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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.2

22 April 2020

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Response to COVID-19 and any other medical condition at this time is based on science that is new, often uncertain, subject to change, and dependent on context.

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ADULT MEDICINE

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

Clinical Features of COVID-19

<https://www.bmj.com/content/369/bmj.m1470>

The working case definition of coronavirus SARS-CoV-2 used to determine who receives viral testing includes severe acute respiratory illness with fever and related respiratory symptoms of cough and shortness of breath - this strategy captures those with a typical symptomatic profile. However, it doesn't identify those with unusual manifestations such as those without respiratory symptoms or those who remain completely asymptomatic, which are common

- > Gastrointestinal Symptoms
 - Diarrhoea may be the initial manifestation of infection in 2-40%; viral RNA has been detected in stool samples, sometimes at high levels
 - Recommendation: consideration for the possibility of fecal-oral transmission should be made as this would have clear implications for infection control
- > Neurological Symptoms
 - Gustatory and olfactory disorders have been reported (up to 53%); new-onset anosmia is being proposed as a new criteria for viral testing, especially in young patients who lack typical symptoms
 - Ischaemic or haemorrhagic stroke, dizziness, headache, musculoskeletal disturbance, altered mental state, Guillain-Barre syndrome, and acute necrotizing encephalopathy have been reported
 - Recommendation: systematic testing for SARS-CoV-2 should be considered in patients with acute neurological events during the epidemic
- > Ocular Symptoms
 - Conjunctival hyperaemia, chemosis, increased secretions in up to 32% of cases in China. SARS-Cov-2 detected in tears.

- > Cardiovascular Symptoms
 - Myocardial injury has been observed in patients especially with severe infection
 - Myocarditis, myopericarditis with reduced systolic function, cardiac arrhythmias, heart failure and misdiagnosis of acute coronary syndrome have also been observed
 - Hypercoagulable state and associated venous thromboembolic events including pulmonary embolism have been reported
 - Recommendation: Patients presenting with chest pain should alert clinicians to the possibility of COVID-19
- > Few Symptoms or Asymptomatic
 - Similar viral loads have been identified in the upper respiratory tract of both symptomatic and asymptomatic cases
 - Testing strategies that exclude patients with few symptoms are likely to miss a substantial proportion of cases.
 - Recommendation: testing should extend far beyond those patients who present only with typical symptoms

Reviewed by: Professor Fiona Russell

Jenny Pham – 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

Guillain-Barré Syndrome Associated with SARS-CoV-2

<https://www.nejm.org/doi/full/10.1056/NEJMc2009191>

Observational study of 5 patients with Guillain-Barré syndrome, infected with SARS-CoV-2 in northern Italy.

- > First symptoms were lower-limb weakness and paresthesia in 4 patients and facial diplegia, ataxia and paresthesia in one patient.
- > This was followed by generalised, flaccid tetraparesis or tetraplegia over 36 hours to 4 days, resulting in 3 patients requiring ventilation.
- > Interval between onset of COVID-19 symptoms and Guillain-Barré syndrome was 5-10 days. This is similar to the interval seen with Guillain-Barré syndrome that occurs after other infections.
- > In all patients, SARS-CoV-2 was not found in real-time PCR analysis of CSF.
- > Unable to determine:
 - If severe deficits and axonal involvement are typical features of Guillain-Barré syndrome associated with SARS-CoV-2.
 - The degree of respiratory complications secondary to neuromuscular failure from Guillain-Barré syndrome.

Reviewed by: Dr Wonie Uahwatasakul

CLINICAL PAEDIATRICS

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

Characteristics of paediatric SARS-CoV-2 infection and potential evidence for persistent fecal viral shedding

<https://www.nature.com/articles/s41591-020-0817-4.pdf>

Reporting of the epidemiological and clinical features of ten infected paediatric patients with testing of viral excretion through the respiratory and gastrointestinal tracts. Patterns of viral excretion were observed chronologically from both the respiratory and gastrointestinal tracts in all ten patients via nasopharyngeal and rectal swabs using real-time PCR

- > Eight of ten patients demonstrated real time RT-PCR-positive rectal swabs suggesting potential fecal viral excretion
- > Eight of ten patients demonstrated persistently positive real time RT-PCR positive rectal swabs after their nasopharyngeal testing had become negative
- > Four of ten patients were discharged from hospital after two consecutive negative real time RT-PCR rectal swabs (separated by at least 24 hours) - nasopharyngeal and rectal swabs were repeated weekly after discharge with two of four remaining negative on follow-up but one of four testing positive with rectal swab once again 13 days after discharge
- > One of ten patients was in hospital between Jan 27th, 2020 - Feb 11th, 2020
 - patient was discharged after two consecutive negative results each for both nasopharyngeal and rectal swabs
 - patient was readmitted to hospital because of a positive rectal swab on Feb 17th, 2020 - nasopharyngeal swab at that same time remained negative
- > As of February 20th, 2020 six of ten patients were testing positive for rectal swabs and were continued in hospital isolation and observation even though there were symptomatically and clinically well
- > Viral shedding from the gastrointestinal tract may be greater and last longer when compared to the respiratory tract
- > Compared to adult patients, the ten pediatric patients demonstrated milder clinical symptoms and fewer alterations in radiological and laboratory testing parameters
- > Consideration: rectal swab-testing may prove more beneficial when compared to nasopharyngeal swab-testing when judging the effectiveness of treatment and when used to determine the timing of termination of quarantine

Reviewed by: Professor Julie Bines

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

Coronavirus Disease 2019 in Children - Morbidity and Mortality Weekly Report

<https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm>

Data from 149,082 laboratory-confirmed COVID-19 cases reported to the CDC in the United States between February 12 - April 2, 2020 were analysed.

- > Demographics. Among 149,082 cases for which age was known, 2572 (1.7%) occurred in children aged <18 years despite this group accounting for 22% of the US population. Among paediatric cases for which sex was known, the majority (57%) occurred in males.
- > Clinical presentation. Fever, cough and dyspnoea are less reliably present in paediatric cases compared with adult cases - 93% of adults reported at least one of these symptoms compared with only 73% of paediatric patients.
- > Severity. Among children with COVID-19, 147 (estimated range = 5.7-20%) were reported to be hospitalised and 15 (0.58-2.0%) were admitted to ICU. These rates are lower than those reported in adults (10-33% and 1.4-4.5%, respectively). Children aged <1 year were more likely to be hospitalised than children of other ages. Children with underlying medical conditions are also more likely to require hospitalisation. Among cases for which information on both hospitalisation status and underlying medical conditions were available, 77% of hospitalised patients had at least one underlying medical condition compared with only 12% of un-hospitalised patients. 3 paediatric patients died.
- > Limitations. Most cases had missing data which resulted in hospitalisation rates being estimated as a range. Many cases occurred only days before publication, and so the outcomes of these cases are unknown and hospitalisation / ICU admission rates may be underestimated as a result.
- > Implications for Victoria: To put it in perspective, based on this CDC data, in Victoria, if the current highly successful containment measures were not as effective as they are, and we reached 1000 cases per week, then we would expect 17 children per week testing positive in the state, 5 children requiring hospitalisation most of whom would just need oxygen, and only one paediatric case every 3 weeks requiring PICU. We currently have less than 100 new total cases per week in Victoria. This paper should be reassuring for all paediatric health care workers.

