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Melbourne Medical School
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. 11

26th June 2020

BE COVIDSAFE

CURRENT STATUS OF CONFIRMED CASES

7,521 **103** **6,924**

Total cases Total deaths Cases recovered

2

CURRENT CASES
 INTENSIVE CARE UNITS (ICU)

ACT	NSW	NT	QLD	SA	TAS	VIC	WA
0	0	0	0	0	0	2	0

16

CURRENT CASES
 ADMITTED TO HOSPITALS

ACT	NSW	NT	QLD	SA	TAS	VIC	WA
0	8	0	1	0	0	7	0

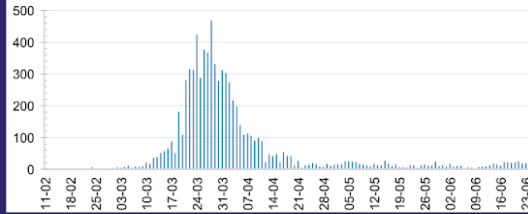
2,180,424

0.3% POSITIVE

TOTAL TESTS
 CONDUCTED

ACT	NSW	NT	QLD
26,937	756,240	12,099	334,084
POSITIVE	POSITIVE	POSITIVE	POSITIVE
0.4%	0.4%	0.2%	0.3%
SA	TAS	VIC	WA
141,630	45,970	696,263	167,201
POSITIVE	POSITIVE	POSITIVE	POSITIVE
0.3%	0.5%	0.3%	0.4%

DAILY NUMBER OF REPORTED CASES

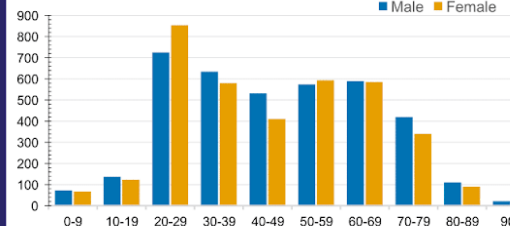


CASES IN AGED CARE SERVICES

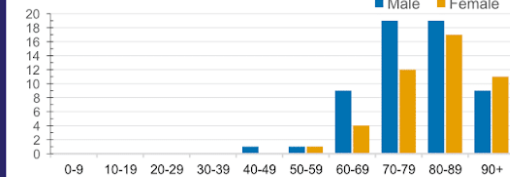
Confirmed Cases	Australia	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
Residential Care	71 [39]	0	61 [34]	0	1 (1)	0	1 (1)	8 [5]	0
Recipients	(29)		(27)						
In Home Care	31 [28]	0	13 [13]	0	8 [8]	1 [1]	5 [3]	3 [3]	1 (1)
Recipients	(3)						(2)		

Cases in care recipients [recovered] (deaths)

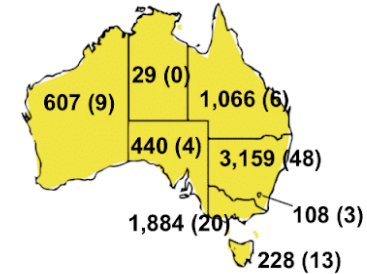
CASES BY AGE GROUP AND SEX



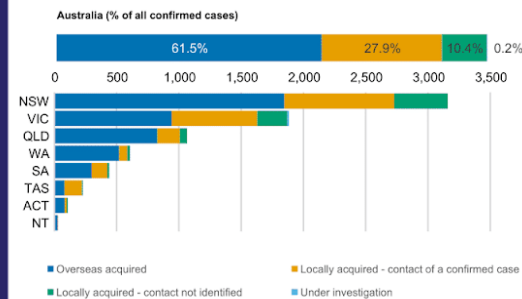
DEATHS BY AGE GROUP AND SEX



CASES (DEATHS) BY STATE AND TERRITORIES

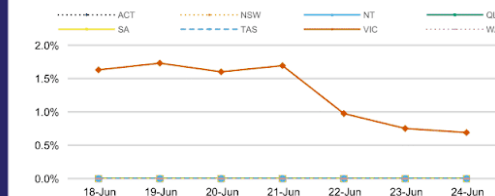


CASES BY SOURCE OF INFECTION



PUBLIC HEALTH RESPONSE MEASURE

Proportion of total cases under investigation



Last updated 24 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 24; cited 2020 June 25]. 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

“How good is social distancing?” you can imagine our Prime Minister saying. Well, it was very, very good, reducing reproductive number (R_0) in Australia from approximately 2.53 to an effective R (R_{eff}) of 0.5 and resulting in incredibly effective suppression of our curve. It was so effective that it also impacted on cases of influenza. Last year there were 313,360 cases of influenza in Australia compared with just 20,575 so far in 2020. In May 2019 there were over 30,000 cases of influenza, but only 197 were reported in May this year. This, in association with suppression of other respiratory viral infections, has contributed to fewer presentations of conditions exacerbated by these viruses such as asthma and cystic fibrosis.

Unfortunately, as restrictions have eased over the past few weeks adherence to social distancing recommendations appears to have also diminished. Social distancing is clearly not working so well in the state of Victoria, with evidence of a recent surge in cases and a jump in R_{eff} to a current value of 2.5. Plans to open up activities and venues have been rescinded and working from home contingencies reinforced.

The global epidemiology is far more depressing of course, with over 9 million cases and nearly 480,000 reported deaths. That's a million more cases and 50 thousand more deaths than last week.

As for young people? Age-structured mathematical modelling of epidemic data from China, Italy, Japan, Singapore, Canada and South Korea confirms the reduced susceptibility to infection in individuals under 20 years of age, which is estimated to be approximately half that of adults aged over 20 years, and that clinical symptoms manifest in 21% of infections in 10- to 19-year-olds, rising to 69% of infections in people aged over 70 years (<https://www.nature.com/articles/s41591-020-0962-9> - see Transmission section of this report). 1.7 billion of the world's population are thought to have a significant co-morbidity that would confer an increased risk of COVID-19. The risk of being hospitalised is < 1% for those < 20-years-old but 20% for those 70-year-old and over.

Modelling has also been used to predict countries that are at greatest risk of severe disease ([https://doi.org/10.1016/S2214-109X\(20\)30264-3](https://doi.org/10.1016/S2214-109X(20)30264-3)). In Africa, the modelling indicates that the country with the greatest proportion of the population at risk is Mauritius, in Latin-America it is Puerto Rico, in Europe - Bulgaria and in Oceania this is Fiji. But of course, it is the populous countries where the greatest tragedies will unfold with socio-economic disparities contributing to mortality, and not just from COVID-19. One such country is our closest neighbour, Indonesia, where child deaths are already being reported. This portends disaster right on our doorstep.

