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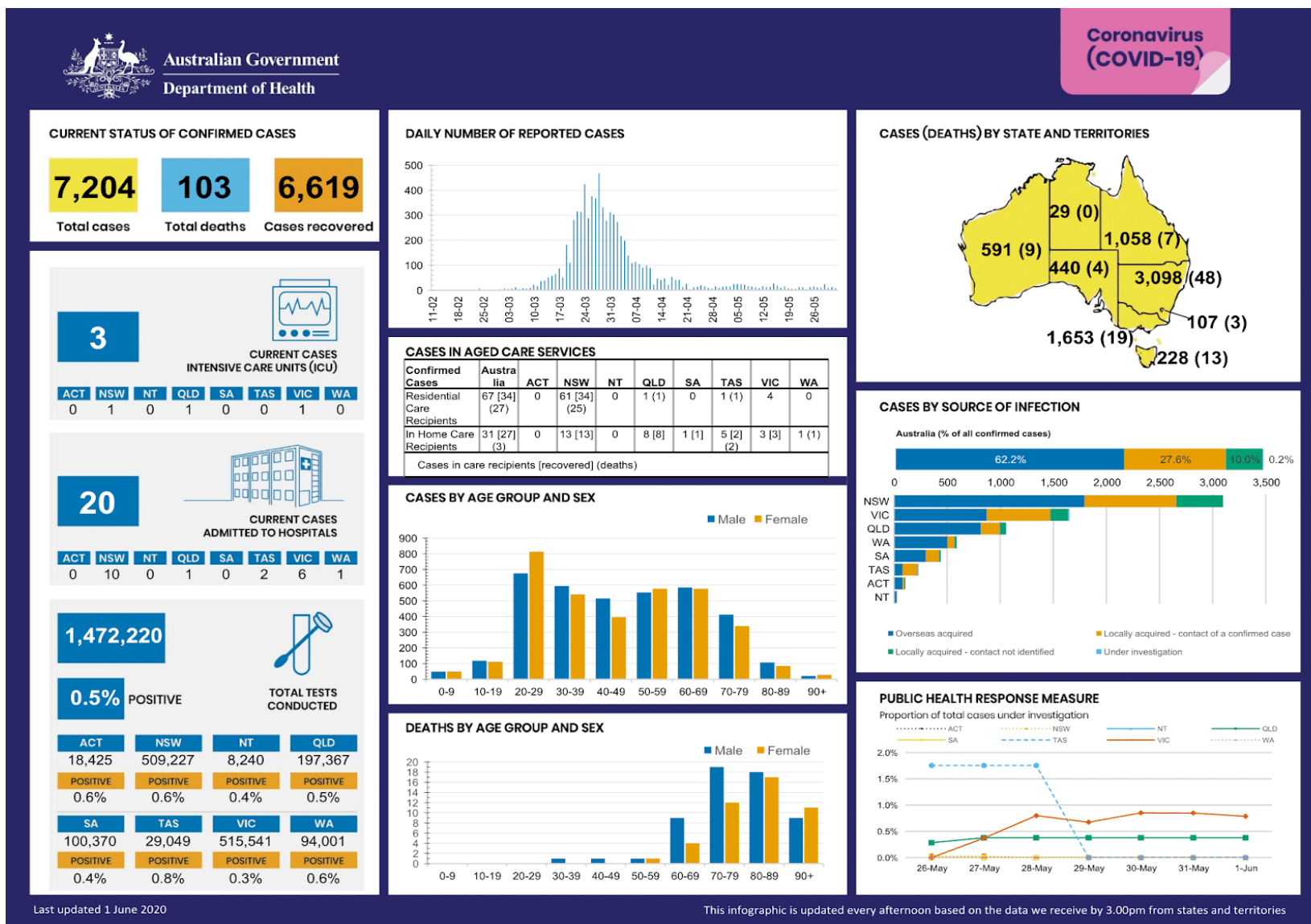
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COVID-19 KIDS EVIDENCE UPDATE

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

Weekly Update No.8

4 June 2020



Source: Australian Government: Department of health [Internet]. 2020 [updated 2020 June 01; cited 2020 June 02. Available from:

<https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-current-situation-and-case-numbers#at-a-glance>

GUEST EDITORIAL

Professor Sarath Ranganathan - Stevenson Chair,
 Department of Paediatrics, University of Melbourne

Welcome to the 8th COVID-19 Kids Research Evidence Update. After eight weeks of producing these reports it is worth pausing to reflect on how significantly our world has changed during this short period of time. From an Australian context, and an anticipated lockdown when we started of up to six months' duration, we have seen instead children now returning to school and an easing of many social distancing restrictions. In several other countries severe restrictions are also being eased, with some balancing economic necessity over direct health needs. Here in Australia we are fortunate that we have not only suppressed the virus, but in some jurisdictions, nearly eliminated it.

For some time, and clearly reiterated again on March 16th 2020, Dr Tedros Adhanom Ghebreyesus, the Director-General of the World Health Organisation has implored us to "Test, test, test". Indeed, if one inspects the table of countries that have heeded this advice and done the most tests to identify each case of COVID-19, a measure of how widely testing is actually done in relation to the extent of disease, the mantra of test, test, test certainly appears to be an important factor in the countries witnessing most success in suppressing the curve and decreasing deaths so far. Mass testing coupled with limiting further spread through contact tracing, isolation of cases and ongoing social distancing measures will be the new normal from here. Although we might be considered a Lucky Country the doubling time for infections a few months ago meant we were on the same trajectory as several other countries that have now suffered many more cases and deaths. So, the lack of circulating infection in Australia is the result of the measures taken and the adherence to the restrictions by all of us. Perhaps soon, we can look forward to safe travel bubbles with our trans-Tasman partners and others.

Total COVID-19 tests for each confirmed case, May 30, 2020



Source: Figure courtesy of Our World in Data <https://ourworldindata.org>

We have all seen the data on COVID-19 in children and they appear reassuring. However, the child pneumonia, and broader global child health experience, provides a forewarning of what may be coming in low and middle income countries where the virus is now circulating and cases increasing in number. The pneumonia mortality rate in low and middle income countries is approximately 70 times higher than in high income countries, with pneumonia the leading infectious cause of under-five deaths globally.

The risk factors for poor outcomes in pneumonia are overwhelmingly more prevalent in low and middle income countries than high income countries. These include severe malnutrition, low immunisation uptake, nutritional anaemia, HIV exposure or infection, air pollution, poverty, low parental education and, crucially, limited access to high-quality acute healthcare. (Ahmed S, Mvalo T, Akech S, et al Protecting children in low-income and middle-income countries from COVID-19 BMJ Global Health 2020;5:e002844). What will this mean for COVID-19? Read a more detailed summary in the global health section of this report.

I would like to congratulate Prof David Tingay of the Melbourne Children's Campus who is co-chairing The European Society for Pediatric and Neonatal Intensive Care (ESPNIC) Covid registry, this is an international, multicentre, and multidisciplinary initiative to study the epidemiology, clinical course, and outcomes of paediatric and neonatal SARS-CoV-2 infections (De Luca, D., Rava, L., Nadel, S. et al. The EPICENTRE (ESPNIC Covid pEdiatric Neonatal Registry) initiative: background and protocol for the international SARS-CoV-2 infections registry. Eur J Pediatr (2020)). More details in the Epidemiology and Public Health section.

Thanks again to all the contributors to this report. Keep it up and stay safe and well!

HIGHLIGHTS

- > Another school contact study, this time in Ireland, fails to show transmission to any of 924 child contacts.
- > 40 children (83%) of those admitted to paediatric intensive care units in the US had a pre-existing medical condition.
- > 87% of people with COVID-19 reported some degree of loss of smell although over-reporting and recall bias likely contribute to these findings.
- > SARS-CoV-2-specific IgG antibody responses in saliva correlate better with serum than IgA and IgM but buccal swabs are not the ideal viral sampling method for detecting SARS-CoV-2 in children.
- > Recovered COVID-19 patients generated a substantial CD4+ T cell response against SARS-CoV-2.
- > SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks, but ferrets and cats are permissive to infection.
- > Implication of SARS-CoV-2 evolution in the sensitivity of RT-qPCR diagnostic assays: viral mutations may indicate need for re-design and optimisation of RT-qPCR oligonucleotides primers.
- > Phase one trial: assessment of replication defective recombinant adenovirus type-five (Ad5) vectored COVID-19 vaccine expressing spike glycoprotein of SARS-CoV-2 strain appears safe and induces antibody responses.
- > Prior to COVID-19, global estimates were that 43% of all children under the age of five years worldwide are at risk of not reaching their developmental potential, based on prevalence of stunting and exposure to extreme poverty. An excellent review informs understanding of short and long-term risk of COVID-19 for child development.
- > Behavioural science approach suggests five main subclasses of intervention in relation to encouraging the maintenance of social distancing: education; persuasion; incentivisation; coercion and environment restructuring.