Reviewed by: Professor Trevor Duke

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

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

Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain

<https://jamanetwork.com/journals/jamapediatrics/fullarticle/2764394>

- > Analysis of 365 children screened for COVID-19 from March 2 to March 16 2020 in Madrid, Spain across 30 different hospitals
- > 41 of 365 children (11.2%) tested positive for COVID-19, which was 0.8% of the total confirmed cases in the time period
- > The median age of children testing positive was 1 year (range 0-15 years)
- > 25 of 41 children (60%) testing positive required hospital admission
- > 4 required PICU (only 1 had a previous condition (recurrent wheezing))
- > The screening recommendations at the time selected for children with more significant disease resulting in a potentially higher proportion of children with COVID-19 requiring hospital admission compared to other studies

Reviewed by: Dr Wonie Uahwatanasakul and Associate Professor Margie Danchin

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

Delayed access or provision of care in Italy resulting from fear of COVID-19 (correspondence)

[https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642\(20\)30108-5/fulltext](https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30108-5/fulltext)

- > During Italy's lockdown for COVID-19, there were significant decreases (from 73% - 83%) in Paediatric Emergency department visits in the period of March 1-27, 2020 compared to the same time period in 2019 and 2018.
- > This can be partly explained by the lower rates of acute infections and trauma as a result of closure of schools and sports activities. However, other reasons such as scarcity of available health resources due to pandemic related redistribution and parents' fear of exposure to SARS-COV-2 in a hospital setting should be considered.
- > Examples of 12 cases were provided to illustrate the detrimental effect on Paediatric health of delayed access to hospital. These included:
 - Children presenting with acute onset of type 1 diabetes and severe ketoacidosis even though parents had recognized abnormal symptoms (e.g. Polydipsia, polyuria).
 - A neonate was kept at home despite vomiting for several days because of hypertrophic pyloric stenosis and arrived in the emergency department with hypovolemic shock.

- A child presenting to the emergency department after being unable to pass faeces for more than a week, got diagnosed with
 - Wilm's tumor. The diagnosis by telephone from his paediatrician had been functional constipation.
- > Of the 12 cases, half of the children were admitted to ICU and four died. Notably, no death occurred in the same hospitals during the same period in 2019, and the total yearly number of paediatric deaths in these hospitals ranges from zero to three.
- > The article calls for the need to provide clear guidance for both the general population and health-care workers in a Pandemic such as COVID-19; Parents should be educated about the risks of delayed access to hospital care and healthcare workers should be made aware of their specific duties and obligations.
- > Important to provide clear messaging around when to stay at home due to social distancing requirements and when to appropriately seek medical care

Reviewed by: Associate Professor Margie Danchin

CO-INFECTION

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

Rates of Co-infection Between SARS-CoV-2 and Other Respiratory Pathogens

[doi:10.1001/jama.2020.6266](https://doi.org/10.1001/jama.2020.6266)

- > 1217 specimens from 1206 symptomatic patients were tested for SARS-CoV-2 and other respiratory pathogens and retrospective analysis performed to compare rates of co-infection between SARS-CoV-2 and other pathogens
 - In total 116 (10.5%) were positive for SARS-CoV-2
 - Of these, 24 (20.7%) had 1 or more additional pathogen detected (as compared to 294/1101, 26.7% of SARS-CoV-2 negative samples showing co-infection)
 - The most common co-infections with SARS-CoV-2 were rhinovirus/enterovirus (6.9%), respiratory syncytial virus (5.2%), non-SARS-CoV-2 Coronaviridae (4.3%) and metapneumovirus (HMPV) (1.6%)
 - The most common co-infections with non-SARS-CoV-2 included rhinovirus/enterovirus (12.1%), HMPV(4.3%), coronaviridae (3.5%) and RSV (2.9%)
 - Differences in rates of non-SARS-CoV-2 pathogens between SARS-CoV-2 positive and negative patients were not statistically significant
- > Rates of co-infection between SARS-CoV-2 and other respiratory pathogens suggest higher rates of co-infection than previously reported however there is no clear pattern of co-infections
- > Limitations: very limited clinical data and no analyses to examine relationship between co-infection and COVID-19 severity.

Reviewed by: Dr Danielle Wurzel

CRITICAL CARE

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

Extracorporeal membrane oxygenation (ECMO): does it have a role in the treatment of severe COVID-19?

[https://www.ijidonline.com/article/S1201-9712\(20\)30191-0/pdf](https://www.ijidonline.com/article/S1201-9712(20)30191-0/pdf)

- > This study aimed to describe and discuss the clinical outcomes of ECMO for ARDS patients, ECMO use for severe COVID-19 in China, the indications of ECMO use, and some important issues associated with ECMO
- > The interim guidance formulated by the World Health Organisation (WHO) supports the use of ECMO as a rescue therapy in patients with refractory hypoxemia, however, the clinical benefit use of ECMO has not been shown in any studies. Based on the entry criteria of EOLIA, indications of ECMO are as follows:
 - PaO₂:FiO₂ < 50mmHg for 3 hours
 - PaO₂:FiO₂ < 80mmHG for > 6 hours
 - pH < 7.25 with PaCO₂ ≥ 60 mmHg for > 6 hours with a respiratory rate increased to 35 breaths per minute, adjusted for plateau pressure ≤ 32 cmH₂O
- > Many factors including the duration of mechanical ventilation, the severity of underlying disease, the experience of trained medical staff, and ECMO equipment could affect the outcomes of ECMO treatment. Without significant evidence on efficacy of ECMO treatment, a shortage of ECMO and the safety of medical staff outweighs the clinical benefit of ECMO in critically ill patients.
- > According to ELSO, the global ECMO registry, there have been over 1000 COVID-19 patients treated with ECMO, only a few children (and several of these went on ECMO for other reasons, such as Staph septic shock or cardiomyopathy). Outcomes of adults on ECMO with COVID-19 are not yet published, but there have been a number of survivors.

