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MELBOURNE

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.10

18 June 2020

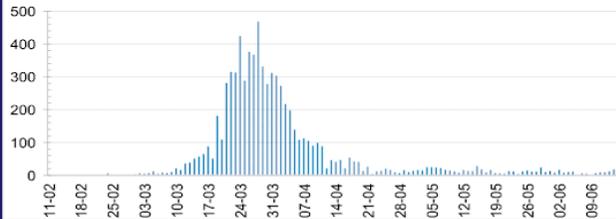


BE COVIDSAFE

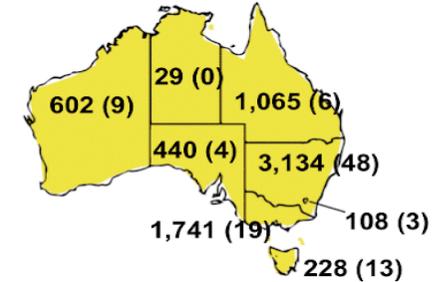
CURRENT STATUS OF CONFIRMED CASES



DAILY NUMBER OF REPORTED CASES



CASES (DEATHS) BY STATE AND TERRITORIES



3

CURRENT CASES INTENSIVE CARE UNITS (ICU)

ACT	NSW	NT	QLD	SA	TAS	VIC	WA
0	0	0	1	0	0	2	0

17

CURRENT CASES ADMITTED TO HOSPITALS

ACT	NSW	NT	QLD	SA	TAS	VIC	WA
0	10	0	1	0	0	6	0

1,848,347

0.4% POSITIVE

TOTAL TESTS CONDUCTED

ACT	NSW	NT	QLD
23,837	649,337	10,665	254,554
POSITIVE	POSITIVE	POSITIVE	POSITIVE
0.5%	0.5%	0.3%	0.4%

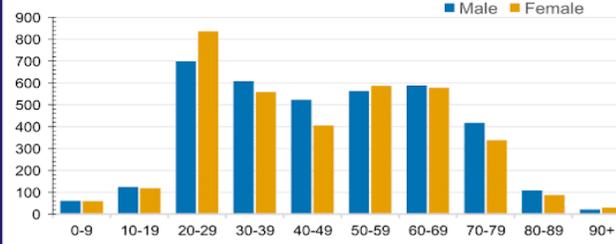
SA	TAS	VIC	WA
127,815	38,826	599,895	143,418
POSITIVE	POSITIVE	POSITIVE	POSITIVE
0.3%	0.6%	0.3%	0.4%

CASES IN AGED CARE SERVICES

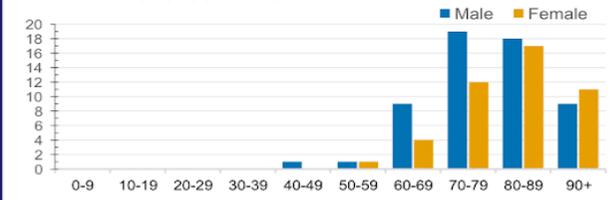
Confirmed Cases	Australia	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
Residential Care Recipients	68 [39] (29)	0	61 [34] (27)	0	1 (1)	0	1 (1)	5 [5]	0
In Home Care Recipients	31 [28] (3)	0	13 [13]	0	8 [8]	1 [1]	5 [3] (2)	3 [3]	1 (1)

Cases in care recipients [recovered] (deaths)

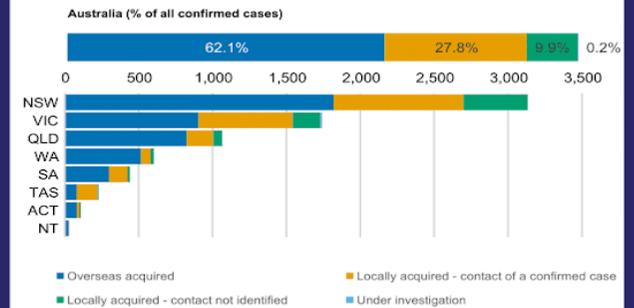
CASES BY AGE GROUP AND SEX



DEATHS BY AGE GROUP AND SEX

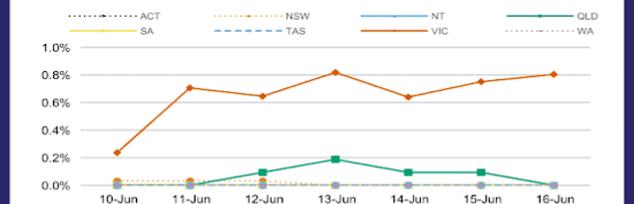


CASES BY SOURCE OF INFECTION



PUBLIC HEALTH RESPONSE MEASURE

Proportion of total cases under investigation



Last updated 16 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 16; cited 2020 June 17. 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

Welcome to the 10th report and congratulations again to the editorial team, students, clinicians, researchers, and professional staff who produce it. A special thanks also to Professor Fiona Russell who is currently looking at extending collaboration and involvement internationally so that the report adds global value, including to those in low- and middle-income countries.

As I write this on 17th June 8,162,276 cases have been reported worldwide with 441,688 deaths. We can see worrying escalations over several continents, especially in India, Brazil, and South Africa. Until this week there was no evidence for any treatment that could decrease the mortality associated with COVID-19, let alone an intervention or vaccine likely to be rapidly available to these parts of the world.

