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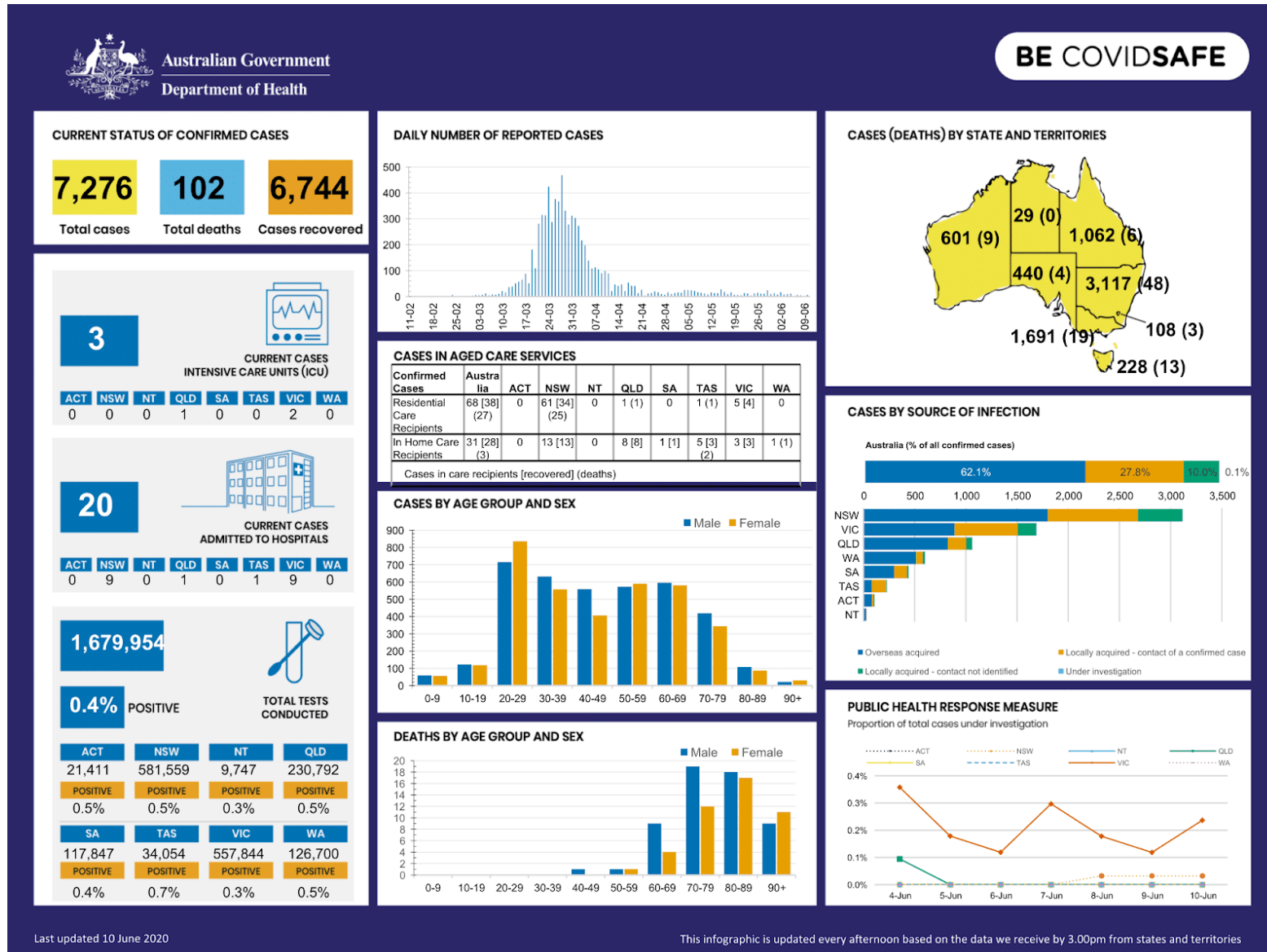
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COVID-19 KIDS EVIDENCE UPDATE

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

Weekly Update No.9

12 June 2020



Source: Australian Government: Department of health [Internet]. 2020 [updated 2020 June 10; cited 2020 June 11. 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>

GUEST EDITORIAL

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

This week New Zealand declared that it has eliminated the disease and has consequently reversed restrictions while maintaining its strict travel and international barriers. Australia is very close although seemingly aiming for control rather than elimination. Other countries have not fared so well. As of 9th June 6.93 million cases have been reported with over four hundred thousand deaths. Therefore, it is very premature to talk about the end of the first wave of the pandemic as we are far from reaching its crest.

During the last week we have also learnt a lot more about the role of hydroxychloroquine in the treatment of those with COVID-19. Chiefly, that it might not, apart from in President Trump's mind, and in the aspirations of many others, have much of one. In this issue are two important reports from randomised trials that studied the role of hydroxychloroquine in treating those infected with SARS-CoV-2 and also its ability to prevent symptoms in those exposed (see also Therapeutic section of the report).

From the open-label RECOVERY trial of patients hospitalised with COVID-19 in the UK preliminary data were reported following the unblinding of the study. 1542 patients were randomised to receive hydroxychloroquine compared with 3132 patients randomised to usual care. There was no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs 23.5% usual care, confidence interval 0.98-1.26, $p=0.10$). "It doesn't work" said the authors.

A randomised, double-blind placebo-controlled trial in the US and Canada assessed hydroxychloroquine as post-exposure prophylaxis for COVID-19 in 821 adults recruited via social media who self-reported to be exposed via household or work-related contacts and were allocated to hydroxychloroquine or placebo (folate). There was no difference in the incidence of new illness considered to be compatible with COVID-19 (hydroxychloroquine: 11.8%, placebo: 14.3%; absolute difference -2.4 %, 95% CI -7.0 to 2.2, $p=0.35$). The trial methods did not, however, allow consistent proof of exposure to SARS-CoV-2 or consistent laboratory confirmation that the symptom complex that was reported represented a SARS-CoV-2 infection so it is hard to be certain how many participants in the trial actually had COVID-19. Adherence to the interventions could not be monitored and the intervention was not introduced immediately, but three days after exposure. So, although well-conducted the study had many limitations. Side effects were more common with hydroxychloroquine than placebo (40% vs. 17%). These were mostly gastrointestinal and mild suggesting that the drug is reasonably safe, which is good news for the 203 other COVID-19 trials registered on ClinicalTrials.gov, 60 of which are focused on prophylaxis, including pre-exposure prophylaxis. Trump may yet prevail.

