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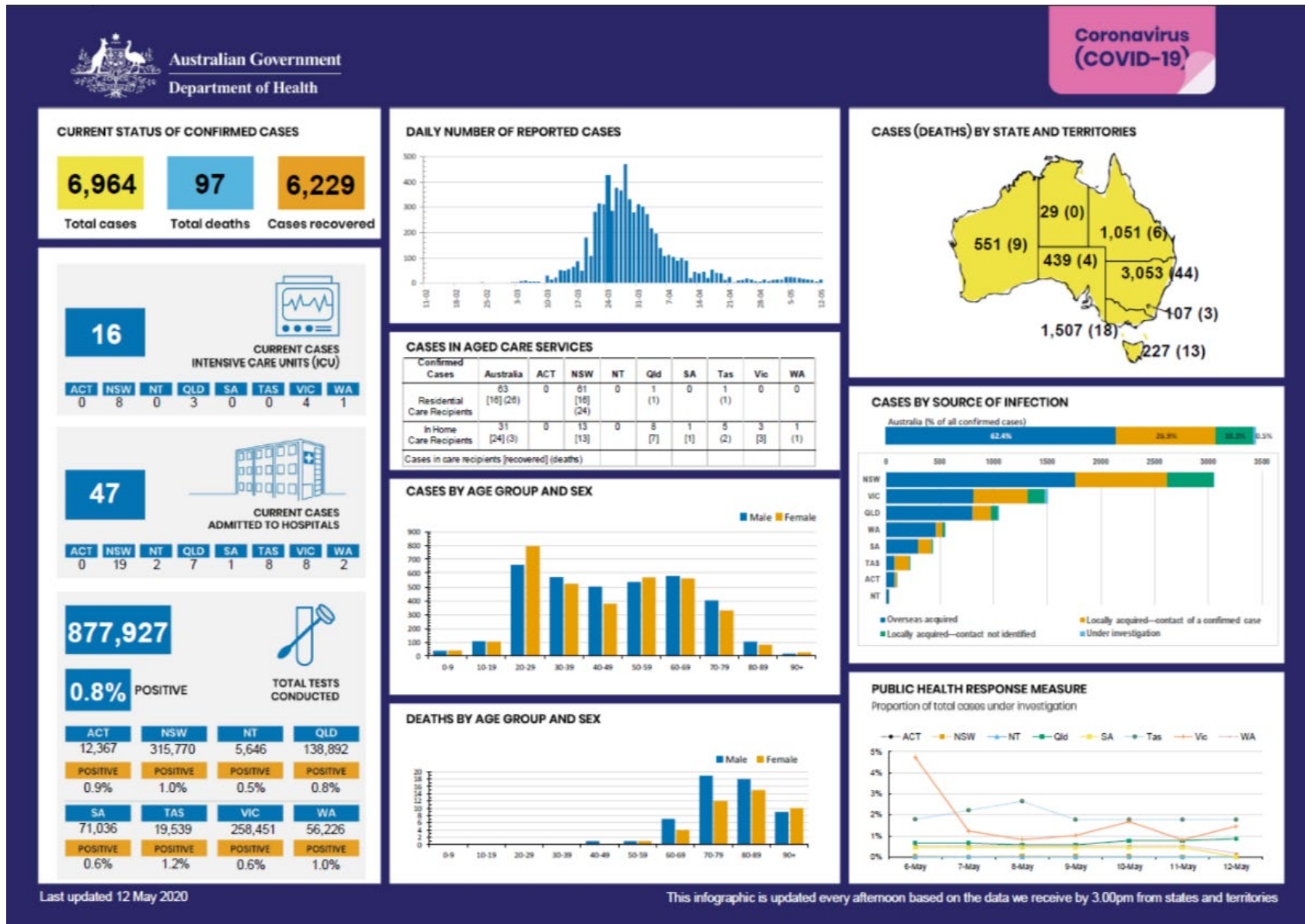
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# COVID19 KIDS EVIDENCE UPDATE

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

**Weekly Update No.5**

13 May 2020



Source: Australian Government: Department of health [Internet]. 2020 [updated 2020 May 11; cited 2020 May 12]. 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>

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# ADULT MEDICINE

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

**OpenSAFELY: Factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients**

<https://www.medrxiv.org/content/10.1101/2020.05.06.20092999v1>

- > Cohort study of 17,425,445 adult NHS patient's primary care electronic health records, pseudonymously linked to the patient-level data from the COVID-19 Patient Notification System using the new OpenSAFELY platform, from 1st February 2020 to 25th April 2020.
- > 5683 deaths attributed to COVID-19 over the time period
- > After full adjustment, death from COVID-19 was strongly associated with:
  - Male
  - Older age
  - Obesity
  - Deprivation - only partially attributable to co-morbidity or other risk factors
  - Most comorbidities- including uncontrolled diabetes, respiratory disease including severe asthma, cardiovascular disease (excluding hypertension), recent cancer (<1 year) and haematological malignancy
  - People of Asian and Black ethnic origin- this was only partially attributable to pre-existing clinical risk factors or deprivation
- > Limitations
  - Using only electronic data from the COVID-19 Patient Notification System relies on hospitals completing a new return under emergency circumstances
  - Only studied in-hospital deaths, and therefore may not be generalisable to those in nursing homes.
  - Method looked for factors correlated with, and not causally related to mortality
  - Discrepancy in the use of electronic health records and entered data related to risk factors in the primary health care setting

