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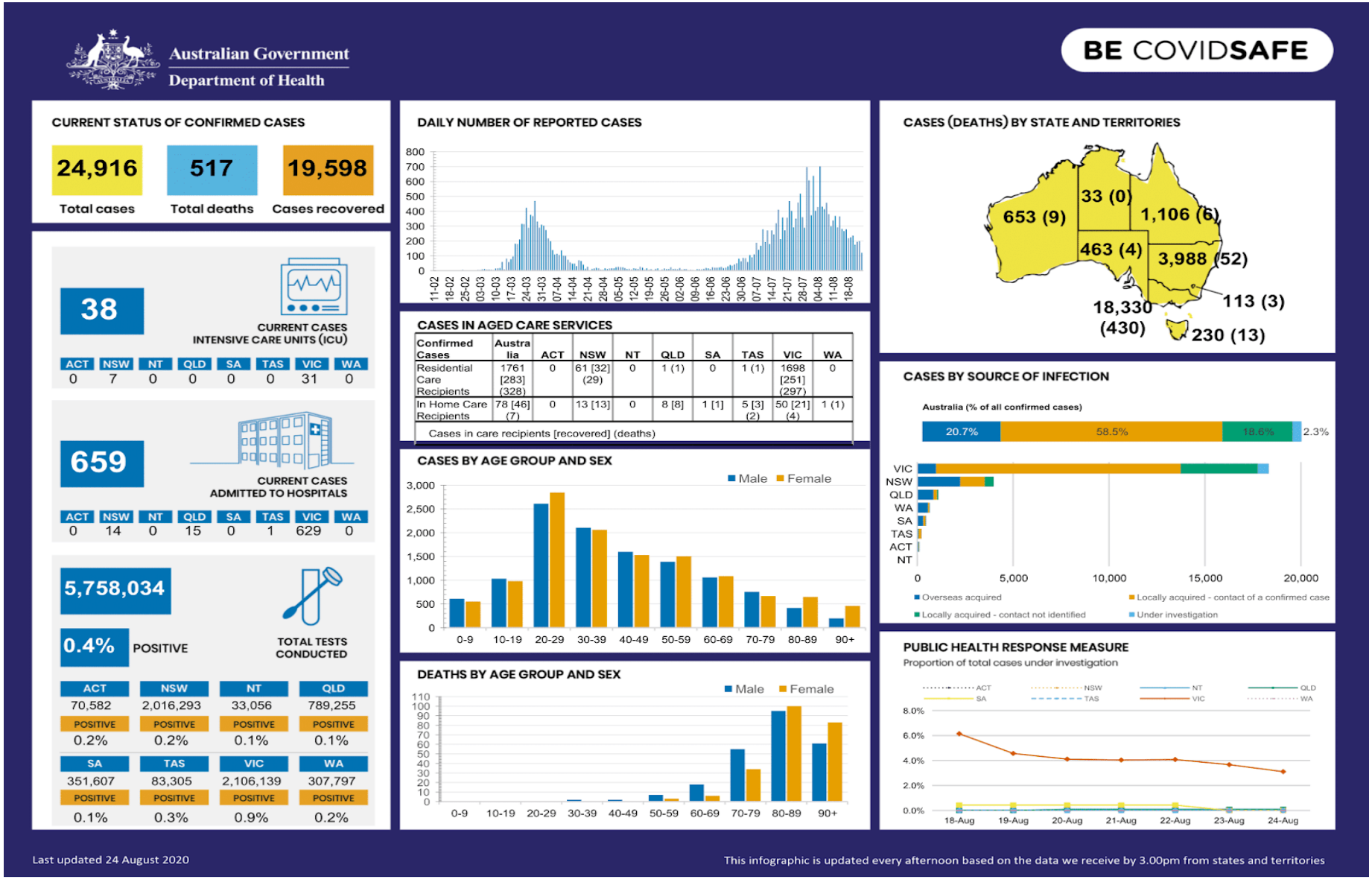
COVID-19 KIDS RESEARCH EVIDENCE UPDATE

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

Weekly Update No.19
28th August 2020



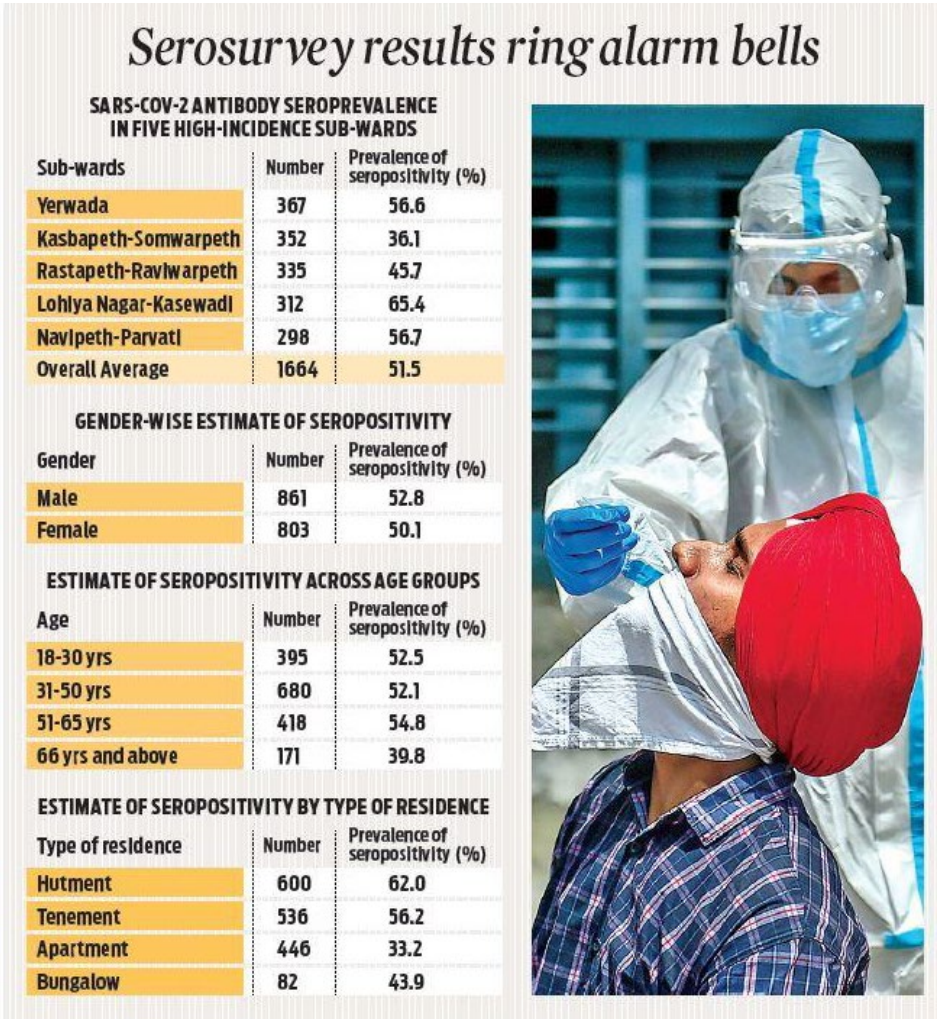
Source: Australian Government: Department of health [Internet]. 2020 [updated 2020 August 24; cited 2020 August 25]. Available from:: https://www.health.gov.au/resources/collections/coronavirus-covid-19-at-a-glance-infographic-collection

GUEST EDITORIAL

Professor Kim Mulholland - Group Leader, New Vaccines, Infection & Immunity, Murdoch Children's Research Institute

The decline in Victorian COVID-19 numbers is steady, but not dramatic. Monitoring death rates is not useful, as most deaths are among cases from aged care facilities, and do not reflect current community transmission. It may be useful to compare daily numbers of new cases with New York State. New York reached a peak of 490 cases / million on 11th April. By 1st May, it was 270 / million, representing a 45% reduction over 20 days. Since then New York has dropped to 32-34 / million, and remains at that level, which is close to the current level in Victoria. Currently, 1% of tests done in New York are positive. The population is wary and compliant, relatively. Small clusters continue to appear and there are predictions of a new wave, but it is not clear that such a wave is a real risk. 32,000 New Yorkers have died (1659/million). In Victoria, where 502 have died (79/million), the state reached a peak of 88 cases / million on 5th August. By 19th August, it was 44 / million, a 50% reduction over 14 days, a more rapid reduction than was seen in New York. So can eradication be achieved now? It is probably possible, but the cost may be substantial. Addressing this question is especially difficult because, unlike most other developed countries and many less developed countries like India and Kenya, Australia has not undertaken detailed studies of the level of seropositivity and other investigations necessary to understand the patterns of illness and transmission.

In India, the government has undertaken systematic serosurveillance to understand the distribution of COVID-19 and the results are surprising. Overall seroprevalence is around 1%, but it is much higher in the major cities. The highest seroprevalence is in Pune, and examination of their results has proved very informative.



