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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.25

8th October 2020



BE COVIDSAFE

CURRENT STATUS OF CONFIRMED CASES



5

CURRENT CASES INTENSIVE CARE UNITS (ICU)

ACT	NSW	NT	QLD	SA	TAS	VIC	WA
0	3	0	1	0	0	1	0

37

CURRENT CASES ADMITTED TO HOSPITALS

ACT	NSW	NT	QLD	SA	TAS	VIC	WA
0	10	0	6	0	0	21	0

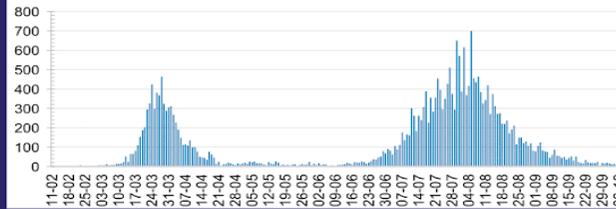
7,819,472

0.3% POSITIVE

TOTAL TESTS CONDUCTED

ACT	NSW	NT	QLD
96,263	2,751,929	49,696	1,133,933
POSITIVE	POSITIVE	POSITIVE	POSITIVE
0.1%	0.2%	0.1%	0.1%
SA	TAS	VIC	WA
483,142	106,374	2,763,802	434,333
POSITIVE	POSITIVE	POSITIVE	POSITIVE
0.1%	0.2%	0.7%	0.2%

DAILY NUMBER OF REPORTED CASES

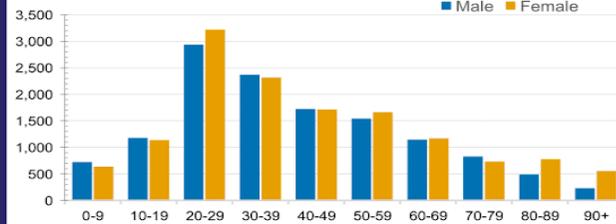


CASES IN AGED CARE SERVICES

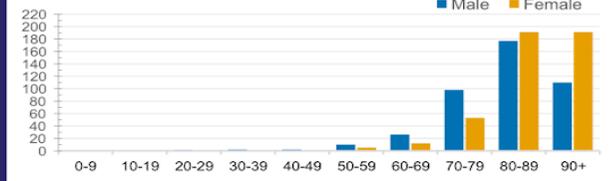
Confirmed Cases	Australia	ACT	NSW	NT	QLD	SA	TAS	VIC	WA
Residential Care Recipients	2050 [1344]	0	61 [33] (28)	0	1 (1)	0	1 (1)	1987 [1311]	0
In Home Care Recipients	82 [72]	0	13 [13]	0	8 [8]	1 [1]	5 [3]	54 [47]	1 (1)

Cases in care recipients [recovered] (deaths)

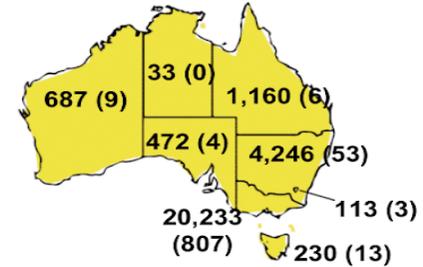
CASES BY AGE GROUP AND SEX



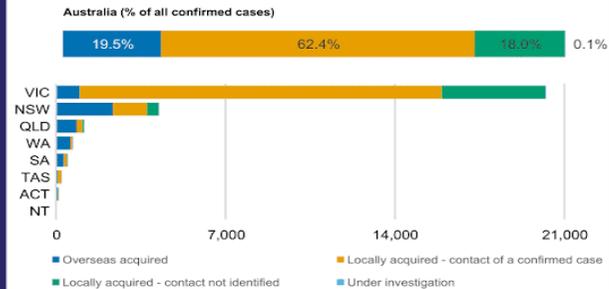
DEATHS BY AGE GROUP AND SEX



CASES (DEATHS) BY STATE AND TERRITORIES



CASES BY SOURCE OF INFECTION



PUBLIC HEALTH RESPONSE MEASURE



Last updated 6 October 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 October 6; cited 2020 October 7]. Available from: <https://www.health.gov.au/resources/collections/coronavirus-covid-19-at-a-glance-infographic-collection>

GUEST EDITORIAL

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

On the second day of the tenth month living with the SARS-CoV-2 pandemic, the whole world has been again shocked by a déjà vu, but this time from the most powerful man on Earth: US President Donald Trump. President Trump, the First Lady and a number of senior staff in the US government have tested positive for the virus. Given a (should-be) strict security tracing/checking as well as (maybe) intense screening tests which should be implemented for this special cluster before the outbreak, this outbreak would be a very interesting to report to provide learning points on SARS-CoV-2 transmission and infection control. Most likely, this report will never be written. Instead, the most recent research data including the herd immunity and re-infections of SARS-CoV-2 (although in pre-print form) covered in this 25th edition of the Weekly may stimulate us to think how can we live safely with SARS-CoV-2, while an effective and safe vaccine is not yet available.

A sensitive, rapid test with an easy and comfortable sample collection is not the complete answer for an effective COVID-19 safe plan, but it is surely is one of the critical, necessary factors of the strategy to get people back to work, and to return children to school, safely.

To et al. from State Key Laboratory for Emerging Infectious Diseases in Hong Kong, was the first group to report saliva for the use in initial diagnosis and subsequently monitoring SARS-CoV-2 load (1). Since February, early in the pandemic, the Hong Kong government has used this approach for screening SARS-CoV-2 in adults, and in children since March (2). In April, Wyllie et al. from Yale School, US, released their pre-print about the performance of saliva in SARS-CoV-2 diagnostics. Their study was later [published in NEJM](#) in September and is covered in this 25th Weekly ([Diagnostics & Sampling](#)). Wyllie's study, together with a number of publications from different settings and countries, highlighted the high sensitivity of saliva specimens compared with nasopharyngeal swab (NPS) specimens in the detection of SARS-CoV-2 during the course of infection (3, 4). Until now, five saliva-based molecular assays using PCR or LAMP platform received FDA emergency use authorisations, but no rapid, saliva-based antigen assay has been developed. In contrast, 47 and 225 commercial, rapid, NPS-based antigen and serum-based antibody assays, respectively, have been submitted for evaluation by FIND, a WHO Collaborating Centre for Laboratory Strengthening and Diagnostic Technology Evaluation (5). The current trend of test kit development should be shifted to saliva-based tests, given the promising diagnostic value of saliva and importantly increasing information on SARS-CoV-2 airborne transmission through saliva (6). We should consider what information is needed from a diagnostic assay of SARS-CoV-2 to enable more rapid and effective investigations of outbreaks.

Having a "Positive/Negative" result seems insufficient for epidemiologists and infectious diseases physicians. Understanding how contagious patients are when people get infected and how long people have been infected are crucial pieces of information for effective outbreak responses. SARS-CoV-2 is an unusual respiratory virus, certainly unlike influenza. SARS-CoV-2 has a long incubation period and the viral load peaks prior to symptom onset.

In the 25th Weekly – [Virology](#), a systematic review by Benefield et al. on 66 studies in 14 countries confirmed SARS-CoV-2 load peaks before symptom onset and remained elevated for up to three weeks after onset. This shedding pattern is different from those of MERS and SARS-CoV-1 and contributes to the transmission speed of the virus. Benefield et al.'s study has raised the alarm regarding the mitigation strategy based only on screening symptomatic people.

Dr Sophie Vankenburg from the Hong Kong Pasteur Institute, presented at the WHO Solidarity Meeting on 2nd October 2020 and showed interesting data on the kinetics of viral proteins expressed during the course of infection (personal note). ORF8, N and ORF3 viral proteins were found to be expressed early and consistently during the infection course. The sensitivity of diagnostic assay depends strongly on the chosen viral target. The majority of current rapid, antigen and antibody tests have targeted either S or N protein. Combinations of different viral proteins or a combination of both antigen and antibody detection into one test will be the next level of new diagnostic assays. This combination would increase the sensitivity of the diagnostic test and would provide additional information on the timeline of the natural infection course, e.g. the timing of the contact with an index case.