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Response to COVID-19 and any other medical condition at this time is based on science that is new, often uncertain, subject to change, and dependent on context.

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ADULT MEDICINE

Renee Cocks - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Loss of smell and taste in 2013 European patients with mild to moderate COVID-19

<https://www.acpjournals.org/doi/10.7326/M20-2428#f1-M202428>

- > The symptoms of loss of smell and taste related to SARS-CoV-2 infection were not extensively reported in early studies. Gaining a better understanding of the frequency of these symptoms could aid in the clinical diagnosis of COVID-19, particularly in countries where there is a lack of generalised testing.
- > The aim of this research letter was to evaluate the prevalence and features of, as well as the recovery from, smell dysfunction in European patients with mild to moderate COVID-19.
- > 2013 patients with mild to moderate SARS-CoV-2 were identified using the electronic health record across 18 European hospitals and took part in an online questionnaire. Among the patients reporting loss of smell, 86 patients in Hainaut Belgium underwent objective olfactory testing.
- > 1754 patients (87%) reported some degree of loss of smell. In 57% of these patients this occurred after other general symptoms (such as headache, myalgia, cough, loss of appetite).
 - Of the 573 patients that had regained their sense of smell during the study 67% regained their smell after five -14 days.
 - 1136 (56%) reported taste dysfunction. Additional aroma disorder occurred in 82.5% of patients.
 - Among the 86 patients who had an objective olfactory evaluation more than a third (38%) showed no objective signs of dysfunction.
 - No significant association was found between loss of smell and otolaryngologic symptoms of nasal obstruction, rhinorrhoea and postnasal drip.
- > Conclusion: loss of smell and taste appear to be common symptoms of SARS-CoV-2 infection.
- > Limitations:
 - Recall bias- mean time from the end of disease to the evaluation was 7.8 days. Now that this symptom has been widely reported, possible that there is “over-reporting”; or perhaps those with no objective signs of changes in smell had symptoms related to other issues (or had recovered)

- Data was collected from hospitalised patients at discharge and non-hospitalised patients after resolution of key symptoms. Due to being questioned after diagnosis there are many confounding factors, such as being influenced by symptoms heard on the news or through the questionnaire
- Most patients had loss of smell after other general and otolaryngologic symptoms, limiting the use of anosmia in early diagnosis

Reviewed by: Professor Allen Cheng

CHILD DEVELOPMENT

Dr Kate Milner - Paediatrician, Neurodevelopment & Disability
Royal Children's Hospital

Effects of the Global COVID-19 pandemic on early childhood development: short- and long-term risks and mitigating policy and program actions (pre-proof)

[https://www.jpeds.com/article/S0022-3476\(20\)30606-5/pdf](https://www.jpeds.com/article/S0022-3476(20)30606-5/pdf)

- > This paper informs the understanding of the short and long-term risk of COVID-19 for early child development (ECD).
- > The early childhood period (defined from the prenatal period to eight years) is a time of particular sensitivity to long-term adverse developmental impact of environmental adversity (i.e. 'toxic stress').
- > Evidence is presented from previous disasters as well as diverse settings in the current pandemic which suggest that short and long-term effects of COVID-19 will substantially increase the number of children worldwide who do not reach their developmental potential, with long-term consequences for health, well-being, education and employment.
- > Immediate potential risks to early child development include:
 - Worsening child health outcomes due to direct and indirect factors, especially disrupted provision and utilisation of routine maternal, newborn and child health services provision, evidenced by data from diverse high and low-and middle-income countries
 - Deteriorating economic circumstances – leading to an additional 42-66 million worldwide children living in extreme poverty over the next year
 - Increased food insecurity, worsening early childhood nutrition
 - Increased migration, displacement and family separation
 - Adverse impact on caregiver stress and mental health, thereby decreasing caregiving capacity and provision of nurturing care, challenges that may be amplified for some groups (e.g. parents of children with disabilities)
 - Confinement and/or crowding during social isolation leading to increases in exposure to family violence as well as increases in other forms of abuse (e.g. sexual violence against girls as evidenced during the Ebola crisis)
- > Additional long-term risks to adult outcomes, relating to the ECD period include;
 - 'Long-term shocks' due to in utero exposure to above, as seen during impact of a number of historical disasters, impacting educational attainment, lifelong earnings and non-communicable disease risks

- Long-term economic downturn beyond the initial pandemic extending duration of exposure to the above risks
- > Data from diverse sources suggests that vulnerability due to these risk factors will be inequitable according to factors such as socioeconomic status, ethnicity and disability.
- > Implications: Suggested mitigating actions for governments, NGOs, civil societies and communities are presented with examples.

CLINICAL PAEDIATRICS

Daniel Lamanna - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

SARS-CoV-2 infection in ambulatory and hospitalised Spanish children
<https://adc.bmj.com/content/early/2020/05/22/archdischild-2020-319366>

- > In the context of limited paediatric data, the effects of SARS-CoV-2 in children suggest that the infection is less frequent and less severe when compared to adults
- > 58 paediatric patients from 11th March - 9th April 2020 at Hospital La Paz (Madrid, Spain) with confirmed SARS-CoV-2 were retrospectively analysed (median hospital stay was three days)
 - 14 received oxygen therapy (median three days)
 - 12 were given antibiotics (ceftriaxone)
 - Three patients with severe disease received remdesivir and tocilizumab was added in ⅓ cases as an inflammatory syndrome developed
- > Overall outcomes were positive, including in five patients who developed outpatient pneumonia
- > However, rates of hospital (57%) and intensive care unit (15%) admission were high; COVID-19 testing was limited over this time period.

Reviewed by: Dr. Wonie Uahwatanasakul

Rose Noble Kizhakekara – 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

The EPICENTRE (ESPNIC COVID pEdiatric Neonatal Registry) initiative: background and protocol for the international SARS-CoV-2 infections registry
<https://link.springer.com/article/10.1007/s00431-020-03690-9>

- > EPICENTRE is an initiative by The European Society for Pediatric and Neonatal Intensive Care (ESPNIC).
- > It is the first international, multicentre, multidisciplinary, meta-data driven, hospital-based, online, prospective cohort registry dedicated to neonatal and paediatric SARS-CoV-2 infections.
- > ~ 100 centres have joined.
- > EPICENTRE aims to study the epidemiology, clinical course, and outcomes of paediatric and neonatal SARS-CoV-2 infections, specifically to:

- Describe the general epidemiology and outcomes of neonatal and paediatric SARS-CoV-2 infections (including the incidence of vertical infection and transmission route).
 - Investigate if SARS-CoV-2 can be transmitted through breast milk and if mother/neonate separation is beneficial or useful
 - Describe the clinical course, need for respiratory, and critical care of severe COVID-19 in neonates and children.
 - Describe the use and side effects of candidate antiviral or other adjunctive therapies for neonatal and paediatric COVID-19 infection.
 - Investigate the value of clinical, laboratory, and imaging findings to predict the clinical severity and other outcomes in the enrolled population.
- > The data are collected through a dedicated database, customized using REDCap® software and hosted by MCRI, Australia.
 - > The registry has also been modelled in order to be able to merge data with similar international registries being launched in other continents.
 - > For more information and to gain access, please write to: epicentre@mcri.edu.au

Reviewed by: Professor Fiona Russell

CLINICAL TRIALS

Dr Amanda Gwee - Infectious Diseases Physician, RCH; Team leader & Clinician-Scientist Fellow in the Infectious Diseases Group, MCRI; and Senior Lecturer, Department of Paediatrics, The University of Melbourne

Importance of paediatric inclusion in COVID-19 therapeutic trials

<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa656/5847864>

- > Commentary on the need to include children in therapeutic trials for COVID-19. Rationale includes.
- > As of 6th May 2020, aside from trials of convalescent plasma, there was only one registered clinical trial (of hydroxychloroquine) for children of all ages.
- > Presentation of SARS-CoV-2 has significantly differed in clinical presentation and severity with age. Therefore, data from adult trials may not reflect the risk versus benefit of therapeutic agents in children.
- > Children should be given equal opportunity to receive potentially active therapeutic agents against COVID-19 in the safest manner possible.
- > Inclusion in well-designed therapeutic trials enables routine, structured safety monitoring and maximises the likelihood of detecting toxicities. It also provides opportunities for pharmacokinetic/pharmacodynamic studies.
- > Inclusion in trials enables parents and children to be fully informed of the risks and benefits associated with the use of therapeutics.

