THE UNIVERSITY OF MELBOURNE

Melbourne Medical School
Department of Paediatrics

Melbourne Children's
A world leader in child and adolescent health

The Royal Children's Hospital Melbourne

murdoch children's research institute

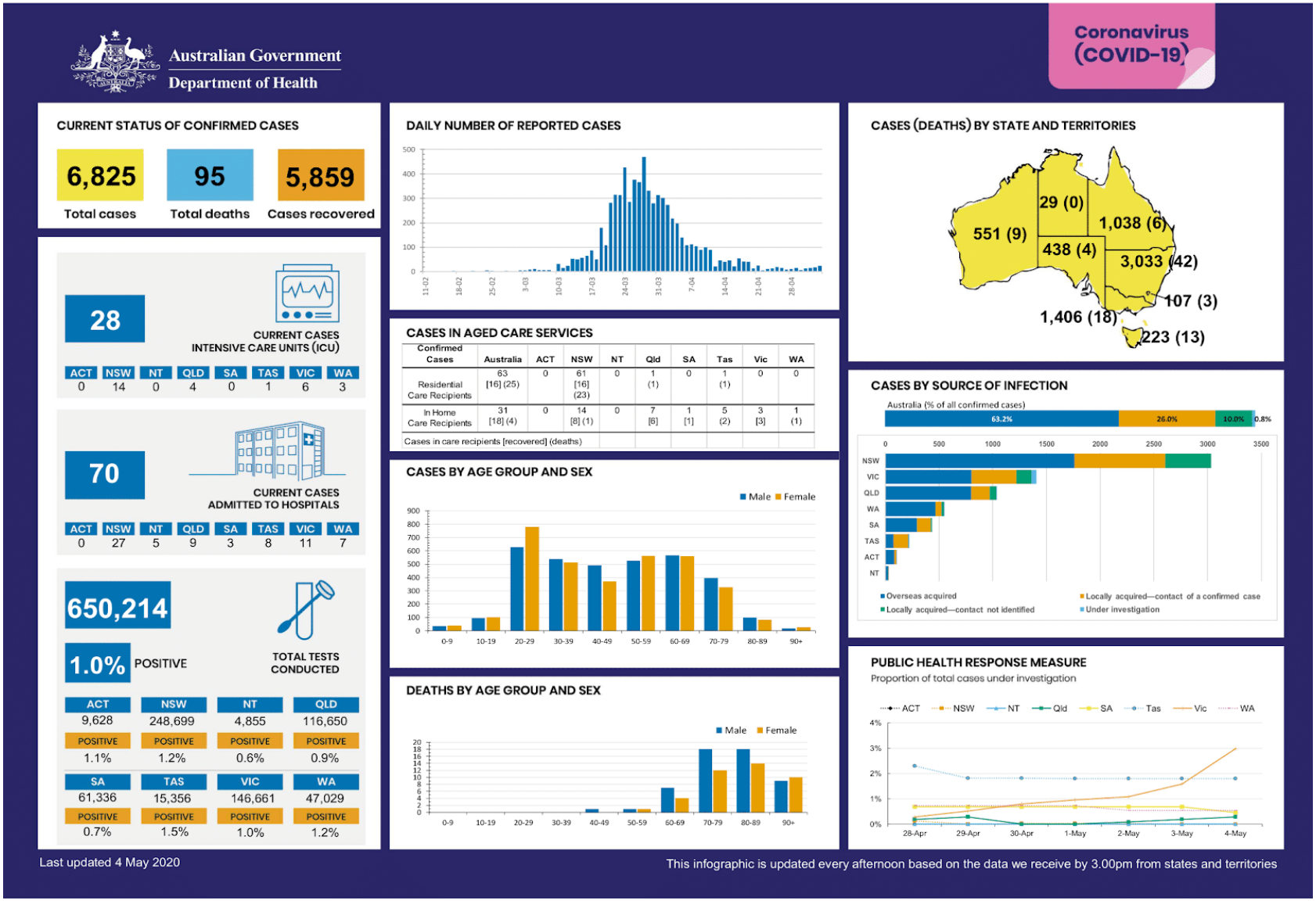
THE UNIVERSITY OF MELBOURNE

Supported by The Royal Children's Hospital Foundation

COVID19 KIDS EVIDENCE UPDATE

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

Weekly Update No.4
6 May 2020



Source: Australian Government: Department of health [Internet]. 2020 [updated 2020 May 4; cited 2020 May 5]. 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

