COVID-19 KIDS RESEARCH EVIDENCE UPDATE

WHAT THE MELBOURNE CHILDREN’S CLINICIANS, SCIENTISTS, EPIDEMIOLOGISTS, AND MEDICAL STUDENTS HAVE BEEN READING THIS WEEK

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FOREWORD TO THE 30th EDITION

Professor Allen Cheng - Deputy Chief Health Officer, DHHS; Medical Adviser, Melbourne Vaccine Education Centre; Infectious Diseases Epidemiology Director of the Infection Prevention and Healthcare Epidemiology, Alfred Health; Infectious Diseases Physician and Epidemiologist, Department of Epidemiology and Preventive Medicine, Monash University | Twitter @peripatetical

Although many academics often think that publishing a paper is the final step of months or years of hard work, published papers are only the starting point for informing practice and policy. For a rapidly evolving field like COVID, it is easy to become overwhelmed by the sheer volume of the literature - PubMed lists more than 70,000 published papers on COVID-19 so far this year.

For policymakers, published papers are like raw data - they need further analysis and synthesis with other published work before we can work out what to do next. Evidence syntheses, like the COVID-19 Kids Research Evidence Weekly Update, are a great resource for clinicians, public health physicians, and others, in that they provide a useful summary and commentary that puts research into context.

It is great to see the breadth of the literature that has been covered, and hopefully, it has been as good a learning experience for the medical students who have written the summaries, as it has been for me reviewing and reading them.
GUEST EDITORIAL

Professor Sarath Ranganathan - Head of the Department of Paediatrics & The Stevenson Chair in Paediatrics, The University of Melbourne; Head of Respiratory Diseases Research Group, MCRI; Director of Respiratory & Sleep Medicine, RCH | Twitter @SarathRanganathan

This week we have reached our thirtieth edition of the COVID-19 Kids Evidence Update. The core backbone of our researchers, our fabulous medical students, have taken a break to sit their examinations (no rest for the brilliant!) while our expert reviewers have been asked to reflect on their specialty areas. For this special edition, we include interviews by the University of Melbourne and University of Ottawa medical students with experts, links to which can be found in the topic areas below.

We are indebted to all our reviewers and our superlative editorial team, and I am especially grateful to one of our reviewers, Professor Allen Cheng, who has taken time out from his role as Deputy Chief Health Officer for the State and contributed a foreword to this bumper issue. Thanks to everyone for volunteering their time, skills, and knowledge throughout the pandemic.

In the last month, despite a one-week hiatus in the COVID-19 Kids Evidence update, there remained a consistently high level of traffic through our website, indicating that the report continues to be of value to clinicians, researchers, and academics around the world. Everyone’s contribution has been of value, so once again - congratulations and well done!
COVID-19 has affected the mental health of all age groups, but the effects have been most prominent in the young. Online surveys of adolescents suggest that around a third report high levels of anxiety and depression during lockdowns. Mental health problems may arise for a range of reasons including worry about other family members, bereavements for some, breaks from school, disruption to friendships, home confinement, increased internet and social media use and heightened concerns about the future. School closures affect not only learning but also the relationships and activities that sustain good mental health with a loss of extracurricular activities, opportunities to socialise with peers and a transition to electronic-based learning platforms. Around a third of adolescents and half of the young adults have reported high loneliness during lockdowns. Families have also been under pressure with parents commonly reporting greater mental health problems. Parental roles have become difficult with juggling work from home with homeschooling with consequences for parental mental health, domestic violence and abuse. Physical inactivity, increased screen time, irregular sleep and poor diets affect adolescent mental health, and all have been altered by lockdowns and school closures. Falls in physical activity have come about from suspension of school-based physical education as well as closures of community-based sporting activities and fitness centres and restrictions in movement beyond local areas. An increase in social and digital media use during lockdowns has been essential for continued engagement with education and maintaining friends. However, social and digital media use might disrupt sleep, heighten vigilance of the news cycle and for some, bring more negative peer interactions.

The pandemic has undoubtedly made pre-existing adolescent mental health problems worse, and this has been compounded by limited access to school counsellors and nurses. For young people, the effects on mental health are likely to be among the most significant in the longer term. We need to know more about the recovery of mental health problems that have emerged during lockdowns. There is also a need to look ahead at the mental health consequences arising from the economic fallout, with disruption to employment, further education and training opportunities likely to have marked mental health consequences.


The COVID-19 pandemic will have long-term consequences on children’s developmental potential worldwide

Pandemics are known to have a substantial and lasting impact on communities, families, and children. While the data on the effects of COVID-19 specifically is only just emerging, we can draw on what we know from previous pandemics and disasters. The COVID-19 pandemic will have long-term consequences on children’s developmental potential worldwide. School closures, physical distancing and lockdown restrictions are known to disrupt children’s routines, cause confusion, anxious and depressive symptoms, and post-traumatic stress symptoms, and negatively impact academic performance and home learning environments. Reduced opportunity to be outside and to engage in daily physical activity, increased screen time, snacking, and weight gain can have long-term impacts on children’s physical health. Household stress and poor parent mental health, associated with unemployment and financial instability, as well as the struggle of balancing employment and child care demands, has a negative impact on children, including in utero.

Rates of child abuse and neglect are expected to increase. Reduced family income and job losses have placed many children into a social and educational disadvantage for the first time. Access to healthcare and services has been heavily impacted, with missed routine health checks, vaccinations delayed and decreased visits to paediatric emergency departments. Meanwhile, there has been a significant increase in children seeking support for mental health problems, including emergency department presentations. The indirect effects of COVID-19 and associated policy responses are disproportionately impacting vulnerable and disadvantaged groups of children in many ways, with the potential for the widening of health and educational disparities. For instance, school engagement and successful remote learning are more significantly compromised among vulnerable and disadvantaged students, and it is more difficult for them to recover. Many underprivileged families lack the resources needed to support their children’s learning. The achievement gap between disadvantaged and advantaged students is reported to have widened to triple the rate in remote learning compared to on-site learning. More evidence is needed about the likely long-term impacts of COVID-19 on children’s health and development outcomes, particularly for those from disadvantaged families. This includes using existing cohorts or surveillance data to understand its impact on vulnerable children and identifying how existing resources (e.g. policies and service interventions) can be optimised to reduce adverse impacts.
COVID-19 pandemic: The impact on vulnerable children and young people in Australia


> The COVID-19 pandemic will have broad, long-lasting implications for society, but also represents an opportunity to address child inequity and improve the health and wellbeing of vulnerable populations of children and young people.

> The pandemic has magnified the issues that vulnerable children experience, such as having more complex needs and barriers to accessing health services.

> The authors conducted a rapid review of the COVID-19 literature to July 2020.

> For children from vulnerable populations, adverse outcomes are more likely to relate to public health measures and mental health than the virus directly.

- Children with a disability may experience difficulty accessing COVID-19 information and following prevention guidelines, and be exposed to more risk factors (e.g., parenting stress) and less protective factors (e.g., respite care) during the pandemic.

- Aboriginal and Torres Strait Islander children may experience limited access to family and community and increased mental health distress.

- Children from migrant and refugee backgrounds may have reduced access to interpreters resulting in lower quality health care.

- Children in the child protection system are likely to have reduced family visits, less access to community support, and delayed court proceedings.

- Children in residential care live in crowded living environments where physical distancing may be impossible, and access to health care may be limited.

- Children living in rural areas may experience increased stress due to recent drought and bushfires, while also experiencing challenges accessing telehealth and specialist health care in urban areas due to travel restrictions.

> There is a need to prioritise children’s health and wellbeing, with a focus on equity and proportionate universalism.