A couple of weeks ago, by contrast, a study published in The Lancet reported significant mortality in those taking hydroxychloroquine but this paper has since been retracted by three of its four authors following worldwide scrutiny of inconsistencies with the data which were, in retrospect, probably fabricated. A previous publication was also retracted from the New England Journal of Medicine this week by the same authors. The sorry event(s) will serve to create mistrust of scientists and scientific processes at a time when the world is at its most reliant on science and the advice of scientists. The episode could be interpreted therefore as bringing medical science into disrepute. There was apparent failure at the editorial level, peer-review and in ethical processes. However, I reserve most opprobrium for the authors themselves who felt comfortable to publish their papers without due diligence with respect to their own data sources. They retracted the paper because they could not independently gain access to validate the data (after they had published!). I have read widely that the first author is well-respected but who publishes without access and scrutiny of their data? Unfortunately, it is actually rather common, especially in studies run by industry where a clinician is given a career-boosting opportunity to front a large consortium of investigators and publish in a high-impact journal. The respected author in this case lists conflicts of interests in relation to receiving personal fees from 12 companies in his retraction letter.

Anti-vaccination protagonists often scream that healthcare workers are in cahoots with Big Pharma. Unfortunately, this may well also be the case.

The Lancet, of course, has history, having fuelled global anti-vaccination clusters through its misconstrued publication of a fallacious study linking autism with measles mumps and rubella vaccine. That paper was retracted twelve years after its publication but enormous harm had been done by then. At least an early retraction of the recent hydroxychloroquine paper might minimise the damage but already the conspiracy hyenas are howling at the moon!

I am proud that The Melbourne Children's always strives for the level of academic rigor necessary to ensure that we contribute to impactful, evidence-based science. I am again grateful to the unconflicted, unrewarded but, hopefully, not unsung posse of people who continue to do a fantastic job putting this report together as a public and professional service.

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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

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

COVID-19-associated hyperviscosity: A link between inflammation and thrombophilia?

[https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736\(20\)31209-5.pdf](https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31209-5.pdf)

- > Case series of 15 critically ill COVID-19 patients with pneumonia admitted to an Atlanta intensive care unit.
- > They were receiving anticoagulation therapy according to the institutional protocol.
- > The 15 patients had plasma viscosity exceeding 95% of normal and substantially increased fibrinogen concentration. The four patients with plasma viscosity above 3.5 cP (normal range 1.4–1.8) had a documented thrombotic complication.
- > The authors noted an elevated fibrinogen, and speculate that other acute phase reactants may contribute.
- > The authors propose that hyperviscosity may link inflammation and thrombophilia in COVID-19.
 - Hyperviscosity is known to cause thrombosis in other diseases, such as Waldenstrom's macroglobulinaemia.
 - They are actively exploring the role of therapeutic plasma exchange, a standard treatment for other conditions associated with hyperviscosity, in clinical management.
- > The association and mechanisms linking hyperviscosity and thrombotic complications of COVID-19 should be studied in larger studies.
- > Additional comments by Professor Paul Monagle:
 - The validity of the measure used to document plasma viscosity is not a great accredited approved measure.
 - Failure to consider chicken and egg; does thrombosis lead to increased viscosity or did increased viscosity lead to thrombosis?

The link to inflammation is not supported by any data provided in the paper.
 - The jump to using plasma exchange seems a big leap of faith.

Reviewed by: Professor Allen Cheng and Professor Paul Monagle

CLINICAL PAEDIATRICS

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

Epidemiological Characteristics of 2143 Paediatric Patients with 2019 Coronavirus Disease in China (pre-print)

<https://pediatrics.aappublications.org/content/pediatrics/early/2020/03/16/peds.2020-0702.full.pdf>

- > This study examined the epidemiological characteristics and transmission patterns of 2143 paediatric patients with COVID-19, reported to the Chinese CDC from 16th January to 8th February 2020.
- > There were 731 (34.1%) laboratory-confirmed cases and 1412 (65.9%) suspected cases. The median time from illness onset to diagnosis was 2 days (range: 0 to 42 days).
- > The median age of all patients was seven years (interquartile range: 2-13), and 1213 cases (56.6%) were boys.
- > Over 90% of all patients were asymptomatic, mild, or moderate cases.
- > Although clinical manifestations of children's COVID-19 cases were generally less severe than those of adult patients, young children, particularly infants, were vulnerable to more severe infection.
- > The distribution of children's COVID-19 cases varied with time and space, and most of the cases concentrated in Hubei province and surrounding areas, providing evidence supporting human-to-human transmission.

Reviewed by: Dr Wonie Uahwatanasakul

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

Children's heart and COVID-19: Up-to-date evidence in the form of a systematic review

<https://link.springer.com/article/10.1007/s00431-020-03699-0>

- > Systematic review aimed at summarising all COVID-19 cases with cardiac involvement in paediatric patients trying to explain the underlying mechanisms for COVID-19 damage.
- > Evidence for cardiac involvement in children is sparse, although a background of surgically treated congenital heart disease seems to be a predisposing factor for severe disease involving admission to ICU.
- > Newborns and infants are less likely to be susceptible for reasons such as the reduced function of the ACE-2 receptor.

- > Theories behind pathophysiology of myocardial injury due to COVID-19:
 - Direct myocardial injury due to direct binding of SARS-CoV-2 to ACE-2 receptors on surface of myocardial cells.
 - Hypoxia – anaerobic metabolism causing metabolic acidosis and induced free radical production destroy the phospholipid bilayer of myocardial cell membranes.
 - Inflammation – direct damage of myocardial cells due to inflammatory molecules.
 - Iatrogenic – antiviral drugs and medications to prevent excessive immune system activation may damage cardiac myocytes.

