Report for the Scottish COVID-19 Inquiry

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Scope of this report

This report was commissioned in May 2023 by the Scottish COVID-19 Inquiry. The Inquiry's Letter of Instruction is reproduced at Appendix 1.

Aim

The aim of this report is to provide the Inquiry with a factual narrative of the currently-accepted scientific knowledge around COVID-19, to highlight the uncertainties that still exist, and to explain how scientific knowledge evolved from late 2019 onwards and how it informed (or alternatively, did not inform) the decisions taken by policymakers at various stages of the COVID-19 pandemic.

Disclaimer

The author of this report is a consultant public health physician and medical epidemiologist with no conflicts of interest. A full CV is at Appendix 2. The report author has no links to any of the research studies cited herein. He is not employed by any UK government department or international agency (e.g. WHO) and nor was he so employed at the time of the COVID-19 pandemic. He has acted in an advisory medicolegal capacity, for both sides, in a number of legal actions relating to COVID-19.

The author of this report does not hold and has not at any time held any directorship or stock in any company specialising in medical devices, or PPE, or diagnostic tests, or antiviral products, or vaccines.

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Abbreviations

ACE2	angiotensin-converting enzyme 2
ARI	acute respiratory illness
CFR	case-fatality rate
CI	confidence interval
COVID-19	coronavirus infectious disease 2019, caused by SARS-CoV-2, a novel coronavirus
DNA	deoxyribonucleic acid
EBM	evidence-based medicine
JCVI	Joint Committee on Vaccines and Immunisations
LNPs	lipid nanoparticles
MERS	Middle East respiratory syndrome, caused by MERS-CoV, a novel coronavirus
MHRA	Medicines and Healthcare products Regulatory Agency
mRNA	messenger RNA
OR	odds ratio
PHEIC	public health emergency of international concern
PPE	personal protective equipment
R_0	the basic reproductive rate (of any given pathogen, or pathogen variant)
RCT	randomised controlled trial
RNA	ribonucleic acid
SARS	severe acute respiratory syndrome, caused by SARS-CoV, a novel coronavirus
TTI	test, trace and isolate
WHO	World Health Organization

Table of contents

Part One

Evidence-based medicine

Footnote citations are to peer-reviewed journals and standard medical textbooks – occasionally an earlier textbook edition is cited, to show the state of knowledge at the time]

[Papers highlighted within the text – e.g. **Torpy 2009** *– are attached to this report as pdf files]*

1.1 What is evidence-based medicine?

Evidence-based medicine (EBM) derives from the understanding that there exists a *hierarchy* of scientific evidence. All clinical and medical policy decisions should be based on the best available research evidence **Torpy 2009**.

Contrary to popular belief, not all scientific evidence is of equal merit. Many scientific studies are prone to *bias* (e.g. commercial bias, in the case of industry-sponsored research). Some scientific evidence is more reliable than other evidence. Many studies, and perhaps the majority, incorporate 'findings' that are false **Ioannidis 2005**.

EBM denotes the principle, now accepted by all modern medical practitioners, that clinical practice and health policy decisions should be informed by high-quality research into the benefits and harms of healthcare interventions, rather than be informed by low-quality studies, theoretical speculation, expert committee reports or anecdote.[1]

While the concept of EBM is simple, an obstacle to its implementation in clinical practice is the uncontrolled explosion that has occurred in scientific data. Over 30,000 biomedical journals are currently in circulation, and over 17,000 biomedical books are published annually. As long ago as 1992 it was calculated that a physician would have to read approximately 11 scientific articles per day to maintain their scientific currency;

[1] Rawlins M, Vale A. Drug therapy and poisoning. In: Kumar P, Clark M, eds. *Kumar & Clark's clinical medicine*. 8th ed. London: Elsevier Saunders, 2012.

the challenge now is exponentially greater.[2]

1.2 What are systematic reviews?

A pragmatic solution is the *systematic review* (also known as an evidence synthesis or *meta-analysis*). Systematic reviews are a relative new form of research. Their aim is to present a balanced and impartial summary of the existing research, enabling decisions on effectiveness to be based on all relevant studies of adequate quality.[3]

The systematic review has established itself at the highest level of evidence in the EBM hierarchy because it summarises the available evidence on a particular topic, in a comprehensive and up-to-date manner. Properly-conducted systematic reviews constitute *Level Ia evidence*. The bottom rung in the EBM hierarchy is *Level IV evidence*, obtained from expert committees, authoritative opinions, and the like. This is demonstrated in the table below, taken from a standard textbook for medical students.[4]

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[2] Minhas R, Feder G, Griffiths C. Using guidance and frameworks. In: Guest C, Ricciardi W, Kawachi I, Lang I, eds. *Oxford handbook of public health practice*. 3rd ed. Oxford: Oxford University Press, 2013.

[3] Clarke M. History of evidence synthesis to assess treatment effects: personal reflections on something that is very much alive. *J R Soc Med* 2016; 109: 154-163.

[4] Cumming AD, Noble SI. Good medical practice. In: Walker B, Colledge N, Ralston S, Penman I, eds. *Davidson's principles and practice of medicine*. 22nd ed. London: Churchill Livingstone, 2014.

1.10 Categories in evidence-based medicine (EBM)*

Levels of evidence (in descending order of strength)

Ia	Evidence obtained from meta-analysis of randomised clinical trials
Ib	Evidence obtained from at least one randomised controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomisation
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities

Grades of recommendation

A	Directly based on level I studies
B	Directly based on level II studies *or* extrapolations from level I studies
C	Directly based on level III studies *or* extrapolations from level I or II studies
D	Directly based on level IV studies *or* extrapolations from level I, II or III studies

1.3 What are randomised controlled trials?

Systematic reviews seek evidence of benefit from *randomised controlled trials* (RCTs).[5]

In an RCT, participants are allocated randomly either to the treatment (or *intervention*) of interest, or to the existing standard treatment, or to a *placebo*. The purpose of randomisation in RCTs is to minimise bias and confounding. In order to minimise patient bias, the participants are unaware of their treatment allocation; this is termed a *single-blind* RCT. In order to minimise doctor bias, treatment allocations are also withheld from investigators; this then is termed a *double-blind* RCT. To recruit sufficient numbers of patients, and to examine the effects of treatment in different settings, it may be necessary to conduct the trial at several locations; this is termed a *multicentre* RCT.[5]

To determine the reliability of a particular RCT, a number of features in the study design need to be assessed. To ensure that there is no selection bias, the process of

[5] Rawlins M, Vale A. Drug therapy and poisoning. In: Kumar P, Clark M, eds. *Kumar & Clark's clinical medicine*. 8th ed. London: Elsevier Saunders, 2012.

randomisation must be seen to be robust. *Blindness of allocation* should be imposed rigorously at the start of the RCT, and it ideally should be maintained throughout the study. This is especially desirable if a subjective outcome is being measured, such as relief of pain, or alleviation of depression. All the patients enrolled into a trial should be properly accounted for, at its conclusion.[6] Finally, the trial must be reported adequately – and as a minimum, it should include a *flow chart* depicting the progress of participants through the trial. The need to report RCTs accurately was recognised in the mid-nineties **Altman 1996** and has been reiterated many times since then.

1.4 *Pooling* scientific evidence

In recent years, systematic reviews have sought to *pool* evidence from RCTs. This is done through meta-analysis, which is a statistical method that quantitatively summarises the systematic review findings **Altman 1996**. Unpublished trials should ideally be identified and included in the meta-analysis to avoid *publication bias* (i.e. non-inclusion of 'negative' trials that are less likely to have been published, on account of their disappointing results).[7]

Meta-analysis results in a pooled estimate of effectiveness which is more precise than the effect estimates from the individual RCTs. This is because the pooled estimate is based on a larger number of participants, and hence is less liable to *random error*.[8]

Increasingly, systematic reviews also assess non-RCT evidence; these additional sources of evidence include qualitative research, animal studies and modelling.[3]

A systematic review should systematically identify and evaluate (i.e. through an explicit and prespecified and well-validated methodology) all appropriately-designed studies

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[6] Brice A, Burls A, Hill A. Finding and appraising evidence. In: Guest C, Ricciardi W, Kawachi I, Lang I, eds. *Oxford handbook of public health practice*. 3rd ed. Oxford: Oxford University Press, 2013.

[7] Mark DB, Wong JB. Decision-making in clinical medicine. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *Harrison's principles of internal medicine*. 19th ed. New York: McGraw-Hill, 2015.

[8] Rawlins M, Vale A. Drug therapy and poisoning. In: Kumar P, Clark M, eds. *Kumar & Clark's clinical medicine*. 8th ed. London: Elsevier Saunders, 2012.

that address the clinical question being considered. Where appropriate, the results of these included studies should be combined.[9]

To be fully valid, a systematic review must satisfy a minimum of three criteria:[10]

i. It must try to identify all relevant studies.

ii. It must assess the quality of the included studies.

iii. It must try to combine the study results, as long as it is reasonable to do so.

1.5 Cochrane reviews

A Cochrane review is a systematic review that uses methodology that has been tested and refined over three decades by the Cochrane Collaboration. Cochrane reviews are prepared and maintained, usually on a *pro bono* basis, by members of the collaboration working in small teams; in 1993 the active members of the Cochrane Collaboration numbered less than 100, but by early 2016 this number had grown to over 30,000 reviewers in more than 100 countries.[11]

Historically, the focus in Cochrane reviews has been on quantitative data, with study results combined using *Revman* software. Since 2003, the quality of included studies in Cochrane reviews has been assessed through the *Cochrane risk of bias tool*; this automatically grades each included study into a *High risk of bias*, *Low risk of bias* or *Unclear risk of bias* category, and allows for a reliable appraisal of the overall robustness or otherwise of the accumulated evidence.[12]

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[9] Brice A, Burls A, Hill A. Finding and appraising evidence. In: Guest C, Ricciardi W, Kawachi I, Lang I, eds. *Oxford handbook of public health practice*. 3rd ed. Oxford: Oxford University Press, 2013.

[10] Brice A, Burls A, Hill A. Finding and appraising evidence. In: Guest C, Ricciardi W, Kawachi I, Lang I, eds. *Oxford handbook of public health practice*. 3rd ed. Oxford: Oxford University Press, 2013.

[11] Clarke M. History of evidence synthesis to assess treatment effects: personal reflections on something that is very much alive. *J R Soc Med* 2016; 109: 154-163.

[12] RevMan. *Review Manager Computer Programme* (Version 5.3). Copenhagen: The Nordic Cochrane Centre, 2015.

An important feature of Cochrane reviews is that they are published electronically in the *Cochrane Library*, and hence are readily available to clinicians, policymakers and researchers. In most countries, Cochrane reviews can be downloaded free of charge.[13]

For better accessibility, every Cochrane review since 2001 has included a *Plain Language Summary*, in addition to the standard abstract which summarises the review and its findings. The collaboration has its own press office, which promotes new reviews that are considered to be especially important. Authors of a Cochrane review also undertake to update their review as and when there is a substantive new body of evidence; in practice and with most current interventions a Cochrane review is likely to be comprehensively updated approximately every 3–5 years.[14]

Three Cochrane reviews, **Jefferson 2011**, **Graña 2022** and **Jefferson 2023**, are of particular relevance to this inquiry. They are discussed at a later point in this report, and are included also as full-text pdf attachments to the report.

[13] Higgins J P, Green S. *Cochrane handbook for systematic reviews of interventions*. London: Wiley-Blackwell, 2011.

[14] Clarke M. History of evidence synthesis to assess treatment effects: personal reflections on something that is very much alive. *J R Soc Med* 2016; 109: 154-163.

Part Two

The COVID-19 pandemic

Footnote citations are to the most recent editions of standard medical textbooks

2.1 What is COVID-19?

COVID-19 is a syndrome (i.e. a multisystem illness) caused by a virus now known as SARS-CoV-2.[15] It is a statutorily-notifiable disease in the UK.[16]

COVID-19 has a varying presentation ranging from asymptomatic or insignificant to respiratory distress and death.[17] The disease is milder in children, with the greatest risk of severe illness and death in those aged 85 years and older.[18]

SARS-CoV-2 was responsible for a global pandemic in 2020–2023; the pandemic has been associated with severe negative impact in most countries, with decreases in gross domestic product and an increase in inequalities among lower socio-economic groups.[19]

A subset of individuals SARS-CoV-2 with infection have progressed to a recurring pattern of physical and cognitive symptoms, known as *long COVID*.[20] The public health measures used to manage the pandemic have also led to social isolation with adverse

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[15] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[16] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[17] Heymann DL. COVID-19. In: Heymann DL, ed. *Control of communicable diseases manual*. Washington DC: American Public Health Association, 2022.

[18] Heymann DL. COVID-19. In: Heymann DL, ed. *Control of communicable diseases manual*. Washington DC: American Public Health Association, 2022.

[19] Heymann DL. COVID-19. In: Heymann DL, ed. *Control of communicable diseases manual*. Washington DC: American Public Health Association, 2022.

[20] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

mental health consequences.[21]

2.2 What are viruses?

Viruses are small (20–150 nm) protein packages.[22] They are much smaller than other infectious agents.[23]

Viruses have a central nucleic acid core (*genome*) surrounded by a protective coat (*capsid*) that is antigenically unique for a particular virus.[24] The virus genome consists of either DNA (i.e. deoxyribonucleic acid) or RNA (i.e. ribonucleic acid), but not both.[25]

Some viruses (e.g. coronaviruses) possess an outer *envelope*, consisting of lipid and protein.[26] Enveloped viruses are less able to survive in the environment and are spread by respiratory, sexual or blood-borne routes; non-enveloped viruses survive better in the environment and are predominantly transmitted by faecal-oral or (less commonly) respiratory routes.[27]

Some viruses contain enzymes (e.g. reverse transcriptase in HIV).[28]

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[21] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[22] Török E, Moran E, Cooke F. *Oxford handbook of infectious diseases and microbiology*. 2nd ed. Oxford: OUP, 2017.

[23] Barlow G, Irving WL, Moss PJ. Infectious disease. In: Feather A, Randall D, Waterhouse M, eds. *Kumar & Clark's clinical medicine*. 10th ed. London: Elsevier, 2021.

[24] Barlow G, Irving WL, Moss PJ. Infectious disease. In: Feather A, Randall D, Waterhouse M, eds. *Kumar & Clark's clinical medicine*. 10th ed. London: Elsevier, 2021.

[25] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[26] Barlow G, Irving WL, Moss PJ. Infectious disease. In: Feather A, Randall D, Waterhouse M, eds. *Kumar & Clark's clinical medicine*. 10th ed. London: Elsevier, 2021.

[27] Sandoe JA, Dockrell DH. Principles of infectious disease. Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[28] Török E, Moran E, Cooke F. *Oxford handbook of infectious diseases and microbiology*. 2nd ed. Oxford: OUP, 2017.

Viruses are grouped into orders, families, subfamilies and genera.[29] Currently, only about half of viruses have been classified in orders.[30]

Viruses have colonised most life forms, including bacteria, plants, insects and animals.[31] However, viruses are not alive.[32] They are metabolically inert, and so must live intracellularly.[33] They are incapable of independent replication, but instead subvert host cellular processes to achieve synthesis of their nucleic acids.[34]

Whereas bacteria may have several thousand genes, the genome of viruses is typically very small, and may comprise only four genes.[35] Each gene codes for one protein, but viruses may produce more than one protein from the same gene by means of RNA splicing, or *frameshifting*.[36]

Viruses evolve rapidly due to the high number of genome duplications undergone in short spaces of time.[37] Genetic sequencing of isolated viruses is important to identify new mutations and variants.[38]

Viruses are obligate intracellular parasites – meaning, they are completely dependent upon the internal environment of the virus-infected host cell to create new infectious

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[29] Török E, Moran E, Cooke F. *Oxford handbook of infectious diseases and microbiology*. 2nd ed. Oxford: OUP, 2017.

[30] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[31] Török E, Moran E, Cooke F. *Oxford handbook of infectious diseases and microbiology*. 2nd ed. Oxford: OUP, 2017.

[32] Louten J. *Essential human virology*. London: 2nd ed. London: Elsevier, 2023.

[33] Barlow G, Irving WL, Moss PJ. Infectious disease. In: Feather A, Randall D, Waterhouse M, eds. *Kumar & Clark's clinical medicine*. 10th ed. London: Elsevier, 2021.

[34] Sandoe JA, Dockrell DH. Principles of infectious disease. Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[35] Török E, Moran E, Cooke F. *Oxford handbook of infectious diseases and microbiology*. 2nd ed. Oxford: OUP, 2017.

[36] Török E, Moran E, Cooke F. *Oxford handbook of infectious diseases and microbiology*. 2nd ed. Oxford: OUP, 2017.

[37] Török E, Moran E, Cooke F. *Oxford handbook of infectious diseases and microbiology*. 2nd ed. Oxford: OUP, 2017.

[38] Heymann DL. COVID-19. In: Heymann DL, ed. *Control of communicable diseases manual*. Washington DC: American Public Health Association, 2022.

virus particles, or *virions*.[39] Periodically, new virions are discharged to the exterior of the infected host cell, thus perpetuating the cycle of viral infection.[40]

2.3 What are coronaviruses?

Coronaviruses, or *Coronaviridae*, are a family of viruses within the order *Nidovirales*, sub-order *Cornidovirineae*.[41] The family of coronaviruses includes the genera *Alphacoronavirus*, *Alphaletovirus*, *Betacoronavirus* and *Deltacoronavirus*, collectively referred to as coronaviruses (CoVs).[42]

Coronaviruses are characterised by the presence of an envelope.[43] The prefix *corona* derives from the crownlike surface projections on the external surface of the virus that can be seen with an electron microscope.[44]

Coronaviruses are further categorised according to a classification scheme developed in the 1970s by Nobel laureate David Baltimore.[45] The Baltimore classification system categorises viruses according to four features, as follows:[46]

- their molecular architecture;
- their genome;
- their replication strategy; and
- whether (in the case of RNA viruses) they are *positive-sense* [+] or *negative-*

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[39] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[40] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[41] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[42] Tille PM. *Bailey & Scott's diagnostic microbiology*. 15th ed. London: St Louis, MI, Elsevier, 2022.

[43] Török E, Moran E, Cooke F. *Oxford handbook of infectious diseases and microbiology*. 2nd ed. Oxford: OUP, 2017.

[44] Tille PM. *Bailey & Scott's diagnostic microbiology*. 15th ed. London: St Louis, MI, Elsevier, 2022.

[45] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[46] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

sense [–].[47]

Positive-sense RNA is able to be immediately *translated* into proteins; negative-sense RNA is not translatable into proteins, but first has to be *transcribed* into positive-sense RNA.[48]

RNA viruses (such as coronaviruses) have high error rates, with genomes diverging by as much as 2% in the course of a year – 1 million times greater than the divergence rate of eukaryotic cell genomes.[49] Many of these viral mutations are non-functional but some will allow the virus to evade host immune responses and medical therapies.[50]

In summary, coronaviruses are enveloped, single-stranded, positive-sense ribonucleic acid viruses that infect mammals and birds and that typically (but not exclusively) target the respiratory tract of their hosts.[51]

2.4 What diseases are caused by coronaviruses?

Coronaviruses infect a range of avian and mammalian hosts, including bats, rodents, cats, dogs and camels.[52] In humans, four coronaviruses have been recognised for many years as causing mild to moderate respiratory tract illness, including the common cold.[53]

Three specific coronavirus genotypes known to infect humans belong to the genus *Betacoronavirus* and emerged recently as a result of *recombination events* (i.e. genetic

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[47] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[48] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[49] Török E, Moran E, Cooke F. *Oxford handbook of infectious diseases and microbiology*. 2nd ed. Oxford: OUP, 2017.

[50] Török E, Moran E, Cooke F. *Oxford handbook of infectious diseases and microbiology*. 2nd ed. Oxford: OUP, 2017.

[51] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[52] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[53] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

'reshuffling') in animals, and subsequent zoonotic transmission from animals to humans; they are:[54]

- SARS-CoV, which caused an epidemic of severe acute respiratory syndrome, first recognised in southern China in November 2002;
- MERS-CoV, which caused an epidemic of Middle East respiratory syndrome, first recognised in Saudi Arabia in 2012; and
- SARS-CoV-2, which caused COVID-19, first reported as a distinct syndrome in China in December 2019.

The characteristics of the seven known human coronaviruses are summarised in the following table.[55]

TABLE 14.4 Human Coronaviruses.

Virus	Year Virus Was Identified	Genome Size (kb)	Entry Receptor
HCoV-229E	1967	27.3	APN (aminopeptidase N)
HCoV-NL63	2004	27.6	ACE2 (angiotensin-converting enzyme 2)
HCoV-OC43	1967	30.7	9-O-acetylated sialoglycans
HCoV-HKU1	2005	29.9	9-O-acetylated sialoglycans
MERS-CoV	2012	30.1	DPP4 (dipeptidyl peptidase 4)
SARS-CoV-1	2003	29.8	ACE2 (angiotensin-converting enzyme 2)
SARS-CoV-2	2020	29.9	ACE2 (angiotensin-converting enzyme 2)

[54] Tille PM. *Bailey & Scott's diagnostic microbiology*. 15th ed. London: St Louis, MI, Elsevier, 2022.

