Melbourne Medical School
Department of Paediatrics

COVID-19 KIDS RESEARCH EVIDENCE UPDATE

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

Weekly Update No.24
1st October 2020

Australian Government
Department of Health

BE COVIDSAFE

CURRENT STATUS OF CONFIRMED CASES

27,063	882	24,583
Total cases	Total deaths	Cases recovered

8 CURRENT CASES INTENSIVE CARE UNITS (ICU)

ACT	NSW	NT	QLD	SA	TAS	VIC	WA
0	3	0	0	0	0	5	0

60 CURRENT CASES ADMITTED TO HOSPITALS

ACT	NSW	NT	QLD	SA	TAS	VIC	WA
0	9	0	5	0	0	46	0

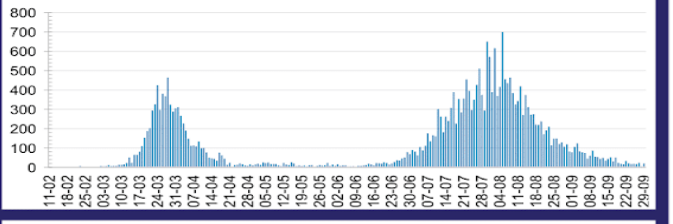
7,589,332 TOTAL TESTS CONDUCTED

0.4% POSITIVE

ACT	NSW	NT	QLD
93,811	2,685,126	47,213	1,104,203
POSITIVE	POSITIVE	POSITIVE	POSITIVE
0.1%	0.2%	0.1%	0.1%

SA	TAS	VIC	WA
465,690	102,821	2,677,022	413,446
POSITIVE	POSITIVE	POSITIVE	POSITIVE
0.1%	0.2%	0.8%	0.2%

DAILY NUMBER OF REPORTED CASES

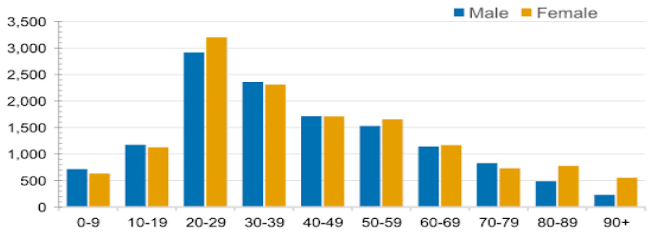


CASES IN AGED CARE SERVICES

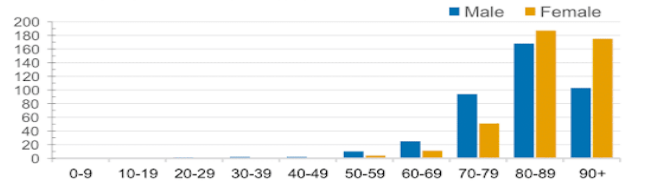
Confirmed Cases	Australia	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
Residential Care Recipients	2049 [1303] (663)	0	61 [33] (28)	0	1 (1)	0	1 (1)	1986 [1270] (633)	0
In Home Care Recipients	82 [72] (7)	0	13 [13]	0	8 [8]	1 [1]	5 [3] (2)	54 [47] (4)	1 (1)

Cases in care recipients [recovered] (deaths)

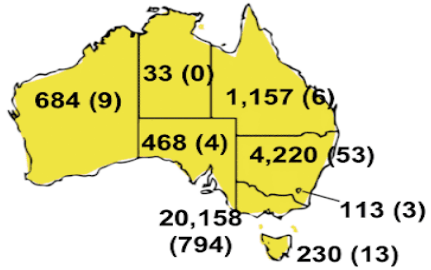
CASES BY AGE GROUP AND SEX



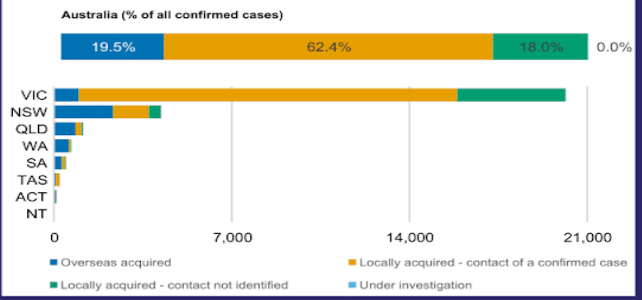
DEATHS BY AGE GROUP AND SEX



CASES (DEATHS) BY STATE AND TERRITORIES

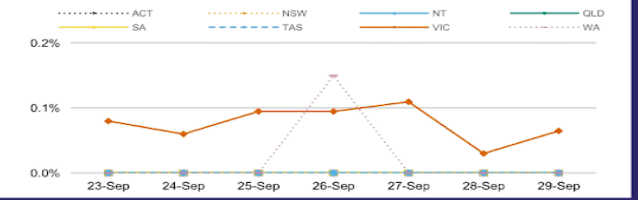


CASES BY SOURCE OF INFECTION



PUBLIC HEALTH RESPONSE MEASURE

Proportion of total cases under investigation



Last updated 29 September 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 September 29; cited 2020 September 30]. Available from: https://www.health.gov.au/resources/collections/coronavirus-covid-19-at-a-glance-infographic-collection

GUEST EDITORIAL

Professor Fiona Russell - Director of the Child and Adolescent Health PhD Program, Department of Paediatrics, The University of Melbourne; Group Leader Asia-Pacific Health Research, Murdoch Children's Research Institute.

Ordinary Victorians have done an extraordinary thing and brought our COVID-19 case numbers down from more than 700 in early August to less than twenty this week by being in Stage 4 lockdown. This has prompted our Premier to announce on the weekend a lightening of restrictions which included the addition of ALL primary school kids returning to school next week, for Term 4. Immediately following that announcement, a Twitter storm ensued- parents (mainly women) went wild- with "of all the changes announced today, this definitely the most exciting" "I actually started crying with relief and joy that all my children can go back to school" "so relieved that my kids can get back to school" "I heard cheering in the park today". The pressure on families has been palpable, particularly for the most vulnerable, and became even more evident when the cork was popped Sunday afternoon when our Premier made this announcement about schools along with the news that "we are ahead of schedule". It's been a long bleak year, and this news has offered a lot of hope for so many.

We read in last week's Weekly (edition number 23, Prof Sharon Goldfeld), how early childhood education and schools play such a critical role not only in providing education but also offer critical support, especially for the most vulnerable of students. With ECEC and schools being closed along with the additional economic and psychological stress on families, family conflict and violence has increased (1) and has led to many children and young people feeling unsafe, with mental health conditions and a feeling of being left behind with their education.

The Premier's announcement was based on analysis that was undertaken by us- a small, and dedicated team from the Melbourne Children's Campus. This analysis and the strategic plan to re-open schools and keep them open was undertaken by yet another "operation warp speed". We worked with colleagues (including the army) from the Department of Health and Human Services (DHHS) and Department of Education and Training (DET) to clean and then analyse the DHHS early childhood education centre (ECEC) and school outbreak data. Our findings prompted updating the mathematical models to predict what would happen if the ECEC and schools went back for Term 4.

We first reviewed the research to understand the role of children in transmission, the global experience in school outbreaks and the school mitigation measures adopted. Here is a summary of what we found:

What do we know about children and transmission? As we know already, children do transmit. The latest evidence shows that children do not play a more significant role than adults in transmission. Children more than ten years old probably transmit the virus at a similar rate to adults; while younger children may transmit less.(2) Children younger than five years old with mild to moderate COVID-19 may have high viral load (3) suggesting that young children can potentially be important drivers of the virus, but it is unclear how long children shed live infectious virus.(2)

Infected children often have no symptoms (asymptomatic) or develop only mild symptoms, so it is harder to detect infection in this age group. At present, it is unclear whether asymptomatic children are infectious.(2) We do need to understand the role of children in transmission better, as the necessary mitigation measures have usually been successful and prevent onward transmission, thereby confounding the understanding of the true natural history of transmission. To become a normal society that can freely mingle again and for children to be able to see their grandparents, it is vital that this is understood. We may even need to vaccinate kids to prevent transmission- but we do not know this yet. Further research is needed.

Schools outbreaks - Internationally, infections in schools are mostly associated with rising case numbers in the broader community. Importantly, data from a number of countries in the European Union (E.U.), the United Kingdom (U.K.), Taiwan, Hong Kong and South Korea suggest that re-opening schools when the transmission is low, and in the context of school mitigation measures and rapid responses, has not been associated with increases in community transmission. This has also been the case in New South Wales, where although infections in schools have occurred in the context of low community transmission, rapid response has prevented single cases progressing to outbreaks (2 or more cases). In England, only 0.01 percent of open schools had an outbreak up until mid-year.(4) Rates of infection in ECEC and school children were no different between Finland (which closed schools) versus Sweden (which did not, except for children >16 years who schooled remotely). Primary school closure and re-opening in Finland did not have any significant impact on infection rates in primary school aged children. Additionally, there was no increased risk of infection in Swedish teachers and child-care workers compared to other professions.(5)

However, school outbreaks do occur, and this has often been associated with high rates of community transmission and lack of adherence to mitigation measures in the school setting. In recent weeks in the U.K., there has been an increase in infections in schools which has coincided with the rise in cases (nearly 6000 cases per day) in the broader community. In Hong Kong, five cases in school age-children were linked to schools, but due to the rapid public health response, there was no evidence of onward transmission. (https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.37.2001671) An uptick in cases in South Korea following mass gatherings in the community in August subsequently resulted in 200 staff and students infected prompting school closures in Seoul. Studies have found that child-to-child transmission in schools is uncommon and not the primary cause of infection in children. The household transmission has been consistently found to be one of the commonest sources of infection for children- in the UK, the seroprevalence in children attending school was the same as for children not attending school.(4) So far, studies have found that schools are not at greater risk of infection than other public places, and are unlikely to drive transmission, if proper and consistent mitigation measures are in place. In this week's Weekly under the School heading, the World Health Organization has guidelines on "Considerations for school-related public health measures in the context of COVID-19".

