Long Covid Update – a threat that continues to demand a strong response

6 March 2025
John D Potter, Michael Baker, Amanda Kvalsvig

APPENDIX – Key questions about Long Covid and summary of recent evidence

This Appendix to our main article lists key questions about Long Covid, including its features, risks, prevention, and management. It summarises more recent published evidence on these points.

A. Features of Long Covid / Post Covid Conditions

1. It is a cluster of chronic illnesses

There are three direct longer-term clinical manifestations of infection with SARS-CoV-2:

- Long Covid (LC), also called Post Covid Conditions (PCC) and Post-Acute Sequelae of Covid (PASC) as defined in the main text – namely, disease present at ≥3 months presenting as a syndrome, a collection of symptoms, or a single symptom.
- Inapparent illness manifest as sudden death – typically during the subsequent 12 months, with or without existing chronic illness, due in part to Covid, but without a formal diagnosis of LC;[1-5] (see: 2. *Increased cardiovascular disease and mortality risk* below).
- Inapparent illness manifesting as pathologic changes (silent cell and organ damage) that may predispose to later illness – including beyond 12 months and particularly among children and young people;[6-8] (see: 3. *Evidence of increased vulnerability to other illnesses* below).

Thus, LC encompasses a constellation of health effects caused by infection with SARS-CoV-2. As noted in the main text, it is a complex, multisystem disorder that can affect nearly every organ system. Pathophysiologic mechanisms include:

- Viral persistence in tissue reservoirs[9-13] and possible replication of SARS-CoV-2 leading to the generation of viral antigens and RNA;[9 12] this results in widespread immune responses,[11] including overactive inflammation, autoimmunity, and reactivation of dormant herpesviruses.[14] Post-Covid auto-immune disorders include lupus, rheumatoid arthritis, and Sjögren's syndrome;[15]
- Downstream pathologies as a result of this immune dysfunction, including:

- mitochondrial dysfunction and impaired energy metabolism:[12 16] as with myelo-encephalitis/chronic fatigue syndrome (ME/CFS),[17] general fatigue and post-exertional malaise are key symptoms and indicators of this mitochondrial pathology;[18]
- dysfunction (dysbiosis) of microbiota[19-21] and intestinal nervous system dysregulation: diarrhoea, vomiting, and abdominal pain are consistent and somewhat neglected symptoms of LC;
- nervous system inflammation which compromises neuronal activity:[22-24] brain fog (including memory dysfunction) is a cardinal LC symptom[25 26] and mental health can be impaired.[27] Specific anatomical changes to brain include:
  - depletion of cortical grey matter;[28]
  - tissue damage to the frontal lobe,[29] known, among many other functions, to be important in moral socialisation and, with damage, the emergence of antisocial behaviour;[30]
  - disruption of connectivity between the hippocampus (known to be important in memory) and other brain areas[31] and enlargement of areas of the hippocampus;[32]
  - damage to the brainstem,[33] central to the control of many involuntary functions such as heart rate, breathing, swallowing, sleep, and balance;
  - persistence of SARS-CoV-2 spike protein at the skull-meninges-brain axis;[34]
- other pathologies, including: complement dysregulation,[35] inflammation of the lining (endothelium) of blood vessels,[7 36 37] and platelet activation and red blood cell breakdown (lysis) leading to clotting (microthrombus formation) and cardiovascular tissue injury.[38 39]

These mechanisms overlap and cause inflammation, tissue dysfunction, and tissue damage in almost all organ systems, leading to the clinical manifestations of LC, especially fatigue, impaired cognition, and breathlessness, which appear to be the three most common symptoms. It has major impacts on individuals and their whanau/family and on health systems and economies.

There are less direct post-infection health outcomes:

- Neurodevelopmental disorders following *in utero* exposure;[40-43]
- The possibility of congenital anomalies as a consequence of viral exposure *in utero,* seen in some registries,[44 45] but not others,[46-48] and perhaps a surveillance artifact;
- Injuries as a secondary consequence of symptomatic illness (e.g., cognitive impairment affecting driving ability[49 50] or workplace safety[51]), perhaps greater susceptibility to injury,[52] and mental distress as a result of being disabled/unable to work.[53-55]

2. Increased cardiovascular disease and mortality risk

LC increases the risk of major cardiovascular events, including myocardial injury, dysrhythmias, coagulation abnormalities, and heart failure; these events, in turn result

in poor health outcomes and elevated mortality. LC-associated cardiovascular complications occur independent of age, hypertension, and diabetes, although these factors influence outcomes.[39 56 57]

During 2020–22, almost 230,000 individuals were included in the COMEGEN (a network of General Practitioners in Naples, Italy) database. More than 30,000 were infected with SARS-CoV-2. The proportion of individuals with a new diagnosis of major adverse cardiovascular and cerebrovascular events was 1.7-fold higher in the 2020–22 Covid-19 group than in the 2017–19 COMEGEN propensity-score-matched comparison group. All major adverse cardiovascular and cerebrovascular events showed a statistically significantly higher risk in Covid-19+ individuals. Thus, there was a persistent excess risk of major cardiovascular and cerebrovascular events over a 3-year observation period, well beyond the acute phase of Covid-19 infection.[38]

In the US, from March 2020 to March 2022, there were more than 90,000 excess deaths due to cardiovascular disease; this represents almost 5% more cardiovascular deaths than would be expected, based on recent years.[5] Two large peaks occurred in March to June 2020 and June to November 2021; these peaks coincided with peaks of Covid-19 deaths, although there were variations by state, age, sex, and race and ethnicity. There were more excess cardiovascular deaths among men than women.

There is evidence that vaccination reduces the risks of major adverse cardiovascular events: a cohort study of >10 million vaccinated and >10 million unvaccinated people across UK, Spain, and Estonia revealed that vaccination was associated with reduced risks of LC-related venous thromboembolism, arterial thrombosis/thromboembolism, and heart failure; e.g., the hazard ratios (HR) at 91–180 days were 0.53, 0.72, and 0.61, respectively.[58]

3. Evidence of increased vulnerability to other illnesses

As noted above, in addition to the accepted World Health Organization (WHO) definition of LC, there was an excess of sudden unexpected death, particularly from heart disease, following acute infection with SARS-CoV-2. Further, there is an excess of several long-term conditions, including diabetes (both type 1[59] and 2[59 60]), neurodegenerative disorders,[34 61] and poorer mental health.[62] It is likely that these events are the early to mid-term overt manifestations of more widespread, less obvious disease processes. Evidence for this can be derived from biomarkers of future risk, as we described in detail earlier: markers of brain injury, metabolic dysfunction, immune-system disturbance, musculoskeletal damage, dysfunctional mitochondria, long-term viral persistence, and some suggestion that there may be an elevated risk of cancer, perhaps as a consequence of immune and metabolic dysfunction.[63]

Evidence of viral persistence as well as complement-system and immune dysfunction continues to accumulate,[9-11 64-66] as does evidence of early manifestations of impaired cognitive (particularly executive) function.[67-69] In this last regard, two studies are of particular relevance:

- University of Otago undergraduates showed post-Covid altered prefrontal-cortex blood-flow patterns during cognitive tasks, patterns reminiscent of those

observed in adults four decades older; these abnormalities were especially marked among those who reported brain fog.[25]

- A challenge study was conducted relatively early in the pandemic, focused on wildtype SARS-CoV-2.[27] Despite this being early in the pandemic, it is important for two reasons. The study closely tracked cognitive function among previously uninfected people and followed them for 12 months. It is also important because it raises (again) the wisdom and the ethics of challenge studies with infectious agents about which little is known. Thirty-four young, healthy, seronegative volunteers were inoculated with SARS-CoV-2 (March 2021 to July 2022). Participants completed daily physiological measurements and computerised cognitive tasks at 30, 90, 180, 270, and 360 days. The main cognitive endpoint was a baseline-corrected composite cognitive score. Eighteen developed infection (evidenced by sustained viral load); one was symptomless; and the remainder had mild illness. Infected individuals showed statistically significantly lower global composite cognitive scores than those uninfected, both acutely and during follow up (up to 360 days). Memory and executive function tasks showed the largest between-group differences.[27] In the Discussion section of their report, the authors remark "Notably, none of the volunteers reported subjective cognitive deficits," suggesting strongly that people may not be aware of cognitive dysfunction even when it is detectable by testing; the true prevalence of cognitive dysfunction in the population may thus be substantially underestimated.

Finally, the emergence of some of these disorders (metabolic, cognitive, etc.) in children and young people raises a concern that there may be even more deeply hidden damage that we have not yet detected and that may emerge as overt disease years or decades hence. Lifecourse impacts of early inflammation on the developing brain were already well-characterised years before the Covid pandemic.[70] There is a great deal of uncertainty of exactly what the post-Covid disease landscape will look like.

B. Risk and consequences of LC

4. Level of LC risk (during current Omicron period)

For now, the dominant SARS-CoV-2 variants are all descendants and cousins of Omicron. Accordingly, we have a picture (albeit blurry, as noted above) of risk of LC associated with infection (particularly in the Omicron era) and reinfection.

Reinfection

The US Department of Veterans Affairs researchers were able to explore, quite early in the pandemic, whether reinfection adds to risks incurred after a first infection.[71] They assembled a cohort of >440,000 individuals with one infection; a cohort of >40,000 with two or more infections, and a cohort of >5.3 million without a history of infection. Compared to those with no reinfection, reinfection contributed additional risks of death (hazard ratio (HR) = 2.2), hospitalisation (HR = 3.3), and LC sequelae including pulmonary, cardiovascular, haematological, gastrointestinal, kidney, mental health, musculoskeletal, and neurological disorders, and diabetes. The elevated risks of these deleterious outcomes of reinfection were independent of a large array of potential confounders and were found among both vaccinated and unvaccinated people.[71]

Data from >2500 essential workers, mainly first responders, with confirmed SARS-CoV-2 infection from March 2020 to February 2024 revealed a prevalence of LC of 18.9%. There was a higher risk of LC among those who experienced multiple SARS-COV-2 infections (relative risk [RR] = 1.4), severe Covid-19 (RR = 3.2), and being unvaccinated at first infection (RR = 3.3).[72]

An online questionnaire study was conducted in China (22 November 2023 to 24 January 2024).[73] The design, particularly because of its online nature, its voluntary participation, and its daisy-chained recruitment, was subject to various biases. However, the pattern of findings, analysing 68,200 valid responses, was similar to other more rigorous studies, namely that:

- 10%–30% of respondents reported LC symptoms
- the most frequent LC symptoms were fatigue (30.5%), memory decline (27.9%), decreased exercise ability (18.3%), and brain fog (16.9%);
- reinfection was, itself, associated with milder symptoms but led to a higher incidence and severity of LC.

Al-Aly commenting on this study, noted that China has a burden of LC similar to that reported elsewhere, that multiple infections increase risk, and that vaccination reduces risk.[74]

A study covering the entire population of Qatar identified two patterns for the impact of natural infection against reinfection for Omicron compared with the pre-Omicron variants.[75] Prior to the Omicron era, natural infection provided strong and durable protection against reinfection, with little waning over time. In contrast, protection following infection with Omicron was robust only for recently infected individuals, declining rapidly over time and largely disappearing within a year. The investigators concluded that "SARS-CoV-2 immune protection is shaped by a dynamic interaction between host immunity and viral evolution, leading to contrasting reinfection patterns before and after Omicron's first wave."[75] This weaker and declining immune response may seem paradoxical given that the frequency of LC[76-78] is lower with the Omicron variant but perhaps these are related: the waning severity of the acute disease may result in a lesser insult to all organs and this, in turn, in a weaker immune response. What it does emphasise is the need, in the current era, for continued episodic vaccine updates to sustain immunity.

