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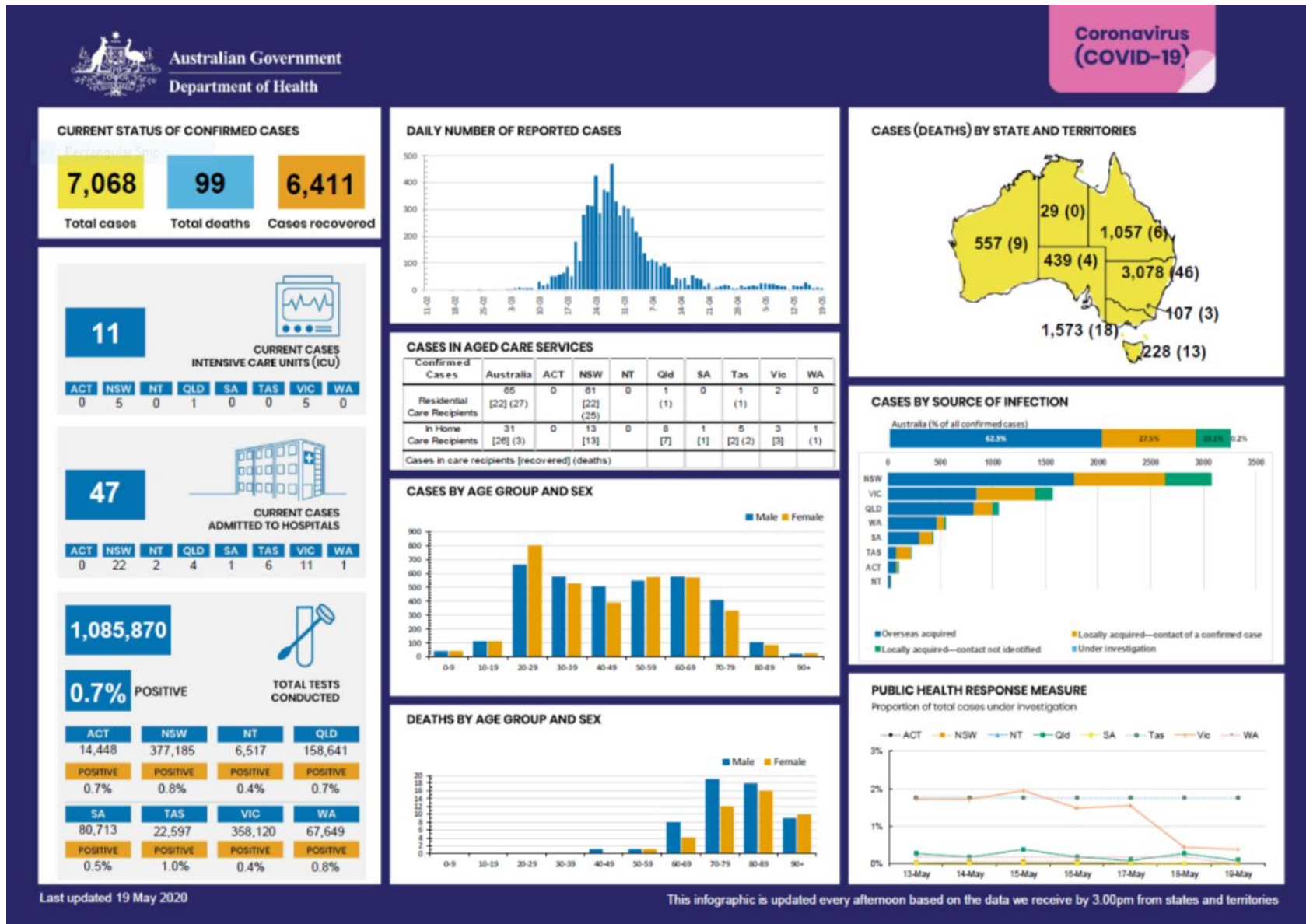murdoch children's research institute

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COVID-19 KIDS EVIDENCE UPDATE

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

Weekly Update No.6
20 May 2020

Source: Australian Government: Department of health [Internet]. 2020 [updated 2020 May 18; cited 2020 May 19]. 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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CLINICAL PAEDIATRICS

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

SARS-CoV-2 testing and outcomes in the first 30 days after the first case of COVID-19 at an Australian children's hospital
https://onlinelibrary.wiley.com/doi/abs/10.1111/1742-6723.13550

The authors described the paediatric patient cohort from the Royal Children's Hospital Emergency Department and Respiratory Infection Clinic.

> Children have comprised a small portion of positive cases, with 1% of all infections <10y and 3% in 10-19y. They typically experience milder disease, lower hospitalisation, ICU admission and mortality.

> 433 patients were tested for SARS-CoV-2 at the Royal Children's Hospital Emergency Department or Respiratory Infection Clinic during the 30 days up to 19th April, 2020.

> These patients met clinical and epidemiological criteria, although 20% of those not meeting epidemiological criteria were also tested to observe community prevalence. All admitted patients eventually received a SARS-CoV-2 swab.

> There were four positive cases detected (0.9%), with none admitted to hospital. All recovered in the community, without requirement for hospitalisation. Their greatest risk factors included overseas travel (3/4) and contact with confirmed cases (4/4). One had a comorbidity (asthma).

> Headache and sore throat were the predominant features of COVID-19 positive patients, with fever only present in 1/4.

> 231/433 were admitted to hospital, none positive for SARS-CoV-2.

> This study is limited by the low number of SARS-CoV-2 positive cases and different testing criteria amongst admitted and discharged patients.

