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. 20
4th September 2020
GUEST EDITORIAL

Professor Julie Bines - Paediatric Gastroenterologist, RCH; Lead Enteric Disease Group MCRI; Victor and Loti Smorgon Professor of Paediatrics, The University of Melbourne and Dr Celeste Donato-Virologist, Enteric Diseases Group, MCRI; Lecturer, Department of Paediatrics, The University of Melbourne

It has been with a huge collective sigh of relief that in Melbourne this week we have seen the daily case numbers fall below 100 in response to lockdowns, masks, physical distancing, and lots of hand sanitising. From a global perspective, this week marked a grim milestone with over 25 million people known to be infected with the SARS-CoV-2 virus - an increase of 1.7 million cases over the preceding week, and 844,000 deaths (http://who.int; August 28 2020). The rate of new cases diagnosed in the Americas have decreased this week, a trend welcome in this region that has contributed 50% of total global cases, and 62% of deaths since the beginning of this pandemic. But we don't need to look far to see upswings in transmission, or stubborn persistence, of this wily virus. Some European countries are reporting a resurgence in community cases with easing of restrictions. In India, there has been a significant increase in new cases, with >70,000 new cases a day reported over the past week – a new record. Despite initial dire predictions, the African region, apart from South Africa, has been relatively spared. However there has been a disturbing increase in cases has been reported this week in Uganda, Ethiopia, Namibia and Nigeria - a sign that this may not yet be all over on the African continent. This pandemic has brought into stark focus the nature of interdependence of our world, and the pivotal role of global agencies and global cooperation to tackle this shared, major global problem. There is much work yet to be done to limit the direct and indirect impact of this global pandemic.

In this issue, the first reported cases of Multi-system Inflammatory syndrome in South Africa have been highlighted https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30272-8/fulltext. Most of the cases had no confirmatory test (serology unavailable) or had experienced suspected COVID-19 infection, but fulfilled diagnostic criteria. Twelve of 23 patients required ICU admission due to myocardial dysfunction, although all have survived to date. The importance of a high level of clinical suspicion was considered critical to avoid the delayed diagnosis, particularly in settings where resources for timely COVID testing may be limited.

The impact of COVID-19 on the provision of routine healthcare, routine immunisation, malnutrition and obstetric services has emerged as a major concern in low resource settings. In Africa, using modelling it has been estimated that for every one death attributable to SARS-CoV-2 infection acquired during a routine immunisation clinic visit, 84 deaths (95% UI 14-267) in children could be prevented by routine immunisation programs (www.thelancet.com/lancetgh Published online 17th July 2020 https://doi.org/10.1016/S2214-109X(20)30308-9). In this issue, the impact of stay-at-home orders to control COVID-19 on families in rural Bangladesh makes disturbing reading https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30366-1/fulltext.
Family income reduced and the proportion of families earning less than $1.90 per day increased from 0.2% to 47.3%, associated with an increase in food insecurity by 51.7%. Anxiety and depression were reported by mothers, as was an increase in intimate partner violence. COVID-19 related anxiety and concerns were frequently reported by mothers attending Obstetric Clinics in Southern India in a survey of 118 Obstetricians included in this week's update. Although placental transmission of SARS-CoV-2 has been postulated there has been limited data to confirm this suspicion. Described in this issue, is a report of the immunohistochemical, electron microscopy and molecular analyses of placenta from 101 mothers who had tested positive, negative, or were not evaluated for COVID-19 infection. One placenta tested positive with strong expression of S and N proteins of SARS-CoV-2 in the syncytiotrophoblast associated with other key features consistent with infection. The mother tested PCR positive. Although born healthy, the infant developed respiratory symptoms on day 1 requiring ICU admission. The infant developed a positive SARS-CoV-2 nasopharyngeal swab 36 hours after birth. Using comprehensive approach to the analysis of the placenta, this study confirms that SARS-CoV-2 can result in placental infection that may be transmitted to the infant at birth (https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30327-3/fulltext). Transmission of infection to the infant via breast milk of an infected mother seems unlikely based on the small study reported in the update this week, although more robust studies are needed to confirm this observation (https://jamanetwork.com/journals/jama/fullarticle/2769825).
HIGHLIGHTS

> Ocular manifestations including conjunctival discharge, eye rubbing or conjunctival injection may occur in children, more commonly when they have systemic disease or cough.

> A high level of suspicion is needed for MIS-C because of non-specific presenting features such as persistent fever, rash, and abdominal pain.

> Out of 33,041 asymptomatic children tested for SARS-CoV-2 in the U.S., there was a pooled prevalence of 0.65%.

> COVID-19 presents an opportunity to invest in telerehabilitation solutions, allowing for continuity of care and support for families and children with neurodevelopmental conditions.

> A meta-analysis calculated an infection fatality rate (IFR) point estimate of 0.68% for COVID-19, with variability in different countries.

> A study from rural Bangladesh highlights the significant impact on families through lockdown with loss of income, food security and increases in maternal depression and anxiety.

> Current guidelines for the use of medical or surgical masks while caring for COVID-19 patients on closed suction system mechanical ventilation if no aerosol-generating procedures (AGPs) are performed is supported by a small study.

> Concerns about hospital visits for antenatal visits and scans, methods for protection from COVID-19, social media messages and safety of the infant from infection after delivery were commonly reported by obstetricians in southern India, about patients, early in the pandemic.

> Survey of adolescents and young adults in India demonstrates variable impacts of lockdown on areas such as screen time, food intake, exercise but a majority trying something new.

