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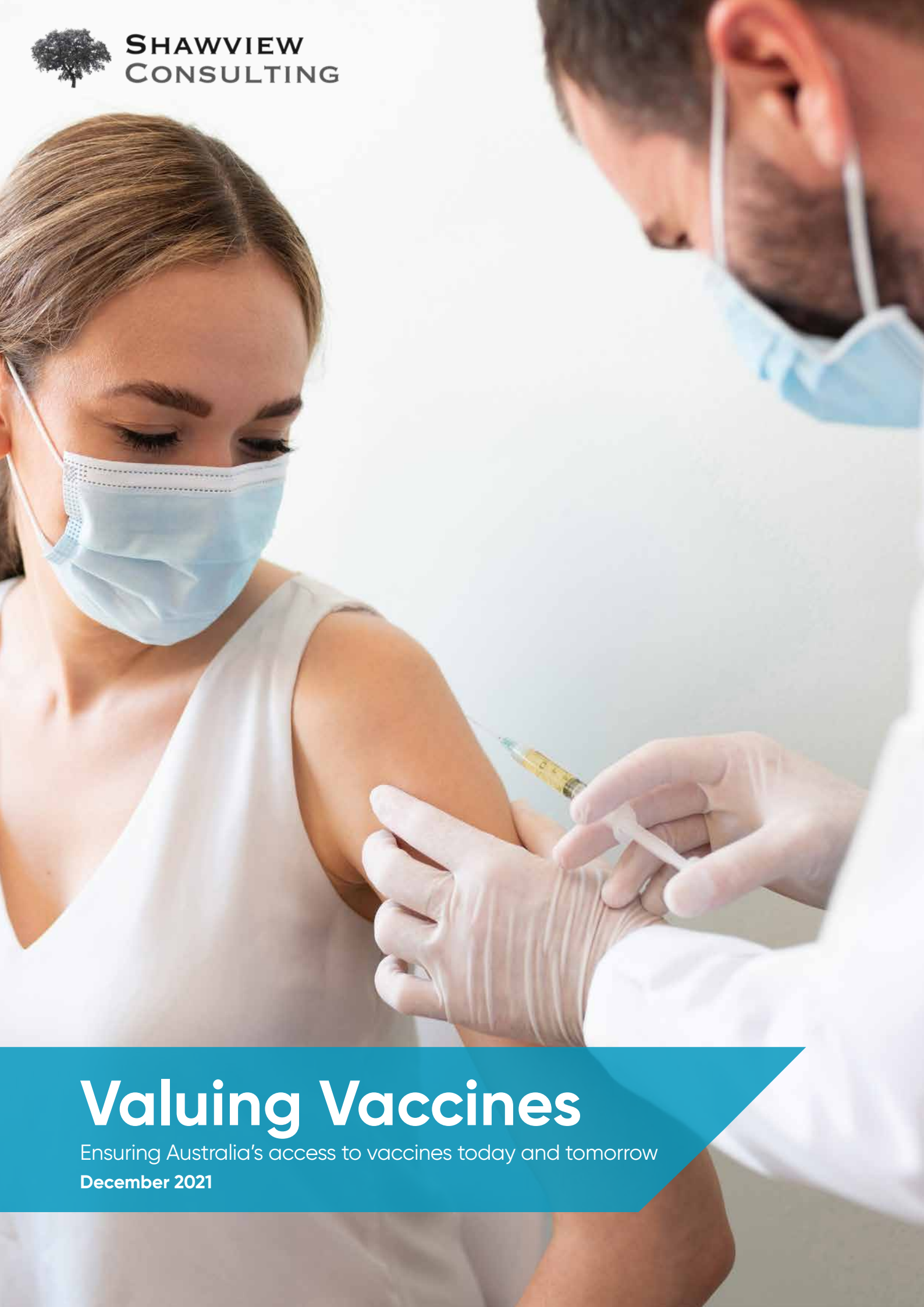

Valuing Vaccines

Ensuring Australia's access to vaccines today and tomorrow

December 2021

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List of Acronyms

ABS	Australian Bureau of Statistics
ACIR	Australian Childhood Immunisation Register
ACV	Advisory Committee on Vaccines
AIHW	Australian Institute of Health and Welfare
AIR	Australian Immunisation Register
ATAGI	Australian Technical Advisory Group on Immunisation
ARTG	Australian Register of Therapeutic Goods
BRAVE	Broad Assessment of Value in Vaccines Engagement
CEA	cost-effectiveness analysis
CE	cost-effectiveness
CHB	chronic hepatitis B
COPD	chronic obstructive pulmonary disease
CPI	Consumer Price Index
CPR	Commonwealth Procurement Rules
CRG	Cost Recovery Guidelines
CRIS	Cost Recovery Implementation Statement
DALY	Disability Adjusted Life Year
DNA	deoxyribonucleic acid
DUSC	Drug Utilisation Sub Committee
DTPa	diphtheria, tetanus and pertussis vaccine
ESC	Economics Sub Committee
GDP	gross domestic product
GMO	genetically modified organism
GP	general practitioner
GST	Goods and Services Tax
GVAP	Global Vaccine Action Plan
HBV	hepatitis B vaccine
HD	high dose HPVhuman papilloma virus
Hib	haemophilus influenzae type b
HIV	human immunodeficiency virus
HTA	health technology assessment
HZ	herpes zoster
ICER	incremental cost-effectiveness ratio
IMD	invasive meningococcal disease
IMF	International Monetary Fund
IPV	inactivated polio vaccine
JCVI	Joint Committee on Vaccination and Immunisation
mAbs	monoclonal antibodies
MBS	Medicare Benefits Scheme
MenB	meningococcal B
MenC	meningococcal C
MMCCV	monovalent meningococcal C conjugate vaccine
MMR	measles, mumps, rubella
mRNA	messenger ribonucleic acid
MS	multiple sclerosis
NDIS	National Disability Insurance Scheme
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIP	National Immunisation Program
NITAG	National Immunisation Technical Advisory Group
NNP	Nationally Negotiated Price
NPEV	National Partnership on Essential Vaccines
OECD	Organisation for Economic Co-operation and Development
OGTR	Office of the Gene Technology Regulator
OHE	Office of Health Economics
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PCV	pneumococcal conjugate vaccine
PS	protein subunits
QAF	quality adjustment factor
QALY	Quality-Adjusted Life Year
R&D	research and development
RFT	Request for Tender
RNA	ribonucleic acid
RSV	respiratory syncytial virus
RV	rotavirus
SPG	special purpose grant
TB	tuberculosis
TGA	Therapeutic Goods Administration
VISES	Victorian Institute of Strategic Economic Studies
VPD	vaccine preventable diseases
VV	varicella vaccine
WHO	World Health Organization
YLD	years lived with disability
YLL	years of life lost
4HPV	quadrivalent human papillomavirus
13vPCV	13 valent pneumococcal conjugate vaccine

Foreword

Vaccines are, without a doubt, one of the most important public health interventions developed in human history. Vaccines have saved literally millions of lives since their introduction several centuries ago and the pipeline of future vaccines holds the potential opportunity to improve the lives of millions more people around the world for decades to come.

Australia's immunisation policies have been one of the major success stories of the country's public health policies. Thousands of lives have been saved since the first vaccines were introduced, the burden of various diseases has been drastically reduced or eliminated, and vaccination has become an important part of Australian life. Most recently, the country's achievement of reaching 95% immunisation targets for Australian children is a testament to the success of its vaccination policies.

Australia's National Immunisation Program and its supporting infrastructure has been one of the major reasons the country has been so successful in vaccination policy. Since its introduction in 1997, the Program has seen significant growth, development and change. The collaboration between the Commonwealth and State and Territory governments, the partnership with advisory committees and other clinical experts, and the strengthening of the evidence and funding base for the Program have all helped to ensure that Australians everywhere can benefit from free access to vaccines to protect themselves, their families and their community.

But as with all good public policy programs, there is a need for regular discussion and review to ensure that the Program continues to meet the needs and expectations of the Australian community.

Now, 25 years on from its inception, with a review underway of Australia's National Medicines Policy and following arguably the worst global pandemic in a century, it is time to consider the National Immunisation Program and Australia's immunisation policies to ensure they continue to provide vaccines to the Australian community in a timely manner.

Australia has a proud history of leading the development of the global vaccine agenda. From the early days of Frank Fenner and the elimination of smallpox through to Ian Frazer and the development of HPV vaccines, Australia has a long tradition of excellence in vaccines. It is this tradition that make it all the more important today to ensure that our National Immunisation Program is fit for purpose for the future.

