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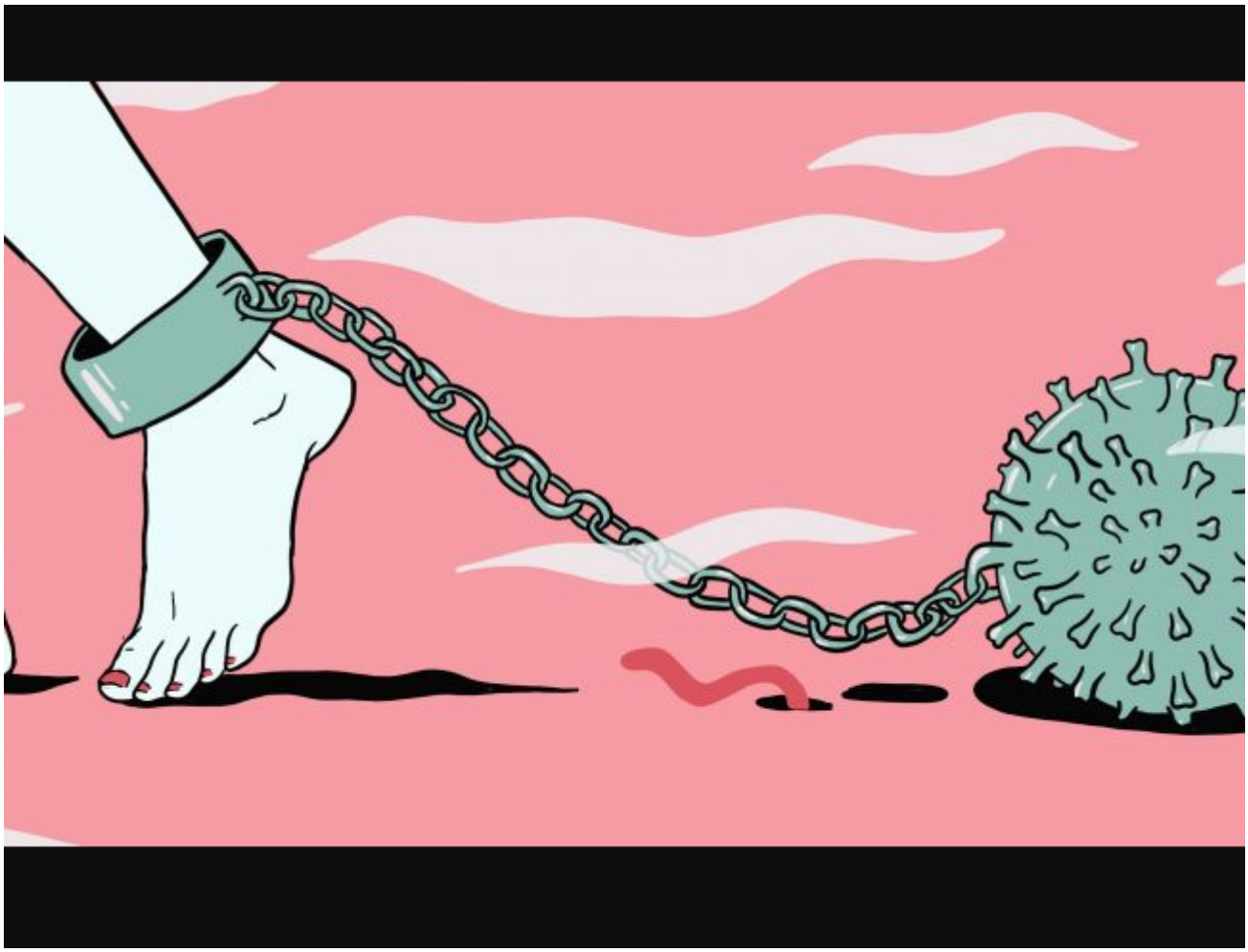

The long-term health burden of COVID-19: further justification for NZ’s elimination strategy

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This blog briefly surveys the emerging scientific evidence on the longer-term burden of symptoms and disease in survivors of the COVID-19 pandemic. Many of these symptoms point to damage in the brain and heart. These long-term harms add to the wide range of other reasons for Aotearoa/New Zealand to persist with its successful COVID-19 elimination strategy.

