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Longer-term harm from Covid-19 in children: The evidence suggests greater efforts are needed to protect children in Aotearoa NZ from infection

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Longer-term (or ‘post-acute effects’) of Covid-19 in children (including multisystem inflammatory syndrome in children [MIS-C] and long Covid) are well-described. But there is a lack of robust evidence about the prevalence of these conditions. In this blog we

summarise findings from a rapid review of the evidence. These findings indicate to us the need for a precautionary approach in Aotearoa New Zealand (NZ) with greater efforts to prevent children from being infected during the current Omicron outbreak. Protections for children could include improvements to ventilation, mask use, and vaccine equity, and a lower threshold for closing schools and early childhood facilities with greater support for temporary home learning when community transmission is high.

Post-acute effects of infection are a well-known phenomenon

The effects of infection are said to be 'post-acute' when they are not part of the original infective illness. Post-acute effects have been described in all infectious diseases of childhood of public health significance. For example, rheumatic fever is a post-acute complication of streptococcal infection of the throat or skin, and multiple sclerosis can occur years after Epstein-Barr infection (glandular fever).[1]

In the 21st century there have been three multi-region coronavirus epidemics/pandemics. In the first two, SARS-CoV from 2002 and MERS-CoV from 2012, post-acute effects have been noted up to 15 years after initial infection.[2] In the third, the current SARS-CoV-2 pandemic causing Covid-19 infection, the full extent of post-acute effects is not yet known.

Overview of post-acute effects of Covid-19 infection in children

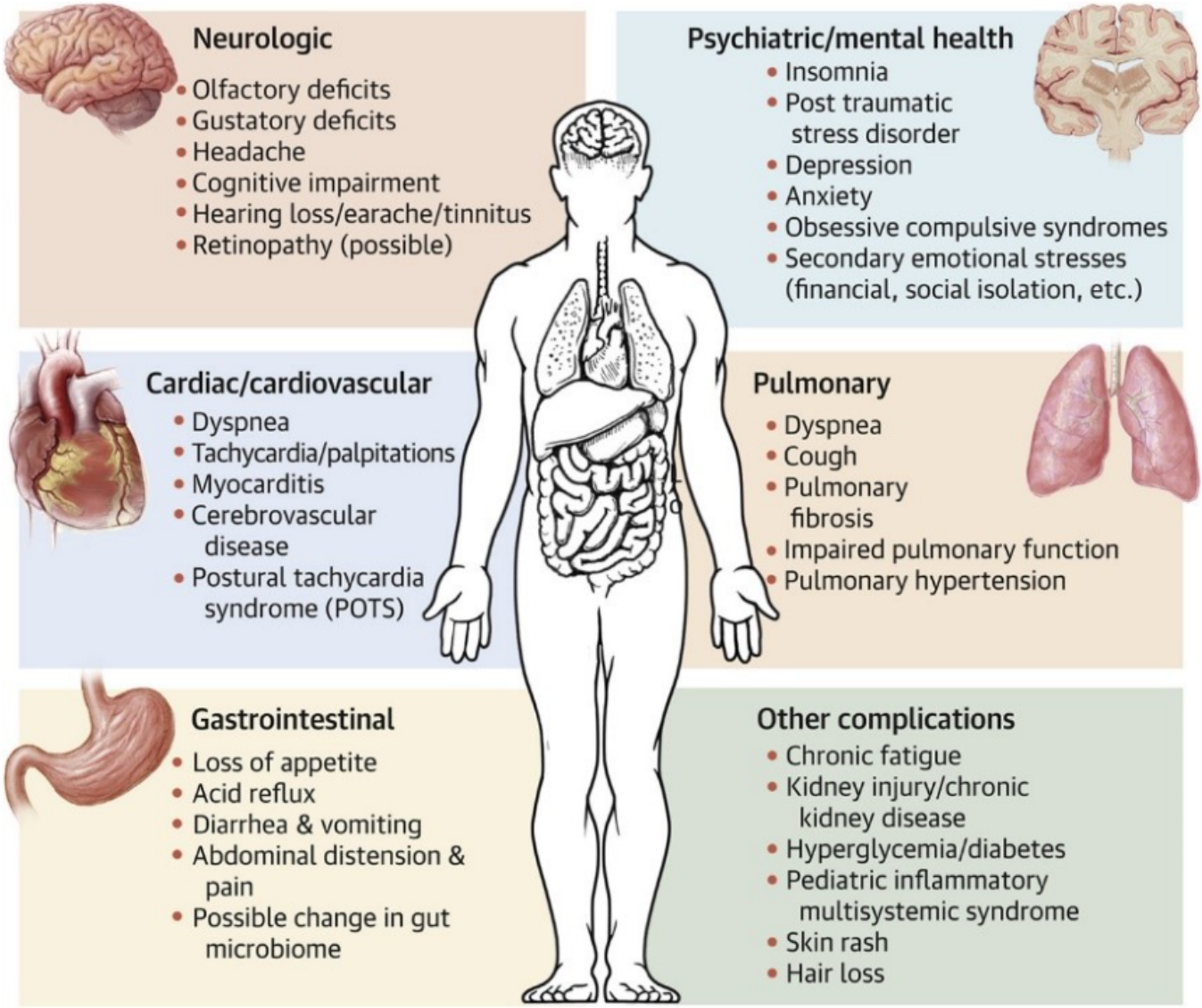
In childhood Covid-19 infection, it is useful to consider post-acute effects in three main groups:

- Multisystem inflammatory syndrome in children (MIS-C), a severe syndrome that occurs from about 2 weeks after the initial illness.
- Longer-term effects grouped under an umbrella term, long Covid; the most common features are fatigue, breathlessness, cognitive dysfunction, and loss of taste or smell, with evidence of multiple organ system involvement.
- Chronic conditions that were known prior to the pandemic and are now being seen with new onset triggered by Covid-19 infection, eg, damage to heart, lungs, and brain.

The above picture which is oriented around symptoms is likely to evolve with further research. Already symptomology shows significant overlap with other post-viral conditions;[3] [4] the associated immune dysfunction is not completely understood but is likely due to both direct viral infection of cells and indirect immune mediated mechanisms.

All of the above post-acute complications of Covid-19 illness appear to share a common underlying mechanism of dysfunction in the immune system (eg, development of autoimmunity, and unresolved inflammation) and/or widespread vascular/endothelial dysfunction resulting in disrupted blood clotting pathways.[5] [6] Viral persistence or debris may also be involved in ongoing inflammation in some cases. While most of this work has been conducted in adults, studies have demonstrated that the same pathways are also activated in children.[7-9]

Figure 1. Post-acute effects of Covid-19 infection in children and adults. Diagram reproduced from Jiang et al.[10]



Multisystem Inflammatory Syndrome in Children (MIS-C)

MIS-C (also known as Paediatric Inflammatory Multisystem Syndrome [PIMS] in some jurisdictions) is a severe inflammatory syndrome unique to Covid-19. Peaks in MIS-C incidence typically occur 2-5 weeks after peaks in acute infections.[11]

The CDC case definition includes a threshold level of clinical severity (hospitalisation, raised inflammatory markers); Covid-19 infection; and involvement of two or more organ systems (cardiac, renal, respiratory, haematologic, gastrointestinal, dermatologic or neurological). When children meet the case definition the majority require ICU care.[11 12]

MIS-C mainly affects primary school aged children with half of cases in the US aged 5-13 years (median age is 9 years). To date, there have been 7,459 cases and 63 deaths from MIS-C in the US (with more cases expected following the recent Omicron peak). Estimates of the population incidence of MIS-C cases during active outbreaks vary widely, from 11 cases per 100 000 population <20 years in New York City over four months in 2020,[13] to a range of 138-627 cases per 1 000 000 SARS-CoV-2 infections in different US states.[14] In NZ, it is currently still too early in the Omicron wave for cases to have been detected.

