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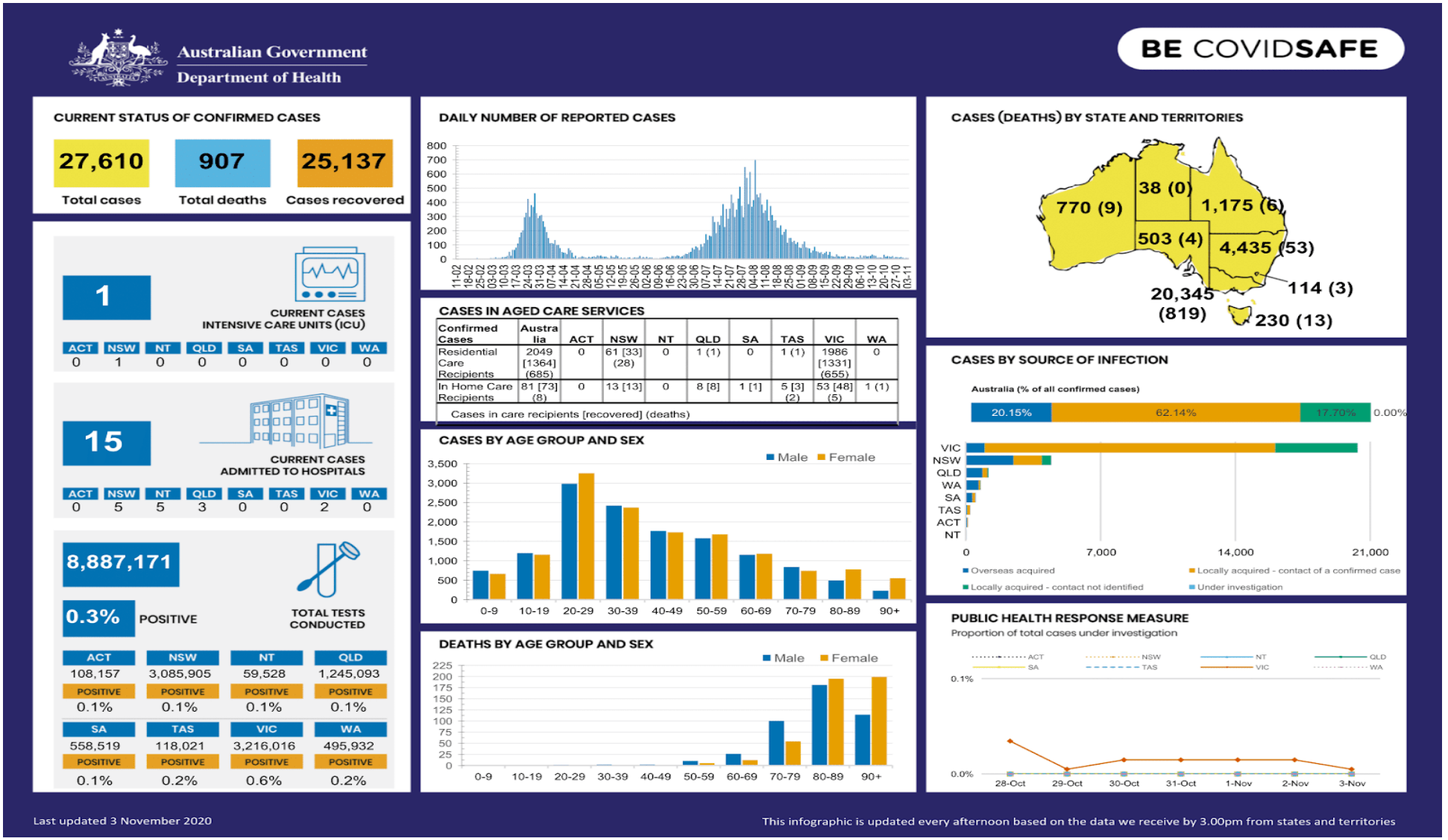
COVID-19 KIDS RESEARCH EVIDENCE UPDATE

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

Weekly Update No.29
5th November 2020



Source: Australian Government: Department of health [Internet]. 2020 [updated 2020 November 3; cited 2020 November 4]
Available from: https://www.health.gov.au/resources/collections/coronavirus-covid-19-at-a-glance-infographic-collection

GUEST EDITORIAL

Associate Professor Paul Licciardi - Team Leader, New Vaccines-Immunology, MCRI; Honorary Fellow, Department of Paediatrics, The University of Melbourne; Honorary Fellow, Menzies School of Health Research, Darwin; Consultant, Singapore Polytechnic

Unravelling the true level of exposure to SARS-CoV-2

As at 2nd November 2020, there have been more than 46 million documented cases and more than 1.2 million deaths from SARS-CoV-2 infections worldwide. Largely, this data is based on laboratory PCR- confirmed detection of the virus, and although highly accurate (and considered the gold standard), does not reveal the true burden of this virus. This is because many SARS-CoV-2 infections do not cause any symptoms (asymptomatic) or produce only very mild symptoms that are not actively tested for. This is particularly true in children where severe illness is rare.

Since the early stages of the pandemic, there has been a major effort to understand the 'true' burden of SARS-CoV-2 infections based on antibody or serological testing. Initial studies were quick to identify that antibodies to SARS-CoV-2 could be generated as early as 7 days post-infection in some individuals, but that reliable detection of antibodies could be achieved after around 14-20 days. These antibodies, namely IgG (but also IgM and IgA), have been measured in many studies as a means to not only determine the nature of the antibody response to those who we know were infected (PCR-confirmed) but also to identify those individuals who were infected but asymptomatic. In particular, neutralising antibodies are typically measured as these are considered the most functional type of antibody produced (1). However, not all laboratories can measure these due to the need for specialised facilities, so SARS-CoV-2-specific antibodies in serum have been measured primarily by commercial or in-house ELISAs or by hospital-based platforms as well as lateral-flow rapid tests (although these have not performed as well to date). Data from serological studies suggested that antibodies primarily targeted the Spike protein, and more specifically, the Receptor-binding domain (RBD) of the Spike protein (2) as this is the main target of neutralisation. It also became clear that in general, these antibodies appeared to develop quicker and to a higher magnitude based on disease severity. This provided the first clue that in cases with mild or asymptomatic infection, these antibodies may be at lower levels or possibly be undetected.