Change over time

We also now know how risk has changed over time, across the dominant SARS-CoV-2 eras. The US Veterans study (which has been one of the most informative sources on the Covid pandemic and its consequences) assembled a population of >440,000 veterans with SARS-CoV-2 infection between March 1, 2020, and January 31, 2022, and >4.7 million noninfected contemporaneous controls.[77] The cumulative incidence of LC at one year after SARS-CoV-2 infection and the differences among the outcomes of pre-Delta, Delta, and Omicron infections were reported. Among the unvaccinated, the cumulative incidence of LC during the first year was 10.42 events per 100 persons in the pre-Delta era, 9.51/100 in the Delta era, and 7.76/100 in the Omicron era. The researchers concluded that there were 2.66 fewer episodes of LC per 100 persons

(Omicron vs. pre-Delta) and 1.75 fewer/100 (Omicron vs. Delta). Among the vaccinated, the one-year cumulative incidence of LC was 5.34 events/100 persons during Delta and 3.50 /100 persons during Omicron (1.83 fewer events/100). Those vaccinated had a lower cumulative incidence of LC at one year than the unvaccinated (4.18 events/100 persons fewer during Delta and 4.26/100 fewer during Omicron). At one year, there were 5.23 fewer LC events per 100 persons during Omicron than during pre-Delta and Delta combined. Over a quarter (28.1%) of this decline was attributed to era-related effects (including changes in the virus) and 71.9% to vaccines.[77]

Risk in children and young people

By the beginning of 2024, it was established that children and adolescents could present with LC, albeit, perhaps, in smaller numbers,[79-81] (although see below for some of the problems estimating prevalence in children and young people) and with milder disease than adults,[80 81] but with a symptom profile that overlaps that of adults.[82 83] Risk was reported to be higher in older children and lower following infection with the Omicron variant.[81] Specific manifestations included an excess risk of diabetes[59 84 85] and of abnormal coagulation profiles,[86] and the presence of anxiety, depression, and sleep disturbance.[87]

Pinto Pereira et al. had previously shown, in children and adolescents at 3- and 6-months post infection, that 12–16% of those infected with the Omicron variant of SARS-CoV-2 met the research definition of LC, with no differences between first-positive and reinfected children and adolescents.[88] At 12 months post-infection with the Omicron variant, the most common symptoms in first-positive and reinfected children and adolescents (12-months post-testing) were fatigue (35.7% and 33.6% respectively) and sleeping difficulties (27.5% and 28.3% respectively). Symptom profiles, severity, and impact were similar in the two infection-status groups. Overall, by 12-months, 17.4% of first-positives and 21.9% of reinfected children and adolescents fulfilled the research consensus LC definition (p=0.13).[89]

A total of 898 school-age children (mean age, 8.6 years), 751 with previous SARS-CoV-2 infection (infected) and 147 without (uninfected) and 4469 adolescents (mean age, 14.8 years), 3109 infected and 1360 uninfected, were studied to establish the most common LC symptoms, how these symptoms differed by age, and how they clustered into distinct phenotypes.[90] In models adjusted for sex and race/ethnicity, 14 symptoms in both school-age children and adolescents were more common in the infected than the uninfected, with four additional symptoms only in school-age children and three only in adolescents; these symptoms affected almost every organ system as has been shown more generally.[91] LC indices – emphasising neurocognitive, pain, and gastrointestinal symptoms in school-age children and change or loss of smell/taste, pain, and fatigue/malaise in adolescents – correlated with poorer overall health and quality of life. Clustering analyses identified four LC phenotypes in school-age children and three in adolescents.[90]

Using data from the 2023 US National Health Interview Survey (NHIS), just over one million (1.4%) of children were reported to have ever experienced LC and just fewer than 300,000 (0.4%) were reported to be currently experiencing LC. Prevalence of both

ever and current LC were higher among older children. Among children currently experiencing LC, 80.0% had some limitation of activity compared with their pre-Covid habit.[92]

Estimating the true prevalence of LC in children and young people is challenging for several reasons:

- It is difficult to estimate prevalence accurately in studies: i) that assess only symptoms when many are not unique to LC; and ii) in which the controls are children who are defined as never having had an infection (even an asymptomatic infection). These limitations blur differences between cases and controls and make true differences harder to see;
- LC symptoms in children and young people are often misattributed to simple anxiety, so surveys such as the NHIS (cited above) that depend on parents or practitioners identifying LC as the cause for ill-health will also tend to underestimate prevalence;[93]
- Children and adolescents have a far lower prevalence of chronic disease than adults, so their functional reserve is much higher. As a result, LC biomarkers detected in research studies, such as endothelial dysfunction and persistently elevated blood pressure,[36] are less likely to cause medical events such as heart attack and stroke in the short term, compared with the same risks in older adults. The potential for accumulation of hidden pathology is particularly concerning given the number of reinfections (many perhaps undetected) to which children and young people are likely to be exposed during their lifetimes;
- Young children, in particular, move rapidly through developmental stages, so they may lack a stable pre-Covid baseline for comparison; further, core LC experiences such as 'brain fog' are likely to be difficult for young children to identify or describe. These factors are again likely to cause under-ascertainment of LC in these age groups, despite evidence that early life is a critical period for brain development and that infections and inflammation are well-established causes of neurodevelopmental disorders,[70 94 95] including high-quality evidence emerging for Covid-19.[96]

The observed high prevalence of LC in children and young people are serious enough to indicate an urgent need for action, including better treatment modalities and measures to reduce the number of Covid-19 infections that children experience. The probably very large number of unobserved cases creates additional urgency because of increasing evidence suggesting that the Covid-19 pandemic may have decades-long impacts for this generation.

Severity of initial infection

A clear relationship between severity of the initial acute infection and the subsequent risk of developing LC was established early in the pandemic, with evidence of a gradient of risk that increased with that severity across: not hospitalised, hospitalised, admitted to intensive care.[97] This relationship has persisted into the Omicron era,[60] including in studies of specific manifestations of LC. For instance, severity of the initial infection was associated with the greatest degree of cognitive deficit (which was also identified by elevated brain-injury markers) one year after Covid-19.[67] Several studies have

reported a higher risk of gastrointestinal disorders following acute infection with SARS-CoV-2,[98] including evidence of excess risk even among people who were not hospitalised during the acute phase of Covid-19. As earlier, these risks increased in a graded fashion across the severity spectrum of the acute phase of Covid-19.[99 100]

As noted above, overall prevalence of LC has declined from the Delta era to the Omicron era.[76] However, there is complicated knot of relationships around the severity of acute disease, primary infection, reinfection, and prevalence of LC:

- Reinfections are consistently reported to be less severe than primary infections, including when both infections involve Omicron;[75 101 102]
- Risk of LC is, however, related to repeated infection,[72 100 103] although somewhat less obviously in children and adolecents.[103]

Sex differences

A key sex difference is the higher risk of LC among women.[73 104 105] The NIH Researching Covid to Enhance Recovery (RECOVER)-Adult cohort consists of individuals across the US followed prospectively. Data were explored (29 October 2021 to 5 July 2024) to establish differences between the sexes among those who had a study visit six months or more after an initial SARS-CoV-2 infection.[106] Among >12,000 participants (73% female) who had been infected, female sex was associated with 31-44% (depending on the statistical model) higher risk of LC. This finding was consistent across all age groups except those 18-39 years, for which the female and male prevalence was similar.[106]

Other risk factors

There are good data on which other risk factors contribute to the likelihood of developing LC. The pattern appears consistent across recent studies. A UK study of >5000 healthcare workers reported that risk factors for LC included direct contact with Covid-19 patients, pre-existing respiratory illnesses, female sex, and older age.[105] A meta-analysis of >200 eligible studies and >13 million individuals identified female sex, older age, severe illness during the acute phase of Covid-19, multiple comorbidities, extended hospital stay, and a high body mass index.[104] An online study in China using 68,200 valid responses reported the presence of underlying diseases, female sex, alcohol consumption, smoking, and the severity of acute infection.[73]

Subtypes of LC

As noted above for children and adolescents,[90] it is also possible to identify several subclasses of LC among adults. For instance, data from >13,000 adults participating in the Researching Covid to Enhance Recovery (RECOVER-Adult) study allowed a recent update to a research index that classifies symptomatic LC into subtypes that differ in demographic features and quality of life.[107] Symptoms that contributed to the updated 2024 index included post-exertional malaise, fatigue, brain fog, dizziness, palpitations, change in smell/taste, thirst, chronic cough, chest pain, shortness of breath, and sleep apnoea. Five subtypes were identified:

- fatigue and postexertional malaise were prominent in all but subtype 1;
- additional prominent features included:
    - change in smell or taste (subtype 1);

    - chronic cough (subtype 2);
    - brain fog (subtype 3);
    - palpitations (subtype 4); and
    - postexertional soreness, dizziness, and gastrointestinal symptoms (subtype 5);
- participants with a high burden of multisystem symptoms (subtype 5) more frequently reported poorer quality of life, physical health, and daily function than those with the other subtypes.

Long Covid vs. Long Influenza

Finally, as has been noted, there are post-viral syndromes associated with infection and with many other viruses. What has made LC stand out is essentially that many more people have been infected over a short period, giving rise to a global cumulative incidence of perhaps 400 million people with LC. However, it is also possible that SARS-CoV-2 infections have a higher risk of causing long-term effects than other infections. This possibility can be assessed by comparing aspects of LC with the downstream consequences of another common infection, namely influenza. The US Department of Veterans Affairs study allowed such a comparison between longer-term outcomes following SARS-CoV-2 and seasonal influenza. More than 80,000 participants admitted to hospital for Covid-19 between March 1, 2020, and June 30, 2022, and almost 11,000 admitted for seasonal influenza between October 1, 2015, and February 28, 2019 were followed for up to 18 months to compare risks of death and other outcomes.[108] Compared to those with seasonal influenza, the Covid-19 group had an increased risk of death (hazard ratio [HR]:1.5). Those with Covid-19 had an increased risk of 68.1% (64 of 94) of a pre-specified set of health outcomes; seasonal influenza was associated with an increased risk of 6.4% (6 of 94) including three of four pre-specified pulmonary outcomes. Organ-systems data showed that Covid-19 was associated with a higher risk across all organ systems except pulmonary, which was higher among those with influenza. In both Covid-19 and seasonal influenza, there was a greater burden of health loss in the post-acute than the acute phase. Finally, Covid-19 had a higher burden of health loss across all organ systems (except pulmonary) than influenza. Hospital readmission and admission to intensive care were higher for the SARS-CoV-2 group. The researchers note that although rates of death and adverse health outcomes following hospital admission for seasonal influenza are high, hospital admission for Covid-19 was associated with higher long-term risks of death and adverse health outcomes in nearly every organ system.[108]

5. Duration of LC and prevalence

Duration of LC

Earlier data from the US Department of Veterans Affairs population (studying almost 140,000 infected and almost 6 million noninfected individuals followed for two years), showed that increased risk of post-Covid death was not statistically significantly elevated beyond six months after infection among those who were not hospitalised but remained statistically significantly elevated throughout the two years among hospitalised individuals.[109] Within the 80 prespecified sequelae, 69% and 35% of them became statistically non-significant at 2 years after infection among non-hospitalised and hospitalised individuals, respectively. Although risks of many sequelae declined

two years after infection, these findings showed that there is a substantial long-term cumulative burden of health loss due to LC.[109]

The US Department of Veterans Affairs researchers undertook a further follow-up of this cohort to establish the risks of LC at three years after the initial infection.[110] A cohort of >135,000 people with SARS-CoV-2 infection and >5.2 million controls were followed to estimate risks of death and LC. Among the non-hospitalised, the elevated risk of death was no longer present after the first year of infection and risk of incident LC declined over the 3 years but still contributed 9.6 disability-adjusted life years (DALYs) per 1,000 persons in the third year. Among the hospitalised, risk of death declined but remained statistically significantly elevated (incidence rate ratio: 1.29) in the third year. Risk of incident LC among the hospitalised declined over the three years, but substantial risk remained in the third year, accounting for 90.0 DALYs per 1,000 persons. Thus, elevated risks of death and LC decline over time, but the burden of LC remains in the third year among those who had been hospitalised.[110]

A cohort of 3663 participants with SARS-CoV-2 infection were followed from early in the pandemic (December 2020 to August 2022) to April 2024. They were classified according to vaccination status and LC status: 2604 (71.1%) never-had; 994 (27.1%) current; 65 (1.8%) resolved.[111] Compared to never having LC, those with current LC had poorer physical and mental health and a higher, statistically significant, likelihood of moderate-to-high stress (adjusted odds ratio [aOR]=2.0); moderate-to-high loneliness (aOR=1.6); moderate-to-severe fatigue (aOR=3.0); insufficient activity (aOR for Exercise Vital Sign ≤150 min/week=0.7); and worse dyspnoea (aOR=5.0). Central to the findings were that: i) the vast majority of those with LC did not resolve, with less than 2% having resolved over an observation period of 19-39 months; ii) those with resolved LC still had poorer physical and mental health than the never-had-LC group; and iii) the number of Covid-19 vaccinations was associated with better outcomes across all measures.[111]

Cumulative incidence and prevalence of LC

Cumulative incidence is a measure of new cases over a defined passage of time; with Covid-19, it is usually dated from the beginning of the pandemic. Prevalence is the number of cases at a particular point in time and is a function of both incidence of new cases and duration of illness.

Greenhalgh et al. note that estimates of the initial incidence of LC after acute SARS-CoV-2 infection range from 50–85% among those both unvaccinated and hospitalised, 10–35% among the unvaccinated who were not hospitalised, and 8–12% for people who had been vaccinated.[112]

CDC analysed US data on adults aged ≥18 years using the 2022 Behavioral Risk Factor Surveillance System (BRFSS) cross-sectional survey and reported that 6.4% of non-institutionalised adults had experienced LC.[113]

Based on a "conservative estimated incidence of 10%" of those initially infected with SARS-CoV-2 and more than 651 million documented Covid-19 cases globally, Davis et al suggested in 2023 that at least 65 million individuals around the world would have

LC, but acknowledged that this was likely to be a marked underestimate because of the large number of undocumented acute infections and LC cases.[114]

In some contrast and perhaps with a more realistic estimate of global incidence, in 2024, Al-Aly estimated the cumulative global incidence of LC at about 400 million (i.e. approximately 5% of the global population).[12]

A 2023 meta-analysis of 194 studies with 735,006 participants <18 years of age reported that at least 45% of Covid-19 survivors, regardless of hospitalisation status, experienced at least one unresolved symptom at four months post-infection.[115]

Using a random-effects model to pool prevalence of persistent symptoms and risk ratios comparing Covid-19 patients with non-Covid-19 individuals, across 211 eligible studies published from December 2019 to January 2023 and covering >13 million individuals (almost 3.5 million with a history of Covid-19 and almost 10 million unaffected controls), Luo et al concluded that fatigue, dyspnoea, post-traumatic stress disorder, anxiety, and depression were the most frequently reported LC symptoms, many of which continued to be highly prevalent even one year after the initial SARS-CoV-2 infection. The authors declined to provide an overall estimate of prevalence but noted that these five symptoms showed prevalences between 14.8% and 25.7% of individuals (see the paper's Appendix).[104]

What the wide range of these figures for cumulative incidence and prevalence shows is that we still do not have a reliable estimate of the prevalence of LC. The estimate of 5% (as proposed by Al-Aly) is very much a lower bound. This uncertainty is partly a consequence of the fact that population prevalence is, as noted above, a function of incidence (here, new LC cases) and duration of illness; therefore, individuals can both join the numerator of the prevalence estimate when they develop LC as well as exit that numerator if/when their LC resolves or they die. The uncertainty is also a consequence, again as noted above, of not having an accurate estimate of incidence (many unreported cases) and, finally, although we have a minimum duration in order to define LC, its maximum duration remains, necessarily, unspecified because we do not yet have the relevant data.

