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Department of Paediatrics

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COVID-19 KIDS EVIDENCE UPDATE

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

Weekly Update No.12

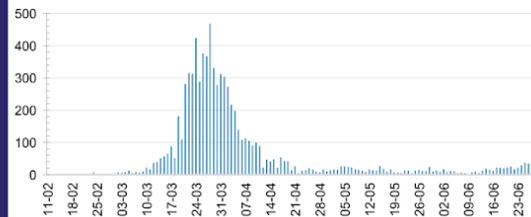
2nd July 2020

BE COVIDSAFE

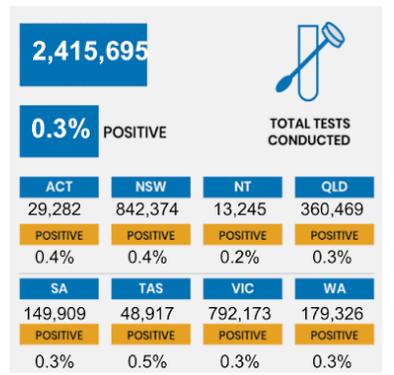
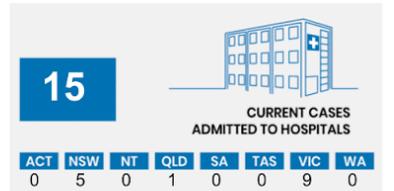
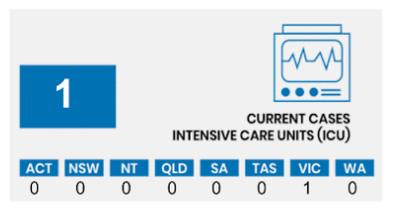
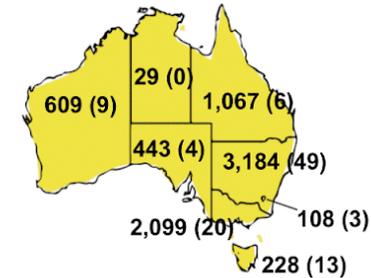
CURRENT STATUS OF CONFIRMED CASES



DAILY NUMBER OF REPORTED CASES



CASES (DEATHS) BY STATE AND TERRITORIES

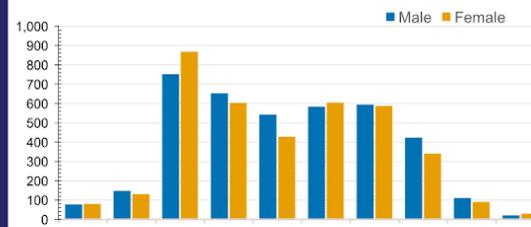


CASES IN AGED CARE SERVICES

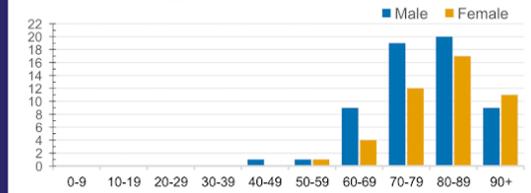
Confirmed Cases	Australia	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
Residential Care Recipients	71 (39)	0	61 (33)	0	1 (1)	0	1 (1)	8 (6)	0
In Home Care Recipients	31 (28)	0	13 (13)	0	8 (8)	1 (1)	5 (3)	3 (3)	1 (1)

Cases in care recipients [recovered] (deaths)

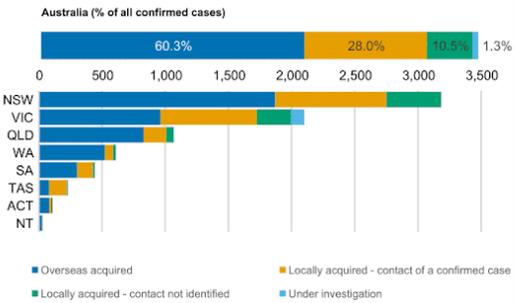
CASES BY AGE GROUP AND SEX



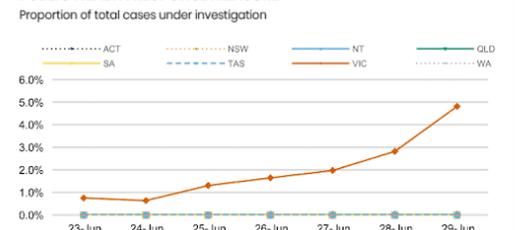
DEATHS BY AGE GROUP AND SEX



CASES BY SOURCE OF INFECTION



PUBLIC HEALTH RESPONSE MEASURE



Last updated 29 June 2020

This infographic is updated every afternoon based on the data we receive by 3.00pm from states and territories

Source: Australian Government: Department of health [Internet]. 2020 [updated 2020 June 29; cited 2020 June 30]. Available from: <https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-current-situation-and-case-numbers#at-a-glance>

HEAD OF DEPARTMENT EDITORIAL

Professor Sarath Ranganathan - Stevenson Chair,
Department of Paediatrics, University of Melbourne

It has been a difficult week in the global defence against COVID-19. As of July 1st there are now 10,585,110 cases and 513,913 reported deaths worldwide. That's almost 1.5 million cases more than last week.

We have also witnessed a continuing surge of cases here in Melbourne. This is not a resurgence, as viral genomics indicates spread of a recently imported virus - one which has effortlessly breached the rather poor infection-control activities practiced in quarantine hotels. Re-institution of lockdown restrictions in ten postcodes affecting 36 suburbs has been mandated.

As foretold in previous reports, children are being impacted in our neighbouring countries as, for example, reported by the Indonesian Paediatric Society who identified 200 deaths of children < 5-years-old infected with SARS-CoV-2, compounding deaths from pneumonia, diarrhoea, malnutrition and tuberculosis.

It was a tuberculosis network, the Paediatric Tuberculosis Network European Trials Group, that this week reported the first multi-national, multi-centre study pertaining to clinical findings in children. Data were reported from 82 participating tertiary health-care institutions in 25 European countries on 582 hospital-affiliated individuals aged 18 years or younger with confirmed SARS-CoV-2 infection identified between April 1st and April 24th 2020 (before multi-system inflammatory syndrome cases were first reported).

Cases had a median age of 5 years and a sex ratio of 1:15 males per female. Only 145 (25%) had pre-existing medical conditions. 507 (87%) individuals did not require respiratory support at any stage. 363 (62%) individuals were admitted to hospital. 75 (13%) patients required oxygen support and 48 (8%) required ICU admission: 31 (5%) were started on continuous positive airway pressure (CPAP) and 25 (4%) on mechanical ventilation (including 14 who had been managed with CPAP initially). Significant risk factors for requiring ICU admission in multivariable analyses were being younger than 1-month, male sex, pre-existing medical conditions, and presence of lower respiratory tract infection signs or symptoms at presentation. [Götzinger et al. Lancet Child Adolesc Health ([https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642\(20\)30177-2/fulltext?utm_campaign=tlcoronavirus20&utm_content=132800378&utm_medium=social&utm_source=twitter&utm_channel=tw-27013292](https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30177-2/fulltext?utm_campaign=tlcoronavirus20&utm_content=132800378&utm_medium=social&utm_source=twitter&utm_channel=tw-27013292))]

See the Clinical Paediatrics section of the report.

