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COVID19 KIDS EVIDENCE UPDATE

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

Weekly Update No.3
29 April 2020

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ADULT MEDICINE

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

How does coronavirus kill? Clinicians trace a ferocious rampage through the body, from brain to toes

[doi:10.1126/science.abc3208](https://doi.org/10.1126/science.abc3208)

- > Summarises the current opinion on how SARS-CoV-2 affects different organ systems.
- > The infection begins as an infected person expels virus laden droplets and some else inhales them. The virus uses the ACE2 receptor to enter cells in the respiratory epithelium of the nose and throat and replicates causing fever, dry cough sore throat, loss of taste and smell, head and body aches
- > Transmitted to the lungs that may result in:
 - An overreaction of the immune system or “Cytokine storm”.
 - Alveoli can become filled with fluid, white blood cells, mucus and cell debris and blood oxygen levels rapidly decline resulting in ARDS
 - There is no consensus regarding the role of immunosuppressive drugs aimed at dampening a cytokine response vs concerns that this may facilitate more viral replication
- > Damage to the heart (heart damage in ~20% hospitalised in Wuhan, Arrhythmias in 44%), blood vessels (?impact on vascular biology particularly related to alveolar oxygen exchange) and on blood clotting (blood clots detected in ~one third ICU patients)
- > If ACE2 receptors on blood vessels are targeted by SARS-CoV-2 it may explain why patients with pre-existing vascular pathology (e.g. diabetes or hypertension) face a higher risk of serious disease
- > Renal disease: ACE2 receptors are also abundantly expressed on kidneys. Renal failure was identified in 27% of hospitalised patients in Wuhan, proteinuria and hematuria also common. Mortality in COVID-19 patients with acute kidney injury was five times higher compared to other COVID-19 patients.
- > Neurological disease: Strokes, seizures, confusion and encephalitis have been observed in COVID-19 patients. It is yet unknown if this is due to the virus itself or the “cytokine storm” associated with infection. ACE2 receptors are present in the cortex and brainstem and virus has been identified in CSF. Observations of lack of smell and lack of gasping for air despite severe hypoxia has led some to postulate that infection may depress brain stem reflexes.

- > Gastrointestinal tract: ACE 2 receptors are abundant in the gut. An estimated 20% of patient's experience diarrhea and viral RNA has been found in up to 53% of patients. Faecal transmission is likely to be low based on experience with SARS and MERs.

Reviewed by: Professor Julie Bines

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

Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized with COVID-19 in the New York City Area

<https://jamanetwork.com/journals/jama/fullarticle/2765184>

What are the clinical features, characteristics and outcomes of patients hospitalised with COVID-19 in the US?

Descriptive case-series study of 5700 consecutive COVID-19 patients admitted to 12 hospitals in the NYC area. Data were collected from electronic health records.

- > The median age of patients was 63 years (Interquartile range 52 – 75). 60.3% were male.
- > The three most common comorbidities were hypertension (56.6%), obesity (41.7%) and diabetes (33.8%).
- > Presenting features included fever in 30.7% and tachypnoea in 17.3%. 27.8% received oxygen supplementation on presentation.
- > As of April 4, 2020, for patients requiring mechanical ventilation (n = 1151, 20.2%), 38 (3.3%) were discharged alive, 282 (24.5%) died, and 831 (72.2%) remained in hospital.
- > Electronic health record data were limited to basic clinical features and unadjusted for confounders, thus limited to descriptive studies.

Reviewed by: Professor Julie Bines

CLINICAL PAEDIATRICS

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

Clinical Characteristics of Children and Adolescents with SARS-CoV-2 Infection <https://jamanetwork.com/journals/jamapediatrics/fullarticle/2765169>

Systematic review of articles about SARS-CoV-2 infection in paediatrics published from December 1, 2019 – March 3, 2020. 18 studies with 1065 participants (444 patients younger than 10 years and 553 were aged 10-19 years) who tested positive for SARS-CoV-2 by nasopharyngeal swab were included in the final analysis.

- > Children at any age were mainly asymptomatic or had mild respiratory symptoms (fever, dry cough, fatigue). Gastrointestinal symptoms (nausea, vomiting, and diarrhoea) were reported in a few cases, particularly in a newborn and infants.
- > There was only 1 case of severe COVID-19 infection in a 13-month-old infant who developed vomiting, diarrhoea, fever, and pneumonia complicated by shock with metabolic acidosis and kidney failure. The infant was successfully treated with intensive care, including assisted ventilation.
- > Main radiological features on chest radiograph and/or CT were bronchial thickening and ground-glass opacities. These findings were evident in both symptomatic and asymptomatic patients.
- > No patients, apart from the 13-months-old with severe COVID-19, required oxygen or assisted ventilation. Most recovered within 1-2 weeks.
- > 1 death was reported in children aged 10-19 years. No deaths were reported in the 0-9 years' age groups.
- > Study limitation: All studies included were conducted in China and 1 was in Singapore. European and US studies in children with COVID-19 were not available to the authors' best knowledge at the time the review was conducted.

Reviewed by: Dr Wonie Uahwatanasakul

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

Late-Onset Neonatal Sepsis in a Patient with COVID-19

<https://www.nejm.org/doi/full/10.1056/NEJMc2010614>

- > Case of a 3-week old boy presented with 2-day history of: nasal congestion, tachypnea, and reduced feeding
 - Previously received 48-hour course of antibiotics for suspected neonatal sepsis (temperature, 38.5C), full workup was negative and was discharged home
- > Initial vital Signs: Temperature 36.1, pulse 166bpm, BP 89/63mmHg, RR 40, Oxygen % saturation 87% (ambient air)
- > Radiography (CXR): bilateral linear opacities + RUL consolidation
- > Treatment: oxygen + empirical antibiotics (ampicillin & gentamicin) + transfer to paediatric hospital
- > Required transfer due to: hypotension, hypothermia, tachycardia, tachypnea
- > At Paediatric Intensive Care Unit (PICU)
 - Transferred to negative pressure room & intubated
 - Crystalloid solution (60mL/kg body weight) + vasopressors administered
 - Chest radiography (performed after intubation): bilateral infiltrates + partial collapse of RUL
 - WBC count = 4,000/mm³ (55% lymphocytes) + elevated inflammatory markers
 - Nasal swabs obtained testing for SARS-CoV-2 were positive on PCR
 - Completed 5-day course of hydroxychloroquine and azithromycin
- > Children are less likely to have severe SARS-CoV-2
- > Children can be managed successfully using standard ICU protocols - only exception was a decision to not use noninvasive mechanical ventilation
- > Source of transmission unknown

Reviewed by: Dr Wonie Uahwatanasakul

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

UK Doctors Issue Urgent Alert as Coronavirus-linked health problems ‘may be emerging in children

<https://www.independent.co.uk/news/health/coronavirus-children-illness-nhs-doctor-warning-health-alert-a9485441.html>