CONTENTS

ADULT MEDICINE

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

Large-vessel stroke as a presenting feature of COVID-19 in the young
https://www.nejm.org/doi/full/10.1056/NEJMc2009787

- Case report describing 5 patients <50 years (age range 33-49 years) in New York over a two-week period who had concurrent severe SARS-CoV-2 infection and large-vessel ischaemic stroke
- 1 patient had a history of stroke, 2 other patients had risk factors for stroke
- A retrospective study from China looking at hospitalised patients with COVID-19 reported the incidence of stroke as 5%
- Large-vessel stroke was reported in association with the 2004 SARS-CoV-1 outbreak in Singapore
- Coagulopathy and vascular endothelial dysfunction are possible complications of COVID-19 and could explain an increased risk of stroke in these patients, but further research is needed

Reviewed by: Professor Fiona Russell

CLINICAL PAEDIATRICS

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

Coronavirus and Kawasaki disease in children: it's an intriguing but unproven link
https://theconversation.com/coronavirus-and-kawasaki-disease-in-children-its-an-intriguing-but-unproven-link-137415

An article in The Conversation discussing the possible link between COVID-19 and Kawasaki disease

- Cases reported from the United Kingdom and other European countries
- Small but increasing numbers of cases
- Clinical presentation:
  - Multi-system inflammatory states
  - Features of Kawasaki disease and toxic shock syndrome (TSS)
  - Both COVID-19 positive and negative
  - Many older than typical of Kawasaki disease
- Kawasaki shock syndrome can resemble severe infection or TSS
- New Haven coronavirus (HCoV-NH) isolated from 8 of 11 children with Kawasaki disease in 2005 by Yale University: Unable to replicate results in other groups of children with Kawasaki disease
- Possible pathophysiology:
  - COVID-19 triggering Kawasaki disease -> Kawasaki shock syndrome
  - Bacterial superinfection in COVID-19 patients -> TSS
- Summary: Possible link between COVID-19 and Kawasaki disease or Kawasaki shock syndrome but this needs to be explored in further research

Reviewed by: Associate Professor Margie Danchin

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

Chilblain-like lesions on feet and hand may be associated with COVID-19 (commentary)
https://onlinelibrary.wiley.com/doi/10.1111/ijd.14937

- Skin lesions may be a late manifestation of COVID-19.
- A series of 6 patients were reported, of which 2 had PCR confirmed COVID-19 and one was a symptomatic close contact of a case.
- Characteristics of the lesions: initially reddish and papular resembling chilblains. Next, in the span of about 1 week, they become more purpuric and flattened. Finally, they seem to resolve by themselves without requiring any treatment. Classic location: toes, soles, fingers, extremities and/or heels.
- These lesions were mainly reported in children (median 13 years) and young adults (median 31 years).
- The majority of patients did not present with coronavirus symptoms. Most of those who were symptomatic had mild symptoms (ex. Low grade fever or congestion) occurring weeks prior to the appearance of the skin lesions.
- Similar lesions have been reported in the media ("COVID toes"). However, the association between these lesions and COVID-19 is hypothetical and needs confirmation.
- If confirmed, this would support the hypothesis that COVID-19 may be associated with a vasculitis.

Reviewed by: Professor Allen Cheng

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

Management of infantile hemangiomas during the COVID-19 pandemic
https://onlinelibrary.wiley.com/doi/10.1111/pde.14196

- Infantile haemangiomas can require urgent evaluation and risk stratification to determine which infants need treatment with beta blockers to prevent medical complications and disfigurement.
- In the setting of COVID-19, these clinicians present recommendations for providing assessment, initiating treatment, beta blocker dosage change, and continued monitoring via telemedicine.
- Key inclusion and exclusion criteria were developed for the use of telemedicine in clinical decision making around the use of beta-blockers,
  - A new referral for infantile haemangioma results in a virtual visit or teletriage to risk-stratify assessment,
  - These are either managed expectantly - which may require reassurance or virtual follow up - or they may be problematic with a high risk of needing treatment.

- For those needing treatment, risk stratification into high-risk and low risk groups was considered helpful.
- For low-risk populations, initiation via telemedicine was appropriate.
- For high-risk populations, in-person visits were thought to be better, not only for propranolol initiation, but also to discuss management, risk of extra-cutaneous disease, and to arrange for imaging studies if needed.

> There was consensus that in settings where there are no disruptions of ambulatory care delivery, in-person evaluation for new patients remains the best approach.

