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Australia's COVID-19 vaccine journey: progress and future perspectives

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ABSTRACT

COVID-19 vaccines have played a pivotal role in reducing SARS-CoV-2 disease severity and mortality. However, evolutionary pressure has resulted in viral variants with increased fitness, greater capacity for immune evasion and higher infectivity. This evolution is exemplified by the emergence of the Omicron subvariants, all of which demonstrate significant escape from vaccine- or infection-induced immunity. Broadly protective vaccines are urgently needed to fight current, emerging and future SARS-CoV-2 variants. Australia is actively contributing to these efforts through the development of innovative vaccination approaches and vaccine delivery platforms.

Introduction

The strict public health measures implemented across Australia during the early phase of the COVID-19 pandemic kept rates of SARS-CoV-2 infection extremely low, until most of the population had received at least two doses of an approved vaccine. Since the relaxation of these measures in late 2021, a combination of waning immunity post-vaccination and the highly infectious and immunoevasive nature of the Omicron variants has driven waves of infection. The initial emergence of Omicron was characterised by the dominance of a single subvariant, BA.1, which was rapidly replaced by BA.2 and then BA.5 by mid-2022[1] (Fig. 1*a*). Subsequently, infection waves in Australia have consisted of a diverse mix of Omicron subvariants that has been termed the Omicron 'soup' (Fig. 1*a*). Thus, immunity to SARS-CoV-2 across the Australian population is highly variable, depending on both the number of vaccine doses received or breakthrough infections.

The COVID-19 vaccine rollout in Australia and its effect on population immunity

Over 95% of adults in Australia had received the initial two doses of an approved COVID-19 vaccine by the end of 2021. Over time, the levels of SARS-CoV-2 neutralising antibodies (NAbs) naturally decline. This, coupled with the emergence of viral variants carrying mutations that diminish antibody recognition, contributes to a reduction in vaccine effectiveness. Australian researchers were the first to establish a correlation between the efficacy of COVID-19 vaccines and the titres of NAbs targeting the SARS-CoV-2 spike protein.[2–4] To counter waning immunity, 'booster' vaccine doses are recommended by the Australian Technical Advisory Group on Immunisation (ATAGI); 3rd vaccine doses were initially introduced at the end of 2021 for high-risk groups, before being expanded in 2022 to all adults whose second dose had been received more than 6 months prior. Clinical data from the Australian population have shown that such booster vaccine doses can restore NAb levels after waning, broaden cross-recognition of SARS-CoV-2 variants and improve protection against symptomatic infection and severe disease.[5] Importantly, Australia served as a distinctive case for evaluating booster efficacy, as prior to Omicron, the Australian population had low rates of previous SARS-CoV-2 infection but high levels of vaccination. In older Australians (65+ years), vaccination is highly effective against COVID-19 mortality, although effectiveness wanes quickly with time since last dose.[6] Accordingly, ATAGI recommends an additional booster dose for those 75+ years, if their previous vaccination was more than 6 months prior.[7] However, uptake of booster doses has been slow; as of 6 December 2023, only

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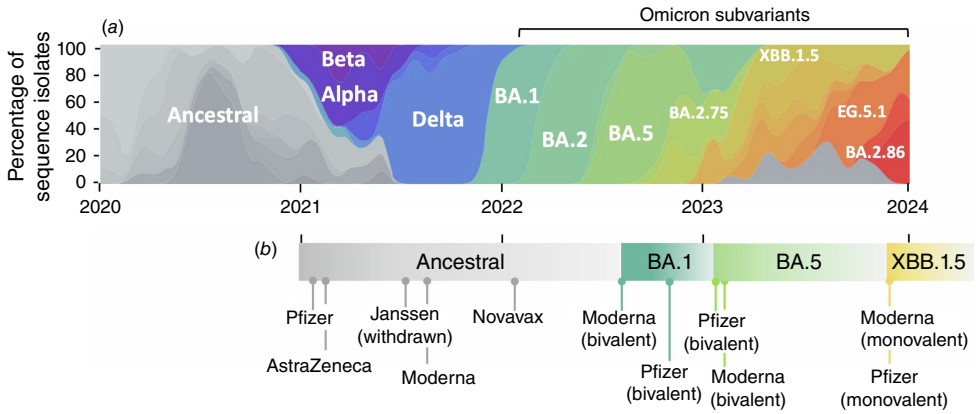

Fig. 1. SARS-CoV-2 variants and vaccination in Australia. (*a*) Overview of SARS-CoV-2 variants circulating in Australia over time as percentage of total infections. Only representative variants shown for clarity. Data from CoVariants.org. (*b*) Timing of the vaccine rollout in Australia. The date of provisional approval for each vaccine (by company and variant) is approximated on the timeline. Full details can be found at www.tga.gov.au/products/covid-19/covid-19-vaccines/covid-19-vaccines-regulatory-status.