[55] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

2.5 What characterises SARS-CoV-2?

SARS-CoV-2 is a single-stranded RNA virus from the genus *Betacoronavirus*.[56] It comprises four major structural proteins, the spike (S), membrane (M), envelope (E) and a helical nucleocapsid (N).[57] Its architecture is shown below:[58]

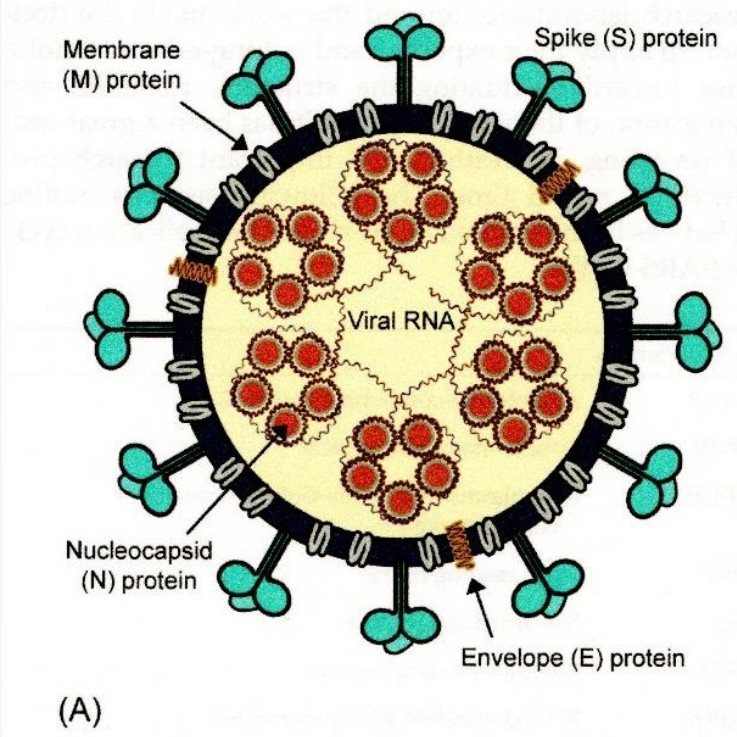

FIGURE 14.6 **SARS-CoV-2 virion architecture and proteins.** (A)

To penetrate a new host, SARS-CoV-2 makes use of a surface protein on the host's cells, known as *angiotensin-converting enzyme 2* (ACE2).[59] ACE2 receptors are found on the surface of cells in many human tissues and organ systems, including (but not limited to) the respiratory tract.[60]

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[56] Heymann DL. COVID-19. In: Heymann DL, ed. *Control of communicable diseases manual*. Washington DC: American Public Health Association, 2022.

[57] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[58] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[59] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[60] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

SARS-CoV-2 accumulates frequent mutations as it passes through human and animal populations (e.g. mink).[61] Some mutations of SARS-CoV-2 occur in the region of the *spike protein*, the glycoprotein projecting from the lipid layer of the surface envelope; it is this protein that attaches to the ACE2 receptor on the surface of host cells, in order to effect entry into the cells.[62]

The mutations that SARS-CoV-2 accumulates facilitate the phenomenon of *immune escape* – meaning, that re-infection with the virus can occur after natural infection, and also after vaccination.[63]

The same phenomenon of recurring immune escape is seen with influenza A viruses.[64] Like coronaviruses, influenza viruses are structurally unstable RNA viruses that frequently and unpredictably transform into new *variants*; this occurs with influenza A viruses that cause seasonal influenza, such that in each new influenza season people may have very little immunity to that season's predominant circulating influenza A virus.[65]

2.6 Airborne spread versus droplet spread of respiratory pathogens

In describing the transmission of respiratory pathogens, a distinction is made between *airborne spread* (known also as aerosol spread) and *droplet spread*; the distinction is based on the size of the infecting particles, as follows:[66]

- Airborne spread. Very small particles infective of < 5 μm diameter (i.e. *aerosol*

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[61] Heymann DL. COVID-19. In: Heymann DL, ed. *Control of communicable diseases manual*. Washington DC: American Public Health Association, 2022.

[62] Heymann DL. COVID-19. In: Heymann DL, ed. *Control of communicable diseases manual*. Washington DC: American Public Health Association, 2022.

[63] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[64] Donaldson LJ, Rutter PD. *Donaldson's essential public health*. 4th ed. London: CRC Press, 2018.

[65] Peiris M. Respiratory tract viruses. In: Firth JD, Conlon CP, Cox TM, eds. *Oxford textbook of medicine*. 6th ed. Oxford: OUP, 2020.

[66] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

particles) are discharged from an infected person's airways – or alternatively, are produced during some medical procedures carried out on infected patients. Being very small, the infective particles can remain suspended in the air for long periods of time and travel long distances and be inhaled into the air passages of potential new hosts.

– Droplet spread. Large infective particles of 5–10 μm diameter (i.e. *droplet nuclei* or *respiratory droplets*) tend to fall out of the air soon after being produced; they are therefore unlikely to travel more than 1 metre or so from the source patient and they infect others either by landing directly on the mucous membranes of healthy hosts (i.e. *direct transmission*), or else by contaminating environmental surfaces or inanimate objects (i.e. *fomites*), and being transported from these inanimate objects to mucous membranes (i.e. *indirect transmission*, occurring if an uninfected person touches a fomite and then touches their mouth).

For any given respiratory pathogen, the range of infective particle size (and hence the predominant mode of spread) will be affected by factors such as:[67]

– the volume of the nasopharyngeal or respiratory secretions being produced by the infected individual;

– the character of the secretions;

– the extent to which droplets are converted to aerosol particles by evaporation;

– the duration of airborne suspension (itself influenced by environmental factors such as temperature, humidity and prevailing air currents); and

– the distance travelled (itself also influenced by environmental factors).

In reality, both the size of respiratory particles produced by an infected person and the

[67] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

distance they can travel are likely to fall within a spectrum; for any given respiratory pathogen, therefore, disease acquisition may occur through both the airborne and the droplet mechanisms of spread.[68]

2.7 How is SARS-CoV-2 transmitted? (1) Aerodynamic factors

Perplexingly, and although COVID-19 is generally thought of as an acute respiratory illness, there are very low levels of SARS-CoV-2 in the respiratory tract during the early phase of disease; this is the case with all coronavirus infections.[69]

In infected humans, SARS-CoV-2 is found in the highest concentration in the nasal passages, where it infects the nasal epithelial cells.[70] COVID-19 is therefore thought to be acquired mainly from the oropharyngeal and respiratory secretions of infected patients.[71]

SARS-CoV-2 is primarily transmitted from person to person following close (≤ 6 feet, ≈ 2 metres) exposure to respiratory fluids carrying infectious virus.[72] When an infected person breathes, sings, talks, coughs or sneezes, they release large infective particles (*droplet nuclei*) into the air; these large particles may land on the exposed mucous membranes of a new host, causing infection.[73]

Infection from touching contaminated surfaces or objects (*fomites*) is also possible, although the evidence suggests that this is not a major route of infection.[74]

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[68] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[69] Tille PM. *Bailey & Scott's diagnostic microbiology*. 15th ed. London: St Louis, MI, Elsevier, 2022.

[70] Tille PM. *Bailey & Scott's diagnostic microbiology*. 15th ed. London: St Louis, MI, Elsevier, 2022.

[71] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[72] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

[73] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

[74] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

Finally, SARS-CoV-2 exposure can occur when very small infective particles (*aerosol particles*), suspended in the air, are inhaled directly.[75] Aerosol-generating procedures commonly take place in hospitals, and in dental surgeries; hospital procedures in this category include (but are not limited to) tracheal intubation, manual ventilation, non-invasive ventilation and the use of certain high-flow oxygen treatments.[76]

2.8 How is SARS-CoV-2 transmitted? (2) Environmental factors

The risk of COVID-19 transmission is enhanced in poorly-ventilated indoor spaces.[77] Densely populated settings such as prisons, cruise ships, nursing homes, aeroplanes and large indoor gatherings facilitate high transmission efficiency.[78] Health care workers and those working in dentistry have high potential for exposure.[79]

Transmission of SARS-CoV-2 in outdoor settings is thought to be much less common.[80]

COVID-19 outbreaks on buses and trains have been described.[81] On buses, COVID-19 *attack rates* (i.e. the proportion of people exposed who go on to develop infection) have been as high as 36%.[82] On trains, attack rates among passengers within 3 rows of an index patient were lower, ranging from 0% to 10%, with an overall attack rate of <

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[75] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

[76] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[77] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

[78] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[79] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[80] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[81] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

[82] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

1%.[83]

COVID-19 attack rates on flights range from 0% to 8% but can be as high as 60% in subsections of an aircraft, as was observed on a 10-hour flight in a business class cabin.[84]

The experience in Wuhan shows that transmission can be massive in a short space of time, with thousands of new patients diagnosed daily.[85]

2.9 How is SARS-CoV-2 transmitted? (3) Patient-specific factors

Individuals with mild to moderate COVID-19 may shed infectious virus in respiratory secretions for up to 10 days following the onset of symptoms; this was known from early on in the pandemic.[86] Immunocompromised people with severe disease may shed the virus for longer (potentially, for up to 20 days).[87] However the concentrations of SARS-CoV-2 RNA are highest one day before symptoms appear, leading to extensive spread of the virus by asymptomatic people not yet showing any signs of illness.[88]

Most people who test positive for SARS-CoV-2 but are asymptomatic eventually do show symptoms, but many individuals remain asymptomatic during the entirety of their infection; in the case of infected children, at least one-third are likely to remain truly asymptomatic during infection.[89]

In February 2020, 3711 passengers and crew members on a cruise ship named the

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[83] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

[84] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

[85] Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

[86] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[87] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[88] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[89] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

Diamond Princess were quarantined off the coast of Japan, due to an outbreak of SARS-CoV-2 infection on the ship.[90] Researchers found that 52% of the 634 people who were laboratory-confirmed cases were initially asymptomatic.[91] Most began to show symptoms, but an estimated 17.9% of infected individuals never showed any symptoms of infection.[92]

2.10 Origins of COVID-19

COVID-19 first came to public attention in December 2019 in the form of an outbreak of severe respiratory illness in Wuhan, Hubei Province, China.[93] Since the disease was caused by a novel virus newly emerged in humans, the world's population was completely immune-naïve to the pathogen and therefore highly vulnerable to infection.[94]

The Wuhan disease outbreak of December 2019 was initially associated with an animal market.[95] In January 2020 the Chinese authorities confirmed that the outbreak was caused by a novel coronavirus, initially termed *2019 novel coronavirus* (2019-nCoV).[96]

Subsequent genome sequencing of the novel coronavirus would demonstrate that it has 79.5% similarity to SARS-CoV (i.e. the betacoronavirus that in 2002–2003 had caused an epidemic of severe acute respiratory syndrome, or SARS), and 96% similarity, at a

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[90] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[91] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[92] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[93] Barlow G, Irving WL, Moss PJ. Infectious disease. In: Feather A, Randall D, Waterhouse M, eds. *Kumar & Clark's clinical medicine*. 10th ed. London: Elsevier, 2021.

[94] Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

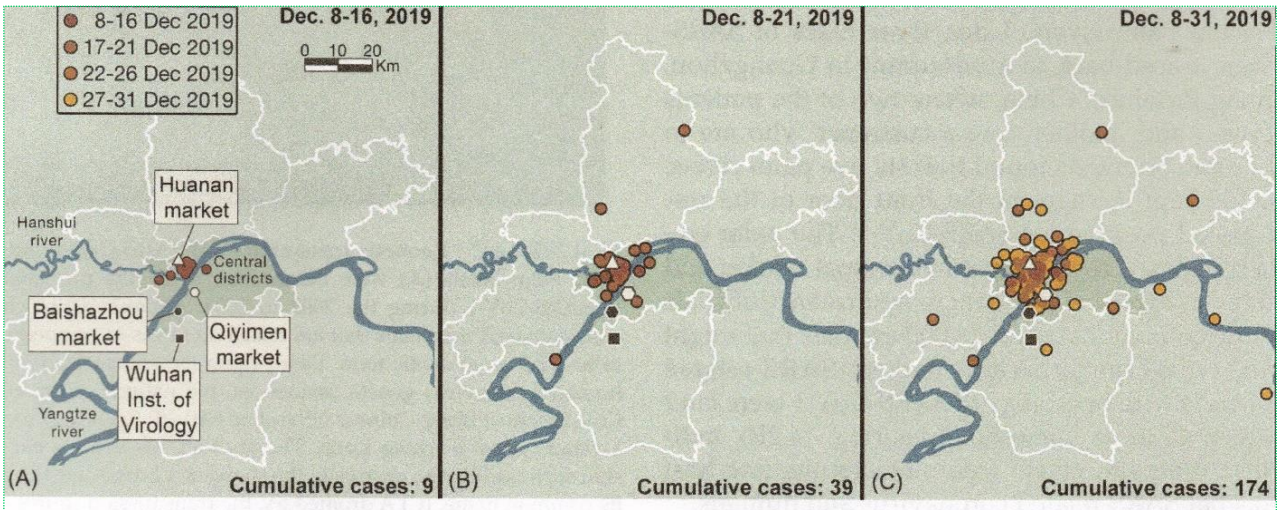
[95] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[96] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

whole-genome level, to a bat coronavirus.[97]

It is now believed by many that the novel Wuhan virus was transmitted to humans via horseshoe bats (*Rhinolophus sinicus*), and potentially other intermediate hosts, to whom individuals may have been exposed at wild food markets in the centre of Wuhan; an alternative theory is that the virus resulted from a 'lab leak'.[98]

The locations of the first documented COVID-19 cases in Wuhan are shown in the disease progression maps, below; 55% of all cases reported in December 2019 were traced back to the Huanan Seafood Wholesale Market in Wuhan or other nearby markets that sold wild animals and their meat:[99]



E 14.3 **First COVID-19 cases in Wuhan, China, in December 2019.** The locations of the first known global COVID-19 cases c

2.11 COVID-19 initial spread

SARS-CoV-2 appeared to be more transmissible than SARS-CoV and MERS-CoV (i.e. the previously identified novel coronaviruses); early efforts to contain SARS-CoV-2 were

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97 Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

98 Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

99 Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

unsuccessful and it spread rapidly throughout the world.

The *basic reproductive rate* (R_0) for the original wild-type strain of SARS-CoV-2 was estimated as 2.8.[100] The R_0 denotes the number of persons directly infected by an infectious case during his or her entire infectious period, on entering a totally susceptible population.[101] By comparison, the R_0 of seasonal influenza is typically 1–2.[102]

On 8th December 2019 an individual with what would become the first known case of SARS-CoV-2 infection began showing symptoms in Wuhan.[103]

On 31st December 2019 China reported the presence of 27 cases of atypical pneumonia to the World Health Organization (WHO).[104]

On 10th January 2020 the Chinese authorities released the genomic sequence of the novel coronavirus; this provided the necessary information for the immediate development of vaccines against the virus.[105]

On 23rd January 2020 China imposed a strict *lockdown* of Wuhan and took similar measures in 15 other cities in the subsequent days.[106] The repressive measures taken in China appeared to slow the progression of the epidemic, though they failed to 'contain' it.[107]

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[100] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[101] Giesecke J. *Modern infectious disease epidemiology*. 3rd ed. London: CRC Press, 2017.

[102] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[103] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[104] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[105] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[106] Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

[107] Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

During January 2020 the first secondary outbreaks of the new disease were identified in Iran, Italy and Spain; within a few weeks, most of the world was affected.[108]

The first two people in the UK to be infected with 2019-nCoV were diagnosed in late January 2020.[109]

On 30th January 2020, and owing to the rapid international spread of 2019-nCoV, WHO declared a public health emergency of international concern (PHEIC).[110]

The new disease at first had no specific name.[111] On 11th February 2020 WHO termed it *Coronavirus Disease 2019*; this term was later contracted to COVID-19.[112]

2.12 Progression of the pandemic – March 2020

On 11th March 2020 WHO declared that the extent and global distribution of COVID-19 constituted a pandemic.[113] By this time cases were being reported throughout the world and severe epidemics in some countries in Europe threatened to overwhelm demand on the national health systems.[114]

The global progression of COVID-19 by 31st March 2020 is shown below:[115]

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[108] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[109] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[110] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

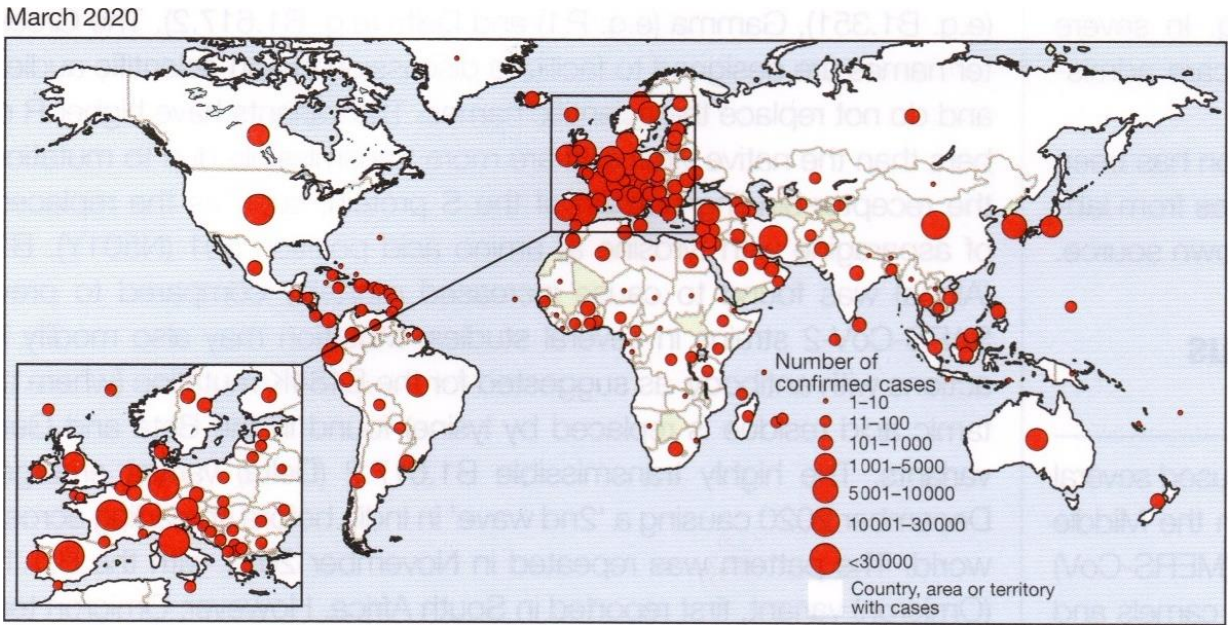
[111] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[112] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[113] Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

[114] Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

[115] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP,



As at May 2020 there were approximately 5 million COVID-19 cases and 300,000 deaths recorded globally.[116]

By August 2021 the virus had caused ≥ 200 million confirmed cases and > 4.3 million deaths worldwide.[117]

As at April 2022 there were an estimated 400 million cases and 6 million deaths reported worldwide.[118]

International travel has played a continuing role in the epidemiology of the pandemic, facilitating the initial global spread of the virus as well as each successive SARS-CoV-2 variant.[119]

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eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[116] Barlow G, Irving WL, Moss PJ. Infectious disease. In: Feather A, Randall D, Waterhouse M, eds. *Kumar & Clark's clinical medicine*. 10th ed. London: Elsevier, 2021.

[117] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[118] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

[119] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

2.13 Emergence of variants – late 2020

By late 2020 new variants of SARS-CoV-2 had emerged carrying several amino acid substitutions.[120] The variants mostly had higher R_0 numbers than the original wild-type strain and were said to be more transmissible due to mutations in the receptor-binding domain of the spike (S) protein.[121] The *Delta* variant had an estimated R_0 of 5.1 and the *Omicron* variant, which emerged in late 2021, had an estimated R_0 of 9.5.[122]

The nomenclature of the new variants developed alongside the pandemic; initially they were assigned alphanumeric lineage codes (e.g. B.1.7) but the public found these codes difficult to use and so the variants tended to be referred to according to the geographic location where they were first identified (e.g. 'Kent', 'South Africa', 'Brazil', etc).[123]

The first SARS-CoV-2 variant to be detected, in Autumn 2020, was the B.1.7 or 'Kent' variant; it was noted for its increased transmissibility over the original, ancestral virus.[124]

The highly transmissible B.617.2 ('India') variant emerged in December 2020 causing a COVID-19 second wave in India before spreading across the world.[125] It was first detected in the UK in April 2021 and became dominant by July 2021.[126]

In May 2021, to both simplify the nomenclature and avoid the pejorative connotations of geographical names, WHO started to assign Greek characters to the variants, as

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[120] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[121] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[122] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[123] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[124] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[125] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[126] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

follows:[127]

- *Alpha* (formerly, B.1.7 or 'Kent');
- *Beta* (formerly, B.1.351 or 'South Africa');
- *Gamma* (formerly, P.1 or 'Brazil'); and
- *Delta* (formerly, B.617.2 or 'India').

