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Department of Paediatrics

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COVID-19 KIDS RESEARCH EVIDENCE UPDATE

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

Weekly Update No. 14

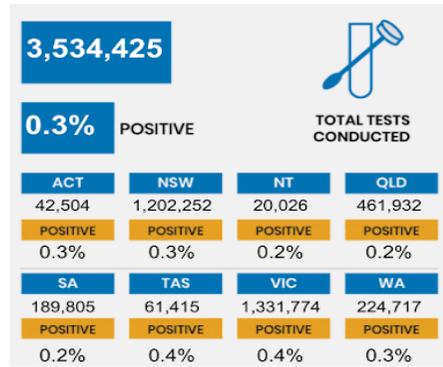
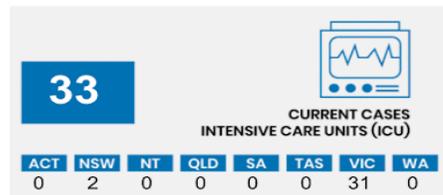
23rd July 2020



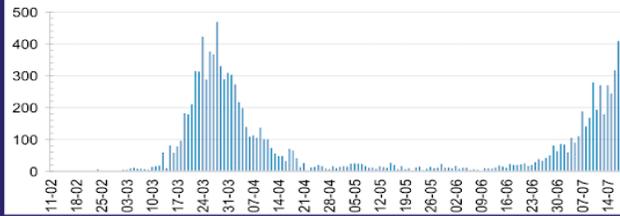
Australian Government
 Department of Health

BE COVIDSAFE

CURRENT STATUS OF CONFIRMED CASES



DAILY NUMBER OF REPORTED CASES

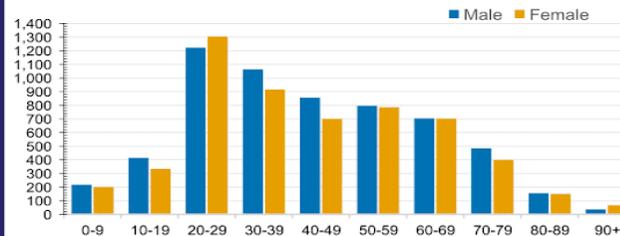


CASES IN AGED CARE SERVICES

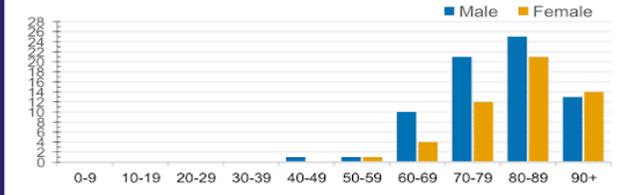
Confirmed Cases	Australia	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
Residential Care Recipients	205 [40]	0	61 [32]	0	1 [1]	0	1 [1]	142 [8]	0
In Home Care Recipients	36 [28]	0	13 [13]	0	8 [8]	1 [1]	5 [3]	8 [3]	1 [1]

Cases in care recipients [recovered] (deaths)

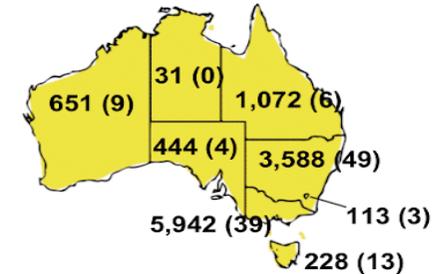
CASES BY AGE GROUP AND SEX



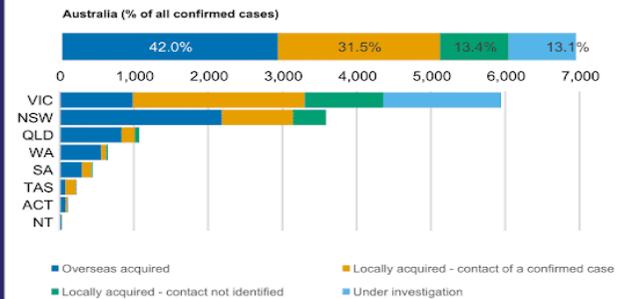
DEATHS BY AGE GROUP AND SEX



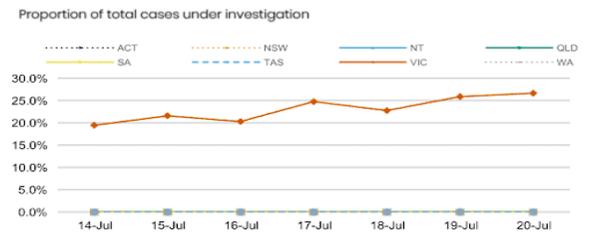
CASES (DEATHS) BY STATE AND TERRITORIES



CASES BY SOURCE OF INFECTION



PUBLIC HEALTH RESPONSE MEASURE



Last updated 20 July 2020

This infographic is updated every afternoon based on the data we receive by 3.00pm from states and territories

Source: Australian Government: Department of health [Internet]. 2020 [updated 2020 June 29; cited 2020 July 20]. 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>

HEAD OF DEPARTMENT EDITORIAL

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

Welcome to the 14th edition of the report and congratulations to the team who keep the production line going with such alacrity. There were plans to move to a fortnightly report but the number of important papers being published, coupled with the surge of cases locally, mean that we need more than ever to keep up to date with the scientific evidence in order to plan our public health responses, clinical care and research in children.

During the past week there has been much talk about elimination versus suppression policies being targeted in our State. To a certain extent it is an arbitrary discussion at the present time, given case numbers are increasing exponentially. As it is now compulsory to wear a mask outside for those over twelve-years-old we can only hope this leads to better success at suppression in the weeks to come, despite revelations that 9 out of 10 people were not self-isolating when they started experiencing symptoms of COVID-19. This is a significant problem because the virus is more likely to be detected between 0 and 4 days after onset of symptoms (see <https://doi.org/10.1101/2020.07.13.20152793> reviewed in the Diagnostic Sampling section of the current report). Unfortunately, we may have missed our one chance at elimination. Of course, the debate is far more nuanced and I recommend reference to a paper summarised in the Epidemiology and Public Health section by Daniel Lamanna and Professor Fiona Russell (<https://doi.org/10.1101/2020.07.13.20152793>) on this topic.

If any further inducement towards good social behaviours is required also see the Adult Medicine section in which a report describes that 87% of patients with COVID-19 discharged from hospitals in Rome still had symptoms two months later! Many still reported fatigue (53%), dyspnoea (43%), joint pain (27%) or chest pain (22%) (<https://www.bmj.com/content/370/bmj.m2815>). Infection fatality risk, by contrast, may not discourage the young. Estimates of the infection fatality risk are key to understanding the true pandemic burden and for comparing different risk-reduction strategies but of course vary in different settings. A Swiss study, published as a research letter, estimated infection fatality rate based on the population-based seroprevalence data collected each week for five consecutive weeks in Geneva. Population-wide infection fatality rate was 0.64% (which is viewed as a best case scenario given their excellent health care system). In young people this was 0.0016% for 5-9 years-old and 0.00032% for 10-19 years-old (see [https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099\(20\)30584-3.pdf](https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(20)30584-3.pdf) in the Epidemiology and Public Health Section of the report). How are your thought and behaviours influenced by such knowledge?