Reviewed by: Dr Wonie Uahwatanasakul

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

An outbreak of severe Kawasaki-like disease at the Italian epicenter of the SARS-CoV-2 epidemic: an observational cohort study
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31103-X/fulltext

> This is a retrospective review of paediatric Kawasaki disease (KD) cases admitted to Hospital Papa Giovanni XXIII (Bergamo, Italy) during the five-year period from January 1, 2015 to April 20, 2020. Definition of classical type and incomplete type of KD cases was based on 2017 American Heart Associations. Kawasaki Disease Shock Syndrome (KDSS) was based on systolic blood pressure and concentrations of troponin I and pro-B-type natriuretic peptide (proBNP). Macrophage activation syndrome (MAS) was defined using the Paediatric Rheumatology International Trials Organisation criteria. KDSS and MAS are markers of severity of KD.

> The review compared the hospital-based incidence and clinical features of KD cases between the two periods: the 5 years-period before the local SARS-CoV-2 epidemic (the pre-epidemic period) and the epidemic period from 18th Feb to 20th April 2020.

> During the epidemic period, 33-fold increased incidence of KD (10 KD cases per month, 10 cases during one month) was observed, versus to the pre-epidemic period (0.3 per month, 19 cases during 5 years). KD cases during the epidemic period were significantly older and showed increased markers of disease severity, including abnormal echocardiogram in 6 of 10 (60%), and fulfilment of clinical criteria for KDSS and biochemical criteria for MAS in 5 of 10 (50%). This is compared with 2 of 19 (10%) and zero of 19 respectively in the pre-epidemic group.

> However, the KD presentation remains a rarity, representing only 3.5% of all paediatric emergency presentations during the epidemic period.

> 8 of the 10 KD cases (80%) presenting during the epidemic showed evidence of current or previous SARS-CoV-2 infection (2 positive nasal RT-PCR, 8 positive serology). One of the two negative cases was tested shortly after treatment with IV Immunoglobin, potentially affecting serology results.

> All patients in the epidemic group responded to aspirin and IV Immunoglobin therapy, with 8 of 10 (80%) fulfilling criteria for adjunct steroid treatment (Kobayashi score≥5).

> The authors report a strong temporal association between the KD outbreak and SARS-CoV-2 epidemic in Bergamo. The findings support the hypothesis that the immune response to SARS-CoV-2 precipitates KD in susceptible patients. The authors maintain that the disease remains rare, estimating incidence of Kawasaki disease at 1 in 1000 children exposed to SARS-CoV-2.

> These cases are likely to be PIMS-TS.

Reviewed by: Dr Lien Anh Ha Do

CLINICAL TRIALS

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

Waste in COVID-19 research
https://www.bmj.com/content/369/bmj.m1847

> Whilst the research response to COVID-19 can be lauded for its speed, collaboration, and open-access nature, it has amplified the systematic issues which lead to wasted research.

> Of the 1087 COVID-19 trials registered at ClinicalTrials.gov, many ask poorly thought out research questions, are badly designed and underpowered, or fail to accurately report their findings.

> Hydroxychloroquine trials highlight these issues: of 145 trials, 32 have a planned sample size of <100, 10 were without a control group, 12 were not randomised, and most were single-center trials. Only one study protocol was provided.

> There is a striking lack of non-pharmaceutical trials. Only two trialed masks, and none examined a range of employed measures to avoid transmission (such as social distancing and hand-hygiene).

> The poor quality of preprints in the COVID-19 academic response is also discussed, especially the way that this leads to inappropriate findings being disseminated by the media whilst robust evidence fails to be widely communicated.

> Excessive study duplication in the COVID-19 response is also highlighted. For example, there were 5 concurrent systematic reviews on face masks for people in the community conducted.

> The article reinforces that whilst an urgent response to the poor standard of COVID-19 research is needed, this pandemic has also shone a spotlight on the systematic issues which result in 85% of research being wasted.

Reviewed by: Professor Fiona Russell

CO-INFECTION

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

Co-infections: potentially lethal and unexplored in COVID-19
https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30009-4/fulltext

> Respiratory viral infections predispose patients to co-infection, thus increasing disease severity and mortality.

> Studies have shown that 50% of patients with COVID-19 who have died had secondary bacterial infections, some with fungal co-infections.

> 71% of admitted patients with COVID-19 received antibiotics.

> Currently, antibiotic use is high (74.5%) among patients with COVID-19 who are admitted to ICU, rendering culture-based microbiological testing less sensitive.

> Diagnosing co-infections is complex. This difficulty is because it can be hospital-acquired (e.g. patients on mechanical ventilation), or carried by patients before the viral infection.

> To accurately diagnose and study co-infection in COVID-19, patients need to be recruited on admission to ICU and sampled longitudinally throughout the disease course.

> Such a study will be valuable to identify the pathogens causing co-infection, antibiotic resistance and inform antibiotic prescribing policy.

Reviewed by: Associate Professor Margie Danchin

DIAGNOSTICS & SAMPLING

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

Real-time tracking of self-reported symptoms to predict potential COVID-19
https://doi.org/10.1038/s41591-020-0916-2

> 2,618,862 participants from the UK and US reported their potential COVID-19 symptoms on a smartphone-based app between 24 March and 21 April 2020.

> The authors used self-reported symptoms and SARS-CoV-2 test results to identify the combination of symptoms most predictive of COVID-19.

> The self-reported symptoms most strongly associated with COVID-19 were: loss of smell and taste, fatigue, persistent cough and loss of appetite.