> Breast milk may not be a source of infection for infants (small study numbers).

> Although schools reopening is beneficial for children, it can put vulnerable adults at risk for severe COVID-19 illness if adequate protective measures are not considered.

> ‘Healthy Buildings’ explains key strategies that should be implemented by schools to keep buildings clean and thus, reduce the risk of spreading COVID-19.

> Use of ACEi and ARBs not found to be associated with an increased risk of COVID-19 disease requiring ICU care.

> Recommendations for social distancing are suggested to be based on circumstances and the risks of the environment, ventilation, occupancy, use of face coverings etc.

> Report of a newborn that developed infection shortly after birth, indicating a source of infection was almost certainly placental transmission.
Prevalence of SARS-CoV-2 infection in children without symptoms of coronavirus disease 2019 (Research Letter)
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2769878

Asymptomatic children (0-18 years) presenting for ENT (operative or outpatient) care at 28 hospitals across the U.S. were routinely tested for SARS-CoV-2 infection using RT-PCR during an unspecified time-frame leading up until 29th May.

Results:
- Out of 33,041 asymptomatic children tested, 250 were positive for SARS-CoV-2. Prevalence varied from 0% - 2.2% across hospitals with a pooled prevalence of 0.65% (95% CI, 0.47%-0.83%).
- Prevalence of SARS-CoV-2 in asymptomatic children presenting to a hospital was significantly associated with the weekly incidence of COVID-19 in the general population around that hospital.

Limitations:
- Results may not be generalisable for the general paediatric population as they only include children presenting for medical/surgical care who may differ by demographics, health and immunological status.
- Children presenting with symptoms that overlapped with SARS-CoV-2 disease were sometimes considered symptomatic and thus not included in this study; even though their symptoms may have been the result of another primary condition.
- Variations in symptom screening and testing protocols between hospitals.

Ocular manifestations and clinical characteristics of children with laboratory-confirmed COVID-19 in Wuhan, China
https://jamanetwork.com/journals/jamaophthalmology/fullarticle/2769877

Cross-sectional study of 216 children infected with SARS-CoV-2 (confirmed with RT-PCR) and hospitalised at Wuhan, China between 26th January and 18th March 2020.

Most common symptoms were fever (37.5%) and cough (36.6%). 43.1% had no systemic or respiratory symptoms.
Ocular manifestations were seen in 22.7% of children and were uncommonly seen as the initial complaint (9 children). Ocular symptoms were mild and included conjunctival discharge, eye rubbing and conjunctival congestion. Children’s ocular symptoms improved or recovered without treatment.

Children with systemic disease or cough were more likely to develop ocular symptoms.


Limitations: the study did not determine the cause of conjunctivitis, description of ocular symptoms are subjective and may be difficult to elicit from children, ophthalmological examinations were limited to COVID-19 isolation units, which did not contain eye examination instruments.

Reviewed by: Dr Wonie Uahwatanasakul

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

**Multisystem inflammatory syndrome in children in South Africa**

https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30272-8/fulltext

- The authors summarise the first 23 cases of multisystem inflammatory syndrome in children (MIC-S) treated in a Cape Town children’s hospital from 4th June to 24th July 2020.

- There was over-representation of black children in the cohort (unable to determine if statistically significant).

- A high level of suspicion is needed for MIS-C because of non-specific presenting features such as persistent fever, rash, and abdominal pain.

- 12 out of the 23 children (52%) required ICU admission, mostly due to myocardial dysfunction.

- There was often a delayed diagnosis due to the degree of cardiac dysfunction being underappreciated (anecdotal). This warrants closer attention to age-appropriate tachycardia and relative hypotension.

- All children were treated with IV immunoglobulin. 15 (65%) children needed additional drugs (e.g. methylprednisolone, a second IV immunoglobulin dose, or tocilizumab). Further studies of drug therapy are required.

- All children with MIC-S admitted to the hospital have survived to date, and no irreversible disease sequelae have been observed yet.

Reviewed by: Dr John Cheek
DIAGNOSTICS & SAMPLING

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

Saliva or nasopharyngeal swab specimens for detection of SARS-CoV-2
(letter to the Editor)

> The current standard is testing of nasopharyngeal swabs by RT-qPCR to detect SARS-CoV-2. Further evaluation of the role of saliva specimens is needed.

> 70 inpatients with Covid-19 (confirmed with a positive nasopharyngeal swab) had further self-collected saliva specimens, and healthcare worker collected nasopharyngeal specimens taken at the same time.

  - More SARS-CoV-2 RNA copies were detected in saliva specimens (5.58 mean log copies/mL) than in nasopharyngeal swab specimens (4.93 mean log copies/mL).

  - A higher percentage of saliva samples than nasopharyngeal swab samples were positive up to ten days after initial diagnosis. At 1-5 days after diagnosis, 81% of saliva samples and 71% of nasopharyngeal swab samples were positive.

  - There was less variation in the levels of SARS-CoV-2 in saliva (SD 0.98 virus RNA copies/mL) than in nasopharyngeal samples (SD 2.01 virus RNA copies/mL).

> 495 asymptomatic healthcare workers had saliva and nasopharyngeal samples taken on the same day.

  - SARS-CoV-2 RNA was detected in 13 saliva samples. Nine of these had matched nasopharyngeal swab specimens, of which seven tested negative. The diagnosis in the 13 healthcare workers was later confirmed via diagnostic testing of additional nasopharyngeal samples.

> Variation in nasopharyngeal sampling may explain false negatives.

