Australian Academy of Health and Medical Sciences

COVID-19 KEY TOOLS AND MEASURES: WHERE ARE WE NOW?

AAHMS COVID-19 BACKGROUND BRIEF

15 December 2020

This background briefing underpins and outlines the evidence base for our position statement, *'Maintaining strong foundations and building resilience: planning Australia's path through the COVID-19 pandemic'*. It summarises the current evidence in the areas highlighted in that document.

Public health measures

SARS-CoV-2 can be spread via multiple routes, including direct contact with an infected person; airborne transmission through droplets (e.g. when speaking or coughing) and under certain conditions, aerosols; and via contaminated surfaces (although transmission via surfaces is not thought to be the main route of spread).[1,2] Virus survival varies under different conditions, e.g. temperature and type of surface. Australian researchers recently reported that under laboratory conditions the virus can remain infectious on a range of surfaces for longer than previously thought.[3]

Masks, if made and used correctly, are an effective means of preventing transmission and thorough, regular handwashing with soap and water minimises the risk of spread.[1] Alcohol-based hand sanitisers which contain at least 60% alcohol can replace soap and water.[4] Good ventilation of spaces also reduces the accumulation of aerosols and therefore reduces transmission.[5] Quarantine has proven to be an effective tool for containment of COVID-19 and early implementation of effective quarantine and other public health measures helps slow the spread of COVID-19.[6]

The most common or infectious routes of transmission – and therefore the most effective combination of measures – is still under investigation. The World Health Organization (WHO) has therefore recommended a comprehensive package of preventive measures as the best strategy, including the use of masks, frequent hand hygiene, physical distancing when possible, respiratory etiquette, environmental cleaning and disinfection.[1]

Vaccines

WHO has recommended that an effective vaccine should reduce the risk of symptomatic infection with SARS-CoV-2 by at least 50% in a relevant target population.[7] Evidence from animal studies and emerging data from clinical trials indicates that while the vaccines currently in clinical trials have a good chance of preventing COVID-19 illness, they are less likely to completely prevent infection with the SARS-CoV-2 virus.[8] This means that it is unlikely that virus transmission will be greatly suppressed through vaccination with this first generation of vaccines. The public health measures currently in place will therefore need to continue to be used to control the spread of infection. Recent announcements from Pfizer and BioNTech, Moderna, and Astra Zeneca are encouraging for our vaccine prospects, particularly because their findings suggest that the SARS-CoV-2 spike protein, which is targeted by most other vaccines in development, is an appropriate target.[9–11]

Potential role of vaccines

A vaccine will be most useful if it can achieve overall population, or 'herd' immunity, which occurs when a large enough proportion of the population is immune to a pathogen to provide indirect protection to those still susceptible.[12] This reduces the spread of disease and is therefore a path to tackling the pandemic. Once a vaccine is approved, modelling will be crucial to understand if and how it can be used to achieve this goal.

The level of immunity in a population is a product of vaccine efficacy and uptake, i.e.:

Efficacy x uptake = level of immunity

Modelling will need to consider these sorts of calculations. For instance, if a vaccine with 50%

efficacy is given to 70% of people, then 35% of the population will be immune (i.e. 50% x 70% = 35%). A vaccine with 90% efficacy taken up by 70% of people will deliver 63% immunity. The key question is – what level of immunity is required for herd immunity? This is known as the herd immunity threshold. The simplest way of answering this is to look at the virus reproduction number (R_0), which is the average number of people to whom an infected individual will pass the virus.[12] However, this model is too simplistic for use in the real world, where many other factors have come into play, including:

- The extent to which it prevents virus transmission or whether it only stops those infected from getting sick or progressing to severe disease.
- Efficacy – what proportion of those vaccinated are protected and for how long?
- Access and uptake within the community, which will depend on vaccine performance, local transmission rates, appropriate storage, available doses and distribution, and public health goals, as well as attitudes towards vaccination (see below).
- Patterns of infection – for example whether it is occurring in clusters or cases are dispersed.
- Levels of pre-existing immunity or cross-protection, since immunity acquired as a result of having had COVID-19 also contributes to herd immunity.