Australia should also ensure it takes an active role at the global level in ensuring that the vaccines of the future that will protect us against future pandemics and epidemics are developed today. Australia has for many decades been a leader in global vaccines policy, so it is important that as a nation we lead global efforts to invest in such future vaccine technologies through organisations like the Coalition for Epidemic Preparedness Innovations.

If there is one lesson coming out of the last two years, it has been the reminder of the value of vaccination for human society. Now is the right time to discuss Australia's vaccine policies and programs to confirm they are sufficiently flexible, expansive and adaptable for the future. We need to ensure that Australia sufficiently prioritises and values early vaccination of all the population for the ever-expanding range of diseases that vaccines will help treat and prevent.

This report, *Valuing Vaccines: Ensuring Australia's access to vaccines today and tomorrow*, is an important step in encouraging that dialogue and reflection about the National Immunisation Program and Australia's vaccination policies more generally. There will always be a variety of views about how Australia should best provide vaccines to its people. This report provides a timely catalyst for debate and a comprehensive perspective on these issues.

Vaccination is one of our most important tools for protecting and supporting the community, so we need to ensure we do the best we can for present and future generations of Australians.

Jane Halton AO PSM
Chair of Coalition for Epidemic Preparedness Innovations

December 2021

Executive Summary

Since 1997, Australians have been the beneficiaries of our National Immunisation Program (NIP) Schedule. The NIP aims to provide Australians with the best possible protection by ensuring they can access immunisations on time, every time, from birth through to adulthood, resulting in a reduction, and in some cases, elimination of communicable diseases.

The NIP has been a major factor in driving childhood vaccination rates of up to 95% for many vaccine-preventable diseases and has undoubtedly saved lives, improved the quality of life for the Australian community, and delivered a variety of broader social and economic benefits for the nation.

As we look to a post-pandemic world, the time is right to consider the way Australia makes decisions about investing in immunisation. The NIP will continue to provide Australians' access to the next wave of innovative vaccines; however, changes need to be made now to improve policy settings to support the ongoing success of the NIP. This will ensure that Australians continue to be able to access new and innovative vaccines on time and every time.

This report sets out the case for change. The recent House of Representatives Standing Committee on Health, Aged Care and Sport inquiry into approval processes for new drugs and novel medical technologies, 'The New Frontier', has recommended that there be a review of the National Immunisation Program to, amongst other things, reform existing approaches used to value vaccines. This report's findings and recommendations would provide a valuable contribution to such a review. There are currently over 10,000 clinical trials for vaccines underway worldwide and a multitude of new vaccines will be developed in coming years to prevent illnesses, such as cancer, Alzheimer's disease, coronaviruses, multiple sclerosis, and allergies.

Emerging opportunities from new vaccine technologies abound. Universal vaccines and treatments for non-infectious diseases, the development of more vaccines for adolescents and adults resulting in an increasing emphasis on a "whole-of-life" approach to vaccination, changing community expectations about the value of life and preventative health, important considerations regarding the viability and attractiveness of Australia's vaccine market, a constrained and competitive global supply environment, and lessons from the COVID-19 pandemic all point to the need for reform of Australia's system of evaluating and funding vaccines.

Such reforms will be critical to ensuring the NIP's continued success in the future and should be integrated with the current reform agenda being shaped by the National Medicines Policy review and Health Technology Assessment review included in the new Strategic Agreement between the Australian Government and Medicines Australia.

New vaccine technology platforms in the pipeline that could be of particular interest to Australia include DNA and mRNA technologies, recombinant technologies, monoclonal antibodies, universal vaccines, new delivery platforms and longer-acting vaccines. These technological developments may provide new opportunities for Australians to be vaccinated against a range of diseases for which there are currently no available vaccines or will provide better vaccines than those that exist today.

Without policy reform, access to these new vaccines is not assured. This is because the processes Australia uses to evaluate, value and fund vaccines are increasingly out of step with international best practice, are administratively cumbersome, and do not sufficiently take the full value of vaccination and disease prevention into account when making investment decisions.

Ensuring Australia's funding levels are sufficient, that our evaluation and decision support frameworks are best practice, and that government procurement processes are focussed on both the short- and long-term benefits to the individual, healthcare system and society, will be critical to Australia's ability to benefit from emerging vaccine technologies.

Key findings

- At a broad historical level, Australia's immunisation policies have been successful in achieving broad coverage and uptake in funded programs; however, there are several issues which could impede continued success in suppressing disease and improving health outcomes in the future.
- Australia's system differs from that of many other countries by requiring ATAGI to advise the health technology assessment body, the PBAC, on NIP listings rather than making such recommendations directly to government.
- At around $450 million a year, the level of investment in the National Immunisation Program (NIP) is relatively low in comparison to other federally funded health and social programs and may not be sufficient to meet the needs of Australia's future requirements given the pipeline of new vaccines in development.
- Challenges caused by delays to access to new and innovative vaccines, problems with the current evaluation system and its ability to appropriately assess and value emerging future vaccine technologies, inadequate funding levels, all of which have been highlighted by the COVID-19 pandemic, point to a need to reform Australia's vaccine policies.
- How Australia values and funds vaccines must be reformed and enhanced to ensure that Australians can continue to access innovative and best in class vaccines now and in the future.
- A suggested four-point plan to reform Australia's vaccine policies is presented in the report.

A four-point-plan for Australia's future vaccines policy

Considering the findings of this report, all stakeholders should work together to upgrade the way Australia's vaccines policies value and fund vaccines for Australians, supported by an appropriate level of investment.

The post-COVID environment provides a unique opportunity for governments, industry, patients, health care professionals, vaccine experts and others to work together collaboratively to enhance Australia's NIP and vaccines funding policies for the long-term future benefit of the Australian community.

The following four-point-plan provides key recommendations that should be implemented.

1. **Long-term strategic plan for vaccines**
2. **Reform Australia's vaccine health technology assessment methodology**
3. **Reform the post-HTA procurement process for NIP vaccines**
4. **Create a framework to develop a pandemic vaccination plan and ensure it remains operationally ready in the face of rapidly evolving risk**

1. Long-term strategic plan for vaccines

The Commonwealth along with a broad range of industry stakeholders should develop a long-term strategy for vaccines and the NIP. This strategic plan should complement the existing National Immunisation Strategy and preventative health strategies by covering gaps such as overarching principles and objectives, mechanisms to enhance government-industry dialogue and information exchange, horizon scanning, measures to maintain and improve the long-term viability of the Australian vaccines market, manufacturing and supply chain integrity and strategic procurement relations.

The development of the plan should be supported by collaboration with patient groups, clinical and public health experts and others. This could be achieved by reconstituting and revamping Australia's National Immunisation Committee or creating a new strategic consultative committee on Australia's vaccination policies. Any committee should include vaccine industry representation and delivery channels for vaccine distribution on the Committee.

2. Reform Australia's vaccine health technology assessment methodology

Introduce changes to Australia's health technology assessment (HTA) methodology for evaluating vaccines to ensure that the full value of vaccines is appropriately assessed and considered when deciding on funding vaccines in Australia.

These changes could be implemented to support the new Commonwealth government and Medicines Australia Strategic Agreement, the government's upcoming HTA Review and the current review of the National Medicines Policy. Changes that the Commonwealth government should make include:

- Consolidate, streamline, and strengthen the HTA evaluation of vaccines to remove duplication, improve administrative efficiency, reduce the time to listing and increase recognition of the value of vaccines. This could be achieved either through a more efficient and integrated evaluation system involving ATAGI and PBAC, or by adopting a model similar to many countries where ATAGI makes the HTA recommendation direct to the Minister for Health.

- Reduce the 5% discount rate used by the PBAC to be consistent with rates used in other high-income countries, in order to properly assess/value the future economic and social benefits of vaccines. Ensure that considerations specific to vaccines are included in the review of discount rates announced as part of the new Strategic Agreement.

- Require PBAC to consider the broader economic and productivity benefits of vaccines in the base case of vaccine submissions where appropriate rather than consigning them to supplementary analyses and consider the appropriate use of real-world evidence and local evidence generation to address concerns regarding uncertainty in valuing the full benefits to Australian society which accrue beyond the directly vaccinated cohort, such as herd immunity.

- Increase Australia's incremental cost-effectiveness ratio (ICER) implicit threshold for vaccines to not disadvantage vaccines against other medical technologies, and

- Benchmark Australia's HTA evaluation of vaccines against international best practice, in consultation with industry, patient groups and other health stakeholders.

3. Reform the post-HTA procurement process for NIP vaccines

Reform the objectives and approach of the post-PBAC NIP price negotiation process to remove duplicative processes and to shift procurement from a 'transactional' to 'strategic' approach with industry. This will help to ensure long-term market and supply chain viability is given equal weight to short-term cost-saving priorities.

