to 250 beds) caring for around 500,000 older and working-age adults (though older people outnumber working-age people by a ratio of 2.5 to 1). There is a high turnover of care workers, and many work in multiple settings or for agencies.[footnote 4], [footnote 5]

Residents in care homes typically have multiple needs and require a range of frequent close care and support interactions – for example, support with cleaning themselves, getting dressed or going to the toilet. This care is provided by staff trained in adult social care, with clinical input provided by on-site nursing staff (nursing homes only) and visiting health professionals. The complexity and severity of medical and nursing needs is even greater in nursing homes than in residential homes. Spread of less severe but highly infectious pathogens such as norovirus and influenza has been known to present challenges to the resident population.

Initial priorities prior to the introduction of a vaccine concentrated on trying to prevent ingress and minimise transmission, as treatment options for infection were limited. However, reducing risk of transmission in care homes involved some of the most complex trade-offs of risk to individuals of any part of the pandemic. These included considering the needs and rights of individuals as well as those of the wider resident population. This in turn meant balancing the risk of COVID-19 outbreaks in a very vulnerable group with maintaining staffing, access to healthcare, close contact needs of residents, visiting by relatives and friends in what are often the last months of life, and dignity and quality of life among a group with high prevalence of dementia. For example, it became clear early on that there was a need to reduce transmission from staff moving between care homes, but an intervention that reduces staffing levels in an already pressured sector could in turn harm quality of care and therefore introduce different risks to residents. Stopping visiting by relatives reduced infection risks to all residents, but inevitably reduced the quality of life of residents and their families. There were existing issues with staffing levels and capacity in the sector prior to the pandemic. Other factors such as limited sick pay (making it financially difficult for staff to take time off if they needed to self-isolate) were common. It was therefore evident from early in the pandemic this was one of the most at-risk sectors but also one where mitigation of risk was not easy in a fragmented sector operating under multiple pressures.

Many staff came from communities experiencing higher transmission and so were also at heightened risk of exposure in the community despite their extensive efforts to reduce risk for residents. This epidemiological trend introduced both transmission risk and a risk to staffing levels in the event of large-scale absences due to COVID-19 sickness. The close links between both staff and visitors and their local communities meant that transmission risks in care homes generally reflected transmission risks in linked communities – and so it was essential to reduce community transmission in order to support vulnerable populations within care homes.[footnote 1], [footnote 6]

These are just some examples of issues explored in more detail in working papers by the Scientific Advisory Group for Emergencies (SAGE) Social Care Working Group (SCWG) referenced in this chapter, and others.

This chapter reviews key public health interventions in UK care homes during this pandemic, first setting out an overview of the epidemiology of the pandemic in care homes as this is important context for interventions.

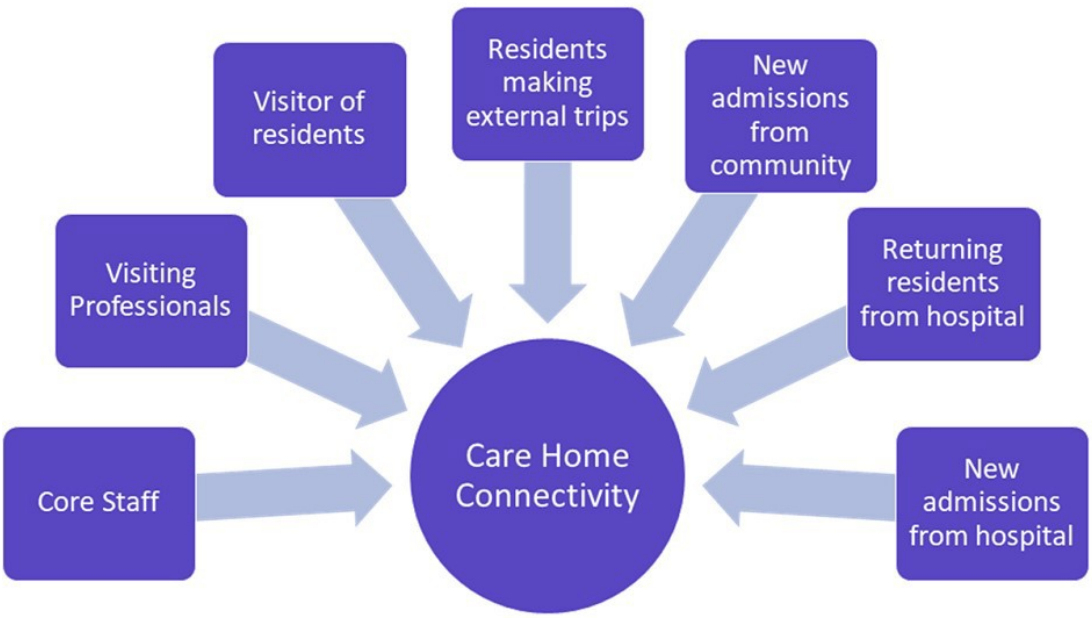
Epidemiology of the pandemic in care homes

In spring 2020, there was widespread recognition that ‘3 epidemics’ were occurring:

- in the community
- in hospitals
- in care homes – with high care home transmission following around 2 weeks after high community transmission

Outbreaks in care homes were closely correlated with community prevalence throughout the pandemic, and there is genetic evidence that the majority of outbreaks were introduced unintentionally by staff members living in the wider community.[footnote 7], [footnote 8], [footnote 9], [footnote 10], [footnote 11], [footnote 12], [footnote 13], [footnote 14], [footnote 15] Care homes were, at this point, largely closed to visitors, but ingress of infection through staff living in the wider community and moving between care homes was readily amplified by the close contact networks required in the provision of care.

Figure 1: schematic showing the potential routes of ingress of COVID-19 into care home settings[footnote 16], [footnote 17]



Larger care homes were more badly affected, which likely reflects their greater number of points of ingress as well as greater risk of resident and staff movement. Staff shortages, worsened by the pandemic, exacerbated risks of staff movement between care homes. Interventions to mitigate this through asymptomatic testing and avoidance of cross-deployment were only partially successful at times of high community prevalence.[footnote 18]

Epidemiological and genetic evidence from across the UK suggests that for COVID-19 while some care home outbreaks were introduced or intensified by discharges from hospital, hospital discharge does not appear to have been the dominant way in which COVID-19 entered most care homes.[footnote 19]

Prior to testing being widely available, the risk of keeping care home residents in hospital at a time of increasing nosocomial infection risk needed to be balanced with the risk that they might already have acquired COVID-19 and introduce it to the care home. Nevertheless, hospital discharge to care homes connects 2 high-contact environments, and it was and should remain a high priority for preventive actions in similar pandemics.

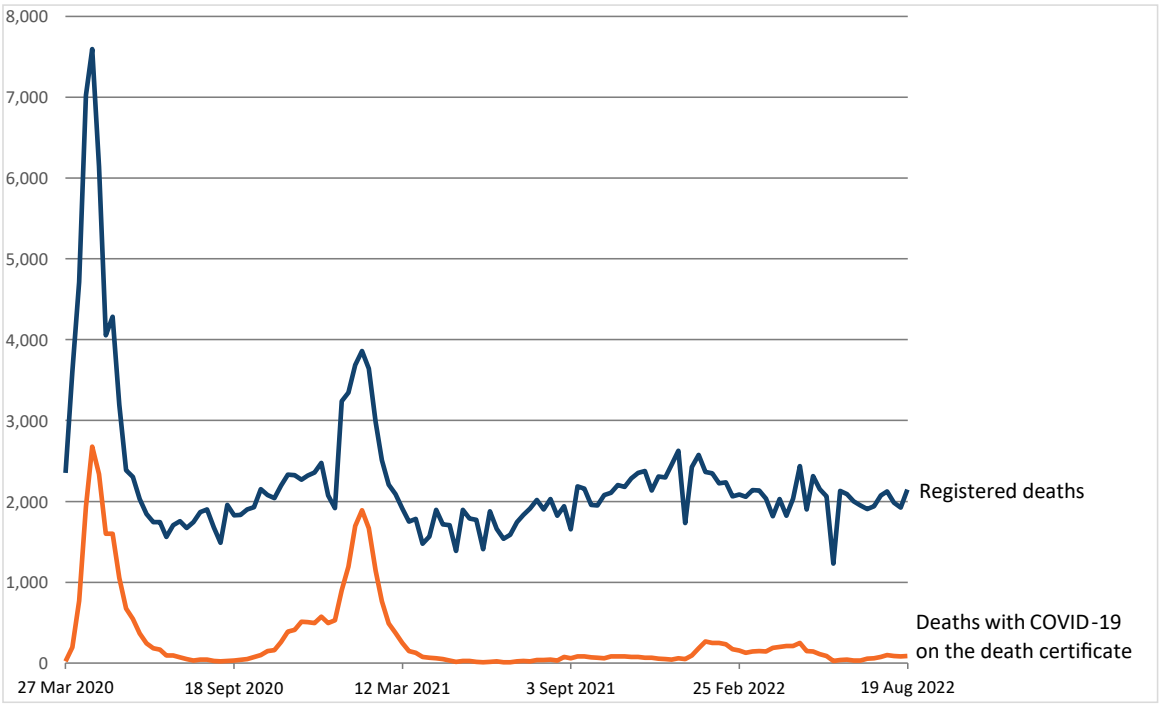
The impact of this pandemic on care homes

The first and second waves of the COVID-19 pandemic had a profound impact on the health of residents of care homes for older people, with high attack rates and a large number of deaths as shown for England in Figure 2 below.[footnote 20] In this pandemic, residents of care homes for older adults were particularly vulnerable due to their age, the presence of multiple high-risk co-morbidities, and the transmission potential inherent in frequent close physical contact through care (which resulted in large numbers of outbreaks).

The measures taken to reduce transmission, like reductions in visiting, also impacted residents – in particular loneliness, isolation and deconditioning as well as stress and distress for residents, staff and loved ones.

Staff in care homes were shown early in the epidemic to have high levels of COVID-19 antibodies in early studies, consistent with high infection rates.[footnote 21], [footnote 22] Vaccine efficacy data subsequently confirmed a high prevalence of pre-existing antibodies, and by the end of waves 1 and 2 at least a quarter of staff and a third of surviving residents had already been infected.[footnote 23], [footnote 24] Infections in care home staff were closely related to community prevalence, a relationship which continued as vaccines and boosters were rolled out and reduced the risk of severe outcomes. A number of risk factors for infection were also over-represented in care home staff, such as socio-economic status (see Chapter 2: disparities).

Figure 2: registered deaths and deaths with COVID-19 on the death certificate taking place in care homes (nursing and residential) in England from week ending 27 March 2020 to week ending 18 August 2022 [footnote 25], [footnote 26]



Note: due to limited availability of testing during the first wave, not all deaths attributed to COVID-19 were confirmed by diagnostic testing.

The risk of severe outcomes varied over time, with a decline in case fatality as vaccines were rolled out and immunity increased due to a combination of vaccination and infection. It also probably reflects the impact of high early mortality among the most vulnerable residents.

Emerging understanding of case fatality rates by age and other factors such as dementia, physical frailty and co-morbidities informed differentiated approaches, particularly in care homes for people of working age in which residents have different patterns of needs and comorbidities to older age homes. In homes for people of working age, case fatality was much lower than care homes for older people, but in some groups (such as those with Down's Syndrome) there was a high risk of severe outcomes.[footnote 27]

Public health interventions in care homes

Relatively enclosed communities such as care homes broadly face 4 kinds of hazard from infectious threats like COVID-19:

- ingress of infection through connection to community and other care settings
- transmission via contacts between staff and residents
- outbreak in closed, densely networked settings
- severe outcomes among residents vulnerable through age, frailty and co-morbidity

This hazard framework is generalisable to other pandemics and epidemics, although specific aspects may be less relevant. For example, testing may be less important in circumstances when symptoms of an infection are highly specific and transmission tends to occur after they first appear.

Addressing these hazards required both non-pharmaceutical interventions (NPIs) and pharmaceutical interventions (PIs). It is important to emphasise that these interventions were implemented by multiple partners within and beyond the care home system to protect both individuals and collective cohorts of residents, staff and visitors. They involved public health, social care and medical care delivery arrangements.

Non-pharmaceutical interventions

As noted elsewhere in this report, PIs were not available in the early stages of the pandemic and so the focus was on NPIs initially. These focused primarily on reducing ingress and transmission of SARS-CoV-2 in care home settings to reduce the frequency and size of outbreaks.

As the first wave rose, NPIs included new and more stringent use of personal protective equipment (PPE) by care home staff and reduction or prevention of visiting, which was sometimes implemented by care homes in advance of official guidance to this effect. Shielding, an option for similarly vulnerable people living at home to reduce their contact with others, was not feasible. The appropriate use of PPE was an important part of mitigating the risks of close contact needed in care homes. This will be explored by the public inquiries on COVID-19 and so it is not explored in detail here, except to highlight some important points for a future CMO or GCSA to be aware of:

- although PPE had been used in the care sector before the pandemic for specific activities and hazards, universal use in the pandemic required updates in knowledge, skills and practices in care homes in line with practices previously standard only in specific acute healthcare settings

- appropriate provision of supplies and training on universal PPE used to support care homes in their role was complex in a fragmented sector with multiple differently sized homes and a mobile workforce; the sector and supporting organisations such as local authorities made huge efforts to rapidly roll out mutual aid networks and training provision to address this issue

Avoiding the deployment of non-permanent staff who might move between homes and ensuring sick pay for affected staff sought to reduce risks of ingress, while higher staff-to-resident ratios and cohorting staff to avoid caring for both infected and uninfected residents helped reduce the risk of transmission from staff to residents.[footnote 28]

Testing was also an important intervention in this pandemic. It was not a routine intervention prior to the pandemic and was initially limited – scaling of systems did not meet demand at the outset of the first wave (see Chapter 6: testing). However, as testing became more widely available in April 2020, care home staff and their household members with symptoms were given access. This helped identify and exclude the staff most likely to be infectious at a given time. This was followed by routine asymptomatic testing of care home staff. Over summer 2020, as more testing capacity became available, whole care home testing was implemented to assess the force of infection in care homes once an outbreak was identified, to guide infection prevention and control (IPC) measures and to judge when an outbreak was successfully controlled and allow some response measures to be stood down.

There were some important developments during this pandemic for care home response management. In particular, data systems and reporting were key, and many new systems and processes were set up across the UK. In Scotland in late 2020, for example, management data (such as on staffing, screening, PPE, IPC and escalation points) was captured daily and published internally for care homes, health boards and health and care partnerships to review and use. It was modelled on a hospital ward safe staffing tool with additional information such as on home capacity, resident or staff test positivity or symptoms and numbers of affected residents. The tool supported multidisciplinary teams working across multiple care homes to provide further supervision if needed, highlight where training in IPC might be needed (and ensure it was delivered), track PPE supply needs and redeploy staff from the acute sector to care homes in times of high pressure. Local health board nurse directors provided clinical governance to review these activities, aligning governance in a previously fragmented sector and giving an overview of frequent challenges through regular ‘look back’ exercises. There is no formal evaluation of these changes in the sector, but aligned governance and systems to track need and provide mutual aid were undoubtedly helpful in managing the care home response in this pandemic and likely to be so in a future one.