Reviewed by: Professor Allen Cheng

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

### Lupus Anticoagulant and Abnormal Coagulation Tests in Patients with COVID-19

<https://www.nejm.org/doi/full/10.1056/NEJMc2013656>

A study to determine the cause of abnormal coagulation tests in COVID-19 patients

- > COVID-19 patients have a profound hypercoagulable state leading to increased venous thrombotic events
- > Prolonged activated partial-thromboplastin time (aPTT) may be seen as a reason to avoid anticoagulation at therapeutic and prophylactic doses
- > Of 216 patients with severe acute respiratory syndrome associated with COVID-19, 44 (20%) had a prolonged aPTT
- > Results of further studies of coagulation status were reported in 35 of the 44 patients
- > Epidemiology: median age 57 years; 24 male patients
- > Venous thrombotic events. Pulmonary embolism in 1 patient and suspected thrombosis in 1 patient. No arterial thrombosis or significant bleeding
- > Coagulation studies:
  - No factor VIII or factor IX deficiencies
  - Marginal factor XI reduction (n = 5) unlikely of clinical significance
  - Factor XII levels  $\leq$  50 IU per decilitre (n = 16)
  - Lupus anticoagulant assays: 31/34 patients positive (91%)
    - 18/34 (53%) had lupus anticoagulant detected on 2 assays (dilute Russell's viper-venom time [DRVVT] and lupus anticoagulant sensitive aPTT)
    - 7/34 (21%) by DRVTT assay alone
    - 6/34 (18%) Lupus anticoagulant-sensitive aPTT alone
    - All Lupus anticoagulative-positive specimens had prolonged aPTT with a 50:50 mix of patient plasma and normal plasma
  - Heparin was detected in 28/35 samples
    - DRVTT assay contains heparinase which neutralises any heparin effect that may lead to false positive detection of Lupus anticoagulant
- > Comparison to a historical control cohort of 540 specimens for Lupus anticoagulant testing: aPTT  $\leq$  30 seconds; 43 patients (8%) and Lupus anticoagulant positive: 11/43 (26%)
- > Summary: a prolonged aPTT should not be a barrier to the use of anticoagulant therapies in the prevention and treatment of venous thrombosis in COVID-19 patients

Reviewed by: Professor Julie Bines

# CLINICAL PAEDIATRICS

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

## **Hyper inflammatory shock in children during COVID-19 pandemic (commentary)**

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31094-1/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31094-1/fulltext)

- > In April 2020, a Paediatric ICU retrieval and support service in the UK identified a cluster of 8 children (aged 4-14 years) with hyperinflammatory shock syndrome; showing features similar to Kawasaki disease.
- > All children were previously fit and well
- > Clinical presentations were similar with persistent fever (38-40°C), rash, conjunctivitis, peripheral oedema, generalised extremity pain, significant gastrointestinal symptoms, development of small pleural, pericardial, and ascitic effusions
- > All progressed to warm, vasoplegic shock, refractory to volume resuscitation; requiring inotropes for haemodynamic support
- > Respiratory involvement was not significant, although 7/8 children required mechanical ventilation for cardiovascular stabilisation
- > Cardiovascular involvement was common with elevated cardiac enzymes during the illness and abnormal echocardiogram showing echo-bright coronary vessels that progressed to a giant coronary aneurysm in 1 child
- > At presentation, all children tested negative for SARS-CoV-2 on bronchoalveolar lavage or nasopharyngeal aspirates. However, 2 children later tested positive and 4 of them had known family exposure to COVID-19
- > There was one death
- > Conclusion: This hyper inflammatory syndrome could be a new manifestation of COVID-19 in previously asymptomatic children.

Reviewed by: Dr Wonie Uahwatanasakul



# DIAGNOSTICS & SAMPLING

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

## **Sensitivity of nasopharyngeal swabs and saliva for detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)**

<https://www.medrxiv.org/content/10.1101/2020.05.01.20081026v1.full.pdf>

- > Participants: 53 consecutive COVID-19 positive inpatients in 6 hospitals in Toronto, Canada
- > Epidemiology: Median age – 63 years old (27-106); Median time from illness onset to collection of tested specimen – 11 days; 21 females (40%); 47 had fever on admission (89%); 44 had a cough on admission (83%)
- > Paired sample timing: At time of enrolment; 3 subsequent paired samples at 72-hour intervals if patient remained hospitalised
- > Main results:
  - Nasopharyngeal (NP) swab sensitivity: 89%
  - Saliva sample sensitivity: 77%
  - Difference in sensitivity greatest when samples collected later in disease, with NP having higher sensitivity than saliva
  - Saliva may be a reasonable alternative to NP for SARS-CoV-2 sampling
- > Irrespective of sampling technique used however, a single specimen is not 100% sensitive and a repeat sample or serologic testing should be performed where there is a high index of suspicion of COVID-19
- > More data is required to assess the utility of saliva for detection SARS-CoV-2 in asymptomatic or non-hospitalised patients as well as determine if NP swabs and saliva are truly equivalent in early disease
- > Study limitations: Likely bias towards NP swabs due to their use for the original diagnosis (“gold-standard” in this study); Single detection system (Seegene) used, other platforms may have shown different results; Other saliva specimen collection techniques (e.g., throat washing) may have increased yield compared to spitting