Current estimates for the COVID-19 herd immunity threshold are between 55% and 82%. Vaccine uptake by individuals could therefore be crucial, especially if approved vaccines are only just above the 50% efficacy threshold set by WHO.[13,14]

Access and uptake in the community

In Australia, current survey data indicate that the majority of individuals are comfortable with the idea of being vaccinated. However, the proportion of the population unwilling or unsure about doing so is substantial, with data from June 2020 suggesting that 24·2% may be unwilling or unsure about it. Common concerns related to safety and efficacy or a belief that it was not necessary.[15] Worryingly, this figure may be rising – April 2020 data suggested a figure closer to 14%.[16] These surveys were not carried out in the same population, but nevertheless indicate that attitudes towards vaccination will need to be closely monitored and concerns addressed appropriately.

Uptake in Australia will not be the only factor, of course – since this is a global pandemic, worldwide uptake will also impact on Australians and whether, for example, we can consider opening international borders. Global data show that 71.5% of people are very or somewhat likely to accept the vaccine, but rates varied substantially – from almost 90% (in China) to less than 55% (in Russia).[17]

Research is the best way to obtain the insights needed to understand and address misconceptions and concerns. For instance, studies have shown that age, education-level and gender impact on attitudes, and that one of the most important factors is trust in government.[17] Governments should, in liaison with experts and with community consultation, aim to:

- Develop clear and consistent messaging to build public confidence, explaining how vaccines work and how they are developed.
- Build vaccine literacy and address specific concerns and misconceptions, which are expected to vary in individuals from different risk groups and cultural backgrounds.

Ongoing public health measures will help here because lower levels of 'mixing' within the community (e.g. because people are practicing physical distancing or using masks), will mean that lower levels of herd immunity may be sufficient to reduce spread, providing a basis to open up the economy while the vaccine is rolled out across the population.

Safety and efficacy

To determine whether efficacy and safety requirements are met, we need large, placebo-controlled trials – reassurance of safety is only as good as the controlled data gathered from robustly designed and delivered studies. Vaccine trials assess safety by comparing the frequency of adverse events in vaccine and placebo recipients. The US Food and Drug Administration has said that to issue emergency use authorization, at least half of participants involved in phase 3 trials must have been monitored for at least two months after vaccination, and they have made it clear that they expect trials to continue beyond this timeframe to assess longer term safety and efficacy.[18]

Most vaccine trials include longer follow up of representative cohorts, often for more than a year.[19]

However, even robust trials are unlikely to detect rare side effects because they do not involve enough participants. Should there be any such effects, they will only be detected once a vaccine is delivered to many more people, including specific socio-demographic groups who might be more susceptible to adverse vaccine events.[20,21] Similarly, since the first trial results will be based on data from only a few months, they will not detect adverse events that occur in the longer-term. The process of active pharmacovigilance is therefore crucial as vaccines are rolled out following approval – in parallel to the process of ongoing clinical trials. This will be challenging due to the scale of the rollout but is a normal part of post-marketing drug development and there are mechanisms and responsible bodies in place in Australia that can be expanded for this purpose.

Once a vaccine is approved, how it is deployed by government will depend on vaccine performance (i.e. safety and efficacy data), local infection transmission rates, availability of doses, distribution logistics (e.g. stability and cold-chain requirements) and public health goals. Equitable distribution of vaccine will need to consider the efficacy of the vaccine in different populations and balance access for people at high risk of severe morbidity and mortality, those at higher risk of exposure (e.g. health professionals) and groups for whom there would be negative social impacts (e.g. some essential workers) against those with the highest burden of disease and disease transmission.[22]

Treatments

If infection progresses to COVID-19 disease, treatment remains our best line of defence. However, treatment options are currently very limited and further research and investigation are vital if we are to introduce new ones.[23] Mechanical ventilation and similar methods have been used successfully to support severely ill patients. Treatments that enhance our ability to manage COVID-19 disease are gradually emerging, with more than 300 potential COVID-19 therapeutics undergoing pre-clinical testing.[23] However, while many are in trials, only two have so far shown evidence of effect in the general population, and they do not work for everyone:

- Corticosteroids such as dexamethasone and hydrocortisone reduce deaths in severely and critically ill patients, and are recommended for use in Australia and by WHO.[24–27]
- There is some evidence remdesivir may result in faster recovery in some hospitalised patients, but it does not seem to reduce mortality. However it is still under investigation and in Australia, the recommendation is that it should only be given to certain hospitalised patients in the context of a clinical trial.[23,27,28]