Greater priority should be given to ensuring that developing, manufacturing and supplying the latest vaccines in Australia is commercially attractive to companies and ensures Australia is sufficiently prioritised in international markets by the vaccines industry.

4. Create a framework to develop a pandemic vaccination plan and ensure it remains operationally ready in the face of a rapidly evolving risk

The Commonwealth should work with stakeholders, including industry, delivery channels and other stakeholders to collaboratively develop a pandemic vaccination plan to complement existing pandemic plans and better operate in tandem with the more normal NIP processes of regular community vaccination.

While providing many instructive lessons for Australia's broader more routine vaccination programs, the COVID-19 pandemic and the government's vaccine response to it have demonstrated the need to develop a pandemic vaccination plan for future pandemics.

The pandemic vaccination plan should complement existing plans such as the Emergency Response Plan for Communicable Disease Incidents of National Significance and the Australian Health Management Plan for Pandemic Influenza and look at overseas models of vaccine-based pandemic responses, including a Centre for Disease Control.

This pandemic vaccination plan should be reviewed in close collaboration with industry to ensure Australia is able to develop, manufacture and purchase vaccines for future pandemics in a timely manner.

1 Introduction

"Speeding up vaccine production and rollout is the best economic policy available today to boost growth and job creation."

OECD, Economic Outlook, Interim Report, March 2021[1]

"The challenges for the Australian economy from the virus remain significant. Further outbreaks of the virus are likely until a vaccine is developed and widely available."

Australian Government, Budget 2020-21, October 2020[2]

"Global economic activity is expected to recover as the increasing vaccine coverage reduces both the need for containment measures and serious health impacts arising from the pandemic."

Australian Government, Budget 2021-22, May 2021[3]

When the COVID-19 pandemic arrived in Australia in 2020, the way that Australia values vaccines was fundamentally challenged.

COVID-19 vaccines were approved by regulatory authorities in a matter of weeks, whereas normally such approvals take months. COVID-19 vaccines were publicly funded by government almost instantly on regulatory approval, whereas under normal circumstances Australians wait 1,375 days on average for a vaccine to be funded once approved by the Therapeutics Goods Administration (TGA). Commonwealth government funding for purchasing COVID-19 vaccines was in the billions of dollars, a factor of 10 to 20 times higher than the normal level of funding for all other vaccines combined.

If the COVID-19 pandemic has taught Australia and the world anything, it is the value to society and the economy from investing in vaccine research and development, manufacturing, supply and ultimately having early access to vaccines that can protect Australians from preventable diseases.

The societal and economic value of vaccines and of ensuring they are available to populations in a timely fashion has been known for a long time. It has been demonstrated and readily accepted for generations by most health experts and the broader community that vaccines are one of the most cost effective and important public health interventions in the health system.

Preventing disease through the development of vaccines has protected lives, supported society and driven economic growth. It has protected lives, supported society and driven economic growth. Be it ridding the world of smallpox, all but eliminating polio, battling influenza, or stopping needless childhood deaths from measles, vaccines have been an important part of human development worldwide and a major reason Australia enjoys a high health status.

The COVID-19 pandemic, its economic aftershocks and the subsequent rollout of COVID-19 vaccines have been a demonstrable example of the societal and economic value of vaccines. As well as saving millions of lives around the world, it is readily accepted by organisations such as the Organisation for Economic Cooperation and Development[4] (OECD) and the International Monetary Fund[5] (IMF) that the global economic recovery hinges critically on the availability and rollout of COVID-19 vaccines.

Similarly, in Australia the key economic issue facing the Australian economy today is having timely and effective access to COVID-19 vaccines for all Australians. The Australian Government's October 2020 and May 2021 budgets readily recognise that Australia's post-pandemic economic recovery hinges on the availability of vaccines to beat the disease. For example, the 2021-22 Federal Budget forecasts for economic recovery in Australia through the fiscal year hinge on key assumptions, including that a nation-wide vaccination program for COVID-19 is in place by the end of 2021[6]. The best economic strategy for Australia and the world today is to fully recognise the value of vaccines.

There is now overriding evidence of the value of investing early in vaccine development and access. However, the question is what has Australia learned that it can apply in the future, to increase efficiency of development and access for vaccines more generally, and how does Australia change its governance structures to ensure timely access to new vaccines? How do the public and private sectors come together where there is an overriding public benefit to make this happen?

How Australia values vaccines

The reality is that many of the problems in Australia's system of evaluating and funding vaccines existed long before the COVID-19 pandemic. Given the social and economic payoff for Australian society and the economy, how the country assesses the value of vaccines, makes decisions on pricing and funding levels, decides who in the community should and should not have access to vaccines and how to ensure that people actually receive the vaccines are all important processes.

In Australia these decisions are made through a complex and, at times, confusing and contradictory series of processes where the reasons why vaccines are funded or not are not always clear.

This report highlights Australia's processes for assessing and funding vaccines do not recognise the economic and societal value of vaccination to the extent they should.

Even before COVID-19, there were tensions buried in the system that have operated for years which constrained thinking and delayed access to vaccines. Prior to COVID-19, Australia's system of evaluating and valuing vaccines routinely downplayed or undervalued the social and broader economy-wide value of vaccination. This system was complex and slow and relied on a system of constrained bargaining and drawn-out negotiation to arrive at a price that routinely undervalued a vaccine. Limited budgets, conflicting processes, convoluted federal-state financial relations, inflexible evaluation criteria and low value attached to preventative health interventions all existed before COVID-19.

Moreover, Australia's policy and bureaucratic systems, admittedly to varying degrees, did not always sufficiently and consistently prioritise government support for and engagement with the vaccine industry. The pandemic shone a spotlight on all these issues.

It was perhaps for these reasons why the entire valuing and decision-making process for COVID-19 vaccines to combat the biggest pandemic to hit Australia since the birth of the modern vaccines industry was conducted entirely outside the normal Australian vaccines evaluation system.

A series of issues and reforms need to be considered to ensure that Australia's system of evaluating and funding vaccines is appropriate for the 21st century.

This report

This report reviews the policies and processes used in Australia to value and fund vaccines for the Australian population. These policies and processes have evolved over the last few decades but there has been little strategic thinking about how those policies and processes are working.

This report concludes that it is time for government, industry, health sector stakeholders and the broader community to come together to revamp Australia's vaccination funding policies and how Australia values vaccines.

The study was conducted up to September 2021 and reviews how Australia makes decisions about the value and funding of vaccines in Australia and focuses on the National Immunisation Program.

The scope of the report is limited to the economic evaluation and funding decisions about vaccines and does not focus on the safety and efficacy approval of vaccines that is conducted through the regulatory processes of the Therapeutic Goods Administration (TGA). Nor does the report examine epidemiological issues about vaccination in Australia in detail, but only to the extent they inform the policy discussion.

The report compares Australia's system of evaluating vaccines against the international experience of other countries of similar income and development levels. The evidence suggests that while Australia broadly funds new and innovative vaccines and provides these to its population, the processes used to make these decisions are complicated by comparison to international standards and result in delays to access and investment decisions which devalue or plays down the broader societal and economic value of vaccines.

The research for this report used a variety of methods to assess this including literature reviews, examination of data, reviewing Australia's systems of evaluating and funding medicines, informal discussions with experts in the vaccines policy space in Australia and internationally, economic modelling of the economic and productivity benefits of vaccines and case studies of vaccines that have gone through Australia's evaluation system.

This report examines these issues across several sections:

- Section 2: Provides an overview of Australia's vaccines reimbursement system and how that system has evolved over time,
- Section 3: Provides a review of the benefits of vaccination for the community and the economy, looking at both international and Australian experience and models the economic benefits to Australia of some key vaccines funded through the NIP,
- Section 4: Provides a detailed review of the issues in Australia's vaccine funding processes, looks at issues and implications in these processes and examines how Australia compares to its international counterparts in terms of community access to vaccines,
- Section 5: Looks at new, emerging vaccine technologies in the pipeline to gain insight into what new vaccines might be potentially available to the Australian population in the next 5 to 10 years,
- Section 6: Reviews the recent experience of the COVID-19 pandemic, how Australia's COVID 19 vaccines were funded and the lessons for Australia's normal vaccine policy processes, and
- Section 7: Provides key finding and recommendations for improving the processes and frameworks for evaluating the value of vaccines in Australia.

This report by Shawview Consulting was commissioned by Sanofi Australia, a global pharmaceutical company that manufactures and supplies a range of vaccines worldwide and is an important supplier of vaccines to the Australian market. Final editorial control and responsibility for the content in this report is with Shawview Consulting, and the views contained in this report may not represent those of Sanofi Australia.