Reviewed by: Associate Professor Margie Danchin

EPIDEMIOLOGY & PUBLIC HEALTH

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

Early analysis of the Australian COVID-19 epidemic (pre-print)
https://www.medrxiv.org/content/10.1101/2020.04.25.20080127v1.full.pdf+html

- As of 18 April 2020, there were 6,533 confirmed cases of COVID-19 in Australia., with 67 deaths
- The daily count of new confirmed cases is declining, suggesting that the COVID-19 actions of the public and government authorities were sufficiently early and assiduous to avert a public health crisis — for now.
- Analysing factors, such as the intensity and timing of public health interventions, that contribute to experiences of COVID-19 will assist in the next stage of response planning
- Using data from the Australian national COVID-19 database, the epidemic and public health responses are described up to 13 April 2020.
- It was estimated that the effective reproduction number was probably < 1 (the threshold value for control) in each State since mid-March and forecasted that hospital ward and intensive care unit occupancy will remain below capacity thresholds over the next two weeks
- Australia's strategy of early, targeted management of the risk of importation, case targeted interventions, and social distancing measures applied prior to the onset of detected widespread community transmission has substantially mitigated the first wave of COVID-19
- More detailed analyses needed to assess the relative impact of specific response measures, and this information will be crucial for the next phase of response planning
- "There are difficult decisions ahead for governments, and for now Australia is one of the few countries fortunate enough to be able to plan the next steps from a position of relative calm as opposed to crisis."

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

Coronavirus disease outbreak in call center, South Korea.
https://wwwnc.cdc.gov/eid/article/26/8/20-1274_article

The authors present the epidemiology of an outbreak in Seoul and its containment efforts.

> Extensive testing of all employees, residents and visitors of a building (total 1143) revealed 97 positive cases (8.5% of all tests), 94 of whom worked on the same floor; 43.5% of this floor was infected. 4 cases were asymptomatic across the 14 days.

> The building was closed, all positive cases were isolated and negative cases were quarantined for 14 days. Extensive contact tracing tested 225 household contacts and requested another 16,628 visitors of this building to present for screening.

> Containment mostly to one floor despite interaction across floors suggests that transmission correlates with the duration of contact.

> This large-scale screening of all close contacts has allowed identification of all cases and further contact tracing to disrupt chains of transmission.

> This reinforces the epidemiology of COVID-19 as being a disease transmitted in crowded, indoor settings with prolonged contact.

Reviewed by: Professor Allen Cheng

Australia's national COVID-19 primary care response
https://www.mja.com.au/journal/2020/australias-national-covid-19-primary-care-response

The authors summarise the primary care framework which is key in protecting at risk groups of Australians.

> Our existing primary care workforce reiterates the need for provision of regular acute and chronic disease and mental health management within this new COVID-19 world order, as well as a single trusted source of information during this state of flux.

> The Primary Care Response (PCR) was defined following lessons learnt from failed responses in previous pandemics. The primary objectives were:

- Protection of vulnerable populations;
- Preservation of functional capacity of the healthcare system for both COVID-19 and non-COVID-19 matters;
- Management of those with symptoms of COVID-19;
- Managing PPE access in primary care and supporting workforce wellbeing.

> Several key projects were rolled out to achieve these objectives:

- Telehealth: Heavily funded under the Medicare Benefits Schedule, telehealth has now delivered 4.3 million primary care, antenatal care, and mental health consultation services to Australians.

> Respiratory Clinics: Network of GP-headed exclusive clinics for patients with fever and respiratory symptoms to redirect potential COVID-19 infections to specific centres and ensure other patients can receive routine care at their GP practices.

- Public Information: A national call centre service providing health advice for those with respiratory symptoms and fever has seen a peak of 37,000 interactions per week during mid-March. A more recent online COVID-19 symptom checker has also been used by up to 370,000 people per day since the end of March.

- HCP Information: Several online modules have been designed to educate Health Care Professionals about basic infection prevention and control. This has engaged half a million healthcare workers to date. There are also various online sources with up-to-date information, including Government-released Fact Sheets with recommendations.

- Protection of remote Indigenous communities: Early travel bans to remote communities have been enacted as an attempt to protect these areas from COVID-19. A National Aboriginal and Torres Strait Islander Advisory Group was also created to represent Indigenous health interests.