> There are several barriers to widespread adoption of saliva tests - first, testing saliva isn’t covered under the regulatory approvals for each test; second, each lab will need to check that this can be done on the tests that they are using to make sure it is as accurate as claimed under their lab conditions and protocol.

> Not all studies have shown that saliva is as good as swabs, e.g., https://jcm.asm.org/content/58/8/e00776-20

> That said, there would be considerable advantages to using saliva instead of swabs, and further work is proceeding.

Reviewed by: Professor Allen Cheng
DISABILITY

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

Potentials of telerehabilitation for families of children with special health care needs during the Coronavirus disease 2019 emergency
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2769776

> A comment in JAMA Paediatrics on the 24th August in response to the article from Thompson and Rasmussen "What does the coronavirus disease 2019 mean for families".

> Children with severe neurodevelopmental conditions and their families are particularly exposed to the risks of unsupervised rehabilitation support as a consequence of closing rehabilitation centres and programs.

> The authors argue that COVID-19 presents an opportunity to invest in telerehabilitation solutions, allowing for continuity of care and support for families and these children.

> Telerehabilitation could involve consultations, sharing interactive materials, promoting joint parent-professional observations, granting active listening to parents’ daily hassles, and supporting caregiving needs.

> These initiatives may still be beneficial after the COVID-19 pandemic to reduce disparities in access to child and family health care, ultimately promoting inclusive rehabilitation communities worldwide.

Reviewed by: Dr Martin Wright
EPIEMIOLOGY & PUBLIC HEALTH

Rafael Lee - 3rd Year Medical Student, 
Department of Paediatrics, The University of Melbourne

A systematic review and meta-analysis of published data on COVID-19 infection fatality rates (not peer reviewed) 
https://www.medrxiv.org/content/10.1101/2020.05.03.20089854v4

> This is a systematic review and meta-analysis of COVID-19 infection fatality rates (IFR).

> Pubmed, Medline, SSRN and medRxiv were searched on 25/4/2020 and again on the 
13/5/2020 and 16/6/2020. Pre-print server SSRN was searched on 25/05/2020, and 
grey literature was assessed using Google and Google scholar search and social 
media.

> The screening was conducted by two authors and meta-analysis performed using a 
random-effects method (metan command in Stata 15.1).

> Included:
  - Studies regarding COVID-19/SARS-CoV-2 (i.e. not SARS-CoV-1 extrapolations).
  - Studies that presented an estimated population infection-fatality rate or allowed 
calculation of such from publicly-available data, including serological data.

> Excluded:
  - Studies that only including COVID-19 incidence rather than the prevalence of 
  antibodies. Studies that are only having targeted populations in their 
seroprevalence.
  - Studies where it was difficult to determine the numerator (i.e. number of deaths) 
  associated with the seroprevalence estimate, or the denominator (i.e. population) 
  was not well defined, and IFR could not be calculated.
  - Studies where confidence bounds could not be calculated for IFR.

> A total of 269 citations were screened with 42 assessed for eligibility and 26 included 
in qualitative and quantitative synthesis (according to PRISMA flowchart – some 
numbers differ in the text).

> IFRs from 26 studies were included in the primary meta-analysis. These were from a 
wide variety of countries, published between February and June 2020.
  - IFR point estimate was 0.68% (0.53-0.82%) with extremely high heterogeneity (I² 
exceeding 99%, p<0.0001).
  - IFR varied between February and May (earlier estimates were lower).
- IFR estimates varied between serosurveys and modelled/PCR-based estimates.
- Five studies had a high risk of bias.

> Although the meta-analysis calculated an IFR point estimate of 0.68% (0.53-0.82%) it is difficult to know if this is the ‘true’ point estimate due to the high degree of heterogeneity in included studies.

- Different countries have varied death rates due to government response, the age distribution in the population, rates of underlying comorbidities in the population, resulting in differences in IFR calculations.
- Methodology differed between included studies.
- Issues with mortality recording mean this likely represents an underestimate of the true IFR figure.
- More research addressing age-stratified IFR is needed to inform policymaking.

Reviewed by: Dr Claire von Mollendorf

Juliana Wu - 3rd Year Medical Student, Department of Paediatrics, The University of Melbourne

Face coverings for COVID-19: from medical intervention to social practice
https://www.bmj.com/content/370/bmj.m3021

The authors discuss the reframing of face coverings as a social practice rather than a medical intervention.

> Face coverings are now widely recommended for public use as an infection control measure to reduce COVID-19 transmission.

> Face coverings work by capturing respiratory droplets from the wearer who may be an asymptomatic carrier of COVID-19.

> Face coverings have become a social practice that carries a range of different meanings and symbolisms across different cultures.

> Social meanings tied to face coverings can often dictate whether face coverings are successfully adopted or not.

- For instance, at the beginning of the COVID-19 pandemic, those wearing face masks in the United Kingdom were largely of Asian ethnicity and hence face coverings became synonymous with those who were carriers of the disease.

- In the United States, face coverings are often interpreted as an infringement of civil liberties, and individual autonomy and those wearing them are often accused of being weak and bowing down to authority.

- Contrastingly, in Asia, face coverings are widely adopted. This may be due to the deeply ingrained cultural belief that emphasises the boundaries between a clean self and a polluted outside.