Inequities in risk are commonly seen: 58% of the total cases in the US have been children identifying as “Hispanic/Latino” or “Black, Non-Hispanic” ethnicity; these are minority

populations in the US. An earlier US series also reported increased risk in children with 'Asian or Pacific Islander' ethnicity.[14] The risk of clotting/thrombosis, a serious complication, is strongly associated with ethnicity.[8] The CDC reports that vaccination appears protective against MIS-C in 12-18 year-olds, although with the caveat that this analysis was of a Delta outbreak.[15]

Long Covid

Long Covid is a condition that can occur following severe, mild, or even asymptomatic SARS-CoV-2 infection. It is also known as post-acute sequelae of SARS-CoV-2 infection (PASC). Long Covid is characterised by symptoms and pathology that persist beyond the acute episode. Almost any organ system can be involved, but common features in children are fatigue, sleep disturbances, headache, poor concentration, and loss of smell or taste.[10] The proportion of child Covid-19 cases that progress to long Covid is difficult to ascertain because of a range of methodological challenges, in particular, accurately identifying children with no previous Covid-19 infection as controls, and the fact that Covid-19 pathology (eg, hypoperfusion) needs specialist investigations not usually performed by paediatric services.[16,17] Our review has not identified any studies that have been able to overcome these difficulties and provide a valid and precise estimate of the proportion of child Covid-19 cases experiencing ongoing symptoms. More information is needed before we can quantify the likely impact in Aotearoa NZ.

However, as an indication of the potential scale of children experiencing prolonged symptoms, the most recent ONS study analysis in England shows that in the period March 2020 to November/December 2021 (ie, just before the Omicron peak), 1% of all primary school aged children and 2.7% of all secondary school aged children (ie, the full child population, not just Covid cases) met the study Delphi criteria for long Covid. This definition is a positive test for Covid-19 infection, the presence of symptoms continuously over a 12-week period or longer; and everyday life affected by these symptoms.[18]

Case data show that long Covid may make children feel unwell for months and some have not recovered two years after infection, with impacts on their physical and social development, education attainment, and mental health. As each individual experiences different patterns and varied severity of symptoms, accessing appropriate support from health providers can be difficult. In the UK some patients report receiving misguided assessment and treatment or dismissive behaviour from some health professionals.[19,20] There is some evidence of a reduction in long Covid symptoms after vaccination in adults, but all previous studies were based on protection from the Delta variant, and as yet there are no study results for children.

Chronic conditions

Some examples of organ-specific damage in children that may lead to long-term impairment include:

- **Brain and nervous system:** A wide spectrum of neurological impacts of Covid-19 infection has been described in children,[21,22] raising concerns about the impact of Covid-19 on the developing brain.
- **Respiratory:** Ongoing symptoms (eg, feeling short of breath) can occur in children following a mild initial infection[23] and lung pathology may not be detectable using common investigations.[16]

- **Gastrointestinal:** Markers of viral persistence and inflammation in the gut in MIS-C[24] and disruption of the gut microbiome[25] indicate potential for future gastrointestinal disease.
- **Cardiovascular system:** Post-acute cardiovascular risks in adults are well-studied and are highly concerning.[26] In children, myocarditis can occur as a component of MIS-C or in isolation. On average children experience milder cardiac symptoms than adults in the acute phase, but abnormal heart rhythms (measured by ECG) and raised inflammatory and cardiac markers can be detected in children in the post-acute phase,[27] [28] [29] [30] raising questions about ongoing subclinical levels of risk.
- **Diabetes:** The case is building for a causal impact of Covid-19 infection on onset of Type 1 diabetes. Type 1 diabetes has a genetic and immune origin. It is a lifelong condition, and onset is often associated with a previous infectious disease episode.[31] Clinical reports[32] [33] are supported by research showing direct damage to β-cells (insulin-producing cells in the pancreas) by the SARS-CoV-2 virus.[34] [35]

Chronic conditions may have serious and lifelong effects and the extent of these effects is still unknown. While most children are showing resolution of post-acute symptoms with time, there are children still experiencing significant symptoms two years after the initial infection in early 2020. Tissue-level effects such as endothelial damage may not develop into clinical disease until much later in life.[36]

Findings in adults suggest that vaccination is likely to provide some protection against long Covid risk, with the caveat that studies were based on the Delta variant where vaccination provided excellent protection against symptomatic infection. Given symptomatic infection from Omicron is common even when vaccinated, extrapolating these results may not predict protection accurately. A layered ‘vaccine plus’ approach to protection will be needed.