As a respiratory paediatrician I am very familiar with the use of corticosteroids to treat some common conditions of childhood. In our hospital you will find recommendations on the use of dexamethasone, for example, in numerous clinical practice guidelines. Here are some links:

Croup

https://www.rch.org.au/clinicalguide/guideline_index/Croup_Laryngotracheobronchitis/

Nausea and Vomiting

https://www.rch.org.au/anaes/pain_management/Post-operative_Nausea_Vomiting_PONV/

https://www.rch.org.au/rchcpg/hospital_clinical_guideline_index/Chemotherapy_induced_nausea_and_vomiting/

Meningitis

https://www.rch.org.au/clinicalguide/guideline_index/Meningitis_encephalitis/

Pharyngitis

https://www.rch.org.au/clinicalguide/guideline_index/Sore_throat/

This week we learnt that compared with standard care, mortality was significantly decreased in ventilated adult patients (by a third), or adult patients receiving oxygen (by 20%), who were randomised to receive 6mg dexamethasone either intravenously or orally in the RECOVERY trial (see **Therapeutics section** of the report). This is the same trial that identified no benefit with hydroxychloroquine (as reported in last week's report). The dexamethasone data are as yet unpublished but released in a preliminary report due to their potential to save lives.

There was no benefit from dexamethasone in less severe patients who were not receiving oxygen suggesting that the benefits may be restricted to its anti-inflammatory actions in suppressing the overzealous immune response in those with severe infections (the so-called "cytokine storm"). The number needed to be treated to prevent a death in ventilated patients was 8 and in those on oxygen but not ventilated this figure was 25. There are no data as yet for children and adolescents.

The only other trial showing benefit of a pharmacological therapeutic intervention so far is that with the antiviral, Remdesivir. This drug is by contrast relatively expensive, in short supply and, as it is given by injection over the course of several days, is likely not to be helpful in resource poor countries with poor access to hospitals. Moreover, R_0 did not decrease mortality but shortened time to recovery by a few days. It is dexamethasone, and not Remdesivir that will help treat those infected in India, Brazil and South Africa and other countries globally in the very near future.

Finally, congratulations to Professor Paul Monagle from the Melbourne Children's Campus, who this week provided commentary on the likely role of the endothelium and micro vascular thrombosis in COVID-19 to the news section of the journal, Nature. We look forward to the results of his experiments, including his investigation of how endothelial cells infected with SARS-CoV-2 impact on coagulation in plasma obtained from children, adults with vascular disease and controls. The findings in children have the potential to inform treatment of adults at risk of severe disease. (See [Clinical Paediatrics](#) section of the report)

HIGHLIGHTS

- > Press release of RECOVERY trial showing improved survival outcomes for COVID-19 for ventilated adults and those on supplementary oxygen following treatment with dexamethasone.
- > Global modelling study shows 4% of the world's population has at least one risk factor for severe COVID-19. In Oceania, Fiji has the highest risk, followed by many other Pacific Island Countries.
- > Evidence is mounting that healthy blood vessels protect children from serious effects of COVID-19, such as stroke.
- > Development of coronary artery aneurysm in paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) may not relate to the level of inflammation or markers of cardiac injury.
- > Evidence of SARS-CoV-2 neurotropism with likely invasion of neuro-mucosal interface via olfactory mucosa and persistence of virus up to 53 days in olfactory mucosa.
- > Current evidence from Denmark does not suggest a need to withdraw well-indicated use of NSAIDs during the current SARS-CoV-2 pandemic.
- > Public health interventions of lockdown in France were associated with a significant decrease in paediatric emergency visits and hospital admissions due to infectious diseases.
- > German study suggests the public health intervention of using masks reduced infection rates.
- > Imaging findings in COVID-19 resemble those of MERS and SARS, supporting the notion that viral pneumonia contributes to acute lung injury.
- > Point of care rapid diagnostic testing for SARS-CoV-2 has high sensitivity and sensitivity when compared to RT-PCR in a UK study.

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Unless specifically stated, the authors do not recommend or endorse any procedures or processes described in this resource.

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.

The Owners of this resource do not wish to use this resource as a means of communication with the general public (i) regarding questions or issues of a medical nature; (ii) to establish physician-patient relationships. Email communications regarding such matters will not be responded to and will be discarded unread.

ADULT MEDICINE

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

Olfactory transmucosal SARS-CoV-2 invasion as port of central nervous system entry in COVID-19 patients (pre-print)

<https://www.biorxiv.org/node/1344414.abstract>

- > Anatomically mapped viral loads in oropharyngeal regions and brains of 32 patients who died from COVID-19 with acute infarction due to CNS thromboembolic events in Germany.
- > SARS-CoV-2 neurotropism: invades nervous system via neuro-mucosal interface in olfactory mucosa.
 - Viral RNA loads present in olfactory mucosa, trigeminal ganglion, medulla oblongata, cerebellum.
 - Lower loads found in cornea, conjunctiva, oral mucosa.
- > Persistence of SARS-CoV-2 RNA in olfactory mucosa up to 53 days after initial symptoms, allowing replication and replenishment of viral load in CNS.
- > This may explain neurological symptoms in COVID-19 patients: alterations in smell and taste perception.
- > Virus may spread more widely to brain regions, contributing to more severe or even chronic disease.

Reviewed by: Dr Wonie Uahwatanasakul

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

ACE2 levels are altered in comorbidities linked to severe outcome in COVID-19 (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.06.04.20122044v1.full.pdf>

- > A single centre population-based study of 5457 Icelanders (66-96 year old Caucasians).
- > ACE2 is the cellular entry point for SARS-CoV-2.
- > In this study ACE2 serum levels were measured using the aptamer-based protein profiling platform.