- Health professionals should utilise telehealth in a way that is appropriate and accessible for children and young people; they should be prepared for increased rates of child protection and family violence cases, and they should advocate for enhanced access to resources and services for children from vulnerable populations.

- Government action should complement the health system by considering scaling up cash transfer programs, with particular consideration of the vulnerable groups (e.g., asylum seekers) who are ineligible for payments like JobKeeper and JobSeeker.

- Researchers can contribute by incorporating the voices of children and young people in research, to understand their experience of the pandemic better.

> Every health service plays a role in ensuring children and young people have their needs supported during the pandemic, using strategies that address inequity and build a better future for vulnerable children and young people.
While limiting the spread of COVID-19, the essential public health measures used (e.g., school closures) threaten the rights of children and may worsen existing inequities.

- Children are at risk of lower educational attainment and reduced access to services.
- Many marginalised families in Canada rely on home visitation programs for mental health support; many of these programs have been suspended during the pandemic.
- Children with complex health needs or disabilities are more susceptible to a deterioration in their physical and mental health, leading to an increased risk of hospitalization.
- Children in foster care may experience cancelled family visits and precarious transitions, leaving them vulnerable to homelessness and food insecurity, as well as poorer mental health outcomes.
- Children who live in substandard housing or who experience homelessness or are dependent on shelters may experience increased household dysfunction or family violence.
- Many families living in poverty are worried about employment and ability to pay for housing, utilities or food.
- Structural inequities have been magnified by the pandemic; there has been a disproportionate impact of COVID-19 on Canadian Indigenous populations and increased reported of xenophobia and racism, with negative impacts on children’s mental health and development.

The authors proposed a tiered action plan, centred on the UN Convention of the Rights of the Child, for child health providers:

- Tier 1: Child health providers should take a comprehensive screen for the social determinants of health during all assessments with children, and facilitate access to additional services and programs while including the child in decision-making.
- Tier 2: Child health providers should find creative ways to connect with families (e.g., telehealth), that are flexible and focus on what is essential to the family; this should be a collaborative approach with other service providers.
- Tier 3: Child health providers should advocate for more flexible definitions of “essential” services, allowing for a more patient-centred approach (e.g., access to a home visiting program by public health nurses for new mothers living alone in isolation).
- Tier 4: Child health providers should support community initiatives to buffer stress and build resilience (e.g., develop partnerships with teachers who check in with their students regularly).

The COVID-19 pandemic will impact children far beyond the infectious period; by “building back better” there is the potential to emerge from this pandemic with strengthened future generations.
Statute of Limitations

**CHILD PROTECTION**

Dr Trusha Brys (MBBCh, FRACP, GradCertForensMed), VFPMS
Paediatrician

**Child maltreatment - the impact of COVID-19**

A study looking at the COVID-19 impact on children in domestic violence refuges showed that 56% of the respondents of the study reported a reduction in the number of requests from clients and many expressed concern that it is "too quiet out there". (1) This had been our experience in Melbourne and likely all around the world at the beginning of the pandemic. Although cases presenting to our service have increased, there is concern that we might have a "second pandemic" in the form of child abuse and neglect with "an irreversible scarring of a generation". (2)

The child protection system was significantly impaired during the lockdown and with school closures. Reasons included decreased exposure of children to mandatory reporters, limitations of telehealth consultations in identifying children at risk and cases not seen due to reluctance to attend the general practitioner or emergency department with fear of contracting the disease. Policy changes of child protection departments and forensic units, to balance staff safety with service delivery, likely also had an impact. A paradoxical decrease in child protection reporting rates is not unexpected, as illustrated by data from international conflicts and disasters. (3)

Although COVID-19 is exceptional in modern history due to its global exposure, a rapid review on the impacts of epidemics and pandemics (COVID-19, Ebola, Zika, SARS [Severe Acute Respiratory Syndrome], MERS [Middle East Respiratory Syndrome], HIV/AIDS and H1N1/swine flu) on child protection and lessons learned showed an increase in child labour, child marriage and sexual violence and exploitation. (4)

Policy guidance, media commentary and initial empirical research highlighted negative impacts of COVID-19 and its infection control measures on children and their families as follows:

- Health, financial and socio-economic stressors. (5)
- Effects on wellbeing, development, safety and protection (6) particularly those already vulnerable to socio-economic exclusion. (7, 8)
- School closures affect the reporting of child maltreatment. (9)
- Increase in violence against women and children. (10)

Unemployment is mounting. Associations between unemployment and increased child abuse have been reported even when the economy is healthy. (11) Parental job loss was identified as a primary factor contributing to future psychological maltreatment and physical abuse in a recent systematic review of prospective longitudinal studies. (12)

Global research which was implemented in 46 countries resulted in the largest and most comprehensive survey of children and families during the COVID-19 crisis to date (September 2020) with 31 683 public responses which included 13477 child responses between 11-17 years. (13)
> **Violence at home** – higher rates were reported when schools were closed and there was a significant association with household income, the length of confinement, the number of children in the family, the numbers of activities parents participated in with their children and parent access to support.

> **32%** of households had a child/caregiver report violence had occurred which included physical and/or verbal abuse.

> **Child labour** – 2/3 girls (63%) reported an increase in household chores compared to less than half boys (43%). 1 in 5 girls reported that this was stopping them from learning compared to 1 in 10 boys.

> Over ¾ program participants (77%) reported an increase in their use of positive parenting methods, and 1 in 5 caregivers (22%) reported an increase in the use of negative or violent parenting methods.

Lockdowns, school closures and movement restrictions have left many children stuck with their abusers and concerns were raised that COVID-19 has been detrimental to the disclosure of intrafamilial child sexual abuse, with reducing child abuse reports.(14)

Increasing harmful online behaviours, including cyberbullying, risky online behaviour and sexual exploitation, have been identified. An INTERPOL assessment on the impact of COVID-19 on child sexual abuse showed the following (15):

> Increased discussions on child sexual exploitation and abuse (CSEA) forums on the Darknet.

> Sex offenders with technical expertise to administrate forums have had more time to create new ones and additional time online to organise their CSEA collections.

> Live streaming of child sexual exploitation for payment has been on the rise in recent years, with demand likely to increase as a result of travel restrictions.

> The supply of live-streamed CSEA material is likely to rise as victims are locked down with abusers/facilitators, and as economic hardship increases.

Ongoing research and knowledge are needed to assess the immediate, intermediate and long-term impact of the pandemic on children. The prevalence of child maltreatment (physical abuse, sexual abuse, emotional abuse and neglect) in the context of COVID-19 is not yet known and factors, both causative and protective, need to be explored. In the meantime, we need to be vigilant in our care for the most vulnerable part of our society and fierce in our protection of their rights.


CLINICAL PAEDIATRICS

Kieren Fahey - 4th Year Medical Student, Department of Paediatrics, The University of Melbourne

Interview with Professor Jim Buttery - Child Informatics, Department of Paediatrics, University of Melbourne; Infectious Diseases Physician, Royal Children’s Hospital; Group Leader, SAFEVIC, Population Health, Murdoch Children’s Research Institute

Interview with Dr John Cheek, Deputy Director Emergency Medicine at The Royal Children’s Hospital Melbourne, Research Associate at MCRI, Honorary Senior Fellow Department of Paediatrics at the University of Melbourne

Dr Martin Wright - Paediatrician, Joan Kirner Women’s and Children’s, Sunshine Hospital and Senior Lecturer, Department of Paediatrics, The University of Melbourne

COVID-19 Summary - Clinical Paediatrics

Age influences the likelihood of contracting an infection from SARS-CoV-2, the severity, and the risk of transmitting it to others. The older the child/adolescent, the closer they present to the (young) adult pattern. Most recent data from the US suggests that children overall account for about 11.3% of COVID-19 infections, but about 0.0006% of deaths.