The greatest global threat according to Dr Tedros Adhanom Ghebreyesus, Director-General of the World Health Organisation is “the lack of global solidarity and global leadership”. As the data accrues regarding where the world faces disaster, it is time for us all to consider how we might employ our clinical, research and academic skills to add value and support our neighbours and other countries more significantly impacted than ourselves in a show of global solidarity.

HIGHLIGHTS

- > Obstetricians should be aware that pregnant women with contact to a COVID-19 patient or suggestive symptoms may be at risk of developing pre-eclampsia.
- > Differences between the child and adult respiratory systems may explain why children are protected from severe COVID-19 disease.
- > COVID-19-response measures in Africa in relation to the management of children with cancer and blood disorders may provide an opportunity for sustainable improvement in care.
- > SARS-CoV-2 appears to be more transmissible in households than SARS-CoV (secondary attack rate 4.6–8.0%) and Middle East respiratory syndrome coronavirus (secondary attack rate 4.0–5.1%).
- > Chilblain like lesions may be a manifestation of milder COVID-19 in younger patients, though PCR is likely to be negative by the time of presentation.
- > High cortisol concentrations on admission of adult patients were associated with increased mortality and a reduced median survival from a UK cohort study, possibly because this is a marker of the severity of illness.
- > Asymptomatic individuals have been observed to have a reduced immune response to SARS-CoV-2 infection and this may lead to indicate a shorter duration of immunity after SARS-CoV-2 infection.

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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 healthcare 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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CLINICAL PAEDIATRICS

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

Negative SARS-CoV-2 PCR in patients with chilblain-like lesions (correspondence)
[https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099\(20\)30518-1.pdf](https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(20)30518-1.pdf)

- > The prospective cohort study was conducted evaluating 40 consecutive patients with chilblain-like lesions.
 - Tested for SARS-CoV-2 via RT-PCR and tested for SARS-CoV-2-specific IgA, IgM, and IgG antibodies.
 - 25/40 patients were asymptomatic on physical examination with the remaining demonstrating mild symptoms.
- > Serology was positive in 12/40 (30%) of patients.
- > No patient was PCR positive at the time of consultation.
- > Suggestions:
 - SARS-CoV-2 in young patients may be completely suppressed before a humoral response is induced.
 - Chilblain-like lesions are associated with mild or asymptomatic infection, and those presenting with such lesions will likely have negative PCR results at the time of presentation.

Reviewed by: Dr Wonie Uahwatanasakul

Outbreak of chilblain-like acral lesions in children in the metropolitan area of Milan, Italy, during the COVID-19 pandemic (pre-proof)

<https://www.sciencedirect.com/science/article/pii/S0190962220310793>

- > Development of chilblain-like acral lesions has been described in young COVID-19 patients.
- > 13/30 patients experienced systemic symptoms a median of 6 days prior to lesion onset.
- > Lesions were erythematous-violaceous patches or slightly infiltrated plaques, no blisters, crusts, or ulcers were observed.
- > Lesions are likely vasculopathic and, although aetiology is unclear and seem to be related to COVID-19 (number of diagnoses of chilblain significantly increased from the same time last year).
- > This manifestation usually appears in asymptomatic or paucisymptomatic children, who do not often undergo SARS-CoV-2 testing in Italy for economic reasons.
- > The recognition of chilblain-like lesions may facilitate diagnosis of COVID-19 in asymptomatic/paucisymptomatic paediatric patients.

Reviewed by: Dr Wonie Uahwatanasakul

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

Physiological advantages of children against COVID-19 (letter)
<https://onlinelibrary.wiley.com/doi/10.1111/apa.15410>

- > Differences between the child and adult respiratory systems may explain why children are protected from severe COVID-19 disease.
- > COVID-19 can enter the human body through the Angiotensin converting enzyme 2 (ACE2). More than 80% of total ACE2 expression is found in type II alveolar cells in the lungs. As children have fewer alveoli (only three million in newborn, compared to 500 million in adults) they may be protected from mounting an excessive immune reaction compared to adults.
- > TMPRSS2 (a cellular serine protease) is also required to allow the entry of COVID-19 into host cells. TMPRSS2 is largely expressed in type II alveolar cells. The gene encoding this protein is upregulated by androgenic enzymes which could explain why children (at the pre-pubertal stage) have decreased entry of coronavirus to type II alveolar cells.
- > Collateral ventilation is the ventilation of the alveoli via pathways that bypass the normal airways. These pathways are absent in neonates and develop during the first five years of life. These collateral pathways may facilitate the excessive spread of virus in adults compared to children.
- > Children have smaller functional residual capacity and larger alveolar ventilation compared to adults. Therefore, the decreased alveolar clearance rate may facilitate viral attachment in adults.

Reviewed by: Dr Wonie Uahwatanasakul

DIAGNOSTICS & SAMPLING

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

Association between high serum total cortisol concentrations and mortality from COVID-19 (correspondence)

[https://www.thelancet.com/pdfs/journals/landia/PIIS2213-8587\(20\)30216-3.pdf](https://www.thelancet.com/pdfs/journals/landia/PIIS2213-8587(20)30216-3.pdf)

- > A cohort study from the UK with 535 patients.
- > It has been suggested that severe acute respiratory syndrome coronavirus (SARS-CoV), the predecessor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), might trigger an immunogenic response to adrenocorticotrophic hormone because of mimicry.
- > Similar mechanisms might apply to SARS-CoV-2, theoretically amplifying morbidity and mortality by inducing a cortisol insufficiency related to critical illness.
- > Multivariable analysis showed that a doubling of cortisol concentration was associated with a significant 42% increase in the hazard of mortality, after adjustment for age, the presence of co-morbidities, and laboratory tests.
- > Patients with COVID-19 whose baseline cortisol concentration was equal to or less than 744 nmol/L had a median survival of 36 days, and those with COVID-19 whose cortisol value was more than 744 nmol/L had a median survival of 15 days
- > This data suggests that it is appropriate for patients with hypoadrenalism—a situation quite commonly encountered in the 3% of the population taking systemic glucocorticoid therapy — to be given supplemental glucocorticoids at a high dose to prevent an acute adrenal crisis if they acquire a SARS-CoV-2 infection.
- > High cortisol concentrations were associated with increased mortality and a reduced median survival, probably because this is a marker of the severity of illness.