In November 2021 the *Omicron* variant (formerly, B.1.1.529, first reported in South Africa) caused a new rise in incident cases.[128] However *Omicron* tended to cause disease of less severity than earlier variants, presumably because of a combination of altered virulence factors and herd immunity from vaccination and natural infection.[129]

Following the recognition of the *Omicron* variant becoming the dominant circulating strain during 2022, many vaccine manufacturers rapidly developed second-generation vaccines against both the wild-type and the *Omicron* strains of SARS-CoV-2; these are known as *bivalent* vaccines.[130]

Further variants of SARS-CoV-2 emerged in 2022 and in 2023.[131]

2.14 How quickly does COVID-19 develop?

Those exposed to an infected patient typically develop symptoms of COVID-19 between

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[127] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[128] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[129] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[130] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[131] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

4 to 5 days post-exposure.[132]

The median incubation period of COVID-19 (i.e. the time interval between the individual becoming infected with SARS-CoV-2 and him or her then developing overt symptoms of disease) is 4 days (with an interquartile range of 2–7 days).[133] The incubation period can be as long as 14 days.[134]

2.15 Who is at high risk for severe COVID-19 infection?

Individuals who are older, male, from deprived areas, or from black, ethnic or minority groups are at higher risk of severe disease and death from COVID-19.[135] Substance use (e.g. alcohol, opioid or cocaine use disorder), and current or former smoking both increase the risk.[136]

The risk of severe COVID-19 also increases with the following conditions:

- obesity;
- certain underlying co-morbidities (e.g. diabetes, hypertension, cardiac disease);
- frailty;
- impaired immunity; and

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[132] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[133] Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

[134] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[135] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[136] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

– reduced ability to cough and clear bronchial secretions.[137]

People with chronic liver disease, especially cirrhosis, are at high risk of severe COVID-19.[138]

In the early stages of the pandemic the crude (i.e. all-age) *case-fatality rate* (CFR) from COVID-19 was reported as ranging from 1% to 13%–14%; this very wide variation in a key measure of pathogenicity was explained at the time as being possibly due to different case definitions used and, to some extent, the intensive care capacity of hospitals.[139]

2.16 COVID-19 and pregnancy

Early in the pandemic, pregnant and recently-pregnant women who acquired COVID-19 were more likely to be admitted to an intensive care unit, have invasive ventilation or extracorporeal membrane oxygenation (ECMO) in comparison to non-pregnant women of reproductive age.[140] The risk was higher if they were overweight or obese, were of black or Asian minority ethnic background, were > 35 years old, or had severe co-morbidities (e.g. diabetes, hypertension, asthma).[141]

In the *Omicron* era, by contrast, pregnant women were substantially less likely to have a preterm birth or maternal critical care; fewer stillbirths and no maternal deaths were observed in the UK in this period.[142]

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[137] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[138] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[139] Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

[140] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[141] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[142] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

2.17 Who is at low risk for severe COVID-19 infection?

In general, COVID-19 has a milder disease course in children and young adults than it does in older adults.[143] The majority of children recover completely after acute SARS-CoV-2 infection and any persistent symptoms will improve with time.[144]

Following the emergence and rapid spread of the *Omicron* variant and subvariants since November 2021, nearly all children in the UK now have antibodies against SARS-CoV-2, mostly due to natural infection in the youngest age groups.[145]

The *case-fatality rate* (CFR) of COVID-19 for different age cohorts in England during 2020 is shown in the table (the Scottish *counts* are lower than the English counts, but the *rates* are likely to be broadly similar); of note, the CFR for those aged under 18 was 0.0003% (i.e. effectively zero, in respect of otherwise healthy children), and for those aged 18 to 49 it was 0.006% – only in the case of people aged ≥ 85 did it rise to 1.9%:[146]

Table 1: Cumulative deaths within 28 days of a positive test for SARS-CoV-2 in England, 2020

	Male		Female		Total	
	Count (n)	Rate (per 100,000)	Count (n)	Rate (per 100,000)	Count (n)	Rate (per 100,000)
Under 18	15	0.24	17	0.29	32	0.26
18 to 49	809	6.94	525	4.56	1334	5.76
50 to 64	3751	70.34	2008	36.50	5759	53.16
65 to 74	6822	253.45	3772	129.77	10594	189.23
75 to 84	13307	845.38	8773	465.39	22080	638.30
85 and over	13134	2498.24	13820	1569.24	26954	1916.51
Total	**37838**	**135.22**	**28915**	**101.22**	**66753**	**118.04**

[143] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[144] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[145] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[146] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

A very small minority of children infected with SARS-CoV-2 (approximately 1 in 3,000) developed a multi-system inflammatory syndrome with Kawasaki disease-like features; this is known also as mucocutaneous lymph node syndrome and as paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS).[147] In the US, the syndrome was mainly seen in black and Latino children.[148]

PIMS-TS risk in the UK declined during the *Delta* wave, and again during the *Omicron* wave, it is likely that this was due to high levels of natural and vaccine-induced immunity in children, and key mutations in the more recent SARS-CoV-2 variants.[149]

2.18 What pathological processes occur in COVID-19?

Early in the course of COVID-19 infection, viral replication occurs; the virus then disseminates to multiple organ sites.[150]

Later in the course of infection disease is driven by an exaggerated immune or inflammatory response to the virus (a phenomenon sometime termed the *cytokine storm*); this results in widespread tissue damage.[151]

For SARS-CoV-2, activation of the clotting cascade in association with marked inflammation appears to be a distinct feature.[152] Microthrombi occur around the body, and both venous thromboembolism and arterial clots in the brain may be prominent

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[147] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[148] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[149] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[150] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[151] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[152] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

features.[153]

2.19 What are the clinical features of COVID-19? (1) Early features

In patients with symptomatic COVID-19 infection, the initial symptoms are non-specific and appear after an incubation period of approximately 2 to 7 days; typically, the symptoms will include:[154]

- fever;
- headache;
- *myalgia* (i.e. muscle pain); and
- *malaise* (i.e. general unwellness).

At the same time, the patient may experience *anosmia* (i.e. loss of smell), and *dysgeunia* (i.e. distortion of taste).[155]

2.20 What are the clinical features of COVID-19? (2) Later features

The majority of individuals with COVID-19 infection will recover spontaneously; up to 80% of those infected in China had mild symptoms not requiring hospitalisation.[156]

In other patients, and over a matter of days or weeks, COVID-19 may progress to one or more severe syndromes (i.e. symptom clusters) including:[157]

- severe acute respiratory disease, characterised by dry cough, sore throat,

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[153] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[154] Tille PM. *Bailey & Scott's diagnostic microbiology*. 15th ed. London: St Louis, MI, Elsevier, 2022.

[155] Tille PM. *Bailey & Scott's diagnostic microbiology*. 15th ed. London: St Louis, MI, Elsevier, 2022.

[156] Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

[157] Tille PM. *Bailey & Scott's diagnostic microbiology*. 15th ed. London: St Louis, MI, Elsevier, 2022.

nasal congestion, shortness of breath and low oxygen saturation;

- cardiac abnormalities;
- coagulopathies (i.e. clotting disorders); and
- immune syndromes that pose significant treatment difficulties.

Other symptoms, such as profound fatigue and skin rashes may also be present.[158]

50% of patients with confirmed COVID-19 will report one or more gastrointestinal symptoms; the leading gastrointestinal symptoms are diarrhoea (in 38% of those who are sick) and vomiting (in 13%).[159]

Some patients with severe COVID-19 may deteriorate rapidly and develop life-threatening complications, including:[160]

- thromboembolic events;
- cardiac disease;
- acute kidney injury;
- sepsis;
- septic shock; and
- multi-organ failure.

Natural immunity due to previous infection with SARS-CoV-2 lasts up to 1 year before beginning to wane, although new strains and variants, such as *Omicron*, appear to

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[158] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[159] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

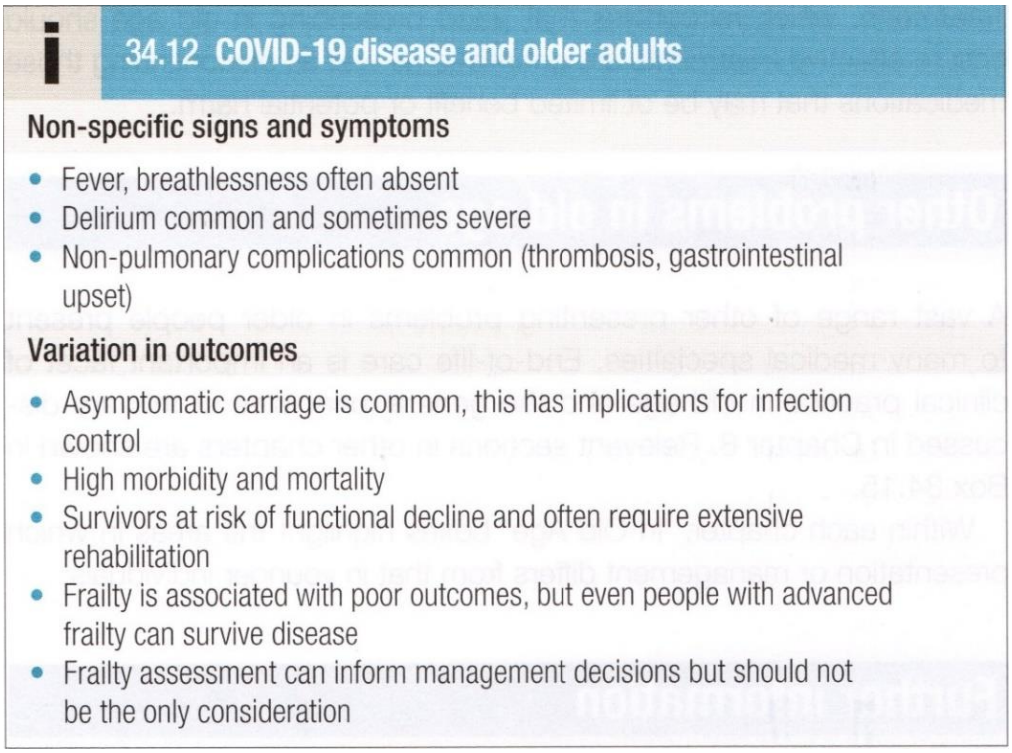
[160] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

exhibit greater immune escape, making reinfection more common:[161]

2.21 How does COVID-19 present in the elderly?

Atypical symptoms of COVID-19 such as delirium and reduced mobility may be present in the elderly (and in immunocompromised individuals also), often without a fever.[162]

The general features of COVID-19 in the elderly are summarised in the following table:[163]



34.12 COVID-19 disease and older adults

Non-specific signs and symptoms

- Fever, breathlessness often absent
- Delirium common and sometimes severe
- Non-pulmonary complications common (thrombosis, gastrointestinal upset)

Variation in outcomes

- Asymptomatic carriage is common, this has implications for infection control
- High morbidity and mortality
- Survivors at risk of functional decline and often require extensive rehabilitation
- Frailty is associated with poor outcomes, but even people with advanced frailty can survive disease
- Frailty assessment can inform management decisions but should not be the only consideration

2.22 What is *long COVID*?

As is the case also with other viral infections, such as infectious mononucleosis (i.e.

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[161] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[162] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[163] Quinn TJ. Ageing and disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

Epstein-Barr virus infection, or 'glandular fever'), COVID-19 may give rise to prolonged symptoms that persist for more than 4 weeks; this is known as *long COVID*.[164] In the UK, 4.5% of COVID-19 cases report long-term symptoms 12–16 weeks after initial infection.[165]

Other terms for long COVID include post-COVID syndrome, and post-acute sequelae of COVID-19 (PASC).[166]

Reported symptoms of long COVID are varied, involving most organ symptoms and affecting both physical and mental health.[167] Commonly-reported long COVID symptoms are:[168]

- shortness of breath;
- fatigue;
- headache; and
- difficulty thinking or concentrating.

In addition to the above, there is growing evidence of long-term cardiovascular sequelae of COVID-19, including cerebrovascular disorders, cardiac dysrhythmias, heart failure, ischaemic and non-ischaemic heart disease, myocarditis, pericarditis and thromboembolic disease.[169]

2.23 What diagnostic tests are available?

[164] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[165] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[166] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

[167] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[168] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

[169] Guagliardo SA, Friedman C. COVID-19. In: Nemhauser J, ed. *CDC health information for international travel*. Oxford: OUP, 2023.

There are currently three types of point-of-care blood tests for COVID-19, as follows:[170]

- Antibody tests. These tests detect antibodies to SARS-CoV-2 that are circulating in the serum (i.e. the liquid component of the blood), rather than detecting the virus itself; this type of testing is known as *serology*, or as 'indirect testing'.

- Antigen tests. These tests detect fragments of proteins of the SARS-CoV-2 virus; because such fragments can persist long after the acute infection, they can wrongly suggest that the individual tested is still infectious, even though this is in fact no longer the case.

- Nucleic acid amplification tests (NAATs). These test directly for the pathogen and represent the gold standard for COVID-19 point-of-care testing.

In a nucleic acid amplification test (NAAT) specific sequences of microbial DNA or RNA are identified using a nucleic acid primer that is then amplified exponentially by enzymes, to generate multiple copies of a target nucleotide sequence.[171]

The most commonly used NAAT uses polymerase chain reaction (PCR).[172] Reverse transcription PCR (RT-PCR) is used to detect RNA from RNA viruses.[173] Fluorescent labels in the reaction enable real-time detection of amplified DNA; crude quantification of the viral load is based on the assumption that the time taken to reach the detection threshold is proportional to the number of copies of the target nucleic acid sequence.[174]

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[170] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[171] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[172] Sandoe JA, Dockrell DH. Principles of infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[173] Sandoe JA, Dockrell DH. Principles of infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[174] Sandoe JA, Dockrell DH. Principles of infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

2.24 What are the laboratory findings?

Severe COVID-19 is associated with the following laboratory abnormalities:[175]

- *lymphopenia* (i.e. a low blood count of circulating lymphocytes);
- *neutrophilia* (i.e. a high blood count of circulating neutrophils);
- elevated serum *alanine aminotransferase* and *aspartate aminotransferase*; and
- elevated *lactate dehydrogenase*.

Elevated *D-dimer* has been associated with high mortality from COVID-19.[176]

2.25 What are the radiological abnormalities?

Ground glass opacity is a common radiological finding (56.4%) on chest computerised tomography (CT) upon hospital admission for COVID-19.[177] However in a large observational study, neither radiographic nor CT abnormality was found in 157 of 877 patients (17.9%) with non-severe COVID-19, and in 5 of 173 patients (2.9%) with severe disease.[178]

2.26 How is COVID-19 treated? (1) Medical supportive care

In the early stages of the pandemic, COVID-19 patients with severe respiratory distress were often treated aggressively with intravenous fluids and mechanical ventilation; it

[175] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[176] Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

[177] Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

[178] Khan OA, Hui DS, Azhar E, Zumia A. SARS, MERS, COVID-19 and other coronavirus infections. In: Khan OA, Heymann DL, eds. *Control of communicable diseases – clinical practice*. Washington DC: American Public Health Association, 2020.

became apparent however that intravenous fluids could exacerbate fluid in the lungs and further reduce oxygenation.[179]

Another early clinical observation was that lying in a *prone position* (i.e. on the stomach, as compared to the customary *supine position* on the back) led to improved oxygenation in patients who were receiving supplemental oxygen therapy through a face mask or nasal tubes.[180] This resulted in fewer intubations (i.e. insertion of a breathing tube into the patient), which themselves were a cause of morbidity and mortality.[181]

The current mainstay of COVID-19 management is medical supportive care.[182]

COVID-19 patients who are coughing should initially be managed using simple non-drug measures (e.g. honey).[183] For cough that is distressing in a patient with COVID-19, short-term use of a cough suppressant (e.g. codeine phosphate) may be indicated.[184]

COVID-19 patients with a fever should be advised to drink fluids regularly to avoid dehydration, and to take antipyretics (e.g. paracetamol or ibuprofen) as appropriate.[185]

2.27 How is COVID-19 treated? (2) Pharmacological therapy

Most drugs tested have shown marginal or disappointing efficacy against SARS-CoV-2.[186]

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[179] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[180] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[181] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[182] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[183] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[184] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[185] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[186] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

Passive immunisation with *human monoclonal antibodies* against SARS-CoV-2 has been used in some centres as therapy in hospitalised patients with severe COVID-19.[187] Convalescent plasma has also been used, although the typical overall composite titre of SARS-CoV-2 neutralising antibodies in convalescent plasma following a single infection is low, limiting its effectiveness and reproducibility.[188]

In the US, the combination of *remdesevir* (an antiviral agent) plus *dexamethasone* (a steroid) was endorsed in early 2020 for those COVID-19 patients requiring supplemental oxygen.[189] The same treatment combination was endorsed in the UK for these patients, at around the same time.[190] Dexamethasone is an 'off-label' (i.e. non-proprietary) drug that costs approximately 9 pence per tablet.[191]

In the UK four antiviral drugs, as follows, have been 'repurposed' from their pre-pandemic treatment indications and are currently approved for critically ill COVID-19 patients; the drug trade names and their respective manufacturers are in parentheses:[192]

- Molnupiravir *(Lagevrio – Merck, Sharp & Dohme)*. Molnupiravir is a ribonucleoside analogue that increases the number of mutations in viral RNA, thus preventing multiplication of the virus *[cost of this drug not publicly available]*.

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[187] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[188] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[189] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[190] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[191] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[192] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

- Nirmatrelvir with ritonavir *(Paxlovid – Pfizer)*. Nirmatrelvir is a peptidomimetic inhibitor of coronavirus 3C-like protease which prevents multiplication of SARS-CoV-2; ritonavir increases the plasma concentrations of nirmatrelvir *[cost of this drug combination not publicly available]*.

- Remdesivir *(Veklury – Gilead)*. Remdesivir is an RNA polymerase inhibitor that disrupts the production of viral RNA, preventing multiplication of SARS-CoV-2; a single vial of remdesivir costs £340.00.

- Sotrovimab *(Xevudy – GlaxoSmithKline)*. Sotrovimab is an engineered human immunoglobulin monoclonal antibody that binds to the spike protein receptor binding domain of SARS-CoV-2, preventing the body from entering human cells; a single vial of sotrovimab costs £2,209.00.

The safety of COVID-19 antiviral treatment during pregnancy has not been established.[193]

Anticoagulation in the face of COVID-19-associated thromboembolic events is an especially complex situation and requires expert consultation.[194]

2.28 How is COVID-19 prevented? (1) General public health measures

COVID-19 may be prevented through standard infection control measures, along with the public health management of infected cases.[195]

The most basic public health measure against COVID-19, which was implemented in all

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[193] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[194] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[195] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

countries during the 2020–2023 pandemic, was promoting frequent handwashing.[196] Large-scale frequent surface decontamination efforts were deployed in public spaces, but the effect of these cleanings on reducing transmission was and remains uncertain.[197]

2.29 How is COVID-19 prevented? (2) Personal protective equipment

All countries advised the use of personal protective equipment (PPE) by frontline healthcare staff during the COVID-19 pandemic.[198] Challenges included the rapid depletion of PPE, the lag between the spread of infection and the acquisition of evidence required to inform precautions to control its spread, and frequent changes in PPE guidance in response to its availability.[199]

Most countries recommended, and in some cases enforced, the use of face coverings by all adults (and not simply healthcare staff), in places where close contact was likely.[200]

2.30 How is COVID-19 prevented? (3) *Lockdowns*

A major strategy for attempting to limit the spread of SARS-CoV-2 was the introduction by some governments, starting with China, of extreme physical distancing measures; these have been termed *lockdowns*.[201]

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[196] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[197] Crowe JE. Common viral respiratory infections, including COVID-19. In: Loscalzo J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Jameson JL, eds. *Harrison's principles of internal medicine*. 21st ed. New York: McGraw-Hill, 2022.

[198] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[199] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[200] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[201] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

The components and restrictiveness of lockdowns varied, and not all countries employed lockdowns.[202] Where lockdowns against COVID-19 were introduced, they typically included:[203]

- the closure of schools, workplaces, non-essential shops, sporting and entertainment venues;
- a move to 'remote' (i.e. computer-based) working where possible;
- banning mass gatherings;
- curfews;
- stay-at-home orders; and
- other local, national and international travel restrictions.

In some countries where extreme physical distancing measures were employed early in the COVID-19 pandemic (e.g. New Zealand), they resulted in complete, although temporary, eradication of virus in the community.[204]

2.31 How is COVID-19 prevented? (4) *Social distancing*

In countries where extreme physical distancing measures (i.e. *lockdowns*) were not considered necessary, or else were temporarily relaxed, *social distancing* strategies were employed instead; these involved keeping people physically separate (a target of ≥ 2 metres was used in the UK).[205]

Vulnerable adults, including older and immunocompromised people, were advised to

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[202] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[203] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[204] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[205] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

curtail all social interactions; this strategy was termed *shielding*, in the UK.[206]

2.32 How is COVID-19 prevented? (5) *Test, trace and isolate* measures

Other measures used to limit, or attempt to limit, the spread of SARS-CoV-2 were high levels of case identification, with widespread testing in order to identify cases and ensure public health follow-up of potential cases, and enforcing quarantine measures for cases, contacts and travellers from high-incidence countries.[207] The combination of such strategies has been termed *test, trace and isolate* (TTI).[208]

More novel approaches to limit, or attempt to limit, the spread of SARS-CoV-2 included the use of mobile phone apps, and (depending on jurisdiction and legal constraints) use of CCTV footage and tracking of a contact's digital signature.[209]

In the UK (including Scotland), and in other countries also, the processes of death certification were streamlined in early 2020, to deal with anticipated surges in deaths.[210]

2.33 How is COVID-19 prevented? (6) Vaccination

During 2020–2021 the COVID-19 vaccine was developed at record speed, mainly due to four factors: prior research, the state of vaccine technology, abundant funding, and a large group of willing volunteers.[211]

Clinical trials of a new drug or vaccine typically have three or four phases (*Phase 1*,

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[206] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[207] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[208] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[209] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[210] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[211] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

Phase 2, etc) and these phases are normally run sequentially, with each phase costing between $10 to $50 million; for the COVID-19 vaccine development the phases were often run concurrently, speeding up the process.[212] Vaccine companies were able to take this commercial risk because they were mostly receiving government money; for instance, *Operation Warp Speed* in the United States provided nearly $1.5 billion of support to Moderna, Janssen, Sanofi / GSK, and Merck towards their vaccine efforts.[213]

Phase 3 trials of the Moderna vaccine, and also of the Pfizer-BioNTech vaccine (which was funded entirely in-house), began on 27th July 2020; both trials initially enrolled over 30,000 participants.

Globally, vaccines against COVID-19 fall into one of three categories, as follows:[214]

- *component* vaccines (i.e. conventional vaccines);
- *viral vector* vaccines (i.e. using novel technology); and
- *nucleic acid* vaccines (known as *messenger RNA* or *mRNA* vaccines, and also constituting novel technology).