Following clear and focused scientific advice, New Zealand chose to meet the current

COVID-19 pandemic with an elimination strategy. As we have discussed on multiple occasions in the scientific literature and public media, this strategy seeks to reduce the community transmission of the pandemic virus, SARS-CoV-2, to zero by a series of public-health interventions and rapid responses to any outbreak. Borders remain tightly controlled, incoming travellers are isolated or quarantined as appropriate, hygiene and behavioural guidelines have been promulgated and widely followed, all supported by extensive testing and a nationwide capacity to track and trace contacts associated with any outbreak. To date, since the initial outbreak was controlled, this well-poised system has been invoked once to control the recent Auckland outbreak: a perimeter was rapidly established and community transmission restricted.

Despite the success, to date, of this approach – as evidenced by numbers of cases, mortality (the lowest in the OECD), and even the impact on the economy – there are voices that insist that we should pursue a much less restrictive approach to managing this pandemic. The advocacy for this approach is based on an erroneous (but regularly repeated) claim that the current pandemic results in no greater mortality than seasonal influenza when, in fact, SARS-CoV-2 is more than an order of magnitude more lethal[1].

More crucially, the long-term consequences of infection with SARS-CoV-2 are simply being ignored by those who imagine that pandemic control aimed at everyone's wellbeing is an attack on their freedom – a failure, in truth, to understand that we are a community, a society, not a collection of isolated individuals.

Long-COVID

Some are beginning to call it "long-COVID"[2] and refer to the misery of "the long haulers"[3]. There are many aspects to this persistence of symptoms after a diagnosis of what was initially assumed to be just an acute illness. Although we lack large robust studies of the phenomenon, there is enough coherence to the current evidence to establish that long-COVID is a real phenomenon and that, for many, the burden of infection with SARS-CoV-2 does not end with discharge from hospital, with the disappearance of the virus, or with the fading of acute symptoms.

Essentially, all the studies to date have no denominators. What is available are individual case-reports and collated case-reports both from clinician-scientists and from patient groups. Therefore, there is no accurate measure of prevalence of the prolonged outcomes or of specific diagnoses and no more than a general idea of the distribution of individual manifestations.

Indeed, the earliest reports were anecdotal and the product of good non-specialist reporting. For instance, in June 2020, the *Washington Post* described multiple long duration cases: individuals who had spent more than 60 days with serious symptoms[4]. In July 2020, the *Guardian* reported on a current study of individuals at St Vincent's Hospital in Sydney, where 94 apparently recovered patients agreed to be involved and are undergoing tests every three months to determine whether SARS-CoV-2 is associated with any lasting effects in the immune system, blood, lung, gut, and brain[5]. No data are yet published but St Vincent's head of Infectious Diseases, Associate Prof Gail Matthews, reported that, currently, one third of the study group are showing symptoms three to four months after being initially infected. Matthews also noted that, of the 10% who were admitted to hospital, "around 80%" still had some symptoms.

The UK Covid-19 Symptom Study, which uses an app to collect symptom information from

nearly four million users, says that their data show that one in 10 people with COVID-19 are sick for three weeks or more[6]. The app was developed by a health-science company and the data are being analysed in collaboration with King's College London researchers.

Data on 640 individuals across Europe and US – derived from a survey on prolonged symptoms organised by a decentralised team of COVID-19 patients – were uploaded in May 2020[7]. Self-reported symptoms included fatigue, difficulty concentrating, insomnia, chills/sweats, loss of appetite, and headache, as well as fever, cough, and shortness of breath.

A more comprehensive study of the persistence of symptoms involved 143 patients in Italy who were assessed at a mean of 60 days after symptom onset[8]. Only 18 (12.6%) were completely free of COVID-19 symptoms; 32% had 1-2 symptoms and 55% had three or more. The prolonged symptoms included fatigue, breathing difficulties, joint pain, and chest pain.

Larger formal studies are now underway, including the UK-based "Post-Hospitalisation COVID-19 Study" (PHOSP-COVID) of 10,000 COVID-19 patients who, after discharge from hospital, are being followed for 12 months[9]. The aim is to establish a clearer picture of the prevalence and persistence of long-term outcomes and to develop appropriate treatment protocols.

The Reggio Emilia (Italy) Covid-19 working group assembled and reported on a cohort of 2653 patients who were initially diagnosed between 27 February and 2 April 2020[10]. This research group are now re-contacting survivors to participate in a follow-up study[11]. The data are not published in the scientific literature but the researchers have established that there exists, among their patients, a variety of persistent symptoms: pain, paraesthesiae, depression, fatigue, short-term memory loss, hair loss, and the need for hours of extra sleep. "Almost half the patients" say they are not cured.