- They produced a model to predict probable infection using the above symptoms as well as gender and age.

> Interestingly their data showed that loss of smell and taste was the strongest predictor of infection.

- Of 18,401 participants tested for SARS-CoV-2 participants who reported loss of smell and taste was higher in those with a positive test result (4,668 of 7,178 individuals; 65.03%) than in those with a negative test result (2,436 of 11,223 participants; 21.71%).

- Excluding this symptom from their predictive model reduced its sensitivity but increased its specificity.

> This work suggests that loss of sense of smell and taste could be included as part of routine screening for COVID-19.

Reviewed by: Dr Wonie Uahwatanasakul

EMERGENCY MEDICINE

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

Preparedness and response to paediatric COVID-19 in European emergency departments: A survey of the REPEM and PERUKI networks
https://www.annemergmed.com/article/S0196-0644(20)30366-8/pdf

> Retrospective cross-sectional analysis of 102 paediatric centers from 18 countries (across Europe, UK and Ireland) using point-prevalence surveys: aimed to have a representative sample by adjusting the number of centers responding per country based on population, however may still be difficult to generalise results outside of this area.

> Whilst the infection rate of children with COVID-19 was relatively low, the challenge for paediatric centers has been the logistical arrangements of managing potential cases and protecting staff and other patients.

   - Logistical problems that can be changed over the long-term: 34% did not have an ED contingency plan for pandemics and 36% had never had simulations for pandemic response; only 17% of EDs had negative pressure rooms.

   - Logistical problems that required a fast response: wide variation in the recommendation of type of PPE to be used in the ED; 62% of centers experienced a shortage in one or more PPE items (most frequently FFP2/N95 masks).

> 25% of centers reported COVID-19 positive staff.

> The study highlights the need for centers to develop pandemic response plans for any possible future events to ensure that the response is fast, coordinated and safe for all.

Reviewed by: Dr John Cheek

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

The importance of effective communication about COVID-19 for children
https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30097-3/fulltext

> Children are being exposed to high levels of media and social conversations about the COVID-19 pandemic, and big changes to their daily routines, with the adults in their lives experiencing stress and anxiety.

> Children experience heightened anxiety when their caregivers are absent or demonstrate unpredictable behavior; further, adults' worries about the pandemic may also limit their ability to respond sensitively to their children's distress.

> Talking to children about life-threatening illnesses has important benefits for their wellbeing; this communication must be appropriate for their age and developmental stage, and should aim to provide them with information that is accurate and meaningful so they don't feel frightened or blame themselves.

> It is also important for adults to engage in authentic emotion-focused conversations with children, setting an example by sharing some of their feelings, without overwhelming them with their fears; this allows children to understand the emotional state of the adults in their lives, and gives them permission to talk about their own feelings.

> The authors argue for the importance of prioritising communication with children as an essential component of the mental health response to the pandemic.

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

Estimating the burden of SARS-CoV-2 in France
https://science.sciencemag.org/content/early/2020/05/12/science.abc3517.full

A report on the burden of COVID-19 in France with modelling of future burden

> Approach combined reported hospitalisations in France, with estimated mild infections from the Diamond Princess investigation.

> Situation in France, 7th May 2020: 95,210 hospitalisations; 16,386 hospital deaths.

> Key results

  - Overall predicted prevalence consistent with 3% seroprevalence previously estimated among Hauts-de-France blood donors.

  - Hospitalisation: 3.6% - mean age 68y.

  - ICU: 19% of hospitalised after 1.5-day mean delay.

  - Mortality:

    • Rate: 0.7% (18.1% of hospitalised) - 0.001% in >20y; 10.1% in >80y.

> Epidemiology: 70y mean age; 60.3% male.

  - 2 clear subpopulations: Die early after admission (15%; 0.67 days' mean time to death) and die after long period (85%; 13.2 days' mean time to death).

> Males: Increased hospitalisation, intensive care, and mortality rates.

> Lockdown from 17 March 2020:

  - Reduced R_0 from 2.90 to 0.67 (77% reduction).

  - End of March cf. 7 May: Daily ICU admissions 700 -> 66; Hospital admissions 3600 -> 357.

> Estimates for 11 May 2020 (when restrictions scheduled to ease):

  - 3900 daily infections.

  - 2.8 million (1.8-4.7 million) people or 4.4% (1.8-4.7%) of the population to have been infected.

> Concerns:

  - Widespread "silent" transmission in younger individuals.

  - Population immunity appears insufficient to avoid second wave if all control measures released.

  - Not clear if all infected are immune (and for how long), but clearly a long way before herd immunity might be possible.

  - Generalisability of Diamond Princess population to general French population unclear (but various sensitivity analyses were performed).

Reviewed by: Professor Allen Cheng

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

Guiding principles by the Australian Government on how to maintain safe immunisation services during the COVID-19 pandemic
https://www.health.gov.au/sites/default/files/documents/2020/05/atagi-guiding-principles-for-maintaining-immunisation-services-during-covid-19-pandemic.pdf

> Ensuring on-time vaccination according to the current recommended vaccination schedules is essential during the COVID-19 pandemic.

> Delaying or missing scheduled vaccines increases the risk of re-emergence of vaccine preventable diseases and puts a further strain on the healthcare system.

> This is especially important for the influenza vaccine, where reducing diagnostic uncertainty for COVID-19 is important for the individual and to reduce testing.