As discussed in Cevik et al.'s viewpoint ([Transmission](#)) understanding transmission dynamics can inform an effective mitigation strategy, and the timing of contact with an index case is a key factor influencing the transmission dynamics. Of note, rapid identification of infectious cases seems insufficient, as no test can identify 100% of potential infections (the White House outbreak is a good example). Cevik et al. clearly showed the presence of any of the three Cs as identified early in the pandemic by the Japanese government (closed-spaces, crowded places, and close-contact settings) can spark a new outbreak. Interrupting the three Cs is a must for COVID-19 transmission reduction policy implementation. Karaivanov et al. ([Global Health](#)) presented convincing data on the impact of interrupting the three Cs through Canadian government policies, including mask mandates and other non-pharmaceutical interventions (NPI) (e.g., business regulations on businesses and gatherings, school closures, travel and self-isolation). The analysis showed mask mandates are associated with an approximate reduction of 31% in weekly COVID-19 cases. Indoor mask mandates can be a powerful preventative measure.

However, in certain countries, mandatory masks and other NPIs are not always implemented easily. The same countries tend to rely on herd immunity through natural SARS-CoV-2 infections, although this is an unlikely achievement. Brazil is adopting this strategy. But it is unclear what percentage of a population must be infected with SARS-CoV-2 before herd immunity is reached and so far there is very little indication that this is at all achievable. Moreover, Buss et al. (and other studies) showed that antibody levels declined over time. This leads to the million-dollar question - "what level of antibodies is required to be protective?" - the answer is unknown and needs a global effort on harmonising standard use of antibody assays and reference sera. Currently, this effort is led by the WHO Solidarity II group.

The herd immunity role in reducing SARS-CoV-2 transmission can be challenged by recent reports on re-infection cases, although these events are rare. Two reports of re-infection have been published, one case from Hong Kong and two from health care workers in India ([Adult Medicine](#)). The three cases were re-infected by genetically distinct SARS-CoV-2 strains compared with the first infection. The authors of the two reports were concerned about the possibility of antibody escape from the mutations of these SARS-CoV-2 strains. Many evolutionary virologists and immunologists work together to monitor SARS-CoV-2 evolution and monitor this issue (7).

Over the past ten months of the COVID-19 pandemic, we have witnessed heavy disruption to infectious disease prevention and health programs, such as vaccination, in many countries. More than 100 million children globally are now at risk of measles infection. However, with the NPIs, such as lockdowns, first time ever, no measles cases have been reported in Ho Chi Minh City, Vietnam, and all hospitalisations associated with acute respiratory infections (ARI) have been reduced by at least one third (data before 21st September 2020, personal communication). This phenomenon has been observed in Sydney Children's Hospitals Network, Australia, specifically, ARI associated with respiratory syncytial virus (RSV) infections (Britton et al., [Epidemiology & Public Health](#)). Will this golden opportunity to eradicate measles with intense vaccination catch on globally? Will the opportunity to examine the potential causal impact of RSV on asthma be taken up, as there is a rare, large cohort of infants who are unexposed to RSV during their first year of life?

I feel optimistic reading the review from Prof Florian Krammer ([Vaccines](#)) on SARS-CoV-2 vaccine development. Prof Krammer gave me some hope, as he believes an effective, safe vaccine might become available within months rather than years, based on available data of phase I/II of 6 leading vaccine candidates (Sinovac's CoronaVac, CanSino's AdV5-based vaccine, AstraZeneca's ChAdOxCoV-19, Moderna's mRNA-1273, Pfizer BNT162b1 and 162b2, Novavax' NVX-CoV2373).

Under intense public pressure for a vaccine, and politicisation of vaccine development efforts, trade-offs between safety, effectiveness, and availability may occur. But what will the future be, when only a few vaccines are found to be effective and safe? In our group meeting, Professor Kim Mulholland asked us to vote which vaccine we want to receive. Most voted for Moderna's vaccine (no conflicts of interests to be declared). Our group has people from different places where maybe different SARS-CoV-2 vaccines will be distributed. We hope all vaccines will have similar safety and effectiveness profiles, and that they will be freely accessible to everyone in the world. This may be a big dream - but being scientists, we are already the professional dreamers.

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2. RTHK: English news. Saliva tests for COVID-19 could also cover children [Internet]. [2020 27th February; cited 2020 6th October]. Available from: <https://news.rthk.hk/rthk/en/component/k2/1511249-20200227.htm>
3. Azzi L, Carcano G, Gianfagna F, et al. saliva is a reliable tool to detect SARS-CoV-2. J Infect. 2020 Jul;81(1):e45-e50. doi: 10.1016/j.jinf.2020.04.005. Epub 2020 14th April. PMID: 32298676; PMCID: PMC7194805.
4. Chau N.V.V., Thanh Lam V, Thanh Dung N, et al; OUCRU COVID-19 research group. [The natural history and transmission potential of asymptomatic SARS-CoV-2 infection](#). Clin Infect Dis. 2020 Jun 4:ciaa711. doi: 10.1093/cid/ciaa711. Epub ahead of print. PMID: 32497212; PMCID: PMC7314145.
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6. The National Academies of Sciences, Engineering, Medicine. Airborne transmission of SARS-CoV-2: a virtual workshop. [Internet] [2020 August 26-27; cited 2020 October 6]. Available from: <https://www.nationalacademies.org/event/08-26-2020/airborne-transmission-of-sars-cov-2-a-virtual-workshop>
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HIGHLIGHTS

- > Given the potential direct and indirect benefits of COVID-19 vaccination for children, Phase II paediatric vaccine clinical trials should start now.
- > Analysis trends in weekly COVID-19 incidence during 1st March to 19th September 2020 among 277,285 laboratory-confirmed cases in school-aged children in the United States found more infections in adolescents compared to younger children.
- > Dried blood spot samples can be used for the detection of SARS-CoV-2-specific antibodies with results comparable to serum samples.
- > Saliva specimens and nasopharyngeal swab specimens have similar sensitivity in the detection of SARS-CoV-2.
- > Fabric face masks have varying efficiency in blocking ultrafine particles at coughing velocity, and the best fabrics are those that block high proportions of particles with low breathing resistance: felted wool, quilting cotton, and cotton flannel.
- > A European report for non-pharmacological interventions to prevent SARS-CoV-2 transmission suggested the COM-B model for aiding compliance and creating community-wide behavioural change.
- > Re-infection with SARS-CoV-2 (with nine unique variant differences between the virus) has been reported in two asymptomatic healthcare workers in India.
- > The Sydney Children's Hospitals Network reported fewer than expected acute respiratory illness presentations and admissions during the early phase of the COVID-19 pandemic.
- > The current state of vaccine development is reviewed: whilst a vaccine may be available in months, there remain a range of challenges to its effectiveness at protecting the world from COVID-19.
- > Data from contact tracing studies should inform public policies that aim to reduce viral transmission.
- > There is likely a rapid reduction in anti-SARS-CoV-2 antibodies following a mild infection of COVID-19; however, this is debated in the literature, and ongoing research is required.
- > Improving the basics of acute care, including oxygen systems, is an achievable priority for hospitals.
- > Transmission of SARS-CoV-2 infection is determined by a variety of viral, host and environmental factors.
- > A study on the mucosal immune response to SARS-CoV-2 confirms that systemic and mucosal IgG antibodies are maintained in the majority of COVID-19 patients for at least three months post-symptom onset, and thus saliva may serve as a surrogate measure of systemic immunity.
- > A Californian study on employing RT-qPCR of municipal wastewater has been found to be useful in epidemiological surveillance and aiding in tracking exact viral strains.
- > Our evidence for COVID-19 transmission using contact tracing studies has improved - now it's time to see it in the policy.

