MICROBIOLOGY AUSTRALIA, 2021, 42, 30–34
https://doi.org/10.1071/MA21009

Vaccination for COVID-19 control and considerations for Australia

Raina MacIntyre

Kirby Institute, Level 6, Wallace Wurth Building, UNSW Sydney, NSW 2052, Australia. Email: r.macintyre@unsw.edu.au

Abstract. Vaccines remain the main prospect for an exit strategy from the COVID-19 pandemic, and may, depending on efficacy, duration of protection and uptake, make herd immunity feasible. If herd immunity is not achievable, SARS-COV-2 will circulate long-term. There are many vaccine candidates in development and choices between vaccines that will vary in efficacy and safety. The efficacy of available vaccines is compared and ranges from 62–95% against symptomatic infection with the G614 variant. Efficacy is reduced against new variants of concern and is uncertain against asymptomatic infection. Some vaccines show a better protective immune response than natural infection. The principles of herd immunity and prerequisites for achieving it, such as vaccine efficacy, duration of protection and coverage, are discussed. The alternative vaccine strategies including mass vaccination, targeted risk or age-based vaccination and ring vaccination, as well as speed of vaccination are reviewed. Finally, the impact of variants of concern on vaccine programs and the logistics of mass vaccination are discussed.

Received 17 January 2021, accepted 13 February 2021, published online 12 April 2021

Introduction

Australia has controlled COVID-19 well, but people live with intermittent restrictions such as social distancing, masks and lock-downs, and health authorities must maintain testing and contact tracing infrastructure. Vaccines remain the main prospect for an exit strategy and may, depending on efficacy, duration of protection and uptake, make herd immunity feasible[1]. There are over 62 vaccine candidates in clinical development and over 170 in pre-clinical development[2], so we will have a diverse choice of vaccines which will vary in efficacy and safety. Some vaccines show a better protective immune response than natural infection, which is promising[3].

There are four basic technologies being used for vaccine development:

(1) Protein subunit;
(2) Whole virus (inactivated or live attenuated);
(3) Vectored (including adenovirus and measles vectors); and
(4) RNA or DNA.

Vaccine candidates with published phase three trials show efficacy of 62–95% against symptomatic infection, and almost 100% efficacy against severe infection and death for all three vaccines[4–6]. There is less confidence about this because the trials were not powered for severe infection and death as end-points. Table 1 summarises these results.

The mRNA vaccines[5,6] show much higher efficacy against symptomatic infection than the ChAdOx1 nCoV19 vaccine. The ChAdOx1 nCoV19 vaccine has published data on prevention of asymptomatic infection, but measurement of this end-point varied between the trial sites for that vaccine, and analysis was restricted to UK sites. If sites which did not include weekly testing are excluded, the efficacy of this vaccine appears to be between 38–50% against all infection depending on which data are included in the calculation[4]. There was no significant reduction in asymptomatic infection seen with 2 standard doses of the Astra Zeneca vaccine. However, the efficacy of the Astra Zeneca vaccine was 80% when two standard doses were given at least 12 weeks apart[8]. Of mRNA vaccines, only the Moderna vaccine trial included data on asymptomatic infection demonstrating a reduction even after a single dose from 39 in placebo to 15 in the vaccine group[9]. A post-licensure study in Israel showed 92% efficacy of the Pfizer vaccine against all infection[10]. When vaccine development began in early 2020, the importance of asymptomatic infection was not recognised – now thought to account for up to half of infections[11]. This may explain the design of clinical trials with symptomatic infection as the primary end-point, when the end-point of interest for herd immunity is prevention of all infection, which includes symptomatic and asymptomatic infection. From an immunological standpoint, symptomatic disease is prevented by good humoral and cell mediated immunity induced by vaccination but immunity at mucosal surfaces in the upper airway may also be important, a still poorly understood mechanism with these current vaccines. The relative importance of systemic and mucosal immunity for prevention of asymptomatic infection is unknown.

Table 1. Published phase three clinical trial results of four vaccines.