Several other important features of LC[116 117] add to the difficulty of understanding its impact and its real prevalence, notably LC:

- can follow SARS-CoV-2 infection at all levels of severity including asymptomatic and even unrecognised;
- can itself be of varying severity;
- can begin at the time of acute infection or be delayed for weeks or months;
- is not restricted by age group; health, disability, or socioeconomic status; sex; race/ethnic group; or geographic location;
- can resolve over a period of months or can persist for years; and
- can be diagnosed only on clinical grounds in routine primary or secondary healthcare settings because biomarkers remain available only within research studies or in highly specialised clinics (e.g., signatures of neurological,

mitochondrial, and immune dysfunction plus viral persistence); even in these settings, these biomarkers remain indicative not definitive.

6. Economic impact of LC

In 2024, Al-Aly estimated the cumulative global incidence of LC at about 400 million (i.e., approximately 5% of the global population), carrying an annual economic impact of approximately $1 trillion - about 1% of the global economy.[12]

A recent simulation model covering clinical course, health effects, and associated costs for a person with LC produced the following picture for the US:

- assuming symptoms last only 1 year, average total cost of an LC case would be US$5,084-$11,646 with >90% of these costs being loss of productivity;
- the current number of LC cases would cost:
    - US society at least US$2.0-$6.6 billion per year;
    - employers at least $2.0-$6.5 billion per year in productivity losses; and
    - third-party payers $21.0-$68.5 million per year;
- every 10-point increase in Covid incidence would result in an additional $365 million per year.

The authors concluded that the current health and economic burden of LC may already exceed that of a number of chronic diseases from other causes and "will continue to grow each year as there are more and more Covid-19 cases."[118]

If the assumptions underlying this model hold for Aotearoa New Zealand (NZ), the yearly cost to society would be NZ$55-$180 million. LC is conservatively costing the Australian economy approximately 0.5% of GDP in reduced productivity.[119] In NZ, a comparable GDP loss would amount to around NZ$2 billion per year.[120]

In one modelling exercise regarding future mortality from pathogens of epidemic and pandemic potential, Madhav et al correct the perception that an event having the mortality level of the Covid-19 pandemic can be considered a "once in a century" risk. They note that it should rather be thought of as having an annual probability of 2–3% and hence being a one in 33–50-year occurrence.[121]

Prevention of LC

7. Public Health and Social Measures

In the early stages of a pandemic, particularly if it is caused by a novel agent, the only available interventions are public health and social measures (PH&SM).[122] In the prevention of primary disease to reduce the risk of LC, they are still crucial. Such interventions begin with the individual and involve masking,[123] physical distancing, and choosing to avoid crowded places to slow spread.[124] Structural-level protections include ensuring better quality ventilation and air filtration, especially in healthcare settings and schools;[63 123 124] provision of high-quality respirator masks and requirement for their use in health settings; and paid sick leave. Sometimes there is a case for contact tracing and quarantine.[124] These measures have been shown to be sufficient to interrupt transmission of SARS-CoV-2 in multiple jurisdictions and to protect a sizeable proportion of the world's population from infection, particularly in the Asia Pacific region.[125] They were effective in high-income island jurisdictions such as Australia, New

Zealand, Taiwan, and Singapore; they were also effective in low- and middle-income countries with long land borders, such as Vietnam, Thailand, Laos, and Mongolia during the early stages of the pandemic. These actions were largely taken by individual jurisdictions, without either global or regional coordination.

Also central to protection are steps to protect others – particularly the social acceptance and wide employment of testing[126] and of self-isolation.[124] More recent work indicates the effectiveness and safety of using far-UV-C systems (i.e., using ultraviolet light with wavelengths between 200 and 230 nanometers), to remove airborne viruses in indoor settings.[127]

Central to everything, we need clear and succinct information/education and specific guarding against, and rebuttal of, mis- and dis-information.[26 128]

In the management of a pandemic, PH&SM is typically the key strategy that is the least dependent on access to high-cost resources and, thus, least plagued by inequities. Nonetheless, the effectiveness of PH&SM would be greatly enhanced if WHO provided strategic and operational support and international coordination for their use when appropriate. Such support would include documenting their role and providing guidance on the legal and practical aspects of effective implementation. One benefit of better coordinating these responses, particularly at a regional level, is the capacity to create 'green zones' where neighbouring countries have all eliminated the emerging pandemic, resulting in easing of travel restrictions among them.[129 130]

8. Vaccines

Protective effectiveness of vaccines

Consistent with observations earlier in the pandemic,[77 131] vaccinated individuals have been consistently shown to be at lower risk of LC after an acute SARS-CoV-2 infection in the Omicron era,[132-134] including children and adolescents,[135-137] and against specific manifestations of LC, including cardiac and thromboembolic disorders,[58] diabetes,[60 132] and impairment of mental health.[62 138] Covid vaccines have also been shown to be safe following *in utero* exposure.[48 139 140]

9. Antivirals

Protective effectiveness of antivirals targetting SARS-CoV-2

A retrospective cohort study of ~39,000 patients aged ≥18 years who tested positive for SARS-CoV-2 between March 11, 2022, and October 10, 2023, and who were admitted to hospital with Covid-19 was undertaken in Hong Kong.[141] Those treated with molnupiravir were excluded. Those prescribed nirmatrelvir-ritonavir (N-R) within five days of symptom onset (>15,000) patients and a control group with no exposure to N-R (>23,500) were compared. Outcomes were post-acute inpatient death and 13 sequelae, evaluated starting at 21 days after a positive diagnosis of SARS-CoV-2. They were followed for a median of 393 days. In the N-R group, compared with the control group, there was a statistically significantly lower risk of post-acute inpatient death, congestive heart failure, atrial fibrillation, coronary artery disease, chronic pulmonary disease, acute respiratory distress syndrome, interstitial lung disease, and end-stage

renal disease. N-R treatment of acute Covid-19 of patients admitted to hospital reduced the risk of early death and of LC cardiovascular and respiratory disorders.[141]

The PANORAMIC trial was a UK multicentre, primary care, open-label, multi-arm, prospective randomised controlled trial of participants aged ≥ 50 years (or ≥18 years with a comorbidity) and ill for five days or fewer with confirmed Covid-19 in the community. Participants were randomly assigned to the usual care (~13,000) vs. molnupiravir (800 mg twice a day for five days) plus usual care (~13,000). Molnupiravir reduced time to recovery in acute Covid-19 over 28 days.[142] However, although the decrease in initial viral load was faster with molnupiravir vs. usual care, five days of the antiviral failed to clear the virus in some cases, resulting in substantial viral mutation and greater persistence at day 14, as well as blunting the boost to anti-SARS-CoV-2 spike antibody concentrations usually associated with acute infection.[143] The primary outcome of the initial trial was hospitalisation or death at 28 days;[142] all longer term outcomes were considered secondary. Long-term follow-up data were available for >23,000 (89·2%). Almost 23,000 (99·1%) had at least one previous dose of a SARS-CoV-2 vaccine. Any severe or persistent symptoms (three months: adjusted risk difference –2·1%) were reduced in severity, and health-related quality of life was better, in the molnupiravir arm at three months and six months. Ratings of wellness, experiencing severe symptoms, and healthcare use were superior among those with molnupiravir treatment. There were statistically significant differences in persistence of any symptom at six months and reported time off work. There were no differences in hospitalisations at long-term follow-up. The absolute differences in this open-label study were small.

A meta-analysis covering a broader period (14 papers) across the pandemic concluded that antiviral treatment had an overall protective efficacy against LC of 61% (meaning risk was reduced by 39%);[144] in contrast, corticosteroid and monoclonal-antibody treatments did not show efficacy. Subgroup analysis revealed that antivirals provided stronger protection among older people, males, unvaccinated individuals, and people without diabetes. Antivirals reduced 8 of the 22 analysed LC symptoms.

Protective effectiveness of Metformin

Metformin has been shown to have antiviral activity against RNA viruses including SARS-CoV-2, probably by suppressing protein translation via targeting the host mTOR pathway.[145] In a randomised trial of treatment of outpatient Covid-19, metformin (in addition to reducing emergency department visits, hospitalisations, and death) reduced the odds of LC through 10 months by 42%.[146]

A retrospective cohort analysis using databases of both the National Covid Cohort Collaborative (N3C) and Patient-Centered Clinical Research Network (PCORnet) electronic health records examined metformin-exposed individuals versus those taking other diabetes medications. After six months, risk of death or LC was statistically significantly lower by 15-21% among N3C participants who were taking metformin but not statistically different among individuals included in the PCORnet data.[147]

Weakly confirmatory evidence comes from another study of >5500 people with diabetes, showing that those who were prevalent users of metformin compared with other diabetes medications, had a 20% (not statistically significant) lower risk of LC.[148]

C. Treatment and management of LC

10. Diagnosis

At the present time, the capacity to diagnose LC in routine primary and secondary care settings is largely restricted to clinical presentation. Diagnostic suspicion is raised by the appearance of specific symptoms, particularly fatigue, impaired cognition, and breathlessness but, as noted in the main text, essentially every system can be affected: cardiovascular,[38 57 149] musculo-skeletal,[150] nervous,[23 55 62 151-154] immune,[11 35 155-157] gastrointestinal,[19 98 99 158] endocrine[60 84 159-161], renal,[162] and reproductive systems.[163] In the face of the widespread pathology (as discussed above and previously[63], there is a steadily growing catalogue of imaging, cellular, and tissue data) and in the absence of definitive diagnostic tests or biomarkers, definitions and attempts at clinical models are continuing to evolve.[164 165] As noted above, there appear to be identifiable phenotypic subsets of LC among both adults[107] and children,[90] but these are not associated with specific approaches to disease management.

At a practical level, what is urgently needed in NZ are specialised LC clinics including a focus on children.

11. Treatment and management

There is much that can be learned from the treatment and management of ME/CFS as LC is either essentially the same cluster of chronic manifestations or a cousin with closely overlapping characteristics.[32 166-168]

SARS-CoV-2 is capable of widespread persistence with autopsy and tissue-biopsy studies showing SARS-CoV-2 RNA and protein across body sites weeks or months after acute Covid-19.[169 170] Hence, one particular target to manage or even cure LC might be to find ways to target the virus itself.[171]

At present, symptomatic treatment/management is the best that current medical practice has to offer; definitive treatment is somewhere in the future. However, to reiterate, there is an urgent need for well conducted, well informed clinical services at primary and secondary level. Many quite basic questions are still being actively debated, such as the place of exercise after LC.[172]

D. Surveillance, research, coordination, policy, communication

12. Establishing comprehensive layered surveillance

One of the achievements of the International Health Regulations (IHR) was that it provided a high-level plan for a global health-surveillance system for emerging infectious diseases that have the potential to become a Public Health Emergency of International Concern (PHEIC).[173] This international law was prescriptive in some areas of surveillance, even at the level of member states; these key functional requirements have yet to be met. Because LC is necessarily downstream of acute Covid infection, it

is relevant that jurisdictions, including Aotearoa NZ, now have a wide array of infectious-disease surveillance methods from which to choose:

- Reports to a central registry, which have been in use since the 17th century[174] (*e.g.:* https://www.cdc.gov/nndss/index.html);
- Sentinel systems, which usually involve a representative subset of the population of interest, have been used to monitor pandemic,[175-178] epidemic,[179-181] endemic,[182 183] sexually transmitted,[184 185] and food-borne[186] diseases in low-, middle, and high-income countries. They have also been used to monitor vaccine effectiveness in more-or-less real time;[187]
- Waste-water monitoring for virus,[188-192] which can be established as a sustainable and equitable nationwide surveillance system;[193]
- Genomic surveillance,[194-197] which can be used to augment sentinel systems and waste-water testing by monitoring the prevalence of organisms of interest (including identifying bacteriophages associated with specific infectious organisms;[198 199]) and, as with SARS-CoV-2, establishing the emergence, prevalence, behaviour, and impact of variants;[200-210]
- Social-media monitoring as an early warning of the spread of queries regarding specific symptoms and other relevant internet activity.[211-216]

We do not yet have data that point to: i) which combinations of these systems would provide optimal surveillance based on well established criteria,[217] sufficient redundancy, or the most cost-effective layered surveillance system; ii) if or how these systems should be selected in relation to the organism and disease under surveillance; iii) how surveillance systems might vary by level of economic and infrastructure development. Accordingly, there is an urgent need to undertake the relevant research to augment the WHO surveillance handbook, recently updated.[218]

The Covid-19 pandemic has produced highly responsive, accessible, essentially real-time reporting of cases, mortality, and vaccination uptake in many countries and coordinated global reporting; for example, the WHO Coronavirus (Covid-19) dashboard and Our World in Data. Despite the increasing sophistication of such reporting systems over time,[219] which accelerated during the Covid-19 pandemic, retrospective exploration of data shows that earlier notification could have been made of the Covid-19 pandemic.[215 220] Further, the real burden of mortality associated with infection with SARS-CoV-2 has been substantially underestimated[221-223] and this excess burden is inequitably shared;[2] see also other literature.[224-227] Additionally, some important descriptive data such as race/ethnicity are poorly recorded.[228 229]

Specifically considering surveillance of LC, it is worth noting that there are systems in place elsewhere. For instance, the UK has a routine Covid surveillance, which includes questions on the proportion of individuals with, and living in households with, LC by time from the initial acute infection. The US CDC currently still reports that it is monitoring Long Covid; more details here.[230] Data on LC are also gathered across OECD countries.[231]

Aotearoa NZ has some relevant capacity in place for Covid-19 surveillance, e.g., routine waste-water testing but no surveillance of LC. At the very least, we need substantive

surveillance drawing on experience with high quality systems used internationally. Aotearoa NZ has an LC registry[232] that invites voluntary registration by those affected. Expanding this system to match something like the sophistication and reporting requirements of our cancer registry could be considered.

