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Long COVID: a crucial reason for vax, mask, and distance

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Long COVID occurs in at least 20-30% of individuals who have been infected with SARS-CoV-2 and is strongly related to the severity of the initial illness. There are insufficient data to provide a trajectory or a timeline for duration and resolution.

The downstream damage can affect: brain, heart, lungs, pancreatic beta cells (resulting in diabetes), muscles, the immune system, eyes, kidneys, and erectile tissue. There is, to date, quite consistent evidence that vaccination is wholly or partly protective against long COVID, whether vaccination occurs before or after COVID-19. A society wanting to minimise the health and cost burden of managing long COVID would therefore choose to maximise vaccination coverage as well as minimise risk of infection with standard public health and social measures.

Introduction

In the earlier PHE blogs[1,2] on long COVID – now increasingly also called Post-Acute Sequelae of COVID (PASC) – we established the following:

- The disorder was initially described as a result of sufferers talking to each other and reported first in the Washington Post[3];
- It began to be studied by both epidemiologic and clinical researchers, who set up cohorts and reported on cross-sectional studies;
- Major common long-COVID symptoms (see for instance[4-7]) included: fatigue; disturbed sense of smell or taste; shortness of breath; “brain fog”; and anxiety and depression
- There were hints that long COVID deserved more attention than it was getting (this may now be improving) because it was much more common than many initially thought;
- We reported on seven studies that gave a quite imprecise (15-65%) estimate of prevalence of long COVID among those initially diagnosed with acute disease. This variation probably related to initial disease severity: Al-Aly et al[8] reported that their analysis of a series of prespecified outcomes among those who survived 30 days after an initial diagnosis showed a risk gradient that increased across: those who were infected but not hospitalised; those hospitalised; and those admitted to intensive care;
- There was evidence that some individuals experienced symptoms that began at the time of the initial infection and that, for others, symptoms arose some time after the initial infection had resolved[9] and that one of the key features was a pattern of remitting/relapsing symptoms[10];
- New chronic diseases emerged among those with long COVID, suggesting that it could well be a serious burden on individuals, family and whanau, communities, and the healthcare system well into the future: lung fibrosis[11], cardiac damage[12], multi organ damage on MRI[13], abnormal brain metabolism[14] and cognitive impairment[15], thrombo-embolism[16], and questions about diabetes[17].
- There was essentially no research on long COVID in children but the very recent blog by Kvalsvig et al. provides an excellent overview of what we know now[18].
- Although the UK National Institute for Health and Care Excellence (NICE) has produced a Rapid Guideline on management[19], little had been written clearly on the kinds of services we need in Aotearoa for long-COVID patients. This gap has now been well addressed by Whittaker et al[20].

Shortly after the second blog[2], some results began to emerge from the studies that had been established in the previous 12 months. A great deal more began to become clear. There are now multiple reports across the world but many are still small and not yet peer-reviewed. Indeed, one preprint presents a meta-analysis of 29 studies, of which 14 are themselves still preprints[21].

Any attempt to summarise these studies would result in an unwieldy long essay, in which important trees became lost in a forest of detail. Accordingly, this blog takes several different slices through the available data. Firstly, we briefly summarise the findings from large studies that presented overall prevalence data on symptoms, signs, and organ systems affected – and provide more details on the studies in an appendix. Secondly, we discuss studies that focused in more detail on key organ systems in order to relate symptoms to possible pathology; we pay particular attention to the brain and the cardiovascular system because it seems likely that, along with diabetes and the respiratory system, these will result in the largest burden on individuals, family, whanau, community,

and the healthcare system. Thirdly, we move from this more detailed discussion of organs to summarise briefly what is currently known or hypothesised about mechanisms. Finally we discuss the impact of vaccination on long COVID.

Definition of Long Covid

As noted above, the scope of Post-Acute Sequelae of COVID (PASC) is very broad. There is no universally accepted definition of long Covid that covers the key features that are needed in a working case-definition based on clinical criteria (symptoms, signs, investigation findings), severity threshold, or time window for onset and duration. However, a useful working definition has been proposed by NICE[19]: Signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post-COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed.

Risk Factors

Long-Covid risk is higher in those with more severe viral disease. It is more common in women than men. There is no consistent relationship with age; it is of particular note that although the initial viral illness is more severe at older ages, that is not true for long COVID. There are some associations among risk factors but the patterns vary across studies. There is a suggestion that risk may vary by ethnicity but, again, patterns are not stable. Vaccination is highly protective, as is discussed later in this blog.

Prevalence of Long-COVID Symptoms

More detail on each of the individual studies is presented in an appendix.

In most of the studies summarised below, there was a general pattern of stepwise higher prevalence of long COVID across those who were asymptomatic, those symptomatic but not hospitalised, those hospitalised, and those in intensive care. There was an essentially universal finding that symptoms were more common in women than men. The diversity of study designs, of definitions of long COVID, of symptoms and symptom clusters used to define the disorder, of the duration of follow-up (although most focus on symptoms that persist for more than 30 days post-acute illness), of the populations studied, and of the recruitment methods – in addition to the problems of selection and other biases – make any sort of summarised single prevalence figure difficult – and perhaps misleading. Chen et al's meta-analysis presents a prevalence of 43% overall and 57% among those hospitalised[21].

Electronic-Health-Record Studies

The large studies of long COVID that use electronic health records (EHR) rely on some further contact(s) with individuals with diagnosed COVID-19: readmission to hospital or outpatient care. Inasmuch as not everyone will present to a healthcare provider with prolonged or newly emerged symptoms (especially in the US), the very nature of this repeat-contact approach to identifying individuals with long COVID establishes these estimates as a lower bound of prevalence across the population.