Vaccine	N subjects	VE symptomatic infection	VE any infection
ChAdOx1 nCoV-19 (Astra- Zeneca)[4]	23 848 in the efficacy analysis for standard dosing	62.1% (66%)	~40–55%
BNT162b2 (Pfizer)[5]	43 548	95.0%	Data not available
mRNA1273 (Moderna)[6]	30 420	94.1%	Data not available
rAd26 and rAd5 heterologous prime-boost Gam-COVID-Vac (Gamaleya)[7]	21 977	91.6% (after 1 dose)	Data not available

Prevention of all infection will prevent transmission, which is necessary for herd immunity and elimination of infection. Elimination and eradication are terms which have specific technical definitions[12]. Eradication means a pathogen is removed globally, with smallpox being an example. Eradicable pathogens should ideally have no animal host, an effective vaccine and minimal asymptomatic transmission – all of which were met for smallpox. Elimination is the prevention of sustained community transmission in a country or region, and requires herd immunity. Outbreaks may still occur, as we see with measles in Australia, but do not become sustained[12]. Australia has achieved WHO certified elimination of measles and polio using vaccines[13].

SARS-COV-2 is unlikely to be eradicable because of a presumed animal host and substantial asymptomatic transmission. In the absence of a goal for eradication by WHO, countries require technical definitions for elimination with measurable end-points, including time elapsed without community transmission, level of immunity and good surveillance systems[12]. When elimination and eradication are not possible, "control" is the next best option to reduce the spread[14].

The most ambitious and aspirational goal of vaccination programs would be herd immunity and elimination of local transmission. Other goals would be prevention of severe infection and death, which are important in countries experiencing a high incidence of disease. Herd immunity is achieved when vaccination rates are high enough to stop community transmission within a defined population and protects the entire population, whether individuals have been immunized or not, because the number of susceptible individuals is too small for sustained transmission. The required population immunity for herd immunity (H) depends on the basic reproductive number, R0, and can be calculated by the formula:

$$H = 1-(1/R0)$$

The higher the R, the higher the herd immunity required to control disease, which is a key concept for control of infections through vaccination. Figure 1 shows an elimination graph, and the relationship of R0 to required population immunity for herd immunity, comparing measles (R0 15), smallpox (R0 3), SARS CoV 2

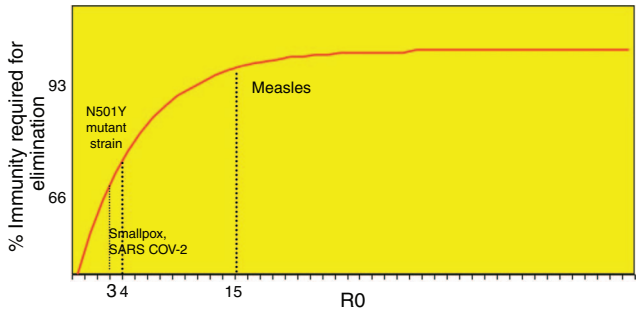

Figure 1. Elimination graph – required population immunity for herd immunity by R0 value for measles, smallpox, SARS-COV-2 and the N501Y mutant strain.

(R0~3)[15], and the N501Y mutant strains of SARS-COV-2, which is estimated to be 75% more infectious than the D614G strain, which was dominant globally for most of 2020[16]. Vaccine escape has also been shown against the South African B.1.351 variant, with efficacy of 10% for the Astra Zeneca vaccine[17]. Elimination of SARS-COV-2 is feasible with a high efficacy vaccine, but if highly transmissible variants become dominant, this will require higher vaccine coverage or even higher efficacy vaccines.

The concept of herd immunity arose from vaccination programs, and yet has been subject to misinformation during the COVID-19 pandemic with theories of 'natural' herd immunity being possible by allowing unfettered transmission of SARS-COV-2[18,19]. An unmitigated second wave in Brazil demonstrated this to be false[20]. Further, the history of epidemic infections such a smallpox, measles and rubella in the pre-vaccine era demonstrates that such infections do not eliminate themselves by 'natural herd immunity' – instead, in the absence of vaccines or other control measures, they cause substantial, cycling epidemics which continue indefinitely[21]. Ongoing cycling epidemics, tempered by intermittent lockdowns and other non-pharmaceutical measures, are also predicted for SARS-COV-2 without vaccines[22].