In recognition of the clear correlation between care home size and risk of

outbreaks and poor outcomes, segregation of larger care homes into smaller sealed units with discrete staffing teams was also deployed in periods of higher prevalence. It was hard to evaluate the impact of these changes and we are not aware of any comprehensive evaluation of how effective they were – but the logic behind such measures is sound.

Finally, ventilation was a key NPI for care homes in this pandemic. While many IPC measures are well understood in the health and adult social care sectors, little scientific attention has to date been given to air quality in care homes as a mitigation and key element of IPC, and it is not an aspect of the environment well understood or easily controlled by carers. A good understanding of the ventilation characteristics of care homes and other closed settings is key to mitigating the impacts of acute respiratory infections generally, and of future pandemics. The importance of this may go beyond viral respiratory pathogens. There is however a tension in that very cold or very hot environments are particular risks to elderly patients, so optimising ventilation has to be balanced against thermoregulation.

As the pandemic progressed, vaccines became a primary mitigation, reducing both severe outcomes and infection risk (see Chapter 8: pharmaceutical interventions). High levels of vaccine uptake among residents (typically 95% among older adults) following prioritisation of care homes for vaccine rollout led to a marked reduction in hospitalisations and deaths, as shown in Figure 2.

Building the evidence base

The UK scientific response to the emerging high impact of COVID-19 on at-risk care settings required fast-paced, collaborative and multidisciplinary research programmes at scale.

The Vivaldi study, for example, established a network of over 300 care homes to gather evidence on a range of issues in care homes from early in the pandemic.[footnote 29] This included a cross-sectional survey showing an increased risk of resident infection associated with use of non-permanent staff, not paying sick pay for staff, new admissions to the care home, and difficulty in isolating residents.[footnote 30], [footnote 31] These risks were often in tension with the economic and workforce features of the sector, including staff turnover and vacancy rates, along with frequent use of non-permanent agency staff.[footnote 32] This meant that prevention of staff movement could risk reducing care to some residents. They also had to be balanced with other issues such as the importance of having visitors to resident wellbeing; there were difficult trade-offs in managing transmission risk within homes.

The Easter 6 (later named the ‘London Care Homes Network’), meanwhile, used detailed genomic testing and contact tracing analysis to understand transmission networks in care homes. These bespoke studies have provided rapid and high-quality evidence on a range of topics including vaccine efficacy, the emergence of variants, and their comparative outcomes, and the

high prevalence of antibodies to SARS-CoV-2 in both residents and, to a lesser extent, staff early in the pandemic.[footnote 33], [footnote 34], [footnote 35], [footnote 36] Beyond the Vivaldi and 'Easter 6' networks, much of the evidence on the impacts of interventions on care home residents, positive and negative, has been indirect. Evidence drawn from modelling studies and existing studies of community or hospital populations of older adults highlighted the vulnerability of older people to physical deconditioning and the impact of ageing on vulnerability to other infections.[footnote 37]

To interpret study outputs and provide science advice informing social care policy decisions, the SCWG complemented work conducted by the Scientific Pandemic Influenza Group on Modelling Operations (SPI-M-O) to understand the impact of SARS-CoV-2 on vulnerable populations and settings such as care homes. Modelling approaches were used to understand the key determinants of ingress and transmission of SARS-CoV-2 in high-risk adult social care settings. A key focus was ongoing assessment of effective options for the most appropriate testing and isolation regimens for care home staff and residents to mitigate the risk of transmission of SARS-CoV-2 and to reduce hospital admissions and avoidable mortality due to COVID-19.

There remain, however, important gaps in the evidence. Always a challenging setting for research, infection control policies have made care homes even less accessible during this pandemic. Evidence on best practice to address social isolation and loneliness in care homes is still emerging and not yet synthesised or well understood,[footnote 38] while there remains a striking lack of directly gathered evidence from residents on their perceptions and preferences. Importantly, understanding of the wider impacts of NPIs needs further development. Their impact in care homes for older people is likely to be different from the general population due to the high prevalence of cognitive impairment, some degree of deafness, and physical frailty. There are not yet high-quality studies which allow comprehensive quantification of the balance of benefits and harms of different NPIs in a care home setting.

Reflections and advice for a future CMO or GCSA

Point 1

> Residents of care homes for older adults are very likely to be at high risk of serious disease in any respiratory disease epidemic.

Measures to reduce ingress to care facilities (via staff or visitors) and minimise transmission while maintaining quality of care will be a high priority.

Point 2

> NPIs that reduce personal contacts, particularly isolation from family and loved ones will have a considerable impact on residents' (and families') quality of life.

Balancing the benefits and harms is not straightforward. The length and extent of limits on visiting (inward and outward), on social interactions of residents, and the use of masks at all times by staff during the COVID-19 pandemic were unprecedented in care homes. Useful measures to mitigate the harms of isolation included use of technology to support social contact and designated 'essential carer' visitors even during outbreaks (with appropriate protective measures and supports).

Point 3

> The control of transmission in care homes also depended on alignment with wider public health, social care and healthcare systems.

Preventing ingress into care homes proved extremely difficult during periods of high prevalence in the community. High case rates in hospitals required careful management of discharges into care homes. The structure of the care sector presented challenges: there is enormous diversity of facilities and many staff move from one facility or care role to another within the same week or even day. The adult social care workforce, although trained to provide care, lacks the status of registered professionals and is relatively poorly paid and insecurely employed, with high vacancy rates and poor sick pay provision.[footnote 39]

Point 4

> The value of reliable and comprehensive routine population and health data describing the population living and working in residential care to inform policy decisions and evaluate the impact of interventions cannot be overstated.

Routine and bespoke data sources enable calibration of interventions to vulnerability and impact, through an understanding of:

- ingress routes
- attack rates
- case fatality

- hospitalisation in different groups of residents[footnote 40], [footnote 41]

Testing early and often is of course key in understanding (and responding to) ingress routes, although if testing capacity is limited there will need to be careful prioritisation of available capacity.

Point 5

> Advice from behavioural and social science was essential in informing good practice in the support and management of care staff and in protecting residents.

This highlighted, for example, that there was a risk of stigmatisation and fear, and the need for financial and other support for staff when isolating.[footnote 42]

Point 6

> Research and innovation to improve care homes' resilience to respiratory and other infections is needed and could inform, among other things, building regulation and best practice.

There are challenges conducting research in care homes, particularly during a pandemic, with limited evaluative evidence available on intervention impacts.[footnote 43]

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Chapter 9: pharmaceutical interventions: therapeutics and vaccines

Contents

Introduction

In the first weeks and months of the COVID-19 pandemic no evidence-based therapeutic options (drugs) or vaccines were available, and there was uncertainty about which existing treatments should be prioritised for clinical trials and where research efforts should be focused to develop novel therapeutics and vaccines. Procurement of potential treatments was challenging, with rapidly changing and competitive global markets and a need to act fast with very limited data. These needs were addressed through collaboration between the NHS, funders, academia, the pharmaceutical industry and the general public.

This chapter sets out the experience in researching, developing and deploying therapeutics and vaccines in the COVID-19 pandemic in the UK. The science behind research, development and manufacturing of COVID-19 medical countermeasures was global, and will be in any future pandemic. The UK was, however, a significant contributor to the evidence base in COVID-19, and relying on others rather than instigating research would have led to significant delays in the deployment of several countermeasures in the UK and globally.

Research

General principles on research in the UK effort are given in Chapter 3: research.

Early in the pandemic, the World Health Organization (WHO) and major drug regulators highlighted the situation in previous epidemics (such as SARS-CoV-1 and Ebola virus) in which a multitude of small trials provided no meaningful new knowledge, or where large quantities of unproven treatments were given to patients outside the context of clinical trials. They emphasised the need for a relatively small number of large, randomised trials comparing the effects of possible therapeutic options with usual care alone.

The UK followed this approach, and a jointly funded National Institute for Health Research (NIHR) and UK Research and Investment (UKRI) Medical Research Council (MRC) rapid call for research into vaccines and therapeutics was launched on 4 February 2020, 4 days after the first UK case.[footnote 1]

Strong existing research infrastructure (especially NIHR, MRC and UKRI) was important for the rapid start-up of research, as were linked data systems, which built on learning from the 2009 H1N1 influenza or ‘swine flu’ pandemic and subsequent independent review of governmental response. The start-up of all NIHR-supported non-COVID-19 studies was temporarily paused.

Resumption as soon as feasible was encouraged, recognising the lifesaving treatment clinical trials can offer (such as oncology therapies), although this proved harder than anticipated.

There was also early direction to clinicians in the form of a UK CMO letter (1 April 2020, see Appendix A: examples of public letters and statements from UK CMOs) to the NHS to prioritise recruitment to highest priority clinical trials, and to desist from prescribing unproven off-licence drugs outside of trials. [footnote 2] While both in theory and in retrospect this was sensible, at the time it was controversial as clinicians had no proven COVID-19 therapeutics options.

Trials were set up as early as possible and in advance of the UK's first wave. COVID-19 clinical trials were embedded as a core component of NHS care, with data collection and surveillance of patients continuing following treatment and discharge – for example, to capture incidence of long-term side effects and survey for emerging drug resistance where possible. Generally, the UK was stronger on phase 3 and 4 trials than on phases 1 and 2.

Observational studies provided key evidence on the impact of vaccines and pharmaceuticals throughout the pandemic, often ahead of results from clinical trials. For example, the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) provided early reports of complications and treatment outcomes reported in hospitalised patients through analysis of data of over 70,000 patients recruited through their COVID-19 Clinical Information Network (CO-CIN).[footnote 3] CO-CIN built on the inFLUenza Clinical Information Network (FLU-CIN) established during the 2009 to 2010 H1N1 influenza pandemic, and it provided the first open-access comprehensive clinical–epidemiological data at scale in this pandemic, reporting weekly to the Department of Health and Social Care (DHSC) and the Scientific Advisory Group for Emergencies (SAGE).

Similarly, the SARS-CoV-2 immunity and reinfection evaluation (SIREN) study, a large, national, multicentre prospective cohort study conducting serial asymptomatic SARS-CoV-2 testing of NHS workers, provided some of the earliest real-world estimates of vaccine effectiveness and reinfection rates in the working age population.[footnote 4] The Vivaldi study investigated SARS-CoV-2 transmission, infection outcomes and immunity in residents and staff care homes in England, providing information on the impact of booster and primary vaccination on immunity and transmissibility in older age groups and in this vulnerable setting.[footnote 5]

From the outset a 4-nation joint approach was taken to leadership, research, governmental delivery and procurement in therapeutics and vaccines. This combined resource facilitated faster and more diverse trial recruitment, supported equity of access for therapeutics, and strengthened the UK's negotiating position in a globally competitive market.

Therapeutics development and research

Based on emerging knowledge of SARS-CoV-2 and the pathophysiology of similar viruses (both of which are outlined in Chapter 1: understanding the pathogen), potential pharmaceutical agents fell broadly into 3 categories:

- those with direct activity against SARS-CoV-2 (in other words, direct-acting antiviral agents)
- those modulating the host immune response to the pathogen such as monoclonal antibodies targeting a specific cytokine (such as TNF inhibitors, IL-1 inhibitors) or corticosteroids (such as dexamethasone)
- those modulating other organ system responses to the pathogen (such as renin-angiotensin, aldosterone and antithrombotic activities)[footnote 6], [footnote 7], [footnote 8]

Identifying candidates for clinical trials

There was an initial need to rapidly identify existing drugs that could be safely and effectively repurposed. Hundreds of candidate therapeutics were proposed in the first days and weeks of the pandemic, and prioritisation was necessary to maximise use of limited resources and ensure adequately powered clinical trials that delivered fast results. Initially, The New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG), a committee advising the CMO and DHSC, carried out an assessment of potentially viable existing pharmaceuticals that could be repurposed. The group recommended prioritisation of potential therapeutics for formal evaluation in clinical trials based on key criteria (see table 1 below).

Table 1. NERVTAG recommendations on potential therapeutics

Consideration	Recommendation	Rationale
Inclusion criteria for consideration	Pharmaceutical agent is available or acquirable, with demonstrated efficacy against similar or comparable pathogens	Rapid trial initiation, efficacious agents identified will be readily available for wider deployment

Consideration	Recommendation	Rationale
Prioritisation of potential therapeutics for clinical trial	Greatest weighting for treatments showing efficacy in SARS-CoV-2 > SARS-CoV-1 > MERS-CoV	Maximise use of resources by focusing on agents hypothesised to have highest chance of efficacy
Prioritisation of potential therapeutics for clinical trial	Human > animal > in-vitro data	Maximise use of resources by focusing on agents hypothesised to have highest chance of efficacy
Outcome measure	Mortality > ICU admission > hospital admission > length of stay	Focus on biggest impact on reducing mortality and serious complications
Priority population for clinical trial	Mildly ill outpatients at high risk of complications	Reducing hospital admission in this group would have high impact in reducing demand on secondary care services.
Priority population for clinical trial	Moderately ill inpatients	Decreasing the rate of hospital complications (such as requirement for ventilation) and shortening length of stay would have a high impact on the ability for hospitals to manage demand
Encouraged trial characteristics	Randomisation, blinding, flexibility (regarding intervention arms and sample sizes), data minimisation and use of routinely collected data	Ensure high-quality results, minimise demand on healthcare and research staff

Consideration	Recommendation	Rationale
Encouraged trial characteristics	Explicitly consider need to include children and pregnant women where possible	Unknown if these are vulnerable groups at particular risk for severe disease or poor outcomes who would benefit from therapeutics. Need to establish pharmacokinetics or safety profiles which may be different to general population

To further support prioritisation of therapeutic candidates for clinical trials, the COVID-19 Therapeutic Advisory Panel (UK-CTAP) was then established which built on NERVTAG's initial work. Potential pharmaceutical agents for treatment and prophylaxis of COVID-19 and, latterly, chronic disease commonly known as 'long COVID' were nominated through an open web portal. Prioritisation was based on several factors, including:[footnote 9]

- scientific rationale (well defined modality of action relevant to pathophysiology of COVID-19 based on in vitro, pre-clinical and clinical data)
- pharmacokinetics and pharmacodynamics (to establish whether therapeutically relevant drug concentrations would be plausible and at what dose and regimen)
- safety and possible drug interactions
- availability and supply, including cost
- emerging evidence in human studies globally
- practicalities of giving the treatment (for example, intravenous drugs can be potentially useful but impractical at scale)

Recommendations were made to the CMO in England (at that time also CSA for DHSC) and trial investigators as to which drugs to trial, in which population and at what stage of the trials pipeline – and these were published online for transparency. This independent and centrally coordinated process minimised duplication of effort across the rapidly evolving clinical trial landscape.

Setting up clinical trials rapidly

Trial recruitment at speed and scale was crucial, and existing organisations rapidly pivoted to focus on COVID-19 in advance of the UK's first wave.