Three EHR studies provide estimates of 27% to 57% prevalence of long-COVID symptoms[6,22,23], with one providing evidence of a clear relationship between initial disease

severity and the prevalence of symptoms: 50% of those hospitalised experienced long-COVID symptoms; 27.5% among the symptomatic but non-hospitalised; and 19% among the asymptomatic[22]. The prevalence of post-COVID symptoms was much lower in 2 other EHR-based studies[24,25] and the reasons for the differences are not obvious.

Cohort and Cross-sectional Studies

We focus here on the 10 cohort and cross-sectional studies with more than 1000 participants, undertaken in China[26,27], Denmark[28], France[29], India[30], Mexico[31], Russia[32], Spain[33], and the UK[34] and one in which individuals (mostly UK) self-reported symptoms prospectively online in the COVID Symptom Study app[7]. Relatively consistent with the EHR studies, these provide estimates of prevalence from 13% to 55% (with one outlier at >80%[33]) with the three largest studies estimating prevalence at 19%[34] to 30%[28,31]. In a smaller Dutch study, of survivors one year post-discharge from ICU, 74% (n=182/245) reported physical symptoms, 26% reported mental symptoms, and 16%, cognitive symptoms[35]. The most common symptoms (which were, however, inconsistent in their prevalence across studies) were fatigue (consistently the most common complaint), muscle weakness, shortness of breath and cough, sleep difficulties, headache, hair loss, joint and muscle pain, brain fog, memory loss, loss of sense of smell, and anxiety and depression.

Duration and Resolution

Although some symptoms resolve over time[6,30], others may persist or re-emerge[31]. There are many individuals whose symptoms persist for at least six[26,29], even 12[28,35] months. To date, there are insufficient data from the cohorts to provide a clear picture of trajectories or timelines toward resolution.

More Detailed Studies of Organ Systems

Symptoms often point to specific organ damage but are, by definition, essentially self-reported. The more closely focused studies discussed below provide some insight into the organ damage that is the result both of infection with SARS-CoV-2 and the body's response. As noted above, we pay particular attention to the nervous and cardiovascular systems because it seems likely that, along with diabetes and the respiratory system, damage to these organs will result in the largest long-term burden.

Multi-organ Impacts

Ayoubkhani et al. undertook a retrospective cohort study across English NHS hospitals and identified 47,780 individuals (mean age 65; 45% women) who were discharged alive by 31 August 2020 and exactly matched to controls from a pool of about 50 million people[36]. The individuals were followed up for a mean of 140 days until 30 September 2020, by which time 12.3% (n=5875) of the individuals who were discharged after acute COVID-19 had died and 29.4% (n=14,060) had been readmitted. These events were 7.7 and 3.5 times the respective rates in the matched controls. New-onset respiratory disease was diagnosed in 21.5% of cases (n=6085) and in 0.8% of controls (n=240) (P<0.001); new-onset diabetes (1.1% vs 0.3%); and new-onset major adverse cardiovascular events such as heart attacks and strokes (2.6% vs 0.5%). Kidney and liver disease were also more common among those discharged after COVID-19. Rate ratios (RR) for these comparisons were higher among individuals aged <70 years than for those aged ≥70 and in ethnic minority groups compared with whites: the largest differences were seen for respiratory disease: RR=10.5 for age <70 years v 4.6 for age ≥70; and RR=11.4 for non-whites v 5.2 for whites.

Neurologic, Neurocognitive, and Mental Health Outcomes

From a wide trawl through the literature, Wildwing and Holt identified two types of neurologic symptoms among those with a diagnosis of COVID-19: life-threatening (eg, Guillain–Barré Syndrome and encephalitis) and less devastating symptoms such as fatigue and muscle pain[37]. They noted that the latter pattern was emerging as longer-term outcomes for some who had been diagnosed with SARS-CoV-2 infections.

However, it is clear from the detailed studies of COVID-19 survivors that far more widespread damage is actually occurring.

Taquet et al. undertook a retrospective cohort study using the TriNetX electronic health records (EHR) network, which includes data from 62 (primarily USA) healthcare organisations with 81 million patients[38]. The cohort of primary interest included patients with a COVID-19 diagnosis. There were 2 propensity-score matched comparison cohorts, one of patients with influenza, the other of patients with any respiratory tract infection (RTI) (including influenza) over the same time period; those with COVID-19 or who were SARS-CoV-2-positive were excluded from the comparison cohorts. The study subjects were aged >10 years with an index event after Jan 19, 2020 and still alive Dec 13, 2020. Among 236,379 patients diagnosed with COVID-19, the incidence of a neurologic or psychiatric diagnosis in the following 6 months was 33·6% and of a new-onset diagnosis, 12·8%. For ICU patients, the estimated overall incidence was 46·4% and 25.8% for new onset disorders. Specific outcomes for the COVID-19 cohort were: intracranial haemorrhage (a form of stroke): 0·6%; ischaemic stroke: 2·1%; Parkinsons: 0·1%; dementia: 0·7%; anxiety disorder: 17·4%; and psychotic disorder: 1.4%. For the ICU COVID patients, the proportional incidence were, respectively: 2·7%; 6·9%; 0·3%; 1·7%; 19·2%; and 2·8%. New-onset diagnoses were statistically significantly more common among the COVID-19 cohort than among the influenza cohort: hazard ratio (HR)=1·8; and the “other RTI” cohort: HR=1·3. Hazard ratios were stepwise higher across increasing severity.