Reviewed by: Dr Claire von Mollendorf

GLOBAL HEALTH

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

Why a campaign to champion all vaccines matters now more than ever
https://theconversation.com/why-a-campaign-to-champion-all-vaccines-matters-now-more-than-ever-137502

> The current COVID-19 pandemic reminds us of what a world without vaccines would look like, therefore, while in search of a COVID-19 vaccine, this article stresses the need to continue existing research and development of other vaccines for diseases such as HIV and malaria.

> The response to the global pandemic threatens the success of existing vaccination programs, including steps towards polio eradication. Therefore, existing vaccines need to be continually delivered to all who need them, to prevent future outbreaks of vaccine-preventable diseases, especially in low-income settings.

> The WHO estimated that around 20 million children globally remained unvaccinated or under-vaccinated in 2018, emphasising that limited access to services was already an issue in some regions, before the COVID-19 pandemic began.

- Staff and supplies are being redirected to attend to COVID-19, leaving limited resources available to continue routine immunisation services.
- In addition, it is becoming increasingly difficult for parents and families to access care, due to uncertainty of service delivery, workplace closures and reduced transport options globally.

> If vaccine rates decline, there is likely to be an increase in deaths due to vaccine preventable diseases such as bacterial meningitis and pneumonia, measles and rotavirus diarrhoea. Hence, it is crucial that health workers and parents work to maintain routine vaccinations during this time to continue to save millions of children's lives.

Reviewed by: Professor Fiona Russell

IMMUNOCOMPROMISED / CANCER

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

COVID-19 in solid organ transplant recipients: initial report from the US epicenter
https://onlinelibrary.wiley.com/doi/epdf/10.1111/ajt.15941

Report of clinical characteristics of 90 solid-organ transplant patients with COVID-19 over a 3-week period.

- Impact of chronic immunosuppression on outcomes of COVID-19 is unknown.
- Patients in this cohort had a mean age of 57. Most were infected via community transmission. Of 90 patients, 68 patients were hospitalised.
- Most common presenting symptoms were: fever, cough, and dyspnoea. No significant difference between severity of disease and type of organ transplant.
- Treatment included hydroxychloroquine (91%), azithromycin (66%), remdesivir (3%), tocilizumab (21%), and bolus steroids (24%).
- After three weeks 16 patients died and 37 patients were discharged.
- When compared to hospitalised non-transplant patients with COVID-19 in international cohorts, this cohort had higher rates of severe disease (39% vs 6.1%) and mortality (24% vs 1.4-4.3%).
- It is difficult to interpret data on outcomes, as there is likely to be under-ascertainment of mild/asymptomatic cases due to testing limitations. This report is a small heterogeneous cohort of different organ transplant types and treatment strategies.
- An open question is the management of immunosuppression in this patient group - while some immune function may be desirable to achieve viral control, modulation of the immune response has been proposed as a potential treatment, and there is the obvious risk of organ rejection.

Reviewed by: Professor Allen Cheng

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

COVID-19 in solid organ transplant recipients: a single-center case series from Spain.
https://www.ncbi.nlm.nih.gov/pubmed/32301155

Experiences of managing 18 adult solid organ transplant (SOT) recipients diagnosed with COVID-19 in Madrid.

- Demographics. The median age was 71 years (range: 38-80 years) with a median interval of 9.3 years since transplantation (range: 2-30 years). Patients in this cohort had received kidney (44%), liver (33%) or heart (22%) transplantation.
- Presentation. Most patients presented with fever (83%) and radiographic abnormalities on chest X-ray (72%).
- Therapeutics. The most common therapy was lopinavir/ritonavir (LPV/r) and hydroxychloroquine (HCQ) co-therapy (44%), followed by HCQ monotherapy (28%). Most patients (56%) underwent transitory discontinuation or dose reduction of their calcineurin inhibitor. LPV/r therapy seemed to precipitate tacrolimus-induced nephrotoxicity in one patient.
- Outcomes. At the time of writing, 5/18 (28%) patients had died, 4/18 (22%) experienced ongoing progressive respiratory failure, 1/18 (6%) was stable in hospital, and 8/18 (44%) had been discharged. No patients developed acute graft rejection. Compared with the general Spanish population, SOT recipients have higher rates of pneumonia (72.2% versus 31.1%), ARDS (38.9% versus 5.6%) and ICU admission (11.1% versus 5.1%).
- Limitations. Small sample size, mixed transplant population, and short follow-up period (median of 18 days).