For most children, SARS-CoV-2 infection is asymptomatic or only mild. Most symptoms are nonspecific, such as fever, mild respiratory and systemic symptoms such as headaches and body aches. Reports of severe respiratory symptoms are uncommon. It is difficult to clinically differentiate COVID-19 from other common viral infections.

The risk of having symptomatic (and especially severe) infection does not seem to be modified by child-related or environmental risk factors in children to the degree it is in adults; however, obesity becomes vital with increasing age.

A minimal number of children will have a severe inflammatory reaction (late) Paediatric Inflammatory Multisystem Syndrome – Temporally associated with SARS-CoV-2 (PIMS-TS) or Multisystem Inflammatory Syndrome in Children and Adolescents (MIS-C). More long-term symptoms have not been reported, and the likelihood is not clear. There is the potential for cardiac, coagulopathy, and neurological complications.

The major burden of disease in children is because of the effects COVID-19 on adults and society, and efforts to limit its spread. Children have significantly been affected by (to name some); delayed or missed vaccination; delay in presentation, diagnosis, and management of developmental and behavioural, and acute or chronic health problems; the impact on schooling; increased family violence and parental mental health problems. Children report increased mental health concerns, social isolation, concerns about the impact on education, family life, and changes to plans and usual activities. Unfortunately, the negative effects of poverty and social disadvantage on child health and wellbeing have been magnified. Note, even though during periods of lockdown and school closures there have been decreased injuries, and decreased infectious disease (due to less activity and interaction) this has been far outweighed by the above negative effects, which will likely become even more evident over time.
EPIDEMIOLOGY & PUBLIC HEALTH

Daniel Lamanna - 3rd Year Medical Student, Department of Paediatrics, The University of Melbourne
Interview with Professor Harriet Hiscock - Group Leader, Health Services, Population Health; Principal Research Fellow, Murdoch Children’s Research Institute; Sessional Principal Specialist, Centre for Community Child Health; Honorary Fellow, Department of Paediatrics, The University of Melbourne

Dr Claire von Mollendorf - Senior Research Officer, New Vaccines and Asia-Pacific Health Research Groups, MCRI; Honorary Senior Fellow, Department of Paediatrics, The University of Melbourne

Risk factors for COVID-19 infection, transmission and death

There are several factors which have been found to affect COVID-19 transmission (setting, climate, age, and public health measures), infection (age, underlying conditions) or risk of death (age, sex, weight, economic inequality, health investment, and race).

More severe outcomes of SARS-CoV-2 infections and higher death rates have been documented in elderly patients, while younger patients, especially children, are often asymptomatic or mildly symptomatic and are less likely to die when infected with SARS-CoV-2. Susceptibility to SARS-CoV-2 infection generally increases with age, with young children having significantly lower estimated susceptibility, while adults over 60 years of age have elevated susceptibility to infection. Sex has been shown to be a positive predictor of COVID-19 death, with the magnitude of this difference increasing in older age groups. The black race has been identified to be a positive predictor of COVID-19 infection and death.

Infection risk is increased in specific settings. Household transmission remains the most widely recorded setting of spread, with the spouse and household contacts with underlying conditions most at risk. Healthcare workers are at a high risk of COVID-19 infection because of more frequent exposure to COVID-19 cases. Other occupational settings which involve working in confined indoor spaces, with lack of social distancing, such as meat processing plants, have been shown to be the source of multiple outbreaks. Aged care facility residents are both a medical and socially vulnerable group who are both at increased risk of infection and death from COVID-19. Crowded, indoor settings with poor ventilation, mixing of groups and singing/loud speech volumes, alcohol consumption, such as pubs and clubs, are also high-risk settings. In settings with high community transmission and limited or no mitigation measures, the spread of SARS-CoV-2 has been seen to occur in secondary/high schools, with a more limited spread in primary schools. However, it has been well documented that mitigation measures prevent large outbreaks. It is important that community mitigation measures to decrease COVID-19 transmission are multi-faceted and tailored to the local setting.
RCH National Child Health Poll: COVID-19 testing in kids - what concerns parents?

The Royal Children's Hospital National Child Health Poll of 1434 parents who care for 2553 children, has found a range of barriers which may impact on the willingness of parents to attend a testing clinic for their child.

Australian parents are in support of COVID-19 testing for kids with 79% understanding the important role it plays in stopping the spread, however, despite these high levels, many parents think twice before getting their child tested.

Almost three-quarters of parents (74%) are concerned the COVID-19 test might be stressful, painful or uncomfortable for their child with 30% indicating these worries are very likely to stop them from taking their child to have a test. The highest level of concern is among parents of children aged zero to less than five years (80%). Among those children who had been tested for COVID-19, parents told us that 53% of children found the experience only mildly or not at all stressful.

“As a parent myself, I understand the concerns parents have. There are several ways you can help ease anxiety in your kids, including having them sit on your lap or talking to them calmly about what’s happening without too many details. It can be stressful for parents too – by staying calm yourself, you will help your child to cope with the experience. Testing is critically important in stopping the spread of COVID-19,” said Dr Anthea Rhodes, Paediatrician and Poll Director.

Despite knowing where to attend testing (83%), parents still hold concerns about access and logistics.

One in three parents (32%) said that the idea of getting their child tested and having to keep them isolated at home would be overwhelming. One in three parents (31%) said it is a hassle to take their child for a COVID-19 test, and two-thirds (61%) said that testing their child every time they had a cold would result in too many tests. Fifteen percent of parents said they would be very likely to be deterred from taking their child for a COVID-19 test because they believed their child would refuse to be tested.

Unsurprisingly, parents from Victoria (43%) and New South Wales (38%) are more likely to take their child to get tested compared to all other states and territories combined (16%).

The stigma attached to a positive test has 40% of parents indicating that they may not take their child for a test due to fears of what people would think if their child tested positive. More than a quarter of parents (29%) also indicated they would not want people to know if their child tested positive.

“Fear and anxiety about a disease can lead to negative attitudes and beliefs toward people, places, or things. Stigma hurts everyone by creating more fear or anger toward ordinary people instead of focusing on the disease that is causing the problem.

Worryingly, almost half of parents (46%) are still unsure about which symptoms would mean their child needed a COVID-19 test and 48% of parents indicated that if their child had a runny nose or cough it was likely to be the common cold, and they did not need a test.
Starting to unravel the reasons behind unexpectedly severe COVID-19 infection

It has been well established that apart from age over 50 years, there are a number of factors that can predispose an individual to severe COVID-19 infection, including pre-existing obstructive lung disease, obesity, diabetes mellitus, cardiovascular, renal or hepatic disease, malignancy and previous bone marrow transplant. However, there is a small proportion of younger individuals who have none of the risk factors who nonetheless go on to develop a severe infection, as defined by admission to ICU with a clinical diagnosis of acute respiratory distress syndrome or encephalitis. Two recent papers in the prestigious journal Science, have shed light on possible reasons for this unexpectedly severe COVID-19 infection in younger individuals.