- > Main results:
 - ACE2 levels were significantly elevated in serum from individuals who are smokers, overweight, obese, diabetic, or have impaired fasting glucose levels.
 - ACE2 levels were higher in severely obese but not significantly ($p=0.087$).
 - ACE2 levels were significantly reduced in males.
 - ACE2 serum levels are positively associated with the Framingham risk score ($\beta=0.0726$, $P=0.08$).
- > Individuals with comorbidities associated with severe outcomes in COVID-19 have altered serum levels of ACE2 that may influence productive infection of SARS-CoV-2.
- > **Limitations:** Further studies in independent study populations warranted for smokers, diabetic and obese individuals; study does not show that altered ACE2 serum levels cause worse clinical outcomes; results presented may be limited to serum and may not reflect the effect of comorbidities on ACE2 pulmonary tissue levels; measured circulating ACE2 levels may not reflect its cell surface receptor levels in solid tissues; all participants were Caucasian limiting the transferability and generalisability of the results across races and ethnicities; ACE2 levels lower in males despite males being at higher risk of a death.

Reviewed by: Professor Fiona Russell

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

Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs (NSAID) tested positive for SARS-CoV-2: A Danish nationwide cohort study (pre-print)

<https://protect-au.mimecast.com/s/4SBuC91ZVBSkYE5Rrs0VAQG?domain=medrxiv.org>

- > Population based cohort study (using Danish administrative and health registries) of whether the use of NSAIDs prior to infection with SARS-CoV-2 is associated with adverse outcomes and mortality.
- > Participants: Individuals tested positive for SARS-CoV-2 between 27th February 2020 and 29th April 2020. Treated individuals were defined as those with a filled NSAID prescription up to 30 days before the SARS-CoV-2 test. Up to four non-treated individuals were matched to each NSAID user on propensity scores based on age, sex, relevant comorbidities, and prescription fills.
- > Main results in the matched analyses:
 - No difference in 30-day mortality (RR 1.02, 95% CI 0.57 to 1.82).
 - No difference in hospitalisation (RR 1.16, 95% CI 0.87 to 1.53).
 - No difference in ICU-admission (RR 1.04, 95% CI 0.54 to 2.02).
 - No difference in mechanical ventilation (RR 1.14, 95% CI 0.56 to 2.30).
 - No difference in acute renal replacement therapy (RR 0.86, CI 0.24 to 3.09).
- > This study does not provide evidence to withdraw well-indicated use of NSAIDs during the current SARS-CoV-2 pandemic.

- > Limitations: Potential for exposure misclassification as there was no information on adherence, intended duration and dose (a filled prescription was equated to NSAID use and individuals were not stratified for duration or dose). There may be some over-the-counter purchase of low dose NSAIDs which can also cause exposure misclassification (however, there is limited availability and use of over the counter NSAIDs in Denmark). Confounding due to indication was not mitigated by an active comparator as there was no adequate comparator. It should also be noted that this is a preprint article and it has not yet been peer reviewed.

Reviewed by: Dr Amanda Gwee

CLINICAL PAEDIATRICS

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

Why children avoid the worst coronavirus complications might lie in their arteries

<https://www.nature.com/articles/d41586-020-01692-z>

- > Evidence is mounting that healthy blood vessels protect children from serious effects of COVID-19, such as stroke.
- > Many adults with serious COVID-19 experience clotting in their blood vessels, which leads to heart attacks or strokes. The clotting seems to be linked to a malfunctioning endothelium, the smooth tissue that lines blood vessels and normally prevents clotting.
- > This hypothesis could also explain why people with conditions that compromise the endothelium, such as diabetes and hypertension, are at a greater risk of serious COVID-19.
- > Children have healthier endothelium than adults.
- > Professor Paul Monagle is undertaking research to try to better understand this mechanism and see whether there is something protective about children's blood vessels that makes them less likely to produce excess clots in response to SARS-CoV-2 infection.

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

Clinical characteristics of 58 children with a paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2

<https://jamanetwork.com/journals/jama/fullarticle/2767209>

- > The study comprised 58 patients from eight different hospitals in England with a median age of nine years old who met the criteria for paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) as outlined by the UK, CDC or WHO guidelines.
- > 78% of the cohort showed evidence of current or prior SARS-CoV-2 infection.
- > Clinical findings included.
 - Fever (100%), vomiting (45%), abdominal pain (53%), diarrhoea (52%), rash (52%) and conjunctival infection (45%).
 - 29 of the 58 children developed shock requiring inotropes and resuscitation, and of these, 23 required mechanical ventilation.
- > Laboratory findings showed marked inflammation in all patients.
 - Elevated C-reactive protein in all cases.

- Elevated ferritin in 53 of the 58 children.
- Other findings included profound lymphopenia, anaemia, elevated fibrinogen levels, lower platelet count and a greater elevation of troponin compared to children with KD or KD shock syndrome.
- > 13 out of 58 children met the American Heart Associated definition of Kawasaki Disease (KD). Eight out of 55 patients assessed via echocardiography developed coronary artery dilatation or aneurysm. The development of coronary artery aneurysm was not found to correlate with the level of inflammation or markers of cardiac injury. Sequential follow up of coronary arteries through echocardiography, similar to the management of KD is recommended.
- > Limitations include the retrospective collection of data during time of developing case definition. Kawasaki Disease is a clinical diagnosis; thus, it is not possible to exclude that the cohort includes children with KD and not PIMS-TS.