- > An urgent alert has been issued to doctors by the NHS England warning of a potential COVID-19 related multi-system inflammatory syndrome requiring intensive care throughout various regions across England.
- > The condition, which has been described in children with and without COVID-19, is described as sharing features of severe COVID-19, toxic shock syndrome and atypical Kawasaki disease.
- > The NHS and Paediatric Intensive Care Society (PICS) both maintain that there are only a handful of critically unwell children with COVID-19 requiring admission to PICU in the UK at the moment.
- > The article quotes Professor Adilia Warris, a paediatric infectious disease specialist, who states that children with compromised immune systems and those on immunosuppressive treatment are not at increased risk for developing severe COVID-19 disease, at this stage
- > Further data collection is required to determine whether a true clinical association exists between COVID-19 and the multi-system inflammatory response.
- > Summary: numbers are tiny and alert was placed so that clinicians are aware of this atypical presentation and therefore to recognise illness to instigate early treatment

Reviewed by: Dr Wonie Uahwatanasakul

CLINICAL TRIALS

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

A real-time dashboard of clinical trials for COVID-19

[https://www.thelancet.com/journals/landig/article/PIIS2589-7500\(20\)30086-8/fulltext?utm_campaign=tlcoronavirus20&utm_source=twitter&utm_medium=social#relAudio](https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30086-8/fulltext?utm_campaign=tlcoronavirus20&utm_source=twitter&utm_medium=social#relAudio)

- > An urgent need exists to track clinical trials, avoid unnecessary duplication of efforts, and understand what trials are being done and where
- > A COVID-19 clinical trials registry has been developed
- > Data were extracted from the International Clinical Trials Registry Platform, including those from the Chinese Clinical Trial Registry, ClinicalTrials.gov, Clinical Research Information Service - Republic of Korea, EU Clinical Trials Register, ISRCTN, Iranian Registry of Clinical Trials, Japan Primary Registries Network, and German Clinical Trials Register
- > To ensure completeness of the search 3 methods were utilised:
 - Manual review by 2 separate reviewers before being entered into the registry;
 - Artificial intelligence (AI)-based methods for data searches to identify potential clinical studies not captured in trial registries
 - Use content aggregator services, such as LitCovid
- > These methods provide estimates of the likelihood of importance of a study being included, such that the study can then be reviewed manually for inclusion
- > Use of AI-based methods saved 50–80% of the time required to manually review all entries without loss of accuracy
- > Results are displayed as a real time digital dashboard: <https://www.covid-trials.org/>
- > With this three-step process, the probability of missing important publications is greatly reduced and so the resulting data are representative of global COVID-19 research efforts

CRITICAL CARE

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

Intensive care management of coronavirus disease 2019 (COVID-19): Challenges and recommendations

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(20\)30161-2/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30161-2/fulltext)

Review of Asian ICU practices describing the challenges in management of COVID-19 and their recommendations, published on the 6th of April

- > One million people worldwide were diagnosed with COVID-19 by the 2nd of April, and the fatality rate was estimated to be 5.2% - which is lower than in the SARS and MERS epidemics, though rates varied across different areas and do not account for undiagnosed patients.
- > Estimated time course of disease progression: median of 5 days from symptom onset to pneumonia, median of 7-12 days from symptom onset to ICU admission, median ICU length of stay was 8 days, viral shedding continues beyond 10 days after symptom onset in severe cases
- > Critically ill patients are older (>60 years) and have more comorbidities, particularly hypertension, diabetes, cardiovascular disease, chronic lung disease and cancer
- > The most common complications in ICU are acute respiratory distress syndrome (ARDS) (60-70% of patients admitted to the ICU), shock (30%), myocardial dysfunction (20-30%) and acute kidney injury (10-30%)
- > ICU practitioners should develop a high index of suspicion and low threshold for diagnostic testing for any patient with severe respiratory infection given the exponential rise in community transmission – sampling from the lower respiratory tract is recommended, but to avoid bronchoscopy to minimise risk of exposure to staff
- > Non-invasive ventilation (NIV) and high-flow nasal cannula (HFNC) are recommended to be used only in mild ARDS cases until more information is available due to risk of aerosol transmission; fluids should be used cautiously given the high incidence of myocardial dysfunction
- > The use of corticosteroids are not recommended due to lack of available evidence – a small study found that patients given methylprednisolone had a lower mortality, but the sample size was only 84 patients and there were other possible confounders to the study.

- > While a lot has changed in the last 3 weeks since this paper was written, the epidemiology seems to stand up well, and is fairly consistent from one high burden country to another. The current estimated case fatality rate for COVID-19 is 3.4%. This paper describes the most common ICU complications, of course 80% of people with the infection are asymptomatic or have mild symptoms only and do not need ICU level care. There are several different severe disease manifestations in adults, from a viral pneumonitis, severe hypoxaemia and VQ mismatching, ARDS, with multiple pulmonary microemboli. Different forms of respiratory support are relevant in different types of pathophysiology and different stages of the disease. Some adults, particularly those who stay in ICU on ventilators develop hyper-inflammatory escalation with shock: elevated D-dimer, ferritin, hypercoagulable, pulmonary emboli, renal failure, and hypotension. Some of these have secondary bacterial sepsis, most just have a severe inflammatory cascade related COVID-19. Risk factors for such deterioration are unclear, but if they have sustained a period of hypotension seems more likely to spiral into this inflammatory / shock cascade.
- > In children (who make up far less than 1% of all ICU admissions for COVID-19 in every country affected) there is no evidence that standard forms of respiratory support, such as high flow nasal cannula oxygen therapy, pose any greater risk to health workers than oxygen therapy. However optimal aerosol PPE is needed in caring for all patients with COVID-19. There are no reports of transmission from an infected child to a health care worker, although of course many tragic cases of healthcare workers being infected while caring for adult patients. Intubation, especially emergency intubation in a general ward is a large risk, but not wearing standard aerosol-level PPE is an even bigger risk, and in the UK there have been nurses, doctors and other health workers who work outside ICUs becoming infected, perhaps from inadequate PPE or dealing with a case that was unsuspected, or infected from colleagues, or community transmission.

Reviewed by: Professor Trevor Duke

DIAGNOSTICS & SAMPLING

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

Saliva as a non-invasive specimen for detection of SARS-CoV-2

<https://jcm.asm.org/content/jcm/early/2020/04/17/JCM.00776-20.full.pdf>

Accurate diagnostic methods for detection of SARS-CoV-2 are crucial in the context of the pandemic currently, nasopharyngeal (NP) swabs (and/or sputum) are the current gold-standard non-invasive method for detection of SARS-CoV-2

- > Advantages of using saliva for detection:
 - Reduced risk to healthcare workers
 - Collection does not require specialised consumables
 - Less patient discomfort
 - Potential for self-collection
- > 622 paired nasopharyngeal swabs and saliva samples were obtained from patients with suspected COVID-19 at The Royal Melbourne Hospital
- > 39 cases were positive on RT-PCR from nasopharyngeal swabs
- > Of the 39 positive nasopharyngeal swabs, 33 also had SARS-CoV-2 detected in their saliva
- > 1 patient who was negative on NP swab had positive saliva sample (although this was felt to be due to sampling technique)
- > Saliva should be considered as an alternative screening option to NP swab based on its feasibility, acceptability, and scalability of prospective collection in busy ambulatory clinics and low-resource environments