13. Research

There is a crucial need to develop an LC research strategy that can be coordinated with the rest of the world and bringing to bear relevant resources that allow the investigation of questions specific to NZ.[12] Included in this scope is a need for research on LC management, particularly clinical trials, again taking advantage of opportunities to collaborate internationally.

14. Coordination, policy, communication

The NZ Royal Commission of Inquiry into *Covid-19: Lessons Learned* is an assessment of the way in which the acute early stages of the pandemic were handled in Aotearoa NZ. It has important implications for future government policy regarding the prevention and management of pandemics, which, in turn, have important implications for the prevention of LC (or its future relatives), particularly the need:[233]

- to stop the spread of misinformation …;
- to stockpile or manufacture personal protective equipment and testing kits locally to improve future pandemic preparedness;
- for a future pandemic plan, including lessons from other countries;
- for increased funding and resourcing of the health system;
- for more research and science funding to help prepare for future pandemics.

More specifically, there was a brief reference (p110) to the need for "support for those suffering from long-term health impacts from Covid-19, especially people with Long Covid, and that more should be done to raise awareness of the condition".[233]

In useful contrast, the comparable Australian inquiry report focused considerable attention on LC itself,[234] expending several pages defining and describing the disorder (pp260-263). That report also noted the lack of relevant data and preparedness: "There remain large gaps in our knowledge about long Covid, and about vaccine effectiveness in preventing long Covid. Identifying control groups early in the pandemic would have helped to address potential evidence gaps in advance. Established data linkages would have allowed for early monitoring and analysis of long Covid and supported the translation of evidence into clear public health messaging," a conclusion that applies essentially without modification to the need in Aotearoa NZ.

Throughout, the Australian report reiterated the recommendation (Action 25) that there is a need "to invest in monitoring and evaluating the long-term impacts of Covid-19, including long Covid …".[234]

A recent Nature Editorial reminded us not to forget or distort the lessons of the Covid pandemic, concluding, "Public-health authorities must learn how to better communicate uncertainty to both policymakers and the public, so that changes in guidance during the next pandemic do not give rise to distrust. But, ultimately, the first

step is to hold on to the urgency of 2020. Do not let history be forgotten — or worse, rewritten."[235]

References

1. Scholey J, Aburto JM, Kashnitsky I, et al. Life expectancy changes since COVID-19. *Nat Hum Behav* 2022;6(12):1649-59. doi: 10.1038/s41562-022-01450-3 [published Online First: 20221017]
2. Stokes AC, Lundberg DJ, Elo IT, et al. COVID-19 and excess mortality in the United States: A county-level analysis. *PLoS Med* 2021;18(5):e1003571. doi: 10.1371/journal.pmed.1003571 [published Online First: 20210520]
3. Iwashyna TJ, Seelye S, Berkowitz TS, et al. Late Mortality After COVID-19 Infection Among US Veterans vs Risk-Matched Comparators: A 2-Year Cohort Analysis. *JAMA Intern Med* 2023;183(10):1111-19. doi: 10.1001/jamainternmed.2023.3587 [published Online First: 20230821]
4. Bilinski A, Emanuel EJ. COVID-19 and Excess All-Cause Mortality in the US and 18 Comparison Countries. *JAMA* 2020;324(20):2100-02. doi: 10.1001/jama.2020.20717 [published Online First: 2020/10/13]
5. Han L, Zhao S, Li S, et al. Excess cardiovascular mortality across multiple COVID-19 waves in the United States from March 2020 to March 2022. *Nat Cardiovasc Res* 2023;2(3):322-33. doi: 10.1038/s44161-023-00220-2 [published Online First: 20230227]
6. Østergaard L. SARS CoV-2 related microvascular damage and symptoms during and after COVID-19: Consequences of capillary transit-time changes, tissue hypoxia and inflammation. *Physiol Rep* 2021;9(3):e14726. doi: 10.14814/phy2.14726
7. Wu X, Xiang M, Jing H, et al. Damage to endothelial barriers and its contribution to long COVID. *Angiogenesis* 2024;27(1):5-22. doi: 10.1007/s10456-023-09878-5 [published Online First: 20230427]
8. Yonts AB. Pediatric Long-COVID: A Review of the Definition, Epidemiology, Presentation, and Pathophysiology. *Pediatr Ann* 2022;51(11):e416-e20. doi: 10.3928/19382359-20220913-06 [published Online First: 20221101]
9. Menezes SM, Jamoulle M, Carletto MP, et al. Blood transcriptomics reveal persistent SARS-CoV-2 RNA and candidate biomarkers in Long COVID patients. *medRxiv* 2024:2024.01.14.24301293. doi: 10.1101/2024.01.14.24301293
10. Zuo W, He D, Liang C, et al. The persistence of SARS-CoV-2 in tissues and its association with long COVID symptoms: a cross-sectional cohort study in China. *Lancet Infect Dis* 2024;24(8):845-55. doi: 10.1016/S1473-3099(24)00171-3 [published Online First: 20240422]
11. Peluso MJ, Ryder D, Flavell RR, et al. Tissue-based T cell activation and viral RNA persist for up to 2 years after SARS-CoV-2 infection. *Sci Transl Med* 2024;16(754):eadk3295. doi: 10.1126/scitranslmed.adk3295 [published Online First: 20240703]
12. Al-Aly Z, Davis H, McCorkell L, et al. Long COVID science, research and policy. *Nat Med* 2024;30(8):2148-64. doi: 10.1038/s41591-024-03173-6 [published Online First: 20240809]

13. Zhang Y, Bharathi V, Dokoshi T, et al. Viral afterlife: SARS-CoV-2 as a reservoir of immunomimetic peptides that reassemble into proinflammatory supramolecular complexes. *Proc Natl Acad Sci U S A* 2024;121(6):e2300644120. doi: 10.1073/pnas.2300644120 [published Online First: 20240202]
14. Chen B, Julg B, Mohandas S, et al. Viral persistence, reactivation, and mechanisms of long COVID. *Elife* 2023;12:e86015. doi: 10.7554/eLife.86015 [published Online First: 20230504]
15. Heo YW, Jeon JJ, Ha MC, et al. Long-Term Risk of Autoimmune and Autoinflammatory Connective Tissue Disorders Following COVID-19. *JAMA Dermatol* 2024;160(12):1278-87. doi: 10.1001/jamadermatol.2024.4233
16. Wang PY, Ma J, Kim YC, et al. WASF3 disrupts mitochondrial respiration and may mediate exercise intolerance in myalgic encephalomyelitis/chronic fatigue syndrome. *Proc Natl Acad Sci U S A* 2023;120(34):e2302738120. doi: 10.1073/pnas.2302738120 [published Online First: 20230814]
17. Marshall-Gradisnik S, Eaton-Fitch N. Understanding myalgic encephalomyelitis. *Science* 2022;377(6611):1150-51. doi: 10.1126/science.abo1261 [published Online First: 20220908]
18. Vernon SD, Zheng T, Do H, et al. Incidence and Prevalence of Post-COVID-19 Myalgic Encephalomyelitis: A Report from the Observational RECOVER-Adult Study. *J Gen Intern Med* 2025 doi: 10.1007/s11606-024-09290-9 [published Online First: 20250113]
19. Su Q, Lau RI, Liu Q, et al. Post-acute COVID-19 syndrome and gut dysbiosis linger beyond 1 year after SARS-CoV-2 clearance. *Gut* 2023;72(6):1230-32. doi: 10.1136/gutjnl-2022-328319 [published Online First: 20220808]
20. Zhang D, Zhou Y, Ma Y, et al. Gut Microbiota Dysbiosis Correlates With Long COVID-19 at One-Year After Discharge. *J Korean Med Sci* 2023;38(15):e120. doi: 10.3346/jkms.2023.38.e120 [published Online First: 20230417]
21. Zhang J, Zhang Y, Xia Y, et al. Microbiome and intestinal pathophysiology in post-acute sequelae of COVID-19. *Genes Dis* 2023;11(3):100978. doi: 10.1016/j.gendis.2023.03.034 [published Online First: 20230619]
22. Braga J, Lepra M, Kish SJ, et al. Neuroinflammation After COVID-19 With Persistent Depressive and Cognitive Symptoms. *JAMA Psychiatry* 2023;80(8):787-95. doi: 10.1001/jamapsychiatry.2023.1321 [published Online First: 20230531]
23. Greene C, Connolly R, Brennan D, et al. Blood-brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment. *Nat Neurosci* 2024;27(3):421-32. doi: 10.1038/s41593-024-01576-9 [published Online First: 20240222]
24. VanElzakker MB, Bues HF, Brusaferri L, et al. Neuroinflammation in post-acute sequelae of COVID-19 (PASC) as assessed by [(11)C]PBR28 PET correlates with vascular disease measures. *Brain Behav Immun* 2024;119:713-23. doi: 10.1016/j.bbi.2024.04.015 [published Online First: 20240418]
25. McNeill R, Marshall R, Fernando SA, et al. COVID-19 may Enduringly Impact cognitive performance and brain haemodynamics in undergraduate students. *Brain Behav Immun* 2024;125:58-67. doi: 10.1016/j.bbi.2024.12.002 [published Online First: 20241219]
26. Kavanagh KT, Cormier LE, Pontus C, et al. Long COVID's Impact on Patients, Workers, & Society: A review. *Medicine* 2024;103(12)

27. Trender W, Hellyer PJ, Killingley B, et al. Changes in memory and cognition during the SARS-CoV-2 human challenge study. *EClinicalMedicine* 2024;76:102842. doi: 10.1016/j.eclinm.2024.102842 [published Online First: 20240921]
28. Rothstein TL. Cortical Grey matter volume depletion links to neurological sequelae in post COVID-19 "long haulers". *BMC Neurol* 2023;23(1):22. doi: 10.1186/s12883-023-03049-1 [published Online First: 20230117]
29. Crunfli F, Carregari VC, Veras FP, et al. Morphological, cellular, and molecular basis of brain infection in COVID-19 patients. *Proc Natl Acad Sci U S A* 2022;119(35):e2200960119. doi: 10.1073/pnas.2200960119 [published Online First: 20220811]
30. Blair RJ. The roles of orbital frontal cortex in the modulation of antisocial behavior. *Brain Cogn* 2004;55(1):198-208. doi: 10.1016/S0278-2626(03)00276-8
31. Dacosta-Aguayo R, Toran-Monserrat P, Carmona-Cervello M, et al. Multimodal neuroimaging in Long-COVID and its correlates with cognition 1.8 years after SARS-CoV-2 infection: a cross-sectional study of the Alianca ProHEpiC-19 Cognitiu. *Front Neurol* 2024;15:1426881. doi: 10.3389/fneur.2024.1426881 [published Online First: 20240913]
32. Thapaliya K, Marshall-Gradisnik S, Eaton-Fitch N, et al. Hippocampal subfield volume alterations and associations with severity measures in long COVID and ME/CFS: A 7T MRI study. *PLoS One* 2025;20(1):e0316625. doi: 10.1371/journal.pone.0316625 [published Online First: 20250113]
33. Rua C, Raman B, Rodgers CT, et al. Quantitative susceptibility mapping at 7 T in COVID-19: brainstem effects and outcome associations. *Brain* 2024;147(12):4121-30. doi: 10.1093/brain/awae215
34. Rong Z, Mai H, Ebert G, et al. Persistence of spike protein at the skull-meninges-brain axis may contribute to the neurological sequelae of COVID-19. *Cell Host Microbe* 2024;32(12):2112-30 e10. doi: 10.1016/j.chom.2024.11.007 [published Online First: 20241129]
35. Cervia-Hasler C, Bruningk SC, Hoch T, et al. Persistent complement dysregulation with signs of thromboinflammation in active Long Covid. *Science* 2024;383(6680):eadg7942. doi: 10.1126/science.adg7942 [published Online First: 20240119]
36. Peng J, Guo W, Li P, et al. Long-term effects of COVID-19 on endothelial function, arterial stiffness, and blood pressure in college students: a pre-post-controlled study. *BMC Infect Dis* 2024;24(1):742. doi: 10.1186/s12879-024-09646-w [published Online First: 20240727]
37. Thomas D, Noishiki C, Gaddam S, et al. CCL2-mediated endothelial injury drives cardiac dysfunction in long COVID. *Nat Cardiovasc Res* 2024;3(10):1249-65. doi: 10.1038/s44161-024-00543-8 [published Online First: 20241014]
38. Battistoni A, Volpe M, Morisco C, et al. Persistent increase of cardiovascular and cerebrovascular events in COVID-19 patients: a 3-year population-based analysis. *Cardiovasc Res* 2024;120(6):623-29. doi: 10.1093/cvr/cvae049
39. Kole C, Stefanou E, Karvelas N, et al. Acute and Post-Acute COVID-19 Cardiovascular Complications: A Comprehensive Review. *Cardiovasc Drugs Ther* 2024;38(5):1017-32. doi: 10.1007/s10557-023-07465-w [published Online First: 20230520]