We have seen and commented on the data for both remdesivir and dexamethasone in prior reports. In the Clinical Trials section of the current report you will find data from a small, single-centre, non-randomised study that provides support for another anti-inflammatory approach using mavrilimumab, an anti-granulocyte colony-stimulating factor alpha-receptor monoclonal antibody ([https://www.thelancet.com/pdfs/journals/lanrhe/PIIS2665-9913\(20\)30170-3.pdf](https://www.thelancet.com/pdfs/journals/lanrhe/PIIS2665-9913(20)30170-3.pdf)). The adult patients treated with mavrilimumab showed greater clinical improvement and in a shorter time-frame (8 versus 19 days) compared with controls, were discharged earlier (10 versus 20 days) and were less likely to need mechanical ventilation (8% vs 35%) or die (0% versus 27%). The study was small, non-randomised and conducted on the background of a cocktail of treatments but indicates promise and the need for a formal randomised controlled trial. More details in the Therapeutics section of the report.

In order to maintain therapeutic optimism I would also like to mention an excellent study reviewed in the Virology section that used mass spectrometry based phosphoproteomics approaches to assess cellular processes that are hijacked during SARS-COV-2 infection. The researchers identified dramatic rewiring of phosphorylation on host and viral proteins that reflect altered activities of kinases ([https://www.cell.com/cell/fulltext/S0092-8674\(20\)30811-4](https://www.cell.com/cell/fulltext/S0092-8674(20)30811-4)) They identified 87 drugs already approved by the FDA that might have a role in preventing such virus-induced dysfunction. They tested 68 drugs and identified that many had anti-viral activity in vitro. That leaves a lot of work to do....

As it emerges just how protracted our current situation is likely to be I was interested to learn from a review of 63 relevant studies (18 of which were longitudinal) that it is the duration of loneliness that is more strongly associated with mental health issues than the intensity of loneliness itself (<https://www.sciencedirect.com/science/article/pii/S0890856720303373>) - see Mental Health section of the report. At least our schools remain open to provide some social connection for young people, even in the once-again locked down suburbs. However, rather than guiding someone who is vulnerable to a web-link for support why not contact your colleague, friends or acquaintance directly and provide some human support and connection in an effort to try to minimise the duration of their preventable loneliness? This is going to be increasingly important during the long haul ahead.

HIGHLIGHTS

- > COVID-19 has a significant effect on paediatric health and wellbeing through the repercussions of lockdowns and school closures and inequities these impose.
- > In Sweden, where schools for children <15 years remained open, there was a low incidence of severe illness due to COVID-19 among children, suggesting that the direct outcomes for children in Sweden were not worsened when compared to other countries where schools were closed.
- > Global coordination and increased funding of high-quality research may enhance the progress of discovering safe and effective treatments.
- > A multi-centre cohort study across Europe found COVID-19 is generally a mild disease in children, although a small proportion may develop severe disease requiring ICU admission and prolonged ventilation and the fatal outcome remains rare.
- > Indirect effects on the wellbeing of children and adolescents likely to be huge, including poverty and financial instability that can lead to malnutrition, child labour, and foregoing school.
- > Assessment of both saliva and serum may increase the detection of individuals who have an antibody response to SARS-CoV-2.
- > Singapore pre-school and secondary school-based study suggest that children are unlikely to be the primary drivers of SARS-CoV-2 transmission.
- > Ten considerations to effectively manage the COVID-19 transition including the de-escalation of social and physical distancing measures in high income, well-resourced countries.
- > Despite Geneva having a rapid first wave of infection, weekly seroprevalence surveys found a small increase in seroprevalence over five weeks, and most people had no evidence of past infection.
- > The modelling paper predicts the increased child deaths from missed immunisations and supports the need to continue routine immunisation services to further prevent vaccine preventable deaths.
- > Early intervention with preventative support is recommended to protect the mental health of young people during COVID-19 pandemic and social distancing measures.
- > The optimal definition of vertical transmission is proposed.
- > Consensus report released on the assessment of risk of disease enhancement with COVID-19 vaccines.
- > The need to build public trust in potential COVID-19 vaccines requires government officials to implement a vaccination policy through a transparent & inclusive process, working closely with stakeholder groups.

- > Animal reservoirs of SARS-CoV-2 could include domestic species such as dogs and cats, farmed wildlife such as mink and pigs, in addition to wild animals such as bats and rodents.
- > Potential targets for COVID-19 treatment suggested through global phosphoproteomics approaches to highlight cellular processes hijacked during SARS-CoV-2 infection.
- > Viral load correlates, at least partially, with the infectivity of an individual and a study from Germany indicates that transmission by children is a distinct possibility and schools and kindergartens should be considered as potential sources of infection.
- > Possible benefits of using GM-CSF blockade with mavrimumab in severe COVID-19 pneumonia and systemic hyperinflammation (small study from Milan, Italy).

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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.

Always seek the advice of your physician or another qualified health provider properly licensed to practice medicine or general health-care in your jurisdiction concerning any questions you may have regarding any information obtained from this publication.

Never disregard professional medical advice or delay in seeking it because of something you have read in this publication. Information obtained in this publication is not exhaustive and does not cover all possible manifestations of COVID-19 nor its interaction with other conditions, diseases, ailments, or their treatment.

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CHILD DEVELOPMENT

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

Generation coronavirus?

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31445-8/fulltext?utm_campaign=tlcoronavirus20&utm_source=twitter&utm_medium=social](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31445-8/fulltext?utm_campaign=tlcoronavirus20&utm_source=twitter&utm_medium=social)

- > COVID-19 has a large effect on paediatric health and wellbeing despite children who may not be directly affected by it.
- > The children of today will grow up during a crisis and inherit its aftermath.
- > 90% of the world's students were unable to physically attend school by April 2020.
 - Short term risks to wellbeing (e.g., exacerbation of existing mental health issues and increased risk of psychological disorders) which could affect their entire life.
 - School provides meals for many children worldwide.
- > Poverty and financial instability can lead to malnutrition, child labour, and foregoing school.
- > Maltreatment of children increases during times of conflict.
- > We must prepare for possible repeated closures and replace what is missing (e.g., meals, vaccinations, examinations) whilst investing in children and adolescents beyond just formal education but also with community engagement and participation.

Reviewed by: Dr Wonie Uahwatanasakul

CLINICAL PAEDIATRICS

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

Children with COVID-19 at a specialist centre: initial experience and outcome (correspondence)

<https://www.thelancet.com/action/showPdf?pii=S2352-4642%2820%2930204-2>

- > Examined a cohort of paediatric patients, presenting to Great Ormond Street Hospital, UK with suspected COVID-19 to document their clinical characteristics and outcomes with regard to the presence of underlying medical conditions associated with vulnerability, over a two week period.
- > 65 COVID-19 cases; 31 were vulnerable.
- > Sepsis, fever and pneumonia were the commonest diagnoses.
- > 29 (45%) admitted to ICU; of whom 14 were classified as vulnerable.
- > Of the 29 patients admitted to ICU, 18 (62%) required mechanical ventilation, of whom ten (56%) were classed as vulnerable.
- > The average length of stay for vulnerable cases was 11 days (compared to four days for non-vulnerable patients).
- > During the study, with a daily average of 326 inpatients, on average ten were positive for SARS-CoV-2 at any time, representing around 3% of the hospital inpatient population, much lower than the estimated 25% COVID-19-positive population reported across adult London hospitals.
- > The findings from this study are not applicable to the general paediatric population, as the participants were highly preselected and include children with severe disease and those with underlying medical conditions.
- > The possible effects of lockdown and shielding of the vulnerable population remain undetermined.
- > This study raises the possibility that underlying medical conditions may place children at increased risk of COVID-19 disease or complications.
- > Susceptibility for COVID-19 in vulnerable groups might be both disease-specific and related to patient age.