Serosurvey results ring alarm bells

SARS-COV-2 ANTIBODY SEROPREVALENCE IN FIVE HIGH-INCIDENCE SUB-WARDS

Sub-wards	Number	Prevalence of seropositivity (%)
Yerwada	367	56.6
Kasbapeth-Somwarpeth	352	36.1
Rastapeth-Ravlwarpeth	335	45.7
Lohiya Nagar-Kasewadi	312	65.4
Navipeth-Parvati	298	56.7
Overall Average	1664	51.5

GENDER-WISE ESTIMATE OF SEROPOSITIVITY

Gender	Number	Prevalence of seropositivity (%)
Male	861	52.8
Female	803	50.1

ESTIMATE OF SEROPOSITIVITY ACROSS AGE GROUPS

Age	Number	Prevalence of seropositivity (%)
18-30 yrs	395	52.5
31-50 yrs	680	52.1
51-65 yrs	418	54.8
66 yrs and above	171	39.8

ESTIMATE OF SEROPOSITIVITY BY TYPE OF RESIDENCE

Type of residence	Number	Prevalence of seropositivity (%)
Hutment	600	62.0
Tenement	536	56.2
Apartment	446	33.2
Bungalow	82	43.9

Pune serosurvey results. Source: The New Indian Express [Internet]. 2020 [2020 August 18; cited 2020 August 25]. Available from: https://www.newindianexpress.com/nation/2020/aug/18/52-in-pune-exposed-to-covid-19-2184885.html

In Delhi the authorities are undertaking serosurveys monthly. Currently, 27% of Delhi residents show serological evidence of having had the infection. Within cities, authorities have identified "red areas" where there have been a large number of cases. Targeted serosurveys have shown seroprevalence rates of over 58% in some "red areas", such as Dharavi, Mumbai, where 850,000 people live in extremely crowded conditions. In Dharavi transmission seems to have stopped. Is this the herd immunity threshold that the mathematical modellers have been talking about?

Mathematical modellers have been major casualties of the pandemic. In general, modelling is useful for understanding what has happened after the event. It is much less useful for predicting the outcome of a pandemic, especially when there are as many unknowns as there are with COVID-19. In April, Christopher Murray's Seattle based Institute of Health Metrics and Evaluation predicted that the U.S. epidemic would eventually cause 60,000 deaths, based on a regression model using European data.
They have since upgraded the prediction to 300,000 deaths. Other models use the Susceptible Exposed Infected Recovered (SEIR) approach. For this approach, two key parameters are required to estimate the impact of an epidemic: the average number of new cases generated by each case in a non-immune population (Basic Reproduction Rate or R_0), and the Case fatality Rate (CFR).

In March 2020 senior U.K. mathematical modeller Professor Sir Roy Anderson estimated the R_0 for the COVID-19 epidemic to be about 2.5, and the case fatality rate to be 0.3-1.0%. It is important to recognise that R_0 is not simply a characteristic of a particular pathogen. It is a function of the social patterns in the society that is affected, which varies between communities and with time. This reflects efforts by a community and the government, and socio-demographic factors, particularly crowding. From the R_0, the proportion of the population that must be infected for the number of cases to begin to decline (the herd immunity threshold) can be calculated. Anderson predicted that with an R_0 of 2.5 this would be about 60%. Once this level was reached numbers would begin to decline, and the eventual number that would be infected would be higher and dependent on the rate of the decline. The prospect of an effective vaccine can be added to this equation. The key figure then, is the proportion of a population that must be immune to stop transmission, which will depend on both natural and vaccine-derived immunity.

As the IHME model fades into the distance, and countries struggle with repeated waves as containment measures are relaxed and enforced, the SEIR models start to look more realistic. So how are we to interpret the Dharavi experience? In this crowded slum, interpersonal transmission must be much higher than in Europe or Australia. Does this mean we could get away with a much lower herd immunity threshold than was predicted by Anderson?

Before considering this, we should look at some of the unknowns in this complex equation:

The process of infection – For most infectious diseases exposed individuals may either become infected or not infected, but this is probably an oversimplification. It is known that adults who have had measles may see an antibody boost on exposure without any sign of illness. With SARS-CoV-2, children, who usually suffer only mild symptoms if any, may have no sign of infection other than a mild increase in serum antibodies, or even only an increase in salivary antibodies (https://www.researchsquare.com/article/rs-47021/v1). Whilst these children clearly are infected, it is unlikely that they have significant lasting immunity, so they may be susceptible to future infections. At the other extreme, older adults who have suffered significant disease have robust antibody responses, probably indicating immunity, which may last 1-2 years or more. In between these extremes, there may be many variations.

The timeline – The incubation period is said to be 1-14 days, usually 5-7 days. This is shorter for children leading to potentially erroneous conclusions when a child is the first in a family to become sick. The problem here is the outliers. Longer incubation periods of up to 4 weeks have been described, and in some cases it may be even longer, as it is very difficult to know this period for certain.

The pre-symptomatic infectious period usually is said to be up to 48 hours, but again outliers may occur. Asymptomatic cases are believed to be minimally infectious, while mild cases may be infectious for up to 10 days following symptom onset (https://www.cdc.gov/coronavirus/2019-ncov/hcp/duration-isolation.html). Severe cases may be infectious for up to 20 days. These times are based on studies measuring the recovery of viable virus from patients. Many patients are positive by PCR for much longer. They are probably not infectious, but this is not known for certain, as it is difficult to culture the virus when the viral load is low.

Immunity – Generally, infection produces antibody. IgM and/or IgG are first to become elevated, and usually antibody following disease is neutralising. More severe illness produces higher antibody levels, so, unusually, older patients tend to generate more robust immune responses.

Curiously, the duration of immunity appears to depend on the antigen target that is used for the assay. The longest duration seems to be seen with full length S-protein, which is fortunate, as this seems to be the assay that correlates best with protection.

Asymptomatic individuals tend to produce mild immune responses, and exposed children have been found who produce antibody responses, often only mucosal, but are PCR negative. These individuals probably are infected for a short time, and this is not detected by the usual PCR test. Their immune responses may be relatively short lived.

Back to India – For unclear reasons, Indians in India appear to suffer less severe illness with SARS-CoV-2 than Europeans. In Delhi, 27% of the population of 30 million has been infected, yet there have been only 4,235 confirmed deaths, for an infection mortality rate of 0.05% - much lower than the 0.68% estimated from a recent, pre-published meta-analysis (Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection-fatality rates. 2020). It follows that a much larger fraction of the cases are asymptomatic, but they still produce enough antibody to be rated as positive for serosurveillance. Perhaps, in a setting like Dharavi the immune fraction may be even larger. Perhaps a large proportion of that population, maybe 80 or 90%, have sufficient immunity to hold off the virus based on mucosal immunity or trained innate immunity.

And about the vaccines – There are many vaccines in trials. Most rely on the S-protein, either in a stabilised form, expressed by a vector, or manufactured by the host with an RNA vaccine. It remains possible, perhaps likely that most will be partially effective. With varying systems and methods of evaluation between countries, often using different endpoints in different populations, it is likely to be very difficult for countries to interpret results of different trials. Two decades ago, albeit with a much smaller repertoire of pneumococcal conjugate vaccines (PCVs), WHO was able to align trial methods and endpoints such that the pneumococcal vaccine trials produced similar results that were ultimately predictive of the impact when PCVs were introduced. This seems impossible in the present SARS-CoV-2 vaccine environment. Concerns about vaccine safety are being voiced already. These are likely to translate into high refusal rates and sub-optimal coverage. Countries will then rely on a combination of community immunity following infection, and vaccine derived immunity to generate the herd immunity required to prevent transmission. This will present another challenge for modellers. But modellers can only hope to estimate the level of vaccine coverage required to protect a community if they know the level of community immunity. This must not just be the average level, but the data will need to have sufficient granularity to understand the required level, by district. Detailed serosurveillance is required. For large countries, indirect methods can be used whereby serosurveillance is undertaken in several sites to establish the infection mortality rate, which can then be applied to other areas of the same country to determine the likely seroprevalence, avoiding the vagaries of identification of cases. Either way serosurveillance is the cornerstone.

Back to Victoria – There is no reason why the rate of community transmission cannot be brought close to zero, but to do this we need to know much more about the pattern of disease in our community. This requires ongoing serosurveillance. Once we understand the disease and understand our levels of population immunity in our diverse community, then we can prepare for rational use of a vaccine, should an effective vaccine become available. In addition, we need a much more aggressive strategy for investigating future outbreaks in schools, meatworks and other institutions. This is not research but basic public health epidemiology in the tradition of John Snow (the anaesthetist/epidemiologist, not the cricketer!).