- > The pandemic shows that sustainable development goes beyond National strategies - every individual needs to make health decisions that meet personal needs, as well as the needs of the broader community (such as wearing a facemask, observing social distancing, self-quarantining when necessary.)
- > Follow-up testing should be performed more than 34 days from the first positive swab to reduce the false-negative rate.
- > The CDC reports that during June to August, the pandemic affected a larger proportion of younger persons than during January to May; this trend was true for all four US census regions, regardless of changes in incidence during this period.
- > According to the REACT-1 September report, the reproduction rate for 20th August to 26th September 2020 was estimated to be 1.47, slightly lower than that measured during August (1.7).

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ADULT MEDICINE

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

Asymptomatic re-infection in two healthcare workers from India with genetically distinct SARS-CoV-2

<https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1451/5910388>

- > There have been previous reports of genetically characterised SARS-CoV-2 re-infection. In all of these reports, patients were symptomatic in one or both episodes.
- > This manuscript reports two cases of genetically characterised re-infection wherein both patients were asymptomatic for both episodes. The patients were healthcare workers, and infection was detected upon routine screening.
- > One individual was a 25-year-old male healthcare worker.
 - The first incidence of infection was detected on 5th May 2020 by RT-PCR, and the patient was confirmed SARS-CoV-2 negative on 13th May 2020.
 - The second incidence of infection was detected on 21st August 2020 by RT-PCR, and the patient was confirmed SARS-CoV-2 negative on 4th September 2020.
 - Analysis of both SARS-CoV-2 genomes revealed nine unique variant differences between the virus isolates from the two episodes of infection.
 - Seven variants mapped to predicted immune epitopes.
- > One individual was a 28-year-old female healthcare worker.
 - The first incidence of infection was detected on 17th May 2020 by RT-PCR, and the patient was confirmed SARS-CoV-2 negative on 27th May 2020.
 - The second incidence of infection was detected on 5th September 2020 by RT-PCR, and the patient was confirmed SARS-CoV-2 negative on 11th September 2020.
 - Analysis of both SARS-CoV-2 genomes revealed ten unique variant differences between the virus isolates from the two episodes of infection.
 - Seven variants mapped to predicted immune epitopes.
- > Both patients had a higher viral load on the second episode of infection.
- > This report highlights the possibility of undetected asymptomatic SARS-CoV-2 re-infections, as well as the need for routine surveillance for re-infections in healthcare workers.
- > There have been several reports of recurrent infection where the second strain can be distinguished from the first using genomic analyses.
- > Given the intense transmission in many countries, this appears to be an uncommon event but highlights that immunity following infection may not be complete and/or may wane over time.

Reviewed by: Professor Allen Cheng

DIAGNOSTICS & SAMPLING

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

Performance characteristics of five immunoassays for SARS-CoV-2: a head-to-head benchmark comparison

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30634-4/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30634-4/fulltext)

- > Global interest exists in the use of serology for population-level surveillance of SARS-CoV-2 infection and to inform individual-level management and risk stratification.
- > The urgent demand for serological testing with few data available has led to a relaxation of typical assessment criteria (FDA Emergency Use Authorisation programme) with several assays obtaining regulatory approvals for emergency use in the USA and EU.
- > It is unclear which of the commercially available assays perform to the standards required to inform public health policy during the pandemic.
- > Aim: To investigate the performance of five immunoassays: four high-throughput commercial SARS-CoV-2 antibody immunoassays and a novel 384-well ELISA.
- > Methods: The study did a head-to-head assessment of SARS-CoV-2 IgG assay (Abbott, U.S.A.), LIAISON SARS-CoV-2 S1/S2 IgG assay (DiaSorin, Italy), Elecsys Anti-SARS-CoV-2 assay (Roche, Switzerland), SARS-CoV-2 Total assay (Siemens, Germany), a novel 384-well ELISA (the Oxford immunoassay).
 - Sensitivity and specificity derived from:
 - 976 pre-pandemic blood samples from adult (>18 years) patients (collected Sep 2014 - Oct 2016).
 - 536 samples from adult (>18 years) patients with laboratory-confirmed SARS-CoV-2 infection >20 days post symptom onset (collected Feb-May 2020).
 - Three known high-volume plasma samples obtained from SARS-CoV-2 positive patients with high, medium and low titre SARS-CoV-2 IgG antibodies as assessed by the SARS-CoV-2 IgG ELISA (EUROIMMUN, Germany).
 - ROC curves used to assess assay thresholds
- > Results:
 - Abbott assay: sensitivity 92.7% (95% CI 90.2–94.8), specificity 99.9% (99.4–100%).
 - DiaSorin assay: sensitivity 95.0% (92.8–96.7); specificity 98.7% (97.7–99.3).
 - Roche assay: sensitivity was 97.2% (95.4–98.4); specificity was 99.8% (99.3–100).

- Siemens assay: sensitivity was 98.1% (96.6–99.1); specificity was 99.9% (99.4–100%).
- Oxford immunoassay: sensitivity 99.1% (97.8–99.7); specificity 99.0% (98.1–99.5).
- All assays achieved a sensitivity of at least 98% with thresholds optimised to achieve a specificity of at least 98% on samples taken 30 days or more post symptom onset.
- > Four commercial, widely available assays and a scalable 384-well ELISA can be used for SARS-CoV-2 serological testing to achieve sensitivity and specificity of at least 98%.
- > The Siemens assay and Oxford immunoassay achieved these metrics without further optimisation.
- > Differences in observed assay performance translate into thousands of additional incorrect diagnoses between the best and worst-performing assays if used on a population-scale.
- > Although these assays can effectively detect SARS-CoV-2 antibodies, the durability and nature of immunity conferred by these antibodies remain unclear.

Reviewed by: Dr Samantha Bannister

Min Zhang - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Sensitive detection of SARS-CoV-2-specific antibodies in dried blood spot samples

https://wwwnc.cdc.gov/eid/article/26/12/20-3309_article

- > The authors investigate the viability and potential role of using dried blood spot (DBS) sampling for studying SARS-CoV-2 seroprevalence.
- > 87 blood samples from 80 healthy volunteers at the University Hospitals Birmingham N.H.S. Foundation Trust were collected.
 - 31 matched samples were from PCR-positive volunteers, on average, 54 days (SD + 17 days) from reported symptom onset and 45 days (SD + 15 days) from PCR testing.
 - Capillary blood samples were used for DBS collection, while SARS-CoV-2-specific antibody levels were determined by blinded PCR analysis of collected venous blood.
 - Statistical analysis was performed by using Prism 8 to assess correlations using Spearman's rank test.
- > Significant correlation between matched serum and DBS samples ($r = 0.96$ [95% CI 0.93–0.97]; $p < 0.0001$) and minimal differences in results observed by sample type (Bland-Altman bias $0.11 + 0.20$).
 - DBS samples achieved 98.11% sensitivity and 100% specificity for detecting S glycoprotein antibodies relative to serum samples.
- > DBS samples can be used for the detection of SARS-CoV-2-specific antibodies with results comparable to serum samples.
 - This is useful since DBS sampling is simple, inexpensive, and can be self-collected and then sent by postal services to laboratories for processing.

Reviewed by: Dr Wonie Uahwatanasakul

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

Saliva or nasopharyngeal swab specimens for detection of SARS-CoV-2

<https://www.nejm.org/doi/full/10.1056/NEJMc2016359>

- > Rapid and accurate diagnostic tests are crucial for effectively controlling COVID-19 outbreaks. Saliva specimens which are easy to collect by patients may be an alternative sampling approach.
- > This study compared the performance of SARS-CoV-2 detection between saliva specimens (self-collected by patients) and nasopharyngeal (NP) swabs (collected by healthcare workers) over the course of infection in 70 confirmed COVID-19 inpatients. The performance was assessed between self-collected saliva and self-collected NP among 495 asymptomatic health care workers.
- > Same RNA extraction protocol and real-time RT-PCR protocol (from US CDC) were used for both sample types.
- > More SARS-CoV-2 R.N.A. copies were detected in the saliva specimens (mean log copies per millilitre, 5.58) compared to the NP. swab (mean log copies per millilitre, 4.93).
 - At 1 to 5 days after diagnosis, 81% of saliva samples were positive compared to 71% of the NP. swab specimens.
 - A higher percentage of saliva than NP was positive up to ten days after the first confirmed positive.
 - There was less variation of SARS-CoV-2 R.N.A. load in the saliva specimens.
 - There was greater variation in human RNase P cycle threshold values in NP. swabs (SD 2.89) than in saliva specimens (SD 2.49), showing the integrity (quality of samples) of NP was less than saliva.
 - 13 of 495 asymptomatic workers tested positive on saliva specimens. When NP. samples were collected in these 13 workers; only seven specimens tested negative.
- > Conclusion: Saliva specimens have similar sensitivity in the detection of SARS-CoV-2 compared to NP. swabs. Self-collected saliva alleviates demands for supplies of swabs and personal protective equipment.