In the first paper by Paul Bastard and colleagues from the COVID Human Genetic Effort (1), it had been observed that three individuals with autoimmune polyendocrinopathy syndrome type 1 (APS-1) developed unexpectedly severe COVID-19 infection. APS-1 individuals are known to have neutralising IgG auto-antibodies against type 1 interferons (IFNs). This led to the hypothesis that auto-antibodies to type 1 IFNs might predispose individuals to severe COVID-19 infection. It was found that of around 1,000 individuals with severe COVID-19 infection, approximately 10% were found to have auto-antibodies against IFN-a2, IFN-w or both (whereas auto-antibodies were seen in only 0.33% of around 700 control individuals). They went on to show that auto-antibody positive serum abolished STAT1 phosphorylation (indicating that activation of type I IFN pathways was impaired), and neutralised the capacity to block SARS-CoV-2 infection in a cell model. Most intriguing, it was found that of those who had severe COVID-19 infection and had auto-antibodies, 95% were male, potentially raising a partial explanation for the observed male excess of severe COVID-19 infection (could there be a predisposing factor encoded on the X-chromosome?). The authors conclude that in the presence of auto-antibodies to type 1 IFNs, this adaptive auto-immunity has impaired innate and intrinsic viral immunity against SARS-CoV-2.

The second paper by Zhang and colleagues, also from the COVID Human Genetic Effort (2) hypothesised that inborn errors of genes involved in the type 1 IFN pathway could predispose otherwise healthy individuals to develop unexpected severe COVID-19 infection. Around 650 individuals < 50 years of age who had severe COVID-19 infection, but who had none of the risk factors, had either exome or genome sequencing performed, with the analysis focused on genes that are involved in the Toll-like Receptor 3 (TLR3) and Interferon Regulator Factor 7 (IRF7) pathways. They found 118 variants in 13 genes and following in silico analyses and the application of a number of cell-based functional tests, they found 24 deleterious variants in 8 genes in 23 individuals, amounting to around 3.5% of individuals sequenced. This included four individuals who had biallelic loss-of-function variants in two known disease genes (IRF7 and IFNAR1), and 19 individuals with presumed autosomal dominant loss-of-function variants in four known disease genes (TLR3, TICAM1, TBK1 and IRF3) and four genes that had not been previously known to be associated with an autosomal dominant predisposition to severe viral infection (UNC93B1, IRF7, IFNAR1, IFNAR2).
Importantly, these genotypes had been silent until exposure to SARS-CoV-2, and none of these individuals had auto-antibodies to type 1 IFNs, strongly indicating that the gene variants identified were the primary contributor to the severe COVID-19 infection in these individuals.

Together these papers highlight that TLR3-and IRF7-dependent intrinsic and innate type 1 IFN immunity are essential for protection against SARS-CoV-2 infection, and raise interesting ideas for treating individuals with severe COVID-19 infection. Firstly, it has been suggested that convalescent serum from survivors of severe COVID-19 infection could be used to treat individuals with severe disease. The results from the first paper would indicate that using serum from individuals who had auto-antibodies could be potentially dangerous. Secondly, for individuals with severe COVID-19 infection who are also auto-antibody positive, potential treatments to reduce the auto-antibodies such as plasmapheresis or plasmablast (antibody-secreting B cells) depletion using monoclonal antibodies, could ameliorate disease severity. Finally, the results of both papers suggest that provision of recombinant type 1 IFNs not targeted by the auto-antibodies (e.g. IFN-b) or those not produced because of an underlying genetic defect of the relevant pathway, could be of potential therapeutic value.

GLOBAL HEALTH

Professor Steve Graham - Group Leader, International Child Health, Infection & Immunity, Murdoch Children’s Research Institute; Centre for International Child Health, Department of Paediatrics, University of Melbourne

What I have learnt - or not learnt - about the impact of COVID-19 respiratory disease in children in low-income settings

The commonest presentation of COVID-19 in children is as an acute respiratory disease. Respiratory disease is the major cause of morbidity and mortality in children globally, and the incidence and case-fatality along with the prevalence of the many risk factors are highest in low-income settings. The burden on health outcomes and systems is largely due to infections and disease of the lower respiratory, and the main cause is acute pneumonia, but the list includes asthma, croup, tuberculosis and chronic lung disease such as bronchiectasis. Poverty with inadequate access to prevention and optimal case management strategies are consistent challenges. At the same time, host risk factors for incidence and mortality include young age and comorbidities such as HIV infection and malnutrition. The impact of most causes of severe respiratory disease in childhood on long-term lung health in these vulnerable populations is unknown. My COVID-19 perspectives are threefold.

The first may still largely be extrapolation for literature from well-resourced settings supported by direct observations from low-income settings. Nonetheless, from the early stages of the epidemic through to more recent experience in a wide range of populations, COVID-19 as a specific respiratory pathogen is not causing a major increase in the overall burden of acute severe respiratory disease such as pneumonia in children. The long-term impact on lung health is not known.

The second observation is that the measures applied to control the COVID-19 pandemic do appear to be resulting in changing epidemiology - such as reduction of incidence and hospitalisations from other common causes - of acute respiratory disease in children. The main unintended consequence may be a reduction in seasonal viral illness, reduced exposure and transmission of potential pathogens and, especially in low-income populations, this may also result in a reduction in secondary bacterial pneumonia. However, analysis of this impact over full years of observation will be needed, with the interpretation of findings considering a wide range of potential confounders and variable settings.

The third and most concerning impact of COVID-19 on the epidemiology of childhood respiratory disease are likely to be the multiple indirect consequences. These include economic downturn, greater nutritional insecurity, reduction or delays in immunisation coverage, reduced access to care, and interruption of health services for established pandemics such as providing prevention and management of tuberculosis and HIV in children. The evidence is mounting that via this indirect route, and the COVID-19 pandemic will have a major negative impact that overshadows the more positive previous two scenarios, especially in low-income settings. Thereby, the overall impact of the COVID-19 pandemic is not just to stall but likely to significantly reverse recent critical progress in child lung health globally.
Dr Vanessa Clifford - Infectious Diseases physician and Microbiologist, RCH/RWH; Honorary Research Fellow in the Infection and Immunity Group, MCRI; and Honorary Senior Fellow, Department of Paediatrics, The University of Melbourne

Infection control and the COVID-19 pandemic

The SARS-CoV-2 pandemic is shining a spotlight on infection control practices around the world, and particularly the issue of health care worker (HCW) safety.(1) Several overseas studies have shown a high proportion of HCWs infected in high-risk health care settings; in one UK study, around 44% of frontline HCWs had evidence of prior SARS-CoV-2 infection by June 2020.(2)

Efforts to improve staff and patient safety rest on the principles of the hierarchy of controls: elimination, substitution, engineering controls, administrative controls and personal protective equipment. The most effective solution will always be elimination (removing the risk). In Victoria, suppression of the second wave of SARS-CoV-2 via lockdown measures and universal mask-wearing has been associated with a corresponding reduction in HCW infections.

Recent reports have highlighted an increased risk of HCW infections when working in poorly ventilated areas with a high density of infected patients.(3) Engineering controls, such as building design and improved hospital ventilation systems, contribute significantly to risk reduction. There has been a renewed focus on standard precautions. Although the contribution of fomite transmission remains uncertain, evidence suggests that SARS-CoV-2 survives on surfaces for long periods,(4) emphasising the importance of careful hand hygiene and environmental cleaning.

The relative contributions of various modes of transmission (contact/droplet/airborne) have been a focus of much recent research, with evidence suggesting that under some circumstances (particularly in the context of aerosol-generating procedures and behaviours), the virus may transmit via aerosols.(5, 6) A precautionary approach suggests that where uncertainty exists, HCWs should wear PPE appropriate to protect against airborne transmission. Adequate staff training in donning and doffing personal protective equipment (PPE) is paramount. Fit testing may be a useful adjunct to fit checking in ensuring the safe use of high-efficiency particulate filter (N95/P2) masks.(7)

Successful implementation of these multi-level strategies requires a high level of cooperation and communication between all craft groups within the healthcare workforce and government.