Reviewed by: Dr Danielle Wurzel

# EMERGENCY MEDICINE

**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.

**Where have all the children gone? Decreases in paediatric emergency department attendances at the start of the COVID-19 pandemic of 2020**  
<https://adc.bmj.com/content/early/2020/05/05/archdischild-2020-319385>

- > During the COVID19 pandemic, significant decreases in Paediatric ED attendances at 2 hospitals in Manchester in the United Kingdom; one a large district hospital and one a tertiary paediatric hospital.
- > Up to 70% less than usual attendances after the UK entered its lockdown phase.
- > The authors raise concern about unwell children with serious pathology remaining at home rather than seeking care.
- > There have now been several articles noting this trend to lower ED presentations; however, none have explored the reasons behind this other than opinion and case presentations. Possible reasons include delayed care seeking in significantly unwell children, seeking care elsewhere or delaying care for non-urgent complaints, and decreased social interaction resulting in less illness and injury in children. As the authors of this letter point out, more research is required before accurate conclusions can be drawn.



# EPIDEMIOLOGY & PUBLIC HEALTH

Professor Sharon Goldfeld – Paediatrician, public health physician, Co-Group Leader of Policy and Equity at the MCRI and Director of the Centre for Community Child Health at The Royal Children's Hospital Melbourne

## **Prevention and early intervention for mental health problems due to COVID-19**

<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2764404>

- > Disasters are associated with an increase in post-traumatic stress, depression, and other mental health problems, both in the short- and long-term
- > With the practice of physical distancing being instituted across the world during the COVID-19 pandemic, there will likely be increased levels of anxiety, depression, loneliness, domestic violence, and child abuse
- > A pandemic of mental illness will soon follow the COVID-19 pandemic
- > Three proactive steps are proposed for preparing for the increased mental health demands following the pandemic:
  - Aim to alleviate increased loneliness and meet social needs via the use of digital technologies, and approaches for outreach and screening
  - Have mechanisms in place for supporting people who are at risk of domestic violence and child abuse
  - Strengthen the mental health system, and consider creative strategies during the pandemic, such as up-skilling the lay public to check in with each other, and using technology platforms to deliver services

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

## **The coronavirus crisis could end in one of these four ways**

<https://www.theguardian.com/commentisfree/2020/apr/08/how-will-the-coronavirus-crisis-end-lockdown-pandemic>

Opinion Piece from April 9th by Professor Devi Sridhar (Chair of Global Public Health at the University of Edinburgh) on the four possible scenarios of how the coronavirus crisis may end:

- > Eradicating the virus – All countries simultaneously close borders for an agreed amount of time and mount an aggressive campaign to identify carriers of the virus to prevent transmission. This is unlikely right now since the virus has already spread aggressively, and global cooperation is difficult to achieve.
- > While waiting for a vaccine, delaying the spread of the virus over the next 12-18 months with intermittent lockdowns – Need to anticipate healthcare capacity three weeks in advance. This is moderately more likely but there are high social and economic costs of lockdown, especially in poorer countries.
- > While waiting for a vaccine, increasing testing and contact tracing so carriers and contacts can be quarantined – Needs large-scale planning and resource mobilisation. Even more likely scenario with potential for more relaxed physical distancing measures.
- > Using the best therapies to manage COVID-19 (including potential antiviral and prophylactic therapies), ideally in combination with rapid diagnostic testing – This is in the absence of a viable vaccine in the foreseeable future. This may be sustainable in countries with the resources, but it is almost impossible for poorer countries.

Reviewed by: Dr Claire von Mollendorf

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

**COVID-19: implementing sustainable low cost physical distancing and enhanced hygiene**

<https://onlinelibrary.wiley.com/doi/10.5694/mja2.50602>

- > The authors discuss that routine employment of low-cost hygiene and physical distancing interventions early in the epidemic will slow disease transmission, potentially decrease case severity and permit more restrictive lockdown measures to be relaxed.
- > Differing transmission dynamics and an earlier viral load peak in SARS-CoV-2 cases has made COVID-19 more difficult to contain than the 2003 SARS epidemic.
- > Large-scale city lockdowns, including cancellation of events and closure of schools, were often implemented late and have had a huge social and economic impact that may not be sustainable.
- > Low-cost measures focusing on social distancing and improved hygiene measures may be enforced pre-emptively and are more sustainable in flattening the curve long-term. These interventions assume that community transmission of SARS-CoV-2 may occur undetected and interventions at this time will be less effective.
- > Some suggested low cost measures include:
  - Workplace: no handshaking, defer large meetings, enforce hand sanitisation
  - School: avoid mixing classes and year levels, strict sick days, food preparation hygiene

- Retail/Commercial: avoid using cash, open windows where possible
- Home: only allow well guests to visit, quarantine ill person at home
- > There is no evidence for the effectiveness of individual interventions in preventing COVID-19; however, observations and simulation from other infectious diseases have shown that, adopted en bloc, they are efficacious in halting the spread of disease.

