Infectious Diseases RESEARCH REVIEW™ Focus on COVID-19

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Abbreviations used in this issue:

COVID-19 = coronavirus disease 2019; **CRP** = C-reactive protein; **CV** = cardiovascular; **NT-proBNP** = N-terminal pro-brain natriuretic peptide; **PPE** = personal protective equipment; **RCT** = randomised controlled trial; **SARS/SARS-CoV** = severe acute respiratory syndrome (coronavirus).

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Welcome to this special issue of Infectious Diseases Research Review with a focus on COVID-19.

The world is learning at lightning speed the importance of epidemiology, the efficacy of PPE (personal protective equipment) and is desperately searching for treatment options. We are learning new greeting rituals, creating 'home offices' with minimal notice, and even universities seem to be able to adjust their curricular. Our internet giants Google, Twitter, Microsoft, Reddit and even Instagram/Facebook/WhatsApp have lifted their game to facilitate information exchange, curate threads and help minimise 'fake news'.

There is just so much news! JAMA reported more than 100 submissions each day (mainly from China), and many journals offer pre-peer-review articles. We thought we would stick to our format of summaries and commentaries with a hyperlink to the original work. In addition, we have collated a few links to government websites, the WHO and key medical journals. I would also like to highlight the dedicated service of the Centre for Evidence-Based Medicine at Oxford University.

Links for healthcare professionals

- NZ Ministry of Health
- Australian Government, Department of Health
- WHO
- N Engl J Med Coronavirus: a collection of articles focussed on COVID-19
- Lancet COVID-19 resource centre
- JAMA Network, COVID-19 collection
- Centre of Evidence-Based Medicine at Oxford University is summarising the evidence on key clinical questions. For example, the evidence for hand disinfectant and PPE, and how to assesses breathlessness by phone or video.

Links for patients

- WHO myth busters: COVID-19 advice for the public
- GINA FAQs on asthma management
- European Lung Foundation; COVID-19 – your questions answered by respiratory experts.

The papers selected include key epidemiological papers, an exploration of the available evidence on transmission (including via surfaces), a touch on the big debate of PPE and two papers on possible treatment options.

Please all stay safe during these difficult times. Our intentions are to provide a little drop of evidence in this torrent of news. Please let us know if we have succeeded, whether we just added to the noise, or whether we should update this review in a few weeks.

Kind Regards,

Dr Janette Tenne
Medical Research Advisor
janette.tenne@researchreview.com.au

Impact of non-pharmaceutical interventions (NPIs) to reduce COVID19 mortality and healthcare demand

Authors: Ferguson N et al., on behalf of the Imperial College COVID-19 Response Team

Summary: These authors presented results of epidemiological modelling that has informed COVID-19 policymaking in the UK and other countries over recent weeks. They assessed the potential of nonpharmaceutical interventions aimed at reducing population contact rates and thereby viral transmission. They applied previously published mitigation and suppression microsimulation models, each of which presents major challenges, to Great Britain and the US. Optimal mitigation policies (which focus on slowing but not necessarily stopping viral transmission) might potentially reduce peak healthcare demand by two-thirds and halve deaths, but there would still be hundreds of thousands of deaths and health systems would be overwhelmed many times over. Therefore, suppression (minimally requiring a combination of physical distancing for the entire population, home isolation of cases and household quarantine of their family members, supplemented with institutional closures) would be the preferred policy for countries able to achieve it. However, it was concluded that the effectiveness of any one intervention in isolation is likely to be limited, and multiple interventions would need to be combined for transmission to be substantially impacted.

Comment: This paper by the Imperial College London was published on the 16th March and gave enough modelling details for governments around the world to change their policies. The authors call COVID-19 the most serious respiratory threat since 1918 H1N1 influenza. With the lack of a vaccine and pharmaceutical treatments, they discuss the social impacts of the strategies to mitigate or suppress the epidemic growth. Their modelling is chilling at times, like estimating 40 million worldwide deaths without intervention (Nature News). **Bottom line: intermittent physical distancing with short periods of relaxation is likely to be the most successful strategy for the next 18 months.**

Reference: Imperial College of London; published online March 16, 2020
Abstract

Incidence, clinical characteristics and prognostic factor of patients with COVID-19

Authors: Zhao X et al.