MENTAL HEALTH

Dan Lindholm - 4th Year Medical Student, Department of Paediatrics, University of Melbourne

Interview with Professor Dave Coghill - Financial Markets Foundation Chair of Developmental Mental Health, The University of Melbourne

Dr Louise Crowe - Team Leader, Brain and Mind, Clinical Sciences; Psychology Services, Royal Children’s Hospital; School of Psychological Sciences, University of Melbourne

Professor Vicki Anderson - Theme Director, Brain and Mind, Clinical Sciences; Psychology Services, Royal Children’s Hospital; School of Psychological Sciences, University of Melbourne

Lessons learnt from COVID-19 for children with chronic health conditions

Victorian children have experienced great upheaval to their lives with the COVID-19 pandemic. For example, remote education, the closure of playgrounds, play centres, cultural and recreation centres (i.e., museums, zoos, cinema, etc.) organised sports and activities (i.e., music lessons, dancing) and restrictions on socialising with extended family and friends. In vulnerable children, including children with chronic health conditions (CHC), psychological disorders and neurodevelopmental disorders, the stressors of COVID-19 pandemic are likely to be magnified. Our study, conducted at Murdoch Children’s Research Institute, focused on the impacts of the COVID-19 pandemic on the mental health and wellbeing of these patients. Preliminary findings from the children with CHC demonstrated that their parents felt that their children’s healthcare needs were not being met as well as pre-pandemic.

Further, the majority felt that the move to telehealth appointments were of lesser quality than face-to-face contacts. Other findings specific to children with CHC include reduced access to therapy and respite services, which was associated with major stress in around half of the families. When we investigated children’s mental health, loneliness was the biggest change, with 40% of children described by the parents as lonely, and missing friends, peers and extended family. Recruitment is ongoing with 3- and 6-month follow-ups planned. The findings provide valuable insights for clinicians and policymakers on the support families of vulnerable children need during pandemics.
COVID-19 pandemic and the impact on infant mental health and changed maternity care practices

The COVID-19 pandemic has had a significant effect on the availability of face-to-face support services for families through pregnancy and in the postnatal period. In Victoria, there have been major limitations on the number, and time at the hospital, of support persons available through labour and the postnatal period. Similar restrictions have been applied in many overseas countries. Limited data are available about the consequences for the development of the infant-parent relationship and perinatal and infant mental health, but there is considerable anecdotal evidence that the necessary contact restrictions have led to adverse mental health consequences for new mothers, infants and fathers.

In Australia, there are regular reports of increased referrals to family violence support services. The national helpline for parents experiencing anxiety or depression in the perinatal period (PANDA) has reported a doubling of telephone mental health crisis referrals from women. This is in the context of vulnerable mothers and infants being isolated and restricted from accessing the support of friends and family. Maternal and child health services have often had to rely on telephone consultations, being unable to provide a face-to-face assessment of vulnerable infants and mothers, unable to provide new mothers groups or home visits.(1) Early parenting centres have had to adapt to initially providing only telephone and telehealth services before moving to a hybrid of virtual assessment and counselling for infants with significant feeding and sleep problems and for infants at high risk. Some limited residential and face-to-face services are now available, but many very vulnerable infants have had limited access to specialist services. Many families have been able to use the virtual media for interventions that are at least partially affected, and even babies can make lively, engaged, connections through the small screen. Australia has a long history of effective tele-psychiatry.(2)

Pregnant women in China after the outbreak of the pandemic experienced higher rates of depressive symptoms (26%), including thoughts of self-harm.(3) In New York, Hermann described the impact of the pandemic on the comprehensive care of birthing women with pre-existing anxiety and depressive disorders, as well as those whose mental health problems were precipitated or intensified by the pandemic.(4) Managing transmission risk with essential public health measures interferes with crucial psychosocial needs in the peripartum period. Women giving birth are likely to be especially fearful and anxious as partners, and other close carers have very limited contact, are all surrounded by illness and fearful of becoming infected themselves, compromising delivery and baby. Telephone and telehealth consultations are recommended to compensate for rapid discharge from the hospital. Maternity clinicians may need to provide some acute interventions to manage patient stress as mental health clinicians are drawn to activities beyond their previous role. Women with pre-existing problems may be especially vulnerable to relapse and because of fear of infection and overstretched resources, may not seek early treatment. Detailed recommendations have been made to support the provision of trauma-informed mother-infant mental health clinical services in the US.(5)

The care of infants and families in Special Care and NICU context has been very much influenced by the presence of the COVID-19 pandemic, Lemmon (6) describes three broad areas that present challenges for optimal physical and emotional care of babies and their parents:

1. Inpatient care: visitors, development care and communication between parents and staff; parents receive complex, crucial and frightening information without the support of their partner.

2. Outpatient care: reduced access to high-risk infant follow-up early intervention.
3. Parent psychosocial stress: mental health, social support and financial toxicity.

Infant mental health: clinical experience suggests that there is a significantly increased attendance at paediatric hospital emergency departments for infants with regulatory problems, poor feeding, crying and irritability, sleep disturbance and parents feeling anxious, distressed, and overwhelmed. Access to face-to-face home-based or centre-based services has been extremely limited. Infants and toddlers pre-COVID-19 have a significant prevalence of diagnosable mental health problems, in the order of 16%.(7)

Although there seem few data in respect of mental health community prevalence and outcome for Australian infants in the first year of life, Children’s Health Queensland has undertaken an Australian wide community survey of 998 parents (phase 1) and found that many young children, aged 1 to 5 years, express fears and worries in relation to COVID-19; 15 to 20% of the children had mild-to-moderate emotional or behavioural difficulties and 5 to 10% of children may need more intensive and specialised mental health support. A 2nd phase of the research project is currently underway across Australia. The researchers, however, said that families reported many positive experiences about initial lockdown in Australia, with parents closer to their children and undertaking more mutual pleasure and other activities than previously, and 80% of children described as having good mental health. Eighteen to 25% of parents reported moderate to severe anxiety depression and/or stress symptoms, and were concerned about their ability to juggle the multiple demands of lockdown.(8)

There is an ongoing international collaboration to undertake the “COVID-19 unmasked” survey in 7 other countries.

Given the extreme vulnerability of infants in the context of the pandemic major social stress and disruption, there is a real need for further investment in research into the impact upon, and effective interventions for vulnerable infants and families. There is very limited research into the impact of COVID-19 upon the mental health of children (9), but clearly, there is a high need for effective supports and interventions for parents in the perinatal period and their infants in the context of the current pandemic which will continue to cause chaos and disruption around the world for a long time to come.

The psychosocial impact of the COVID-19 pandemic on socially and economically disadvantaged children and families

Children and families experiencing social and economic disadvantage are at the greatest risk of poor mental health and stressful life circumstances, including family conflict and violence during the COVID-19 pandemic. Due to its unprecedented scale and protracted nature, many families will continue to experience significant economic hardship and poor mental health long after the initial crisis period.

During the pandemic, our community health partners (Tweddle Child & Family Health Service; Berry Street; Merri Health) transitioned to providing telehealth services via video-conferencing. This has been a very different way of working with families experiencing significant social health issues, including family conflict and violence, and child maltreatment concerns. Our team embedded COVID-19 research into our work with these organisations to capture the experiences of families and health professionals supporting families during the pandemic. The key aims are to:

- Identify the perceived impacts of the pandemic on parents, children and families, how they have coped, and what support they have needed or used
- Explore parents’ experiences of receiving telehealth interventions
- Explore health professionals’ experiences of delivering telehealth interventions to families

Qualitative interviews with 30 clinicians and 29 parents have identified notable perceived impacts on (a) parent stress and mental health difficulties, (b) strain and conflict in family relationships, and (c) concerns about child health and development (see Figure 1).
Figure 1: Parent experiences of the COVID-19 pandemic

Figure 2 presents the key themes related to parents’ and clinician’s experiences of telehealth interventions. Parents and clinicians indicated high acceptability for telehealth interventions, viewing it as a way to overcome barriers to accessing support and services. Strong support for telehealth intervention in a ‘COVID normal’ or post-COVID world was indicated. For clinicians, there were perceived challenges in conducting child and family safety and risk assessments via telehealth. They highlighted the need for organisational strategies to support their wellbeing and the need for informal and formal debriefing opportunities when working from home.