Reviewed by: Dr Danielle Wurzel

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

Effect of throat washing on detection of 2019 novel coronavirus

<https://www.ncbi.nlm.nih.gov/pubmed/?term=effect+of+throat+washings+on+detection+of+2019+novel+coronavirus>

Nasopharyngeal (NP) and oropharyngeal (OP) swabs (+sputum when possible) are currently recommended for the detection of SARS-CoV-2

- > NP swab has higher sensitivity than OP swabs (89% vs 54%; $P < 0.001$) however its limitations include: aerosol production; inconsistency between collections and patient discomfort
- > Sputum specimen: Non-invasive however only 28% of COVID-19 patients are productive of sputum
- > Throat washing has advantages: Non-invasive; easy-access sample; reduced risk to healthcare workers; increased epithelial cells.
- > Study:
 - 11 laboratory-confirmed COVID-19 subjects; 24 paired throat washings and NP swabs
 - Sample collection date after symptom onset: Median: 53 days, (range: 48-57 days) after symptom onset
 - Method:
 - Specimen acquisition: Oscillation of 20ml of sterile normal saline over the posterior pharyngeal wall by the subject for 5-10 seconds before being spat out into a sterile container
 - Laboratory technique:
 - Nucleic acid extraction and real-time reverse transcription-quantitative polymerase chain reaction (RT-PCR)
 - RT-PCR used focused on NP and ORF1ab SARS-CoV-2 genes
 - Positive test rate of throat washing determined to be higher than that of NP swabs ($P=0.031$)
 - Limitations: Small sample size; low positive detection rate due to decline in viral loads due to late timing of sampling

Reviewed by: Dr Danielle Wurzel

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

Current considerations for laboratory diagnosis of SARS-CoV-2

<https://jcm.asm.org/content/jcm/early/2020/04/03/JCM.00512-20.full.pdf>

- > Commentary outlining issues around laboratory diagnosis of SARS-CoV-2.
- > Nasopharyngeal swabs are recommended over oropharyngeal swabs as they are higher-yield diagnostic tests, better tolerated by patients and are safer to the operator.
- > Self-collected saliva and nasal washes could be used for community-based screening if supply of swabs is limited.
- > Repeat testing or obtaining lower respiratory tract samples may be necessary.
- > Viral loads determined by RT-PCR should not be used to determine disease severity or therapeutic response. However, low cycle threshold values (Ct-value) may indicate transmissibility.
- > To avoid potential cross-reaction with other coronaviruses and genetic drift of SARS-CoV-2, using at least two molecular targets for RT-PCR. The ideal would be to include one conserved and one specific region.
- > Serological methods such as rapid lateral flow assays will play an important role in COVID-19 epidemiology, checking the immune status of asymptomatic patients and confirming diagnosis when available, but will not play a role in early diagnostic screening or management.
- > Rectal swabs may be used as tests of infectivity/cure, but further evaluation is needed.
- > Note that the authors clearly disclose that they are employed by Cepheid, the manufacturer of the Xpert SARS-CoV-2 test.

Reviewed by: Associate Professor Catherine Satzke

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

Saliva is more sensitive for SARS-CoV-2 detection in COVID-19 patients than nasopharyngeal swabs

<https://www.medrxiv.org/content/10.1101/2020.04.16.20067835v1.full.pdf>

Paired nasopharyngeal swabs and saliva samples were collected from COVID-19 inpatients (38 matched paired samples, mean age 59) and asymptomatic healthcare workers with moderate to high risk of COVID-19 exposure (98 self-collected samples, mean age 36) at Yale New-Haven Hospital, Connecticut, USA.

- > SARS-CoV-2 titres from saliva were higher than nasopharyngeal swabs
- > SARS-CoV-2 was detected through saliva sample but not nasopharyngeal swabs from 8 matching samples (21%), compared to 3 matching samples (8%) detecting SARS-CoV-2 through nasopharyngeal swab but not saliva sample

- > Saliva samples demonstrated less temporal variability of SARS-CoV-2 titers, with no instances where a sample tested negative then was later followed by a positive result, compared with 5 instances for nasopharyngeal swabs.
- > SARS-CoV-2 was detected through saliva samples in two asymptomatic healthcare workers who were negative by nasopharyngeal swab upon repeat testing two days later.
- > Alternative options to nasopharyngeal swabs through saliva samples would provide an ability for self-testing, reducing the risk posed to health care workers during sample collection and provide a less resource intensive sample
- > Limitations:
 - Viral loads differs between mild and severe cases, limiting the study as primarily COVID-19 inpatients with severe disease were tested
 - A larger sample size is needed to confirm if saliva is more sensitive for detecting asymptomatic or pre-symptomatic infections.
- > Summary: Saliva samples provide comparable, if not superior detection of SARS-CoV-2 compared with nasopharyngeal swabs, and may provide a more consistent true negative result that can track patient improvements and aid decision making regarding discharges.

Reviewed by: Associate Professor Catherine Satzke

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

What are the impacts of natural disasters on academic performance in primary school?

<https://www.ncbi.nlm.nih.gov/pubmed/30675903>

- > Experiencing natural disasters in childhood can impact physical, mental, cognitive and social development, as well as academic performance
- > Two to four years after Black Saturday, expected gains in reading and numeracy were reduced for those students in schools with higher bushfire impact
- > The same cognitive skills needed for learning are known to be impacted by early trauma experiences
- > Parents and schools need to recognise there may also be delayed impacts of disaster experience
- > Disasters may also affect parent mental health for a number of years, which could create a lower quality home learning environment (e.g., with less supported reading at home)

Which policies and practices promote social distancing in schools during influenza pandemics?

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5870081/>

- > Social distancing interventions within schools during influenza pandemics tend to focus on full school closures
- > Little research identifies more sustainable, less costly, interventions
- > Practices identified from the literature include cancelling activities with a high rate of contact, increasing spacing between students, implementing shorter school days or weeks, implementing social distancing practices for staff, and reducing load in common areas.
- > Further research is needed to determine feasibility and effectiveness

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

COVID-19, Australia: Epidemiology Report 11 (Reporting week to 23:59 AEST 12 April 2020)

[https://www1.health.gov.au/internet/main/publishing.nsf/Content/1D03BCB527F40C8BCA258503000302EB/\\$File/covid_19_australia_epidemiology_report_11_reporting_week_ending_23_59_aest_12_april_2020.pdf](https://www1.health.gov.au/internet/main/publishing.nsf/Content/1D03BCB527F40C8BCA258503000302EB/$File/covid_19_australia_epidemiology_report_11_reporting_week_ending_23_59_aest_12_april_2020.pdf)

- > Comprehensive descriptive epidemiology of COVID-19 cases in Australia up until 12 April, 2020.
- > There was a 65% decrease in the number of weekly reported COVID-19 cases (n=589) compared to the previous week.
- > In the reporting period, NSW continued to have the highest rate of notifications, followed by Victoria; there were no cases reported in the Northern Territory. Most cases occurred in urban areas.
- > 44 cases were reported in people who identify as Aboriginal and/or Torres Strait Islander. Indigenous Identification status was only completed in 78% of cases.
- > 20-29 year olds continue to have the highest number of cases, whilst 60-69 year olds have the highest rates of disease.
- > Only 1% of cases were in children under 10, and 3% in those between 10 and 19 years of age.
- > Despite some variation across age groups, the notification rates in males and females remain approximately equal overall.
- > 65% of cases had recent travel history, whereas 33% of cases were likely to be locally acquired.
- > The symptom profile remains similar to the previous reporting period; 70% had cough, 47% had fever, 40% had sore throat and 36% had headaches. Data on loss of smell and taste is likely under-reported, but 8% of cases reported these symptoms which was increased from the week prior (5.5%).
- > Hospitalisation rates increased from 11% to 12% of total cases (n=6,394) in this reporting period, whilst ICU admissions increased from 13% to 17% of hospitalised cases (n=752).
- > The median age of deceased patients was 78.5 years, and 61% of deceased patients (n=46) were male.
- > There are a number of useful resources published in this weekly update, including international updates, an up-to-date timeline of Australian public health responses to COVID-19, heatmaps of cases around the nation, and case number graphics annotated with the timing of public health interventions.