ISARIC used co-developed pandemic preparedness plans and standardised trial protocols developed over the previous decade for MERS-CoV, avian influenza, Ebola virus and Zika virus, to rapidly facilitate recruitment for many trials.[footnote 10], [footnote 11], [footnote 12]

The NIHR also built on established research processes such as the Urgent Public Health (UPH) process established in 2012 for the rapid set-up and delivery of research into unexpected and severe infections with the potential to cause widespread disease in the UK. Under the process, research studies designated highest priority were 'UPH badged', and eligible for prioritised support and resources.[footnote 13] Such support included:

- prioritisation for recruitment within the NHS and clinical research networks (CRNs)
- favourable access to research delivery resources across the UK nations
- expedited regulatory review through Health Research Authority (HRA) (https://www.hra.nhs.uk/) and Medicines and Healthcare products Regulatory Agency (MHRA) (https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency)

This process was activated in January 2020, and in February 2020 the CMO instructed NIHR to scale up the UPH process and lead on identification, funding and delivery of COVID-19 studies. The initial priority was testing existing, licenced drugs designed for other purposes ('repurposed') while waiting for COVID-19 specific therapies.

Within days of the UPH process being announced on 4 February, UK researchers submitted applications for research to be set up at hospitals, GP practices and non-NHS settings including schools, prisons and care homes. Over 1,500 submissions were reviewed and 101 studies recommended by an expert panel to the CMO in England and subsequently designated as priority studies. This resulted in full approvals being granted within an average of 8 days. The process meant that:

- competition for recruitment between trial platforms was minimised
- existing processes were sped up substantially
- access to national resources for trial recruitment and delivery was facilitated

Platform trials and the role of RECOVERY and other national trials

Priority national clinical platform trials to assess therapeutic candidates were set up in a range of patient cohorts. They were coordinated by NIHR and streamlined so that treatments could move through phase 1 to 3 trials rapidly. Trials included a number of patient groups:

1. The Randomised Evaluation of COVID-19 Therapy (RECOVERY) study included hospitalised patients.[footnote 14]
2. The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) study, a repurposed platform trial used originally for patients with severe pneumonia in intensive care units (ICUs) pre-pandemic, included severely ill patients in ICUs.[footnote 15]
3. The Platform Randomised trial of INterventions against COVID-19 In older peoPLE (PRINCIPLE) study for repurposed oral medicines, and the Platform Adaptive trial of Novel antiviRals for eArly treatment of COVID-19 In the Community (PANORAMIC) study for novel oral antivirals, both included patients in the community.[footnote 16], [footnote 17]
4. The PROphylaxis for paTiEnts at risk of COVID-19 infecTion (PROTECT-V) study tested prophylactic interventions in vulnerable renal and immunocompromised patients.[footnote 18]
5. The HElping Alleviate the Longer-term Consequences of COVID-19 (HEAL-COVID) study included discharged hospitalised patients recovering from COVID-19.[footnote 19]
6. The Symptoms, Trajectory, Inequalities and Management: Understanding Long-COVID to Address and Transform Existing Integrated Care Pathways (STIMULATE ICP) study included patients with long COVID.[footnote 20]

Clear support from senior leaders in the clinical system was essential – this included but was not limited to the CMOs and medical directors (see Appendix A: examples of public letters and statements from UK CMOs) as well as professional bodies such as the medical royal colleges. Without this clear guidance clinicians were under considerable pressure to prescribe untried treatments in the absence of proven treatments. It was not, however, uncontroversial.

The RECOVERY trial was one of the first and most successful UPH-badged studies, and was (and remains at time of writing) the world's largest randomised controlled clinical trial for patients hospitalised with COVID-19. RECOVERY was designated a UPH study on 11 March 2020. It had received

MHRA and HRA approval and recruited its first patient by 19 March 2020. It is an example of the constituent trials, but not the only successful one.

RECOVERY built on trials initially set up in China using pre-prepared MERS-CoV protocols, before migrating to the UK when COVID-19 incidence decreased in China in order to ensure continued rapid recruitment. To ensure results were applicable to the national population, RECOVERY was deliberately inclusive, recruiting nearly 50,000 patients, ranging in age from less than 6 months to over 100 years old, one-third of whom were female, and one-sixth of whom were black, Asian or minority ethnic background. It had broad geographic spread across 195 hospital sites using in part established NIHR CRN infrastructure. Importantly it was a platform trial; drugs could enter and exit the trial on a rolling basis to allow multiple drugs to be tested simultaneously but with different start and stop points.

RECOVERY's scale and breadth allowed for rapid, flexible and efficient testing of multiple treatments at the same time. Rolling analysis enabled rapid identification and reporting of results. The NHS, largely using existing NIHR CRN architecture, played an essential role, recruiting patients into RECOVERY as an integral part of clinical care including in non-academic centres not traditionally involved in delivering research of this type. To support rapid recruitment, biological and data collection requirements were kept to a minimum, reducing work for very stretched healthcare staff. Finally, data linkage of each recruited patient through their NHS record enabled progress to be tracked over time and across different healthcare facilities, enabling assessment of any long-term effects of the treatments on health outcomes.

The heavy emphasis on trials in the UK proved valuable. Within the first 100 days, 3 changes of practice were recommended. First, dexamethasone was recommended – contrary to understandable previous caution regarding the use of corticosteroids. Dexamethasone was the first drug to improve survival in COVID-19, reducing deaths by about one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]) and by one-fifth in other patients receiving oxygen only (rate ratio 0.80 [95% confidence interval 0.67 to 0.96]).[footnote 21], [footnote 22] This result was disseminated rapidly, and 4 hours after the first announcement of results UK CMOs wrote to all NHS hospitals recommending this become the standard of care (see Appendix A: examples of public letters and statements from UK CMOs).[footnote 23] It is now recommended for patients with severe COVID-19 worldwide.[footnote 24] Dexamethasone had the advantages of being well known to all clinicians, relatively safe, widely available and cheap, giving global applicability. There was, however, a risk calculation to be made between rapid dissemination and full peer review; this balance is explored in Chapter 3: research.

RECOVERY subsequently identified effective repurposed drugs including tocilizumab and sarilumab, immunomodulatory drugs used for rheumatoid arthritis which also reduced immune damage.

Equally importantly, RECOVERY ruled out repurposed drugs for which there

was scientific and/or wider support but that showed no benefit such as hydroxychloroquine, lopinavir-ritonavir, aspirin, antibiotics and convalescent plasma – a treatment that had been used in over 100,000 patients before this finding was disseminated.[footnote 25] These results were contrary to some prevailing expectations, emphasising the critical role that adequately large randomised control trials play in differentiating treatments hoped to work from those with rigorous evidence of effect. These highly powered trials meant that subset analysis identified several drugs that were effective in subpopulations, but had no or negative effect in others (such as heparin, which reduced mortality in moderately but not severely ill patients in ICU).

As the pandemic progressed, focus shifted from repurposed disease-modifying therapeutics (largely with impact on the immune system) to specific antiviral treatments and prophylaxis such as monoclonal antibodies against the virus and directly acting antiviral drugs. These were not available earlier in the pandemic.

New treatments under development by pharmaceutical companies since the start of the pandemic were approved in the second year of the pandemic after demonstrating safety and efficacy in clinical trials. These included:

- ronapreve, a novel monoclonal antibody combination product for use in the prevention and treatment of hospitalised patients
- sotrovimab, a monoclonal antibody for high-risk, non-hospitalised people and those with hospital-onset COVID-19

Collectively, these drugs reduced hospitalisations, had mortality advantage and reduced pressures on the NHS, although to date none with as large an effect as dexamethasone.

Antibody drugs against antigens had the advantage that they could be identified rapidly. They had the disadvantage that with each significant viral mutation it took time to identify whether the antibody still worked. Non-antibody antivirals against fundamental viral processes were much more likely to remain effective as the virus evolved.

Therapeutics deployment

Limited supply of drugs in a globally competitive supply situation meant that rapid decisions regarding procurement and stockpiling needed to be taken, often well ahead of efficacy results, to avoid the UK facing a market shortage when efficacy was proved. To address this, a multiagency collaboration called the ‘Rapid C-19 initiative’ was established between:

- NHS England and Improvement (NHSE/I)
- the National Institute for Health and Care Excellence (NICE)
- NIHR

- MHRA
- the Scottish Medicines Consortium
- All Wales Therapeutics and Toxicology Centre
- All Wales Medicines Strategy Group
- Department of Health in Northern Ireland
- DHSC's new Therapeutics Taskforce (TTF)

The Rapid C-19 initiative sped up access to safe, efficacious treatments through horizon scanning to identify:

- credible or plausible therapeutic candidates (led by NIHR and NICE)
- health technology assessments (led by NICE)
- clinical policy development (led by NHSE/I)
- expedited regulatory processes (led by MHRA)
- simplified purchase and supply agreements followed by deployment at scale to the patient population (led by TTF and the NHS)

The TTF was established in April 2020 followed by a specific antiviral taskforce (ATF) one year later. As well as working with NIHR to support therapeutics trials, the TTF and ATF worked with industry and academia to identify and procure therapeutics and novel antivirals at pace and scale. They took strategic decisions on procurement and stockpiling of drugs at an early stage based on scientifically informed best guesses, working closely with the Deputy CMO for England on behalf of all the CMOs to ensure access to drugs for UK patients in the case of a successful trial outcome. Generally, sufficient confidence to put a repurposed drug into one of the key national clinical trials was taken as a strong enough signal that it should be purchased in bulk in advance at risk. This initial 'no regrets policy' has meant that where a NHS patient was eligible for treatment with a proven therapeutic, it was available.

As the pandemic progressed and vaccines were deployed, an advisory group supported by the NHS England Rapid-C19 team was constituted, which conducted evidence reviews, evaluating risk of poor outcomes using QCOVID© (a risk stratification tool) and ISARIC data to generate indicative risk groups, and triangulating these with a review of immunological evidence of the efficacy of vaccines in the context of primary disease or therapeutics that might compromise immune-competence. The work identified groups that were deemed to be at highest risk of hospitalisation and death, and who would be most likely to benefit from targeted treatment deployment.

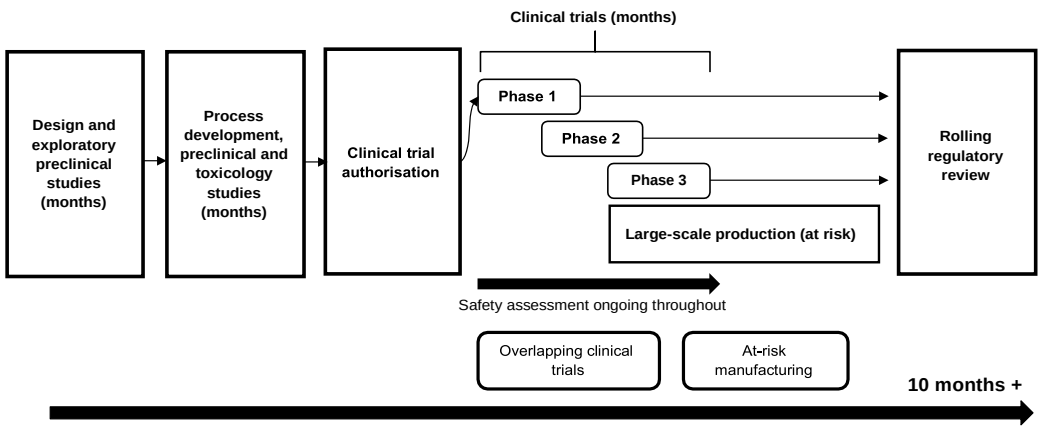
Vaccines

How candidate vaccines were developed and deployed

Strengthening and speeding up existing processes

The development of vaccines for SARS-CoV-2 built on decades of global research and preparation, benefitting from previous work to develop prototype vaccines for SARS-CoV-1 and MERS-CoV and decades of research to develop mRNA vaccines, many of which were conceived as cancer vaccines. It was also supported by pre-existing protocols for rapid vaccine implementation in the face of a new global pandemic, and existing networks such as the UK Vaccine Network (UKVN) which was established in 2015 to address the lack of incentive for the pharmaceutical industry to develop vaccines for intermittent infectious disease outbreaks. Discovering, developing and approving a new vaccine has in recent history generally taken between 10 and 20 years. In developing a vaccine for SARS-CoV-2, there was an unprecedented universal mission focus on speeding up and expediting existing processes and creating agile alternatives in order to deliver a safe and efficacious vaccine to the population as soon as possible (Figure 1).

Figure 1: SARS-CoV-2 vaccine development timeline[footnote 26]



There were important actions taken to speed up the process: the NIHR and UKRI rapid research call released in February 2020, for example, funded Oxford University to reorientate their adenovirus vector vaccine platform against the partially UKVN-funded MERS-CoV vaccine to develop a COVID-19 vaccine. Other developers used similar approaches to expedite development, using modified production processes from pre-existing vaccine candidates, or preclinical and toxicology data from related vaccines. mRNA platforms were initial frontrunners, building on 30 years of vaccine research

that had resulted in mRNA vaccine candidates for influenza A, respiratory syncytial virus and cytomegalovirus, among others, but with no marketable products.

Use of this existing technology and learning cut research time and allowed mRNA vaccines to enter trials very quickly. Moderna, for example, started phase 1 trials in March 2020.[footnote 27] Rather than running phase 1 to 3 trials sequentially, many developers ran phase 1 and 2 in parallel, such as Pfizer running phases 1 and 2 in May 2020. They also mass manufactured vaccine bulk substance ahead of efficacy results, substantially speeding up timelines, albeit at financial risk. Trials were targeted at high prevalence areas such as the USA, the UK, South Africa and Brazil, to accelerate recruitment. By autumn 2020, clinical trial data indicated that all 3 of the vaccines outlined above were highly effective at preventing symptomatic disease.

The UK, using NIHR CRN infrastructure, tested several vaccines developed in the private sector in other nations, including Novavax, Janssen, Valneva and Medicargo/GSK. Key institutions also supported an expedited vaccine development and deployment process. The National Institute for Biological Standards and Control (NIBSC) ensured quality of the final vaccine product through independent testing of each vaccine batch, and also developed reagents to support quick and reliable vaccine evaluation. NIBSC routinely conduct similar batch release testing for all licensed vaccines in the UK.

MHRA undertook a rolling review of data from clinical trials and manufacturing data as it became available to accelerate approval – the first time MHRA had instigated this process. By reviewing data from ongoing studies after initial analyses rather than as a package of all trial data at programme completion, blockages were identified and resolved earlier. MHRA authorised Pfizer, AstraZeneca and Moderna vaccines for emergency use on a temporary basis just under 8 months after trials started, and less than one year after the UK’s first case.

Mission-focused taskforces also helped speed up vaccine and drug development by setting direction for complex cross-agency working and bringing considerable external expertise into government. The Vaccine Taskforce (VTF), set up in March 2020, established formally in April and with a full-time leader appointed by late May, brought together experts from industry, academia and the civil service to secure an effective vaccine for use in the population by the end of 2020. It also worked with NIHR on the development and funding of post-authorisation trials to inform ongoing UK vaccine strategy (such as on boosters). The taskforce brought together government officials in DHSC and the Department of Business, Energy and Industrial Strategy alongside vaccinology and manufacturing experts drawn from industry and academia to provide expertise and credibility and to drive rapid decision-making. VTF’s due diligence team also supported rapid triage by recommending vaccines for clinical trial based on time to availability and plausible efficacy; with over 200 vaccine candidates in development, this was crucial.