Reviewed by: Professor Michael Sullivan

IMMUNOLOGY

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

Antibodies in infants born to mothers with COVID-19 pneumonia
https://jamanetwork.com/journals/jama/fullarticle/2763854

Clinical records and laboratory results were reviewed for six pregnant women with confirmed COVID-19

- All mothers had clinical manifestations of infection and underwent Cesarean deliveries in their third trimester in negative pressure isolation rooms
- All 6/6 infants returned negative results with neonatal throat swab and RT-PCR
- All 6/6 infants had detectable antibodies in their serum
  - 2/6 infants had IgG and IgM concentrations higher than normal levels
  - The mothers of these 2/6 infants also had elevated levels of IgG and IgM
- Inflammatory cytokine IL-6 was markedly increased in all infants
- Issues include antibody kit used not formally evaluated despite manufacturer's recommendations, also unknown if the virus had crossed the placenta to induce IgM or just antibody.

Reviewed by: Associate Professor Paul Licciardi

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

Trained immunity could be a tool for reducing susceptibility and severity of SARS-CoV-2 infection
https://www.cell.com/cell/fulltext/S0092-8674(20)30507-9?rss=yes

- The innate immune system plays an important role in the pathophysiology of COVID-19: it triggers host defence mechanisms necessary for viral elimination but may also contribute to hyperinflammation and tissue damage responsible for causing severe disease in some patients.
- Elderly and individuals with co-morbidities are at an increased susceptibility to severe SARS-CoV-2 infection, potentially due to a defect in innate immune responses.
- Live vaccines (BCG, oral polio, measles) can induce epigenetic, transcriptional, and functional reprogramming of innate immune cells, leading to improved antiviral host responses. This is called 'trained immunity' and could be explored as a potential tool for reducing susceptibility and severity to SARS-CoV-2.

> This mechanism of inducing trained immunity will only provide partial protection for a limited period of time. Yet, it can contribute to reducing the rapid spread of infection while a specific vaccine against SARS-CoV-2 is being developed.

Reviewed by: Dr Wonie Uahwatanasakul

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

What role do neutrophil extracellular traps (NETs) play in COVID-19 pathophysiology?
https://df6sxcketz7bb.cloudfront.net/manuscripts/138000/138999/cache/138999.1-20200430160226-covered-253bed37ca4c1ab43d105aefdf7b5536.pdf

Role of NETs in severity of COVID-19 was evaluated on sera of 50 hospitalised patients and 30 healthy control individuals

> Significantly elevated levels of cell-free DNA, myeloperoxidase (MPO)-DNA complexes (MPO-DNA), and citrullinated histone 3 (Cit-H3) - the latter two are specific markers of NETs in sera of COVID-19, compared in sera of healthy control

> In a subset of COVID-19 patients (n=22) with longitudinal sera samples, increased NETs markers significantly associated with increased oxygenation intervention

> Cell-free DNA positively correlated with clinical biomarkers observed in severe COVID-19 (C-reactive protein, D-dimer, LDH, absolute neutrophil count), while MPO-DNA only correlated with neutrophil count and Cit-H3 correlated with platelet count

> Hydroxychloroquine did not show any effect on NETs markers

> Cell-free DNA and MPO-DNA significantly higher in patients requiring mechanical ventilation versus in patients breathing room air

> Sera from COVID-19 patients triggered NETosis from control neutrophils in vitro.

> Authors concluded it was unclear if NETs remnants were drivers of COVID-19 disease severity or a consequence of inflammation.

Reviewed by: Dr Lien Anh Ha Do

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

What is the important role of serology for COVID-19 control?
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30322-4/fulltext

Background:

> Coronavirus is still growing at an alarming rate. Currently there are just under 2 million cases of reported cases.

> Singapore and Taiwan have been successful in slowing down the epidemic growth using broad testing strategies to identify and contain cases

Summary of findings:

> In early 2020, the missing link between three clusters of COVID-19 in Singapore was successfully identified using serological analysis - an individual who had twice tested negative for RT-PCR.

> This highlights the success of serology testing in contrast to the failing of RT-PCR as a sole diagnostic method in surveillance.

  - RT-PCR fails to detect past infection, whilst with the added value of serological testing, it can capture both the timeframe after disease onset, including both active and past infections. (NB. Serology testing test for prior exposure and cannot determine active/infectious nature of the patient). Main issue is validation of appropriate methods and understanding the duration of immunity.

  - In public health practice, serological testing is helpful in contact tracing due to its sensitivity to timing, particularly in highly dense populations.

> Also, serological data can also be used to set control policies.