Full or emergency approvals have been granted in many countries for vaccines, mostly those with phase three clinical trial data published such as Pfizer, Moderna and Astra Zeneca vaccines. However, some countries are rolling out vaccines such as CoronaVac (Sinovac) in Indonesia or Covaxin (Bharat Biotech) without published phase three data.

The choice of vaccine strategies for Australia and other countries include:

- Mass vaccination
- Targeted vaccination (age or risk group)
- Ring vaccination

There may be vaccine shortages initially, so that targeted vaccine is needed initially. Healthcare, aged care and hotel quarantine workers who are at high risk of infection have been prioritised in Australia, followed by groups at significantly higher risk of severe disease, such as older adults[23]. In Indonesia, young people have been prioritised, as transmission is highest in young adults, so this strategy will impact epidemic growth the most[24]. Alternatively, a ring vaccination strategy could be used as a dose-sparing strategy. Ring vaccination is the use of vaccines as post-exposure prophylaxis (PEP) to close contacts of cases, who may have been exposed to the virus. Many vaccines, such as measles, hepatitis A and smallpox do have efficacy as PEP[25], and are used for outbreak control. Eradication of smallpox was achieved in the last remaining hotspot, India, using ring vaccination[26]. The long incubation period of SARS-COV-2 may mean there is efficacy as PEP, but no published data are available yet. We showed that ring vaccination would be the best use of limited doses, if there is efficacy as PEP, and that targeted vaccine strategies would have minimal impact on epidemic growth[1]. However, herd immunity can only be achieved with mass vaccination.

We do not know yet if herd immunity is achievable. However, given the R0 of SARS-COV-2 in the range of 2–4[15], it should be feasible with a high efficacy vaccine. If vaccine-induced immunity wanes over time, booster doses may be an option. We do not know the safety or efficacy of giving two different vaccines serially, and this is not always straightforward. For example, conjugate followed by polysaccharide pneumococcal vaccines provide immune boosting, but the reverse causes a diminished response[27]. Antibody dependant enhancement (ADE)[28] is another concern, and was seen with MERS Coronavirus vaccines. The effect of serial administration of different vaccines on the risk of ADE is unknown.

For Australia, aiming for herd immunity requires choosing the highest efficacy vaccines, and planning for at least 70% of the population vaccinated[1]. A vaccine of less than 70% efficacy against all infection is unlikely to achieve herd immunity, and a vaccine that is very poor at preventing infection will result in ongoing transmission of SARS-COV-2 in the community[1]. This will place unvaccinated people and people who have vaccine failure such as immunocompromised people, at risk of illness. Unpublished data from Novavax show reduced efficacy for people with HIV infection, for example. The risk of infected people in hotel quarantine is higher now than in March or July 2020, given the pandemic is much worse now. Therefore, the risk of breaches resulting in community outbreaks is now higher. The burden of living with ongoing restrictions and intermittent outbreaks points to the importance of a strategic vaccination policy. Further, the risk of an outbreak of a more transmissible variant is increasing, and such outbreaks will be harder to control than any we have faced previously[16].

Vaccine escape is another concern, with unpublished data from Novavax, Johnson and Johnson and Astra Zeneca showing reduced efficacy against variants of concern, particularly the South African and Brazilian variants. The Novavax efficacy in the UK is 95% against G614 but 85% against B117, whilst in South Africa, efficacy against B1351 was 60% (49% when HIV positive subjects included). The Johnson and Johnson single dose vaccine was 66–72% in the UK and US, but 57% against moderate to severe disease in South Africa. However, the Astra Zeneca vaccine was reported to have only 10% efficacy against the South African variant, prompting the South African government to pause plans to roll out that vaccine. On the basis of these developments, the WHO and COVAX have stressed that vaccine manufacturers 'must be prepared to adjust to the SARS-CoV-2 viral evolution, including potentially providing future booster shots and adapted vaccines, if found to be scientifically necessary'[29]. The emergence of vaccine escape mutants makes the case for mass vaccination with high efficacy vaccines stronger, as higher population immunity will reduce the selective pressure for further variants to emerge.