Reviewed by: Dr Lien Anh Ha Do

EPIDEMIOLOGY & PUBLIC HEALTH

Julian Loo Yong Kee - 3rd Year Medical Student,
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COVID-19 public health measures and respiratory syncytial virus

[https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642\(20\)30307-2/fulltext](https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30307-2/fulltext)

- > The Sydney Children's Hospitals Network (SCHN) reported fewer than expected acute respiratory illness presentations and admissions during the early phase of the COVID-19 pandemic which New South Wales (NSW) was highly effective in controlling.
- > SCHN records analysed from 1st January 2015 to 30th June 2020 for children <16 years.
- > Significantly decreased frequency of respiratory syncytial virus (RSV) detection (94.3% lower), bronchiolitis admission (85.9% lower), and emergency department attendance for acute respiratory illness (70.8% lower) in 2020 compared to previous years.
- > Double the number of RSV testing compared to previous years not accounting for the decrease in detection in 2020.
- > A strong association is shown between RSV disease among children in Sydney, N.S.W. and public health interventions.
- > Limitations: Generalisability due to unique context in NSW; Individual measures were not directly assessed; brief study period.
- > Further research should be undertaken to identify which components of the public health interventions were most effective in preventing RSV in 2020 and may contribute to future primary prevention of seasonal respiratory diseases.

Reviewed by: Dr John Cheek

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

Guidelines for the implementation of non-pharmaceutical interventions against COVID-19

<https://www.ecdc.europa.eu/en/publications-data/covid-19-guidelines-non-pharmaceutical-interventions>

- > These ECDC guidelines detail available options for non-pharmaceutical interventions (NPI) in various epidemiologic scenarios, assess the evidence for their effectiveness and address implementation issues, including potential barriers and facilitators.
- > Considerations in the event of community transmission.
 - They are promoting and facilitating physical distancing.
 - Voluntary self-isolation if experiencing COVID-19 symptoms.

- Advising keeping social circle small (i.e. social bubble).
- They are limiting the size of indoor and outdoor gatherings.
- They are promoting telework where possible.
- Closing selected business that limit the possibility of physical distancing.
- Pro-active school closure is NOT recommended, as there is little evidence that this affects transmission.
- Regular cleaning of indoor spaces, especially in healthcare industries.
- > Considerations in the event of widespread transmission.
 - Stay at home measures are a last resort option.
 - Population-wide testing strategies may be appropriate in local settings with high incidence.
 - Reactive school closure may be necessary due to high absenteeism and operational issues but has little effect on the impact of the epidemic.
- > Most NPI can have a negative impact on general well-being and the functioning of society so their use should be carefully guided by the local epidemiological situation.
- > Addressing NPI compliance
 - The COM-B model system*, which identifies that three factors (capability, opportunity and motivation) are required for behaviour to occur, can be employed to influence behavioural change, i.e. the idea that behavioural change occurs when both the capability and opportunity are present and when the individual concerned is more motivated to adopt that behaviour than any other.

Reviewed by: Dr Wonie Uahwatanasakul

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

**Genome sequencing of sewage detects regionally prevalent SARS-CoV-2 variants
(not peer reviewed)**

<https://www.medrxiv.org/content/10.1101/2020.09.13.20193805v1>

- > SARS-CoV-2 viral genomes are usually sequenced from nasopharyngeal swabs of individual patients to track viral spread.
- > However, meta-transcriptomic sequencing of wastewater can be used to profile the viral genetic diversity across infected communities.
- > This study looked to sequenced RNA directly from sewage collected by municipal utility districts in the San Francisco Bay Area to generate complete and near-complete SARS-CoV-2 genomes.
- > The significant consensus SARS-CoV-2 genotypes detected in the sewage were identical to clinical genomes from the region. Using a pipeline for single nucleotide variant (SNV) calling in a metagenomic context, this study characterised minor SARS-CoV-2 alleles in the wastewater and detected viral genotypes which were found within clinical genomes throughout California.

- > Observed wastewater variants were more similar to local California patient-derived genotypes than they were to those from other regions within the US or globally.
- > Additional variants detected in wastewater have only been identified in genomes from patients sampled outside of CA, indicating that wastewater sequencing can provide evidence for recent introductions of viral lineages before they are detected by local clinical sequencing.
- > Obtaining genomic sequences from wastewater is technically challenging - in this study, sequences were only obtained from 7 of 22 samples.
- > This would be further complicated if multiple strains were present in a single sample.
- > These results demonstrate that surveillance through wastewater sequencing can aid in tracking exact viral strains in an epidemic context and determining the epidemiology of outbreaks.

Reviewed by: Dr Martin Wright and Professor Allen Cheng

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

Changing age distribution of the COVID-19 pandemic – United States, May-August 2020

https://www.cdc.gov/mmwr/volumes/69/wr/mm6939e1.htm?s_cid=mm6939e1_w

- > The CDC examined the change in the age distribution of the COVID-19 pandemic during May to August 2020 for fifty US states using three indicators: COVID-19-like illness-related ED visits, positive SARS-CoV-2 PCR results, and confirmed COVID-19 cases.
- > National case counts, percentage distributions, and estimated incidence of confirmed COVID-19 cases were calculated by ten-year age increments and by month.
- > The median age of confirmed COVID-19 cases decreased from 46 years in May to 37 years in July, and 38 years in August.
 - During June to August, the incidence was highest among adults aged 20-29 years.
- > During June to August, the pandemic affected a larger proportion of younger persons than during January to May; this trend was true for all four US census regions, regardless of changes in incidence during this period, and was reflected in all three study indicators
 - A similar age shift was described in Europe over the same period.
- > This study provides preliminary evidence that younger adults contributed to community transmission of COVID-19 to older adults.
- > The findings have public health implications:
 - Occupational and behavioural factors may put younger adults at higher risk for exposure; younger adults make up larger proportions of frontline workers.
 - Younger adults may be less likely to follow community mitigation strategies.
 - Younger adults with little or no symptoms can unknowingly contribute to pre-symptomatic or asymptomatic transmission to others.

- > Limitations to this report include the:
 - Underestimation of true incidence due to case reporting by state health departments.
 - Batch reporting of historical cases by some states may have led to spikes in median age trend lines.
 - The three included data sources varied in their geographical coverage.
 - Data was analysed at a regional level and in wide age groups which may mask changes at the local level or among smaller age groups.
- > Despite these limitations, consistent trends were observed across the three indicators

Reviewed by: Dr Claire von Mollendorf

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

REACT-1: real-time assessment of community transmission of Coronavirus (COVID-19) in September 2020

<https://www.gov.uk/government/publications/react-1-study-of-coronavirus-transmission-september-2020-results/react-1-real-time-assessment-of-community-transmission-of-coronavirus-covid-19-in-september-2020>

- > The REACT-1 study is a population-based surveillance study that examines levels of SARS-CoV-2 infection in the general population in England by testing over 150,000 participants each month over a two-week period.
- > A randomly selected representative sample of participants are invited to participate. Those who volunteer are sent a swab kit in the post. The swabs are couriered to a lab and analysed using RT-PCR.
- > The preliminary report for round 5 of the study identified 363 positives from 84,610 samples (weighted prevalence 0.55% [0.47%, 0.64%]).
- > The reproduction number for this period of the study (20th August to 26th September 2020) was estimated to be 1.47, slightly lower than that measured during August (which was 1.7).
- > Prevalence of infection increased across all age groups in this round.
- > Highest prevalence of infection was 0.96% (0.68%, 1.36%) in the 18-24 year age group.
- > In volunteers ≥ 65 years, the prevalence increased 7-fold from 0.04% to 0.29% compared to the last report.
- > Asian and Black ethnicity was associated with a higher prevalence of infection - these ethnicities had a two-fold higher rate of infection compared with White participants.
- > Prevalence was highest amongst those who reported classic COVID-19 symptoms (high temperature, new continuous cough, loss of smell or taste).