40. Duan L, Yin H, Liu J, et al. Maternal COVID-19 infection associated with offspring neurodevelopmental disorders. *Mol Psychiatry* 2024 doi: 10.1038/s41380-024-02822-z [published Online First: 20241109]
41. Veloso AHN, Barbosa AM, Ribeiro MFM, et al. Neurodevelopment in the first year of children exposed to SARS-CoV-2 during intrauterine period: systematic review. *Rev Gaucha Enferm* 2024;45:e20240020. doi: 10.1590/1983-1447.2024.20240020.en [published Online First: 20241125]
42. Hill RA, Gibbons A, Suwakulsiri W, et al. Investigating the impact of severe maternal SARS-CoV-2 infection on infant DNA methylation and neurodevelopment. *Mol Psychiatry* 2024 doi: 10.1038/s41380-024-02808-x [published Online First: 20241030]
43. Fajardo-Martinez V, Ferreira F, Fuller T, et al. Neurodevelopmental delay in children exposed to maternal SARS-CoV-2 in-utero. *Sci Rep* 2024;14(1):11851. doi: 10.1038/s41598-024-61918-2 [published Online First: 20240524]
44. Khalil A, Painter I, Souter V. Congenital heart defects during COVID-19 pandemic. *Ultrasound Obstet Gynecol* 2024;n/a(n/a) doi: 10.1002/uog.29126 [published Online First: 20241114]
45. Auger N, Arbour L, Lewin A, et al. Congenital anomalies during Covid-19: artifact of surveillance or a real TORCH? *Eur J Epidemiol* 2024;39(6):613-21. doi: 10.1007/s10654-024-01122-8 [published Online First: 20240409]
46. Hernandez-Diaz S, Smith LH, Wyszynski DF, et al. First trimester COVID-19 and the risk of major congenital malformations-International Registry of Coronavirus Exposure in Pregnancy. *Birth Defects Res* 2022;114(15):906-14. doi: 10.1002/bdr2.2070 [published Online First: 20220805]
47. Calvert C, Carruthers J, Denny C, et al. A population-based matched cohort study of major congenital anomalies following COVID-19 vaccination and SARS-CoV-2 infection. *Nat Commun* 2023;14(1):107. doi: 10.1038/s41467-022-35771-8 [published Online First: 20230106]
48. Magnus MC, Soderling J, Ortqvist AK, et al. Covid-19 infection and vaccination during first trimester and risk of congenital anomalies: Nordic registry based study. *BMJ* 2024;386:e079364. doi: 10.1136/bmj-2024-079364 [published Online First: 20240717]
49. Redelmeier DA, Wang J, Thiruchelvam D. COVID Vaccine Hesitancy and Risk of a Traffic Crash. *Am J Med* 2023;136(2):153-62 e5. doi: 10.1016/j.amjmed.2022.11.002 [published Online First: 20221202]
50. AAA Foundation for Traffic Safety. Traffic Safety Impact of the COVID-19 Pandemic: Fatal Crashes in 2020–2022. *Driver Behavior and Performance* 2024 Jul 2024. https://content.presspage.com/uploads/2983/6f7c6f70-f7e5-475f-a7c0-5e1963d3c91e/ftsresearchbrief-covidtrafficsafety0724final.pdf?10000 (accessed Feb 3 2025).
51. Anon. In the time of COVID-19, how fit to fly are you? *Vector* 2022; (Spring 2022). https://aviation.govt.nz/assets/publications/vector/vector-2022-3-spring-web.pdf.
52. Bullock GS, Emery CA, Nelson VR, et al. Higher rates of concussion following COVID-19 infection in high school athletes. *Br J Sports Med* 2023;57(10):590-94. doi: 10.1136/bjsports-2022-106436 [published Online First: 20230208]

53. Perlis RH, Lunz Trujillo K, Safarpour A, et al. Association of Post-COVID-19 Condition Symptoms and Employment Status. *JAMA Netw Open* 2023;6(2):e2256152. doi: 10.1001/jamanetworkopen.2022.56152 [published Online First: 20230201]
54. Bach K. New data shows long Covid is keeping as many as 4 million people out of work. 2022 August 24, 2022. https://www.brookings.edu/articles/new-data-shows-long-covid-is-keeping-as-many-as-4-million-people-out-of-work/ (accessed 2 Jan 2025).
55. Zhao S, Martin EM, Reuken PA, et al. Long COVID is associated with severe cognitive slowing: a multicentre cross-sectional study. *EClinicalMedicine* 2024;68:102434. doi: 10.1016/j.eclinm.2024.102434 [published Online First: 20240125]
56. DePace NL, Colombo J. Long-COVID Syndrome and the Cardiovascular System: A Review of Neurocardiologic Effects on Multiple Systems. *Curr Cardiol Rep* 2022;24(11):1711-26. doi: 10.1007/s11886-022-01786-2 [published Online First: 20220930]
57. Xie Y, Xu E, Bowe B, et al. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022;28(3):583-90. doi: 10.1038/s41591-022-01689-3 [published Online First: 20220207]
58. Mercade-Besora N, Li X, Kolde R, et al. The role of COVID-19 vaccines in preventing post-COVID-19 thromboembolic and cardiovascular complications. *Heart* 2024;110(9):635-43. doi: 10.1136/heartjnl-2023-323483 [published Online First: 20240415]
59. Lee DH, Kim HY, Park JY, et al. New-Onset Type 1 and Type 2 Diabetes Among Korean Youths During the COVID-19 Pandemic. *JAMA Pediatr* 2025;179(2):155-62. doi: 10.1001/jamapediatrics.2024.5068
60. Taylor K, Eastwood S, Walker V, et al. Incidence of diabetes after SARS-CoV-2 infection in England and the implications of COVID-19 vaccination: a retrospective cohort study of 16 million people. *Lancet Diabetes Endocrinol* 2024;12(8):558-68. doi: 10.1016/S2213-8587(24)00159-1
61. Hu WT, Kaluzova M, Dawson A, et al. Clinical and CSF single-cell profiling of post-COVID-19 cognitive impairment. *Cell Rep Med* 2024;5(5):101561. doi: 10.1016/j.xcrm.2024.101561 [published Online First: 20240513]
62. Walker VM, Patalay P, Cuitun Coronado JI, et al. COVID-19 and Mental Illnesses in Vaccinated and Unvaccinated People. *JAMA Psychiatry* 2024;81(11):1071-80. doi: 10.1001/jamapsychiatry.2024.2339
63. Kvalsvig A, Brooks AES, Potter JD, et al. Long Covid in Aotearoa NZ: Risk assessment and preventive action urgently needed. *Public Health Expert Briefing* 2024 26 Mar 2024. https://www.phcc.org.nz/briefing/long-covid-aotearoa-nz-risk-assessment-and-preventive-action-urgently-needed (accessed 26 Mar 2024).
64. Ruf W. Immune damage in Long Covid. *Science* 2024;383(6680):262-63. doi: 10.1126/science.adn1077 [published Online First: 20240118]
65. Machkovech HM, Hahn AM, Garonzik Wang J, et al. Persistent SARS-CoV-2 infection: significance and implications. *Lancet Infect Dis* 2024;24(7):e453-e62. doi: 10.1016/S1473-3099(23)00815-0 [published Online First: 20240207]
66. Burkard T, López-Güell K, Català M, et al. The risks of autoimmune- and inflammatory post-acute COVID-19 conditions: a network cohort study in six

European countries, the US, and Korea. *medRxiv* 2024:2024.05.15.24307344. doi: 10.1101/2024.05.15.24307344
67. Wood GK, Sargent BF, Ahmad ZU, et al. Posthospitalization COVID-19 cognitive deficits at 1 year are global and associated with elevated brain injury markers and gray matter volume reduction. *Nat Med* 2025;31(1):245-57. doi: 10.1038/s41591-024-03309-8 [published Online First: 20240923]
68. Zhao Y, Liang Q, Jiang Z, et al. Brain abnormalities in survivors of COVID-19 after 2-year recovery: a functional MRI study. *Lancet Reg Health West Pac* 2024;47:101086. doi: 10.1016/j.lanwpc.2024.101086 [published Online First: 20240509]
69. Nasir SM, Yahya N, Yap KH, et al. Executive function deficit in patients with long COVID syndrome: A systematic review. *Heliyon* 2025;11(3):e41987. doi: 10.1016/j.heliyon.2025.e41987 [published Online First: 20250120]
70. Green HF, Nolan YM. Inflammation and the developing brain: consequences for hippocampal neurogenesis and behavior. *Neurosci Biobehav Rev* 2014;40:20-34. doi: 10.1016/j.neubiorev.2014.01.004 [published Online First: 20140121]
71. Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nat Med* 2022;28(11):2398-405. doi: 10.1038/s41591-022-02051-3 [published Online First: 20221110]
72. Babalola TK, Clouston SAP, Sekendiz Z, et al. SARS-COV-2 re-infection and incidence of post-acute sequelae of COVID-19 (PASC) among essential workers in New York: a retrospective cohort study. *Lancet Reg Health Am* 2025;42:100984. doi: 10.1016/j.lana.2024.100984 [published Online First: 20250108]
73. Qin S, Zhang Y, Li Y, et al. Long COVID facts and findings: a large-scale online survey in 74,075 Chinese participants. *Lancet Reg Health West Pac* 2024;52:101218. doi: 10.1016/j.lanwpc.2024.101218 [published Online First: 20241011]
74. Al-Aly Z. Long Covid is a significant health crisis in China too. *Lancet Reg Health West Pac* 2024;52:101223. doi: 10.1016/j.lanwpc.2024.101223 [published Online First: 20241014]
75. Chemaitelly H, Ayoub HH, Coyle P, et al. Differential protection against SARS-CoV-2 reinfection pre- and post-Omicron. *Nature* 2025 doi: 10.1038/s41586-024-08511-9 [published Online First: 20250205]
76. de Bruijn S, Tulen AD, Rodenburg J, et al. Post-acute sequelae of COVID-19 3 to 12 months after infection: Delta vs Omicron. *Int J Infect Dis* 2025;150:107302. doi: 10.1016/j.ijid.2024.107302 [published Online First: 20241115]
77. Xie Y, Choi T, Al-Aly Z. Postacute Sequelae of SARS-CoV-2 Infection in the Pre-Delta, Delta, and Omicron Eras. *N Engl J Med* 2024;391(6):515-25. doi: 10.1056/NEJMoa2403211 [published Online First: 20240717]
78. Hernandez-Aceituno A, Garcia-Hernandez A, Larumbe-Zabala E. COVID-19 long-term sequelae: Omicron versus Alpha and Delta variants. *Infect Dis Now* 2023;53(5):104688. doi: 10.1016/j.idnow.2023.104688 [published Online First: 20230228]
79. Vahratian A, Adjaye-Gbewonyo D, Lin JS, et al. Long COVID in Children: United States, 2022. *NCHS Data Brief* 2023(479):1-6.