What can be done to prevent infections in schools? The single best policy to support school re-opening prior to the development of a vaccine or treatment is the suppression of COVID-19 to near zero case incidence in the broader community.(6) This can be achieved via universal mask wearing, social distancing, reduction or elimination of indoor gatherings, staying home when sick, and rigorous and timely Testing, Tracing and Isolation within 48 hours of a notification. For schools, additional mitigation strategies (6) and a rapid response by public health authorities to an infection are crucial to prevent a single case from progressing to an outbreak as has been successfully demonstrated in the previous examples given- New South Wales and Hong Kong.

DHHS school outbreak findings - The summary of our findings is in our "Report Summary: COVID-19 in Victorian Schools: An analysis of ECEC and school outbreak data and evidence-based recommendations for re-opening schools and keeping schools open" which can be found https://www.dhhs.vic.gov.au/emerging-lockdown-victorian-schools-covid-19

In brief:

> Infections linked to ECECs and schools peaked at the time when community transmission was highest during July and then declined in August, suggesting that infections in ECECs and schools are driven primarily by transmission in the broader community

> Schools are not inherently a dangerous place

  – Of one million students enrolled, only 337 may have acquired COVID via outbreaks at schools

  – Cases associated with schools accounted for 8 percent of all infections in Victoria

  – Of 139 staff & 373 students who may have acquired infection via outbreaks at ECEC or schools, eight (four staff and four students) were admitted to hospital and all recovered

  – Infections in ECEC and schools were rarely linked to infections in the most vulnerable population, the elderly

  – There were 1,635 infections linked to ECECs and schools, out of a total of 19,901 cases in Victoria

> The DHHS and DET response was effective as

  – 66 percent involved only a single case in a staff member or student

  – 91 percent involved fewer than ten cases (total)

> Children less than 12 years old seem to transmit less than adolescents & adults- if the first case was a child (<12 years), an outbreak (2 or more cases) was less common.

> Many cases associated with ECECs and schools are in households, but we were unable to determine the direction of transmission

Our recommendations for Victorian schools - Based on our review of the literature and analysis of DHHS data we recommend (7):

> ECEC and schools should be prioritised for re-opening and staying open to guarantee equitable learning environments and lessen social and educational effects of school closure.

> Closing schools should be a last resort, especially for ECEC and primary schools as children in these age groups are less likely to transmit and be associated with an outbreak.

> There should be a staged mitigation approach to opening up and staying open.

  – Schools across Victoria could be opened up safely and stay open to protect the health, safety, and well-being of students, teachers, and ECEC staff and should be based on the incidence of community transmission and as this varies by geographical location could be eased or progressed depending on Victoria's Coronavirus Road to Recovery Step level and proportionate to the incidence of infection in each geographic area.

  - Proposed mitigation strategies have been provided that augment existing DET policy and align with the Harvard Healthy Building Programs which focuses on Healthy buildings, classrooms, policies, schedules and activities.(6)

> Gathering data and evidence in term four is recommended to inform future education and health policy.

  - As there are a number of gaps in our knowledge such as transmission in asymptomatic children, the direction of transmission and how best to inform school closures based on balancing safety against the associated potential academic and well-being impacts, we have recommended additional monitoring and investigation of transmission in Term 4 together with well-being and mental health impacts in ECEC and schools to inform medium term policy decisions.

> Testing, tracing and isolation within 48 hours of a notification is the most important strategy to prevent an outbreak.

When risk reduction strategies are in place ECECs and schools are controlled environments, with no greater risk of infection than other places. Infections in schools and ECECs were well contained with existing controls and rapid closure, contact tracing and cleaning. When infections did occur, serious infections were rare in both students and staff, and very rarely involved the elderly.

So will outbreaks occur in Victorian schools in Term 4? Cases in ECEC and schools may well occur in Term 4. But there are likely to be fewer of these events because community transmission is low, the public health response to an infection in a school has been rapid and this has already prevented many single infections from progressing to an outbreak (this was demonstrated even during the peak of the epidemic in July/August); and provided additional school mitigation strategies are adopted by all ECECs and schools, these measures will also prevent infections. It is important that all of these measures are in place to ensure the health, safety, and well-being of students, teachers, and other ECEC and school staff.

So in summary - There is no doubt that children transmit the virus, but mitigation measures are key to preventing transmission and outbreaks. This works. And with these measures all in place, Victorian kids can go back to school. Infections may occur in Term 4 but are much less likely to progress to an outbreak. Further research is needed to fully understand the role of kids in transmission as in order to see their grandparents again, they may actually need to get vaccinated. But for now, this is not a reason to hold children back from returning to school.

With thanks - It has been a great honour to lead a small team (epidemiologists Dr Kathleen Ryan, MCRI and DHHS, and Dr Katherine Snow, DHHS and MSPGH) with an Advisory Committee including Professor Sharon Goldfeld, Prof Kim Mulholland and Associate Professor Margie Danchin and colleagues from the Department of Education and Training and DHHS. We were fortunate to have a team of nine University of Melbourne medical students of whom many contribute to the Weekly (Alastair Weng, Angela Zhu, Anthea Tsatsaronis, Benjamin Watson, Julian Loo Yong Kee, Natalie Commins, Nicholas Wu, Renee Cocks, Timothy O'Hare), and research assistant Kanwal Salee to clean the data. Thanks also to Belle Overmars.

With an onslaught of papers, fake news and marginal quality studies, our Weekly provides an important snapshot of some of the latest discoveries relating to COVID-19 in Kids, and provides expert oversight to sift the wheat from the chaff. Moreover, children have often been overlooked in this pandemic but are suffering considerably from the indirect effects. Our Weekly has global reach, has about 1-2000 downloads each

month and positive feedback is important to keep us motivated- so thank you. I wish to thank the Weekly Editorial team- my co-Editor Dr Wonie U and Editorial Assistant Eleanor Neal, and recent co-Editor A/Prof Amy Gray, along with our volunteer University of Melbourne medical students, including Daniel Lamanna (student coordinator) and our many other medical students for their important contributions. Last week, we welcomed University of Ottawa medical students to join the review team. Additionally, many thanks to our many Melbourne Children's Campus experts, who review the students work and ensure quality is maintained.

1. Maryland: Substance Abuse and Mental Health Services Administration. Intimate Partner Violence and Child Abuse Considerations During COVID-19 2020 [cited 2020 29th September]. Available from: https://www.samhsa.gov/sites/default/files/social-distancing-domestic-violence.pdf.

2. Han MS, Choi EH, Chang SH, Jin B-L, Lee EJ, Kim BN, et al. Clinical Characteristics and Viral R.N.A. Detection in Children With Coronavirus Disease 2019 in the Republic of Korea. JAMA Pediatrics. 2020.

3. Heald-Sargent T, Muller WJ, Zheng X, Rippe J, Patel AB, Kociolek L.K. Age-Related Differences in Nasopharyngeal Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Levels in Patients With Mild to Moderate Coronavirus Disease 2019 (COVID-19). JAMA Pediatrics. 2020;174(9):902-3.

4. Ismail SA, Saliba V, Lopez Bernal JA, Ramsay ME, Ladhani SN. SARS-CoV-2 infection and transmission in educational settings: cross-sectional analysis of clusters and outbreaks in England. medRxiv. 2020:2020.08.21.20178574.

5. Public Health Agency of Sweden. Covid-19 in schoolchildren: A comparison between Finland and Sweden. [Internet] [cited 2020 29 September]. Available from: https://www.folkhalsomyndigheten.se/contentassets/c1b78bffbfde4a7899eb0d8ffdb57b09/covid-19-school-aged-children.pdf

6. Harvard Global Health Institute. The Path to Zero and Schools: Achieving Pandemic Resilient Teaching and Learning Spaces 2020. [Internet] [cited 2020 September 29]. Available from: https://globalepidemics.org/wp-content/uploads/2020/07/pandemic_resilient_schools_briefing_72020.pdf

7. Russell FM, Mulholland EK, Ryan K, Snow K, Danchin M, Goldfeld S. Behind Victoria's decision to open primary schools to all students: report shows COVID transmission is rare 2020 [updated 2020 28th September; cited 2020 29th September]. Available from:https://theconversation.com/behind-victorias-decision-to-open-primary-schools-to-all-students-report-shows-covid-transmission-is-rare-147006#comment_2345617.

HIGHLIGHTS

> A RCT of B.C.G. administration vs placebo in the elderly in Greece pre-COVID-19 resulted in a 79% reduction in respiratory infections of probable viral origin at 12 months.