For mass vaccination, a slow implementation of vaccine roll out will result in the population living with COVID-19 longer and higher morbidity and mortality[1]. If vaccination can be delivered at scale rapidly, this will deliver the best outcomes. However, the logistics of rapid delivery are complex and includes vaccination infrastructure, adequate numbers of accredited vaccinators, mass vaccination clinics, a communication and health promotion strategy and a high capacity to deliver large numbers of vaccine doses rapidly.

While many countries have started their COVID-19 vaccination programs, the last time any country conducted mass vaccination was more than 40 years ago, for smallpox. Current EPI programs[30] are for infants. In Australia, for example, approximately 4–5 million people a year are vaccinated under the National Immunisation Program, including influenza vaccine for people aged 65 years and over, but mass vaccination would require vaccination of 25 million people. There is no living memory among people in the health workforce on mass vaccination of all age groups. We have excellent knowledge and experience of vaccinating infants and older adults, as well as some high-risk groups. Working age adults are especially challenging, as they are mobile and may not routinely seek healthcare[31]. The infrastructure and skilled personnel requirements to ensure rapid uptake of mass vaccination, rather than a slow trickle,

are significant. We need to be training and accrediting more nurse and pharmacist vaccinators, making plans for public vaccination clinics, ensuring widespread infrastructure for cold chain requirements, especially for vaccines that require deep freezing[32], and working proactively on health promotion and communication to ensure high acceptance of vaccination. We could also model the capacity to vaccinate rapidly in each state and territory and expand capacity accordingly. Given the number of good vaccine candidates to come, and the unforeseen circumstances such as those which led to the loss of the University of Queensland vaccine from the Australian planned stockpile, we could diversify our vaccine portfolio. We could also be using vaccines as PEP and collecting data on effectiveness as PEP during outbreaks. Adverse events monitoring is the final component of a vaccine program, as rare side effects may only become apparent post-licensure. Public confidence could be further enhanced with a no-fault vaccine compensation scheme, which is a part of many vaccination programs around the world[33].

Conflicts of interest

Raina MacIntyre has consulted for Astra Zeneca and Janssen for COVID-19 vaccines and been on an advisory board on COVID-19 vaccines for Seqirus.

Acknowledgements

This paper did not receive any specific funding. Raina MacIntyre is funded by a NHMRC Principal Research Fellowship.