Reviewed by: Dr Claire von Mollendorf

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

Connecting clusters of COVID-19: an epidemiological and serological investigation

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30273-5/fulltext#.Xp_6SyUko0Y.twitter](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30273-5/fulltext#.Xp_6SyUko0Y.twitter)

Can SARS-CoV-2 serological assays assist in outbreak control through identification of convalescent cases?

Epidemiological study in Singapore which used active case-finding and contact tracing of COVID-19 cases to identify three disease clusters. A combination of RT-PCR and serological assays were used to confirm active and convalescent cases respectively.

- > Utilising Singaporean disease-notification registers, three disease clusters involving local transmission were identified between January 19 and February 18, linked to two churches and one family gathering.
- > Two subsequently diagnosed travellers from Wuhan were linked to the initial disease cluster in a church service.
- > SARS-CoV-2 serology was instrumental in confirming the link between two disease clusters. Serology identified a single subclinical case who had since convalesced and returned two negative RT-PCR tests. It is a key method in the COVID-19 pandemic response.
- > The epidemiological findings suggest that risk of transmission is increased in situations of prolonged close contact, and support the public health measures focussed on this area.

Reviewed by: Dr Claire von Mollendorf

Nicholas Baxter - 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

Incidence, clinical outcomes, and transmission dynamics of hospitalized 2019 coronavirus disease among 9,596,321 individuals residing in California and Washington, United States: a prospective cohort study (not peer-reviewed article)

<https://medrxiv.org/cgi/content/short/2020.04.12.20062943v1>

- > Study assessing the incidence, clinical outcomes, and transmission dynamics of 1277 patients hospitalised with acute COVID-19.
 - Identified as part of a prospective cohort of individuals enrolled in a US healthcare plan
- > Key findings
 - Cumulative incidence of COVID-19 hospitalisation ranged from 10.6 to 14.6 per 100,000 individuals within the three cohorts.

- Mean duration of hospital stay was 10.7 days for survivors and 13.7 days among non-survivors.
 - Median age of all cases was 60 years (range 1-103 years), 50% of patients aged between 47-72 years.
 - Mortality higher in men than women.
 - Estimated probability of ICU admission was 41.9% and mortality 17.8% across all age groups.
 - Effective reproductive number declined to around 1 following social distancing implementation.
- > Modelling considerations
- Some models used by the UK and US to anticipate and predict clinical resource needs are based on incidence and length of ICU admission data from Chinese studies.
 - ICU admission length is longer in this cohort of patients in America (13.7 days among non-survivors) compared to (cited) studies in China (7.5 days), which may reflect alternative approaches to extending end-of-life care in the two settings.
 - ICU admission rate higher in this study (42%) c.f. hospitalised patients in Chinese studies (30%).
- > Study limitations
- Patients discharged at the end of the most recent hospitalisation were considered to be survivors if they did not die by April 9. Hospitalisations were complete for only 64% of patients.
 - Laboratory diagnosis of COVID-19 only available in 91.7% of COVID-19 cases, otherwise clinical diagnosis were accepted
 - Patient comorbidities not captured
 - Only includes commercially-insured patients treated by Kaiser Permanente

Reviewed by: Dr Claire von Mollendorf

Su Lee - 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

Cluster of COVID-19 in Northern France: A retrospective closed cohort study (not peer-reviewed)

[Cluster of COVID-19 in northern France: A retrospective closed cohort study](#)

- > A retrospective closed cohort study was conducted to estimate the infection attack rate (IAR) and its determinants in an area of France affected by COVID-19.
- > 661 participants (median age: 37 years) completed a questionnaire that included history of fever and/or respiratory symptoms since 13 January 2020 and who had blood tested for the presence of anti-SARS-CoV-2.

- > Of the 661 participants, 171 participants had anti-SARS-CoV-2 antibodies, giving an overall IAR of 25.9%. The IAR was defined as the proportion of all participants with confirmed SARS-CoV2 infection based on antibody detection.
- > Among the 171 participants who had positive serology results, participants with major, minor or no symptoms were 121 (70.8%), 21 (12.3%), and 29 (17%) participants respectively.
- > IAR did not differ by sex, but a difference was seen by age (highest in the 15-17 years' age group). IAR was the highest in the high school group.
- > Major symptoms - anosmia and ageusia - showed high positive predictive values (84.7% and 88.1% respectively) for SARS-CoV-2 infection
- > Smokers had lower risk of infection (7.2% versus 28.0% for smokers and non-smokers respectively) with no significant increase in IAR among those who had comorbidities, otherwise known to be associated with severe forms of COVID-19.
- > Major study limitations were low participation rate and retrospective symptom reporting.
- > In summary, as the study was conducted in an area of active SARS-CoV-2 circulation prior to confinement measures, the low IAR may suggest that herd immunity will not be established quickly. Therefore, lifting of confinement measures may be complicated in this setting prior to the availability of effective therapeutics or ultimately vaccines specific to SARS-CoV2.

Reviewed by: Dr Claire von Mollendorf

GLOBAL HEALTH

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

Hard fought gains in immunization coverage at risk without critical health services, warns WHO

<https://www.who.int/news-room/detail/23-04-2020-hard-fought-gains-in-immunization-coverage-at-risk-without-critical-health-services-warns-who>

This is a WHO news item, not a peer-reviewed article

- > Issue:
 - The secondary or indirect consequences of the COVID-19 pandemic on child health is a major concern, likely to have a greater impact than primary infection on child health globally. Immunisation services can be disrupted during a pandemic, and such disruptions can lead to outbreaks of vaccine-preventable diseases such as measles, pertussis and polio.
 - To conserve immunisation services, need to ensure strong supply chains are in place, facilitate urgent catch-up programmes where disruptions have occurred, undertake disease surveillance and have adequately trained health care workers.
- > Current WHO guidelines:
 - Temporarily pause preventive immunization campaigns where there is no active outbreak of a vaccine preventable disease
 - Prioritise the continuation of routine immunisation of children in essential service delivery, as well as adult vaccinations such as influenza for groups most at risk
 - Reschedule urgent catch-up vaccinations as soon as possible, prioritizing those most at risk
- > Main message:
 - Emphasises the importance of maintaining essential health services and immunisation at this time, to prevent further disease outbreaks overwhelming health systems that are already fragile due to COVID-19 pandemic, and to prevent more death.