Reviewed by: Dr Wonie Uahwatanasakul

EPIDEMIOLOGY & PUBLIC HEALTH

Dr Claire von Mollendorf - Senior Research Officer, New Vaccines and Asia-Pacific Health Research Groups, MCRI and honorary Senior Fellow, Department of Paediatrics, The University of Melbourne

Household secondary attack rate of COVID-19 and associated determinants in Guangzhou, China: a retrospective cohort study

[https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099\(20\)30471-0.pdf](https://www.thelancet.com/pdfs/journals/laninf/PIIS1473-3099(20)30471-0.pdf)

- > Retrospective cohort study using a contact tracing dataset from the Guangzhou Center for Disease Control and Prevention.
- > The study aimed to estimate the secondary attack rate of SARS-CoV-2 among household and non-household close contacts in Guangzhou.
- > Between 7th January - 18th February 2020, there were 349 laboratories confirmed SARS-CoV-2 infections with 195 unrelated close contact groups (215 primary cases, 134 secondary or tertiary cases, and 1964 uninfected close contacts) identified on contact tracing.
- > In 138 (71%) of close contact groups, no secondary cases were identified.
- > Most patients with COVID-19 were adults (aged 20–59 years).
- > The overall secondary attack rates were 13·2% (95% CI 10·9–15·7) among household contacts and 2·4% (1·6–3·3) among non-household contacts.
- > Individuals aged 60 years and older were the groups most susceptible to SARS-CoV-2 infection.
- > Within households, the secondary attack rates were lower in the youngest age group (age < 20 years; 5·2% [95% CI 2·4–9·7]) than the 20–59 years age group (14·8% [95% CI 11·7–18·4]; P = 0·0009) and the oldest age group (age ≥60 years; 18·4% [12·5–25·6%]; P = 0·0003).
- > Secondary attack rate estimates decreased between January and February 2020.
- > For household contacts defined as close relatives: using a mean incubation period of five days and maximum infectious period of 13 days and assuming no case isolation, the estimated secondary attack rates were 12·4% (95% CI 9·8–15·4%) among household contacts and 7·9% (95% CI 5·3–11·8%) among non-household contacts.

- > A longer incubation period was associated with a slightly lower secondary attack rate estimate than a shorter incubation period, and a longer infectious period was associated with a slightly higher secondary attack rate estimate than a shorter infectious period.
- > SARS-CoV-2 appears to be more transmissible in households than SARS-CoV (secondary attack rate 4·6–8·0%) and Middle East respiratory syndrome coronavirus (secondary attack rate 4·0–5·1%).

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

Epidemiological features and viral shedding in children with SARS-CoV-2 infection (pre-proof)

<https://onlinelibrary.wiley.com/doi/abs/10.1002/jmv.26180>

- > Children with COVID-19 had mild or asymptomatic disease accompanied by pneumonia in approximately half of the cases.
- > Data was collected in multiple centres by the Chinese CDC on paediatric patients (less than 14 years old).
- > Incubation periods ranged from four days to 21 days, with a mean of 9.1 in the 43 cases included in this study.
- > On day seven and day 14 after being discharged, the results of faecal RT-PCR were now negative in 17.6% (3/17) and 33.3% (6/18) of the children, respectively.
- > The study also investigated contacts in the same families of the affected children and found that the incidence of SARS-CoV-2 infection in children contacts was 13.2% - this was much lower than that in adult contacts, which is in accordance with previous literature.
- > The possible progress of SARS-CoV-2 in children, was not clear, which might have led to over examination with the use of chest CT - upon review of these cases, the necessity of chest CT in most cases with mild/no symptoms is questioned.
- > Paediatric patients were given anti-virals in hospital - the effectiveness of these drugs was difficult to analyse, but there was no difference in viral shedding.
- > Susceptibility of SARS-CoV-2 infection in children was lower, and the incubation periods were longer than that in adults.

Reviewed by: Dr Wonie Uahwatanasakul

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

Risks to children during the COVID-19 pandemic: some essential epidemiology
<https://www.bmj.com/content/bmj/369/bmj.m2290.full.pdf>

- > Shielding children as a precaution against COVID-19 is not risk-free, and children cannot be kept at home if they are to thrive.
- > There were 44 deaths from COVID-19 in 0-19-year-olds (total population 135,691,226) up to 19th May 2020, accounting for just 0.333% of deaths in 0-19-year-olds.
- > The medical community should inform parents, carers, teachers, clinicians, and decision-makers that the direct impact of COVID-19 on children is currently small in comparison with other risks.
- > The main reason we are keeping children at home is to protect adults.
- > This conclusion might change as the pandemic evolves, so the epidemiology of COVID-19 in children should be closely monitored.

Reviewed by: Dr Wonie Uahwatanasakul

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

Open with care: Minimising COVID-19 super spreading settings in Australia
https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3625655

- > Next phase of COVID-19 crisis may be characterised by superspreading events in high-risk settings.
- > High-risk settings (e.g. night clubs, karaoke rooms, gymnasiums, ski resorts, cruise ships and religious gatherings) inherently have an increased risk of transmission due to factors such as large crowds, close proximity of attendees, long duration of exposure, loud vocalisation (e.g. singing or yelling), poor ventilation, aerobic activity, sharing of objects, food or drinks, and alcohol or other drug use.
- > A simple relative risk assessment shows a potential 200-fold (multiplicative) increased risk of COVID-19 transmission in night clubs compared to restaurants:
 - Louder vocalisation: 3-10 fold increased risk of viral dose excretion.
 - Communicating closely together (30 cm versus 1 m): 8-fold increased risk of viral dose excretion and inhalation.
 - Light exercise (dancing): 3-fold increased risk of viral dose excretion.
 - Mixing of patrons: the 3-fold increase in clubs.
- > Opening of high-risk venues should be managed through robust risk-benefit analysis, with enhanced surveillance for super spreading events and rapid response.

- > The authors suggest four principles for safely opening up public settings:
 - Ensure the increase in COVID-19 cases do not overwhelm the healthcare system, and reasonable non-urgent non-COVID-19 healthcare can be maintained.
 - Seek the maximum social and economic benefit with the least number of COVID-19 cases.
 - Situations favourable to opening up the economy:
 - Low-level transmission with easy contact tracing and control and low risk of causing large uncontrollable outbreaks.
 - Low viral dose exposures that are less likely to cause severe disease and potentially result in less infectious cases.
 - No venue with higher risk should be opened until all lower risk venues are opened under normal (or adapted) operating conditions and the impact has been observed.