Reviewed by: Dr Wonie Uahwatanasakul

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

Acute myocardial injury: a novel clinical pattern in children with COVID-19
[https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642\(20\)30168-1/fulltext](https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30168-1/fulltext)

- > Case series of five children with cardiac injury and mild to moderate cardiac dysfunction in the setting of COVID-19 admitted to a paediatric intensive care unit (PICU) in Italy.
- > These previously healthy children had initial symptoms of fever and gastrointestinal symptoms (severe diarrhoea with or without abdominal pain and vomiting).
- > Tachycardia and hypotension were the main clinical signs on PICU admission.
- > Cardiac enzymes, especially NT-proBNP, were substantially elevated. All five children had a mild to moderate heart dysfunction; ejection fraction was reduced (mean 47.8%) and four children required a short course of intravenous adrenaline. One child developed atrial fibrillation and reversible acute kidney injury. All children were discharged to the ward with normal cardiac function.
- > This clinical picture may be a mild form of the COVID-19-related shock described in the UK, now being labelled as paediatric multisystem inflammatory syndrome.
- > This case series reinforces the need for close monitoring of children with COVID-19 for cardiac involvement.

Reviewed by: Dr Wonie Uahwatanasakul

DIAGNOSTICS & SAMPLING

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

False Negative Tests for SARS-CoV-2 Infection- Challenges and Implications
<https://www.nejm.org/doi/full/10.1056/NEJMp2015897?source=nejmtwitter&medium=organic-social>

- > The performance of a test is based on its sensitivity and specificity.
- > Analytic sensitivity indicates the likelihood that the test will be positive for material containing any virus strains and the minimum concentration the test can detect.
- > Analytic specificity indicates the likelihood that the test will be negative for material containing pathogens other than the target virus.
- > For testing, the FDA prefers clinical specimens to determine a test's sensitivity and specificity, however it permits "contrived specimens"- those produced by adding viral RNA or inactivated virus to leftover clinical material. It has also allowed companies to establish clinical performance by using an authorised real time PCR test in known positive material (symptomatic swabs or contrived samples) rather than against a 'reference standard' (usually a clinical diagnosis) to determine their true state. Using known positive samples or contrived samples may lead to overestimates in test sensitivity as in practice swabs may miss infected material.
- > The paper also discusses false negative real time-PCR tests in patients with apparent COVID-19 illness, expressed through two studies from China.
 - In one study 11% of sputum samples (n=142), 27% of nasal swabs (n=490) and 40% of throat samples (n=205) were deemed falsely negative in 213 patients hospitalised with COVID-19.
 - In the second study antibody seroconversion was observed in 93% of 173 patients hospitalised with acute respiratory symptoms and chest CT 'typical' of COVID-19.
- > The other conclusions come from modelling the chance of infection given a negative result (using sensitivity and specificity) against the pretest probability that a person is infected. The pretest probability is based on local SARS-CoV-2 prevalence in the area, patient exposure and symptoms. This can influence whether to find a negative test result reassuring, and highlights the importance of high sensitivity. Pretest probability can be reduced through social distancing and other public health measures.

> Conclusions

- Diagnostic tests need to be highly sensitive and validated under realistic conditions against a clinically meaningful reference standard.
- Designing a reference standard for measuring test sensitivity in asymptomatic patients is an urgent priority as of June 1st there is no way to assess clinical sensitivity of a test in asymptomatic people.
- Developing methods of determining pretest probability of infection for asymptomatic and symptomatic individuals could allow calculation of post-test probabilities after positive and negative results.
- Negative results, even on highly sensitive tests, cannot rule out infection if the pretest probability is high- clinicians are advised not to trust unexpected negative results.
- Thresholds for ruling out infection need to be developed, and as this is a value judgement public input is important.

Reviewed by: Professor Fiona Russell

DISABILITY

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

**Intellectual and developmental disability and COVID-19 case fatality trends:
TriNetX analysis**

<https://www.sciencedirect.com/science/article/pii/S1936657420300674?via%3Dihub>

- > Despite higher prevalence of co-morbidities and risk of severe outcomes from SARS-CoV-2, there have been limited COVID-19 reports regarding people with intellectual and developmental disability (IDD).
- > This study compared COVID-19 trends amongst people with and without IDD using 55 million electronic medical records from 42 health care organisations.
- > The overall case-fatality rate was similar in patients with and without IDD (5.1% vs 5.4%).
 - Within the IDD population, a greater proportion of cases were in the 0-17-year age group compared to the non-IDD population (26.7% vs 1.6%), and a lower proportion were in the >75-year age group (8% vs 15.3%).
 - People with IDD aged 0-17 years of age had higher COVID-19 case-fatality rates (1.6% vs <0.1%) than their non-IDD counterparts, however these figures were based on very small numbers (Two deaths in the IDD population and one death in the non-IDD population).

Reviewed by: Professor David Amor

EPIDEMIOLOGY & PUBLIC HEALTH

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

The Role of Children in the Dynamics of Intra Family Coronavirus 2019 Spread in Densely Populated Area

https://journals.lww.com/pidj/Abstract/9000/The_Role_of_Children_in_the_Dynamics_of_Intra.96128.aspx

- > The dynamics of COVID-19 transmission within families was investigated in 13 family clusters of infection in a crowded city in Israel.
- > Index cases were omitted from the analysis to prevent biased higher rates in adults since in almost all index cases were adults.
- > SARS-CoV-2 positivity rates: 21/36 adults (58.3%); 13/40 children 5–17y (32.5%); 2/18 children, 0–4y (11.8%).
- > There were significantly lower rates of COVID-19 positivity in children compared with adults residing in the same household.
- > Supportive evidence of less adult-child transmission compared with adult-adult transmission within households.

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

COVID-19 in Great Britain: Epidemiological and clinical characteristics of the first few hundred (FF100) cases: A descriptive case series and case control analysis

<https://europepmc.org/article/ppr/ppr166002>

- > Following detection of the first virologically confirmed cases of SARS-CoV-2 in Great Britain, an enhanced surveillance study was initiated to map the clinical presentation, disease course, and underlying health conditions associated with the infection in the first few hundred cases (FF100).
- > Case questionnaires were completed via interview for those who were identified as case positive - demographic details, medical history, and travel history details were gathered.
 - Cases were then followed-up for 14 days from the initial report seeking information on potential medical complications and clinical outcomes
- > .