Reviewed by: Professor Trevor Duke

DIAGNOSTICS AND SAMPLING

Kieren Fahey – 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne.

What is the sensitivity of self-collected throat washing samples for detecting SARS-CoV-2?

<https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa416/5818370>

24 paired throat washing and nasopharyngeal swab samples were collected from 11 confirmed SARS-CoV-2 patients in Guangzhao, China. (aged 26-83, median 53 days after onset of symptoms).

- > For 5 paired samples, throat washing samples returned positive for SARS-CoV-2 nucleic acid, whilst nasopharyngeal swabs returned negative results
- > Analysis (chi-squared test) indicated the positive testing rate of throat washing samples was significantly higher than that of nasopharyngeal swabs
- > Nasopharyngeal swabs present a significant risk for healthcare worker infection during collection, highlighting the need for alternative, safer, methods of detection
- > Limitations
 - Small sample size (only 11 unique patients)
 - As testing was performed between 48 and 57 days after symptoms onset, these results may not be reflective of screening sensitivity at time of symptom onset.
 - Larger studies will need to be performed on the efficacy of throat washing samples as a diagnostic test at the time of symptom onset

Summary: In a small study 53 days after symptom onset, throat washing samples have been shown to be a more sensitive test for detecting SARS-CoV-2 when compared to nasopharyngeal swabs. Adopting this method may have the additional benefit of reduced healthcare worker infections during collection.

Reviewed by: Dr Danielle Wurzel

DISABILITY

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

The COVID-19 Response Must Be Disability Inclusive (Correspondence)

<https://www.thelancet.com/action/showPdf?pii=S2468-2667%2820%2930076-1>

- > There are more than one billion people living with a disability who face a disproportionate increased risk of morbidity and mortality during the COVID-19 pandemic.
- > The inherent healthcare access inequities, disruption of essential assistant services (such as personal care, medication and food deliveries) and pre-existing comorbidities all contribute significantly to this risk.
- > To mitigate this, the following must be implemented:
 - All public health communication pertaining to COVID-19 should be presented in plain language across multiple accessible formats including mass digital media channels and sign language interpretation.
 - Care workers and family members must be provided with protective measures that allow them to safely continue supporting people living with disabilities.
 - Rapid awareness training of healthcare staff regarding the diverse needs of people living with disabilities must occur.
- > It is essential that people living with disabilities be included in the preparation and response planning of COVID-19 strategies to minimise widening of the existing health disparities.

Reviewed by: Dr Kate Milner

EPIDEMIOLOGY AND PUBLIC HEALTH

Daniel Lindhom – 4th Year Medical Student,
Department of Paediatrics, The University of Melbourne

COVID-19, Australia: Epidemiology Report 10 (Reporting week to 5 April 2020)

[https://www1.health.gov.au/internet/main/publishing.nsf/Content/1D03BCB527F40C8BCA258503000302EB/\\$File/covid_19_australia_epidemiology_report_10_reporting_week_ending_23_59_aest_5_april_2020.pdf](https://www1.health.gov.au/internet/main/publishing.nsf/Content/1D03BCB527F40C8BCA258503000302EB/$File/covid_19_australia_epidemiology_report_10_reporting_week_ending_23_59_aest_5_april_2020.pdf)

- > Comprehensive descriptive epidemiology of COVID-19 cases in Australia up until 5 April, 2020
- > NSW has highest rate; most cases in urban areas
- > 41 cases of COVID-19 have been reported in Aboriginal and Torres Strait Islander persons, with the majority of these cases in major cities. The completion of the Indigenous Identification status was 79% (ie incomplete reporting)
- > Number of cases was highest in the 20–29 years age group, and the highest rate of disease was among those in the 60–69 years age group
- > Number of Males vs females for case detection is equal
- > Acquisition: 66% had recent international travel history and 32% locally acquired. Cruise ships account for a substantial proportion.
- > Symptoms: Cough (71%); fever (49%), sore throat (44%), and headache (39%). Only 4% or fewer of all cases reported either pneumonia or acute respiratory disease (ARD); and loss of taste was reported from 324 cases and loss of smell from 322 cases. These conditions were reported in at least 5.5% of cases, noting that this is currently not a standard field in NNDSS, and is likely to under-represent those presenting with these symptoms.
- > Of the total cases of COVID-19 (n = 5,805) notified, 11% (n = 628) were admitted to hospital: median age of hospitalised cases was 59.5 years (range 0–94 years), with the highest proportion of hospitalised cases in the 60–69 years age group. Of the hospitalised COVID-19 cases, 13% (n = 82) were admitted to an intensive care unit (ICU), with 29 cases requiring ventilation.
- > 33 COVID-19 associated deaths up to 5 April 2020: median age of cases who died was 80 years (range 60–94 years); 21 of the cases were male and 12 were female.

- > Preliminary findings suggest low onward transmission among children with 1.9% of close contacts who were children testing positive for the virus from an investigation into the transmission of SARS COV-2 in school and child-care centre settings in NSW.
- > Includes a good summary of the global situation too.

Reviewed by: Professor Fiona Russell

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

Spread of SARS-CoV-2 in the Icelandic Population

<https://www.nejm.org/doi/full/10.1056/NEJMoa2006100?query=RP>

- > Targeted testing in Icelandic people who were at high risk for infection and population screening using two strategies: an open invitation to 10,797 persons and sending random invitations to 2283 persons
- > 1221 of 9199 persons (13.3%) were positive for SARS-CoV-2. Of those tested in the general population, 0.8% in the open-invitation screening and 0.6% in the random-population screening tested positive for the virus. In total, 6% of the population was screened.
- > Children under 10 years of age were less likely to receive a positive result than were persons 10 years of age or older (6.7% vs 13.7%), for targeted testing; in the population screening, no child under 10 years of age had a positive result, as compared with 0.8% of those 10 years of age or older
- > Fewer females than males received positive results both in targeted testing (11.0% vs. 16.7%) and in population screening (0.6% vs. 0.9%)
- > The haplotypes of the sequenced SARS-CoV-2 viruses were diverse and changed over time
- > Very low levels of population immunity which could be due to effective public health measures in halting community transmission
- > Still need a valid serological test

What can we learn from school closures and the impact on disease control during the 1918-1919 Influenza Pandemic in the USA?

<https://jamanetwork.com/journals/jama/fullarticle/208354>

- > Historical data was used to examine cities in the US from 1918-1919 to determine whether city-to-city variation in mortality was associated with the timing, duration, and combination of nonpharmaceutical interventions; altered population susceptibility associated with prior pandemic waves; age and sex distribution; and population size and density.
- > School closure and public gathering bans were the most common combination implemented in 34 cities (79%); this combination had a median duration of 4 weeks and was associated with reductions in weekly excess pneumonia and influenza deaths.