> For the successful uptake of face coverings, policies should reflect a specific region’s socio-cultural beliefs. They should either draw on these to promote their use or work to actively reframe the negative social meanings attached to face coverings.
An example of a successful reshaping of cultural beliefs surrounding face coverings is Czech Republic’s #Masks4All campaign. Community-made masks were hung on trees as a way of boosting community morale whilst also ensuring the wide dissemination of masks. Social media campaigns involved many celebrities that promoted various public health slogans such as “keep your droplets to yourself” and “my mask protects you, your mask protects me.” The success of this campaign sparked similar movements in the United States, South Africa and the United Kingdom.

Reviewed by: Dr Claire von Mollendorf
GLOBAL HEALTH

Adolescent experiences of COVID-19
https://www.gage.org/adolescent-experiences-of-covid-19/

Burnet COVID-19 Global Trends and Analyses Health Care Workers, Aerosol Spread

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

WHO Coronavirus disease (COVID-19) Weekly Epidemiological Update
https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200831-weekly-epi-update-3.pdf?sfvrsn=d7032a2a_4

Sophia Moshegov - 3rd Year Medical Student, Department of Paediatrics, The University of Melbourne

The immediate impact of stay-at-home orders to control COVID-19 transmission on socioeconomic conditions, food insecurity, mental health, and intimate partner violence in Bangladeshi women and their families: an interrupted time series
https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30366-1/fulltext

> An interrupted time series was utilised to investigate the effects of COVID-19 lockdown on income, food security, mental health and women’s experiences of intimate partner violence in Bangladesh, a low-middle income country

> Participants from Rupganj upazila, rural Bangladesh were randomly selected from those enrolled in a separate randomised control trial of the benefits and risks of iron interventions in children (BRISC) on cognitive development. The BRISC trial was set in a rural area about 35km northeast of Dhaka, which comprises approximately 82,000 households. Residents work in agriculture, the garment industry, and other industrial activities. For this trial, data provided from mothers of enrolled children included levels of income, family food security and maternal depression - at enrolment and 12 months post-randomisation.

> This current study contacted mothers to repeat the baseline questionnaires from the BRISC trial, but also assessed levels of anxiety and intimate partner violence before and since lockdown.

> Between May 19th and June 18th 2020, the mothers of 3,016 children were randomly selected and invited to participate in the study, 2,424 of whom provided consent.

> Results: 2,424 mothers participated:
  - 96% reported a reduction in paid work for the family.
  - Median monthly family income fell from US$212 at baseline to $59 during lockdown.
- The proportion of families earning less than $1.90 per day rose from 0.2% to 47.3%.
- Moderate and severe food insecurity increased from 5.6% to 36.5%, and 2.7% to 15.3% respectively.
- The number of families experiencing any level of food insecurity increased by 51.7%.
- Mothers’ depression and anxiety symptoms increased during lockdown.
- Emotional, physical and sexual intimate partner violence increased.

> Limitations: Anxiety and intimate partner violence data was only collected during lockdown (no baseline data) retrospectively introducing recall bias. Generalisability to urban settings may be limited.

> The data represent stark and important findings, even with acknowledged limitations.

> Welfare delivery should be broader to reach all families experiencing a reduction of income, even if not below the poverty line.

> Local community services to protect the safety of women must be supported and remain accessible, even during the lockdown.

> Qualitative research to further explore and understand experiences under lockdown may be of value in future studies.

Reviewed by: Professor Steve Graham
Sex differences in immune responses that underlie COVID-19 disease outcomes
https://www.nature.com/articles/s41586-020-2700-3_reference.pdf

There is a growing body of evidence that suggests that male sex is a risk factor for more severe COVID-19 disease, including death. This article examined the sex differences in viral loads, SARS-CoV-2-specific antibody titres, plasma cytokines, as well as blood cell phenotyping in COVID-19 patients at baseline (n=39) and over the disease course (n=98, includes additional patients in ICU). A control group of COVID-19 uninfected health care workers (HCWs) was recruited for comparison.

> No clear differences in viral RNA concentrations and amount of IgG or IgM against S1 protein between male and female patients.

> Compared to female patients, male patients had:
  - Elevated innate inflammatory cytokines and chemokines (IL-8 and IL-18) and CCL-5.
  - Higher levels of CD14loCD16+ non-classical monocytes (ncMono).
  - Lower T cell level decrease in male patients.

> Compared to male patients, female patients had
  - Higher levels of CD38 and HLA-DR-positive activated T cells, as well as PD-1 and TIM-3-positive terminally differentiated T cells.

> Factors in disease progression
  - CXCL10 (IP-10) and M-CSF were elevated in patients that went on to develop worse disease regardless of sex.
  - In women, higher innate immune cytokines, such as TNFSF10 and IL-15, were positively correlated with disease progression.
  - In men, higher age, higher BMI, and poor CD8 T cell activation were associated with disease progression.
> Limitations:
  - Healthy HCWs used as the control population were not matched to patients based on age, BMI or underlying risk factors.
  - Small numbers in those with both baseline and longitudinal data.

> Significance:
  - To understand differential COVID-19 disease progression between gender, and inform vaccine and therapies for male and female patients (i.e. elevate T cell immune response and dampening innate immune activation in male and female patients, respectively).