CO-INFECTION

Natalie Commins - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Prevalence of putative invasive pulmonary aspergillosis in critically ill patients with COVID-19

[https://www.thelancet.com/pdfs/journals/lanres/PIIS2213-2600\(20\)30237-X.pdf](https://www.thelancet.com/pdfs/journals/lanres/PIIS2213-2600(20)30237-X.pdf)

- > Adult patients hospitalised with severe COVID-19 infection are at risk of developing secondary infections such as invasive pulmonary aspergillosis (IPA).
 - IPA was noted as a secondary infection after H1N1 influenza infection. It was present in 20-30% of critically ill patients and led to significant illness severity and mortality (40-60%).
 - Most cases involved patients who were not immunocompromised.
- > Prospective observational study looking at the risk of developing IPA in critically ill COVID-19 patients.
- > Due to concerns that the EORTC-MSG criteria used to define aspergillosis risk may not capture all affected patients, the authors developed an algorithm that can be used to distinguish *Aspergillus* spp colonisation from putative IPA in ICU patients.
 - Patients in the study were classified using one of the below criteria to determine risk: The EORTC-MSG criteria for immunocompromised patients; Influenza-associated IPA criteria.
 - Mycological investigations were undertaken.
 - Putative IPA should be considered if
 - If *Aspergillus* spp identified in BAL culture, or
 - Two of the following conditions were met: presence of *Aspergillus* spp in BA culture; positive *Aspergillus fumigatus* qPCR in BAL, BA or serum; Galactomannan index >0.8 in BAL; Galactomannan index >0.5 in serum; β -D-glucan >80pg/mL in serum.
- > Using the above algorithm in 27 patients with COVID-19 (all mechanically ventilated, 18 males, nine females, median age 63).
 - Suspected IPA in one patient (8%); putative IPA in eight patients (30%); a history of hypertension was more common in patients with putative IPA than those without; mortality rate was unchanged between patients with putative IPA and those without; three patients had *Aspergillus fumigatus* cultured without positive qPCR or galactomannan antigen in the BAL or BA; four of the nine affected patients died, though from bacterial shock and multiorgan failure, rather than aspergillosis.

- > Adding β -D-glucan and qPCR to the mycological workup for suspected IPA can help aid in diagnosis, especially given that other forms of testing (CT and BAL) are difficult to perform in these patients

Reviewed by: Dr Wonie Uahwatanasakul

CRITICAL CARE

Julian Loo Yong Kee - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Characteristics and outcomes of children with coronavirus Disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units

<https://jamanetwork.com/journals/jamapediatrics/fullarticle/2766037>

- > A cross-sectional study across 46 North American paediatric intensive care units (PICUs) from 14th March – 3rd April 2020.
- > PICU admissions: USA: 48 admissions to 14 PICUs; Canada: 0 admissions.
- > Epidemiology: Median age: 13 years old (4.2-16.6); Male: 25 children (52%); Pre-existing medical condition: 40 children (83%); ≥ 2 organ system failure: 11 children (23%); Respiratory symptoms present: 35 children (73%); invasive ventilation: 18 children (38%); target therapy: 28 children (61%); median length of stay for those discharged: PICU – five days (3-9); hospital – seven days (4-13); hospital mortality rate: 4.2%.
- > Prehospital comorbidities appear to be an important paediatric factor.
- > Data indicates that children are at greater risk of critical illness from influenza than from COVID-19.

Reviewed by: Dr Wonie Uahwatanasakul

DIAGNOSTICS & SAMPLING

Dr Celeste Donato - Senior Research Officer, Enteric Diseases, Infection & Immunity Theme, MCRI and Honorary Fellow, Department of Paediatrics, The University of Melbourne

Implication of SARS-CoV-2 evolution in the sensitivity of RT-qPCR diagnostic assays

<https://www.sciencedirect.com/science/article/pii/S1473309920304357?via%3Dihub>

- > Whilst SARS-CoV-2 mutates slower than some other RNA viruses, it may become necessary to redesign the oligonucleotides used in the SARS-CoV-2 diagnostic RT-qPCR assays if primer-RNA mismatches occur.
- > The alignment based on 1,825 SARS-CoV-2 genome sequences available in the GISAID database at the time of this study (March 2020) was annotated with the binding sites of the 33 published RT-qPCR oligonucleotides (primers and probes) designed for the detection of SARS-CoV-2. The nucleotide diversity was calculated in the binding region of each oligonucleotide.
- > A total of 79% (26/33) of the oligonucleotides used in the RT-qPCR assays exhibited mutations in the binding sites.
- > The primer with the most substantial mismatch was the Chinese National Institute for Viral Disease Control and Prevention's forward primer designed against the gene encoding for the nucleocapsid phosphoprotein. This primer had a substitution of three nucleotides (GGG substituted to AAC) at the start of the binding site. The AAC variant has been detected in 14% (258/1825) of the genomes sequenced from 24 different countries. The authors suggest this primer is now likely to be ineffective at detecting some virus variants.
- > The observed mutations highlight the need for continued sequencing of variants as well as the continued re-design and optimisation of RT-qPCR oligonucleotides

Dr Danielle Wurzel - Respiratory Physician, RCH; Honorary post-doctoral Research Fellow in the Respiratory Diseases Group, MCRI; and honorary Senior Fellow, Department of Paediatrics, The University of Melbourne.

Clinical utility of buccal swabs for SARS-CoV-2 detection in COVID-19-infected children

<https://academic.oup.com/jpids/advance-article/doi/10.1093/jpids/piaa068/5848122>

- > The optimal sampling method for detection of SARS-CoV-2 in children with respect to diagnostic yield and tolerability is unknown
- > Nasopharyngeal (NP) and oropharyngeal specimens are currently the recommended mode of sampling however NP samples are often poorly tolerated in children and may induce cough resulting in risk to healthcare workers performing the test.
- > Buccal swabs are less invasive and better tolerated than NP swabs however no studies to date have compared their respective diagnostic yields.
- > Over a ten-day period (23rd March - 3rd April 2020) all confirmed COVID-19 paediatric inpatients (PCR from NP swabs) were recruited and had daily paired NP and buccal swabs.
- > Cycle threshold (Ct) values were obtained for all samples and presence/absence of symptoms recorded.
- > Eleven COVID-19-infected children were included in this study: six (54.5%) children were asymptomatic (median age 8.4 years), and five (45.5%) symptomatic children (median age 3.8 years) had mild illness.
- > SARS-CoV-2 was detected from at least one buccal specimen in 9/11 children (81.8%)
- > Viral load, inferred from Ct values was significantly lower in buccal compared to NP swabs [mean difference in Ct value 10.7 (range: 6.1 to 16.1); $p < 0.001$]
- > Sensitivity of buccal swabs for detecting SARS-CoV-2 in NP swabs ranged from 25% to 71.4% depending on timing of sampling with respect to duration of illness
- > Limitations: Small sample size, limitation duration of testing, indirect measurement of viral loads using Ct-values.
- > Conclusion: Buccal swabs are not the ideal viral sampling method for detecting SARS-CoV-2 in children and have lower sensitivity than NP swabs

Thomas Hill - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

How does the epidemic stage influence RT-PCR findings in children and adults? (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.05.18.20098863v1.full.pdf>

- > This study aimed to identify if RT-PCR-positive SARS-CoV-2 rates in children and adults changed during the stage of the COVID-19 epidemic in France.
- > The authors conducted a prospective multicentre study involving 45 paediatric wards and emergency centres and analysed 52,588 RT-PCR tests.
- > Consistent with other studies, the RT-PCR positive rate was higher for adults than for children. At the start, the peak and after the peak of the epidemic the RT-PCR-positive rates in adults were 4.5, 2.8 and 2.2-fold higher than in children, respectively.
- > In Paris, a region greatly affected by COVID-19, RT-PCR-positive rates in adults were seven fold higher at the start of the epidemic and three fold higher at the peak of the epidemic than in children.
- > For adults, the proportion of positive tests changed over time, and were higher at the peak of the epidemic.
- > RT-PCR testing varied across centres and local guidelines relating to the testing of children may have changed during the study, potentially resulting in imprecise surveillance.