Reviewed by: Dr Claire von Mollendorf

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

Importance of advancing SARS-CoV-2 vaccines in children

<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa712/5850904>

- > The role of children in SARS-CoV-2 transmission and the true burden in this group is still poorly defined.
- > Retrospective data demonstrate that children were infected early on in the outbreak, with children < 4 years old accounting for the highest percentage of hospitalisation (the majority of which have at least one underlying medical condition).
- > Children, in general, are asymptomatic or have mild/moderate symptoms, although an increasing number of children are presenting with an inflammatory syndrome with Kawasaki disease-like features in the setting of recent or past infection.
- > Epidemiological studies of similar respiratory viruses have shown a higher percentage of positive viral episodes and a longer duration of shedding in children.
- > Childhood vaccination in similar respiratory infections has been effective in reducing community spread through the development of herd immunity.
- > Based on current data, children should be included early in SARS-CoV-2 vaccine, clinical trials – planning should begin as soon as data is available about safety in adults from phase 2 clinical trials.
- > If determined safe and immunogenic, these vaccines should be integrated into childhood immunisation programs.

Reviewed by: Dr Claire von Mollendorf

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

**Coronavirus disease 2019 case surveillance - The United States, January 22-
May 30, 2020**

https://www.cdc.gov/mmwr/volumes/69/wr/mm6924e2.htm?s_cid=mm6924e2_e&deliveryName=USCDC_921-DM30615

- > This report describes demographic characteristics, underlying health conditions, symptoms, and outcomes among 1,320,488 laboratory-confirmed COVID-19 cases from 22nd January until 30th May, 2020.
- > The most common underlying health conditions among COVID-19 cases were cardiovascular disease (32%), diabetes (30%), and chronic lung disease (18%).
- > Hospitalisations were six times higher and deaths 12 times higher for COVID-19 patients with reported underlying conditions compared to those without.
- > Severe outcomes such as hospitalisations, ICU admissions and deaths increased by age, regardless of underlying conditions.

Reviewed by: Dr Wonie Jahwatanasakul

GLOBAL HEALTH

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

Caring for children with cancer in Africa during the COVID-19 crisis: implications and opportunities

<https://www.tandfonline.com/doi/full/10.1080/08880018.2020.1772913>

- > As a result of the COVID-19 pandemic, a shift in healthcare priorities has left children with cancer and blood disorders in low- and middle-income countries at an even higher risk of detrimental outcomes than before.
- > Additional challenges that have arisen during the pandemic include reduced detection and referral of cancer patients, shortages in therapeutic drugs, blood donors and staff availability. Similarly, travel restrictions, loss of income and additional psychosocial strain on families of children with cancer adds to the worsening outcomes.
- > The continuation of the following COVID-19-response measures may provide considerable and sustainable improvement in the management of children with cancer and blood disorders during and following the pandemic:
 - Persistence of infection control measures such as hand hygiene, PPE availability, and physical distancing.
 - Decentralisation of care by delivering treatment in outpatient settings or at primary hospital level reduces travel time to access healthcare.
 - Increased recruitment, training and retention of health professionals in the government sector.
 - Additional funding to healthcare systems in African countries and maintaining adequate stocks of essential consumables.

Reviewed by: Dr Wonie Uahwatanasakul

An urgent call to address the nutritional status of women and children in Nepal during COVID-19 crises

<https://equityhealthj.biomedcentral.com/articles/10.1186/s12939-020-01210-7>

- > Women and children stand to be the most disadvantaged during the current (24th March - 14th June) COVID-19 nation-wide lockdown in Nepal.
- > Infants are at an increased risk of morbidity and mortality secondary to malnutrition and dehydration due to low immunity, gastrointestinal or respiratory tract infections.

- > Lockdown restricts household jobs/ incomes and subsequently access to food where food insecurity and hunger are already significant challenges faced within Nepal (Global hunger index score of 20.8). Conversely, lockdown may also increase the rate of obesity in childhood due to behaviours, such as consuming unhealthy food and reduced physical activity.
- > Moreover, lockdown disrupts health promotion campaigns and access to healthcare services both as inpatients and at outpatient centres.
- > The following preventative measures have been proposed:
 - Subnational development and implementation of mitigation strategies against food insecurity in the most affected areas.
 - Promote and support optimal breastfeeding and complementary feeding practices. Ensure food security and distribute specialised nutritious food where required.
 - Continue maternal child health services to offer preventative services, treat acute malnutrition and provide counselling and psychological support to mothers and caregivers of under 5-year-old children.

Reviewed by: Associate Professor Margie Danchin

IMMUNOLOGY

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

Neutralising antibodies responses to SARS-CoV-2 in COVID-19 inpatients and convalescent patients

<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa721/5851474>

- > This is a study aimed at characterising the changing levels of neutralising antibodies in patients with COVID-19 infection at different stages of infection.
- > The study design consisted of 70 COVID-19 positive patients from two hospitals, 12 of whom were inpatients, and 58 of whom were convalescent. The mean age was 45.1 years, and 58.6% were female. Indicators for the assessment of immunogenicity included the seropositivity rate and the geometric mean titre (GMT).
- > A small percentage of patients had co-morbidities, including cardiovascular disease, hypertension and diabetes.
- > In terms of disease severity, one patient was asymptomatic, 22 had mild clinical manifestations, 43 were moderate, and four had severe clinical manifestations.
- > The study characterised a ‘typical’ response to COVID-19 viral infection in all patients, involving a seropositivity rate of 100% at around day ten as well as a peaked GMT between days 31-40.
- > Neutralising antibody titres were found to increase significantly with increasing age; thus, further studies are needed to elucidate whether high titre levels are protective against moderate to severe disease.
- > Overall, antibody levels were also shown to be higher in convalescent patients than in inpatients; however, a small number of convalescent patients showed recovery with a low GMT, suggesting that other immunological factors are at play in achieving recovery.
- > Several limitations of the study are noted, including convenient sampling (not random), a small sample size as well as inconsistencies with the number of follow up testing and follow-up period.