- > 381 confirmed cases were included in the analysis - 16.8% of cases were resident in London, England.
- > Of the FF100: 51.4% of the cases included were imported, 24.7% were secondary, and 23.9% were sporadic cases.
 - 38.3% reported travel to Italy in the 14 days prior to symptom onset (71.4% of imported cases).
 - Of the secondary cases, almost all people reported close contact with a confirmed case (93/94, 98.9%).
 - Close household contact (39.8%), healthcare setting (10.8%), other settings including work and social gatherings (47.3%)
- > When occupation was recorded (n = 357), 42 cases were healthcare workers (11.8%).
- > Demographics: male (56.7%), female (43.3%), age ranged between one year - 94 years (mean 47.7), ethnicity breakdown was comparable to the general population.
- > Underlying health conditions: 32.1% of cases had an underlying health condition, and 11.7% of cases demonstrated multimorbidity; most commonly asthma, diabetes, and chronic heart disease.
- > No association of COVID-19 with diabetes, chronic respiratory disease (excluding asthma), chronic neurological disease, organ transplant or history of malignant cancer was found.
- > Clinical features: the most frequent symptoms were cough (77.75), fatigue (70.9%), fever (60.1%), headache (56.7%), myalgia (50.9%), and anorexia (44.1%).
 - Some variation existed in symptomatology across age groups, symptoms by sex were relatively consistent (excluding headache as more females reported).
- > Association with symptoms: non-linear relationships were observed with age and fever.
- > Symptom sensitivity & specificity varied by age.

Reviewed by: Associate Professor Margie Danchin

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

Greater risk of severe COVID-19 in non-White ethnicities is not explained by cardiometabolic, socioeconomic, or behavioural factors, or by 25(OH)-vitamin D status: study of 1,326 cases from the UK Biobank (not peer-reviewed)
<https://www.medrxiv.org/content/10.1101/2020.06.01.20118943v1>.

- > Participants identified through prospective cohort UK Biobank Study. Data linked with hospitalisation records and Public Health England COVID-19 test results.
- > Of 4510 hospitalised patients tested for COVID-19, 1326 were positive. Participants were grouped according to COVID-19 status: test positive, test negative, and untested.
- > This study used multivariate logistic regression to assess whether cardiometabolic, socio-economic, or behavioural factors explained the greater severity of COVID-19 in men and non-White ethnicities in the UK.

- > Both men and patients of non-White ethnicity were most likely to test positive for COVID-19.
- > Cardiometabolic comorbidities were more common in the non-White and male groups, whilst smoking was more common in the White cohort. Townsend deprivation scores and overcrowding measures were worse for non-White groups.
- > On univariate analysis male sex, non-White ethnicity, higher BMI, greater material deprivation, and greater household overcrowding were associated with increased odds of a positive COVID-19 test.
- > On multivariate analysis, none of the cardiometabolic, socio-economic, or behavioural factors explained the strong association with sex or ethnicity.
- > This study aggregates all non-White ethnicities into one cohort, which may overlook unique differences in these populations. Causal relationships can't be inferred, and confounding may have occurred despite the wide range of covariates which were included in the analysis.
- > Overall, the study might suggest that other mechanisms which are as yet untested could be responsible for the increased burden of COVID-19 on those of certain ethnicities.

Reviewed by: Dr Claire von Mollendorf

Effects of non-pharmaceutical interventions on COVID-19 cases, deaths and demand for hospital services in the UK: A modelling study

[https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667\(20\)30133-X/fulltext](https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30133-X/fulltext)

- > This age-structured dynamic transmission model investigated the potential impact of different intervention packages on the number of COVID-19 cases, deaths and ICU admissions projected out to December 2021.
- > The authors included eight intervention scenarios: Baseline – no intervention; school closures; physical distancing; shielding of people over 70 years of age; self-isolation of symptomatic cases; combined – school closures, physical distancing, shielding and self-isolation; intensive interventions; and lockdown.
- > A model with no interventions in place, estimated 23 million cases, with 350,000 deaths (CFR 1.5%), not including those who would die due to the health service capacity becoming overwhelmed. Projected ICU bed needs were 13-80 times actual capacity.
- > None of the shorter-duration interventions (school closures, physical distancing, shielding, self-isolation) on their own were able decrease projected healthcare needs to below actual capacity.
- > School closures were negated by potential impact of children cared for by grandparents.
- > Combination strategy did not demonstrate a sustained impact on the epidemic.
- > Intensive strategies delayed the epidemic peak, but did not reduce it to below capacity.
- > Intensive interventions with lockdowns triggered by COVID-19 ICU bed requirement thresholds, reduced ICU load.

- > The most stringent intervention program, with combined measures and lockdown, resulted in a projected 50,000 deaths. The capacity of the health services was still exceeded in this scenario.
- > Whilst this article discusses a model which was updated with current knowledge about transmission of COVID-19, the conclusions on the relative effectiveness of the interventions are the same as that which the research team presented to decision makers in real time (mid-March).
- > The modelling highlights the necessity of extreme measures to avoid health services becoming overwhelmed during COVID-19.

Reviewed by: Dr Claire von Mollendorf

INFECTION CONTROL

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

Detection of air and surface contamination by SARS-CoV-2 in hospital rooms of infected patients

<https://www.nature.com/articles/s41467-020-16670-2>

- > Current evidence suggests that SARS-CoV-2 is primarily spread via droplet and contact transmission; the role of airborne transmission remains uncertain.
- > This study aimed to identify patient level risk factors for environmental contamination by SARS-CoV-2 in hospitalised COVID-19 patients (n=30) at different stages of illness.
- > The investigators collected surface samples (~9 samples/room) from the patient environment, and air samples (n=5 rooms; using NIOSH BC 251 bio aerosol sampler), and tested samples by PCR (Qiagen, Hilden, Germany).
- > 57% of hospital rooms had at least one environmental surface contaminated.
- > The floor (65%), bed rail (59%) and bedside locker (47%) were most likely to be contaminated. Air samples were positive in three out of five rooms (60%).
- > Airborne SARS-CoV-2 particles and high touch surfaces contamination were highest during the first week of symptoms and associated with nasopharyngeal viral load.
- > Limitations: Small study; viral culture was not done, so it was not possible to determine whether SARS-CoV-2 detected on surfaces was capable of causing infection; only single time point sampling was done for each patient; clinical samples were collected at a different time to environmental sampling; findings are not necessarily representative of environmental contamination in community settings.