As noted previously[2], evidence of possible cognitive deficits have emerged. In a large cross-sectional study (n=84,285), members of the general public – largely within the UK – took part in the Great British Intelligence Test. Hampshire et al[15] found that participants in this study who had recovered from confirmed or suspected COVID-19 (n=13,050) exhibited statistically significantly more cognitive deficits, which were more marked among people who had been hospitalised but also found among those with mild, but biologically confirmed, disease.

Wuhan was the Chinese city of origin of the pandemic. Liu et al. recruited 3233 COVID-19 survivors 60 years and older who had been discharged from three COVID-19-designated hospitals in Wuhan, from February 10 to April 10, 2020, to investigate patterns of cognitive changes[39]. Their uninfected spouses were recruited as controls. Cognitive status at 6 and 12 months was classified as: stable cognition; early-onset cognitive decline; late-onset cognitive decline; and progressive cognitive decline. The incidence of cognitive impairment in survivors 12 months after discharge was 12.5%. Impairment was related to initial disease severity: severe COVID-19 was associated with a higher risk of early-onset cognitive decline (odds ratio [OR] =4.9; 95%CI: 3.3-7.2), late-onset decline (7.6; 3.6-16.0), and progressive decline (19.0; 9.1-39.5). In contrast, adjusting for confounders, non-severe COVID-19 was associated with a higher risk of early-onset decline (1.7; 1.3-2.3).

Xie et al., in one of the studies undertaken in the healthcare system of the US Department of Veterans Affairs, studied 153,848 people who survived the first 30 days of a SARS-CoV-2

infection and two comparison groups: a contemporary group (n=5,637,840) with no evidence of SARS-CoV-2 and a historical group (n=5,859,251) who predated the pandemic[40]. They reported that those with a history of SARS-CoV-2 infection were at increased risk of any incident mental-health diagnosis or prescription (HR=1.6; 95% confidence interval: 1.6-1.7); with a risk difference of 64.4 per 1000 people at one year compared to the contemporary comparison group. More specifically, there was a higher risk in the COVID-19 survivors of: new-onset anxiety disorders (1.4; 1.3-1.4); depressive disorders (1.4; 1.3-1.4); stress and adjustment disorders (1.4 (1.3-1.4); and use of both antidepressants (1.6; 1.5-1.6) and benzodiazepines (1.7; 1.6-1.7) as well as a higher risk of new opioid prescriptions and opioid-use and other substance-use disorders. The COVID-19 survivors also showed an increased risk of incident neurocognitive decline (1.8; 1.7-1.9) and sleep disorders (1.4; 1.4-1.5). The risks of these outcomes were elevated even among those not admitted to hospital and highest among those hospitalised. The findings were consistent when the COVID survivors were compared with the pre-pandemic historical comparison group.

Because there was strong and growing evidence that long COVID included a sizable proportion of individuals with neurologic, neurocognitive, and mental-health abnormalities, Douaud et al. established an imaging study that took advantage of the fact that participants in the UK Biobank had undergone multimodal brain imaging[41]. Data had originally been obtained from 42,729 participants >45 years[42]. From February 2021, hundreds of participants who had already taken part before the pandemic were invited for a second scan. 785 participants (aged 51-81 years) were imaged twice, including 401 cases who tested positive for SARS-CoV-2 between scans (an average of 141 days separated diagnosis and second scan) and 384 controls. This provided the first imaging study of SARS-CoV-2 consequences where participants were initially scanned pre-infection, ensuring interpretable relationships across time. Statistically significant longitudinal effects in the COVID-19-affected group included: (i) greater reduction in grey matter thickness and tissue-contrast (change in diffusion measures are proxies for tissue damage) in the orbitofrontal cortex and parahippocampal gyrus; (ii) greater changes in markers of tissue damage in regions functionally connected to the primary olfactory cortex; and (iii) greater reduction in global brain size. The researchers hypothesise that this mainly limbic brain damage may result from: a spread of the disease via olfactory pathways; neuroinflammatory events; or the loss of sensory input due to anosmia (loss of sense of smell). (In an unrelated study, Song et al. used three different approaches to demonstrate that SARS-CoV-2 can invade brain tissue[43] but see also the section on mechanisms below.) In summary, using before-and-after imaging, there was clear evidence of a substantial, deleterious impact on the brain following SARS-CoV-2 infection. The infected participants also showed a larger cognitive decline between time points. Douaud et al. note that whether the changes can be partially reversed or will persist in the long term remains unknown.

Cardiovascular Disease

The most comprehensive study of cardiovascular complications of infection with SARS-CoV-2 was undertaken using the national healthcare databases of the US Department of Veterans Affairs. As with the study on mental health[40], Xie et al. assembled a cohort of 153,760 individuals with COVID-19 and 2 comparison cohorts of 5,637,647 (contemporary) and 5,859,411 (historical) individuals[44]. They reported that – on the basis of the difference between the estimated incidence rate in individuals with COVID-19 and the contemporary comparison group – beyond the first 30 days following SARS-CoV-2 infection, there was both an elevated risk of incident cardiovascular disease (CVD) and an elevated disease

burden. The CVD outcomes including cerebrovascular disorders (HR=1.5; 95% confidence interval: 1.5-1.6); excess burden=5.5 per 1000 persons at 12 months; dysrhythmias (HR=1.7; 1.6-1.8; excess burden=19.9/1000); pericarditis (HR=1.9; 1.6-2.1; excess burden=1.0/1000); myocarditis (HR=5.5; 3.8-7.6; excess burden=0.3/1000); ischaemic heart disease (HR=1.7; 1.5-1.8; excess burden=7.3/1000; heart failure (HR=1.7; 1.7-1.8; excess burden=11.6/1000; and thrombo-embolic disease (HR=2.4; 2.3-2.5; excess burden=9.9/1000. The comparisons with the historical cohort were consistent with the above analyses. The risks and burdens were evident even among individuals who were not hospitalised during the acute phase of the infection and increased in graded fashion across non-hospitalised, hospitalised, and admitted to intensive care.