There was more positive news on vaccines this week with two phase 1/2 studies being published in the Lancet (see Vaccines section of the report). The Oxford University vaccine utilises a genetically-modified chimpanzee adenovirus that expresses the coronavirus spike protein whereas the Cansino Biologics vaccine developed in China harnesses a modified human adenovirus. The vaccines appeared to be safe with some evidence of inducing both a humoral and cellular response immune response. Four vaccines are now progressing to phase 3 clinical trials. Stock up on your mask supplies and cross your fingers!

HIGHLIGHTS

- > The Oxford ChAdOx1 nCoV-19 vaccine showed an acceptable safety profile, and homologous boosting increased antibody responses. These results, together with the induction of both humoral and cellular immune responses, support a large-scale evaluation in an ongoing phase 3 trial
- > The Chinese Ad5-vectored COVID-19 vaccine is safe and induced significant immune responses in the majority of recipients after a single dose.
- > A study suggests that elimination in Victoria is achievable, and that mandatory wearing of masks can greatly assist its chances.
- > Multicentre cohort European study of children <18 years found that risk factors for ICU admission included age <1 month, pre-existing medical conditions and symptoms or signs of the lower respiratory infection at presentation.
- > European consensus recommendations for neonatal and paediatric retrievals of positive or suspected COVID-19 patients have been detailed from the initial assessment of patient risk for COVID-19 through transportation and ensuring clear coordination with receiving units.
- > Epidemiological data from Italy suggests that paediatric cases of COVID-19 are less severe than adults, however, age <1 year and the presence of underlying conditions represent risk factors for more severe disease.
- > Lack of studies on medium and long term symptoms of COVID-19.
- > Vertical transmission occurs, although uncommon, although defining case criteria and systematic methodology of evaluation of potential cases is needed.
- > Hispanic and non-Hispanic black pregnant women in the U.S. appear to be disproportionately affected by SARS-CoV-2; among women aged 15-44 y with COVID-19, pregnancy is associated with an increased risk of ICU admission and mechanical ventilation, but not an increased risk of mortality.
- > Very limited data regarding the relationship between Treg/Th17 cell imbalance and pregnancy outcomes as a result of COVID-19.
- > The infection fatality rate (IFR) characterises the severity of infection across a population and for specific demographic groups. The IFR is lower in children compared to adults. However, the IFR is context-specific, as access to care and quality of care (key determinants of outcome) is highly variable between settings.
- > Testing samples from many people at once has been suggested as a method to save time, reagents, and money.
- > Highest percentage of virus detection via nasopharyngeal swab occurred 0 to 4 days post-symptom onset at 89%, after 10 to 14 days this drops to 54%.
- > Possible genetic determinants of innate immune response and symptom severity in other coronaviruses pre-COVID-19.

- > To improve handwashing in young children, a combination of antecedent and consequence strategies can be used, e.g., demonstrating handwashing effectiveness, ongoing performance feedback, handwashing song, frequent and immediate consequences such as feedback or rewards after handwashing.

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Unless specifically stated, the authors do not recommend or endorse any procedures or processes described in this resource.

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.

Always seek the advice of your physician or another qualified health provider properly licensed to practice medicine or general health-care in your jurisdiction concerning any questions you may have regarding any information obtained from this publication.

Never disregard professional medical advice or delay in seeking it because of something you have read in this publication. Information obtained in this publication is not exhaustive and does not cover all possible manifestations of COVID-19 nor its interaction with other conditions, diseases, ailments, or their treatment.

The Owners of this resource do not wish to use this resource as a means of communication with the general public (i) regarding questions or issues of a medical nature; (ii) to establish physician-patient relationships. Email communications regarding such matters will not be responded to and will be discarded unread.

ADULT MEDICINE

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

Covid-19: What do we know about “long covid”?

<https://www.bmj.com/content/370/bmj.m2815>

- > Ongoing COVID-19 symptoms are not well described.
- > Aside from anecdotal evidence, there is as yet little research on this topic.
- > A report from Italy found that 87% discharged from a Rome hospital after recovering from COVID-19 were still experiencing at least one symptom 60 days after onset.
 - 13% were completely symptom-free.
 - 32% had 1-2 symptoms, and 55% had 3+ symptoms.
 - Although none of the patients had a fever or any signs or symptoms of acute illness, many still reported fatigue (53%), dyspnoea (43%), joint pain (27%), and chest pain (22%). Two-fifths of patients reported a worsened quality of life.
- > The UK COVID-19 Symptom Study app collects symptom information from nearly 4 million users and found 10% with COVID-19 are sick for 3+ weeks.
- > U.K. G.P. college requests rapid review of requirements needed.
- > The Post-hospitalisation COVID-19 Study (PHOSP-COVID) aims to recruit 10,000 patients across the U.K., who will be followed for more than a year but excludes those with milder symptoms. It is unclear whether infants, children and adolescents are included in this study.

CLINICAL PAEDIATRICS

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

COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study

[https://www.thelancet.com/pdfs/journals/lanchi/PIIS2352-4642\(20\)30177-2.pdf](https://www.thelancet.com/pdfs/journals/lanchi/PIIS2352-4642(20)30177-2.pdf)

- > This study aims to capture key data on children and adolescents (< 18 years) with SARS-CoV-2 across Europe to inform physicians and health-care service planning during the ongoing pandemic.
- > Methods:
 - Multicentre cohort study involved 82 health-care institutions in 21 European countries.
 - Include individuals aged 18 years or younger with confirmed SARS-CoV-2 infection between 1st April and 24th April 2020, during the initial peak of European COVID-19 pandemic.
 - Explore factors that associated with the need for ICU admission and initiation of drug treatment for COVID-19.
- > Findings:
 - 582 individuals are included. 145 (25%) had pre-existing medical conditions. 363 (62%) individuals were admitted to the hospital. 48 (8%) individuals require ICU admission. 25 (4%) mechanical ventilation. 19 (3%) inotropic support, and 1 (<1%) extracorporeal membrane oxygenation.
 - Risk factors associated with ICU admission: Younger than one-month, male sex, pre-existing medical condition, presence of lower respiratory tract infection signs or symptoms.
 - Frequently used anti-viral treatment: hydroxychloroquine (7%), remdesivir (3%), lopinavir-ritonavir (1%), oseltamivir (1%).
 - Frequently used immunomodulatory: corticosteroids (4%), IVIG (1%), tocilizumab (1%), anakinra (1%), siltuximab (<1%).
 - Fever and cough were the predominant clinical features at presentation
 - Four children died.

- > Discussion:
 - This study mostly includes children and adolescents who were seen in hospitals, thus representing individuals at the more severe end of the disease spectrum. Notably, a recent letter from 171 PCR-confirmed cases in Wuhan suggests 20% of children and adolescents with COVID-19 are asymptomatic.
 - Nevertheless, the study concludes that children and adolescents are overall less severely affected by COVID-19, particularly older patients. However, a small proportion develop a severe disease that requires ICU admission, although a fatal outcome is overall rare.
 - Severe COVID-19 can occur in both young children and adolescents. Individuals with viral co-infections were more likely to require ICU support than having SARS-CoV-2 alone. This means influenza season can result in a greater number of paediatrics patients to require ICU admission.
 - Data also reflects current uncertainties regarding specific treatment options, highlighting additional data on antiviral and immunomodulatory drugs are urgently needed.