References

1. MacIntyre, C.R. *et al*. (2020) Modelling of COVID-19 vaccination strategies and herd immunity, in scenarios of limited and full vaccine supply in NSW, Australia. *medRxiv*. doi:2020.12.15.20248278
2. World Health Organization (2021) Draft landscape of COVID-19 candidate vaccines. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines (accessed 17 January 2021).
3. Poland, G.A. *et al*. (2020) SARS-CoV-2 immunity: review and applications to phase 3 vaccine candidates. *Lancet* **396**, 1595–1606. doi:10.1016/S0140-6736(20)32137-1
4. Voysey, M. *et al*. (2021) Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* **397**, 99–111.
5. Polack, F.P. *et al*. (2020) Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N. Engl. J. Med.* **383**, 2603–2615. doi:10.1056/NEJMoa2034577
6. Baden, L.R. *et al*. (2021) Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N. Engl. J. Med.* **384**, 403–416.
7. Logunov, D.Y. *et al*. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. *Lancet* **397**, 671–681.
8. Voysey, M. *et al*. (2021) Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials. *Lancet* **397**, 881–891. doi:10.1016/s0140-6736(21)00432-3
9. Food and Drug Administration (2020) Vaccines and Related Biological Products Advisory Committee Meeting December 17, 2020. US Department of Health and Human Services, FDA, Silver Spring, MD, USA.
10. Dagan, N. *et al*. (2021) BNT162b2 mRNA Covid-19 vaccine in a nationwide mass vaccination setting. *N. Engl. J. Med.* doi:10.1056/NEJMoa2101765
11. Oran, D.P. and Topol, E.J. (2020) Prevalence of asymptomatic SARS-CoV-2 infection. *Ann. Intern. Med.* **173**, 362–367. doi:10.7326/M20-3012
12. Heywood, A.E. and Macintyre, C.R. (2020) Elimination of COVID-19: what would it look like and is it possible? *Lancet Infect. Dis.* **20**, 1005–1007. doi:10.1016/S1473-3099(20)30633-2
13. Heywood, A.E. *et al*. (2009) Elimination of endemic measles transmission in Australia. *Bull. World Health Organ.* **87**, 64–71. doi:10.2471/BLT.07.046375
14. Dowdle, W.R. (1998) The principles of disease elimination and eradication. *Bull. World Health Organ.* **76**, 22–25.
15. CDC (2020) COVID-19 Pandemic Planning Scenarios. https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html
16. Leung, K. *et al*. (2021) Early transmissibility assessment of the N501Y mutant strains of SARS-CoV-2 in the United Kingdom, October to November 2020. *Euro Surveill.* **26**, 2002106.
17. Madhi, S.A. *et al*. (2021) Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa. *medRxiv* [Preprint]. doi:10.1101.2021.02.10.21251247
18. Aschwanden, C. (2020) The false promise of herd immunity for COVID-19. *Nature* **587**, 26–28. doi:10.1038/d41586-020-02948-4
19. Vogel, G. (2020) Sweden's gamble. *Science* **370**, 159–163. doi:10.1126/science.370.6513.159
20. Buss, L.F. *et al*. (2021) Three-quarters attack rate of SARS-CoV-2 in the Brazilian Amazon during a largely unmitigated epidemic. *Science* **371**, 288. doi:10.1126/science.abe9728
21. MacIntyre, C.R. *et al*. (2019) Evidence of long-distance aerial convection of variola virus and implications for disease control. *Viruses* **12**, 33. doi:10.3390/v12010033
22. Kissler, S.M. *et al*. (2020) Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science* **368**, 860–868. doi:10.1126/science.abb5793
23. Australian Government, Department of Health (2020) Preliminary advice from ATAGI on general principles for the COVID-19 vaccination program.
24. Giubilini, A. *et al*. (2020) COVID-19 vaccine: vaccinate the young to protect the old? *J. Law Biosci.* **7**, lsaa050. doi:10.1093/jlb/lsaa050
25. Gallagher, T. and Lipsitch, M. (2019) Postexposure effects of vaccines on infectious diseases. *Epidemiol. Rev.* **41**, 13–27. doi:10.1093/epirev/mxz014
26. Mohanty, B. *et al*. (2020) Modelling the impact of a smallpox attack in India and influence of disease control measures. *BMJ Open* **10**, e038480. doi:10.1136/bmjopen-2020-038480
27. Greenberg, R.N. *et al*. (2014) Sequential administration of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naïve adults 60-64 years of age. *Vaccine* **32**, 2364–2374. doi:10.1016/j.vaccine.2014.02.002
28. Arvin, A.M. *et al*. (2020) A perspective on potential antibody-dependent enhancement of SARS-CoV-2. *Nature* **584**, 353–363. doi:10.1038/s41586-020-2538-8
29. WHO (2021) COVAX statement on new variants of SARS-CoV-2. https://www.who.int/news/item/08-02-2021-covax-statement-on-new-variants-of-sars-cov-2
30. Hoest, C. *et al*. (2017) Vaccine coverage and adherence to EPI schedules in eight resource poor settings in the MAL-ED cohort study. *Vaccine* **35**, 443–451. doi:10.1016/j.vaccine.2016.11.075
31. MacIntyre, C.R. *et al*. (2016) Equity in disease prevention: vaccines for the older adults – a national workshop, Australia 2014. *Vaccine* **34**, 5463–5469. doi:10.1016/j.vaccine.2016.09.039
32. Callaway, E. (2020) What Pfizer's landmark COVID vaccine results mean for the pandemic. *Nature*. doi:10.1038/d41586-020-03166-8
33. Halabi, S. *et al*. (2020) No-Fault compensation for vaccine injury – the other side of equitable access to Covid-19 vaccines. *N. Engl. J. Med.* **383**, e125. doi:10.1056/NEJMp2030600