HIGHLIGHTS

- The latest Royal Children's Hospital National Child Health Poll summarises Australian families' experiences during COVID-19 https://www.rchpoll.org.au/
- The importance of clear and effective public health messaging requires knowledge about the audience's concerns and beliefs.
- Evidence consistently suggests that transmission of COVID-19 within school settings may be low, however, this is based on a small number of studies and the evidence is considered to be weak.
- A comparison between Finland (schools closed) and Sweden (schools open) found no difference in COVID-19 infection rates in children and no increased risk in infection in Swedish teachers compared with other professions.
- Despite the large number of children tested in the U.K., children accounted for a very small proportion of positive cases, although the role of asymptomatic children contributing to the spread of COVID-19 needs further investigation.
- SARS-CoV-2 infections and outbreaks were uncommon in educational settings during the first month after the easing of national lockdown in England, and there was a strong correlation with regional SARS-CoV-2 incidence, emphasising the importance of controlling community transmission to protect educational settings.
- Modelling studies calibrated U.K. and E.U. data predicted the reopening of schools at reduced capacity, particularly for younger children, may not increase the R_0 greater than 1, but the evidence is considered to be weak.
- A survey in the U.S. found 31% parents would probably or definitely keep their children at home from school if they reopened.
- Four factors are most heavily influencing parents' decision-making on return to school in the U.S.: fears of COVID-19, multisystem inflammatory syndrome, ability to home-school and confidence in the school system; and critical to apply an 'equity lens' when assisting families and schools deliver online or in-person learning during the pandemic.
- MIS-C may be a distinct immunopathogenic illness associated with SARS-CoV-2
- Patients with the Δ382 SARS-CoV-2 variants had a milder disease and mounted a more effective immune response compared with those infected with the wild-type virus
- It is speculated that SARS-CoV-2-specific T cells in unexposed individuals might originate from memory T cells derived from exposure to 'common cold' coronaviruses (CCC); more than 90% of the human population is seropositive for at least three of the CCC, and may explain differences in severity by age and setting.
- Both symptomatic and asymptomatic individuals with mild-moderate COVID-19 carry the infectious virus, and the duration of shedding of the infectious virus suggests infection control measures are required immediately after symptom onset until at least day 10.

- The time to PCR negativity is correlated with age: children aged 6-15 years took longer to achieve negativity compared with those aged 16-22 years.
- Robust SARS-CoV-2 specific T cell responses were detectable months after exposure, even in the absence of detectable circulating antibodies, in exposed family members and convalescent individuals with a history of asymptomatic and mild COVID-1.
- CovidNudge, a point of care diagnostic, has 94% sensitivity and 100% specificity when compared with standard laboratory-based RT-PCR.
- Intranasal administration of replication-defective human adenovirus type 5-based COVID-19 vaccine is immunogenic in animal models.
- Close follow up for medium and long term sequelae of MIS-C such as coronary artery formation is important as these outcomes remain unknown.
- 74% of adults reported ongoing symptoms at 12 week follow up in the U.K. patients in the more severe disease group reported more breathlessness, fatigue, myalgia and insomnia.

CONTENTS

ADULT MEDICINE

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

Patient outcomes after hospitalisation with COVID-19 and implications for follow up: results from a prospective U.K. cohort (not peer reviewed)
https://www.medrxiv.org/content/10.1101/2020.08.12.20173526v1

> This is a prospective cohort study that aims to assess longer-term complications of COVID-19 in previously hospitalised patients to inform appropriate follow up guidelines for these patients.

> Inpatient participants >18 years old were recruited via the DISCOVER study, baseline assessment of demographics, physiological dysfunction, biochemistry, haematology and chest radiography on admission were collected. 28-day remote follow up of hospital and/or general practice notes were collated and 8-12-week face-to-face outpatient follow up with a clinician, chest radiograph, spirometry, exercise testing, routine blood and observations and health related QoL questionnaires were conducted.

> Findings: 163 participants with a median age of 60 were recruited. 91 were male (56%). 110 attended the 8-12 week follow up. 19 patients died.

- 74% (n=81) reported ongoing symptoms at follow up with patients in the more severe disease group reporting more symptomatic breathlessness, fatigue, myalgia and insomnia.
- 15 patients (ten in a moderate group) and (five in a severe group) had abnormal chest radiography with two having worsened since hospital admission.
- Forced vital capacity was lower in more severe disease. In the moderate to severe groups 11 had restrictive pattern spirometry, and 15 patients had significant desaturation during the sitting to standing test.
- The more severe the disease, the lower the health-related quality of life scores reported across all domains. However, wellbeing scores were on par with age-matched population norms.
- Blood test abnormalities had returned to normal in 104/110 patients. No relationship between abnormal blood results and the severity of disease was identified.

> Conclusion: more intensive follow up may only be appropriate for people with severe disease. Rehabilitation and physiological services may be better suited to ease persisting symptoms.

> Limitations: a single centre study with small sample size and the availability of cross-sectional imaging and the full pulmonary functioning test was sometimes limited.

Reviewed by: Dr Wonie Uahwatanasakul

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

Longitudinal analyses reveal immunological misfiring in severe COVID-19
https://www.nature.com/articles/s41586-020-2588-y

- Immune profiling revealed an overall increase in innate cell lineages, with a concomitant reduction in T cell number in the serially analysed immune responses in 113 patients with moderate or severe COVID-19.
- An early elevation in cytokine levels was associated with worse disease outcomes.
- Following an early increase in cytokines, patients with moderate COVID-19 displayed a progressive reduction in type 1 (antiviral) and type 3 (antifungal) responses.
- By contrast, patients with severe COVID-19 maintained these elevated responses throughout the course of the disease.
- Moreover, severe COVID-19 was accompanied by an increase in multiple type 2 (anti-helminths) effectors, including interleukin-5 (IL-5), IL-13, immunoglobulin E and eosinophil.
- Unsupervised clustering analysis identified four immune signatures, representing growth factors (A), type-2/3 cytokines (B), mixed type-1/2/3 cytokines (C), and chemokines (D) that correlated with three distinct disease trajectories.
- The immune profiles of patients who recovered from moderate COVID-19 were enriched in tissue reparative growth factor signature A, whereas the profiles of those with who developed the severe disease had elevated levels of all four signatures.
- Thus, this study has identified a maladapted immune response profile associated with severe COVID-19 and poor clinical outcome, as well as early immune signatures that correlate with divergent disease trajectories.

Reviewed by: Professor Julie Bines

CLINICAL PAEDIATRICS

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

Peripheral immunophenotypes in children with multisystem inflammatory syndrome associated with SARS-CoV-2 infection
https://www.nature.com/articles/s41591-020-1054-6?utm_source=other&utm_medium=other&utm_content=null&utm_campaign=JRCN_2_DD01_CN_NatureRJ_article_paid_XMOL#change-history

> This study undertook peripheral leukocyte phenotyping in 25 children who fulfilled the clinical definition of a multisystem inflammatory syndrome (17 of whom were seropositive for SARS Co-V-2 antibodies and eight who were seronegative) in three phases of illness: the acute, resolution and convalescence phases.
  - Acute: worst illness within 72 hours of admission.
  - Resolution: clinical improvement (improved respiratory status or cardiac support and CRP < 100 mgl-1).
  - Convalescence: first outpatient follow-up after recovery.

> Samples were compared with seven age-matched controls..

> Acute phase: high levels of IL-1β, IL-6, IL-8, IL-10, IL-17, IFN-γ and lymphopenia
  - High CD64 expression on neutrophils and monocytes.
  - High HLA-DR (marker of T cell activation) expression on γδ and CD4+CCR7+ T cells.
  - This suggested activation of these immune cell populations.
  - Meanwhile, antigen-presenting cells had low HLA-DR and CD86 expression potentially indicating impaired antigen presentation.
  - Features normalised over resolution and convalescence phases.

> The 17 SARS CoV-2 seropositive children had more severe clinical manifestations:
  - Greater prevalence of gastrointestinal symptoms.
  - Worse left ventricular fractional shortening.
  - Increased use of immunomodulatory treatment.
  - Coronary artery aneurysms in seven seropositive children (30% of the entire cohort), which is higher than the other reports (of larger groups) from USA or U.K. of MIS-C (7-8%).

> Differences from Kawasaki disease (K.D.):
  - MIS-C patients had procoagulant states in acute phase characterised by raised fibrinogen, D-Dimer, and low platelets, the procoagulant state is not a common feature of K.D.

- Age of affected children (median 12.5 years) was considerably older than peak incidence of 1-3 years in K.D.
- Gastrointestinal symptoms and myocardial dysfunction in SARS Co-V 2 seropositive children, less common in K.D.
- K.D. characterised by neutrophilia and raised monocytes, not observed in the current study, as well as higher CD4 and CD8 counts, and lower HLA-DR-positive CD4+ T cells.
- K.D. characterised by activation of IL-1 pathways, while altered IFN responses may be more relevant in MIS-C.

> In reality, hyper-inflammation is also seen in severe COVID-19 disease in adults (also characterised by cytokine storm, multi-organ failure and lymphopenia), but these authors highlighted some differences.