Reviewed by: Dr Wonie Uahwatanasakul

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

European consensus recommendations for neonatal and paediatric retrievals of positive or suspected COVID-19 patients

<https://www.nature.com/articles/s41390-020-1050-z>

17 recommendations specifying pertinent aspects of neonatal and paediatric COVID-19 patient transport:

- > Determine the status of the patient, COVID-19 positive or suspected, at the referral of the patient.
- > Full PPE for transport staff involved in clinical patient care during transport.
- > Reduced PPE for assisting transport staff not involved in patient care but within < 2 m of the patient.
- > Transport teams to train and simulate donning and doffing procedures of PPEs.
- > The patient should, whenever feasible, wear a surgical mask to minimise aerosol spread.
- > Use cuffed endotracheal and tracheostomy tubes, including for newborn infants, to avoid aerosol spread by an air leak.
- > Use video-laryngoscopy whenever possible for intubation.
- > Use strict protocol/checklist for airway management/intubation.
- > Use HEPA filters on the inspiratory limb of the ventilation circuit.
- > Use HEPA filters on the expiratory limb to avoid spreading contaminated air from the patient.

- > No recommendation for or against the use of humidified air or heater/humidifier.
- > Provide non-invasive ventilation with the use of a ventilator and a dual-limb system and filters as recommended above.
- > Any incubator transport is to be handled like an open stretcher transport from a PPE point of view.
- > Place a newborn infant in a suitable sized plastic bag to prevent heat loss and to reduce the need for incubator humidification.
- > Transport infants and children without parents or relatives, regardless if symptomatic or not.
- > Assure a secure and dedicated pathway for entering the receiving unit.
- > Decontaminate any exposed transport equipment, including equipment left within the transport vehicle.

Reviewed by: Dr Wonie Uahwatanasakul

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

COVID-19 disease severity risk factors for paediatric patients in Italy

<https://pediatrics.aappublications.org/content/pediatrics/early/2020/07/11/peds.2020-009399.full.pdf>

- > This research looked at the epidemiological and clinical characteristics of COVID-19 in paediatric cases (n=3,836) below 18 years old in Italy.
- > Demographics were summarised by age groups, and risk factors for disease severity were evaluated using a multilevel multivariable logistic regression model.
- > Paediatric cases accounted for 1.8% of total infections with.
 - The median age being 11 years.
 - 51.4% were males.
 - 13.3% were hospitalised, and 5.4 had previous underlying medical conditions.
 - The disease was mild in 32.4% of cases and severe in 4.3% especially in children under six.
 - 3.5% of hospitalised cases were admitted to ICU, and there were four deaths.
- > Overall, the data suggests that paediatric cases of COVID-19 are less severe than adults, however, age <1 year and the presence of underlying conditions represent risk factors.

Reviewed by: Associate Professor Margie Danchin

CRITICAL CARE

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

The impact of coronavirus disease 2019 pandemic on the U.S and Canadian PICUs
https://journals.lww.com/pccmjournal/Abstract/9000/The_Impact_of_Corona_virus_Disease_2019_Pandemic_on.97990.aspx

- > This report summarises the national experience of PICUs in the U.S. and Canada, emphasising geographical patterns in PICU admissions and identifying hypotheses for further research. The results draw on a national data collaborative known as Virtual Paediatric Systems, which was expanded to all Canadian and U.S. PICUs for data collection related to COVID-19.
- > In 183 reporting ICUs there were 530 admissions and 30 deaths. Almost one-quarter of admissions were adults (24%), suggesting some PICU beds were being repurposed for where needed. There was a predominance of cases in eastern regions. Admission data suggests that cases plateaued in early May. The form of respiratory support required for 70% of patients' care days requiring advanced support, as well as detailed outcome data is reported.
- > Most of this epidemiology and clinical outcomes are well reported in other countries, and some of the differences are related to practice (such as "high rates of ventilation" may reflect the early intubation practices and recommendations early in the COVID-19 pandemic).
- > The report offers eight suggestions for future research which may help to inform policy on the use of PICUs during current and future pandemics.
- > With several published reports using different databases and surveys in one country or region, there is a risk of double-counting of numbers of children admitted to ICUs.

Reviewed by: Professor Trevor Duke

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

COVID-19 PICU guidelines: for high and limited resource settings
https://www.nature.com/articles/s41390-020-1053-9_reference.pdf

- > This international collaboration details “evidence-based” guidelines, or where there was insufficient evidence, consensus-based guidelines, on the care of critically-ill children with COVID-19. It is an evolving area, and the authors liberally extrapolate from the more common adult evidence and experience, and the general intensive care of critically ill children without COVID-19. There is some undue generalising from case series, rather than a recognition of the heterogeneity of context and the pitfalls of small numbers. There are some instances of implying research has been done on children with COVID-19 (such as with CPAP) when this is just an extrapolation of guidelines for seriously unwell children with other forms of viral or bacterial pneumonia. Given that most of the management of children with COVID-19 is the same as with other respiratory pathogens, one wonders why a guideline covering all aspects of intensive care is needed. Might be best to state that, apart from a few key areas that the management should be the same, and hospitals should do what they do best.
- > Guidelines on respiratory support are given according to disease severity. They emphasise the importance of non-invasive ventilation means such as bubble CPAP where there is a shortage of ventilators. They also reinforce that intubation should be conducted by the most-skilled available provider, as well as other mechanisms to avoid risk for care providers. There is an under-recognition of epidemiology and accumulated clinical experience as it applies to children with COVID-19; that in the vast majority of children with pneumonia, oxygen is all that is needed.
- > Guidelines on hemodynamic support, adjuvant therapy, CPR, ECMO, the recently described Multisystem Inflammatory Syndrome in Children (MIS-C) and pharmacologic treatments are discussed in detail. There is an unusual recommendation against the use of nitric oxide, but no explanation of why it is less likely to work in COVID-19 than in other children with refractory hypoxaemia or pulmonary hypertension from severe pneumonia. The review also recommends “compassionate use” of convalescent plasma treatment (or in research protocol), which is too premature as a global recommendation.
- > The document also discusses the differing regional experiences of PICUs during the COVID-19 pandemic.
- > The guideline is marked “Author Accepted”, so it is not clear that it has gone through a process of peer review.

Reviewed by: Professor Trevor Duke

DIAGNOSTICS & SAMPLING

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

The mathematical strategy that could transform coronavirus testing

https://www.nature.com/articles/d41586-020-02053-6?utm_source=tw_t_nnc&utm_medium=social&utm_campaign=naturenews&utm_medium=social&utm_content=organic&utm_source=twitter&utm_campaign=NatureNews_&sf235848250=1

- > Group testing, testing samples from many people at once, has been suggested as a method to save time, reagents, and money.
- > Method 1: Samples tested in groups, with those testing positive getting retested individually.
 - Was used in Wuhan, China with ≤ 5 samples per group testing ~10 million people in two weeks.
 - More efficient with low levels of infection (~1%).
- > Method 2: Same as Method 1 with an additional interim test group if the original group tests positive.
- > Method 3: Two rounds of testing using different group allocations each round to allow an individual positive sample to be located (e.g., sample present in group A in round 1 and group C in round 2).
- > Method 4: Samples distributed into a matrix of overlapping groups for one round of testing, allowing an individual positive sample to be located.
- > Proposed method one followed by Method 3 for positive groups.
- > Not recommended to have >30 samples per group due to decreased sensitivity with larger groups.
- > Apps and A.I. being developed to support this method.