- > Cities that implemented nonpharmaceutical interventions earlier had greater delays in reaching peak mortality, lower peak mortality rates, and lower total mortality. There was an association between increased duration of nonpharmaceutical interventions and a reduced total mortality burden.
- > Second peaks frequently followed the sequential activation, deactivation, and reactivation of nonpharmaceutical interventions, highlighting the transient protective nature of nonpharmaceutical interventions and the need for a sustained response. See Figure 3.
- > Although these urban communities had neither effective vaccines nor antivirals, cities that were able to execute classic public health interventions before the pandemic appeared to have an associated mitigated epidemic experience.
- > Can these lessons be applied to COVID-19? Yes, however COVID-19 differs in many ways to influenza eg. we do not know how much transmission occurs by children in the school setting.

GLOBAL HEALTH

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

What are the risks and benefits of sustaining routine childhood immunisation programmes in Africa during the Covid-19 pandemic?

<https://cmmid.github.io/topics/covid19/control-measures/EPI-suspension.html> (not peer reviewed)

- > Aim: To weigh the health benefits of continuing routine infant immunisation delivery in Africa against the risk of acquiring coronavirus infections through visiting vaccination services.
- > Method: Using previously reported child mortality rate to approximate the deaths caused by discontinuation of childhood vaccination during a 6-month COVID-19 risk period. Benefit-risk ratios for sustaining routine childhood immunisation were used.
- > Key finding: For one case of COVID-19 death attributable to an infection acquired during a child vaccination visit, there would be 128 (34 - 1 247) future deaths in children from vaccine preventable diseases if routine childhood vaccination is not sustained. Benefit-risk ratio increases to 52,000 (3,000 - 46,487,000).
- > Limitations: a number of assumptions including (i) assuming the unvaccinated cohort of children during COVID-19 period is at similar risk of contracting vaccine preventable disease as a completely unvaccinated children cohort; (ii) assuming no catch-up administration once the pandemic ends; and (iii) assuming contact reducing measures have limited effect on measles and pertussis transmission.

Reviewed by: Associate Professor Margie Danchin

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

Estimates of the Potential Impact of the COVID-19 Pandemic on Sexual and Reproductive Health in Low- and Middle-Income Countries

<https://www.guttmacher.org/journals/ipsrh/2020/04/estimates-potential-impact-covid-19-pandemic-sexual-and-reproductive-health>

- > Due to lockdown associated with physical distancing measures, the potential annual impact of a 10% proportional decline in the use of sexual and reproductive health care services was estimated in 132 low- and middle-income countries
- > For example, a 10% decline in service coverage of essential pregnancy-related and newborn care was estimated to result in:
 - 1,745,000 additional women experiencing major obstetric complications without care
 - 28,000 additional maternal deaths

- 2,591,000 additional newborns experiencing major complications without care
- 168,000 additional newborn deaths
- > Clear need to continue routine essential services during COVID-19 pandemic

IMAGING

Associate Professor Simone Mandelstam, Senior Specialist
Paediatric Radiologist RCH, Departments of Paediatrics and
Radiology University of Melbourne

Chest CT and Coronavirus Disease (COVID-19): A Critical Review of the Literature to Date

<https://www.ajronline.org/doi/abs/10.2214/AJR.20.23202>

- > Is there a role for CT in screening and diagnosis of COVID-19 and can it replace RT-PCR when testing availability is limited?
 - Critical review of multiple CT publications including Fang et al (51 patients) and Ai et al (1014 patients)
- > Overestimation of Sensitivity and Specificity of CT in all publications
 - Low quality evidence - retrospective reviews and case series
 - Selection bias
 - Faulty design characteristics
 - CT used as a binary test with no defined threshold for positive findings and abnormally low thresholds different to usual clinical practice
 - No objective CT criteria to define positive COVID-19
 - No singular or unique CT findings - “characteristic” ground- glass peripheral lower lobe changes can be seen in many infectious and non- infectious conditions
 - No control groups for comparison of conditions other than viral pneumonias
- > Implications for CT in Clinical Practice
 - No data to support use of CT as screening tool
 - CT should be reserved for evaluating complications of COVID-19 or if an alternate diagnosis is suspected.

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

The Role of Chest Imaging in Patient Management during the COVID-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society

<https://pubs.rsna.org/doi/10.1148/radiol.2020201365>

Multidisciplinary panel composed of radiologists and pulmonologists from 10 countries evaluated the value of imaging adult patients in the context of COVID-19.

- > Imaging is not indicated:
 - As a screening tool for COVID-19 in asymptomatic patients.
 - For patients with suspected disease or mild clinical features, unless they are at risk of disease progression.
- > Imaging is indicated for:
 - Patients with COVID-19 and worsening respiratory symptoms.
 - Patients presenting with moderate/severe features of COVID-19 regardless of COVID-19 test results.
 - Patients who have functional impairment/hypoxaemia following recovery from COVID-19.
- > Chest X-ray is insensitive in mild or early infection.
- > Daily CXR are not indicated in stable intubated patients with COVID19 - no difference in outcomes and increased exposure of radiographers.
- > CT is more sensitive for early lung disease, disease progression and can be used to detect alternative diagnoses such as heart failure secondary to COVID-19 myocardial injury or other treatable pathologies.
- > COVID-19 testing is indicated in patients with CT findings that are suggestive of COVID-19 in areas of high prevalence or with high pre-test probability.

Reviewed by: Associate Professor Simone Mandelstam

IMMUNOLOGY

Professor Philip Sutton – Group Leader, Mucosal Immunology Group, MCRI

Associate Professor Paul Licciardi, Team Leader, New Vaccines Group, MCRI

Dr Dan Pellicci- Group Leader, Cellular Immunology Group, MCRI

SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor

[https://www.cell.com/cell/fulltext/S0092-8674\(20\)30229-](https://www.cell.com/cell/fulltext/S0092-8674(20)30229-4?returnURL=https%3A%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867420302294%3Fshowall%3Dtrue)

[4?returnURL=https%3A%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867420302294%3Fshowall%3Dtrue](https://www.cell.com/cell/fulltext/S0092-8674(20)30229-4?returnURL=https%3A%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867420302294%3Fshowall%3Dtrue)

This study made a number of very important findings. The key one related to the finding that the SARS-CoV-2 virus infects cells by using its spike protein to attach to ACE2 on host cells. From an immunological perspective, the important findings were:

- > Sera from people who had recovered from SARS infection contained neutralising antibodies that were shown to reduce the ability of SARS-CoV-2 to infect human cells in culture
- > Similarly, antisera from rabbits raised against the S1 portion of the spike protein from SARS-CoV-2 strongly reduced the ability of this virus to infect mammalian cells.
- > The importance of these immunological observations is that they provide the first direct proof that antibodies, in particular against the spike protein, could protect against SARS-CoV-2 infection, at least in culture. This supports firstly, the idea that antibodies were likely to be the mechanism of protection against this infection and secondly, that the spike protein was a viable candidate antigen for use in a vaccine against SARS-CoV-2.
- > It also supports the use of convalescent sera in the treatment of patients with severe infection.