Reviewed by: Professor Steve Graham

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

What are the lessons learned from Vietnam's policy response, social media and science journalism for the sustainability of public health amid the COVID-19 outbreak?

<https://www.mdpi.com/2071-1050/12/7/2931>

> Background:

- As of 4th April 2020, Vietnam had detected only 239 confirmed cases, with no reported deaths.
- This analysis is a review to date of Vietnam's policy highlighting strengths and weakness of responses, the extensive and seemingly effective utilisation of social media, and input from science journalism within Vietnam.

> Summary of findings:

- Previous experience with national responses to epidemics/pandemics - SARS 2003, H5N1 flu 2008, A/H1N1 2009 - is identified as having possible positive affect on efficient decision-making for prevention and treatment of COVID-19 and community and health sector response.
- The government introduced mandatory mask-wearing, health checks, self-quarantine, social distancing, restrictions of mobility between provinces, school closures and border closures, while continuing to maintain the supply of fundamental goods for its citizens.
- Effective uptake and adherence by the population is attributed to communication such as through the media response to complement government policy promoting public awareness of the disease and providing information as to how people can protect themselves and their communities.
- The authors also highlighted certain missteps that the government has made. In the education sector, there was a lack of clear guidelines for students as well as indecisive policies regarding school shutdowns during the early phase of the pandemic. The tourism sector initially underestimated the extent of the pandemic, initially promoting Vietnam as a "safe haven" from COVID-19 for tourists, with a subsequent increase in national COVID-19 cases due to foreign tourists.

> Critical review:

- By April 26th, 270 confirmed cases occurred with no reported deaths, while Vietnam has done around 213,000 tests - a ratio of around 2,200 tests per 1 million population which is about one-tenth of that in Australia.
- Being close to China could have been of benefit for earlier response than other countries, as Vietnam health authorities were already aware of the reporting of unusual cases of pneumonia in China as early as December 2019 - and with previous recent experience of viral epidemics in the region.
- While the paper provides extensive documentation of a range of policies, communication and activities, seemingly strictly applied and adhered to, the relative contribution of each to an effective response is difficult to define.
- The findings are observational and so prone to bias

- While important, the contribution of locally authored scientific papers is likely to be limited with only four papers listed at this point
- Vietnam's experience to date might provide valuable lessons for other countries
- Early response only reported and it will be interesting to monitor future epidemiology with ease of restrictions, including re-opening of schools.

Reviewed by: Professor Steve Graham

INFECTION CONTROL

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

Facemasks and similar barriers to prevent respiratory illness such as COVID-19: A rapid systematic review

<https://www.medrxiv.org/content/10.1101/2020.04.01.20049528v1>

- > Systematic review of 28 studies (including 12 RCTs), including a narrative synthesis and random-effects meta-analysis of attack rates for primary and secondary prevention of influenza like illness (ILI).
- > This review specifically examined the efficacy of face masks (including a variety of face coverings) outside of healthcare settings
- > 3 RCTs found that wearing a facemask may very slightly reduce the odds of developing ILI/respiratory symptoms, by around 6% (low certainty evidence). In observational studies, the evidence in favour of wearing facemasks was stronger.
 - It is expected that RCTs under-estimate the protective effect and observational studies exaggerate it.
- > In a household setting, when an infected person and uninfected housemates wore face masks, the odds of further household members becoming ill may be modestly reduced by around 19% (low certainty evidence). The protective effect was very small if only the well person or the infected person wore the facemask.
- > Summary: There is insufficient evidence to support widespread use of facemasks as a protective measure against COVID-19. However, the evidence supports the use of facemasks for short periods of time by particularly vulnerable individuals when in temporary high-risk situations.

Reviewed by: Professor Allen Cheng

IMAGING

Ben Watson - 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

International Expert Consensus Statement on Chest Imaging in Pediatric COVID-19 Patient Management: Imaging Findings, Imaging Study Reporting and Imaging Study Recommendations

<https://pubs.rsna.org/doi/10.1148/ryct.2020200214>

A group of international experts from 5 continents convened to create a consensus statement describing imaging manifestations of COVID-19 in the paediatric population and generating consensus recommendations, listed here:

- > Initial Chest imaging evaluation in Paediatric Patients with COVID-19
 - Imaging is not generally indicated as a screening tool for symptomatic or asymptomatic paediatric patients with suspected COVID-19 infection
 - Imaging is not indicated for paediatric patients presenting with mild clinical symptoms unless the patient has risk factors for disease progression or develops worsening clinical symptoms
 - Initial imaging with CXR may be appropriate in paediatric patients with moderate-to-severe clinical symptoms regardless of COVID-19 infection status, and chest CT may be considered if the results would potentially impact clinical management
 - Repeating a RT-PCR test for COVID-19 may be considered in paediatric patients with moderate-to-severe symptoms who initially had a negative lab result but demonstrate imaging findings typically seen in COVID-19
 - In a resource constrained environment, chest imaging may be utilized as an initial step in work-up for COVID-19 infection in triage decision making
- > Sequential Chest Imaging Evaluation in Paediatric Patients with COVID-19
 - Sequential CXR examinations, ordered as needed on a clinical basis, may be appropriate for paediatric COVID-19 patients to assess response to therapy, evaluate clinical deterioration, or assess positioning of life support devices
- > Post Recovery Follow-Up Chest Imaging Evaluation in Paediatric Patients with COVID-19
 - Post recovery follow-up imaging is not recommended for asymptomatic paediatric patients with a mild COVID-19 disease course, however may be considered in asymptomatic individuals with initial moderate-to-severe course depending of level of clinical concern for long term lung injury

Comments:

The report contains a detailed summary of structured CXR/CT reporting for paediatric COVID-19 patients, and imaging findings (typical and atypical), noting that even typical features could be caused by many other conditions.

Note that most children with suspected COVID-19 infection would require no imaging or CXR only if moderate-to-severe symptoms. This is important as many initial reports of COVID-19 reported CT chest imaging findings which likely reflected local practice and early diagnostic uncertainty in those settings with initial experience with pandemic, rather than that CT chest is commonly indicated.

Reviewed by: Professor Steve Graham and Associate Professor Simone Mandelstam

IMMUNOCOMPROMISED / CANCER

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

The COVID-19 PANDEMIC: A Rapid Global response for Children with Cancer from SIOF, COG, SIOF-E, SIOF-PODC, IPSO, PROS, CCI and St Jude Global
<http://doi.org/10.22541/au.158777298.87289192>

How can the diagnosis and treatment of children with cancer be adapted during periods of increased strain on hospital resources associated with the COVID-19 pandemic?

Collaborative project from paediatric oncology experts representing the leading global childhood cancer organisations to provide guidance on methods to adapt diagnostic and treatment protocols, ensure the safety of patients and healthcare workers, and prepare for the recovery period. This rapid global collaboration on COVID-19 was initiated to foster the goals of the WHO Global Initiative for Childhood Cancer to support the care of children with cancer wherever they may live.