Reviewed by: Professor Fiona Russell

Jun Hua Bowen Lim - 3rd year Medical student,
Department of Paediatrics, The University of Melbourne

At what times during infection is SARS-CoV-2 detectable and no longer detectable using RT-PCR based tests? A systematic review of individual participant data

<https://doi.org/10.1101/2020.07.13.20152793>

- > The authors performed a systematic review of longitudinal studies of RT-PCR test results in symptomatic SARS-CoV-2 patients, with the aim of finding the percentage of positive test results by time and the duration of the detectable virus by sampling site.
- > 32 studies were included with 1023 SARS-CoV-2 infected participants and 1619 test results.
- > Their analysis shows that positive test results from RT-PCR with nasopharyngeal sampling decline over time.
 - The highest percentage of virus detection was between 0 to 4 days post-symptom onset at 89%.
 - After 10 to 14 day, this drops to 54%.
- > The duration of the detectable virus was longer with lower respiratory tract sampling compared with the upper respiratory tract.
- > The duration of faecal and respiratory tract virus detection varied greatly within individual participants.
- > Overall the results suggest that early RT-PCR sampling minimises false-negative results and after ten days post-symptoms onset lower respiratory tract or faecal testing may be preferred sampling site.
- > The authors note that the included studies are open to a substantial risk of bias, so the positivity rates are probably overestimated.

Reviewed by: Dr Celeste Donato

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

An approach to estimating seroprevalence: an example from British Columbia (not peer-reviewed)

<https://www.medrxiv.org/content/10.1101/2020.07.13.20153148v1.full.pdf>

- > Serial cross-sectional analyses were conducted before (March) and after (May) the first wave of COVID-19 assessing seropositivity in anonymised residual patient sera (children and adults) from multiple outpatient centres in Lower Mainland, British Columbia.
- > Sera were screened with two chemiluminescent immune-assays (CLIA): detection of total antibody (IgM, IgA, IgG) to recombinant spike (S1) protein and detection of IgG antibody to nucleocapsid.
- > Two further assays were conducted on positive samples: CLIA detection of the total (IgG, IgM) to the S1 receptor binding domain, and the gold-standard virus neutralisation assay. A positive result on either secondary assay confirmed seropositivity.

- > Of the suitable samples collected in March.
 - 2/869 showed dual-assay positivity.
 - Age-standardised seroprevalence of 0.28%.
 - Neither specimen had detectable neutralising antibodies.
- > Of the suitable samples collected in May.
 - 4/885 showed dual-assay positivity.
 - Age-standardised seroprevalence of 0.55% (95%CI=0.15-1.37%).
 - All four specimens had detectable neutralising antibodies.
- > Using this surveying technique, the estimated seroprevalence in the population was eightfold higher than actual reported cases.
- > It was estimated that <1% of the population of British Columbia had been infected with SARS-CoV-2 when first-wave mitigation measures were relaxed in May 2020
- > Limitations: Using residual clinical specimens, patients are more likely to have underlying co-morbidities and differ in their exposure risk and immunological status; reported surveillance tallies may over-represent samples that were imported or acquired in care facilities and thus not reflect actual community tallies; only one from 375 collected samples were positive in children limiting the ability to conduct subset comparisons.

Reviewed by: Dr Celeste Donato

EPIDEMIOLOGY & PUBLIC HEALTH

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

Maximising the probability that the 6-week lockdown in Victoria delivers a COVID-19 free Australia

<https://www.mja.com.au/journal/2020/maximizing-probability-6-week-lockdown-victoria-delivers-covid-19-free-australia>

- > Victoria is the unlucky state in an otherwise lucky country - most other states and territories (excluding NSW) have achieved elimination of community transmission of the pandemic SARS-CoV-2 virus. There are three general strategic policy responses to control COVID-19: no response is free of economic, social and health harms – rather, it is about minimising harm.
- > Elimination:
 - Advantages: citizen freedom (despite international border closures and the use of facial masking), more normal function of society and economy.
 - Challenges: required much effort to achieve with no guaranteed success, risk of viral re-entry via quarantine breaches, uncertain about long-term sustainability and impact on the country.
 - Outline four scenarios to determine whether elimination is possible in Victoria during the six-week lockdown.
 - Need at least 85% of people observing physical distancing measures at least 85% of the time, with 93% of people who are asked to isolate for whatever reason actually doing so, 20% uptake of the COVID-Safe App, and the strict and mandatory wearing of masks. Increasing the stringency of mask use and restricting the proportion of essential workers to 20% further improves the chances of eliminating community transmission.
 - Living in a state or country that has achieved elimination is a far better option than suppression in the short- to medium-term, compared to the high likelihood of recurrent outbreaks precipitating recurrent lockdowns with attendant social and economic disruption

- > Suppression:
 - May have to pivot to this strategy if a timely vaccine does not arrive, or if treatment options do not vastly improve.
- > Mitigation (herd immunity): Largely rejected mitigation response given inherent morbidity and mortality, and no immunological basis for this approach.
- > Results suggest that elimination is achievable, and that mandatory wearing of masks can significantly assist its chances.

Reviewed by: Professor Fiona Russell

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

Serology-informed estimates of SARS-CoV-2 infection fatality risk in Geneva, Switzerland

[https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099\(20\)30584-3.pdf](https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(20)30584-3.pdf)

- > The infection fatality risk (IFR) of COVID-19 is the average number of deaths per SARS-CoV-2 infection and is key to characterising the severity of COVID-19 across the population and for specific demographic groups.
- > The study estimated IFR of COVID-19 in Geneva from 24th February to 2nd June 2020. This estimation was based on the population-based seroprevalence data collected each week for five consecutive weeks and inferred from the Bayesian framework.
- > Population-wide IFR was 0.64%.
- > IFRs by age group:
 - 5-9 years old: 0.0016%.
 - 10-19 years old: 0.0032%.
 - 20-49 years old: 0.0092%.
 - 50-64 years old: 0.14%.
 - >65 years old: 5.6%.
- > Limitations of the study: 50% of those >65 years old who died were residents of assisted care facilities (0.8% of Geneva population) and were likely severely under-represented or absent in the serosurvey. This under-representation would lead to an overestimation of the IFR in the 65 years and older age group if seroprevalence in this institutionalised population were higher than in the general population of the same age; the IFR estimation could not taking account the difference of antibody kinetics between mild and severe COVID-19 cases.
- > The IFR is key to characterising the severity of infection across a population and for specific demographic groups; and a key parameter in mathematical models. However, the IFR is highly likely to be context-specific as access to care and quality of care (key determinants of outcome) is highly variable between settings.

Reviewed by: Dr Lien Anh Ha Do and Professor Fiona Russell

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

How much may COVID-19 school closures increase childhood obesity?