As the performance of these assays improved over time, more reliable data started to emerge on the seroprevalence of SARS-CoV-2 antibodies in different populations. The WHO established the Solidarity II and Unity groups to develop and share reagents and methods so that countries could undertake serosurveys to estimate the true exposure of populations to this virus. SeroTracker, a global SARS-CoV-2 seroprevalence dashboard, has since become available with up to date information from global serosurveillance studies (3). Data from several studies have suggested that virus exposure is higher than first realised, with regional estimates for some hotspot cities almost 40%, and possibly even higher. Understanding who has been exposed to the virus is critical to answering key questions around susceptibility and transmission as well as for policy and decision making around social restrictions and who to vaccinate. No such data has been reported from Australia on this dashboard. One important question that remains unanswered is the seroprevalence in children, as this would inform whether children are indeed reservoirs of the virus in the community and a source of transmission, the so-called silent spreaders.

Data from school outbreaks suggest that children do not transmit as efficiently as adolescents and adults, but data is limited, and mitigation measures are in place to prevent them spreading the virus.

However, as important as serological studies are, they do not account for other aspects of immunity that may also be involved in response to SARS-CoV-2 infection. There is accumulating evidence for the role of different T cell populations during infection, similar to many other viruses. We also know that up to 20% of SARS-CoV-2 infected individuals do not 'seroconvert', or in other words produce antibodies that can be detected in blood (4). Intriguingly, up to half of these individuals have been shown to elicit specific T cell responses to different antigens on the virus, suggesting that T cells (both CD4+ and CD8+) might also play a key role in protection against SARS-CoV-2. This points to the involvement of a much broader immune response (5). Mucosal immunity is also likely to be important, with an early family case study from RCH/MCRI, suggesting that salivary antibodies might play a role in protecting children (6). It also raises the question of whether measuring serum antibodies alone provides a true level of exposure within the population. Measuring T cells (and other responses) as part of serosurveillance studies is very challenging, from both a technical and logistical perspective, particularly in remote and hard-to-reach settings. Another important observation that has been made is the finding that SARS-CoV-2 specific T cells have been detected in samples collected from individuals prior to the pandemic (7). The role of these 'cross-reactive' T cells is unclear, but it is speculated that they might provide some degree of natural protection. The potential implications of T cell immunity on herd immunity is being debated and more studies are needed to address this question.

Probably the two most important immunological questions related to SARS-CoV-2 at the moment is how long do these antibodies or T cells last and do they actually protect against re-infection? We are beginning to understand the kinetics and duration of the immune response to SARS-CoV-2 in greater detail. In a modelling study from the U.K., it was reported that certain antibodies (particularly those to the Spike protein) could theoretically persist for more than 500 days (8). Recent findings from the REACT-2 study in the U.K., however showed that antibodies declined by 26% after 3 months (9). This is consistent with our knowledge of antibody responses to other human coronaviruses where immune responses are generally short-lived and reinfection common. A recent preprint posted yesterday (2nd November) reported for the first time that SARS-CoV-2 specific T cells could still be detected after six months in adult patients with mild-to-moderate or asymptomatic infection in the U.K., and in some individuals, outlasts antibody responses (10). This is reassuring, but it is important to note that a decline in antibodies is a natural feature of the response to any infection and so this should not necessarily be viewed negatively. Immunological memory in the form of memory B cells and memory T cells is a fundamental aspect of the immune response (to infection and vaccines) and so protection is still possible even with the decline of serum antibodies.

Our understanding of the immune response to SARS-CoV-2 infection is increasing at pace. Accurate documentation of virus exposure in the community is a critical part of public health and so unravelling the contributions of antibody, cellular and mucosal immunity in response to this virus will be critical. This also has relevance for vaccines, in terms of whether both antibodies and T cells should be measured, and also whether booster doses are needed to provide long-term protection.

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HIGHLIGHTS

- 3 case studies of children aged <16 years with pancreatitis.
- G.I. symptoms are independent predictors of PICU admission in hospitalised paediatric patients with COVID-19.
- A recent retrospective case series describes increased coagulopathy in paediatric patients with acute SARS-CoV-2 infection.
- A case report of a seven-year old with COVID-19 who developed fatal paediatric multisystem inflammatory syndrome (PMIS) associated with cerebral oedema.
- Catheter directed thrombolysis for 24 hours provided a resolution of bilateral pulmonary emboli in a 15-year-old patient.
- General care providers and paediatricians must join forces and find new ways of working to avoid care delays in a possible second peak of COVID-19.
- A pooled testing strategy based on the geometry of a hypercube may be a way to maximise the speed of SARS-CoV-2 testing while minimising associated costs.
- HIV-positive individuals with COVID-19 have an increased risk of day-28 mortality due to HIV compared with HIV-negative groups.
- Mandatory face masks may reduce COVID-19 disease severity.
- The U.K. government's Scientific Advisory Group for Emergencies offers guidelines around the role of ventilation in preventing COVID-19 transmission and options for improving ventilation in closed spaces.
- A small percentage of infected people cause most of the COVID-19 transmission. Stopping superspreading is key to infection control, and backward contact tracing will help with this.
- Vertical transmission of SARS-CoV-2 through breast milk is unlikely and that any viral particles detected in breast milk are unlikely to be infectious.
- Reverting to online learning should be based on linked in-school transmission and less on case incidence/test positivity thresholds.
- In adults with mild COVID-19, symptom resolution did not differ between nitazoxanide and placebo groups after 5 days of therapy. Early nitazoxanide therapy was safe and reduced viral load compared to placebo.
- Simulating airborne transmission using the Covid Airborne Transmission Estimator demonstrates that adequate ventilation, mask-wearing, and halving contact times radically reduces transmission.
- Examining the potential for airborne spread of COVID-19 by inhalation exposure to the virus in microdroplets at medium room-sized distances and advocating for increased preventative measures to mitigate airborne transmission route.

- Household transmission of SARS-CoV-2 is common between adults and children, and strategies to mitigate risk to other household members should be implemented.
- A systematic review explored the effect of age on the transmission of SARS-CoV-2 in households, schools and the community.
- The European CDC details key considerations for deployment of a COVID-19 vaccine.
- According to a recent study, the highest infectious potential of SARS-CoV-2 is just before and within the first five days of symptom onset; transmission after the first week of illness is unlikely.
- SARS-CoV-2 has been mutating, but little is known about what is significant and what is background noise.