Reviewed by: Professor Fiona Russell

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

Paediatric COVID-19 admissions in a region with open schools during the first 2 months of the pandemic (Brief report)

<https://onlinelibrary.wiley.com/doi/abs/10.1111/apa.15432>

- > School closures have been implemented by most countries as a way to combat the COVID-19 pandemic. In Sweden however, daycare centres and schools for children up to 15 years of age remained open.
- > In this article, a two month review of paediatric admissions of children aged 0-17 years who tested positive for SARS-CoV-2 in Stockholm, Sweden was carried out to assess the impact of leaving schools open on the incidence and severity of paediatric COVID-19 admissions.
 - A total of 63 admitted children tested positive for SARS-CoV-2 during the study period.
 - Of the 63 paediatric admissions, 30 had a primary COVID-19 diagnosis, 14 had concurrent illnesses, and 19 had incidental positive SARS-CoV-2 findings.
 - 39/63 (62%) presented with fever and 32/63 (51%) had respiratory symptoms. Four children (6%) required oxygen treatment and one patient with immunosuppression was admitted to the ICU.
 - More than half of all symptomatic admissions (16/30, 53%) were infants.
- > Conclusion: Even though daycare centres and primary schools remained open in Sweden, there still remains a low incidence of severe illness due to COVID-19 among children, which suggests that allowing schools to remain open did not worsen the pandemic outcomes for children in Sweden compared to other countries where schools were closed.
- > Limitations: The impact of allowing schools to remain open on the overall transmission of SARS-CoV-2 from children to adults and its consequences for adult hospitalisations and deaths was not studied.

Reviewed by: Dr Wonie Uahwatanasakul

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

COVID-19 in children and adolescents in Europe: a multinational, multi-centre cohort study

[https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642\(20\)30177-2/fulltext?utm_campaign=tlcoronavirus20&utm_content=132800378&utm_medium=social&utm_source=twitter&hss_channel=tw-27013292](https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30177-2/fulltext?utm_campaign=tlcoronavirus20&utm_content=132800378&utm_medium=social&utm_source=twitter&hss_channel=tw-27013292)

- > This study aimed to capture key data on children and adolescents with SARS-CoV-2 virus infection diagnosed at any anatomical site by RT-PCR across Europe, involving 82 participating health-care institutions across 25 European countries (between 1st - 24th April).
- > 582 individuals were included in the study.

- > Findings:
 - Median age of 5.0 years old.
 - Sex ratio of 1.15 males per female.
 - 25% had pre-existing medical conditions.
 - 8% required ICU admissions with 4% required mechanical ventilation, 3% requiring inotropic support and <1% requiring extracorporeal membrane oxygenation.
 - Significant risk factors for ICU admission in a multivariable analysis: younger than one month, pre-existing medical conditions, and presence of lower respiratory tract infection signs or symptoms at presentation.
 - Four children died.
 - Most frequently used antiviral drugs: Hydroxychloroquine, Remdesvir, lopinavir-ritonavir, and oseltamivir.
 - Most frequently used immunomodulatory drugs: Corticosteroids, IVIG, tocilizumab, anakinra and siltuximab.
- > COVID-19 is generally a mild disease in children, including infants.
- > However, a small proportion develops severe disease requiring ICU admission and prolonged ventilation, although the fatal outcome is rare overall.

Reviewed by: Dr Wonie Uahwatanasakul

CLINICAL TRIALS

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

Characteristics of registered clinical trials assessing treatments for COVID-19: a cross-sectional analysis

<https://bmjopen.bmj.com/content/10/6/e039978>

- > Due to the impact of the pandemic, there has been a wave of biomedical research to identify safe and effective treatments for COVID-19. This study aims to characterise registered clinical trials assessing drugs or plasma treatment for COVID-19.
- > Both new molecular entities and previously approved therapies for other diseases are being evaluated for their therapeutic effect, including the use of convalescent plasma to treat COVID-19.
- > Cross-sectional analysis of clinical trials of drugs or plasma for the treatment of COVID-19, using the WHO's clinical trial registry network and US clinical trials downloaded on 26th March 2020.
- > 201 clinical trials were registered for testing therapeutic benefits.
- > Eight products or combinations (8.7%) involved new molecular entities. Other test therapies had a wide range of prior medical use: 18.8% antivirals, 14.1% immunosuppressants other than corticosteroids, 6.3% anticancer drugs, 4.7% antimalarials, 3.1% corticosteroids, 3.1% immunostimulant, 3.1% antithrombotic agents.
 - 152 trials (75.7%) involve randomising patients to treatment or comparator.
 - Most trial designs featured multiple endpoints, including COVID-19 symptoms, death, recovery, required intensive care and hospital discharge.
 - 33 trials (16.4%) use clinical scales such as oxygenation and critical illness.
 - 88 trials (37.8%) use surrogate endpoints or biomarkers, primarily viral load.
- > Data shows the current primary focus of clinical trials is to assess whether a wide range of existing therapeutic products might also be effective against acute COVID-19 infection.
- > Current scientific activity is concentrated in China and the USA, accounting for 87.6% of the studies. Several multi-centre trials of therapies against COVID-19 are also underway, testing remdesivir, hydroxychloroquine, ritonavir/lopinavir.
- > Many registered COVID-19 trials were designed expediently. While case series and single-arm trials have value and may provide early signals, randomised study designs provide higher quality evidence and will maximise chances for finding effective and safe treatment.

- > It is important to implement surrogate outcomes, biomarkers and clinical scales to trials.
- > There is a remarkable scientific activity to investigate existing antiviral, antimalarial, immunosuppressants and oncology treatment against COVID-19. However, many trials lack features to optimise their scientific value.
- > Global coordination and increased funding of high-quality research may help to maximise the progress of discovering safe and effective treatments.

Reviewed by: Dr Wonie Uahwatanasakul

CRITICAL CARE

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

Reshaping of Neonatal Intensive Care Units to avoid the spread of COVID-19 to high-risk infants

https://www.cambridge.org/core/services/aop-cambridge-core/content/view/C7726CC632A98CE5472E584D3457D08B/S0899823X20003104a.pdf/reshaping_of_neonatal_intensive_care_units_to_avoid_the_spread_of_covid19_to_highrisk_infants.pdf

- > An observational study (15th March – 15th May 2020) on how an Italian Neonatal Intensive Care Unit (NICU) reorganised admissions during the COVID-19 outbreak.
- > Adopted procedures:
 - Neonates isolated on arrival until negative COVID-19 swab.
 - COVID-19 ruled out before admission via nasopharyngeal swab and Allplex 2019-nCoV Assay.
 - COVID-19 positive neonates managed in a dedicated paediatric COVID-19 unit.
 - Gloves, eye protection and gowns used while managing neonates in addition to surgical masks, or N95 masks if suspected or confirmed to have COVID-19.
 - Daily body temperature measurement of health care workers (HCWs).
 - Limitations to one parent per day visiting up to 6 hours after signing self-certification about fever, suspicious symptoms or contact: Visitation forbidden if febrile or have respiratory symptoms.
 - Parents wore masks, gloves, and disposable clothing.
- > Results: 101 newborns: 71 interhospital referrals and 30 via the emergency department (ED).
 - One neonate admitted from ED tested positive: Managed in dedicated paediatric COVID-19 unit given stable condition.
 - No referred neonates tested positive.
 - No neonates or HCWs acquired COVID-19 while the adopted procedures were implemented/study period.
- > Conclusion:
 - The fight against the pandemic should not affect the quality of care to high-risk infants.
 - Newborns should be tested for SARS-CoV-2 before NICU admissions, especially if admitted from the ED.
- > Limitations: Single centre site in a medium-risk region.