What are the potential long-term impacts of the pandemic for Aotearoa NZ?

Although Covid-19 is spread by the respiratory route, it is best considered as a multisystem disease. Research to date shows that serious effects are less common in children than in adults, but they can be life-changing or life-limiting. As more children become infected with Omicron, post-acute effects have the potential to generate population-level impacts. These impacts may be experienced throughout the life-course in underserved communities living with intergenerational history of chronic illnesses due to inadequate living standards and poor access to quality health care.

These new health problems could place additional demands on health and education services in NZ,[37] and on workplaces through caregiver absenteeism. There is a high probability that post-acute impacts of Covid-19 will be focused in communities that were already at crisis point in health, education, justice, and overall wellness. Māori and Pacific children are likely to be at a significantly higher risk because vaccine coverage is lower and Covid-19 rates are higher (compared to Asian and European children in NZ), incidence of MIS-C is likely to be higher,[11] [13] and they will likely experience greater barriers to supportive health care.

Potential next steps for Aotearoa NZ

The current policy of the NZ Government that “closing schools is the last resort” is

potentially problematic in that it allows for exposing a large number of children, families, and teachers to infection during the Omicron outbreak. Because post-acute effects have a time lag following acute infection, it will be many months before the impact of post-acute effects from the Omicron outbreak can be estimated in NZ. We propose the following measures to minimise the risk of post-acute effects of Covid-19 in NZ children:

- Until more is known, a precautionary approach should be taken, ie, we should try to minimise widespread Covid-19 infection in children. This position is supported by a child rights-focused and whānau-centred approach for children in the pandemic with particular protections for whānau at higher risk of infection and post-acute effects.
- Specific measures are needed to protect children's health and wellbeing during the Omicron outbreak including reducing transmission in schools and early childhood education settings (eg, improving ventilation and appropriate mask use), and supporting online learning.
- Vaccination may reduce risk and should be actively promoted for children, and Government needs to better support and work alongside Māori leadership to achieve high equity in vaccine coverage.
- It is vital that parents and clinicians are provided with information about these conditions and that clinicians listen to family concerns.[38 39] Because Omicron has often been mis-portrayed as a "mild" variant, families and clinicians may be unaware of the symptoms of post-acute effects.[37] MIS-C is less common but straightforward to diagnose. Long Covid is more common, but can be difficult to identify.[37 40] Research on treatment of post-acute effects of Covid is promising but it will likely require early diagnosis for optimum treatment efficacy; in the meantime families should be advised that children should not 'push through' fatigue and to seek professional care.
- NZ should use modelling with careful sensitivity analyses to estimate the range of possible impacts of post-acute effects of Covid-19 on NZ children, particularly those with existing acute and chronic conditions including disabilities. This modelling could inform further risk assessment and infection control policies relevant to children, eg, vaccine strategy and mask wearing. There are varying estimates of the prevalence of post-acute effects but there is reasonable understanding of the mechanisms by which different study designs under- or -overestimate prevalence,[17 40 41] and there is enough evidence to indicate that this issue requires serious attention to both prevention and ongoing management.
- NZ needs a national survey (similar to the UK ONS survey) and utilisation of existing population surveys in NZ to monitor wellbeing including post-acute symptoms, with data linkage to follow this cohort of children over the coming decades using NZ's Integrated Data Infrastructure (IDI). It is important to collect high-quality data on differential impacts by ethnicity in view of likely inequities in incidence and access to care.

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