CONTENTS

CLINICAL PAEDIATRICS

Daniel Lamanna - 3rd Year Medical Student,
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Pancreatitis in paediatric patients with COVID-19
https://academic.oup.com/jpids/advance-article/doi/10.1093/jpids/piaa125/5930830

- The respiratory effects of COVID-19 have been well documented; however, extra-pulmonary disease, including gastrointestinal symptomatology, are becoming more apparent. To date, there are only a few case reports demonstrating an association between COVID-19 and pancreatitis in adults. The following three cases describe pancreatitis in children with a recent diagnosis of COVID-19.
- Case #1 - 15-year-old male, previously healthy, obese, presenting to the emergency department with non-bloody, non-bilious emesis, epigastric abdominal pain, and fever.
  - Recent history: one-week history of nasal congestion, anosmia, and ageusia.
  - Laboratory results: normal WBC, normal ESR, normal CRP, normal HbA1c, normal triglycerides, and elevated AST, ALT and lipase.
  - Imaging: abdominal C.T. demonstrated mild stranding around the head of the pancreas and proximal duodenum with scattered ground glass opacities bilaterally in the lower lung fields.
  - Treatment: admission to hospital, liquid diet, IV fluid resuscitation, pain medications were prescribed for abdominal pain.
  - Discharge: occurred day three post-admission with a resolution of pain, improving lipase level, and tolerance to a normal diet.
- Case #2 - 11-year-old male, overweight, presenting to the emergency department with periumbilical abdominal pain and poor oral intake for the past two days.
  - Recent History: 8-day history of headache, chills, fever, intermittent hematochezia, epistaxis.
  - Laboratory Results: normal cholesterol, leukocytosis, elevated AST, ALT, amylase, lipase and triglycerides.
  - Imaging
    - Abdominal CT demonstrated diffuse fatty infiltration of the liver, enlarged appendix (uncomplicated appendicitis), normal pancreas
    - Chest radiography demonstrated central interstitial opacities with peribronchial thickening

- Treatment: admission to hospital, nothing by mouth, intravenous fluid, piperacillin-tazobactam.
- Discharge: occurred day 4 post-admission and demonstrated improvement of abdominal pain with advancement of diet.

> Case #3 - 16-year-old female with a history of pancreatitis (one year prior), presenting to emergency with a 3-day history nausea and epigastric abdominal pain radiating to her back.

- Recent history: one-week history of intolerance to foods or drinks, subjective fever, cough.
- Laboratory results: leukopenia, neutropenia, elevated lipase, normal liver enzymes, triglycerides and cholesterol.
- Imaging: abdominal ultrasound demonstrated mild hepatomegaly, single gallstone, and prominence of the pancreatic head, tail, and duct.
- Treatment: admission to hospital, commenced on IV fluid therapy, pain medication, clear liquid diet.
- Discharge: occurred on day 3 post-admission.

> Conclusion: Though other causes of pancreatitis could not be excluded; this is further evidence supporting that clinicians should consider SARS-CoV-2 as a possible cause of extra-pulmonary symptoms.

Reviewed by: Dr Martin Wright

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

COVID-19 gastrointestinal manifestations are independent predictors of PICU admission in hospitalised paediatric patients
https://pubmed.ncbi.nlm.nih.gov/33105340/

> Multicentre retrospective observational study conducted across 15 hospitals in Spain to describe the gastrointestinal (G.I.) manifestations of COVID-19 in hospitalised paediatric patients. A total of 101 children (aged one month - 18 years) admitted from 1st March to 3rd June 2020 with a COVID-19 diagnosis were included.

> G.I. symptoms (abdominal pain, nausea, vomiting, diarrhoea):

- Were present in 57% of patients.
- Were the first manifestation of the disease in 14%.
- Occurred in the absence of respiratory symptoms in 25% of cases.
    - Patients with G.I. symptoms had:
- Higher levels of C-reactive protein (CRP) and procalcitonin (PCT).
- Higher risk of PICU admission; regardless of age, gender, immunosuppressive therapy and previous underlying conditions. This is more specifically for G.I. symptoms of nausea and vomiting.

- Conclusions: G.I. symptoms are common manifestations of COVID-19 in hospitalised paediatric patients and are predictors of disease severity, independent of other confounding factors.

Reviewed by: Dr Martin Wright

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

Are children with SARS-CoV-2 infection at high risk for thrombosis? Viscoelastic testing and coagulation profiles in a case series of paediatric patients
https://onlinelibrary.wiley.com/doi/10.1002/pbc.28737

- There are not many studies that explore coagulopathic effects in the setting of SARS-CoV-2 infection in paediatric patients nor guidelines that guide the use of prophylactic anticoagulation in children at risk of thrombotic events.
- Retrospective case series describing increased coagulopathy in paediatric patients with acute SARS-CoV-2 infection as demonstrated by viscoelastic testing and coagulation profiles.
- In this series, ROTEM (rotational thromboelastography) was added on to coagulation profiles for hospitalised paediatric patients with SARS-CoV-2 to determine thrombosis risk and to ascertain if similar coagulopathic changes occur in children compared to adults.
- Case series was comprised of eight patients < 21 years (average age 12 years) with acute SARS-CoV-2 infection admitted to a single paediatric hospital in New York.
- Whole blood for ROTEM analysis was obtained within four days of admission to hospital and included EXTEM (evaluation of the extrinsic pathway), INTEM (intrinsic pathway), FIBTEM (fibrogen activity) and APTEM (fibrinolysis).
- The following parameters were analysed: clotting time, clot formation time and maximum amplitude in mm.
- Routine bloods: lymphopaenia (37.5%), mild thrombocytopaenia (13%), prolonged P.T. (50%).
  - ROTEM analysis: showed a predominance of hypercoagulable profiles comparable to SARS-CoV-2 infected adults, with elevated extra EXTEM MCF (50%), elevated INTEM (38%) and elevated FIBTEM MCF (75%).
  - All patients admitted to ICU had a 3-10 fold elevation in fibrinogen levels, and 80% had elevated FIBTEM parameters.
  - In the early stages of infection, elevated fibrinogen, D-dimer and CRP are noted, as well as lymphopaenia and prolonged P.T.
- This series demonstrates hypercoagulability in paediatric patients with acute SARS-CoV-2 infection and also increased thrombin generation in patients admitted to the ICU compared to other inpatients.
- Despite evidence of hypercoagulability, there were no thromboembolic events and no increased mortality due to coagulopathy in this population.

- This case series has a small sample size, and so no definitive conclusions can be drawn from these results. However, there may be a role for using ROTEM in evaluating clinical risk for thrombotic events in paediatric patients to guide the use and choice of anticoagulation.

