COVID-19 Evidence Update

COVID-19 Update from SAHMRI, Health Translation SA and the Commission on Excellence and Innovation in Health

11 April 2020

Viral load, inoculum dose and severity of COVID-19

Executive Summary

The evidence clearly indicates that minimisation of exposure to SARS-COV-2 (and similar viruses) is key to reducing the chance of infection and developing disease. Viral load is positively correlated with severity of COVID-19. There is an **absence of evidence about inoculum dose and severity** for COVID-19 but extrapolation from MERS, SARS and influenza could suggest that the higher the initial inoculum the more severe the subsequent disease.

Health Care Workers (HCW) are more likely than the general public to come into contact with people (patients, visitors, other HCW) who are infected with SARS-COV-2; both known cases and potentially unknown cases. Notably, those who work in ICU with COVID-19 patients, undertaking procedures such as intubation and extubation which generate aerosols, are at increased risk of exposure to the virus, and therefore contracting COVID-19. However, the available data on HCW in hospitals shows that staff from a range of departments have become infected, not just those directly exposed to patients with COVID-19 in ICU.

It cannot be substantiated (or conclusively refuted) by the current literature, that healthcare workers may be developing disproportionately severe COVID-19 disease. However, the international reports indicate that the apparent increased risk of contracting disease and subsequent severe outcomes may be due to: lack of awareness of patients' SARS-COV-2 positive status; surface contamination and lack of social distancing in hospitals; and/or inadequate PPE, especially early in the pandemic.

While it is clear that **cruise ships** are places of very high social contact, causing high spread of SARS-COV-2, the implementation of quarantine rules reduced the reproductive rate. It cannot be substantiated (or conclusively refuted) by the current literature, that cruise ship passengers are developing disproportionately severe COVID-19 disease. One paper (not peer reviewed) reports that the deaths from the Diamond Princess cruise ship occurred in those aged 70 years and over (average age of passengers was 58 years). The apparently high cases of severity and mortality is likely to be a function of demographics of the passengers (e.g. age and comorbidity).

There is an **absence of evidence about inoculum dose and severity of SARS-COV-2.** However, there is a correlation between viral inoculum and disease severity for **SARS and influenza** [1-3]. Health care workers were at a greater risk during the SARS epidemic, which has been attributed to similar factors as COVID-19 (e.g. inadequate PPE, exposure to undiagnosed patients) [4, 5]. There is also animal data on MERS and SARS [6, 7].

Context

Media reports from across the world are highlighting the high number of severe cases and deaths of health care workers infected with COVID-19. Medscape are now compiling an in memoriam list [8]. There are multiple news articles reporting COVID-19 outbreak clusters in hospitals in Victoria, Tasmania, Queensland and NSW, however, minimal information is available and the source of infection and severity of disease cannot be determined (e.g. [9]).

While it cannot yet be substantiated or refuted by the current literature, concern has been expressed that healthcare workers may be developing disproportionately severe COVID-19 disease, which may be a result of a higher infectious dose (e.g. the amount of virus at the start of infection), which may then increase the severity of the illness. If this is demonstrated to be the case (which it has not yet been), it is hypothesised that this is influenced by:

a) Conducting or being present during aerosol generating procedures (e.g. intubation), or
a) Being present for a series of exposures to smaller viral loads, such as the presence of virus particulates in rooms and on surfaces within healthcare settings.

Healthcare workers may also be at higher risk of infection during the early stages of an outbreak (when initial contacts may not be recognised because they are asymptomatic or have atypical clinical manifestations) due to inadequate protective measures.