Reviewed by: Professor Fiona Russell

INFECTION CONTROL

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

Clinical and immunological assessment of asymptomatic SARS-CoV-2 infections <https://www.nature.com/articles/s41591-020-0965-6>

- > Viral shedding and immune response in asymptomatic patients has not been well characterised, but has implications for shield immunity and easing physical distancing restrictions if understood.
- > This paper is a case-control study involving 37 asymptomatic individuals (mean age 41 years) in Wanzhou District. Patients were matched using sex, age-frequency and co-morbidities to mild symptomatic patients for comparison, along with matched RT-PCR negative patients for cytokine comparison.
- > Results:
 - The median duration of viral shedding was 19 days (6-45) for the asymptomatic group versus 14 days for the symptomatic group. Note- viral shedding does not equate to infectivity.
 - The virus-specific IgG levels in the asymptomatic group were significantly lower ($P = 0.005$) in the acute phase (when viral RNA can be found in the respiratory specimen).
 - In the early convalescent phase (8 weeks after they were discharged from the hospital) IgG levels in 93.3% of the asymptomatic group and 96.8% of the symptomatic group declined. IgG levels were still significantly higher in the symptomatic group ($P = 0.002$).
 - A decrease in neutralising serum antibodies by 81% of the asymptomatic group and 62.2% of the symptomatic group was observed.
 - 40.0% of asymptomatic individuals became seronegative for IgG compared to 12.9% of symptomatic individuals.
 - Asymptomatic individuals exhibited lower levels of 18 pro- and anti-inflammatory cytokines compared to symptomatic individuals.
- > Conclusion:
 - Asymptomatic individuals had a reduced immune response to SARS-CoV-2 infection, and this may lead to a shorter duration of immunity after SARS-CoV-2 infection.

- > Limitations:
 - Small sample size.
 - Further long term follow up would aid in furthering understanding in this area.
 - The true infection rate of asymptomatic patients needs further investigation.

Reviewed by: Dr Wonie Uahwatanasakul

PERINATAL HEALTH

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

COVID-19 and maternal pre-eclampsia: a synopsis

<https://onlinelibrary.wiley.com/doi/abs/10.1111/sji.12918>

- > The hyperinflammatory state in COVID-19 may be associated with hypoxic injury of the placenta and development of the pre-eclamptic state in pregnant women.
- > Possible COVID-19 intrauterine infection may alter the expression of ACE2 receptors, the entry receptor for SARS-CoV-2, in human placental villi and cause vasoconstriction and altered blood flow.
- > There are similarities between COVID-19 positive patients and pre-eclamptic women at an immunological and laboratory basis. COVID-19 and pre-eclampsia are both associated with an increase in pro-inflammatory cytokines serum ferritin.
- > Thrombocytopenia, a characteristic of severe COVID-19, is an independent risk factor for severity in pre-eclampsia.
- > The authors recommend further studies to show the association between COVID-19 and development of pre-eclampsia.
- > Obstetricians should be aware that women who were in contact with a confirmed COVID-19 patient or those who have a history of suggestive symptoms may be at risk of developing pre-eclampsia.

Reviewed by: Dr Wonie Uahwatanasakul

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

The collateral damage of the COVID-19 pandemic: A Dutch perinatal perspective

<https://www.bmj.com/content/bmj/369/bmj.m2326.full.pdf>

- > Pregnant women may be more hesitant to visit the hospital, as they perceive an increased risk of infection.
- > Hospitals are not allowing partners to be present during labour.
- > In many hospitals, only one visitor per day can visit a child in the neonatal intensive care unit - this may lead to long term neonatal bonding problems as well as parental psychosocial complications and depression.
- > After discharge, the new family is isolated from family and friends owing to social distancing rules - women, especially those who are vulnerable, need monitoring for postpartum depression and domestic abuse.

- > The less obvious consequences of COVID-19 not described in guidelines should be registered in a timely manner for further understanding of these adverse sequelae, and secondary prevention programmes should be implemented.

Reviewed by: Professor Fiona Russell

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

A systematic review on the levels of antibodies in COVID-19 virus exposed but negative newborns: a possible vertical transmission of IgG/ IgM (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.06.09.20127118v1?%253fcol=lection=>

- > This was a systematic review to determine the immunoglobulin G and M (IgG/IgM) levels among infants born to mothers with COVID-19.
- > Data were extracted by two independent authors in accordance with the PRISMA-P guidelines.
- > 486 abstracts were screened, and 63 full-text articles were assessed, of which nine met the inclusion criteria for qualitative analysis.
- > The median antibody levels was 75.49 AU/mL (range: 7.25 AU/mL- 140.32 AU/mL) and for 3.79 AU/mL (range: 0.16 AU/mL-45.83 AU/mL) for anti-SARS-CoV-2 IgG and IgM, respectively.
- > There were high levels of IgG but low IgM against SARS-CoV-2 (using < 10 AU/mL as a reference range) among COVID-19 virus exposed but negative newborns.
- > This review suggests a possible natural passive immunity (IgG/ IgM) against COVID-19 virus.

Reviewed by: Professor Fiona Russell

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

SARS-CoV-2 in first-trimester pregnancy - does it affect the fetus? (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.06.08.20125195v1>

- > There are few documented cases of infection during the first trimester by SARS and MERS, hence implementing public health policies for pregnant women in the setting of COVID-19 is challenging. However, women infected by SARS/MERS in the first trimester were shown to have an increased risk of adverse obstetric outcomes and maternal morbidity.
- > This study investigated two cohorts of pregnant women in Denmark. The first (n = 1019) had a double test (PAPP-A and β -hCG) taken during February and April. The second cohort (n=36) included women with a first-trimester loss prior to the double test. SARS-CoV-2 antibodies were correlated with nuchal translucency thickness.

- > Sera collected from these two cohorts were analysed for SARS-CoV-2 antibodies IgG and IgM. No specimens were collected for virus PCR.
- > Results: infection during the first trimester did not seem harmful, with no increased risk of severe COVID-19 disease, as defined by serology. Nuchal translucency was not significantly different in pregnant women with COVID-19. Of the 36 women with first-trimester loss, none had SARS-CoV-2 antibodies.
- > Limitations: use of serological assays, which are limited by the low prevalence of positive results, for the assessment of disease; selection bias as not all women invited to participate responded.