Reviewed by: Dr Ryan Toh
Environmental contamination in the isolation rooms of COVID-19 patients with severe pneumonia requiring mechanical ventilation or high-flow oxygen therapy.

https://www.journalofhospitalinfection.com/article/S0195-6701(20)30401-1/fulltext

- To investigate the extent of environmental contamination in the isolation rooms of severe COVID-19 patients requiring ventilatory support.
- To compare sites and degrees of contamination around patients receiving different types of ventilatory support.
- Environmental swabs (n=76) and air samples (n=3) were collected from the rooms of three patients with severe COVID-19 at a single time point.
- Air sampling was performed 1.2m above ground level and 1m away from each patient at an airflow rate of 10-12.5L/min for 20 minutes.
- Environmental swabs were taken of fomites, nasal prongs, outside surfaces of the ventilator circuit, ceiling ventilation grills and fixed structures in the room.
- Participants: Three patients with severe COVID-19 receiving intensive care in individual negative-pressure rooms.
  - Patients one and two: mechanically ventilated with a closed suction system.
  - Patient three: a combination of high flow oxygen therapy (HFNC), non-invasive ventilation (NIV) via facial mask and manual ventilation.
- Contamination was defined by a positive rRT-PCR detection of SARS-CoV-2 from air samples or environmental swabs. Viable virus was detected by viral culture.
- Patients one and two: 2/48 environmental swabs positive - outside surface of the endotracheal tubes (ETT) from each patient. Viable virus was detected from ETT surface swab from Patient one.
- Patient three: 13/28 swabs positive including fomites, fixed structures and ceiling ventilation grill. Viable virus detected in eight samples.
- Air samples were negative for all patients.
- Increased environmental contamination of SARS-CoV-2 in the room of the patient receiving HFNC and NIV compared with mechanical ventilation with a closed suction system.
- All PCR-positive samples from surfaces were within droplet distance of the patients. ETT surfaces likely contaminated by oropharyngeal secretions.
- Positive swabs from the floor >2 m from the patient and a ceiling ventilation grill raise the possibility of airborne transmission from aerosols and secondary contamination by healthcare workers.

- The study supports current guidelines for the use of medical or surgical masks while caring for patients on closed suction system mechanical ventilation if no aerosol-generating procedures (AGPs) are performed.

- Small sample size.

- Absence of temporal relationship between environmental contamination and procedure performance.

- No AGPs were performed at the time of air sampling.

Reviewed by: Dr Samantha Bannister
MENTAL HEALTH

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

Child and adolescent psychiatry research during the COVID-19 pandemic (correspondence) https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(20)30314-X/fulltext

> The pandemic has had a far-reaching impact on a child and adolescent mental health researchers, particularly those early in their careers.

> Interventional studies have been suspended due to physical distancing requirements. Cohort studies, longitudinal studies and randomised controlled trials being most affected. School-based studies have also been halted due to school closures.

> The priority of new grants is directed towards COVID-19 research, which could have long term implications for already under the resourced child and adolescent mental health research.

> In the extra time afforded to researchers, attention has been directed towards understanding mental health impacts of physical distancing, identifying risk and resilience factors, and establishing prevention measures to mitigate long term impacts of the COVID-19 pandemic.

> The pandemic has also provided researchers with the opportunity to improve technical skills in online research, networking and collaboration.

> Although child and adolescent mental health research has been widely affected, new opportunities have also arisen. The skills acquired during the pandemic may be used commonly in the future.

Reviewed by: Professor David Coghill

COVID-19 related anxiety and concerns expressed by pregnant and postpartum women to obstetricians (pre-print) https://assets.researchsquare.com/files/rs-38004/v1/c7d8d894-d19d-4845-87dd-baf775ce9fdd.pdf

> 118 obstetricians in Southern India completed an online survey in April – May, regarding anxieties and concerns expressed by pregnant and postpartum women during the COVID-19 pandemic.

> A response to each question was measured using a Likert scale, with responses ranging from ‘very often’, ‘often’, ‘occasionally’ to ‘not at all’.

> Of the obstetricians that completed the survey, 89.83% were women, 87% had over ten years of experience, 45.76% had delivered at least ten children during the pandemic.
Obstetricians reported that concerns about the following were expressed ‘very often’ or ‘often’: hospital visits for antenatal visits and scans (72.65%), methods for protection from COVID-19 (60.17%), social media messages (52.14%), and safety of the infant from infection after delivery (52.14%).

Obstetricians reported the following anxieties were raised ‘very often’ or ‘often’: excessive worrying about social media messages (40.68%) and excessive worry about contracting COVID-19 (39.83%).

The most common methods implemented by obstetricians to address COVID-19 related anxiety were providing reassurance (88.89%), education about COVID-19 (80.34%) and recommending meditation and relaxation techniques (40.17%).

Limitations: the study was completed early on during the pandemic; small sample size limiting the generalisability of the findings; the possibility of recall bias.

Reviewed by: Professor David Coghill

How has pandemic led lockdown impacted the lifestyle of adolescents and young adults? (not peer reviewed)

https://www.medrxiv.org/content/10.1101/2020.08.22.20180000v1?collection=content

Online questionnaire-based survey (based on the FANTASTIC Lifestyle Questionnaire) distributed by social media and completed by 1,065 Indian adolescents and young adults aged 13-25 (mean age 19.9 years).

Average self-reported sleep duration increased from 6.86 hours prior to lockdown to 8.18 hours during the lockdown.

Average self-reported daily screen time was 5.13 hours. Pre-lockdown data estimate an Indian average of 3.5 hours per day.

51.9% of respondents felt their stress had increased, while 48.1% felt their stress had decreased since living in lockdown.

76% reported that their daily quantity of food intake increased during the lockdown.

38.6% of respondents indicated exercising less, while 37.0% exercised the same as prior to lockdown, and 24.4% exercised more.

79.3% reported trying something new or creative.