DIAGNOSTICS & SAMPLING

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

Antibody response to infectious diseases and other risk factors accurately predict COVID-19 infection and severity risk 10-14 years later: a retrospective UK biobank study (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.06.09.20127092v2>

- > This study used machine learning to determine what combinations of baseline measures (demographics, body compositions, health conditions/behaviours, vital signs, biochemistry, serology of non-COVID-19), collected 10-14 years ago from UK Biobank cohorts, could best predict which older adults developed COVID-19 and its severity.
- > 7,539 total test cases for COVID-19 were conducted among 4,510 UK Biobank participants, 2,210 of 7,539 were positive cases. Of the positive cases, there were 996 mild and 1,214 presumptively severe disease outcomes, defined as a test case occurring in a hospital setting. A sub-group of 124 test cases among 7,539 total test cases, with serology data, was used for testing the predictive model of COVID-19 infection, while the whole cohort was used for validation of the model.
- > From the models, antibody titres, reflecting pathogen exposure history and past host immunity, age, biological factors related to lipids and kidney health as well as innate immune cells (neutrophils, monocytes) were strong predictors of COVID-19 infection and severity.
- > In the subgroup with serology, final models predicted infection with high accuracy (93.5%) but severity with modest accuracy (74.4%).
- > Among all test cases, accuracy was modest for both predictions of COVID-19 infection (70.2%) severity (58.3%).
- > Serological titres for non-COVID-19 infectious diseases and other risk factors could help policymakers and clinicians better identify who may get COVID-19 and require hospitalisation, as well as influence host immunity.

Reviewed by: Dr Lien Anh Ha Do

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

How can detection of an antibody response to SARS-CoV-2 spike glycoprotein be enhanced? (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.06.16.20133025v1.full.pdf>

- > Antibodies against SARS-CoV-2 spike (S) glycoprotein and nucleocapsid (N) protein were tested in sera of hospitalised patients, symptomatic non-hospitalised patients and asymptomatic non-hospitalised patients, all of which had a confirmed diagnosis by PCR. Results were compared to the convalescent sera of pre-pandemic controls.
 - Purified trimeric S protein was more sensitive in precipitating an antibody response in patients with less severe disease than N protein.
 - Merging secondary antibodies to detect IgG, IgA, and IgM enhanced detection in higher dilutions, suggesting that using a combined approach may be more effective in discriminating between low-level infected patients and non-infected patients.
- > Saliva samples were assessed for an antibody response to SARS-CoV-2 in a separate cohort that self-reported COVID-19 symptoms.
 - IgG and IgA antibodies against S glycoprotein provided the strongest signal.
 - Antibodies against N protein were not detected in higher amounts compared to pre-pandemic controls.
- > Paired serum and saliva samples were collected from health-care workers (n = 39), of which half had reported COVID-19 symptoms.
 - While saliva and serum responses did correlate with each other when a large antibody response was present, there was a poor relationship between serum and saliva antibody positivity in many subjects, suggesting that assessment of both saliva and serum may increase the detection of individuals who have an antibody response to SARS-CoV-2.

Reviewed by: Professor Phil Sutton

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

An analysis of SARS-CoV-2 Viral Load by Patient Age

<https://www.medrxiv.org/content/10.1101/2020.06.08.20125484v1>

- > RT-PCR threshold cycle data from 3303 patients who tested positive for SARS-CoV-2, out of 77,996 samples, from across Germany were analysed to examine the relationship between patient age and estimated viral load.
- > Two separate systems PCR systems were utilised over the period of this study, with each utilising a separate method to determine viral load.
 - A viral load threshold of 250,000 copies/ml, which has previously been established for the isolation of the infectious virus in cell culture, was used to determine which samples would likely be infectious

- > Infectious viral loads in PCR positive SARS-CoV-2 patients were found in:
 - 29.0% of children aged 0-6 (n=8).
 - 37.3% of children aged 0-19 (n=150).
 - 51.4% of those aged 20 and above (n=3153).
- > Although 29.0% of children aged 0-6 were found to have infectious viral loads, this is unlikely to tell the full story and should not be viewed in isolation.
 - The level of symptoms an individual has (i.e. coughing, sneezing) has been shown in other viruses, such as influenza, to influence infectivity.
 - Despite this, the findings of this study do not indicate that children are significantly less infectious than adults, and the transmission potential in schools and kindergartens should be considered as a potential source of infection.
- > Limitations:
 - As children are largely asymptomatic, or mildly symptomatic, or they may be less likely to present to testing centres even if they do have symptoms, they are likely being underrepresented in this study population.
 - As two separate PCR systems were used over the period of this study, variation is likely to be present in how they determine the viral load, resulting in inconsistencies between the two groups.
- > Viral load correlates, at least partially, with the infectivity of an individual. When stratifying by age group, 29.0% of children aged 0-6 were found to be carrying an infectious viral load. This indicates that transmission by children is a distinct possibility, and schools and kindergartens should be considered as potential sources of infection.

Reviewed by: Dr Wonie Uahwatanasakul

EPIDEMIOLOGY & PUBLIC HEALTH

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

Novel coronavirus 2019 transmission risk in educational settings

<https://academic.oup.com/cid/article/doi/10.1093/cid/ciaa794/5862649> (pre-print)

- > Comprehensive nationwide surveillance and contact tracing as part of Singapore's public health strategy identified three potential SARS-CoV-2 seeding incidents in three separate school settings.
- > All index cases were in the pre-school or school prior to being tested following household transmission. Once results were known, the index cases were quarantined, and all symptomatic school contacts were tested, and one pre-school all asymptomatic contacts were also tested. All close contacts were also placed under quarantine – and these individuals who developed symptoms sent for medical evaluation and admitted for isolation.
- > Data was obtained with regards to attack rate, date of symptom onset and illness duration, and viral load.
- > There were no cases of child-child transmission in the pre-school or secondary school setting.
- > Results suggest that children are unlikely to be the primary drivers of SARS-CoV-2 transmission in schools (especially in pre-schools) and could help inform exit strategies for lifting lockdown.
- > Based on these findings, more targeted control measures for pre-school settings such as keeping symptomatic children away from schools instead of blanket-wide closures could be considered.

Reviewed by: Professor Fiona Russell

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

Ethnicity and outcomes from COVID-19: the ISARIC CCP-UK prospective observational cohort study of hospitalised patients (pre-print)

<https://protect-au.mimecast.com/s/60HIC2xZLrcp8KIO9hv8miY?domain=papers.ssrn.com>

- > This paper builds on the narrative of recent studies which suggest a link between ethnicity and confirmed infection, hospitalisation as well as mortality from COVID-19.
- > This is the largest prospective study investigating ethnic differences between critical care admissions and mortality for 30,693 patients with COVID-19 in the UK.
- > Patients were classified into the following ethnic groups: South Asian (n=1,388, 5%), East Asian (266, 1%), Black (1,094, 4%), Other Ethnic Minorities (2,398, 8%), and White (25,547, 83%).
- > Ethnic minorities were younger and more likely to have diabetes compared to the White group. Whites were more likely than Ethnic Minorities to have other comorbidities such as chronic cardiac disease, non-asthmatic chronic pulmonary disease and dementia.
- > Overall, 4,353 patients (14%) were admitted to a critical care facility. The South Asian (odds ratio (OR) 1.28, 95% confidence interval (CI) 1.09 - 1.52), Black (OR 1.36 95% CI 1.14-1.62), and the other ethnic minority groups (OR 1.29, 95% CI 1.13-1.47) all had higher odds of critical care admission than the White group.
- > A total of 9,145 (30%) patients died. When age, sex and location were accounted for, South Asians had a higher adjusted mortality (hazard ratio 1.19, 95%CI 1.05-1.36) than Caucasians, approximately 18% (95%CI 9% - 56%) of which can be explained by higher rates of type 1 and 2 diabetes mellitus (based on mediation analysis).
- > Although this article is still in pre-print, it provides some of the most robust evidence to date on the relationship between ethnicity and COVID-19, and may have implications for policy on the prioritisation of prevention treatment as well as other aspects of the COVID-19 response.