80. Dun-Dery F, Xie J, Winston K, et al. Post-COVID-19 Condition in Children 6 and 12 Months After Infection. *JAMA Netw Open* 2023;6(12):e2349613. doi: 10.1001/jamanetworkopen.2023.49613 [published Online First: 20231201]
81. Morello R, Mariani F, Mastrantoni L, et al. Risk factors for post-COVID-19 condition (Long Covid) in children: a prospective cohort study. *EClinicalMedicine* 2023;59(22):101961. doi: 10.1016/j.eclinm.2023.101961 [published Online First: 20230414]
82. Lopez-Leon S, Wegman-Ostrosky T, Ayuzo Del Valle NC, et al. Long-COVID in children and adolescents: a systematic review and meta-analyses. *Sci Rep* 2022;12(1):9950. doi: 10.1038/s41598-022-13495-5 [published Online First: 20220623]
83. Sansone F, Pellegrino GM, Caronni A, et al. Long COVID in Children: A Multidisciplinary Review. *Diagnostics* 2023; 13(12).
84. Weiss A, Donnachie E, Beyerlein A, et al. Type 1 Diabetes Incidence and Risk in Children With a Diagnosis of COVID-19. *JAMA* 2023;329(23):2089-91. doi: 10.1001/jama.2023.8674 [published Online First: 20230522]
85. D'Souza D, Empringham J, Pechlivanoglou P, et al. Incidence of Diabetes in Children and Adolescents During the COVID-19 Pandemic: A Systematic Review and Meta-Analysis. *JAMA Netw Open* 2023;6(6):e2321281. doi: 10.1001/jamanetworkopen.2023.21281 [published Online First: 20230601]
86. Di Gennaro L, Valentini P, Sorrentino S, et al. Extended coagulation profile of children with Long Covid: a prospective study. *Sci Rep* 2022;12(1):18392. doi: 10.1038/s41598-022-23168-y [published Online First: 20221101]
87. Mat Hassan N, Salim HS, Amaran S, et al. Prevalence of mental health problems among children with long COVID: A systematic review and meta-analysis. *PLoS One* 2023;18(5):e0282538. doi: 10.1371/journal.pone.0282538 [published Online First: 20230517]
88. Pinto Pereira SM, Nugawela MD, Rojas NK, et al. Post-COVID-19 condition at 6 months and COVID-19 vaccination in non-hospitalised children and young people. *Arch Dis Child* 2023;108(4):289-95. doi: 10.1136/archdischild-2022-324656 [published Online First: 20230104]
89. Pinto Pereira SM, Nugawela MD, Stephenson T, et al. Post-Covid-19 condition (Long Covid) in children and young people 12 months after infection or reinfection with the Omicron variant: a prospective observational study. *Sci Rep* 2024;14(1):9957. doi: 10.1038/s41598-024-60372-4 [published Online First: 20240430]
90. Gross RS, Thaweethai T, Kleinman LC, et al. Characterizing Long COVID in Children and Adolescents. *JAMA* 2024;332(14):1174-88. doi: 10.1001/jama.2024.12747 [published Online First: 20240821]
91. Rao S, Gross RS, Mohandas S, et al. Postacute Sequelae of SARS-CoV-2 in Children. *Pediatrics* 2024;153(3):e2023062570. doi: 10.1542/peds.2023-062570
92. Ford ND, Vahratian A, Pratt CQ, et al. Long COVID Prevalence and Associated Activity Limitation in US Children. *JAMA Pediatr* 2025 doi: 10.1001/jamapediatrics.2024.6206 [published Online First: 20250203]
93. Simpson F, Chew-Graham C, Lokugamage A. Long COVID in children: the perspectives of parents and children need to be heard. *Br J Gen Pract*

2021;71(706):216. doi: 10.3399/bjgp21X715769 [published Online First: 20210429]
94. Al-Haddad BJS, Jacobsson B, Chabra S, et al. Long-term Risk of Neuropsychiatric Disease After Exposure to Infection In Utero. *JAMA Psychiatry* 2019;76(6):594-602. doi: 10.1001/jamapsychiatry.2019.0029
95. Yates EF, Mulkey SB. Viral infections in pregnancy and impact on offspring neurodevelopment: mechanisms and lessons learned. *Pediatr Res* 2024;96(1):64-72. doi: 10.1038/s41390-024-03145-z [published Online First: 20240320]
96. Jiang Q, Feldman N, Koire A, et al. Infant neurodevelopment during the COVID-19 pandemic: Associations with maternal pandemic-related experiences, parenting stress, and self-efficacy. *Early Hum Dev* 2024;193:106018. doi: 10.1016/j.earlhumdev.2024.106018 [published Online First: 20240425]
97. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021;594(7862):259-64. doi: 10.1038/s41586-021-03553-9 [published Online First: 20210422]
98. Elmunzer BJ, Palsson OS, Forbes N, et al. Prolonged Gastrointestinal Manifestations After Recovery From COVID-19. *Clin Gastroenterol Hepatol* 2024;22(5):1098-107 e3. doi: 10.1016/j.cgh.2023.11.009 [published Online First: 20231122]
99. Xu E, Xie Y, Al-Aly Z. Long-term gastrointestinal outcomes of COVID-19. *Nat Commun* 2023;14(1):983. doi: 10.1038/s41467-023-36223-7 [published Online First: 20230307]
100. Ma Y, Zhang L, Wei R, et al. Risks of digestive diseases in long COVID: evidence from a population-based cohort study. *BMC Med* 2024;22(1):14. doi: 10.1186/s12916-023-03236-4 [published Online First: 20240110]
101. Chemaitelly H, Nagelkerke N, Ayoub HH, et al. Duration of immune protection of SARS-CoV-2 natural infection against reinfection. *J Travel Med* 2022;29(8) doi: 10.1093/jtm/taac109 [published Online First: 20220930]
102. Bobrovitz N, Ware H, Ma X, et al. Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression. *Lancet Infect Dis* 2023;23(5):556-67. doi: 10.1016/S1473-3099(22)00801-5 [published Online First: 20230118]
103. Stephenson T, Pinto Pereira SM, Nugawela MD, et al. A 24-month National Cohort Study examining long-term effects of COVID-19 in children and young people. *Commun Med (Lond)* 2024;4(1):255. doi: 10.1038/s43856-024-00657-x [published Online First: 20241204]
104. Luo D, Mei B, Wang P, et al. Prevalence and risk factors for persistent symptoms after COVID-19: a systematic review and meta-analysis. *Clin Microbiol Infect* 2024;30(3):328-35. doi: 10.1016/j.cmi.2023.10.016 [published Online First: 20231020]
105. Dempsey B, Blake HA, Madan I, et al. Post COVID-19 syndrome among 5248 healthcare workers in England: longitudinal findings from NHS CHECK. *Occup Environ Med* 2024;81(9):471-79. doi: 10.1136/oemed-2024-109621 [published Online First: 20241008]

106. Shah DP, Thaweethai T, Karlson EW, et al. Sex Differences in Long COVID. *JAMA Netw Open* 2025;8(1):e2455430. doi: 10.1001/jamanetworkopen.2024.55430 [published Online First: 20250102]
107. Geng LN, Erlandson KM, Hornig M, et al. 2024 Update of the RECOVER-Adult Long COVID Research Index. *JAMA* 2024;333(8):694-700. doi: 10.1001/jama.2024.24184 [published Online First: 20241218]
108. Xie Y, Choi T, Al-Aly Z. Long-term outcomes following hospital admission for COVID-19 versus seasonal influenza: a cohort study. *Lancet Infect Dis* 2024;24(3):239-55. doi: 10.1016/S1473-3099(23)00684-9 [published Online First: 20231214]
109. Bowe B, Xie Y, Al-Aly Z. Postacute sequelae of COVID-19 at 2 years. *Nat Med* 2023;29(9):2347–57. doi: 10.1038/s41591-023-02521-2 [published Online First: 20230821]
110. Cai M, Xie Y, Topol EJ, et al. Three-year outcomes of post-acute sequelae of COVID-19. *Nat Med* 2024;30(6):1564-73. doi: 10.1038/s41591-024-02987-8 [published Online First: 20240530]
111. Gottlieb M, Yu H, Chen J, et al. Differences in Long COVID severity by duration of illness, symptom evolution, and vaccination: a longitudinal cohort study from the INSPIRE group. *The Lancet Regional Health - Americas* 2025;44 doi: 10.1016/j.lana.2025.101026
112. Greenhalgh T, Sivan M, Perlowski A, et al. Long COVID: a clinical update. *Lancet* 2024;404(10453):707-24. doi: 10.1016/S0140-6736(24)01136-X [published Online First: 20240731]
113. Ford ND, Agedew A, Dalton AF, et al. Notes from the Field: Long COVID Prevalence Among Adults - United States, 2022. *MMWR Morb Mortal Wkly Rep* 2024;73(6):135-36. doi: 10.15585/mmwr.mm7306a4 [published Online First: 20240215]
114. Davis HE, McCorkell L, Vogel JM, et al. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023;21(3):133-46. doi: 10.1038/s41579-022-00846-2 [published Online First: 20230113]
115. O'Mahoney LL, Routen A, Gillies C, et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *EClinicalMedicine* 2023;55:101762. doi: 10.1016/j.eclinm.2022.101762 [published Online First: 20221201]
116. Ely EW, Brown LM, Fineberg HV, et al. Long Covid Defined. *N Engl J Med* 2024;391(18):1746-53. doi: 10.1056/NEJMsb2408466 [published Online First: 20240731]
117. Boufidou F, Medić S, Lampropoulou V, et al. SARS-CoV-2 Reinfections and Long COVID in the Post-Omicron Phase of the Pandemic. *International Journal of Molecular Sciences* 2023; 24(16).
118. Bartsch SM, Chin KL, Strych U, et al. The Current and Future Burden of Long COVID in the United States (U.S.). *J Infect Dis* 2025:jiaf030. doi: 10.1093/infdis/jiaf030 [published Online First: 20250122]
119. Costantino V, Grafton Q, Kompas T, et al. The public health and economic burden of long COVID in Australia, 2022-24: a modelling study. *Med J Aust* 2024;221(4):217-23. doi: 10.5694/mja2.52400

120. Kvalsvig A, Kerr J, Lorgelly P, et al. Long Covid: High economic burden justifies further preventive efforts. *Public Health Expert Briefing* 2024 9 Sept 2024. https://www.phcc.org.nz/briefing/long-covid-high-economic-burden-justifies-further-preventive-efforts (accessed 9 Sept 2024).
121. Madhav NK, Oppenheim B, Stephenson N, et al. Estimated Future Mortality from Pathogens of Epidemic and Pandemic Potential. 2023. https://www.cgdev.org/sites/default/files/estimated-future-mortality-pathogens-epidemic-and-pandemic-potential.pdf.
122. The Royal Society. COVID-19: examining the effectiveness of non-pharmaceutical interventionsThe https://royalsociety.org/-/media/policy/projects/impact-non-pharmaceutical-interventions-on-covid-19-transmission/the-royal-society-covid-19-examining-the-effectiveness-of-non-pharmaceutical-interventions-report.pdf: The Royal Society, 2023.
123. Greenhalgh T, MacIntyre CR, Baker MG, et al. Masks and respirators for prevention of respiratory infections: a state of the science review. *Clin Microbiol Rev* 2024;0(0):e0012423. doi: 10.1128/cmr.00124-23 [published Online First: 20240522]
124. World Health Organization. Global guidance on monitoring public health and social measures policies during health emergencies. https://iris.who.int/bitstream/handle/10665/378470/9789240094444-eng.pdf: World Health Organization, 2024.
125. Baker MG, Wilson N, Blakely T. Elimination could be the optimal response strategy for covid-19 and other emerging pandemic diseases. *BMJ* 2020;371:m4907. doi: 10.1136/bmj.m4907 [published Online First: 2021/02/10]
126. Honigsbaum M. Virologist Wendy Barclay: 'Wild avian viruses are mixing up their genetics all the time. It's like viral sex on steroids'. *Guardian* 2025 1 Feb 2025.
127. Blatchley ER, Brenner DJ, Claus H, et al. Far UV-C radiation: An emerging tool for pandemic control. *Critical Reviews in Environmental Science and Technology* 2022;53(6):733-53. doi: 10.1080/10643389.2022.2084315
128. Hassan I, Fernandes G, Mukaigawara M, et al. Lessons from COVID-19 must be learned before the next outbreak. *Nat Med* 2023;29(9):2171-73. doi: 10.1038/s41591-023-02377-6
129. Oliu-Barton M, Pradelski BSR. Green zoning: An effective policy tool to tackle the Covid-19 pandemic. *Health Policy* 2021;125(8):981-86. doi: 10.1016/j.healthpol.2021.06.001 [published Online First: 20210609]
130. Sun X, Wandelt S, Zhang A. Why are COVID-19 travel bubbles a tightrope walk? An investigation based on the Trans-Tasmanian case. *Communications in Transportation Research* 2023;3:100089. doi: 10.1016/j.commtr.2022.100089
131. Potter JD, Baker M, Ingram J. Covid-19 vaccines still protect us: How do we get the best out of them? *Public Health Expert Briefing* 2024 1 Aug 2024. https://www.phcc.org.nz/briefing/covid-19-vaccines-still-protect-us-how-do-we-get-best-out-them (accessed 1 Aug 2024).
132. Trinh NT, Jodicke AM, Catala M, et al. Effectiveness of COVID-19 vaccines to prevent long COVID: data from Norway. *Lancet Respir Med* 2024;12(5):e33-e34. doi: 10.1016/S2213-2600(24)00082-1 [published Online First: 20240410]
133. Catala M, Mercade-Besora N, Kolde R, et al. The effectiveness of COVID-19 vaccines to prevent long COVID symptoms: staggered cohort study of data from