Reviewed by: Dr Vanessa Clifford

MENTAL HEALTH

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

How does lockdown impact loneliness? (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.05.29.20116657v1.full.pdf>

- > This study aimed to assess the trajectory of loneliness over the lockdown period. Risk factors for loneliness and resilience factors were also assessed.
- > The UCLA 3-point loneliness scale was used to determine loneliness in 35,712 participants at three separate time points over a six-week period during isolation in the United Kingdom.
- > Participants were recruited from the UCL COVID-19 social study, which did not use a random sample.
- > Participants were ranked into four loneliness classes ranging from low to high using a growth mixture modelling approach.
- > Individuals with pre-existing mental health issues, younger adults (18-29) and women were more likely to experience heightened loneliness during isolation. Students also had greater odds of being in the highest loneliness class.
- > Living with other people, having a close friendship group, and having higher perceived social support appeared protective against loneliness. People living in rural areas were also less likely to be in the highest loneliness class.
- > This study identified young adults to be at particular risk of loneliness during lockdown, suggesting greater intervention is needed to prevent loneliness in this group.

Reviewed by: Professor David Coghill

PERINATAL HEALTH

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

Preeclampsia-like syndrome induced by severe COVID-19: a prospective observational study

<https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1111/1471-0528.16339>

A prospective observational study of 42 pregnancies investigating the use of clinical, ultrasonographic and biochemical findings to differentiate between preeclampsia (PE) and PE-like syndrome associated with COVID-19 during the study period of 31 days in March 13th to April 10th, 2020 in Barcelona, Spain.

- > Some systemic effects of COVID-19 (eg. hypertension; kidney disease) are thought to be due to vasoconstriction resulting from renin-angiotensin system dysfunction.
- > PE is mainly the consequence of endothelial damage due to placental oxidative stress and antiangiogenic status.
- > Reports of increased PE incidence in COVID-19 patients.
- > Participants:
 - Singleton pregnancies with COVID-19 at >20+0 weeks' gestation.
 - Median gestational age: 32 weeks.
 - Median maternal age of cases with severe COVID-19 was significantly higher than in non-severe cases (39.4 vs 30.9, $p=0.006$).
 - Split into severe and non-severe COVID-19 according to severe pneumonia.
- > 75% (six of eight) of severe COVID-19 cases developed PE features, all requiring antihypertensive treatment.
- > Abnormal sFlt-1/PIGF and UtAPI demonstrated in one of the six women, who still met PE diagnostic criteria following recovery from severe pneumonia.
- > Two women remained pregnant after recovering from severe pneumonia and had spontaneous resolution of PE-like syndrome; No PE cases in non-severe women.
- > Pregnant women with severe COVID-19 may present with a PE-like syndrome which can be distinguished from actual PE by sFlt-1/PIGF, LDH and UtAPI.
- > Limitations: Small series; only five women with PE-like syndrome are reported; only two of five women who developed a PE-like syndrome remained pregnant after severe pneumonia; Cannot affirm that the three cases with PE-like syndrome that improved during severe pneumonia did not improve due to delivery; sFlt-1/PIGF and UtAPI are not diagnostic of PE. Authors suggest therefore that the PE-like syndrome alone may not be an obstetric indication for delivery.

Reviewed by: Professor Suzanne M Garland

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

Safety of Breastfeeding in Mothers with SARS-CoV-2 Infection (pre-print)
<https://www.medrxiv.org/content/10.1101/2020.05.30.20033407v1.full.pdf>

- > 23 pregnant women (in the third trimester) and in the puerperium were enrolled in the study (14 had confirmed SARS-CoV-2 infection and nine had suspected infection).
- > The presence of SARS-CoV-2, IgG and IgM in breast milk, maternal blood and infant blood were assessed.
 - All breast milk samples (collected largely one postpartum and several 12-15 days) were negative for detection of SARS-CoV-2 nucleic acid by RTPCR.
 - SARS-CoV-2 IgM in breast milk generally correlated with maternal blood results. SARS-CoV-2 IgG was negative in all milk samples regardless of whether it was positive or negative in maternal blood. (Testing for SARS-CoV-2 IgG and IgM was only performed in seven patients).
 - SARS-CoV-2 detection of throat swab was performed in 21 neonates at or shortly after birth. Eight infants also received IgM/IgG antibody testing one month after birth. All results were negative.
- > Conclusion: The study suggests no evidence for mother-to-child transmission via breastfeeding in women with COVID-19 in the third trimester and puerperium. It is noteworthy that the mothers were not particularly ill from COVID-19 (cough, fever and one had diarrhoea).
- > Limitations: Small sample size and short interval for medical observation. Further studies are needed to prove the safety of breastfeeding.

Reviewed by: Professor Suzanne M Garland

THERAPEUTICS

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

COVID 19 rapid evidence summary: Remdesivir for treating hospitalised patients with suspected or confirmed COVID-19

<https://www.nice.org.uk/advice/es27/chapter/Key-messages>

- > UK NICE guidelines on use of Remdesivir.
- > Remdesivir has not been studied in the paediatric population or in pregnant women with COVID-19 and there are currently limited safety data.

Chan Ying Zhen Charissa –3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for COVID-19

<https://www.nejm.org/doi/full/10.1056/NEJMoa2016638>

- > Randomised, double-blind, placebo-controlled trial in the USA and Canada.
- > 821 asymptomatic, uninfected adult participants: 87.6% reported moderate to high-risk exposure to confirmed COVID-19 contact (household or workplace setting).
- > Participants recruited and enrolled via the internet.
 - Allocated to placebo (folate) or HCQ (800mg once, then 600mg six to eight hours later, then 600mg daily for four more days).
- > No significant difference in incidence of new illness (HCQ: 11.8%, Placebo: 14.3%; absolute difference -2.4 percentage points, 95% CI -7.0 to 2.2, p=0.35).
- > No significant difference in incidence of symptoms and hospitalisations.
- > Side effects more common with HCQ than placebo (40.1% vs. 16.8%), gastrointestinal intolerance most common, but discontinuation due to side effects less common.
- > No serious intervention-related adverse reactions or cardiac arrhythmias.
- > Limitations: Lack of availability of diagnostic testing in the United States for participants, however trial represents real-world implementation after exposure. Data obtained by means of participant report from an internet-based approach of recruitment. Less than half of participants started HCQ within two days.
- > Conclusion: hydroxychloroquine use within four days of exposure is not effective as postexposure prophylaxis for COVID-19.