This distinction between *conventional* (the first three categories in the table) and novel-technology vaccines (the two final categories) is shown in the table below:[215]

[212] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[213] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[214] Sandoe JA, Dockrell DH. Principles of infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[215] Sandoe JA, Dockrell DH. Principles of infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

6.14 Vaccines in current clinical use

Live attenuated vaccines

- Measles, mumps, rubella (MMR)
- Oral poliomyelitis (OPV, not used in UK)
- Rotavirus
- Tuberculosis (bacille Calmette–Guérin, BCG)
- Typhoid (oral typhoid vaccine)
- Varicella zoster virus

Inactivated (killed) whole-cell vaccines

- Cholera
- Hepatitis A
- Influenza
- Poliomyelitis (inactivated polio virus, IPV)
- Rabies

Component vaccines

- Anthrax (adsorbed extracted antigens)
- COVID-19
- Diphtheria (adsorbed toxoid)
- Hepatitis B (adsorbed recombinant hepatitis B surface antigen, HBsAg)
- *Haemophilus influenzae* type B (conjugated capsular polysaccharide)
- Human papillomavirus (recombinant capsid proteins)
- Meningococcal, quadrivalent A, C, Y, W135 (conjugated capsular polysaccharide)
- Meningococcal, serogroup C (conjugated capsular polysaccharide)
- Pertussis (adsorbed extracted antigens)
- Pneumococcal conjugate (PCV; conjugated capsular polysaccharide, 13 serotypes)
- Pneumococcal polysaccharide (PPV; purified capsular polysaccharide, 23 serotypes)
- Tetanus (adsorbed toxoid)
- Typhoid (purified Vi capsular polysaccharide)

Viral vector vaccines

- Dengue virus (containing Yellow fever 17D vaccine strain with dengue virus genes)
- Ebola virus (vesicular stomatitis virus expressing Ebola virus glycoproteins)
- COVID-19

Nucleic acid vaccines

- COVID-19 (RNA vaccines)
- Ebola virus (DNA in clinical trials)

The first round of COVID-19 vaccines, approved for emergency use in 2020–2021, were nucleic acid vaccines using novel gene technology; prior to their emergency use approval, no nucleic acid vaccines had been licensed for therapeutic use in any

country.[216]

In the US two mRNA vaccines, as follows, received Emergency Use Authorisation in December 2020 from the Food and Drug Administration (FDA):[217]

- the Moderna COVID-19 vaccine (for use in individuals 18 years of age and older).
- the Pfizer-BioNTech COVID-19 vaccine (for use in individuals 16 years of age and older); and

2.34 Initial COVID-19 vaccines procured in the UK

In the UK, COVID-19 vaccination was made available from mid-January 2021, initially for high-risk groups only.[218] During 2021 four COVID-19 vaccines were authorised for use in the UK; two of these products were viral vector vaccines and two were mRNA vaccines, as follows:[219]

- the AstraZeneca COVID-19 vaccine, *Vaxzevria* (adenovirus vector);
- the Janssen COVID-19 vaccine (adenovirus vector);
- the Moderna COVID-19 vaccine, *Spikevax* (mRNA); and
- the Pfizer / BioNTech COVID-19 vaccine, *Cominarty* (mRNA).

Although the UK government announced in April 2021 that 20 million doses of the Janssen (adenovirus vector) vaccine had been ordered from the manufacturer, the vaccine has never been issued in the UK.[220] Since early 2023 the AstraZeneca

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[216] Dockrell DH, Sundar S, Angus BJ. Infectious disease. In: Penman ID, Ralston SH, Strachan MW, Hobson RP, eds. *Davidson's principles and practice of medicine*. 24th ed. London: Elsevier, 2022.

[217] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[218] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[219] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 81*. London: Pharmaceutical Press, 2021.

[220] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

(adenovirus vector) vaccine has been no longer available in the UK, either.[221]

2.35 Later COVID-19 vaccines procured in the UK

In late 2022 *Nuvaxovid*, an adjuvanted, protein-based monovalent COVID-19 vaccine (i.e. a conventional vaccine) manufactured by Novavax, was authorised for use in the UK.[222] Only a small supply of *Nuvaxovid* is currently available, at a limited number of sites.[223] The use of *Nuvaxovid* is restricted to 'booster' doses, in those vaccine recipients where an mRNA vaccine is considered unsuitable.[224]

Another vaccine recently approved in the UK for 'booster' use only is *VidPrevtyn Beta*, manufactured by Sanofi Pasteur (and also a conventional vaccine); as its name suggests, *VidPrevtyn Beta* is targeted against the *Beta* variant of SARS-CoV-2.[225]

2.36 Current UK vaccination programme against COVID-19

The aims of the current COVID-19 vaccination programme in the UK are:[226]

- to provide protection for individuals who are considered at highest risk of severe illness or death from COVID-19 infection;
- to reduce hospitalisations; and
- to protect frontline health and social care staff from exposure.

All UK adults, and children aged 5½ years and over, are currently eligible for a primary

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[221] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[222] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 83*. London: Pharmaceutical Press, 2022.

[223] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[224] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[225] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[226] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

vaccination course.[227] Most eligible individuals should receive two doses of COVID-19 vaccine for their primary course; three doses are required for individuals aged 5 and above who are severely immunosuppressed at the time of their vaccination.[228]

The manufacturers' initial advice during 2021 was that COVID-19 vaccines should be administered as a 2-dose schedule, with 3–4 weeks between each dose.[229]

Current UK advice, based on a better understanding of how the vaccines achieve immunity, is that there should be a minimum 8-week interval between doses, unless rapid immunisation is required in specific circumstances (e.g. in individuals about to receive immunosuppressive treatments).[230] However for healthy individuals aged < 18 years who are not health and social care workers, carers, or household contacts of immunosuppressed individuals, a minimum 12-week interval between doses is recommended.[231]

Where possible, the same COVID-19 vaccine should be used for the entire primary course.[232]

From 2021 onwards, as SARS-CoV-2 variants emerged and were genetically sequenced, vaccine manufacturers responded by developing vaccines that were *bivalent* (i.e. that targeted the original, 'ancestral' version of the virus, as well as the variant of greatest public health concern at that specific point in time).[233] Earlier formulations of the same vaccine were referred to as *monovalent*.[234]

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[227] Pierson BC, Cardile AP, Pittman PR. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. *Netter's infectious diseases*. 2nd ed. Philadelphia: Elsevier, 2021.

[228] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[229] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2021.

[230] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[231] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[232] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[233] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[234] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

2.37 How do the novel COVID-19 vaccines work? (1) Adenovirus vector vaccines

Adenovirus vector vaccines (e.g. AstraZeneca, Janssen) work by using a non-pathogenic viral vector to enter host cells and deliver the SARS-CoV-2 spike (S) protein genetic sequence to the nucleus of the cell, as double-stranded DNA.[235]

The AstraZeneca and Janssen vaccines contain a live non-replicating adenovirus vector (chimpanzee and human, respectively), grown in a human cell-line.[236]

Once the adenovirus vector is in the cell nucleus of the vaccine recipient, mRNA encoding the spike protein is produced and this then enters the cytoplasm of the same cell.[237] This in turn results in *translation* of target spike protein within the ribosomes of the cell, and the spike protein thereafter acts as an intracellular antigen (or immunogen).[238]

Neutralising antibodies against the spike protein are then produced by the vaccine recipient's *B lymphocytes*, as prompted by the *T lymphocytes*, and these antibodies block any circulating SARS-CoV-2 virus from interacting with the ACE-2 receptor, and thereby gaining entry to the cell.[239]

2.38 How do the novel COVID-19 vaccines work? (2) mRNA vaccines

mRNA vaccines (e.g. Moderna, Pfizer) target the SARS-CoV-2 spike (S) protein found on the surface of SARS-CoV-2.[240]

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[235] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[236] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[237] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[238] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[239] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[240] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

The Moderna and Pfizer vaccines comprise messenger RNA (mRNA) for the S protein, contained within lipid nanoparticles (LNPs); each dose of vaccine delivers trillions of mRNA-containing nanoparticles to the vaccine recipient.[241] The nanoparticles deliver a genetic instruction to ribosomes in all the tissues of the recipient to manufacture S protein; the recipient's T lymphocytes then detect the S protein that has been auto-manufactured, identify it as an immunogen and instruct the B lymphocytes to create neutralising antibodies against it.[242]

2.39 COVID-19 vaccine 'booster' doses

In around September 2021 Israel became the first country to demonstrate waning protection from Pfizer vaccine, showing a decline in protection, even against severe disease, at around 6 months.[243]

By the end of 2021 it became apparent that on account of waning vaccine immunity, and the emergence of SARS-CoV-2 variants, fully-vaccinated individuals could still become infected with SARS-CoV-2; at that point 'booster' doses (in reality, additional doses in the primary vaccine course against COVID-19) were introduced.[244]

Protection against hospitalisation after an mRNA 'booster' reaches over 90% in the 2 weeks after vaccination and then declines towards a stable plateau of around 60% by 6 months.[245]

Current UK practice is to offer a first 'booster' dose at least 3 months after completion of primary immunisation to the following groups:[246]

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[241] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[242] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[243] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[244] Royal Pharmaceutical Society of Great Britain. Viral infection. In: *British National Formulary No 81*. London: Pharmaceutical Press, 2021.

[245] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[246] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

- all individuals aged 16 years and over;
- children aged 12–15 years in clinical at-risk groups or who are household contacts of immunosuppressed individuals; and
- children aged 5–11 years with severe immunosuppression.

Current UK practice is that seasonal 'booster' doses (spring, autumn), in addition to any 'booster' dose already received, should be offered provided there has been an interval of at least 3 months from the previous dose to the following groups:[247]

- residents of, and staff working in care homes for older adults;
- frontline health and social care workers;
- all individuals aged 50 years and over;
- individuals aged 5 years and over in a clinical at-risk group;
- individuals aged 5 years and over who are household contacts of immunosuppressed individuals; and
- individuals aged 16 years and over who are carers.

2.40 COVID-19 vaccines and specific patient groups

Current UK advice is that pregnant females should be offered immunisation against COVID-19, as pregnancy is a risk factor for severe COVID-19 infection.[248]

Individuals with severe immunosuppression may have an inadequate immune response to a primary course of vaccination and may therefore remain at high risk of severe

[247] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[248] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

COVID-19.[249] Current UK advice is that individuals aged 5 years and over who were severely immunosuppressed at the time of receiving their first or second dose of COVID-19 vaccine should be offered a third dose as part of their primary course; they should also be offered 'booster' doses, to extend protection.[250]

Current UK advice is that people with HIV infection, regardless of their CD4 count, should likewise be offered a third dose of COVID-19 vaccine as part of their primary course, along with subsequent 'booster' doses.[251]

2.41 How safe are COVID-19 vaccines? (1) Thromboembolic (clotting) events

In early 2021 there were multiple reports of vaccine-induced immune thrombocytopaenia and thrombosis (VITT) with the adenovirus vector vaccines *Vaxzevria* (AstraZeneca) and *Nuvaxovid* (Janssen).[252] VITT is a severe but rare blood clotting condition; it develops within 5 to 30 days of receiving vaccination.[253]

As from early 2023, *Vaxzevria* (AstraZeneca) was not routinely supplied in the UK.[254] *Nuvaxovid* (Janssen) vaccine was initially procured for use in the UK, but has not ever been supplied.[255]

2.42 How safe are COVID-19 vaccines? (2) Myocarditis

The mRNA that is delivered to cells following challenge with COVID-19 nucleic acid

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[249] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[250] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[251] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[252] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[253] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[254] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[255] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

vaccines (i.e. mRNA vaccines) is said to be normally degraded within a few days.[256]

There have been reports of vaccine-associated myocarditis with all COVID-19 mRNA vaccines.[257] Although the mRNA monovalent vaccine *Spikevax* (Moderna) is licensed in the UK for use in children aged ≥ 6 years, current guidance is that the preferred COVID-19 vaccine for use in children is the mRNA monovalent *Cominarty* (Pfizer), due to a lower reported rate of myocarditis.[258]

2.43 How safe are COVID-19 vaccines? (3) Other adverse events

A two-year analysis of Yellow Card reports (i.e. spontaneously-reported vaccine adverse events), published in December 2022 by the Medicines and Healthcare products Regulatory Agency (MHRA), documented 2,362 spontaneous reports suggesting a fatal outcome following COVID-19 vaccination; while of concern, the association does not prove causality.[259]

Other adverse events commonly reported to the MHRA in association with COVID-19 vaccines included:[260]

- Bell's palsy (i.e. unilateral facial paralysis);
- Guillain-Barré syndrome (i.e. ascending paralysis);
- transverse myelitis (i.e. spinal cord inflammation); and
- menstrual disorders and vaginal bleeding.

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[256] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[257] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[258] Royal Pharmaceutical Society of Great Britain. Vaccination. In: *British National Formulary No 85*. London: Pharmaceutical Press, 2023.

[259] Medicines and Healthcare products Regulatory Agency. *Coronavirus vaccines – summary of Yellow Card reporting*. London: MHRA, December 2022.

[260] Medicines and Healthcare products Regulatory Agency. *Coronavirus vaccines – summary of Yellow Card reporting*. London: MHRA, December 2022.

2.43 What is the likely future course of COVID-19?

On 5th May 2023 the World Health Organization declared that COVID-19 no longer constituted a public health emergency of international concern (PHEIC).[261]

Epidemiological surveillance suggests that SARS-CoV-2 is now becoming *endemic* (i.e. the virus is circulating at about the same incidence over a long period of time); endemicity is a feature of the four coronaviruses that have been known for many years to cause mild to moderate respiratory tract illness, including the common cold.[262] Potentially, SARS-CoV-2 can still cause severe illness in those not previously exposed to the virus, either through natural infection or through vaccination.[263]

It is possible to *model* the possible future behaviour of SARS-CoV-2 infection; no model however will be better than the assumptions on which it was built, and disease models are typically phrased in mathematical terms which can make them difficult to understand for the non-mathematician, and also lend them an air of exactitude that they seldom merit.[264]

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[261] Department of Health. *Immunisation against infectious disease ('The Green Book')*. London: DoH, 2023.

[262] Heymann DL. COVID-19. In: Heymann DL, ed. *Control of communicable diseases manual*. Washington DC: American Public Health Association, 2022.

[263] Louten J. *Essential human virology*. 2nd ed. London: Elsevier, 2023.

[264] Giesecke J. *Modern infectious disease epidemiology*. 3rd ed. London: CRC Press, 2017.

Part Three

Physical measures taken against COVID-19

[Papers highlighted in the text – e.g. **Jefferson 2011** *– are attached to this report as full-text pdf files. Key epidemiological concepts are explained in Appendix 2. Odds, odds ratios and confidence intervals are explained in Appendix 3.]*

Scientific knowledge – pre-pandemic

Do physical measures such as hand-washing or wearing masks stop or slow down the spread of respiratory viruses?

Cochrane review, *Physical interventions to interrupt or reduce the spread of respiratory viruses* **Jefferson 2011**

Key messages	*Supporting statistics*
• *Respiratory virus spread can be reduced by hygienic measures (such as handwashing), especially around younger children.*	3 cluster-RCTs in children showed handwashing to be effective; 1 RCT in households showed it to be effective if implemented < 36 hours after onset of illness
• *Frequent handwashing can also reduce transmission from children to other household members.*	7 studies assessed frequent handwashing; 4 found it to be effective on multivariable analysis
• *Implementing barriers to transmission, such as isolation, and hygienic measures (wearing masks, gloves and gowns) can be effective in containing respiratory virus epidemics or in hospital wards.*	1 RCT showed that surgical masks had no effect. 2 cluster-RCTs showed that mask wearing added to handwashing had no effect. 1 cluster-RCT showed that mask wearing added to handwashing was effective if implemented < 36 hours after onset of illness.
• *We found no evidence that the more expensive, irritating and uncomfortable N95 respirators were superior to simple surgical*	1 cluster-RCT found no effect with a P2 mask

masks.

- *It is unclear if adding virucidals or antiseptics to normal handwashing with soap is more effective.*

1 cluster-RCT found a small effect with virucidal tissues. 2 cluster-RCTs were non-significant.

- *There is insufficient evidence to support screening at entry ports and social distancing (spatial separation of at least 1 metre between those infected and those non-infected), as a method to reduce spread during epidemics.*

"A disappointing finding was the lack of proper evaluation of global and highly resource-intensive measures such as screening at entry ports and social distancing"

Authors' overall conclusion. *Routine long-term implementation of some of the measures assessed in this review would be problematic, particularly maintaining strict hygiene and barrier routines for long periods of time. This would probably only be feasible in highly motivated environments, such as hospitals.*

Scientific knowledge – post-pandemic

Do physical measures such as hand-washing or wearing masks stop or slow down the spread of respiratory viruses?

Cochrane review, *Physical interventions to interrupt or reduce the spread of respiratory viruses* **Jefferson 2023**

Key messages	*Supporting statistics*
• *We are uncertain whether wearing masks or N95/P2 respirators helps to slow the spread of respiratory viruses based on the studies we assessed.*	(See Appendix 4 to this report)
• *Hand hygiene programmes may help to slow the spread of respiratory viruses.*	(See Appendix 5 to this report)

Authors' overall conclusion. *There should be a deliberate emphasis and directed funding opportunities to conduct well-designed RCTs to address the effectiveness of*

many of the physical interventions in multiple settings and populations, especially in those most at risk, and in very specific well-defined populations with monitoring of the adherence to the interventions.

3.1 Physical measures taken in Scotland against COVID-19

Historically, a range of physical (or non-pharmacological) measures have been employed to try to prevent the spread of respiratory viruses – such as influenza A virus, which recurs every year as seasonal influenza. These physical measures have included the following **Jefferson 2023**:

- washing hands often;
- not touching your eyes, nose, or mouth;
- sneezing or coughing into your elbow;
- wiping surfaces with disinfectant;
- wearing masks, eye protection, gloves, and protective gowns;
- avoiding contact with other people (i.e. isolation or quarantine);
- keeping a distance of at least one metre away from other people (i.e. social distancing); and
- examining people entering a country for signs of infection (i.e. point-of-entry screening).

When the COVID-19 pandemic was declared, in March 2020, the response of most governments around the world was to safeguard their citizens by simultaneously advocating multiple protective physical measures (sometimes referred to as a 'layered' approach to population protection) that had been deployed in earlier epidemics of acute

respiratory illness. This section describes how in Scotland, as in most counties, a wide range of physical measures against COVID-19 was either recommended or else mandated, from early 2020 onwards. Some of the measures were undoubtedly effective. Others were harmful.

> **Comment.** As the pandemic struck, in early 2020, SARS-CoV-2 was treated as an acute respiratory virus. At that time, the best evidence for the effectiveness or otherwise of physical measures to prevent the spread of respiratory viruses was from a decade-old Cochrane review **Jefferson 2011**. This review was updated as the pandemic progressed, and was reissued in revised form towards the end of the pandemic **Jefferson 2023**.

3.1.1 Physical measures advised or mandated in March to July 2020

On 1 March 2020 the first positive case of COVID-19 was confirmed in Scotland.

On 13 March 2020 the first confirmed death of a COVID-19 patient was confirmed in Scotland.

During March and April 2020, cases of COVID-19 increased exponentially. Vaccines against the new disease were already under development, but they were not expected to become available for general use until September 2020; in the event, the first vaccinations in care homes in Scotland occurred on 14 December 2020, but COVID-19 vaccines did not become generally available in Scotland until early 2021. During 2020, therefore, the Scottish Government mandated a variety of physical measures to stop or slow down the spread of COVID-19.

The physical measures mandated in Scotland during March to July 2020 were as follows.

- **13 March 2020.** People with symptoms of COVID-19 told to stay at home for seven days.

- **16 March 2020.** Cancellation of all mass indoor and outdoor events of 500 people or more.

- **20 March 2020.** All schools and nurseries closed by the end of this week.

- **23 March 2020**. The UK Prime Minister, Boris Johnson, broadcast to the nation, "You must stay at home"; this was to take effect from the next day.

- **24 March 2020.** Start of *lockdown* in Scotland.

- **11 May 2020.** People told they can go outside more than once a day to exercise. However, people should stay local and either go alone or with members of their household.

- **22 June 2020.** Face coverings become mandatory on public transport.

- **10 July 2020.** Face coverings become mandatory in shops.

- **30 July 2020.** Advice on self-isolation changed from 7 to 10 days.

  Comment. See the first 'Scientific knowledge' box, above. During March to July 2020 there was limited scientific evidence and in some cases no scientific evidence (e.g. as regards *lockdowns*) to support the physical measures that were mandated in Scotland against COVID-19. Such evidence as there was (e.g. for mask wearing) mostly came from hospital settings, rather than community settings – and arguably was not applicable to the general, non-hospital population.

3.1.2 Physical measures advised or mandated in August to December 2020

In the summer of 2020 the number of new COVID-19 cases across the UK declined. This was attributed, in part, to the effectiveness of the physical measures that had been mandated earlier that year.

From August 2020 onwards, these was some relaxation of the existing mandates in the UK. On 3 August 2020 the UK Government introduced the 'Eat Out to Help Out' scheme.

With the onset of the autumn / winter influenza season, and the fear of a COVID-19 'second wave', some new and more restrictive physical measures were mandated in Scotland, as follows.

- **25 August 2020.** Face coverings introduced in schools and dedicated school transport.

- **14 September 2020.** Indoor and outdoor gatherings are limited to six people from two households.

- **23 September 2020.** Ban on gatherings in homes.

- **25 September 2020.** 10 pm curfew introduced in hospitality sector.

- **29 October 2020.** Face covering exemption cards introduced.

- **20 November 2020.** New travel regulations prevent people who live in a Level 3 or Level 4 area from travelling outside their local authority except for an essential purpose. Travel between Scotland and the rest of the UK also becomes illegal except for essential purposes..

  Comment. Again, see the first 'Scientific knowledge' box, above. During August to November 2020 there was little scientific evidence to support the physical measures that were mandated in Scotland against COVID-19.

3.1.3 Temporary easing of physical measures in run-up to Christmas 2020

In the run-up to Christmas, there was a temporary easing of the physical measures that had previously been mandated in Scotland. This temporary easing was as follows.

- **24 November 2020.** Scottish Government announce details of a UK-wide "limited relaxation" of restrictions over the Christmas period.

- **14 December 2020.** The self-isolation period for positive contacts and overseas arrivals is reduced from 14 days to 10 days.

- **19 December 2020.** Easing of restrictions around Christmas is limited to Christmas Day only.

  Comment. The easing of the centrally-mandated COVID-19 restrictions over the 2020 Christmas period differed, in different parts of the UK. It is not clear to what extent, if at all, the easing of the restrictions was based on a better understanding of the pathogenicity and transmission characteristics of SARS-CoV-2.

3.1.4 Continuation of physical measures in Scotland in early 2021

From 14 December 2020 onwards, COVID-19 vaccination became available in Scotland. However due to limited supplies of vaccine, vaccination was for some weeks restricted to specific high-risk groups only (e.g. residents and staff in care homes, other front-line healthcare workers, people with high-risk clinical conditions, etc).

New cases of COVID-19, and deaths from COVID-19 remained at high levels. In early 2021 a new series of physical measures was mandated in Scotland, as follows.

- **05 January 2021.** Mainland Scotland goes into *lockdown*.

- **18 January 2021.** All travel corridors are suspended.

- **18 January 2021.** Scotland introduces pre-departure testing for international travellers.

- **17 February 2021.** Scottish Government announce an expansion of testing to include anyone who is identified as a close contact of somebody who has tested

positive for COVID-19, from 18 February 2021.

- **22 February 2021.** Children in early learning and childcare, and primaries 1 to 3, return full-time to classrooms.