Indeed, from observations made so far in multiple places, the symptoms of long-COVID cover a wide range from the non-specific to some particular and rare manifestations[12]. They include pain, fever, "brain fog" (loss of the ability of concentrate), shortness of breath, heart arrhythmias, and hypertension. Also included is Guillain-Barré syndrome, a neurological syndrome which was already known to be one of the late complications of infection with Zika virus and *Campylobacter* (see here for a NZ study). It may be relevant that a study of 78 medical personnel over 15 years showed that SARS-CoV-1 (the coronavirus that caused the SARS pandemic in 2003) also provides evidence of persistence of long-term consequences, specifically, in this case, lung damage and bone damage[13].

There are some studies that provide evidence of specific organ damage, particularly the brain and heart, that may explain some of the persistent symptoms – see Appendix.

Mechanisms for the harm

As discussed in the Appendix, the specific manifestations of COVID-19 damage in both brain and heart (as well as other organs) appear to be associated with:

- tissue damage consequent upon invasion, virus replication and tissue destruction (e.g., encephalitis; myocarditis);
- the immune response involving extensive systemic release of inflammatory cytokines with resulting microvascular damage from thrombosis (e.g., stroke; myocardial

infarction);

There are also data on the persistence of the virus itself. Anecdotal reports[14] [15] have been supported by an as-yet non-peer-reviewed study in the Netherlands[16] of 129 patients. Infectious virus shedding was detected in 23 (17.8%) and the median duration of shedding was 8 days after onset of symptoms. The probability of detecting infectious virus dropped below 5% after 15 days after onset of symptoms. In one patient, however, infectious virus was detected up to 20 days after onset of symptoms. Whether any of the individuals with prolonged symptoms also show persistence of the virus itself has not, as far as I can tell, been reported.

Conclusions

A central issue with the current pandemic is that we have not seen anything like SARS-CoV-2 before. It shows this spectrum of behaviours:

1. highly infectious
2. capable of airborne spread
3. an illness that is often not so devastating that it allows many infectious individuals to still mix with the susceptible
4. especially spreadable by the young who epitomise (even more so) point 3
5. an infection fatality risk (IFR) between 0.5 and 2%, much more lethal than typical seasonal influenza epidemics
6. increasingly lethal with age and with widespread – more recently increasingly common across world – co-morbidities

Many who advocate “routine” responses to the COVID-19 pandemic do not grasp how different this virus is. As this blog post is intended to convey, there is a 7th feature that can be added to this list – a wide spectrum of multi-organ symptoms that persist long after the virus has cleared.

So, those who mistakenly (or, more worryingly, deliberately) argue that the IFR is much lower than is actually the case[1] need also to expand their understanding to embrace the fact that there are long-term sequelae. These are manifestations that may lay an increasing burden not only on individuals, whanau, and community but also on the health system and thus, on the New Zealand economy. This is additional evidence, if any were needed, that elimination is the only appropriate response in Aotearoa/New Zealand – it is the most rational, most humane, and, in the end, most economical approach to the control of this pandemic.

APPENDIX: Specific impacts on the brain and heart

Specific impacts – Brain

Early in the pandemic in the UK, a group of researchers developed an online network of case-report notification portals across major UK neuroscience bodies, representing neurology, stroke, psychiatry, and intensive care[17]. Physicians were encouraged to report both catch-up cases that had occurred before the portals were up and prospective cases as they were diagnosed. Complete clinical datasets were available for 125 (82%) of 153 patients, median age 71 years. Seventy-seven (62%) presented with a stroke event, three-

quarters of which were ischaemic strokes; 13 (18%) of these patients were younger than 60 years. Altered mental status was the second most common presentation, accounted for by encephalopathy or encephalitis and primary psychiatric diagnoses, often occurring in younger patients; 21 (92%) of the psychiatric presentations were new diagnoses. In the absence of a denominator but against the background of the total UK case-load, the neuropsychiatric diagnoses represent a small spectrum of the total disease load but the specific outcomes will contribute strongly to individual long-term sequelae of SARS-CoV-2 infection.

A smaller radiology-based study of 43 patients, (29 SARS-CoV-2 PCR-positive, eight probable and six possible) reported: encephalopathies with no distinct magnetic resonance imaging (MRI) or cerebrospinal fluid (CSF) abnormalities; inflammatory central nervous system (CNS) syndromes including encephalitis and encephalomyelitis; ischaemic strokes associated with a prothrombotic state; peripheral neurological disorders, almost all Guillain-Barré syndrome; as well as other CNS disorders[18].

There is also evidence of demyelinating disease[19], meningitis/encephalitis[20], and the possibility that encephalopathies, particularly presenting as delirium, are underdiagnosed[21].