> To ensure vaccinations continue to be delivered safely, immunisation providers must implement measures to reduce the transmission of COVID-19. The following are guiding principles to achieve this:

  - Implement the full hierarchy of COVID-19 infection prevention and control measures, including physical distancing, according to the national and state/territory guidelines.

  - Consider telecommunications for scheduling appointments, separate staff administering vaccinations, and alternative locations such as outdoor areas for vaccinations ie the car park of general practices for flu vaccine.

  - Use screening questions/procedures to identify all attendees for vaccinations who may have COVID-19. Use of PPE is recommended for vaccinations of individuals who have symptoms or risk factors for COVID-19. Otherwise, standard precautions are sufficient.

  - A safe post-vaccination observation period of 15 minutes still needs to be maintained, where possible.

> If the immunisation service does not have the capacity to safely meet the immunisation needs of its clients, it should:

  - Suggest alternative immunisation providers to facilitate timely vaccination.

  - Prioritise population groups at risk including: newborns, children < 2 years, pregnant women, Aboriginal and Torres Strait Islander people, older individuals ≥65 years, individuals with conditions that increases the risk of vaccine preventable diseases.

Reviewed by: Associate Professor Margie Danchin

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

Estimating excess 1-year mortality associated with the COVID-19 pandemic according to underlying conditions and age: a population-based cohort study
https://w ww.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30854-0/fulltext

> Population-based cohort study from England using linked electronic health records and incorporating individuals aged ≥30 years to estimate the excess COVID-19-associated mortality.

> See the online, publicly available, prototype risk calculator for excess death estimations (concise and visually appealing graphical representation of the results): http://covid19-phenomics.org/PrototypeOurRiskCoV.html

> The study aimed to:

- Provide initial estimates of excess COVID-19-related deaths over a 1-year period based on differing rates (full suppression – 0.001%, partial suppression – 1%, mitigation – 10% and do nothing – 80%) and relative levels of impact of infection (relative risk [RR] of 1.5, 2.0 or 3.0);

- Provide parameters (prevalence and background pre-COVID-19 1-year mortality risk by age and underlying conditions) and interactive tools to assist exploration and modelling of COVID-19 related deaths by research, public health and other groups.

> COVID-19 related mortality was defined as deaths from both direct and indirect effects of the pandemic.

> The study included data for 3,862,012 individuals; 50.7% female, 13.7% >70 years of age and >20% with one or more high risk conditions.

> Do nothing: 146,996 (RR 1.5), 293,991 (RR 2.0) and 587,982 (RR 3.0) excess deaths.

> Initial model estimates – excess COVID-19-related deaths (vs baseline deaths) in 1 year for different scenarios in the UK population:

- Full suppression: two (RR 1.5), four (RR 2.0) and seven (RR 3.0) excess deaths.

- Partial suppression: 1,837 (RR 1.5), 3,675 (RR 2.0) and 7,350 (RR 3.0) excess deaths.

- Mitigation: 18,374 (RR 1.5), 36,749 (RR 2.0) and 73,498 (RR 3.0) excess deaths.

> Estimated deaths were also detailed according to the number of underlying conditions and age categories for each of the different scenarios. This will assist in targeting preventive interventions to groups most at risk of death.

> Limitations: underestimation of deaths may occur using this method as other causes of death eg. road accidents may occur less frequently during lockdown; overestimation may occur as not all deaths that occur are a direct result of COVID-19 (eg. people with heart attacks, strokes etc may be reluctant to come to hospital).

Reviewed by: Dr Claire von Mollendorf and Professor Fiona Russell

GLOBAL HEALTH

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

A wake-up call: COVID-19 and its impact on children's health and wellbeing
https://www.thelancet.com/journals/langlo/article/PIIS2214-109X%2820%2930238-2/fulltext

The author highlights six priority areas to address with regards to global maternal and child health during this pandemic.

> Background

  - Modelling has predicted dramatic rates in maternal and child mortality in low and middle income countries. Most of this is attributed to the disruption of basic health services due to access restrictions, and patient/parent hesitancy to access services during this pandemic.

  - UNICEF aims to prevent transmission of COVID-19, ensure continuity of health services, and strengthen health systems affected.

  - Apart from the virus itself, the primary threats to global child health include childcare and safety, water and sanitation, education, and access. Economic destruction is the primary long-term factor affecting health.

> Call to action

  - Keep children healthy and well-nourished.

  - Prioritise funding for maintaining water, sanitation, and hygiene.

  - Promote continual education.

  - Recognise families as front-line workers.

  - Protect against gender-based violence.

  - Protect refugee and migrant children.

Reviewed by: Professor Fiona Russell

INFECTION CONTROL

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

Screening of health care workers for SARS-CoV-2 highlights the role of asymptomatic carriage in COVID-19 transmission
https://elifesciences.org/articles/58728

> A study involving the screening of health care workers and their symptomatic household contacts for SARS-CoV-2 in a large UK teaching hospital.

> Samples were collected via nasopharyngeal swab and tested by real-time RT-PCR.

> The median age of the health care workers (HCW) was 34 years of age. 71% percent were female; 29% were male.

> The group was stratified into high, medium, low or asymptomatic probability groups based on clinical criteria for estimating pre-test probability of COVID-19

  - It is not made clear in the article how the clinical criteria were developed.

> Furthermore, health care workers were categorised according to the anticipated risk of exposure to COVID-19 in the clinical areas they worked in. It was found that those working in the 'amber' or 'red' wards were significantly more likely to test positive for the virus than those working on 'green' (low risk) wards.

> Of 1032 participants, 31 asymptomatic health care workers (3%) tested positive for SARS-CoV-2 at the time of testing.