Reviewed by: Dr Claire von Mollendorf

GLOBAL HEALTH

gage: data collection in COVID-19 restrictions

<https://www.gage.odi.org/multimedia/data-collection-in-covid-19-restrictions/>

Our world in data: statistics and research: Coronavirus pandemic (COVID-19)

<https://ourworldindata.org/coronavirus>

WHO COVID-19 dashboard

<https://covid19.who.int/>

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

COVID-19 paediatric mortality rate is heterogeneous between countries (not peer reviewed)

<https://www.medrxiv.org/content/10.1101/2020.09.17.20196832v2.article-info>

- > This study aimed to compare the paediatric COVID-19 mortality rate in 23 countries that have populations of at least 5 million.
- > Peru had the highest mortality rate per million in children <15 years (12.1), followed by Brazil (8.8) and Ecuador (5.5).
- > Australia, South Korea, Greece, Finland and Austria had 0 reported deaths in children <15 years.
- > Peru has the highest mortality rate per million in children 0-4 (16.04) and 5-9 (10.96), and Brazil had the highest in children aged 10-14 (15.33).
- > Spearman correlation coefficient was calculated between paediatric COVID-19 mortality rates, general mortality rates and neonatal mortality rate (all causes in 2018).
- > A correlation was identified between COVID-19 paediatric mortality and neonatal mortality.
- > Although the paediatric mortality rate is low, there is still an essential variation between countries suggesting that social determinants of health and the quality of health care systems play a role in the differences of paediatric COVID-19 mortality rates.

Reviewed by: Dr Wonie Uahwatanasakul

Celina DeBiasio- 3rd Year Medical Student, University of Ottawa

Improving hospital oxygen systems for COVID-19 in low-resource settings: lessons from the field (technical note)

<https://www.ghspjournal.org/content/early/2020/09/28/GHSP-D-20-00224>

- > This article describes practical guides on how hospitals, in the face of the need for more resources for respiratory support and intensive care can:
 - Improve pulse oximetry and oxygen use.
 - Optimise existing oxygen supplies.
 - Expand existing oxygen systems with robust equipment and smart design.
- > The authors' collated field experience from African and Asia-Pacific contexts detail how hospitals can rapidly improve their oxygen systems through the following practical strategies:
 - Support health care workers to use pulse oximetry and oxygen through training and protocols.
 - Pulse oximetry can enable health care workers to target oxygen to those who need it, dramatically improving oxygen access and clinical outcomes.
 - The authors recommend using oxygen saturation as the “fifth vital sign”.
 - The authors have created practical training materials.
 - Assist biomedical engineers to optimise existing oxygen supplies through training, protocols, and logistic support.
 - Biomedical engineers and technologists need to be included in the decision-making process.
 - Hospital staff can use the article's practical installation guidance provided in supplement four to create smart and efficient ward oxygen systems to put this influx of equipment to use rapidly and effectively.
 - Expand on existing oxygen systems using robust equipment and smart design.
 - WHO and UNICEF have released guidance on oxygen-related equipment and specific advice for COVID-19, which includes low low-cost oxygen concentrator-based systems that use simple plastic piping and flowmeter stands to provide oxygen to multiple patients simultaneously.
- > Conclusion: improving the basics of acute care like oxygen systems is an achievable priority for hospitals. The authors provide free downloadable resources here: (<https://bit.ly/OxygenResources>).

Reviewed by: Professor Trevor Duke

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

COVID-19 and Sustainable Development Goals

<https://www.who.int/bulletin/volumes/98/10/20-263533.pdf?ua=1>

- > The COVID-19 pandemic has highlighted that the world is dealing with a crisis of immense proportions that is fuelled by poverty, hunger, weak health systems and lack of clean water and sanitation, education, and global cooperation.
- > The global recession caused by COVID-19 response is alarming and raises questions whether the sustainable development goals (SDGs) are fit for the post-pandemic age - some claim that specific SDG targets are counterproductive because they enhance growth rather than development.
- > There is no pandemic response plan in the SDGs; the World Health Organization believes it is essential not to de-link the response plan from the SDGs - the COVID-19 crisis demonstrates the need to integrate the SDGs at a national level, as well as in individual healthcare decisions.
- > Achieving the SDGs requires balancing three dimensions of sustainable development: economic growth, social inclusion, environmental protection.
- > The pandemic shows that sustainable development goes beyond national strategies - every individual needs to make health decisions that meet personal needs, as well as the needs of the broader community (such as wearing a facemask, observing social distancing, self-quarantining when necessary).
- > This global crisis reveals that community needs can be immediate (in contrast to the 2030 horizon of the SDGs).
- > How can emergency strategies be consistent with targets like universal health coverage (i.e. free health care) that may reduce the risk for future pandemics?.
- > These issues should be addressed in national strategies, and in the choices made by individuals when we comply with health authorities' recommendations.

Reviewed by: Professor Fiona Russell

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

Face masks, public policies and slowing the spread of COVID-19: evidence from Canada (not peer reviewed)

<https://www.medrxiv.org/content/10.1101/2020.09.24.20201178v1>

- > This study examined the effectiveness of mandated mask-wearing and other non-pharmaceutical interventions (NPIs) on slowing the weekly growth of COVID-19 cases in 34 regions of Ontario, Canada's most populated province, and compared this with other provinces and across Canada using data collected between 11th March and 13th August 2020.
- > Data included weekly new COVID-19 cases, when specific policies including mandatory indoor masks were enacted (17 in total), self-reported mask use and other behaviours such as handwashing and social distancing collected through regular public opinion surveys, and proxy behaviour changes using Google Community Mobility reports (this does not capture hand hygiene and social distancing).
- > A 14-day lag between behaviour and policy changes and COVID-19 cases was used.

- > Face masks were made mandatory in public spaces in Ontario's 34 public health regions over a period of two months, which allows for comparison of the intra-provincial policy variation while most other NPIs, such as regulations on school, social gatherings, etc. were standard across the province. These other non-pharmaceutical interventions were compared between provinces.
- > Data supports a 25-31% reduction in COVID-19 cases within the first few weeks of a mask-wearing mandate.
- > Mask mandates increase self-reported mask-wearing in the general population by on average 31.5% from a baseline of 29.8%, indicating that mandated masking is likely a powerful tool for slowing the spread of the virus.
- > No evidence that community masking decreases other preventative measures such as hand washing in Canada.
- > NPIs were grouped into five policy aggregates: travel, school, business/gathering, long term care, and masks.
 - Stringent restrictions on gatherings and businesses strongly correlated to decreased weekly COVID-19 numbers (48-57%, though not the same degree of confidence in this estimate).
 - School closures appeared to lead to a large decrease in numbers; however, these changes happened at the same time as many others and over a concise period so the results should be interpreted with caution.
- > Limitations: the study does not examine whether the initial alterations in behaviour, such as mask-wearing, persist into the future as the pandemic continues.