The VTF also took a portfolio approach for research and development, manufacturing and procurement. Investment was made across multiple vaccine platforms. Contracting was centralised, and establishment of new flexible governance models sped up signing-off processes. The UK provided a relatively small commercial market for overseas companies. To strengthen its position, the VTF offered manufacturers troubleshooting across the development pathway, including linking with the UK's considerable trials infrastructure to help companies prove efficacy, and with MHRA and HRA to prioritise and expedite regulatory approval processes.

JCVI and vaccine safety

Review and recommendation of novel vaccinations to UK health departments has been the responsibility of the Joint Committee on Vaccination and Immunisation (JCVI) since 1963. However, the need for expedient decision-making in a pandemic forced greater intensity. JCVI met twice weekly (compared with twice annually pre-pandemic), reviewing emerging evidence on a rolling basis to allow timely recommendations when appropriate. Weighting of JCVI's usual priorities in decision-making also evolved, with vaccine supply, procurement and delivery capacity becoming higher priority considerations than usual, and programmatic cost lower priority than usual.

Issues of supply, procurement and delivery were more important than usual because of intense market competition globally and the need to make the UK market attractive. For the same reason, there was a need to pre-buy many vaccines, and so the question with programmatic cost was no longer whether to buy a vaccine but whether to use or discard a vaccine.

A guiding principle for JCVI was to maintain public confidence in a rapidly evolving environment through transparency while carefully considering any changes to advice in order to avoid confusion. This was particularly important for very rare side effects which are not ordinarily detected in vaccine trials and only observed and reported once the vaccine is being rolled out to the general population. During the first 2 days of vaccine rollout in the UK, more people had been vaccinated than in all clinical trials in the UK up to that point. When very rare complications of thrombosis and thrombocytopenia were reported after rollout of the Oxford/AstraZeneca vaccine first dose, JCVI initially recommended alternative vaccines for those under 30 years, later raising this limit to 40 years.[footnote 28]

Vaccination in children and vaccination in pregnancy were both important questions that needed to be addressed in this pandemic. This is likely to be the case in a future pandemic as both groups are not ordinarily included in vaccine trials, though this depends on the pathogen in question. If, for example, a future pathogen impacted children more severely then the risk–benefit calculation would look very different.

Vaccination in pregnancy

JCVI also exercised caution when giving advice on issues with evolving

evidence but updated such advice when further evidence came to light. In December 2020 at the start of vaccine rollout, for example, JCVI did not initially recommend vaccination for women who were pregnant or breastfeeding. At the time, although the available data did not indicate any safety concern or harm to pregnancy, JCVI noted that there was insufficient evidence to recommend routine use. As further data were obtained, guidance was updated, initially recommending consideration of use where the risk of exposures to SARS-CoV2 infection was high, or where women had underlying conditions that put them at very high risk of serious complications of COVID-19, before moving to recommending vaccination in all women in pregnancy.

Pregnant women were designated as a priority group in December 2021 following evidence of increased risk of complications, including maternal death and stillbirth, following COVID-19 infection in the third trimester.[footnote 29], [footnote 30], [footnote 31] While this constituted an evidence-based approach to vaccine rollout in a potentially vulnerable group, the evolving messaging was misused by some groups to undermine vaccine confidence in pregnancy. With the benefit of data available later in the pandemic the decision to encourage vaccination in pregnancy would have come earlier, but that is with the benefit of hindsight.

Vaccination in children

Similarly, JCVI did not originally recommend vaccination of children, instead prioritising those most at highest risk from COVID. In December 2020 there were very limited data on adolescents, with no data on vaccination in younger children, and population data showing almost all children who were infected having asymptomatic infection or mild disease.

As the pandemic progressed, data accumulated on vaccine efficacy and safety, including incidence and severity of suspected adverse events, as well as on the incidence of rare complications following COVID-19 infection in children and young people (myocarditis, paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), long COVID). There was also growing evidence of the impact the measures taken to control COVID-19 had on children's mental health and education.

JCVI made incremental recommendations in response to expand inclusion groups for vaccination to children aged over 12, and then offer (rather than recommend) the vaccine for 5 to 11 year olds. Decision-making regarding this group was much slower than for older age groups due to the finer benefit–risk balance as a result of the comparatively very low risks associated with COVID-19 infection in children compared with adults. On the question of vaccinating 12 to 15 year olds, as JCVI considered harms and benefits primarily from a health perspective, they asked UK CMOs to provide advice from a broader perspective (for example, considering impacts to education).[footnote 32] The advice, supported by a range of expert input, found that taking into account both JCVI findings on marginal but positive health benefits alongside the likely benefits of reducing educational disruption and the

consequent reduction in lifelong public health harm from educational disruption, vaccination in this group was recommended.

Vaccine scheduling

The National Immunisation Schedule Evaluation Consortium (NISEC) was formed in 2017 in response to a DHSC research call for vaccine evaluation to inform policy and decision-making for the national immunisation programme. The programme pivoted to COVID-19, establishing several national multicentre trials to evaluate emerging vaccines and inform choice of booster regimens (COV-Boost), mix and match regimes in case of vaccine shortages (Com-Cov), co-administration with seasonal influenza vaccination (ComFluCOV) and vaccination in pregnancy (Preg-CoV). Research design and priorities were codeveloped with DHSC, VTF, the UK Health Security Agency (UKHSA) and JCVI, with an emphasis on communication to ensure policy and guidance aligned in timing and content with emerging research. [footnote 33] For example, JCVI and DHSC worked with COV-Boost chief investigators to agree the timing of key trial milestones so that timely data was available to inform JCVI decision-making regarding choice of vaccine candidates for the autumn 2021 booster campaign.

Vaccine deployment

The last stage of vaccine development – getting doses to the right people with equitable uptake – was critical, and depended on planning for the entire supply chain at the outset of the pandemic. Delivery of nearly 120 million vaccines across the UK within one year required advance procurement and provision of large amounts of vaccine cold storage, including minus 70°C freezers for mRNA vaccines and consumables (including hundreds of millions of needles, syringes and vials) at the start of the pandemic, to avoid deployment being slowed by a bottleneck caused by global shortages.

Workforce was equally important. Aided by an unprecedented effort from tens of thousands of NHS volunteer vaccinators and stewards, vaccination centres were set up across the UK in general practices, sports stadiums, places of worship, high street pharmacies and roaming mobile vaccination units (in England, for example, this was done with the aim that all residents were within 10 miles of a centre). The work was supported by Public Health England (PHE, subsequently UKHSA) and devolved equivalents and partners who distributed vaccines and components across the country and pre-assessed the UK's infrastructure to ensure safe storage and supply.

UKHSA's laboratory and population-based research informed vaccine research and development. Assessment of neutralising antibody titres and levels required for protection from infection were key early markers for evaluation of vaccine efficacy and, later, assessment of likely vaccine efficacy against emerging variants. The UKHSA laboratories worked closely with studies like COV-Boost and with vaccine manufacturers to facilitate much of their research. Close working between the UKHSA laboratories, DHSC and

JCVI was important in aligning priorities and providing data at the right times.

UKHSA delivered the first real-world data on the effectiveness of the Pfizer vaccine from population data, further supported by its observational cohort SIREN study of over 40,000 healthcare workers, who were among the first to receive the vaccine. This provided among the first population evidence globally that the vaccine protected against infection, finding that healthcare workers were 70% (95% confidence interval 55% to 85%) less likely to develop asymptomatic and symptomatic disease after one dose of the vaccine, rising to 85% (95% confidence interval 74% to 96%) after the second dose.[footnote 34] In the months that followed, UKHSA's gathering of data on vaccine efficacy, safety in pregnancy and assessment of emerging variants and waning immunity informed governmental decisions on future vaccination policies and the wider global policy landscape.

Emerging considerations

Vaccine scheduling with limited supplies

The interval between first and second doses employed in phase 3 trials ranged from 3 to 4 weeks and was recommended for use by manufacturers and most regulators including MHRA. However, throughout December 2020, rising case numbers and the establishment of a new variant (Alpha) contributed to increased pressure to ensure as many people as possible received a first dose of vaccine rather than half as many receiving 2 doses, in order to save more lives overall.

On 30 December 2020, following MHRA agreement, the JCVI gave advice on extending the interval between the first and second dose from 3 to 4 weeks to up to 12 weeks, stating that the delivery of the first dose should initially be prioritised over the delivery of a second vaccine dose. The UK CMOs set out the rationale in a joint letter (see Appendix A: examples of public letters and statements from UK CMOs) explaining that the great majority of the initial protection from clinical disease came after the first dose of vaccine and that "in terms of protecting priority groups, a model where we can vaccinate twice the number of people in the next 2 to 3 months is […] preferable in public health terms than one where we vaccinate half the number but with only slightly greater protection".[footnote 35]

This deviation from trial protocol and manufacturers' recommendations initially met with opposition from some professional groups as well as manufacturers. However, the decision was ultimately supported by surveillance and laboratory data proving higher effectiveness of the 12-week interval strategy compared with 3 to 4 weeks.[footnote 36], [footnote 37], [footnote 38], [footnote 39]

Prioritisation

The reality of a situation where novel vaccines are being developed during a global pandemic is that supplies will be limited initially, with increasing stock over time to meet demand. This is likely to be repeated in any subsequent pandemic. Prioritisation of specific population groups, therefore, was a necessary step in the planning process to ensure that those most at risk of severe consequences of COVID-19 had early access to vaccine.

JCVI reviewed UK epidemiological and clinical data, including:

- disease incidence, mortality and hospitalisation from COVID-19
- data on occupational exposure
- a review of inequalities associated with COVID-19
- mathematical modelling
- a review of evidence from different vaccination programmes

Based on this, it advised that the first priorities for the vaccination programme should be prevention of mortality, and protection of health and social care systems and staff with high occupational exposure and interaction with vulnerable patients, with secondary priorities including vaccination of those at increased risk of hospitalisation and at increased risk of exposure.[footnote 40], [footnote 41], [footnote 42], [footnote 43], [footnote 44], [footnote 45], [footnote 46], [footnote 47]

A programme combining clinical risk stratification, an age-based approach and prioritisation of health and social care workers was developed to optimise delivery and uptake by focusing on the highest risk groups (Table 2). Nine priority groups were identified and JCVI “estimated that taken together, these groups represent around 99% of preventable mortality from COVID-19”. [footnote 48]

Table 2: summary of population groups and considerations for prioritisation[footnote 49]

Population group	Scientific evidence	Ethics	Deliverability and implementation
Older age groups	Highest absolute risk of morbidity and mortality	Maximises benefit and reduces health inequalities	Age is almost universally recorded on NHS records, so easy to identify individuals; flexible delivery model to reduce inequalities in vaccine uptake

Population group	Scientific evidence	Ethics	Deliverability and implementation
People with high-risk clinical conditions	Elevated relative risk; comorbidities increase with age; mediated/driven by other factors	Maximises benefit and reduces health inequalities	High-risk clinical conditions are well recorded on NHS records, so individuals are easy to identify; flexible delivery model to reduce inequalities in uptake
Health and social care workers	Elevated relative risk – mediated or driven by other factors not just occupation; vaccination of staff protects vulnerable patients	Contributes to individual benefit and population benefits: protect patients and ensure NHS and adult social care resilience	Health and social care workers can be identified through occupational health structures; established delivery model in occupational settings
Men	Elevated relative risk – mediated or driven by other factors, not just biological or genetic	Some benefit achieved by vaccinating older age groups and those with high-risk clinical conditions	Sex is almost universally recorded on NHS records, so men would be easy to identify
Black, Asian and minority ethnic groups	Elevated relative risk – mediated or driven by other factors, not just biological or genetic	Risks further increasing stigma; some benefit achieved by vaccinating health and social care workers	Ethnicity recording on NHS electronic systems is poor quality, so individuals would be difficult to identify; communications strategy and flexible delivery model to reduce inequalities in vaccine uptake

The JCVI prioritisation was supported by the COVID-19 Actuaries Response Group who explored the rationale for the priority order, demonstrating significant differences in vulnerability between the groups, with the number of

vaccinations required to save one life increasing rapidly from vaccination of 20 care home residents to prevent one COVID-19 death, to 8,000 vaccinations of 50 to 55 year olds to prevent the same (table 3).[footnote 50]

Table 3: overview of the number needed to vaccinate to prevent one death, per priority vaccine group[footnote 51]

Vaccination group	Number of COVID-19 deaths as of 20 November 2020	Approximate population number (million)	Number needed to vaccinate to prevent one COVID death
Care home residents	22,800	0.5 million	20
80 years old or over	18,900	3.0 million	160
75 years old or over	6,300	2.2 million	350
70 years old or over	5,600	3.3 million	600
65 years old or over	3,100	3.3 million	1,000
60 years old or over	2,000	3.8 million	2,000
55 years old or over	900	4.4 million	4,000
50 years old or over	500	4.7 million	8,000
Everyone else	600	37.0 million	47,000

> Note: some groups are not included because of limited data – for example, care home residents' carers, frontline health and social care workers, the clinically extremely vulnerable, and 16 to 64 year olds with underlying health conditions.

Health and social care workers were also included. Although not highly vulnerable to severe disease, they had high exposures and interacted with a

high number of those who were likely to die from COVID-19, so even a modest impact on transmission could have a significant impact on mortality in their patients. An evidence-based approach to prioritisation was essential and will be in future pandemics.

The prioritisation process then needed to be communicated, operationalised and above all accepted by the public and professionals. This took a lot of communication. The UK public in all 4 nations were extremely accepting of the need to prioritise, but rightly wanted to have a clear rationale laid out for why the prioritisation should be for others before their vulnerable family members and themselves. Once the logic was accepted the virtual queue based on risk was widely supported by the public, even when they were quite a long way down the priority list. Having national leaders visibly wait in (virtual) line based on this prioritisation was central to the perception and reality of fairness that clinical risk alone drove the priority.

An evolving virus, and population

Over the course of 2020 and 2021, the UK population had changed from an immunologically naïve population to a situation where the great majority had vaccine-derived and/or infection-derived immunity, especially against severe disease. Evidence generated from trials on an immunologically naïve population in 2020 was very challenging to extrapolate to this new population, with the challenge compounded by the emergence of multiple new variants. For example, the advent of the Omicron variant, with multiple spike protein mutations that partially or fully evaded monoclonal antibody targets, resulted in ronapreve being removed from clinical guidelines in the UK due to lack of efficacy. It also resulted in sotrovimab, one of the only remaining effective monoclonal antibodies, no longer being recommended by the US Food and Drug Administration due to similar concerns.[footnote 52]

The loss of a large proportion of a previously effective drug class necessitated a change in focus of therapeutic strategy away from neutralising monoclonal antibodies to emerging small molecule directly acting antivirals, and a new ATF was established with the specific aim of securing 2 new effective antivirals. Antivirals were sensible to aim at as they are variant-agnostic and there were antivirals on the horizon. The UK government secured 5 million courses of oral antivirals to treat COVID-19 (paxlovid and molnupiravir), with over 80% of courses procured after the emergence of Omicron. Both antivirals have been shown to reduce the risk of hospitalisation and death significantly in trials. However, these trials had taken place in an unvaccinated population prior to the advent of Omicron.