2 Outline of Australia's vaccines reimbursement system

"Immunisation is one of the most significant public health interventions of the past 200 years, and the National Immunisation Program (NIP) is one of Australia's great health success stories."

Australian Government, National Immunisation Strategy for Australia, 2019 - 2024[7]

Key points

- The process for getting a vaccine funded under the NIP has become more complicated and costly since 1997.
- Increasing levels of expenditure control have been added since 1997 with responsibility for recommending vaccines for funding shifting from ATAGI to the PBAC and the centralisation of vaccine purchasing with the Commonwealth government through the National Partnerships for Essential Vaccines.
- Costs for vaccine companies have increased with the introduction of cost recovery for the evaluation process.
- Companies seeking to have a vaccine listed on the NIP now need to go through four evaluation processes: TGA, ATAGI, PBAC and NIP tendering.

Historical context

Australia has developed a high-quality immunisation system that is recognised for its contribution to global immunisation[8]. The routine immunisation of infants in Australia started in the 1950s. In 1975 the first nationally funded program for immunisation of infants against three diseases – diphtheria, tetanus and polio – was introduced[9,10]. Prior to 1997, an expert sub-committee within the National Health and Medical Research Council (NHMRC) was tasked to create national clinical guidelines on immunisation for health professionals[11]. This sub-committee developed the National Immunisation Handbook which provided guidance on the inclusion of vaccines in Australian immunisation programs. However, the recommendations of the National Immunisation Handbook were not directly linked to the Australian government's vaccine funding decisions.

As a part of larger reforms to Australia's immunisation program, in 1997 a National Immunisation Program (NIP) was established as a joint Commonwealth – state and territory government initiative with the objective to improve national immunisation coverage to reduce the incidence of diseases that are preventable by vaccination in Australia[12]. Around the same time, the Commonwealth removed the expert sub-committee from the governance of NHMRC and created the Australian Technical Advisory Group on Immunisation (ATAGI) under the aegis of the Department of Health to advise the Minister for Health on the inclusion of vaccines in the NIP and the administration of NIP.

The NIP is administered in a collaborative effort by the Commonwealth, states, and territories. A range of committees and advisory bodies advise the Commonwealth government on immunisation and assist in making new vaccines available under the NIP. Through the NIP the Commonwealth government provides free vaccines to eligible people, based on age and/or medical risk, as detailed in the NIP Schedule[13]. At the time of its establishment in 1997, the NIP provided vaccines against nine childhood diseases which today has expanded to cover 17 diseases (constituting 20 antigens) for infants, children, young adults, vulnerable adults, older people, and the Aboriginal and Torres Strait islander population (Table 1).

Table 1 – Vaccines available under the NIP schedule

Chickenpox (varicella)	Diphtheria	Haemophilus influenzae type b (Hib)
Hepatitis A†	Hepatitis B	Human papillomavirus (HPV)
Influenza	Measles	Meningococcal disease (invasive)
Mumps	Pneumococcal disease (invasive)	Poliomyelitis
Rotavirus	Rubella	Shingles (herpes zoster)
Tetanus	Whooping cough (pertussis)	

† Vaccine is available under the NIP for Aboriginal and Torres Strait Islander children living in Queensland, Western Australia, South Australia and the Northern Territory.

Source: Department of Health. "National Immunisation Program Schedule", https://www.health.gov.au/health-topics/immunisation/immunisation-throughout-life/national-immunisation-program-schedule, accessed 10/6/2021.

Immunisation, as a public health issue, was traditionally the responsibility of the states and territories, in line with Australia's federal system of government. As demand for immunisation and its availability increased in the latter half of the 20th century, a range of disparities in funding for, and access to, vaccines appeared between states and territories.

National surveys in the 1980s suggested that only about 53% of Australian children were adequately immunised[14]. This gave rise to the first National Immunisation Strategy in 1993; the establishment of the Australian Childhood Immunisation Register (ACIR) in 1994, initially as a pilot before being adopted in 1996, and the introduction of the Immunise Australia Program In 1997 which included the NIP[15].

The most recent National Immunisation Strategy 2019 – 2024[16] is consistent with the World Health Organization's Global Vaccine Action Plan[17]. It aims to encouraging a greater focus in the health system on health rather than illness and improve Australia's preventive health system. Its aim is to prevent disease and severe outcomes of disease by maximising immunisation coverage in people of all ages.

The Strategy comprises eight strategic priority areas to complement and strengthen the NIP:

1. Improve immunisation coverage
2. Ensure effective governance of the National Immunisation Program
3. Ensure secure vaccine supply and efficient use of vaccines for the National Immunisation Program
4. Continue to enhance vaccine safety monitoring systems
5. Maintain and ensure community confidence in the National Immunisation Program through effective communication strategies
6. Strengthen monitoring and evaluation of the National Immunisation Program through assessment and analysis of immunisation register data and vaccine-preventable disease surveillance
7. Ensure an adequately skilled immunisation workforce through promoting effective training for immunisation providers
8. Maintain Australia's strong contribution to the region

Various arrangements for the funding and management of the NIP have been in place since its inception in 1997. Coordination between the Commonwealth and state and territory governments has increased, leading to consistent funding for all vaccines on the NIP. Funding was initially agreed under the Public Health Outcome Funding Agreements and subsequently the Australian Immunisation Agreements.

Following changes to federal financial arrangements between the Commonwealth and the state and territory governments as a result of the Intergovernmental Agreement on Federal Financial Relations and the *Federal Financial Relations Act 2009*, the Australian Immunisation Agreements were replaced with the National Partnership on Essential Vaccines (NPEV) in 2009.

The NPEV is an agreement between the Commonwealth government and the states and territories, which aims "to protect the Australian public from the spread of vaccine-preventable diseases (VPD) through the cost-effective and efficient delivery of immunisation programs under the National Immunisation Program"[18].

The NPEV describes the arrangements for the funding and delivery of a national, coordinated, and integrated approach to maintaining and improving effective immunisation coverage for VPD covered by the NIP[19]. It delineates the roles and responsibilities of the Commonwealth, and states and territories, and provides the framework for payments to states and territories from the Commonwealth for achieving performance indicators.

The second NPEV commenced in 2017[20]. It introduced stronger incentives for states to achieve higher immunisation coverage rates and to support program sustainability through targets for wastage through loss of vaccines due to cold chain breach or other damage, and leakage through unauthorised use of vaccines. In August 2020, the NPEV published its 2018-19 performance report[21] which provides an assessment of state and territory performance against the performance benchmarks[22] outlined in the National Partnership on Essential Vaccines (NPEV), for the second year of the agreement, covering the assessment period 1 April 2018 to 31 March 2019.

Australia's immunisation program has grown over the years. Funding for vaccine purchasing and services to support immunisation uptake has increased from $10 million[23] per year in the mid-1970s to $454 million in 2020-21 (Figure 9). Importantly, the range, scope and size of Australia's immunisation programs has expanded in that time. When the NIP Schedule was created in 1997, it only supported 9 childhood vaccines[24], whereas today the program reflects the course of vaccination throughout life by providing at least 17 vaccines for infants, children, young adults, vulnerable adults, and older people (Table 1). These new vaccines cover a range of additional diseases where a person can be preventatively immunised today where they could not be immunised for them back in 1997. Today, for example, Australians can be immunised against diseases such as pneumococcal disease, meningococcal disease, rotavirus, and cancer-inducing human papillomavirus whereas in 1997 no vaccines for these diseases were available.

The National Immunisation Program (NIP)

The NIP is the cornerstone of Australia's vaccination system. It aims to increase national immunisation coverage to reduce the number of cases of diseases that are preventable by vaccination in Australia. All vaccines listed in the NIP Schedule are free for Australians. Eligibility for free vaccines under the NIP is linked to eligibility for Medicare benefits[25].

Vaccines must go through several stages to ultimately be funded under the NIP. These are the regulatory process, the health technology assessment process, and the procurement process.

The regulatory process

The Therapeutic Goods Administration (TGA)

The TGA rigorously assesses vaccines for safety, quality, and efficacy before they can be used in Australia. Vaccines receive the same high level of scrutiny as other prescription medicines and related therapeutic goods. The TGA regulates therapeutic goods through:

- pre-market assessment
- post-market monitoring and enforcement of standards, and
- licensing of Australian manufacturers and verifying overseas manufacturers' compliance with the same standards as their Australian counterparts.

Therapeutic goods are divided broadly into two classes: medicines and medical devices. Vaccines are categorised as medicines. Medicines must be entered as either 'registered' or 'listed' medicines on the Australian Register of Therapeutic Goods (ARTG) before they may be supplied in or exported from Australia.