Notes: Viral load is the measure of the number of viral particles present in an individual. Viral inoculum is the amount of virus that patient first experiences from someone/somewhere that caused their infection. We refer to the virus as SARS-CoV-2 and the disease as COVID-19

International review (discussion piece)

The Centre for Evidence-Based Medicine, at the University of Oxford published a rapid review on 'SARS-CoV-2 viral load and the severity of COVID-19' (26th March 2020) [10]

This review is not specific to healthcare workers, but discussed evidence in SARS, SARS-CoV-2 and Influenza. Authors noted that there is association of viral load with the severity of the disease however many of the studies are of poor quality. The authors refer to studies that have found a relationship between the severity of SARS and proximity to initial case [2], and the severity of influenza and exposure to high infectious dose [3]. The authors list numerous news reports of healthcare worker deaths across multiple countries, but highlight that such reports lack context and insight into what is contributing to the deaths. Overall, authors recommended that the more monitoring and observation needs to occur before conclusions can be drawn.

Healthcare workers (HCW) susceptibility to COVID-19

<u>Statistics on prevalence of COVID-19 among healthcare workers (HCW) and disease severity</u>

- A summary report from the Chinese Center for Disease Control and Prevention showed that, of 44,672 infected cases, **3.8% were HCW**. Of the infected HCW, **14.8% classified as severe or critical** and there were **5 deaths**. In the overall sample, 14% of cases were severe, 5% were critical and the case-fatality rate was 2.3% [11]. Another study showed that **2.1% of HCW** were infected [12].
- Of 138 patients treated in Wuhan hospital, **29% were HCW**. Among affected HCW, 78% worked on general wards, 18% worked in ED and 5% worked in ICU. There was potentially a super-spreader patient who infected more than 10 HCW in the surgical department after presenting with abdominal symptoms [13].

- An investigation of a cluster of cases from a single thoracic department involving 13 patients and 12 HCW. Of the HCW, 2 (17%) were classified as severe, whereas for hospitalised patients, 7 (46%) were severe. HCW were significantly younger than hospitalised patients. The study identified a potential 'super spreader' who had a chest operation before the implementation of quarantine and comprehensive protection. During the hospitalisation of 'patient 01', 8 HCW had positive exposure with him and 6 subsequently tested positive for SARS-CoV-2, and 5 post-operational patients had positive exposure and all tested positive for SARS-CoV-2. In the second generation of transmission, 1 HCW tested positive for SARS-CoV-2 after exposure from another HCW. Two patients tested positive for SARS-CoV-2 after exposure from other patients, and both died [14].
- Chu et al. [15] retrospectively analysed 54 cases of SARS-CoV-2 infected medical staff who were admitted to hospital (22 Jan to 3 Feb, Tongji Hospital, China). Only 3.7% were from the emergency department and 18.5% were from medical technology departments and the rest were from other clinical departments. Most patients were classified as severe type (74%), with 20% classified as common-type and 6% as critical-type. There was no relationship between disease severity and occupation/department.
- A study investigated 30 HCW with COVID-19 who had been involved in clinical front-line work (close contact within 1m of infected patients); 26 were common-type and 4 were severe. Of the 30 cases, 19 were infected during the unprotected period (10-20 Jan, 2020). Severe cases had a greater number of contacts and accumulated contact time than common-type cases. However, all 4 severe cases were infected during the unprotected period [16].
- A retrospective study of 64 confirmed HCW cases admitted to Union Hospital, Wuhan between 18 Jan and 15 Feb found that 6% had family members with confirmed COVID-19 and a small proportion had contact with specimens (5%), and patients in fever clinics (8%) and isolation wards (5%). Only 1 case was severe. The authors reported that "The exact mode of medical staff infection remains unclear". The HCW had similar signs and symptoms with general confirmed infection patients which may have been due to their medical expertise, younger age and less underlying disease [17].
- A study tracking the proportion of severely ill medical staff in Wuhan over time showed that there was a gradual decline over time, from a peak of 38.9% in January to 12.7% in early February [18].
- In Wuhan, about **3.8% of cases were HCW**. It was reported that "unexpectedly, a large portion of nosocomial transmissions occurred through contacts between clinicians and visitors with no or mild symptoms of COVID-19 at the early phase of this outbreak" [19].
- A study from The Netherlands showed that **6% of 1353 HCW** tested for SARS-CoV-2 were positive; the 86 cases were employed in 53 different hospital departments, including 36 medical wards. **The majority were mild cases**. Seven HCW were symptomatic before the first dutch patient was diagnosed, and 54 (63%) mentioned that they worked while being symptomatic [20].
- There was a hospital cluster in South Korea comprising 118 cases and 7 deaths. The confirmed cases were mainly from the psychiatric ward and included 9 HCW. The route of infection was unknown [21].
- An investigation of HCW treating 42 confirmed cases in Hong Kong showed that, of the 413 HCW caring for the patients before confirmation of SARS-CoV-2, 11 (2.7%) had been in close contact with unprotected exposure and required 14 days of quarantine, but none of them was infected by the end of the quarantine [22].
- An internet search on physician deaths resulted in the identification of 198 cases, of which 194 were analysed (age details missing for 49 individuals). Physicians aged 57 years and over accounted for the majority of COVID-19 related deaths. It was not possible to identify pre-existing medical comorbidities in most cases. Deaths were reported across a wide range of specialties, with the highest number reported among general practitioners and emergency room doctors (41%), medicine (6%), dentistry (5%) and otorhinolaryngology (4%) [23].