Reviewed by: Dr Martin Wright

IMMUNOLOGY

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

Loss of anti-SARS-CoV-2 antibodies in mild COVID-19

<https://www.nejm.org/doi/full/10.1056/NEJMc2027051>

- > There is ongoing concern surrounding the possibility of re-infection with SARS-CoV-2 due to rapid waning immunity and the possible consequences of this on herd immunity.
- > This correspondence included three responses to the paper, Rapid Decay of Anti-SARS-CoV-2 Antibodies in Persons with Mild COVID-19 by Ibarondo et al. (10th September 2020). The original study reported IgG antibodies to the anti-receptor-binding domain of spike proteins had a half-life of 36 days (n=31, investigation over 90 days).
- > One response to the original paper had found IgG levels remained high until 50-60 days after the onset of symptoms (n=151). In contrast, the other two responses had suggested a rapid decline in anti-SARS-CoV-2 antibodies after recovery (n=74 and n=46, antibody testing over 60 days from symptom onset).
- > The authors of the original paper responded with some possibilities for inconsistencies in the literature, including:
 - Varying methods used to measure SARS-CoV-2 antibodies in studies- Ibarondo et al. used anti-receptor-binding domain of spike proteins as opposed to whole spike or nucleocapsid, yielding greater specificity.
 - Ibarondo et al. used a monoclonal antibody control standard curve for each assay, which controls for inter-experiment variability (as seen when using optical density readings).
 - Differences between study participants may change the degree of antibody decay. Ibarondo et al. used a homogeneous group with mild infection.
- > Conclusions: more research into the stability of anti-SARS-CoV-2 antibodies in mild COVID-19 infection will aid in public health decisions around the likelihood of ongoing herd immunity and re-infection. Likewise, further study will be required when a vaccine becomes available as to whether the vaccine can provide a more prolonged antibody response.

Reviewed by: Dr Ryan Toh

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

Mucosal versus systemic antibody responses to SARS-CoV-2 antigens in COVID-19 patients (not peer-reviewed)

<https://www.medrxiv.org/content/10.1101/2020.08.01.20166553v2>

- > This study examined the antibody response in serum (n=496) and saliva (n=90) from acute and convalescent COVID-19 patients. Samples collected ranged from 3-115 days post-symptom onset (PSO).
- > Antibody responses in serum against SARS-CoV-2 Spike, receptor-binding domain (RBD) and N protein (NP).
 - Automated and manual enzyme-linked immunosorbent assays (sensitivities of 95.6% and 95.5% for spike and 93.8% and 91.3% for RBD, respectively) was used to detect IgG, IgA and IgM responses.
 - Peak IgG levels attained by 16-30 days PSO and sustained over 115 days (IgG decline 25% and 46% by day 105 and 115, respectively).
 - IgA and IgM antibodies peak at 16-30 days POS, rapidly decayed; IgA levels against RBD/S1 decline >74% for a while IgM decline >66% by day 115.
 - A protein-based surrogate neutralisation ELISA (snELISA) was used to measure neutralising antibodies.
 - Neutralising antibodies peak at 31–45 day PSO, and decreases to an intermediate median plateau in the 46–105 day.
 - Antibodies to the spike was more stable over time than those to the RBD and NP.
- > Antibody responses in saliva.
 - Optimised an ELISA method to detect SARS-CoV-2 antibodies in saliva.
 - Total IgG levels, but not IgA or IgM levels, were found to be higher in COVID-19 patients compared to pre-COVID-19 samples.
 - The sensitivity of the saliva assay to spike and RBD, respectively for:
 - IgG antibodies were 89% and 85%.
 - IgA antibodies were 51% and 30%.
 - IgM antibodies were 57% and 33%.
 - IgG, IgA and IgM were detectable in saliva against the spike and RBD antigens, with only the IgG response persisting beyond day 60.
- > IgG, IgM and to a lesser extent, IgA responses to spike and RBD in the serum positively correlated with matched saliva samples (based on saliva %AUC values and serum antibody ratios).
- > Limitations:
 - The sensitivity of the saliva assay to IgA and IgM was low.
 - A number of samples in the later time points was small.

- > This study found that systemic and mucosal humoral IgG antibodies are maintained in the majority of COVID-19 patients for at least three months PSO. Based on their correlation between antibodies in saliva and serum, IgG responses in saliva may serve as a surrogate measure of systemic immunity.
- > Measuring the nature and kinetics of salivary antibodies will be essential to determine potential correlates of protection against SARS-CoV-2.

Reviewed by: Dr Ryan Toh

INFECTION CONTROL

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

The ability of fabric face mask materials to filter ultrafine particles at coughing velocity <https://bmjopen.bmj.com/content/10/9/e039424>

- > A shortage of PPE was and continues to be, for some countries and communities, one of the most significant challenges of dealing with COVID-19.
- > Many governments have either advised or mandated the wearing of face masks, which has necessitated many people to create homemade masks.
- > This study assessed the ability of different materials to filter ultrafine particles (0.02-0.1 μm ; size range includes SARS-CoV-2) at coughing velocity, as well as the impact of moisture on filtration ability.
- > Tube-shaped apparatus was constructed with two-particle counters on either side of the fabric sample. Airflow was controlled with suction.
- > An N95 respirator, hospital-grade surgical mask, HEPA vacuum bag, and 18 fabrics were tested either as a single layer or in combinations with other fabrics.
- > The average filtration efficiency of single-layer and layered combinations of materials were 35 and 45%, respectively.
- > HEPA vacuum bags blocked the highest percentage of particles (61%), followed by the N95 mask (52%).
- > Potential for great material as an emergency face mask, however, concern over the safety of potential inhalation of layers of the bag particularly when it is cut (releases fibres), as this is not its primary purpose.
- > Of the fabrics, windbreaker and jean denim materials blocked the most particles (47% and 46%, respectively), but were very difficult to breathe through.
- > The fabrics which blocked the lowest proportion of particles were: light-weight t-shirt (10%), fusible interfacing (material for collar stiffening, 15%), and Lycra (22%).
- > The best materials were those that blocked a high proportion of particles, while having low resistance to breathing, including felted wool, quilting cotton and cotton flannel.
- > Layering the materials was found to improve particle blocking: however, these combinations were found to be harder to breathe through than the N95 mask.
- > Moisture played a minor role in changing efficiency, most notably in denim where a 15% decrease in particle blocking was observed.
- > Summary: in times where masks must be worn, and surgical masks are not available; layering standard fabrics is the best way to block a significant proportion of ultrafine particles: however, they can create challenges to breathability, especially in situations where masks must be worn for any length of time.

- > Limitations: This study did not differentiate between pathogenic and non-pathogenic particles; breathing resistance with various materials was based on qualitative feedback.

Reviewed by: Professor Suzanne M. Garland

SCHOOLS

Celina DeBiasio - 3rd Year Medical Student, University of Ottawa

COVID-19 trends among school-aged children - the United States, 1st March-19th September 2020

<https://www.cdc.gov/mmwr/volumes/69/wr/mm6939e2.htm>

- > In September 2020, 56 million school-aged children (aged 5–17 years) resumed education in the United States.
- > The authors collected and analysed data from 1st March to 19th September 2020 among 277,285 laboratory-confirmed cases in school-aged children:
 - Average weekly incidence (cases per 100,000 children) among adolescents aged 12–17 years (37.4) was approximately twice that of children aged 5–11 years (19.0).
 - During July and August, test volume and incidence decreased then plateaued (school holidays); incidence decreased further during early September and might be increasing.
 - Weekly incidence, SARS-CoV-2 test volume, and percentage of tests positive among school-aged children varied over time and by region of the United States.
 - Among school-aged children with laboratory-confirmed SARS-CoV-2, 58% reported at least one symptom, 5% reported no symptoms, and information on symptoms was missing or unknown for 37%.
 - Hospitalisations due to COVID-19 among school-aged children:
 - Overall, 3,240 (1.2%) of school-aged children with COVID-19 were hospitalised: 404 (0.1%) who required ICU admission; 51 (<0.01%) school-aged children died.
 - For those with complete information on race/ethnicity who were hospitalised (2,473 [76%]) or admitted to an ICU. (321 [80%]), Hispanic ethnicity was most commonly reported (45% and 43%, respectively), followed by Black (24% and 28%, respectively) and White (22% and 17%, respectively) races.
 - At least one underlying condition was reported for 16%: 27% of those admitted to an ICU, and 28% of those who died.
 - At least one underlying condition was reported for 7,738 (3%), including ~3% of adolescents and 2% of younger children. Among those with an underlying condition, chronic lung disease, including asthma, was most commonly reported (55%), followed by disability (9%), immunosuppressive conditions (7%), diabetes (6%), psychological conditions (6%), cardiovascular disease (5%), and severe obesity (4%).