The TGA's decision to register a vaccine for use in Australia is informed by the advice of the Advisory Committee on Vaccines (ACV). The ACV is an independent committee appointed by the Commonwealth Minister for Health and is composed of members with expertise in science, medicine and public health, together with a consumer representative.

The ACV complements expertise in the TGA, ensuring that assessments of vaccines are as robust as possible. The TGA uses the best available scientific evidence to assess the risks and benefits of each vaccine. Evidence requirements are based on international guidelines developed by the European Medicines Agency.

The Office of the Gene Technology Regulator (OGTR)

The OGTR is responsible for the regulation of genetically modified organisms (GMOs) in accordance with the Gene Technology Act 2001. The objective of the Act is to protect the health and safety of people, and to protect the environment, by identifying risks posed by or because of gene technology, and by managing those risks through regulating certain dealings with GMOs. For example, the OGTR is required to approve and license any COVID-19 vaccines being administered in Australia that use GMOs. These include all the adenovirus vaccines and mRNA vaccines. Protein subunit vaccines will not generally require OGTR approval.

The health technology assessment (HTA) process

The Australian Technical Advisory Group on Immunisation (ATAGI)

ATAGI is a ministerially appointed committee established to advise both the Commonwealth Minister for Health as well as the Department of Health. It comprises medical and scientific experts of varying fields and expertise in immunisation from around the nation and includes consumer representation. It provides advice on the medical administration of vaccines for the NIP as well as vaccine policy generally, including through the development of the comprehensive Australian Immunisation Handbook[26]. The Handbook provides clinical advice for health professionals on the safest and most effective use of vaccines in their practice.

ATAGI provides technical interpretation of the safety and efficacy of the new vaccine under consideration and provides contextualised advice regarding the suitability and feasibility of any proposed change to the NIP.

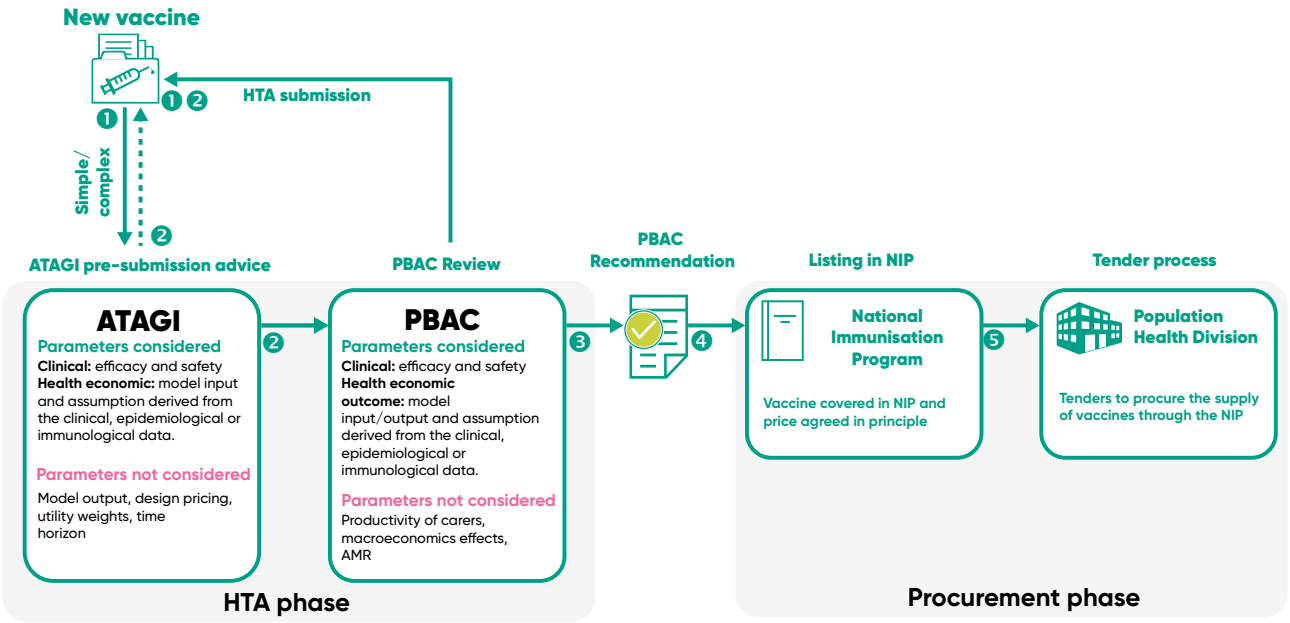
While ATAGI may periodically undertake general horizon scanning exercises for potential new vaccine candidates for Australian practice, these are not automatically considered for funding under the NIP[27]. Unlike many other vaccine advisory committees in other countries that pro-actively scan for potential vaccines to be funded, the NIP process and ATAGI's role is reactive in so far as its considerations of potential vaccines is triggered by a submission from sponsor, usually a pharmaceutical company sponsoring its vaccine.

One of the major roles of ATAGI is to provide the PBAC and its Economic Subcommittee with technical advice in relation to the consideration of listing a vaccine on the NIP. ATAGI has several horizon-scanning methods and may be aware of the existence of a new vaccine before being approached for advice to be prepared on a submission. The horizon scanning includes:

- presentations by vaccine manufacturers at the annual ATAGI Industry Day
- reviews of literature and decisions by regulatory authorities in other countries, and
- TGA advice to ATAGI regarding new applications for registration.

A preliminary meeting is available for companies prior to application to obtain ATAGI advice to ensure the proposed vaccine is suitable for public funding.

Figure 1 – Assessment of vaccine for inclusion in NIP and subsequent funding



Source: Department of Health. Procedure guidance for listing medicines on the Pharmaceutical Benefits Scheme. http://www.pbs.gov.au/info/industry/listing/listing-steps, accessed 10/6/2021; Department of Health. Guidelines for preparing a request for advice from the Australian Technical Advisory Group on Immunisation (ATAGI) to support Pharmaceutical Benefits Advisory Committee (PBAC) consideration of vaccines. https://www.health.gov.au/sites/default/files/documents/2020/05/atagi-pre-submission-advice-for-industry-sponsors-wishing-to-make-a-pbac-submission-guidelines_0.pdf, accessed 10/6/2021; Department of Health. Procedures for Australian Technical Advisory Group on Immunisation (ATAGI) advice to the Pharmaceutical Benefits Advisory Committee (PBAC). https://www.health.gov.au/sites/default/files/documents/2020/05/atagi-pre-submission-advice-for-industry-sponsors-wishing-to-make-a-pbac-submission-procedures_0.pdf, accessed 10/6/2021.

Following a 2018[28] review of ATAGI advice, procedures and requirements, new processes were introduced into the NIP listing process from July 2020. These include:

- the establishment of a vaccine evaluation panel
- development of new documents for sponsors seeking ATAGI advice including:
  - guidelines for preparing a request for pre-submission advice from ATAGI to support PBAC consideration of vaccines
  - procedures for ATAGI advice to the PBAC
  - templates for obtaining pre- and post-submission advice to the PBAC, and
- defined timeframes and submissions calendar for ATAGI advice.

This is the first time there have been explicit timelines and information requirements for the ATAGI advice process.

The provision of ATAGI advice prior to a submission broadly involves:

1. notifying the Department of Health of an intention to request ATAGI advice
2. producing the *request for pre-submission advice* following the guidance document
3. an external Vaccine Evaluation Group producing a draft advice document
4. ATAGI considering the draft advice, led by ATAGI discussants, and
5. ATAGI endorsing the advice and returning it to the sponsor and PBAC.

ATAGI members themselves rarely engage directly with the sponsor company and there is little opportunity for the company to discuss technical or scientific elements of its submission with ATAGI directly. The ATAGI secretariat of the Department does, however, take on this role of answering questions for companies.

The Pharmaceutical Benefits Advisory Committee (PBAC)

The Pharmaceutical Benefits Advisory Committee (PBAC) is a statutory independent expert body appointed by the Commonwealth, one of whose primary functions is to recommend new vaccines to the Commonwealth Minister for Health for funding under the NIP[29]. Its members include doctors, health professionals, health economists and consumer representatives. As with ATAGI, the PBAC is in one sense reactive in that it is up to sponsoring companies to make a submission to the PBAC to have vaccines listed on the NIP.

For vaccines, the PBAC follows an established process and decision-making criteria for listing a new vaccine on the NIP[30]. As explained in the PBAC guidelines, industry sponsors of vaccines seeking a listing on the NIP schedule are first required to obtain advice from the Australian Technical Advisory Group on Immunisation (ATAGI) before proceeding with the submission to PBAC[31]. Favourable ATAGI advice, however, is not a guarantee of the inclusion of a vaccine on the NIP. Since 2005 a positive recommendation is also required from the PBAC as a condition of listing a vaccine on the NIP.