Reviewed by: Dr Claire von Mollendorf

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

Ten considerations for effectively managing the COVID-19 transition

<https://www.nature.com/articles/s41562-020-0906-x>

- > In this perspective piece, the authors discuss ten considerations to effectively manage the COVID-19 transition, including the de-escalation of social and physical distancing measures in high income, well-resourced countries.
- > WHO recommends that communities have a voice (points 2-4 below), be informed (8-10) and engaged and participate (5-7) in the transition process.
 1. Implement a phased approach to a new normal (at the centre of the transition process)
 - Example: Plan a detailed transition strategy – set goals for each phase with red, yellow, and green signs for pandemic response adjustment scenarios with ongoing monitoring and adjustment. Transparently communicate these goals and the criteria used for making decisions.
 2. Balance individual rights with the social good
 - Example: Focus messages on identified prevailing norms and values; for example, emphasise the substantial impact of measures on protecting the community, individual families and/or workers.
 3. Prioritise people at highest risk of negative consequences
 - Example: Prioritise people who are most severely affected, either mentally, physically, or financially.
 4. Provide special support for health-care workers and caring staff
 - Example: Provide guidance on the rights and entitlements of health-care and caring workers.
 5. Build, strengthen and maintain trust
 - Example: Acknowledge uncertainty, be transparent about unanswered questions and balance the need for clarity with acknowledgement of uncertainty regarding the evolution of the outbreak.
 6. Enlist existing social norms and foster healthy new norms
 - Example: Work with influencers to amplify messages about the transition aimed at different population groups.
 7. Increase resilience and self-efficacy
 - Example: Produce proactive advice about the importance of self-care, stress management, healthy habits, social interactions and prioritising rest, sleep, and exercise, considering diversity in health literacy.

8. Use clear and positive language
 - Example: Communicate clearly and focus on the benefits and gains.
 9. Anticipate and manage misinformation
 - Example: Advise people that they are likely to receive misinformation and inform them where they can access trustworthy facts.
 10. Engage with media outlets
 - Example: Proactively reach out to media outlets to engage them as partners in the response, respect their independence and highlight their role and potential influence.
- > Where possible, each consideration should be monitored, informed, and qualified using real-time empirical evidence.

Reviewed by: Dr Claire von Mollendorf

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

Associations of Global Country Profiles and Modifiable Risk Factors with COVID-19 Cases and Deaths (pre-print)

<https://doi.org/10.1101/2020.06.17.20133454>

- > The study aimed to determine the association of modifiable risk factors with total cases and excess deaths due to COVID-19 using global data.
- > Authors obtained COVID-19 case and death data from the European Centre for Disease Prevention and Control (ECDC) and the prevalence of modifiable risk factors in each country from the WHO Noncommunicable Diseases Country Profiles 2018.
- > Data on cases and excess deaths were available for 181 countries, with fewer countries having data for confounders (167-181) and risk factors (133-168), depending on the variable.
- > Overall there was a median (IQR) of 1.21 (0.41, 2.24) excess deaths per case and male sex was associated with nearly twice as many deaths compared to women [481 (143, 2,970) vs. 277 (120, 1,670), $P < 0.001$].
- > Obesity was the only major modifiable risk factor independently associated with SARS-CoV-2 infection. The association was stronger in men.
- > After adjusting for confounders, older age, male sex, physical inactivity and low salt consumption were associated with excess death. Obesity was not a risk factor for excess death after adjusting for physical inactivity.
- > The most novel finding was that countries with higher salt intake had lower COVID-19 mortality. The authors hypothesised that high salt intake induced lower levels of ACE2 in the lungs and myocardium, which reduced viral damage and subsequently reduced mortality rates.

Reviewed by: Dr Claire von Mollendorf

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

Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study

<https://www.thelancet.com/action/showPdf?pii=S0140-6736%2820%2931304-0>

- > Gaining a greater understanding of who may be potentially protected against subsequent infections through studying the proportion of the population that has developed SARS-CoV-2 antibodies, could inform public health responses. This is important as initial limits on swabs meant that asymptomatic and mildly symptomatic patients were not being tested around the world.
- > This is a population-based study in Geneva, Switzerland that randomly selected 1300 patients per week from those already enrolled in the Bus Santé trial (which had tried to recruit a representative sample of the population) and their families. Participants could only participate once in the study. Participants had 3ml of blood taken at a self-booked appointment. This paper analyses the data from the first five weeks of the study (planned to continue for 12 weeks).
- > Results:
 - Over the course of the five weeks, 219 of 2766 participants tested positive for SARS-CoV-2 antibodies on ELISA.
 - Seroprevalence was estimated for the first week as 4.8% (n=341). The estimate increased to 8.5% (n=469) in the second week, 10.9% (n=577) in the third week, 6.6% (n=604) in the fourth week, and 10.8% (n=775) in the fifth week.
 - Compared to the number of confirmed cases in Geneva, the authors estimated that for every confirmed case in the study, there were 11.6 cases in the community.
 - The risk of being seropositive was similar between men and women (RR 1.26 [95% CI 1.00–1.58]).
 - In young children and those over 65 years, the risk of being seropositive was lower than adults aged 20-49 years (young children RR 0.32 [0.11–0.63], over 65 years RR 0.50 [0.28–0.78]).
 - There was strong evidence of clustering in households (intracluster correlation coefficient 67.6%).
- > Conclusions:
 - Despite high levels of infection, only one in ten people had developed detectable antibodies against SARS-CoV-2.
 - Young children (5-9 years) had significantly lower seroprevalence than other groups, suggesting young children are infected less, have less severe disease, and don't generate antibody for these reasons.
 - Despite Geneva having a rapid first wave of infection, and a small increase in seroprevalence over five weeks, most people had no evidence of past infection. The reduction in numbers of a susceptible population can't be relied upon to play a major role in slowing transmission.

> Limitations:

- The study included randomly selected patients and their households, making the study not completely randomly selected. Post-stratification adjustment for age and sex differences compared with Geneva population.
- Recruitment was initially done through email, limiting the study to those who were more technically proficient. Recruitment moved to postal mail from week four of the study.
- Confirmatory testing was not done, but the same testing was used throughout.
- There is potential for selection bias (30-40% participation rate) with those who had experienced symptoms or those less confined by lockdown more likely to participate in the study, potentially leading to an overestimation in prevalence.
- The sample had an over-representation of 50-64 year olds than the general Geneva population, more individuals with a tertiary education and fewer non-Swiss nationals.
- No indication in the study regarding whether participants had symptoms or known exposure to SARS-CoV-2.