- > Although mortality and hospitalisation in school-aged children was low, Hispanic ethnicity, Black race, and underlying conditions were more commonly reported among children who were hospitalised or admitted to an ICU, providing additional evidence that some children might be at increased risk for severe illness associated with COVID-19.
- > Limitations: data may underestimate the actual incidence of disease among school-aged children because testing was frequently prioritised for persons with symptoms and is from a single reporting system; data on race/ethnicity, symptom status, underlying conditions, and outcomes had high rates of missing or unknown values; delays in reporting may cause lags in trend data; State reporting of laboratory data and case surveillance is not uniform; therefore laboratory data presented here may underrepresent the volume of laboratory tests.
- > It is important for schools and communities to monitor multiple indicators of COVID-19 among school-aged children and layer prevention strategies to reduce COVID-19 disease risk for students, teachers, school staff, and families. These results can provide a baseline for monitoring trends and evaluating mitigation strategies.

Reviewed by: Professor Fiona Russell

TRANSMISSION

Alastair Weng – 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne &
Rebecca Seliga – 3rd Year Medical Student, University of Ottawa

SARS-CoV-2 transmission dynamics should inform policy

https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3692807

The authors describe the known transmission dynamics of SARS-COV-2 in detail and argue that social policy around Coronavirus should be driven by the risk and severity of transmission.

- > Evidence about transmission dynamics is generated through contact tracing and household studies, a crucial element of understanding this novel virus to reach an effective reproductive number (R) of less than one.
- > The risk of transmission is dependent on several key factors:
 1. Host factors, e.g. age, the severity of illness, host defence.
 - There is an early viral load peak with higher viral titres from symptom onset until day five, translating to increased infectiousness.
 - Symptomatic cases are more likely to spread the virus to others than asymptomatic cases (0.7-16.2% vs 0-2.8%), with a lower risk ratio of asymptomatic: symptomatic of 0.35.
 2. Contact pattern, e.g. proximity to index, contact frequency
 - Household contacts (especially spouses), close friends, and taking public transport were far more likely to result in infection spread than work or shopping.
 - Large clusters may stem from pubs, church services, nursing homes, and friendship group gatherings.
 - Isolation from non-infected family, hand hygiene, and social distancing could limit spread even amongst family members.
 3. Environment, e.g. indoor/outdoor, ventilation
 - Contact indoors results in 18.7 x greater risk of transmission compared to outdoor settings.
 - Long-term care facilities (e.g. nursing homes, homeless shelters, prisons) are most susceptible to cluster spreading due to their crowding and enclosed environment.
 4. Socio-economic, e.g. household crowding, poverty, work hours
 - This is the driving force behind many of the household and environmental factors described above, and this virus has disproportionately affected the poor.
 - It is contributed to by access to healthcare, lifestyle and disease comorbidities, structural racism, etc.

- > Having data is not enough; this must be translated into policy and action. These may include:
 1. Addressing systemic social inequities in order to allow even those least well off to be able to follow isolation and quarantine recommendations without financial or social consequence.
 2. Prioritising contact tracing and testing for interactions most high risk of spread, including early disease (high viral load), household contacts, and contacts in crowded spaces.
 3. Educating the community about low versus high-risk activities and environments to encourage self-quarantining and community-led detection and tracing.
 4. Redesigning high risk indoor and overcrowded environments to ensure social distancing and/or ventilation is possible.

Reviewed by: Dr John Cheek

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

Transmission of SARS-CoV-2: a review of viral, host, and environmental factors

<https://www.acpjournals.org/doi/10.7326/M20-5008>

A review of viral, host, and environmental factors affecting SARS-CoV-2 transmission:

- > Environmental viability of the virus.
 - Under experimental conditions, viable SARS-CoV-2 was isolated for up to 3 hours from aerosols and up to 72 hours from various surfaces with the longest viability being on plastics and stainless steel (half-lives = 6 hours). The virus was stable at low temperatures but was inactivated by heat and various disinfectants.
- > Viral and host factors affecting transmission.
 - Host cell entry requires binding of the viral spike (S) protein to the host ACE2 receptor. Decreased ACE2 expression in children compared to adults may be one of the reasons why children are less susceptible to SARS-CoV-2 infection.
 - The likelihood of viral transmission from an infected child compared to that from an infected adult is still unclear. Some studies have suggested that children are less likely to transmit the virus; however, this may be due to the fact that children are often asymptomatic and thus less likely to be identified as index cases.
 - Certain viral mutations, such as the D614G mutation, may increase the likelihood of transmission.
- > Modes of SARS-CoV-2 transmission.
 - The respiratory route is the most common mode of transmission. Factors such as proximity and poor ventilation increased transmission risk while wearing masks decreased transmission.
 - There is no conclusive evidence that transmission via fomites or direct contact. However, circumstantial evidence and reports of the value of hand hygiene on reducing the risk of transmission is suggestive.

- Infected domestic animals, in particular cats, can transmit SARS-CoV-2 infection amongst each other. However, there are no confirmed cases of transmission from domestic animals to humans.
 - Vertical transmission of SARS-CoV-2 infection is rare. Transplacental transmission has been reported in a few studies.
 - The live virus has been isolated from the stool and saliva samples, and viral RNA has been isolated from semen and blood. However, transmission via faecal-oral, sexual or blood-borne routes has not been reported aside from one cluster of potential faecal-oral transmission.
- > Period of infectiousness for a person with SARS-CoV-2 infection
- Both symptomatic and asymptomatic people can transmit the virus, although transmission is less likely from those who are persistently asymptomatic. Increased disease severity and the presence of fever and expectoration in the index case were associated with increased rates of viral transmission.
 - The period of infectiousness is much shorter than the duration of viral RNA shedding. The period of infectiousness was estimated to start 2.3 days before symptom onset, peak at about one day before symptom onset and rapidly decline within seven days. The median duration of viral RNA shedding from the nasopharynx was 22 days for mild disease and 33 days for severe disease.
- > Population-level transmission dynamics.
- R_0 (average number of secondary cases generated from the index case in an entirely susceptible population) was estimated to be 2-3 for SARS-CoV-2.
 - Increasing evidence suggests that SARS-CoV-2 transmission is over-dispersed where most index cases do not cause secondary transmission, but only a small minority lead to many secondary transmissions in clusters (superspreading events). Such transmissions mainly occurred in indoor settings.

Reviewed by: Professor Julie Bines

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

Epidemiology and transmission dynamics of COVID-19 in two Indian states

<https://science.sciencemag.org/content/early/2020/09/29/science.abd7672.full>

- > Current understanding of COVID-19 transmission comes from disease surveillance undertaken in early phases of the pandemic in China, and in high-income countries in Europe and North America.
- > However, most confirmed cases of COVID-19 have now occurred in low and middle-income countries, where a large proportion of individuals may be at risk of severe outcomes, and face barriers to accessing quality healthcare services.
- > This study analysed surveillance and contact tracing data for two states (Tamil Nadu & Andhra Pradesh) in South India to understand transmission dynamics and clinical outcomes, as well as to provide insight into controlling SARS-CoV-2 in similar low and middle-income countries.