<https://onlinelibrary.wiley.com/doi/abs/10.1002/oby.22960>

- > Letter to the editor in response to the recent article “COVID-19 related school closings and risk of weight gain among children” Rundle et al (2020) which discussed the effects the pandemic may have on childhood obesity rates, as a possible consequence of:
 - Increased food insecurity.
 - Increased reliance on processed food.
 - Reduced opportunities to be outside and exercise.
- > The disruption to school time due to the pandemic and the increased time at home could increase childhood obesity rates.
- > A 2016 study demonstrated that obesity rates increased from 8.9% to 11.5% in a group of kindergarten students over the summer break, related to out of school time.
- > On the other hand, the author considered that the pandemic could have effects that reduce the risk of developing obesity, such as a decrease in families dining out at restaurants.
- > More research into the effects of the pandemic on childhood obesity would be useful in determining if the risk is increased and by what magnitude.

Reviewed by: Associate Professor Margie Danchin

Grace Newman – 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Direct observation of repeated infections with endemic Coronavirus

<https://academic.oup.com/jid/article/doi/10.1093/infdis/jiaa392/5868459>

- > Mechanisms for adaptive immunity to SARS-CoV-2 still unknown but the immune response to endemic coronaviruses HKU1, 229E, NL63, OC43 able to provide a reference for understanding repeat infection risk.
- > Method:
 - Proactive sampling performed between October 2016 and April 2018 of 214 healthy individuals in Manhattan, NY – all participants younger than 65 years.
 - Only 191 included in analysis.
 - Weekly nasopharyngeal samples and screened for 18 respiratory viruses using PCR (including coronavirus 229E, NL63, OC43, HKU1) and daily self-reports of symptoms.
- > Results:
 - 86 individuals tested positive at least once for any coronavirus.
 - 12 individuals tested positive multiple times during the study for the same coronavirus.

- Nine children aged 1-9 at enrolment, three adults aged 25-34.
 - The median time between reinfection events was 37 weeks (shortest = 4 weeks and longest = 48 weeks).
 - The significant association between severity of symptoms and belonging to the same family cluster.
- > Discussion:
- Reinfection with same coronavirus type occurs in time window shorter than one year.
 - No significant association between repeat infections and symptom severity.
 - Possible genetic determinants of innate immune response and symptom severity.
- > Limitations:
- Seasonality of endemic coronaviruses and relative magnitude across years of seasonal coronavirus epidemics.
 - The occurrence of weekly swabs missed by participants.
 - Possible missed infections of short duration between consecutive weekly tests.
 - Self-reporting of symptoms and parents reporting symptoms for their dependents.
 - The high sensitivity of PCR may detect virus not causing an active infection.
 - Without virus sequencing cannot exclude possibility that subsequent positives are resurgence of same infection.

Reviewed by: Dr Wonie Uahwatanasakul

GLOBAL HEALTH

WHO Coronavirus disease (COVID-2019) situation report 182, 20th July 2020
https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200720-covid-19-sitrep-182.pdf?sfvrsn=60aabc5c_2

Dahlia Hawari – 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Addressing challenges for clinical research responses to emerging epidemics and pandemics: a scoping review
<https://bmcmecine.biomedcentral.com/articles/10.1186/s12916-020-01624-8>

- > This is a scoping review aimed at identifying the challenges involved in delivering essential clinical research during an acute epidemic or pandemic. Inclusion criteria included published, peer-reviewed quantitative and qualitative studies describing the political, economic, administrative, regulatory, logistic, ethical and social (PEARLES) challenges in designing and implementing clinical research during a pandemic. Opinion articles based on clinical research responses were also included, as were conference abstracts. Studies related solely to public health responses were excluded, as studied presenting study outcomes without reflection on challenges/solutions.
- > 76 articles were included in the final review - most from Africa (n=37), “global” (n=22), only one from Asia. Most articles related to Ebola or H1N1 outbreaks.
- > Key political and economic actions identified in the review include the coordinated collaboration between public health emergencies at the national and international level, dedicated funding, investment in health systems, infrastructure and sustainable clinical research centres as well as incentivising clinical research response networks and engaging stakeholders in affected countries early.
- > Key administrative and logistical actions identified include the training of researchers, clinicians and other stakeholders for rapid deployment, the establishment of accelerated pathways for regulatory and ethical joint approvals as well as means of allowing open data sharing.
- > Ethical actions include the development of frameworks for ethical and scientifically robust study designs for various epidemic/pandemic scenarios as well as the development of international guidelines on ethical standards and conduct for emergencies.
- > Highlighted the need to strengthen global collaborations and coordination at all levels and develop pre-approved protocols and equitable frameworks, protocols and standards for emergencies - such as through clinical trial networks, expedited funding and approvals, with key elements being national ownership and community engagement from the outset.

- > The article identified a long list of challenges, but none of the wide range of recommended solutions had been formally evaluated. It is essentially a “call to action” for an internationally coordinated effort in optimising the global response to pandemics.

Reviewed by: Professor Steve Graham

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

The tragedy of COVID-19 in Brazil: 124 maternal deaths and counting
<https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/ijgo.13300>

- > Brazil has a leading number of COVID-19-related maternal deaths in the world, with 124 pregnant or postpartum women having died at the time of writing this brief communication.
- > In the Brazilian obstetric population, the mortality rate is high (12.7%) in women infected with COVID-19, BUT only women with severe symptoms usually get tested.
- > 978 pregnant and postpartum women had diagnosed ARDS caused by COVID-19 between 26th February 2020 and 18th June 2020.
- > 207 (21.2%) of these women were admitted to ICU (134 recovered, 73 died).
- > Of the fatal cases, 22.6% were not admitted to ICU - only 64% had invasive ventilation, 21.4% received non-invasive ventilation only, and 14.6% had no ventilatory support.
- > Cases identified during the postpartum period had a higher mortality rate (22.3%) compared with those identified during pregnancy (9.8%.)
- > It was observed that co-morbidities such as diabetes, cardiovascular disease, and obesity were associated with mortality.
- > The high maternal mortality rate associated with COVID-19 may be due to direct or more indirect, care-related factors - long-standing problems including poor quality antenatal care, insufficient resources to manage emergency and critical care, high rates of caesarean sections, barriers to accessing appropriate intensive care in the COVID-19 positive obstetric population.

Reviewed by: Professor Steve Graham

IMMUNOLOGY

Dr Ryan Toh – Post-doctoral researcher, New Vaccines, Infection & Immunity Theme, MCRI and Honorary Fellow, Department of Paediatrics, The University of Melbourne

SARS-CoV-2 infection induces robust, neutralising antibody responses that are stable for at least three months (not peer-reviewed)

<https://www.medrxiv.org/content/10.1101/2020.07.14.20151126v1.full.pdf>

- > The functionality and longevity of the antibody response generated following SARS-CoV-2 infection remains unknown.
- > This observational study of 19,763 examined the antibody response in infected individuals with mild-to-moderate symptoms.
- > The vast majority (97%) have moderate to high IgG antibody level to the SARS-CoV-2 spike protein using ELISA.
 - Neutralising antibody titres significantly correlated with spike-ELISA titres; 50% of the sera in the lower ELISA range have neutralising activity.
 - At approximate three months post symptom onset (82 days), those with moderate-high antibody levels had a slight drop in antibody levels; there was a slight increase for those with low antibody levels, which may be due to mild COVID-19 cases, taking a long time to mount an antibody response.
- > Significance: Important implications when considering protection against reinfection with SARS-CoV-2; informs correlate of protection and vaccine development.
- > Limitations: Individuals that had been infected with SARS-CoV-2 and did not seroconvert may have been missed as they were not PCR-confirmed positive; neutralising antibodies were not examined on samples at three months post symptom onset.