In a small post-COVID-only imaging study of myocardial injury (damage to heart muscle), myocardial inflammation was identified on fluorodeoxyglucose–positron emission tomography (18F-FDG PET) in 8 of 47 participants; was associated with cardiac MRI abnormalities and elevated inflammatory blood markers at baseline; and resolved or improved at follow-up performed a mean of 52 days after baseline PET/MRI[45].

A study of 10 patients without a prior history of cardiovascular or pulmonary disease revealed that recovery from COVID-19 was accompanied by markedly reduced peak exercise aerobic capacity (oxygen consumption [VO_2]) compared with control participants[46]. This reduction in peak VO_2 was associated with impaired systemic oxygen extraction; i.e., a peripheral rather than central problem, suggesting peripheral vascular damage in addition to the direct effects on the lungs described below.

The Respiratory System

Autopsies on 13 individuals (10 males) with COVID-19 revealed characteristic pathologic changes in the lungs, with the main histologic finding being sequential alveolar damage apparently due to focal capillary microthrombus formation[47]. In a separate study, the immune and proteomic patterns of airway and peripheral blood among COVID-19 patients 3 to 6 months after hospital discharge (n=38) were compared with normal volunteers (n=10)[48]. The bronchoalveolar lavage (but not peripheral blood) proteome was abnormal in patients with post-COVID19 lung disease with elevated concentrations of proteins associated with apoptosis, tissue repair, and epithelial injury, findings that were associated with an increase in cytotoxic lymphocytes (especially tissue-resident $CD8^+$ T cells) and biomarkers of cell death. In three patients followed up at one year, some of these changes had partly resolved[48]. Taken together, these two studies indicate that COVID-19 can result in prolonged changes in both the respiratory vascular and immune systems that sometimes result in lethal lung disease and seem likely to cause persistent lung damage in those who recover.

Diabetes

A meta-analysis of eight studies with more than 3700 patients reported a pooled proportion of 14.4% for newly diagnosed diabetes in hospitalised COVID-19 patients[49]. Thus, in addition to the observation that patients with pre-existing co-morbidities, including Type 2 diabetes, are at higher risk, this analysis is highly suggestive that infection with SARS-CoV-2 can cause new-onset diabetes. Pancreatic autopsy tissue from COVID-19 patients revealed SARS-CoV-2 viral infiltration of beta-cells in all patients and *in vitro* studies showed that human islet cells are susceptible to infection[50]

Muscles

In a case-control study of 43 patients who had died with COVID-19 and 11 without COVID, most individuals with severe COVID-19 showed signs of inflammation of skeletal muscles, which was associated with the duration of illness. No evidence was found for direct viral infection of muscle fibres. Aschman et al. concluded that SARS-CoV-2 may be associated with a post-infectious, immune-mediated, myopathy[51]. This myositis plausibly explains much of the very common long-COVID symptoms of fatigue and muscle pain.

The Immune System

Patients with poorer outcomes and evidence of long COVID show immune abnormalities, such as: i) persistence of a cytotoxic programme evident in CD8+ T cells as well as elevated production of type 1 cytokines and interleukin-17[52]; ii) a specific immunoglobulin signature, based on total IgM and IgG3 levels[53]; and iii) highly activated innate immune cells, lack of naive T and B cells, and prolonged elevated levels of specific interferons (signalling molecules that are part of the body's antiviral defences)[54]. Some of these changes probably contribute to the chronic inflammatory and other manifestations of COVID-19.

Eyes

A meta-analysis estimated that 11% of 8,219 COVID-19 patients presented with ocular symptoms[55]. A separate study of 40 long-COVID patients used direct visualisation of nerve damage via corneal confocal microscopy to identify corneal small-nerve-fibre loss and the presence of increased immune cells (specifically dendritic cells) in patients with long COVID, especially those with neurologic symptoms[56]. The full implications for vision in long COVID patients are not clear but the related optic neuritis in multiple sclerosis can result in loss of vision and, in that disorder, corneal confocal microscopy can be used as a way of quantifying nerve damage. It may thus have a role in the longer term monitoring and management of long COVID.

Kidney Disease

Bowe et al., similar to the other US Veterans studies by this group of researchers[8,40,44], established a cohort of 1,726,683 (March 1, 2020-March 15, 2021): 89,216 30-day survivors of COVID-19 and 1,637,467 non-infected controls[57].They examined risks of acute kidney injury (AKI), decline in estimated Glomerular Filtration Rate (eGFR), end-stage kidney disease (ESKD), and major adverse kidney events (MAKE – defined as eGFR decline ≥50%, ESKD, or all-cause mortality). 30-day COVID-19 survivors exhibited a higher risk of AKI (HR=1.9), eGFR decline ≥30% (HR=1.3) eGFR decline ≥40% (HR=1.4), eGFR decline ≥50% (HR=1.6), ESKD (HR=3.0), and MAKE (HR=1.7). Compared to non-infected controls, 30-day survivors exhibited an excess decline in eGFR that was positively related to the severity of the acute infection, increasing stepwise across the spectrum of non-hospitalised, hospitalised, and those who were admitted to ICU[57]. In a separate smaller study, Hirsch et al. used the health records of a cohort of 5,449 patients admitted with COVID-19 (March 1-April 5, 2020) to 13 hospitals in New York City to establish that AKI developed in 1,993 (36.6%) and was seen largely in patients with respiratory failure (89.7% of those on mechanical ventilation developed AKI compared to 21.7% of non-ventilated patients)[58]; of the AKI patients in this study, 694 (35%) died. These two studies show that kidney damage occurs early and in temporal association with respiratory failure, is associated with a poor prognosis, and, among those who recover, there is a substantially elevated risk of kidney disease.