Reviewed by: Dr Claire von Mollendorf

Jim Owens – 4th Year Medical Student,  
Department of Paediatrics, The University of Melbourne

**Enhanced contact investigations for nine early travel-related cases of SARS-CoV-2 in the United States (preprint, not peer reviewed)**

<https://www.medrxiv.org/content/10.1101/2020.04.27.20081901v1>

- > How can enhanced contact tracing increase understanding of transmission risk factors and aid in public health efforts to control the spread of COVID-19?
- > Summary of the findings of enhanced contact tracing investigations, including in-depth interviews and rRT-PCR testing, for 553 close contacts of nine imported cases across multiple jurisdictions of the US, in the period between January 19 and January 30.
- > 404 contacts met the criteria for active surveillance and 338 contacts had adequate demographic and exposure data. Of these, 15 (4%) were household contacts, 163 (48%) were healthcare personnel, 95 (28%) were community contacts exposed in the healthcare setting, and 65 (19%) were exposed in other settings.
- > Two secondary cases (both spouses) were identified among household contacts in the 14-day monitoring period. The measured secondary attack rate was 13% for household contacts, 0% for healthcare personnel, and 0% for community contacts.
- > Household contacts were observed to display high levels of adherence to home isolation guidelines, and all primary cases employed transmission-control practices including wearing facemasks, practicing social distancing and seeking care, likely reducing secondary transmission.
- > The findings support previous research showing that individuals having prolonged close contact with cases are at higher risk for developing COVID-19.

Reviewed by: Dr Claire von Mollendorf

Sarah Jackson – 3rd Year Medical Student,  
Department of Paediatrics, The University Of Melbourne

**A strategic framework to ease community-wide COVID-19 suppression measures**

<https://www.mja.com.au/journal/2020/strategic-framework-ease-community-wide-covid-19-suppression-measures>

- > Already implemented measures have suppressed sustained transmission of COVID-19 in Australia. As the country recovers from direct health, and indirect socio-economic impacts, an evidence-based, and community-engaging strategic response is required.
- > A framework for research and public health action is proposed, building on the Australian Health Sector Emergency Response Plan, for aid in control-measure decision making as we exit societal “lockdown”.
- > This consists of three ‘Phases’ to be implemented in a stepwise progression, as key predefined targets are met rather than at arbitrary time-points.
- > A transition period precedes each phase, to determine if further release can proceed or if a return to tighter restrictions is warranted.
- > Phase 1: Suppress – optimise existing suppression strategy and prioritise segments of the community to be ‘released’.
- > Phase 2: Release – limited socio-economic restoration with prioritisation of economic and educational sectors prior to recreational; alongside heightened monitoring for disease resurgence in vulnerable populations.
- > Phase 3: Restore – precedes complete exit of lockdown, consisting of broader restoration of activities, continued protection of health care workers and vulnerable populations, and preparation for introduction of novel tools and strategies in our response.
- > The 3-phase framework runs concurrently with optimisation of existing tools and strategies, and a ‘whole-society approach’ to harness and integrate the collective expertise of all facets of the community, and ensure correct information, governance and approach.

Reviewed by: Professor Steve Graham

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

**Herd immunity is not a realistic exit strategy during a COVID-19 outbreak (preprint, not peer-reviewed)**

<https://www.researchsquare.com/article/rs-25862/v1>

The authors examine the likelihood of achieving herd immunity against COVID-19 in The Netherlands.

- > Natural herd immunity is thought possible when half to two-thirds of the population has been infected, recovered and produced antibodies against SARS-CoV-2.

- > This strategy was examined in The Netherlands, with a population of 17.4 million, and approx. 37000 infections and 4500 deaths as of 25th April, 2020.
- > From a total of 7361 blood donors without a history of COVID-19, 188 (with a previous sample) demonstrated IgM seroconversion. Including those without a previous sample (total=200) translated into a seroprevalence of 2.7%, far shy of that required for herd immunity.
- > Seroprevalence was highest in the 18-30-year age group (4.2%) and the hardest-hit areas (9.5%).
- > The authors recommended against an immediate herd immunity strategy, but rather proposed an exit strategy based on risk stratification of the population.
- > This study has notably excluded seroconversion data in the known COVID-19 positive population, as well as age extremes (<18 years and > 72 years). It also did not examine the correlation between seroconversion and immunity against COVID-19.

Reviewed by: Dr Claire von Mollendorf

Jim Owens – 4th Year Medical Student,  
Department of Paediatrics, The University of Melbourne

### **Quantifying the impact of physical distance measures on the transmission of COVID-19 in the UK**

<https://doi.org/10.1186/s12916-020-01597-8>

- > Are physical distancing measures leading to a reduction in transmission of SARS-CoV-2?
- > Online social-mixing survey (CoMix) of 1356 adult participants 1 day after implementation of 'lockdown' in the UK. Comparison of contacts made with pre-intervention statistics from the POLYMOD study. Incorporated updated social mixing patterns into deterministic transmission models to estimate the reduction in basic reproduction number  $R_0$ .
- > The mean number of reported physical and non-physical contacts were reduced by 74% compared with POLYMOD data.
- > Pre-intervention mean  $R_0$  estimated to be 2.6 based on a meta-analysis of current literature. Computed  $R_0$  was reduced below 1 (0.62 incorporating all types of contact, 0.39 incorporating only physical contact) when using updated social-mixing patterns reported in the CoMix survey.
- > Results strongly support the hypothesis that 'lockdown' with physical distancing will reduce the transmission of SARS-CoV-2 in the UK. Results will however be delayed.
- > Study limitations include the omission of child respondents, assumptions regarding age-dependent transmission dynamics, and the possibility of selection and recall bias introduced by the survey format.