> Modelling estimates the way that varied immune dynamics and public health interventions may affect a range of potential COVID-19 futures.

> Women in labour with SARS-CoV-2 are more likely to have pre-eclampsia, and less likely to undergo induction of labour.

> Gastrointestinal symptoms are more frequently associated with severe or critical presentations of COVID-19 in children and are positively correlated with subsequent cardiac complications.

> The evidence of protection from neutralising antibodies is emerging, with implications for therapeutics and vaccines.

> A prospective cohort study in Turkey found that symptomatic neonates with COVID-19 had high rates of respiratory support requirements and that high C.R.P. and prothrombin time were associated with more severe disease.

> Pool testing is one way to increase efficiency and decrease the costs associated with COVID-19 testing.

> Delaying Phase II vaccine clinical trials in children will delay our recovery from COVID-19 and unnecessarily prolong its impact upon children's education, health and emotional well-being, and equitable access to opportunities for development and social success.

> Countries should prepare for the worst-case scenario when lifting restrictions, while still moving forward (with a clear and explicit plan) on the basis of epidemiology, monitoring infection, community measures, and effective testing/tracing/isolation.

> Governments must not politicise the decision regarding when and how to open schools - children cannot be used as a political ploy, and all leaders have a responsibility to focus on children and young people's well-being and long-term future, even at cost to some sections of the economy.

> Four widely available, commercial assays can be effectively used for SARS-CoV-2 serological testing to achieve sensitivity and specificity of at least 98%.

> A Swiss study found that seroprevalence was inversely related to age.

> Lack of preventative dental services due to COVID-19 restrictions may have long-term effects on the oral health of children, highlighting the need for dental services in tertiary care centres.

> US COVID-19 related deaths in those <21 years old are rare (0.08% total), but certain populations are higher risk: underlying medical condition, 10-20 years old, and Black and Hispanic ethnicity.

> U.C. San Diego reports that statins are associated with reduced risk of developing severe COVID-19 disease, as well as faster recovery times - it is proposed that the statins role in removing cholesterol from cell membranes prevents the Coronavirus from getting in.

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ADULT MEDICINE

Rebecca Seliga – 3rd Year Medical Student, University of Ottawa

Reduced maximal aerobic capacity after COVID-19 in young adult recruits, Switzerland, May 2020
https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.36.2001542

> In March 2020 there was a COVID-19 outbreak amongst young, healthy Swiss recruits (median age 21; 87% male).

> This study aimed to compare physical fitness in COVID-19 confirmed and symptomatic (termed COVID-19 convalescent), COVID-19 confirmed and asymptomatic, and COVID-19 negative individuals both before and after the outbreak.

- Baseline fitness testing was done 3 months before the COVID-19 outbreak.
- Follow-up fitness testing was done a median of 45 days (31-58) after COVID-19 diagnosis
  Fitness was measured in 3 ways:
  1. Progressive endurance running, whereby the final running velocity could be used to predict maximal aerobic capacity (VO2 max).
  2. Prone bridge testing, a measure of trunk strength.
  3. Seated shot-put testing, a measure of upper extremity strength.

> Follow-up fitness testing revealed a significant decrease in VO2 max (-0.9 mL/min/kg) in COVID-19 convalescent individuals compared to their baseline test result.

> There was no significant difference in VO2 max for COVID-19 asymptomatic nor COVID-19-negative individuals.

> 19% of COVID-19 convalescent individuals had a decrease of >10%.

> Trunk strength and upper extremity strength did not significantly differ between the three groups before and after the outbreak.

> This study does not explain the pathophysiology of these findings, or whether these observed changes are different from those following other significant illness.

> Further long-term follow-up studies are needed to determine if these changes in VO2 max are reversible.

> It is possible that the findings of this study could be explained by either physical deconditioning or demotivation. This is made more likely by the fact that quarantine, physical distancing, and social isolation both restrict exercise possibilities and lower the morale of individuals.

> One would expect that both deconditioning and demotivation would result in lower scores on all fitness tests (VO2 max, trunk strength, and upper body strength); however, strength test scores did not vary significantly.

> The fitness testing methods used in this study are not as specific or well-validated as tests such as spirometry.

Reviewed by: Professor Allen Cheng

CLINICAL PAEDIATRICS

Angela Zhu - 3rd Year Medical Student, Department of Paediatrics, The University of Melbourne

Gastrointestinal symptoms in severe COVID-19 children
https://pubmed.ncbi.nlm.nih.gov/32932333/

- This is a retrospective analysis of children and adolescents hospitalised with COVID-19 across 23 centres in Italy from 21st February 2020 to 1st May 2020.
- Of 127 cases, the median age was 4.8 years, 57 (45%) were < 12 months of age.
- 84.4% were assessed as asymptomatic, mild or moderate severity, 8.7% were severe, and 7.1 % critical.
- 8 (6.7%) were admitted to I.C.U., 14 (12%) required oxygen therapy, 5 (4%) received non-invasive ventilation, and one patient required mechanical ventilation.
- There was no significant difference between I.C.U. admission rates amongst children with or without coexisting co-morbidities.
- G.I. symptoms (vomiting, diarrhoea and abdominal pain) were present in 28.3% of the children.
- G.I. symptoms were more commonly associated with more severe or critical illnesses (P= 0.029) and with the development of cardiac complications.
- Limitations:
  - Small study size.
  - The severity score classification used was mainly for respiratory symptoms.
  - Limited temporal data of G.I. symptoms and its relationship with disease severity.

Reviewed by: Professor Julie Bines

Julia Sweet - 3rd Year Medical Student, University of Ottawa

SARS-CoV-2-Associated deaths among persons aged <21 years - the United States, 12th February - 31st July 2020
https://www.cdc.gov/mmwr/volumes/69/wr/mm6937e4.htm?s_cid=mm6937e4_w

- This report summarises characteristics of those under 21 years of age who have died due to COVID-19 in the U.S. between February and July 2020.
- COVID-19 is known to be milder in those <21 years old, but the severity is known to be associated with increasing age.
- The U.S. has seen over 190,000 deaths, but only 121 deaths identified in the <21 years age group (0.08%):

  - 91 cases (75%) had underlying medical conditions.
  - Chronic lung disease, obesity, neurologic/developmental conditions, and cardiovascular conditions.
  - 74% of cases were Black or Hispanic persons.
  - Disproportionately affected; these groups account for 41% of the U.S. population.
  - 70% of the cases were aged 10-20 years.

> Multisystem inflammatory syndrome in children (MIS-C), a severe illness characterised by fever, multiorgan system involvement, laboratory evidence of inflammation, and laboratory or epidemiologic evidence of SARS-CoV-2 infection or exposure, was associated with 15 (12%) of reported deaths.

  - Early recognition and treatment of MIS-C is an important take-home message from this paper.

> Racial and ethnic minority overrepresentation in identified deaths <21 years of age, is an important finding with significant public health implications, noting 42 decedents were not admitted to hospital with 16 (38%) dying at home, 23 (55%) were critically ill and died in the E.D.

> Potential contributory factors include:

  - These groups are also overrepresented in a number of essential workers unable to work from home, increasing the risk of exposure to COVID-19 and thus potential secondary transmission among family members.
  - Challenges seeking health-care due to difficulties or delays.
    - Lack of insurance.
    - Lack of childcare or transportation.

> Limitations:

  - Not all deaths may have been reported as due to COVID-19 due to incomplete testing, reporting delays, etc.
  - Autopsy findings and death certificates were not available for verification.
  - No standard data collection procedures among states; individual states manually submitted their data via case-based surveillance data and aggregated case reports.
  - Case-based surveillance may underestimate the number of deaths compared to aggregated reports; some data was missing from case reports.

> Ongoing evaluation of deaths associated with SARS CoV2 is essential, including follow-up strategies that aim to minimise morbidity and mortality in the paediatric population.

Reviewed by: Associate Professor Nigel Crawford

Alastair Weng – 3rd Year Medical Student, Department of Paediatrics, The University of Melbourne

Clinical experience on video consultation in preterm follow-up care in times of the COVID-19 pandemic
https://pubmed.ncbi.nlm.nih.gov/32961545/

The authors describe their clinical perspective of routine developmental care for preterm infants.

> Preterm birth is a significant contributor of morbidity and mortality in children, especially within the respiratory and neurodevelopmental domains. Ex-premature children undergo regular screening through clinical review and validated tools for early intervention where necessary.

> COVID-19 social distancing measures help protect ex-premature children from respiratory complications but created a barrier to routine preventative care.

> Clinicians in Germany utilised telehealth, not only for history-taking but also for examination of neurological and neurodevelopmental function. They achieved this by instructing the parents to perform several simple tests that can be interpreted through videoconference.

> Children were found to be more cooperative in the home environment, parents felt empowered in their inclusion in the process, and there were lower costs associated with health-care resource utilisation.

> Some limitations included not being able to perform specific examination elements (e.g. muscle tone and strength assessment, auscultation, percussion) and lack of interaction between child and health-care professionals.

> Video consultation is not a replacement but may improve access to preterm follow-up in families with previously poor engagement.

Reviewed by: Dr Wonie Uahwatanasakul

Julia Sweet - 3rd Year Medical Student, University of Ottawa

COVID-19: implications for paediatric dental care in the hospital setting - Letter to the Editor
https://onlinelibrary.wiley.com/doi/10.1111/jpc.15198

> Concern that paediatric dental care restrictions due to COVID-19 are creating a crisis in the future of paediatric dental health.