Erectile Dysfunction

Consistent with the observation that a key characteristic of COVID-19 is small-vessel thrombus formation, there are several studies that have identified erectile dysfunction as a component of long COVID[59-61].

Duration and Resolution

The duration and possible resolution of tissue and organ damage remains unclear. Although there is evidence that some changes can resolve[45,48], the probable outcome of COVID-induced diabetes[49], many of the thrombo-embolic events[62], and perhaps the brain and cognitive changes[41] is persistence of damage and resulting long-term disability.

Mechanisms

The widespread nature of the symptoms and the already extensive catalogue of tissues and organs involved point to long COVID as a cluster of diseases, not a single entity or even a clearly definable syndrome. Long COVID itself is related to the severity of the initial disease and whether or not an individual has been vaccinated. Together, these suggest that viral load is important. There are a variety of ways in which infection with SARS-CoV-2 can contribute to long COVID but the exact mix of mechanisms that produce damage in specific tissues and in any one individual is yet to become clear.

Direct Damage to Tissue

SARS-COV-2 invades via cell receptors (particularly ACE2) and its own Spike protein. It then replicates, turning each cell into a viral factory, which bursts to release the new generation of viral particles and destroys the cell in the process. Direct damage to tissue seems to play a part in the long-COVID manifestations that involve: i) blood vessels generally[63] as well as in the peripheral nerves that supply small blood vessels[46]; ii) muscles[64]; iii) the autonomic nervous system[65]; and iv) the brain[43,66], although there is strong evidence that damage to the brain involves almost all the mechanisms discussed here (see below).

Microscopic Blood Clots

Thrombo-embolic processes are key players in tissue damage and may themselves be the result of immune reactions. Focal capillary microscopic blood clots are found in the lung and result in alveolar damage and markedly reduced oxygenation of blood[47]. Amyloid microclots have been reported as a common feature in serum of COVID-19 patients[67]. Microthrombus formation is probably the primary cause of long-COVID-related erectile dysfunction[59]. Damage to the central nervous system includes thrombo-embolic ischaemic infarction[66]. Capillary flow disturbances limit oxygen diffusion exchange both in the lungs and in peripheral tissue and plausibly result in low oxygen levels in both blood and tissue (hypoxia). The result is a vicious cycle: infection and hypoxia result in inflammation that causes capillary function to deteriorate, which then accelerates hypoxia-related inflammation and tissue damage[68]. Ultimately, in patients with COVID-19, the endothelial inflammation and accumulation of leukocytes, along with the initiation of immune responses, culminate in microthrombotic complications and sometimes deep vein thrombosis, pulmonary embolism, and stroke[62].

Immune Damage

The immune system can, itself, cause damage when it begins to attack normal tissue or produce a cytokine storm[69]. Damage can be seen in: i) mitochondria (the cell's energy generator)[70]; ii) muscles – this is likely to be a key cause of long-COVID fatigue[71]; and iii) lung[48]. Although virus can be found in neural tissue, some of the central features of the changes in the brain involve activation of microglia (the brain's macrophages and part of the immune system) in the presence of very low levels of detectable virus; this suggests that activation does not result from direct viral infection but, rather, from systemic inflammation, perhaps with a synergistic contribution from hypoxia/ischaemia[72,73]. Thus COVID-19-related brain damage is likely to be the result of infection, microclots and hypoxia, and an activated immune response.

Viral Reactivation

In some individuals, there is evidence of reactivation of Epstein-Barr virus (EBV, a virus that causes glandular fever) as well as bystander activation (no evidence of a viraemia) of cytomegalovirus (CMV)-specific CD8+ T cells[74]. Whether these processes contribute to the fatigue that resembles Chronic Fatigue Syndrome, which can also present with peripheral nerve damage, is not clear[75].

Impact of Vaccination on the Risk of Long COVID

To estimate the impact of vaccination on long COVID is to chase a moving target because the continued emergence of new variants means that we may not yet have full data on the relationship between all variants and long COVID.

Acknowledging the large heterogeneity among studies in the definition of long COVID and noting that all results were observational, the UK Health Security Agency summarised data from 15 studies (to 12 January 2022) of the effectiveness of vaccination against long COVID. Seven of these studies asked whether vaccination before infection reduced the symptoms or incidence of long COVID; 7 explored whether vaccination after a diagnosis of long COVID reduced or cleared symptoms; and 1 examined both[76]. Six of 8 studies of the effectiveness of vaccination before COVID-19 infection suggested that vaccinated cases (1 or 2 doses) were less likely to develop symptoms of long COVID after breakthrough infection, early (4 weeks after infection), later (12-20 weeks after infection), and longer term (6 months after infection). These studies were only of participants who had had COVID-19 so the impact of vaccination via reducing incidence of COVID-19 itself is not accounted for. However, that means that these studies underestimate the population-wide effectiveness of vaccines against long COVID because those who were never infected with SARS-CoV-2 cannot, by definition, get long COVID. Data from 2 of the studies show that fully vaccinated cases were less likely to have the following symptoms in the medium or long term than unvaccinated cases: fatigue, headache, limb weakness, persistent muscle pain, hair loss, dizziness, shortness of breath, loss of sense of smell, interstitial lung disease, and other pain[76].

