COVID-19 Science Report:
What’s New

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What’s New
For regular readers, this section has all the new content across all sections.
References for new content outlined below are located in the main reports.

Clinical Characteristics
The update to the report this week continued to focus on highlighting novel presentations of COVID-19, risk factors for disease susceptibility and severity, as well as clinical characteristics in vulnerable sub-populations.

Disease Susceptibility
An analysis suggested that SARS-CoV-2 has a receptor-binding domain that may bind well to human ACE-2, and that pericytes in cardiac cells with a high expression of ACE2 may be targeted.

Clinical Presentation
A study of 417 mild-to-moderate COVID-19 patients in Europe found that 85.6% of patients had infection related olfactory dysfunction, of which 79.6% were anosmic and 20.4% were hyposmic. 12.6% of patient developed phantosmia, while 32.4% developed parosmia. The majority of patients (65.4%) developed olfactory dysfunction after general or ENT symptoms, although 11.8% olfactory dysfunction before other symptoms. On the other hand, 88.0% of patients reported gustatory dysfunctions. Olfactory and gustatory dysfunctions were found to have a statistically significant association. 44.0% of patients recovered their olfactory in the short-term, of which 72.6% recovered within 8 days following disease resolution.

In a study in China, out of 38 patients with clinically confirmed COVID-19 (of which 73.7% tested positive based on RT-PCR from nasopharyngeal swab), 31.6% (95% CI 17.5-48.7) had ocular abnormalities consistent with conjunctivitis. However only one of 30 patients had conjunctivitis in another study, and only 9 out of 1099 patients had conjunctival congestion in the study by Guan et al.

There was a case reported of uncomplicated spontaneous vaginal delivery in a pregnant mother diagnosed with COVID-19 in US.

Asymptomatic Presentation
In Korea, 3 of the 28 initial laboratory confirmed COVID-19 cases were asymptomatic. In Singapore, pre-symptomatic cases accounted for 6.4% of the 157 locally acquired cases recorded between January 23 and March 16.

In a study of 1012 non-critically ill patients in Wuhan, 30 patients (3.0%) were asymptomatic from exposure to admission, of which 53.3% developed symptoms during follow-up. 14 patients (1.4%) remained asymptomatic during the follow-up period lasting a median of 24 days (IQR 22-27).

A study in Shanghai classified 13 patients who tested positive for COVID-19 on RT-PCR but with no symptoms into 4 categories: (1) patients in incubation period, (2) patients with signs of disease (eg chest CT findings) but no subjective symptoms, (3) patients with subclinical infection, and (4) asymptomatic chronic carriers. Out of 13 patients who did not have subjective symptoms, 3 patients fell under both category (1) and (2), 10 under category (2)
only, 1 patient under category (3), and none under category 4 as all patients tested negative within 3 weeks.

**Radiographic Findings**

An enlarged subsegmental vessel (>3mm diameter) was noted in 89% of 58 patients in Italy. Han et al noted rapid increase in mean CT score from first to third week, with a peak of 8.2 in the second week, as well as increasing presentation of consolidation and mixed patterns in the second week, which become less prevalent as compared to ground glass opacities again in the third and fourth week during recovery.

Another study in Rome, Italy, found the sensitivity, specificity and accuracy of CT to be 97% (95% CI 88-99), 56% (95% CI 45-66), and 72% (95% CI 64-78). A case report noted a diagnosis of COVID-19 in an initially asymptomatic patient after findings of “bilateral, diffuse and intense FDG uptake” on a ^18^F-FDG PET/CT scan for malignancy, which correlated with ground-glass opacities seen on a low-dose CT scan.

**Laboratory Findings**

One study noted that multi-functional CD4+ T cells are significantly reduced in the severe group. A study found that lower levels of lymphocytes, CD4+ T-cells, CD8+ T cells, B cells and NK cells were noted in severe cases as compared to milder cases, with a decrease in CD8+ T cells and B cells, as well as an increase in CD4+/CD8+ ratio, associated with poor recovery and clinical efficacy. One study found elevated lymphocyte counts and CRP levels in a 10 month old boy with co-infection with Influenza A.

In an ex-vivo study, SARS-CoV-2 infection upregulated the expression of 5 out of 13 pro-inflammatory cytokines and chemokines, as compared to 11 by SARS-CoV infection, although the SARS-CoV-2 replicated more efficiently in human lung tissue.