INFECTION CONTROL

Dr Vanessa Clifford - Infectious Diseases physician and Microbiologist, RCH/RWH; Honorary Research Fellow in the Infection and Immunity Group, MCRI; and honorary Senior Fellow, Department of Paediatrics, The University of Melbourne

Aerosol and Surface Distribution of Severe Acute Respiratory Syndrome Coronavirus 2 in Hospital Wards, Wuhan, China, 2020

https://wwwnc.cdc.gov/eid/article/26/7/20-0885_article

Single hospital study from Wuhan, China. Investigators measured the presence of SARS-CoV-2 in surface and air samples from an intensive care unit (ICU) and a general COVID-19 ward.

- > SARS-CoV-2 RNA frequently detected on high-touch surfaces and the floor, particularly in the ICU environment
- > SARS-CoV-2 RNA detected in air samples from both ICU (14/40; 35%) and general COVID-19 ward (2/16; 12.5%)
- > Patient care and treatment areas were most likely to have SARS-CoV-2 detected in air samples, however it was also occasionally detected up to 4m from patient bedside
- > This study supports recommendations to use airborne precautions when caring for patients with COVID-19 undergoing aerosol generating procedures
- > The study does not provide direct evidence around transmission of viral RNA present in air samples, as viability of virus, and infective dose, are unknown

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

Masks for all? The science says yes.

<https://www.fast.ai/2020/04/13/masks-summary/>

- > A summary of literature and modelling on use of masks during COVID-19 pandemic, including comparing trajectories of countries with/without mask-wearing policies.
- > Modelling suggests that if most people wear a mask in public, the transmission rate ('effective R') will reduce below 1.0, stopping the spread of the disease (anything above 1.0 permits spread).
 - Effectiveness of mask-wearing to reduce disease spread depends on: how well the mask blocks the virus, proportion of public wearing masks, and transmission rate (i.e. if masks block 50% of virus particles, high rates of mask-wearing could contain the disease)

- > If you have COVID-19 and cough on someone from 8 inches away, wearing a cotton mask will reduce the amount of virus you transmit to that person by 36 times, and is even more effective than a surgical mask.
- > Real-world evidence shows that countries with mask-wearing policies have reduced transmission and number of cases, when compared to countries that do not have mask-wearing policies
 - South Korea had rapid community spread initially, similar to Italy, but in late February the South Korean government provided masks to all citizens. The numbers of reported cases then decreased significantly and remain at low levels, compared to Italy's numbers which have increased (without mask policy).
 - Comparing Austria and Czechia: both introduced social distancing at same time, Czechia also introduced mandatory mask wearing. The Austrian case rate continued to increase, whilst Czechia's flattened.

Summary: Keep your droplets to yourself – wear a mask. Instructions on how to make a cloth mask from home materials included.

Reviewed by: Professor Fiona Russell

MENTAL HEALTH

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

How to mitigate the effects of home confinement on children during the COVID-19 outbreak?

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30547-X/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30547-X/fulltext)
(Correspondence)

- > Prolonged school closure and home confinement can have negative effects on children's mental and physical well-being
- > Studies suggest when children are not at school, there is an increase in screen time, less physical activities, irregular sleep patterns and less healthy diet. These can result in weight gain and poorer physical health
- > Psychological stressors such as fear of infection, confinement frustration, lack of contacts with friends and family financial loss can impact on their mental health. Sprang and Silman showed the mean post-traumatic stress scores were four times higher in children who had been quarantined than those who were not quarantined
- > To minimise these consequences, online materials need to be effective at meeting the course requirements yet not overburden children, this allows more time for physical activities outside of the study and alleviates the stress burden
- > An online platform that includes advice on healthy lifestyle and psychological support should be promoted for children and adolescence. Psychologists can offer online counselling to cope with the mental health issues of domestic conflicts and tensions with parents and domestic conflicts
- > Due to the large volume of epidemic-related news children are exposed to, parents play a key role in having a direct conversation with children and alleviate their anxiety. With the right parenting approach, this is an important time where family bonding can be strengthened and child psychological needs met

Reviewed by: Professor David Coghill

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

Collaboration is key in addressing mental health research priorities during the COVID-19 pandemic

<https://www.thelancet.com/action/showPdf?pii=S2215-0366%2820%2930168-1>

Research priorities for the United Kingdom have been outlined utilising the insight of experts, people with a lived experience of mental health issues and the public to identify the immediate and long-term psychological, social and neuroscientific impacts of the pandemic to mechanistically inform intervention.

- > Psychological: identify causal precipitators of anxiety, depression, distress, and suicide; optimise personal care plans during social distancing and isolation using methods that promote alternative social engagement, resilience and altruism.
- > Social: identify unique contributors to mental illness in vulnerable groups; understand the potential burden of traditional and social media exposure; identify the most effective method of communicating behavioural interventions to slow viral transmission and promote well-being.
- > Neuroscience: build a neuropsychiatric database of COVID-19 patients; expand the capacity of infected tissue handling for post-mortem analysis, building pathology and molecular neuroscience networks; understand how SARS-CoV-2 might travel through and propagate in the nervous system, and how the immune response may contribute to illness; validate possible clinical biomarkers of neurological sequelae using MRI and other modalities; investigate the long-term relationship between SARS-CoV-2 and post infectious fatigue and depression.
- > The authors stressed the importance of multidisciplinary collaboration, quality and standardisation of research design and the need to coordinate pre-existing infrastructure to centralise and track data in real-time. Pre-existing cohorts could be recruited for longitudinal studies and robust population-based novel studies should be designed.
- > These research objectives aim to guide intervention and public health policy during the current outbreak, potential secondary outbreaks of COVID-19 and in future pandemics.

What is the impact of shutting down school based mental health services?

<https://jamanetwork.com/journals/jamapediatrics/fullarticle/2764730>

The authors highlighted the importance of schools in providing mental health services, and suggested strategies to overcome their shutdown.