In studies examining the effect of vaccination among people after a diagnosis of long COVID, the overall evidence identified an improvement in symptoms after vaccination, either immediately or over several weeks; however, some people reported a worsening of symptoms post-vaccination. One study suggested that being vaccinated sooner, rather than later, after diagnosis was much more likely to reduce symptoms of long COVID than remaining unvaccinated. In 3 of the 5 studies that reported on symptom changes following vaccination of those with long COVID, a higher proportion reported unchanged symptoms

following vaccination than reported improved or worsened symptoms[76].

The UK Office of National Statistics summarised data to 5 September 2021 on the impact of vaccination after a diagnosis of COVID-19[77]. They noted that a first vaccination was associated with an initial 13% decrease in the likelihood of self-reported long COVID among study participants aged 18-69 years in the UK who had confirmed COVID-19 prior to vaccination. Receiving a second COVID-19 vaccination was associated with a 9% decrease in the likelihood of self-reported long COVID – relative to having received the first vaccination – and a sustained improvement after that.

Ayoubkhani et al. investigated the impact of vaccination on the likelihood of developing long-COVID symptoms 12 weeks after infection[78]. 3,090 double-vaccinated participants (mean age 49 years; 54% female; 92% white; median post-infection follow-up=96 days) were propensity-score-matched to control participants who were unvaccinated at the time of infection. Long-COVID symptoms were reported by 294 participants who were double-vaccinated before infection (prevalence 9.5%) compared with 452 unvaccinated participants (14.6%). This corresponds to a significant protective effect of vaccination with an adjusted OR for long-Covid symptoms of 0.6 (95% CI: 0.5 to 0.7).

Simon et al. used data from the COVID-19 Patient Recovery Alliance to undertake a retrospective analysis of the medical history of 240,648 COVID-19-infected persons[79]. They reported that patients who received at least one dose of a COVID vaccine before diagnosis with COVID-19 were 7-10 times less likely to report two or more long-COVID symptoms than unvaccinated patients. Furthermore, unvaccinated patients who received their first COVID-19 vaccination after but within four weeks of SARS-CoV-2 infection, were 4-6 times less likely to report multiple long-COVID symptoms. Furthermore, those who received their first dose within 4-8 weeks after diagnosis were 3 times less likely to report multiple long-COVID symptoms than those who remained unvaccinated.

Thus, there is, to date, quite strong and consistent evidence that vaccination is wholly or partly protective against long COVID, whether people receive their vaccination before or after infection and that this protection is found even if vaccination occurs up to 12 weeks after a COVID-19 diagnosis.

In summary, long COVID occurs in at least 20-30% of individuals who have been infected with SARS-CoV-2 and is strongly related to the severity of the initial illness. Fortunately, there is, to date, quite consistent evidence that vaccination is wholly or partly protective against long COVID, whether vaccination occurs before or after COVID-19. A society wanting to minimise the health and cost burden of managing long COVID would therefore choose to maximise vaccination coverage as well as minimise risk of infection with standard public health and social measures.

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Appendix – more detail on the studies of symptoms

Electronic-Health-Record Studies

Almost 2 million individuals were followed using the US FAIR Health database of healthcare claim records[22]. Of those diagnosed with COVID-19, 23.2% had at least one post-COVID condition ≥30 days later. The frequency showed a relationship with severity: 50% of the

hospitalised reported at least one symptom, 27.5% of the symptomatic but not hospitalised, and 19% of the asymptomatic. The most common reports, in descending order, were: pain, breathing difficulties, hyperlipidaemia, malaise/fatigue, and hypertension. There was also an excess of anxiety and depression. The symptoms were more common amongst women.

Taquet and colleagues conducted a retrospective cohort study based on linked EHR data from 81 million patients, largely in the US, including 273,618 COVID-19 survivors[6]. Incidence within 6 months as well as in the second 3 months (i.e., exploring symptoms that persisted after 90 days) after diagnosis was calculated for 9 central features of long COVID (breathing difficulties/shortness of breath, fatigue/malaise, chest/throat pain, headache, abdominal symptoms, myalgia, other pain, cognitive symptoms, and anxiety/depression). These data were compared with a matched cohort of patients diagnosed with influenza during the same time period. Among survivors (mean age: 46.3; 55.6% female), 57.0% had one or more long-COVID feature during the whole 6-month period (i.e., including the acute phase), and 36.6% between 3 and 6 months. The incidence of each feature was: abnormal breathing (18.7% in the 1-180-day period; 7.9% in the 90-180-day period), fatigue/malaise (12.8%; 5.9%), chest/throat pain (12.6%; 5.7%), headache (8.7%; 4.6%), other pain (11.6%; 7.2%), abdominal symptoms (15.6%; 8.3%), myalgia (3.2%; 1.5%), cognitive symptoms (7.9%; 4.0%), and anxiety/depression (22.8%; 15.5%). All 9 features were more frequently reported after COVID-19 than after influenza (with an overall excess incidence of 16.6% and hazard ratios between 1.4 and 2.0, all $p< 0.001$). The symptoms co-occurred more commonly and formed an interconnected network. Statistically significant differences in incidence and co-occurrence were associated with sex, age, and illness severity. Thrombo-embolic long-COVID clinical features occurred and co-occurred frequently and showed some specificity to COVID-19, though they were also observed after influenza. The incidence of any long-COVID symptom varied from 46.4% in the 10- to 21-year age group, to 61.1% in those >65. They also varied by severity: 63.6% among those who were hospitalised and 73.2% for persons admitted to ICU. Women were statistically significantly more likely to have headaches, abdominal symptoms, and anxiety/depression, whereas men had more breathing difficulties and cognitive symptoms. Younger patients were more likely to have headaches, abdominal symptoms, and anxiety/depression, whereas older patients were more likely to have breathing difficulties, cognitive symptoms, pain, and fatigue.