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

COVID-19 and Treg/Th17 imbalance: potential relationship to pregnancy outcomes

<https://onlinelibrary.wiley.com/doi/abs/10.1111/aji.13304>

- > This mini-review article provides an overview of the cellular immune response to COVID-19, with a focus on the Th17 and Treg immune responses and the potential implications in adverse pregnancy outcomes.
- > In severe COVID-19 disease, the increased number of Th17 cells (pro-inflammatory) and reduced numbers of Treg cells (anti-inflammatory, maintenance of self-tolerance) may contribute to the uncontrolled systemic inflammatory response, leading to tissue damage, multiorgan failure and death.

- > The role of Treg and Th17 cells are important in pregnancy for immune tolerance and defence, respectively.
- > Dysregulation of Treg/Th17 balance can lead to foetal allograft rejection and/or increase inflammation, which may result in adverse outcomes of pregnancy, including premature labour, foetal distress and spontaneous abortion.
- > Although studies have reported adverse pregnancy outcomes in women infected with SARS-CoV-2, there is no evidence demonstrating the direct effects of the virus on pregnancy outcomes.
- > The authors underline the importance of monitoring and early intervention to prevent maternal and perinatal complications.
- > There are minimal data regarding the relationship between Treg/Th17 cell imbalance and pregnancy outcomes as a result of COVID-19.

Reviewed by: Dr Ryan Toh

INFECTION CONTROL

Grace Newman – 3rd Year Medical Student,
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Increasing handwashing in young children: a brief review

<https://onlinelibrary.wiley.com/doi/full/10.1002/jaba.732>

- > Hands are the most common mode of transmission of pathogens, and handwashing with soap and water for at least 20 seconds the most effective method for decreasing transmission.
- > Antecedent strategies for teaching handwashing in young children.
 - Provide rationale and instructions – should be used in conjunction with other strategies.
 - Model proper handwashing behaviour.
 - Provide vocal and visual prompts.
- > Consequence strategies for teaching handwashing in young children.
 - Providing visual feedback – for example, using U.V. sensitive lotions to demonstrate the efficacy of handwashing technique.
 - Implementing error correction – for example allowing an opportunity to rewash hands.
 - Providing rewards – provided intermittently during follow up observations.
- > Combination of both antecedent and consequence strategies should be used.
- > Suggested treatment package: demonstrating handwashing effectiveness, ongoing performance feedback, handwashing song, frequent and immediate consequences such as feedback or rewards after handwashing, products such as U.V. sensitive lotions or nutmeg and lotion to provide visual feedback.
- > Further research is required to determine which elements are essential to teaching handwashing in young children.

Reviewed by: Dr Celeste Donato

PERINATAL HEALTH

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

Pregnancy and postpartum outcomes in a universally tested population for SARS-CoV-2 in New York City: A prospective cohort study

<https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/1471-0528.16403>

- > A prospective cohort study of all pregnant women admitted for delivery to three facilities in New York City with universal testing for SARS-CoV-2 by RT-PCR. Infants of mothers with positive RT-PCR results also had a nasopharyngeal swab taken after birth for SARS-CoV-2.
- > A total of 675 women were admitted for delivery at >20 weeks gestation within the first 28 days of universal testing; 70 (10.4%) tested positive, of which 55 (78.6%) were asymptomatic. The median gestational age of all patients on admission was 39 weeks.
- > Only three COVID-19 positive women developed hypoxia during their admission.
- > The authors compared symptomatic SARS-CoV-2 RT-PCR positive patients, asymptomatic SARS-CoV-2 RT-PCR positive patients and those that tested SARS-CoV-2 RT-PCR negative with regards to obstetric and neonatal outcomes:
 - No difference was seen in live births and preterm births.
 - Among symptomatic positive patients, 7 (46.7%) had a caesarean section, compared with 25 (45.5%) asymptomatic positive patients and 30.9% (n=187) of negative patients. Most caesarean sections were scheduled repeats.
 - Postpartum complications (fever, hypoxia, and readmission) occurred more frequently in women with vs. without COVID-19 (12.9% vs. 4.5%). No woman required mechanical ventilation, and no maternal deaths occurred.
 - The median length of stay was slightly longer in symptomatic positive patients.
- > Placental pathology findings were compared between a sample of SARS-CoV-2 RT-PCR positive (n=29) and negative (n=106) patients:
 - Increased frequency of fetal vascular malperfusion, indicative of thrombi in fetal vessels, was observed in women with vs. without COVID-19 (48.3% vs 11.3%, p<0.001).
- > Neonatal outcomes:
 - Among 71 infants tested, none were positive for SARS-CoV-2.

Reviewed by: Dr Claire von Mollendorf

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

Characteristics of women of reproductive age with laboratory-confirmed SARS-CoV-2 infection by pregnancy status – United States, 22nd January-7th June, 2020

<https://www.cdc.gov/mmwr/volumes/69/wr/mm6925a1.htm>

- > This retrospective observational study in the U.S. aims to further understand the prevalence and severity of COVID-19 among pregnant women compared with non-pregnant women.
- > Data was collected between 22nd January - 7th June through electronic reports to the CDC or the National Notifiable Diseases Surveillance System.
- > Data on pregnancy status for women between 15-44 y with laboratory-confirmed SARS-CoV-2 infection was available for 91,412 women, of which 8,207 (9%) were pregnant. This is higher than the percentage of reproductive women who are pregnant at any one time, which is 5%.
- > Among women with known symptom status, similar percentages of pregnant and non-pregnant women were symptomatic (97.1% pregnant women and 96.9% non-pregnant women).
- > A similar frequency was reported between pregnant and non-pregnant women for the symptoms cough (51.8% vs 53.7%) and shortness of breath (30.1% vs 30.3%).
- > Symptoms of fever, muscle aches, chills, headache and diarrhoea were reported less frequently in pregnant women than non-pregnant women.
- > Hospital admissions: more frequent for pregnant women than non-pregnant women (31.5% vs 5.8%).
 - After adjusting for age, underlying conditions and ethnicity pregnant women were 5.4 times more likely to be hospitalised than non-pregnant women.
- > ICU admissions: more frequent in pregnant women than non-pregnant women (1.5% vs 0.9%) and mechanical ventilation more common (0.5% vs 0.3%).
 - After adjusting for age, underlying conditions and ethnicity ICU admission was 1.5 times more likely in pregnant women, and mechanical ventilation 1.7 times more likely.
- > Mortality risk was the same for pregnant and non-pregnant women (0.2% both groups).
- > Of those with SARS-CoV-2 infection 46% were Hispanic, 22% were black, and 23% were white, which differs from the demographics of women who gave birth in 2019 in the U.S. (24% Hispanic, 15% black and 51% white).