- > In principle, all efforts must be made to ensure diagnosis is timely, and medical treatment schedules continue unaltered. In-depth modification charts are provided for the six most common good-prognosis malignancies: ALL, Burkitt lymphoma, Hodgkin lymphoma, retinoblastoma, Wilms tumour and low grade glioma.
- > Delaying surgical procedures may be considered when the anticipated risk of blood-loss or ICU care is high, concomitant with extensions to chemotherapy regimens.
- > Strict infection control in hospitals must be maintained, incorporating supervised hygiene procedures, visitor limitations, isolation of oncology wards and adequate provision and training for PPE use.
- > To address the lack of data to inform clinical decision-making, a global COVID-19 resource centre and registry has been established for clinicians to register COVID-19 cases in childhood cancer patients. The web-based registry is hosted by St Jude Children's Research Hospital.

Reviewed by: Professor Michael Sullivan

IMMUNOLOGY

Associate Professor Paul Licciardi – Team Leader,
New Vaccines-Immunology, MCRI

A serological assay to detect SARS-CoV-2 seroconversion in humans
<https://doi.org/10.1101/2020.03.17.20037713>
(not peer reviewed-medRxiv preprint)

This paper presents the results of an in-house ELISA method to measure SARS-CoV-2 specific antibodies.

- > Serological assays are needed to understand level of exposure in a population as well to determine individual protection
- > ELISA method based on recombinant spike protein, which is the major target for neutralising antibodies produced during infection. Both full-length spike protein and receptor binding domain was used for assays.
- > Assessed a large number of pre-COVID-19 negative samples (N=51 healthy adults and N=50 HIV+ samples) as well as samples from COVID-19 patients (N=16 samples total, acute and convalescent) and different IVIG preparations
- > Demonstrated good specificity and sensitivity although did not formally assess this
- > Good correlation with microneutralisation assays (considered gold standard)

Main message is the development of a sensitive and specific assay that could be used as the basis of serosurveys to estimate the true burden of infection in the community. The assay can be readily adapted in many laboratories worldwide and will facilitate standardisation of ongoing studies that use this assay.

INDIGENOUS HEALTH

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

Are Aboriginal and Torres Strait Islander communities prepared for COVID-19? “Bullet proofing Aboriginal and Torres Strait Islander communities from COVID-19”

<https://croakey.org/bullet-proofing-aboriginal-and-torres-strait-islander-communities-from-covid-19/>

- > Professor James Ward is a Pitjantjatjara and Narungga man, and Director of the Poche Centre for Indigenous Health. He describes how Aboriginal and Torres Strait Islander communities are preparing to withstand COVID-19.
- > 44 cases (0.7%) of 6,394 cases in Australia had been reported in Aboriginal and Torres Strait Islander persons.
- > Internationally, Indigenous populations have been particularly impacted by COVID-19. The Navajo Nation mortality rate is greater than that of other states with larger populations. Elsewhere, the first death of a Yanomami person in the Amazon was a 15 year old, and highlighted concerns for people residing on traditional and isolated lands close to mining sites in the Amazon.
- > Prof Ward calls for firm, clear, consistent and optimistic messaging around COVID-19, rather than causing unnecessary fear
- > National Aboriginal Community Controlled Health Organisation (NACCHO) recently convened an Aboriginal and Torres Strait Islander Advisory Group within the Department of Health which is critical in ensuring that communities are prepared.
- > The Advisory Group cemented Indigenous Australians as a priority population in the Series of National Guidelines for Public Health Units (SoNG), with special considerations for cases of COVID-19 detected in remote communities. Furthermore, they created a COVID-19 National Management Plan for Aboriginal and Torres Strait Islander communities.
- > Access to remote communities has been restricted to minimise exposure to COVID-19. The Advisory Group has also been working with mining companies to further minimize risk of transmission. Stricter measures could be put in place, especially since detection of COVID-19 cases in the Kimberley.
- > The Advisory Group is helping to open GP-led respiratory clinics in Aboriginal Community Controlled Health Organisations, as well as to adapt care systems to minimise the risk of transmission, such as employing telehealth.
- > Perhaps most critically, testing capacity has been established in 83 remote communities, test results in 45 minutes.
- > A number of other interventions are discussed.

Reviewed by: Professor Fiona Russell and Dr Wonie Uahwatanasakul

INFECTION CONTROL

Dr Aleisha Anderson - Microbiology Registrar RCH,
Advanced trainee paediatric infectious diseases

Asymptomatic Transmission, the Achilles' Heel of Current Strategies to Control COVID-19.

<https://www.nejm.org/doi/pdf/10.1056/NEJMe2009758?articleTools=true>

- > Early public health responses to COVID-19 were based on symptom-based case detection leading to testing and case/contact isolation.
- > A Washington State nursing facility outbreak was used to assess the role asymptomatic patients may play in transmission by conducting point prevalence PCR screening (nasopharyngeal swabs).
- > Of 76 residents tested, 48 (63%) were SARS-CoV2 PCR positive; 27 (56%) of whom were deemed asymptomatic (note, 24 subsequently developed symptoms and thus were actually pre-symptomatic; virus was cultured in 71% of these patients prior to symptom onset).
- > Conclusion- asymptomatic/pre-symptomatic individuals may play a role in transmission of COVID-19, representing an infection control opportunity which may be missed by symptom-based screening strategies alone. Broader testing may be indicated in nursing facilities/similar residential care, in areas with high rates of community transmission.
- > Limitations- accuracy of symptom history may have been impacted by cognitive impairment of some residents; applicability to areas with low rates of community transmission is uncertain.

Reviewed by: Dr Vanessa Clifford

MENTAL HEALTH

Associate Professor Margie Danchin - General and Immunisation Paediatrician, RCH; Group leader, Infection and Immunity Theme, MCRI; Clinician Scientist Fellow, Department of Paediatrics, The University of Melbourne

Mental Health Status Among Children in Home Confinement During the Coronavirus Disease 2019 Outbreak in Hubei Province, China

<https://jamanetwork.com/journals/jamapediatrics/fullarticle/2765196>

- > Study on impact on mental health of primary school students due to school closures over a 34-day period
- > Students in Hubei province, China were restricted to home from January 23 to April 8 in Wuhan and January 24 to March 23 in Huangshi (city 85 km from Wuhan)
- > Overall 180 million students were restricted to their homes due to school closures in China
- > Study investigated depressive and anxiety symptoms in 2330 primary school students in grades 2 to 6 from 2 primary schools in Hubei province - 845 students from the city of Wuhan and 1485 Huangshi
- > Survey completed between Feb 28 and March 5 2020 – survey sent to guardian’s cell phone for consent and then passed to students
- > Screened for depressive symptoms (Children’s Depression Inventory short form – CDI-S) and anxiety through the Child Anxiety Related Emotional Disorders
- > Response rate 76%, 57% boys, approx. 20% of children in each grade level (2 to 6)
- > Students had been restricted to home for a mean of 34 days
- > 23% of students reported depressive symptoms and 19% anxiety symptoms
- > Students in Wuhan were more likely to be depressed (OR 1.4, 95% CI 1.13 to 1.79)
- > Those who were not optimistic about the epidemic had significantly higher depressive scores with an increased risk of depression (OR 2.26, 95% CI 1.64 to 3.11)
- > Caution about protecting the mental health of children restricted to home due to school closure is warranted and raises even more concern for vulnerable and disadvantaged children

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

How can children affected by the response to the pandemic be assisted?