In 2005, the *National Heath Act 1953* was amended to provide for the evaluation of the cost-effectiveness of vaccines by the PBAC, to provide a more consistent and transparent process for recommending vaccines for Commonwealth government funding[32]. While medicines have required a positive PBAC recommendation for listing on the PBS since the early 1990s, it was only since 2005 with these legislative changes that vaccines submitted for reimbursement under the NIP also required a similar positive recommendation from the PBAC.

Under these arrangements, the *National Health Act 1953* requires that before a medicine (such as a vaccine) is provided to Australians for free through the NIP or subsidised under the Pharmaceutical Benefits Scheme (PBS), the PBAC must undertake a thorough and objective assessment of its clinical efficacy and cost-effectiveness in comparison with other available treatments. The PBAC then provides advice to the Minister for Health. No new medicine or vaccine can be listed unless the Committee makes a positive recommendation. The PBAC meets three times a year, usually in March, July and November. PBAC recommendations are given in response to vaccine sponsor submissions.

As part of the legislative changes in 2005, existing vaccines that were already on the NIP prior to the change were listed on the *National Health (Immunisation Program – Designated Vaccines) Determination*[33]. With these legislative changes, ATAGI was given a new role in providing technical advice to the PBAC on new vaccines and specific vaccines expertise was added to the PBAC.

When recommending a medicine for listing, the PBAC considers the medical conditions for which the vaccine was registered for use in Australia, its clinical effectiveness, safety, and cost-effectiveness compared with other treatments. The PBAC has a set of guidelines relating to vaccine submissions[34]. PBAC has two sub-committees to assist with analysis and advice in these areas: the Drug Utilisation Sub Committee[35] (DUSC) and the Economics Sub Committee[36] (ESC). To minimise duplication between the ATAGI advice and PBAC evaluation processes ATAGI advice does not address:

- economic models, incremental cost-effectiveness ratios (ICERs), pricing information or financial estimates.
- indirect treatment comparisons or meta-analyses.
- other broader issues, such as full baseline demographics, risk of bias assessment, literature search methodology and flow of patient diagram.

The price outcome coming out of the PBAC process becomes what is termed the Nationally Negotiated Price (NNP), for the purposes of the further procurement process for the NIP. Following the assessment by PBAC a vaccine can be listed on the NIP, the PBS or it can be simultaneously listed under the NIP and funded under the PBS for different indications.

The PBAC guidelines for vaccines[37] state that several factors affect whether vaccines will be listed on the PBS or funded under the NIP. A vaccine should generally be proposed for funding under the NIP where there is expected to be an additional health benefit to the community beyond the individuals vaccinated, which would be improved by maximising coverage rates of the proposed vaccine in the identified individuals.

The guidelines note that PBS listing is a less common route for subsidised vaccine provision, but might be appropriate when the proposed vaccine is 'discretionary' for the majority of the population (e.g. to vaccinate an individual against a disease that is not sufficiently prevalent in Australia to justify maximising the use of the proposed vaccine), or where vaccination relates to a higher disease risk associated with the presence of specific risk factors, for which assessment of eligibility is less straightforward (e.g. where an assessment of immune system status is required). A vaccine may be simultaneously listed on the PBS and funded under the NIP for different indications. In practice, most vaccines have been gradually migrated to the NIP and few vaccines today remain on the PBS.

Cost recovery

Cost recovery activities and fees associated with evaluation of submissions and the listing of medicines, vaccines and other products or services on the PBS and the NIP commenced on 1 January 2010. From 1 January 2010 to 30 June 2019, fees rose annually in line with the consumer price index (CPI) based on the approved 2008-09 cost model.

In 2015, the Commonwealth government's Charging Framework and the Cost Recovery Guidelines (the CRGs) were introduced. The 2008-09 cost model was inconsistent with these requirements and, as a result, the Department of Health was required to undertake a full review of cost recovery arrangements, update the cost model, and provide these for Government approval. This model and the revised cost recovery arrangements was approved by Government in the 2018-19 Mid-Year Economic and Fiscal Outlook and commenced on 1 July 2019.

The Cost Recovery Implementation Statement (CRIS)[38] provides information on how the Department of Health implements cost recovery for submissions to the PBAC for medicines seeking to be listed on the PBS and for vaccines to be listed on the NIP. Cost recoverable activities from ATAGI processes include providing advice to support the PBAC's evaluation of vaccines for the NIP, including the provision of advice on clinical, technical and implementation matters. Fees for this service were first introduced in mid-2020. For PBAC processes, cost recoverable activities include pre-submission advice provided by the Department to assist applicants in the development of their PBAC submission and evaluation activity to support the PBAC's evaluation of medicines for listing on the PBS and for vaccines on the NIP. Fees for evaluation activity and advice provided to support the PBAC's evaluation of medicines for listing on the PBS have been in place since 2010, while the fee for pre-submission meetings was first introduced in 2019.

There are two types of vaccine submissions - complex and simple. The ATAGI procedures document outlines the criteria for complex and simple submissions (Table 2).

Table 2 – ATAGI pre-submission evaluation activity description[35]

Free Category	Description
NIP: Simple submission	An ATAGI application is in the simple category if the Secretary determines the application is not in the complex category.
NIP: Complex submission	An ATAGI application is in the complex category if the Secretary determines that considering the application will require extensive, or complex, data analysis and review.

In the Cost Recovery Implementation Statement (Table 3), a complex vaccine which is first in class (Category 1) can incur total fees for its first submission of more than $400,000. If a resubmission to the PBAC is required, further costs are incurred.

Table 3 – 2020-21 fees with estimated volumes and revenue for 1st Jan 2021 to 30th June 2021

Charge	Type	Fee from January 2021	Estimated Volume	Est. Revenue for 1 Jan – 30 Jun 2021 ($m)
ATAGI Pre-Submission Evaluation				
Complex Submission	Fee	$180,950	2	$0.27
Simple Submission	Fee	$103,270	2	$0.16
Pre-Submission Meetings				
1st Pre-Submission Meeting	Fee	$15,580	30	$0.47
2nd Pre-Submission Meeting	Fee	$21,180	5	$0.11
Intent to Apply Submissions				
Intent to Apply/Notice of Intent	Fee	$430	144	$0.06
Submission Services (PBAC Evaluation)				
Category 1	Fee	$222,910	8	$1.67
Category 2	Fee	$168,270	24	$4.04
Category 3	Fee	$42,590	17	$0.73
Category 4	Fee	$33,280	16	$0.53
Resubmission - Standard re-entry	Fee	$166,220	12	$2.00
Resubmission - Facilitated resolution pathway	Fee	$238,230	1	$0.24
Resubmission - Early resolution	Fee	$41,400	3	$0.11
Resubmission - Early re-entry	Fee	$41,250	9	$0.37
Secretariat Submission	Fee	$12,300	3	$0.04
Generic Submission	Fee	$6,450	80	$0.52
Independent Review	Fee	$168,270	0	$0.00

PBS Pricing Services				
Pricing Pathway A*	Fee	$140,980	3	$0.35
Pricing Pathway B*	Fee	$111,490	4	$0.45
Pricing Pathway C*	Fee	$73,660	10	$0.70
Pricing Pathway D	Fee	$19,870	13	$0.26
Pricing Secretariat	Fee	$12,740	3	$0.04
PBS List Management Services				
Deed Variations	Fee	$1,970	3	$0.01
Deed Renewals*	Fee	$10,330	11	$0.11
Price Increases	Fee	$5,040	185	$0.93
Ministerial Discretion Request	Fee	$7,040	7	$0.05
Total				**$14.17**

The Intent to Apply/Notice of Intent fee is payable in addition to the fees specified in the table above.

* These fees include the five year rebate management fee of $8,275.

Source: Department of Health. "2020-21-Cost-Recovery-Implementation-Statement-1-Jan-to-30-Jun-2021", https://www.pbs.gov.au/industry/listing/elements/fees-and-charges/2020-21-Cost-Recovery-Implementation-Statement-1-Jan-to-30-Jun-2021.pdf, accessed 10/6/2021.

The procurement processes

The Commonwealth, acting through the Department of Health, has implemented a coordinated vaccine procurement arrangement with the states and territories to secure an assured supply of essential vaccines to the NIP. The NIP operates through the National Partnership on Essential Vaccines (NPEV) between the Commonwealth and states and territories[39]. This arrangement is intended to administer the supply of vaccines in a simple and efficient manner which provides cost savings to the Commonwealth and the states and territories.