Reasons for greater risk to HCW

- Numerous studies reporting on healthcare workers in China noted that medical staff were not adequately protected during the **initial outbreak** because of asymptomatic and atypical clinical manifestations and insufficient reserves of protective equipment [15, 16, 22, 24].
- **Shortage of PPE** and lack of provision for **training** for infection prevention and control [25].
- Potential risk of **transmission between HCWs**: case discussions and handovers, lunch breaks, work in confined spaces to not able to maintain social distancing. Can also spread through **contacts outside of work**, just like the general community [26].
- **Aerosol generating procedures** for critically ill patients: intubation, manual ventilation by resuscitator, noninvasive ventilation, high-flow nasal cannula, bronchoscopy examination, suction and patient transportation [19]. This is supported by research on SARS showing that procedures capable of generating aerosols have increased risk of transmission [27-29].
- Complete muscle relaxation during endotracheal intubation in coronavirus disease (COVID-19) patients using intravenous lidocaine is recommended is to reduce coughing [30].
- A self-report recall survey of HCW which tested predisposing factors on COVID-19 outcomes showed that having a **diagnosed family member** increased the relative risk of a COVID-19 diagnosis whereas having a diagnosed or suspected patient decreased the relative risk. There was no relationship with medical operation, but **suboptimal handwashing** before and after contact with patients and **improper PPE** increased the relative risk. The results also suggested that those working in a **high-risk department** compared to low-risk department, and those working **longer duty hours**, were at greater risk [24].
- A theoretical model used to calculate the risk of being infected in health care facilities suggested that the results supported the following: decrease the rate of patient encounters and interaction time per HCW, increase clean and safe space for social distancing, and provide effective PPE [31].

Evidence linking viral dose, load and disease severity

Viral load and shedding

- High viral loads associated with more severe clinical outcomes [32-36].
- Reports of highest viral load near initial symptom presentation but can also remain high throughout infection for severe cases [37-40].
- Viral shedding can be prolonged (one study reported median duration 20 days, longest observed was 37 days [39, 41].
- SARS-CoV-2 can actively replicate in the upper respiratory tract [42]
- Mixed results on the median duration of SARS-CoV-2 RNA remaining detectable, but results suggest that patients may remain infectious for long periods. (Higher viral loads detected in the nose than in the throat; shedding in the nose, sputum and stools had median duration of 12, 19 and 18 days, respectively; detectable in through swab until day 11, rectal swab until day 18) [32, 42-44].
- An editorial in Cell Stress uses an analogy to other CoVs to make hypotheses about the relationship between exposure to mild and severe cases and subsequent disease development. It is hypothesised that the initial dose of viral inoculum leading to infection may have a decisive impact on all subsequent events [45]. See Figure 1:

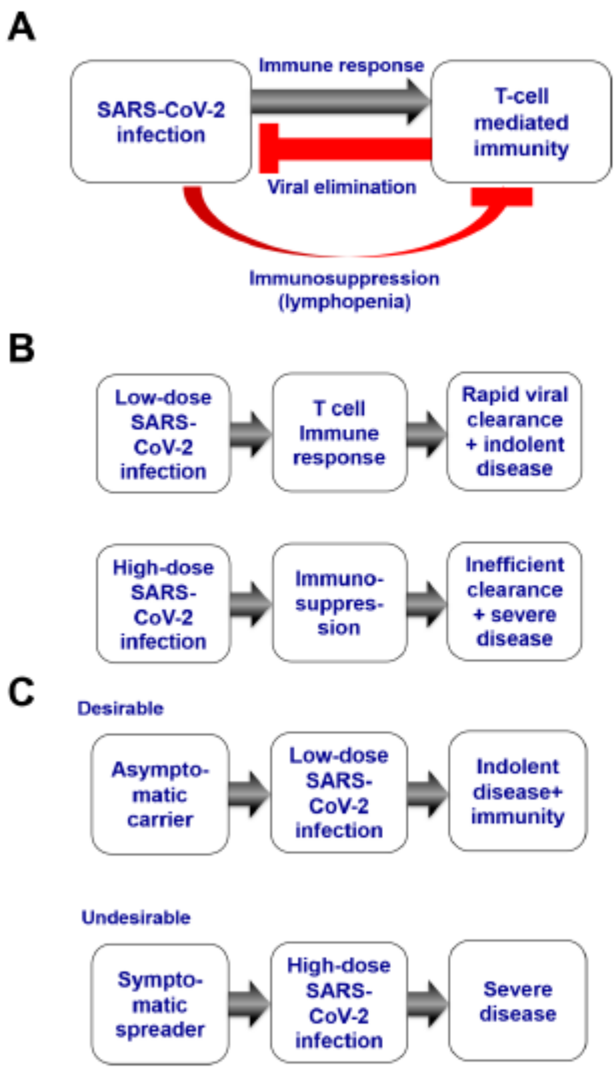

FIGURE 1: Proposed relationships between COVID-19 and anti-SARS-CoV-2 immune responses. (A) The precarious equilibrium between SARS-CoV-2 and the immune system. While the virus elicits an immune response leading to elimination of infected cells (and hence clearance of the infection), it tends to suppress the immune response. Therefore, the outcome of infection is determined by the kinetics of the immune response leading to viral elimination versus viral replication leading to immunosuppression. **(B)** Hypothetical effect of the initial contagion on the course of the infection caused by SARS-CoV-2. A low-level contagion would favor an efficient immune response and indolent infection, leading to immunity of the infected person. Transmission of a large number of viral particles would tend to cause multifocal respiratory infection leading to immunosuppression and severe illness and possibly death. **(C)** Possible modes of transmission of SARS-CoV-2. Indolent carriers would tend to transmit a low viral load to their contacts, leading to indolent disease and antiviral immune responses in immunocompetent individuals. This mode of transmission might be considered as desirable because it leads to population immunity if it attains a large fraction of the population. In contrast, symptomatic carriers might transmit larger amounts of viral particles with a higher probability of leading to severe disease.

Expert reaction to questions about COVID-19 and 'viral load', (incl. dose and severity)

Source: Science Media Centre (UK) Dated: Thursday 26 March [46]

Dr Michael Skinner, Reader in Virology, Imperial College London:

- *"...infection can start with just a small number of articles (the 'dose'). The actual minimum number varies between different viruses and we don't yet know what that 'minimum infectious dose' is for COVID-19, but we might presume it's around a hundred virus particles.*
- *"It is unlikely that higher doses that would be acquired by being exposed to multiple infected sources would make much difference to the course of disease or the outcome. It's hard to see how the dose would vary by more than 10 fold.*
- *"We must be more concerned about situations where somebody receives a massive dose of the virus (we have no data on how large that might be but bodily fluids from those infected with other viruses can contain a million, and up to a hundred million viruses per ml), particularly through inhalation.*
- *"For most of us, it's hard to see how we could receive such a high dose; it's going to be a rare event. In the COVID-19 clinic, the purpose of PPE is to prevent such large exposures leading to high dose infection. Situations we should be concerned about are potential high dose exposure of clinical staff*