> Limitations of the study: SARS-CoV-2 seronegative children were assumed to have been infected due to a number of risk factors, but the connection to COVID-19 could not be confirmed.

> The authors conclude that MIS-C may be a distinct immunopathogenic illness associated with SARS-CoV-2.

Reviewed by: Professor Trevor Duke

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

COVID-19 and multisystem inflammatory syndrome in children and adolescents
https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30651-4/fulltext

> Review of the multisystem inflammatory syndrome in children (MIS-C), including epidemiology, causes, clinical features, current treatment protocols and possible pathological mechanisms for the disease.

> MIS-C is suspected but not confirmed to be a post-viral illness resulting from SARS-CoV-2 approximately four weeks prior.

> There is considerable overlap with Kawasaki disease however MIS-C has some distinguishing features (older age of patients, a higher proportion of African or Hispanic children affected and more pronounced cardiovascular involvement), and the relationship between Kawasaki disease and MIS-C is still unclear.

> Possible pathological mechanisms include viral mimicry resulting in autoantigens, antibody or T cell recognition of viral antigens expressed on infected cells, inflammation mediated by the formation of immune complexes and viral superantigen sequences that activate host immune cells.

> There is no single agreed-upon diagnostic criteria for MIS-C, but several institutions have developed their own guidelines of which most include the following criteria.

- The person is a child or young adult.
- Fever.
- Some criteria include elevated inflammatory markers.
- Single or multiple organ dysfunction.

- Some criteria include the presence of symptoms consistent with Kawasaki disease.
- No other cause or infection to explain symptoms.
- SARS-CoV-2 infection diagnosed via RT-PCR, antigen test or serology (or history of exposure to a known person with COVID-19).

> Most cases of MIS-C have been managed similarly to Kawasaki disease - supportive care, with fluids and possibly inotropes for hypotension, steroids and other immunotherapy (biologics, IVIG) and anticoagulants/antiplatelets for the coagulopathy seen in many patients, prophylactic antibiotics and antiviral agents in certain patients where they may be of benefit.

> The long-term effects of MIS-C are unclear, but patients should have continued to follow up, mainly if they had cardiovascular disease (etc. coronary aneurysms).

Reviewed by: Dr Wonie Uahwatanasakul

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

Multisystem Inflammatory Syndrome in U.S. children and adolescents
https://www.nejm.org/doi/full/10.1056/NEJMoa2021680

> A descriptive study looking at multisystem inflammatory syndrome in children (MIS-C), and the temporal association with COVID-19.

> The authors conducted a retrospective targeted surveillance study across numerous hospital systems and states in the U.S., including patients who met six criteria: serious illness leading to hospitalisation, an age of less than 21 years, fever that lasted at least 24 hours >38.0 °C, laboratory evidence of inflammation, multisystem organ involvement, and evidence of infection with SARS-CoV-2 based on reverse-transcriptase polymerase chain reaction (RT-PCR), antibody testing, or exposure to persons with COVID-19 in the past month.

> Patient characteristics

- The median age was 8.3 years.
- Positive for SARS-CoV-2 PCR by RT-PCR or antibody testing (70%).

> Treatment characteristics: mechanical ventilation (20%); vasoactive support (48%); intravenous immune globulin (77%); glucocorticoids (49%); IL-6 or 1RA inhibitors (20%).

> Organ system involvement: gastrointestinal system (92%); cardiovascular system (80%); haematologic (76%); mucocutaneous (74%); respiratory (70%).

> Complications: death (2%); coronary-artery aneurysms (z scores >2.5) (8%); intensive care (80%).

> Differences between Kawasaki's disease and SARS-CoV-2 MIS-C highlighted (Kawasaki's - 5% present in shock, 25% coronary artery aneurysms, MIS-C 50% in shock, 8% aneurysms).

> MIC-C is uncommon in this age group with COVID-19 infection but can cause life-threatening inflammatory responses in children when it occurs.

Reviewed by: Dr John Cheek

DIAGNOSTICS & SAMPLING

Jun Hua Bowen Lim - 3rd Year Medical Student,
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CovidNudge: diagnostic accuracy of a novel lab-free point-of-care diagnostic for SARS-CoV-2 (not peer reviewed)
https://www.medrxiv.org/content/10.1101/2020.08.13.20174193v1

- The authors describe the diagnostic accuracy and development of a novel point of care diagnostic RT-PCR test which does not require a laboratory or sample pre-processing, named the CovidNudge.
- Traditional RT-PCR lab tests are time-consuming (4-6 hours to complete) and require a laboratory, and this may delay treatment or the implementation of infection control precaution.
- CovidNudge seeks to address this issue by offering a fully-automated direct sample-to-answer platform, targeting seven SARS-CoV-2 gene targets (rdrp1, rdrp2, e-gene, n-gene, n1, n2 and n3) with a run-time under 90 minutes and a validated positive control (human ribonuclease P gene).
- Swab samples were tested in parallel to compare RT-PCR and CovidNudge (n=386 samples from three groups: Group 1 -self-referred healthcare workers with suspected COVID-19, n=280/386; Group 2- patients attending the emergency department with suspected COVID-19, n=15/386; Group 3 - hospital inpatient admissions with or without suspected COVID-19, n=91/386).
- Overall, CovidNudge has a 94% sensitivity and 100% specificity when compared with standard laboratory-based RT-PCR; however, the sensitivity varied by the group. Group 1 had good sensitivity and a close confidential interval (CI), while group 2 and 3 had wide CI, 48%-100% and 20%-100%, respectively.
- Limitations: CovidNudge has a low throughput compared with RT-PCR therefore multiple processing units (Nudgebox) may be needed depending on the clinical setting. Only assessed on oropharyngeal/ nasopharyngeal swabs, other sample types need to be examined.

Reviewed by: Dr Lien Anh Ha Do

EPIDEMIOLOGY & PUBLIC HEALTH

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

Influenza in the COVID-19 Era
https://jamanetwork.com/journals/jama/fullarticle/2769676

- The threat of concurrent influenza and COVID-19 epidemics is a major concern.
- Studies have shown decreased influenza cases from January – May 2020; however, ongoing decreased transmission relies on continued adherence to non-pharmaceutical interventions (e.g., face masks).
- Limitations: Testing for non-SARS-CoV-2 respiratory viruses were reduced during the initial pandemic wave.
- Influenza and COVID-19 have different management, course and required infection control measures.
- Influenza is a source of significant paediatric morbidity and mortality compared with the typically mild disease experienced by COVID-19 paediatric patients.
- Increased importance for seasonal influenza vaccination to minimise viral reservoir in population.
- Patients presenting with nonspecific respiratory symptoms should be tested for SARS-CoV-2.
- Note that coinfection of influenza and SARS-CoV-2 is possible

Reviewed by: Dr Wonie Uahwatanasakul

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

The importance of testing messages
https://www.who.int/bulletin/volumes/98/8/20-030820.pdf

- The author discusses the importance of communication in the time of a global pandemic for the purpose of public action and decision-making.
- A clear and effective message requires knowledge about the audience's concerns and beliefs.
- Testing draft messages on a sample of the population will quickly provide ample information about likely public interpretation and reaction.
- In today's climate, the evidence is being generated at a rapid speed, so filtering and simplification is required to disseminate to the public.

- Especially when issues are complicated, communication should focus on the decisions people make in daily life.
- WHO has consistently produced high-quality communication targeted at a diverse population that is assumed to be responsible in decision making.
- In some circumstances, Coronavirus has been used as a political football, making scientific communication all the more difficult.

Reviewed by: Dr Martin Wright

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

Population-wide testing of SARS-CoV-2: country experiences and potential approaches in the EU/EEA and the United Kingdom
https://www.ecdc.europa.eu/en/publications-data/population-wide-testing-sars-cov-2-country-experiences-and-potential-approaches

- This document from the European Centre for Disease Prevention and Control summarises the experiences of population-wide testing practices in over 53 countries and how they can be applied in the context of the EU/EEA and the U.K.
- A literature review was performed on 11/08/2020, as well as a direct request to 53 countries on 24th July 2020.
- Population-wide testing of SARS-CoV-2 involves screening for SARS-CoV-2 in people irrespective of symptoms or whether they are in a high-risk setting.
- Possible reasons for population-wide testing are to decrease incidence to manageable levels, where one of the public health goals of the country is to eliminate the disease or to understand disease prevalence by age, ethnicity, setting, and location to target public health measures.
- Six countries identified that they were performing some type of population-wide testing. However, many more are performing targeted testing of populations in specific settings - such as health care workers.
- Different approaches to population-wide testing adopted in countries include household testing, individual-initiated testing and testing incoming travellers.
- To be able to perform enough tests, strategies also include pooled or group testing, and the use of screening tests.
- Population-wide testing strategies are more effective when paired with case isolation and contact tracing.
- Countries should increase testing availability and coverage along with robust contact tracing before relaxing physical distancing measures to achieve similar control of the pandemic compared with when stringent physical distancing measures were in place.
- Challenges to population-wide testing include individual's compliance with (repeated) testing irrespective of symptoms, logistics (especially time barriers), test performance (especially when low rates of infection in the community), and resource limitations.