- **30 March 2021.** Scottish Government announce non-essential journeys within the local authority area are allowed from Friday 2 April 2021, when a requirement to Stay Local will replace the Stay at Home rule.

- **30 March 2021.** Hairdressers, garden centres, car showrooms and forecourts, homeware stores and non-essential click and collect services can open from Monday 5 April 2021.

- **13 April 2021.** Scottish Government announce Travel within Scotland for outdoor socialising, recreation and exercise, and outdoor meetings in groups of up to six adults from up to six households will be allowed from Friday 16 April 2021.

- **20 April 2021.** Scottish Government announce all parts of the country will move to Level 3 from Monday 26 April 2021; hospitality venues such as cafés, pubs and restaurants can reopen, along with tourist accommodation.

- **14 May 2021.** Scottish Government announce most of mainland Scotland (with the exception of Moray) will move to level 2 from Monday 17 May, with eased restrictions on hospitality, entertainment, education and sport.

- **22 June 2021.** First Minister Nicola Sturgeon announces a new indicative date for the whole of Scotland to move to level 0 on 19 July 2021, provided all necessary vaccination and harm reduction measures are met.

Comment. Physical measures intended to restrict the spread of SARS-CoV-2 remained in place in Scotland throughout 2021, and some were still in place in 2022. The relevant milestones are summarised in Appendix 9 to this report.

Part Four

Vaccines used against COVID-19

[Papers highlighted within the text – e.g. **Graña 2022** *– are attached to this report as full-text pdf files. Key epidemiological concepts are explained in Appendix 2. Odds ratios, risk ratios and confidence intervals are explained in Appendix 3]*

Scientific knowledge – post-pandemic

What are the benefits and risks of vaccines for preventing COVID-19?

Key messages

- *Most vaccines reduce, or probably reduce, the number of people who get COVID-19 disease and severe COVID-19 disease.*
- *There is insufficient evidence to determine whether there was a difference between the vaccine and placebo in terms of death because the numbers of deaths were low in the trials.*
- *Many vaccines likely increase number of people experiencing events such as fever or headache compared to placebo (sham vaccine that contains no medicine but looks identical to the vaccine being tested). This is expected because these events are mainly due to the body's response to the vaccine; they are usually mild and short-term.*
- *Many vaccines have little or no difference in the incidence of serious adverse events compared to placebo.*
- *Most trials assessed vaccine efficacy over a short time, and did not evaluate efficacy to the COVID variants of concern.*

Cochrane review, *Efficacy and safety of COVID-19 vaccines* **Graña 2022**

4.1 Vaccines procured against COVID-19

During 2020, over one hundred vaccines against SARS-CoV-2 were in development in various parts of the world. The candidate products included a large number of *component vaccines* (i.e. conventional vaccines), and a limited number of *gene technology vaccines* (i.e. novel or relatively novel technology, using either viral vector

transportation for vaccinating against COVID-19, or else an mRNA-based approach).

In or around the latter half of 2020 the UK government purchased or pre-purchased four gene technology candidate vaccines against COVID-19, as follows:

- the AstraZeneca COVID-19 vaccine (*adenovirus vector*) **Folegatti 2020**;
- the Janssen COVID-19 vaccine (*adenovirus vector*) **Sadoff 2021**;
- the Moderna COVID-19 vaccine (*mRNA*) **Polack 2020**; and
- the Pfizer-BioNTech COVID-19 vaccine (*mRNA*) **Baden 2020**.

All the COVID-19 vaccines procured in the UK required a two-dose schedule. The chosen vaccine manufacturers mostly recommended an interval of 21 days between the first and second injections; for logistical reasons, this was not always adhered to.

4.1.1 The AstraZeneca vaccine

AstraZeneca received approval to supply their COVID-19 vaccine (*Vaxzevria*) in the UK from the Medicines and Healthcare products Regulatory Agency (MHRA) on 30 December 2020.

The AstraZeneca vaccine is an adenovirus vector product. The 'pivotal' study that preceded conditional approval for use of the vaccine in the UK was published in August 2020, in the *Lancet* **Folegatti 2020**. A follow-up report on the same study was published in the *Lancet* in December 2021 **Ramasamy 2021**.

There were 1077 participants in the AstraZeneca 'pivotal' study **Folegatti 2020**. The participants were healthy adults aged between 18–55 years. Half were randomised to receive the vaccine, and half received the control injection (i.e. meningitis ACWY vaccine). The initial period of follow-up was 4 weeks. Preliminary findings showed that

neutralising antibodies to SARS-CoV-2 were induced at day 14 and 28 after the first vaccination, and titres increased after a second dose. The vaccine appeared to be safe.

> **Comment.** Strengths of the AstraZeneca study are that it is a randomised controlled trial. It appears not to be sponsored by industry. Limitations include (i) the relatively small number of participants *[543 people in the vaccine arm]*; (ii) the use of a different vaccine as the control, rather than saline *[this would tend to result in an unrealistically favourable assessment of the study vaccine's true tolerability]*; (iii) the short period of follow-up *[4 weeks]*; and (iv) the lack of a study flow chart in the published report *[even though this is mandatory* **Altmann 1996** *in the reporting of RCTs]*.

4.1.2 The Janssen vaccine

Janssen received approval to supply their COVID-19 vaccine in the UK from the Medicines and Healthcare products Regulatory Agency (MHRA) on 28 May 2021.

> **Comment.** In May 2021 the UK government announced that 20 million doses of the Janssen vaccine had been procured, and their delivery was expected later in the year. It is unclear however as to whether or not the Janssen vaccine was ever administered in the UK (as it was, for example, in the Republic of Ireland). The MHRA report on vaccine adverse events **MHRA 2022** makes no mention of the Janssen vaccine. The Janssen vaccine is not currently supplied in the UK and may never have been supplied. The reasons for this are unclear.

The Janssen vaccine is an adenovirus vector vaccine. The 'pivotal' study that preceded conditional approval for use of the vaccine in the UK was published in June 2021 in the *New England Journal of Medicine* **Sadoff 2021**. A follow-up report on the same study was published in the *New England Journal of Medicine* in March 2022 **Sadoff 2022**.

There were 39,321 participants in the Janssen 'pivotal' study **Sadoff 2021**. Half were randomised to receive the vaccine, and half received placebo (i.e. saline). The period

of follow-up was 15 weeks (but this applied only to approximately 1000 participants – most were followed up for a few weeks only). The study showed that the vaccine induced an antibody response to SARS-CoV-2. The vaccine appeared to be safe.

> **Comment.** Strengths of the Janssen study are that it is a randomised controlled trial. It uses a true placebo. Limitations include (i) it is an industry-sponsored study *[and hence its reporting is liable to commercial bias]*; (ii) short period of follow-up for most participants ("this was necessitated… by the urgent need for vaccine"); (iii) the differing follow-up periods for different participants groups is confusing; and (iv) there is no study flow chart in the published report *[even though this is mandatory* **Altmann 1996** *in the reporting of RCTs]*.

4.1.3 The Moderna vaccine

Moderna received approval to supply their COVID-19 vaccine (*Spikevax*) in the UK from the Medicines and Healthcare products Regulatory Agency (MHRA) in January 2021.

The Moderna vaccine is an mRNA vaccine. The 'pivotal' study that preceded conditional approval for use of the vaccine in the UK was published in December 2020 in the *New England Journal of Medicine* **Baden 2020**. A follow-up report on the same study was published in the *New England Journal of Medicine* in September 2021 **El Sahly 2021**.

There were 30,420 participants in the Moderna 'pivotal' study **Baden 2020**. Half were randomised to receive the vaccine, and half received placebo (i.e. saline). The period of follow-up varied from a few weeks in 4% of participants to a maximum (in an unspecified, but again a minority of participants) of 120 days. The study showed a vaccine efficacy of 94.1% against symptomatic illness due to wild-type (i.e. ancestral strain) SARS-CoV-2. Efficacy was similar in those over 65 years. Vaccine efficacy against severe COVID-19 was 100% (95% CI 87.0 to 100%). All the severe COVID-19 cases that occurred were in the placebo group. The vaccine appeared to be safe.

Comment. Strengths of the Moderna study are that it is a randomised controlled trial. It uses a true placebo. The trial report incorporates a study flow chart. Limitations include (i) it is an industry-sponsored study *[and hence its reporting is liable to commercial bias]*; (ii) the differing follow-up periods for different participants groups is confusing.

4.1.4 The Pfizer vaccine

Pfizer BioNtech received approval to supply their COVID-19 vaccine (*Cominarty*) in the UK from the Medicines and Healthcare products Regulatory Agency (MHRA) on 2 December 2020.

The Pfizer vaccine is an mRNA vaccine. The 'pivotal' study that preceded conditional approval for use of the vaccine in the UK was published in December 2020 in the *New England Journal of Medicine* **Polack 2020**. A follow-up report on the same study was published in the *New England Journal of Medicine* in September 2021 **Thomas 2021**.

There were 43,548 participants aged 12 years and above in the Pfizer 'pivotal' study **Polack 2020**. Half were randomised to receive the vaccine, and half received placebo (i.e. saline). A few participants (number unspecified) were followed up for 119 days but the median period of follow-up was 2 months. The study showed that the vaccine induced an antibody response to SARS-CoV-2. In naïve participants aged between 65 and 75 years, and in those aged 75 years and over, the efficacy was 94.&% (95% CI 66.7 to 99.9%). Ten cases of severe COVID-19 cases were observed, but nine of these were in the placebo group. The vaccine appeared to be safe.

Comment. Strengths of the Pfizer study are that it is a randomised controlled trial. It uses a true placebo. It incorporates a study flow chart. Limitations include (i) it is an industry-sponsored study *[and hence its reporting is liable to commercial bias]*; (ii) short period of follow-up for the majority of participants.

Further comment. By the time of the September 2021 follow-up study **Thomas 2021** (and as occurred also with the other vaccine follow-up studies), there were multiple drop-outs from the original 'pivotal' Pfizer study; the study in effect had shrunk in size. The follow-up study found that vaccine efficacy declined at "an average… of 6% every 2 months". The lack of transparency in the data presented by Pfizer in their follow-up study was strongly criticised in an online editorial in the *British Medical Journal* **Doshi 2021**.

4.1.5 COVID-19 vaccination timeline in Scotland

On 8 December 2020 the first vaccinations against COVID-19 were given in Scotland to those who would be carrying out the subsequent population-wide vaccination programme; this included both medical and non-medical personnel.

Care home residents and staff in Scotland were vaccinated from 14 December 2020 onwards, and high-risk clinical groups were offered vaccination in early 2021.

Subsequent 2021 milestones in Scotland were as follows.

- **24 January 2021.** Scottish Government announce invitations for COVID-19 vaccine appointments for people aged 70-79 will commence from Monday 25 January 2021.

- **10 February 2021.** The number of first-dose vaccinations in Scotland reaches the 1 million mark.

- **22 February 2021.** People with underlying health conditions and unpaid carers begin to receive COVID-19 vaccinations.

- **25 February 2021.** More than 1.5 million people in Scotland (a third of those eligible) have received first doses of the COVID-19 vaccine.

- **March 2021.** Vaccination with the AstraZeneca COVID-19 vaccine is temporarily paused in many European countries due to reports of increased rates of thrombo-

embolic events; this is confirmed in a registry-based study of vaccine harms, carried out in Denmark and Norway **Pottegård 2021**.

- **April 2021.** The European Medicines Agency, and the US Food and Drug Administration, investigate embolic and thrombotic events with the Janssen COVID-19 vaccine; the use of this vaccine is temporarily paused.

- **7 May 2021.** JCVI issues updated advice on the use of AstraZeneca vaccine; it could be offered to those over 40.

- **28 May 2021.** Medicines and Healthcare products Regulatory Agency (MHRA) approves the one-dose Janssen Covid-19 vaccine for use in the UK.

- **19 July 2021.** JCVI issues advice on COVID-19 vaccination of children and young people – children at increased risk of serious COVID-19 disease should be offered the Pfizer-BioNTech vaccine (this includes children aged 12 to 15 with severe neurodisabilities, Down's syndrome, immunosuppression and multiple or severe learning disabilities).

- **4 August 2021.** Scottish Government announce all young people 16 to 17 years of age to be offered the coronavirus (COVID-19) vaccination in Scotland from 6 August 2021.

- **14 September 2021.** Scottish Government announce children and young people aged 12 -15 years old will be offered a dose of the Pfizer-BioNTech vaccine from Monday 20 September 2021.

- **20 September 2021.** Scottish Government launch the COVID-19 booster vaccination programme; residents in care homes for older people are the first to be offered COVID-19 booster vaccinations.

- **15 November 2021.** JCVI issues advice on COVID-19 booster vaccines for those aged 40 to 49 and second doses for 16- to 17-year olds. All adults aged 40 to 49

years should be offered an mRNA booster, 6 months after their second dose, irrespective of the vaccines given for the first and second doses. All 16 to 17 year olds who are not in an at-risk group should be offered a second dose of the Pfizer vaccine. The second vaccine dose should be given 12 weeks or more following the first vaccine dose.

- **29 November 2021.** First cases of the COVID-19 *Omicron* variant are identified in Scotland.

- **29 November 2021.** JCVI issue advice on COVID-19 booster vaccines for those aged 18 to 39 and a second dose for ages 12 to 15. The booster will now be given 3 months after the primary course. In addition, a second dose of the Pfizer-BioNTech vaccine for young people aged 12 to 15 years is advised 12 weeks after the first dose.

- **8 December 2021.** One-year anniversary of the first COVID-19 vaccination in Scotland. Since then, 4,355,063 first doses, 3,962,203 second doses and 1,922,604 boosters and third doses have been administered from around 1,200 locations.

  Comment. The COVID-19 vaccination programme in Scotland continued throughout 2022 and is still in place in 2023. In autumn 2022, MHRA approved bivalent vaccines from Moderna and Pfizer. The vaccination milestones are summarised in Appendix 9 to this report.

4.1.6 Vaccine adverse events reported in the UK

On 1 December 2022 the UK Medicines and Healthcare Products Regulatory Agency (MHRA) published a summary of the spontaneously-reported adverse events (Yellow Card reporting) that had been received by the agency between 9 December 2020 to 23 November 2022 **MHRA 2022**.

The December 2022 MHRA publication lists 2,362 Yellow Card reports with a fatal

outcome from COVID-19 vaccination. 1044 of the reported fatalities (47%) were in females, and 1189 (53%) were in males. 809 of the reported fatalities (34%) occurred in people aged < 69 years **MHRA 2022**.

During the 2-year period of assessment, vaccine-associated adverse events (other than fatal events) were reported to the MHRA as follows:

- AstraZeneca COVID-19 vaccine (*adenovirus vector*) – 246,866 reports;
- Moderna COVID-19 vaccine (*mRNA*) – 47,045 reports; and
- Pfizer-BioNTech COVID-19 vaccine (*mRNA*) – 177,925 reports

Comment. A reported adverse event from a drug or vaccine (e.g. sudden death) does not prove causality – although adverse events that are reported frequently and consistently often do point to a true causal association. The risk of vaccination need to be weighed against the risks of severe COVID-19. Historically, the UK's Yellow Card system for reporting adverse events has resulted in under- rather than over-reporting; the MHRA's December 2022 report on the potential harms of COVID-19 vaccines may therefore have underestimated the scale of the vaccine-associated harms, rather than overestimating it.

Aside from fatal events, analysis by the MHRA of two consecutive years of Yellow Card reports suggests that COVID-19 vaccination may cause an increased risk of the following serious adverse events **MHRA 2022**:

- Anaphylaxis (i.e. immediate-onset, life-threatening allergic reaction) *[number of reports to MHRA – 990 in total, most (90%) with AstraZeneca]*;
- Bells' palsy (i.e. unilateral facial nerve paralysis) *[number of reports to MHRA – not disclosed (but "continuously reviewed")]*;
- Guillain-Barré syndrome (i.e. ascending paralysis of the lower limbs) *[number of*

reports to MHRA – not disclosed];

- immune thrombocytopaenia *[number of reports to MHRA – not disclosed]*;

- major thrombo-embolic events (i.e. life-threatening blood clots) *[number of reports to MHRA – 486 in total, most (91%) with AstraZeneca]*;

- menstrual disorders and vaginal bleeding *[number of reports to MHRA – 51,695 in total ("mostly transient [and] MHRA will continue to review")]*;

- myocarditis *[number of reports to MHRA – 1241 in total, 15 with a fatal outcome ("reports… are being monitored closely")]*;

- pericarditis *[number of reports to MHRA – 954 in total]*;

- transverse myelitis (i.e. spinal cord inflammation) *[number of reports to MHRA – 179 in total, most (72%) with AstraZeneca ("the product information has been updated")]*;

Comment. See the 'Scientific knowledge' box, on Page 62 of this report. At a population level, all of the currently-available COVID-19 vaccines are effective (or "probably" effective) in reducing the incidence of COVID-19 and severe COVID-19. The Cochrane review of COVID-19 vaccines states that it is unclear as to whether or not vaccination has made any difference to the numbers of deaths from COVID-19 ("there is insufficient evidence to determine whether there was a difference between the vaccine and placebo in terms of death because the numbers of deaths were low in the trials"); future updates of the review may resolve this important point. Minor adverse events (e.g. fever, headache) occur commonly with many of the currently-available COVID-19 vaccines. For many of the currently-available COVID-19 vaccines, serious adverse events (e.g. cardiac and neurological events, and sudden death) appear to be few, based on the reported RCTs. However this apparently low number may be due to (i) the very short follow-up period in many of the reported vaccine RCTs, (ii) the fact that the candidate vaccine was not compared against a true placebo, (iii) the number of participants in the reported RCTs was

small, (iv) the RCT participants were optimally healthy at time of vaccination, or were otherwise unrepresentative of the majority of the UK population, or (v) a combination of any or all of the foregoing. In early 2023 MHRA announced that it would no longer be issuing special publications on the spontaneously-reported adverse events associated with COVID-19 vaccines. The reasons for this announcement are unclear. Around this same time, and for reasons that are also unclear, the December 2022 report **MHRA 2022** was removed from the agency's website.

Summary – what do we now know?

The COVID-19 pandemic of 2020–2023, caused by a novel coronavirus, was a national emergency which threatened the lives of certain groups in society: the very old, and the very sick.

Other groups (children, healthy young adults) were not ever at risk of severe disease.

By early 2023 the pandemic had abated but there were reports of many people with long COVID and of other people with long-term cardiovascular sequelae of COVID-19 infection.

Physical measures against COVID-19

- From March 2020 onwards, and in common with many other governments, the Scottish government recommended or mandated a range of physical measures intended to limit the spread of SARS-CoV-2, the novel coronavirus which was the cause of COVID-19.

- The physical measures recommended or mandated by the Scottish government ranged from simple public health practices (the encouragement of frequent handwashing, cleaning of environmental surfaces, the use of PPE in hospitals and care homes) to coercive and / or intrusive measures (face mask mandates outside of healthcare settings; *lockdowns*; enforced social distancing; *test, trace and isolate* measures).

- In 2020 there was scientific evidence to support the use of some of the physical measures (e.g. frequent handwashing, the use of PPE in hospital settings) adopted against COVID-19.

- For other measures (e.g. face mask mandates outside of healthcare settings,

lockdowns, social distancing, *test, trace and isolate* measures) there was either insufficient evidence in 2020 to support their use – or alternatively, no evidence; the evidence base has not changed materially in the intervening three years.

- It has been argued that the restrictive measures introduced during the COVID-19 pandemic resulted in individual, societal and economic harm that was avoidable and that should not have occurred.

Vaccines against COVID-19

- Vaccines against COVID-19 became available to the UK general public in December 2020; initially only the high-risk groups (the very old, the very sick) were targeted.

- All the COVID-19 vaccines procured by the UK government during 2020 and 2021 were nucleic acid vaccines using novel gene technology.

- As additional vaccine supplies became available, vaccination was extended to young, middle-aged and elderly adults, and to children.

- Vaccination against COVID-19 became a prerequisite of travel to many countries, and some UK employers made it obligatory for their workforce.

- It remains unclear as to whether or not COVID-19 vaccination has resulted in fewer deaths from COVID-19.

- COVID-19 vaccines have been shown in randomised controlled trials to be effective, or probably effective, in reducing the number of people acquiring COVID-19 or severe COVID-19; however vaccine-induced protection against COVID-19 is short-lived.

- Because of the antigenic variability of all coronaviruses, including SARS-CoV-2, it was foreseeable that COVID-19 vaccines would only provide short-term protection against COVID-19 (as is the case also with current vaccines against seasonal

influenza).

- Because the novel gene technology vaccines procured by the UK government had been tested on relatively small study populations, and had been assessed for safety over short follow-up periods only, rare and sometimes serious adverse effects (including reported fatal events) emerged, once the vaccines had been used on a mass scale in the UK and in other countries.

Twenty-two key scientific papers cited in this report

All papers are attached as full-text pdf files

[This series of 22 key papers has been compiled expressly to assist the Inquiry. The list is indicative only. It does not purport to be a comprehensive bibliography of COVID-19.]