- > 13% school students aged 12-17 years in the United States accessed school-based mental health services last year.
- > Of students that require mental health care 57% receive part of their care from school-based services and up to 35% receive support exclusively from school-based services, making these students particularly vulnerable.
- > Telemental health services are a recommended immediate replacement, but with caution regarding accessibility and privacy. Mobile mental health apps have shown limited effectiveness and need further validation.
- > Public health policy should address the need to expand telehealth services and cater for inequities amongst minority groups.
- > In future schools could liaise with community based mental health services to deliver care in schools allowing students to engage with these services in multiple settings.

Reviewed by: Professor David Coghill

PERINATAL HEALTH

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

Pregnant versus non-pregnant COVID-19 Hospital Admissions

[https://www.ajog.org/article/S0002-9378\(20\)30437-3/pdf](https://www.ajog.org/article/S0002-9378(20)30437-3/pdf)

Comparison of test-positivity rates in pregnant and non-pregnant patients over a 4 week period in March 2020 in New York State

- > Total of 21,980 admissions (3,064 pregnant/postpartum and 19,299 not pregnant) at 14 hospitals
- > Routine SARS-CoV-2 testing was not conducted
- > Increase in percent testing positive for SARS-CoV-2 in pregnant/postpartum group from 0.14% of all admissions in week 1 to 5.65% in week 4 (RR 14.81 95% CI: 2.07-107.38).
- > Increase in percent testing positive for SARS-CoV-2 in non-pregnant group from 1.21% of all admissions in week 1 to 56.79% in week 4 (RR: 46.99 95%CI: 36.72-60.15).

Study had intrinsic issues, most importantly that non-pregnant patients were admitted because of symptoms and pregnant patients for delivery; however, study reinforces the findings from other studies that pregnant women are mostly asymptomatic and will not be detected by the current testing regimen.

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

Universal Screening for SARS-CoV-2 in Women Admitted for Delivery

<https://www.nejm.org/doi/full/10.1056/NEJMc2009316?query=RP>

Between March 22 and April 4 2020, all pregnant women presenting for delivery were tested for SARS-CoV-2 at a New York Hospital.

- > 215 patients were tested for SARS-CoV-2. 15.4% were positive. Of the 33 positive women, 29 were asymptomatic.
- > Of 29 asymptomatic women, 3 developed a fever prior to discharge
- > Prevalence of SARS-CoV-2 in this study has limited generalisability in regions with lower rates of infection. True infection prevalence may also be underreported due to false negative results.

- > During high periods of community transmission, universal screening is important to determine use of PPE, isolation practices, bed assignments and inform neonatal care, as many women had no symptoms and the potential for asymptomatic women to transmit infection in the hospital setting and to their baby during delivery is significant but unknown.

Reviewed by: Professor Fiona Russell

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

Hope, and New life, in a Brooklyn Maternity Ward Fighting Covid-19

<https://www.nytimes.com/2020/04/12/nyregion/coronavirus-births-mothers.html?referringSource=articleShare>

NY Times article focusing on a New York Hospital at the centre of the crisis and several personal stories recounted by Doctors and patients

- > Nearly 200 babies have arrived since March 1, with 29 pregnant or delivering women having suspected or confirmed cases of COVID-19
- > These women have been kept isolated from other patients
- > Even healthy pregnant women are anxious and aren't feeling the happiness and joy usually associated with this experience
- > Some pregnant patients have even avoided coming into hospital, for fear of the virus, and a few of them have become dangerously ill
- > However, not one mother or baby has been lost, although several very ill requiring ICU and ventilation and one an emergency LUSC for maternal reasons
- > Unlike many hospitals in the New York area, Brooklyn hospital doesn't separate mothers and babies – even allowing mothers to nurse their newborns whilst wearing PPE
- > One critically ill lady was approved to receive remdesivir, and showed significant improvement – although it is difficult to assess whether this was due to the drug itself

Reviewed by: Professor Suzanne M Garland

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

Clinical Characteristics of Pregnant Women with COVID-19 in Wuhan, China (correspondence)

<https://www.nejm.org/doi/full/10.1056/NEJMc2009226?query=RP>

From December 8, 2019 – March 20, 2020, a total of 118 pregnant women with COVID-19 were identified using the medical records of 50 hospitals in Wuhan.

- > Median age of all included women was 31 years. 52% (55/106) were nulliparous, and two-thirds (64%, 75/118) were infected in the third trimester.

- > 112 women were symptomatic, with the most common symptoms being fever (75%) and cough (73%). 88 of the 111 women (79%) who underwent chest CT had infiltrates in both lungs.
- > Out of the 118 women: 92% had mild disease and 8% had severe disease (with tachypnoea and hypoxaemia); 1 of whom required non-invasive mechanical ventilation. Most women (including all those with severe disease) were discharged. No deaths occurred.
- > There were 3 spontaneous abortions, 2 ectopic pregnancies, and 4 induced abortions (all due to concerns regarding COVID-19).
- > Of the 68 women who delivered during the study period:
 - 93% underwent a caesarean section. More than half had the procedure due to concerns about the effects of COVID-19 on the pregnancy.
 - 21% were premature deliveries; 8 were induced (7 owing to concerns regarding the effects of COVID-19).
 - No babies had neonatal asphyxia.
- > Neonatal throat swabs of 8 newborns and breast milk samples of 3 mothers were tested for SARS-CoV-2; all results were negative.
- > In contrast to influenza, the current study did not demonstrate any increased risk of severe disease with SARS-CoV-2 among pregnant women compared to the general population, but very limited sample size to determine this and more data required.

Reviewed by: Dr Claire von Mollendorf

THERAPEUTICS

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

When should ACE-1 inhibitors and angiotensin receptor blockers (ARB) be continued in relation to SARS-CoV-2 infection status?