Under the NIP, the Commonwealth is responsible for the procurement of all essential vaccines on the NIP, while the states and territories aid the Commonwealth in the tender process and have responsibility for the delivery of the NIP to the community. The supply of essential vaccines is in accordance with the *Commonwealth Procurement Rules* (CPRs)[40], a key principle of which is achieving value for money to provide cost savings to the Commonwealth.

AusTender

AusTender is the Commonwealth Government's procurement information system for all procurement. It manages the centralised procurement of essential vaccines, to support efficiencies in administration and value for money. Tenders are evaluated by a Tender Evaluation Committee against four criteria which include quality, efficacy, and useability of the supplies; manufacture, storage, and delivery of the supplies; and price and risk (see below for criteria weightings). AusTender will issue a Request for Tender (RFT) for the supply of the proposed vaccine where the sponsor company (or companies) can submit tenders to supply the NIP.

The evaluation process comprises the following stages:

Stage 1	***Compliance:*** The receipt and registration of the tender, screening of the tender to determine it complies with requirements.
Stage 2	***Assessment:*** Assessment of the tender against the weighted technical evaluation criteria and identification of risks.
Stage 3	***Price evaluation and overall evaluation of risk:*** Review of the price proposed against pricing criteria and previous PBAC recommendation, together with assessment of the range of risks for government.
Stage 4	***Determination of value for money:*** Evaluation of overall value for money, tender evaluation report, and decision by a delegated government official with the responsibility for approval.

The two weighted[41] technical evaluation criteria in priority order are:

- quality, efficacy, and useability of the supplies, which is weighted at 60% and includes details of any new or emerging data arising since the TGA registration of the vaccine, and
- manufacture, storage, and delivery of the supplies, which is weighted at 40%.

The unweighted evaluation criteria relate to price and risk. In terms of price, the RFT states that "Health's expectation is that prices from the suppliers will be at or below the Nationally Negotiated Price"[42,43]. The NNP that comes out of the HTA process therefore essentially sets a ceiling price for a vaccine, based on cost-effectiveness methodology, to be used in tender and procurement negotiations between the Department of Health and a sponsor company.

There is a specific provision in the Request for Tender document[44] to outline the broader benefits to the Australian economy, which states:

> *"In line with Australian Government policy Health seeks to understand the extent to which the Tender provides an economic benefit to the Australian economy. Accordingly, the Tenderer should detail in its Tender the extent to which the Tenderer contributes to the production of economic benefit to the Australian economy in the provision of the Supplies".*

Note that this request for information about the broader economic impact is focussed on the production of the vaccines themselves in Australia, rather than the broader economic productivity benefits that may arise from a vaccine being administered to the Australian population.

Usually, the company supplying a vaccine will be engaged by the Commonwealth Department of Health and each state and territory under Vaccine Agreements. Each Vaccine Agreement will allow the Commonwealth and each state and territory to obtain supplies by placing orders with the supplier company. The supplier will deliver the vaccines to designated sites where the relevant state or territory will store and distribute them to the eligible cohorts of the community as required.

Under the Australian system, the Commonwealth, through the Department of Health, is responsible for paying a supplying company for vaccines supplied to the NIP under each supply order, including those made by the states and territories. These payments by the Commonwealth on behalf of the states and territories are made up to an agreed Payment Cap. The Commonwealth effectively operates as a payment agent on behalf of the relevant state or territory. Prior to 2010 when the NPEVs commenced operation, states and territories themselves were responsible for directly purchasing vaccines from supplier companies, with the Commonwealth funding states and territories' purchasing activities.

However, Australia's vaccine purchasing for the NIP was centralised with the Commonwealth from 2009 with the introduction of the National Partnership on Essential Vaccines, the first of which ran from 2009- 2016. Today, the states and territories retain responsibility for the day-to-day arrangements and issues related to providing the supplied vaccines to the broader eligible community in their jurisdictions.

Transparency

The Department of Health is required to publish the award of all contracts, agreements and standing offers valued at $10,000 (GST inclusive) or more on AusTender. This includes details to whom the contract, agreement or standing offer was awarded and the contract price.

The Department of Health is also required in accordance with the *Senate Order on Departmental and Agency Contracts* to publish on the Internet with access through their websites, a report listing of all agreements, standing offers and contracts with a value $100,000 (GST inclusive) or more, which has not been fully performed or which has been entered into in the previous 12 months.

3 The benefits of vaccination for the community and the economy

"While the vaccine discovery was progressive, the joy I felt at the prospect before me of being the instrument destined to take away from the world one of its greatest calamities (smallpox), blended with the fond hope of enjoying independence and domestic peace and happiness, was often so excessive that, in pursuing my favourite subject among the meadows, I have sometimes found myself in a kind of reverie."

Edward Jenner, 1749 – 1823, developer of first vaccine (for smallpox)

"Chance favours only the prepared mind."

Louis Pasteur, 1822 - 1895

"In the last 25 years, there has been a 'second-wave' explosion in the availability of new vaccines resulting from protein conjugates, acellular approaches, new molecular strategies and adjuvants."

Terry Nolan, Former Chair ATAGI, 2010[45]

Key points

- Vaccines provided under the NIP and its predecessors have substantially reduced and, in some cases, eliminated the incidence and burden of disease in Australia over many years, including for diseases that imposed substantial burdens on Australian society.
- The NIP has helped deliver childhood vaccination rates of up to 95% for many vaccine-preventable diseases.
- A sample of vaccines supplied though the NIP has provided up to $31 billion in economic benefits to Australia at a cost of $5 billion since their listing, providing substantially positive benefit-cost ratios.
- Calculations of the broader longer-term benefits and costs of vaccines can be affected by the value society places on future benefits and costs.

The development of vaccines and the implementation of immunisation programs are public health interventions that have made an immense contribution to global health. Globally, vaccines prevent more than 20 life-threatening diseases that affect people of all ages and avert 2-3 million deaths per year[46]. Yet, despite tremendous contribution to improving global health, the development of vaccines and their adoption has had its share of challenges[47].

The first serious efforts to develop a vaccine and its use as a public health tool date back to 1796 when Edward Jenner successfully used a cowpox virus to provide immunisation against the smallpox and called this new procedure "*vaccination*"[48]. Evidence suggests that smallpox inoculation was practised in China, Africa, and India as early as 1000 CE; however, Edward Jenner's work was the first scientific attempt to control an infectious disease by using vaccination. Almost one and a half-centuries later in 1958 the World Health Organization (WHO) started its first global smallpox eradication campaign. With decades of intensive effort smallpox became the first and only disease to be completely eradicated in the world, allowing the discontinuation of routine smallpox immunisation globally[49].

During the mid-to-late 19th century Louis Pasteur, while working on fermentation, challenged the two-millennium-old theory of spontaneous generation and furthered the theory of germs[50,51]. Reinforcing germ theory had a tremendous effect in the subsequent two decades as the causative bacteria for leprosy, tuberculosis, diphtheria, cholera, and bubonic plague were discovered, and the emphasis then moved to how to prevent the spread of the disease using new techniques.

Later, Pasteur successfully developed vaccines to prevent fowl cholera in chicken, anthrax in livestock, and erysipelas in swine. However, Pasteur's most notable contribution was the development of the anti-rabies vaccine in 1885, and his work on rabies vaccines led scientific advancement in vaccinology[52].

Since this time many improvements have occurred to the anti-rabies vaccines making this once deadly disease preventable if people are vaccinated on time. Subsequently, other advancements in vaccinology rapidly followed including the development of vaccines for diphtheria, tetanus, anthrax, cholera, plague, typhoid, and tuberculosis. By the mid-20th century vaccines for measles, mumps, and rubella (MMR), and polio had significantly reduced the global burden of disease for these illnesses.