Summary: This was a systematic review with meta-analysis of 30 studies (n=53,000) reporting data on the clinical characteristics of patients with COVID-19 infection and predictors of disease severity and mortality. The patients' mean age was 49.8 years and 55.5% were male. The respective pooled severity and mortality incidences were 20.2% and 3.1%. Predictors for disease severity were age ≥50 years (odds ratio 2.61 [95% CI 2.29-2.98]), male gender (1.348 [1.195-1.521]), smoking (1.734 [1.146-2.626]) and any comorbidity (2.635 [2.098-3.309]), particularly chronic kidney disease (6.017 [2.192-16.514]), chronic obstructive pulmonary disease (5.323 [2.613-10.847]) and cerebrovascular disease (3.219 [1.486-6.972]). Laboratory parameters significantly associated with severe COVID-19 infection were elevated LDH, CRP and D-dimer levels, and decreased blood platelet and lymphocyte counts (p<0.001 for all). Independent predictors of COVID-19-related mortality were age ≥60 years (relative risk 9.45 [95% CI 8.09-11.04]), CV disease (6.75 [5.40-8.43]), hypertension (4.48 [3.69-5.45]) and diabetes (4.43 [3.49-5.61]).

Comment: This is one of three articles picked from a so-called preprint server, meaning the paper has been submitted for publication but hasn't been accepted or peer reviewed. This meta-analysis from Shanghai includes 30 studies and 53,000 patients. The average time between infections and symptoms was 7 days. Risk factors for severe disease include older age (≥50 years), male, smoking, and any comorbidity, especially chronic kidney disease, chronic obstructive pulmonary disease and cerebrovascular disease. Laboratory markers like raised CRP, D-dimer and LDH levels and reduced platelet or lymphocyte counts were associated with severe COVID-19. **Bottom line: this is a comprehensive summary of prognostic data for COVID-19.**

Reference: medRxiv 2020.03.17.20037572
Abstract

Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak

Authors: Bagheri SHR et al.

Summary: Patients from Iran who self-reported anosmia or hyposmia and who completed an online checklist within 4 weeks of the start of the country's COVID-19 epidemic were included in this cross-sectional study. Of the 10,069 respondents (aged 32.5 ±8.6 years; range 7–78), 71.13% were female, 81.68% were nonsmokers, 10.55% reported a history of a trip out of their home town and 1.1% had been hospitalised due to respiratory problems. Among respondents' family members, 12.17% had a history of severe respiratory disease in recent days and 48.23% had experienced anosmia or hyposmia. A highly significant correlation was seen between the number of olfactory disorders and patients with documented COVID-19 across all 31 Iranian provinces until March 16, 2020 (Spearman correlation coefficient, 0.87 [p<0.001]). Around three-quarters of those with anosmia reported rapid onset, and up to the time they completed the questionnaire, 60.90% reported constant decreased sense of smell, and 83.38% also reported decreased taste sensation.

Comment: This is another non-peer-reviewed article, this time from researchers in Iran. This study is methodologically weak. It surveyed for loss of smell in the general population and then correlated it to the published number of COVID-19 cases. No firm conclusions can be drawn. However, there is anecdotal evidence from ENT colleagues. The Centre for Evidence-Based Medicine also reviewed data on anosmia as a clinical feature of COVID-19 and gave us the **bottom line: the current evidence base to suggest olfactory sensation changes as a feature of COVID-19 is limited; however, a clinical question around olfactory sensation changes could be integrated when assessing patients.**

Reference: medRxiv 2020.03.23.20041889
Abstract

Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV2)

Authors: Li R et al.