<https://doi.org/10.1136/bmj.m1313>

- > Editorial providing advice on ACE-1 inhibitor and ARB use in patients who are positive, negative or have recovered from COVID-19
- > Decisions are complex because
 - ACE-1 inhibitors and ARBs increase ACE-2 activity, which would theoretically increase SARS-CoV-2 entry into cells
 - ACE-2 activity could increase angiotensin II conversion to angiotensin-(1-7) which has anti-inflammatory properties of unclear benefit in COVID-19
- > The following recommendations are summarised in Fig 1 and are the authors suggestions until more clinical evidence is available
 - Patients taking these drugs for long term benefits (e.g. managing mild hypertension), should have medication withheld only if they get an infection.
 - For patients in this group with increased risk of SARS-CoV-2 infection, it may be appropriate to defer treatment to reduce a theoretical short-term risk of continuing treatment while infected
 - Patients who would deteriorate rapidly if ACE-1 inhibitor or ARB therapy were discontinued should continue to receive them even during active infection

Reviewed by: Dr Amanda Gwee

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

Compassionate Use of Remdesivir for Patients with Severe Covid-19

<https://www.ncbi.nlm.nih.gov/pubmed/32275812>

- > A small cohort study supported by Gilead Sciences reporting the outcomes of 53 patients in different treatment facilities in the UK, Europe, Japan and the US who received compassionate access IV remdesivir therapy (200 mg day 1, then 100 mg daily for 9 days).
- > The baseline characteristics for patients were variable:
 - At baseline 64% were receiving mechanical ventilation; median age 64 years (interquartile range 48 to 71)

- Variable length of hospitalisation and clinical course before receiving remdesivir
- Variety of coexisting medical conditions (hypertension, diabetes, hyperlipidaemia, asthma)
- > The results largely showed clinical improvement:
 - Clinical improvement in oxygen support requirements described in 68% of patients with a median of 18 days (max 30 days) follow up
 - Mortality rate 13% overall (18% for those requiring invasive ventilation, 5% for those requiring non-invasive ventilation)
 - Outcomes worse in those with co-existing medical conditions or those requiring invasive ventilation at baseline
- > Limitations:
 - Lack of appropriately matched controls. Therefore, is it unclear whether patients improved due to the natural history of the disease or due to remdesivir treatment.
 - The viral load was not determined and so no data is available to assess the in vivo effect on the viral load.

Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial (not peer reviewed)

<https://www.medrxiv.org/content/10.1101/2020.04.10.20060558v1>

- > Open label multicenter RCT of patients hospitalised with COVID-19 in China.
- > 150 patients included in analysis and randomised 1:1 to receive standard of care vs standard of care + hydroxychloroquine
- > Treatment regimen for hydroxychloroquine group: loading dose 1,200 mg daily for 3 days, followed by 800 mg daily. Treatment duration 2 weeks (mild/moderate) or 3 weeks (severe patients).
- > Primary endpoint was negative respiratory tract PCR by 28 days and was similar in both groups (85.4% in hydroxychloroquine group and 81.3% in standard of care group)
- > Secondary endpoints included
 - Negative PCR at day 4, 7, 10, 14 or 21 - similar at each time point between both groups
 - Normalisation of CRP, elevation of blood lymphocyte counts - more rapid normalisation in treatment group but similar by day 28. May indicate that the clinical benefit is through anti-inflammatory activity
 - Symptom alleviation - median time to alleviation of symptoms 19 days in the treatment group vs 21 days in the standard of care group
 - Safety - adverse events 30% in the treatment group vs 8.8% in the standard of care group
- > This manuscript reports a planned interim analysis due to promising trial results.

- > Limitations
 - Open label study
 - Patients in the standard of care group received a variety of other antiviral drugs: lopinavir-ritonavir, arbidol, oseltamivir, virazole, entecavir, ganciclovir, and interferon-alpha
- > Manuscript not peer reviewed

Reviewed by: Dr Diana Zannino and Dr Amanda Gwee.

VACCINES

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

Coronavirus vaccines: five key questions as trials begin

<https://www.nature.com/articles/d41586-020-00798-8>

What are the major concerns facing the coronavirus vaccine in its unprecedented rapid development?

- > There is a need for evidence that humans develop immunity from SARS-CoV-2 infection; assumptions that this occurs are based on other coronaviruses and limited evidence in rhesus monkeys infected with SARS-CoV-2. A preprint from China looked at two rhesus macaques (monkeys) that recovered from SARS-CoV-2 infection, which caused them only mild illness. The monkeys did not seem to become re-infected when researchers exposed them to the virus for a second time four weeks after their initial exposure. Studies looking for evidence that humans react in the same way are underway eg. studying people potentially exposed multiple times and looking at re-infection rates.
- > There is even less data around the longevity of an immune response to SARS-CoV-2 - evidence from previous SARS and MERS outbreaks on the longevity of the immune response is equivocal
- > Whilst a vaccine that generates antibodies to the S-spike of the SARS-CoV-2 is assumed to be the initial solution, it's unclear whether other antibodies or immune function will be needed
- > It is difficult to predict which candidate is likely to be successful at this stage. This is largely due to a lack of animal and initial human trial results which, in many cases, are occurring in parallel
- > The risk of disease enhancement is a very real safety concern for a SARS-CoV-2 vaccine. Need for animal studies to rule this out before moving to human trials. However, the risk of expediting development at the expense of definitively ruling out disease enhancement needs to be weighed against the risk of not having a vaccine quickly available

Reviewed by: Professor Fiona Russell

If a coronavirus vaccine arrives, can the world make enough?<https://www.nature.com/articles/d41586-020-01063-8>

How can we design production pipelines in preparation for a coronavirus vaccine? This article interrogates the potential issues with the production of a COVID-19 vaccine. It updates us on all the aspects that governments and industry need to consider in preparation for bringing whichever vaccine is successful to market.

- > The infrastructure needed to bring a successful vaccine to market hinges entirely on the type of vaccine. Whilst technology already exists to produce inactivated vaccines at scale, the facilities needed to make these are scarce. Conversely, RNA/DNA vaccines may be easier to scale up.
- > The Bill & Melinda Gates Foundation have pledged to fund building production facilities in advance to ensure preparedness, and other agencies are similarly shoring up funding to scale up the supply capacity of their vaccine candidates. Industry is requesting governments declare how much they plan to purchase, and some players are calling for advanced market commitments similar to what has occurred in the distribution of pneumococcal vaccines through Gavi.
- > There are a number of concerns around countries hoarding vaccines; whilst the Pandemic Influenza Preparedness Framework resolved to protect the supply of vaccines for those in the greatest need, no such resolution exists for pandemics like COVID-19. Australia was accused of this activity in 2009.
- > Balancing the need for the production of other vaccines, such as influenza, will remain a major concern.
- > The paper states that “It is possible that by the time a vaccine arrives, much of the world will already have been infected with the new coronavirus.” This seems unlikely based on current rates of infection.

Reviewed by: Professor Kim Mulholland

Single-Dose, Intranasal Immunization with Recombinant Parainfluenza Virus 5 Expressing Middle East Respiratory Syndrome Coronavirus (MERS-CoV) Spike Protein Protects Mice from Fatal MERS-CoV Infection

<https://mbio.asm.org/content/mbio/11/2/e00554-20.full.pdf>

Is there any evidence in support of Parainfluenza Virus 5 (PIV5) as a vector for a coronavirus antigen? This original research investigated PIV5 as a vector for MERS Coronavirus.