the UK, Spain, and Estonia. *Lancet Respir Med* 2024;12(3):225-36. doi: 10.1016/S2213-2600(23)00414-9 [published Online First: 20240111]
134. Spiliopoulos L, Sorensen AIV, Bager P, et al. Postacute symptoms 4 months after SARS-CoV-2 infection during the Omicron period: a nationwide Danish questionnaire study. *Am J Epidemiol* 2024;193(8):1106-14. doi: 10.1093/aje/kwad225
135. Wu Q, Zhang B, Tong J, et al. Real-world Effectiveness and Causal Mediation Study of BNT162b2 on Long COVID Risks in Children and Adolescents. *medRxiv* 2024;79:2024.02.19.24302823. doi: 10.1101/2024.02.19.24302823 [published Online First: 20241206]
136. Razzaghi H, Forrest CB, Hirabayashi K, et al. Vaccine Effectiveness Against Long COVID in Children. *Pediatrics* 2024;153(4):e2023064446. doi: 10.1542/peds.2023-064446
137. Yousaf AR, Mak J, Gwynn L, et al. COVID-19 Vaccination and Odds of Post-COVID-19 Condition Symptoms in Children Aged 5 to 17 Years. *JAMA Netw Open* 2025;8(2):e2459672. doi: 10.1001/jamanetworkopen.2024.59672 [published Online First: 20250203]
138. Rover MM, Scolari FL, Trott G, et al. Association between vaccination and persistent COVID-19-related symptoms among patients with mild Omicron infection: A prospective cohort study. *Vaccine X* 2024;21:100579. doi: 10.1016/j.jvacx.2024.100579 [published Online First: 20241104]
139. Jaswa EG, Cedars MI, Lindquist KJ, et al. In Utero Exposure to Maternal COVID-19 Vaccination and Offspring Neurodevelopment at 12 and 18 Months. *JAMA Pediatr* 2024;178(3):258-65. doi: 10.1001/jamapediatrics.2023.5743 [published Online First: 20240122]
140. Kharbanda EO, DeSilva MB, Lipkind HS, et al. COVID-19 Vaccination in the First Trimester and Major Structural Birth Defects Among Live Births. *JAMA Pediatr* 2024;178(8):823-29. doi: 10.1001/jamapediatrics.2024.1917
141. Wang H, Wei Y, Hung CT, et al. Association of nirmatrelvir-ritonavir with post-acute sequelae and mortality in patients admitted to hospital with COVID-19: a retrospective cohort study. *Lancet Infect Dis* 2024;24(10):1130-40. doi: 10.1016/S1473-3099(24)00217-2 [published Online First: 20240503]
142. Butler CC, Hobbs FDR, Gbinigie OA, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. *Lancet* 2022;401(10373):281-93. doi: 10.1016/S0140-6736(22)02597-1 [published Online First: 20221222]
143. Standing JF, Buggiotti L, Guerra-Assuncao JA, et al. Randomized controlled trial of molnupiravir SARS-CoV-2 viral and antibody response in at-risk adult outpatients. *Nat Commun* 2024;15(1):1652. doi: 10.1038/s41467-024-45641-0 [published Online First: 20240223]
144. Olliaro P. What does 95% COVID-19 vaccine efficacy really mean? *Lancet Infect Dis* 2021;21(6):769. doi: 10.1016/S1473-3099(21)00075-X [published Online First: 20210217]
145. Howell JJ, Hellberg K, Turner M, et al. Metformin Inhibits Hepatic mTORC1 Signaling via Dose-Dependent Mechanisms Involving AMPK and the TSC

Complex. *Cell Metab* 2017;25(2):463-71. doi: 10.1016/j.cmet.2016.12.009 [published Online First: 20170112]
146. Bramante CT, Beckman KB, Mehta T, et al. Favorable Antiviral Effect of Metformin on SARS-CoV-2 Viral Load in a Randomized, Placebo-Controlled Clinical Trial of COVID-19. *Clin Infect Dis* 2024;79(2):354-63. doi: 10.1093/cid/ciae159
147. Johnson SG, Abedian S, Sturmer T, et al. Prevalent Metformin Use in Adults With Diabetes and the Incidence of Long COVID: An EHR-Based Cohort Study From the RECOVER Program. *Diabetes care* 2024;47(11):1930-40. doi: 10.2337/DCa24-0032
148. Olawore O, Turner LE, Evans MD, et al. Risk of Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Among Patients with Type 2 Diabetes Mellitus on Anti-Hyperglycemic Medications. *Clin Epidemiol* 2024;16(null):379-93. doi: 10.2147/CLEP.S458901 [published Online First: 20240531]
149. Wan EYF, Mathur S, Zhang R, et al. Association of COVID-19 with short- and long-term risk of cardiovascular disease and mortality: a prospective cohort in UK Biobank. *Cardiovasc Res* 2023;119(8):1718-27. doi: 10.1093/cvr/cvac195
150. Appelman B, Charlton BT, Goulding RP, et al. Muscle abnormalities worsen after post-exertional malaise in long COVID. *Nature Communications* 2024;15(1):17. doi: 10.1038/s41467-023-44432-3 [published Online First: 20240104]
151. Xie Y, Xu E, Al-Aly Z. Risks of mental health outcomes in people with covid-19: cohort study. *BMJ* 2022;376:e068993. doi: 10.1136/bmj-2021-068993 [published Online First: 20220216]
152. Xu E, Xie Y, Al-Aly Z. Long-term neurologic outcomes of COVID-19. *Nat Med* 2022;28(11):2406-15. doi: 10.1038/s41591-022-02001-z [published Online First: 20220922]
153. Atchison CJ, Davies B, Cooper E, et al. Long-term health impacts of COVID-19 among 242,712 adults in England. *Nat Commun* 2023;14(1):6588. doi: 10.1038/s41467-023-41879-2 [published Online First: 20231024]
154. Seighali N, Abdollahi A, Shafiee A, et al. The global prevalence of depression, anxiety, and sleep disorder among patients coping with Post COVID-19 syndrome (long COVID): a systematic review and meta-analysis. *BMC Psychiatry* 2024;24(1):105. doi: 10.1186/s12888-023-05481-6 [published Online First: 20240206]
155. Altmann DM, Whettlock EM, Liu S, et al. The immunology of long COVID. *Nat Rev Immunol* 2023;23(10):618-34. doi: 10.1038/s41577-023-00904-7 [published Online First: 20230711]
156. Ewing A. COVID-19 and Immune Dysregulation, a Summary and Resource. *WHN Science Communications* 2023 5 March, 2023. https://whn.global/scientific/covid19-immune-dysregulation/ (accessed 27 Dec 2023).
157. Klein J, Wood J, Jaycox JR, et al. Distinguishing features of long COVID identified through immune profiling. *Nature* 2023;623(7985):139-48. doi: 10.1038/s41586-023-06651-y [published Online First: 20230925]
158. Golla R, Vuyyuru S, Kante B, et al. Long-term Gastrointestinal Sequelae Following COVID-19: A Prospective Follow-up Cohort Study. *Clin Gastroenterol Hepatol* 2023;21(3):789-96 e1. doi: 10.1016/j.cgh.2022.10.015 [published Online First: 20221021]

159. Rathmann W, Kuss O, Kostev K. Incidence of newly diagnosed diabetes after Covid-19. *Diabetologia* 2022;65(6):949-54. doi: 10.1007/s00125-022-05670-0 [published Online First: 20220316]
160. Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol* 2022;10(5):311-21. doi: 10.1016/S2213-8587(22)00044-4 [published Online First: 20220321]
161. Kendall EK, Olaker VR, Kaelber DC, et al. Association of SARS-CoV-2 Infection With New-Onset Type 1 Diabetes Among Pediatric Patients From 2020 to 2021. *JAMA Netw Open* 2022;5(9):e2233014. doi: 10.1001/jamanetworkopen.2022.33014 [published Online First: 20220901]
162. Bowe B, Xie Y, Xu E, et al. Kidney Outcomes in Long COVID. *J Am Soc Nephrol* 2021;32(11):2851-62. doi: 10.1681/ASN.2021060734 [published Online First: 20210901]
163. Subramanian A, Nirantharakumar K, Hughes S, et al. Symptoms and risk factors for long COVID in non-hospitalized adults. *Nat Med* 2022;28(8):1706-14. doi: 10.1038/s41591-022-01909-w [published Online First: 20220725]
164. Chou R, Herman E, Ahmed A, et al. Long COVID Definitions and Models of Care : A Scoping Review. *Ann Intern Med* 2024;177(7):929-40. doi: 10.7326/M24-0677 [published Online First: 20240521]
165. National Academies of Sciences Engineering and Medicine. A Long COVID Definition: A Chronic, Systemic Disease State with Profound Consequences. Washington, DC: The National Academies Press, 2024.
166. Walitt B, Singh K, LaMunion SR, et al. Deep phenotyping of post-infectious myalgic encephalomyelitis/chronic fatigue syndrome. *Nat Commun* 2024;15(1):907. doi: 10.1038/s41467-024-45107-3 [published Online First: 20240221]
167. Unger ER, Lin JS, Wisk LE, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome After SARS-CoV-2 Infection. *JAMA Netw Open* 2024;7(7):e2423555. doi: 10.1001/jamanetworkopen.2024.23555 [published Online First: 20240701]
168. Annesley SJ, Missailidis D, Heng B, et al. Unravelling shared mechanisms: insights from recent ME/CFS research to illuminate long COVID pathologies. *Trends in Molecular Medicine* 2024;30(5):443-58. doi: 10.1016/j.molmed.2024.02.003 [published Online First: 20240304]
169. Peluso MJ, Ryder D, Flavell R, et al. Multimodal Molecular Imaging Reveals Tissue-Based T Cell Activation and Viral RNA Persistence for Up to 2 Years Following COVID-19. *medRxiv* 2023:2023.07.27.23293177. doi: 10.1101/2023.07.27.23293177 [published Online First: 20230731]
170. Proal AD, VanElzakker MB, Aleman S, et al. SARS-CoV-2 reservoir in post-acute sequelae of COVID-19 (PASC). *Nat Immunol* 2023;24(10):1616-27. doi: 10.1038/s41590-023-01601-2 [published Online First: 20230904]
171. Proal AD, Aleman S, Bomsel M, et al. Targeting the SARS-CoV-2 reservoir in long COVID. *Lancet Infect Dis* 2025 doi: 10.1016/S1473-3099(24)00769-2 [published Online First: 20250210]
172. Saris CGJ, van Engelen BGM, Janssen MCH, et al. Should we be careful with exercise in post-exertional malaise after long COVID? *Nat Commun* 2025;16(1):1724. doi: 10.1038/s41467-025-56427-3 [published Online First: 20250218]

173. Baker MG, Fidler DP. Global public health surveillance under new international health regulations. *Emerg Infect Dis* 2006;12(7):1058-65. doi: 10.3201/eid1207.051497
174. Potter JD. Epidemiology informing clinical practice: from bills of mortality to population laboratories. *Nat Clin Pract Oncol* 2005;2(12):625-34. doi: 10.1038/ncponc0359
175. Zwald ML, Lin W, Sondermeyer Cooksey GL, et al. Rapid Sentinel Surveillance for COVID-19 - Santa Clara County, California, March 2020. *MMWR Morb Mortal Wkly Rep* 2020;69(14):419-21. doi: 10.15585/mmwr.mm6914e3 [published Online First: 20200410]
176. Ward H, Cooke GS, Atchison C, et al. Prevalence of antibody positivity to SARS-CoV-2 following the first peak of infection in England: Serial cross-sectional studies of 365,000 adults. *Lancet Reg Health Eur* 2021;4:100098. doi: 10.1016/j.lanepe.2021.100098 [published Online First: 20210502]
177. Ward H, Atchison C, Whitaker M, et al. SARS-CoV-2 antibody prevalence in England following the first peak of the pandemic. *Nat Commun* 2021;12(1):905. doi: 10.1038/s41467-021-21237-w [published Online First: 20210210]
178. Riley S, Ainslie KEC, Eales O, et al. Resurgence of SARS-CoV-2: Detection by community viral surveillance. *Science* 2021;372(6545):990-95. doi: 10.1126/science.abf0874 [published Online First: 20210423]
179. Choi WS. The National Influenza Surveillance System of Korea. *Infect Chemother* 2019;51(2):98-106. doi: 10.3947/ic.2019.51.2.98
180. Nuvey FS, Edu-Quansah EP, Kuma GK, et al. Evaluation of the sentinel surveillance system for influenza-like illnesses in the Greater Accra region, Ghana, 2018. *PLoS One* 2019;14(3):e0213627. doi: 10.1371/journal.pone.0213627 [published Online First: 20190314]
181. Ortiz JR, Sotomayor V, Uez OC, et al. Strategy to enhance influenza surveillance worldwide. *Emerg Infect Dis* 2009;15(8):1271-8. doi: 10.3201/eid1508.081422
182. Girond F, Randrianasolo L, Randriamampionona L, et al. Analysing trends and forecasting malaria epidemics in Madagascar using a sentinel surveillance network: a web-based application. *Malar J* 2017;16(1):72. doi: 10.1186/s12936-017-1728-9 [published Online First: 20170213]
183. Jayaraman Y, Veeraraghavan B, Chethrapilly Purushothaman GK, et al. Burden of bacterial meningitis in India: Preliminary data from a hospital based sentinel surveillance network. *PLoS One* 2018;13(5):e0197198. doi: 10.1371/journal.pone.0197198 [published Online First: 20180516]
184. Frerichs RR, Ungchusak K, Htoon MT, et al. HIV Sentinel Surveillance in Thailand — An Example for Developing Countries. *Asia Pac J Public Health* 2016;8(1):20-26. doi: 10.1177/101053959500800105
185. Alagiyawanna AMADK, Gajaweera NDCRC, Benaragama APS. HIV Sentinel Surveillance Survey 2019/ Prevalence and Characteristics of HIV Cases in Sri Lanka; Experience from Sentinel site Surveillance 2019. *Sri Lanka Journal of Sexual Health and HIV Medicine* 2020;6(0):9-14. doi: 10.4038/joshhm.v6i0.99
186. Bolwell CF, Gilpin BJ, Campbell D, et al. Evaluation of the representativeness of a sentinel surveillance site for campylobacteriosis. *Epidemiol Infect* 2015;143(9):1990-2002. doi: 10.1017/S0950268814003173 [published Online First: 20141127]