22% of those aged 75+ years in Australia have received a COVID-19 booster within the last 6 months, leaving a large number of vulnerable individuals at risk.[7]

Currently, population immunity to SARS-CoV-2 in Australia is being shaped by a mix of responses to both vaccination and infection,[8] largely with the Omicron subvariants (Fig. 1*a*). The ability of Omicron subvariants to cause breakthrough and re-infections can be attributed to key mutations within the viral spike protein that render them antigenically distinct from the ancestral spike antigen used in the original COVID-19 vaccines. Therefore, to improve responses against these subvariants updated bivalent (ancestral + BA.1 and ancestral + BA.5) booster vaccines were developed (Fig. 1*b*). Bivalent booster vaccines were provisionally approved in Australia in August 2022, and were recommended by ATAGI as the booster of choice in early 2023. A study of Australians aged over 65 showed bivalent boosters provide better protection against mortality from the diverse Omicron subvariants XBB and BA.2.75 than ancestral-based vaccines.[9] Owing to the persistent global dominance of the Omicron subvariants, particularly the recombinant XBB lineage, monovalent XBB.1.5 booster vaccines were developed and approved for use in Australia in October 2023. Currently there are limited studies describing the efficacy of XBB.1.5 monovalent vaccines; however, current data suggest the XBB lineage, which includes EG.5 variants, could be soon replaced by JN.1 variants.[10] Therefore, the development of next-generation COVID-19 vaccines that can provide pan-variant protection, as well as more durable responses, are required to reduce SARS-CoV-2 infection rates.

Australia's contribution to the next-generation of SARS-CoV-2 vaccines

Australia's dependence on 'imported' COVID-19 vaccines significantly influenced the pace of the initial vaccine rollout, highlighting vulnerabilities in our sovereign vaccine manufacturing capabilities.[11] Nevertheless, the pandemic has catalysed increased investment, both domestically and globally, in advancing not only COVID-19 vaccines but also tools to combat diseases with pandemic potential. This investment, coupled with the high quality of Australian science, has given rise to several research programs addressing these issues, as outlined in Table 1 and discussed below.

Improved variant-based vaccines

The emergence of the SARS-CoV-2 Beta variant in late 2020, the first variant of concern (VOC) to display significant immune evasion, initiated the development of variant-based vaccines that could induce cross-protection. We showed that in animal models, booster vaccines based on the Beta variant could broaden immunity against divergent VOCs.[12] Researchers at The University of Melbourne and Monash Institute of Pharmacological Sciences (MIPS) developed two Beta-based vaccine candidates (protein and mRNA respectively) that showed promise in Phase I clinical testing[13] (Table 1). In individuals who had already received three COVID-19 vaccine doses, both candidates were able to boost antibody responses, including against the highly immune-evasive Omicron subvariants XBB.1.5 and BQ.1.1.[13]

Vaccines targeted to circulating variants have been the basis for all authorised COVID-19 booster shots. However, the virus has demonstrated the ability to surpass the pace of vaccine development and distribution, as illustrated in Fig. 1*b*. Consequently, significant attention has been directed towards creating broadly protective, pan-variant candidates to 'futureproof' against both existing and emerging SARS-CoV-2 variants. Supporting these programs has been a major focus of the Coalition for Epidemic Preparedness Innovations (CEPI), a global partnership dedicated to accelerating the development of vaccines against epidemic and pandemic threats. With the support of CEPI, and in collaboration with Bharat Biotech International and ExcellGene SA, we have developed chimeric spike antigens (CSAs) that display broad immunological cross-reactivity and high-yield

Table 1. Overview of COVID-19 vaccine development in Australia.

Lead organisation	Technology	Status	Reference
Improved variant-based vaccines			
The University of Melbourne	Beta variant receptor binding domain (RBD) in MF59 adjuvant	Phase I complete	13
Monash Institute of Pharmacological Sciences	Beta RBD mRNA vaccine	Phase I complete	13
The University of Sydney	Pan-variant, chimeric spike protein in SWE adjuvant	Pre-clinical, Phase I scheduled for Q3 2024	14
Garvan Institute of Medical Research	Pan-variant mRNA	Pre-clinical	15
New vaccine formulations and delivery approaches			
Vaxine	Spike protein in Advax adjuvant	Approved for use in Iran	16
Vaxxas	Spike protein and QS21 adjuvant coated skin nanopatch	Phase I ongoing	20
University of Sydney	DNA vaccine. Needle-free injection system	Phase I ongoing	22
University of Adelaide	DNA vaccine. Needle-free injection system	Phase I ongoing	23
University of Sydney	Spike protein in Advax adjuvant. Mucosal delivery	Pre-clinical	17
Centenary Institute	Spike protein with Pam2Cys adjuvant. Nose-only mucosal delivery	Pre-clinical	18
Griffith University	Codon de-optimised, live attenuated SARS-CoV-2. Mucosal delivery	Pre-clinical	19
Novel vaccine platforms			
The University of Queensland	S-CLAMP spike protein and MF59 adjuvant	Second generation CLAMP2 phase I for proof-of-concept complete	24
EnGeneIC	Nanocell packaged with spike protein plus a-galactosyl ceramide adjuvant	Phase I/IIa ongoing	27
Sementis	Non-replicating vaccinia virus vector encoding spike protein	Pre-clinical	26