Reviewed by: Dr Wonie Uahwatanasakul

DIAGNOSTICS & SAMPLING

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

Rapid point of care nucleic acid testing for SARS-CoV-2 in hospitalised patients: a clinical trial and implementation study (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.05.31.20114520v1.full.pdf>

- > 149 patients admitted to Cambridge University Hospitals NHS Foundation Trust were included in this analysis of the efficacy of the SAMBA II SARS-CoV-2 rapid POC test.
 - The SAMBA II test is a nucleic acid amplification test which uses loop mediated isothermal amplification to detect SARS-CoV-2 RNA.
 - 21.6% (32/149) tested positive by the standard lab RT-PCR Testing and 31 tested positive on the SAMBA II SARS-CoV-2 test.
 - Sensitivity & specificity of the SAMBA II against the RT-PCR was found to be 96.9% and 99.1% respectively, with a mean duration of symptoms being three days.
 - The major benefit of the SAMBA II SARS-CoV-2 test is the fast time to result, with a median time of 2.6 hours compared to the 24 hours + waiting period for RT-PCR tests.
- > After this initial clinical trial, the SAMBA II SARS-CoV-2 rapid POC test was implemented as the preferred method of COVID-19 screening in the hospital.
 - During the initial 10-day period of utilising the SAMBA II, median time to result was 3.6 hours.
 - The authors state this fast turnaround allowed for ward closures to be prevented, patient flow to non-COVID-19 clinical areas to be improved and discharges to nursing homes be expedited safely.
- > Limitations:
 - This study would have benefited from separating analysis of the sensitivity and specificity in relation to date of symptom onset. It is well known that other POC tests (mainly antibody-based tests) sensitivity and specificity decrease significantly in the earlier phase of disease.
 - It does not appear that during the roll out of the SAMBA II in clinical areas, matched nasal swabs were taken for RT-PCR testing. This prevented an analysis of real-world sensitivity and specificity.

- > The SAMBA II SARS-CoV-2 rapid POC test was found to be a highly sensitive and specific test whilst returning results in a matter of hours, which allows for smoother patient flow.

Reviewed by: Dr Wonie Uahwatanasakul

EMERGENCY MEDICINE

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

COVID-19 pandemic: Impact caused by school closure and national lockdown on paediatric visits and admissions for viral and non-viral infections in France (pre-print)

<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa710/5850910>

- > A time series analysis of 871,543 paediatric emergency visits across six hospitals in France was conducted to study the impact of public health interventions (Nationwide lockdown and school closure) due to COVID-19 on several paediatric infectious diseases that usually spread through social contact. Urinary tract infections were used as a control as this disease does not generally spread through social contact.
- > It was found that these public health interventions were associated with a significant decrease in paediatric emergency visits and hospital admissions due to infectious diseases disseminated through airborne or faecal-oral transmission. These include common cold, gastroenteritis, bronchiolitis, and acute otitis media. No change was found for urinary tract infections.
- > Study limitations:
 - Changes in the clinical management due to COVID-19 (ex. Avoidance of ENT examination) which could have impacted the diagnosis of certain infections was not evaluated.
 - The decrease in number of emergency paediatric visits and admissions could be due to other factors such as transportation limitations, fear of visiting a hospital, and an increase in the use of telemedicine rather than solely due to the lack of social contact as a consequence of COVID-19 public health interventions.

Reviewed by: Dr John Cheek

EPIDEMIOLOGY & PUBLIC HEALTH

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

Infection prevention guidelines and considerations for paediatric risk groups when reopening primary schools during COVID-19 pandemic, Norway, April 2020

https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.22.2000921#html_fulltext

- > Guidelines developed for the reopening of primary schools in Norway.
- > Schools were closed in Norway on the 13th March 2020 as part of the government's COVID-19 response to reduce community transmission.
- > Evidence suggests that school closures may not be indicated for reduction of COVID-19 disease burden.
 - Evidence for the effect of school closures on disease transmission is based on influenza studies.
 - School closures more effective for viruses with:
 - Low reproduction number ($R_0 < 2$): SARS-CoV-2 $R_0 \approx 2.2-3.6$.
 - Higher attack rates in children than adults: 93% of cases >19 years old on 11th May in Norway.
- > Based on available scientific evidence the government decided to reopen schools in a graded fashion from the 20th April to the 11th May depending on school grade. Guidelines for infection control and prevention and high-risk groups were developed for schools.
- > Infection prevention guidelines for primary schools:
 - Included the following principles: Self-isolation of sick individuals, hygiene measures, and physical distancing measures.
 - Schools were encouraged to establish procedures for individuals who become symptomatic at school.
 - Recommended cohorts (smaller, fixed groups of children and employees).
 - Takes into account that physical distancing measures are difficult for children and physical contact is an important part of their development and wellbeing.
 - Can prevent whole school closures by confining an outbreak to a cohort.

- Cohort size based on children's age and need for care, national teacher-pupil ratio relations, and ability for compliance with preventative measures.
- Increasing space available: Outdoor teaching, larger rooms and facilities, and smaller cohort numbers.
- > Children and staff at risk for severe COVID-19:
 - Children are likely to develop mild disease even with severe comorbidities.
 - Recommended >65-year-old staff to continue preventative self-isolation and others with comorbidities to consult their physician.
- > Urgent need to evaluate the effect of school closures on disease transmission versus the negative effects on children in the context of the COVID-19 pandemic.
- > Students and teachers will be prioritised to evaluate impact of school opening on SARS-CoV-2 transmission as part of the national surveillance strategy in Norway.