Reviewed by: Dr Claire von Mollendorf

# GLOBAL HEALTH

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

## **The potential impact of the COVID-19 response on tuberculosis in high burden countries: a modelling analysis**

[http://www.stoptb.org/assets/documents/news/Modeling%20Report\\_1%20May%202020\\_FINAL.pdf?utm\\_source=The+Stop+TB+Partnership+News&utm\\_campaign=4bee55b759-partner+survey+2019\\_COPY\\_01&utm\\_medium=email&utm\\_term=0\\_75a3f23f9f-4bee55b759-189991929](http://www.stoptb.org/assets/documents/news/Modeling%20Report_1%20May%202020_FINAL.pdf?utm_source=The+Stop+TB+Partnership+News&utm_campaign=4bee55b759-partner+survey+2019_COPY_01&utm_medium=email&utm_term=0_75a3f23f9f-4bee55b759-189991929)

- > Tuberculosis is the major infectious disease causing death globally - in 2018, there were an estimated 1.5 million deaths due to tuberculosis, including a quarter of a million deaths in children and adolescents
- > Global and national disease control programmes including for tuberculosis are being affected by the indirect effects of the COVID-19 pandemic
- > Short-term impacts include an increase of missed opportunities for diagnosis and treatment initiation (with fewer notifications), for follow-up and treatment support, and for prevention through household contact screening and management
- > Long-term implications include increased community transmission of drug-susceptible and drug resistant tuberculosis due to undetected and untreated cases, and poorer treatment outcomes (death and lost-to-follow-up) due to a potential shortage in availability of drugs for treatment as well as challenges in providing treatment support until completion.
- > This modelling analysis was published by the Stop TB Partnership in collaboration with Imperial College, Avenir Health, Johns Hopkins University and USAID.
- > With a 3-month lockdown and 10-month recovery, it is estimated that there will be an additional 6.3 million cases and 1.3 million deaths due to tuberculosis globally over the next 5 years.
- > This equates to a reversal of the recent progress with tuberculosis pandemic control to a return to levels before 2013.
- > To minimise the impact of the COVID-19 lockdown response, intensive community engagement, maintaining importance of TB services while reemerging from the COVID-19 response, and active case finding including contact tracing may help compensate for missed diagnoses during the lockdown period.
- > Limitation: important to note that for this modelling analysis, it was assumed that there would be no interaction between tuberculosis and SARS-CoV-2, as no data yet to inform modelling.

Reviewed by: Professor Steve Graham

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

**The art of medicine - Has COVID-19 subverted global health?**

<https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931089-8>

This is a perspective published by authors from Harvard School of Public Health. In summary:

- > The global approach to controlling the COVID-19 pandemic has largely hinged upon enforcing widespread lockdowns, and a focus on high-technology health-care.
- > These strategies have been applied near-universally to both high- and low-income countries, with little regard for their vastly different population structures, public health needs, access to health-care resources, and economies.
- > Enforcing widespread lockdowns in low income countries may unintentionally be increasing morbidity and mortality from other causes, and is likely to disproportionately affect the poor.
- > Lockdowns in these countries have already resulted in:
  - Reduced healthcare accessibility - including reduced clinical presentations for acute cardiac events, and increased numbers of home-deliveries;
  - Interruptions to public health interventions - including reduced childhood vaccination rates, and decreased distribution of insecticide-treated bed nets and antimalarial medications; and,
  - Exacerbated hunger - the UN estimates that over 300 million children may be at risk of acute hunger due to inability to access meals during school closures.
- > A community-based approach is needed in these countries, focusing on active-case finding through syndromic diagnosis, banning of mass gatherings, and encouragement of personal hygiene practices. Targeted lockdowns may be used sparingly to contain small outbreaks.
- > This perspective highlights the issues of concern that are becoming widely acknowledged, and are already very much on the agenda for national planning of sustaining health service delivery in resource-limited countries. Certainly through necessity, the COVID-19 pandemic provides an important opportunity to strengthen the decentralised delivery of health services, but just to illustrate some of the challenges: for the community health worker - greater responsibility, wider skill-set, fear and stigma, limited remuneration and lack of measures to protect the health worker at the community level from being infected or spreading infection - or for the process of effective and cohesive community engagement and communication in many settings without a “gathering”.

Reviewed by: Professor Steve Graham



# MENTAL HEALTH

**Professor Sharon Goldfeld** – Paediatrician, public health physician, Co-Group Leader of Policy and Equity at the MCRI and Director of the Centre for Community Child Health at The Royal Children's Hospital Melbourne

## **Trauma-informed schools following disaster exposure in childhood**

<https://www.ncbi.nlm.nih.gov/pubmed/29945077>

- > To help schools respond to the impact of disasters on children, policies are needed that integrate screening for children in disaster affected areas, including an assessment of children's past exposure to community violence
- > Disaster exposure is linked to post-traumatic stress symptoms (PTSS), and anxiety and depressive symptoms
- > Schools can help reduce the impact of the trauma associated with disasters on children by responding to children's needs and referring when appropriate
- > The authors investigated whether exposure to community violence prior to a disaster contributed to children's vulnerability to developing symptoms of distress after a disaster
- > They found that community violence exposure was associated with an increased in PTSS following Hurricane Katrina

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

## **How did the epidemic in China influence the behaviour of children and the mental health of their parents? (pre-print)**

<https://www.researchsquare.com/article/rs-22686/v1>

- > 30,861 children under the age of 18 and their parents completed a survey during the peak of the epidemic to assess the behaviour of children and the mental health of their parents. Higher scores positively correlated with unhealthier behaviour or indicators of mental ill-health.
- > Children in cities had higher behavioural scores than aged matched children in towns and rural areas. Similarly, parents in cities scored higher than parents in rural areas in physical, emotional and cognitive predictors of mental ill-health.
- > Children 3 years of age or younger had the lowest behavioural score, children 4-6 scored highest, children 7-12 and older scored second highest. Parents with children 3 years of age or younger scored higher in all predictors of mental ill-health.