> In individuals testing positive for SARS-CoV-2, viral load was significantly lower compared to symptomatic individuals i.e. those tested due to the presence of symptoms.

> Of the health care workers who tested positive for SARS-CoV-2 in the absence of symptoms, 12 had symptoms commencing ≤ 7 days prior to screening and another 12 had symptoms > 7 days prior to screening.

> This study concluded that testing should expand to include asymptomatic health care workers in all areas of the hospital to prevent an increase in the hospital transmission in the setting of reduced community transmission rates.

> The study was limited by the small sample of positive cases, a short timeframe, lack of behavioral data and the absence of detailed workplace and community epidemiological data.

Reviewed by: Associate Professor Margie Danchin

IMMUNOCOMPROMISED / CANCER

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

Updated advice for paediatric oncology and BMT patients during the COVID-19 pandemic
https://anzchog.org/wp-content/uploads/2020/05/Update-Guidance-COVID-19-8th-of-May-2020.pdf

> Evidence summary document targeting parents of paediatric oncology and BMT patients receiving chemotherapy or who have undergone BMT to provide public health recommendations regarding sending their children, and siblings of patients, back to school as schools are reopened.

> The key message is that "If it was medically safe to attend school prior to COVID-19, it is recommended that it is now safe for the majority of paediatric oncology and BMT patients and their siblings to return to school in discussion with the child's individual medical team." This is based on the following:

  - In Australia and New Zealand, there have been few cases of SARS-CoV-2 infection, despite high testing rates indicating that community transmission is low.

  - Younger children appear less likely to transmit the disease than adults or older teenagers. The evidence also shows that transmission of COVID-19 in schools is rare and improved contact tracing and testing capabilities in Australia and New Zealand enables prompt containment and isolation of any potential outbreaks.

  - The evidence to date suggests that paediatric oncology patients infected with SARS-CoV-2 are not at increased risk of developing severe disease. Being neutropenic should not increase the risk of contracting COVID-19 or any other viral illness.

> There is concern that infection with influenza concurrently with COVID-19 infection increases the risk of severe illness, and the flu vaccine is recommended for patients and all family members.

> Increased focus on hand washing and general hygiene will be introduced with schools reopening. Social distancing measures are not considered practical with younger children, however should be encouraged and practiced by older teenagers and amongst adults, all staff and parents inclusive. Masks are not recommended routinely for the protection of paediatric oncology and BMT patients attending school as there is not widespread community transmission in Australia and New Zealand currently, masks are advised in areas with significant community transmission to reduce the spread of COVID-19 from asymptomatic or mildly symptomatic adults in the community.

Reviewed by: Dr Gabrielle Haeusler

IMMUNOLOGY

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

Final Report: post-market validation of three serological assays for COVID-19
https://www.health.gov.au/sites/default/files/documents/2020/05/post-market-validation-of-three-serological-assays-for-covid-19-final-report.pdf

The final report on three serological assays for COVID-19 prepared for the Office of Health Protection and the TGA
https://www.health.gov.au/resources/publications/post-market-validation-of-three-serological-assays-for-covid-19-final-report

> Assays:

  - Lateral flow assays: AKA Serological point of care test (PoCT)

    • Onsite IgM/IgG Rapid Test

    • VivaDiag IgM/IgG Rapid Test

  - Laboratory based enzyme immunoassay: EUROIMMUN EIA

> Gold standard:

  - Molecular testing (RT-PCR) for positives (n=137 samples in 90 patients).

  - Non COVID-19 infections (n=36) and pre-pandemic samples (n=56).

> PoCT:

  - Sensitivity:

    • Onsite IgM/IgG Rapid Test: 56.9% (95% CI 48.6-64.9%) but rising to 84.8 [73.9, 92.5] in patients >20 days after onset of illness.

    • VivaDiag IgM/IgG Rapid Test: 51.8% (95% CI 43.1-60.4%) but 78.8 [67.0, 87.9] in patients >20 days after onset of illness .

  - Specificity:

    • Onsite IgM/IgG Rapid test: 95.6% (95% CI 89.2-98.8%).

    • VivaDiag IgM/IgG Rapid Test: 97.8% (95% CI 92.4-99.7%).

> EUROIMMUN EIA: 208 samples from 167 patients.

  - Sensitivity: 68.1% (95% CI 58.8-76.5%) but IgG 92.7 [82.4, 98.0] in patients >20 days after admission.

  - Specificity: 72.8% (95% CI 58.8%-76.5%) but IgG 97.8 [92.4, 99.7].

> Onsite IgM/IgG Rapid Test and EUROIMMUN EIA returned positive to SARS-CoV-1 serum and negative to MERS-CoV serum (VivaDiag IgM/IgG Rapid Test was not tested).

> Summary:

- Findings suggest performance characteristics below those reported by manufacturer for both PoCT.

- EUROIMMUN EIA: Performance characteristics findings in line with manufacturers updated performance criteria (22nd April 2020).

- Poor sensitivity of serological assays in acute infection, but still significant false negatives at 14 days.

- Findings support PHLN and RCPA statements that serological assays have limited or no role in acute COVID-19 infection diagnosis.

- Specificity of all tests reasonable but positive predictive value would be very high in low prevalence situations, so probably not suitable for serosurveys.

- Other test types are being evaluated.

Reviewed by: Professor Allen Cheng

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

The humoral immune response to SARS-CoV-2
https://www.medrxiv.org/content/10.1101/2020.04.30.20085613v1.full.pdf

> SARS-CoV-2 antibody tires were measured in 1343 individuals with either confirmed or suspected infection.