Reviewed by: Dr Claire von Mollendorf

GLOBAL HEALTH

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

Benefit-risk analysis of health benefits of routine childhood immunisation against the excess risk of SARS-CoV-2 infections during the COVID-19 pandemic in Africa (not peer reviewed)

<https://www.medrxiv.org/content/10.1101/2020.05.19.20106278v3?%253fcollection=>

- > One risk of the ongoing COVID-19 pandemic is a global suspension of routine immunisation programs.
- > This modelling paper compared the health benefits of sustaining routine childhood immunisation in Africa against the risk of acquiring SARS-CoV-2 virus during routine vaccination service delivery points.
- > Data indicates that for every one excess COVID-19 death attributable to SARS-CoV-2 infections acquired during routine vaccination visit, there could be 84 deaths in children prevented by sustaining routine childhood immunisation in Africa.
- > Analysis suggests that the health benefits of deaths prevented by sustaining routine childhood immunisation in Africa far outweigh the excess risk of COVID-19 deaths associated with vaccination clinic visits, especially for vaccinated children.
- > Limitations: did not consider BCG birth dose this vaccine provides non-specific effects, so disruption to administration is likely as it is predicted that many more pregnant women will be delivering at home due to public health containment measures and therefore their infants will not receive birth dose BCG; assumes SARS-CoV-2 transmission will infect ~60% of the population which is very high and has not been demonstrated in any setting despite widespread community transmission; assumes that the potential disruption to health services will last for six months, but this may be highly variable; assumes a 12.5% chance of a measles outbreak during the six-month suspension period; age-stratified infection fatality risk for SARS-CoV-2 used was estimated from reported cases and their severity in China in combination with the proportion of asymptomatic infections estimated among international residents repatriated from China.
- > Nevertheless, this paper supports the need to continue routine immunisation services and catch-up measles SIAs to prevent further vaccine-preventable deaths.

Reviewed by: Professor Fiona Russell

MENTAL HEALTH

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

What is the impact of social isolation and loneliness on the mental health of young people in the context of COVID-19? (pre-proof)

<https://www.sciencedirect.com/science/article/pii/S0890856720303373>

- > A rapid systematic review was conducted to assess the impact of social isolation and loneliness on the mental health of previously healthy children and adolescents.
- > Social isolation increased the risk of depression and possibly anxiety, at the time that loneliness was measured and 0.25 to 9 years later.
- > The duration of loneliness shared a stronger correlation with mental health issues than the intensity of loneliness.
- > Young people are at ongoing risk of mental health issues both during and after loneliness is experienced.
- > The authors suggest that early intervention with preventative support is recommended to protect the mental health of young people.
- > 63 studies were included in the review. Many studies had a high risk of bias, although longitudinal studies (n=18) were of better methodological quality than the cross-sectional ones.

Reviewed by: Professor David Coghill

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

Perinatal mental health and COVID-19 in Japan (Letter to the Editor)

<https://onlinelibrary.wiley.com/doi/10.1111/pcn.13091>

- > The novel coronavirus disease (COVID-19) outbreak has had a wide range of effects on perinatal mental health.
- > A group of 2872 pregnant women responded to a survey regarding their concerns about being infected by COVID-19, complications if infected, lack of therapeutic drugs to treat COVID-19, and infection of children after childbirth.
- > A common cultural delivery in Japan is called Satogaeri, which involves returning to their parents' home for assistance in the care of mother and baby - this has been advised against given the physical distance guidelines imposed by COVID-19.
- > Not being able to deliver their children in this manner has caused anxiety for some pregnant women.

- > The implications of having to change birthing plans have had widespread effects on perinatal mental health.
- > The survey limitations include it may have been a non-representative sample of pregnant women.

Reviewed by: Professor Fiona Russell

PERINATAL HEALTH

Daniel Lamanna - 3rd Year Medical Student,
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Maternal and Neonatal Response to COVID-19

<https://journals.physiology.org/doi/pdf/10.1152/ajpendo.00287.2020>

- > SARS-associated coronavirus resulted in high rates of miscarriage, maternal death, and preterm birth.
- > Majority of outcomes in studies on pregnant women infected with SARS-CoV-2 are no different than the general population.
- > While most COVID-19 infections in pregnant women are mild, data are emerging that demonstrate significant placental pathology in SARS-CoV-2 pregnancies despite the lack of detectable (or very low) levels of mRNA or protein SARS-CoV-2.
- > An important remaining question is whether SARS-CoV-2 replicates in the placenta and is a cause of the described placental abnormalities, or whether it is an innocent bystander.
- > Placental abnormalities described include diffuse perivillous fibrin, foetal vascular malperfusion, multifocal infarctions.
 - In the vast majority of cases, placentas were negative for SARS-CoV-2 - therefore, abnormalities on pathology suggest placenta is susceptible to the effects of maternal COVID-19 disease largely in the absence of infection.
 - Many of these abnormalities could be due to maternal comorbidities - careful, systematic studies to determine the prevalence of infection & replication of SARS-CoV-2 in the placenta and its association with placental abnormalities.
- > It also remains to be determined if vertical transmission of SARS-CoV-2 is possible.
- > Most case series report normal term newborns to mothers with mild-moderate SARS-CoV-2.
 - Preterm births occur fairly often in women with severe illness (mostly as a result of early delivery for maternal indications).
 - Sporadic reports of spontaneous preterm births.
 - Spontaneous abortion has also been reported twice in early pregnancy.
 - Foetal demise has been reported six times.
 - Case reports have also described newborns with symptoms that require admission to NICU.

- > Considerable evidence demonstrates a lack of vertical transmission - neonatal testing has infrequently been reported positive for the virus.
 - Interestingly, despite lack of virus detected in neonate at delivery, antibodies have been detected in neonatal blood (particularly IgM was reported to be elevated, suggesting foetal exposure to the virus in utero).
- > The virus requires ACE2 for entry, and TMPRSS2 cellular protease for priming - the placenta has robust expression of ACE2, but not TMPRSS2.
- > If SARS-CoV-2 changes the expression of ACE2 in the placenta, as SARS-CoV-1 has been shown to do in the lung, there is potential for placental abnormalities and pregnancy complications.

Reviewed by: Professor Fiona Russell

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

Vertical Transmission of SARS-CoV-2: What is the Optimal Definition?

<https://www.thieme-connect.de/products/ejournals/pdf/10.1055/s-0040-1712457.pdf>

- > Standardised definitions are important for defining and managing mother to child transmission and have implications for research and management of infection, particularly in describing clinical courses.
- > Authors distinguish vertical transmission as antepartum (would correlate with maternal viraemia which is rare), intrapartum (ascending infection or infection during the birth process from genital secretions /faeces), or postpartum (maternal / others respiratory secretions, breast milk).
- > In all cases, vertical transmission should be considered if the mother is positive for SARS-CoV-2 between 14 days prior to birth and two days after birth.
- > Early exposure consistent with the antepartum transmission is defined as detection of the virus in the neonatal respiratory tract, amniotic fluid, umbilical cord blood or blood sample persistently after birth.
- > Persistence is defined as a positive swab of the neonatal respiratory tract after 24 hours of life or a positive SARS-CoV-2 IgM assay in the first few weeks of life.
- > If early exposure and persistence is found, together with an immune response of IgM and G, this is considered as likely 'intrauterine transmission'.
- > If early exposure is found, but there is no evidence of persistence, nor immune response, this is defined as 'superficial exposure or transient viraemia'.
- > If there is nil evidence of early exposure, but persistence is found (+PCR and immune response shortly after birth, this is known as 'intrapartum or early postnatal transmission'.
- > Recommendation: initial swab on 1st and 2nd day of life; a SARS-CoV-2 antibody assay during days 5-14; a repeat of antibody titres at 2-3 weeks of life if initial IgM negative.