conducting procedures on patients who are not known to be infected. I read about a Chinese description of an early stage COVID-19 infection of the lung, which only came about because lung cancer patients (not known to be infected) had lobectemies. There have been suggestions that such situations contributed to the deaths of medics in Wuhan, who were conducting normal procedures (including some that could generate aerosols of infected fluids) before the spread and risk had been appreciated.

Prof Wendy Barclay, Action Medical Research Chair Virology, and Head of Department of Infectious Disease, Imperial College London:

- *"In general with respiratory viruses, the outcome of infection – whether you get severely ill or only get a mild cold – can sometimes be determined by how much virus actually got into your body and started the infection off.*
- *"So standing further away from someone when they breathe or cough out virus likely means fewer virus particles reach you and then you get infected with a lower dose and get less ill. Doctors who have to get very close to patients to take samples from them or to intubate them are at higher risk so need to wear masks.*
- *"But there is no evidence for any suggestion that if everyone in a family is already sick they can they reinfect each other with more and more virus. In fact for other viruses once you are infected it's quite hard to get infected with the same virus on top."*

Professor Willem van Schaik, Professor in Microbiology and Infection at the University of Birmingham

- *"The minimal infective dose is defined as the lowest number of viral particles that cause an infection in 50% of individuals (or 'the average person'). For many bacterial and viral pathogens we have a general idea of the minimal infective dose but because SARS-CoV-2 is a new pathogen we lack data. For SARS, the infective dose in mouse models was only a few hundred viral particles. It thus seems likely that we need to breathe in something like a few hundred or thousands of SARS-CoV-2 particles to develop symptoms. This would be a relatively low infective dose and could explain why the virus is spreading relatively efficiently.*
- *"On the basis of previous work on SARS and MERS coronaviruses, we know that exposure to higher doses are associated with a worse outcome and this may be likely in the case of Covid-19 as well. This means that health care workers that care for Covid-19 patients are at a particularly high risk as they are more likely to be exposed to a higher number of viral particles, particularly when there is a lack of personal protective equipment (PPE) as is reported in some UK hospitals*
- *"It seems unlikely that people can pick up small numbers of viruses from others (e.g. in a crowd) and that will tip the infection over the edge to become symptomatic as that must happen around the same time.*

Transmission

- A prospective case-ascertained study on laboratory confirmed COVID-19 cases and their close contacts was conducted between January 15 and February 26. Thirty-two confirmed cases were enrolled. The secondary clinical attack rate was 0.9% (95%CI 0.5-1.7%). The attack rate was also higher among household contacts (13.6%, 95% CI 4.7-29.5%) and non-household family contacts (8.5%, 95% CI 2.4-20.3%) than that in healthcare or other settings [47].
- A study on household versus non-household transmission found that the risk of being infected outside of households is higher for those aged 18-64 years. The majority of transmission clusters were smaller than five, but there was evidence of pre-symptomatic transmission [48].
- Environmental
    - A study of environmental contamination in airborne infection isolation rooms of 3 symptomatic patients in Singapore found that samples were negative after routine cleaning for patients A and

B. For patient C, whose samples were collected prior to cleaning, 13 (87%) of 15 room sites (including air outlet fans) and 3 (60%) of 5 toilet sites (toilet bowl, sink, and door handle) returning positive results. Only 1 PPE swab was positive (surface of front shoe) and all air samples were negative. Viral culture was not done to demonstrate viability [49].

- Samples were taken from 11 isolation rooms to examine viral shedding from 13 isolated individuals with confirmed COVID-19. There was evidence of viral contamination on many commonly used items, toilet facilities, and air samples. Size range of SARS-CoV-2 droplets and particles was not measured [50].