Summary: These authors reported observations of reported COVID-19 infections within China, along with mobility data, a networked dynamic metapopulation model and Bayesian inference, to infer critical epidemiological characteristics associated with the virus, including the fraction of undocumented infections and their contagiousness. It was estimated that 86% of all infections were undocumented before travel restrictions were implemented on Jan 23, 2020. While the per-person undocumented infection transmission rate was 55% that of documented infections, the greater numbers resulted in undocumented infections being the infection source for 79% of documented cases.

Comment: This article is a little more difficult to read as the authors used different mathematical models to estimate the number of undocumented infections. Undocumented infection in patients with minimal symptoms is probably an important driver of the pandemic. Using data from 31 cities, the authors estimated that up to 86% of all infections are caused by undocumented/minimally symptomatic individuals. Influenza also causes many mild cases and can also quickly spread globally. **Bottom line: countries that don't identify symptomatic cases and isolate them pay a high social price. These mathematical data suggest that prolonged geographical mobility restrictions are needed to contain the SARS-CoV-2 pandemic.**

Reference: Science; published online Mar 16, 2020
Abstract

Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China

Authors: Dong Y et al.

Summary: Epidemiological characteristics and transmission patterns were reported for 2143 paediatric patients with laboratory-confirmed (34.1%) or suspected (65.9%) COVID-19 infection in China. The patients' median age was 7 years, and 56.6% were male. The vast majority of patients (>90%) were asymptomatic, mild or moderate cases. Diagnoses were made a median of 2 days (range 0–42) after symptom onset. A rapid increase in paediatric patients with COVID-19 was seen early in the epidemic, after which there was a gradual, steady decrease. The Hubei province, from where paediatric COVID-19 cases rapidly spread, had more paediatric COVID-19 cases than any other province.

Comment: The role of children in the current COVID-19 pandemic is still unclear. Are they not affected/infected or will they become eventually the key for building a 'herd immunity' for this virus? This retrospective study from China provides good-quality data and a weak ethics statement. Overall, more than 90% of infected children were asymptomatic or had mild/moderate disease. The highest incidence of severe/critical disease (11%) occurred in children aged <1 year. **Bottom line: transmission of this virus between children seems to occur rapidly and widely. Families should be urged to adhere to physical distancing and hand hygiene.**

Reference: Pediatrics 2020:e20200702
Abstract

Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19)

Authors: Guo T et al.

Summary: Associations of underlying CV disease and myocardial injury with fatal outcomes from confirmed COVID-19 infection were investigated for a retrospective cohort of 187 patients (mean age 58.5 years) in China, 23% of whom died. Underlying CV diseases were present in 35.3% of the patients, and 27.8% had myocardial injury (elevated troponin T level). The respective in-hospital mortality rates for patients with and without underlying CV disease and normal troponin T levels were 13.33% and 7.62%, and the respective rates for those with elevated troponin T levels were 69.44% and 37.50%. Patients with versus without underlying CV disease were more likely to have an elevated troponin T level (54.5% vs. 13.2%). Significant positive linear correlations were seen between plasma troponin T level and plasma high-sensitivity CRP and NT-proBNP levels (respective β values 0.530 and 0.413 [$p<0.001$ for both]). Patients who died experienced significant increases in plasma troponin T and NT-proBNP levels during hospitalisation ($p\leq0.001$), whereas survivors did not. Compared with patients whose troponin T levels remained normal during hospitalisation, greater proportions of those whose levels increased experienced malignant arrhythmias and required glucocorticoid therapy (71.2% vs. 51.1%) and mechanical ventilation (59.6% vs. 10.4%). The respective mortality rates for angiotensin-converting enzyme inhibitor/angiotensin receptor blocker recipients and nonrecipients were 36.8% and 25.6%.

Comment: This article from Wuhan is focussing on CV manifestations of 187 patients diagnosed with COVID-19. The median illness duration was 28 days. Even without clinical features of ischaemic heart disease, an elevated troponin T level was associated with an increased risk of mortality of 37%. Patients with a raised troponin T level and cardiac risk factors like hypertension, coronary heart disease or cardiomyopathy had a mortality rate of 69%. The picture of a raised troponin T level, raised NT-proBNP level and cardiac arrhythmias suggests possible direct damage of the cardiomyocytes by the virus. **Bottom line: myocardial injury is associated with impaired cardiac function, arrhythmias and fatal outcomes in COVID-19.**

Reference: JAMA Cardiol: published online March 27, 2020
Abstract

Physical interventions to interrupt or reduce the spread of respiratory viruses

Authors: Jefferson T et al.