Our research has highlighted the critical role of community health services in minimising the psychosocial impacts of the pandemic on families. In particular, family-based interventions targeting children’s home environments are important, and the potential for telehealth services to overcome barriers to engagement for some families has been realised. Future research is planned to test the effectiveness and cost-effectiveness of these telehealth interventions during the pandemic and other community-wide crises. Importantly, this work has highlighted the need to safeguard and promote the mental health of the community health workforce, who are also managing their own experiences and impacts of the pandemic on them and their families.
PERINATAL HEALTH

Professor Suzanne Garland - Reproductive & Neonatal Infectious Diseases, Department of Obstetrics and Gynecology, University of Melbourne; Director Centre Women’s Infectious Diseases Research; Honorary Research Fellow, Infection & Immunity, Murdoch Children’s Research Institute

COVID-19 and perinatal health

Overall, pregnant women with SARS-CoV-2 diagnosed in the hospital are less likely to manifest symptoms of fever and myalgia than age-matched non-pregnant women. This may relate to many obstetric centres overseas implementing universal screening rather than symptom-based testing. However, of those positive for SARS-CoV-2, there is a reported increase in admissions to the intensive care unit and the need for invasive ventilation compared with infected nonpregnant women of reproductive age. Risk factors for severe COVID-19 in pregnancy included increasing maternal age, high body mass index, and pre-existing comorbidities such as chronic hypertension and pre-existing diabetes. Pregnant women with COVID-19 were more likely to experience preterm birth, and their neonates are more likely to be admitted to a neonatal unit. Some pregnant women with COVID-19 have evidence of placental pathology such as villitis, thrombotic vasculopathy, and vascular malperfusion.

Routes of transmission to the neonate can occur transplacentally (documented rarely and via maternal viraemia), intrapartum (maternal genital secretions or via faeces) or postpartum (via maternal respiratory droplet or contact transmission route) and most common. Current evidence suggests that neonates are more at risk of developing severe COVID-19 than children. Still, the overall infection risk is low if the infected mother practices good hand hygiene and infection prevention with respiratory secretions and cleaning of surfaces. Breastfeeding is to be encouraged. In the setting of breast milk banks, in vitro testing of breast milk following holder pasteurisation inactivates SARS-CoV-2.
Challenges for biostatistical methods posed by a global pandemic

The sudden advent of COVID-19 as a global pandemic on a scale unprecedented for at least a century brought abrupt challenges to the normally deliberate processes of clinical and epidemiological research. Biostatistical methods underpin the conclusions drawn from research data, but the difficulties of ensuring high-quality application and interpretation of such methods are under-recognised at the best of times and raise serious dangers in the pressure-cooker environment of a pandemic. Perhaps the most prominent and egregious case of poor quality research to appear so far during the pandemic was the publication of a paper in The Lancet (1) claiming to document risks associated with the use of hydroxychloroquine in hospitalised COVID-19 patients using complex statistical methods in a large database of electronic records. Questions raised initially by several statisticians worldwide led to the recognition that this work was fraudulent, and this and a related publication in the New England Journal of Medicine were retracted, exposing serious flaws in the processes of peer review at both journals. (2) In the early days of the pandemic, there was a rush to publish small clinical trials that arguably produced more confusion than enlightenment, but the biostatistical community has been increasingly engaged as time goes on with efforts to address challenges in the conduct and analysis of COVID-19 trials. (3) Similarly, in a recent review in Nature Communications (4), epidemiologists and biostatisticians highlighted that many observational studies of risk factors for COVID-19 infection and outcomes have been at high risk of bias due to the way in which participants are selected into cohorts. Yet another challenging area for clinical research has been the development of prediction models for outcomes of COVID-19, with some particularly poor studies plagued by inadequate sample size on top of numerous other problems. (5) An early biostatistical contribution was the establishment of a “living systematic review” (6) although to date the review has concluded that despite more than 100 published studies all models have been at high risk of bias and none are recommended for use! Overall, a scarcity of high-quality biostatistical thinking and methodology has been a particular challenge in the COVID-19 era.


RESPIRATORY MEDICINE

Kieren Fahey - 4th Year Medical Student, Department of Paediatrics, The University of Melbourne

Interview with Dr Danielle Wurzel - Paediatric Respiratory and Sleep Medicine Physician, Royal Children’s Hospital; Honorary, Department of Paediatrics, University of Melbourne; Honorary Fellow, Respiratory, Infection & Immunity, Murdoch Children’s Research Institute
SCHOOLS

Professor Fiona Russell - Director of Child and Adolescent Health PhD Program, Department of Paediatrics, The University of Melbourne; Group Leader, Asia-Pacific Health, Murdoch Children’s Research Institute | Twitter @Fiona_M_Russell

Schools and their role in transmission

Schools play a critical role not only in providing education and social and emotional development in children, but also offer critical support, especially for the most vulnerable of students. In this Edition of the Weekly (under Mental Health), the impact of school closures on the wellbeing of children and families is disturbing. It is vital to prioritise early education centres (ECEC) and schools in the pandemic response to prevent unintended harms to children and families, but we also need to understand the role of children in transmission and the role of schools in feeding the broader community epidemic.

Role of children in transmission - Children get infected and transmit SARS-CoV-2. Emerging evidence suggests that children under 10-12 are at a lower risk of transmitting SARS-CoV-2 than adolescents and adults. Our analysis from Victorian ECEC and schools also supports these findings. However, many infections in children are asymptomatic, and the role of asymptomatic children in the transmission is unclear. Although a recent review found that asymptomatic cases transmit less than symptomatic and pre-symptomatic cases.

Role of schools in broader community transmission - We found that SARS-CoV-2 events in Victorian ECEC and schools occurred in a very similar temporal pattern and in similar geographical locations as the broader community. Although we were unable to determine the direction of transmission, it is highly unlikely that school infections were driving the broader community epidemic in the surrounding local area. Rather the opposite - that cases in the community were spilling over into schools. This is further supported by the fact that, in late July and early August, infections linked to ECEC and schools fell after more stringent restrictions were implemented in the broader community but before ECEC services closed and senior high school students returned to remote learning. Although school outbreaks do occur, there are fewer reports of widespread SARS-CoV-2 infection or transmission in preschools and primary schools, especially when compared to other institutions such as hospitals, aged care facilities, prisons, and some workplaces. UK surveillance data found schools were not a common location of contacts for any person testing positive: 3.5% from secondary schools, 1.8% from primary schools and 1.1% from preschool. Moreover, Ireland recently entered lockdown but kept schools open (with mitigation measures in place), and community infections have already declined by ~75% in one month. Listen to Victorian Chief Medical Officer, Brett Sutton, talk to Ireland on the Victorian approach https://www.youtube.com/watch?v=N8DSUo2mdVU (schools discussed at 30:15 and 1:16:00). Iceland kept schools open all year whilst successfully managing their two epidemic waves. Taken together, these observations suggest that schools are unlikely to play a predominant role in broader community transmission, provided school mitigation measures are in place.
Nevertheless, there are observations that transmission increases when schools reopen. Schools and children do contribute to community transmission, but implicating schools as a major contributor for this increase does not take into account the simultaneous effects of other loosened restrictions on adults (parents) work and social activities, which almost always occurs simultaneously when children return to school. In the US, mobility data from mobile phone use from 98 million people found that in metropolitan areas, full-service restaurants, gyms, hotels, cafes, religious organisations, and limited-service restaurants produced the largest predicted increases in infections when reopened.(5) Schools were not listed. In Victoria, schools were closed not because they were deemed high risk, but to minimise the movement of people, especially adults. A number of countries and NSW have found that reopening schools in the context of low transmission and school mitigation measures, has not been associated with increases in community transmission.(6,7)