Cheng et al found that peak Cre was 91±67 μmol/L. After adjustment for age, gender, disease severity, comorbidity and leukocyte count, higher baseline Cre at admission (HR 2.10, 95% CI 1.36-3.26), AKI stage 2 (HR 3.51, 95% CI 1.49-8.26), and AKI stage 3 (HR 4.38, 95% CI 2.31-8.31) were found to be associated with mortality. Wang et al reported that although 10.8% of patients without chronic kidney disease showed mild increase of blood urea nitrogen or serum creatinine, and 7.2% of patients showed trace or 1+ albuminuria, the patients “did not meet the diagnostic criteria of AKI”.

A case report noted delayed antibody response in a COVID-19 patient with existing co-infection with HIV-1 and HCV.

**Viral Load**

Based on testing using RT-PCR cycle threshold (Ct) and droplet digital PCR (ddPCR), viral loads are said to be higher in the “early and progressive stages” (46800 ± 17272) as compared to the recovery stage (1252 ± 1027).

While uncommon, a study detected SARS-CoV-2 from conjunctival swabs from 2 patients with ocular manifestations suggestive of conjunctivitis, and another yielded positive RT-PCR results from tear and conjunctival secretions from a patient with conjunctivitis.

Another study of 10 female postmenopausal patients with severe COVID-19 disease in China did not find the presence of SARS-CoV-2 virus in vaginal fluids obtained from vaginal swab samples taken 17-40 days after onset of infection.
The Korea Centers for Disease Control and Prevention reported that 51 people tested positive again for COVID-19 after discharge, likely due to viral reactivation, although further studies are required. There are reports that between 3-10%, and approximately 14% of patients test positive after recovery in China. A study in Shenzhen found that 14.5% of 172 discharged patients (after achieving two consecutive negative RT-PCR test results 24 hours apart) in Shenzhen tested positive again without symptom aggravation after 2-13 days.

**Morbidity/ Complications**

Acute kidney injury was noted in 5.1% of patients in a prospective cohort study of 701 patients.

Pulmonary embolism has been reported to occur in patients with COVID-19 without notable risk factors for venous thromboembolism. Pulmonary embolism may be associated with respiratory deterioration, elevated serum D-dimer levels, and hemoptysis. There are also case reports of clinically significant coagulopathy and antiphospholipid antibodies (anticardiolipin IgA, anti-β₂-glycoprotein I IgA and IgG) in COVID-19 patients in ICU.

An adult COVID-19 patient with sickle cell disease developed Acute Chest Syndrome, and underwent exchange transfusion before recovery.

**Risk factors for Disease Progression**

Another study found that independent risk factors for disease progression include comorbidity (HR 3.9, 95% CI 1.9-7.9), age above 60 years (HR 3.0, 95% CI 1.4-6.0), lower lymphocyte levels ≤1.0 x 10⁹/L (HR 3.7, 95% CI 1.8-7.8), and higher lactate dehydrogenase levels between 250-500 U/L (HR 2.5, 95% CI 1.2-5.2) and above 500 U/L (HR 9.8, 95% CI 2.8-33.8) at presentation. The study proposed the use of a CALL scoring model incorporating the risk factors, for the prediction of risk of progression of disease. Based on ROC analysis, the AUC was 0.91 (95% CI 0.6-0.94).

France has added obesity to its list of risk factors for severe disease, on top of older age, and co-morbidities including hypertension, diabetes, and coronary artery disease.

Based on RNA sequencing, patients with heart failure were found to have increased myocardial ACE2 expression which may result in a higher risk of heart attack.

**Diagnostics**

In March 2020, FIND launched an evaluation of SARS-CoV-2 immunoassays using a standardized independent protocol.⁵⁵ Although the initial round of submissions allowed for manual ELISA and machine-based or lateral flow rapid tests, the first selection announced prioritised evaluation of only rapid diagnostic tests (RDTs). The final list of this first selection covered 27 RDTs for detection of antibodies targeting SARS-CoV-2. Five RDTs for detection of SARS-CoV-2 antigen will also be tested. Results are not available as of 11 April 2020.

**Therapeutics**

Numerous clinical trials have commenced based on possible treatment candidates. Lists of the clinical trials can be found at the following databases:

- [US Clinical Trial Registry](#)
- [Chinese Clinical Trial Registry](#)
WHO hosts a web base application to analyse clinical trials to evaluate therapeutics for COVID-19. Therefore, the report no longer lists the clinical trials.