Reviewed by: Professor Suzanne Garland

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

Voices from the frontline: global survey of maternal and newborn health professionals facing the COVID-19 pandemic

<https://www.medrxiv.org/content/10.1101/2020.05.08.20093393v1.full.pdf>

- > Cross-sectional study via an online survey involving 714 maternal and newborn health-care professionals from 81 different countries.
- > The main outcomes studied were preparedness for and response to COVID-19, experiences of health workers providing care to women and newborns, and adaptations to outpatient and inpatient care processes during the pandemic.
- > Results:
 - Only one-third of respondents reported receiving training on COVID-19 from their health-care facility. Most respondents actively sought information relating to COVID-19 through personal searches.
 - 50% of respondents in low- and middle-income countries (LMICs) received updated guidelines for providing maternal and newborn care during the pandemic compared with 82% in high-income countries (HICs).
 - Only 47% of participants in LMICs and 69% in HICs felt mostly or completely knowledgeable about how to care for COVID-19 maternity patients.
 - 90% of respondents reported higher levels of stress due to changed working hours, difficulties in reaching health facilities, and staff shortages.
 - Respondents reported concerns about the rapidly changing care practices on health outcomes such as reduced access to antenatal care, fewer outpatient visits, shorter length of hospital stay in facilities after birth, banning birth companions, separating newborns from COVID-19 positive mothers and postponing routine immunisations.
 - Respondents also reported challenges in the shift to telemedicine for the provision of both antenatal and postnatal care.
- > Conclusion: there are knowledge gaps in guidance on the management of maternity cases with or without COVID-19 and steps need to be undertaken to ensure greater support and guidance is available for health-care workers.

Reviewed by: Professor Suzanne Garland

THERAPEUTICS

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

GM-CSF blockade with mavrilimumab in severe COVID-19 pneumonia and systemic hyperinflammation: a single-centre, prospective cohort study
[https://www.thelancet.com/pdfs/journals/lanrhe/PIIS2665-9913\(20\)30170-3.pdf](https://www.thelancet.com/pdfs/journals/lanrhe/PIIS2665-9913(20)30170-3.pdf)

- > A single-centre prospective cohort study in Italy of 13 non-mechanically ventilated patients who received mavrilimumab compared with 26 patients with similar baseline characteristics receiving standard of care.
- > Mavrilimumab: Granulocyte–macrophage colony-stimulating factor (GM-CSF) receptor inhibitor. Hypothesised to be useful in treating the subset of patients with SARS-CoV-2 infection by preventing the development of a sustained hyperinflammatory response similar to a cytokine storm which resembles haemophagocytic lymphohistocytosis due to virally triggered hyperinflammation.
- > Population:
 - Inclusion criteria: Over 18 years; PCR confirmed COVID-19; Radiological findings on CXR or CT; Hyperinflammation as defined by the elevation of CRP to 100 mg/L or more, or ferritin to 900 ug/L or more, in the presence of any increase in LDH > 220 U/L.
 - Exclusion criteria: Management in intensive care unit; Evidence of bacterial infection; Concomitant administration of other immunosuppressive biological agents or corticosteroids.
 - Baseline characteristics of treatment group (N=13): Age 57 (IQR 52-58); Male sex 12 (92%); Respiratory support: low-flow oxygen 4 (31%), high-flow oxygen 6 (46%), non-invasive ventilation with CPAP 3 (23%); Patients with fever 11 (85%); Fever duration, days 11 (10-12); Duration of hospital stay before enrolment, days 2 (1-2); C-reactive protein.
- > Intervention: All patients admitted to the hospital with COVID-19 pneumonia received on-admission treatment with oral HCQ (200 mg BD), intravenous azithromycin (500 mg OD), oral lopinavir-ritonavir (400 mg and 100 mg, respectively, twice a day), and respiratory support with supplemental O₂ or non-invasive ventilation with CPAP. Patients in the mavrilimumab group received 6 mg/ kg intravenously, once.
- > Comparison: Control group had similar baseline characteristics, carefully selected for age, sex, comorbidities (tobacco smoking, arterial hypertension, coronary artery disease, diabetes, chronic obstructive pulmonary disease, dyslipidaemia and obesity), baseline inflammatory markers, and respiratory dysfunction.

- > Outcomes:
 - The clinical improvement observed in 100% of mavrilimumab patients vs 65% of the control group
 - Days to clinical improvement 8 (5 to 11) in mavrilimumab group vs 19 (11 to >28) in the control group
 - Days to hospital discharge 10 (9 to 12) in mavrilimumab group vs 20 (12 to >28) in the control group
 - Fever resolution by day 14 10 (91%) in mavrilimumab group vs 11 (61%) in the control group
 - Mechanical ventilation or death 1 (8%) in mavrilimumab group vs 9 (35%) in the control group
 - Death 0 (0%) in mavrilimumab group vs 7 (27%) in control group
 - CRP reduction >75% 11 (85%) in mavrilimumab group vs 11/25 (44%) in the control group (NB: only patients with post-baseline assessments were included in the analysis)
- > Limitations: Small population size; Patients could not be randomly assigned to receive mavrilimumab or institutional standard of care, due to the expedited design and delivery of the study under pandemic circumstances, and due to constraints such as limited drug availability, shortage of the drug, and absence of patient consent. This, therefore, may have introduced selection bias, treatment bias, and placebo effect; Other clinical variables besides mavrilimumab treatment may have affected clinical outcomes despite the matching of baseline characteristics.

Reviewed by: Dr Wonie Uahwatanasakul

TRANSMISSION

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

Host range of SARS-CoV-2 and implications for public health

[https://www.thelancet.com/pdfs/journals/lanmic/PIIS2666-5247\(20\)30069-0.pdf](https://www.thelancet.com/pdfs/journals/lanmic/PIIS2666-5247(20)30069-0.pdf)

- > A comment discussing concerns of possible anthroponosis of SARS-CoV-2.
- > Data regarding an animal's susceptibility may be derived from real-world reports of infections, experimental evidence of infections or modelling of spike-ACE2 interactions.
- > There have been real-world reports (e.g., cats and dogs), experimental evidence (e.g., monkeys, ferrets, and cats) as well as computer modelling (e.g., rabbits and sheep) suggesting the possible susceptibility of certain animals to SARS-CoV-2.
- > A combination of approaches, including real-world epidemiology and diagnostics, with large sample numbers, is required to determine an animal's infectibility.
- > It will be difficult to trace natural transmission between species after SARS-CoV-2 circulates more widely beyond humans due to the viral genome being essentially identical in humans.
- > Our ability to isolate, protect, or contain animals in a domestic, agricultural, and wildlife setting is important for assessing risk.
- > Animal reservoirs of SARS-CoV-2 could include domestic species such as dogs and cats, farmed wildlife such as mink and pigs, in addition to wild animals such as bats and rodents.