What can be done to prevent infections in schools? The single best policy to support ECEC and school reopening prior to the development of a vaccine or treatment is the suppression of SARS-CoV-2 to near-zero case incidence in the broader community. School mitigation measures including prevention (improved personal hygiene, enhanced environmental cleaning, improved ventilation, physical distancing for staff etc.) which can be dialed up or down depending on the degree of local community transmission; and rapid public health responses to a school case.(2) Countries need to have school mitigation plans in place in anticipation of the next wave, which prioritises schools staying open. Additionally, vaccinating children to prevent transmission (if a safe and effective vaccine is available that prevents transmission) may be the ultimate solution.

TRANSMISSION

Victoria Ivankovic - 3rd Year Medical Student, University of Ottawa

Interview with Dr Shidan Tossif - Research Fellow, Centre for International Child Health, Department of Paediatrics, University of Melbourne; Infection & Immunity, Murdoch Children’s Research Institute; Paediatrician, Department of General Medicine, The Royal Children’s Hospital
VACCINES

Rebecca Seliga - 3rd Year Medical Student, University of Ottawa
*Interview with Associate Professor Margie Danchin* - Group Leader / Honorary Fellow Manager, Vaccine Uptake, Infection & Immunity, Murdoch Children’s Research Institute; Consultant Paediatrician, General Medicine and Immunisation Service, Royal Children’s Hospital; Associate Professor and David Bicart Clinician Research Fellow, Department of Paediatrics, University of Melbourne; Honorary Senior Research Fellow, Telethon Kids Institute

Dan Lindholm - 4th Year Medical Student, Department of Paediatrics, University of Melbourne
*Interview with Associate Professor Nigel Crawford* - General Paediatrician, The Royal Children’s Hospital; Medical Head, Immunisation Services, Department of General Medicine, The Royal Children’s Hospital; Director of SAEFVIC (Surveillance of Adverse Events Following Vaccination in the Community); Senior Fellow, Department of Paediatrics, University of Melbourne

Melbourne Vaccine Education Centre - COVID-19 Road to a vaccine
*Podcast with Associate Professor Nigel Crawford* - General Paediatrician, The Royal Children’s Hospital; Medical Head, Immunisation Services, Department of General Medicine, The Royal Children’s Hospital; Director of SAEFVIC (Surveillance of Adverse Events Following Vaccination in the Community); Senior Fellow, Department of Paediatrics, University of Melbourne

On Coronacast with Dr Norman Swan - Why the next big vaccine milestone might be only 4-6 weeks away
*Podcast with Professor Terry Nolan* - Group Leader, Vaccine and Immunisation Research Group (VIRGo), Infection & Immunity, Murdoch Children’s Research Institute; Senior Staff Specialist, Department of General Medicine, Royal Children’s Hospital; Head, Melbourne School of Population and Global Health, University of Melbourne
BCG vaccination and COVID-19

The possibility of using the off-target effects of BCG vaccine to reduce the impact of COVID-19 has received a lot of attention, with over 160 publications to date on PubMed and many more on preprint servers. In recent years, an increasing number of laboratory and human challenge studies have shown the beneficial effects of BCG vaccination on the immune response to a variety of (non-TB) pathogens, including viruses. Recent studies have begun to unravel the immunological basis for BCG’s off-target effects, focusing on the ability of BCG to enhance the innate immune response (‘trained immunity’ or ‘TRIM’) (1) and increase granulopoiesis.(2)

Randomised trials have shown that BCG vaccination reduces all-cause mortality in infants in high-mortality settings by protecting against respiratory infections and sepsis. Small randomised controlled trials (RCT) provide encouraging, though limited, evidence that BCG also protects against respiratory infections in adults.

Early in the pandemic, it was hypothesised that BCG’s ability to induce trained immunity might protect against SARS-CoV-2 and could be used to reduce the impact of COVID-19 in healthcare workers and other vulnerable groups, providing a stopgap measure before coronavirus vaccines become widely available.(1,3) A number of RCT are underway including the BRACE trial that is recruiting over 10,000 healthcare workers in Australia, The Netherlands, Spain, UK and Brazil.

In the hiatus before these trials are complete, a spate of ecological studies have been published purporting to provide evidence for or against the notion that the incidence and/or severity of COVID-19 in different countries correlates with BCG vaccination coverage. However, many of these studies are of low quality (4) and, despite some valiant attempts,(5) all suffer from the inaccuracy of national BCG records and the inability to fully account for critical confounders, including differences in populations (e.g., age distribution), stage of the epidemic in each setting, local testing policies, rates and availability, etc.

Studies have compared the rate of COVID-19 in those who have previously received BCG and those who have not.(6,7) However, such studies test the wrong hypothesis as it is unlikely that BCG vaccine given many years earlier protects against COVID-19 because trained immunity induced by BCG might not be long-lasting and is likely abrogated by other intervening vaccines and infections.

Recent studies provide grounds for optimism for BCG’s ability to reduce the impact of COVID-19. An interim analysis of an RCT in elderly patients in Greece (done prior to the COVID-19 pandemic) reported that BCG vaccination provided 79% (95% CI 28-94%) protection against presumed viral respiratory infections.(8) Less strong evidence comes from a preprint that reported a protective effect of a BCG ‘booster’ against COVID-19 in a small non-randomised study in healthcare workers in the UAE.(9)

Two studies provide some reassurance that enhanced innate immunity induced by BCG will not paradoxically worsen COVID-19. The first found no increased incidence of COVID-19 in adult trial participants vaccinated with BCG in the five years prior to the pandemic (10). In the second, patients with COVID-19 admitted to a hospital in India were randomised to receive BCG vaccine or not as part of their therapy. A preprint reports that the BCG-vaccinated patients had more ‘favourable outcomes’ without any adverse effects.(11)
To avoid jeopardising the global supply of BCG vaccine for its proven indication (i.e., preventing TB in infants and young children), BCG vaccination for COVID-19 should only be used in the context of an RCT.(12)


Vaccine confidence and uptake in Australia

The pandemic has shone a light on vaccines as we have never experienced before. COVID-19 vaccines are being heralded as the solution to control the pandemic and resume our previous way of life. With over 200 vaccines currently under development and 11 in phase III trials, a safe and effective COVID-19 vaccine doesn’t appear to be very far away. Extensive planning is now underway to establish the priority groups, develop an implementation and rollout plan and ensure vaccine safety, confidence and evaluation of the program in Australia. GPs and nurses in primary care will be at the forefront of vaccine delivery and acceptance, but COVID-19 vaccines will also be deployed through pharmacies, hospitals and other workplaces as well as non-health settings such as community centres. Ensuring public confidence in the COVID-19 vaccines will be crucial to facilitate uptake. Low intention to refuse COVID-19 vaccines by adults has been reported in Australia (7.6%) compared to the USA (20%) and France (27%), but we know that population attitudes towards the COVID-19 vaccines will fluctuate with the perception of disease severity and the waves of the pandemic, necessitating regular tracking of vaccine confidence amongst different population groups. Effective risk communication by all providers, scientific institutions and public health officials, along with a strong endorsement from the government, will be crucial to achieving sustained vaccine confidence and uptake. We will need strong community engagement and both broad and tailored communication campaigns to ensure that messaging around the COVID-19 vaccines reaches all sectors of the community, through community and religious leaders and regular and non-mainstream communication channels.