This study has major limitations: relatively small sample size likely to be not representative as a result of the sampling process; limited demographic and other information about the sample; lack of statistical analysis of the results; no attempt to consider the potential for recall bias; lack of consideration of confounders (such as the extent to which educational expectations influenced the increased screen time); lack of longitudinal data to assess if lifestyle changes are sustained.

Reviewed by: Dr Martin Wright and Professor David Coghill
PERINATAL HEALTH

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

Evaluation for SARS-CoV-2 in breast milk from 18 infected women
https://jamanetwork.com/journals/jama/fullarticle/2769825

- 18 women in the U.S. who had SARS-CoV-2 infection detected by RT-PCR (self-reported) provided a total of 64 samples of self-collected breast milk between 27th March and 6th May 2020.

- Offspring ranged in age from newborn to 19 months, with individual women donating 1-12 samples.

- Breast milk samples were processed for SARS-CoV-2 RNA by PCR and tissue culture. In addition samples of breast milk were spiked with SARS-CoV-2 RNA and then held at Holder pasteurisation (heated to 62.5 °C for 30 minutes and then cooled to 4 °C) as commonly used in human milk banks.

- One breast milk sample had SARS-CoV-2 RNA detected, collected on the day of symptom onset. However, there was no replication-competent virus detectable in that sample. The breastfed infant was not tested.

- Two control samples spiked with the replication-competent virus and Holder pasteurised, had no replication-competent virus or viral RNA detected.

- These findings suggest that breast milk may not be a source of infection for the infant.


Reviewed by: Professor Sue Garland

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

SARS-CoV-2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of the placenta
https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30327-3/fulltext

- There have been some reports of placental transmission of SARS-CoV-2, but it is unclear what effect the virus has on foetal tissues and newborns.

- The placentas of 101 women were evaluated in the study. Of these women,
  - 15 women tested positive for SARS-CoV-2 infection.
  - 34 women tested negative.
  - 52 women were not evaluated for SARS-CoV-2 infection.
All placentas were screened for SARS-CoV-2 spike (S) protein expression.

Immunostaining for SARS-CoV-2 nucleocapsid (N) was performed on the placentas from women with COVID-19.

Only one placenta tested positive and was positive for both S and N SARS-CoV-2 proteins, with the symptomatic mother also testing positive for SARS-CoV-2.

Further testing on this placenta revealed:

- Immunohistochemistry: strong expression of both S and N proteins in the syncytiotrophoblast.
- In situ hybridisation for SARS-CoV-2 RNA: intense signal in the syncytiotrophoblast and a prominent intervillous inflammation and mixed monocyte-macrophage and neutrophil composition.
- Ultrastructural analysis demonstrated particles morphologically consistent with SARS-CoV-2 in the cytoplasm of syncytiotrophoblast cells, endothelium of the foetal capillaries, fibroblasts and foetal intravascular mononuclear cells. The placental tissue contained an inflammatory infiltrate occupying the intervillous spaces, as earlier reports.
- Histology: an intervillous inflammatory infiltrate with neutrophils and monocyte-macrophages.

The newborn of this mother was born healthy at term, but one day after birth developed interstitial pneumonia consistent with COVID-19, requiring ICU admission and 18-day hospital admission. Initial testing was inconclusive, but a positive nasopharyngeal swab was returned at 36 hours post-birth, at 72 hours age. The mother at delivery had pneumonia and severe thrombocytopenia, requiring induction of labour.

This study reveals the histological and immunohistochemical findings of SARS-CoV-2 infection in the placenta; including the location of infection and the types of cells involved.

Further studies are needed to further characterise the pathological findings and identify typical changes in placentae that are positive for SARS-CoV-2 infection.

The newborn (born to the mother with the positive placenta) developed infection shortly after birth, confirming the source of infection was almost certainly placental transmission.

Unfortunately, the article does not mention measuring for maternal or neonatal viraemia which would have been conclusive for trans-placental transmission.

Reviewed by: Professor Sue Garland
Limited secondary transmission of SARS-CoV-2 in child care programs - Rhode Island, June 1-July 31, 2020
https://www.cdc.gov/mmwr/volumes/69/wr/mm6934e2.htm?s_cid=mm6934e2_w

- Childcare programs reopened on 1st June 2020 following declines in COVID-19 cases and hospitalisations in Rhode Island.

- Requirements before reopening: reduce enrolment: 12 people maximum initially; stable groups in physically separated spaces; mask use in adults; daily symptom screening; enhanced cleaning and disinfection; classes with a symptomatic person were required to close for 14 days or until the case was ruled out by testing.

- High compliance with RIDHS requirements was observed but maintaining stable staff was reported as the most difficult requirement and continued adherence to small, stable classes might not be feasible without additional funding.

- Cases occurred in 29 childcare programs, with 69% having a single case with no apparent secondary transmission.

- 75% of cases occurred from mid- to late July when incidence in the state was increasing.

- 101 possible child-care associated COVID-19 cases reported.

  - 52 probable or confirmed cases:
    - Children: 58% (30 cases) – 5 years median age.
    - Adults: 42% (22 cases – 20 teachers, 2 parents) – 30 years median age.
  
  - Resulted in the closure of 89 classes, quarantining of 687 children and 166 staff members, including contacts.

- Case study: Two years old, attended childcare for six days while potentially infectious (three days before symptom onset and three days after symptom resolution) with none of the ten tested childcare contacts testing COVID-19 positive (one additional childcare contact not tested).

- Secondary transmission in some childcare programs could not be ruled out with some having possible secondary transmissions identified.