Reviewed by: Associate Professor Catherine Satzke

EPIDEMIOLOGY & PUBLIC HEALTH

Professor Fiona Russell - Director of the Child and Adolescent Health PhD Program, Department of Paediatrics, The University of Melbourne; Group Leader Asia-Pacific Health Research, MCRI

No evidence of secondary transmission of COVID-19 from children attending school in Ireland, 2020

<https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.21.2000903>

- > Examined the evidence of paediatric transmission in the Republic of Ireland in the school setting.
- > The first Irish case of COVID-19 was notified in a school-going child at the beginning of March 2020.
- > Schools closed from 12th March, 2020.
- > All SARS-CoV-2 notifications were screened to identify children and adults who had attended the school setting.
- > Three children and three adult cases of COVID-19 were identified.
- > The epidemiological investigation indicated that all six cases had not been infected with SARS-CoV-2 in the school setting.
- > Among 1,001 child contacts of these six cases there were no confirmed cases of COVID-19. In the school setting, among 924 child contacts and 101 adult contacts identified, there were no confirmed cases of COVID-19.
- > Limitations: Small numbers; only symptomatic contacts were tested, and so asymptomatic secondary cases were not captured.
- > Summary: Concurs with supportive evidence from Iceland, Italy and NSW that children are likely to play a small role in transmission; although further larger studies are warranted.

Jun Hua Bowen Lim -3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

COVID-19 in children and the dynamics of infection in families

<https://pediatrics.aappublications.org/content/early/2020/05/22/peds.2020-1576>

- > This study aimed to describe the clinical presentation of the first 40 pediatric cases of COVID-19 in Geneva and the dynamics of their familial clusters.
- > Among a total of 4310 SARS-CoV-2 cases, 40 were <16 years old (0.9%)
- > Most children had mild or atypical presentations
- > In 79% of households, at least one adult family member was suspected or confirmed for COVID-19 prior to symptom onset in the study child, confirming other reports that children are infected mainly inside familial clusters
- > In 33% of households, symptomatic household contacts tested negative despite belonging to a familial cluster with confirmed SARS-CoV-2 cases
- > In only 8% of households did a child develop symptoms prior to any other household contacts

Reviewed by: Dr Shidan Tosif

Samar Hikmat - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

How long does SARS-CoV-2 remain viable on different surfaces?

<https://www.science.org.au/covid19/viability-on-surfaces>

- > Report convened by the Australian Science Academy Australian Rapid Research Information Forum to inform the Minister for Health
- > Understanding how long SARS-CoV-2 remains viable on different surfaces and how to efficiently clean surfaces is important for informing public health and infection control measures.
- > At standard room temperature and humidity (21-23°C, 40% relative humidity), SARS-CoV-2 remains viable up to: four days on glass; three days on stainless steel and plastic; two days on clothes; one day on cardboard/paper; four hours on copper.
- > For the same temperature and initial viral load, the half-life of the virus is shortened with increased humidity.
- > Disinfection of contaminated surfaces:
 - Household bleach and solutions containing at least 70% alcohol inactivate SARS-CoV-2 on surfaces within five minutes. Heat and simulated sunlight can also reduce the viability of the virus on surfaces.

- The survival of SARS-CoV-2 on the hands is yet to be determined. Thorough cleansing (for 20s) with alcohol-based hand rubs or soap and water should be sufficient to reduce the likelihood of infection.
- Laundry with hot water, bleach and detergent is sufficient to reduce contamination on clothes.

Reviewed by: Professor Fiona Russell

Benjamin Watson - 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

SARS-CoV-2 RNA concentrations in primary municipal sewage sludge as a leading indicator of COVID-19 outbreak dynamics (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.05.19.20105999v1>

- > This is a report of the time course of SARS-CoV-2 RNA concentrations in primary sewage sludge during the Spring COVID-19 outbreak in a north-eastern U.S. metropolitan area.
- > This study uniquely utilised primary sewage sludge instead of raw wastewater for virus RNA measurements. Sewage sludge is comprised of solids that are removed during primary sedimentation steps and typically gravity thickened.
- > SARS-CoV-2 RNA concentrations were a seven day leading indicator ahead of compiled COVID-19 testing data and led local hospital admissions data by 3 days
- > This study demonstrates:
 - The utility of SARS-CoV-2 primary sludge monitoring to accurately track outbreaks in a community.
 - Primary sludge SARS-CoV-2 RNA concentrations can be a leading indicator over other commonly used epidemiology approaches including summarised COVID-19 test results and hospital admissions.
- > SARS-CoV-2 concentrations in raw wastewater or sludge may be utilised to pre-empt community outbreaks or provide an additional basis for easing restrictions, especially in countries with limitations in clinical testing.

Reviewed by: Dr Wonie Uahwatanasakul

Batsho Mandlebe - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Reducing SARS-CoV-2 transmission in the UK: A behavioral science approach to identifying options for increasing adherence to social distancing and shielding vulnerable people

<https://onlinelibrary.wiley.com/doi/full/10.1111/bjhp.12428>

- > Reducing transmission of SARS-CoV-2 in the UK requires the population to accept and adhere to public health measures implemented by the government.
- > The aim of this research was to produce a systematic method for a very rapid response to a UK government policy question in the context of reducing SARS-CoV-2 transmission.
- > The APEASE criteria and Behaviour Change Wheel were used to evaluate and structure the interventions of increasing general social distancing and shielding of vulnerable people in the UK.
- > There are ten options in five subclasses to consider when promoting general social distancing:
 - Education – Information regarding recommended behaviours must be specified and rationalised to communities.
 - Persuasion – People must perceive a personal threat or responsibility to others while receiving positive messaging around their actions and tailored measures for their community.
 - Incentivisation – Social approval can both highlight good practices and mutual social encouragement.
 - Coercion – Compulsory measures and social disapproval from community can promote prosocial behaviours amongst communities.
 - Environment restructuring – Ensure adequate access to social contact and resources from home and identify and reduce inequities in disadvantaged communities.
- > Considerations when shielding vulnerable people for at least 12 weeks are:
 - Education – Specific rationalised behavioural recommendations must be stated. The information must be tailored not only to people living with vulnerable persons, but vulnerable people themselves.
 - Enablement – Practical support must be offered to assist new living arrangement, routines and adherence to guidelines.
- > Conclusion: using a framework can assist in rapidly responding to policymakers during the COVID-19 pandemic.

Reviewed by: Associate Professor Margie Danchin

GLOBAL HEALTH

Professor Fiona Russell - Director of the Child and Adolescent Health PhD Program, Department of Paediatrics, The University of Melbourne; Group Leader Asia-Pacific Health Research, MCRI

Protecting children in low-income and middle-income countries from COVID-19
<https://gh.bmj.com/content/5/5/e002844>

- > While yet unknown, COVID-19, a viral pneumonia syndrome, may impact children in low- and middle-income countries (LMIC) more severely than what has been observed to date in high income countries as the rate of pneumonia in LMICs is 200 per 100 000 populations, with pneumonia the leading infectious cause of under-five deaths globally.
- > The risk factors for poor outcomes in pneumonia are overwhelmingly more prevalent in LMICs: severe malnutrition, low immunisation uptake, nutritional anaemia, HIV exposure or infection, air pollution, poverty, low parental education and, crucially, limited access to high-quality acute healthcare.
- > The indirect effects of the COVID-19 response need attention: widespread parental unemployment, disrupted education, food and housing insecurity and threats to vital preventive health programmes, like immunisation, antenatal care, infant feeding and mental health. The acute care workforce may soon be overwhelmed.
- > 4 approaches outlined:
 - Prevent the collapse of vital acute care (oxygen, antibiotics, PPE), preventive services (immunisation, maternity care, breastfeeding and nutrition programmes, HIV and malaria prevention) and supply chains and take opportunities for system strengthening that could be a legacy of the pandemic.
 - Upscale COVID-19 testing.
 - Tailor local lockdown strategies to maintain vital access to care and to suit the particular social, economic and health environments.
 - Research to better understanding COVID-19 in children, including their role in transmission dynamics, spectrum of illness and outcomes, the impact of comorbidities and common coinfections (viral, bacterial, mycobacterial and parasitic) and how broader pandemic responses impact on health behaviours and outcomes.