1. **Abaluck 2022**
   Abaluck J, Kwong LH, Styczynski A, *et al*. Impact of community masking on COVID-19: A cluster-randomized trial in Bangladesh. *Science* 2022; 375.
   https://doi.org/10.1126/science.abi9069

2. **Altman 1996**
   Altman DG. Better reporting of randomised controlled trials - the CONSORT statement. *BMJ* 1996; 313: 570-571.
   https://doi.org/10.1136/bmj.313.7057.570

3. **Baden 2021**
   Baden LR, El Sahly HM, Essink B, *et al*. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med* 2021; 384: 403-416.
   https://doi.org/10.1056/NEJMoa2035389

4. **Bundgaard 2021**
   Bundgaard H, Bundgaard JS, Raaschou-Pedersen DE, *et al*. Effectiveness of adding a mask recommendation to other public health measures to prevent SARS-CoV-2 infection in Danish mask wearers – a randomized controlled trial. *Ann Intern Med* 2021; 174: 335-343.
   https://doi.org/10.7326/M20-6817

5. **Doshi 2021**
   Doshi P. Does the FDA think these data justify the first full approval of a COVID-19 vaccine? *BMJ online* (Aug 23, 2021).
   https://blogs.bmj.com/bmj/2021/08/23/does-the-fda-think-these-data-justify-the-first-full-approval-of-a-covid-19-vaccine/

6. **Folegatti 2020**
   Folegatti PM, Ewer KJ, Aley PK, *et al*. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. *Lancet* 2020; 396: 467-478.
   https://doi.org/10.1016/S0140-6736(20)31604-4

7. **El Sahly 2021**
   El Sahly HM, Baden LR, Essink B, *et al*. Efficacy of the mRNA-1273 SARS-CoV-2 Vaccine at completion of blinded phase. *N Engl J Med* 2021; 385: 1774-1785.
   https://doi.org/10.1056/NEJMoa2113017

8. **Godlee 2010**
Godlee F. Conflicts of interest and pandemic flu. BMJ 2010; 340: c2947.
https://doi.org/10.1136/bmj.c2947

9. **Graña 2022**
Graña C, Ghosn L, Evrenoglou T, *et al*. efficacy and safety of COVID-19 vaccines. *Cochrane Database Syst Rev* 2022; 12.
https://doi.org/10.1002/14651858.CD015477

10. **Jefferson 2011**
Jefferson T, Del Mar CB, Dooley L, *et al*. Physical interventions to interrupt or reduce the spread of respiratory viruses. *Cochrane Database Syst Rev* 2011; 7.
https://doi.org/10.1002/14651858.CD006207.pub4

11. **Jefferson 2023**
Jefferson T, Dooley L, Ferroni E, *et al*. Physical interventions to interrupt or reduce the spread of respiratory viruses. *Cochrane Database Syst Rev* 2023; 1.
https://doi.org/10.1002/14651858.CD006207.pub6

12. **Ioannidis 2005**
Ioannidis JP. Why most published research findings are false. *PLoS Med* 2005; 2: e124.
https://doi.org/10.1371/journal.pmed.0020124

13. **Mandeville 2014**
Mandeville KL, O'Neill S, Brighouse A, *et al*. Academics and competing interests in H1N1 influenza media reporting. *J Epidemiol Community Health* 2014; 68: 197-203.
https://doi.org/10.1136/jech-2013-203128

14. **MHRA 2022**
Medicines and Healthcare products Regulatory Agency. *Coronavirus vaccines - summary of Yellow Card reporting*. London: MHRA, December 2022.
(This document was previously publicly available on the MHRA website in pdf format, but appears now to have been removed from the website)

15. **Polack 2020**
Polack FP, Thomas SJ, Kitchin N, *et al*. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N Engl J Med* 2020; 383: 2603-2615.
https://doi.org/10.1056/NEJMoa2034577

16. **Pottegård 2021**
Pottegård A, Lund LC, Karlstad Ø, *et al*. Arterial events, venous thromboembolism, thrombocytopenia, and bleeding after vaccination with Oxford-AstraZeneca ChAdOx1-S in Denmark and Norway: population-based cohort study. *BMJ* 2021; 373: n1114.
https://doi.org/10.1136/bmj.n1114

17. **Ramasamy 2021**
Ramasamy MN, Minassian AM, Ewer KJ, *et al*. Safety and immunogenicity of ChAdOx1 nCoV-19 vaccine administered in a prime-boost regimen in young and old adults (COV002) - a single-blind, randomised, controlled, phase 2/3 trial. *Lancet* 2021; 396: 1979-1993.
https://doi.org/10.1016/S0140-6736(20)32466-1

18. **Sadoff 2021**
Sadoff J, Gray G, Vandebosch A, *et al*. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. *N Engl J Med* 2021; 384: 2187-2201.
https://doi.org/10.1056/NEJMoa2101544

19. **Sadoff 2022**
Sadoff J, Gray G, Vandebosch A, *et al*. Final analysis of efficacy and safety of single-dose Ad26.COV2.S. *N Engl J Med* 2022; 386: 847-860.
https://doi.org/10.1056/NEJMoa2117608

20. **Starko 2009**
Starko KM. Salicylates and pandemic influenza mortality, 1918-1919 pharmacology, pathology, and historic evidence. *Clin Infect Dis* 2009; 49: 1405-1410.
https://doi.org/10.1086/606060

21. **Thomas 2021**
Thomas SJ, Moreira ED Jr, Kitchin N, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. *N Engl J Med* 2021; 385: 1761-1773.
https://doi.org/10.1056/NEJMoa2110345

22. **Torpy 2009**
Torpy JM, Lynm C, Glass RM. Evidence-based medicine. *JAMA* 2009; 301: 900.
https://doi.org/10.1001/jama.301.8.900

Appendix 1

Letter of Instruction

Scottish COVID-19 Inquiry
Email: contact@covid19inquiry.scot
Post: FREEPOST Scottish COVID-19 Inquiry
Web: www.covid19inquiry.scot

Dr Ashley Croft

By email only to: ashleycroft@doctors.org.uk

Dear Dr Croft

As the interim Deputy Solicitor to the Scottish COVID-19 Inquiry ("the Inquiry") I would be grateful if you would accept this letter as your instruction to utilise your expertise as an independent Consultant in Public Health Medicine and provide the Inquiry with a written report which will subsequently form the basis of oral evidence to be given at a hearing of the Inquiry which is likely to take place in late July 2023.

The scope of your report and the oral evidence which you will give in support of the report has been the subject of email correspondence passing between you and Claire Soper, Co-Secretary and Head of Policy of the Inquiry, and in discussions you have had with Stuart Gale KC, Co-Lead Counsel to the Inquiry. The report that the Inquiry wishes you to provide is one which will provide the Inquiry with a factual narrative detailing the state of accepted scientific knowledge concerning Coronavirus and COVID-19 as that knowledge was understood by public health practitioners in the period between late 2019 and the end of 2022. In particular, your report will include the evolving state of scientific knowledge around (a) the nature of Coronavirus and COVID-19 and its pathogenicity; (b) the ability or otherwise of masks and other forms of PPE or other measures as recommended to medical, nursing and care practitioners and the public at various stages during the period from late 2019 to the end of 2022 to prevent or restrict transmission of the virus; and (c) the utility or otherwise of handwashing, social distancing rules or guidance, social isolation measures or guidance for those at risk and/or those infected, COVID-19 specific treatments and vaccines at various stages during the period from late 2019 and the end of 2022 to prevent or restrict transmission of the virus.

In the preceding paragraph I have mentioned the period from late 2019 to the end of 2022. If it is necessary for you to stray outwith those dates in order to give your report proper and necessary context, then that is a matter for your professional discretion.

Your report will contain references to and be supported by scientific papers and other information/documents which you in your professional judgment and discretion consider necessary and/or appropriate.

As indicated to you in conversation with Mr Gale the Inquiry is in the process of scheduling its first oral hearings. The oral hearing at which you will provide oral evidence under reference to your report will be the Inquiry's first oral hearing, and that hearing is tentatively scheduled for late July 2023. That date has not been publicly announced and is therefore communicated to you in confidence. It is therefore essential that your report and supporting documentation is available to me by at the latest mid-June 2023 in order that I and my team have sufficient time to produce it for publication to interested parties by the end of June 2023.

You will continue to have regular meetings with Mr Gale and his Counsel Team.

A formal contract securing your services will be prepared by Harper MacLeod LLP, solicitors acting on behalf of the Inquiry and will be sent to you for agreement and your signature in the near future.

Yours sincerely,

Eilidh Clements
Interim Deputy Solicitor
Scottish COVID-19 Inquiry

Mobile: [redacted]

Appendix 2

Curriculum vitae

CURRICULUM VITAE

Dr Ashley M. Croft

MA (Oxon) MBBS MSc PhD DMCC DTM&H MIL FFPHM

Consultant Public Health Physician and Medical Epidemiologist

Correct as at 10th July 2023

Contents

Personal details

Name	Ashley Marcel John CROFT
Nationality	British
Address – consulting rooms	10 Harley Street London W1G 9PF United Kingdom Tel +44 (0)20 7467 8300 Fax +44 (0)20 7636 8789 e-mail AshleyCroft@doctors.org.uk
General Medical Council number	3013254
Professional body	Faculty of Public Health Medicine of the Royal College of Physicians of London
Responsible body for appraisal and revalidation	Independent Doctors' Federation, London, UK

Education and qualifications

School	St George's College, Weybridge, UK	1964–70
Universities	Facultad de Filosofía y Letras, Madrid University, Spain	1970
	Oxford University	1971–74
	London University	1978–02
	Portsmouth University	2010-22
Medical school	Guy's Hospital Medical School, London University, UK	1978–84
Postgraduate school	London School of Hygiene & Tropical Medicine, London University, UK	1990–02

Registrable qualifications

MBBS *(Bachelor of Medicine – Bachelor of Surgery – London University)*	December 1984
MFPHM *(Member of the Faculty of Public Health Medicine of the Royal College of Physicians of London)*	July 1995
FFPHM *(Fellow of the Faculty of Public Health Medicine of the Royal College of Physicians of London)*	February 2001

Non-registrable qualifications

MA *(Master of Arts – Oxford University)*	March 1984
MSc *(Master of Science – Community Medicine – London University)*	November 1990
DMCC *(Diploma in the Medical Care of Catastrophes – London University)*	June 1995
DTM&H *(Diploma in Tropical Medicine and Hygiene – London University / Gambia)*	January – June 2002
MIL *(Member of the Institute of Linguists – accredited interpreter in French and Spanish)*	December 1996
PhD *(Doctor of Philosophy – Portsmouth University)*	January 2022

Professional appointments

	Start	*End*
House Physician / Surgeon, Guy's Hospital, London	2/85	1/86
General Duties Medical Officer, Falkland Islands	6/86	10/86
Regimental Medical Officer, First Regiment Royal Horse Artillery, Hohne, West Germany	11/86	1/89
Senior Lecturer in Preventive Medicine, Royal Army Medical College, London	2/89	6/91
Public Health Specialist Registrar, Army Medical Services Training Centre, Aldershot	7/91	8/93
Public Health Specialist Registrar / Consultant, Army Medical Directorate, Camberley	9/93	11/95
NATO Public Health Consultant Adviser, Multinational Division Southwest, Bosnia	12/95	07/96
Consultant Public Health Physician, Defence Secondary Care Agency, London	08/96	04/99
Consultant Public Health Physician, Surgeon General's Department, Ministry of Defence, London	05/99	04/02
Director of Public Health, HQ British Forces Germany Health Service	05/02	06/05
Consultant Public Health Physician, Headquarters Fifth Army Division, Shrewsbury	07/05	09/07
ISAF Public Health Consultant Advisor, Regional Command South, Afghanistan	10/07	04/08
Consultant Public Health Physician, Headquarters Fifth Army Division, Shrewsbury	05/08	06/09

Visiting Fellow, Effective Health Care Research Programme Consortium, Liverpool University, UK	06/08	10/09
Editor-in-Chief, *Human Parasitic Diseases*	10/08	10/17
Consultant Public Health Physician, Surgeon General's Department, London	06/09	04/10
Honorary Lecturer in Travel Medicine, Leicester de Montfort University, UK	06/09	10/17
Consultant Public Health Physician, Headquarters Surgeon General, Lichfield	04/10	04/13
Postdoctoral Research Fellow, Portsmouth University, UK	04/13	02/22
Appraiser *[of GMC-registered consultants and general practitioners]*, General Medical Council, UK	04/21	–

Postgraduate awards and decorations

The Parkes Memorial Prize — 1995

This prize commemorates the late Dr Edmund Parkes MD, assistant surgeon in the 84th Regiment and the first Professor of Hygiene in the Army Medical School from 1860 to 1876. The prize is awarded annually to the officer who has done most by professional work of outstanding merit to promote the study of military hygiene.

Joint winner – the Bayer Scientific Prize — 1995

This prize is awarded annually in open competition at the Royal Society of Medicine to the Army, Navy or RAF trainee presenting research of outstanding scientific merit.

NATO Medal — 1996

For active service in Bosnia, 1995–1996.

The North Persian Forces Memorial Prize — 1996

This prize is provided from a fund raised in 1921 by regular officers of the Royal Army Medical Corps who took part in, and wished to commemorate, the withdrawal and dissolution of the forces in North Persia in that year. The prize is awarded for the best paper on tropical medicine or tropical hygiene published in any journal during the year.

The Alexander Memorial Prize — 1997

This prize commemorates Thomas Alexander CB FRCS(Ed), Director General Army Medical Department 1858-60, who reorganised the Army Medical Department after the Crimean War. The prize is awarded annually for professional work of outstanding merit to promote the study and improvement of military medicine.

The North Persian Forces Memorial Prize — 1998

Citation as above.

The Parkes Memorial Prize — 2000

Citation as above.

The North Persian Forces Memorial Prize — 2002

Citation as above.

Royal Society of Medicine Essay Prize — 2006

This prize is awarded annually by the Pharmaceutical Medicine and Research section of the Royal Society of Medicine, in open competition, for an essay of outstanding merit on a given topic of current scientific importance.

Campaign Medal — 2008

For active service in Afghanistan, 2007–2008.

The North Persian Forces Memorial Prize — 2010

Citation as above.

The ISTM Prize — 2011

This prize is awarded annually by the International Society of Travel Medicine, to the authors of the best review paper published on any travel health related topic, in the *Journal of the Society of Travel Medicine*.

The ‘Cochrane Club’ award 2012

Awarded each year at the conclusion of the annual Colloquium of the Cochrane Collaboration (held in 2012 in Auckland, New Zealand). Awards are given to the authors of the best podcasts published during the preceding year, in the *Cochrane Library*.

Main scientific publications

Research papers

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National and international scientific presentations

Major presentations at scientific conferences

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- Croft AM. The influence of physiological factors (food, diarrhea) on the bioavailability of mefloquine. Abstract No 221. 5th Conference of the International Society of Travel Medicine, Geneva, Switzerland. March 1997 *[oral presentation]*.
- Croft AM. Hospitalisation in British troops during Operation Joint Endeavour (Bosnia). 1st NATO Scientific Symposium on Army and Communicable Disease Control, Hradec Králové, Czech Republic. September 1998 *[oral presentation]*.
- Croft AM. Strategies to prevent malaria: Ensuring the best evidence for travellers. Abstract No 114. 2nd European Congress on Tropical Medicine, Liverpool University, UK. September 1998 *[oral presentation]*.
- Croft AM. Monitoring skin reactions to antimalarial drugs. Abstract No 78. 31st Indian Pharmacological Society Meeting, Lucknow, India. December 1998 *[oral presentation]*.
- Croft AM. Identifying the harms of mefloquine. Abstract No C19. 6th Conference of the International Society of Travel Medicine, Montréal, Canada. June 1999 *[oral presentation]*.
- Croft AM. Handsearching military medical journals for trials. Abstract No F04. 6th Conference of the International Society of Travel Medicine, Montréal, Canada. June 1999 *[poster presentation]*.
- Croft AM. Travelling to the tropics? How to enrich a systematic review with good observational evidence about adverse effects. Abstract No O-19. 7th Cochrane Colloquium, Rome, Italy. October 1999 *[oral presentation].*
- Croft AM. Trends in post-deployment mental disorders. Serial 9. NATO COMEDS scientific session – 5th meeting of Military Preventive Medicine Working Group. Washington, USA. November 1999 *[oral presentation]*.
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Prophylaxis Antipaludique, Marseilles, France. May 2000 *[oral presentation]*.

- Croft AM. Antimalaria drugs: the British military experience. Abstract No 12. Giornata di studio: Il rischio infettivo nelle missioni militari in ambiente tropicale. Rome, Italy, November 2000 *[oral presentation]*.
- Croft AM. Evidence-based policy making for international preventive medicine. Serial 11. NATO COMEDS scientific session – 7th meeting of Military Preventive Medicine Working Group. Quebec, Canada. October 2001 *[oral presentation]*.
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- Croft AM. Systematic review of mosquito coils to protect against mosquito bites and malaria in adults and children. Abstract No FC09.04. 8th Conference of the International Society of Travel Medicine, New York, USA. May 2003 *[oral presentation]*.
- Croft AM. Two-year audit of imported malaria cases in a military population in Europe. Abstract No PO07.02. 8th Conference of the International Society of Travel Medicine, New York, USA. May 2003 *[poster presentation]*.
- Croft AM. Systematic review of vaporising mats to protect against mosquito bites and malaria transmission. Abstract No 46. 4th European Conference on Travel Medicine, Rome, Italy, March 2004 *[oral presentation]*.
- Croft AM. Preventing Lyme disease in an expatriate British population in Germany: when education is not enough. Abstract No 60. 4th European Conference on Travel Medicine, Rome, Italy, March 2004 *[oral presentation].*
- Croft AM. Patterns of sickness and health in British Forces Germany. Research Forum, Department of Public Health & Epidemiology, University of Birmingham, England, May 2004 *[oral presentation]*.
- Croft AM. Double-blind randomised controlled trial of malaria chemoprophylaxis in British soldiers, with extended follow-up. Abstract No 108. World Conference on Magic Bullets, Nürnberg, Germany, September 2004 *[oral presentation]*.
- Croft AM. Direct health costs of occupationally acquired malaria in a military population in Europe. 9th Sharing Best Practice Workshop, Herford, Germany, October 2004 *[oral presentation].*
- Croft AM. Cutaneous leishmaniasis in British soldiers following military deployment to Iraq. Abstract No PO06.29. 9th Conference of the International Society of Travel Medicine, Lisbon, Portugal. May 2005 *[poster presentation]*.
- Croft AM. Why research is needed to improve the health of military populations. 1st British Forces Germany Health Service Research Conference, Herford, Germany. May 2005 *[keynote address]*.
- Croft AM. Developing evidence-based tobacco cessation guidelines for the UK military. 1st Symposium of Military Tobacco Surveys and Cessation Programs, Taipei, Taiwan. May 2005 *[keynote address]*.

- ✈ Croft AM. Mefloquine to prevent malaria: updating a systematic review. Abstract No O-351. 4th European Congress on Tropical Medicine and International Health, Marseilles, France. September 2005 *[oral presentation]*.
- ✈ Croft AM. Cysticercosis in a female Nicaraguan traveller. Abstract No P44. 5th European Conference on Travel Medicine, Venice, Italy, March 2006 *[poster presentation]*
- ✈ Croft AM, Leaver C, Gauron M. Using routine meteorological data to determine leishmaniasis and malaria risk in southern Afghanistan. 6th European Conference on Travel Medicine, Rome, Italy, April 2008 *[oral presentation]*.

Invited expert advisor to official inquiries

- Invited expert advisor to UK Parliamentary inquiry, House of Commons, Westminster: *The use of Lariam (mefloquine) for military personnel* (October 2015 – February 2016).
- Invited expert advisor to UK Parliamentary inquiry, House of Commons, Westminster: *Mental health and the Armed Forces Part 2: the provision of care* (September 2017 – July 2018).
- Invited expert advisor to Canadian Parliamentary inquiry, House of Commons, Ottawa: *The effects of mefloquine use among Canadian veterans* (October 2018 – June 2019).
- Invited expert advisor to Scottish COVID-19 inquiry (May 2023 – *ongoing*).

Scientific advisory activities

Standing scientific committees

- Publications Committee (2005–2016): International Society of Travel Medicine.
- Member (1999–2004) Part 1 Examiners' Executive Committee: Faculty of Public Health Medicine of the Royal College of Physicians of London.
- Member (1999–2002): UK Department of Health Joint Committee on Vaccinations and Immunisations.
- Member (1998–1999): King's Fund Working Group on Clinical Governance.
- Technical adviser (1997–1999): World Health Organization Special Programme for Research and Training in Tropical Diseases (TDR).
- Member (1998–1999): British Medical Association Steering Group for Clinical Effectiveness.
- Honorary member (1996–2002): US Interagency Group on Malaria Prophylaxis.
- Advisory member (1996–1999): UK Public Health Laboratory Service Committee for Malaria Prevention Guidelines.

Scientific research editing

- Editor-in-Chief (2008–2016): *Human Parasitic Diseases.*
- Honorary Guest Editor (2015): *Journal of Parasitology Research .*
- Editorial reviewer / peer reviewer / section author for:
  - *ACP Medicine.*
  - *American Journal of Clinical Dermatology.*
  - *American Journal of Infection Control.*
  - *American Journal of Medicine*.
  - *BMC Central.*
  - *British Medical Journal.*
  - *Cochrane Library.*

- *Drug Safety.*
- *Journal of the Royal Army Medical Corps.*
- *Lancet.*
- *McMaster Evidence-based Journals.*
- *Medical Journal of Australia.*
- *Open Tropical Medicine.*
- *Thorax.*
- *Trends in Parasitology.*

- Section Adviser in Public Health and Epidemiology: *PubMed Central*.
- Technical Adviser and Section Author: *BMJ Best Practice*.
- Technical Adviser and Section Author: *BMJ Clinical Evidence*.
- Technical Adviser and Section Author: *NHS Choices*.