There is not yet sufficient high quality evidence to draw firm conclusions about convalescent plasma, monoclonal antibodies, or anticoagulation therapies (which prevent blood clots), but some emerging data show promise, for instance that virus-neutralizing monoclonal antibodies might reduce hospitalisation.[29]

Research has helped to rule out certain treatments. For example, hydroxychloroquine, lopinavir/ritonavir (an antiviral combination used in HIV), and interferon (an immune enhancer) have not improved survival in hospitalised patients.[23,30–32]

Prophylactic treatments are used for some infectious diseases to prevent illness and secondary transmission.[33] They can be administered either before or after exposure to the virus. However, at present, there is no clear evidence for an effective prophylactic treatment option in COVID-19, though it remains under investigation and monoclonal antibodies are of particular interest.[27]

An important longer-term consideration is the extent to which COVID-19 patients experience long COVID, and the severity of their ongoing symptoms. Individuals with long COVID experience health complications lasting several weeks or even months after the acute infection. Long COVID can affect individuals whether they had mild or severe disease.[34] One study (not yet peer reviewed) that monitored ongoing symptoms of patients found that 13% of them had symptoms lasting more than 28 days and 4% for more than eight weeks.[35] Research is needed to understand how to diagnose and treat long COVID and whether it is possible to predict which patients are more likely to experience prolonged illness, so that they can be helped by better targeted prevention and treatment measures.

Diagnostic tests

The success of contact tracing systems, which are an essential component of public health programs, depends on efficient access to diagnostic testing. Active case funding through targeted testing and screening strategies can help to provide confidence that cases will be detected if they exist. The most common mode of confirming the presence of virus (i.e. confirming active infection) currently involves taking a nose or throat swab and sending this to a laboratory for processing. However, new tests are emerging that could improve testing speeds and access, for example more rapid laboratory tests for virus detection or detection of proteins (antigens) that are part of the virus or specific antibodies produced by individuals in response to infection, enabling tests to be undertaken in the community.[36,37] These kinds of tests will substantially enhance tracking and tracing efforts, and reduce the time needed for individuals to isolate while waiting for results, which can act as a disincentive to individuals getting tested.

The nature of these rapid tests is that they are unlikely to be as sensitive as the existing lab-based tests, i.e. they may not pick up low levels of virus; rapid antigen tests are most reliable during the early stages of infection, when viral load is at its highest.[36] Any decision to introduce such tests will need to be informed by data about their sensitivity – there may be situations where less sensitive tests are still valuable, such as in individuals at high risk of exposure. When numbers are low, as is currently the case in Australia, false negative tests could potentially lead to missed cases and cause outbreaks, but there may still be instances where the tests are useful – where rapid tests are still better than no tests. Specificity is the other key characteristic of diagnostic tests, i.e. whether the test correctly identifies SARS-CoV-2 (rather than something else). In a population with low infection rates, even a small number of false positives can be problematic – picking up more false positives than actual infections. Continuous improvements to tests will enable more rapid detection of patients and enhance prevention and treatment.[38]

However, the most important factors driving the effectiveness of testing and surveillance systems appear to be the frequency of testing and the speed of reporting, rather than high test sensitivity, meaning that tracing systems should be designed to maximise access, frequency and speed.[39,40]

Addressing social and health inequalities

Certain risk factors increase the chance of infection with SARS-CoV-2 and the likelihood that infection will progress to severe disease. Data show that low socio-economic status is one of the biggest risk factors due to the higher prevalence of comorbidities (co-existing diseases) in these communities and our first nations people are also at particular risk.[41] Comorbidities such as heart disease and chronic obstructive pulmonary disease increase the risk of hospitalisation, admission to ICU and death. Similarly, immunosuppressed people (e.g. post organ transplant or after treatment for certain cancers) fare worse than healthy people.[41] Health inequalities reflect a range of underlying social determinants, such as access to healthcare, housing and employment, which also need to be tackled, and care must be appropriate and in addition, culturally safe – noting that such safety is of particular importance for Aboriginal and Torres Strait Islander peoples.

Reducing impacts of these social and health inequalities on infection rates, morbidity and mortality can therefore significantly impact on efforts to address the pandemic. We should therefore implement and expand measures that protect and support these vulnerable populations and ensure they receive the appropriate care for their chronic conditions, which could also bring longer term benefits in improving health in such communities.