- > Limitations: Pregnancy status was unknown for 72% of SARS-CoV-2 infected women of reproductive age; other missing information included ethnicity, symptom status (1/3 pregnant women) and underlying conditions; pregnancy trimester and birth outcomes were unavailable; data was unable to distinguish if the chronic disease was present before pregnancy or if it was new during pregnancy (gestational diabetes and pregnancy-induced hypertension); data was unable to distinguish the reason for hospitalisation so that hospitalisation may be COVID-19 related or pregnancy-related (including delivery); pregnant women may be tested more frequently than non-pregnant women due to a lower threshold for testing or more frequent health encounters- increasing the detection of SARS-CoV-2.
- > Conclusions: Hispanic and non-Hispanic black pregnant women appear to be disproportionately affected by SARS-CoV-2; among women aged 15-44y with COVID-19, pregnancy is associated with an increased risk of ICU admission and mechanical ventilation, but not an increased risk of mortality.
- > There is a need for complete data collection and longitudinal data collection from pregnant women.

Reviewed by: Professor Fiona Russell

Evelyn Andrews - 4th year Medical Student,
Department of Paediatrics, The University of Melbourne

In-utero mother-to-child SARS-CoV-2 transmission: viral detection and fetal immune response

<https://www.medrxiv.org/content/10.1101/2020.07.09.20149591v1.article-info>

- > This study aimed to investigate the possible mechanisms of vertical transmission in SARS-CoV-2 affected pregnancies.
- > 31 COVID-19 positive pregnant women were enrolled across three maternity centres in Lombardy, Italy. Real-time PCR was performed on maternal and newborn nasopharyngeal swabs, vaginal swabs, maternal and umbilical cord plasma, placental and umbilical cord biopsies, amniotic fluid and breast milk. Plasma and milk samples were tested for anti-SARS-CoV-2 antibodies. Gene expression was analysed in select placental biopsies.
- > Results were strongly suggestive of in-utero vertical transmission in 2 out of 31 enrolled women (6% and both had severe clinical disease). One of these subjects demonstrated SARS-CoV-2 in the vagina, umbilical cord plasma, and placenta. The presence of the virus in the umbilical cord plasma strongly suggests in-utero transmission. The other subject was SARS-CoV-2 positive on placental biopsy and had SARS-CoV-2 specific IgM and IgG in umbilical cord plasma. The presence of anti-SARS-CoV-2 IgM in cord plasma strongly suggests in-utero infection, as IgM is not usually transferred across the placenta.
- > SARS-CoV-2 RNA was detected in the breast milk of one subject.
- > The placentae of infected patients displayed a generalised immune activation profile, compared with a control. The placenta of a patient who had fully recovered from the disease four weeks before delivery still showed an increased inflammatory profile compared with the control. This is suggestive of a persistent inflammatory state in the placenta, even after clinical resolution.

- > This study is the first to find SARS-CoV-2 in the vagina of a pregnant woman, in at-term placentae and the umbilical cord blood. This provides strong evidence for in-utero transmission of SARS-CoV-2. That the virus was discovered in the vagina and breast milk of infected women also suggests the possibility of intrapartum transmission during vaginal delivery, and transmission via breastfeeding.

Reviewed by: Professor Suzanne Garland

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

Transplacental transmission of SARS-CoV-2 infection
<https://www.nature.com/articles/s41467-020-17436-6.pdf>

- > The article presents a case study demonstrating vertical transmission of SARS-CoV-2 from a pregnant woman (affected by COVID-19 in the last trimester) to her offspring.
 - The mother presented with fever and severe productive cough. Due to evidence of fetal distress on cardiotocography, a caesarean section was performed to deliver the baby at 35+5 weeks. Neonatal resuscitation was required due to low Apgar scores.
 - According to a recent article by Prakesh et al, a neonatal congenital infection with SARS-CoV-2 is considered proven if the virus is detected in the amniotic fluid collected prior to the rupture of membranes and/or in blood drawn early in life. This case met both of these criteria. Amniotic fluid collected prior to rupture of the membranes at C-section was positive on PCR for SARS-CoV-2, as were neonatal nasopharyngeal and rectal swabs at one hour of life, day 3 and 18 of life.
 - In the first two days of life, the neonate was asymptomatic, and all laboratory tests were unremarkable. However, on day 3 of life, the neonate suddenly presented with irritability, poor feeding, neurological symptoms (axial hypertonia and opisthotonos), and inflammatory findings in the CSF. All other viral/bacterial infections and neonatal disorders potentially causing these clinical manifestations were excluded.
 - MRI at 11 days of life showed bilateral gliosis of the deep white periventricular and subcortical matter which can be caused by vascular inflammation induced by SARS-CoV-2 (similar findings were reported in adult patients infected with SARS-CoV-2)
 - The neonate recovered gradually, requiring no specific treatment and was discharged after 18 days.
- > Transplacental transmission of SARS-CoV-2 occurs via the following steps: (1) Maternal viraemia; (2) Placental infection and inflammation (demonstrated by histological examination, immunohistochemistry and high viral load); (3) Neonatal viraemia. Amniotic fluid collected prior to rupture of the membranes at C-section was also positive on PCR for SARS-CoV-2.
- > In this case, transmission most likely occurred as vertical transmission through the placenta because the placental tissue, maternal and fetal blood samples were all positive for SARS-CoV-2 using RT-PCR. In fact, Angiotensin-converting enzyme 2 (ACE2); known to be a receptor of SARS-CoV-2, is highly expressed in placental tissue.

Reviewed by: Professor Suzanne Garland

Natalie Commins - 3rd Year Medical Student,
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Probable vertical transmission of SARS-CoV-2 infection

https://journals.lww.com/pidj/Abstract/9000/Probable_Vertical_Transmission_of_SARS_CoV_2.96098.aspx

- > Case report detailing likely vertical transmission of SARS-CoV-2 to a neonate.
- > The pregnant mother (38 weeks + 5) tested positive to SARS-CoV-2 several days after admission to hospital for fever and respiratory symptoms, eventually requiring intubation and an emergency caesarean.
- > The caesarean was performed eight days after the mother's admission to hospital and was performed under COVID-19 precautions: in a large operating room, with all staff in PPE (airborne precautions).
- > The neonate initially had some irregular respiratory efforts and spent ten minutes in an incubator, but then was transferred into an isolation room. There was no contact with family members, and the neonate was exclusively formula-fed.
- > The mother remained intubated for 17 days and required ECMO. A retrospective review of the mother's blood taken at LUSC and a couple of days post-delivery (she was not screened on admission for SARS-CoV-2) was low positive on PCR.
- > The neonates PCR for SARS-CoV-2 was negative on the first day of life, and CXR was clear on the first day of life.
- > On day 3 of life, PCR on NPA was positive for SARS-CoV-2, while testing at the same time on faecal and blood samples were negative.
- > On Day 5, the neonate developed a fever, and mild respiratory symptoms which abated and a full recovery was made.
- > The genetic sequences from the mother and child were identical across the entire genome apart from a single nucleotide difference.
- > Therefore, this case describes good evidence for vertical transmission of SARS-CoV-2.
- > Route of transmission either transplacentally or intrapartum via contact with maternal blood (mother had viraemia).
- > Most other reports of neonatal COVID-19 infection most likely occurred postnatally, and only one other probable case of vertical transmission has been published.