> The study examined dental services provided at a tertiary Australian children's hospital between January-May 2020 and compared it to rates of 2019 services.

> Overall there were 40.2% fewer patients during this period compared to 2019.

> March, April, and May faced the largest reductions with approximately 35, 91, and 91% reduction in routine dental services, including preventative services.

> Lack of available preventative services such as routine check-ups and fluoride application could have long-standing effects in children's dental health, leading to more advanced oral disease, more complex treatments, and poorer health outcomes.

> With the closure of most community dental practices, tertiary care became critical and remains essential in the COVID-19 era.

Reviewed by: Dr Martin Wright

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

Rhabdomyolysis and acute kidney injury as leading COVID-19 presentation in an adolescent
https://journals.lww.com/pidj/Fulltext/2020/10000/Rhabdomyolysis_and_Acute_Kidney_Injury_as_Leading.23.aspx

> A case report of an adolescent in Belgium with COVID-19, severe rhabdomyolysis and A.K.I., without respiratory symptoms and fever.

> The course of illness for the 15-year-old patient;

- Initial symptoms (D0): intense proximal muscle pain.
- D3: sought assistance at E.D., no abnormal physical or laboratory findings.
- D4-5: abdominal pain, vomiting and mild diarrhoea.
- D6: developed haematuria, polyuria, polydipsia and general fatigue.
- D10: representation and admission to paediatric I.C.U., positive SARS-CoV-2 swab and negative for all SARS-CoV-2 class immunoglobulins.
- Recovered with supportive care.
- D19: discharged from hospital

> The patient's vital signs were normal on admission to I.C.U., however, he had lab findings demonstrating severe renal failure, mild hypocalcaemia, mild hepatic cytolysis, elevated C.R.P., severe rhabdomyolysis with a positive SARS-CoV-2 PCR test. SARS-CoV-2 IgG serology became positive on day 29.

> Extensive testing did not reveal any other viral illness, testing for drugs (amphetamines, cocaine, benzodiazepines, opioids) was negative, and there was no suspicion of connective tissue or inherited metabolic disorders.

> This is the first known report of COVID-19-associated rhabdomyolysis in the paediatric population, with two reported cases in adults.

> Rhabdomyolysis in the paediatric population is usually secondary to viral myositis or inherited metabolic disorders.

> A viral cause is expected in this patient due to the acute onset of gastrointestinal symptoms and is likely to have been precipitated by a SARS-CoV-2 infection (given extensive testing did not reveal any other known causes of myositis).

> Viral myositis is a common cause of rhabdomyolysis in the paediatric population and clinicians should consider SARS-CoV-2 infection in the workup of rhabdomyolysis associated with an acute viral illness.

Reviewed by: Dr Martin Wright

EPIDEMIOLOGY & PUBLIC HEALTH

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

Universal screening for SARS-CoV-2 infection: a rapid review
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013718/full

> Rapid review to assess:

1. The effectiveness of universal screening of SARS-CoV-2 infection compared with no screening.
2. The accuracy of universal screening in people who have not presented to clinical care for symptoms of COVID-19.

> Results:

– 22 publications: Two modelling studies on universal screening; 17 cohort studies and three modelling studies on screening test accuracy.

> Effectiveness of screening: symptom screening at travel hubs may reduce the importation of infected cases, and screening of health-care workers (H.C.W.) in emergency departments using laboratory tests may reduce transmission to patients and other H.C.W.

– The certainty of the evidence was very low and assessed to have a high risk of bias and indirectness.

> Screening test accuracy:

– Single time-point strategies:

- Symptom assessment (n=524): sensitivity 0.00-0.60; specificity 0.66-1.00.
- Direct temperature measurement (n=822), international travel history (n=13080), exposure to known infected people (n=13205), exposure to suspected infected people (n=954): sensitivity 0.00-0.23; specificity 0.90-1.00.
- Combined symptom assessment plus direct temperature measurement (n=779): sensitivity 0.12-0.69; specificity 0.90-1.00.
- Rapid PCR text (n=21): sensitivity 0.8 (95% CI: 0.39-0.94); specificity 0.74 (95% CI: 0.44-0.96).

– Repeated screening with symptom assessment (n=76): sensitivity 0.44 (95% CI: 0.29-0.59); specificity 0.62 (95% CI: 0.43-0.79).

– Screening at airports: sensitivity 0.3 (95% CI: 0.1-0.53).

  - The majority of studies were assessed as very-low to low-certainty evidence.

> Conclusions: The evidence base for the effectiveness of screening comes from two modellings studied and is limited by their assumptions.

  - The review highlight the uncertainty and variation inaccuracy of screening strategies.

> Recommendations: Further studies need to evaluate the utility of rapid laboratory tests, combined screening and repeated screening. More research also needed on reference standards with greater accuracy than RT-PCR.

> Due to the poor sensitivity of existing approaches, there is a need for greater emphasis on other ways to prevent transmission such as face coverings, physical distancing, quarantine and adequate P.P.E. for frontline workers.

Reviewed by: Dr Samantha Bannister

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

Immune life history, vaccination, and the dynamics of SARS-CoV-2 over the next five years
https://science.sciencemag.org/content/early/2020/09/18/science.abd7343.full

> This modelling work uses a Susceptible-Infected-Recovered(-Susceptible) or S.I.R. (S) model to explore how the pandemic trajectory might unfold for different assumptions regarding the nature of the adaptive immune response to SARS-CoV-2.

> The authors consider how immune differences, seasonal variation, changing rates of non-pharmaceutical interventions (such as school and business closures and lockdown restrictions) and the development of a vaccine may impact a range of COVID-19 futures.

  - Seasonal transmission rates and non-pharmaceutical interventions: social distancing can cause a delay in the timing of the secondary peak of the pandemic and can also allow for further accumulation of fully susceptible individuals.

  - Vaccination: modelling illustrates that both high vaccination rates and relatively long durations of vaccine-induced immunity are required to achieve the largest reductions in secondary infection burdens.

    - An imperfect vaccine with short-lasting transmission-blocking immunity in the setting of short-lasting partially protective natural immunity could reduce the peaks of future outbreaks.

    - A vaccine with longer-lasting transmission-blocking immunity in the setting of longer-lasting more protective natural immunity could eliminate future outbreaks.

  - Transmission dynamics: the authors further consider how variation in the way that people transmit COVID-19 may impact this modelling.

    - Vaccine hesitancy: disease burden is higher if vaccine refusers have higher contact rates.

> Conclusions: many factors influence the pandemic trajectory, including seasonal variation in transmission, the immunology of secondary infection and nature of the adaptive immune response, efficacy of any vaccine and vaccine hesitancy.

> Future research should focus on establishing:

1. The duration and strength of transmission-blocking and clinical immunity following primary (and subsequent) infection and vaccination.
2. Population and individual variation in these parameters (age, sex, etc.).
3. The impact of viral evolution, coinfection and other pathogen characteristics on COVID-19 infection and disease.

> Limitations: this work necessarily simplifies certain aspects of the COVID-19, but highlights the massive variation in potential COVID-19 futures. It offers the reader opportunities to consider a range of aspects of the pandemic in unique ways and apply this thinking at the population level.

Reviewed by: Dr Samantha Bannister

Rafael Lee - 3rd Year Medical Student, Department of Paediatrics, The University of Melbourne

Susceptibility to SARS-CoV-2 infection among children and adolescents compared with adults: a systematic review and meta-analysis
Susceptibility to SARS-CoV-2 Infection Among Children and Adolescents Compared With Adults

> The aim of this systematic review and meta-analysis was to examine the susceptibility of children and adolescents to SARS-CoV-2 compared to adults.

> 18 contact tracing, and 14 population-based prevalence studies from 21 countries, comprising in total 41,640 children and adolescents <20 years and 268,945 adults, were identified through searches of PubMed and medRxiv from database inception to 28th July 2020.

> Findings:

- The pooled odds ratio of being an infected contact in children and adolescents versus adults was 0.56 (95% CI, 0.37-0.85) with substantial heterogeneity ($I^2 = 94.6$).
- In the eight contact tracing studies that allowed estimation, children younger than 10-14 years of age had a lower odds of being an infected contact (0.52, 0.33-0.82) than adolescents (1.23, 0.64-2.36), the later not being significantly different to that in adults.
- Three school-based studies found minimal transmission from child or teacher index cases.
- Seroprevalence among children was lower compared with adults, whilst similar in adolescents compared to adults.

> Discussion:

- This suggests that children have a lower susceptibility to SARS-CoV-2 infection compared with adults.

- This meta-analysis does not directly assess the role of children and adolescents in the transmission of SARS-CoV-2.

> Limitations:

- Most of the studies were assessed as low or medium quality.
- The COVID-19 pandemic is ongoing, and data will continue to evolve (already in places such as the U.S., prevalence rates for SARS-CoV-2 in children and adolescents are much greater than was the case when these studies were performed).
- There is significant heterogeneity within those <20 years and though there was some attempt to separate into different age groups, the ability to do so with any accuracy was limited.
- The secondary infection rates of contact tracing studies were low, which may represent an underestimation.
- Most contact tracing studies were undertaken after strict social distancing measures had been implemented, which may have reduced children and children contact but increased children and adult contact.
- The number of contacts nominated and traced for those younger than 20 years was low compared to adults in some studies.