  - assess how much community transmission has occurred (including subclinical and past infection) and its burden

  - strategically deploy immune health-workers to reduce exposure risk of susceptible people

  - assess the effect of non-pharmaceutical interventions, thus informing policy changes

  - identify individuals who have a strong immune response, whose antibody isolates can be used for plasma therapy as treatment.

> This is a comment on another article so this should also be consulted for details on the methods and study design.

Reviewed by: Associate Professor Paul Licciardi

INDIGENOUS HEALTH

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

First Nations people leading the way in COVID-19 pandemic planning, response and management
https://www.mja.com.au/journal/2020/first-nations-people-leading-way-covid-19-pandemic-planning-response-and-management

- Aboriginal and Torres Strait Islander peoples of Australia were disproportionately impacted by the 2009 H1N1 pandemic. The number of interrelated factors which led to this are discussed in this article, including the omission of First Nations peoples from the 2009 National Action Plan for Human Influenza Pandemic.
- Interventions to prevent the spread of COVID-19 severely impact the cultural life of many First Nations people, and are particularly difficult to achieve in communities where overcrowded housing is a prominent issue.
- The Australian Government Department of Health convened an Aboriginal and Torres Strait Islander Advisory group to lead, and provide advice on the preparation and response to COVID-19 - discussed in detail in the previous issue of this research update.
- The Advisory Group has led, or been involved in a number of initiatives to this end. These include:
    - Legislative changes and the development of national guidelines
    - Health service planning and rapid testing capacity building
    - Infrastructure and workforce planning
    - Health promotion, epidemiological tracking, infectious disease modelling and advocacy across all levels of government
- The model discussed in this article, which privileges First Nations voices and results in culturally informed strategies to reduce inequities, could be replicated in future crises.

Reviewed by: Professor Fiona Russell

MENTAL HEALTH

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

What is the ADHD management guidance during COVID-19 pandemic? From European ADHD Guidelines Group
https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30110-3/fulltext

Background:

> Individuals with ADHD are particularly vulnerable to the restrictions and physical distancing measures imposed due to the pandemic, and might display increased behavioural problems.

Key messages:

> Service provision should continue via telephone or appropriate online video technology.
  - However, routine cardiovascular check-up, especially ADHD patients without risk factors can often be postponed. Monitoring using blood pressure machines is recommended for those with potential risk factors and encouraging patients to contact their health provider if concerns arise.

> Schools and teachers should monitor students with ADHD during distance learning, especially adolescents, because of their disorganisation and increased level of risks (e.g. monitor their attendance to online classes, tasks submission, concerns about social or emotional well-being).

> For families, behavioural parenting strategies can improve parenting, reducing oppositional defiant and disruptive behaviour, which is common in ADHD. These training can now be achieved via certified online courses.

> Neuro-feedback or cognitive training should be encouraged to continue.

> Individuals with ADHD, if clinically appropriate, should start pharmacological treatment after initial assessment or continue on medications if already started.
  - Parents or adults with ADHD should avoid increasing doses (beyond prescriptions) to manage crisis or stress related to confinement.
  - This reduces ADHD-related risk thus better compliance with requirements for physical distancing.
  - No strong rationale to introduce weekend drug holidays during the current crisis.

> Sleep-onset delay can be more prevalent (in addition to side effects from psycho-stimulant treatment) due to stress, late-morning waking and disruption of daily routines. Appropriate sleep hygiene or increasing the doses of melatonin beyond therapeutic range (5-6 mg nocte per night) can be implemented.

Reviewed by: Professor David Coghill

THERAPEUTICS

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

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31022-9/fulltext

Randomised, double-blind, placebo-controlled, multicentre trial in ten hospitals in Wuhan, Hubei, China.

> Participants: Hospitalised patients aged ≥ 18 years with severe COVID-19 (laboratory confirmed SARS-CoV-2, enrolled within 12 days of symptom onset, oxygen saturation ≤ 94% in room air or PaO2/FiO2 ≤ 300 mm Hg, and radiologically confirmed pneumonia).

> Intervention: Randomised in 2:1 ratio to intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions) vs placebo. Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids.

> Primary endpoint: Time to clinical improvement up to 28 days.

> Allowed for interim statistical testing (though never performed) that would stop the trial early if remdesivir was deleterious or likely to be ineffective.