> Of the 624 individuals with confirmed SARS-CoV-2 infection, 71 (11%) were antibody negative. These were retested along with the weakly positive samples (N=42).

> The greater the number of days between symptom onset and antibody test correlated with higher antibody titers. IgG titers did not decrease with repeat testing.

> In patients with suspected SARS-CoV-2 infection (N=719), only 36% had a positive IgG result. This could mean either not infected, false negative rate of the assay or too early to mount an antibody response.

> In 19% of individuals SARS-CoV-2 could be detected in nasopharyngeal samples two weeks after symptom resolution. It is unclear if virus detected at this stage was infectious.

> Moving forward it is important to understand if IgG produced against SARS-CoV-2 protects individuals from reinfection.

Reviewed by: Associate Professor Paul Licciardi

INFECTION CONTROL

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

Asymptomatic seroconversion of immunoglobulins to SARS-CoV-2 in a paediatric dialysis unit
https://jamanetwork.com/journals/jama/fullarticle/2766215

> This study describes SARS-CoV-2 seroconversion in asymptomatic patients and health care workers in a paediatric dialysis unit at Riley Hospital for Children, Indianapolis, Indiana.

> One week before the study began, a single patient presented for haemodialysis with fever and generalised symptoms, and was found to be positive by RT-PCR test for SARS-CoV-2.

> This patient returned for dialysis on Day 7, 14, and 21 in an isolation room, and was cared for by a range of dialysis nurses, nurse practitioners, and physicians, in addition to the interactions with other children on the paediatric dialysis unit.

> Serial SARS-CoV-2 antibody levels were measured in 13 patients and 25 healthcare workers (HCW) attending and working in the paediatric dialysis units on days 7, 14, and 21. Only 1 patient and 2 HCWs had COVID-19 like symptoms.

> By day 21, 11 of 25 health care workers (45%) and 3 of 13 patients (23%) had SARS-CoV-2 antibodies, indicating a high prevalence of subclinical seroconversion in the unit.

> The one, symptomatic, PCR-positive patient may have been the source of the spread, but other health care environment or community transmission may have contributed.

> The authors feel that the prevalence of subclinical seroconversion in healthcare workers may be higher than would otherwise be expected, and replication in additional sites can help to define the broad applicability of these findings.

Reviewed by: Dr Lien Anh Ha Do

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

Children's mental health during COVID-19 quarantine
https://www.ncbi.nlm.nih.gov/pubmed/32224303

> In China, some children who have been quarantined due to COVID-19 have been separated from their caregivers. This includes children who have been infected with the virus, and those whose caregivers have been infected or died from the disease.

> Separation from caregivers has short- and long-term effects on mental health, including grief, post-traumatic stress, and mood disorders.

> In some cities in China, during the COVID-19 pandemic, children who are in isolation wards or medical observation centers have 24-hour care by nurses, access to nutritionists and psychiatrists, night lights, small gifts, and communication with their caregivers via mobile devices at any time.

> Where caregivers are not able to care for children after their discharge (e.g., due to their own quarantine, or death), local volunteers often act as temporary mothers. However, most of these efforts focus on children's basic daily needs.

> The authors argue for the need for additional training for paediatric healthcare workers to assist with early intervention and referral for mental health problems, and improved access to mental health services.

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

An update on starting ADHD medication during the COVID-19 pandemic
https://www.thelancet.com/action/showPdf?pii=S2352-4642%2820%2930144-9

> Recommendations from the European ADHD Guidelines Group (EAGG) on prescribing psychostimulants and atomoxetine during the pandemic in patients who have not had a face-to-face cardiovascular screen.

> The EAGG deems it appropriate to start treatment if the patient satisfies the following considerations:

 - No concerning or confirmed history of shortness of breath on exertion, palpitations, syncope, cardiovascular disease or hypertension.

 - The patient does not have a family history of sudden death <40 years, suggesting cardiovascular disease.

 - Blood pressure and heart rate are measured by a family member remotely on three separate occasions (with telephonic assistance if required).

> A referral to a cardiologist should be made prior to commencing pharmacological treatment if the first or second considerations are not met.

> If the third consideration is not met, the prescriber should assess the risk of a face-to-face consultation against the risk of withholding treatment.

> A revision to the 2013 EAGG guidelines in the current circumstances is that if the first two conditions are met, cardiac auscultation is not necessary before prescribing.

Reviewed by: Professor David Coghill

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

COVID-19 racism is making kids sick
https://insightplus.mja.com.au/2020/18/covid-19-racism-is-making-kids-sick/

> Children's lives have undergone massive changes due to the pandemic, impacting their mental, social, emotional and physical health in the long term. However, children who also experience racisms are likely to feel these effects to a greater extent.

> Racism experienced by children was an issue before the COVID-19 pandemic began, but has been exacerbated in two main groups, Asian and Aboriginal and Torres Strait Islander populations.

  - In addition to Aboriginal and Torres Strait Islander children experiencing high levels of racism in everyday life, there are concerns in the context of COVID-19 about over-policing and unequal consequences of families in relation to quarantine requirements.

> Experience of racial discrimination have been linked both mental and physical illness in children, some which may be associated with increased risk of severe illness of COVID-19.

  - Second hand racism, that is, children witnessing others' experiences of racism, as well as the flow-on effects of their families and communities experiencing racism, can also harm child mental and physical health.

> Recommendations to address the impacts of racism on child health during COVID-19:

  - Health care professionals working with children and families must be able to discuss the effects of exposure to racism and support children and families.