Reviewed by: Dr Martin Wright

Victoria Ivankovic - 3rd Year Medical Student, University of Ottawa

Lessons learnt from easing COVID-19 restrictions: an analysis of countries and regions in Asia Pacific and Europe
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32007-9/fulltext?utm_campaign=tlcoronavirus20&utm_content=140781846&utm_medium=social&utm_source=twitter&hss_channel=tw-27013292#%20

> Countries around the world have implemented varying degrees of restriction on population movement to slow the spread of COVID-19 and prevent systems from being overwhelmed.

> Such measures may have saved lives; however, lockdowns and other extreme restrictions are not sustainable in the long term.

> When and how countries should ease restrictions are the most common challenges governments now face, as they seek to balance the health, social, and economic concerns.

> This study has identified five prerequisites for easing COVID-19 lockdowns and restrictions:

- Knowledge of infection status:
    - Indicators to monitor the epidemiological situation - high surveillance of infection of high quality confirming that infections are being suppressed.
- Community engagement

        - Safe policies for physical distancing (varies from 1-2m) & mask-wearing, precautionary measures in schools and workplaces, communication to secure public trust and cooperation, protecting vulnerable populations, providing socioeconomic support.

    - Adequate public health capacity
        - Testing, tracing, isolating - robust systems to monitor infection situation is key: find, test, trace, isolate, and support system needs to be supported by sustained investment in public health and health-system capacities.

    - Adequate health system capacity
        - Treatment facilities, medical equipment, health-care workforce.

    - Border controls
        - Inbound travel restrictions - as countries gradually re-open borders, the inflow of travellers should be managed to reduce the risk of people with COVID-19 travelling into the area.

> Governments should be explicit about their goals and transparent in their decision making when lifting restrictions.

> Several countries have produced dashboards of indicators of factors being considered.

> Two broad approaches emerge:

    - Politicians draw on expert advice and decide which restrictions to relax, without explicit and public criteria.

    - Other nations included in the study are lifting restrictions based on epidemiological thresholds (e.g. Germany: local authorities are in charge of lifting lockdowns in individual states depending on the situation faced locally).

> There is increasing realisation that removing COVID-19 restrictions is about cautiously and gradually transitioning to a “new normal” while being able to reimpose measures if, and when, necessary.

> With few exceptions countries have struggled to secure public trust, however, overall female leaders have been reported to achieve higher confidence and adherence than their male counterparts.

> While data and digital tracking has a role, countries such as South Korea highlight the importance of “shoe-leather epidemiology” - use of tracers which have detailed local knowledge.

> Countries should prepare for the worst while still moving forward on the basis of:

    - Epidemiology, or epidemiology in combination with other considerations; a clear and transparent plan that describes which factors are being considered is essential.

    - Robust monitoring systems.

    - Community measures to reduce transmission.

    - Effective testing, tracing, and isolation (with local knowledge).

Reviewed by: A/Prof Amy Gray

GLOBAL HEALTH

gage: doing long-distance research with vulnerable adolescents under COVID-19 lockdown
https://www.gage.odi.org/multimedia/doing-long-distance-research-with-vulnerable-adolescents-under-covid-19-lockdown/

Our world in data: statistics and research: Coronavirus pandemic (COVID-19)
https://ourworldindata.org/coronavirus

WHO COVID-19 dashboard
https://covid19.who.int/

Rebecca Seliga – 3rd Year Medical Student, University of Ottawa

Uruguay is winning against COVID-19. This is how.
https://www.bmj.com/content/370/bmj.m3575

> This is a feature article in the B.M.J. by a freelance journalist that reports on the relative success to date of COVID-19 containment in Uruguay, as compared to other countries in the Latin American region including neighbouring Brazil and Argentina and reflecting on possible reasons. Uruguay has a population of around 3.5 million and 14% are 65 years and older. Recognition in the region: "Uruguay continues to provide hope", says Marcos Espinal, the head of the Communicable Diseases and Health Analysis department at the Pan American Health Organisation (PAHO).

> This article attributes Uruguay's success to the following:

- Rapid response:
    - Political leadership with early and decisive lockdown and border closures.
    - Outbreaks were traced by epidemiologists to ensure that exposed contacts were tested and isolated within 24 hours.
- Developing a nationally-produced testing kit: Latin America relies heavily on medical supplies produced abroad, but Uruguay developed a testing kit so as to not be affected by global shortages.
- Pool testing: Once infection prevalence reached <1%, Uruguay began pool PCR testing to increase efficiency and decrease costs. Pool testing means that multiple samples are pooled and tested together. If the result is negative, all samples that were combined are negative. If positive, then individual samples are re-tested to identify the positive case. This allowed a decrease in tests required by 80%. Matrix pooling takes this one step further and overlaps samples in such a way that it is easier to find an individual infected sample if there is a positive result.

> While not highlighted in the article, context should also be noted that pre-COVID-19, Uruguay had better health and education indicators, higher G.N.I. per capita, and more equitable distribution of wealth than its neighbours - and political leadership in COVID-19 response stands in sharp contrast to Brazil.

Reviewed by: Professor Steve Graham

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

Building resilient societies after COVID-19: the case for investing in maternal, neonatal, and child health
https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(20)30200-0/fulltext

> An opinion piece that argues for greater investment in maternal, neonatal and child health (MNCH). They highlight that this will promote resilience in societies, allowing rapid and effective responses to health challenges and the associated economic consequences.

> The global economic recession after the COVID-19 pandemic is likely to result in reduced investment in MNCH. The short term impact in low-middle income countries is likely to be an increase in mortality of children under five years, child wasting and stunting and maternal mortality. In high-income countries, this is likely to lead to an increase in preterm and low birth weight babies, along with negative impacts on child-health facilities and routine immunisation. Long-term impacts are likely to include an increase in non-communicable diseases, as seen in past events of socioeconomic shock.

> This viewpoint argues that the priority actions for policies to invest in MNCH include:

- Greater public awareness of the importance of promoting and investing in MNCH services.
- Initiate immediate pre-emptive interventions including sustained access to contraception and reproductive health services, pre-conception care, antenatal care and child health and developmental programs.
- Strengthen primary care and sustain community-based interventions, including home visits during and after pregnancy, breastfeeding supports and immunisation.
- Develop new policies to drive gender equity and reduce the penalties of motherhood.
- Increase and sustain training and capacity building for community health workers in MNCH.
- Invest in research and data collection to monitor the immediate and longer-term effect of COVID-19 and the related socio-economic crisis on MNCH.

> Investing in MNCH has high rates of return in the medium and long term through reducing long term non-communicable disease (such as obesity), while providing a unique opportunity to empower women through reducing the gender pay, career and status gaps that make women more susceptible to the effect of socioeconomic shocks.

Reviewed by: Professor David Coghill

IMMUNOLOGY

Thang Dao - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Antibody response to SARS-CoV-2 infection in humans: a systematic review (not peer reviewed)
https://protect-au.mimecast.com/s/QKdWC91ZVBSkxMN3Etooh7C?domain=medrxiv.org

> This systematic review aimed to:
  - Characterise the antibody response to SARS-CoV-2 infection over time and explore the effects of potential correlates of immune activity on this response.
  - Consider the relationship between different variables influencing antibody responses and quantification of SARS-CoV-2 antibodies.
  - Duration of post-infection antibody response.

> Using designated search terms and articles between 1st January to 26th June 2020, 9223 articles were identified and screened. 150 articles were deemed eligible and were included in the review.

> Most studies were observational cohort studies, focused on hospitalised patients, and were of moderate quality.

> Kinetics of antibody response.
  - Majority of individuals mounted a SARS-CoV-2 specific antibody response during the acute phase (≤28 days).
  - Antibody response followed typical immunological paradigms: the appearance of IgM isotype first, followed by IgG.
  - IgM peaks two to five weeks post-symptom onset and then decreases to undetectable levels by a further six weeks. IgG peaked later in three to seven weeks post-symptom onset, plateau, and persisted at lower levels for at least eight weeks.
  - Fewer studies reported IgA; reported to peak between 2-3 weeks post symptom onset.

> Correlates of antibody response (i.e. disease severity, co-morbidities, and symptom profile, age, sex, and ethnicity) were inconclusive due to on the lack of consistency in methods, comparison groups and study design in most studies.

> Neutralising antibodies (nAb) antibody response.
  - Most subjects developed detectable SARS-CoV-2 nAb, despite generally low titres and short-lived responses. They were detectable between seven to ten days, peaking at three weeks after disease onset, plateauing, before decreasing over six weeks.
  - nAb response was associated with disease severity.

  - Neutralisation ability was associated with different specific IgG antibodies against spike (S), receptor-binding domain (RBD), and nucleocapsid (N)-specific. Potent nAb has been isolated from convalescent plasma.
  - Data on long-term protection due to nAbs are limited, and the titres required for protection are not identified.
  - Limited evidence on cross-reactivity between SARS-CoV-2 and other HCoVs, and cross-neutralisation is rare.