- > Educational status of the parents positively correlated with higher scores in all predictors of mental ill-health, attributed to a greater awareness of the implications of the epidemic.
- > Parents with a family member working in the medical field also scored higher in all categories.
- > The analysis only provided a snapshot during the peak of the epidemic in China. Follow-up is needed to assess the long-term mental health implications of the epidemic.

Reviewed by: Professor Dave Coghill

# PERINATAL HEALTH

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

## **COVID-19 in a 26-week preterm neonate**

[https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642\(20\)30140-1/fulltext](https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30140-1/fulltext)

- > A female neonate was born by Caesarean section at 26+4 weeks in Brussels and tested positive for COVID-19 on day 5 of life after suspected vertical transmission from the mother
- > The neonate was admitted to the NICU and received NIPPV and surfactant therapy. NICU stay was notable for PDA (treated with ibuprofen) and a pneumothorax (which required drainage), although it is unclear if these are related to the neonate's eventual confirmed COVID-19 diagnosis.
- > The mother felt ill with cough and fever on day 1 after delivery, and so wore a surgical mask when visiting her infant in the NICU. She was discharged on day 5. She was not tested for SARS-CoV-2 until day 6 when she presented to the ER.
- > The mother received the COVID-19 diagnosis via PCR on day 7, at which point the neonate was tested and confirmed positive.
- > The neonate displayed no temperature instability, no signs of parenchymal infiltrates on chest radiographs, nor clinical or biochemical signs of sepsis. Considering her stable condition, no specific therapy was targeted for COVID-19.
- > The case illustrates the need for a high index of suspicion for pregnant women developing fever, and/or respiratory symptoms
- > The authors recommend neonatal cases of SARS-CoV-2 infection should be thoroughly documented, followed, and reported to create a database for neonatal COVID-19.

Reviewed by: Professor Jim Buttery

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

## **Effectiveness of a COVID-19 screening questionnaire for pregnant women at admission to an obstetric unit in Milan**

<https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1002/ijgo.13191>

- > Observational study involving 139 women, of which only 6 patients were suspected of having COVID-19 based on their responses. Suspected cases were isolated, whilst patients with unremarkable responses were managed using current standards.

- > To validate the questionnaire, all women were tested for SARS-CoV-2: 3 returned positive nasopharyngeal tests, 2 of which were in the suspected group.
- > Prevalence of COVID-19 amongst women with unremarkable responses to the questionnaire was 0.8%.
- > Universal screening is important to reliably detect COVID-19, however performing nasopharyngeal swabs for all patients is not feasible for hospitals that have fewer resources and less efficient laboratories. A specific questionnaire is inexpensive however is unlikely to be of sufficient sensitivity or specificity to replace universal screening.
- > Although this may be an alternative approach, it may be less effective in regions with higher rates of positive tests, such as that of New York (15.3% vs. 2.2% in Milan).

Reviewed by: Professor Jim Buttery

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

#### **SARS-CoV-2 Infection of the placenta (pre-print)**

<https://www.medrxiv.org/content/10.1101/2020.04.30.20083907v2>

- > Laboratory analysis was performed on a placental tissue of a COVID-19 patient in the USA who opted for the termination of her pregnancy after developing severe pre-eclampsia and placental disruption in the second trimester at 22 weeks.
- > The patient was admitted after presenting with vaginal bleeding and abdominal pain on a background of worsening COVID-19 symptoms (fever, cough, myalgias, anorexia, nausea and diarrhoea). Her blood pressure was elevated to 150/100 and lab results were consistent with severe preeclampsia and disseminated intravascular coagulation.
- > Histopathological examination of the placenta revealed high levels of SARS-CoV-2 and intervillitis (fibrin deposits and mononuclear cell infiltration of the intervillous spaces). Similar immunopathological findings were observed in lung tissue examined at autopsy from patients with severe COVID-19. This raises the possibility that COVID-19 may have contributed to placental inflammation that ultimately resulted in placental abruption and early-onset pre-eclampsia and worsening maternal disease. PCR and electron microscopy were performed and positive in placental tissue.
- > Mechanism of placental invasion remains unclear. Given that the patient had very high serum titres of anti-SARS-CoV-2 antibodies, a potential mechanism could be antibody dependent transcytosis mediated by the foetal Fc receptor (FcRn), which has been observed for other viruses (CMV, HIV, Zika). The similarity between the SARS-CoV-2 genome sequenced from the placenta of this case to others sequenced from around the world further suggests that no adaptation is required for the virus to invade. Virus was not detected in foetal liver, lung tissues.
- > Conclusion: The study demonstrates SARS-CoV-2 infection of the placenta, which may be responsible for precipitating severe early-onset pre-eclampsia in pregnancy.