Julian Loo Yong Kee - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Oxygen for all, during COVID-19 (coronavirus) and beyond
<https://blogs.worldbank.org/health/oxygen-all-during-covid-19-coronavirus-and-beyond>

- > An article by Kevin Watkins, Director of Save the Children UK, discusses the need for accessible medical oxygen for all.
- > Medical oxygen is a key treatment for many conditions eg. severe pneumonia: Biggest killer of children; 148,000 deaths of under-five in the 15 counties with the highest pneumonia burden could be averted.
- > During COVID-19, fixing ventilator supply is futile if medical oxygen supply is not there. WHO recommends focusing medical oxygen systems and provision of pulse oximeters, which are often overlooked.
- > Accessibility for all: Medical oxygen is often unaffordable to poorest and most disadvantaged (\$40-60 worth of medical oxygen for a child with severe pneumonia).
 - Many first world hospitals have industrial quantities of high-grade liquid oxygen that are linked to patients via miles of piping and valves.
 - National health service (NHS) in the UK provides medical oxygen for free.
 - Hospitals in poorer and underdeveloped countries often rely on oxygen cylinders delivered by truck and charge for the cost of refilling.
- > Increasing investment and commitment to put oxygen at the centre of strategies for universal health coverage is required.
- > COVID-19 is an opportunity to spotlight the need for medical oxygen for health equity.

Reviewed by: Professor Fiona Russell

Ha My Ngoc Nguyen - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Paediatric care in the time of COVID-19 in countries with under-resourced healthcare systems
<https://adc-bmj-com.ezp.lib.unimelb.edu.au/content/early/2020/05/17/archdischild-2020-319333>

- > Children from lower-income countries have significant health risk factors such as malnutrition, overcrowded housing, inadequate sanitation and income insecurity. In these countries, there is also a lack of personal protective equipment (PPE) and testing capacity.
- > To overcome these barriers, three primary health interventions were suggested, including that hospitals should do what they can do, really well.

- > Doing oxygen well:
 - Oxygen supplies are often limited, especially in rural settings, which contribute to high mortality from pneumonia and other critical illnesses.
 - Provision of oxygen alone without CPAP or mechanical ventilation has been shown to reduce mortality in children with pneumonia by 35%.
 - Countries should urgently assess their capacity to provide oxygen, identify gaps, in order to procure equipment to treat all people requiring oxygen therapy due to COVID-19.
- > Protecting staff:
 - Measures such as allocating a separate ward for paediatrics patients with severe pneumonia and keeping children with non-severe pneumonia out of hospital are essential.
 - Doing oxygen well, rather than scaling up mechanical ventilation is also a protective measure for staff. Emergency intubation is the highest risk of transmission to a healthcare worker.
- > Maintain routine services:
 - High-risk children (HIV, tuberculosis, newborns) need frequent monitoring to treat acute infections and receive special care.
 - Disruption to immunisation services have had disastrous consequences in recent years (e.g. deadly measles outbreaks, eroding efforts to eliminate polio).

Reviewed by: Dr Wonie Uahwatanasakul

Rachel Leong - 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

COVID-19: Pandemic exposes inequalities in global food systems
<https://www.bmj.com/content/369/bmj.m1915>

- > A comment on the Global Nutrition Report 2020 in the context of the COVID-19 pandemic.
- > There is already vast inequity between food systems around the world, where many people cannot afford healthy food, and only have access to staple grains (rice/wheat/maize) and highly processed foods.
- > Increasingly, countries are experiencing the 'double burden of malnutrition', where both undernutrition and obesity and other diet-related diseases (diabetes, cardiovascular disease) co-exist.
 - One in nine people in the world are hungry or undernourished; whilst one in three is overweight or obese.

- > No country is on course to meet all ten of the 2025 Global Nutrition Targets (anaemia, low birthweight, exclusive breastfeeding, childhood stunting, childhood wasting, childhood overweight, adult obesity (men/women), adult (men/women) diabetes); → there is risk that progress made towards these goals will be lost during this pandemic.
- > Existing vulnerability is amplified in the current COVID-19 pandemic.
 - Undernourished people with weaker immune systems are at greater risk of severe illness.
 - People with metabolic disease (diabetes, cardiovascular disease) are strongly associated with worse outcomes.

Reviewed by: Dr Wonie Uahwatanasakul

IMMUNOLOGY

Thomas Hill - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

The role of spike in priming the innate immune response to SARS-CoV-2 (pre-print)

<https://assets.researchsquare.com/files/rs-30407/v1/84b04e7c-44c9-4f6d-a6a1-360b9f87e48e.pdf>

- > Authors speculated the SARS-CoV-2 spike (S) glycoprotein functions as a pathogen associated molecular pattern (PAMP) for macrophages priming the NLRP3 inflammasome.
- > Incubation with S-protein followed by nigericin resulted in increased secretion of IL-1 β by ex vivo derived macrophages from circulating monocytes of COVID-19 patients but not SARS-CoV-2 naïve controls.
- > This indicates that SARS-CoV-2 may possibly induce trained innate immunity, but for this to be confirmed the elevated response would need to be shown to be non-specific (e.g. in response to LPS), which was not the case in this study.
- > Incubation with LPS, nigericin or S-protein alone had no differential effect on IL-1 β expression, suggesting S-protein functions to prime the NLRP3 inflammasome requiring a second signal for activation.
- > S-protein also triggered NLRP3-independent release of proinflammatory cytokines including IL-6, IL-8 and TNF α similarly in both COVID-19 patients and naïve controls groups, suggesting that SARS-CoV-2 specifically primes the NLRP3 pathway.
- > Chemical inhibition of the NLRP3 inflammasome blocked secretion of IL-1 β in COVID-19 patient derived macrophages, suggesting a potential therapeutic target for the hyperinflammatory syndrome seen in COVID-19.

Reviewed by: Dr Boris Novakovic

Samar Hikmat - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

COVID-19 serology at population scale: SARS-CoV-2-specific antibody responses in saliva (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.05.24.20112300v1.full.pdf>

- > Large scale monitoring of SARS-CoV-2 is important for guiding public health policies pertaining to COVID-19 prevention and control. Currently, population level serological testing is mainly performed using serum samples which may be too invasive, uncomfortable or unacceptable among particular groups.
- > Salivary antibodies (particularly IgG) to SARS-CoV-2 could serve as a non-invasive alternative to serological testing for large-scale monitoring of SARS-CoV-2 infection.
- > Salivary SARS-CoV-2-specific antibody responses were compared to that of sera.
- > A multiplex antibody immunoassay containing different SARS-CoV-2 antigens was created.
- > 167 saliva and 324 serum samples were tested. Out of these, 134 saliva and 118 serum samples were negative (collected before the COVID-19 pandemic); 33 saliva and 206 serum samples were SARS-CoV-2 positive (collected <10 days and ≥10 days' post symptom onset).
- > Saliva samples were collected from the space between the gums and teeth as it is enriched with gingival crevicular fluid which contains antibodies resembling that of serum.
- > Antigen specific IgG levels in 28 matched saliva and serum samples were significantly correlated for all SARS-CoV-2 and SARS-CoV-1 antigens. Antigen-specific IgA and IgM had weaker correlation between the samples.
- > Salivary SARS-CoV-2-specific IgG can be used to detect a prior SARS-CoV-2 infection with improved sensitivity and specificity compared to serum (peaking at 100% sensitivity ≥10 days post symptom onset for GenScript N antigen and 100% specificity for Mt. Sinai RBD antigen). However, SARS-CoV-2-specific IgM and IgA in saliva had lower sensitivity compared to that of serum.
- > The temporal kinetics of SARS-CoV-2-specific IgG responses in saliva are consistent with those observed in serum and indicate that most individual seroconvert approximately ten days after COVID-19 symptom onset or approximately two weeks post-presumed infection.
- > Limitations: Small sample of matched saliva and serum samples. Severity of SARS-CoV-2 disease, sociodemographic and medical history information from study participants were not known and therefore not taken into consideration in the analysis.

- > Additional comments: There are two main ways antibodies get into saliva. The majority of salivary antibodies are secreted into saliva via plasma cells in salivary glands; these are studied by collecting drool (spit). However, some of the antibodies found in saliva come from the blood by leaking across the gums. As this study collects “saliva” by swabbing the gums, they are predominantly measuring the antibodies that cross the gums, i.e. are from the blood, rather than antibodies from the salivary glands, which can be quite different. This doesn’t alter the value of the study regarding the potential use of saliva as a diagnostic tool, but as full saliva was not analysed, care must be taken with these results and interpreting the true salivary antibody response to COVID-19.