Summary: This was a 2011 Cochrane review of 67 RCTs and observational studies reporting on the effectiveness of physical interventions to interrupt or reduce respiratory virus spread; five of the RCTs and most cluster RCTs had a high risk of bias, and the quality of the observational studies was mixed. A meta-analysis was possible only for case-control data. Data from the highest quality cluster RCTs suggested that spread of respiratory viruses can be prevented by hygiene measures, such as handwashing, especially around younger children. The benefit from reduced transmission from children to household members was broadly supported with other study designs, although they have greater potential for confounding. Data from nine case-control studies suggested effectiveness of transmission barriers, isolation and hygienic measures for containing respiratory virus epidemics. Surgical masks and N95 respirators were consistent, comprehensive supportive measures, and were noninferior to each other, although respirators had the disadvantages of being more costly, uncomfortable and irritating to the skin. It was not clear if adding virucidals or antiseptics to normal handwashing decreased respiratory disease transmission. Global measures (e.g., entry point screening) were associated with a nonsignificant, marginal delay in respiratory virus spread, and evidence for the effectiveness of physical distancing was limited, especially if related to exposure risk.

Comment: The use of facemasks in public is a topic of intense debate. Their use is influenced by cultural traditions, epidemiology, environmental science and the need to ration the limited resource of PPE. Published during a less pressured time, this Cochrane review was suggesting some efficacy of N95 respirators and simple surgical masks to reduce infections. The authors found no evidence that the more expensive, irritating and uncomfortable N95 respirators were superior to simple surgical masks. The Czech Republic is an example of a European country embracing masks (YouTube). **Bottom line: in addition to physical distancing and handwashing, facial masks may reduce the spread of infections.**

Reference: Cochrane Database of Syst Rev. 2011;7:CD006207
Abstract

Testing the efficacy of homemade masks: Would they protect in an influenza pandemic?

Authors: Davies A et al.

Summary: The effectiveness of home-made facemasks, as an alternative to commercially available facemasks, was investigated in this research. Masks made from cotton t-shirts by 21 healthy volunteers were tested for fit, and compared with surgical masks or no mask for isolation of micro-organisms from coughs using several air-sampling techniques. Compared with surgical masks, the home-made masks had one-half the median fit factor. While both the homemade and surgical masks were associated with significant reductions in the number of micro-organisms expelled during coughing, surgical masks were three times more effective for blocking transmission.

Comment: If you watched this YouTube video, endorsed by the Minister of Health of the Czech Republic, the YouTube algorithm will have suggested an array of videos on how to make your own facial mask using a variety of fabrics. This study from London scientists was published in 2013 and compared a variety of home-made masks with surgical masks. Even so, the authors only recommend home-made masks as a measure of 'last resort'; the reduction in droplets producing colony-forming units was impressive (Tables 3 and 4). **Bottom line: a home-made facemask could be considered in conjunction with other measures, such as isolation of infected cases, good respiratory etiquette and regular hand hygiene.**

Reference: Disaster Med Public Health Prep. 2013;7:413–8
Abstract

Treatment of 5 critically ill patients with COVID-19 with convalescent plasma

Authors: Shen C et al.