Reviewed by: Dr Martin Wright

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

Prioritising children's rights in the COVID-19 response
https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(20)30172-3/fulltext

> An editorial discussing the wide-ranging impacts of the COVID-19 pandemic on child health.

> Shortages in essential medicines, medical equipment, and health services as resources are diverted to tackle the pandemic.

- Eighty million children under one year are now at risk of vaccine-preventable diseases.
- Over 42,000 additional child deaths each month is predicted across 118 low to middle-income countries.

> Widespread school closures, with 86% of the world's children being out of school during April 2020.

- Risks malnutrition for those who are dependent on school meals.
- Long-lasting impacts on development, wellbeing, and future earning potential.

> Reduced economic activity and household income.

- An additional 42-66 million children may fall into extreme poverty.
- Increased risk of child labour and child marriage.

> Recommendations for overcoming these issues:

- Prioritise the rights of children in the pandemic response and recovery.
- Consider the opportunities that the recovery provides for advancing human development and reducing disparities.
- Ensure health systems are more equitable and resilient.
- Prioritise education, especially in the early years of childhood.
- Establish strong social protection for children, particularly those at the margins of society.

Reviewed by: Dr Martin Wright

GLOBAL HEALTH

WHO situation report 209
https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200816-covid-19-sitrep-209.pdf?sfvrsn=5dde1ca2_2

Burnet COVID-19 Global Trends and Analyses Health Care Workers, Aerosol Spread
https://burnet.edu.au/system/asset/file/4183/8.2_Know_C-19_Hub_Global_Analysis_August_21_FINAL.pdf

Adolescent experiences of COVID-19
https://www.gage.odi.org/adolescent-experiences-of-covid-19/

IMMUNOLOGY

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

Pre-existing immunity to SARS-CoV-2: the knowns and unknowns
https://www.nature.com/articles/s41577-020-0389-z

> A comment article discussing the T cell reactivity against SARS-CoV-2 observed in unexposed people as reported by five different studies.

> The source of T cells and whether they are memory T cells as well as their role in protection against COVID-19 remains unknown.

> It is speculated that SARS-CoV-2-specific T cells in unexposed individuals might originate from memory T cells derived from exposure to 'common cold' coronaviruses (CCC); more than 90% of the human population is seropositive for at least three of the CCC.

> Potential implications for pre-existing T cell cross-reactivity against COVID-19:

- Influence COVID-19 severity; high level of pre-existing memory CD4+ T cells may recognise SARS-CoV-2 and mount a faster and stronger immune response, limiting disease severity.
- CCC exposure and disease severity; it will become important to understand the patterns of CCC exposure in space and time, such that differences in CCC geo-distribution may have a different burden of COVID-19 disease severity.
- Influence vaccination outcomes. Pre-existing T cell memory may lead to a faster or better immune response, particularly the development of neutralising antibodies, which generally depend on T cell help. This may also confound small phase I vaccine trials, leading to skewed conclusions.
- Detrimental to protection through immune mechanisms such as 'original antigenic sin' (the propensity to elicit potentially inferior immune responses owing to pre-existing immune memory to a related pathogen), or through antibody-mediated disease enhancement.

Reviewed by: Dr Ryan Toh

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

Robust T cell immunity in convalescent individuals with asymptomatic or mild COVID-19 (pre-proof)
https://www.sciencedirect.com/science/article/pii/S0092867420310084?via%3Dihub

- This study aimed to characterise SARS-CoV-2-specific memory T cells in unexposed individuals, exposed family members, and in individuals with acute or convalescent COVID-19.
- Acute phase SARS-CoV-2-specific T cells displayed a highly activated cytotoxic phenotype (CD8+CD38+PD1+/HLA-DR+/Ki67+), that correlated with various markers of clinical severity.
- Convalescent phase SARS-CoV-2-specific T cells were polyfunctional and displayed a stem-like memory phenotype (CCR7+ CD127+ CD45RA−/+ TCF1+).
- Cross-reactive T cell responses against SARS-CoV-2 were detected in 30% of unexposed individuals, which may be due to seasonal coronaviruses.
- Robust SARS-CoV-2 specific T cell responses were detectable months after exposure, even in the absence of detectable circulating antibodies, in exposed family members and convalescent individuals with a history of asymptomatic and mild COVID-19.
- Limitations included the cross-sectional design of the study, preventing follow-up and the limited sample size in each donor group. Consequently, it is unable to be determined if robust memory T cell responses, in the absence of detectable antibodies, can protect against severe forms of COVID-19.

Reviewed by: Dr Ryan Toh

MENTAL HEALTH

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

Child and adolescent mental illness during COVID-19: a rapid review
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7363598/pdf/main.pdf

- A rapid review of child and adolescent anxiety, depression, and traumatic stress experienced during the COVID-19 pandemic.
- To date, there is a paucity of literature estimating the prevalence of child and adolescent mental illness during the COVID-19 pandemic.
- However, findings from published studies (six articles met full inclusion criteria) suggest an increase in anxiety and depressive symptoms.
- The results of studies that assessed risk factors for developing mental illness are limited or mixed but suggest external factors (such as virus prevalence in the community, parental anxiety) are significant.
- Only two studies reported consideration of protective factors, suggesting that awareness of COVID-19 and life-style factors such as physical exercise were effective.
- Limitations include a lack of pre-COVID-19 pandemic baseline data, that all studies were from early in the pandemic, failing to estimate the number of children and adolescents that meet clinically relevant phenotypes, and a lack of longitudinal studies that assess if behavioural changes are persistent over time.
- Further methodologically strong studies are needed to assess the consequences of the COVID-19 pandemic on child and adolescent mental health.

Reviewed by: Dr Martin Wright and Professor David Coghill

PERINATAL HEALTH

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

Anatomical and timely assessment of protein expression of angiotensin-converting enzyme 2, SARS-CoV-2 specific receptor, in fetal and placental tissues: new insight for perinatal counselling
https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1002/uog.22178

- It was hypothesised that low rates of perinatal infection may be related to low expression of ACE2 (the receptor for SARS-CoV-2) in the placenta and fetal organs.
- Using immunohistochemistry, the group assessed levels of ACE2 expression in paraffin-embedded tissues of organs (kidneys, brain, lungs, GIT, heart) from 5 medical terminated pregnancies (15-38 weeks gestation) in healthy women obtained from a registered biobank. This was matched to an eight-year-old child (n=4) as controls. Seven placentas, including those from the five cases, were analysed. One placenta was obtained from a symptomatic SARS-CoV-2 infected pregnancy at 34 weeks.
- ACE2 protein expression was detected in fetal kidneys, testis, rectum and ileum from 15 weeks + 5 weeks onwards. This was also seen in the paediatric controls.
- In the lung, weak expression ACE2 was detectable at 15 weeks in type 2 pneumocytes and absent thereafter. In paediatric controls, ACE2 expression was detected in type 2 pneumocytes.
- No ACE2 expression was found in the cortex or ependymal of the brain or in cardiac tissue.
- ACE2 expression was observed in the syncitiotrophoblast and cytotrophoblast from 7 weeks but not in the amnion. It was also found in the maternal placenta.
- Possible clinical implications: expression of ACE2 in placental tissues supports the notion that SARS-CoV-2 is able to cross the placenta at any gestational time. However, as the expression is absent in the fetal brain, risk of neurological sequelae may be less likely as a result of perinatal infection. As the amnion was not observed to have ACE2 expression, the chorioamnionitis reported in association with SARS-CoV-2 infection likely results from ascending infection following prolonged rupture of membranes.
- As this is a limited observational study, further studies are required to validate these observations and explore clinical implications.

Reviewed by: Professor Julie Bines

SCHOOLS

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

SARS-CoV-2 infection and transmission in educational settings: cross-sectional analysis of clusters and outbreaks in England
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/911267/School_Outbreaks_Analysis.pdf

- Public Health England initiated enhanced national surveillance following the reopening of educational settings during the summer mini-term on 1st June 2020.
- There were 67 single confirmed cases, four co-primary cases and 30 COVID-19 outbreaks during June 2020, with a strong correlation between the number of outbreaks and regional COVID-19 incidence (0.51 outbreaks for each SARS-CoV-2 infection per 100,000 in the community; p=0.001).
- Overall, SARS-CoV-2 infections and outbreaks were uncommon across all educational settings.
- Staff members had an increased risk of SARS-CoV-2 infections compared to students in any educational setting, and the majority of cases linked to outbreaks were in staff.
- The probable transmission direction for the 30 confirmed outbreaks was: staff-to-staff (n=15), staff-to-student (n=7), student-to-staff (n=6) and student-to-student (n=2).
- SARS-CoV-2 infections and outbreaks were uncommon in educational settings during the first month after the easing of national lockdown in England. The strong correlation with regional SARS-CoV-2 incidence emphasises the importance of controlling community transmission to protect educational settings. Additional interventions should focus on reducing transmission in and among staff members.