Reviewed by: Professor Allen Cheng

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

No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19

<https://www.recoverytrial.net/news/statement-from-the-chief-investigators-of-the-randomised-evaluation-of-covid-19-therapy-recovery-trial-on-hydroxychloroquine-5-june-2020-no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19>

- > A statement from the chief investigators of the Randomised Evaluation of COVID-19 therapy (RECOVERY) trial on 5th June 2020 advising that they have found no benefit in the use of hydroxychloroquine therapy and will no longer be enrolling patients in this arm of the study.
- > The RECOVERY trial was established as an open-label randomised clinical trial to test a range of potential drugs for the treatment of COVID-19, including hydroxychloroquine. The trial is enrolling patients from 175 NHS hospitals in the UK.
 - The study protocol has been published online:
<https://www.recoverytrial.net/files/recovery-protocol-v6-0-2020-05-14.pdf>.
 - Hydroxychloroquine was administered at a dose of 800mg (0, 6h) then 400mg (12h then bd until day nine).
 - Other interventions being tested in this trial include lopinavir/ritonavir, corticosteroids, azithromycin, convalescent plasma.
- > Every two weeks the data monitoring committee has reviewed the data to determine if there is evidence strong enough to affect global health outcomes. Upon request from the UK MHRA, an additional review was performed by the data monitoring committee, who then recommended the chief investigators review the unblinded data on the hydroxychloroquine arm of the trial. The chief investigators concluded that there is no beneficial effect of hydroxychloroquine in patients hospitalised with COVID-19.
- > Preliminary results:
 - 1542 patients were randomised to hydroxychloroquine compared with 3132 patients randomised to usual care alone.
 - There was no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs 23.5% usual care, confidence interval 0.98-1.26, p=0.10).
 - There was no evidence of beneficial effects on hospital stay duration or other outcomes.
- > Limitations: Detailed results have not been published yet, and further detail (including the characteristics of patients and results in subgroups) will be important to consider; toxicity data will also be important to consider.

Reviewed by: Professor Allen Cheng

TRANSMISSION

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

Estimating the extent of asymptomatic COVID-19 and its potential for community transmission: systematic review and meta-analysis (pre-print)
<https://www.medrxiv.org/content/10.1101/2020.05.10.20097543v2>

- > The rate of asymptomatic COVID-19 cases is critical to policy makers considering the effectiveness of mitigation measures against SARS-CoV-2.
- > This study aims to synthesize all available research on the asymptomatic rates and transmission rates.
- > Meta-analysis used fixed effect and random effects models.
- > Included nine low risk-of-bias studies from six countries that tested 21,035 at-risk people, of which 559 were positive and 83 were asymptomatic.
- > Diagnosis was confirmed using a RT-qPCR.
- > The proportion of asymptomatic cases ranged from 4% to 41%.
- > Meta-analysis found that the proportion of asymptomatic cases was 15% overall; higher in non-aged care 16%, and lower in long-term aged care 8%.
- > Four studies provided direct evidence of forward transmission of the infection by asymptomatic cases but suggested considerably lower rates than symptomatic cases.
- > These estimates of the prevalence of asymptomatic COVID-19 cases and asymptomatic transmission rates are lower than many highly publicized studies.
- > Further robust epidemiological evidence is urgently needed, including in sub-populations such as children, to better understand the importance of asymptomatic cases for driving spread of SARS-CoV-2.

Chan Ying Zhen Charissa – 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31142-9/fulltext?utm_campaign=tlcoronavirus20&utm_content=130650663&utm_medium=social&utm_source=twitter&utm_channel=tw-27013292](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31142-9/fulltext?utm_campaign=tlcoronavirus20&utm_content=130650663&utm_medium=social&utm_source=twitter&utm_channel=tw-27013292)

- > Systematic review: 172 observational studies, 16 countries, 6 continents, 25,697 patients; Meta-analysis: 44 comparative studies.
- > Studies on COVID-19, SARS, or MERS.
- > Transmission of viruses was lower with physical distancing of 1 metre or more, compared with a distance of less than one.
- > Protection was increased as distance was lengthened.
- > Face mask use by both healthcare workers and the general public could result in a large reduction in risk of infection.
- > Stronger associations with N95 or similar respirators compared with disposable surgical masks or similar (eg. reusable 12–16-layer cotton masks).
- > Eye protection might provide additional protection.
- > However, none of these interventions provide complete protection from infection.
- > Limitations: all studies were non-randomised, not always fully adjusted. Recall and measurement bias.

Reviewed by: Dr Celeste Donato

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

Exhaled breath is a significant source of SARS-CoV-2 emission (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.05.31.20115154v1.full.pdf>

- > Exhaled breath condensate (EBC), air samples, and surface swabs collected from 35 COVID-19 subjects and analyzed using quantitative reverse transcription-polymerase chain reaction (RT-qPCR).
- > EBC: 16.7% positive rate (n=30).
- > Surface swabs: 5.4% positive rate (n=242).
- > Air samples: 3.8% positive rate (n=26).
- > SARS-CoV-2 exhaled into air at ~103-105 RNA copies/minute.
- > Toilet (16.7%) and floor surfaces (12.5%) are important SARS-CoV-2 reservoirs.
- > Surfaces frequently used by COVID-19 patients had very low probabilities of SARS-CoV-2 presence: Mobile phones = 9% (n=22); various handles = 0% (n=35).
- > Study implies that airborne transmission plays a major role COVID-19 spread, especially during early stages of disease.