- The possible secondary transmission was identified in 4/666 programs that had been allowed to reopen, all in the last two weeks of July, when community transmission increased. The apparent absence of secondary transmission within the other 662 child care programs was likely the result of response efforts to contain transmission and child care programs’ adherence to requirements, in particular maximum class sizes and use of face masks for adults.
Community efforts are essential to safeguard childcare programs with adherence to recommendations (e.g., face masks, stable groups, disinfection, etc.) being important to reducing transmission in childcare setting in addition to timely public health action.

Reviewed by: Professor Fiona Russell

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

The risk for severe COVID-19 illness among teachers and adults living with school-aged children

In this study conducted in the U.S., the authors used representative data from the 2018 National Health Interview Survey to estimate the prevalence of risk factors (definite and possible) for severe COVID-19 disease among three groups: non-teacher adult workers, teacher adult workers, and adults living with school-aged children (5-17 years old).

Definite risk factors included cancer, a serious heart condition, obesity, type 2 diabetes, age >64 years. Possible risk factors included moderate/severe asthma, cerebrovascular disease, hypertension, dementia, liver disease, pregnancy, smoking, type 1 diabetes.

Results:
- Among the 5.8 million teacher adult workers, 39.8% had definite, and 50.6% had definite or possible risk factors for severe COVID-19 disease.
- Among the 150.3 million non-teacher adult workers, 41.4% had definite, and 55.8% had definite or possible risk factors for severe COVID-19 disease.
- Among the 69.74 million adults living with school-aged children, 41.0% had definite, and 54.0% had definite or possible risk factors for severe COVID-19 disease.
- The most common risk factor in all groups was BMI >/= 30 (27.9% of teachers).

Conclusion: although schools reopening is beneficial for children, it can put vulnerable adults at risk for severe COVID-19 illness if adequate protective measures are not considered.

Limitations: Some risk factors for severe COVID-19 disease (ex. chronic kidney disease, thalassemia) were not accounted for. School personnel other than teachers were not identified. Different levels of obesity carry different levels of risk.

Reviewed by: Dr Martin Wright
Healthy buildings: risk-reduction strategies for reopening schools, Schools For Health; Harvard, School of Public Health

> ‘Schools For Health’ website (from the Harvard School of Public Health) focuses on how school buildings influence school health, thinking, and performance.

> It provides information, including risk reduction strategies for reopening schools.

> 'Healthy Buildings’ explains key strategies that should be implemented by schools to keep buildings clean and thus, reduce the risk of spreading COVID-19 (other sections include; Healthy Classrooms and Healthy Policies):

- Increase outdoor ventilation: prioritise circulation of fresh air and minimise recirculation of air;
- Filter indoor air: ensure air is filtered to MERV13 or higher and that filters are checked regularly;
- Supplement with portable air cleaners: with high-efficiency particulate air (HEPA) filters that can be placed in individual rooms;
- Ensure filtration and ventilation performance: verify the standard of air filtration by engaging with experts and conducting tests;
- Advanced air quality techniques: consider additional techniques such as humidification or ultraviolet germicidal irradiation (UGVI);
- Plexiglass as a physical barrier: especially in areas where social distancing is challenging, e.g. cafeteria checkout or reception;
- Prioritise adequate and regular deep cleaning of surfaces;
- Keep the bathroom hygienic; by staggering use and closing toilet lids/doors;
- Install no-contact infrastructure: to reduce spread through fomites, for example, automatic sanitiser dispensers.

> For a more detailed guide, Schools for Health recommends viewing the materials produced by ASHRAE Epidemic Task Force.

> These strategies should be employed within a layered COVID-19 response at all schools, which include:

- Healthy policies: Building a culture of health, safety, and shared responsibility.
- Healthy buildings: Breathing clean air in the school building.
- Healthy classrooms: Following safe practices in classrooms.
- Healthy schedules: Moving between rooms and locations safely.
- Healthy activities: Enjoying modified activities.

Reviewed by: Dr Martin Wright and Professor Fiona Russell
THERAPEUTICS

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

Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: Cohort study including 8.3 million people
https://heart.bmj.com/content/early/2020/07/31/heartjnl-2020-317393

> This study aimed to investigate whether the use of ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs) alter the risk of developing severe COVID-19 disease requiring ICU care.

> Prospective cohort study using data from 1205 general practices in England with 8.28 million participants aged 20-99 years.

> Results from 19,486 patients who had COVID-19 disease:

- Use of ACEi and ARBs were associated with a significant reduction in the risk of RT-PCR-confirmed COVID-19 disease.

- Use of ACEi and ARBs not associated with an increased risk of COVID-19 disease requiring ICU care.

- Risk of COVID-19 disease with ACEi was higher in Caribbean and Black African patient groups than the white group.

- Risk of COVID-19 disease with ARBs was higher in Black African than the white group.

> Limitations:

- Exposure to ACEi and ARBs was based on prescriptions rather than dispensed medication.

- Data on deaths occurring in the community, care homes, or in hospital but not in ICU were not available.

- Death data is not included, which may bias analyses if not taken into account in the hazard analysis.

- Interactions may exist among confounding variables.

- Propensity matching analysis could have been performed to mimic an RCT.

Reviewed by: Dr Amanda Gwee and Dr Diana Zannino
Two metres or one: what is the evidence for physical distancing in COVID-19?

https://www.bmj.com/content/370/bmj.m3223

- Current recommendations vary between countries but are generally 1-2m between people for physical distancing to reduce the risk of contracting COVID-19 through the airborne spread.