Reviewed by: Professor Suzanne Garland

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

SARS-CoV-2 maternal-child transmission: can it occur before delivery, and how do we prove it?

https://journals.lww.com/pidj/Citation/9000/SARS_COV_2_Maternal_Child_Transmission_Can_It.96096.aspx

- > As the pandemic of COVID-19 has expanded globally, concerns regarding the potential for mother-to-child transmission has been expressed by clinicians and patients – and proving this has been a challenge.
- > There have been no confirmed cases of maternal-fetal transmission, although there have been a small number of suspected vertical SARS-CoV-2 infections reported – this paper analyses 3.
- > Case 1: The infant nasopharyngeal SARS-CoV-2 RT-PCR test at age 12 hours was indeterminate, earliest documented SARS-CoV-2 RNA detection at 36 hours of life. Given the vaginal route of delivery, this case was more likely intrapartum or early horizontal infection than intrauterine transmission. Moreover, in this case, there was no PCR performed on placenta, amniotic fluid to refine the assessment.
- > Case 2: SARS-CoV-2 RT-PCR results were negative from nasopharyngeal, stool, urine, and blood specimens obtained from the infant on the day of birth, essentially excluding intrauterine infection. NPA tested positive on day 3 of life, and no amniotic fluid or placental tissue studies were available. Because the infant was delivered by caesarean section, the intrapartum transmission is unlikely.
- > Case 3: the first specimen was obtained by 24 hours of life, and that nasopharyngeal specimen was SARS-CoV-2 RT-PCR positive. The evidence for intrauterine infection was strengthened by the histologic, immunohistochemical, and electron microscope findings of the fetal side of the placenta; however, direct SARS-CoV-2 RNA detection was not attempted on the placenta, amniotic fluid, or infant blood. Furthermore, rupture of membranes 8 hours prior to birth increases the potential intrapartum exposure risk. Thus, while this case could represent intrauterine or intrapartum infection, the early and persistent SARS-CoV-2 RNA detection in this infant placental tissue findings and careful infection prevention measures suggest the intrauterine infection is more likely.
- > The inconsistency in these cases supports the need for defining case criteria and systematic methodology of evaluation of potential intrauterine cases.

Reviewed by: Professor Suzanne Garland

VACCINES

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

Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31604-4/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31604-4/fulltext)

- > Safety, reactogenicity, and immunogenicity of a viral vectored coronavirus vaccine was assessed in a single, blind phase 1/2 clinical trial in healthy adults in the U.K.
- > The chimpanzee adenovirus-vectored vaccine (ChAdOx1 nCoV-19) expressing the SARS-CoV-2 spike protein was used and compared with Meningococcal ACWY vaccine as a control.
- > Ten participants assigned to a non-randomised, unblinded ChAdOx1 nCoV-19 prime-boost group received a two-dose schedule, with the booster vaccine administered 28 days after the first dose.
- > 1077 participants were enrolled.
- > Local and systemic reactions were more common in the ChAdOx1 nCoV-19 group, and many were reduced by the use of prophylactic paracetamol, including pain, feeling feverish, chills, muscle ache, headache, and malaise.
- > There were no serious adverse events related to ChAdOx1 nCoV-19.
- > In the ChAdOx1 nCoV-19 group, spike-specific T-cell responses peaked on day 14
- > Anti-spike IgG responses rose by day 28 and were boosted following a second dose.
- > Neutralising antibody responses against SARS-CoV-2 were detected in 32/35 participants after a single dose when measured in MNA80 and all 35 participants when measured in PRNT50.
- > After a booster dose, all participants had neutralising activity. It was neutralising antibody responses correlated strongly with antibody levels measured by ELISA.
- > Conclusion: ChAdOx1 nCoV-19 showed an acceptable safety profile, and homologous boosting increased antibody responses. These results, together with the induction of both humoral and cellular immune responses, support a large-scale evaluation in an ongoing phase 3 trial.

Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31605-6/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31605-6/fulltext).

- > A randomised, double-blind, placebo-controlled, phase 2 trial of the Ad5-vectored COVID-19 vaccine was done in China.
- > Healthy adults were randomly assigned to receive the vaccine at a dose of 1×10^{11} viral particles per mL or 5×10^{10} viral particles per mL, or placebo.
- > 508 eligible participants (50% male; mean age 39.7 years, S.D. 12.5) were assigned to receive the vaccine (1×10^{11} viral particles n=253; 5×10^{10} viral particles n=129) or placebo (n=126).
- > In the 1×10^{11} and 5×10^{10} viral particles dose groups, the RBD-specific ELISA antibodies peaked at 656.5 and 571.0, with seroconversion rates at 96% and 97%, respectively, at day 28.
- > Both doses of the vaccine induced significant neutralising antibody responses to live SARS-CoV-2, with GMTs of 19.5 and 18.3 in participants receiving 1×10^{11} and 5×10^{10} viral particles, respectively.
- > Specific interferon γ enzyme-linked immunospot assay responses post vaccination were observed in 227 (90%) and 113 (88%) of 129 participants (subgroup) in the 1×10^{11} and 5×10^{10} viral particles dose groups, respectively.
- > Solicited adverse reactions were reported by 183 (72%) of 253 and 96 (74%) of 129 participants in the 1×10^{11} and 5×10^{10} viral particles dose groups, respectively. Severe adverse reactions were reported by 24 (9%) participants in the 1×10^{11} viral particles dose group and one (1%) participant in the 5×10^{10} viral particles dose group. No serious adverse reactions were documented.
- > The Ad5-vectored COVID-19 vaccine at 5×10^{10} viral particles is safe and induced significant immune responses in the majority of recipients after a dose.

VIROLOGY

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

No evidence of viral polymorphisms associated with Paediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS) (not peer reviewed)

<https://www.medrxiv.org/content/10.1101/2020.07.07.20148213v1.full.pdf>

- > Severe illness and death due to SARS-CoV-2 infection in children is rare. However, a small number of cases of shock and multisystem inflammation have been reported in children who have either been tested positive for SARS-CoV-2 (by PCR or serology) or had epidemiological links to it.
- > This new syndrome is called the paediatric inflammatory, multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS).
- > It has been suggested that part of the SARS-CoV-2 viral spike (S) protein may resemble a superantigen which could drive the development of PIMS-TS and triggers a cytokine storm in adults.
- > Polymorphisms in S including A831V and D839Y/N/E have been predicted to enhance binding affinity to T cell receptors have been observed in lineages circulating in Europe and North America, where the majority of PIMS-TS cases have been described. The 614G Spike protein polymorphism may be associated with increased transmission.
- > Full-length SARS-CoV-2 genome sequences were generated from 5 PIMS-TS children and eight non-PIMS-TS children using Illumina sequencing and were compared with local community cases.
- > Using the reference genome, there were no observed single nucleotide polymorphisms (SNPs) unique to the PIMS-TS or the other childhood cases and no difference in the distribution of SNPs between PIMS-TS, non PIMS-TS and community cases.
- > All childhood and local cases exhibited A831 and D839 in the S protein. The majority of PIMS-TS (3/5), non PIMS-TS (6/8) and community cases (118/130) had the 614G polymorphism.
- > Overall, the data suggested that the viruses causing PIMS-TS in these patients were representative of locally circulating SARS-CoV-2. There was no evidence for an association of PIMS-TS with the presence of new or unusual sequence polymorphisms.

Reviewed by: Dr Celeste Donato

OTHER RESOURCES

Burnet Institute research findings, policy and technical reports

https://www.burnet.edu.au/covid-19//36_know_c19_hub

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_z2uWV7r3FaPzAO86q9ZXBcTZ1OcCE_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 U.S. 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 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/>

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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