The pandemic has also highlighted that globally under-vaccination is an urgent problem, with disruption to routine immunisation services from the COVID-19 pandemic leaving more than 80 million children < 1 year of age at risk from diseases such as measles, diphtheria and polio. In 2019 there were an estimated 19.7 million children that missed out on recommended vaccines and outbreaks of measles and other vaccine-preventable diseases have been increasing globally, with a 300% global increase in measles cases alone in 2019. Lack of access and practical barriers to vaccination remain the leading cause of low vaccine coverage in most settings. However, vaccine hesitancy, or the delay in acceptance or refusal of vaccines despite the availability of vaccination services, is escalating and was named as one of the 10 threats to global health by WHO in 2019. In the face of rising vaccine misinformation and anti-vaccination activity, and disruption to routine vaccination services, we will need strategies to increase and maintain vaccination routine and COVID-19 vaccine uptake in Australia and globally. It is imperative that we prepare the public for the advent of COVID-19 vaccines and that we respond quickly to ensure catch-up and maintenance of routine vaccination to optimise the health and wellbeing of Australian children and families for the future.
Thanks to the University of Melbourne, Department of Paediatrics weekly literature review, as it has been an important way to keep up to date in my own area of special interest (vaccines), but also public health more broadly, including the impact of the COVID-19 pandemic on schools, families and mental health. On a practical level, the Royal Children’s Hospital (RCH) Immunisation service, also appreciated the support provided by medical students in administering the staff seasonal influenza vaccine program. This helped facilitate a high uptake of the flu vaccine in 2020 and mitigated the potential for seasonal influenza outbreaks in 2020. As a paediatrician specialising in immunisations, I had an early interest in ‘vaccine preparedness’ and explored some of these topics in our Melbourne Vaccine Education Centre podcast series [https://mvec.mcri.edu.au/podcasts/covid19-road-to-a-vaccine/](https://mvec.mcri.edu.au/podcasts/covid19-road-to-a-vaccine/). Our camps research team based at MCRI has recruited via our ‘COVID kids’ platform to try and better understand the immunological, virological and serological features of the SARS-CoV-2 infection in children and their families. We still have much to learn about the virus, including the reason increasing age correlates so strongly with increasing morbidity and mortality. Duration of protection and risk of re-infection is another important area to continue to monitor. As the 1st SARS-CoV-2 phase 3 vaccine trial results emerge, unknowns include the vaccine effectiveness in the real world and medium to longer-term vaccine safety data. Correlates of protection from COVID-19 disease will also be important, especially as the trial and vaccine programs progress to include children and pregnant women. Efforts should continue to be made to avoid ‘vaccine nationalism’ and ensure global equitable access. Lastly, vaccine safety efforts will need to be coordinated nationally and internationally, as this will be crucial in our efforts to maintain confidence in the eventual COVID-19 vaccine roll-out.
VIROLOGY

Professor Julie Bines - Victor and Loti Smorgon Professor of Paediatrics University of Melbourne, Paediatric Gastroenterologist Royal Children’s Hospital, Group Leader Enteric Diseases MCRI

Unlocking the secrets in the stool: SARS-CoV-2 in the gut

SARS-CoV-2 is a multisystem disease that involves the gastrointestinal tract. Gastrointestinal symptoms are common in patients with COVID-19 infection (18% adults, 25% in children) with a reported 12.5% of patients experiencing diarrhoea. Up to 28% patients with SARS-CoV-2 RNA detected in the stool do not report respiratory symptoms. Shedding of SARS-CoV-2 RNA in the stool is reported within three days of initial infection and up to 4 weeks prior to the development of significant respiratory symptoms. Faecal shedding can also occur in otherwise asymptomatic individuals infected with SARS-CoV-2. Fifteen % of adults have RNA in stool on admission with COVID-19, and this increases to ~50% with a positive stool RNA during the course of their hospitalisation. The duration of RNA shedding in the stool is longer than observed in respiratory samples (<33 days in adults), with 70% of participants in one study having a positive RNA in stool despite negative respiratory samples. Interestingly the severity of COVID-19 disease is not correlated with the duration of RNA shedding in the stool with a report of shedding for 42 days in an asymptomatic child. However, the potential role of faecal transmission - either through faecal-oral spread or aerosolisation of infected faeces - has been suspected but has not been fully explored to date. It could be particularly relevant in low- and middle-income countries, where wastewater systems and sewerage handling is poor, and contamination of water sources and the environment with infectious agents is common. Wastewater has been used to assess the presence of infectious agents (such as polio, typhoid), antimicrobial resistance and chemical substances (such as illicit drugs). SARS-CoV-2 RNA has been identified in the sewerage in the Netherlands, US, Australia and elsewhere and has been linked to the community burden of disease. Currently, wastewater surveillance is being explored as a mechanism to inform COVID-19 control strategies – including as an early warning system to flag a community outbreak. In low- and middle-income countries where testing of individuals to determine the community burden of COVID-19 is impractical and/or unaffordable, assessment of community burden by testing of wastewater may be a cost-effective option.
OTHER RESOURCES

All COVID-19 literature

A pandemic primer on excess mortality statistics and their comparability across countries
https://ourworldindata.org/covid-excess-mortality

Australian Government Department of Health Webinars on the COVID-19 response for primary care practitioners

Australian Government

Burnet Institute research findings, policy and technical reports
https://www.burnet.edu.au/covid-19//36_know_c19_hub

COVID-19 and the kidney, currently the recommended U.S. resource
http://www.nephjc.com/covid19

Daily updates on COVID-19 literature compiled by Canadian medical students
https://docs.google.com/forms/u/0/d/e/1FAIpQLSfOxCoVuLV0aJdf_z2uWV7r3FaPzAOIr86qg9ZXBcTZ1DcCE_Nw/formResponse

Focuses on paediatric clinical, epidemiological, transmission and neonatal aspects

Global summary, identifying changes in the reproduction number, rate of spread, and doubling time during the course of the COVID-19 outbreak whilst accounting for potential biases due to delays in case reporting both nationally and sub-nationally
https://epiforecasts.io/covid/posts/global/

Introduction to Coronavirus: free, online course aimed at teenagers and young adults: scientists and experts from the London School of Hygiene & Tropical Medicine explain research to understand the virus and guide the global response to coronavirus
https://www.open.edu/openlearncreate/course/view.php?id=5319

Lancet COVID-19 papers

National COVID-19 clinical evidence taskforce: continually updated evidence-based clinical guidelines
https://covid19evidence.net.au/

Our world in data: statistics and research: Coronavirus pandemic (COVID-19)
https://ourworldindata.org/coronavirus

Oxford COVID-19 Evidence Service
https://www.cebm.net/oxford-covid-19/

https://philibrary.koha-pts.co.uk/covid19rapidreviews/

Retracted coronavirus (COVID-19) papers

Scimex.org – breaking science news portal: COVID-19 stories (research and expert commentary)
https://www.covid19-hpc-consortium.org/

University of Birmingham COVID-19 Research Briefing

Victorian Department of Health and Human Services

WHO Rolling updates on COVID-19

WHO COVID-19 dashboard
https://covid19.who.int/
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