**NICE** (UK National Institute for Health and Care Excellence) has published COVID-19 rapid guidelines covering:

- Critical care in adults
- Managing symptoms (including at the end of life) in the community
- Haematopoietic stem cell transplantation
- Managing suspected or confirmed pneumonia in adults in the community
- Severe asthma
- Rheumatological autoimmune, inflammatory and metabolic bone disorders
- Dialysis service delivery
- Delivery of systemic anticancer treatments
- Delivery of radiotherapy

Further rapid guidelines will be published shortly.

**Drug updates:**

- **Chloroquine** - Some Swedish hospitals have stopped their usage of chloroquine for COVID-19 patients after reports of severe side effects such as loss of peripheral vision.
- **Hydroxychloroquine and azithromycin** - Re-analysis of the positive hydroxychloroquine and azithromycin study has been published in Pre-Print. Questions were raised regarding the study’s data integrity, statistical analyses, and experimental design. Re-analysis of the study suggested that there was a positive effect of Hydroxychloroquine on viral load reduction, and a further improvement by adding and Azithromycin. However, the re-analysis also highlighted the limitations and concluded that randomised controlled trials will be essential in resolving uncertainty as to whether hydroxychloroquine and azithromycin are effective as a treatment for COVID-19.

Another study of Azithromycin has also shown to have possible inhibitory effect on SARS-CoV-2 replication.

- **Darunavir/Cobicistat** - Study has found no in-vitro efficacy of Darunavir/Cobicistat at clinically relevant concentrations.
- **Emtricitabine/Tenofovir** - The triphosphates of Emtricitabine and Tenofovir has been shown to act as terminators for the SARS-CoV-2 RdRp catalysed reaction, thus making it a potential drug against COVID-19.
- **Atazanavir** - Atazanavir is an antiretroviral drug of the protease inhibitor class, typically used in the treatment of HIV. Atazanavir has been shown in molecular dynamic analysis to bind more strongly to SARS-CoV-2 Mpro active site than Lopinavir. In-vitro assays with different cell types showed that Atazanavir with or without ritonavir inhibited SARS-CoV-2 replication. Furthermore, Atazanavir performed better than chloroquine in reducing virus-induced IL-6 and TNF α levels.
• **Tocilizumab** - A pre-publication meta-analysis has shown that tocilizumab has appeared to be efficacious and safe so far, but concludes that the above clinical trials need to be concluded before defining the role of the drug in COVID-19.

• **Baricitinib** - A *lancet* article suggests that Baricitinib could directly block the penetration of SARS-CoV-2 into host cells.

• A pre-publication paper has suggested that Azithromycin, Opipramol, Quinidine, and Omeprazole might be suitable for repurposing for the inhibition of SARS-CoV-2 based on in-vitro tests.

• Teicoplanin, a glycopeptide antibiotic that inhibits bacterial cell wall synthesis, was recently found to have actions against MERS-CoV and Ebola virus in cell culture. The role of Teicoplanin in COVID-19 is still under investigation.

**Prophylaxis**

So far, there has been a lack of clinical guidance for the use of chloroquine for pre or post-exposure prophylaxis due to absence of clinical trials. Similarly, the John Hopkins University JHMI Clinical Guidance for COVID-19 does not recommend any prophylaxis.

A Chinese retrospective case-control study looked at the potential of Arbidol to be used as a post-exposure prophylaxis. The small study included 27 families and 124 health care workers who had been exposed to patients with confirmed COVID-19 infections. Arbidol was found to reduce the likelihood of developing COVID-19 (Oseltamivir was also studied and not found to be beneficial in preventing infection).

**Vaccines**

There are well-established databases listing the potential COVID-19 vaccine candidates. Therefore this report has been shortened to focus on the vaccines funded by CEPI and those in clinical trials, as well as some of the key issues. Therefore the search criteria shifted to a more targeted approach.

Vaccines in development:

• The WHO has a collection of the latest vaccine reports related to COVID-19, which includes a regularly updated landscape of COVID-19 vaccine candidates

• Regulatory Affairs Professional Society has a [COVID-19 Vaccine Tracker](#)

The report has new content around the difference between normal linear development of vaccines and the approach in pandemics. The following diagram outlines the two approaches.
Issues around the manufacture of vaccines and serological testing within a vaccine strategy are also flagged.