> A limitation of the review was the methodology that it might have missed relevant or unpublished negative results. There were also shortcomings from the evidence base due to moderate quality, heterogeneity, lack of study on longer duration, small sample sizes, and lack of statistical analysis in some studies.

> Implications: humoral response against SARS-CoV-2 infection and sterilising immunity, seroprevalence studies, immunity passports as well as vaccine development and strategies.

> Research gaps:

  - relationship between antibody response and correlates including age, sex, ethnicity and disease severity.
  - data on antibody dynamics for mild and asymptomatic cases.
  - Long term data beyond three months following primary infection or vaccination.

> Conclusion: Published literature on immune responses to SARS-CoV-2 is of variable quality with considerable heterogeneity. Longer-term and more comprehensive assessment of immune responses is required.

Reviewed by: Dr Ryan Toh

PERINATAL HEALTH

Maria Gladkikh - 3rd Year Medical Student, University of Ottawa

Infant outcomes following maternal infection with SARS-CoV-2: first report from the PRIORITY study
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1411/5908705

> This is a report of early findings from the U.S. prospective cohort PRegnancy CoronavIrus Outcomes RegIsTrY (PRIORITY) study

- This earlier report includes 263 infants (179 SARS-CoV-2 positive mothers and 84 negative mothers) recruited nationally from multiple sources between 22nd March and 22nd June 2020.
- PRIORITY enrolment and follow-up are ongoing as the sample size aim is 1200.
- Enrolment criteria: individuals ≥13 years old with suspected or confirmed SARS-CoV-2 during pregnancy or in the first six weeks after pregnancy.
- Control group: mothers who tested negative for SARS-CoV-2.
- Information was from parent report and hospital electronic medical records and was collected up to 6-8 weeks after birth.

> Early findings:

- Among the 263 infants currently enrolled in the PRIORITY study, adverse outcomes (preterm birth, NICU admission, respiratory disease) did not differ between those born to mothers testing positive and those born to mothers testing negative for SARS-CoV-2.
- No pneumonia or lower respiratory tract infection reported in the cohort through 6-7 weeks of age.
- In mothers who tested positive = estimated incidence of a positive infant SARS-CoV-2 test is 1.1% (0.1%, 4.0%) and infants had minimal symptoms.

> Limitations:

- Infant testing was incomplete and might be biased by false-negative and false-positive results.
- PRIORITY currently underrepresents maternal Latina ethnicity and Black races.

Reviewed by: Dr Martin Wright

Sophia Moshegov - 3rd Year Medical Student, Department of Paediatrics, The University of Melbourne

Association of SARS-CoV-2 test status and pregnancy outcomes
https://jamanetwork.com/journals/jama/fullarticle/2771110?guestAccessKey=a0c6fc98-25bb-44bd-853f-ef3b7f62786c

- Research letter comparing outcomes in pregnant women in labour infected with SARS-CoV-2 compared with those uninfected.
- Included all patients presenting in labour at Karolinska University Hospital, Stockholm, Sweden from 25th March to 24th July, 2020. SARS-CoV-2 was confirmed via RT-PCR testing of nasopharyngeal swabs performed on all patients in labour regardless of symptoms.
- Measured the associations between SARS-CoV-2 infection and adverse pregnancy, delivery and neonatal outcomes.
- Among 2682 patients presenting in labour, 5.8% were SARS-CoV-2 positive, 65% of those were asymptomatic.
- Patients testing positive were more likely to have pre-eclampsia (7.7% vs 4.3%) and less likely to undergo induction of labour (18.7% vs 29.6%).
- Mode of delivery, postpartum haemorrhage, preterm birth did not significantly differ between groups.
- No difference in neonatal outcomes; 5-minute Apgar score and birth weight for gestational age.
- SARS-CoV-2 is less severe in pregnancy than the two previous coronavirus infections: SARS and MERS.
- Results of the current study are consistent with previous literature regarding the absence of an increased prevalence of preterm birth and lack of difference in neonatal outcomes.
- Limitations: Uncertainty regarding generalisability to other countries with different obstetric care, and limited statistical power for rare outcomes.

Reviewed by: Professor Suzanne Garland

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

A multicentred study on epidemiologic and clinical characteristics of 37 neonates with community-acquired COVID-19
https://journals.lww.com/pidj/Fulltext/2020/10000/A_Multicentered_Study_on_Epidemiologic_and.2.aspx

- A prospective multicentre cohort study involving 24 neonatal intensive care units across Turkey to describe the epidemiological and clinical characteristics of neonates with community-acquired COVID-19.
- A total of 37 neonates with RT-PCR confirmed SARS-CoV-2 infection between 9th March to 15th June were included. Neonates whose mothers were diagnosed with COVID-19 during pregnancy were excluded.

> Epidemiology: all neonates were born with APGAR scores of 8 or more. The delivery mode was vaginal in 19/37 (51%) and caesarean section in 18/37 (49%). 3/37 (8%) were premature while the remaining were full term. two neonates had congenital anomalies.

> Clinical characteristics: all patients were symptomatic with 16/37 (43%) having severe/critical disease. The most common clinical findings were fever (18/37, 49%), hypoxemia (15/37, 41%), cough (10/37, 27%) and tachypnoea (9/37, 24%). Other findings included poor feeding, retractions, rales, diarrhoea, rhinorrhoea and exanthema.

> Laboratory results: the median C-reactive protein (C.R.P.) and prothrombin time (P.T.) values were higher in patients who needed supplemental oxygen or had severe/critical disease.

> Imaging results: 31 neonates had a chest x-ray, and five had C.T. Abnormalities were seen in 11/31 (36%) of the C.X.R.s (consolidation/infiltration) and 4/5 (80%) of the C.T.s (ground-glass opacities or consolidation with surrounding halo sign).

> Management:

- Neonates were only admitted if they had respiratory distress, feeding difficulty or were suspected of having bacterial sepsis. Otherwise, they were followed up as ambulatory patients. 73% were admitted to the NICU.
- 15 neonates (41%) required oxygen administration and 6 (16%) required non-invasive ventilation. Only one neonate (3%) required mechanical ventilation.
- Therapies given included: intravenous antibiotics (54%), azithromycin (38%), oseltamivir (32%), corticosteroid (11%), IVIG (3%), and surfactant (3%).

> Complications:

- Three (8%) had myocarditis, two (5%) had disseminated intravascular coagulopathy, and one (3%) had multiple organ dysfunction.
- One patient with Down syndrome and congenital cardiovascular disease died due to neonatal respiratory distress syndrome and co-infection with MRSE (methicillin-resistant Streptococcus epidermidis).

> Conclusions: symptomatic neonates with COVID-19 had high rates of respiratory support requirements. High C.R.P. and prothrombin time were associated with more severe disease.

> Limitations: study only included neonates seeking medical attention and may, therefore, overestimate the severity of COVID-19 disease in neonates.

Reviewed by: Professor Suzanne Garland

Maria Gladkikh - 3rd Year Medical Student, University of Ottawa

***Ready, Set, BABY Live* Virtual Prenatal Breastfeeding Education for COVID-19**
https://journals.sagepub.com/doi/10.1177/0890334420959292?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed&

> COVID-19 has disrupted families' access to perinatal care services, including breastfeeding education and lactation support.

> Ready, Set, BABY (R.S.B.) Live is a free online interactive education class taught by graduate lactation students with assistance from International Board Certified Lactation Consultants (IBCLC).

- It offers education for pregnancy/postpartum care, reflects updated breastfeeding guidelines, and includes COVID-19 guidance and recommendations.
- It is adapted from the R.S.B. open-access curriculum created by the Carolina Global Breastfeeding Institute (CGBI) in 2012.

> R.S.B. Live is hosted on a secure virtual teleconferencing platform that is HIPPA-compliant.

- R.S.B. Live is offered in English and Spanish.
- The platform supports both verbal and written interactions.
- It is primarily designed for a US-based audience, but participants from other countries can also join.

> R.S.B. Live has two purposes in the pandemic:

1. Education resource for expectant parents.
2. Clinical training opportunity for students in the CGBI training program who need clinical hours to register for the 2020 IBCLC examination.

Reviewed by: Professor Suzanne Garland

SCHOOLS

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

Considerations for school-related public health measures in the context of COVID-19
https://apps.who.int/iris/bitstream/handle/10665/332052/WHO-2019-nCoV-Adjusting_PH_measures-Schools-2020.1-eng.pdf?sequence=1&isAllowed=y

> An Annex by the World Health Organization regarding minimising the risk of COVID-19 to students and staff in the educational setting for children <18 years old.

> Principles underlying considerations for school-related public health measures:

  – Ensuring safe, adequate and appropriate educational and social learning and development of children.

  – Minimise SARS-CoV-2 transmission risk and prevent schools from being amplifiers of transmission.

  – Ensure school-related public health and social measures (PHSM) are integrated and supported at the community level.

> COVID-19 appears to have limited direct burden on children's health compared to school closures; as such, closure of educational facilities should only be considered when there is community transmission in an area.

> Multi-layered measures to prevent SARS-CoV-2 transmission in the educational setting at the community, school, classroom and individual level.

> Ongoing adherence to PHSM in the education setting including physical distancing between groups and individuals (<12 years not required to adhere at all times depending on risk), use of masks (<5 years excluded; 6-11 years based on risk), adequate ventilation, personal hygiene, environmental cleaning, and screening and management of sick students and staff.