To ensure comprehensive trials of novel antivirals in the real-world context of a heavily vaccinated population, drugs were entered into PANORAMIC, an interventional randomised controlled trial delivered through primary care for higher-risk patients in the community. Out of trial, targeted deployment of antivirals was reserved for patients at the very highest risk (such as severely immunocompromised, recent chemotherapy or radiotherapy). The first set of results from PANORAMIC came out in October 2022.

Antiviral resistance

Experience with HIV and hepatitis C virus, among other chronic infections, had highlighted the propensity of antiviral resistance to develop, particularly in immunosuppressed individuals on long-term treatment. While there is less evidence of resistance in acute viral infections (such as influenza), this was a plausible concern and so UKHSA expanded their antimicrobial surveillance programme to support and monitor appropriate use of therapies and mitigate antiviral resistance risk. Antiviral resistance risk needed to be balanced with the need to treat patients with available effective drugs, and it is important to have protocols to achieve this alongside antimicrobial surveillance. In the event of future viral evolution conferring resistance to directly acting drugs or vaccines, untargeted but broader acting pharmaceuticals (such as corticosteroids) have the potential to remain useful.

Vaccine equity

For vaccine programmes to work and be fair, uptake needs to be high across the population, geographically and in all ethnic and social groups. In common with vaccination programmes in other nations, COVID-19 vaccine uptake was lower, with higher rates of hesitancy, in more deprived areas and in minority ethnic groups which had also been disproportionately affected by COVID-19, potentially exacerbating existing health inequalities (see Chapter 2: disparities). It was important to tackle misinformation and disinformation swiftly, using trusted voices and communication channels to ensure all communities were getting scientifically accurate information (see Chapter 11: communications).

A number of barriers to uptake were identified,[footnote 53], [footnote 54] including:

- pre-existing mistrust in governments and institutions
- lack of information about the vaccine’s safety through trusted channels
- misinformation, including from country of origin in first generation migrants
- complex and changing UK guidance
- inaccessible communications, including language
- conflicting information from different information sources
- practical barriers such as the location of vaccine centres

Narrative syntheses have reported that reasons for vaccine hesitancy varied by ethnic group, with black groups more likely to cite mistrust of vaccines broadly and Pakistani or Bangladeshi groups more likely to cite concerns about possible side effects.[footnote 55]

Work to address vaccine hesitancy and uptake in these communities was

undertaken from the start of the vaccination programme but took time fully to develop. Strategies included a nationally funded Community Champions programme which supported local public health teams to work with communities and community engagement using ‘hyper local’ peer educators and trusted communicators. This helped amplify the voices of trusted local health and social care workers and religious representatives, remove practical barriers through provision of outreach teams in convenient places, including student unions and places of worship, and ensure communications were accessible, in a range of languages, locally appropriate and culturally sensitive.

While vaccine uptake increased across all minority groups over the course of 2021 and 2022, it has remained lower among certain communities, with booster uptake lowest among black African, black Caribbean and Pakistani adults, and in the most deprived populations.[footnote 56], [footnote 57] This reinforces the need for ongoing work to improve vaccine and health equities, but also for long-term engagement on health.

Reflections and advice for a future CMO or GCSA

Point 1

> Speed of decision-making was crucial, particularly at the outset of the pandemic.

Decisions regarding research and procurement needed to be made early, and often ahead of complete information.

Point 2

> An adequately powered trial with a faster result will prevent more deaths than an apparently perfect trial with later results.

Point 3

> On the other hand, too many trials would have led to few or none reporting.

Some nations internationally experienced an explosion of trials, but with few getting to robust endpoints. Prioritisation of trial infrastructure based on realistic power calculations and patient flow and uptake were essential.

Point 4

> The pressure to ‘just do something’ was intense on individual clinicians especially early in the pandemic.

High-profile senior support of research and pharmaceutical development (including CMOs) was needed for united and oriented cross-agency work and to ensure that the NHS prioritised enrolment of patients in trials.

Point 5

> Existing research infrastructure (such as NIHR and MRC) and relationships (such as NHS and the academic community) were built on rather than setting up new organisations wherever possible.

This meant that the structures were functional and built on established relationships, resulting in rapid and more flexible work and, ultimately, better results.

Point 6

> CMOs and GCSA are not responsible for procurement, but the rapid procurement of potentially useful drugs and vaccines at risk was essential and cannot wait for the final published trial results in an emergency.

Point 7

> The model of the VTF, which integrated research and development, procurement and manufacturing, was important for rapid development and delivery of vaccines.

The VTF had a clear remit, single point accountability, brought in industry expertise and was empowered to make rapid decisions and deal directly with manufacturers.

Point 8

> Balancing early dissemination of initial results against proper peer review of final results was never satisfactorily resolved in this fast-moving emergency.

The use of pre-prints, a novelty in the clinical (although not the academic) literature, was controversial. The dissemination of results just based on first reads of the data was even more so. UK CMOs only did this once, for dexamethasone. Their logic was that the drug was well known and relatively safe and the size of effect so large it was unlikely to unravel. It was, however, controversial at the time.

Point 9

> Independent scientific and clinical advice was especially important for decision-making in areas where risk and benefit were less clear cut, or where there was more scientific uncertainty.

This included decisions regarding vaccination, especially of less vulnerable groups, particularly children, where JCVI had a critical role. The public understand the need for prioritisation of medical interventions such as drugs or vaccines based on clinical need. But they need to see the logic laid out, and fairness in execution.

Point 10

> Vaccine uptake has proven to be the most important factor in reducing the impact of epidemic.

Uptake has, however, been particularly low in historically marginalised and ethnic minority communities which has widened inequalities, especially initially. Vaccination rates have also been influenced by deliberate disinformation and misinformation.

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Chapter 10: improvements in care of COVID-19

Contents

Introduction

The introduction of a novel disease with rapid transmission and severe sequelae will always be a significant challenge for the health and care sector to adapt to, and in this pandemic health and care staff have gone to extraordinary efforts to confront those challenges. In this pandemic, as with other new health threats, rapid innovation by clinicians and spreading of new best practice steadily improved outcomes. We would like to pay tribute to all those people who worked under significant pressure to deliver care and to innovate. Formal studies are the gold standard of evidence-based care but much of the initial reduction in mortality and improvement in delivery of care was in advance of these. Without their contributions many thousands more may have died.

Innovation occurred and spread through the NHS, public health and the wider health and social care sector by several routes. For clinical management, initially the sharing of contemporary best practice by clinicians and scientists from countries hit early in the pandemic, including from China, Singapore and Italy, allowed the early management of people with COVID-19 in the UK to be based on some prior knowledge. Clinical trials and formal observational studies were launched in the UK at almost the same time the first cases were imported. While these provided the most robust testing of drugs and other interventions, clinicians adapted rapidly as they observed patients' progress and learned.

Examples where clinical practice changed early in advance of formal trials include:

- the recognition of the high rates of pulmonary embolism and substantial use of empiric prophylactic and therapeutic doses of anticoagulants
- a systematic approach to the use of high flow oxygen therapy (including the continuous positive airway pressure (CPAP) approach) based on oxygen levels
- the regular adoption of proning in intensive care units (ICUs)
- a move away from mechanical ventilation
- the identification of several distinct COVID-19 related syndromes

Later in the pandemic the syndromes of 'long COVID' and paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in children were recognised. As major observational studies like SARS-CoV2 immunity and reinfection evaluation (SIREN) and the COVID-19 Clinical Information Network (CO-CIN) and then therapeutic trials including the Randomised Evaluation of COVID-19 Therapy study (RECOVERY) started to publish, change in clinical practice was increasingly and rightly

driven by formal scientific methodologies and outcomes. The NHS and equivalents across the UK were relatively systematic at insisting that novel treatments were used in formal trials where possible (see Chapter 9: pharmaceutical interventions: therapeutics and vaccines). The importance of initial changes in practice as clinicians in the UK and globally learned and adapted to a new disease and shared best practice, however, should not be underestimated and may have contributed significantly to the fall in mortality of cases between the first and second waves.

There was also widespread and rapid change to the delivery of care. This included:

- ventilation and ICU care expanding widely outside its normal footprint in hospitals, with whole floors being taken over for care of severe COVID-19 patients
- the move of specialists to completely different areas of work
- new ways of delivering care at home, in the community and remotely
- a substantial increase in telemedicine
- the construction of additional hospital capacity (in England called ‘Nightingale’ hospitals)

Infection prevention and control (IPC) also evolved during the pandemic as the epidemiological situation changed, other elements of the response came on-stream and new evidence emerged. For example, changing case definitions and limited testing in the first 3 months of the pandemic made it challenging for healthcare settings to identify and confirm cases and therefore to put appropriate IPC precautions in place. The first few cases were managed according to high consequence infectious disease (HCID) protocols but, as numbers of patients with COVID-19 in hospital and community spread occurred, proportionate and deliverable care throughout health and care settings was essential. During the first wave, nosocomial transmission was a particular concern as healthcare settings worked to manage surging demand while rapidly identifying cases and implementing relevant IPC actions in response. Limited testing early in the first wave complicated this picture but, as testing capacity grew and IPC guidance adapted in response to the changing situation, nosocomial transmission reduced.

This chapter outlines changes to clinical care, changes to delivery of care and finally changes in IPC. There are of course many important operational considerations here, many of which are outside the remit of the CMOs and GCSA and beyond the scope of this report. Some operational matters – for example, regarding health system response – are set out below for context, but this account is by no means exhaustive. We anticipate public inquiries will

give a more complete overview of health system responses and improvements in care across the 4 nations, and set out where the key lessons learned are.

Clinical practice evolution

In the first 2 months of the pandemic, when only a small number of known COVID-19 cases had entered the UK, health services adopted existing HCID protocols to prevent any transmission risk within healthcare settings, delivering support to a small number of cases in highly specialised settings. The aim was to prevent any spread from known cases while optimising care for the patients involved. This is likely to be the priority for the first cases of any new pandemic or epidemic as it serves several purposes:

- it contributed to delaying the establishment of the pandemic
- it allows knowledge and experience of clinical management to accumulate in specialist centres which can then be disseminated
- it provides assurance to the public that these cases are less likely to transmit at a time of very high concern

There are, however, a limited number of HCID beds and this will only be a realistic response when numbers needing hospitalisation are small and community transmission is limited. Clinical management in HCID units was based on existing knowledge of broadly similar diseases, as well as emerging evidence from outbreaks and case reports across the world.

As cases began to rapidly rise following widespread seeding of cases in the community leading to the first wave, health services saw a surge in needs across the population as high volumes of COVID-19 patients presented to healthcare settings. At this point it was necessary simultaneously to:

- manage rising demand alongside existing health needs
- reduce transmission risk within healthcare settings
- rapidly scale up clinical care for a cohort of patients with a variety of care requirements, including for intensive care

Routine and non-urgent services were paused and care for COVID-19 patients with urgent and extensive needs prioritised. At this point, the disease was still relatively new and evidence on appropriate clinical care still emerging. Oxygen delivery was a priority. As the wave progressed, clinicians rapidly developed and shared best practice, including on the importance of proning, anticoagulation and effective use of high-flow oxygen guided by pulse oximetry. Again, this accumulation of clinical experience is likely to be replicated in any new pandemic or novel epidemic.

Following the first wave, formal evidence based on studies and then trials of effective pharmaceutical interventions began to emerge and was implemented rapidly and effectively. So, too, did approaches to IPC and the balance of transmission risk with the impact of highly specified IPC guidance on service delivery. The broader management of healthcare services also adjusted and routine and non-urgent care was then expanded alongside continuing support for COVID-19 patients. Delivering this wider range of services alongside rising case rates in the second wave put huge pressure on health services and professionals, and there was a continuing need to support workforce morale.

At the same time, an improved understanding of COVID-19 and shared developments in clinical practice, alongside available therapeutics, helped manage this second wave in clinical settings. The impact of the second wave on non-COVID-19 care was smaller, despite larger numbers of cases because of this adaptation.

As the pandemic and subsequent waves progressed and the seroprevalence of the population rose through a combination of vaccine rollout and infection-derived immunity, rates of severe disease reduced, and clinicians became increasingly familiar with management of COVID-19 as part of regular practice. They also increasingly saw patients with COVID-19 who were in healthcare settings with, rather than due to, the disease. Being able to distinguish between the 2 was important not only for clinical management but also national surveillance of severe disease, and it was difficult to achieve in a timely way.

Throughout the pandemic, health and care staff have gone to extraordinary efforts in highly pressured environments to deliver care and protect patients and colleagues, even when this presented potential risk to their physical and mental health, and the impact on morale has been considerable. Support has been important – from the public, from local mental health support offers, by adapting services to manage surges, and most importantly by wider efforts to reduce infection rates in the community. Research – from early case studies to wider network intelligence such as through CO-CIN, to large clinical trials – has been critical. Emerging evidence has informed guidance and clinical practice, alongside shared expertise as clinicians have developed and shared new ways to treat and support patients with COVID-19 through local groups and clinical networks.

There has been a continual evolution during this pandemic: in clinical management, managing surges in demand alongside competing healthcare priorities, and in IPC practices. The rest of this chapter sets out these processes in more detail.

To inform this chapter, we discussed experiences with the royal colleges of physicians, general practice, intensive care, emergency medicine, psychiatry, obstetrics and gynaecology and the Faculty of Public Health. We had discussions with trainees and consultants from these specialties. All

specialties have been important to the response in different ways, and it was a critical part of our role to link into a range of specialties and understand their experiences.

Weekly discussions with the Academy of Medical Royal Colleges (AoMRC) throughout the pandemic have been seen both by the royal colleges and the CMOs as invaluable in highlighting issues, innovations and pressure points across the professions as the pandemic evolved. Of course, there were many differences in the experience of different specialties, and indeed of individuals within specialties. Which areas come under what types of pressure may also look different in a future pandemic depending on the pathogen itself, health and social care structures and the population's health characteristics.

People working across health and social care have been critical to this pandemic, including public health teams, other keyworkers and those working in community and voluntary sector organisations, as well as recognised health and social care professionals. As CMOs, however, we were professional leaders for doctors – and so we focus on healthcare settings and healthcare professionals (particularly doctors) in this section. Here, we have focused on reflections from our collective professional leadership role rather than from the perspective of directing the health system response.

It is worth noting that these issues were complex and rarely have a single answer, and as a consequence collective leadership of the medical profession and shared decision-making has been an important part of the response.