  - Ensuring all children and families know they are welcome in health care settings.

  - Advocating for community initiatives and collaboration.

  - Position statements on racism and child health from peak representative groups.

  - Address data gaps: collect and report Indigeneity, ethnicity and racism in child health data.

> Racism must be seen as a priority issue for child public health and health inequities research, policy, practice and evaluation. This is even more urgent with COVID-19, but will extend long beyond the current pandemic.

Reviewed by: Professor David Coghill

PERINATAL HEALTH

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

Placental pathology in COVID-19 (Pre-Print)
https://www.medrxiv.org/content/medrxiv/early/2020/05/12/2020.05.08.20093229.full.pdf

> Histopathologic findings in the placentas of women with COVID-19 during pregnancy in US were described.

> Placentas were examined and compared to historical controls and women with placental evaluation for a history of melanoma.

> 16 placentas from patients with SARS-CoV-2 were included (15 with live birth in the 3rd trimester 1 delivered in the 2nd trimester after intrauterine fetal demise).

> Compared to controls, third trimester placentas were significantly more likely to show at least one feature of maternal vascular malperfusion, including abnormal or injured maternal vessels, as well as delayed villous maturation, chorangiosis, and intervillous thrombi.

> Rates of acute and chronic inflammation were not increased.

> The placenta from the patient with intrauterine fetal demise showed villous edema and a retroplacental hematoma.

> COVID-19 placentas showed an increase in maternal vascular malperfusion, a pattern of placental injury reflecting abnormalities in oxygenation associated with adverse perinatal outcomes including preeclampsia, fetal growth restriction, preterm birth, and stillbirth.

> Only one COVID-19 patient was hypertensive despite the association of maternal vascular malperfusion with hypertensive disorders and preeclampsia.

> These changes may reflect a systemic inflammatory or hypercoagulable state.

> Increased antenatal surveillance for women with COVID-19 is needed.

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

Characteristics and outcomes of pregnant women hospitalised with confirmed SARS-CoV-2 infection in the UK: a national cohort study using the UK Obstetric Surveillance System (Pre-Print)
https://www.medrxiv.org/content/10.1101/2020.05.08.20089268v1

> This was a prospective national population-based cohort study using the UK Obstetric Surveillance System (UKOSS). The study was designed in 2012 and hibernated pending a pandemic.

> The study involved all 194 obstetric units.

> During the study period 86,293 births were recorded and 630 women were hospitalised with SARS-CoV-2. Of these, 427 pregnant women were admitted to one of the obstetric units with confirmed SARS-CoV-2 infection between 01/03/20 and 14/04/20. For comparison 694 women who gave birth between 01/11/17 and 31/10/18 (and were enrolled as controls in a previous influenza study) were used as controls.

> Findings:

  - Pregnant women were more likely to be admitted to hospital with COVID-19 if they were:

    • Obese or overweight;

    • Had pre-existing medical comorbidities, particularly diabetes or hypertension;

    • Were from black, South Asian or other ethnic groups.

  - Majority of pregnant women hospitalised with SARS-CoV-2 were in the late second or third trimester – supporting guidelines for continued social distancing measures in later pregnancy. However, the authors noted that they may have missed hospitalisations in early pregnancy.

  - 40 women (9%) required ICU admission, of whom 4 required ECMO. At the time of writing 9 remained in a critical condition. Five women died. This is a higher fatality rate than would be seen in young women, but the numbers are small so no conclusions can be drawn as to whether or not pregnancy increases the risk of death in COVID-19. If it does it is a small increase. The study was not designed to address this question.

  - 5 babies died, 3 of whom were stillborn.

> At the time of writing 100 pregnant women were being hospitalised in the UK each week with COVID-19.

> There was a strong association between admission with infection and black or minority ethnicity which warrants urgent investigation and explanation.

Reviewed by: Professor Kim Mulholland

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

Consider pregnancy in COVID-19 therapeutic drug and vaccine trials
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31029-1/fulltext?utm_content=129361061&utm_medium=social&utm_source=twitter&hss_channel=tw-27013292

> Pregnant women have been systematically excluded from clinical trials for therapeutics and vaccines.

> Many of the drugs being invested are safe and widely used in pregnancy. These drugs include: hydroxychloroquine, lopinavir and ritonavir combination, azithromycin, interferon beta 1-a.

> Without evidence informed by clinical trials, pregnant women may be vulnerable to having limited access to therapeutics. Further, the importance of vaccination during pregnancy, as it confers protection to mother, fetus and baby, warrants the inclusion of pregnant women in vaccine trials.

Reviewed by: Professor Suzanne M Garland

VACCINES

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

SARS-CoV-2 rates in BCG-vaccinated and unvaccinated young adults
https://jamanetwork.com/journals/jama/fullarticle/2766182

> In Israel, BCG was routinely given to all infants born before 1982. After this, only immigrants from high TB prevalence countries received the vaccine.

> COVID-19 testing occurs for all people with symptoms.

> The study aimed to address the potential for the childhood vaccination with BCG vaccine to contribute to the fewer confirmed cases and lower death toll reported in some countries, as the BCG vaccine has been shown to have non-specific benefits protecting against other infectious diseases.

> This study compared COVID-19 positivity in a likely BCG vaccinated population (born between 1979-1981, n=361) and a likely BCG unvaccinated population (born between 1983-1985, n=299).

> There was no statistically significant difference in the proportion of positive nasopharyngeal swabs between the vaccinated and unvaccinated group (11.7% vs 10.4%) or positivity rates per 100,000 (121 vs 100 per 100,000).