Reviewed by: Dr Claire von Mollendorf

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

Using mHealth to support COVID-19 education, self-assessment, and symptom monitoring: an observational study in The Netherlands (pre-print)
<https://preprints.jmir.org/preprint/19822/accepted>

- > The concept of Mobile health (mHealth) and using apps to provide the latest information to patients and allow symptom tracking opens the potential for aiding patients, healthcare workers and policy makers through the pandemic.
- > This is an observational study conducted in The Netherlands.
- > Studied the number of users of the new COVID-19 app and its functionality.
- > The COVID-19 app was added to the already existing app the 'ETZ Treatment guide' in Tilburg, The Netherlands on 1st April 2020. All ETZ patients and residents of the Tilburg area were able to download the app from 1st April.
- > 6194 people used the app between 1st April and 20th April (5698 new downloads and 496 existing downloads).
- > The average number of views per day increased from 178 to 611 in the period.
- > The health self-assessment function was used most often: 5326 (86%) people.
- > The 7-day symptom diary feature was initially used by 1378 people, however this dropped to 21%, 31% and 34% of the original number in the three areas studied.
- > Satisfaction was answered by 718 users, reporting on average an 8/10.
- > Conclusions: There is a need for patients to have access to clear and trusted information; a large number of people are willing to voluntarily share personal information regarding demographics; there is a limited use for tracking information over seven days as compliance is an issue.

- > Limitations: Recruitment/advertising for people to download the app is unclear, and the proportion of uptake of the app vs the actual population in this area is not given; the usability by healthcare professionals developed through maps is a concept that needs further exploration.

Reviewed by: Professor Fiona Russell

GLOBAL HEALTH

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

Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study
[https://www.thelancet.com/pdfs/journals/langlo/PIIS2214-109X\(20\)30264-3.pdf](https://www.thelancet.com/pdfs/journals/langlo/PIIS2214-109X(20)30264-3.pdf)

- > The risk of severe COVID-19 is higher in older people and those with underlying health conditions.
- > Understanding the number of individuals at increased risk of severe COVID-19 and how this varies between countries should inform the design of possible strategies to shield or vaccinate those at highest risk.
- > This modelling study estimated the number of individuals at increased risk of severe disease by age, sex, and country.
- > 1.7 billion people, comprising 22% of the global population, have at least one underlying condition that puts them at increased risk of severe COVID-19 if infected (ranging from <5% of those younger than 20 years to >66% of those aged 70 years or older).
- > 349 million people (4% of the global population) are at high risk of severe COVID-19 and would require hospital admission if infected (ranging from <1% of those younger than 20 years to approximately 20% of those aged 70 years or older).
- > 6% of males to be at high risk compared with 3% of females.
- > The share of the population at increased risk was highest in countries with older populations, African countries with high HIV/AIDS prevalence, and small island nations with high diabetes prevalence.
- > Estimates of the number of individuals at increased risk were most sensitive to the prevalence of chronic kidney disease, diabetes, cardiovascular disease, and chronic respiratory disease.
- > ~20% of individuals worldwide could be at increased risk of severe COVID-19, should they become infected, due to underlying health conditions, but this risk varies considerably by age. The estimates are uncertain, and focus on underlying conditions rather than other risk factors such as ethnicity, socioeconomic deprivation, and obesity, but provide a starting point for considering the number of individuals that might need to be shielded or vaccinated as the global pandemic unfolds.
- > In Oceania, Fiji has the highest risk, followed by many other Pacific Island Countries.

IMAGING

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

CT in coronavirus disease 2019 (COVID-19): a systematic review of chest CT findings in 4410 adult patients

<https://link.springer.com/article/10.1007/s00330-020-06975-7>

- > This systematic review included 45 studies consisting of 4410 patients who underwent 4733 CT scans.
- > Cumulative percentage of the imaging findings out of the total number of CTs rather than the total number of patients.
- > The most common lesions were bilateral (84%), peripheral/subpleural, posterior ground glass opacities (GGO), in isolation (50.2%) or seen with consolidations (44.4%).
- > Important ancillary findings included pulmonary vascular enlargement (64%; 353/550), intralobular septal thickening (60%; 310/2053), adjacent pleural thickening (41.7%; 213/511), air bronchograms (41.2%; 572/1388), subpleural lines (25%; 98/388), crazy paving (19.5%; 266/1364), bronchus distortion (18.6%; 21/113), bronchiectasis (18%; 69/385), and interlobular septal thickening (15.1%; 310/2053).
- > Serial CT imaging demonstrated a progression of GGO to a mixed pattern with consolidation increasing in the second week (peak at 10-11 days after symptom onset), followed by GGO in the fourth week prior to resolving or persisting as patches of fibrosis.
- > Younger populations tended to have more ground glass opacities. This is compared to CT findings in older patients or patients with severe disease (respiratory distress and hypoxia at rest), which demonstrated extensive ground glass opacities and consolidations. In critically severe disease, extensive 'white lung' with atelectasis and pleural effusions were seen.
- > Imaging findings in COVID-19 resemble those of MERS and SARS, supporting the notion that viral pneumonia contributes to acute lung injury. CT findings in COVID-19 are attributed to infection of type II alveolar epithelial cells via ACE2 receptors by the SARS-CoV-2 virus.
- > Limitations: most studies included are descriptive and non-blinded, studies were limited to those published in English, articles describing manifestations in children were not reviewed, individual case reports which may represent atypical manifestations were also not included, temporal progression data is based on only two studies, different scanners, acquisition parameters and reporting experience of radiologists was not taken into account.