Reviewed by: Dr Martin Wright

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

Bilateral pulmonary emboli in a teenager with positive SARS-CoV-2 antibody
https://onlinelibrary.wiley.com/doi/10.1002/ppul.25132

- This case study explored the case of a 15-year-old obese female (BMI 34.29) and a past medical history of asthma who developed bilateral pulmonary emboli three days following a laparoscopic appendectomy.
- On arrival to the E.D., she was febrile with supraventricular tachycardia (220 bpm), an echocardiogram showed moderately depressed right ventricular function.
- Bilateral catheters were placed in pulmonary arteries for localised TPA infusion, as well as systemic heparin.
- She suffered a severe hypoxic brain injury, with ischemia noted on MRI of the brain in occipital, parietal, frontal grey-white matter bilaterally.
- CTA of the chest showed resolution of bilateral P.E. on day three of admission.
- Infectious workup was positive for SARS-CoV-2 IgM antibody, IgG remained negative on three tests (PCR was negative on six tests during admission).
- This case highlights the relationship between SARS-CoV-2 and thrombotic complications; the case fits criteria for MIS-C (multisystem inflammatory syndrome in children).
  - A negative PCR is not unusual in MIS-C cases; recent studies demonstrate only 70% of patients have PCR or antibody evidence of SARS-CoV-2.
- Despite the successful treatment of pulmonary emboli in this patient, due to her associated cardiac arrest, her overall neurologic outcome remains poor.

Reviewed by: Dr John Cheek

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

Fatal cerebral oedema in a child with COVID-19
https://www.pedneur.com/article/S0887-8994(20)30339-8/fulltext

- A case report of a seven-year-old male with COVID-19 infection who developed fatal paediatric multisystem inflammatory syndrome (PMIS) associated with cerebral oedema.
- Initial presentation: The patient presented to the hospital with 3/7 of fever (39.1°C) headaches, abdominal pain, and intractable emesis. He tested positive for SARS-CoV-2 infection on nasopharyngeal PCR and had no prior medical history.
  - Initial blood tests were normal except for increased inflammatory markers: CRP, ESR and D-dimer.

- 2/7 after admission, the patient developed severe neck pain and headache. He received hydroxychloroquine and then developed a facial rash, altered mental status, expressive aphasia, and pinpoint but reactive pupils.
- The patient then became unresponsive with left gaze deviation, positive Brudzinski's sign, and decreased range of neck motion. He received anticonvulsants and broad-spectrum antibiotics.
- He deteriorated further with extensor posturing, dilated pupils and absent brainstem reflexes, and was intubated.
- A CT scan revealed a loss of grey-white matter differentiation with diffuse cerebral oedema.
- Repeat blood tests demonstrated severe inflammation: ferritin 1601, CRP 22, D-dimer 17.65, with ESR of 14 and normal WCC.
- Post-mortem histopathological analysis of brain tissue revealed diffuse cerebral oedema in both grey and white matter with perivascular mononuclear infiltrates, consistent with diffuse inflammation (including in the meninges). There were no features of viral encephalitis and no evidence of SARS-CoV-2 infection in the brain parenchyma or CSF.

> PMIS results in multi-organ inflammation and overproduction of pro-inflammatory cytokines which can lead to vascular injury, cell death and increased vascular permeability, which could account for the histopathological changes and clinical course seen in this patient.

Reviewed by: Dr Martin Wright

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

Delayed presentation to regular Dutch paediatric care in COVID-19 times: a national survey
https://dx.doi.org/10.1136/bmjpo-2020-000834

> The authors from this paper sought reports from members of the Dutch Paediatric Society of instances of collateral harm to Dutch children and adolescents due to the COVID-19 pandemic from two weeks since the initiation of the Dutch lockdown, which occurred from the end of March, till the first week of July.

> 1,400 paediatricians (93% of the total in the Netherlands) are affiliated with the Dutch Paediatric Society.

> Members were asked to report; '… if, in your opinion, a child was presented too late to acute, regular or chronic care due to parental or healthcare provider concerns about Corona, and which resulted in unnecessary harm.'

> 51 reports were received from 38 paediatricians.

> Most reports (54%) were for young children < 4 years of age with mainly acute physical problems, but also some social problems.

> In older children, several cases of diabetic ketoacidosis were reported.

> The authors believe that their results indicate that delaying care can lead to seriously ill children, life-threatening situations and that in some cases, it can even lead to death.

- General care providers and paediatricians must join forces and find new ways of working to avoid care delays in a possible second peak of COVID-19.
- Systematic data collection of collateral harm in children is needed to be able to intervene adequately.

Reviewed by: Dr Martin Wright

DIAGNOSTICS & SAMPLING

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

A pooled testing strategy for identifying SARS-CoV-2 at low prevalence
https://dx.doi.org/10.1038/s41586-020-2885-5

- This paper proposes an algorithm for sample pooling that is based on the geometry of a hypercube in order to maximise the speed of testing (by testing in parallel) and minimise associated cost (based on pooled sample size). It also uses proof of concept experiments to prove that one positive sample out of 100 can be reliably detected using this method.
- The suggestions made here are for population screening, where the pre-test probability is relatively low. This method is not recommended for testing in clinics or for those presenting with symptoms.
- First, there is a large round of group tests. If a large group test positive, it proceeds onto the second round of smaller 'slice tests' to efficiently identify all infected individuals.
- A balance must be struck between increasing sample size and maintaining adequate test sensitivity since, by increasing sample size, any theoretically positive sample is diluted by other negative samples.
- Note, the positive samples most affected by the dilution (and becoming potential false negatives) would be those with low RNA molecule count, and therefore potentially less infectious in the first place.
- PCR is generally very sensitive. The authors of this paper investigated if known positive specimens would still test positive after being diluted 20, 50, and 100 times via pooling with negative specimens in a 40-cycle RT-PCR test.
  - This resulted in 91%, 88%, and 85% sensitivities respectively.
- The authors suggest several ways in which the loss of sensitivity due to dilution can be mitigated:
  - Re-test individuals sufficiently often to ensure that the window in which the specimen is obtained occurs during the period of highest viral load.
  - Increase the number of PCR cycles, e.g., to 44.
  - Increase the volume of the sample used, e.g., from 5uL to 10uL.
  - Increase viral concentration in the pooled sample either physically or chemically (ex: centrifugation, precipitation).
  - Re-engineer PCR machines to allow for larger sample volumes to be tested.
- The authors also show that it is possible to use this testing algorithm to identify all infected individuals, even if up to five samples in the pool are positive.
- Field trials of the algorithm described here are being conducted in Rwanda and South Africa.