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

COVID-19 in schoolchildren: a comparison between Finland and Sweden
https://www.folkhalsomyndigheten.se/contentassets/c1b78bffbfde4a7899eb0d8ffdb57b09/covid-19-school-aged-children.pdf

- A comparison between Finland and Sweden infection rates in school-age children was undertaken.
- Finland: All schools closed 18th March – 13th May, except children in grades one to three whose carers were essential workers.
    - Confirmed cases did not fluctuate with school closure or change in testing policy in Finland.
    - Children not contributing to transmission.
    - Primary school reopening did not increase child infection rates.

> Sweden: Daycare and primary schools remained open throughout the pandemic.
  - A number of confirmed cases affected by a change in testing policy.
  - No increased risk of COVID-19 in teachers.
> No overall incidence difference of COVID-19 cases between the countries in 1-19 year olds.
> Negative effects of a school closure: Primary effects (e.g. social character) and secondary effects (e.g., parents having to home school children).
> School closures have no measurable direct impact on confirmed cases of COVID-19 in school-aged children.
> Negative effects of school closures may outweigh the positive effects on COVID-19 cases.
> Public health mitigation measures are still required.

Reviewed by: Professor Fiona Russell

Emma Tovey Crutchfield - 3rd Year Medical Student, Department of Paediatrics, The University of Melbourne

Returning to School in the Era of COVID-19
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2769633

> The following four factors are most heavily influencing parents' decision-making on return to school: fears of COVID-19, a multisystem inflammatory syndrome in children, ability to home-school and confidence in the school system.
> Other considerations of families and schools include:
  - The success of virtual learning. Research shows that Black, Latinx and Native American students have experienced an additional three-month loss of learning compared with other students, owing to inequities such as poor internet, quality of online learning programs and reduced access to electronics;
  - The burden of COVID-19 disease and death which has been disproportionately higher amongst Black, Latinx and Native American communities;
  - Parental employment. Socioeconomically disadvantaged families are more likely to depend on inflexible jobs. In response, families intend to keep their children home. Ironically, many of these same families depend on critical services supplied by the school: physical activity, health services and nutrition;
  - Educated parents were found to have more confidence in school's safety standards and hence, are more likely to send their children back to school;
  - Children with disabilities who often heavily depend on school services for learning and healthy development.
> It is critical to apply an 'equity lens' when assisting families and schools deliver online or in-person learning during the COVID-19 pandemic.
> The authors contend that it is the responsibility of schools to assist families in their decision-making on return to school during the COVID-19 pandemic.

Reviewed by: Professor Fiona Russell

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

Transmission of COVID-19 in school settings and interventions to reduce the transmission: a rapid review
https://phe.koha-ptfs.co.uk/cgi-bin/koha/opac-retrieve-file.pl?id=45d305bc223d425af0fcbd60e8108a32

- A rapid review of nine studies (three epidemiological and six modelling studies (including five preprints) which aimed to identify and assess direct evidence on the transmission of COVID-19 within school settings, and on the effectiveness of school-based interventions in reducing transmission.
- Evidence consistently suggests that transmission of COVID-19 within school settings may be low, however this is based on a small number of studies and the evidence is considered to be weak. Further research and analysis is needed.
- Evidence on the effectiveness of school-based interventions is currently limited to modelling studies which considered the population impact of school closures or reopening. The modelling studies calibrated with U.K. and E.U. data predict the reopening of schools at reduced capacity, particularly for younger children, may not increase the R_0 greater than one. However, this is based on six studies, of which five were preprints so the evidence is considered to be weak.

Reviewed by: Professor Fiona Russell

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

Plans of U.S. parents regarding school attendance for their children in the fall of 2020: a national survey
https://jamanetwork.com/journals/jamapediatrics/fullarticle/2769634

- Cross-sectional convenience sample between 2nd June and 5th June 2020 of 730 parents, sampled to reflect U.S. population norms for race and ethnicity.
- Parents surveyed online to examine factors influencing their decision whether or not to send their child to school in fall 2020.
- 31% parents would probably or definitely keep children home. 49% indicate probably or definitely send their children to school.
- Factors associated with plans to keep children at home: lower income, being unemployed, having a flexible job, fear of COVID-19, fear of multisystem inflammatory syndrome, and decreased confidence in schools being able to manage the risks of COVID-19.
- Socio-economic and family characteristics contributed moderately to the variability in plans to send children to school (R2 =16%).
- Parent attitudes and beliefs explained moderately more variation (ΔR2= 11%)
- Race and ethnicity were not significantly associated with plans to keep children home.

> Conclusions; some of the reasons parents might consider keeping their child home are amenable to education and supports from school. Others relate to broader factors such as the economic effects of COVID-19 on employment.

Reviewed by: Dr Martin Wright

THERAPEUTICS

Nicholas Wu – 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

The impact of sofosbuvir/daclatasvir or ribavirin in patients with severe COVID-19
https://academic.oup.com/jac/advance-article/doi/10.1093/jac/dkaa331/5889946

> This was an open-label, non-randomised, parallel clinical trial at Taleghani Hospital in Abadan, Iran that evaluated the effectiveness of sofosbuvir/daclatasvir versus ribavirin in treating hospitalised patients with severe COVID-19 between the 18th March and 16th April 2020.

- The inclusion criteria were hospitalised patients with either positive nasopharyngeal swab RT-PCR for SARS-CoV-2 or bilateral multi-lobar ground-glass opacity on chest C.T., and signs of severe COVID-19 (oxygen saturation < 94%, respiratory rate > 24/min or decreased level of consciousness).
- The exclusion criteria were patients < 18 years, pregnant and breastfeeding women, severe anaemia (haemoglobin < 7 mg/dL), prior COVID-19 treatment, and patients not consenting.
- Treatment allocation was based upon which clinician was in charge at admission.

> Thirty-five patients received sofosbuvir/daclatasvir 400 mg/60 mg daily, and 27 patients received ribavirin 600 mg every 12 hours. Both arms also received the national standard treatment protocol of lopinavir/ritonavir 200/50 mg every 12 hours and a single dose of hydroxychloroquine 400 mg on admission.

> The median duration of hospital stay was five days for the sofosbuvir/daclatasvir arm versus nine days for the ribavirin arm.

- The mortality rate was 2/35 (5.7%) for the sofosbuvir/daclatasvir arm versus 9/27 (33%) for the ribavirin arm.
- The relative risk of death for the sofosbuvir/daclatasvir arm versus the ribavirin arm was 0.17 (95% CI 0.04-0.73, P=0.02).
- The number needed to treat (NNT) for the benefit for the sofosbuvir/daclatasvir arm was 3.6 (95% CI 2.1-12.1, P<0.01).

> Treatment of hospitalised patients with severe COVID-19 with sofosbuvir/daclatasvir is significantly more effective than ribavirin with a shorter duration of both hospital and ICU stay, lower mortality rate, improved clinical symptoms, and fewer adverse effects.

- These preliminary results potentially warrant further investigation in double-blind, randomised clinical trials.

> Limitations: Although there was no statistically significant difference in baseline observations, the inability to perform a blinded and fully randomised clinical trial is a significant shortcoming.

- Treatment allocation was linked to treating doctor.
- Sofosbuvir is not available as monotherapy in Iran, so it is indeterminate as to whether both sofosbuvir and daclatasvir are active molecules, or if it is only one of these that is active.
- There was no sample size calculation performed, and the numbers were small.

Reviewed by: Professor Jim Buttery

Grace Newman – 3rd Year Medical Student, Department of Paediatrics, The University of Melbourne

Convalescent Plasma Therapy for COVID-19: State of the Art (review)
https://cmr.asm.org/content/33/4/e00072-20

> If a new pathogen induces an immune response with the production of neutralising antibodies, passive transfusion of convalescent plasma (C.P.) is a feasible therapeutic strategy by clearance of viraemia.

> C.P. donor recruitment should be based on neutralising antibody titre assessed with a plaque reduction neutralisation test or ELISA. The donor should ideally live in the same area as the intended recipient to address possible mutations of the target viral antigens. Possible approaches include screening general regular blood donor population, recruitment of hospital-discharged patients or calls to positive cases under home-based quarantine.

> C.P. should be collected by apheresis with plasmapheresis additionally benefitting convalescent COVID-19 donors.

> Additional pathogen reduction technologies would be required, such as solvent/detergent filtered plasma (>4 log inactivation of most enveloped viruses), photoinactivation, or fatty acids.

> A mini pool fractionation scale process based on caprylic acid precipitation has been under development in Egypt since 2003 and has proved effective at purifying coagulation factors.