Reviewed by: Professor Phil Sutton

Daniel Lamanna - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Targets of T-cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals

[https://www.cell.com/cell/fulltext/S0092-8674\(20\)30610-3](https://www.cell.com/cell/fulltext/S0092-8674(20)30610-3)

- > An understanding of the human T cell response to SARS-CoV-2 is lacking as a result of the rapid emergence and evolution of the pandemic. There is an urgent need for foundational information regarding the T cell response to the virus.
- > Identification and quantitation of SARS-CoV-2 Specific CD4+ T cell responses.
 - SARS-CoV-2 spike-specific CD4+ T cell responses (OX40+CD137+) were detected in 100% of COVID-19 cases.
 - Cytokine secretion was used to assess the functionality and polarisation of CD4+ T cell response.
 - Production of IL-2 in response to non-spike and spike MPs confirmed functionality.
 - Polarisation of the cells appeared to classically be the TH1 type as substantial interferon (IFN)-gamma was produced, while little to no IL-4, IL-5, IL-13, or IL-17a was expressed.
 - Recovered COVID-19 patients generated a substantial CD4+ T cell response against SARS-CoV-2.
 - Total CD4+ T cell response per donor; 50% of the detected response was directed towards the spike protein, and 50% was directed against the MP representing the remainder of the SARS-CoV-2 orfome.
- > Identification & quantitation of SARS-CoV-2 specific CD8+ T cell responses.

- Assays detected IFN- γ + SARS-CoV-2 specific CD8 + T cells in the majority of COVID-19 cases.
 - Majority of IFN- γ + cells co-expressed granzyme B and tumor necrosis factor, but not IL-10.
 - The majority of recovered COVID-19 patients generated a CD8+ T cell response.
- > Relationship between SARS-CoV-2 specific CD4+ T cell responses and IgG and IgA titres.
 - COVID-19 patients make anti-spike RBD antibody responses commensurate with the magnitude of their spike-specific CD4+ T cell response.
 - SARS-CoV-2 specific CD4+ and CD8+ T cell responses and antibody were well correlated.

Reviewed by: Professor Fiona Russell

INDIGENOUS HEALTH

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

Critical condition: the impact of COVID-19 policies, policing and prisons on First Nations communities

<https://drive.google.com/file/d/18XF70q-ILvvpfe9arDLqGoZev2sCxMxt/view>

- > This Report is by Australia's only national Aboriginal led justice coalition of Aboriginal peak bodies and non-Indigenous allies. They work to end the incarceration of, and family violence against, Aboriginal and Torres Strait Islander people.
- > This Report details the indirect social impacts of COVID-19 on Indigenous Australians.
- > The ongoing impacts of colonisation, poverty and inequality result in Aboriginal and Torres Strait Islander peoples having poorer health outcomes than non-Indigenous Australians, as well as increased risk of the severe impacts of COVID-19.
- > There is an over-representation of Aboriginal and Torres Strait Islanders peoples in criminal justice systems, and the increased risk of COVID-19 spreading in incarcerated populations. They recommend that those who are low-risk to the community or who may be at increased risk of COVID-19 be released.
- > Acknowledging reports of reduced access to a range of supports and increased use of isolation and lock down measures during the COVID-19 pandemic, this Report recommends "protecting the human rights of Aboriginal and Torres Strait Islander peoples by ensuring access to oversight and monitoring agencies and other rehabilitative services.
- > The pandemic has highlighted the particular absence of culturally appropriate and trauma-informed legal services
- > Recognising high rates of COVID-19 in incarcerated children overseas (up to 46%), this Report recommends raising the age of criminal responsibility from ten to 14 years old and urgently releasing children as a part of the public health response.
- > Rates of family violence increase during disasters - the report recommends connecting Aboriginal and Torres Strait Islander peoples with culturally appropriate services, as well as increasing access to safe housing for families fleeing violence.
- > The Report recommends short term changes to legislation to bypass some of the barriers to family unification which have been exacerbated by COVID-19. They also recommend enacting a culturally safe national child protection notification and referral scheme to prevent the removal of children, particularly newborns, from their families.
- > Acknowledging the disproportionate impact that travel restrictions, over-policing in public spaces, and overcrowding issues have on Aboriginal and Torres Strait Islander peoples, this Report recommends that police and policy-makers resist punitive responses against people in these circumstances.

Reviewed by: Dr Renata Kukuruzovic

INFECTION CONTROL

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

Predicting infectious SARS-CoV-2 from diagnostic samples

<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa638/5842165>

- > Canadian study investigating whether infectious virus could be cultured from SARS-CoV-2 samples that were positive by nucleic acid testing.
- > 26/90 SARS-CoV-2 RT-PCR positive samples were culture positive on Vero cell culture, suggesting presence of infectious virus
- > Samples were more likely to be culture positive if shorter time from onset of symptoms to testing.
- > There was no viral growth in samples with symptom to test time > eight days, suggesting that patients were unlikely to be infectious more than eight days after symptom onset.
- > Limitations: small sample size, samples were frozen then cultured two - four weeks after collection, did not include children.
- > These findings are consistent with previous small studies, and support existing public health guidelines that recommend quarantine of SARS-CoV-2 positive patients for at least ten days from onset of symptoms.

MENTAL HEALTH

Professor David Coghill - Chair of Developmental Mental Health,
Department of Paediatrics, The University of Melbourne

COVID-19 and the need for perinatal mental health professionals: now more than ever before

<https://www.nature.com/articles/s41372-020-0696-z>

- > Comment on the mental health impacts of the COVID-19 pandemic on the babies, their parents and the staff that are looking after them in neonatal intensive care units (NICU).
- > Highlights the already high, but often under recognised, impact on parents of having a baby in NICU with rates of diagnosable mental disorders in NICU parents the first partum year of at least 20-30% with depression and post traumatic stress being the most common problems.
- > Argues that these rates are almost certain to rise as a result of the restrictions on visiting, skin to skin care and breastfeeding that have been introduced as a consequence of COVID-19 restrictions
- > Pre COVID-19 rates of burnout among NICU staff were already high with a mean across California of 26.7% and a range of 7.5-42.9%.
- > Believes that the additional stresses of supporting babies and their parents during the pandemic, often through telehealth rather than face to face contact, will increase these rates further.
- > Argues that an increased focus on funding social work and psychology posts in NICUs should be a priority.
- > An observation on this comment is that the focus was on parents and staff with little discussion of the direct and indirect impacts of the babies. Although I am sure this was unintentional it might have been good to have made the ultimate goal of supporting the babies more explicit.

Chan Ying Zhen Charissa - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Prevalence of depression, anxiety, and insomnia among healthcare workers during the COVID-19 pandemic: A systematic review and meta-analysis
<https://www.sciencedirect.com/science/article/pii/S088915912030845X?via%3DiHub>

- > 13 cross sectional studies; 33062 participants: 12 studies in China (two in Wuhan), one in Singapore.
- > Only studies evaluating prevalence rates of depression, anxiety, and/or insomnia using validated assessment methods were eligible.
- > Male representation 18%.
- > Anxiety prevalence (n=12): pooled 23.2%.
 - Among low risk of bias studies (n=9), pooled prevalence of 24.1%.
- > Depression prevalence (n=10): pooled 22.8%.
 - After excluding studies that affected outcome by over 2% (n=2), pooled prevalence of 16.9%.
 - Among low risk of bias studies (n=8), pooled prevalence 22.9%.
- > Insomnia prevalence (n=5): pooled 34.3%; low risk of bias in all five studies
- > Subgroup analysis revealed higher pooled prevalence of anxiety and depression in females than males. Nurses exhibited higher prevalence estimates for both anxiety and depression than doctors.
- > Conclusion: Early evidence suggests that a considerable proportion of healthcare workers experience mood and sleep disturbances during this outbreak.
- > Limitations: Inherent heterogeneity across studies. Generalisability of findings limited as all studies were conducted in Asia, majority in China. All studies included were cross-sectional, hence did not compare prevalence of anxiety, depression and insomnia with pre-COVID-19 baseline. Future research should evaluate the changes in prevalence of mental health conditions in the context of COVID-19.

Reviewed by: Professor David Coghill

PERINATAL HEALTH

Professor Suzanne M 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.