Reviewed by: Professor Suzanne M Garland

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

Appropriate care for neonates born to mothers with COVID-19 disease (pre-proof)
<https://onlinelibrary.wiley.com/doi/abs/10.1111/apa.15413>

- > Current data suggests the risk of vertical transmission from infected mothers to babies, or through breastmilk is very low.
- > Feasible that maternal SARS-CoV-2 antibodies can be transferred through the placenta, either conferring immunity against virus or reduce disease severity. Antibodies may also be transferred via breastmilk, which is important for IgA isotype antibodies which do not pass through the placenta. Breastmilk also contains other bioactive molecules which inhibit viral entry into cells.
- > The limited separation between mother and baby allows prolonged skin-to-skin contact, increases the likelihood of early and exclusive breastfeeding, and reduces potential exposure to harmful practices and infected surfaces, staff and carers.
- > Data suggests relatively few newborn infants born to mothers with COVID-19 get the disease as long as good infection prevention practices are followed by the mum.
- > Mothers with COVID-19 should be managed in delivery and recovery areas separate from main patient care areas (as recommended by WHO).
- > Mothers with COVID-19 who keep their infants with them after birth need to adopt appropriate infection prevention and control practices to limit the risk of infecting baby: PPE, masks, hand hygiene resources, careful counselling of mother and family members.

Reviewed by: Professor Fiona Russell

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

Maternal transmission of SARS-CoV-2 to the neonate, and possible quotes for such transmission: a systematic review and critical analysis (accepted)

<https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/1471-0528.16362>

- > A systematic review (49 studies, 666 neonates) to evaluate the risk of transmission to the neonate from mothers infected with SARS-COV-2.
- > The following factors that may contribute towards the risk of transmission were included and discussed in the review: mode of delivery, type of feeding and mother-infant interaction.
- > Postnatal SARS-CoV-2 infection was detected in 28/666 (4%) of neonates - eight had symptoms, of which four were premature, and the cause of symptoms was difficult to identify.
- > 291 women delivered vaginally with 8 (2.7%) neonates testing positive for SARS-COV-2. 364 women delivered by Caesarean with 20 (5.3%) neonates testing positive. Whether infection occurred via vertical transmission or was transmitted postnatally is unclear.
- > Whether breastfeeding contributed to risk was difficult to estimate as most neonates (460/666) had no feeding data collected. Of the 28 infected neonates, seven were breastfed, three formula-fed, one was given expressed milk, and the remaining 17 had no information collected.
- > For the COVID-19 positive neonates, seven were kept isolated from their mother, five were in the same room as their mother, and the isolation status for the remaining 16 was unknown.
- > The findings and overall consensus so far is that neonatal COVID-19 infection is not common and is usually asymptomatic.
- > The rate of infection does not appear to be affected by the mode of delivery, breastfeeding or mother-baby contact.
- > Other studies have demonstrated that neonates can be infected early in life, but as the severe infection is rare, the benefits of breastfeeding and contact with the mother are thought to outweigh the risks.
- > A number of issues in the review are present: there is some overlap with the same cases and neonates in multiple studies (though attempts to mitigate this were made), asymptomatic mothers and babies may be missed due to lack of testing, symptomatic mothers may have not been tested, testing methods vary, and there was missing data for some of the variables included (breastfeeding, neonate isolation).

Reviewed by: Professor Fiona Russell

THERAPEUTICS

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

ICON (Ivermectin in Covid Nineteen) study: use of Ivermectin is associated with lower mortality in hospitalised patients with COVID-19 (pre-print)
<https://www.medrxiv.org/content/10.1101/2020.06.06.20124461v2.full.pdf>

- > A retrospective cohort study of 280 consecutive COVID-19 patients hospitalised at four Broward Health hospitals in South Florida from 15th March – 11th May 2020.
- > Cohort:
 - Epidemiology: Mean age – 59.6 years old; Female – 45.4%.
 - Ivermectin (≥ 1 dose 200 $\mu\text{g}/\text{Kg}$) group: 173 patients.
 - Normal care group: 107 patients.
 - Treatment received was at the discretion of treating physicians.
 - 27 patients not reviewed (multiple admissions, lack of confirmed COVID-19 results during hospitalisation, <18 years old, pregnant, or incarcerated).
- > Severe pulmonary involvement defined as requiring $\text{FiO}_2 \geq 50\%$, or non-invasive or invasive mechanical ventilation (n = 75).
- > Main results:
 - Lower mortality in ivermectin group even after adjusting for between-group differences and mortality risk factors (OR 0.27, 95% CI 0.09-0.85, P = 0.03; HR 0.37, 95% CI 0.19-0.71, P = 0.03).
 - Severe pulmonary involvement:
 - Lower mortality rates in ivermectin group (38.8% vs 80.7%; OR 0.15, 95% CI 0.05-0.47, P = 0.001).
 - No significant difference in successful extubating rates between groups (36.1% vs 15.4%; OR 3.11, 95% CI 0.88-11, P = 0.07).
 - No significant side effects from ivermectin use were observed.
- > Ivermectin was associated with lower mortality during COVID-19 treatment, especially in patients with severe pulmonary involvement.

- > Limitations:
 - Retrospective nature of the study; relatively small sample size, the unusually high proportion receiving ivermectin.
 - Unmeasured confounding factors cannot be excluded; use of stepwise variable selection not favoured by statisticians as may exclude confounders from the final model.
 - Implausible that anti-virals would be more effective late in illness; this may reflect possible “immortal time” bias - those who received ivermectin survived at least long enough to receive it.
 - Unable to determine the additional benefit of hydroxychloroquine with or without azithromycin which was received by most patients (although recent clinical trials suggest that HCQ is not effective).
 - Unknown appropriate dosing of ivermectin for COVID-19; previous studies have suggested that toxic doses are required to achieve viral inhibition.
 - Unknown effect of ivermectin on viral load or in milder COVID-19.
- > Ivermectin cannot currently be recommended for routine use; clinical trials would be required to demonstrate efficacy and safety.

Reviewed by: Professor Allen Cheng

TRANSMISSION

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

Age-dependent effects in the transmission and control of COVID-19 epidemics
<https://www.nature.com/articles/s41591-020-0962-9>

- > Evaluation based on an age-structured mathematical model to epidemic data from China, Italy, Japan, Singapore, Canada and South Korea.
- > Susceptibility of infection in individuals under 20 years old is approximately half of adults over 20 years old.
- > Clinical symptoms manifest in 21% of infections in 10-19-year-olds (95% CI 12-31%) but are 69% in those over 70 years (95% CI 57-82%).
- > Interventions aimed at children might have a relatively small impact in SARS-CoV-2 transmission.
- > Global burden of COVID-19: regions with older population could see disproportionately more cases.