Appendix 3

Key epidemiological concepts

airborne spread	In the case of a respiratory pathogen, spread that occurs when very small particles of < 5 μm diameter (i.e. aerosol particles) are discharged from an infected person's airways – or alternatively, are produced during a medical procedure; being very small, the infective particles can remain suspended in the air for a long period of time and travel long distances and be inhaled into the air passages of potential new hosts
angiotensin-converting enzyme 2 (ACE2)	a cell surface protein found in human tissues and organ systems, utilised by SARS-CoV-2 to gain entry to the cell
antigen	That component (or components) of a bacterium or virus that is usually found on the external surface of the pathogen, and that is recognised by the host's immune system and serves to stimulate an immune response; sometimes referred to as the 'immunogen'
attack rate	For a given infectious disease, the proportion of people exposed to that disease who go on to develop infection
bacterium *(plural, 'bacteria')*	A microscopic, single-celled living organism that is found on or in other living organisms and that in some cases is pathogenic; bacteria can be treated with antibiotics
basic reproductive rate (R_0)	For any given pathogen (or variant of a pathogen), the number of persons directly infected by an infectious case during his or her entire infectious period, on entering a totally susceptible population
B lymphocytes	Class of lymphocytes (i.e. specialised white blood cells) that produce antibodies against specific antigens; they are primed to do so by the T lymphocytes
case-fatality rate (CFR)	For a given infectious disease, the proportion of patients who present to hospital with that disease, who subsequently die from the disease; in the case of COVID-19 the case fatality rate for those aged under 18 in England during 2020 was 0.0003% (i.e. effectively zero, in respect of otherwise healthy children)
cluster-randomised controlled trial	A randomised controlled trial where the unit of randomisation is not an individual participant, as is the case with most RCTs, but instead is a 'cluster' (e.g. a village, or a household)

Cochrane review	A systematic review of scientific evidence in a particular area, produced by the Cochrane international research collaboration and prepared to a very high standard of scientific rigour; Cochrane reviews include a plain language summary of the main findings of the review, and are updated every few years as new evidence becomes available
coronaviruses	A family of viruses found in animals and birds, causing a wide variety of diseases (including SARS, MERS, COVID-19)
COVID-19	A multi-system viral illness, first recognised in China in December 2019, that spread throughout the world during 2020, resulting in a pandemic lasting 3 years
direct transmission	In the case of a respiratory pathogen, disease transmission that occurs directly and from person to person – either through airborne spread, or else through droplet spread; most respiratory pathogens spread through both mechanisms
deoxyribonucleic acid (DNA)	The relatively stable genetic constituent of some viruses (e.g. smallpox viruses)
droplet spread	In the case of a respiratory pathogen, spread that occurs as a result of large infective particles of 5–10 μm diameter (i.e. droplet nuclei or respiratory droplets) falling out of the air soon after being produced; these large particles rarely travel more than one metre or so from the source patient and infect others either by landing directly on the mucous membranes of healthy hosts, or by contaminating inanimate objects (fomites), which then act as sources of indirect transmission
epidemiology	The monitoring and study of factors related to health conditions, and the implementation of control measures to prevent disease occurrence
evidence-based medicine	An approach to medical practice, now universally adopted, which postulates a hierarchy of scientific evidence; the 'gold standard' of scientific evidence, at the top of the hierarchy, is the randomised controlled trial (RCT)
fomites	Inanimate objects such as towels or utensils that have become contaminated by a virus, or other pathogen; if an uninfected person touches a fomite and then touches their mouth (or some other mucous membrane), they may acquire infection
herd immunity	The protection of unvaccinated individuals as a consequence of a high rate of vaccination within the population that eliminates (or largely eliminates) susceptible hosts

immune escape	Phenomenon whereby a pathogen evades the host's immune system; in the case of a virus, this can result from mutation of its antigenic structure
indirect transmission	In the case of any pathogen, disease transmission that occurs indirectly – such as, when an uninfected person touches a fomite and then touches their mouth, or some other mucous membrane
lockdown	Umbrella term for a range of extreme physical distancing measures, first introduced in China in 2002–2003 against SARS, and including: the closure of schools, workplaces, non-essential shops, sporting and entertainment venues; a move to 'remote' (i.e. computer-based) working where possible; banning mass gatherings; curfews; stay-at-home orders; and other local, national and international travel restrictions
long COVID	Symptoms of COVID-19 that persist for more than 4 weeks after the acute illness
MERS	Term applied to the 2012 self-limited epidemic of novel coronavirus infection, first recognised in Saudi Arabia and then seen sporadically in a number other countries (e.g. UK, France, Italy, South Korea); the virus is thought to have originated from an animal source
myocarditis	Inflammation of the heart muscle; myocarditis is often self-healing, but the damaged heart muscle (myocardium) does not regenerate
observational studies	Studies that do not have a control group and that therefore are of poor scientific quality and likely to yield biased or misleading result; known also as 'non-experimental studies', 'anecdotal studies', etc
pathogen	A micro-organism that can cause infection; pathogens include viruses, bacteria, fungi and protozoa
pericarditis	Inflammation of the fibrous sac that encloses the heart and great vessels
randomised controlled trial (RCT)	The 'gold standard' research study in evidence-based medicine (EBM); study participants are assigned to the intervention group or to the control group in a random fashion
ribonucleic acid (RNA)	The relatively unstable genetic constituent of some viruses (e.g. coronaviruses, influenza viruses)
SARS	Term applied to the 2002-2003 epidemic of novel coronavirus

	infection, first recognised in China and then seen in 28 other countries; the virus is thought to have originated from an animal source
SARS-CoV-2	A novel coronavirus; the cause of COVID-19
shielding	Advice given to vulnerable adults, including older and immunocompromised people, to curtail all social interactions
social distancing	A strategy to keep people physically separate; during the 2020–2023 COVID-19 pandemic a target of ≥ 2 metres, which at times (but in Scotland only) was relaxed to 1 metre, was used in the UK
'Spanish flu'	Term applied to the 1918-1919 pandemic of seasonal influenza, first recognised in Spain and characterised by unusually high mortality in young adults in some countries (e.g. UK and USA); this high mortality is now thought to have been in large part due to harmful treatment protocols used in those countries
spike protein	The glycoprotein projecting from the lipid layer of the surface envelope of SARS-CoV-2; this protein attaches to the ACE2 receptor on the surface of host cells, in order to effect entry into the cells
swine flu	A WHO-declared influenza pandemic that spread rapidly throughout the world in 2009 but reached a state of natural equilibrium in early 2010
systematic review	A type of scientific study which summarises the existing research in a particular area in a comprehenisve and impartial way; known also as an 'evidence synthesis' or 'meta-analysis'
test, trace and isolate	Term applied to a combination of test-based measures against COVID-19, including widespread testing to identify cases and ensure follow-up of potential cases, and enforcing quarantine measures for cases, contacts and travellers
thrombo-embolic events	Blood clots
transmission	How a virus (or some other pathogen) is passed from one susceptible host to another
vaccination	The process of inducing immunity by administering a vaccine against a pathogen; this is referred to as 'artificially-acquired immunity' (as opposed to 'naturally-acquired immunity', which results from natural exposure to a pathogen)

vaccine	An antigen-containing agent that is injected into a human or animal (or sometimes sprayed onto the host's mucosal surfaces) in order to induce immunity against a particular pathogen; vaccines may be component (or 'conventional') products, or novel-technology products (e.g. viral vector vaccines, and nucleic acid – or 'mRNA' – vaccines)
variant	In the case of viruses, a virus with an altered antigenic structure; this alteration may confer different properties on the virus (e.g. it may be more infective, or less infective)
virus	A sub-microscopic, non-living organism containing genetic material and found on or in living organisms; viruses are sometimes pathogenic and while they are not susceptible to treatment with antibiotics, their replication can sometimes be slowed with antiviral drugs
Yellow Card reporting	In the UK, a system whereby health professionals (and more recently, members of the public) can report a suspected adverse reaction to a drug or a vaccine

Appendix 4

Odds ratios, risk ratios and confidence intervals

1. *What is meant by* odds *and* odds ratio*?*

Odds and *odds ratio* are effect measures which are commonly used in the statistical analysis of research findings.

The odds for a particular group is defined as the number of patients in the group who achieve the stated end point, divided by the number of patients who do not. For example, the odds of acne resolution during treatment with an antibiotic in a group of 10 patients may be 6 to 4 (6 with resolution of acne divided by 4 without = 1.5); in a control group the odds may be 3 to 7 (0.43).

The odds ratio, as the name implies, is a ratio of two odds. It is simply defined as the ratio of the odds of the treatment group to the odds of the control group. In our example, the odds ratio of treatment to control group would be 3.5 (1.5 divided by 0.43).

An odds ratio of 1 means that there is no effect. The intervention of interest is no different to the comparator, or *control* intervention.

2. *What is meant by* risk *and* relative risk*?*

Risk and *relative risk* are other effect measures used in statistical analysis of research findings.

Risk, as opposed to odds, is calculated as the number of patients in the group who achieve the stated end point, divided by the total number of patients in the group.

Risk ratio or relative risk is a ratio of two risks. In the example above the risks would be 6 in 10 in the treatment group (6 divided by 10 = 0.6) and 3 in 10 in the control group (0.3), giving a risk ratio, or relative risk of 2 (0.6 divided by 0.3).

Again, a relative risk of 1 means that there is no effect. The intervention of interest is no different to the comparator, or *control* intervention.

3. *What is meant by* confidence intervals*?*

The *confidence interval* is a measure of uncertainty. Strictly, it should be called the 'uncertainty interval'.

Because all studies with a control group, such as randomised controlled trials (RCTs), are based on a sample of the population, instead of the entire population, it follows that there will always be some uncertainty around the reliability of the effect measures that are calculated on the basis of the chosen sample. The true effect measure may be larger than the estimated effect measure – or alternatively, it may be smaller.

At the same time as estimating the effect measure (e.g. the odds ratio) for the intervention of interest, it is customary nowadays to calculate the parameters within which the true effect measure must lie, with a 95% degree of confidence. These parameters are known as *the 95% confidence interval* (95% CI). The true effect measure may be higher than the estimated effect measure, or it may be lower – but there is a 95% chance that it will lie somewhere between the upper boundary and the lower boundary of the 95% CI.

In general terms, the larger the sample size of a given controlled study, the greater the likelihood of the estimated effect measure being close to the true effect measure, and the smaller the size of the corresponding confidence intervals. The same applies to meta-analyses. Large RCTs with many participants, and large meta-analyses, are more likely to yield accurate results than small RCTs, and small meta-analyses.

Appendix 5

The Bundgaard (Denmark) and Abaluck (Bangladesh) studies

[The two studies discussed – **Bundgaard 2020** *and* **Abaluck 2022** *– are attached as pdf files]*

1. *The Bundgaard study*[265]

The Bundgaard study was a randomised controlled trial carried out in Denmark in April–May 2020 (i.e. at the start of the COVID-19 pandemic). At that time, mask wearing was not amongst the recommended public health measures in Denmark.

There were 6024 participants in the study. They were community-dwelling adults, previously uninfected with SARS-CoV2, who did not wear masks in their daily work. They were randomised into either (i) wearing a surgical mask outside the home for > 3 hours, or (ii) not wearing a mask, i.e. control group. Testing for SARS-CoV-2 was carried out at 1 month.

At 1 month, 42 (1.8%) of the mask-wearing participants tested positive for COVID-19, whereas 53 (2.1%) of the non-mask wearers tested positive. The odds ratio was 0.82 (i.e. suggesting a benefit from mask wearing), but statistically this result was not significant (CI 0.54 to 1.23). The study results were inconclusive, therefore.

2. *The Abaluck study*[266]

The Abaluck study was a cluster-randomised controlled trial carried out in rural Bangladesh in November 2020 – April 2021. The unit of randomisation was villages.

There were 600 villages in the study. They were randomised into either (i) wearing a mask + shown a video and given a brochure on how to use them, or (ii) no intervention, i.e. control group. SARS-CoV-2 infection was determined by (i) self-reported symptoms, and (ii) laboratory testing.

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[265] Bundgaard H, Bundgaard JS, Raaschou-Pedersen DE, *et al*. Effectiveness of adding a mask recommendation to other public health measures to prevent SARS-CoV-2 infection in Danish mask wearers – a randomized controlled trial. *Ann Intern Med* 2021; 174: 335-343.

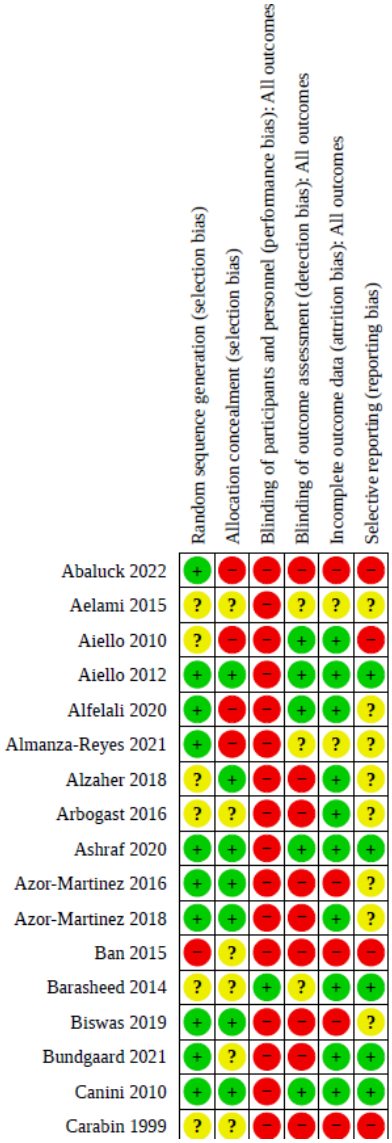
[266] Abaluck J, Kwong LH, Styczynski A, *et al*. Impact of community masking on COVID-19: A cluster-randomized trial in Bangladesh. *Science* 2022; 375.

The study authors concluded that the intervention reduced symptomatic seroprevalence (i.e. a composite measure of positive symptoms and positive antibody tests). The all-age odds ratio was 0.91 (CI 0.82 to 1.00). The results were only just significant therefore – because the upper boundary of the 95% confidence interval touched 1, and an odds ratio of 1 means that there is no effect.

Assessment of the two studies by the Cochrane reviewers Cochrane 2023

The 2023 Cochrane reviewers Cochrane 2023 interpreted the Bundgaard and Abaluck studies in the context of pre-existing evidence from earlier RCTs of mask use. They applied the standards of scientific rigour that are routinely used in Cochrane reviews.

Using the *Cochrane risk of bias* tool, the Bundgaard study was found to be at low-to-moderate risk of bias, and the Abaluck study at high risk of bias. This is shown below:



When the findings of the Bundgaard and Abaluck studies were combined through meta-analysis with the findings of other medical / surgical mask RCTs, they contributed modestly to the overall finding that mask wearing may be effective in preventing the acquisition of SARS-CoV-2 infection – but statistically, and because the confidence intervals for the various pooled effect measures, shown below as black diamonds (the pooled effect measure in this analysis was the risk ratio, which is equivalent to the odds ratio), in all cases include 1, the results are not significant. This is shown here:

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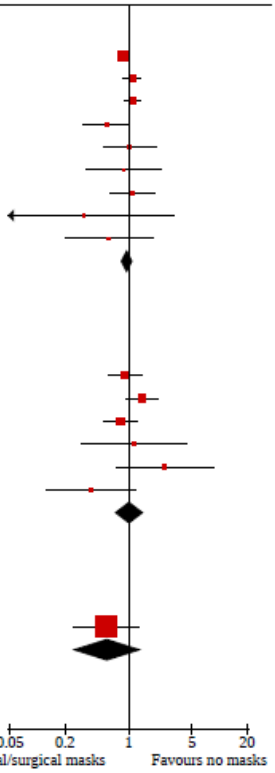
Analysis 1.1. Comparison 1: Randomised trials: medical/surgical masks versus no masks, Outcome 1: Viral illness

Study or Subgroup	log[Risk Ratio]	SE	Medical/surgical masks Total	No masks Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Influenza/COVID-like illness						
Abaluck 2022 (1)	-0.135	0.036	111525	155268	41.4%	0.87 [0.81 , 0.94]
Aiello 2012	0.095	0.115	392	370	19.8%	1.10 [0.88 , 1.38]
Alfelali 2020	0.095	0.105	3864	3823	21.9%	1.10 [0.90 , 1.35]
Barasheed 2014	-0.55	0.3	75	89	4.6%	0.58 [0.32 , 1.04]
Canini 2010	0.025	0.342	148	158	3.6%	1.03 [0.52 , 2.00]
Cowling 2008	-0.128	0.483	61	205	1.9%	0.88 [0.34 , 2.27]
MacIntyre 2009	0.1	0.28	186	100	5.2%	1.11 [0.64 , 1.91]
MacIntyre 2016	-1.139	1.16	302	295	0.3%	0.32 [0.03 , 3.11]
Suess 2012	-0.494	0.571	26	30	1.4%	0.61 [0.20 , 1.87]
Subtotal (95% CI)			**116579**	**160338**	**100.0%**	**0.95 [0.84 , 1.09]**
Heterogeneity: Tau² = 0.01; Chi² = 11.44, df = 8 (P = 0.18); I² = 30%						
Test for overall effect: Z = 0.71 (P = 0.48)						
1.1.2 Laboratory-confirmed influenza or SARS-cov-2						
Aiello 2012	-0.083	0.223	392	370	25.9%	0.92 [0.59 , 1.42]
Alfelali 2020	0.34	0.215	3864	3823	26.7%	1.40 [0.92 , 2.14]
Bundgaard 2021 (2)	-0.2	0.208	2392	2470	27.4%	0.82 [0.54 , 1.23]
Cowling 2008	0.148	0.674	61	205	5.8%	1.16 [0.31 , 4.34]
MacIntyre 2009	0.92	0.6225	186	100	6.6%	2.51 [0.74 , 8.50]
Suess 2012	-0.942	0.57	26	30	7.7%	0.39 [0.13 , 1.19]
Subtotal (95% CI)			**6921**	**6998**	**100.0%**	**1.01 [0.72 , 1.42]**
Heterogeneity: Tau² = 0.07; Chi² = 8.52, df = 5 (P = 0.13); I² = 41%						
Test for overall effect: Z = 0.07 (P = 0.95)						
1.1.3 Laboratory-confirmed other respiratory viruses						
Bundgaard 2021	-0.55	0.42	2392	2470	100.0%	0.58 [0.25 , 1.31]
Subtotal (95% CI)			**2392**	**2470**	**100.0%**	**0.58 [0.25 , 1.31]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						



Footnotes
(1) Covid-like-illness
(2) SARS-cov-2

Appendix 6

Hand hygiene compared to control

*[The Cochrane review cited here – **Jefferson 2023** – is attached as a pdf file]*

Assessment of hand hygiene by the Cochrane reviewers **Cochrane 2023**

The 2023 Cochrane reviewers **Cochrane 2023** used meta-analysis to combine the results of 20 RCTs of hand hygiene, in different settings. The risk ratio (i.e. a pooled effect measure that is equivalent to the odds ratio) shows that hand hygiene prevents acute respiratory illness, or influenza-like illness, or influenza (RR 0.89, 95% CI 0.83 to 0.94). Because the confidence interval for the calculated risk ratio does not include 1, this is likely to be a true finding. This is shown here:

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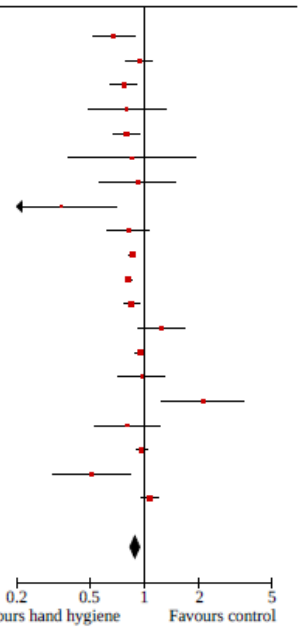
Analysis 3.2. Comparison 3: Randomised trials: hand hygiene compared to control, Outcome 2: ARI or ILI or influenza (including outcome with most events from each study)

Study or Subgroup	log[Risk Ratio]	SE	Hand hygiene Total	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Ashraf 2020	-0.39	0.135	588	1123	3.7%	0.68 [0.52 , 0.88]
Azor-Martinez 2018 (1)	-0.062	0.086	274	149	6.1%	0.94 [0.79 , 1.11]
Azor-Martinez 2018	-0.261	0.086	339	149	6.1%	0.77 [0.65 , 0.91]
Biswas 2019	-0.223	0.249	5077	5778	1.4%	0.80 [0.49 , 1.30]
Correa 2012	-0.223	0.084	794	933	6.3%	0.80 [0.68 , 0.94]
Cowling 2008	-0.151	0.408	84	205	0.6%	0.86 [0.39 , 1.91]
Cowling 2009	-0.083	0.243	257	279	1.5%	0.92 [0.57 , 1.48]
Hubner 2010	-1.05	0.36	64	65	0.7%	0.35 [0.17 , 0.71]
Larson 2010	-0.199	0.134	946	904	3.7%	0.82 [0.63 , 1.07]
Little 2015	-0.151	0.02	8241	8667	10.8%	0.86 [0.83 , 0.89]
Millar 2016	-0.198	0.016	10000	10000	11.0%	0.82 [0.80 , 0.85]
Nicholson 2014	-0.163	0.05	847	833	8.8%	0.85 [0.77 , 0.94]
Ram 2015	0.215	0.149	193	184	3.2%	1.24 [0.93 , 1.66]
Roberts 2000	-0.051	0.03	299	259	10.2%	0.95 [0.90 , 1.01]
Sandora 2005	-0.03	0.15	602	451	3.2%	0.97 [0.72 , 1.30]
Simmerman 2011	0.737	0.263	292	302	1.3%	2.09 [1.25 , 3.50]
Stebbins 2011	-0.211	0.212	1695	1665	1.8%	0.81 [0.53 , 1.23]
Swarthout 2020	-0.03	0.037	1496	4769	9.8%	0.97 [0.90 , 1.04]
Teesing 2021	-0.67	0.248	976	886	1.4%	0.51 [0.31 , 0.83]
Zomer 2015	0.068	0.052	278	267	8.6%	1.07 [0.97 , 1.19]
Total (95% CI)			**33342**	**37868**	**100.0%**	**0.89 [0.83 , 0.94]**

Heterogeneity: Tau² = 0.01; Chi² = 83.20, df = 19 (P < 0.00001); I² = 77%
Test for overall effect: Z = 3.83 (P = 0.0001)
Test for subgroup differences: Not applicable



Footnotes
(1) Azor 2018 included 2 treatment groups: soap and water (RR 0.94); and hand sanitizer (RR 0.77)

Appendix 7

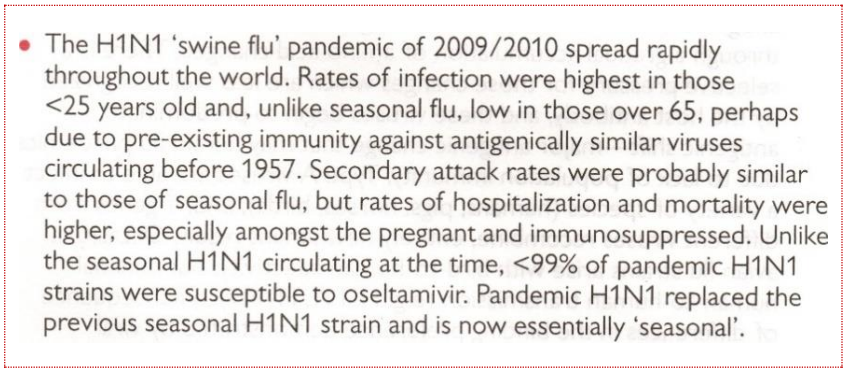
The 1918–1919 influenza pandemic

[The 1918-1919 influenza pandemic, known also as the 'Spanish flu', has been described as being among the most deadly events in recent human history. The pandemic killed between 50–100 million people. In countries such as the UK and USA, and for reasons that have never adequately explained, there was a high case-fatality rate at all ages, including amongst 20–40-year-old individuals, an age group normally at low risk for severe influenza. Conversely, in some countries (e.g. in Spain itself) the influenza took the form of 'normal' seasonal flu, with average or close-to-average mortality.]