The impact of thermal pasteurization on viral load in human milk and other matrices: a rapid review (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.05.23.20111369v2?%253fcollection>

- > The primary aim of this review was to characterise studies conducted in human milk to determine how certain viral families that are either present in human milk, or used as surrogates, respond to thermal pasteurisation as assessed by viral load or live virus detection. To expand the scope of viruses tested, the secondary objective was to summarise studies conducted in non-human milk matrices that have examined the effect of thermal pasteurisation on any virus. This review also aims to compare viruses that have been assessed in studies using both human milk and nonhuman milk matrices to ascertain any trends in susceptibility to thermal pasteurisation.
- > This was a systematic review performed following milk banking associations call for guidance to determine whether SARS-CoV-2 is inactivated by Holder pasteurisation (62.5°- 63°C C, 30 min). It was performed by one author only.
- > For studies conducted in human milk (18 unique studies), where eight different virus families were spiked into human milk (all capsid enveloped viruses),
- > For those in other matrices (90 unique studies and 21 viral families studied, the majority were non-enveloped viruses in the families of picornaviridae), it was found to completely inactivate non-enveloped viruses, such as hepatitis A or porcine parvovirus in human milk or in other matrices, temperatures above 63°C (70°C -90°C) or a significantly longer duration at 60°C-63°C was required. Notably, viruses in the coronaviridae family, SARS-CoV, and SARS-CoV-2, showed significant reductions in infectivity (>5-7-log reduction in TCID50/mL) following pasteurization; complete inactivation was observed at temperatures between 56°C-60°C for a 5-60 min duration.
- > In general, their results were that irrespective of matrix, enveloped (e.g. CMV), compared to non-enveloped viruses, generally require less input of thermal energy in order to achieve similar reductions in viral load or live virus concentration.
- > The authors concluded that based on the literature review, Holder pasteurisation (62.5°C, 30 minutes) may be sufficient to inactivate non-heat resistant viruses that may be present in human milk, including coronaviruses.

Jenny Pham - 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

Horizontal transmission of severe acute respiratory syndrome coronavirus 2 to a premature infant: multiple organ injury and association with markers of inflammation

[https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642\(20\)30166-8/fulltext](https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30166-8/fulltext)

- > A male infant, born at 27 weeks' gestation presented at eight weeks of age (then 35 weeks corrected), presented with severe symptoms of poor feeding and dyspnoea on a background of neonatal respiratory distress syndrome requiring three days of ventilation.
- > Clinical course of respiratory failure, progressive changes on X-ray was consistent with acute respiratory distress syndrome seen in severe adult COVID-19 disease. The child had severe sepsis syndrome with unrecordable BP, severe lactic acidosis. Day eight of admission the infant was thought to have hyperinflammatory syndrome (raised IL6).
- > Remdesivir was trialled in the infant but had little contribution to the clinical improvement of the infant as viral load remained stable.
- > Rather than a decreasing viral load, respiratory improvement was associated with reduced IL-6 levels, ferritin and lactate dehydrogenase, suggesting that host inflammatory response plays a role in the pathophysiology of respiratory failure.
- > This is the first detailed description of a premature infant with COVID-19 and suggests that, like adults, infants are at risk of severe multisystem disease. As the host inflammatory response is implicated in the mechanism of respiratory disease, monitoring of inflammation is recommended.

Reviewed by: Professor Suzanne M Garland

THERAPEUTICS

Nicholas Baxter - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Hydroxychloroquine (HCQ) in patients with mainly mild to moderate coronavirus disease 2019: open label, randomized controlled trial

<https://www.bmj.com/content/369/bmj.m1849>

- > Open label RCT in China.
- > Population: 150 patients aged 18 years and above, with SARS-CoV-2 infection confirmed by respiratory PCR. Majority (148/150, 99%) had mild symptoms.
- > Intervention: Randomised in a 1:1 ratio to standard of care (control) or standard of care + high dose HCQ (1200_{mg} for three days followed by 800_{mg} daily) for two weeks if mild or moderate symptoms; or three weeks if severe symptoms. 75 in each arm.
- > Results: Trial terminated early due to decline in eligible cases in China
 - Primary outcome: 56/70 standard of care vs 53/70 standard of care + HCQ had negative conversion of SARS-CoV-2 by 28 days.
 - Secondary outcome: No significant difference in the probability of negative conversion of SARS-CoV-2 the probability of alleviation of symptoms by 28 days.
 - Adverse events: diarrhoea reported in 7/70 (10%) of patients in the HCQ group. Other adverse events: blurred vision (One patient requiring dose reduction); thirst (One patient). Both side effects were transient.
- > Limitations
 - Change of primary endpoint from negative conversion rate by day ten to negative conversion by day 28.
 - Treatment initiated late in the illness - median duration from onset of symptoms to randomisation was 16.6 days.
 - 90 (60%) of patients received other drugs prior to randomisation including steroids, antibiotics, and antivirals, in both the Standard of Care and Standard of Care + HCQ arm.
 - Doses of HCQ were modified (decreased) if treating practitioners believed HCQ to be the cause of adverse events, meaning not all participants were consistently dosed.
 - 99% of study participants had mild-moderate disease limiting the broad applicability of these findings for those with severe infection.

Reviewed by: Dr Amanda Gwee

TRANSMISSION

Dr Lien Anh Ha Do, Virologist - New Vaccines, Infection & Immunity Theme, MCRI and Honorary Fellow, Department of Paediatrics, The University of Melbourne

Maximum daily temperature, precipitation, ultraviolet light, and rates of transmission of SARS-CoV-2 in the United States

<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa681/5849063>

- > This study reports the effects of daily maximum temperature, precipitation, and UV Light on community transmission of SARS-CoV-2 in the US from 22nd January to 3rd April 2020 using data from 50 US states and Washington D.C and adjusting for a number of state level factors such as state population, population density, gross-domestic product, median family income, the proportion of uninsured, obesity rates, graduation rates, the proportion of African-Americans, and the proportion of older adults and children.
- > A daily maximum temperature greater than 52° F (11°C) was associated with a significantly lower rate of COVID-19 cases at five days.
 - A significant inverse association between the maximum daily temperature (per one-degree F) and the rate of COVID-19 cases at five days was also observed.
 - A one unit higher UV index was associated with a lower rate of COVID-19 cases at five days.
 - A presence of precipitation was not associated with the rate of COVID-19 cases at five days.
- > Significance: The study provided additional data on the effect of temperature and also a new data on the effect of UV on community transmission of SARS-CoV-2, although both effects are modest and would not provide significant effects beyond the current mitigation strategies.
- > Limitations: The different scales of COVID-19 testing, the introductions of containment at different time-points and the definition of incubation duration of COVID-19 could confound the findings.

Benjamin Watson - 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

Susceptibility of ferrets, cats, dogs, and other domesticated animals to SARS-coronavirus 2

<https://science.sciencemag.org/content/368/6494/1016.full>

- > SARS-CoV-2 is thought to have originated in bats; however, the intermediate animal sources of the virus are unknown.
- > Cats in Wuhan have been reported to be seropositive for SARS-CoV-2.
- > This study found that SARS-CoV-2 replicates poorly in dogs, pigs, chickens, and ducks, but ferrets and cats are permissive to infection.
- > Additionally, cats are susceptible to airborne transmission.
- > The fact that SARS-CoV-2 replicates efficiently in the upper respiratory tract of ferrets makes them a candidate animal model for evaluating the efficacy of antiviral drugs or vaccines against COVID-19.

Reviewed by: Dr Wonie Uahwatanasakul

Alastair Weng - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Susceptibility to and transmission of COVID-19 amongst children and adolescents compared with adults: a systematic review and meta-analysis (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.05.20.20108126v1>

- > The prevalence, infectivity and transmission of SARS-CoV-2 in children has been a source of debate amongst healthcare professionals and the community alike, with little convincing evidence presented.
- > This systematic review looked at what is the susceptibility to and transmission of SARS-CoV-2 by children and adolescents compared with adults?
- > Contact tracing studies: Using pooled data from eight studies, the odds ratio of being an infected close contact as a child vs an adult was 0.44 (0.29, 0.69), suggesting children may be 56% less susceptible than adults. Using data from another systematic review, 3/31 (9.7%) household clusters identified a child as the index case.
- > Population screening studies: Studies included populations from Iceland, Italy, Sweden, Netherlands, Germany, Switzerland, Spain, and the United Kingdom. Some included national data, others only certain municipalities. Some studies were conducted prior to social distancing measures, but others only during lockdown policies.
- > There was no consensus regarding prevalence of SARS-CoV-2 amongst children compared to adults. Some studies suggested a positive correlation between prevalence and age, and others found no link whatsoever.