> Limitations: Includes populations not born in Israel with unknown immunisation status; low number of severe cases in each population group (1 in each group).

> In conclusion, this study does not support the idea that BCG vaccination in childhood has a protective effect against COVID-19 in adulthood. However, sample size was limited to determine any protective effect of birth BCG against severe disease.

> These findings are consistent with what experts had expected as trained immunity from a birth dose of BCG is unlikely to continue long term due to other environmental exposures.

Reviewed by: Professor Fiona Russell

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

The online competition between pro- and anti-vaccination views
https://www.nature.com/articles/s41586-020-2281-1#Sec1

> Social media companies are struggling to control online health dis- and misinformation, which has also been seen during the COVID-19 pandemic.

> This study provides a map of the contention surrounding vaccines that has emerged from the global pool of around 3 billion Facebook users.

> Although similar in overall size, anti-vaccination clusters manage to become highly entangled with undecided clusters, whereas pro-vaccination clusters are more peripheral.

> Undecided individuals are highly active and have the highest growth of out-links, as opposed to being passively persuaded by either camp.

> Anti-vaccination clusters dominate the main network patch in which they are heavily entangled with a very large presence of undecided clusters (more than 50 million undecided individuals). This means that the pro-vaccination clusters in the smaller network patches may remain ignorant of the main conflict and have the wrong impression that they are winning.

> Anti-vaccination populations provide a larger number of sites for engagement than the pro-vaccination population and thus many anti-vaccination clusters manage to increase their network centrality.

> Additionally, anti-vaccination clusters offer a wide range of potentially attractive narratives that blend topics such as safety concern, conspiracy theories and alternative health and medicine, whereas pro-vaccine narratives are more monothematic.

> Anti-vaccination clusters show the highest growth during outbreaks, by offering negative narratives with regards to vaccinations ie during the measles outbreaks in 2019.

> Strongest growth is in medium sized anti-vaccination clusters, which may go unnoticed by pro-vaccination clusters and thus allow certain narratives to gain significant traction.

> This simulation predicts that anti-vaccination views will dominate in approximately 10 years.

> This complex dynamic between anti, pro and undecided individuals means that traditional mass-action modelling cannot be used reliably for predictions or policies.

Reviewed by: Associate Professor Margie Danchin

VIROLOGY

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

Transmission of SARS-CoV-2 in domestic cats
https://www.nejm.org/doi/full/10.1056/NEJMc2013400?source=nejmtwitter&medium=organic-social

> This correspondence describes an infection and direct transmission of SARS-CoV-2 between domestic cats.

> SARS-CoV-2 was inoculated to three cats and continuously detected in nasal swabs from all three cats until day 5 after inoculations.

> Another three cats with no previous SARS-CoV-2 infections were co-housed in pair with the three infected cats on day 1 of inoculation.

> SARS-CoV-2 was also detected in all the three cohoused cats on 3 or 5 or 6 days later and the viral shedding in these three cats continued for 5 days.

> None of those infected cats showed any symptoms.

> Significance: Cats could be a silent intermediate host of SARS-CoV-2 and play an important role in SARS-CoV-2 transmission.

> CDC US issued a recommendation for cat owners www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/animals.html. opens in new tab).

Multiorgan and renal tropism of SARS-CoV-2
https://www.nejm.org/doi/full/10.1056/NEJMc2011400?query=featured_coronavirus

> This study reports the autopsy results from 27 COVID-19 patients.

> SARS-CoV-2 targeted multiple organs, including the lungs, pharynx, heart, liver, brain, and kidneys.

> The respiratory tract had the highest levels of SARS-CoV-2 copies per cell while the kidneys, liver, heart, brain, and blood had lower levels of virus. Specifically, glomerular cells were found to be a preferential target of the virus.

> The in-silico analysis of publicly available data sets of single-cell RNA sequencing of RNA of genes that are considered to facilitate SARS-CoV-2 infection, showed these RNAs are enriched in multiple kidney-cell types from fetal development through adulthood.

> Significance: SARS-CoV-2 is a systemic virus, targeting multiple organs.

> Limitations: No data on the correlations of SARS-CoV-2 detections in different organs and the onset of illness; no data on the presence of SARS-CoV-2 in salivary gland while increased data support the use of saliva for SARS-CoV-2 detection.

OTHER RESOURCES

Lancet COVID-19 papers
https://www.thelancet.com/coronavirus?utm_campaign=tlcoronavirus20&utm_content=1263835
02&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

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

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- Immunisation service RCH, MD Child and Adolescent Health Program Lead Coordinator, Department of Paediatrics, The University of Melbourne

Dr Lien Anh Ha Do

Postdoctoral Fellow, Infection and Immunity Theme, MCRI

Associate Professor Margie Danchin

General and Immunisation paediatrician, Department of General Medicine, RCH, Group Leader, Vaccine Uptake, MCRI, Clinician Scientist Fellow, Department of Paediatrics and School of Population and Global Health, 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 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

Professor Allen Cheng

Medical Adviser, Melbourne Vaccine Education Centre

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

Dr Gabrielle Haeusler

Paediatrician and Infectious Diseases Physician at Monash Medical Centre and Peter MacCallum Cancer Centre

Associate Professor Paul Licciardi

Team Leader, New Vaccines-Immunology, MCRI

Professor David Coghill

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

Professor Kim Mulholland

Group Leader, New Vaccines, MCRi

Professor Suzanne M Garland

Group Leader, Infection and Immunity, MCRI