Reviewed by: Dr Celeste Donato

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

Asymptomatic Transmission, the Achilles' Heel of Current Strategies to Control COVID-19
<https://www.nejm.org/doi/full/10.1056/NEJMe2009758>

- > Whilst there are many similarities between SARS-CoV-2 and SARS-CoV-1 (SARS of 2003) (genetics, respiratory droplet transmission and lower respiratory symptoms), SARS-CoV-2 has resulted in much higher infection rates around the world - the authors contend that relying on intervention strategies used during SARS is insufficient to control the spread of COVID-19.
- > Reasons for the much higher infection rates of SARS-CoV-2 include:
 - High levels of upper respiratory tract SARS-CoV-2 shedding (making the virus more transmissible compared to the lower respiratory tract replication of SARS-CoV-1).
 - Viral load peak occurs earlier in COVID-19 so viral load is higher at symptom onset compared with SARS.
- > A case study in a nursing facility in Washington State:
 - 76 residents tested: 48 were positive for SARS-CoV-2 and 27 of these were asymptomatic at testing (56%).
 - Of the 27 asymptomatic patients, 24 developed symptoms within four days of testing, however 17 of them had a viable virus culture one to six days before the development of symptoms.
- > The authors recommend mass testing of residents in nursing homes and other vulnerable facilities (congregate living situations), as relying on symptomatic testing is inadequate due to the high rates of asymptomatic infection and transmission.
 - Mass testing will allow for appropriate quarantine of infected patients and reduce the number of deaths.
 - One in ten nursing homes in the US have reported COVID-19 cases.
 - They also recommend the use of face masks by the general public in crowded areas in light of this evidence.

Reviewed by: Dr Celeste Donato

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

What explains the high rate of SARS-CoV-2 transmission in meat and poultry facilities?

<https://www.cebm.net/covid-19/what-explains-the-high-rate-of-sars-cov-2-transmission-in-meat-and-poultry-facilities/>

- > Numerous COVID-19 outbreaks have been described related to meat and poultry processing facilities in different countries.
- > The working environment in meat and poultry facilities is favourable to SARS-CoV-2 persistence (metallic surfaces, low temperature and relative humidity).
 - Low temperature and high humidity rates promote the stability of SARS-CoV-2 in the environment.
 - SARS-CoV-2 persists better on metallic or plastic surfaces and meat factories often use stainless steel surfaces.

The working environment may help SARS-CoV-2 transmission (crowded working place, shared transportation, production of aerosols, droplets, fomites. In some countries, workers often live in overcrowded housing environments, which contribute to the spread of the virus.

- > There is a high time pressure in meat factories and intense physical demands, which make it difficult for workers to comply with proper PPE use or high cleaning standards.
- > Speaking loudly in a noisy environment also increases the release of droplets, which may facilitate the spread.
- > In the wet environment, there is an increasing need to regularly change PPE, which is often not possible due to the shortage during COVID-19 pandemic.

A vulnerable, low-paid workforce may be under pressure to keep working despite having symptoms of COVID-19.

- > Meat industry is an important infrastructure and important to remain open.
- > Many workers are immigrants with a significant language barrier and limited health literacy. They are often fearful of losing their job and thus under pressure to continue working despite their symptoms.

Reviewed by: Dr Lien Anh Ha Do

VIROLOGY

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

Introductions and early spread of SARS-CoV-2 in the New York City area

<https://science.sciencemag.org/content/early/2020/05/28/science.abc1917>

- > This study describes how the introduction and early spread of SARS-CoV-2 occurred in the New York City (NYC) area, by analysing the 90 SARS-CoV-2 whole genome sequences from COVID-19 patients seeking care at the Mount Sinai Health System, between February 29th, 2020 and March 18th, 2020, together with 2,363 sequences from GISAID database (up to April 1st, 2020). Of note, the authors used the clade nomenclature from the NextStrain tool (an open source project to pathogen genomic research <https://nextstrain.org/>).
- > 87% of sequences were clustered with clade A2a – a clade largely composed of isolates from COVID-19 patients in Europe. Within the A2a clade, there were two mutations distinguishing clusters of sequences from NYC and elsewhere. This suggests there were two separated introductions of COVID-19 cases from Europe into NYC.
- > 6% were clade A1a – this is also a clade composed of 82% isolates from COVID-19 patients in Europe.
- > 7% were clade B, B1 and B4 – Clade B was composed of 50% isolates from COVID-19 patients in Asia.
- > Phylogeny analysis shows strong evidence of untracked transmission of COVID-19 cases between Europe and U.S in the early March, while a limited evidence of direct introductions from China where the virus originated.
- > Limitations: Absence of detailed epidemiological data on travel history and contacts has challenged the analysis of the association between untracked transmission periods and specific countries/regions.

Emergence of SARS-CoV-2 through recombination and strong purifying selection

<https://advances.sciencemag.org/content/early/2020/05/28/sciadv.abb9153.full>

- > This study presents a potential mechanism of SARS-CoV-2 origin by using 43 representative and complete genome sequences of coronavirus (CoV) selected from GenBank and GISAID, while the animal source of SARS-CoV-2 is still unknown.
- > Authors focused on recombination breakpoints and selection evolution analysis as recombination is an important mechanism of CoV evolution. The two-previous human CoVs (SARS and MERS) are the result of recombination among CoVs.