> Main results - Total 237 randomised. Intention-to-treat analysis of 236 (158 remdesivir group vs. 78 placebo group):

- Time to clinical improvement in the remdesivir group was not significantly different to that of the placebo group (median 21·0 days vs 23·0 days; HR 1·23 [95% CI 0·87–1·75]).
- Weak evidence that those receiving remdesivir within 10 days of symptom onset had a numerically faster time to clinical improvement than those receiving placebo within the same time frame (median 18·0 days vs 23·0 days; HR 1·52 [0·95–2·43]).
- Mortality was 14% (remdesivir) vs 13% (placebo), difference 1.1% (−8.1 to 10.3)
- There were no differences in viral load in upper or lower respiratory tract samples

> Major limitation: Insufficient power (58%) to detect assumed differences in clinical outcome. This is because of the early termination of the study before attaining the prespecified sample size due to the control of the outbreak in Wuhan.

Summary: This intravenous dose regimen of remdesivir was not associated with statistically significant clinical benefits in adults with severe COVID-19 compared with placebo. However, there was an observed reduction in time to clinical improvement in those treated earlier. This will require confirmation in larger studies.

Reviewed by: Professor Allen Cheng

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

Concentration-dependent mortality of chloroquine in overdose
https://www.medrxiv.org/content/10.1101/2020.04.24.20078303v1 (pre-print)

- High concentrations of chloroquine/hydroxychloroquine can potentially result in lethal cardiovascular and nervous system toxicity.
- This study used data collected from the national clinical toxicology unit in Paris of self-poisonings with hydroxychloroquine as well as data extracted from 12 case reports of chloroquine poisoning.
- Pharmacokinetic-pharmacodynamic modelling was used to predict likely exposures and risk of toxicity for chloroquine dosing regimens that are being evaluated for COVID-19.
- The probability of death was modelled as a function of the log whole blood peak chloroquine concentration. This was used to determine the risk of mortality for 5 potential chloroquine COVID-19 adult treatment dosing regimens.
    - Whole blood peak chloroquine concentration of 13 umol/L (95% CI, 10-16) associated with 1% mortality. Peak concentrations >20 umol/L associated with >5% mortality.
    - Doses of 600 mg twice daily for 10 days (used in the CloroCOVID-19 trial) predicted to result in absolute mean fatality ratio between 0.06% and 4.8%. The other four proposed dosing regimens predicted to have a <1% probability of death for an adult weighing 70 kg.
    - Reduced doses should be given to those in the lower end of the adult weight spectrum.
- Toxicity of treatment must be weighed against the severity of COVID-19.
- Limitations: retrospective dataset from self-poisonings (risk of polypharmacy).

Reviewed by: Dr Amanda Gwee

TRANSMISSION

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

The natural history and transmission potential of asymptomatic SARS-CoV-2 infection (not peer-reviewed)
https://www.medrxiv.org/content/10.1101/2020.04.27.20082347v1

> Prospective study of 30 individuals (mean age 29 yrs) testing positive for SARS-CoV-2, of which 13 never developed symptoms and 17 were symptomatic with mild infection, conducted at Cu Chi Hospital quarantine centre outside Ho Chi Minh City, Vietnam.

> Main findings:

- Asymptomatic participants were less likely to have detectable SARS-CoV-2 in nasopharyngeal throat swabs collected at enrolment (8/13 vs 17/17 participants)
- Asymptomatic participants had a faster viral clearance than symptomatic participants via RT-PCR analysis, with the difference most pronounced in the first week of follow-up
- Asymptomatic individuals can still transmit disease, with two asymptomatic individuals appearing through contact tracing to be the "likely" source of infection for two cases, and the "possible" source for another four infections.

> Limitations: very small sample size

Reviewed by: Professor Steve Graham

VACCINES

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

Audio Interview: approaches to COVID-19 vaccines and antivirals
https://www.nejm.org/doi/full/10.1056/NEJMe2012889?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed

> Prefer to listen than read?

> Go here for an insightful discussion between the editors of the New England Journal of Medicine around the path to an effective COVID-19 vaccine and strategies available for the development of therapeutic agents. (length 20 mins)

Reviewed by: Dr Wonie Uahwatanasakul

The COVID-19 vaccine: how do we immunize 7 billion people
https://newatlas.com/health-wellbeing/covid19-coronavirus-vaccine-how-to-immunize-world-seven-billion-people/?amp=true&__twitter_impression=true

> Vaccine development is only one part of the exit strategy to COVID-19. Here, Professor Kim Mulholland discusses the complexity around mass distribution of a successful COVID-19 vaccine.