- > Contact tracing efforts in the states reached 3,084,885 known exposed contacts of confirmed cases by 1st August 2020; individual-level epidemiological data on cases and contacts, and lab test results were available from 575,071 tested contacts of 84,965 confirmed cases.
- > Traced contacts tended to be younger, and were more often female, than their linked index cases.
- > The mean number of contacts tested per index case was 7.3 - numbers of contacts tested varied by district.
- > Assuming that the contacts that tested positive were infected by the index case they were traced to, the overall secondary attack rate was 10.7% for high-risk contacts and 4.7% for low-risk contacts (those who were in the proximity of index cases but did not meet criteria for high-risk exposure).
- > Cases in Tamil Nadu and Andhra Pradesh showed a younger age distribution than cases reported in the United States - age-specific COVID-19 incidence increased sharply in both 5-17 and 18-29 year age groups, incidence declines steadily at ages older than 30-39 years in both Indian states (incidence increases at 65 years and older in the United States).
- > There are many factors that may have contributed to the above observations in these two Indian states:
 - Imperfect surveillance - although unexpected given the strong public and clinical awareness of COVID-19, and the predisposition of older adults to severe disease.
 - Case-based surveillance may underestimate attack rates among younger adults in high-income settings
 - Strict stay at home measures for older Indian adults, coupled with the delivery of essential items contributed to lower exposure to this age group.
- > Limitations included a lack of data on the timing of exposure and symptom onset in relation to testing dates - more robust temporal data would reduce dependence on assumptions, provide greater insight into the directionality of transmission, and reduce the risk for misclassification of infection status.
 - The lack of temporal data prevented estimation of incubation period and serial interval.
 - The serial interval between successive infections is expected to be lower in high-transmission settings - data allowing estimation of these parameters in low & middle-income countries are needed to inform quarantine policies and other response efforts.
 - Contact tracing data analysed only 20% of all reported cases as index cases and represented only 19% of all contacts traced.
- > The study highlights that children are commonly infected and transmit the virus and have the most contacts. The degree to which transmission occurs may vary by setting and be related to household size, living arrangements (higher density living/poor ventilation are likely to contribute to higher attack rates); whether schools were open or closed during this period (prevents transmission); and whether there were school mitigation strategies in place (mitigation also prevents transmission). Important that when sufficient safety data is gained from adult studies, that children are enrolled in vaccine trials (to determine if they are safe and effective), as to stop mitigation measures and return to normal life in the future, children may need to be vaccinated.

Reviewed by: Professor Fiona Russell

VACCINES

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

SARS-CoV-2 vaccines in development

<https://www.nature.com/articles/s41586-020-2798-3>

- > This review details the history of coronaviruses, summarises the pathogenesis and immunology of SARS-CoV-2 and juxtaposes the rapid development of a COVID-19 vaccine against the normal process for licensure.
- > The benefits and challenges of each vaccine type are discussed, as well as the number of candidates of each type at different stages of development. Non-human primate research is also summarised.
- > Of more than 180 candidates, 35 are in clinical trials, of which nine have already reached Phase III. Detailed information is offered for the leading Sinovac, CanSino, AstraZeneca, Pfizer, Moderna and Novavax candidates.
- > The recombinant protein vaccine candidates seem to be most immunogenic, and alongside the inactivated vaccine candidates may be the most tolerable.
- > Overall, the current outlook for a vaccine soon becoming available is reasonably positive. However, none of the candidates in clinical trials are likely to offer mucosal immunity which may result in vaccinated individuals still transmitting Coronavirus despite being protected from severe disease.
- > The longevity of an immune response is unknown, as well as how both children and the elderly will respond to candidate vaccines.
- > Mass production and distribution of any vaccine will be a significant logistical challenge.

Reviewed by: Associate Professor Margie Danchin

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

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>

- > While clinical trials of COVID-19 vaccines for adults have progressed at warp speed into Phase III trials, paediatric Phase II clinical trials have not begun in the US.
- > An approved paediatric COVID-19 vaccine could provide direct benefit, including:
 - Reducing COVID-19 circulation in the community, hospitalisations, burdens of hospitalisation such as racial disparities, and deaths in children.

- Improving childhood education by allowing a safer return to school and adequacy and equity of access to learning. With the easing of social distancing, maintaining their learning environment and extracurricular activities could improve their emotional and psychological development.
- > Potential indirect benefits of vaccinating children include:
 - A vaccine may reduce the risk of adult infection with COVID-19 and the risk of children serving as a reservoir. This would allow more direct contact with grandparents.
 - It may improve the likelihood of ending the pandemic and recovery of the economy.
- > The article suggests strategies to address the safety concerns of a vaccine:
 - For unexpected safety events after vaccination, the authors advocate for a robust process of obtaining FDA licensure with a carefully designed clinical development plan and post-licensure safety surveillance.
 - Monitor carefully for vaccine-associated immune-mediated enhanced disease (VAED) - this has happened with other vaccines, i.e. Dengvaxia, but the authors consider VAED unlikely in COVID-19.
 - Multisystem Inflammatory Syndrome in Children (MIS-C) can be a risk with COVID-19 exposure, but MIS-C is rare to observe in clinical trials. Ongoing surveillance for MIS-C will be necessary after a vaccine approval.
- > The authors make recommendations to advance COVID-19 vaccines in children:
 - Trials should follow the age de-escalating strategy by starting with adolescents and older children before expanding to younger children to establish safety.
 - The FDA, funding agencies, investigators, and manufacturers should join to initiate these studies now.
 - Funders and overseers of US vaccine efforts should ensure paediatric COVID-19 vaccine clinical trials begin simultaneously and occur when adult clinical trials move into Phase III trials.
- > In conclusion, given the potential direct and indirect benefits of COVID-19 vaccination for children, Phase II paediatric vaccine clinical trials should start now.

Reviewed by: Associate Professor Margie Danchin

VIROLOGY

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

Temporal profile and determinants of viral shedding and of viral clearance confirmation on nasopharyngeal swabs from SARS-CoV-2-positive subjects: a population-based prospective cohort study in Reggio Emilia, Italy

<https://bmjopen.bmj.com/content/10/8/e040380>

- > A prospective population-based cohort study that included analysis of 1,162 symptomatic patients with a positive SARS-CoV-2 swab followed up for at least 30 days in the Reggio Emilia province, Italy.
- > Viral clearance was achieved by 60.6% of patients and confirmed in 78.7% of cases of those who had a second swab after the first negative swab (suggesting a 1/5 false-negative rate).
 - The median time to viral clearance was 30 days from the first positive swab and 36 days from symptom onset.
 - When comparing those aged under 50 to those aged over 80; time from symptom onset to viral clearance slightly increased with age (28 to 31 days) and with disease severity (32 to 38 days).
 - The probability of confirmed viral clearance was 86.8% after 34 days from symptom onset and increased with time, even when age and sex were adjusted for.
- > Weaknesses:
 - A negative swab does not indicate when clearance actually occurred.
 - Clinical information was not available for all study subjects; access to the emergency department and hospitalisation were used as a surrogate for disease severity.
- > Takeaway: testing should be performed more than 34 days from the first positive swab to reduce the false-negative rate.

Reviewed by: Dr Celeste Donato

Jun Hua Bowen Lim - 3rd year Medical student,
Department of Paediatrics, The University of Melbourne

SARS-CoV-2 viral load peaks prior to symptom onset: a systematic review and individual-pooled analysis of coronavirus viral load from 66 studies (not peer reviewed)

<https://www.medrxiv.org/content/10.1101/2020.09.28.202028v1>

- > Viral load plays a part in the transmission potential of the SARS-CoV-2.
- > In the present study, the authors collated data from 66 publications which described viral load and shedding of SARS-CoV-2, SARS-CoV and MERS-CoV representing a total of 1,198 patients across 14 countries.
- > They modelled the available data and found that SARS-CoV-2 viral load peaks prior to symptom onset while the viral load for SARS-CoV and MERS-CoV peaked after symptom onset.
- > SARS-CoV-2, MERS-CoV, and SARS-CoV had median viral shedding durations of 4.8, 4.2, and 1.2 days after symptom onset.
- > Disease severity plays a role in determining viral load, where mild cases had on average, 16% of the viral load compared to severe cases.
- > Age and specimen type affected viral load, but sex did not.
- > These findings are consistent with previous reports and have substantial implications for public health policy and contact tracing.

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 US 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_z2uWV7r3FaPzAO86q9ZXBcTZ1OcCE_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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