Reviewed by: Associate Professor Simone Mandelstam

IMMUNOCOMPROMISED / CANCER

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

Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study

[https://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045\(20\)30309-0.pdf](https://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(20)30309-0.pdf)

- > Multicentre, retrospective cohort study of admitted cancer patients, n=232 (malignant solid tumours and haematological malignancy), propensity score matched (on basis of age, sex, and comorbidities) with 519 admitted patients without cancer.
- > Cancer patients were significantly more likely to have severe COVID-19 than those without cancer (OR 3.61, 95% CI 2.59–5.04). Severe disease defined according to WHO recommendations.
- > There was a trend towards higher mortality in cancer patients compared to non-cancer patients, although non-significant (20 v 11%).
- > Patient and disease-related factors significantly associated with illness severity in cancer patients included - increasing age, Increasing ECOG status, advanced tumour stage, targeted therapy, or immunotherapy. Risk of COVID-19 severity and death was highest for patients with last chemotherapy treatment within two weeks of admission and decreased as the time interval since last chemotherapy increased, with significantly reduced risk when last treatment was at least three weeks before hospital admission. Patients with longer time since cancer diagnosis (1–5 years or >5 years) had lower risk of COVID-19 severity and death compared with patients with less than one year of tumour history.
- > The time for viral clearance was longer in patients with cancer (24 [IQR 17–29] days) than in those without cancer (21 days [IQR 15–24]; p=0.045).
- > Proinflammatory cytokines and infection biomarkers were more likely to be elevated in patients with cancer. Lymphopenia and reduced CD-4+ and CD-8+ counts was also more common in patients with cancer.
- > Limitations: Study sample included multiple different cancer types so limited conclusions can be drawn about impact of underlying cancer diagnosis and phase of treatment. The study also included patients with cancer who had completed cancer treatment. The impact of a lot of different variables were also investigated and some results may be due to overfitting.

- > This study has important implications for follow up and monitoring of patients with cancer who are diagnosed with COVID-19. The authors make some recommendations for managing cancer patients, including (i) Consider postponement of adjuvant chemotherapy or elective surgery for stable cancer in endemic areas; (ii) More intensive surveillance of cancer patients with COVID-19 due to potential for deterioration and severe disease in this population

Reviewed by: Dr Gabrielle Haeusler

INFECTION CONTROL

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

Face masks considerably reduce COVID-19 cases in Germany: a synthetic control method approach (pre-print)

<http://ftp.iza.org/dp13319.pdf>

- > Face masks play an important role in the prevention of respiratory borne infections and have been proven to decrease the transmission of SARS and influenza.
- > This paper is the first to systematically analyse the use of face masks during the COVID-19 pandemic and their role in preventing transmission of the virus.
- > Study based in Germany, with data from 401 regions used.
 - Face mask use on public transport and in sales shops became compulsory over the period 20th - 29th April.
 - The study compared the data of a single region (Jena) with other German regions, as it introduced mandatory face masks on 6th April, much earlier than the rest of Germany, while lockdown in Germany had been already instigated and other public health prevention measures were unchanged during the observation period.
 - The timing of mandatory face mask use in each region and the subsequent rates of COVID-19 among these populations was also analysed.
 - Regions were compared against a synthetic control (comprised of the weighted average of control regions that are similar to the regions of interest) to attempt to isolate and study the effect that wearing a face mask has on viral transmission.
- > 20 days after the introduction of face masks on 6th April in Jena, the number of reported COVID-19 cases decreased by 23%.
 - The decrease in transmission was of a greater magnitude in people 60 years and older (reduction of more than 50%) compared with other age groups (reduction of 10-20%).
 - A small anticipation effect was found, though was found not to significantly affect the overall result.
- > When looking at different regions, face masks were found to reduce the number of cases by 2.3-13% over a period of ten days after they became mandatory.
 - Results for the regions were heterogeneous with one region showing an increase in cases after face masks were introduced.
- > The overall estimated reduction in COVID-19 transmission by using face masks was calculated by the authors to be in the order of 40-60%.

- > As this is the first paper directly studying the efficacy of face mask use during the COVID-19 pandemic, more studies are needed to clarify the results. There are regional differences and other interventions and behaviours that may affect disease transmission and cultural differences that impact on the acceptability and uptake of face masks in a given population.

Reviewed by: Professor Fiona Russell

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

Shedding of infectious virus in hospitalized patients with coronavirus-disease-2019 (COVID-19) duration and key determinants (pre-print)

<https://www.medrxiv.org/content/10.1101/2020.06.08.20125310v1>

- > Current evidence suggests that viral RNA cannot be isolated after eight days in patients with mild COVID-19 symptoms. Moreover, it has been suggested that the likelihood of isolating an infectious virus when the viral load drops below $6.51 \text{Log}_{10} \text{RNA/copies/ml}$ is less than 5%.
- > This study aims to determine the duration and determinants of infectious virus shedding in severely ill COVID-19 patients.
- > The investigators collected 690 respiratory samples (n=129) from severe and critically COVID-19 patients and tested them for viral RNA load using PCR. Samples were then cultured for seven days and analysed for the detection of nucleocapsid proteins using immunofluorescent detection. 112 serum samples were collected and analysed for SARS-CoV-2 neutralizing antibodies using a plaque reduction neutralisation test. Generalised estimating equations were used as predictive models.
- > 17.8% of patients had an infectious virus isolated.
- > Median time of virus shedding was eight days post onset of symptoms (IQR 5-11, range 0-20) and dropped below 5% after 15.2 days (CI: 13.4-17.2).
- > The median viral load was significantly higher in culture positive samples than in culture negative samples (8.14 vs 5.88 Log_{10} RNA copies/mL, $p < 0.0001$). Viral loads above $7 \text{Log}_{10} \text{RNA copies/mL}$ were associated with isolation of infection SARS-CoV-2 from the respiratory tract ([OR]; CI 14.7 (.57-58.1; $p < 0.001$).
- > Detection of the sub genomic RNA outlasted the detection of infectious virus and predicted poorly if virus culture was positive. However, a serum neutralizing antibody titre of at least 1:20 was independently associated with non-infectious SARS-CoV-2 isolation (OR of 0.01 (CI 0.003-0.08; $p < 0,001$).
- > Limitations– retrospective virological data collection however rich virology sampling was performed prior to study commencement. In-vitro cell cultures were used as surrogate markers for infectious virus shedding - the infectious dose is not yet known. Quantitative PCR and serological assays are not yet widely available. Finally, only hospitalised symptomatic adults with severe COVID-19 were recruited.