- The authors argue that current recommendations are antiquated and are not supported by our current understanding of the physics and principles of viral spread (acknowledging that there are still significant gaps in what we know).

- Origin of the 1-2m rule:
  - The recommendations for keeping 1-2m between people originated before the 20th century and were reinforced by research performed in the 1940s.
  - Original theory: respiratory droplets are two different sizes - large ("droplets") and small ("airborne"). Droplets fall to the ground quickly before they evaporate and airborne particles evaporate more quickly than they fall. Both cannot move far without airflow.

- Contemporary research.
  - Droplets exist in many sizes.
  - Exhaled air and ambient airflow are integral in determining how far these droplets can travel. Without exhaled airflow, the larger droplets travel furthest (1-2m), and the smaller ones don't travel as far because they encounter high resistance.
  - Depending on airflow, small droplets can travel beyond 2m, and large droplets can travel also travel further than they normally would.
  - Coughing, singing, sneezing, heavy breathing with exercising, etc. can propel droplets 7-8m.
  - 8/10 studies evaluated in a recent systematic review found horizontal projection beyond 2m for respiratory droplets (for particles up to 60μm).
  - Studies reporting on recent outbreaks (SARS-CoV, MERS-CoV and Avian flu) also suspected spread beyond 2m.
  - Respiratory droplets tend to dilute more quickly in well-aerated outdoor settings, and indoor settings confer a higher risk of transmission.
  - Airborne particles (e.g. measles) travel further and in a more concentrated way compared to droplets.
Specific airflow patterns are important - one study detailed how several people became infected with SARS-CoV-2 in a Chinese restaurant which had no contact but was in the same line of airflow from an air conditioning unit.

Studies on whether SARS-CoV-2 infection can occur via airborne transmission have been mixed. It is likely that SARS-CoV-2 can spread via airborne transmission but whether or not these particles remain infectious is less clear.

The author proposes that rather than a 'one size fits all' approach, there should be graded recommendations based on circumstances and the risks of the environment.

Proposed risk-based model

- Takes into account environment, ventilation, occupancy, use of face coverings and the length of time they are worn, and whether people are silent, speaking or shouting/singing.
- Higher risk settings are those have multiple risk factors, etc. a well ventilated outdoor area but with lots of people singing or a poorly ventilated area with a small number of people, but no masks and contact for a prolonged time.

Reviewed by: Dr Martin Wright
OTHER RESOURCES

All COVID-19 literature

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

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

Australian Government

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

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

Daily updates on COVID-19 literature compiled by Canadian medical students
https://docs.google.com/forms/u/0/d/e/1FAIpQLSFOxCoAuLV0aJdf_z2uWV7r3FaPzAQr86g9ZXBcTZ1QcCE_Nw/formResponse

Focuses on paediatric clinical, epidemiological, transmission and neonatal aspects

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

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

Lancet COVID-19 papers

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

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

https://phelibrary.koha-ptsfs.co.uk/covid19rapidreviews/

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

Victorian Department of Health and Human Services

WHO Rolling updates on COVID-19
EDITORIAL TEAM

Leadership group: Professor Fiona Russell & Dr Wonie Uahwatanasakul

Editorial Assistant: Eleanor Neal (Epidemiologist / PhD student)

Librarian: Poh Chua

Production: Kase Anderson, David Pethick & Helen Dedman

Medical Student Committee: Daniel Lamanna
Samar Hikman
Jenny Pham
Rose Noble Kizhakekara
Grace Newman
Renee Cocks
Rafael Lee
Juliana Wu
Sophia Moshegov
Angela Zhu
Thomas Hill
Natalie Commins
Julian Loo Yong Kee
Emma Tovey Crutchfield
Ha My Ngoc Nguyen

Journalists: For any media inquiries, please contact The University of Melbourne media unit, via news@media.unimelb.edu.au

Distribution List: If you would like to be on the distribution list to receive this report, please send an email to Kase Anderson
COVID-19 KIDS EVIDENCE UPDATE
http://go.unimelb.edu.au/qp3r

REVIEWERS

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

Dr Wonie Uahwatanasakul
Paediatrician- Immunization service RCH, MD Child and Adolescent Health Program Lead Coordinator, Department of Paediatrics, The University of Melbourne

Professor Julie Bines
Paediatric Gastroenterologist, RCH; Lead Enteric Disease Group MCRI; Victor and Loti Smorgon Professor of Paediatrics, The University of Melbourne and Dr Celeste Donato- Virologist, Enteric Diseases Group, MCRI; Lecturer, Department of Paediatrics, The University of Melbourne

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

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

Professor Allen Cheng
Medical Adviser, Melbourne Vaccine Education Centre, Infectious Diseases Epidemiology Director of the Infection Prevention and Healthcare Epidemiology, Alfred Health, Infectious diseases and an epidemiologist, Department of Epidemiology and Preventive Medicine at Monash

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

Professor Steve Graham
Centre for International Child Health, Department of Paediatrics, The University of Melbourne, MCRI

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

Dr Samantha Bannister
Paediatric Registrar, The Royal Children’s Hospital, Melbourne, Graduate Research Student, Murdoch Children’s Research Institute, PhD Candidate, Department of Paediatrics, The University of Melbourne

Professor David Coghill
Financial Markets Foundation Chair of Developmental Mental Health, The University of Melbourne

Professor Sue 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

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

Dr Diana Zannino
Biostatistician and Senior Research officer at MCRI