Reviewed by: Professor Suzanne M Garland

# THERAPEUTICS

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

**The race is on for antibodies that stop the new coronavirus**  
[doi:10.1126/science.abc6444](https://doi.org/10.1126/science.abc6444)

- > Convalescent plasma therapy has shown promise as treatment in China, prompting research into monoclonal antibodies as a more targeted antibody therapy for COVID-19
- > Research into monoclonal antibodies involves searching for neutralising antibodies; these reduce SARS-CoV-2 infectivity by binding to a viral protein needed to enter human's cells known as the spike protein
- > Many techniques have been used to identify neutralising antibodies some examples include searching human plasma donated from survivors, injecting mice with spike protein to induce antibody production and designing antibodies using software
- > Some firms aim to identify multiple suitable antibodies as an antibody 'cocktail' helps ensure protection against mutant strains of SARS-CoV-2
- > Unfortunately, widespread use of monoclonal antibody treatments are limited by their cost and difficulty to produce.

Reviewed by: Professor Fiona Russell

# TRANSMISSION

Benjamin Watson – 4th year medical student,  
Department of Paediatrics, The University of Melbourne

**Crowding and the epidemic intensity of COVID-19 transmission (pre-print)**  
<https://www.medrxiv.org/content/10.1101/2020.04.15.20064980v1>

- > An analysis of highly-resolved spatial variables for cities in China together with case count data
- > Crowded cities tend to be more prolonged due to high population density and potential for transmission chains to persist
- > Humidity was negatively associated with epidemic intensity, though it did not explain the majority of variation between cities
- > Rurality was also negatively associated with epidemic intensity, but likewise did not explain the majority of variation between cities
- > There is strong empirical evidence for the role of spatial organisation in determining infectious disease dynamics and the limited capacity of cordon sanitaires (guarded quarantine areas) to control local epidemics

Reviewed by: Professor Suzanne M Garland

Isabella Overmars - 2nd Year Master of Public Health Student,  
The University of Melbourne

**Children are not COVID-19 super spreaders: time to go back to school**  
<https://adc.bmj.com/content/early/2020/05/05/archdischild-2020-319474>

- > This is an Opinion piece
- > Key questions that need answering:
  - Are there low rates of confirmed infection in children because children are not becoming infected and/or infectious?
  - Or is COVID-19 in children usually such a benign upper respiratory illness that does not even cause infants or immune-suppressed children to need hospital admission?
  - If children are infected, are they infectious to each other and/or to adults? If so, how long for?
- > It was presumed that children had the capacity to act as silent spreaders of SARS-CoV-2 during the pandemic due to similar attack rates as adults in individual households in China, and school closures were implemented without concrete evidence, to prevent the possibility of serious community transmission.

- > Recent reviews have revealed that children have not been largely contributing to infection, and that SARS-CoV-2 is mainly spread between adults and from adult family members to children.
  - Widespread community testing in Korea and Iceland showed the rates of infection in children to be lower than the 0.8% in the general population, with Iceland finding no children under 10 to be positive for SARS-CoV-2. Similar data is emerging out of Italy and Japan.
  - A collection of international family clusters found that children were not likely to be the index case in households, only being responsible for around 10% of clusters.
  - In New South Wales, Australia, none of 735 students and 128 staff contracted COVID-19 from nine child and nine adult initial school cases despite close contact. Similar data is emerging out of France and the Netherlands.
- > Many questions still remain about the role of children in this pandemic and until there is high-quality sero-surveillance data, these questions will not be able to be answered with certainty.
- > There has been very little evidence so far on the effects of COVID-19 on children with comorbidities, and if they truly are at greater risk. There is concern that a blanket assumption that 'all immune-suppressed children are at increased risk' will cause considerable long-term educational and social harm to these children.
- > Recommendations: Governments worldwide should allow all children back to school regardless of comorbidities. Detailed surveillance will be needed to confirm the safety of this approach, despite the ineffectiveness of school closures in the recent past. The possible link with the rare new Kawasaki-like vasculitis that may or may not be due to SARS-CoV-2 does not change the fact that severe COVID-19 is as rare as many other serious infection syndromes in children that do not cause schools to be closed. Individualised risk assessment and decision-making by clinicians should occur for those considered at exceptional risk (e.g., immediately after bone marrow transplant) or where there are other older family members at significant risk.

Reviewed by: Professor Fiona Russell



# VACCINES

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

## **The race for coronavirus vaccines: a graphical guide**

<https://www.nature.com/articles/d41586-020-01221-y>

- > If you're someone who prefers pictures over words, then this is the article for you.
- > This nature article delves into vaccine development at a fairly basic level, but is extremely accessible and likely to be a useful teaching tool for experts.
- > Graphical descriptions of:
  - The basics of developing immunity to a virus like COVID-19
  - Vaccine types being developed for COVID-19
  - Weakened and inactivated virus vaccines
  - Viral-vector vaccines
  - Nucleic-acid vaccines
  - Protein-based vaccines
  - Industry based vaccine trials

Reviewed by: Professor Terry Nolan

## **Scores of coronavirus vaccines are in competition - how will scientists choose the best?**

<https://www.nature.com/articles/d41586-020-01247-2>

- > This article lays out the initial proposals from the WHO for an adaptive, head-to-head, rolling trial of vaccine candidates.
- > The "Solidarity Vaccine Trial" would continuously enrol participants, adding vaccine candidates as they become suitable and dropping them as they fail to show efficacy. The opportunities and challenges of such a trial are discussed here.
- > Emergency use of vaccine candidates, and challenge trials are also briefly discussed.
- > This is a WHO aspiration for global coordination of the need for multiple candidate evaluations, to both speed up Phase III trials especially, and to minimise the numbers required for control groups.