- > The receptor binding motifs of SARS-CoV-2 was potentially acquired from recombination events because a significant recombination breakpoint before and after the ACE2 receptor binding motif (RBM) was found in the comparison analysis between Wuhan-Hu-1 (SARS-CoV-2 from human) to Pan_SL-CoV_GD (pangolin) and RaTG13 (Bat) sequences. Likely, a RaTG13-like virus served as a progenitor to generate SARS-CoV-2 by gaining a complete human ACE2 binding RBM from Pan_SL-CoV_GD-like viruses.
 - SARS-CoV-2 has a unique furin cleavage site insertion (PRRA) not found in any other CoVs in the Sarbecovirus group. A similar insertion (PAA) at the same site was reported from a study on CoVs in wild bats in Yunnan, China, although it is not clear if the insertion (PAA) has similar function as the insertion (PRRA), but this indicates that such insertion (PRRA) in SARS-CoV-2 may already be present in wild bats. Hence recombination events helped SARS-CoV-2 to gain the human ACE2 binding RBM and the PRRA motif makes the S1/S2 cleavage in SARS-CoV-2 much more efficient than in SARS-CoV, together then may facilitate the expanding the tropism and/or enhancing the transmissibility of SARS-CoV-2.
 - Evolution analysis of regions containing RBM and the PRRA insertion showed S2 and RBM were highly conserved across SARS-CoV-2, RaTG13, and Pan_SL-CoV with low dN/dS ratio (ratio between non-synonymous and synonymous substitutions) suggesting a strong purifying selection in these regions.
- > Provides a complex pattern of evolutionary recombination and strong purifying selection between CoVs from distinct host species and that cross-species infections could be likely origin of SARS-CoV-2.
 - Highlights the importance of monitoring coronavirus in their natural hosts and in human population in order to control a future outbreak.
 - Highlights the danger of wet market setting where the risk of cross-species spillover infections is high due to close interactions between animals of different species and with human.
- > Limitations: Lack of sequence data from wild bats and other potential wild animals from the wet markets.

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

Proteomic and Metabolomic Characterization of COVID-19 Patient Sera

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7254001/pdf/main.pdf>

- > This retrospective case-control study undertook proteomic and metabolomic analysis of sera from 65 confirmed COVID-19 cases (28 severe and 37 non-severe cases) and 53 control individuals (28 healthy controls and 25 non-COVID-19 individuals).
- > 894 proteins and 941 metabolites (including 36 drugs and their metabolites) were identified and quantified as potential COVID-19 omics profile with high degree of consistency and reproducibility (median coefficient of variance (CV) values for proteomic and metabolomic data were 10% and 5%, respectively). No substantial impact of potential confounding factors (i.e age, sex, the time from disease onset to admission, and the time from sampling to diagnosis of severe cases) to the COVID-19 omics profile.

- The proteomic and metabolomic data from 18 non-severe and 13 severe COVID-19 cases were then used to train a random forest machine learning model => This model had a good predicting performance with an area under curve (AUC) of 0.957.
- The machine learning model was validated on an independent dataset from ten patients => only one patient (a 62-year-old male) and one patient (a 43-year-old male) were incorrectly classified as severe and non-severe, respectively.
- 29 molecules (22 proteins and seven metabolites) randomly selected from the COVID-19 omics profiles (for 1,000 times and for those having relatively low rates of classification correctness) were used to test another independent dataset from 19 COVID-19 patients => 16/19 patients were correctly classified into severe and non-severe groups.
- > 93 differentially expressed proteins in severe COVID-19 were identified and were involved in three major biological pathways i.e activation of the complement system, macrophage function, and platelet degranulation.
- > 204 metabolites were correlated with COVID-19 severity. Among these 204 metabolites, 80 significantly changed metabolites were also involved in the three biological pathways revealed in the above proteomic analysis.
- > Key dysregulated protein molecules and metabolites in each biological pathway were also identified. Interestingly, lipid metabolism (dysregulation of multiple apolipoproteins) was downregulated in severe COVID-19 and associated with macrophage function.
- > This study provided potential biomarkers in serum that could predict progression to severe COVID-19 and also suggested molecular insights on SARS-CoV-2 pathogenesis.

Reviewed by: Dr Lien Anh Ha Do

OTHER RESOURCES

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_z2uWV7r3FaPzAOr86q9ZXBcTZ1OcCE_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>

EDITORIAL TEAM

Leadership group:	Professor Fiona Russell & Dr Wonie Uahwatanasakul
Editorial Assistant:	Eleanor Neal (Epidemiologist / PhD student)
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Journalists: For any media inquiries, please contact The University of Melbourne media unit, via news@media.unimelb.edu.au

REVIEWERS

Professor Fiona Russell	Director of the Child and Adolescent Health PhD Program, Department of Paediatrics, The University of Melbourne; Group Leader Asia-Pacific Health Research, MCRI
Dr Wonie Uahwatanasakul	Paediatrician- Immunisation service RCH, MD Child and Adolescent Health Program Lead Coordinator, Department of Paediatrics, The University of Melbourne
Professor Sarath Ranganathan	Head of the Department of Paediatrics & The Stevenson Chair in Paediatrics, University of Melbourne, Head of Respiratory Diseases Research Group, Infection and Immunity Theme, MCRI, Director of Respiratory & Sleep Medicine, RCH
Professor Allen Cheng	Medical Adviser, Melbourne Vaccine Education Centre, Infectious Diseases Epidemiology Director of the Infection Prevention and Healthcare Epidemiology, Alfred Health, Infectious diseases and an epidemiologist, Department of Epidemiology and Preventive Medicine at Monash
Professor Paul Monagle	Haematologist, The Royal Children's Hospital; Group Leader, Haematology Research, Murdoch Children's Research Institute; Department of Paediatrics, University of Melbourne
Professor David Amor	Department of Paediatrics, The University of Melbourne, Group Lead, Neurodisability and Rehabilitation Research, Murdoch Children's Research Institute
Associate Professor Margie Danchin	General and Immunisation Paediatrician, Department of General Medicine, RCH, Group Leader, Vaccine Uptake, MCRI, Clinician Scientist Fellow, Department of Paediatrics and School of Population and Global Health, The University of Melbourne
Dr Claire von Mollendorf	Senior Research Officer, New Vaccines and Asia-Pacific Health Research Groups, MCRI and honorary Senior Fellow, Department of Paediatrics, The University of Melbourne
Dr 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
Professor David Coghill	Financial Markets Foundation Chair of Developmental Mental Health, The University of Melbourne
Professor Suzanne M Garland	Reproductive & Neonatal Infectious Diseases, Department of Obstetrics and Gynecology, University of Melbourne; Director Centre Women's Infectious Diseases Research; Honorary Research Fellow, Infection & Immunity, Murdoch Children's Research Institute.
Dr Celeste Donato	Senior Research Officer, Enteric Diseases, Infection & Immunity Theme, MCRI and Honorary Fellow, Department of Paediatrics, The University of Melbourne
Dr Lien Anh Ha Do	Virologist, New Vaccines, Infection & Immunity Theme, MCRI and Honorary Fellow, Department of Paediatrics, The University of Melbourne