Spotnitz et al. characterised the post-acute experience for over 448,178 patients who were diagnosed with COVID-19 or tested positive for SARS-COV-2 using the IBM MarketScan Commercial Claims and Encounters, Optum Electronic Health Record, and Columbia University Irving Medical Center databases. Of these, 123,509 (27.6%) had a post-COVID-related symptom within the following 6 months. Five long-COVID diagnoses had higher relative risk in COVID-19 than among concurrently identified Influenza patients: altered smell or taste, myocarditis, acute kidney injury, shortness of breath, and hair loss. Further, the proportions of patients who had post-acute diagnoses or symptoms of lung disorder, chest pain, depression, anxiety, or joint pain in the COVID-19 cohort were greater than 2% in each of the 3 databases.

The prevalence of post-COVID symptoms was much lower in the EHR-based studies of Hernandez-Romieu et al.[24] and Chevinsky et al.[25] Hernandez-Romieu et al. reported that, among persons aged 20 years or older with a positive test, shortness of breath (4.5% non-hospitalised, 10.5% hospitalised, and 16.6% ventilated), fatigue (4.2% non-hospitalised, 8.0% hospitalised, and 19.8% ventilated) were the most common symptoms 31 and 150 days after testing. However, among those in the comparison group who had negative tests

but the same categories of severity, shortness of breath was 4.1% among the non-hospitalised, 5.5% for the hospitalised, and 9.8% for the ventilated and fatigue prevalences were 4.4% non-hospitalised, 5.9% hospitalised, and 10.0% ventilated[24]. Chevinsky et al. reported that 7.0% of hospitalised adults experienced ≥1 of 5 post-COVID conditions and that 7.7% of adult outpatients with COVID-19 experienced ≥1 of 10 post-COVID conditions. The reasons for the differences between these studies and the other EHR-based studies described above are not obvious but choice of investigated symptoms may be relevant.

Cohort and Cross-sectional Studies

Huang et al. undertook a cohort study of confirmed-COVID-19 patients discharged from Jin Yin-tan Hospital (Wuhan, China) Jan 7 – May 29 2020[26]. They enrolled 1733 of 2469 discharged patients with a median age of 57·0 years; 48% were women. Follow-up was June 16-Sept 3 2020 with a median duration after symptom onset of 186 days. Fatigue or muscle weakness (63%; 1038 of 1655) and sleep difficulties (26%; 437 of 1655) were the most common symptoms. Anxiety or depression was reported by 23% (367 of 1617). Patients who had been the most severely ill had greater impairment of pulmonary diffusion capacities and more abnormalities on chest imaging.

Sudre et al. analysed data from 4,182 incident cases of COVID-19, with individuals self-reporting symptoms prospectively in the COVID Symptom Study app[7]. 13.3% (n=558) reported symptoms lasting ≥28 days, 189 (4.5%) for ≥8 weeks, and 95 (2.3%) for ≥12 weeks; the most common were fatigue, headache, shortness of breath, and loss of sense of smell. These were seen more commonly among women, older individuals, and those with a higher body mass index. They reported two main clusters in those with symptoms for ≥28 days: i) those who identified exclusively fatigue, headache, and upper respiratory symptoms (shortness of breath, sore throat, persistent cough, and loss of sense of smell); and ii) those with additional multisystem complaints, including fever and gastrointestinal symptoms. More than five symptoms during the first week of the initial illness was associated with a greater risk of long COVID (OR = 3.5 (2.8–4.5)) with the most predictive of symptoms for ≥28 days being fatigue, headache, shortness of breath, a hoarse voice, and muscle pain.

Munblit et al. collected data via telephone 6 to 8 months post-discharge from 2649 of 4755 (56%) patients from 4 hospitals in Moscow, Russia (8 April – 10 July 2020)[32]. COVID-19 diagnosis was clinical in 1291 and molecular in 1358. Most cases were mild but 902 (34%) required supplemental oxygen and 68 (2.6%), ventilation. Median age was 56 years; 51.1% were women. Persistent symptoms were reported by 1247 (47.1%) participants, with fatigue (21.2%), shortness of breath (14.5%), and forgetfulness (9.1%) the most common. Symptoms were more common among women.

Whitaker et al. reported on rounds 3–5 of the REACT-2 study, involving 508,707 people in the community in England[80]. The weighted prevalence of self-reported COVID-19 was 19.2% with 92,116 people reporting one or more of 29 specific symptoms, of whom 76,155 (82.7%) reported a valid date of symptom onset ≥12 weeks before their survey date. Over a third (37.7%) of these 76,155 symptomatic people experienced at least one symptom and 14.8% experienced three or more symptoms for ≥ 12 weeks. Nearly a third (30.5%) of people with at least one symptom lasting ≥12 weeks reported having had severe COVID-19 symptoms during their acute illness. The prevalence of persistent symptoms was higher in women than men (OR=1.5) and, conditional on reporting symptoms, was higher at older ages. Obesity, smoking or vaping, hospitalisation, and deprivation were also associated with a higher probability of persistent symptoms; Asian ethnicity was associated with a

lower probability. Two stable symptom clusters were identified for symptoms that persisted for ≥12 weeks: a larger cluster in which tiredness predominated and another with a high prevalence of respiratory and related symptoms.