- > Conclusion - A viral load exceeding $7\text{Log}_{10}\text{RNA}$ copies/mL, less than seven days of symptoms, absence of serum neutralizing antibodies and being immunocompromised were all associated with a positive virus culture in univariate analysis. Positive serology and viral load could be useful in determining when patients are no longer infectious, but further work and validated assays are required to confirm this.

Reviewed by: Professor Allen Cheng

MENTAL HEALTH

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

Mental health outcomes from quarantine and isolation in response to infectious disease outbreaks (pre-print)

<https://www.e-epih.org/upload/pdf/epih-e2020038-AOP.pdf>

- > Authors conducted an umbrella review on mental health outcomes from social isolation and quarantine due to infectious disease outbreaks.
- > All reviews reported a high prevalence of anxiety among individuals who had experienced isolation or quarantine.
- > Varying levels of depression were reported amongst six reviews.
- > Four reviews reported increased anger and irritability in participants.
- > Most reviews included in the umbrella review were from high income countries, limiting the generalisability of mental health outcomes in a low- or middle-income context.
- > Isolation and quarantine protocols vary depending on the infectious agent, findings from this umbrella review may not be predictive of mental health outcomes from the current COVID-19 pandemic.

Reviewed by: Professor Dave Coghill

The association between mental ill-health and health-related behaviours during the COVID-19 epidemic in Australian adults

<https://www.mdpi.com/1660-4601/17/11/4065/htm>

- > An online survey completed by 1491 Australian adults assessed mental health and health related behaviours during the COVID-19 epidemic. The mean age of participants was 50.5 years.
- > 48.9% of participants reported a reduction in physical activity, 40.7% reported reduced sleep, 6.9% reported increased tobacco consumption and 26.6% reported increased alcohol consumption since the commencement of social isolation measures.
- > Participants who reported a negative change in any health-related behaviour were marginally more likely to report higher depression, anxiety, and stress related symptoms.
- > Higher levels of psychological distress (i.e. moderate to severe depression, anxiety, or stress) were associated with a greater negative change in health-related behaviours.

- > When compared to normative data collected from Australian adults, participants reported slightly increased depression and stress, and slightly decreased anxiety.
- > Further study in a larger representative sample of the population is needed to assess the association between mental ill-health and health related behaviours during the COVID-19 epidemic.

Reviewed by: Professor Dave Coghill

PERINATAL HEALTH

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

Protecting hard-won gains for mothers and newborns in low-income and middle-income countries in the face of COVID-19: call for a service safety net
<https://gh.bmj.com/content/5/6/e002754>

- > There is concern that the COVID-19 pandemic is reversing the improvement in maternal and perinatal health (MNH) outcomes in the last 30 years, especially in low and middle-income countries.
- > There have been reports of declining use of MNH services and deteriorating quality of care. Based on modelling, it is estimated that this has led to an increase of 8.3-38.6% in maternal deaths per month across 118 low and middle-income countries.
- > To protect women and newborns, MNH services should be routine and maintained alongside management strategies for the COVID-19 pandemic. Further funding is required for facilities to adapt to the pandemic and its associated challenges.
- > The authors present an outline of how to maintain routine essential services (Table 1).
- > Limitation: as population-based surveys have been delayed, reports informing this article were gathered through online tools, hence bias in sample population may exist.

Reviewed by: Professor Fiona Russell

THERAPEUTICS

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

Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19 (not peer reviewed)

https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_v2final.pdf

- > This is a press release.
- > The RECOVERY trial is a large RCT of possible treatments for patients admitted to hospital with COVID-19.
- > Over 11,500 patients have been randomised to the following treatment arms, or no additional treatment:
 - Lopinavir-Ritonavir (commonly used to treat HIV).
 - Low-dose Dexamethasone (a type of steroid, which typically used to reduce inflammation).
 - Hydroxychloroquine (which has now been stopped due to lack of efficacy).
 - Azithromycin (antibiotic).
 - Tocilizumab (an anti-inflammatory treatment given by injection).
 - Convalescent plasma (collected from donors who have recovered from COVID-19 and contains antibodies against the SARS-CoV-2 virus).
- > Follow-up is complete for over 94% of participants.
- > Dexamethasone reduced the 28-day mortality rate by 17% (0.83 [0.74 to 0.92]; P=0.0007) with a highly significant trend showing greatest benefit among those patients requiring ventilation (test for trend p<0.001).
- > Note- no evidence of benefit for patients who did not require oxygen and they did not study patients outside the hospital setting.
- > Important survival benefits found from this readily available low cost therapeutic that can be used immediately and worldwide.

TRANSMISSION

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

Airborne SARS-CoV-2 is rapidly inactivated by simulated sunlight

<https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa334/5856149>

- > Aerosols represent a potential route of transmission of SARS-CoV-2.
- > This study examined the effect of simulated sunlight and relative humidity on the stability of SARS-CoV-2 in aerosols generated from virus suspended in different liquid matrices (simulated saliva or culture medium). All tests were conducted at a constant temperature (20°C) across a range of relative humidity levels (20%, 45% and 70%) and simulated sunlight intensities (darkness, mid-intensity, and high intensity). Regression analysis was utilised to assess the effect of these variables.
- > Simulated sunlight and liquid matrix significantly affected the decay rate of the virus.
- > Relative humidity alone did not affect the decay rate; however, minor interactions between relative humidity and the other factors were observed.
- > The decay rates in simulated saliva, under simulated sunlight levels representative of late winter/early autumn and summer were $0.121 \pm 0.017 \text{ min}^{-1}$ (90% of the virus inactivated in 19 minutes) and $0.379 \pm 0.072 \text{ min}^{-1}$ (90% of the virus inactivated in 6 minutes), respectively. The mean decay rate without simulated sunlight across all relative humidity levels was $0.008 \pm 0.011 \text{ min}^{-1}$ (90% of the virus inactivated in 125 minutes).
- > Overall, these results suggest that the potential for aerosol transmission of SARS-CoV-2 may be dependent on environmental conditions, particularly sunlight.