Reluctance to attend appointments or perceived difficulties in accessing services as a result of the pandemic could delay the presentation and diagnosis of other conditions, such as heart conditions, stroke and cancer, as well as mental ill health. Some such conditions are time-sensitive and urgent, and there is evidence that delays associated with the pandemic have impacted on morbidity and mortality.[42–44] These issues can also impact on the uptake of important health and prevention measures including screening programs and elective surgery.

This background briefing underpins and outlines the evidence base for our report, *'Maintaining strong foundations and building resilience – planning Australia's path through the COVID-19 pandemic'*.

The briefing was developed with advice from the Academy's COVID-19 Expert Committee, membership of which is provided in the main document.

REFERENCES

All web references were access on 2 December 2020.

1. World Health Organization. Transmission of SARS-CoV-2: implications for infection prevention precautions. https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions (2020).
2. European Centre for Disease Prevention and Control. Transmission of COVID-19. https://www.ecdc.europa.eu/en/covid-19/latest-evidence/transmission (2020).
3. Riddell, S., Goldie, S., Hill, A., Eagles, D. & Drew, T. W. The effect of temperature on persistence of SARS-CoV-2 on common surfaces. *Virol. J.* **17**, 145 (2020).
4. Therapeutic Goods Administration. Hand sanitisers: Information for consumers. https://www.tga.gov.au/hand-sanitisers-information-consumers (2020).
5. European Centre for Disease Prevention and Control. *Heating, ventilation and air-conditioning systems in the context of COVID-19 Target audience Evidence for transmission in closed spaces and the role of heating, ventilation and air-conditioning (HVAC) systems*. (2020).
6. Nussbaumer-Streit, B. *et al.* Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review. *Cochrane Database of Systematic Reviews* vol. 2020 (2020).
7. World Health Organization. WHO Target Product Profiles for COVID-19 Vaccines. https://www.who.int/publications/m/item/who-target-product-profiles-for-covid-19-vaccines (2020).
8. Peiris, M. & Leung, G. M. Comment What can we expect from first-generation COVID-19 vaccines? *The Lancet* (2020) doi:10.1016/S0140-6736(20)31976-0.
9. Pfizer and BioNTech. Pfizer and BioNTech Announce Vaccine Candidate Against COVID-19 Achieved Success in First Interim Analysis from Phase 3 Study . https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-vaccine-candidate-against (2020).
10. Moderna Inc. Moderna's COVID-19 Vaccine Candidate Meets its Primary Efficacy Endpoint in the First Interim Analysis of the Phase 3 COVE Study. https://investors.modernatx.com/news-releases/news-release-details/modernas-covid-19-vaccine-candidate-meets-its-primary-efficacy (2020).
11. Astra Zeneca. AZD1222 vaccine met primary efficacy endpoint in preventing COVID-19. https://www.astrazeneca.com/media-centre/press-releases/2020/azd1222hlr.html (2020).
12. Randolph, H. E. & Barreiro, L. B. Herd Immunity: Understanding COVID-19. *Immunity* **52**, 737–741 (2020).
13. Danchin, M., Biezen, R., Manski-Nankervis, J.-A., Kaufman, J. & Leask, J. Preparing the public for COVID-19 vaccines: How can general practitioners build vaccine confidence and optimise uptake for themselves and their patients? *Aust. J. Gen. Pract.* **49**, 625–629 (2020).
14. Sanche, S. *et al.* High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome

Coronavirus 2. *Emerg. Infect. Dis.* **26**, 1470–1477 (2020).

15. Rhodes, A., Hoq, M., Measey, M. A. & Danchin, M. Intention to vaccinate against COVID-19 in Australia. *The Lancet Infectious Diseases* vol. 0 (2020).

16. Dodd, R. H., Cvejic, E., Bonner, C., Pickles, K. & Mccaffery, K. J. Willingness to vaccinate against COVID-19 in Australia. *BMC Public Health* **14**, 484 (2020).

17. Lazarus, J. V. *et al.* A global survey of potential acceptance of a COVID-19 vaccine. *Nat. Med.* (2020) doi:10.1038/s41591-020-1124-9.

18. US Food and Drug Administration. *Emergency Use Authorization for Vaccines to Prevent COVID-19 - Guidance for Industry* . (2020).

19. Krause, P. *et al.* COVID-19 vaccine trials should seek worthwhile efficacy. *The Lancet* vol. 396 741–743 (2020).

20. Crooke, S. N., Ovsyannikova, I. G., Poland, G. A. & Kennedy, R. B. Immunosenescence and human vaccine immune responses. *Immun. Ageing* **16**, 1–16 (2019).