<https://pediatrics.aappublications.org/content/pediatrics/early/2020/04/17/peds.2020-0973.full.pdf>

Children with behavioural needs, in foster care, at risk of maltreatment or with medical complexity were identified as at-risk groups, particularly those from a low socioeconomic family.

- > Timely and reimbursed access to telehealth and virtual emotional support services is essential to meet the needs of these children and their families.
- > Guidelines can be implemented to allow parents to communicate clearly and honestly about COVID-19 appropriate to their child's development level
- > Communicate that vulnerable children are at higher risk of maltreatment to services that have access to families such as schools and faith-based organisations and provide basic trauma informed training to guide their response.
- > Economic support strategies and paid leave could be offered to foster-carers to ensure children are adequately supported in their placements.
- > Promote virtual visits for child welfare workers to assess the safety of the home environment.
- > The pandemic has forced mental health and social support providers to be innovative in reaching children and families in the community in which they live. Further evaluation about the effectiveness of these strategies can be applied to guide practice in the future.

Reviewed by: Professor David Coghill

PERINATAL HEALTH

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

Sequential analysis of viral load in a neonate and her mother infected with SARS-CoV-2

<https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa447/5820869>

Report on the clinical manifestation and viral kinetics of a neonate and her mother, both infected with COVID-19.

- > Full term vaginally delivered neonate 3.73 kg (27 days old) fully breastfed presented with fever, cough and vomiting. Unremarkable laboratory results and nil findings on serial chest x-rays conducted during admission for COVID-19. Parents and neonate lived at her grandparents house with 2 older siblings. Grandparents had become symptomatic with cough at day 20 of the neonates life. Two days later both mother and father developed cough, sore throat and chills. Neither baby nor mother had been out of the home since the birth of neonate. All family cases tested positive for SARS-CoV-2, but not the 2 older siblings. Mother and baby were admitted to hospital. The neonate had nasal stuffiness, cough fever and vomiting. Her chest X-rays were clear.
- > Virus was detected in neonate's nasopharynx (highest load), oropharynx, stool, saliva, plasma, and urine. Overtime, viral load decreased in nasopharynx, but remained high in stools out to day 18.
- > Mother had mild symptoms and virus was detected in respiratory and stool specimens at lower titre.
- > Both baby and mother did not require any antiviral therapy and baby continued to feed and gain weight.
- > Results suggest that COVID-19 could be systemic in neonates, who may therefore be vulnerable to systemic complications. (all tests performed were PCR based: no viral cultures for SARS-CoV-2)
- > Caregivers need to be taught adequate handwashing techniques as stool and urine may be continual routes of spread, but the viability and infectivity of viruses shed in this manner needs to be further investigated.

Reviewed by: Professor Suzanne M Garland

THERAPEUTICS

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

Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection - A Randomized Clinical Trial

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2765499?resultClick=1>

Parallel, double-blinded, randomised, phase IIb clinical trial in the largest public unit dedicated to treat severe COVID-19 in Brazil.

- > Participants: aged ≥ 18 y with tachypnoea, tachycardia, hypoxaemia and/or shock. Randomised if clinical suspicion of COVID-19 (prior to laboratory confirmation).
- > Intervention: randomised in 1:1 ratio to high-dose chloroquine (600 mg twice daily for 10 days) vs low-dose chloroquine (450 mg twice daily on day 1, then 450 mg daily for 4 days). Treatment was given concurrently with azithromycin.
- > Primary end point – death by day 28.
- > Main results – report of preliminary analysis as per DSMB recommendation. Total 81 randomised, 41 high-dose chloroquine group vs 40 low-dose chloroquine group.
 - Death – 16/41 (39%) high-dose group vs 6/40 (15%) low-dose group. High-dose group had increased odds of death (OR 3.6; 95% CI, 1.2-10.6) but exploratory multivariate analysis found that high-dose chloroquine was not associated with death when controlled for age.
 - Viral RNA detection in patients who died - 14/16 (87.5%) high-dose vs 5/6 (83.3%) low-dose chloroquine.
 - Elevated CK – 7/14 (50%) high-dose vs 6/19 (31.6%) low-dose hydroxychloroquine.
 - QTc prolongation (>500 ms) – 7/37 (18.9%) high-dose vs 4/36 (11.1%) low-dose hydroxychloroquine.
- > Key result: High-dose chloroquine given with azithromycin is not considered safe.

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

Initial guidance on the use of antivirals for children with COVID-19

<https://academic.oup.com/jpids/advance-article/doi/10.1093/jpids/piaa045/5823622>

Guiding principles on the use of antivirals for children with COVID-19 were developed by a panel of Paediatric infectious disease physicians and pharmacists from 18 different institutions across North America based on a review of the best available evidence and expert opinion. 4 questions were addressed.

- > Are antiviral agents indicated in children with COVID-19?
 - The use of antiviral therapy should be evaluated on a case-by-case basis, taking into consideration the risks and benefits of treatment.
 - Given that most paediatric COVID-19 cases are mild, supportive care alone is suggested for the majority of cases. This is further supported by a lack of evidence of efficacy for any antiviral therapy and the possible harms of these medications.
 - If antivirals are used, it is recommended that it is done as part of a clinical trial if available.
- > What criteria define the paediatric population in whom antiviral therapy may be considered?
 - Antivirals should be considered only in children with positive virologic COVID-19 testing.
 - Antiviral therapy should be reserved for patients in whom the possibility of benefit outweighs the risk of toxicity. This includes children with more severe illness, such as those with evidence of lower respiratory tract disease; specifically, if they require respiratory support.
- > Does the presence of any underlying medical condition increase the risk of COVID-19 related mortality and thus warrants antiviral use?
 - There is no definitive data to support any specific risk factors for severe COVID-19 in children.
 - However, extrapolations from studies on adults with COVID-19 and studies about other respiratory viral infections in children suggest that certain factors (e.g. immunocompromised state, underlying cardiac or pulmonary disease) may increase the risk of severe disease and thus could be considered when weighing the risks and benefits of antiviral agents.
- > Which antivirals should be considered?
 - There are no antivirals with proven efficacy for the treatment of COVID-19 as of April 14, 2020.

- If a decision to use an antiviral is made, remdesivir is the preferred agent. The rationale for this is the in vitro and animal data supporting the probable efficacy of remdesivir against SARS-CoV-2 and the fact that it is generally well-tolerated.
- Hydroxychloroquine could be considered for patients who are not candidates for remdesivir or when remdesivir is not available.
 - Suggested dosing regimen includes a loading dose on day 1 and a total duration of no more than 5 days of therapy.
 - It is recommended that hydroxychloroquine is not used in combination with azithromycin due to potential prolongation of the QTc.
 - G6PD screening is not routinely recommended prior to initiation of hydroxychloroquine because the risk of haemolysis from short courses of hydroxychloroquine is low. However, patients with known G6PD deficiencies should be monitored for haemolysis during hydroxychloroquine therapy.