- > Despite promising results, this article is limited only to MERS
- > Whilst there are similarities between MERS and SARS-CoV-2, these data should not be extrapolated to COVID-19 as the authors suggest
- > Interesting, but early, mouse model evidence of PIV5 as a vector for engineered MERS CoV spike protein epitope targeted vaccine

- > The authors note that “In the case of a PIV5-based RSV vaccine, extensive studies indicate that PIV5-based RSV vaccine does not cause enhanced diseases. Thus, as a viral vector, PIV5 is not known to cause any enhanced diseases, and in our experiment, we observed no abnormal immune responses in PIV5-MERS-S-immunised mice after MERS-CoV challenge, suggesting that PIV5-MERS-S is unlikely to be associated with enhanced disease”.
- > They state that they are examining this model for SARS-CoV-2, but no data yet available

Reviewed by: Professor Terry Nolan

The COVID-19 vaccine development landscape

<https://www.nature.com/articles/d41573-020-00073-5>

- > This is a brief but complete overview of the Global COVID-19 vaccine R&D Landscape, written by leaders of the, previously obscure but well-funded, coalition for Epidemic Preparedness and Innovation (CEPI)
- > The paper contains a useful link to CEPI’s landscape document that is updated continuously
- > The authors highlight the potential for rapid and flexible development of the novel mRNA and DNA platforms
- > While most vaccines focus on the Spike (S) protein, there is a risk of disease enhancement that needs to be addressed
- > Authors also highlighted the absence of vaccine development in Latin America and Africa

Reviewed by: Professor Kim Mulholland

VIROLOGY

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

Temporal dynamics in viral shedding and transmissibility of COVID-19

<https://www.nature.com/articles/s41591-020-0869-5>

A temporal patterns of viral shedding data together with a transmission-pairs data were used to model the infectiousness profile of COVID-19

- > Viral load from the throat swabs of 94 moderately-ill patients with laboratory confirmed COVID-19 in a hospital in Guangzhou, were monitored from symptom onset up to 32 days after onset.
 - Virus was detected soon after the onset and viral shedding was until day 21
 - No difference in viral load across sex, age group and disease severity
- > Transmission profile of COVID-19 was modeled by using 77 transmission-pairs data from a database within and outside mainland China
 - The model was use 5.8 days for the serial interval (duration between symptom onsets of successive cases in a transmission chain) and 5.2 days for the incubation period (time between infection and onset of symptoms)
 - The model inferred that the infectiousness started from 2.3 days (95% CI, 0.8–3.0 days) before symptom onset, peaked at 0.7 days (95% CI, –0.2–2.0 days) before symptom onset and declined within 7 days. Importantly proportion of presymptomatic transmission was 44% (95% CI 25%–69%)
- > Combined viral shedding data and the inferred model of transmission profile suggested viral shedding may begin 2 or 3 days before the appearance of the first symptoms
- > Significant presymptomatic transmission would probably reduce the effectiveness of control measures initiated by symptom onset:
 - 90% of the contacts should be traced & revising contacts definition is required e.g contacts definition should cover 2-3 days prior to symptom onset
 - Enhanced personal hygiene and social distancing still required

Reviewed by: Dr Lien Anh Ha Do

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

SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion

<https://www.nature.com/articles/s41423-020-0424-9>

Pseudoviruses and live viruses were used to assess susceptibility of T lymphocyte to infection and delineate the mechanism of viral entry.

- > T lymphocytes are more sensitive to infection by SARS-CoV-2 compared to SARS-CoV.
- > Previous studies showed that SARS-CoV-2 enters host cells using angiotensin-converting enzyme 2 (ACE2) as a receptor. However, T lymphocytes have a low expression of ACE2, hence a novel receptor may mediate entry
- > SARS-CoV-2 enters T lymphocytes via receptor-dependent S protein mediated membrane fusion. EK1 peptide can inhibit this activity
- > Like MERS-CoV, SARS-CoV-2 fails to replicate in T lymphocytes
- > Further research is required to investigate replication and whether the virus induces apoptosis in T cells

Reviewed by: Professor Julie Bines

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

Key proteins mediating SARS-CoV-2 cell entry and fusion

<https://www.nature.com/articles/s41467-020-15562-9.pdf>

Research aimed to characterise the SARS-CoV-2 spike glycoprotein (SARS-CoV-2 S) / receptor interaction and identify proteins mediating cell entry and fusion

- > Using a SARS-CoV-2 S protein pseudovirus system confirmed that SARS-CoV-2 uses the human angiotensin converting enzyme 2 (hACE2) as the receptor and enters 293/hACE2 cells primarily through endocytosis
- > PIKfyve, TPC2 and Cathepsin L are required for virus entry. Inhibition of PIKfyve, TPC2 or Cathepsin L have been associated with reduced virus entry and may be potential targets for drug development.
- > SARS-CoV-2 S mediated 293/hACE2 cell fusion and syncytium formation independent of exogenous protease activity unlike SARS-CoV S, possibly providing an explanation for the rapid transmission of the virus.
- > Polyclonal anti-SARS S1 antibodies T62 inhibit entry of SARS CoV but not SARS-CoV-2 pseudovirions. It was also identified that mixed convalescent sera of a SARS patient (n=1) and COVID-19 patients (n=5) showed limited immunological cross-neutralisation suggesting that recovery from one infection may not protect from the other.
- > This research provides vital information regarding viral pathogenesis, vaccine targets and drug development

Reviewed by: Professor Julie Bines

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

SARS-CoV-2 found in untreated wastewater in Australia

<https://doi.org/10.1016/j.scitotenv.2020.138764>

This study reported the detection of SARS-CoV-2 RNA from untreated wastewater and how these data can help for monitoring the infections in communities.

- > Main results:
 - Validation of technique was performed to confirm no presence of RTqPCR inhibitors after concentration and pre-treatment of wastewater samples
 - 22% (2/8) samples collected from wastewater treatment plants representing urban catchments in Southeast Queensland on two sampling events (4 days apart) were positive for SARS-CoV-2 by PCR and confirmed by Sanger & Illumina MiSeq sequencing- viral load ~ 12 and 1.9 copies/100mL
 - Monte Carlo simulation suggested a median SARS-CoV-2 infection prevalence of 0.096% (95%CI: 0.064-0.142) in the catchment basin
- > Significance:
 - Potential for an alternative approach to monitor the COVID-19 infections in communities.
 - Presence of SARS-CoV-2 in untreated wastewater can be used as an early warning of COVID-19 infection in communities.
- > Limitations:
 - Need a highly sensitive test

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

<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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