Some researchers[22] recently summarised what is known from the case reports and case series, describing multiple neurological manifestations across a total of 901 patients, albeit in the absence of many details. Consistent with the above, they identify encephalopathy, Guillain-Barré syndrome, and encephalitis among the direct effects of the virus on neural tissue and note that SARS-CoV-2 has been detected in the CSF of some patients. In addition to manifestations of infection of neural tissue, cerebrovascular events have also been reported, presenting more commonly as ischaemic stroke in the presence of pro-inflammatory state but also as haemorrhagic stroke.

Although the primary receptor to which SARS-CoV-2 binds, Angiotensin Converting Enzyme-2 (ACE-2), has relatively low expression in brain[23], there are studies that show that the virus is capable of infecting and killing neural cells[24 25]. There are also data[25] to show: that SARS-CoV-2 can invade mouse brain tissue; that, in brain organoids, infection was prevented by antibodies against ACE-2 or by CSF from COVID-19 patients; and that virus is found in autopsied brains of individuals who died from COVID-19.

It is clear from all these studies that SARS-CoV-2 infection causes a wide spectrum of neurological abnormalities that involve both neuronal and vascular tissue but, in the absence of data from large well conducted longitudinal studies accompanied by extensive clinical data, we remain in the dark about the prevalence and relative distribution of specific conditions, as well as longer-term outcomes. Nonetheless, these highly visible outcomes plausibly inform our understanding of the development of milder but persistent neurological symptoms such as headache, sleep and mood disorders, loss of appetite, and loss of ability to concentrate.

Specific impacts – Heart

A study of 200 recently recovered patients who underwent cardiac magnetic resonance imaging (CMR) with a median time interval between diagnosis and CMR of 71 (64 to 92) days showed cardiac involvement in 78 (78%) and continuing myocardial inflammation in 60 (60%), independent of pre-existing conditions[26].

CMR on 26 (15 male) competitive college athletes was undertaken after quarantine; four

(all male) had findings consistent with myocarditis[27]. All four showed Late Gadolinium Enhancement (LGE; which characterises regional scar formation and myocardial fibrosis). There were a further eight with LGE but without evidence of prior myocardial injury.

In a study of 101 patients (average age 49 years) admitted to two tertiary-care hospitals in Sichuan Province (China)[28], 16 (15.8%) of them showed acute myocardial injury, evidenced by high-sensitivity troponin T levels above the normal upper limit; nearly half of these had levels five-fold higher than the upper limit. These patients had a higher prevalence of pre-existing cardiovascular disease.

A study of 2736 patients in five hospitals of the Mount Sinai Health System in New York City[29] involved all patients who had had troponin-I measured within 24 h of admission. Of the 2736, 985 (36%) had elevated troponin-I levels, demonstrating that myocardial injury is highly prevalent among those infected with SARS-CoV-2. Patients with pre-existing cardiovascular disease were more likely to present with myocardial injury.

A study to evaluate the risk of cardiac arrest and arrhythmias was conducted in a population admitted to the Hospital of the University of Pennsylvania with a diagnosis of COVID-19[30]. Among the 700 patients (mean age 50±18 years; 45% men; 71% African American), there were 9 cardiac arrests, 25 incident atrial fibrillation events, 9 clinically significant bradyarrhythmias (usually associated with a conduction block in the heart), and 10 cases of non-sustained ventricular tachycardia (a serious heart arrhythmia).

An autopsy study showed that SARS-CoV-2 can be found in the myocardium (the heart muscle)[31]. Viral load in this study was associated with cytokine response but there was no difference in the influx of inflammatory cells into the myocardium.

In summary, the presence of pre-existing cardiovascular disease in patients with COVID-19 is associated with high mortality and COVID-19 can, itself, cause cardiovascular disorders, including myocardial injury and arrhythmias. As with the brain, ACE-2 is the likely point of entry to heart muscle[32 33], which is among the tissues that express ACE-2 at the highest levels[23]. ACE-2 entry is aided by transmembrane protease serine 2 protease. The tissue localisation of the receptors correlates with both presenting symptoms and organ dysfunction[33].

As with the brain, SARS-CoV-2 infection causes a wide spectrum of cardiovascular abnormalities involving both myocardium and vascular tissue. Also, as with the brain, in the absence of well conducted longitudinal studies that include extensive clinical data, we do not have a full picture of prevalence and relative distribution of specific conditions, nor of longer-term outcomes. Nonetheless, these more severe clinical outcomes can inform our understanding of the development of reported persistent symptoms, including arrhythmias, hypertension, and perhaps chest pain and dyspnoea.

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