Aerosol

- The possibility of aerosol transmission has attracted significant media attention [51-53].
- Viral diseases such as SARS and Influenza have been shown to be transmitted via airborne particles [2, 54, 55].
- Results from a small number of studies suggest that the possibility of airborne transmission of COVID-19 cannot be ruled out [50, 56, 57]. Situations most likely to result in airborne transmission include procedures or support treatments that generate aerosols [45, 58].
- Key questions remain: what is the number of SARS-CoV particles needed to cause infection, do people with COVID-19 produce enough particles through aerosol to infect others and is this related to length of exposure? [53].
- The WHO reports that, according to current evidence, SARS-CoV-2 is primarily transmitted between people through respiratory droplets and contact routes [58].

Amplified spread in confined spaces (cruise ships)

- Evidence from **Diamond Princess cruise ship** suggests that the high rate of transmission occurred prior to the implementation of quarantining, probably due to confined space, virus present on surfaces, homogenous interactions, and short serial interval (i.e. the number of days between the reported symptom onset date for the primary case and that for the secondary case). There was also a relatively high number of asymptomatic cases. After quarantine was implemented, new cases arose due to difficulty isolating cases and crew needing to perform essential duties [59-61].
- Number of studies showed that the reproductive rate on cruise ships was greater than the epicentre in Wuhan, but the rate dropped dramatically following quarantining [62-65].
- A recent paper estimated the infection and case fatality ratio of COVID-19 using data from passengers of the Diamond Princess cruise ship, correcting for delays between confirmation-and-death, and age-structure of the population. The average age of passengers on board the ship was 58 years. The case fatality ratio (CFR) was 2.6% and the infection fatality ratio (IFR) was 1.3% (compared to estimates from China: CFR=1.2%; IFR=0.6%). The estimated CFR for passengers aged 70 years and over (33% of passengers on board) was 13%. Raw data indicates that no-one under aged 70 died. It should also be noted that passengers may have a different health status to the general community [66].

What is being done in an attempt to mitigate risks to HCW?

- **Practice changes:**
  It appears that Australian health workers may already be training and introducing measures to reduce potential risks. For example, clinicians in the intensive care unit of the Royal Melbourne Hospital, are practicing intubation using a minimum number of staff to reduce potential exposure [67].

- **International reviews on the correct use of PPE**:
  - Cochrane review on correct PPE for highly infectious diseases (not specific to COVID-19 and published on 1 July 2019) [68]. An updated Cochrane review on PPE is imminent.
  - The World Health Organization has advice on the use of masks in the context of COVID-19 [69].
  - Oxford Evidence series:
    - Standard face masks vs respirator masks (respirator masks are recommended for protection during aerosol generating procedures (AGPs). Rapid reviews on wider PPE measures, and what counts as an AGP, are ongoing) [70].
    - Efficacy of eye protection (for close contact procedures, full PPE should be worn) [71].
    - Should PPE include shoe covers (wear shoe covers where there is a risk of splashing; further research required) [72].

- **Protective barrier enclosures for endotracheal intubation**
  A barrier, known as the aerosol box, has been developed exist [73], but currently no trials on usability or effectiveness. (Not yet in use in Australian hospitals, to our knowledge.)

- **Trial of anti-malaria drug** led by Prof Marc Pellegrini (Walter and Eliza Hall Institute) on the potential preventative effect of the anti-malaria drug hydroxychloroquine (Plaquenil) for healthcare workers. A double-blind trial for 2,250 front line workers for four months. Trial results may be available in as early as 2 months if results are strong [74].

- **Trial of the BCG vaccine (BRACE Trial)** led by Professor Nigel Curtis (University of Melbourne). The Bacille Calmette-Guerin (BCG) vaccine (used widely for TB) will be tested and the trial aims to enrol 4000 healthcare workers from hospitals around Australia. The trial builds on previous studies which showed that BCG reduces the level of virus when people are infected with similar viruses to SARS-CoV-2 [75]. The BRACE trial will shortly commence in South Australian hospitals coordinated by SAHMRI.

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