- > A parallel development was announced last week by the US National Institutes of Health (NIH) which has established the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) partnership. The NIH and the Foundation for the NIH (FNIH) are bringing together more than a dozen leading biopharmaceutical companies, the Health and Human Services Office of the Assistant Secretary for Preparedness and Response, the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration and the European Medicines Agency. See <https://www.nih.gov/news-events/news-releases/nih-launch-public-private-partnership-speed-covid-19-vaccine-treatment-options>

Reviewed by: Professor Terry Nolan

# VIROLOGY

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

## Development and evaluation of a CRISPR-based diagnostic 1 for 2019 novel coronavirus

<https://www.medrxiv.org/content/10.1101/2020.02.22.20025460v2>

- > This study reports the performance of a newly developed isothermal, CRISPR-based assay for SARS-CoV-2 diagnostic, in comparison to the RT-PCR, metagenomics next generation sequencing (mNGS).
- > Main results:
  - Choosing target gene for the new assay: mNGS identified 52/61 suspected cases with COVID-19. The sequences generated from mNGS were used to define the target genes for the identification of COVID-19. Three target genes were identified: two from ORF1ab and one from N gene of SARS-CoV-2.
  - Development of the new isothermal CRISPR-based assay: the newly CRISPR-based assay exploits the polymerase-mediated DNA amplification by recombinase polymerase amplification (RPA) and the CRISPR/Cas-mediated enzymatic signal amplification to increase the sensitivity of the assay. Based on the sensitivity analysis, only one set targeting ORF1ab among three candidate target genes was chosen. This set had 7.5 copies per reaction as its limit of detection.
  - Validation for sensitivity and specificity of the new isothermal CRISPR-based assay: the validations were conducted on serial dilutions of control plasmid and also on clinical samples. The detection performance of the CRISPR-based assay (52/52, 100%) was shown to be superior to the RT-PCR (47/52, 90.4%) and similar to mNGS (52/52, 100%). The turnaround time of the CRISPR-based assay was only 40 minutes while 1.5 hours and 20 hours for RT-PCR and mNGS, respectively. No false positivity found for the CRISPR-based assay when tested on other viruses.
- > Significances: Provide a rapid, high sensitive and specific assay that doesn't require thermocycler machines (a PCR machine).
- > Limitations: It was not clear how the signal from the new isothermal CRISPR-based assay was read and how many samples can be analysed on one analysis. The target ORF1ab gene has been shown to be evolved during the on-going pandemic, hence it's crucial to check if the primers/probes reported here are still matched with the newly evolved viral strains.

## Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2

<https://www.biorxiv.org/content/10.1101/2020.04.29.069054v1>

- > This study reported a three-stage data pipeline analysis (analysis of daily GISAID data, structural modelling of sites of interest, and experimental evaluation) to identify sites of positive selection of Spike protein of SARS-CoV-2. GISAID provides public access to a collection of genetic sequence data of influenza viruses and SARS-CoV-2, related clinical and epidemiological data. The reported analysis was based on 6,346 sequences in the database (April 13th).
- > Main results:
  - The D614G mutation: appeared in early March, 4 of 7 first D614G strains were sampled in Europe, and one each in Mexico, Brazil, and in Wuhan. Lately, the G614 has become globally dominant and shown associated with higher viral load (in clinical data). G614 potentially impacts the antibody response, due to its location on the S protein protomer, between S1 and S2 protomer of S protein (S protein structural).
  - The S943P mutation: potentially impact the transition of S2 unit of the S protein from pre-fusion to post-fusion structure.
  - Other additional sites of S protein: L5F and L8V, V367F, G476S, V483A, H49Y, Y145H/del, Q239K, A831V, D839Y/N/E and P1263L: not clear about the impacts.
- > Significance: A hypothesis could be proposed about the enhanced SARS-CoV-2 fitness of G614 strains. Warning about the importance of monitoring SARS-CoV-2 evolution during the pandemic for antigenic drift and also recombinant events, while Spike protein is the target for vaccine development and many serology diagnostics assays.
- > Limitations: Supportive data (from a subset sequence having all clinical data) was only available for D614G mutation and help to understand the impact of the mutation. Lack of clinical data associated with sequences. At least, age and sex – the two factors are significantly associated with severe disease, should be reported with viral sequences.

# OTHER RESOURCES

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](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\\_z2uWV7r3FaPzAOr86q9ZXBcT\\_Z1QcCE\\_Nw/formResponse](https://docs.google.com/forms/u/0/d/e/1FAIpQLSfOxCoAuLV0aJdf_z2uWV7r3FaPzAOr86q9ZXBcT_Z1QcCE_Nw/formResponse)

Victorian Department of Health and Human Services

<https://www.dhhs.vic.gov.au/coronavirus-covid-19-daily-update>

Australian Government

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

<https://www.health.gov.au/resources/publications/management-and-operational-plan-for-people-with-disability>

COVID-19 and the kidney, which is currently the recommended US resource

<http://www.nephjc.com/covid19>

University of Birmingham COVID-19 Research Briefing

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

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

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

Global summary, identifying changes in the reproduction number, rate of spread, and doubling time during the course of the COVID-19 outbreak whilst accounting for potential biases due to delays in case reporting both nationally and sub-nationally

<https://epiforecasts.io/covid/posts/global/>

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/>

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