Reviewed by: Dr Martin Wright

EPIDEMIOLOGY & PUBLIC HEALTH

Julian Loo Yong Kee - 3rd Year Medical Student,
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Decrease in hospitalisation for COVID-19 after mask mandates in 1083 U.S. counties (not peer reviewed)
https://www.medrxiv.org/content/10.1101/2020.10.21.20208728v1.full.pdf

- Publicly-sourced epidemiological data to observe for changes in the proportion of hospitalisations due to COVID-19 as a result of mandating masks (up to 12 weeks before and 12 weeks) from 10th March – 16th September 2020.
- There was a 7% decrease in COVID-19 hospitalisations following mandating masks.
- Small pre-treatment effect possibly due to uptake of masks prior to the mandate.
- Reduced COVID-19 hospital admissions suggest reduced COVID-19 severity with mandating mask-wearing, may be due to a reduction in the viral inoculum.
- Other factors may have resulted in a decline in severity; however, the model did try to control for some of these factors.
- Limitations: No data on facial mask compliance; no data on specific ages of hospitalised COVID-19 patients; no grading of disease severity other than inpatient admission.

Reviewed by: Dr Wonie Uahwatanasakul

IMMUNOCOMPROMISED / CANCER

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

Outcomes of COVID-19 related hospitalisation among people with HIV in the ISARIC WHO Clinical Characterization Protocol (U.K.): a prospective observational study
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1605/5937133

- This prospective observational study looked at the presentation and outcomes of adults with and without HIV infection who were hospitalised with COVID-19 in the United Kingdom.
- Despite effective antiretroviral therapy (ART), people with HIV (PWH) may continue to experience persistent immune dysfunction that can influence the severity of COVID-19.
- The authors used the existing ISARIC WHO CCP-UK prospective cohort study for their participant selection. Eligible patients were ≥18 years who were admitted to participating hospitals with laboratory-confirmed or highly-likely SARS-CoV-2 infection.
- 47,952 patients were included – 122 had confirmed HIV infection, and 112/122 had a record of ART.
- Findings:
  - PWH were younger than HIV-negative people (median 56 vs 74 years, P<0.001), included a larger proportion of males and patients of Black ethnicity and had fever comorbidities.
  - The cumulative day-28 mortality was similar in PWH and the HIV-negative groups (26.7% vs. 32.1%).
  - There was an age-adjusted 47% increased risk of day-28 mortality among PWH compared to the HIV-negative group (adjusted hazard ratio 1.47, 95% CI 1.01-2.14,) and the association persisted after adjusting for other variables.
  - Among participants <60 years old, mortality was 21.3% in HIV-positive patients vs. 9.6% in HIV-negative patients after adjusting for sex, ethnicity, age, baseline date, comorbidities and severity of COVID-19 infection at presentation.
- Limitations: relatively small PWH sample size, did not address risk factors for COVID-19 diagnosis or hospitalisation among PWH or the modulating role of ART. HIV-positive patients who died were less likely to have ART recorded than those who survived at day 28.
- Conclusion: PWH and COVID-19 have an increased risk of day-28 mortality due to HIV compared to HIV-negative groups.

Reviewed by: Professor Jim Buttery

INFECTION CONTROL

Rose Noble Kizhakekara - 3rd Year Medical Student,
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The science of superspreading
https://vis.sciencemag.org/covid-clusters/

- An online infographic that explains superspreading.
- A small percentage of people seem to cause most of the COVID-19 transmission: one study found that 10% of patients are responsible for 80% of the spread.
- Therefore, stopping superspreading is key.
- The '3 Cs' make superspreading more likely: closed spaces with poor ventilation, crowds and close contact settings.
- Backward contact tracing is recognised to be important in finding more chains of transmission, where superspreading events take place and may thus help prevent them.

Reviewed by: Dr Wonie Uahwatanasakul

PERINATAL HEALTH

Benjamin Watson – 4th Year Medical Student,
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Bench research, human milk, and SARS-CoV-2 (preprint, peer reviewed)
https://pediatrics.aappublications.org/content/pediatrics/early/2020/10/19/peds.2020-033852.full.pdf

- Holder pasteurisation of human milk, i.e. heating to 62.5° C for 30 minutes, can inactivate SARS-CoV-2 by testing the virus in a culture system in the laboratory.
- The authors "spiked" five individual women's expressed milk samples with five different SARS-CoV-2 isolates, conducted Holder pasteurisation (to 63° C), and then assessed tissue culture infectious dose 50 (TCID50) by infecting susceptible cells and monitoring the cytopathic effect.
- Holder pasteurisation effectively inactivated SARS-CoV-2, and additionally, they noted a 40.9-92.8% viral titre decrease in human milk as compared to the control medium, confirming human milk's unique antiviral properties.
- This critical study adds to the limited evidence that pasteurised donor human milk is safe but placing it within the clinical context is key.
- Providers and parents should not leap to any of several possible unfounded conclusions:
  1. That the milk of a mother who has SARS-CoV-2 infection will be infected,
  2. That her milk must be expressed to be fed to her infant, or
  3. That her milk should be Holder pasteurised prior to feeding.
- While much remains to be learned about human milk and SARS-CoV-2 infection, preliminary laboratory and clinical reports have led to professional guidance supporting the safety of breastfeeding if the SARS-CoV-2-infected mother is well enough to care for her infant.
- When she is too ill to feed directly, or her preterm infant cannot directly breastfeed, expressing her milk and feeding it to the infant is preferred.
- These recommendations appropriately acknowledge the extraordinary health benefits of human milk feeding.
- In fact, preliminary evidence from laboratory and clinical studies suggests that
  - SARS-CoV-2 is unlikely to infect human milk, and
  - Any particles detected in human milk are likely not to be infectious.

Reviewed by: Professor Suzanne M Garland

SCHOOLS

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

Executive summary: evidence and guidance for in-person schooling during the COVID-19 pandemic
https://policylab.chop.edu/sites/default/files/pdf/publications/PolicyLab-Executive-Summary-Evidence-Guidance-In-Person-Schooling-During-COVID-19.pdf

- All decision-makers should be mindful that as long as there are cases of SARS-CoV-2 in the community, there are no strategies that can eliminate transmission risk in schools.
- The goal is to keep transmission as low as possible to maximise both safety and in-person learning.
- Recommendations have moved away from case incidence and test positivity thresholds and towards linked in-school transmission for reverting to online learning.
- These guidelines are based on high transmission in the U.S.
- The effectiveness of a successful school safety plan is inherent in the layering of multiple strategies that can reduce the likelihood of linked transmission during the school days: symptom surveillance; quarantine and school absence policies; masks; physical distancing; establishing small group cohorts; increased ventilation; hand hygiene and disinfecting.
- Clear communication is essential.
- Extracurricular activities and school-linked programs should continue if there has not been rapidly accelerating disease transmission in the community.