The clinical trials infrastructure in the UK and the rapid enrolment of patients into trials even at the height of the pandemic provided essential evidence that improved clinical care in the UK and globally. From March 2020 to March 2021, the National Institute for Health and Care Research (NIHR) Clinical Research Network supported recruitment of over 1 million patients from across the UK into urgent public health studies.[footnote 1]

Patient care

In the first weeks of the pandemic, little was known about COVID-19, with correspondingly limited treatment options beyond the use of oxygen and respiratory and general systems support. Clinical understanding rapidly assimilated; early case reports and data from countries further ahead in their first wave (Wuhan, then wider China and Northern Italy) were hugely important in identifying the disease phenotype, progression, multisystem involvement, and outcomes. This learning was supplemented within weeks with practical experience from rapidly increasing case numbers within the UK.

Learning was rapidly disseminated through informal and formalised networks so that regions already experiencing high volumes of patients could share their learning with others further behind in the wave. Clinicians and early case reports drove changes in clinical practice that improved care in wave 1 far

ahead of formal observational trials (wave 2), clinical trials (wave 3) and the deployment of specific pharmaceutical interventions and vaccinations (see Chapter 9: pharmaceutical interventions: therapeutics and vaccines).

Observational studies such as the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) and SIREN (which are explored in Chapter 1: understanding the pathogen and Chapter 9) provided evidence during the early stages of the pandemic, months ahead of results from formal clinical trials.

In-hospital mortality rates, which peaked in the earliest months of the pandemic, declined towards the end of the first wave, further decreasing in subsequent waves. While this reduction can, in part, be attributed to a changing patient demographic (due to shielding of susceptible at-risk patients), accumulating immunity and easier access to testing and medical advice, increased clinical familiarity and improved clinical management also demonstrably improved outcomes, with ISARIC analyses suggesting that one-fifth of the reduction in in-hospital mortality in the first wave could be accounted for by changes in treatment (optimum respiratory support and later, steroid treatment).[footnote 2]

Clinical learning about COVID-19

First wave

Acute hypoxaemic respiratory failure was almost universally seen in severely unwell patients with COVID-19, with senior clinicians describing “a lifetime of acute respiratory distress syndrome (ARDS) patients in 2 years”. At the start of the first wave, there was an emphasis on early intubation for the sickest patients, with differential ventilator management practices based on different presumed phenotypes.[footnote 3] However, international experiences in Lombardy and China reported high mortality in patients requiring invasive mechanical ventilation and highlighted the potential risk that ICU capacity might be exceeded.[footnote 4], [footnote 5], [footnote 6]

In addition to increasing national ICU capacity approximately 3-fold by a number of measures, consideration of non-invasive respiratory support strategies such as CPAP and high-flow nasal oxygen (HFNO) was therefore central to reducing the need for tracheal intubation and invasive ventilation, both to reduce pressures on ICUs and as a potential strategy to reduce mortality.

High rates of failure are reported when treating other viral or bacterial pneumonias with non-invasive ventilation, leading to concern that similarly high failure rates might be observed in patients with COVID-19, with treatment delaying intubation and mechanical ventilation (rather than

preventing it) and exacerbating lung injury.[footnote 7] Over time, however, the approach of delaying intubation for a trial of non-invasive ventilation became a routine part of practice in many centres with general success.

A key component of respiratory support soon became the widespread use of prone positioning of mechanically ventilated patients, a strategy which already had an established evidence base for non-COVID-19 ARDS in ventilated patients.[footnote 8] Informed by this pre-COVID-19 evidence base, anecdotal reports of improved oxygenation and ventilation in COVID-19 patients and, later, formalised guidance, the approach was also extended to include conscious non-ventilated patients. In some ICUs, the volume of patients requiring this management led to the development of 'proning teams' of redeployed staff to reduce workload on ICU staff, standardise the process and maintain patient safety.

While COVID-19 is primarily a respiratory disease in most patients, in the early weeks of the pandemic there was increasing recognition that severe COVID-19 is a complex multisystem disease involving immunological, coagulation, renal and cardiovascular systems. Severe disease requiring ICU admission might therefore present with respiratory failure alone, or with multi-organ impairment or failure, each adding to the burden on ICUs.

The exaggerated immunological response observed was characterised by hyperproduction of proinflammatory cytokines in the most severely affected patients, typically in the second week of their illness. This was closely associated with capillary leak syndrome, disseminated intravascular coagulation, ARDS, and multi-organ failure, ultimately leading to death in the most severe cases.[footnote 9], [footnote 10]

Despite initial understandable concern based on experience with SARS-CoV-1 and MERS-CoV that broadly acting immunosuppressant drugs might impair immune responses, dexamethasone was extensively trialed in hospitalised patients during the first wave as part of the RECOVERY trial.[footnote 11] Less than 6 months after the first UK case, based on trial evidence, dexamethasone was approved for immediate widespread use in hospitalised patients with requirement for supplemental oxygen, substantially reducing morbidity and mortality in second and subsequent waves of the pandemic.

A further component to the multisystem disease observed by clinicians early on in the pandemic was the increased incidence of acute kidney injury among patients hospitalised with COVID-19, which had also been reported in Wuhan.[footnote 12], [footnote 13] This association was particularly pronounced in the first wave, where more than 25% of patients admitted to critical care required renal replacement therapy (RRT), with very high mortality (80%).[footnote 14] In the first wave, in many ICUs it was the availability of RRT (machines and disposables) rather than ventilators that was most challenging in terms of equipment provision. Improved understanding of the disease and less restrictive fluid management strategies likely contributed to this becoming less of a challenge as the pandemic waves progressed.

The acute inflammatory state seen in COVID-19 probably led to the increased risk of thromboembolic events that was a feature of severe COVID-19, and, to a lesser extent, bleeding. This presented as both micro and macro thrombotic phenomena, with up to a third of patients admitted to ICU experiencing thromboembolic events.[footnote 15] Enhanced thromboprophylaxis was rapidly introduced for patients identified as being at risk. However, even with heparin prophylaxis as standard, pulmonary thromboembolism was identified in about one-quarter of COVID-19 patients admitted to ICU, with deep vein thrombosis also observed in one-quarter of patients with pulmonary thromboembolism.[footnote 16]

Cardiovascular compromise was a further challenge of the multisystem disease seen in severe COVID-19 with cardiomyopathy, myocarditis and arrythmias all contributing to advanced cardiovascular support being required for 1 in 3 patients requiring mechanical ventilation.[footnote 17]

By the end of the first wave, the management of hospitalised patients had evolved significantly. Seriously unwell patients were often trialed on non-invasive rather than invasive ventilation, hypovolaemia was avoided, enhanced thromboprophylaxis provided as standard for at risk patients, and many were randomised to receive dexamethasone.

Second and third waves

By the start of the second wave, dexamethasone was in widespread use. As the pandemic progressed in the second and third waves, evidence from other clinical trials mounted, filling in gaps that could not be met by observational studies and clinical networks. As a result of these trials, many patients who were hospitalised during the third wave were also treated with more targeted drugs including small molecule directly acting antivirals and monoclonal antibodies which further improved clinical outcomes, albeit with a smaller, more incremental effect (see Chapter 9: pharmaceutical interventions: therapeutics and vaccines). It was important that in the UK use of unproven medicines outside the setting of a clinical trial was effectively minimised.

Clinical trials also partially addressed the absence of evidence to support the novel widespread use of different modalities of non-invasive ventilation, which had resulted in significant variability both in international guidelines and clinical practice during the first and second waves. The UK RECOVERY-Respiratory Support trial found that an initial strategy of CPAP significantly reduced the risk of tracheal intubation or mortality compared with conventional oxygen therapy, or HFNO in patients with acute hypoxaemic respiratory failure, and provides some support to this approach.

Widespread immunisation, with some additional accumulation of immunity due to prior infection, was the major factor in reducing the number of patients requiring ICU admission for severe COVID-19, with numbers needing ICU falling substantially in spring 2021. However, throughout 2020 to 2021, COVID-19 remained a severe disease for many, with some patients requiring

ICU admission and prolonged care on ICU, and with high associated mortality rates. Despite improvements in understanding of the disease and the introduction of specific therapeutics, for those patients who required tracheal intubation and ventilation, multi-organ support was typically required. Duration of ICU care for such patients typically lasted several weeks, perhaps 5 times the typical stay of many ICU patients and mortality remained close to 1 in 2 patients.[footnote 17]

Understanding of rare and delayed sequelae

Understanding of disease management evolved with the progression of the pandemic, as did recognition of rarer and/or delayed or long-term sequelae of COVID-19 infection. A diverse number of chronic symptoms were reported by approximately 2% of the population weeks or months after their initial acute infection. ‘long COVID’ encompassed multiple symptoms (and, it is thought, syndromes), and the disabling symptoms experienced by some patients challenged their ability to return to normal life. Long COVID likely includes a combination of conditions including organ damage by severe or milder COVID-19 infections, perhaps disease caused by persisting infection, persistent clotting and more traditional post-viral syndromes. Research into the causes, pathophysiology and management of this disorder is ongoing, with recognition and understanding improving over time. However, currently prevention (through vaccination) represents the only evidence-based approach to the condition.

While children make up a very small proportion of COVID-19 hospitalisations and deaths, several countries reported an increased number of children with symptoms similar to Kawasaki disease (KD) and toxic shock syndrome (TSS) in the early months of the pandemic. Prospective enhanced surveillance led by the British Paediatric Surveillance Unit and Public Health England (PHE) demonstrated a strong association between this condition and SARS-CoV-2, with children developing KD or TSS symptoms with single or multi-organ failure several weeks after initial COVID-19 infection. While very rare, PIMS-TS is the most severe recognised complication for children, with 42% of 268 cases detected during the first wave of the pandemic requiring ICU admission, though mortality was relatively low at 1.1%.[footnote 18]

A signal of increased incidence of myocarditis and pericarditis in younger people following COVID-19 infection in younger people was also observed several months into the pandemic, and subsequently also identified following COVID-19 vaccination, albeit much less commonly (commensurate with other routine vaccinations).[footnote 19] While the great majority of cases were mild and self-resolving, nuanced accurate communication of these risks (and thus the relative protection conferred from vaccination) was required in the face of evolving evidence. While in the early months of the pandemic infection in young people and children had been relatively mild with sequalae rarely observed, emerging evidence of PIMS-TS, myocarditis and pericarditis, and long COVID altered the risk-benefit balance in these groups, impacting

decision-making regarding transmission and prevention of infection (for example, Joint Committee on Vaccination and Immunisation and CMO vaccination recommendations).

Measures to manage surging clinical needs

Early in the pandemic, the NHS wrote to all staff initiating the “fastest and most far-reaching repurposing of NHS services, staffing and capacity in our 73-year history”.[footnote 20], [footnote 21] Efforts to meet surging demand throughout the pandemic included:

- the re-prioritisation of healthcare services
- expansion of capacity and equipment
- a shift to remote working for primary care and outpatient services
- substantial transfers of patients (particularly in winter 2020 to 2021)
- perhaps most importantly, large-scale redeployment and upskilling of staff

This section sets out how that process evolved over the pandemic to meet surging clinical needs and enable the health system to ramp up support.

Re-prioritisation of healthcare services

At the outset of the pandemic, when cases were rapidly rising and it was not clear what and when the peak would be (even with control measures in place), services were reprioritised. Owing to both the wider impacts of the pandemic and efforts to reprioritise services to meet surging demand, non-COVID-19, non-urgent care services, including elective operations and screening, were impacted.

The public were encouraged through widespread public communications to avoid healthcare settings unless their care needs were urgent and necessary, and not to present in healthcare settings if they had COVID-19 symptoms.

Alongside this, processes were set up to assess people for COVID-19 before presenting in-person at healthcare settings, such as the network of COVID-19 assessment centres set up in March 2020 in Scotland to assess and treat potential COVID-19 patients in the community. Emergency admissions, urgent cancer treatment and other clinically urgent care was largely maintained.[footnote 22]

Reprioritisation impacted demand differently across different areas of the health system. Primary care presentations, for example, reduced considerably in the first wave. At the same time, intensive care saw rapidly rising patient numbers and required surge staffing. Hospital emergency

admissions were 56% lower in April 2020 than April 2019 as healthcare-seeking behaviour changed, some incidents prompting emergency care reduced (such as sporting and traffic accidents), and healthcare provision shifted to online consultation where possible.[footnote 23] This reduction will have included some who needed urgent care but did not seek it, often for altruistic reasons.

From an early stage it was recognised that advice to avoid unnecessary visits to healthcare could discourage necessary health-seeking behaviours, and so there were early communications reiterating that urgent and necessary health services remained open and encouraging their use. However, there were reports particularly during the first wave of people avoiding health services in an effort to both reduce demand on the health service and manage their own risk of infection with SARS-CoV-2. This is an important point to consider for a future pandemic.

As both therapeutics and vaccines became available, reducing the risk of severe disease associated with SARS-CoV-2 infection, non-COVID-19 and non-urgent services were stepped back up. Between waves, routine non-urgent elective care was offered, while maintaining critical care surge capacity for further waves.

This rapid re-prioritisation of healthcare services enabled the NHS to continue to support COVID-19 patients. However, there was an ongoing need to balance this with other health needs that continued to require services, such as non-communicable diseases or pregnancy-related care.

Expanding ICU and acute bed capacity and equipment

The major focus early in the pandemic was on expanding ICU capacity (staff, space, systems and equipment) both within the existing health estate and beyond. This included repurposing theatres and later taking over other general wards to drive up critical care space, alongside efforts to expand the workforce and equipment outlined below.

In England, for example, between 17 March and 12 April 2020, the number of available critical care beds increased from 12,600 to 53,700.[footnote 24] Expansion of critical care capacity was achieved through:

- urgently discharging all medically fit patients
- providing governmental funding of discharge packages to support the supply and resilience of post-hospital care
- postponement of non-urgent elective operations
- pausing a number of screening programmes
- block-buying capacity in independent hospitals

Routine procedural ‘burdens’ (such as routine Care Quality Commission inspections in England) were removed to enable staff to devote maximum operational effort to COVID readiness and response.

Temporary hospitals (called ‘Nightingale hospitals’ in England) were also set up to provide surge bed capacity in the event of existing hospital capacity being exceeded. In the event, demand for beds was largely managed within the existing NHS estate, but this was not a foregone conclusion due to the extreme pressures observed in other health systems during early 2020. There may well be a similar need to manage the risk of hospital capacity being exceeded in a future pandemic.

There are important lessons from the Nightingale hospitals, such as the need to bring in additional staffing, equipment and digital infrastructure to support expansion of bed capacity. The logistic and staffing pressures of setting up a new clinical setting had to be balanced with existing staffing and system needs across the hospital estate, and the potential disbenefits of moving staff from their usual workplace where they were likely to be maximally effective. That balance was continually evolving. It was also important to ensure these hospitals were as close to existing hospitals as possible so that staff and patients could move between sites easily when needed. Finally there was a need to remain flexible when setting these up so that if they were not needed, resource could be rapidly returned to existing hospital settings.

This had never been done before at such scale since the creation of the NHS, and ICU teams and experts were key in guiding this rapid expansion. So, too, were ICU networks. In the early weeks of the first wave, pre-existing and novel networks were established to facilitate mutual aid and, in the second wave, create transfer teams staffed by ICU doctors and nurses. These teams had regular discussions to assess capacity and reduce pressure in the most severely affected regions, transferring severely unwell patients needing ICU care from hospitals with no available ICU or high dependency unit (HDU) beds to networked hospitals with more capacity. This was particularly important as the epidemic moved across the country and affected different areas at different points in time.