Ghosn et al. reported symptoms that persisted 6 months after admission in a longitudinal prospective French cohort of hospitalised patients with confirmed COVID-19[29]. Planned follow-up involved a physician's visit at month 3 (M3) and M6 after admission. Over a quarter (29%) had been admitted to ICU during the acute phase. M6 data were available for 1137 participants. Median age was 61 years. 68% and 60% of participants had at least one symptom at M3 and M6, respectively, mostly fatigue, shortness of breath, joint pain, and muscle pain. At M6, 24% (n=255) of participants had three or more persistent symptoms. The presence of three or more symptoms at six months was higher in women and those with more severe initial illness but not related to age or having two or more comorbidities. 29% (n=125) of those with a professional occupation were not back to work at six months.

Fernández-de-las-Peñas et al. reported on a multicenter study that assessed post-COVID symptoms and their risk factors seven months after hospital discharge of patients hospitalised with a positive RT-PCR diagnosis of SARS-CoV-2 during the first wave of the pandemic (March 10 – May 31 2020) in four public hospitals in Madrid, Spain[33]. A random sample of 300 patients was selected from each hospital. Follow-up was by telephone interview and included a list of post-COVID symptoms (shortness of breath, fatigue, loss of smell, loss of taste, hair loss, chest pain, palpitations, diarrhoea, skin rashes, brain fog, memory loss, and cough) as well as any symptom that the participants considered relevant. After refusals, non-contact, and deaths, a total of 1142 (48% women; mean age: 61 years) were included and assessed a mean of 7.0 months after discharge. Only 212 (18.6%) were completely free of any post-COVID symptom, 238 (20.8%) had one symptom, 267 (23.4%) had two symptoms, and 425 (37.2%) had 3 or more. The mean number of post-COVID symptoms was 2.5 (SD 1.2). More symptoms were seen among women and those who required ICU care. The most frequent symptoms were fatigue (60.8%), hair loss (26.3%), and shortness of breath (23.5%). Number of comorbidities and number of acute COVID-19 symptoms at admission were also associated with the number of long-COVID symptoms.

Naik et al. described the clinical features of, and risk factors for, post COVID-19 sequelae in a North Indian tertiary healthcare centre (October 2020 – February 2021)[30]. A total of 1234 patients aged >18 years with laboratory-confirmed COVID-19 were recruited within at least two weeks of diagnosis and followed up for a median of 91 days. Of these, 495 (40.1%) had persistent symptoms post-discharge or recovery. In 223 (18.1%), symptoms resolved within four weeks; 150 (12.1%) had symptoms up to 12 weeks, and 122 (9.9%) beyond 12 weeks. Most common symptoms included muscle pain (10.9%), fatigue (5.5%), shortness of breath (6.1%), cough (2.1%), insomnia (1.4%), mood disturbances (0.48%), and anxiety (0.6%). Patients who were hospitalised were more likely to report fatigue. Patients with hypothyroidism and hypoxia during acute illness were at higher risk of long COVID.

Wong-Chew et al. conducted a longitudinal study on the prevalence of, and risk factors for, long-term health consequences of COVID-19 in patients discharged from the Temporary COVID-19 Hospital (TCH) in Mexico City (September 2020 – January 2021)[31]. Self-reported symptom data collected by telephone from 4670 participants showed that neurologic, dermatologic, and mood-disorder symptom clusters persisted in >30% of patients at 90 days post-discharge. Although most symptoms decreased in frequency between day 30 and 90, alopecia (hair loss) and the dermatologic symptom cluster statistically significantly increased. Women were more prone than men to develop long-term symptoms; invasive

mechanical ventilation increased the frequency of symptoms at 30 days post-discharge.

Shang et al. followed up 1174 patients with severe RT-PCR-confirmed COVID-19 who recovered and had been discharged for 6 months from 3 hospitals in Wuhan, China; 55.4% (n=441) had one or more sequelae (February – March 2020)[27]. The most common symptoms were fatigue (25.3%), sleep disorder (23.2%), and shortness of breath (20.4%). Among the symptomatic group, 262 (59.4%) had more than one symptom. Women were statistically significantly more likely to have multiple symptoms as well as fatigue and sleep disorders. Having had a critical illness was found to be an independent risk factor for memory loss.

Vedel Sørensen et al. conducted a nationwide cross-sectional study in Denmark of 61,002 individuals aged ≥15 years with RT-PCR-confirmed COVID-19 (September 2020 – April 2021 and a corresponding test-negative group of 91,878. Web-based-questionnaire data were collected 6, 9, or 12 months after diagnosis[28]. Six to 12 months after the test date, the risks of 18 out of 21 physical symptoms were higher among those who tested positive and 29.6% of these people experienced at least one post-acute symptom. The largest risk differences were observed for loss of sense of smell (risk difference (RD) for prevalence = 10.9%), loss of sense of taste (RD=8.7%) fatigue/exhaustion (RD=8.4%), shortness of breath (RD=4.9%), and reduced strength in arms/legs (RD=4.7%). Over half (53.1%) of those who tested positive reported at least one of the following conditions: concentration difficulties (RD=28.3%), memory disturbance (RD=27.3), sleep disturbance (RD=17.3%), mental exhaustion (RD=32.6%), or physical exhaustion (RD=40.5%) compared to 11.5% of those who tested negative. New diagnoses of anxiety (RD=1.2%) or depression (RD=1.0%) were also more common among those with a history of COVID-19.

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