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

The natural history and transmission potential of asymptomatic SARS-CoV-2 infection

<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa711/5851471>

- > A prospective study comparing the natural history and transmission potential of asymptomatic and symptomatic individuals with confirmed SARS-CoV-2, admitted to Cu Chi Hospital in Ho Chi Minh City (HCMC), Vietnam, between 10th March and 4th April 2020.
- > This study enrolled 30 COVID-19 positive individuals, from a total of 51 reported cases in HCMC during the same period. 13 were asymptomatic and 17 had mild respiratory symptoms. None of the participants developed severe disease or progressed from asymptomatic to symptomatic.

- > A saliva sample was taken at enrolment, and nasopharyngeal throat swabs (NTS) were collected daily from enrolment to discharge. These specimens were assessed for SARS-CoV-2 using RT-PCR.
- > SARS-CoV-2 RNA was detected in the saliva of 64% of the asymptomatic samples and 81% in the symptomatic group. Those with asymptomatic infection were less likely to have detectable SARS-CoV-2 in NTS samples collected at enrolment (62%) compared to symptomatic patients (100%).
- > Asymptomatic patients had a lower viral load over the first 19 days, when compared to symptomatic patients. The asymptomatic group also showed faster viral clearance during the first week of follow up, however after this period, the probability of viral detection quickly fell to near zero in both groups.
- > The researchers found evidence to suggest asymptomatic individuals may transmit the virus to others, through analysis of transmission chains and clusters, despite their data suggesting asymptomatic carriers had lower viral loads and faster viral clearance from the respiratory tract.

Reviewed by: Professor Fiona Russell

VACCINES

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

The online competition between pro- and anti-vaccination views

<https://www.nature.com/articles/s41586-020-2281-1.pdf>

- > System-level analysis of contention surrounding vaccines of three billion Facebook users.
 - Pro-vaccination clusters are numerically larger, but anti- clusters are central in their positioning within the network, as they dominate the main network patch in which they are heavily entangled with a very large presence of undecided clusters.
 - Undecided population are highly active.
 - Anti-vaccination clusters have higher engagement than pro- vaccination clusters.
 - Anti-vaccination cluster content offers wide range of “attractive” narratives: safety concerns, conspiracy theories, alternative medicine, and now the cause and cure of COVID-19.
 - Anti- clusters grew the most during 2019 measles outbreak, attracting more undecided individuals.
 - Medium-sized anti- clusters grow most, contrary to belief that larger sizes attract more recruits.
 - Anti- clusters either self-locate within cities, states, or countries, or remain global.
- > This reproduces recent explosive growth in anti-vaccination views and predicts that they will dominate in a decade.
- > Insights can inform new policies and approaches to interrupt this shift negative views.

Reviewed by: Professor Fiona Russell

VIROLOGY

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

SARS-CoV-2 reverse genetics reveals a variable infection gradient in the respiratory tract

<https://linkinghub.elsevier.com/retrieve/pii/S0092867420306759>

This study provides a protocol to generate recombinant SARS-CoV-2 with a label “green fluorescence protein (GFP)” or “a GFP-fused nanoluciferase (nLuc)” from a US SARS-CoV-2 clinical isolate WA1, by using reverse genetic system. The newly recombinant viruses have a signature mutation e.g., a silent mutation (T15102A) at a conserved region in nsp12 gene, in order to distinguish from the circulating wild-type SARS-CoV-2 strains. The authors describe additional evidence on the host-pathogen interaction and viral pathogenesis of SARS-CoV-2 by using the newly synthesised recombinant SARS-CoV-2.

- > Main results.
 - The recombinant viruses have similar viral fitness as observed in wild-type viruses.
 - The newly recombinant virus was used:
 - For studying which host protease is crucial in viral replications: it showed that only serine proteases like furin and TMPRSS2 enhance the replication efficiency and cytopathology of SARS-CoV-2 in vitro.
 - For studying the cross-reactive neutralising antibodies between SARS-CoV, MERS and SARS-CoV-2: limited cross-reactive responses were observed.
 - For studying if SARS-CoV-2 has a specific region of respiratory system to infect (virus tropism) by using a number of in vitro primary epithelial cell culture systems as well as autopsy lungs from COVID-19 patients:
 - The expression of ACE2- a receptor of SARS-CoV-2 decreased throughout the lower respiratory tract (RNA in situ hybridization data).
 - ACE2 was also reported to be highly expressed in cystic fibrosis patients and ACE2 expressions were modulated by IFN-beta and IL-13.
 - ciliated and type 2 pneumocyte cells were the main target but dominant secretory cell, i.e., the MUC5B+ club cell, was not infected in vitro or in vivo, despite detectable ACE2 and TMPRSS2 expression.

- > Significance:
 - Provided an additional protocol to generate recombinant SARS-CoV-2 with similar viral fitness to the wild-type strain, while a similar protocol published in early May did not. (Thao et al., <https://doi.org/10.1038/s41586-020-2294-9>); Provide further evidences on viral transmission and pathogenesis.
- > Caution: Biosafety and regulations of using the reverse genetic system should be discussed and highlighted.

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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