Summary: These authors reported on a series of five critically ill, mechanically ventilated patients with laboratory-confirmed COVID-19 infection and acute respiratory distress syndrome treated with convalescent plasma transfusions; all five patients had also received antiviral agents and methylprednisolone. The transfusions consisted of convalescent plasma with a SARS-CoV-2-specific antibody (IgG) binding titre >1:1000 and a neutralisation titre >40, obtained from five patients who had recovered from COVID-19 infection. Four of the patients had normalisation of their body temperature within 3 days of receiving the plasma transfusion, their Sequential Organ Failure Assessment scores decreased, and their ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) increased within 12 days. SARS-CoV-2-specific antibody titres increased following the transfusion and viral loads declined and became negative within 12 days post-transfusion. Four patients had experienced resolution of their acute respiratory distress by day 12, and three had been weaned from mechanical ventilation within 2 weeks. At the time of reporting, three patients had been discharged after 51–55 days of hospitalisation, and two were in a stable condition at 37 days post-transfusion.

Comment: It is difficult to judge from this uncontrolled case series of five patients if the effect was related to the plasma infusion or part of the natural history. On first principles, the use of convalescent plasma has been used for SARS, pandemic 2009 influenza A (H1N1), avian influenza A (H5N1) and Ebola. The accompanying editorial by John Roback and Jeannette Guarner explores the five steps that need to be considered if this treatment is confirmed by trial evidence. **Bottom line: five patients with COVID-19 seemed to have improved in this preliminary uncontrolled case series after treatment with convalescent plasma.**

Reference: JAMA; published online March 27, 2020
Abstract

Independent commentary by Professor Lutz Beckert

Professor Lutz Beckert is the Associate Dean Medical Education with the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or with the view of future collaborations.

Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1

Authors: van Doremalen N et al.

Summary: The stability of SARS-CoV-2 and SARS-CoV-1 in aerosols (<5μm) and on various surfaces was evaluated in this research; decay rates were estimated using a Bayesian regression model. SARS-CoV-2 and SARS-CoV-1 in aerosols had similar median estimated half-lives of ~1.1–1.2 hours, and their half-lives were also similar on copper. However, SARS-CoV-2 had a longer half-life on cardboard than SARS-CoV-1, with viable SARS-CoV-2 still present 24 hours after application. Both viruses showed the longest viability on stainless steel and plastic, with respective estimated median half-lives of 5.6 and 6.8 hours for SARS-CoV-2. Estimated differences in the half-lives between the two viruses were small except when applied to cardboard.

Comment: The authors of this letter to the editor in the N Engl J Med aerosolised the SARS-CoV-2 virus, which is not the way it is thought to spread. The virus remained viable on plastic for longer than 72 hours, on stainless steel for longer than 48 hours, and on cardboard for 24 hours. Given the similar survival times to SARS-CoV-1, other factors including high viral loads in the upper respiratory tract and asymptomatic spread may explain the different epidemiological characteristics of these viruses. **Bottom line: the virus has a long survival on plastic and stainless steel, contributing to its spread.**

Reference: N Engl J Med; published online March 17, 2020
Abstract

Hydroxychloroquine and azithromycin as a treatment of COVID-19

Authors: Gautret P et al.

Summary: Patients from France with confirmed COVID-19 infection received hydroxychloroquine 600 mg/day, with azithromycin added depending on their clinical presentation, in this open-label, single-arm trial. Six asymptomatic patients, 22 with symptoms of upper respiratory tract infection and eight with lower respiratory tract infection symptoms were eligible, 20 of whom received treatment; those who refused treatment and untreated patients from another centre served as negative controls. Compared with controls, treated participants had a significant reduction in their viral carriage at day 6, and much lower average carrying duration than has been reported for untreated patients in the literature. Virus elimination was also significantly enhanced by the addition of azithromycin.

Comment: This study is only included because it has been picked up by social media and lay people from a pre-print server. Under normal circumstances, this paper may not have been published, as this was an uncontrolled study, with controls having a higher viral load to start with and only surrogate outcomes being measured. Our colleagues in rheumatology spelled out the shortcomings of this paper and the consequences of a shortage of hydroxychloroquine for the treatment of rheumatological conditions (Ann Intern Med; published online March 30, 2020). **Bottom line: the evidence for the use of hydroxychloroquine/azithromycin is not established. The rapid dissemination of pre-reviewed papers can lead to unintended consequences.**

Reference: Int J Antimicrob Agents; published online March 20, 2020
Abstract