There was also an urgent need to surge equipment. Initially, the focus was on increasing provision of ventilators to support large numbers of severe COVID-19 cases managed in temporary ICUs. As the pandemic progressed, it also became clear that a mainstay of care involved high-flow oxygen. This required both an increase in provision of devices to deliver this therapy and a review of hospital sites to ensure oxygen supplies were not exhausted in the face of unprecedented demands on oxygen supplies. Some hospitals found existing piped oxygen capacity insufficient. Hospital estates teams played an important role in reviewing oxygen supplies capacity and hardware and maintaining safe delivery.

Supply of renal replacement machines and disposables was also a key issue for many units across the country. So, too, were consumables, such as anaesthetic drugs and renal consumables. National and regional teams supported local health services to pool equipment in mutual aid systems. They also supported the scaling up of production and procuring equipment at pace – an important process in the context of high global demand for equipment supporting COVID-19 clinical care. Repurposing equipment to different service areas was important to meet demand but had to be balanced with the risks of healthcare professionals using unfamiliar equipment.

As noted above, staffing was central to the ICU response. To expand resource, large numbers of anaesthetists and theatre staff were redeployed to ICU from theatre work and other staff were redeployed to critical care from ward-based work, bringing numbers up 2 to 3-fold. Redeployed staff were trained and cross-skilled at great pace and supervised by permanent staff. Expansion of ICU capacity led to plans for revised staff-to-patient ratios when needed, to maximise care delivery. Other staff were redeployed to independent sector hospitals to support urgent surgical work being undertaken there. As knowledge of the disease and its treatments increased rapidly, this knowledge was disseminated alongside information from NHS England and PHE through rapidly convened collaborations between critical care and anaesthesia organisations.

Evolving understanding of clinical needs also informed surge procedures – for example, the possible need for renal support or anticoagulation therapies. Continual evaluations and care improvement processes highlighted these needs throughout, and there was important learning on building surged bed capacity that incorporated the breadth of service needs.[footnote 25] The National Audit Office review on surging equipment sets out some important reflections such as the benefits of scaling up existing designs when surging at pace.[footnote 26]

Redeployment

To support this surge, large numbers of trainees and retired healthcare workers came forward to support colleagues at a time when there was a real concern that health service capacity could be exceeded. Over 40,000 students, trainees and learners came forward to support the surge, including medical students, student nurses, midwives and allied health professionals, and over 1.5 million people volunteered to support the NHS and social care. [footnote 27]

Given the increased risks to older practitioners, the return to work by recently retired members of the profession was remarkable, and heartening. As with other recent epidemics including the West African Ebola virus epidemic and the SARS-CoV-1 epidemic when UK medical, nursing and allied professional

staff volunteered to work in West Africa and Canada respectively, the courage and professionalism of staff facing an emergency, including where there is significant personal risk, has been repeatedly demonstrated.

Such mass redeployment carried with it a need to support professionals. Refresher training was offered for all clinical and patient-facing staff. There was also a need to match existing skills and experience of staff to different service contexts during redeployment. The skills and experience of a number of different healthcare professionals was vital to have the right skill mix in surge teams, and this should be properly recognised.

When redeploying staff, there was a need to rapidly match skills (rather than just head count), particularly because untrained staff could represent additional burden on existing staff in some settings. There were, however, some tasks – such as support for proning in ICU – that required minimal training. Workforce readiness for such surge needs is key – for example, with training for surge situations or cross-training between specialties.

Finally, indemnity cover and appropriate fitness-to-practice checks were needed. The UK CMOs, NHS England National Medical Director, the AoMRC and the General Medical Council (GMC) wrote to doctors stressing that it may be appropriate and necessary for clinicians to work beyond their usual disciplinary boundaries and specialisms, and that those who did so would be supported (see Appendix A), with equivalent considerations for nurses and allied health professionals.[footnote 28] The GMC played an important role in ensuring those redeployed were fit to practise, and it was crucial to involve them early in discussions to ensure regulatory issues were addressed at speed. By 27 March 2020 the GMC had granted temporary registration to 11,800 doctors.[footnote 29]

There were challenges in achieving this scale of redeployment, in part owing to the speed of its implementation, the around-the-clock support needed for staff and the context of rapidly changing projections of patient needs. Surging staff towards the needs of COVID-19 patients needed to be continually balanced with delivering support for other health needs, and the relative pressures on different areas of the health service had to be carefully managed.

Remote working

In the first wave, GPs and outpatient services swiftly adapted services to reduce face-to-face appointments and minimise transmission risk by offering remote consultations using video, telephone, email and text services. These changes resulted in around three-quarters of patients being managed remotely by June 2020 compared with one-quarter at the same time the previous year, with the total volume of primary care activity falling by 25%.[footnote 30] Patients with symptoms that may have been due to COVID-19 were seen in dedicated respiratory ‘hot clinics’, often in the form of a dedicated hub of a network of general practices.

This move to remote working relied on the existing digital infrastructure, which within NHS primary care enabled clinicians to work remotely and access records as well as issue electronic prescriptions to patients who had often moved from their usual area of residence. It also relied on supported and digital enablement for both staff and patients. NHS 111 also provided a key role in advising patients and limiting demands on primary care and specialist services. It was, however, initially under pressure from extremely high patient requests, resulting in long waiting times.

There were limits to how far remote consultation could replace in-person services – for example, for those without digital access or with conditions such as dementia. However, early in the pandemic limits on testing capacity meant that safeguards such as pre-testing to enable face-to-face consultation were not possible (see Chapter 6: testing) and so in many cases the balance of risks and benefits still favoured remote support.

Reflections on measures to meet surging demand

Healthcare professionals were working in highly pressured environments with potential significant exposure to transmission risk for a novel and largely unknown pathogen. Particularly during surges in case rates, staff were managing transmission risk both within the workplace and at home, and many fed back that in the first months of the pandemic the fear of harm to patients, colleagues, vulnerable family members and themselves was significant.

Morale across the workforce was understandably closely linked to the overall direction of the pandemic and the broader public mood, and it was important to bear this in mind in communications. Colleagues fed back that public support and workplace mental health and wellbeing support were important to them, though this varied over time and across different workplaces.

For the UK CMOs, regular discussions across the health and care professions have aided better understanding of what was happening on the ground and how it was impacting colleagues, including those in supporting roles or shielding. It was also important to have an early view of risks to health and care workers through national surveillance of morbidity and mortality.

All of these issues required significant operational and clinical expertise.

There was a careful balance to strike in updating guidance on clinical practice while services were busy surging staff, beds and equipment. Routine is important to maintain safety in clinical care, and each change to guidance interrupts this and can cause confusion and therefore potentially risk. At the same time, evidence was emerging every day on best ways to manage COVID-19 cases and there was a need to respond to this. There was and remains debate across the health professions on the appropriate point at which evidence is strong enough to change practice, particularly when pre-

prints were bringing (often very important) evidence into the public domain well ahead of peer review. Clinicians fed back to us that being clear on the scientific or operational rationale for a change, and keeping guidance as simple as possible, was helpful to them.

There was a need to balance the need for surge and service adjustment to meet pandemic needs with maintaining an appropriate level of care and support for other health needs. This evolved over the course of the pandemic – for example, changing to allow birthing partners to attend births or enabling access for advocates of those with a learning disability when wider visitor restrictions were in place.

Shifting to remote consultations, discouraging unnecessary health setting presentations and asking that those with specific symptoms avoid healthcare settings unless necessary has been an effective way to reduce potential transmission risks and additional burden during a time of significant pressure. However, this must be balanced with a risk that health-seeking behaviours were adjusted to such a degree that there was significant unmet need, with resulting impacts on mortality and morbidity.

Additionally, advice discouraging presentation in healthcare settings when people had certain symptoms needed to include caveats and routes for appropriate triage where these symptoms were not highly specific. Without this, there was a risk that people with other conditions with a similar presentation (for example, other febrile infections) were discouraged from accessing the healthcare they needed even though they did not present a threat of SARS-CoV-2 transmission.

Communications to discourage unnecessary visits to healthcare settings therefore needed to be continually adapted and revisited if such issues arose. UK CMOs stressed in public communications that emergency care was always open for business, but emergency presentation rates were much lower than normal during the first wave. Undoubtedly some people who would (and could) have come forward did not because of a sense of altruism or perceived risk of being in hospital.

There is little doubt that delays in presentation, reductions in secondary prevention (such as statins and antihypertensives), postponement of elective and semi-elective care and screening will have led to later and more severe presentation of non-COVID illness both during and after the first 3 waves. The combined effect of this will likely lead to a prolonged period of non-COVID excess mortality and morbidity after the worst period of the pandemic is over.

Infection prevention and control

Context

IPC is a vital patient safety consideration across health and social care interactions. Its importance has been especially evident through the COVID-19 pandemic, with an increased focus on IPC practice not just in health and social care, but across the breadth of community settings (schools, prisons and places of detention). Here, we focus on COVID-19 IPC measures in healthcare settings and set out how IPC guidance evolved during the pandemic, where the evidence base has progressed, and finally our reflections.

The IPC guidance for COVID-19 was developed by the 4 UK nations. This supported consistency in practice and a shared understanding of the scientific evidence across the UK. For wider transmission control measures, see Chapter 8: non-pharmaceutical interventions (NPIs). For measures (including IPC) in educational settings and care homes, see Chapters 8.1 and 8.2 respectively.

The aims of the COVID-19 IPC guidance were to reduce the transmission of SARS-CoV-2 in health and care settings, protecting patients, staff and visitors, while supporting the safe delivery of health and care services. This guidance was produced in the context of an evolving evidence base, with clinical practice adapting in response to emerging health needs, which required the following considerations to be taken into account:

1. Emerging evidence on transmission risks for SARS-CoV-2, which initially was often based on rapid assessments of real-world scenarios and inevitably featured variations in methodology and outcomes.
2. International recommendations regarding best practice in IPC. These built on the established evidence base for IPC practices derived in particular from the World Health Organization (WHO). IPC guidance in the UK was initially based on amended Department of Health and Social Care (DHSC) UK pandemic flu guidance but was adapted throughout the pandemic in accordance with emerging evidence, expert recommendations (such as from UK Scientific Advisory Group for Emergencies (SAGE) and subgroups) and changes in the epidemiology of SARS-CoV-2.[footnote 31]
3. The evolving healthcare situation in the UK. The COVID-19 IPC guidance developed over the course of the pandemic to reflect these changes, moving from initially focusing on managing COVID patients during the first wave to balancing this with supporting the safe restoration of NHS services

from mid-2020 onwards, such as through establishment of risk-based clinical pathways.

4. Ensuring that guidance was consistent with established IPC practice and easily understood by staff and implementable in all health and care settings.
5. The impact of IPC guidance on workforce morale, to support and reassure clinicians who were responding to a novel virus and were concerned for the safety of their patients, colleagues, families and themselves.

These are complex issues with inherent tensions between them. At a national level, strong relationships between organisations across the UK ensured that these tensions were discussed and consensus, evidence-based IPC practice was reflected in the UK COVID-19 IPC guidance. This collaboration brought broad consistency of approach across the 4 national health and care systems. Collaboration and co-operation with external stakeholders, such as the AoMRC, the Health and Safety Executive and ventilation experts, added additional expertise (and credence) to the COVID-19 IPC guidance and over time contributed to increased certainty and standardisation of approach across the system. There was, however, never complete consensus across all professional groups and we consider this is likely to be a feature of any future pandemic as well.

Continual evidence reviews were undertaken by the UK public health bodies to identify changes in the evidence base for IPC interventions and reflected in updated guidance, to provide assurance to all stakeholders that the full range of evidence was being assessed. Creating a systematic and consolidated way of communicating this knowledge from the 4 UK health systems' specialist IPC advice to all frontline workforces was vital, and not always easy. This was done via regular webinars with directors of nursing and directors of IPC in providers, as well as specific communications materials to support implementation of IPC measures. Again, 4-nation alignment on this was important.

Many of the IPC measures recommended across the NHS for COVID-19 were known and established IPC practices:

- standard infection control precautions (SICPs)
- transmission-based precautions (TBPs)

The COVID-19 IPC guidance, as well as outlining when and where SICPs and TBPs should be used, contained a number of specific measures for COVID-19 such as universal masking for source control, COVID-19 specific treatment pathways and physical and social distancing within healthcare settings. There was also an added emphasis on the use of a hierarchy of controls approach, which encompasses a risk assessment of the effectiveness of potential interventions in individual contexts including

consideration of the environment, the patient and the healthcare practitioner.

Together these approaches brought together 3 critical system components: clinical care for patients, IPC, and assessment and management of risks. In addition, the Personal Protective Equipment (PPE) Innovation and Sustainability group and NHS bodies collaborated to develop an educational programme on the safe use of non-sterile gloves, appropriate respiratory protective equipment (RPE) fit testing, and the assessment of novel PPE. [footnote 32]

Evidence

The IPC guidelines were initially informed by experience and evidence of responding to the risks posed by other pathogens, including respiratory infectious diseases (notably, influenza). There is good evidence regarding the effectiveness of SICPs and TBPs to prevent and control the transmission of known pathogens if applied correctly.[footnote 33] The COVID-19 IPC guidance built on this evidence base and added specific measures based on the evidence of the transmission and impact of SARS-CoV-2, such as universal masking in healthcare settings and patient cohorting.

COVID-19 IPC measures were implemented while the epidemiology of the pandemic was changing (for example, emergence of variants of concern, the introduction and effect of population-level public health mitigations, and the availability of licensed vaccines and therapeutics). There was continual adaptation of measures in response to epidemiology and wider measures in place and use of the hierarchy of controls approach to risk assessment across different settings and services.

It is widely accepted that it is very difficult to assess the effectiveness of individual IPC interventions in this context, due to the multi-interventional nature of IPC practice and widespread community transmission during the pandemic response. However, evidence suggests that the application of the established IPC practices was effective in markedly reducing the transmission of SARS-CoV-2 in healthcare settings across the UK.[footnote 34] The evidence (anecdotal and published) also suggests that the effectiveness of IPC practice in preventing transmission was related to their optimised application in the healthcare environment.[footnote 35]

Universal masking (source control) with face coverings or surgical masks (type II or IIR) to prevent the transmission of SARS-CoV-2 and other respiratory infectious agents was implemented in healthcare settings from 15 June 2020. There is evidence to suggest that this intervention was effective in reducing transmission of COVID-19 in the healthcare environment, though importantly as part of the hierarchy of controls and considering possible associated risks if not properly managed.[footnote 36]

It was also important to consider inappropriate use of PPE, the role of other factors such as ventilation or crowding (particularly in high throughput departments), and the potential inability or unwillingness of patients to wear

masks.