Reviewed by: Professor Fiona Russell

THERAPEUTICS

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

Early use of nitazoxanide in mild COVID-19 disease: randomised, placebo-controlled trial (not peer reviewed)
https://www.medrxiv.org/content/10.1101/2020.10.21.20217208v1.full-text

- Multicentre, randomised, double-blind, placebo-controlled trial in Brazil evaluating whether early nitazoxanide therapy can effectively accelerate COVID-19 symptom resolution compared to placebo.
- Nitazoxanide is a clinically approved and commercially available antiparasitic drug that has been found to have broad-spectrum antiviral activity, including against coronaviruses. It has also been shown to inhibit SARS-CoV-2 replication at low micromolar concentrations in Vero CCL81 cells.
- Patients aged ≥18 years old who presented with symptoms (dry cough, fever, or fatigue) for no longer than three days were enrolled. Patients were excluded if they had a negative swab or pre-existing medical conditions precluding the safe conduct of study procedures.
- 392 patients were randomly assigned in a 1:1 ratio to receive either a placebo or nitazoxanide (198 placebo, 194 nitazoxanide). Median time from symptom onset to the first dose of the drug was five days.
- Findings:
  - Complete resolution of symptoms after five days of treatment did not differ between groups. At 1-week follow-up (after treatment cessation), 38 patients (78%) in the nitazoxanide group and 26 (57%) patients in the placebo group reported complete symptom resolution.
  - After five days of treatment, the viral load was lower in the nitazoxanide arm compared to placebo (P=0.006). The percentage reduction in viral load was also higher in the nitazoxanide arm (55%) compared to placebo (45%).
  - 29.9% of patients in the nitazoxanide arm vs. 18.2% in the placebo arm were negative for SARS-CoV-2 on RT-PCR.
  - Nitazoxanide did not prevent hospitalisation or affect change in FBE, CRP levels or serum biomarkers for inflammation compared to placebo.
  - No deaths or life-threatening adverse events were reported in the nitazoxanide arm. Mild-moderate adverse events were reported by patients in both arms (nitazoxanide 30.9%; placebo 30.4%) during the 5-day course.
- Limitations: This has not been peer-reviewed; long-term analysis of therapy effects (>28 days) was nor performed, and only three symptoms (dry cough, fever, fatigue) were considered for analysis of primary outcome.

> Conclusion: In patients with mild COVID-19, symptom resolution did not differ between nitazoxanide and placebo group after five days of therapy. Early nitazoxanide therapy was safe and reduced the SARS-CoV-2 viral load compared to placebo.

Reviewed by: Dr Amanda Gwee

TRANSMISSION

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

On the effect of age on the transmission of SARS-CoV-2 in households, schools, and the community
https://academic.oup.com/jid/advance-article/doi/10.1093/infdis/jiaa691/5943164

- This systematic review reviewed the relevant evidence of transmission based on household, school, and community studies, and drew conclusions regarding the relevant public health policies.
- The studies included found evidence for lower susceptibility to infection in children under ten years old, and higher susceptibility to infection in adults over 60 years old compared to young/middle-aged adults.
  - The review highlights potential biases for these estimates of susceptibility:
    - Estimates based on household attack rates may be influenced (generally downward biased) due to contact patterns - certain adult-adult contacts may be more sustained than adult-child contacts, the higher secondary attack rates in adults vs. children may reflect greater exposure, in addition to differences in susceptibility given the same exposure (this is highlighted in a study where it was found that spousal exposure may face the additional risk of infection due to a shared bed or room - 27% secondary attack rate compared to 17.3% for the rest of the household).
    - The following scenario is a second potential bias (index misclassification): a child is first infected and then infects an adult in the home, but due to the child being asymptomatic, the adult is labelled as the index case, and the child is subsequently tested and labelled as a secondary attack.
- To mitigate these biases, infection between different age subgroups of children among household contacts can be explored.
  - One study reviewed compared secondary attack rates (SAR) in children 0-4 and 5-9 to those of older children: SAR in these younger groups are less than half those children aged 15-19.
- There are limited data regarding age-related differences in infectivity, though point estimates in several studies suggest infectivity may increase somewhat with age.
  - Biases in the infectivity study include errors in ascertaining index cases, as well as the conflation of differences in infectivity with differences in susceptibility and intensity of contacts.
- Age differences in seroprevalence were also explored in this review: serological studies estimate that younger adults (under 35) have the highest seroprevalence of nearly all age groups.

  - Biases included that participants in seroprevalence surveys are almost never fully representative of the source population, as convenience samples might be more likely to reach generally healthy people with unrepresentative risks of exposure.
  - Estimates of sensitivity and specificity for antibody tests are derived from groups of individuals that might be different from the general population, complicating the interpretation of results.

> In school settings with limited mitigation strategies (no reduction in class sizes, no contact limiting, and limited mask use) robust spread of SARS-CoV-2 can occur.

  - There are several examples demonstrating mitigation measures prevent large outbreaks: schools that introduced widespread testing in schools, and schools closing for 24-48 hours following case detection with contacts of detected cases subsequently quarantined exhibited a smaller number of secondary infections.

> Less spread occurs in primary schools, supporting lower susceptibility to infection in children under the age of ten.

Reviewed by: Professor Fiona Russell

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

A room, a bar and a classroom: how the Coronavirus is spread through air (Spanish-language news article; not peer reviewed research)
https://english.elpais.com/society/2020-10-28/a-room-a-bar-and-a-class-how-the-coronavirus-is-spread-through-the-air.html

> Understanding how Coronavirus spreads through airborne transmission will help in developing appropriate public health measures, particularly as lockdowns are eased.

> This infographic utilised the Covid Airborne Transmission Estimator (https://cires.colorado.edu/news/covid-19-airborne-transmission-tool-available) developed by a group of scientists from the University of Colorado and led by atmospheric-chemist Professor José Luis Jiménez.

> The estimator used is based on a standard model of aerosol disease transmission, the Wells-Riley model. It is calibrated to COVID-19 per recent literature on quanta emission rate.

> The model estimates propagation of COVID-19 by aerosol transmission only. It assumes that 2m social distancing is maintained to eliminate transmission through droplets.

> Preventative measures applied in each scenario included correct ventilation, halved encounter times and mask-wearing.