Details of the listed vaccines were obtained by examining published information, including journal articles and press releases. The list is representative and may not include all candidates currently in development.

manufacturability.[14] CSAs are designed to incorporate mutations known or proposed to affect immunity that are present across VOCs, or predicted to arrive in future variants. An alternative approach is to develop universal COVID-19 vaccines by targeting regions of the virus that are more conserved than the spike protein; this is being pursued by a consortium of the Garvan Institute for Medical Research, Kirby Institute (at the University of New South Wales, UNSW) and the UNSW RNA Institute, with support from the NSW Health COVID-19 Vaccine Acceleration Research Grant scheme.[15]

New vaccine formulations and delivery approaches

A major challenge for control of COVID-19 is to develop strategies that can prevent viral transmission and curb the number of infections. In collaboration with the Australian biotech company Vaxine, we developed a mucosal vaccine combining spike antigen adjuvanted with the novel polysaccharide adjuvant Advax, which is a component of Vaxine's SpikoGen COVID-19 vaccine that is approved for use in Iran.[16] Our mucosal vaccine provided sustained generation of NAbs and lung resident T cells, which was not observed with parenteral immunisation, coupled with sterilising immunity against virulent SARS-CoV-2 infection in mice.[17] Additionally, Ashhurst *et al.* demonstrated that intranasal administration of spike antigen with the TLR2-stimulating adjuvant Pam2Cys stimulated anti-spike immunoglobulin A (IgA) production, generated systemic NAbs and protected K18-hACE2 mice from clinical disease and lung viral infection.[18] Progression of this vaccine is supported by the NSW Health COVID-19 Vaccine Acceleration Research Grant scheme. Mucosal delivery of a codon de-optimised, live-attenuated SARS-CoV-2 vaccine is also being explored.[19]

Needle-free delivery platforms are also being investigated to improve vaccine performance and safety. Vaxxas has developed a high-density skin microarray patch (HD-MAP), that when coated with spike protein and the QS21 saponin adjuvant, demonstrated enhanced immunity compared to intradermal delivery and provided complete protection from SARS-CoV-2 challenge in mice.[20] This vaccine has advanced to phase I clinical testing in Australia, and the technology is also being applied to mRNA vaccine delivery.[21] Needle free injection methods are also being tested locally for the delivery of DNA-based COVID-19 vaccines[22,23] (Table 1).

Novel vaccine platforms

The COVID-19 pandemic underscored the urgent need for rapid and equitable vaccine distribution, prompting the development of adaptable vaccine platforms that can be quickly updated in response to emerging threats. The University of Queensland, supported in part by CEPI, has developed a rapid response vaccine platform based on their 'molecular-clamp' technology for antigen stabilisation and manufacture. Initially deployed to create a spike protein-in-adjuvant-based COVID-19 vaccine in 2020, the first candidate faced challenges with the clamp design, limiting progression beyond phase I of clinical testing.[24] Subsequently, clinical assessment of a second-generation clamp has demonstrated viability of the technology as a versatile vaccine platform.[25] Sementis, in collaboration with the University of South Australia, have applied a replication-deficient vaccinia virus platform for SARS-CoV-2 spike protein delivery, with strong immunity observed in preclinical assessment using murine models.[26] EnGeneIC, a Sydney-based company, utilised its bacterial-derived nanocell technology to encapsulate bacterially expressed SARS-CoV-2 spike protein and an α-galactosyl ceramide adjuvant.[27] A phase I/IIa trial of this candidate is currently in progress.

Conclusions

Australia made many valuable scientific contributions during the COVID-19 pandemic that have strengthened our vaccine development and manufacturing capabilities. Continued research and investment in this field will be critical to ensure we are prepared for future pandemic threats.

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Professor James Triccas is a bacteriologist who uses a multidisciplinary approach to define immunity to chronic bacterial pathogens and develop new treatments to control infection. He is Professor of Medical Microbiology and Deputy Director of the Sydney Institute Infectious Diseases (Sydney ID) at The University of Sydney. He leads the recently established vaccine consortium comprising The University of Sydney, ExcellGene and Bharat Biotech, supported by the Coalition for Epidemic Preparedness Innovations (CEPI), to develop a broadly protective SARS-CoV-2 vaccine.

Dr Megan Steain is a virologist with expertise in host-pathogen interactions and using viruses as vectors to address multiple health challenges. She is a senior lecturer in the Infection, Immunity and Inflammation theme within the School of Medical Sciences at The University of Sydney. She has over 20 years' experience working with pathogenic human viruses, including HIV, SARS-CoV-2, varicella zoster virus, herpes simplex virus-1 and human cytomegalovirus.