> The titration of anti-A and anti-B isoagglutinins and the transfusion of low-titre non-ABO-compatible C.P. units is recommended for A.B. recipients.

> SARS-specific neutralising antibodies usually persist for two years, while antibody responses to MERS persist for less than one year. In MERS, patients with mild disease have very low antibody titres.

> In SARS-CoV-2 serum IgM and IgA appear as early as day five and IgG can be detected at day 14; however, their duration in plasma is unknown. Virus shedding can last as long as 37 days, meaning RNA screening is required in C.P. donors.

> Contraindications to C.P. therapy include allergy to plasma protein or sodium citrate, selective IgA deficiency or treatment with immunoglobulins in the last 30 days. Also, concurrent viral or bacterial infections, thrombosis, poor compliance, short life expectancy and pregnancy or breastfeeding.

> Some published studies and case studies regarding COVID-19 and C.P. transfusion

- A series of case studies have demonstrated the efficacy of C.P. in treating COVID-19, including ARDS and patients on mechanical ventilation in some patients, while some showed no improvement in mortality despite viral clearance.
- A significant case series in Wuhan (n=138) with patients transfused with C.P. at a median of 45 days after symptom onset experienced 50% lower ICU admission rate and mortality compared with best supportive care.
- A retrospective RCT in New York transfused 39 patients with severe COVID-19 with ABO-matched CP. Recipients were more likely than control to not increase supplemental O_2 requirements (OR 0.86), but survival only improved for non-intubated patients (HR 0.19).
- An expanded access program in the USA has led to the treatment of more than 30,000 patients. A preliminary report of the first 20,000 patients showed <1% severe adverse events and 14.9% mortality at 14 days and suggested a benefit compared with results with historical cohorts.

> Concerns: transfusion-transmitted infection, TRALI, antibody-dependent enhancement (passive or active antibodies enhancing virion entry into macrophages leading to increased TNF and IL6 production and cytokine storm) and worsening of underlying coagulopathy.

> There are many ongoing clinical trials assessing the use of C.P. in COVID-19 patients.

> C.P. has been approved by the FDA for Emergency Use Authorization for Convalescent Plasma as Potential Promising COVID–19 Treatment.

Reviewed by: Professor Jim Buttery

TRANSMISSION

Juliana Wu - 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

Wrong person, place and time: viral load and contact network structure predict 5 SARS-CoV-2 transmission and super-spreading event (not peer reviewed)
https://www.medrxiv.org/content/10.1101/2020.08.07.20169920v2

- COVID-19 is difficult to contain because most transmissions occur during the pre-symptomatic phase of infection.
- While most infected individuals do not transmit the virus to anyone, there is a small proportion that infect large numbers of people- these are known as super-spreaders events.
- Approximately 10-20% of infected individuals account for 80% of COVID-19 transmissions.
- Authors designed a mathematical model to illustrate the pattern of viral load in an infected individual and investigate the conditions required for a super-spreader event to occur.
- The overarching pattern of infection appeared to be an early viral peak followed by a decelerating viral clearance phase which led to a temporary plateau at a lower viral load and then rapid viral elimination.
- Transmission after the first week of infection is rare and highest during the pre-symptomatic phase of infection.
- A study found that massive super-spreader events occurred almost exclusively when individual viral loads exceeded 107 RNA copies with high levels of concurrently exposed contacts.
- Modelling showed that transmission is unlikely if nasal viral load is below 105 RNA copies and is extremely likely when shedding exceeds 108 RNA copies.
- Those with low nasal viral loads, particularly during late infection, may not need full patient isolation procedures.
- Newly diagnosed individuals may be past the peak of their spreading potential, but their contacts may not be, highlighting the importance of early contact tracing and quarantine measures for contacts of infected individuals.

Reviewed by: Professor Fiona Russell

Evelyn Andrews - 4th Year Medical Student, Department of Paediatrics, The University of Melbourne

Risk of fomite-mediated transmission of SARS-CoV-2 in child daycares, schools, and offices: a modelling study (not peer reviewed)
https://www.medrxiv.org/content/10.1101/2020.08.10.20171629v1

> This study used an adapted version of a published fomite transmission model to assess the potential for spread of SARS-CoV-2 via contaminated surfaces (fomites).

> The primary aims were to explore differences in fomite transmission based on location (child daycares, schools and offices), surface disinfection frequency (hourly, four-hourly and eight-hourly), and surface type (stainless steel, plastic and cloth).

> The fomite R_0 exceeded one in all three locations, ranging from two in offices to about 20 in child daycares.

- Hourly surface disinfection brought the fomite R_0 below one in some office settings but was inadequate in schools and child daycares.
- Surface disinfection was effective in a wider range of settings when paired with reduced viral shedding (such as with mask-wearing), although child daycares remained a high risk.
- Decay rates on cloth are high and unlikely to sustain transmission, compared with stainless steel and plastic.

> Fomite transmission alone could sustain ongoing viral spread in all of the locations examined.

- Hourly surface disinfection in office settings may be enough to interrupt viral transmission.
- Childcare settings are particularly high-risk and remain so even when viral shedding is low, and surfaces are cleaned hourly. The authors suggested that in these settings, additional cleaning interventions directly after shedding events (e.g. after a child coughs directly on a surface) may be beneficial in addition to regular interval cleaning.
- Frequent disinfection is most important for frequently-touched, non-porous surfaces, such as steel and plastic. Porous surfaces, such as plush toys, do not require such frequent cleaning due to low viral persistence.

Reviewed by: Dr Celeste Donato

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

Kinetics of viral clearance and antibody production across age groups in SARS-CoV-2 children (not peer reviewed)
https://www.medrxiv.org/content/10.1101/2020.08.06.20162446v1?%253fcollection=

> 6,324 symptomatic and asymptomatic paediatric patients (< 22 years) presenting to a large children's hospital in Washington, DC.
  - 592 patients with positive SARS-CoV-2 RT-PCR from nasopharyngeal swab, of which 68 had a follow-up negative RT-PCR result.
  - 58 patients with positive anti-SARS-CoV-2 IgG antibody testing, of which 33 had both a positive RT-PCR result and positive serology result.

> The median duration of viral shedding (RT-PCR positivity) was 19.5 days (IQR 12-39; max 62).
  - The median time to RT-PCR negativity from initial positivity was 25 days.
  - The time to negativity was correlated with age:
    - Patients aged 6-15 years took longer to achieve negativity (median 32 days) compared with those aged 16-22 years (median 18 days).
  - The median time to IgG seropositivity from RT-PCR positivity was 18 days.
  - 17/33 patients developed neutralising levels of anti-SARS-CoV-2 IgG antibodies with a median time to reach adequate levels of antibodies for neutralisation of 36 days.

> Anti-SARS-CoV-2 IgG antibodies can be detected in blood samples of children before the viral clearance.
  - This study demonstrated a difference between age groups in the time to SARS-CoV-2 RT-PCR negativity.
  - It remains uncertain whether IgG antibody production correlates with immunity and how long measurable antibodies persist and protect against future infection.

> Limitations: Retrospective study relying on laboratory data only.
  - The timing of symptom onset and collection of samples at defined time intervals could not be performed, thus limiting the ability to create a clear timeline of positivity and negativity.
  - Due to the reliance on RT-PCR the period of 'positivity' does not necessarily correlate with the period of infectivity, as the presence of viral genome detected by RT-PCR may not correlate with transmissibility.
  - Conclusions are drawn between the development of neutralising levels of antibodies and RT-PCR negativity based on small numbers (n=17).

Reviewed by: Dr Samantha Bannister

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

Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020
https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2020.25.32.2001483#html_fulltext

> Understanding how the RT-PCR detection correlates with the presence of infectious SARS-CoV-2 can inform and support infection control measurements. The study investigated:
  - The kinetics of viral RNA detection from respiratory samples over the disease onset.
  - The relationship between Ct-value (a semi-quantitative value representing the viral titre) and the ability to recover infectious virus from clinical samples.
  - The relationship between symptoms onset and the ability of having infectious viruses defined by successful viral isolation.
  - The differences in viral shedding/ viral culture and the presence of symptoms across different age groups.

> The study was based on a real-world dataset in a single laboratory analysing upper respiratory tract (URT) samples of suspected COVID-19 cases.
  - The level of SARS-CoV-2 RNA in the URT was greatest around symptom onset, steadily decreased during the first ten days after illness onset and then plateaued.
  - The estimated odds ratio (OR) of recovering infectious virus decreased by 0.67 for each unit increase in Ct value (95% CI: 0.58–0.77).
  - Culture positive rate peaks at symptom onset (42%), remains high on day seven (40.1%, 95% CI: 22.8–60.4) and gradually declines (6%, 95% CI: 0.9–31.2) by day ten.
  - No difference in Ct values across different age groups (p=0.12). No difference in culture-positive rate between symptomatic and asymptomatic individuals (OR = 0.66; p = 0.23). Both symptomatic and asymptomatic individuals with mild-moderate COVID-19 carry infectious viruses.