> Simulation 1: 6 people in a room:

  - If 6 people spend 4 hours in a room talking loudly, everyone will become infected.
  - With preventative measures, the risk is below one person becoming infected.

> Simulation 2: A bar at 50% capacity with 15 people and 3 staff for 4 hours:

  - If no extra measures are taken 14/18 will become infected.
  - With preventative measures, only one person will become infected.

> Simulation 3: A two hour class with 25 students and the teacher is patient 0

  - If no extra measures are taken half, the students will be infected (12/24).
  - With preventative measures, including the class being stopped after an hour to refresh the air, the risk is roughly that one student will become infected.

> Limitations:

  - This publication is a news article and is not a peer-reviewed research publication. Other than referencing the model used, there are no references included in the article.
  - The calculation used in the model is not exhaustive and does not cover the number of variables that could affect transmission. The model also assumes that no one is immune.
  - The developers of the model acknowledge these limitations and state that 'The model is kept simple so that it can be understood and changed easily. The goal is to get the order-of-magnitude of the effects quickly and to explore the trends.'
  - The methods used to develop the model are not described in detail by the developers.

> Conclusion: The preventative strategies of adequate ventilation, masks and reduced contact time all appear to be useful measures for reducing the spread of COVID-19. This should be taken into consideration when people are indoors; including visiting other homes, indoor dining and in the classroom.

> This infographic provides a visual and thought-provoking perspective on the role of different strategies to reduce airborne transmission of COVID-19. It is a useful strategy for public health messaging, but the scientific evidence behind the model is not clear from the news article or the website for the Covid Airborne Transmission Estimator tool, and thus the conclusions should be interpreted cautiously.

Reviewed by: Dr Samantha Bannister

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

Role of ventilation in controlling transmission - SAGE-EMG
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/928720/S0789_EMG_Role_of_Ventilation_in_Controlling_SARS-CoV-2_Transmission.pdf

> The U.K. Government's Environment and Modelling Group (EMG) of the Scientific Advisory Group for Emergencies (SAGE) detail the role of ventilation in preventing transmission of SARS-CoV-2.

> Ventilation has a role in preventing far-field aerosol transmission but offers no prevention for other modes of transmission. The nature and intensity of ventilation required are determined by the density of occupants and the types of activities being undertaken. CO_2 monitoring can be a useful measure of adequate ventilation in densely occupied spaces.

> Ventilation may be one of a suite of interventions to protect occupants in spaces which may pose a risk of high transmission rates, but this should be considered against noise and carbon pollution as well as other negative consequences of increased ventilation.

> Face covering should be considered alongside ventilation for reducing far-field aerosol transmission risks, hand washing also.

- A menu of options for improving ventilation is offered, alongside summaries of evidence drawn on for these recommendations.

Reviewed by: Dr Lien Anh Ha Do

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

It is time to address airborne transmission of coronavirus disease 2019 (COVID-19)
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa939/5867798

- This article listed increasing evidence of potential airborne spread of COVID-19 by inhalation exposure at short to medium distances (up to several metres) and advocated for the use of preventative measures to mitigate this airborne transmission route.
- Studies demonstrated viruses are released during normal talking, exhaling, etc., in microdroplets that can be small enough to remain aloft in the air and create exposure risk at distances beyond 1-2m from an infected individual.
- Retrospective analysis of SARS-CoV-1 as well as SARS-CoV-2 epidemic showed the airborne transmission seems the most likely mechanism explaining the spatial pattern of infection.
- Authors note that many other viral respiratory illnesses, such as MERS-CoV, RSV, and influenza can be exhaled, and it is expected that SARS-CoV-2 would behave similarly with regards to transmission via airborne microdroplets.
- Authors believe current guidance from public health (in June 2020) is insufficient in the case that COVID-19 is spread via airborne transmission, and advocate the following changes be implemented:
  - Sufficient and adequate ventilation including supplying outdoor air and minimising recirculated air in indoor public environments.
  - General ventilation should be supplemented with germicidal U.V. lights and high-efficiency air filtration systems.
  - Overcrowding should be avoided at all costs, particularly in public buildings and transit.
- Limitations noted in the article include currently incomplete evidence for all the steps in airborne transmission, however, they note that evidence for large droplet and fomite transmission is similarly incomplete.
- Additional comments: After only a few months of the pandemic, many studies have been reported solid evidence on the airborne transmission of SARS-CoV-2, although still many questions more than answers such as infectious doses. There are no randomised trials on the effectiveness of wearing masks on the reduction of transmission in public settings, but many data and models have shown the importance of masks, specifically in school settings. Freely- accessed webinar series on this topic can be watched at https://aerosol-soc.com/covid-19-webinar-series/

Reviewed by: Dr Lien Anh Ha Do

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

Transmission of SARS-COV-2 infections in households — Tennessee and Wisconsin, April-September 2020
https://www.cdc.gov/mmwr/volumes/69/wr/mm6944e1.htm

- This article examines data from a prospective household study on transmission of SARS-CoV-2 among household members in the U.S.
- The index patient (positive COVID-19 test) and household members recorded symptoms and self-collected specimens, including nasal and saliva swabs for 14 days.
- Rate of another household member testing positive after the index patient was 53%.
  - In households where the index case was <12 years old, the secondary infection rate was 53%.
  - 75% of secondary household infections were identified within five days of the index case's illness onset.
  - 69% of index patients reported spending >4 hours in the same room with 1+ household member before illness onset, and 40% reported doing so the day after symptom onset.
  - Rates of symptomatic and asymptomatic laboratory SARS-CoV-2 infection among household members was 36% and 18%, respectively.
  - Secondary infection, as shown to happen quickly, with 75% of infections identified within five days of the index patient's illness onset.
- Prompt isolation of cases can largely decrease transmission, so those with known exposure or any symptoms should isolate, stay home, and use separate bedrooms/bathrooms if possible.
  - Masks should be worn in the communal home areas if someone is self-isolating or there is a concern for potential infection.
  - Close household contacts of the index patient should proactively self-isolate if possible, even if they are asymptomatic.
- Limitations: It is possible that although the index patient was tested first, the household members may have been concurrently infected (same as the index patient) and developed symptoms later or remained asymptomatic. Higher apparent secondary rates could have been due to a household member contracting the virus outside the home, but it is attributed to the index patient. Samples in the study were self-collected and therefore, subject to potential sensitivity.
- Study shows the importance of household transmission; and the challenges to mitigate within the household transmission, especially for houses that are small with shared bedroom facilities etc.