Reviewed by: Professor Fiona Russell

VACCINES

Daniel Lamanna - 3rd Year Medical Student,
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Ensuring Uptake of Vaccines against SARS-CoV-2

<https://www.nejm.org/doi/full/10.1056/NEJMp2020926?source=nejmtwitter&medibaum=organic-social>

- > With the advent of a COVID-19 vaccination, achieving a high enough vaccination rate to achieve herd immunity is of critical importance.
- > One option is to make the vaccination mandatory - this strategy has shown high success in school children, but mandates have not been widely used in adults.
- > The authors suggest six criteria that should be met before a state imposes a SARS-CoV-2 vaccine mandate:
 - COVID-19 is not adequately contained.
 - Advisory committee on immunisation practices have recommended vaccination for the groups for which a mandate is being considered.
 - Currently, available evidence suggests the elderly, health professionals working in high-risk situations or with high-risk patients, and people with specific underlying medical conditions may be considered high-priority groups.
 - The supply of vaccine is sufficient to cover the population.
 - Available evidence about the safety and efficacy of the vaccine has been transparently communicated.
 - The state has created an infrastructure to provide access to vaccination without financial or logistical barriers, compensation to workers who have adverse effects from a required vaccine, and real-time surveillance of vaccine side effects.
 - In a time-limited evaluation, voluntary uptake of the vaccine among high-priority groups has fallen short of the level required to prevent epidemic spread.
 - Principles of public health ethics support trying less burdensome policies before moving to more burdensome ones whenever possible. In this case, the costs of a failed voluntary scheme are sufficiently high that the attempt should be limited to a matter of weeks.
 - If the above criteria were met the authors suggest proposed legislation should be supported by appropriate government officials, public health officers, and another expert committee confirms that all trigger criteria have been met.
 - The need to build public trust requires that government officials implement vaccination policy through a transparent & inclusive process, working closely with stakeholder groups.

Reviewed by: Professor Fiona Russell

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

**Consensus summary report for CEPI/BC March 12-13, 2020 meeting:
assessment of risk of disease enhancement with COVID-19 vaccines**

https://protect-au.mimecast.com/s/ipwUCL7rxDsRYKvW7soC_S1?domain=dx.doi.org

- > Given the safety risks associated with rapid vaccine development, as well as existing evidence of disease enhancement associated with MERS and SARS-CoV-1 vaccine candidates, the Centre for Epidemic Preparedness Innovations (CEPI) and the Brighton Collaboration Safety Platform for Emergency Vaccines (SPEAC) convened an expert group to consider which vaccine designs would best mitigate safety concerns.
- > The group recommends that it is important to monitor the Th responses produced by vaccine candidates, with those that induce a predominant Th2 cell response warranting further research in animal models, especially non-human primates, prior to entering phase I trials, given their increased risk of disease enhancement. For those which induce a predominant neutralising antibody and Th1 response, animal studies are recommended to continue in parallel with Phase I trials.
- > Adjuvants for subunit vaccine candidates offer a number of benefits, including increasing their immunogenicity and drive an immune response that could limit the risk of disease enhancement.
- > Participants expressed the great need for standardisation between protocols, as well as recommended a range of trial design features which may help to develop a more comprehensive understanding of these immune mechanisms.
- > The expert group also emphasised that an indication of disease enhancement in animal models should not immediately arrest the progression of a vaccine candidate, but close monitoring will be required.
- > This report will help inform vaccine safety monitoring as vaccine candidates enter human early phase 1-2 clinical trials.
- > Importantly, this consensus can inform SARS CoV-2 vaccine development, which can contribute to undergoing existing, robust, regulatory processes, all of which will need to be fulfilled before we have an effective and safe vaccine to be used at a population level.

Reviewed by: Associate Professor Nigel Crawford

VIROLOGY

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

The Global Phosphorylation Landscape of SARS-CoV-2 Infection

[https://www.cell.com/cell/fulltext/S0092-8674\(20\)30811-4](https://www.cell.com/cell/fulltext/S0092-8674(20)30811-4)

- > This study using mass spectrometry-based approach to study perturbations in protein abundance and phosphorylation of the host during SARS-CoV-2 infection through an in vitro Vero E6 cells, ACE2-expressing A549 cells, a human lung epithelial cell line model. The authors mapped phosphorylation changes to disrupted kinases and pathways. These identified profiles were then used to rapidly prioritise drugs and compounds with the potential to treat SARS-CoV-2 infection.
- > An increase was observed in the number of significantly regulated phosphorylation sites and proteins over the infection time course, with the majority of regulation occurring at the level of phosphorylation.
- > Several downregulated host proteins are known to be involved in platelet regulation, thrombosis, and in preventing blood coagulation, including APOH, CD9, TSPAN14, AHSG, SERPINA1, and A2M.
- > 49 phosphorylation sites in SARS-CoV-2 viral proteins across seven viral protein were detected. The sites on membrane (M) protein, Nsp9, and nucleocapsid (N) protein of SARS-CoV-2 suggested potential important functions in virus-host interactions favouring viral replications.
- > SARS-CoV-2 infections activated host kinases signalling. Several members of the p38 pathway, including p38 γ (MAPK12), as well as CK2 (CSNK2A1/2), Ca(2+)/calmodulin-dependent protein kinase (CAMK2G), and GMP-dependent protein kinases PRKG1/2 were the strongest activated.
- > Kinase inhibitors were mapped to the most differentially regulated kinase activities and to specific phosphorylation sites. This resulted in a list of 87 drugs and compounds: 10 FDA-approved, 53 investigational new drugs (INDs, undergoing clinical testing), and 24 pre-clinical. Pharmacological inhibitors of CK2, p38 MAP kinase signalling, PIKFYVE, and cyclin-dependent kinases (CDKs) were shown to have strong antiviral efficacy in the in vitro models.
- > Significance: Provided unbiased, global phosphoproteomics approaches to highlight cellular processes hijacked during SARS-CoV-2 infection and then suggested potential targets for COVID-19 treatment.

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

Host-viral infection maps reveal signatures of severe COVID-19 patients

[https://www.cell.com/cell/pdf/S0092-8674\(20\)30568-7.pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867420305687%3Fshowall%3Dtrue](https://www.cell.com/cell/pdf/S0092-8674(20)30568-7.pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867420305687%3Fshowall%3Dtrue)

- > The following article introduces a novel computational tool called Viral-Track. It is designed to perform comprehensive mapping of single-cell RNA sequencing data (scRNA-seq) of a wide range of viruses with the aim of being able to determine host cell types associated with viral infections.
- > Viral-Track differentiates between infected host cells and bystander cells, thereby characterising the type of cells infected by the virus. By differentiating between the gene expression of viral infected cells and their bystander counterparts, Viral-Track is said to be able to determine key host factors required for viral replication.
- > In assessing the SARS-CoV-2 virus, the technology found that the virus mainly infects epithelial and macrophage subsets. The inflammatory process is characterised by a replacement of resident alveolar macrophages with recruited monocytes, neutrophils and macrophages as well as an altered CD8+ T cell cytotoxic response.
- > The exact sensitivity and specificity values of Viral-Track are not mentioned in the article. Furthermore, the technology isn't compared to traditional methods of single cell RNA sequencing for comparison of efficacy and efficiency. As such, further studies are needed to elucidate the clinical applicability of the technology.

Reviewed by: Professor Fiona Russell

OTHER RESOURCES

COVID-19 and adolescent health

https://www.rch.org.au/cah/about_us/COVID-19_and_adolescent_health_%F2%80%93_helpful_resources_to_consider/

Burnet Institute research findings, policy and technical reports

https://www.burnet.edu.au/covid-19//36_know_c19_hub

National COVID-19 clinical evidence taskforce: continually updated evidence-based clinical guidelines

<https://covid19evidence.net.au/>

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/>

Introduction to Coronavirus: free, online course aimed at teenagers and young adults: scientists and experts from the London School of Hygiene & Tropical Medicine explain research to understand the virus and guide the global response to coronavirus

<https://www.open.edu/openlearncreate/course/view.php?id=5319>

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