Reviewed by: Associate Professor Margie Danchin

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

Age-dependent effects in the transmission and control of COVID-19 epi
<https://www.nature.com/articles/s41591-020-0962-9>

- > This was an evaluation of the possibility of fitting an age-structured mathematical model to epidemic data from China, Italy, Japan, Singapore, Canada, and South Korea.
- > Susceptibility to infection in individuals under 20 years of age is approximately half that of adults aged over 20 years, and that clinical symptoms manifest in 21% of infections in 10- to 19-year-olds, rising to 69% of infections in people aged over 70 years.
- > Interventions aimed at children might have a relatively small impact on reducing SARS-CoV-2 transmission, particularly if the transmissibility of subclinical infections is low.
- > In countries with younger population structures—such as many low-income countries—the expected per capita incidence of clinical cases would be lower than in countries with older population structures, although it is likely that co-morbidities in low-income countries will also influence disease severity.
- > Without effective control measures, regions with relatively older populations could see disproportionately more cases of COVID-19, particularly in the latter stages of an unmitigated epidemic.

Reviewed by: Professor Fiona Russell

VACCINES

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

Vaccine repurposing approach for preventing COVID-19: can MMR vaccines reduce morbidity and mortality?

<https://www.tandfonline.com/doi/full/10.1080/21645515.2020.1773141>

- > This commentary suggests that the measles-mumps-rubella (MMR) vaccine could be repurposed for COVID-19 prophylaxis and used to prevent severe disease progression. The suggestion is based on the vaccine's ability to induce natural killer (NK) cells and interferons (IFN), in addition to some cross-reactivity from proteins in the MMR vaccine.
- > They assume that the extensive paediatric vaccination schedule followed globally could have resulted in innate immune responses offering natural immunity to SARS-CoV-2, and that this may describe the low prevalence of COVID-19 infection observed in children.
- > They describe the increase in innate immunity arising from the induction of NK cells and the production of IFNs following childhood vaccination.
 - After viral infection or vaccination, NK cells proliferate and help to reduce the severity and duration of viral infections by lysing virus-infected cells.
 - IFNs have strong anti-viral activities, and IFN production is triggered in response to viral and intracellular bacterial infections.
- > IFNs elicited by vaccine strains are reported to be more efficient in offering protection than wild-type disease strains. Similarly, vaccine-induced NK cells are more potent and robust in their anti-viral activities. IFNs and NK cells induced post-vaccination are also less likely to cause a hyper-inflammatory response upon reinfection.
- > The MMR vaccine that is included in most vaccination programs contains attenuated enveloped RNA viruses that have glycoprotein spikes similar to SARS-CoV-2. The spike glycoprotein sequences in the MMR vaccine share 31-33% similarity with SARS-CoV-2, and therefore may offer some antibody-mediated cross-protection.
- > The potential for cross-protective antibodies along with the advantages of vaccine-induced IFNs and NK cells offered by MMR vaccination could be repurposed to prevent or ameliorate SARS-CoV-2 infection.
- > Limitations: This study was based on a few assumptions that do not identify a causal relationship between MMR vaccination in children and protection from SARS-CoV-2. Any assumptions should be considered with caution. This commentary did not consider other viral vaccines in the vaccination schedule, nor the combination of vaccines in a short time period in early life contributing to the innate protection described. Given the inclusion of MMR in most childhood vaccination schedules RCTs to test this hypothesis will be extremely difficult.

Reviewed by: Associate Professor Margie Danchin

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

Towards intervention development to increase the uptake of COVID-19 vaccination amongst those at high risk (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.06.16.20132480v1.full.pdf>

- > A cross-sectional online survey performed in the UK found that out of 527 participants; where the majority were ‘at-risk adults’ (older than 65 years, those with a chronic respiratory disease):
 - 85% were willing to receive a COVID-19 vaccine once it becomes available.
 - 38% said it would make them more likely to get the annual flu vaccination, and 51% said they will now be more likely to receive the one-off pneumococcal vaccination.
- > The willingness to receive a COVID-19 vaccination was positively associated with the belief that the COVID-19 outbreak is going to continue for a long time and negatively associated with the belief that the media has over-exaggerated the risks of catching COVID-19.
- > Three facilitators to increased vaccine uptake were identified:
 - Personal health: participants (particularly those with co-morbidities, e.g. old age, having a chronic disease) felt that receiving the COVID-19 vaccine would give them a sense of protection.
 - The severity of COVID-19 disease including the contagious nature of the illness and the fear of dying from it.
 - Achieving herd immunity and protecting the health of others.
- > The main barrier to vaccination was concerned about vaccine safety which was primarily centred on the newness of the vaccine, scepticism about its efficacy, feelings that the development of the vaccine may have been rushed and that vaccine safety measures could have been overlooked in the development process.
- > To improve vaccination uptake, strategies such as education about susceptibility and severity of COVID-19 and the effectiveness of vaccination as well as persuasion to change beliefs and encourage action towards vaccination can be used. These could be achieved using a combination of mass media, social media, and working closely with broadcasters and journalists to manage consistent messaging and challenging misinformation.
- > Limitations of the study:
 - Data was collected during the peak of the pandemic and therefore, mainly provides information about a particular stage of the pandemic.
 - The findings may not be generalisable to those at low risk of COVID-19.

Reviewed by: Professor Fiona Russell

VIROLOGY

Dr Celeste Donato - Senior Research Officer, Enteric Diseases, Infection & Immunity Theme, MCRI and Honorary Fellow, Department of Paediatrics, The University of Melbourne

A SARS-CoV-2 infection model in mice demonstrates protection by Neutralising antibodies

[https://www.cell.com/cell/pdf/S0092-8674\(20\)30742-X.pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS009286742030742X%3Fshowall%3Dtrue](https://www.cell.com/cell/pdf/S0092-8674(20)30742-X.pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS009286742030742X%3Fshowall%3Dtrue)

- > Due to species-specific differences in their angiotensin-converting enzyme 2 (ACE2) receptors, laboratory mice strains are not readily infected by SARS-CoV-2. This lack of a small animal model is a limitation in the evaluation of potential therapeutics and vaccines.
- > In this study, BALB/c laboratory mice were transduced with replication-defective adenoviruses encoding for human ACE2 (hACE2) via intranasal administration. Receptor expression was established in lung tissues.
- > The hACE2-transduced mice were infected with SARS-CoV-2, which resulted in high viral titres in the lung, lung pathology consistent with pneumonia, and weight loss.
- > The administration of a SARS-CoV-2 neutralising monoclonal antibody one day prior to intranasal SARS-CoV-2 inoculation decreased viral titre in the lung and mitigated inflammation and weight loss.
- > The limitations of this study include mouse-to-mouse variation in hACE2 expression and tissue distribution as well as possible mild bronchial inflammation associated with adenovirus inoculation.