**Containment Measures**

**Detection/Contact Tracing**

**Isolation/fever tracking in schools.** A recent modelling study showed that with a high rate of fever detection (at 88%), a 1 day post fever isolation reduces COVID-19 attack rate by 8% and a 6 day policy reduces attack rate by 15%. The study recommends at least 6 days of post fever isolation for COVID-19 infection in school settings. (Page 15 of COVID-19 Science Report: Containment Measures)

**Hospital Infection Control and Protection of Healthcare Personnel**

**Practices of a radiology team.** A journal article shared the steps taken by a radiology department in a Singapore hospital to ensure business continuity and patient safety amidst the COVID-19 situation. (Page 20)

**Sterilisation of masks.** A study conducted to evaluate the effectiveness of using Gamma irradiation as a sterilisation method for N95 masks found that irradiated masks performed much more poorly than unirradiated masks in terms of particulate matter filtration, especially for 0.3 μm particles. The study suggests against irradiation as a sterilisation method. (Page 25)
Mask utilisation projections. A modelling study projected the mask shortage numbers for different facemask policies in China for the period up to June (modelling assumes usage of both N95 and non-N95 masks for different users). Facemask shortage and its duration range from 539.5 million (132 days) for the universal facemask wearing policy scenario to 37.5 million (4 days) for the no universal facemask wearing policy. The study pointed out that a universal facemask wearing policy can cause panic throughout the country and lead to more severe shortages that will affect healthcare workers. (Page 27)

Plastic drapes. A study evaluating the use of clear plastic drapes in minimising droplets contamination during aerosol-generating medical procedures such as intubation and extubation during COVID-19 treatment found its use effective, with 3-layer plastic drape configuration - 1. Under the head, 2. Covering the upper torso, 3. Over-head top drape – most effective. (Page 28)

Hospital capacity preparedness. A modelling study estimated that hospitals in half of the states in the US are expected to exceed capacity even if less than the projected proportion of state population requires hospitalization with COVID-19. (Page 29)

Community Hygiene

Facemask usage behaviour. A 2020 study done on 345 online responders in Vietnam found that people who chose to buy masks have higher risk perceptions than those who did not, and are likely to maintain such behaviours. The elderly were also more likely than before to wear masks after the COVID-10 outbreak. Mask characteristics apparently did not influence people’s decision to wear masks. (Page 32)

Wastewater plumbing system. A 2017 study using a model organism to test for the presence of droplet contamination in wastewater plumbing systems showed positive droplet fallout contamination and cross contamination of air from wastewater plumbing systems. High concentration of self-isolation or quarantine individuals can contribute to higher viral load in wastewater plumbing systems and lead to increased spread infection spread. The study recommends ensuring tight seal of leaks and monitoring of whole wastewater plumbing system performance to decrease risk of viral transmission. (Page 32)

Workplace and School Closures

Secondary adverse effects. A review article pointed to some adverse effects of school closure such as increased dropouts, child labour, violence against children, poorer children health with lack of vaccinations and school nurses, and widened inequality due to lack of access to distance learning technologies amongst disadvantaged children.

Populations Contained in High Density Accommodation (PCHDA). A sub-section pointing out the key concerns and higher outbreak risk factors regarding prisons, custodial settings, immigration detention centres and military accommodation settings, possible precautionary measures, and key considerations when there are outbreaks in such settings. (Page 38)

Multi-intervention Strategies

A mass testing and isolation centric strategy. A modelling study found that a much higher detection rate followed by subsequent isolation of cases can be as effective as social distancing measures in bringing RO down to one. This is equivalent to testing the entire susceptible population roughly once every 10 days, after which frequency can be reduced when infected cases drop and surviving cases develop immunity. Mass testing alone or
coupled with less severe social distancing measures can be a strategy which results in less disruption to economy/societal functioning. (Page 47)

**Comparison of effect of combined NPIs across countries.** Measures implemented in China reduced RO more quickly as compared to Italy, Belgium and Spain, where measures enforced resulted in more gradual impact to RO that was not drastic enough to reverse epidemic trend. In Italy, this was likely due to substantial population mobility still taking place after nationwide lockdown, after which mobility further reduced and RO was later brought to 0.69. (Page 53)

**South Korea.** A recent analysis pointed out that while South Korea’s experience provides evidence of less severe measures suppressing an epidemic, observation of metro traffic as a proxy for degree of social distancing showed a 80% decrease in traffic volume in Daegu suggestive of similar strength in social distancing comparable to Wuhan’s. Recent decrease in the number of reported cases in South Korea is driven by the sharp decrease in Daegu and the epidemic may still persist in other regions. (Page 56)

**Timing, duration and impact.** A UK study showed that less strict implementation of social distancing will mean taking a longer time for life to return to normal and with more lives at risk. The epidemic will resolve in 15 months with 22,000 dead in a perfectly implemented lockdown in the UK, 4.5 months with 80,000 dead in a semi-lockdown situation, and 6 months with >300,000 dead in an even more relaxed situation. (Page 57)