Reviewed by: Professor Fiona Russell

VACCINES

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

Key aspects regarding the introduction and prioritisation of COVID-19 vaccination in the EU/EEA and the U.K.
https://www.ecdc.europa.eu/en/publications-data/key-aspects-regarding-introduction-and-prioritisation-covid-19-vaccination

- The European Centre for Disease Prevention and Control (ECDC) is considering how to best introduce a COVID-19 vaccine and how to decide who might be initially prioritised for vaccination.
- Here, the ECDC layout the importance of robust disease and post-marketing surveillance, detailed vaccination coverage data, evidence-based policy development, legal and regulatory frameworks specific to the pandemic context, supply chain logistics, vaccine acceptability studies, clear communication, and equitable introduction of a vaccine.
- At-risk groups will need to be identified and prioritised, targeting vaccination to high-incidence areas, as well as adapting to changing pandemic conditions whilst striving for equity and universal vaccination is discussed.
- The key aspects, especially supply shortages, will likely apply also to our own context, and countries will need flexibility in adapting strategies to manage this as new evidence continues to be generated.

Reviewed by: Dr Wonie Uahwatanasakul

VIROLOGY

Chelsea Haliburton – 3rd Year Medical Student, University of Ottawa

Virology, transmission and pathogenesis of SARS-CoV-2
https://www.bmj.com/content/371/bmj.m3862

- Virology: Both SARS-CoV-2 and SARS-CoV-1 preferentially interact with angiotensin-converting enzyme 2 (ACE2) receptor. However, structural differences in its surface proteins and viral load kinetics during the infectious period of SARS-CoV-2 help to explain its enhanced rate of transmission.
  - Structural differences of the surface proteins spikes allow a stronger bond to ACE-2 and more significant affinity for the upper respiratory tract and conjunctiva.
  - Peak SARS-CoV-2 load is observed just before or within the first five days of symptom onset.
- Transmission: Quantitative reverse transcription polymerase chain reaction technology can detect SARS-CoV-2 RNA in the upper respiratory tract for a mean of 17 days after symptom onset.
  - Viral culture from PCR positive samples has rarely been positive beyond nine days of illness.
  - This suggests that individuals are more likely to transmit infection within the first week of illness compared to later in the course.
  - Symptomatic and pre-symptomatic transmission (before symptom onset) is likely to play a greater role in the spread of SARS-CoV-2 than asymptomatic transmission.
- Route of transmission:
  - Via infected respiratory droplets by direct or indirect contact with nasal, conjunctival or oral mucosa.
    - There is no documentation of infection via faecal-oral transmission.
  - Target host receptors are found mainly in the respiratory tract epithelium; the conjunctiva and gastrointestinal tracts are susceptible to infection.
  - Risk of infection substantially increases in enclosed environments compared to outdoors; a systematic review of transmission clusters found that most superspreading events occurred indoors.
  - SARS-CoV-1 and SARS-CoV-2 can both live on surfaces at a low temperature and humidity, however, both viruses are readily inactivated by disinfectants.
- Pathogenesis:
  - In hamster model, the virus causes transient damage to the cells in the olfactory epithelium, this may explain the temporary loss of taste and smell commonly seen in COVID-19 patients

  - The presence of ACE2 on the epithelium of the intestine and endothelial cells in the kidney and blood vessels, this may explain gastrointestinal symptoms and cardiovascular complications.
  - It is still not clear whether pathological changes in the respiratory tract or endothelial dysfunction are the results of direct viral infection or cytokine dysregulation, coagulopathy.

> Immune response

  - Evidence on inflammatory immune responses in severe COVID-19 patients and on responses differences by sex was reported with higher plasma innate immune cytokines and chemokines at baseline in men, compared in women, while more robust T-cell activation in women compared in men. These findings suggest that adaptive immune response may be a determinant factor of clinical outcome in COVID-19.
  - High viral load correlates with increased severity and disease outcome.
  - Neutralising antibody level correlates with severity of disease but wane overtime.
  - There are cross-reactive CD4- T cell responses between endemic human coronaviruses and SARS-CoV-2, but it is still not clear about their protective role.

Reviewed by: Dr Lien Anh Ha Do

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

Is there evidence for genetic change in SARS-CoV-2 and if so, do mutations affect virus phenotype?
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/928724/S0790_NERVTAG_-_Is_there_evidence_for_genetic_change_in_SARS-CoV-2.pdf

> Using the database of more than 70,000 SARS-CoV-2 genome during the period of 11th March to 25th September 2020, representing >50% of the genomes available in the global repository, the authors describe several common mutations in the SARS-CoV-2 genome that may carry clinical significance such as PCR diagnostics, serology as well as viral transmission and pathogenesis/virulence.

> Evolution of coronaviruses can be the results of point mutations, recombinations and deletions in the genomes, which later were the major process of switching host range and changing pathogenesis/virulence of coronaviruses. SARS-CoV-1, MERS-CoV is thought to have ad recombination in their evolutionary history. Human coronavirus OC43, the same genre beta-coronavirus with SARS-CoV-2 could acquire the hemagglutinin esterase (HE) gene from recombination between a progenitor coronavirus and influenza C virus.

> At the moment, SARS-CoV-2 is mainly accumulating point mutations which are less likely to have consequences to the virus biology. However, some point mutation events in other Coronavirus lead to increased viral virulence such as mutations in the furin cleavage site of the spike glycoprotein of feline enteric Coronavirus.

> The overall rate of evolution of SARS-CoV-2 has been estimated to be approximately 1.0 x 10- substitution/site/year across the entire genome, but this includes both amino acid replacements and ‘silent’ nucleotide changes.

- Two approaches to understanding the effects of genetic changes of SARS-CoV-2:
  - Analysing genomic data together with epidemiological and clinical data.
  - Performing laboratory virological assays to compare the characteristics of different strains of the virus.
- Several mutations have been described in the literature:
  - Spike glycoprotein D614G: enhances ACE2 receptor binding, seemingly confers a selection advantage but has not been demonstrated to have a mortality effect
  - Spike glycoprotein N439K (receptor binding motif): enhances ACE2 receptor binding, sporadic cases worldwide (Romania, Switzerland, Ireland and the U.S.) while initially exclusive to Scotland.
  - Spike glycoprotein deletions around furin cleavage site: less pathogenic and transmissible in vitro, but no data clinically.
  - Viral polymerase P323L: always with D614G, little evidence on the effect.
  - orf8 deletion: lineage was present in Singapore but now eliminated, reportedly milder infection.

Reviewed by: Dr Lien Anh Ha Do

OTHER RESOURCES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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