Biography

Raina MacIntyre (MBBS Hons 1, M App Epid, PhD, FRACP, FAFPHM) is Professor of Global Biosecurity, NHMRC Principal Research Fellow and Head of the Biosecurity Program at the Kirby Institute, UNSW, Australia. She leads a research program in control and prevention of infectious diseases, spanning vaccinology, pandemics and emerging infections, and personal protective equipment. Her area of vaccine expertise is vaccination of older adults and immunosuppressed people, and she has a track record in research on vaccines against measles, influenza, hepatitis A, pneumococcal disease, herpes zoster and smallpox. She has conducted several randomized controlled clinical trials of vaccines and is on the Vaccine Council of 100 for the journal, Vaccine. She has over 400 peer reviewed publications. She has received many awards including the Sir Henry Wellcome Medal and Prize from the Association of Military Surgeons of the US, the Public Health Association of Australia's National Immunisation Award (for her research on adult vaccination), and the Frank Fenner Award for Research in Infectious Diseases.

*MICROBIOLOGY AUSTRALIA, 2021, **42**, 34–38*
https://doi.org/10.1071/MA21010

Long-term and short-term immunity to SARS-CoV-2: why it matters

John Zaunders[A,C] *and Chansavath Phetsouphanh*[B]

[A]Centre for Applied Medical Research, St Vincent's Hospital, Sydney, NSW, Australia
[B]Kirby Institute, UNSW Sydney, Australia
[C]Email: j.zaunders@amr.org.au

Abstract. The adaptive immune system, regulated by CD4 T cells, is essential for control of many viral infections. Endemic coronavirus infections generally occur as short-term upper respiratory tract infections which in many cases appear to be cleared before adaptive immunity is fully involved, since adaptive immunity takes approximately 1.5–2 weeks to ramp up the response to a primary infection, or approximately 1 week for a recurrent infection. However, the adaptive immune response to SARS-CoV-2 infection will be critical to full recovery with minimal long-lasting effects, and to either prevention of recurrence of infection or at least reduced severity of symptoms. The detailed kinetics of this infection versus the dynamics of the immune response, including in vaccinated individuals, will largely determine these outcomes.

Received 29 January 2021, accepted 10 March 2021, published online 13 April 2021

Introduction

SARS-CoV-2 is the third highly pathogenic coronavirus zoonosis from bats, which have evolved interferon and adaptive immune responses that allow many such viruses to co-exist without disease, but still permitting transmission[1]. In humans, transmission of SARS-CoV-2 to other individuals will typically occur at the peak of viral load in the first 5 days of symptoms[2].

Innate immunity

The earliest mechanism combating an acute, short-lived viral infection of an epithelial barrier, such as with SARS-CoV-2, involves type-1 and type-III interferons (IFN-I and IFN-λ)[3], prior to the adaptive immune response. Therefore, the first phase of the current pandemic is likely due to sufficient evasion of the early IFN response. Amongst patients with severe life-threatening pneumonia, 3% have inborn genetic errors in the IFN-I response pathway[4], and 13% have autoantibodies that prevent IFN-I signalling[5], much higher rates than in the general population. Also, it has been reported that COVID-19 patients with severe disease have lower[6], or delayed IFN production[7,8], consistent with evidence that exogenous IFN can limit coronavirus replication *in vitro*, and that these viruses have non-structural proteins that help evade and antagonise innate immunity[9,10].

Highly specialised circulating plasmacytoid dendritic cells (PDCs) also sense dsRNA and produce large amounts of exogenous