**Political factors.** An event history analysis of dataset on five social distancing policies across fifty states in the US reveals that the most important predictors of implementation and timing of the policies are political. All else being equal, Republican governors and governors from states with more Trump supporters were slower to adopt social distancing policies. Poorer states were less likely to adopt social distancing policies and neighbouring state actions increased the likelihood of social distancing policies, while confirmed state-level caseload had only a small effect on social distancing timing. (Page 57)

**Tracking behavioural change as early indicator of impact.** A UK study showed that as there is time lag between decline in cases in response to social distancing measures, tracking behavioural change data can provide rapid assessment of impact of measures. The study observed a 73% reduction in the average daily number of contacts per participant which translates to an RO reduction from 2.6 to 0.62 after lockdown. (Page 57)

**Herd immunity versus suppression (economic and mortality costs).** A modelling study estimated the total costs of 3 different approaches: (1) Laissez-faire approach (no mitigation measures taken) (2) Herd immunity approach (NPIs are implemented to reduce the RO to less than 1 and keep the number of new infections close to the healthcare system capacity) (3) Aggressive approach (strict measures are implemented from April to June to bring the RO down to almost zero). The aggressive approach results in the least total costs for both a low and high value of value of statistical life (VSL). (Page 58)

**Comparing different strategies.** A study considered the effectiveness and mapped out the curves of 5 different strategy scenarios in London, Wuhan, Hubei and UK: (1) no interventions, (2) surveillance and isolation, (3) Suppression intervention (4) Mitigation intervention (see above para. on ‘Herd immunity versus suppression’ section and (5) hybrid intervention of Suppression and Mitigation for every 2/3 weeks over a longer period. The study points out that the choice of strategy is highly challenging and depends on the multiple nature and capabilities of different countries. It also points out that a highly effective surveillance and isolation strategy is necessary to control an epidemic in early stage and if executed excellently, prevents major outbreaks subsequently. A Suppression strategy is highly effective but questionable in practical feasibility. (Page 60)
Availability of online model. An online model, real-time, and interactive simulation model to facilitate local policy making and regional coordination in the US by providing estimates of hospital bed demand and impact of public health measures on COVID-19 spread has been made available by Schools at Stanford University. (Page 60)

Feasibility of the ‘switching’ and herd immunity strategy. A modelling study on New Zealand simulated the scenario of the Mitigation strategy as a combination of a low level of control measures (reducing RO to 1.75) with periods of high control measures (imposed when capacity is close to full and reducing RO to 0.75) to keep the case numbers under hospital capacity. The study cautioned that the theory is tempting but it remains unknown if it is achievable in practice. Less effective than hoped for strong control or small uncertainties in case trajectories can lead to incorrect implementation timing and drastic overshooting of hospital/ICU capacity. The study recommends Suppression to buy time for medical solutions to become available and for learning from unfolding events in other countries. (Page 62)

Two other modelling studies (one of which is a simulation study on Germany and Poland and the other, a Belgium based study) indicated that there is only a narrow feasible interval of epidemiologically relevant parameters within which such a similar strategy of flattening the curve or ‘switching’ while achieving herd immunity is possible. These studies propose the immediate quashing and containment of the epidemic at a minimal level driven by imported cases while awaiting medical solutions, and the imposition of heavy quarantine measures to quash the new epidemic flare when these fail. (Page 63)

Targeted Quarantine strategy. Two modelling studies considered a strategy in which all of society (bar essential workers) are locked down for 2-4 weeks to brake uncontrolled epidemic spread, after which those without risk factors are encouraged to return to work and socialise while at risk individuals remain at home under quarantine. One study pointed out that with threshold age for quarantine at 50 years and one third of the population quarantined, a 6 months duration is sufficient to complete entire course of epidemic without overwhelming ICU capacity. Quarantine measures can then be lowered in stages, with each stage exposing successively higher risk populations. Notwithstanding, the study listed out the pressing issues that need to be resolved to support societal functioning during the period. (Page 62)

Nordic countries. An analysis of infection case doubling time (DT) noted an increase in DT values in all Nordic countries after the governments imposed shutdowns. (Page 64)

China. Further modelling studies estimating that RO in locations outside Hubei reduced to <1 after 30 Jan and implementation of containment measures. Peaks in RO in these locations ranged between 1.08 in Shenzhen to 1.71 in Shandong. (Page 53)

Social Distancing & Lockdowns

This report should be read alongside the COVID-19 Containment Measures evidence report, particularly the ‘Multi-Intervention Strategies’ section.

The case studies have been updated.