Comment. The unusually high mortality in young adults with 'Spanish flu' that occurred in some countries (e.g. UK and USA) is now thought to have been in large part due to harmful treatment protocols that were used in those countries **Starko 2009**. In the early weeks of the COVID-19 pandemic the case-fatality rate was reported to be as high as 15%, causing widespread alarm. This high reported rate may likewise have been due, at least in part, to harmful treatment protocols (e.g. over-enthusiastic use of intravenous fluids, nursing patients in the supine rather than the prone position, etc), such as are no longer implemented. The crude case-fatality rate for COVID-19, averaged across all age groups, is now considered to be around 0.5–1% *[in Scotland it was 0.29%]*; the overwhelming majority of COVID-19 deaths occur in those who are very old, or very sick. In 2020 and 2021 some commentators drew parallels between COVID-19 and the high mortality rates in young people that were reported in some countries during the 1918–1919 influenza pandemic. Arguably, the drawing of these historical parallels was misleading, and contributed to the atmosphere of panic that prevailed in 2020 and 2021 – and that hence facilitated the introduction, in some countries, of repressive and authoritarian response measures against COVID-19 that were often harmful at a societal level, but that were declared as necessary to 'contain' SARS-CoV-2.

Appendix 8

The 2009–2010 swine flu pandemic



- The H1N1 'swine flu' pandemic of 2009/2010 spread rapidly throughout the world. Rates of infection were highest in those <25 years old and, unlike seasonal flu, low in those over 65, perhaps due to pre-existing immunity against antigenically similar viruses circulating before 1957. Secondary attack rates were probably similar to those of seasonal flu, but rates of hospitalization and mortality were higher, especially amongst the pregnant and immunosuppressed. Unlike the seasonal H1N1 circulating at the time, <99% of pandemic H1N1 strains were susceptible to oseltamivir. Pandemic H1N1 replaced the previous seasonal H1N1 strain and is now essentially 'seasonal'.

Comment. The above short summary of the 2009–2010 swine flu pandemic is taken from a standard textbook for medical students.[267] The response to the pandemic by the UK government at the time (i.e. the Labour government of Gordon Brown) was unduly influenced by 'worst-case' modelling and by alarmist predictions in the media that originated from WHO officials and UK academics who had undeclared conflicts of interest **Mandeville 2014**; in fact the swine flu pandemic quickly reached a state of natural equilibrium by early 2010. Important additional mistakes made in 2009–2010 by the UK government included (i) the stockpiling at great expense to the UK taxpayer of ineffective antiviral drugs (notably oseltamivir, or *Tamiflu*) **Godlee 2010**; and (ii) emergency-use authorisation given to inadequately-tested vaccines (notably the GlaxoSmithKline vaccine *Pandemrix*, which in a significant but undisclosed number of children caused narcolepsy, a devastating and lifelong neurological disease). An official review of the pandemic, published in July 2010, criticised the over-use by pandemic planners of the terms "containment" and "reasonable worst-case scenario", and also criticised GlaxoSmithKline for not agreeing to a break clause once vaccine procurement contracts had been signed.[268]

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[267] Török E, Moran E, Cooke F. *Oxford handbook of infectious diseases and microbiology*. 2nd ed. Oxford: OUP, 2017.

[268] Hine D. *The 2009 influenza pandemic – an independent review of the UK response to the 2009 influenza pandemic*. London: Cabinet Office, 2010.

Appendix 9

Previous coronavirus epidemics (SARS and MERS)

Severe Acute Respiratory Syndrome (SARS) coronavirus

SARS was recognized in China in November 2002 and had spread to affect 29 countries across the world by February 2003. The epidemic had died out by July 2003; 8096 cases were reported, with a fatality rate of 11% (43% in those over 60 years of age). Between July 2003 and May 2004, there were four small and rapidly contained outbreaks of SARS, three of which were associated with laboratory releases and the fourth thought to be due to an animal source. The cause was a novel coronavirus. Animals are thought to be the main reservoir. Transmission is by droplets and contact with contaminated surfaces—nosocomial transmission was common in the early stages of the outbreak. The virus is present in stool and may cause diarrhoea.

- Clinical features—incubation is 2–10 days. A 3- to 7-day febrile prodrome follows, notable for the absence of upper respiratory symptoms. The respiratory phase typically starts with a dry cough, progressing to breathlessness and progressive pulmonary infiltrates on CXR.
- Diagnosis—during the outbreak, RT-PCR was performed but sensitivity appeared limited (<70% positive on NPAs in week 2 of illness). No systematic study was performed to validate tests. Serological testing by ELISA at 3 weeks appeared most sensitive.
- Treatment—no specific therapy. Care is supportive. Patient isolation and infection control precautions were key to the control of the 2002/3 outbreak. This was greatly facilitated by the relatively long prodrome that enabled patients to be identified and isolated before they became infectious.

Middle East Respiratory Syndrome (MERS) coronavirus

This betacoronavirus, closely related to several bat coronaviruses was identified in 2012 from a man admitted to hospital in Saudi Arabia with pneumonia and renal failure. Shortly after his admission, an identical virus was identified in Qatar in a patient with similar features who had travelled to Saudi Arabia. Cases followed across the Middle East and were reported in five other countries amongst patients returning from the Middle East. The UK, France, Italy, and Tunisia reported limited human-to-human transmission to close contacts of the index cases. The case fatality rate was reported as 60%.

- Clinical features—incubation around 5 days (but <10 days). Symptoms range from none (positive RT-PCR tests were found in several asymptomatic close contacts), mild respiratory illness, to severe pneumonia requiring ventilation or extracorporeal membrane oxygenation. Other symptoms: pericarditis, renal failure, DIC, diarrhoea. Those with underlying medical problems seem at greater risk of severe disease.
- Diagnosis—RT-PCR testing of lower respiratory tract specimens is most sensitive. Testing multiple specimens taken at different times from different sites increases the likelihood of detecting virus. Guidance should be sought from national public health authorities regarding who to test, based upon contemporary epidemiology.
- Treatment is supportive, and infection control paramount.

Comment. The above short summaries of the SARS and MERS novel coronavirus

epidemics (they were never designated by WHO as pandemics) are taken from a standard textbook for medical students.[269] This knowledge was readily available, when the COVID-19 pandemic was declared, in March 2020. Like the 2009–2010 swine flu pandemic, the MERS epidemic of 2012 proved to be self-limiting – although sporadic cases do still occur. Arguably, the 2002–2003 SARS epidemic, which was first recognised in China in November 2002 and then spread to 28 other countries (e.g. Vietnam, Singapore, Canada, USA), was also self-limiting, since most countries did not adopt emergency measures against SARS and yet the epidemic died out, by July 2013. In China, by contrast, a series of repressive and authoritarian measures, including *lockdowns* (i.e. closure of schools, workplaces and entertainment venues, and government-enforced stay-at-home orders), *social distancing* (i.e. enforced spatial separation of at least 1 metre between those infected and those non-infected) *border closures*, and *compulsory face mask wearing* were mandated by the Communist Party of China. These extreme government-mandated measures were afterwards judged by the Chinese government – but without any scientific evidence to support this judgment – to have resulted in the 'containment' of the SARS epidemic. In respect of SARS, China was the worst-affected country in the world, by a wide margin. Since secondary attack rates of coronavirus infections within households are high, the 'containment' measures against SARS that were adopted by the Communist Party of China may have made their SARS experience worse, not better – for example, by creating hundreds of new foci for the ready acquisition of SARS, in people's homes. Notwithstanding these uncertainties, the same 2002–2003 package of repressive and authoritarian 'containment' measures (and with the additional new measure of population-wide electronic surveillance of citizens' movements), was adopted by the Communist Party of China in 2019–2020, at the start of the COVID-19 pandemic. In early 2020, with high COVID-19 case numbers occurring in most countries – including China itself – the Chinese model of coronavirus 'containment' was adopted by many other governments, including the UK and the Scottish governments. In Scotland, two population-wide electronic surveillance schemes on the Chinese model were procured; these were (i) *Test and Protect*, procured by the Scottish government in May 2020, and (ii) *Protect Scotland*, procured by the Scottish government in September 2020. In England, the population-wide electronic surveillance scheme procured in 2020 by the then Secretary of State for Health, Matt Hancock, was called *Track and Trace*. There is no evidence now, and there was no evidence in 2020, that any of these population-wide electronic surveillance schemes were effective in helping prevent the spread of SARS-CoV-2 infection.

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[269] Török E, Moran E, Cooke F. *Oxford handbook of infectious diseases and microbiology*. 2nd ed. Oxford: OUP, 2017.

Appendix 10

Timeline of COVID-19 events in Scotland

Date	Milestone
1 March 2020	First positive case of COVID-19 confirmed in Scotland.
13 March 2020	First confirmed death of a COVID-19 patient in Scotland.
13 March 2020	People with symptoms of COVID-19 told to stay at home for seven days.
16 March 2020	Cancellation of all mass indoor and outdoor events of 500 people or more.
20 March 2020	All schools and nurseries closed by the end of this week.
24 March 2020	Start of *lockdown* in Scotland.
6 May 2020	National Records of Scotland records the first weekly reduction of registered deaths (for the week ending 3 May) since March 2020.
11 May 2020	People told they can go outside more than once a day to exercise. However, people should stay local and either go alone or with members of their household.
18 May 2020	UK Government announces an update to COVID-19 symptoms to include anosmia or 'the loss of or a change in your normal sense of smell'.
18 May 2020	Testing made available to everyone who is symptomatic over the age of five.
21 May 2020	Scottish Government publishes a COVID-19 'Route Map' to take Scotland through and out of the COVID-19 pandemic.

Date	Milestone
28 May 2020	NHS Scotland's Test and Protect scheme rolled out across Scotland.
29 May 2020	Move to Phase 1 of the route map out of *lockdown*.
19 June 2020	Move to Phase 2 of the route map out of *lockdown*.
22 June 2020	Face coverings become mandatory on public transport.
2 July 2020	Due to a spike in cases in Dumfries & Galloway, the Scottish Government implements the first localised delay in the relaxation of restrictions. Other areas would be impacted in a similar way as the pandemic continued.
10 July 2020	Face coverings become mandatory in shops.
10 July 2020	Move to Phase 3 of the route map out of *lockdown*.
30 July 2020	Advice on self-isolation changed from 7 to 10 days.
3 August 2020	Eat Out to Help Out Scheme introduced by UK Government.
11 August 2020	Pupils return to Scotland's schools.
25 August 2020	Face coverings introduced in schools and dedicated school transport.
10 September 2020	Scottish Government's Protect Scotland app launches, complementing NHS Scotland's Test and Protect system.
22 September 2020	Scottish Government announce new restrictions on household visits and a national curfew for pubs, bars and restaurants.
25 September 2020	10 pm curfew introduced in hospitality sector.

Date	Milestone
23 October 2020	Scotland's Strategic Framework – a five-level tiered framework – is published by the Scottish Government.
29 October 2020	Face covering exemption cards introduced.
20 November 2020	New travel regulations prevent people who live in a Level 3 or Level 4 area from travelling outside their local authority except for an essential purpose. Travel between Scotland and the rest of the UK also becomes illegal except for essential purposes.
24 November 2020	Scottish Government announce details of a UK-wide "limited relaxation" of restrictions over the Christmas period.
2 December 2020	UK medicines regulator authorises first COVID-19 vaccine, developed by Pfizer and BioNTech.
2 December 2020	First Community Asymptomatic Test site opens in Scotland.
8 December 2020	In Coventry, Mrs Margaret Keenan, an 80-year old grandmother, became the first person in the world to receive the Pfizer COVID-19 vaccine.
8 December 2020	The first vaccinations against COVID-19 are given in Scotland to those who will be carrying out the vaccination programme.
14 December 2020	The self-isolation period for positive contacts and overseas arrivals is reduced from 14 days to 10 days.
14 December 2020	First vaccinations in care homes in Scotland.
19 December 2020	First Minister Nicola Sturgeon announces the tightening of COVID-19 restrictions around the festive period.

Date	Milestone
30 December 2020	The Oxford AstraZeneca vaccine is approved for use in the UK.
5 January 2021	Mainland Scotland goes into *lockdown*.
18 January 2021	All travel corridors are suspended.
18 January 2021	Scotland introduces pre-departure testing for international travellers.
24 January 2021	Scottish Government announce invitations for COVID-19 vaccine appointments for people aged 70-79 will commence from Monday 25 January 2021.
10 February 2021	Scottish Government announce the number of first dose vaccinations in Scotland reaches the 1 million milestone.
17 February 2021	Scottish Government announce an expansion of testing to include anyone who is identified as a close contact of somebody who has tested positive for COVID-19, from 18 February 2021.
22 February 2021	Children in early learning and childcare, and primaries 1 to 3, return full-time to classrooms.
22 February 2021	Scottish Government announce people with underlying health conditions and unpaid carers are beginning to receive COVID-19 vaccinations.
23 February 2021	Scottish Government publish the updated Strategic Framework, setting out the broad order of priority for re-opening.
25 February 2021	Scottish Government announce Scotland's vaccination programme has delivered first doses of the COVID-19 vaccine to a third (33.4%) of those eligible – more than 1.5 million people.

Date	Milestone
30 March 2021	Scottish Government announce non-essential journeys within the local authority area are allowed from Friday 2 April 2021, when a requirement to Stay Local will replace the Stay at Home rule.
30 March 2021	Hairdressers, garden centres, car showrooms and forecourts, homeware stores and non-essential click and collect services can open from Monday 5 April 2021.
13 April 2021	Scottish Government announce Travel within Scotland for outdoor socialising, recreation and exercise, and outdoor meetings in groups of up to six adults from up to six households will be allowed from Friday 16 April 2021.
20 April 2021	Scottish Government announce all parts of the country will move to Level 3 from Monday 26 April 2021; hospitality venues such as cafés, pubs and restaurants can reopen, along with tourist accommodation.
14 May 2021	The World Health Organization classifies the COVID19 B.1.617 mutation, first found in India, as a variant of concern.
14 May 2021	Scottish Government announce most of mainland Scotland (with the exception of Moray) will move to level 2 from Monday 17 May, with eased restrictions on hospitality, entertainment, education and sport.
28 May 2021	Scottish Government announce £3 million Destination and Sector Marketing Fund for tourism organisations to promote key visitor destinations in a responsible and sustainable way.
28 May 2021	Medicines and Healthcare products Regulatory Agency (MHRA) approves the one-dose Janssen COVID-19 vaccine for use in the UK.
22 June 2021	First Minister Nicola Sturgeon announces a new indicative date for the whole of Scotland to move to level 0 on 19 July, provided all necessary vaccination and harm reduction measures are met.
13 July 2021	First Minister Nicola Sturgeon announces all of Scotland will move to protection level 0 on Monday 19 July 2021. Social distancing will reduce from 2 metres to 1 metre in all indoor public settings and outdoors, and informal social gatherings of up to 15 people from 15

Date	Milestone
	households will be permitted outdoors without social distancing. Mandatory face coverings will remain in place.
19 July 2021	Scotland moves to protection level 0.
19 July 2021	JCVI issues advice on COVID-19 vaccination of children and young people – children at increased risk of serious COVID-19 disease should be offered the Pfizer-BioNTech vaccine. That includes children aged 12 to 15 with severe neurodisabilities, Down's syndrome, immunosuppression and multiple or severe learning disabilities.
23 July 2021	Scottish Government announce changes to self-isolation rules for close contacts of COVID-19 cases – essential staff in critical roles will be allowed to return to work to maintain lifeline services and critical national infrastructure.
28 July 2021	Scottish Government announce fully vaccinated people from the EU and US will be able to travel to Scotland without quarantining from Monday 2 August 2021.
3 August 2021	First Minister Nicola Sturgeon announces Scotland to move beyond level 0 on 9 August 2021, when the legal requirement for social distancing and limits on gatherings will be removed. Some protective measures will stay in place such as the use of face coverings indoors and the collection of contact details as part of Test and Protect.
4 August 2021	Scottish Government announce all young people 16 to 17 years of age to be offered the coronavirus (COVID-19) vaccination in Scotland from 6 August 2021.
9 September 2021	Scottish Parliament approves vaccine certification plans. From Friday 1 October 2021, Coronavirus vaccination certificates will be required to enter events such as nightclubs, music festivals and some football grounds.
14 September 2021	Scottish Government announce children and young people aged 12 - 15 years old will be offered a dose of the Pfizer-BioNTech vaccine from Monday 20 September.

Date	Milestone
20 September 2021	Scottish Government launch the COVID-19 booster vaccination programme. Residents in care homes for older people are the first to be offered COVID-19 booster vaccinations.
22 September 2021	Scottish Government announce more than 10 million COVID-19 PCR tests have now been carried out in Scotland over the past 19 months since testing got underway.
24 September 2021	Scottish Government announce travellers from non-red list countries who have been fully vaccinated in a country that meets recognised standards of certifications will no longer be required to provide evidence of a negative test result before they can travel to Scotland, from 4 October.
1 October 2021	The Scottish Government's vaccination certification scheme is in operation from 1 October 2021. People attending certain late-night venues and larger indoor and outdoor live events will be required to show proof to staff of their COVID-19 status, or a valid exemption.
28 October 2021	Scottish Government announce the final seven countries to be removed from the international travel red list from 1 November 2021, meaning that travellers to the UK from those destinations will no longer have to stay in hotel quarantine for 10 days on arrival.
4 November 2021	UK Government announce the first oral antiviral for COVID-19, Lagevrio (molnupiravir), has been approved by MHRA.
15 November 2021	JCVI issues advice on COVID-19 booster vaccines for those aged 40 to 49 and second doses for 16- to 17-year olds. All adults aged 40 to 49 years should be offered an mRNA booster, 6 months after their second dose, irrespective of the vaccines given for the first and second doses. All 16- to 17-year olds who are not in an at-risk group should be offered a second dose of the Pfizer vaccine. The second vaccine dose should be given 12 weeks or more following the first vaccine dose.
24 November 2021	More than one and a half million third doses and boosters administered in Scotland by the Autumn / Winter vaccination programme.

Date	Milestone
29 November 2021	First cases of the COVID-19 *Omicron* variant are identified in Scotland.
29 November 2021	JCVI issue advice on COVID-19 booster vaccines for those aged 18 to 39, and a second dose for ages 12 to 15. The booster will now be given 3 months after the primary course. In addition, a second dose of the Pfizer-BioNTech vaccine for young people aged 12 to 15 years is advised 12 weeks after the first dose.
8 December 2021	One-year anniversary of the first COVID-19 vaccination in Scotland. Since then, 4,355,063 first doses, 3,962,203 second doses and 1,922,604 boosters and third doses have been administered from around 1,200 vaccination centres.
12 December 2021	UK Government announce the UK coronavirus (COVID-19) alert level will be increased from Level 3 to Level 4.
21 December 2021	Scottish Government announce that 1-metre rule for social distancing will be reintroduced in indoor hospitality and leisure settings, from 27 December 2021.
23 December 2021	More than 70% of eligible adults in Scotland have received their booster or third dose.
23 December 2021	Scottish Government announce nightclubs are to close from 27 December 2021, subject to a review after three weeks.
14 January 2022	Number of people in Scotland who have died within 28 days of testing positive for COVID-19 passes 10,000.
26 January 2022	The Scottish Government's monthly GDP estimates for November 2021 show Scotland's economy to be 0.6% higher than in February 2020, before the main economic impact of coronavirus (COVID-19) began to be felt. This is the first time Scotland's GDP has been recorded as higher than pre-pandemic levels.
3 February 2022	UK Government announce the Novavax COVID-19 vaccine Nuvaxovid has been approved by MHRA.

Date	Milestone
4 February 2022	Scottish Government announce more than 15 million COVID-19 PCR tests have now been carried out in Scotland since testing began.
10 February 2022	Scottish Government announce high school pupils and staff will not be required to wear face coverings in classrooms from 28 February 2022.
16 February 2022	JCVI updates advice on vaccinations for 5 to 11 age group. The committee recommends a non-urgent offer to all 5 to 11 year olds of 2 (10mcg) doses of the Pfizer-BioNTech paediatric vaccine.
22 February 2022	First Minister Nicola Sturgeon announces vaccine certification will no longer be legally required from Monday 28 February. Current legal requirements on the use of face coverings and the collection of customer details for contact tracing purposes are expected to be lifted on 21 March 2022.
15 March 2022	Scottish Government announce legal requirements to wear face coverings on public transport and most indoor public settings will continue until at least early April. The remaining legal requirements for businesses and service providers will end on Monday 21 March 2022.
30 March 2022	Scottish Government announce the legal requirement to wear a face covering on public transport and most indoor public settings will end on 18 April 2022. Requirements for face coverings at weddings, funerals and places of worship will end on 4 April 2022. In addition, from 18 April 2022 most people without symptoms will not be required to take tests. Lateral flow devices for twice weekly testing will no longer be available. PCR tests for people with COVID-19 symptoms will be available until 30 April 2022, when test sites will close.
27 April 2022	Scottish Government announce the shielding list will end on 31 May 2022. The Chief Medical Officer will write to individuals on the list to advise them of the change and sign post them to ongoing support.
28 April 2022	Scottish Government announce public health advice will change to a 'stay at home' message from 1 May 2022. All contact tracing will end. Testing for the general population will end on 30 April 2022, with test sites closing. Testing will remain available to certain groups. NHS Scotland will be taken out of emergency footing at the end of 30 April 2022.

Date	Milestone
5 May 2023	The World Health Organization declares that COVID-19 no longer constitutes a public health emergency of international concern (PHEIC).