- > The diversity of results here can be attributed to the population viral burden, cultural aspects, and lockdown measures. No meta-analysis was performed, and no consensus was reached.
- > This is a highly dynamic research field, and although the authors attempted to characterise the risk children pose in society, there is still inconclusive evidence. More research and more time is needed to reach a more agreeable consensus.

Reviewed by: Associate Professor Margie Danchin

VACCINES

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

The world needs COVID-19 vaccines. It may also be overestimating their power

<https://www.statnews.com/2020/05/22/the-world-needs-covid-19-vaccines-it-may-also-be-overestimating-their-power/>

- > This article cautions against expecting that a COVID-19 vaccine could induce “sterilizing immunity”. Instead, those interviewed for this article suggest that it is more likely to induce short-term protection against severe disease, similar to that seen in the influenza vaccine, and that such a vaccine might not prevent transmission.
- > Kanta Subbarao (WHO influenza collaborating centre in Melbourne) highlights the importance around public health messaging in this space, and that setting realistic expectations of a COVID-19 vaccine in the community will be essential to avoid the same lack of confidence as is seen for the influenza vaccine.
- > Michael Mina (infectious diseases epidemiologist at Harvard’s TH Chan School of Public Health) optimistically wonders whether low-level circulation of COVID-19 in the community could actually offer natural boosting of immunity. However, Sarah Fortune (Chair of the Department of Immunology and Infectious disease at Harvard’s School of Public Health) reinforced that in the case that we don’t have a sterilizing vaccine, and COVID-19 can’t die out through herd immunity, extremely high rates of vaccination will be needed to protect those who are most vulnerable to COVID-19.

Reviewed by: Associate Professor Margie Danchin

Chan Ying Zhen Charissa - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial

[https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(20\)31208-3.pdf](https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31208-3.pdf)

- > Phase One trial: assessment of a recombinant adenovirus type-5 (Ad5) vectored COVID-19 vaccine expressing spike glycoprotein of SARS-CoV-2.
- > 108 healthy adult participants (51% male; mean age 36.3 years) were recruited in Wuhan, China and received the intramuscular low dose (n=36), middle dose (n=36), or high dose (n=36) of the vaccine: low dose (5×10^{10} viral particles per 0.5 mL), middle dose (1×10^{11} viral particles per mL) or high dose (1.5×10^{11} viral particles per 1.5 mL).

- > Laboratory safety tests measured on day seven included white blood cell count, lymphocyte count, neutrophils, platelets, haemoglobin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, fasting blood glucose and creatinine: No clinically significant, vaccine-related changes in laboratory measurements.
- > Tolerability: No difference in rate of adverse reactions across treatment groups. Overall, 81% experienced an adverse event within 28 days.
 - No serious adverse reactions in all groups within 28 days.
 - Most common were mild or moderate adverse reactions: pain (54%), fever (46%), fatigue (44%), headache (39%), muscle pain (17%).
 - Higher reactogenicity profile of the high dose (17%), as compared to low (6%) and middle dose (6%) groups, presenting as severe, activity-limiting fever, fatigue, muscle pain, or joint pain, which might be associated with viraemia caused by Ad5 vector infection. But transient and self-limiting.
- > Immunogenicity
 - ELISA antibodies and neutralising antibodies increased at day 14, peaked at day 28. The antibody response in the high dose group was slightly greater than that in the middle dose and low dose groups.
 - High proportions of participants with positive T-cell responses occurred in all dose groups post-vaccination.
 - High pre-existing Ad5 neutralising antibody titres compromised seroconversion of neutralising antibody post-vaccine.
 - Recipients aged 45-60 years seemed to have lower seroconversion of neutralising antibody compare to younger recipients.
- > Limitations: Small sample size consistent with phase one studies; no control group. Limited population as only 16% were between 50-60 years old.
- > Conclusion: Ad5 vectored COVID-19 vaccine is tolerable and immunogenic in healthy adults. Specific humoral responses against SARS-CoV-2 peaked at day 28 post-vaccination, and rapid, specific T-cell responses noted from day 14 after one dose. Current ongoing phase two trial in China to provide more information about safety and immunogenicity.

Reviewed by: Professor Fiona Russell

VIROLOGY

Dr Lien Anh Ha Do - Virologist, New Vaccines, Infection & Immunity Theme, MCRI and Honorary Fellow, Department of Paediatrics, The University of Melbourne

Large-scale, in-house production of viral transport media to support SARS-CoV-2 PCR testing in a multi-hospital healthcare network during the COVID-19 pandemic

<https://jcm.asm.org/content/jcm/early/2020/05/11/JCM.00913-20.full.pdf>

- > This study describes a protocol to process for large-scale, implicated quality control, in-house production of viral transport media (VTM) and a validation report of testing different swabs, in the context of worldwide shortage of VTM and swabs and of the US crisis.
- > An adapted formulation of VTM from CDC protocol has been validated, using already and easily access reagents.
 - A well-designed, adapted infrastructure, team organization, and management from research teams successfully provided the service during the on-going crisis.
 - Quality control (QC) process has been implicated by a separated team.
 - In-house VTM demonstrated an accelerated stability, even stored at high temperature 56°C.
 - A list of alternative swabs was presented.
- > Significance: Useful and practical information for choosing swabs or preparing in-house VTM in the context of disrupted worldwide supplies.
- > Limitations: The validation testings were only performed using PCR, while one important aspect of using VTM is for viral culture.

Daniel Lamanna - 3rd Year Medical Student,
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Estrogen regulates the expression of SARS-CoV-2 receptor ACE2 in differentiated airway epithelial cells

<https://journals.physiology.org/doi/abs/10.1152/ajplung.00153.2020>

There is marked sexual dimorphism in the current COVID-19 pandemic - oestrogen can regulate the expression of ACE2, a key component to SARS-CoV-2 cellular entry in differentiated airway epithelial cells.

- > Higher intensive care unit (ICU) admissions and deaths have been reported in males as a result of COVID-19, consistent with epidemiological data collected from previous coronavirus outbreaks (SARS, MERS) - there seems to be an increased susceptibility of males to pathogenic coronaviruses.
- > 17 β -oestradiol (E2) can regulate gene expression of ACE2 and the serine protease TMPRSS2 (responsible for priming of the viral spike protein) in differentiated normal human bronchial epithelial (NHBE) cells.
- > Commercially purchased NHBE donor cells treated with E2 expressed lower levels of ACE2 mRNA.
- > Of note, the concentration of E2 used is only seen under the physiological conditions of pregnancy, and not in non-pregnant females. There was also only one donor used in the study.

Reviewed by: Dr Wonie Uahwatanasakul

OTHER RESOURCES

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

Lancet COVID-19 papers
https://www.thelancet.com/coronavirus?utm_campaign=tlcoronavirus20&utm_content=126383502&utm_medium=social&utm_source=twitter&hss_channel=tw-27013292

Focuses on paediatric clinical, epidemiological, transmission and neonatal aspects
<https://dontforgetthebubbles.com/evidence-summary-paediatric-covid-19-literature/>

All COVID-19 literature
<https://www.ncbi.nlm.nih.gov/research/coronavirus/>

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

Daily updates on COVID-19 literature compiled by Canadian medical students
https://docs.google.com/forms/u/0/d/e/1FAIpQLSfOxCoAuLV0aJdf_z2uWV7r3FaPzAOr86q9ZXBcTZ1QcCE_Nw/formResponse

Victorian Department of Health and Human Services
<https://www.dhhs.vic.gov.au/coronavirus-covid-19-daily-update>

Australian Government
<https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-current-situation-and-case-numbers>
<https://www.health.gov.au/resources/publications/management-and-operational-plan-for-people-with-disability>

COVID-19 and the kidney, which is currently the recommended US resource
<http://www.nephjc.com/covid19>

University of Birmingham COVID-19 Research Briefing
<https://www.birmingham.ac.uk/university/colleges/mds/Coronavirus/COVID-19-research-briefing.aspx>

Australian Government Department of Health Webinars on the COVID-19 response for primary care practitioners
<https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-advice-for-the-health-and-aged-care-sector/webinars-on-the-coronavirus-covid-19-response-for-primary-care-practitioners>

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/>

OTHER RESOURCES

WHO Rolling updates on COVID-19

<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen>

Scimex.org – breaking science news portal: COVID-19 stories (research and expert commentary)

<https://www.scimex.org/info/2019-20-coronavirus>

<https://www.covid19-hpc-consortium.org/>

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>

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