> Infection control measures are required immediately after symptom onset until day ten (minimum timeline).

> Observational epidemiological data of known infector–infectee pairs will further understandings of infectiousness and transmissibility.

Reviewed by: Dr Lien Anh Ha Do

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

Clustering and superspreading potential of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Hong Kong (pre-print)
https://europepmc.org/article/ppr/ppr165671

> The authors used contact tracing data to characterise SARS-CoV-2 clusters in Hong Kong.

> With a super spreading threshold of six to eight secondary cases, five to seven probable superspreading events were identified.

- An estimated 20% of cases were responsible for 80% of local transmission cases.
- Social exposures resulted in a greater number of secondary cases compared with family or work exposures.
- Delays between the onset of symptoms and isolation did not reliably predict the number of individual secondary cases or resulting cluster size.

> Overall there is substantial potential for superspreading events in COVID-19 but less than for SARS and MERS.

- Public health authorities should focus on rapid tracing and quarantine of contacts, along with physical distancing to prevent superspreading events in high-risk social environments such as bars, nightclubs and restaurants.

> Limitations: Incomplete case ascertainment and contact tracing data introduce bias.

- Furthermore, 50 sporadic local infections could not be determined.
- Whilst the evidence supported rapid contact tracing and effectiveness of quarantine, it was found that most chains of transmission did not terminate in quarantine. This must be interpreted in the context of moderate physical distancing in Hong Kong, rather than suggesting quarantine is not essential or effective.

Reviewed by: Professor Julie Bines

VACCINES

Grace Newman – 3rd Year Medical Student,
Department of Paediatrics, The University of Melbourne

A single dose of an adenovirus-vectored vaccine provides protection against SARS-CoV-2 challenge
https://www.nature.com/articles/s41467-020-17972-1

> This study evaluates the protective efficacy of mucosal vaccination, in addition to intramuscular vaccination for SARS-CoV-2 in animal models.

> Methods: the full spike (S) protein based on Wuhan-Hu-1 strain was used as an immunogen in a replication defective human adenovirus type 5-based COVID-19 vaccine.

- BALB/c mice (n=10 per group) received a single immunisation of high dose (5x109), middle dose (5x108) or low dose (5x107) Ad5-nCoV virus particles or control Ad5 vector (5x109) by intramuscular (IM) or intranasal (IN) route. 7/10 vaccinated mice in each group were inoculated intranasally with mouse-adapted SARS-CoV-2 at week ten post vaccination.

- Ferrets were also vaccinated via the IM and IN route (n=6 per group). Ferrets challenged IN with SARS-CoV-2 at week four post vaccination. SARS-CoV-2 can replicate efficiently in the upper respiratory tract of ferrets but not in the lungs.

> S specific IgG, specific neutralising antibody and cellular immune responses detected in each group.

- ELISA IgG titres peaked at day 28 in the IM group and then slightly decreased. The IN group level remained at a steady peak from week four to eight.

- There were higher IgG titres for the high-dose IN than in the IM groups at week six and week eight with no significant difference in the middle or low dose IM and IN groups.

- Neutralising antibody levels peaked at week 6 in the IN group and week eight in the I.M. group. Levels were significantly higher in the high dose IN than IM group at week four and six and week eight. There was no difference in the middle dose group at week six and eight and no difference at any time in the low dose group.

- S-specific IgG was found in the trachea-lung wash in both groups at week two and ten but S-specific IgA was only found in the IN group. Neutralising antibody was also detected in both high dose group trachea-lung washes.

- The middle dose IM and IN caused significant response in splenic CD8 T cells or CD4 T cells with higher levels in the IM group.

- After virus inoculation, no virus was detected in the lungs of all IN and IM vaccinated mice groups at day three and five post inoculation (control IN and IM group demonstrated significant viral load). There was no virus detected in the turbinates of IN vaccinated mice, however, the virus was detected in some of the IM vaccinated mice but with a significant reduction in load compared with controls.

- In the ferrets, no virus was detected in the nose washes of the mucosal vaccination group but was found in all infected controls. Virus was detected in the nose washes of 3, 2 and 0 of the IM vaccinated group at 2, 4, and 6 & 8 days post inoculation with a significant reduction in viral load compared with controls.

> Complete protection for the upper and lower respiratory tract against SARS-CoV-2 infection can be achieved using a single mucosal inoculation of Ad5-nCoV in mice.

- A single IM inoculation of Ad5-nCoV can protect the lungs of mice from SARS-CoV infection and significantly reduce viral replication in the upper respiratory tract of mice and ferrets.

- Different routes of vaccination should be considered in human clinical trials for the development of SARS-CoV-2 vaccines.

> Limitations: Animal infection via the nasal route do not reflect realistic human exposure and humans are a much more permissive host to SARS-CoV-2.

Reviewed by: Professor Fiona Russell

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

COVID-19 vaccine intention in the U.K.: results from the COVID-19 vaccination acceptability study (CoVAccs), a nationally representative cross-sectional survey (not peer reviewed)
https://www.medrxiv.org/content/10.1101/2020.08.13.20174045v1

> Survey of 1,500 participants from the U.K. looking at projected COVID-19 vaccine uptake and acceptability

> A survey was conducted online and explored participant's personal and clinical characteristics, previous history of influenza vaccination, general vaccination beliefs, beliefs and attitudes about COVID-19 and history of COVID-19 infection, as well as demographic information

> Results:

- 64% of participants said they would likely receive a COVID-19 vaccine.

- 27% of participants were unsure whether or not they would get the vaccine.

- 9% of participants reported that they were unlikely to get vaccinated.

- 77% of the variation in vaccine intention was explained by personal and clinical characteristics, previous influenza vaccination, general vaccine beliefs and beliefs and attitudes about COVID-19.

- The factor that explained the greatest proportion of the variance (20%) was attitudes and beliefs about COVID-19.

- Herd immunity could be achieved with 60% vaccine uptake, and so these results indicate that could be achieved, however, vaccination intention is likely to be higher than actual vaccine uptake.
- Attitudes and beliefs about COVID-19, were the strongest factors with intentions to uptake the vaccine - indicating that this is an important issue for public health officials to understand and address to try and improve vaccine uptake.
- Public acceptance of COVID-19 vaccines will vary at different stages of the pandemic and depend of perceived disease severity, vaccine safety and effectiveness.

Reviewed by: Associate Professor Margie Danchin

VIROLOGY

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

Effects of a major deletion in the SARS-CoV-2 genome on the severity of the infection and the inflammatory response: an observational cohort study
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31757-8/fulltext

> Infection with a SARS-CoV-2 variant that has a 382-nucleotide deletion (Δ382) in the open reading frame 8 (ORF8) of its genome was observed in some COVID-19 cases in a number of countries. The function of the ORF8 protein is still unknown, but some studies have suggested that it could help the virus evade some of our immune responses.

> This observational multicentre cohort study was conducted in Singapore to investigate the implications of this deletion on the clinical outcomes of the disease.

> Study population: 131 patients with PCR-confirmed SARS-CoV-2 infection.

- 92 (70%) were infected with only the wild-type virus.
- 29 (22%) were infected with only the Δ382 variant.
- 10 (8%) had co-infection with both the wild type and the Δ382 variant viruses.

> Compared with patients infected with only the wild-type virus, those infected with only the Δ382 variant:

    - Were younger, presented later after symptom onset, with milder symptoms (lower median temperature and less systemic inflammation).
    - Were less likely to develop hypoxia requiring supplemental oxygen.
    - Had lower concentrations of proinflammatory cytokines, chemokines and growth factors associated with severe COVID-19 and more effective T-cell responses and platelet aggregation.

- All three infection groups had similar rates of pneumonia and were similar by sex and comorbidities.

> Limitations: The reported odds ratio for developing hypoxia requiring supplemental oxygen was only adjusted for age and presence of comorbidities; there might have been other confounders not accounted for.

- Results on the differences in the concentration of immune mediators between the groups only include data from 97/131 patients as plasma samples were not available for the rest of patients.

> Patients infected with the Δ382 SARS-CoV-2 variant had a milder disease and mounted a more effective immune response compared with those infected with the wild-type virus. Further studies of SARS-CoV-2 variants with a deletion in the ORF8 region could have implications for the development of treatments and vaccines.

Reviewed by: Dr Celeste Donato

OTHER RESOURCES

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

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

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

Lancet COVID-19 papers
https://www.thelancet.com/coronavirus?utm_campaign=tlcoronavirus20&utm_content=126383502&utm_medium=social&utm_source=twitter&hss_channel=tw-27013292

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

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

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

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

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

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

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

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

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

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

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

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

Introduction to Coronavirus: free, online course aimed at teenagers and young adults: scientists and experts from the London School of Hygiene & Tropical Medicine explain research to understand the virus and guide the global response to Coronavirus
https://www.open.edu/openlearncreate/course/view.php?id=5319

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