> Ensure open communication with guardians of school children outlining PHSM in place and to counter misleading information in addition to explaining to students the reasoning for school-related measures.

> Maintain school-based and school-linked health services, health promotion, school feeding, care and support services where possible and support remote learning when in-person classes are not possible.

> Monitoring of potential and current risk of transmission, the effect of policies and measures on the educational learning outcomes and health of students, staff and families, and the trend in dropouts after lifting of restrictions.

Reviewed by: Professor Sharon Goldfeld

Victoria Ivankovic - 3rd Year Medical Student, University of Ottawa

It's time to put children and young people first during the global COVID-19 pandemic
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2771180

> Children have been relatively spared from the effect of clinical COVID-19, but there is significant uncertainty regarding children and young people's ability to catch, transmit, and spread the virus.

> A previous meta-analysis (Viner et al.) revealed a significantly lower proportion of children acquiring the infection than adults within the household - these data suggest young children (<12-14yrs) are less than half as likely to develop an infection with SARS-CoV-2) than adults are given an equivalent exposure.

> How infectious children are once they have acquired SARS-CoV-2 remains unclear, studies into the precise role of transmission in schools are ongoing.

> How governments make decisions regarding when and how to open schools and keep them open, must avoid politicisation and reductionism of the debate - children cannot be used as a political ploy, and all leaders have a responsibility to focus on children and young people's well-being and long-term future.

Reviewed by: Dr Wonie Uahwatanasakul

Benjamin Watson - 4th Year Medical Student, University of Melbourne

Variation in SARS-CoV-2 seroprevalence in school-children across districts, schools and classes (not peer reviewed)
https;//medrxiv.org/content/10.1101/2020.09.18.20191254v1

> The objective of this study was to determine the variation in SARS-CoV-2 seroprevalence in school children across districts, schools, grades, and classes, and the relationship of SARS-CoV-2 seroprevalence with self-reported symptoms.

> This study performed a cross-sectional analysis of baseline measurements of a longitudinal cohort study (Ciao Corona) from June-July 2020:

- 55 randomly selected schools and classes stratified by district in the canton of Zurich, Switzerland (1.5 million inhabitants).
- Children, aged 6-16 years old, attending grades 1-2, 4-5 and 7-8.
- Exposure to circulating SARS-CoV-2 between February and June 2020 including public lock-down and school closure (16th March to 10th May, 2020).
- In total, 55 schools and 2585 children were recruited (1337 girls, median age 11, age range 6-16 years).

> Results:

- Overall seroprevalence was 2.8 % (95% CI 1.6-4.1%), ranging from 1.0% to 4.5% across districts.
- Seroprevalence was 3.8% in grades 1-2, 2.5% in grades 4-5, and 1.5% in grades 7-8.
- At least one case was present in 36/55 tested schools and in 43/128 classes with ≥50% participation rate and ≥5 children tested.

- 73% of children reported COVID-19 compatible symptoms since January 2020, but none were reported more frequently in seropositive compared to seronegative children.
- Seroprevalence of children was very similar to seroprevalence of randomly selected adults in the same region in June-July 2020, measured with the same Corona Immunitas test, combining IgG and IgA (3.1%, 95% CI 1.4-5.4%, versus 3.3%, 95% CI 1.4-5.5%).

> Thus, seroprevalence was inversely related to age with younger children having a higher seroprevalence, though no difference in reported symptomatology between seropositive or negative children.

Reviewed by: Dr Wonie Uahwatanasakul

THERAPEUTICS

Daniel Lamanna - 3rd Year Medical Student,
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Statins reduce COVID-19 severity, Likely by removing cholesterol that virus uses to infect
https://www.universityofcalifornia.edu/news/statins-reduce-covid-19-severity-likely-removing-cholesterol-virus-uses-infect

> The current standard of care for COVID-19 is fluids and fever-reducing medications - there are currently no F.D.A. approved treatments for COVID-19.

> To speed the search for COVID-19 therapies, researchers are testing repurposed drugs for their abilities to mitigate the virus.

> U.C. San Diego reports that statins are associated with reduced risk of developing severe COVID-19 disease, as well as faster recovery times - it is proposed that the statins role in removing cholesterol from cell membranes prevents the Coronavirus from getting in.

> It was discovered in previous literature that SARS-CoV2 uses ACE2 receptor to enter lung cells and establish respiratory infection.

> The study conducted by Daniels & Messer et al. analysed medical records of 170 patients with COVID-19 and 5281 COVID negative control patients

> Data points included: disease severity, length of stay, outcome, use of statins, angiotensin-converting enzyme (A.C.E.) inhibitors, and angiotensin II receptor blockers (A.R.B.s) within 30 days prior to admission.

> 27% of COVID patients were actively taking statins on admission, 21% were taking A.C.E. inhibitors, 12% were on an A.R.B.

> Researchers found that statin use prior to hospital admission for COVID-19 was associated with more than a 50% reduction in risk of developing severe COVID-19 compared to those with COVID-19 but not taking statins.

> Patients taking statins also recovered faster than those who were not.

> It was concluded that statins are potentially protective by inhibiting SARS-CoV2 infection through its known anti-inflammatory effects and binding capabilities that could potentially stop the progression of the virus - draining cholesterol from cell membranes blocks SARS-CoV2 entry.

> Furthermore, a study conducted by Rana et al. examined the effects of depleting cholesterol using an enzymatic pathway that requires 25-hydroxycholesterol (25HC), to activate an enzyme called ACAT, which then depletes accessible cholesterol on the cells membrane.

  – Adding 25HC to cells inhibited the ability for the virus to enter cells, blocking infection almost completely.

- 25HC is currently not approved for human use - it is a natural product restricted for laboratory work.
- This research team plans to continue to optimise 25HC as a potential antiviral agent; however, many steps remain before it can be tested in human clinical trials.

Reviewed by: Dr Wonie Uahwatanasakul

TRANSMISSION

Chan Ying Zhen Charissa - 3rd Year Medical Student,
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Transmission of severe acute respiratory syndrome coronavirus 2 during long flight
https://wwwnc.cdc.gov/eid/article/26/11/20-3299_article

> Epidemiologic investigation of 16 crews and 201 passengers on a 10-hour commercial flight from London, the U.K. to Hanoi, Vietnam on 2nd March 2020 was conducted with intensive tracing and testing, in order to estimate the probability of transmission and the associated risk factors.

> Prevention background for air travel on 2nd March 2020.

- Use of face masks on board were not required at the time.
- All passengers body temperature were screened by thermal imaging.
- Only passengers arriving from China, South Korea, Iran or Italy required to undergo SARS-CoV-2 testing and a 14-day quarantine.

> Flight setting and the suspected index case: 21 passengers occupied business (75% seats occupied), 35 premium economy (100%), and 145 economy (67%) seats. The suspected index case was a 27 years old woman, seated in the business cabin and had experienced a sore throat and cough 24 hours before attending the flight. She continued to develop more symptoms and sought care 3-days after her arrival at a local hospital in Hanoi where SARS-CoV-2 confirmation by PCR was conducted. All 16 (100%) of the flight crew and 168 (84%) of the passengers who remained in Vietnam had been traced, tested for SARS-CoV-2. All close-contacts (<2 metre distance for >15 minutes) with the passengers on this flight were also asked to be quarantined for 14 days regardless of the PCR results; 33 (16%) passengers had already transited to other countries.

> Results:

- 16 persons with SARS-CoV-2 detected, including the suspected index case. 12 (80%) in business class and two travellers and one flight attendant had been in economy class 12. The attack rate among business class cases was 62% (13/21).
- Seating proximity (<2 metres) strongly associated with increased infection risk (RR 7.3, 95% CI 1.2–46.2).
- 8/12 (67%) cases in business class subsequently developed symptoms; median symptom onset was 8.8 days (interquartile range 5.8–13.5) after arrival. None of these cases had COVID-19 symptoms on the flight.

> Conclusion: Most likely route of transmission during flight is aerosol or droplet transmission, particularly for persons seated in business class.

> Limitations: No genomic sequences data to support the hypothesis of in-flight transmission. Lack of detailed data on activities of cases while onboard (e.g. movements, seat changes, use of toilets, sharing meals). Passengers' pre-flight exposure to other confirmed cases relied on interviews only. No data on individual passenger use of face masks. No environmental samples could be collected from the aeroplane.

> Implications to Vietnam policy: mandatory testing at arrival irrespective of departure location and 14-day quarantine irrespective of a test result or clinical signs/symptoms have been implicated immediately after this outbreak investigation.

Reviewed by: Dr Lien Anh Ha Do

VACCINES

Daniel Lamanna - 4th Year Medical Student,
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Warp speed for COVID-19 vaccines: why are children stuck in neutral?
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1425/5908283

The direct effects of COVID-19 on the paediatric population is greater than that observed for a variety of other pathogens for which there are effective vaccines. The role of children and SARS-CoV-2 transmission seems to be underappreciated - carefully conducted phase II clinical trials can adequately assess potential COVID-19 vaccine safety concerns. Delays in vaccine trials will subsequently delay our recovery from COVID-19 with impacts on child health, education, and emotional well-being.

> During this time of adult phase III clinical trials, paediatric phase II trials to monitor safety and immunogenicity should be conducted in parallel rather than waiting until adult vaccine efficacy is determined.