Reviewed by: Dr Amanda Gwee

TRANSMISSION

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

COVID-19 in schools - the experience in NSW (Report- not yet peer review)

http://ncirs.org.au/sites/default/files/2020-04/NCIRS%20NSW%20Schools%20COVID_Summary_FINAL%20public_26%20April%202020.pdf

- > Important report on an investigation into all COVID-19 cases in New South Wales (NSW) schools
- > 15 schools included: 10 secondary schools and 5 primary schools between 5 March and 3 April, and 863 close contacts (face to face contact at least 15 minutes in same room as infectious case for 2 hours)
- > 18 index cases (9 students and 9 staff): 735 students and 128 staff were close contacts of the 18 index cases
- > No teacher or staff member contracted COVID-19 from any of the initial school cases
- > 2 children were secondary cases and were most likely infected at school: one was diagnosed by nose/throat swab testing and one had a positive antibody test 4 weeks after exposure
- > Limitations: very small number of index cases; study undertaken when school closures were beginning (from 23 March) and majority of cases imported ie not widespread community transmission so difficult to know applicability to that scenario; only 1/3 of close contacts were tested by "swab" and a subset by antibody testing so may underestimate the number of secondary cases; "infectious" contact not defined - many cases are not symptomatic or pre-symptomatic so likely not all cases and contacts identified.
- > Nevertheless, findings show that transmission in NSW schools likely to be limited and have led to policy decisions regarding reopening schools in NSW

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

SARS-CoV-2 is transmitted via contact and via the air between ferrets

<https://www.biorxiv.org/content/10.1101/2020.04.16.044503v1.full>

- > Current COVID-19 epidemiological data suggests the transmission of SARS-CoV-2 via primarily respiratory droplet and contact transmission, week data to support the airborne transmission

- > Using ferret model to assess whether SARS-CoV-2 spreads through direct contact and/or through the air (via respiratory droplets and/or aerosols)
- > Method:
 - 4 index (donor) ferrets who individually housed were inoculated intranasally with a clinical strain of SARS-CoV-2.
 - 1 direct contact ferret was added to each cage where the index ferret stayed, 6 hours post inoculation (dpi)
 - 4 indirect recipient ferrets were later placed in adjacent cages (10cm apart from the cage of index cases), one day pdi
 - Viral titer was measured by qPCR on samples (throat, nasal and rectal swab) collected from all ferrets on alternative days until day 21 pdi
- > Results:
 - In index ferrets, viral titer peaked at 3 days' post-inoculation (dpi) and was shedding up to 11-19 dpi
 - In direct contact ferrets: All 4 ferrets infected 1-3 days after exposure; viral RNA detected up to 13-15 days' post exposure (dpe)
 - In indirect recipient ferrets to understand the air (droplet/airborne) transmission: 3 of 4 infected 3-7 days after exposure; viral RNA detected up to 13-19 days' post exposure
 - Robust replication of SARS-CoV-2 upon transmission via direct contact and via the air, independent of the infectious dose
 - Viral RNA titer in samples was highest in Throat > Nasal > Rectal and only infectious virus found in throat and nasal swabs
 - Seroconversion occurred on 21 dpi/dpe and the antibody levels were similar in index, direct contact and indirect recipient ferrets
- > Conclusion:

First experimental evidence of airborne transmission of SARS-CoV-2 => precautions on current recommendations of community-level social distancing measures applied in many counties

Limitations: Does not determine whether SARS-CoV-2 air transmission was through respiratory droplets, aerosols, or both.

Reviewed by: Dr Lien Anh Ha Do

VACCINES

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

Extraordinary diseases require extraordinary solutions

<https://www.sciencedirect.com/science/article/pii/S0264410X20305326>

What are the ethical implications and potential utility of human challenge studies for COVID-19?

- > This opinion piece comes from distinguished and senior vaccinologist, Stanley Plotkin, and ethicist Arthur Caplan (NYU)
- > This article discussed the ethical implications of human challenge studies for COVID-19, as well as the critical evidence they could provide in informing vaccine development
- > They argue that despite the ethical implications of deliberately infecting healthy individuals with potentially deadly COVID-19, human challenge studies could be ethically achievable in 18-29-year-old volunteers who experience an extremely low mortality rate and whose informed consent was ratified to be free of coercion by ethics governance bodies.
- > These studies should only be undertaken once regulators agree that their evidence can be used to inform vaccine efficacy as well as correlates of protection
- > Although challenge studies might not be necessary if vaccine development accelerates rapidly, data from challenge studies could inform emergency use of vaccine candidates that show some efficacy in challenge studies whilst phase 3 efficacy studies continue to collect data for licensure at a later date
- > Any human challenge study (vaccine or therapeutic intervention) in the absence of effective treatment is of questionable ethical standing
- > They give a recommended age group for subjects (18-29 year olds) in whom the Wuhan CFR experience was 0.03%. But this is a non-zero risk of death.
- > For vaccine licensure, the place of human challenge studies is not yet established, though it has occurred.
- > A major shortcoming for definitive evaluation is in relation to safety. Even for moderate risk rates, the typical sample size of a challenge study can provide no confidence of safety.

Reviewed by: Professor Terry Nolan

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

The VACCINES Act, Deciphering Vaccine Hesitancy in the Time of COVID-19
<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa433/5819529>

What will the vaccine hesitant do in the face of this pandemic?

- > This article describes the benefits of using the language of “vaccine hesitant”, as opposed to “antivax”, as well as the history of vaccine hesitancy.
- > Authors discuss the VACCINES Act, trying to be introduced by Congress in the United States to provide federal funding for vaccine hesitancy surveillance and campaigns to increase public confidence in vaccines, although they also highlight that there are inadequate resources to fund serious communication campaigns
- > Will allow analysis of contextual influences that drive hesitancy at the local levels
- > This article is largely written to support the Vaccines Act, highlighting the potential for COVID-19 to persuade the vaccine hesitant to be in favour of immunization, but also raising fears that hesitancy around a COVID-19 vaccine will likely grow as time goes on
- > Vaccine hesitancy is a persistent global threat and requires solutions - will be important to consider when preparing for new COVID vaccines

Reviewed by: Associate Professor Margie Danchin

VIROLOGY

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

Profile of RT-PCR for SARS-CoV-2: a preliminary study from 56 COVID-19 patients

<https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa460/5822175#.XpxgwySokjA.twitter>

- > Viral RNA shedding was monitored in 56 hospitalised adult patients (median age 55 years (IQR, 42-68) with mild/moderate COVID-19 during the disease course.
- > Serial RT-PCR testing on throat/deep nasal cavity swabs was undertaken for each patient, until two consecutive negative results. The viral nucleic acid conversion time was determined to be the time from the onset of symptoms to the first negative test result
- > The median detection time from the onset of symptoms was 24 days (IQR, 18-31), with the longest time being 42 days
- > Virus can be detected in 100% cases at first week, 89.3% cases at second week, 66.1% cases at third week.
- > Viral shedding was up to 6 weeks after onset of symptoms
- > Those patients who have longer viral shedding were older with more comorbidities
- > 4/56 patients had viral RNA detection after the two consecutive negative samples, this questioned about the possible error in sampling.

Reviewed by: Dr Lien Anh Ha Do

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_z2uWV7r3FaPzAO86q9ZXBcTZ1QcCE_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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