21. Verity, R. *et al.* Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect. Dis.* **20**, 669–677 (2020).

22. US National Academy of Medicine. *Framework for Equitable Allocation of COVID-19 Vaccine*. *Framework for Equitable Allocation of COVID-19 Vaccine* (2020) doi:10.17226/25917.

23. Rapid Research Information Forum. *The most promising therapeutics for COVID-19*. (2020).

24. The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *N. Engl. J. Med.* (2020) doi:10.1056/nejmoa2021436.

25. Sterne, J. A. C. *et al.* Association between Administration of Systemic Corticosteroids and Mortality among Critically Ill Patients with COVID-19: A Meta-analysis. *JAMA - J. Am. Med. Assoc.* **324**, 1330–1341 (2020).

26. World Health Organisation. *Corticosteroids for COVID-19 - Living Guidance 2 September 2020*. (2020).

27. National COVID-19 Clinical Evidence Taskforce. Living Guidelines - Caring for people with COVID-19. https://covid19evidence.net.au/ (2020).

28. Schwartz, I. S., Heil, E. L. & McCreary, E. K. Remdesivir: a pendulum in a pandemic. *Br. Med. J.* **371**, (2020).

29. Chen, P. *et al.* SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. *N. Engl. J. Med.* (2020) doi:10.1056/nejmoa2029849.

30. RECOVERY Collaborative Group. Effect of Hydroxychloroquine in Hospitalized Patients with Covid-19. *N. Engl. J. Med.* (2020) doi:10.1056/nejmoa2022926.

31. Horby, P. W. *et al.* Lopinavir–ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* **396**, 1345–1352 (2020).

32. § WHO Solidarity trial consortium *et al.* Repurposed antiviral drugs for COVID-19 – interim WHO SOLIDARITY trial results. (2020) doi:10.1101/2020.10.15.20209817.

33. Mitjà, O. & Clotet, B. Use of antiviral drugs to reduce COVID-19 transmission. *Lancet Glob. Heal.* **8**, e639–e640 (2020).

34. US Centers for Disease Control and Prevention. Long-Term Effects of COVID-19 . https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects.html (2020).

35. § Sudre, C. H. *et al.* Attributes and predictors of Long-COVID: analysis of COVID cases and their

symptoms 1 collected by the Covid Symptoms Study App. *medRxiv Prepr.* (2020) doi:10.1101/2020.10.19.20214494.

36. Therapeutic Goods Administration. COVID-19 testing in Australia - information for health professionals. https://www.tga.gov.au/covid-19-testing-australia-information-health-professionals (2020).

37. Therapeutic Goods Administration. COVID-19 test kits included in the ARTG for legal supply in Australia . https://www.tga.gov.au/covid-19-test-kits-included-artg-legal-supply-australia (2020).

38. Vandenberg, O., Martiny, D., Rochas, O., van Belkum, A. & Kozlakidis, Z. Considerations for diagnostic COVID-19 tests. *Nature Reviews Microbiology* 1–13 (2020) doi:10.1038/s41579-020-00461-z.

39. Kretzschmar, M. E. *et al.* Impact of delays on effectiveness of contact tracing strategies for COVID-19: a modelling study. *Lancet Public Heal.* **5**, e452–e459 (2020).

40. § Larremore, D. B. *et al.* Test sensitivity is secondary to frequency and turnaround time for COVID-19 surveillance. *medRxiv Prepr. Serv. Heal. Sci.* 2020.06.22.20136309 (2020) doi:10.1101/2020.06.22.20136309.

41. Rapid Research Information Forum. *Morbidity, mortality and sex-specific impacts of COVID-19*. (2020).

42. Maringe, C. *et al.* The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. *Lancet Oncol.* **21**, 1023–1034 (2020).

43. Shah, K. *et al.* Surge in Delayed Myocardial Infarction Presentations. *JACC Case Reports* **2**, 1642–1647 (2020).

44. Czeisler, M. É. *et al.* Delay or Avoidance of Medical Care Because of COVID-19–Related Concerns — United States, June 2020. *Morb. Mortal. Wkly. Report, Centers Dis. Control Prev. US* **69**, 1250–1257 (2020).

Australian
Academy *of* Health and
Medical Sciences

www.aahms.org