PUBLIC HEALTH COMMUNICATION CENTRE AOTEAROA

Science-informed policy: considerations in support of judicious, circumspect changes to Aotearoa/NZ alert levels during the COVID-19 pandemic

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There are a number of characteristics of the novel SARS-CoV-2 virus and the COVID-19 pandemic that make deciding when and how to change the rules regarding lock-down and physical distancing less than straightforward. In this very brief commentary, these considerations do not include the pressures from those who are more concerned with the economy than with human individual, whanau, and population health.

Infectivity

It has been clear from the earliest days of the pandemic that this virus is highly infectious, with estimates of the basic reproduction number (R_0) of greater than 2[1,2] (ie, the average infected case will typically infect more than two other people). A tight estimate of R_0 is difficult in the absence of a good understanding of the prevalence and incidence of disease but the early rapid spread, the nature and size of clusters, especially in residential facilities and resulting from social functions, and the effectiveness of physical distancing all attest to this high infectivity, even in the absence of an exact measure of R_0.

Severity and lethality

Equally obvious from the earliest reports is the lethal nature of the virus, particularly among older individuals and those with existing chronic conditions, including heart disease, diabetes, cancer, etc[3-6].

Silent transmission

Infection with SARS-CoV-2 manifests across a very wide spectrum – from individuals who are asymptomatic through increasing severity of disease to a need for critical care and, finally, death. The asymptomatic and mildly affected are clearly, nonetheless, capable of spreading the virus to others[7], as also evidenced by the emergence of disease without a clear transmission path[8] and by the population pattern of virus mutations. Indeed, the time of early low-symptom infection is probably the period of greatest infectivity (shedding of the virus[9-11]). Routine screening of asymptomatic pregnant women has been shown to reveal a high proportion of infected individuals; not all of these women eventually showed symptoms[12]. In a study of virus transmission, He et al concluded that infectivity probably peaked at or before symptom onset and estimated that 44% (95% CI: 25–69%) of secondary cases were infected during the index cases' presymptomatic stage[13].

It is silent transmission, coupled with the highly infective nature of the virus, that makes lifting restrictions on physical distancing and social contacts most problematic. It speaks to the need for a better understanding of the prevalence of infection in asymptomatic individuals, best accomplished by widening testing out from individuals who present with symptoms, as has now begun in some New Zealand centres[14]. We will eventually know the extent of asymptomatic disease by virtue of establishing retrospectively the immune status of the population, but that does not answer the exigent need to know the prevalence in order to better plan the management of the degree of restriction of non-bubble contact.

Re-emergence of infection?

There are data from China[15], Japan[16], and South Korea[17] attesting to the re-emergence of infection in individuals who were reported to have been COVID-19 positive and, later, negative. One possible explanation is obviously the presence of errors in the testing system[18]. However, others have asked the question as to whether reinfection can occur[19] (which means that immunity is not 100% following infection – see below). A third possibility is reactivation, whereby a virus emerges from a latent state in a host cell and undergoes productive replication and shedding[20]. This occurs particularly among herpes viruses but is currently under investigation as a possible explanation for the apparent behaviour of SARS-CoV-2[19]. Finally, given the widespread list of SARS-CoV-2 target organs (see below), it seems possible that an individual may harbour the virus (undetected by upper-respiratory testing) in, say, the kidney, which later emerges, for a second time, in the respiratory tract.

Whatever the explanation of apparent reinfection, it identifies yet another source of transmission in the population and, again, argues for a careful approach to lifting physical distancing restrictions.

Target organs

COVID-19 has been largely identified as a respiratory viral disease (and can present with a loss of the sense of smell – anosmia[21]); indeed, SARS-CoV-2 is most likely to be fatal as a

result of its impact on the lungs. Nonetheless, it has been shown to target an extensive list of organs, some of which also contribute to the mortality associated with infection. The immune system (see also below) is central to an elevated risk of mortality as a consequence of a cytokine storm[22], a condition (associated with a wide variety of viral infections and auto-immune disorders) in which the immune response is no longer targeting an invading organism but rather acts to induce widespread inflammation and organ damage. The COVID-19 version of the cytokine storm may respond to treatment with an anti-cytokine antibody[23,24]. The difficulty of establishing, in any individual case, exactly how SARS-CoV-2 is threatening life makes decisions about letting natural immunity control the virus versus suppressing an over-reacting immune system very problematic[25]. Other organ systems affected by SARS-CoV-2 include the kidney[26], the cardiovascular system[27-30], the eye[31] and the gastrointestinal tract[32,33], which can also act as a source of viral spread.

Viral load

The body's burden of virus – the viral load – is an established risk factor for the severity of viral infections generally, eg, influenza[34]. This probably provides an explanation for the particular risk of healthcare workers[35] who spend many hours in close contact with multiple infected individuals in settings where the virus is airborne and on multiple surfaces[36]. This particular risk can be mitigated with widespread and well trained use of PPE.

Antibody-dependent enhancement

As already noted, the immune system is not always on our side when it comes to fighting infection, particularly viral infection. It has been known since the 1960s[37] that sometimes the immune system acts in a way that facilitates infection in a variety of ways and across a wide spectrum of viral agents. The phenomenon is associated with the development of antibodies that are not neutralising antibodies and that can actually facilitate the subsequent entry of a different but related virus[38,39]. Known as antibody-dependent enhancement (ADE), its best-known deleterious consequences are described around the development of dengue haemorrhagic fever[38,40-43]. The list of viruses that are associated with ADE includes the coronavirus that causes feline peritonitis[44].

The phenomenon of ADE has not been established for SARS-CoV-2, but it is clear that a cytokine storm can be severe to lethal in COVID-19[23]. This raises yet more questions to which we do not yet have answers but which, again, give us pause in relation to rapidly changing the rules around physical distancing and lock-down. For example, are asymptomatic and low-symptomatic infection associated with an immune response that does not produce neutralising antibodies and that may lay the groundwork for a subsequent more severe infection? Even more speculatively, is the higher risk in older individuals the result of previous multiple exposures and weak responses to other coronaviruses, perhaps those associated with the common cold? ADE is one of the problems associated with the development of a safe and effective vaccine.

Co-infection with other respiratory viruses

An early report from Wuhan suggested that those infected with SARS-CoV-2 were only rarely co-infected with other respiratory pathogens[45]. A very recent study from Northern California found that more than 20% of samples that were positive for SARS-CoV-2 were also positive for other respiratory viruses[46], suggesting higher rates of co-infection than those previously reported. The Southern Hemisphere is rolling into Winter – colds and

influenza season – so it is additionally problematic that establishing the presence of a non–SARS-CoV-2 pathogen provides little reassurance that an individual is not also infected with SARS-CoV-2.

Misinformation

A final problem for population and individual management of COVID-19 is the ubiquity of misinformation — from the US White House, from social media both as a result of ignorance and malice[47], and from deliberate campaigns designed to discredit science and the effectiveness of medical practice[48]. It is not clear whether, as a society, we can ever develop an effective immune response – but we need to work harder at it.

Final thought

Given the complexity of COVID-19, when it comes to establishing policy, it is better to follow those with manifest leadership skills, brightened further by clarity, compassion, and informed counsel, than to follow those with only modest public-health knowledge and even less understanding of infectious disease.

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