Generation of a broadly useful model for COVID-19 pathogenesis, vaccination, and treatment

[https://www.cell.com/cell/pdf/S0092-8674\(20\)30741-8.pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867420307418%3Fshowall%3Dtrue](https://www.cell.com/cell/pdf/S0092-8674(20)30741-8.pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867420307418%3Fshowall%3Dtrue)

- > Various immunocompetent and immunodeficient mice strains were transduced intranasally with a replication-deficient adenovirus (Ad5-hACE2), and hACE2 expression was observed predominantly in the alveolar epithelium with some positive cells in the airway epithelium. Control mice received the Ad5-Empty vector and did not express hACE2.
- > Ad5-hACE2 transduced BALB/c mice that were infected with SARS-CoV-2 showed ruffled fur, hunching, and difficulty breathing from day two post infection. The mice lost up to 20% of their body weight in the first 4–6 days of infection, and the virus grew to high titres in lung tissue - gradually declining over the course of the infection.

- > Ad5-hACE2 transduced C57BL/6 mice infected with SARS-CoV-2 lost 10–15% of their body weight and highest virus titres were observed at one–two days post infection.
- > Histological examination of lung tissues from infected Ad5-hACE2 transduced BALB/c and C57BL/6 mice revealed a variety of lesions. Examination of gross lung specimens revealed increased vascular congestion and haemorrhage.
- > Wild-type and IFNAR^{-/-} (interferon) C57BL/6 mice were transduced with Ad5-hACE2 and then infected with SARS-CoV-2 to investigate interferon (IFN)-I signalling.
 - The mice had delayed virus clearance and diminished inflammation; suggesting IFN signalling may have varied roles in virus clearance, cellular infiltration, and clinical disease.
- > SARS-CoV-2-infected, Ad5-hACE2 transduced STAT1^{-/-} C57BL/6 mice exhibited greater weight loss, enhanced inflammatory cell infiltration into the lungs, and delayed virus clearance.
- > Mice were treated intranasally with poly I:C (inducer of IFN-I) prior to infection with SARS-CoV-2 which resulted in significantly diminished clinical disease and induced more rapid virus clearance.
- > RNA sequencing (RNA-seq) was performed using RNA extracted from lungs of Ad5-Empty and Ad5-ACE2 transduced BALB/c mice at 2 days post infection.
 - SARS-CoV-2 viral RNA was only detected in Ad5-ACE2 transduced mice.
 - 2,142 genes upregulated and 914 genes downregulated in Ad5-ACE2-transduced mice compared with Ad5-Empty-transduced mice.
 - The majority of upregulated genes were associated with inflammation pathways, innate and adaptive immune response pathways - CD4 and CD8 transcript abundance were significantly upregulated as well as several cytokines and chemokines.
- > CD4⁺ and CD8⁺ T cells were depleted individually and together from Ad5-hACE2-sensitised BALB/c and C57BL/6 mice prior to SARS-CoV-2 infection.
 - This revealed that optimal virus clearance required both CD4⁺ and CD8⁺ T cell responses.
 - CD4⁺ and CD8⁺ T cell epitopes were predominantly located in the N protein and the S1 region of the S protein, respectively.
 - The mice also produced neutralising antibodies.
- > Mice administered with human plasma from SARS-CoV-2 recovered patients showed accelerated viral clearance didn't experience weight loss or histological changes in the lung.
- > Ad5-hACE2 transduced mice treated with Remdesivir prior to and during SARS-CoV-2 infection exhibited decreased weight loss, accelerated virus clearance, and diminished cellular infiltration of lung tissue.
- > This study has demonstrated the varied utility of Ad5-hACE2 transduced mice.

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

Genome-wide CRISPR screen reveals host genes that regulate SARS-CoV-2 infection (pre-print)

<https://www.biorxiv.org/content/10.1101/2020.06.16.155101v1>

This study using an in vitro model and genome-wide CRISPR screens, identified host genes that are essential for SARS-CoV-2 infection and cell death. Gene Enrichment (clusters of functional genes) was performed using 10 data sources (including KEGG, GO process).

- > Main results:
 - Performance of the in vitro model of *Chlorocebus sabaeus* (African green monkey) cell line Vero-E6 for genome-wide CRISPR screens: a number of independent screens, using a *C. sabaeus* genome-wide pooled CRISPR library on different conditions defined by cell densities, foetal bovine serum (FBS) concentration and SARS-CoV-2 concentrations (multiplicities of infection – MOI) were conducted and showed a strong correlation between those conditions.
 - Identification of cluster of genes that are pro-viral infections (resistance) as well as those are involved in anti-viral activities (sensitisation), some are highlighted as below:
 - > ACE2 gene was the strongest resistance (pro-viral) hit, SMARCA4 (BRG1), the catalytic subunit of the SWI/SNF remodelling complex was the second-strongest resistance hit, while other member genes such as ARID1A, SMARCE1, SMARCB1, and SMARCC1; CTSL were also identified; (Cathepsin L protease) was identified in all conditions above; HMGB1-like gene was identified as a putative pro-viral role, HMGB1-knockout protected cells from SARS-CoV-2 induced cell death and reduced ~ 2-log of SARS-CoV-2 replications at 24 h/48 h post-infection.
 - > HIRA, CABIN1, and ASF1A – represent three of four components of HUCA histone H3.3 chaperone complex were identified as anti-viral hit.
 - Potential gene target for therapy based on genes revealed from CRISPR screens: inhibitors targeted to identified pro-viral genes (for example: Cathepsin L inhibitor Calpain Inhibitor III, SMARCA4 inhibitor PFI-3) protected cells from SARS-CoV-2 induced death and reduced frequency of viral infection.
- > Significance:
 - Provided a novel CRISPR library tool and additional novo pro-viral genes that could have important implications in enhancing understanding of COVID-19 pathogenesis, therapeutic and vaccine design.
 - Provided a novel role for HMGB1 in SARS-CoV-2 infection. Of note, HMGB1 has been recently reported as a potential biomarker associated with severe respiratory syncytial virus.

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_z2uWV7r3FaPzAOr86q9ZXBcTZ1QcCE_Nw/formResponse

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

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

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

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

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

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

WHO Rolling updates on COVID-19
<https://www.who.int/emergencies/diseases/novel-coronavirus-2019/events-as-they-happen>

Scimex.org – breaking science news portal: COVID-19 stories (research and expert commentary)
<https://www.scimex.org/info/2019-20-coronavirus>
<https://www.covid19-hpc-consortium.org/>

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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