Physical and social distancing were also applied to healthcare settings in response to the pandemic and were reported as being effective in preventing transmission.[footnote 37] Similarly, COVID-19 management pathways (segregating infectious from non-infectious patients, typically via cohorting) were also implemented across the system and have been reported as being effective at mitigating the risk of transmission posed by the SARS-CoV-2 pandemic.[footnote 38]

A computational modelling approach was used to determine the effectiveness of IPC interventions in England in the first wave of the pandemic.[footnote 9] Outputs derived from this model estimated the most effective interventions for the prevention of nosocomial COVID-19 infections in patients to be decreasing occupancy, increasing spacing between beds, and testing patients on admission. Universal mask use was found to be the most effective single intervention for preventing transmission among healthcare workers, although importantly it was the collective impact of all interventions that demonstrated greatest effects. The study found that interventions introduced over the first wave of the SARS-CoV-2 pandemic in England probably reduced healthcare worker infection rates by around 51% (95% confidence interval 43.6% to 55%), with authors estimating that without IPC interventions, nosocomial COVID-19 infections in patients could have been 5-fold higher (5.2% versus 1% of susceptible inpatients).

Importantly, it was difficult to separate aerosols generated by natural respiratory activities, such as coughing, from those generated by procedures. This evidence supported the removal of several aerosol generating procedures (AGPs) from the AGP list in England and Wales, including some oxygen modalities such as high flow nasal oxygen, non-invasive ventilation and manual facemask ventilation.[footnote 40]

Reflections on IPC

At the outset of the pandemic, scientific knowledge of COVID-19 was unavailable, which led to widespread anxiety across society. At the same time, decisions were required about what IPC measures were needed to protect staff, patients and visitors in health and care settings, taking a wide range of considerations into account. Balancing these considerations was a complex process for healthcare leaders, but also for professionals across the healthcare sector who worked extremely hard continually to balance multiple risks throughout this pandemic, including to themselves and their families as well as patients, in order to deliver the best achievable quality care.

Clinicians were understandably concerned that IPC practices and resources should not only protect them from becoming infected at work and subsequently lead to the risk of infecting their patients, but also be appropriately tailored to the levels of risk in different settings and for different activities. Recommendations in IPC guidance were always made using the best available evidence. However, undeveloped supply chains meant that

PPE supplies came under widespread pressure due to increased demand and required prolonged use and in some cases re-use of PPE. This is likely to be repeated in the initial stages of future pandemics and epidemics and should be anticipated.

Especially in the early stages of the pandemic there was widespread concern in some professional groups that IPC measures being recommended were insufficient, based in part on a concern it was being driven by supply constraints rather than science. There were also vigorous debates about what constituted an AGP requiring higher levels of IPC. This was probably the biggest source of tension within the otherwise largely unified healthcare professions in the initial months. Concerns about whether IPC is sufficient are repeated (and legitimate) in many pandemics and epidemics and should be anticipated.

The evidence base for IPC measures to mitigate the risks from COVID-19 continues to develop and evolve as understanding of the pathogen increases. In this context of evolving evidence, and particularly at the outset of the pandemic, some clinicians or groups of clinicians advocated for particular approaches based on an interpretation of latest evidence (for example, in relation to issues such as routes of transmission and the use of RPE). However, the evidence base has continually evolved and so ongoing care is required interpreting latest outputs.

It was important that UK COVID-19 IPC guidance remained consistent with WHO recommendations and that the UK-wide COVID-19 IPC guidance and principles had consistency of strategic approach across the 4 national health and care systems. Collaboration and co-operation between IPC policy and operational leads and external stakeholders, such as the Health and Safety Executive, ventilation engineers and clinical experts, added additional expertise (and independence) to the IPC COVID-19 guidance and thus contributed to increased certainty and standardisation of approach across the system. While there was cross-UK variation in terms of governance, all UK countries had a shared view that there needed to be clear communication, understanding of responsibilities, and ownership of IPC and health protection guidance and its implementation across IPC and health protection stakeholders.

In any pandemic, it is likely that the complexity and rapidity of asks falling on clinicians and healthcare settings means that interpreting IPC guidance at speed is difficult and that as a result IPC guidance is at risk of being inconsistently applied across different settings. Appropriate strategic and educational support was key, not only at a local level but also from regional and national IPC teams, both of which were strengthened in terms of resource during this period. Fit-testing for staff is also an important way to ensure that everyone is aware of relevant RPE requirements and has the appropriate PPE to protect them in different scenarios.

Importantly, the design of buildings and other infrastructure (in both clinical and non-clinical environments) also impacted trusts' and clinicians' ability to implement IPC guidance and to optimise mitigations such as bed spacing, using single or isolation rooms or ventilation during the pandemic. An ongoing collaborative approach between IPC, estates and facilities teams regarding new builds, ventilation and review of technical notes can help mitigate such issues.

The SARS-CoV-2 pandemic highlighted existing disparities between IPC practice and expertise in health and social care, and across different areas of healthcare. IPC measures were embedded in secondary healthcare and elements of primary care (such as dentistry) as part of core business before the pandemic. In other areas, the importance of IPC has become more evident over the course of the pandemic – for example, in mental health and learning disability services where implementing guidance can be particularly difficult. During the pandemic, links between the health and social care sectors to align IPC approaches have strengthened, and programmes of work have been established to share expertise, such as NHS provision of IPC training to all care homes in England under mutual aid arrangements. Such efforts are important legacies of the pandemic.

Robust, standardised, evidence-based IPC guidance along with consistent implementation has been vital to ensuring the safety of healthcare workers, patients and visitors across the health and care system throughout this pandemic. However, there is an ongoing need to balance the direct harms of infection against the unintended consequences and potential harms of control interventions. For example, the introduction of enhanced COVID-19 IPC practices and health protection measures may impact service capacity which in turn risks increasing morbidity through reduced services.

Enhanced IPC practices may also have implications for the wider support needs of patients, such as restricting visiting for advocates supporting people with a learning disability or birthing partners, though again this needs to be balanced with the potentially serious (and, in the early stages of a pandemic, often unknown) impacts of infection in these same groups.

Such decisions required a balanced consideration of multiple factors, such as case rates and the possible direct and indirect health harms of the pandemic, and continual reassessment as new variants emerged, natural immunity increased and therapeutics and vaccines weakened the link between infection and severe outcomes.

Reflections and advice for a future CMO or GCSA

Many of the lessons we learned in clinical management and operational design were likely to be specific to COVID-19 but some key learnings were more general.

Point 1

> Improvements in care reflect the extraordinary efforts of medical, nursing and allied staff.

Their repeated determination to go well beyond their normal practice over prolonged periods, learn and disseminate best clinical practice and redesign operational systems for the benefit of patients was remarkable.

Point 2

> The rapid flow of international experience was absolutely essential, whether through formal routes or through informal networks.

UK clinicians and scientists benefited from the experience of colleagues from China, Singapore, South Korea, Japan, India, the USA, many European nations and South Africa, among others.

There is a difficult balance between learning from others who are most affected, and taking up their time when they are most under pressure, but the experience was that sharing of information worked well. Publications and group briefings (for example, via WHO) should wherever possible be the mechanism for doing this.

Point 3

> Observational studies like CO-CIN and SIREN provided essential insights into severe and mild-moderate disease.

Trials remain the gold standard, especially for therapeutics, but evidence emerges rapidly from clinicians learning by doing, and from systematic observational studies.

Point 4

> Management of PPE and best infection control advice in healthcare settings was very difficult.

The balance between what would be ideal and what is possible was one tension which is likely to be repeated in future, as is the balance between keeping up with the global evidence base and keeping routines stable. This issue probably provided the greatest point of tension between individual medical practitioners and those trying to provide a standardised approach to IPC, not made easier by the practical difficulties of getting PPE in the face of unprecedented global demand.

We anticipate this difficulty will be repeated in any epidemic and pandemic of any size, noting that IPC and PPE needs are not universal between different infections. Certain items such as gloves and aprons are very likely to be needed. These are operational issues that need to be considered by the operational leads.

Point 5

> Training of staff for redeployment was essential, and considering issues of indemnity and registration was central to having staff able to practise safely and legally.

Engaging early with the GMC was essential. The use of recently retired staff has many great advantages, but in the face of a disease whose greatest risks are to older people, some of those volunteering had to consider risks carefully.

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Chapter 11: communications

Contents

During a national medical or public health emergency, the public as well as decision-makers want to hear from clinicians, scientists and public health experts, among them CMOs and GCSA. We will leave in-depth analysis on communications to experts in the field but as it was such a significant part of the pandemic, we set out here some of our reflections for future CMOs or GCSA.

Communicating with the public

There was regular engagement with the communications teams in the health departments and public health agencies across the UK, which had a central role in communicating with the public. There was, at least initially, an almost limitless demand for authoritative medical and scientific information. The media medics, and most specialist health and science correspondents, provided challenge, were well informed and generally relayed accurate technical messages clearly.

Communications took various forms:

- written statements
- press conferences on background and live to camera
- television, radio and social media adverts
- live and pre-recorded interviews with journalists
- question and answer sessions with the public

As CMO or GCSA, many people legitimately want to know your advice on medicine, public health and science, and less constructively answers to questions which are political. Consistently staying in our area of expertise (science and medicine) was important. There was genuine public concern and speaking directly to the public on medical and scientific matters was vital, especially being clear on what was known, the degree of confidence, the balance of risks and just as importantly what was simply not known at different stages.

Many members of the public will not seek information from or know what a CMO or GCSA is. They will use other channels or trusted messengers. It is important that all communities receive accurate information in an accessible way, in the language they speak and through the channels and messengers they trust.

The appetite for data (cases, hospitalisations, deaths) and latest scientific evidence (what is known about transmission, the disease, likely health outcomes and evidence-based ways to reduce risk) was constant. This was most challenging at the outset of the pandemic when reliable information was limited and data flows and visualisations were basic.

Over time, a sophisticated set of timely, accurate data visualisations and easily available summaries (such as the highly successful COVID-19 Dashboard) were developed and curated, which helped fill this need with reliable data. These were used for ministerial briefings and press conferences. We would recommend something similar is developed in a future pandemic.

Transparency

People and Parliament will want, and reasonably expect, to know the science behind advice. It is important this is available and presented in a transparent way. Communicating epidemiological principles was central to helping people understand the reasons for advice, especially early in the pandemic.

Media briefings, Parliamentary scrutiny committees, publication of Scientific Advisory Group for Emergencies (SAGE) minutes, open access to medical journals and publicly available summaries of latest evidence from academic experts all supported informed dialogue. Having all SAGE papers and minutes available to the public was a major advance.

It was important to be clear and open about uncertainties and unknowns throughout as the evidence base, and our understanding of the situation, evolved. Routine summaries for professionals, the public and decision-makers of what is known and unknown will be needed in the future too.

Addressing misunderstandings

Particularly in the early stages and with vaccinations, we found that disinformation and misinformation were issues, especially with social media use at scale unlike previous pandemics. This is likely to be the norm from now on, and gives an equal voice to the highly informed, uninformed and malicious. There is a major difference between people with genuine and legitimate concerns (for example, about vaccines) and those with other agendas. Therefore it is important that sensible, well informed professional colleagues put out information and engage in courteous debate. Scientists and their teams will also be communicating with the media as well as directly to the public in order to correct inaccuracies.

Widespread publication of pre-print research without full peer review presented challenges. Media outlets and journalists in the vast majority of cases made a real effort to understand the science and to communicate this clearly. Inevitably, there were some points at which media translation of the science was not accurate, and in these cases it was important to reiterate the scientific advice.

The work of dedicated journalists and organisations like the Science Media Centre, which sourced high-quality scientific commentary, helped interpret research, put it in context, explain limitations and in doing so support informed debate while being clear where scientific consensus lay. Sometimes independent scientists had strong views on policy choices. Informed debate is important, but the blurring of science advice and policy opinion could cause confusion.

Misunderstandings are a particular risk where new evidence is rapidly coming to light and there is a desire to know more at pace. In particular, the outputs of statistical models were sometimes misunderstood. It is important to be clear about the limitations of modelling and the nuances and assumptions behind model outputs when they are presented, but this is not easy.

Communicating with professionals

During this pandemic, it was extremely helpful to communicate regularly and in both directions with clinical and public health colleagues – for example, through weekly calls with the Academy of Medical Royal Colleges (the presidents or chairs of the medical royal colleges and faculties) or with directors of public health. The learned academies were an important additional source of information.

This helped us better understand the situation our colleagues were facing across the country, hear constructive challenge, and gave us a forum to discuss the latest data, scientific advice or explain the background to policy changes. As travel was difficult or impossible during lockdowns this was even more important as we were unable to conduct visits.

Appendix A: examples of public letters and statements from UK CMOs

Contents

This is not an exhaustive list. It outlines some examples of public statements and letters to the professions from the UK CMOs as a group during the COVID-19 pandemic.

In addition, there were:

- statements from the UK CMOs on updates to alert levels which are available online
- communications from individual CMOs and DCMOs
- press briefings from UK CMOs, the GCSA and the Medical Director of the NHS[footnote 1]

Examples of joint letters from the UK CMOs (along with others) to the medical and public health profession

1. 11 March 2020: letter supporting doctors in the event of a COVID-19 pandemic in the UK (http://www.aomrc.org.uk/wp-content/uploads/2020/03/0320_letter_supporting_doctors_in_COVID-19.pdf).

2. 3 April 2020: letter on novel coronavirus clinical trials (https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103012).

3. 1 May 2020: letter to express gratitude for the efforts of medical and public health professionals across the NHS and public health (https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103034).

4. 6 May 2020: letter on recruitment to clinical trials for COVID-19 therapeutics (https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103037).

5. 11 November 2020: letter in support of doctors during the second COVID-19 wave (https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103114).

6. 4 December 2020: letter outlining winter challenges ahead (https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103122).

7. 31 December 2020: letter to the profession on COVID-19 vaccination programmes dosing schedules (https://www.gov.uk/government/publications/letter-to-the-profession-from-the-uk-chief-medical-officers-on-the-uk-covid-19-vaccination-programmes).

Examples of some key statements and public advice to ministers from the joint UK CMOs

8. 23 August 2020: statement from the UK Chief Medical Officers on schools and childcare reopening (https://www.gov.uk/government/news/statement-from-the-uk-chief-medical-officers-on-schools-and-childcare-reopening).

9. 11 December 2020: UK Chief Medical Officers' statement on the self-isolation period (https://www.gov.uk/government/news/uk-chief-medical-officers-statement-on-the-self-isolation-period-11-december-2020).

10. 30 December 2020: statement from the UK Chief Medical Officers on the prioritisation of first doses of COVID-19 vaccines (https://www.gov.uk/government/news/statement-from-the-uk-chief-medical-officers-on-the-prioritisation-of-first-doses-of-covid-19-vaccines).

11. 13 September 2021: letter from the UK Chief Medical Officers to the UK Health Ministers on COVID-19 vaccination of 12 to 15 year olds (https://www.gov.uk/government/publications/universal-vaccination-of-children-and-young-people-aged-12-to-15-years-against-covid-19).

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1. See, for example, 19 June 2020: update from the UK Chief Medical Officers on the UK alert level (https://www.gov.uk/government/news/update-from-the-uk-chief-medical-officers-on-the-uk-alert-level)

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