> In this unprecedented time, there is scope to accelerate registration of a safe and effective vaccine whilst concurrent clinical trials expand beyond the initial target demographics.

> There is justifiable immense concern that rich nations will buy-up vaccine supply, restricting access to this essential resource for those who cannot afford it.

> Fortunately, many vaccine candidates share a hypothesized mechanism of action and thus, it is likely that multiple candidates will be successful. This would help to mitigate supply issues.

> Global collaboration and funding will be needed to shore up the supply of a COVID-19 vaccine for poorer nations. The ACT Accelerator is one example of a novel initiative working to this end.

> Professor Mulholland emphasises the importance of global bodies such as the WHO being well-funded to be prepared for, and to respond to crises such as these.

> Vaccine acceptance for a new COVID-19 vaccine will also need to be addressed and prepared for

Reviewed by: Associate Professor Margie Danchin

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

Considering BCG vaccination to reduce the impact of COVID-19
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31025-4/fulltext

- RCTs are underway in the Netherlands and Australia (BRACE trial) to assess whether BCG-Danish reduces incidence and severity of COVID-19 in healthcare workers
- Rationale
  - RCTs have provided evidence to suggest that the BCG vaccine's immunomodulatory properties can protect against respiratory infections
  - SARS-CoV-2 virus is a single stranded positive-sense RNA virus and the BCG vaccine has shown to reduce the severity of other viruses with that structure in controlled trials
  - The mechanism of "trained immunity" is a consequence of the live vaccine inducing metabolic and epigenetic changes that enhance the innate immune response to subsequent infections
- Uncertainties
  - Whether BCG is effective is not known
  - There may be differences in potential benefit between BCG strains
- Ecological studies (unpublished) make the observation that there is a lower incidence and severity of COVID-19 in countries where BCG (neonatal) immunisation is routine
- Ecological studies conflate population level data, and potential confounders include timing of observation in relation to the epidemic, contrasting population demographics and testing and reporting practices
- There are major uncertainties of BCG immunisation early in life affecting severity of COVID in the elderly, noting that early BCG was often routine in those born over 50 years ago living in countries currently experiencing a high incidence and mortality due to COVID-19
- Reports of health workers self-administering BCG vaccines intended for newborns in some settings
- There should be no changes to BCG vaccine policy
- The inappropriate use of BCG vaccines will exacerbate global supply challenges and shortages which then lead to increased tuberculosis-related morbidity and mortality in infants and young children in tuberculosis endemic countries
- Recommendation is that until (and if) benefit is clearly established, the BCG vaccine is used for COVID-19 RCTs only

Reviewed by: Professor Steve Graham

VIROLOGY

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

A SARS-CoV-2 protein interaction map reveals targets for drug repurposing
https://doi.org/10.1038/s41586-020-2286-9

- This study presented a systemic approach to evaluate the physical interactions between SARS-CoV-2 and human proteins in order to identify potential human proteins or host factors for the targets of antiviral treatments.
- 26 of 29 proteins of SARS-CoV-2 were successfully cloned and expressed to examine their physical interactions with human proteins, using affinity-purification mass spectrometry (AP-MS).
- 332 high-confidence SARS-CoV2- human protein-protein interactions (PPIs) were identified. Those PPIs connected to multiple biological processes of human cells, including protein trafficking, translation, transcription and ubiquitination regulation.
- 69 ligands against 332 PPIs were found, including some FDA approved drugs or preclinical compounds / compounds on trials. Two potential antiviral candidates were Sigma1 and Sigma2 receptors
- Significance: A ready platform for future screening drugs that target host proteins interacting directly to vital viral proteins. The antiviral strategy based on host-directed intervention could overcome the drug resistance and be used for the next pandemic.
- Limitations: No animal models to test the potential drugs

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

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

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

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

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

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

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

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

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

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

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

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/

EDITORIAL TEAM

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
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
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
Professor Michael Sullivan	Paediatric Oncologist, Children Cancer Centre, RCH and Department of Paediatrics, The University of Melbourne
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
Dr Amanda Gwee	Infectious Diseases Physician, RCH; Team leader & Clinician-Scientist Fellow in the Infectious Diseases Group, MCRI: and Senior Lecturer, Department of Paediatrics, The University of Melbourne
Professor Steve Graham	Centre for International Child Health, Department of Paediatrics, The University of Melbourne
Dr Lien Anh Ha Do	Postdoctoral Fellow, Infection and Immunity Theme, MCRI