> The potential direct benefits of safe and effective paediatric vaccine.

- Dramatic reduction in paediatric hospitalisations, especially in those ethnic groups of Hispanics and Blacks with a disproportionately higher rates of hospitalisation and Multisystem Inflammatory Syndrome in Children (MIS-C).
- The anticipated persistence of SARS-CoV-2 and the associated burden on the health-care system also supports vaccine development.
- Allows for a safer return to school which is an important factor in enabling children to achieve their maximum potential and engage in extracurricular activity which is important for their emotional and psychological development.

> The potential indirect benefits of a safe and effective paediatric vaccine.

- The potential for indirect benefit is reliant on the ability of the vaccine to prevent viral transmission to the unvaccinated population; recent primate data has demonstrated a reduction of both disease and viral titres in the nose. Such non-human primate SARS-CoV-2 challenge data in conjunction with high neutralising antibodies recognise in early human trials support the possibility of the indirect benefit of vaccination.

> Addressing COVID-19 vaccine safety concerns in children.

- When looking at reactogenicity in adult vaccines, there are both local (pain, redness, swelling, induration) and systemic (fever, chills, myalgia) symptoms to consider. Of note, reactogenicity is self-limiting, treatable, and is a reflection of a typical innate immune response to antigen exposure.
- All vaccines have the potential for unknown and unlikely safety issues, and the potential benefit and risk profiles must always be considered.

  - Particular safety concern of note is the potential for the initiation of MIS-C, which frequently presents weeks after the initial infection. It is suspected this results from an immune-mediated injury triggered by the virus. The subsequent viremia that is expected in COVID-19 infection and the response of patients to brief courses of steroids suggest that the response may be due to immunological recognition of viral antigens or live virus rather than the triggering of an autoimmune condition.

> There are only 3 phase I or II and 1 phase II/III paediatric vaccine trial with the Oxford vaccine underway and no phase III only trials in children - more paediatric trials need to be conducted.

Reviewed by: Associate Professor Margie Danchin

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

Activate: randomised clinical trial of B.C.G. vaccination against infection in the elderly
https://www.sciencedirect.com/science/article/pii/S0092867420311399

> Whilst this study began in 2017 and is ongoing, this interim analysis is relevant to the COVID-19 pandemic.

> ACTIVATE is a phase III, double-blind, placebo-controlled randomised clinical trial which assesses the role of B.C.G. in protecting those over 65 years of age against non-Tuberculosis infections.

> Participants of a mean age of 80 years old were vaccinated on discharge from hospital.

> At 12 months of follow-up, those vaccinated with B.C.G. experienced a 79% reduction in the incidence of respiratory infections of probable viral origin, a 45% reduction in the incidence of all infections and delayed the time until next infection (16 versus 11 weeks) compared to placebo.

> Sensitivity and stepwise Cox regression analyses are also presented, and in a sub-group, the protective effect of B.C.G. was associated with cytokine production changes in monocytes.

> B.C.G. was safe when compared to placebo, and there was no difference in the frequency of adverse effects found.

> These findings suggest a role for B.C.G. in protecting the elderly against viral respiratory tract infections.

> The study concluded more extensive studies which focus on the role of B.C.G. in protecting against COVID-19 are needed.

Reviewed by: Associate Professor Margie Danchin

VIROLOGY

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

Free fatty acid binding pocket in the locked structure of SARS-CoV-2 spike protein
https://science.sciencemag.org/content/early/2020/09/18/science.abd3255

> The authors conducted a series of preclinical experiments determining biochemical features of the SARS-CoV-2 spike (S) glycoprotein and its receptor-binding domains (RBDs) through cryo-electron microscopy at 2.85 angstrom resolution. This was produced as a secreted trimer, in MultiBac baculovirus-infected Hi5 insect cells, with mild differences from the native, in vivo S glycoprotein.

> In doing so, they discovered a pocket on the receptor-binding domain which tightly binds to linoleic acid (L.A.), an extremely common free fatty acid which persists throughout nature and is involved in lipid and arachidonic acid metabolism. The identity of L.A. was confirmed through separation using liquid chromatography .coupled with mass spectrometry analysis (ESI-TOF).

> As linoleic acid takes a 3D form of an extended "greasy" alkyl chain with an anionic head, the cryo-EM determined structure in these experiments agreed well with structural motifs aligned with L.A. binding; a neatly chapped series of hydrophobic phenylalanine captured the alkyl chain of the fat, and the anchor for the head group carboxyl was provided by arginine and glutamine.

> The presence of L.A. was confirmed in all three binding pockets in the S protein. This S protein is modified compared to in vivo SARS-CoV-2 S protein, due to the addition of a trimerisation domain and deletion of a polybasic cleavage site, but these alterations do not alter the structure of S in an appreciable way.

> In considering glycosylation susceptibility, the authors report that glycosylation sites are far away from the LA-binding pocket, and thus unlikely to impact the binding of S and L.A.

> The authors compared their insect-derived S and RBD in an ELISA immunosorbent binding assay which demonstrated effective binding of ACE2 at levels similar to a mammalian cell produced S

> SARS-CoV-2 S can adopt an open conformation; previous cryo-EM structures have found about 60-75% of the S adopts an open conformation, which contrasts the authors' findings of 70% in the closed conformation, Surface plasmon resonance experiments demonstrated a reduced signal for LA-bound S as compared to Apo S at the same concentrations (obtained by applying Lipidex to generate the apo S): this correlates with the apo state having a higher percentage of S trimers in the open, ACE2-accessible conformation.

> In addition to surface plasmon resonance studies, computational studies as repeated molecular dynamics simulations of the entire LA-bound spike trimer (locked) using GROMACS-2019 corroborated the persistence of stable interactions between L.A. and the spike trimer. Computational studies further suggested that the slow off-rate observed with the RBD monomer could be maintained when the S trimer transiently converts to the open conformation, given that L.A. was retained during S purification in spite of S trimers adopting the open form 30% of the time, and by molecular dynamics simulations modelling a ligand-bound open spike tetramer in which all three L.A.s remain bound over 500 ns.

> In vitro experiments of human-derived SARS-CoV-2 virus demonstrates L.A. supplementation had a synergistic effect with remdesivir in suppressing SARS-CoV-2 replication.

> Superimposition of the authors LA-bound structure on previous SARS-CoV-2 S structures in the closed conformation revealed a gating helix located next to the binding pocket, which results in a compacted trimer arrangement, locked down over the head group of L.A., in the region formed by the RBDs that give rise to a locked S structure.

> Additional investigations revealed the LA-binding pocket is conserved in all SARS-CoV including the other six coronaviruses which infect humans. The greasy tube with its hydrophilic anchor point appears to be present in MERS-CoV, suggesting convergent evolution.

> In summary, there are four molecular features which mediate L.A. binding to SARS-CoV-2 and its S protein; a conserved hydrophobic pocket, a gating helix, amino acid residues in suitable places for binding the LA-head group, and loosely packed RBDs in the apo form.

> In each of the four common circulating human coronaviruses, one or more of these four architectural prerequisites is missing the S protein structures.

> L.A. binding to SARS-CoV-2 S triggers a locking down of the hydrophilic anchor, compaction of the RBD trimer. In addition to stabilising the closed conformation, this may stabilise the S1 region (including N-terminal) and maintain the RBD and its receptor binding motif (R.B.M.), central to ACE2 binding, which has implications in ACE2 docking.

> In summary, detailed biochemical understanding of the interactions between the apo SARS-CoV-2 S protein lipid-binding motifs provides useful insight into the factors determining ACE2 binding and cellular invasion.

> Finally, the authors hypothesise that L.A. sequestration by SARS-CoV-2 could drive a tissue-independent mechanism by which pathogenic coronaviruses may drive immune and lipid dysregulation and inflammation.

Reviewed by: Dr Celeste Donato

OTHER RESOURCES

All COVID-19 literature
https://www.ncbi.nlm.nih.gov/research/coronavirus/

A pandemic primer on excess mortality statistics and their comparability across countries
https://ourworldindata.org/covid-excess-mortality

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

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

Burnet Institute research findings, policy and technical reports
https://www.burnet.edu.au/covid-19//36_know_c19_hub

COVID-19 and the kidney, currently the recommended U.S. resource
http://www.nephjc.com/covid19

Daily updates on COVID-19 literature compiled by Canadian medical students
https://docs.google.com/forms/u/0/d/e/1FAIpQLSfOxCoAuLV0aJdf_z2uWV7r3FaPzAOr86q9ZXBcTZ1QcCE_Nw/formResponse

Focuses on paediatric clinical, epidemiological, transmission and neonatal aspects
https://dontforgetthebubbles.com/evidence-summary-paediatric-covid-19-literature/

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/

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

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

National COVID-19 clinical evidence taskforce: continually updated evidence-based clinical guidelines
https://covid19evidence.net.au/

Oxford COVID-19 Evidence Service
https://www.cebm.net/oxford-covid-19/

Public Health England COVID-19 Rapid Reviewed - Knowledge & Library Service
https://phelibrary.koha-ptfs.co.uk/covid19rapidreviews/

Retracted coronavirus (COVID-19) papers
https://retractionwatch.com/retracted-coronavirus-covid-19-papers/

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/

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

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

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

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