187. Björk J, Bonander C, Moghaddassi M, et al. COVID-19 vaccine effectiveness against severe disease from the Omicron BA.1 and BA.2 subvariants – surveillance results from southern Sweden, December 2021 to March 2022. *medRxiv* 2022:2022.04.14.22273896. doi: 10.1101/2022.04.14.22273896
188. Chavarria-Miro G, Anfruns-Estrada E, Martinez-Velazquez A, et al. Time Evolution of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Wastewater during the First Pandemic Wave of COVID-19 in the Metropolitan Area of Barcelona, Spain. *Appl Environ Microbiol* 2021;87(7) doi: 10.1128/AEM.02750-20 [published Online First: 20210311]
189. Link-Gelles R, Lutterloh E, Schnabel Ruppert P, et al. Public Health Response to a Case of Paralytic Poliomyelitis in an Unvaccinated Person and Detection of Poliovirus in Wastewater - New York, June-August 2022. *MMWR Morb Mortal Wkly Rep* 2022;71(33):1065-68. doi: 10.15585/mmwr.mm7133e2 [published Online First: 20220819]
190. Editorial. Wastewater monitoring comes of age. *Nat Microbiol* 2022;7(8):1101-02. doi: 10.1038/s41564-022-01201-0
191. Sims N, Kasprzyk-Hordern B. Future perspectives of wastewater-based epidemiology: Monitoring infectious disease spread and resistance to the community level. *Environ Int* 2020;139:105689. doi: 10.1016/j.envint.2020.105689 [published Online First: 20200404]
192. Mello MM, Meschke JS, Palmer GH. Mainstreaming Wastewater Surveillance for Infectious Disease. *N Engl J Med* 2023;388(16):1441-44. doi: 10.1056/NEJMp2301042 [published Online First: 20230415]
193. National Academies of Sciences Engineering and Medicine. Wastewater-based Disease Surveillance for Public Health Action. Washington, DC: The National Academies Press, 2023.
194. Karthikeyan S, Levy JI, De Hoff P, et al. Wastewater sequencing reveals early cryptic SARS-CoV-2 variant transmission. *Nature* 2022;609(7925):101-08. doi: 10.1038/s41586-022-05049-6 [published Online First: 20220707]
195. Brunner FS, Brown MR, Bassano I, et al. City-wide wastewater genomic surveillance through the successive emergence of SARS-CoV-2 Alpha and Delta variants. *Water Res* 2022;226:119306. doi: 10.1016/j.watres.2022.119306 [published Online First: 20221028]
196. Amman F, Markt R, Endler L, et al. Viral variant-resolved wastewater surveillance of SARS-CoV-2 at national scale. *Nat Biotechnol* 2022;40(12):1814-22. doi: 10.1038/s41587-022-01387-y [published Online First: 20220718]
197. Jahn K, Dreifuss D, Topolsky I, et al. Early detection and surveillance of SARS-CoV-2 genomic variants in wastewater using COJAC. *Nat Microbiol* 2022;7(8):1151-60. doi: 10.1038/s41564-022-01185-x [published Online First: 20220718]
198. Hooda Y, Islam S, Kabiraj R, et al. Old tools, new applications: use of environmental bacteriophages for typhoid surveillance and evaluating vaccine impact. *medRxiv* 2023:2023.02.14.23285884. doi: 10.1101/2023.02.14.23285884
199. Shrestha S, Da Silva KE, Shakya J, et al. Detection of *Salmonella typhi* bacteriophages in surface waters as a scalable approach to environmental surveillance. *medRxiv* 2023:2023.02.14.23285806. doi: 10.1101/2023.02.14.23285806

200. Deng X, Gu W, Federman S, et al. Genomic surveillance reveals multiple introductions of SARS-CoV-2 into Northern California. *Science* 2020;369(6503):582-87. doi: 10.1126/science.abb9263 [published Online First: 20200608]
201. Rockett RJ, Arnott A, Lam C, et al. Revealing COVID-19 transmission in Australia by SARS-CoV-2 genome sequencing and agent-based modeling. *Nat Med* 2020;26(9):1398-404. doi: 10.1038/s41591-020-1000-7 [published Online First: 20200709]
202. Cyranoski D. Alarming COVID variants show vital role of genomic surveillance. *Nature* 2021;589(7842):337-38. doi: 10.1038/d41586-021-00065-4 [published Online First: 2021/01/17]
203. Li J, Lai S, Gao GF, et al. The emergence, genomic diversity and global spread of SARS-CoV-2. *Nature* 2021;600(7889):408-18. doi: 10.1038/s41586-021-04188-6 [published Online First: 20211208]
204. Zhao LP, Lybrand TP, Gilbert PB, et al. Tracking SARS-CoV-2 Spike Protein Mutations in the United States (January 2020-March 2021) Using a Statistical Learning Strategy. *Viruses* 2021;14(1) doi: 10.3390/v14010009 [published Online First: 20211221]
205. Viana R, Moyo S, Amoako DG, et al. Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa. *Nature* 2022;603(7902):679-86. doi: 10.1038/s41586-022-04411-y [published Online First: 20220107]
206. Tegally H, San JE, Cotten M, et al. The evolving SARS-CoV-2 epidemic in Africa: Insights from rapidly expanding genomic surveillance. *Science* 2022;378(6615):eabq5358. doi: 10.1126/science.abq5358 [published Online First: 20221007]
207. Happi AN, Ugwu CA, Happi CT. Tracking the emergence of new SARS-CoV-2 variants in South Africa. *Nat Med* 2021;27(3):372-73. doi: 10.1038/s41591-021-01265-1 [published Online First: 2021/03/17]
208. Rockett RJ, Draper J, Gall M, et al. Co-infection with SARS-CoV-2 Omicron and Delta variants revealed by genomic surveillance. *Nat Commun* 2022;13(1):2745. doi: 10.1038/s41467-022-30518-x [published Online First: 20220518]
209. Peng J, Liu J, Mann SA, et al. Estimation of Secondary Household Attack Rates for Emergent Spike L452R Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Variants Detected by Genomic Surveillance at a Community-Based Testing Site in San Francisco. *Clin Infect Dis* 2022;74(1):32-39. doi: 10.1093/cid/ciab283
210. Subissi L, von Gottberg A, Thukral L, et al. An early warning system for emerging SARS-CoV-2 variants. *Nat Med* 2022;28(6):1110-15. doi: 10.1038/s41591-022-01836-w
211. Milinovich GJ, Williams GM, Clements AC, et al. Internet-based surveillance systems for monitoring emerging infectious diseases. *Lancet Infect Dis* 2014;14(2):160-8. doi: 10.1016/S1473-3099(13)70244-5 [published Online First: 20131128]
212. Al-Surimi K, Khalifa M, Bahkali S, et al. The Potential of Social Media and Internet-Based Data in Preventing and Fighting Infectious Diseases: From Internet to Twitter. In: Rezza G, Ippolito G, eds. Emerging and Re-emerging Viral Infections:

Advances in Microbiology, Infectious Diseases and Public Health Volume 6. Cham: Springer International Publishing 2017:131-39.
213. Lopreite M, Panzarasa P, Puliga M, et al. Early warnings of COVID-19 outbreaks across Europe from social media. *Sci Rep* 2021;11(1):2147. doi: 10.1038/s41598-021-81333-1 [published Online First: 20210125]
214. Jang B, Kim M, Kim I, et al. EagleEye: A Worldwide Disease-Related Topic Extraction System Using a Deep Learning Based Ranking Algorithm and Internet-Sourced Data. *Sensors (Basel)* 2021;21(14) doi: 10.3390/s21144665 [published Online First: 20210707]
215. Valentin S, Mercier A, Lancelot R, et al. Monitoring online media reports for early detection of unknown diseases: Insight from a retrospective study of COVID-19 emergence. *Transbound Emerg Dis* 2021;68(3):981-86. doi: 10.1111/tbed.13738 [published Online First: 20200802]
216. Carrion M, Madoff LC. ProMED-mail: 22 years of digital surveillance of emerging infectious diseases. *Int Health* 2017;9(3):177-83. doi: 10.1093/inthealth/ihx014
217. Centers for Disease Control and Prevention. Updated Guidelines for Evaluating Public Health Surveillance Systems: Recommendations from the Guidelines Working Group *MMWR* 2001;50(RR-13):1-36 (https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5013a1.htm).
218. World Health Organization. Surveillance of health care-associated infections at national and facility levels: practical handbook. https://iris.who.int/bitstream/handle/10665/379248/9789240101456-eng.pdf?sequence=1: World Health Organization, 2024.
219. Institute of Medicine. Global infectious disease surveillance and detection: Assessing the challenges—finding solutions. Workshop summary. Washington, DC: The National Academies Press, 2007.
220. Wang W, Wang Y, Zhang X, et al. Using WeChat, a Chinese Social Media App, for Early Detection of the COVID-19 Outbreak in December 2019: Retrospective Study. *JMIR Mhealth Uhealth* 2020;8(10):e19589. doi: 10.2196/19589 [published Online First: 20201005]
221. Kepp KP, Bjork J, Kontis V, et al. Estimates of excess mortality for the five Nordic countries during the COVID-19 pandemic 2020-2021. *Int J Epidemiol* 2022;51(6):1722-32. doi: 10.1093/ije/dyac204
222. Msemburi W, Karlinsky A, Knutson V, et al. The WHO estimates of excess mortality associated with the COVID-19 pandemic. *Nature* 2023;613(7942):130-37. doi: 10.1038/s41586-022-05522-2 [published Online First: 20221214]
223. Ministry of Health Singapore. Report on excess mortality during the COVID-19 pandemic up to June 2022. https://www.moh.gov.sg/docs/librariesprovider5/resources-statistics/reports/report-on-excess-mortality-during-the-covid-pandemic-18sep2022.pdf?sfvrsn=fbdd8ee_2: Ministry of Health Singapore, 2022.
224. *pandemic*. Cumulative excess deaths by income (last 12 months) https://pandem-ic.com/cumulative-excess-deaths-by-income-last-12-months/2023 [Available from: https://pandem-ic.com/cumulative-excess-deaths-by-income-last-12-months/ accessed April 22 2023).
225. *pandemic*. Demography and excess deaths https://pandem-ic.com/the-global-mortality-distribution-simulated-vs-excess-deaths/2023 [Available from:

https://pandem-ic.com/the-global-mortality-distribution-simulated-vs-excess-deaths/ accessed 22 April 2023).
226. Sidik SM. How COVID has deepened inequality—in six stark graphics. *Nature* 2022;606(7915):638-39. doi: 10.1038/d41586-022-01647-6
227. LeWinn KZ, Trasande L, Law A, et al. Sociodemographic Differences in COVID-19 Pandemic Experiences Among Families in the United States. *JAMA Netw Open* 2023;6(8):e2330495. doi: 10.1001/jamanetworkopen.2023.30495 [published Online First: 20230801]
228. Douglas MD, Respress E, Gaglioti AH, et al. Variation in Reporting of the Race and Ethnicity of COVID-19 Cases and Deaths Across US States: April 12, 2020, and November 9, 2020. *Am J Public Health* 2021;111(6):1141-48. doi: 10.2105/AJPH.2021.306167 [published Online First: 20210415]
229. Noppert GA, Zalla LC. Who Counts and Who Gets Counted? Health Equity in Infectious Disease Surveillance. *Am J Public Health* 2021;111(6):1004-06. doi: 10.2105/AJPH.2021.306249
230. Jones RM, Andrews JG, Dalton AF, et al. Tracking the burden, distribution, and impact of Post-COVID conditions in diverse populations for children, adolescents, and adults (Track PCC): passive and active surveillance protocols. *BMC Public Health* 2024;24(1):2345. doi: 10.1186/s12889-024-19772-4 [published Online First: 20240829]
231. Espinosa Gonzalez A, Suzuki E. The impacts of long COVID across OECD countries. 2024. https://www.oecd.org/content/dam/oecd/en/publications/reports/2024/06/the-impacts-of-long-covid-across-oecd-countries_f662b21c/8bd08383-en.pdf.
232. Lorgelly PK, Crossan J, Exeter DJ, et al. The Burden of Long COVID in Aotearoa New Zealand: Establishing a Registry. Final Report to the Ministry of Health. https://lcregistry.auckland.ac.nz/files/2024/06/report_to_MoH.pdf: University of Auckland & Long Covid Support Aotearoa, 2024.
233. New Zealand Royal Commission COVID-19 Lessons Learned. Looking back to move forward: Aotearoa New Zealand's Experiences of the COVID-19 pandemic. https://www.covid19lessons.royalcommission.nz/assets/Report-pdfs/experiences.pdf: New Zealand Royal Commission COVID-19 Lessons Learned, 2024.
234. Commonwealth of Australia, Department of the Prime Minister and Cabinet. COVID-19 Response Inquiry Report. https://www.pmc.gov.au/sites/default/files/resource/download/covid-19-response-inquiry-report.docx: Commonwealth of Australia, 2024.
235. Nature Editorial. Learn COVID pandemic lessons - before it's too late. *Nature* 2025;638(8052):859. doi: 10.1038/d41586-025-00498-1 [published Online First: 20250218]