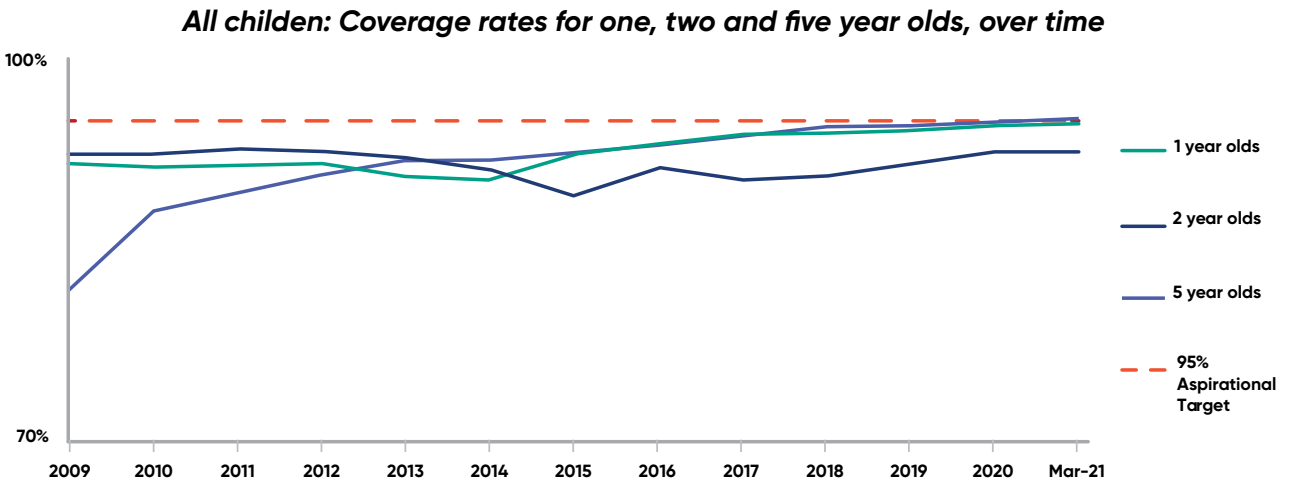
What benefits has the NIP provided to the Australian community so far?

The benefits the NIP and its predecessor programs have provided to individual Australians and the broader Australian community is evidenced by immunisation coverage rates, the impact of individual vaccines on the diseases they are designed to target and the reduction in broader burden of disease across Australian society.

Immunisation coverage

Since its introduction, the NIP has played a central role in improving immunisation coverage in Australia. Childhood immunisation coverage has significantly increased over the last two decades. As at March 2021, coverage had reached rates of 94.91% of 1-year-olds, 92.53% of 2-year-olds and 95.22% of 5-year-olds being fully vaccinated[53] (Figure 2). Reaching the 95% coverage aspirational target for 5-year-olds and almost reaching it for 1-year-olds is a significant public health achievement for Australia. It is testament to the importance of the policies and programs associated with Australia's vaccination program and the NIP.

Figure 2 – Childhood immunisation coverage in Australia, 2009 – March 2021

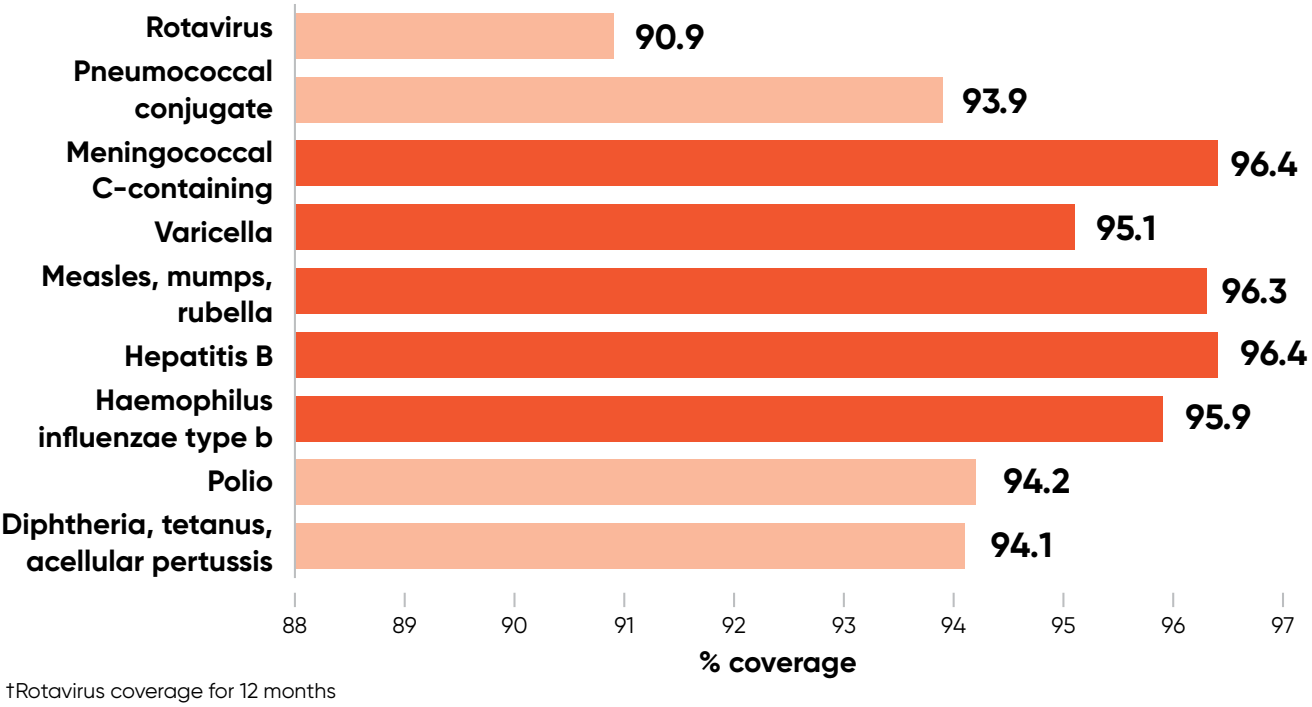


Data for 2009-2020 is at End December quarter. Current quarter data as at 30 March 2021.
Source: Australian Immunisation Register

Source: Department of Health. 2021. "Immunisation Coverage Rates for All Children", May, https://www.health.gov.au/health-topics/immunisation/childhood-immunisation-coverage/immunisation-coverage-rates-for-all-children, accessed 11/6/2021.

The fully vaccinated coverage rate at 12-, 24-, and 60-months in 2018 was estimated to be 93.9%, 90.1%, and 94.0%, respectively. The coverage of individual vaccine/antigen at 60-months was above the recommended 95% coverage for meningococcal C (MenC), varicella, MMR, hepatitis B, and Hib (Figure 3).

Figure 3 – Australian vaccination coverage estimates (%) by vaccine/antigen at 60-months, 2018



†Rotavirus coverage for 12 months

Source: Australian Immunisation Register, data as at 31 March 2018 for 2017 estimates and 31 March 2019 for 2018 estimates. Note: Coverage rates less than 95% are in beige, rates greater than 95% are in orange.

Reduction in the incidence of disease

The success of the NIP is demonstrated by the consistent improvement across a range of immunisation indicators and the fact that diseases such as rubella, tetanus, diphtheria, Hib, and measles are now rare in Australia[54,55]. Various studies over the years have demonstrated the positive impact vaccinations provided under the NIP have had on the Australian population:

- Epidemiological studies assessing the long-term impact of monovalent meningococcal C conjugate vaccine (MCCV) have shown that, after the introduction of MCCV in 2003, with a single dose at 12 months of age and a catch-up at 2-19 years of age, a significant reduction, ranging from 85% to 100% in the incidence of MenC disease was observed[56,57]. Studies have also noted a reduction in the MenC disease incidence in non-vaccine eligible ages (>65 years), through herd immunity, observed 3 to 4 years following the introduction of MCCV in the immunisation program.

- Since 2005, the NIP has included a combined DTPa-HBV-IPV/Hib vaccine against six diseases (diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and Hib) as a three-dose primary vaccination series, given at two, four, and six months of age[58]. A study assessing the 10-year impact of this combined vaccine found that no cases of diphtheria, polio, or tetanus were reported in infants below one year of age and Hepatitis B and Hib remained rare in this age group in the last 10 years.

- A meta-analysis of 36 studies assessing the impact of HBV vaccination reported a 7.3% decrease in the prevalence of chronic hepatitis B (CHB) disease among Aboriginal Australians after implementing HBV vaccination by the NIP in 2000[59].

- Another study examined data on hospitalisation due to varicella and herpes zoster (HZ) infection and compared the trend for before and after the inclusion of HZ vaccine in the NIP[60]. This study found a significant reduction in hospitalisation due to HZ infection in the targeted age group, with the highest reduction noted in children aged 18-59 months, suggesting a substantial impact of the NIP in the reduction of HZ burden.

- The NIP included quadrivalent human papillomavirus (HPV) [4HPV] vaccine in 2007, providing free vaccination for females aged 12-13 years[61]. A systematic review evaluated the impact of 4HPV vaccination on the incidence of genital warts and reported rapid and significant declines in GW incidence in populations below 30 years of age[62].

- A study assessing the indirect impact of pneumococcal conjugate vaccines (PCVs) reported a significant indirect effect of PCVs mediated by reducing the transmission by vaccinated children[63]. The NIP covers the 13-valent pneumococcal conjugate vaccine (13vPCV) in children and adults[64]. A study assessing the benefit of PCV reported a decline in the proportion of community-acquired pneumonia attributable to pneumococcus (both bacteraemic and nonbacteraemic) in Australian adults, providing an incremental benefit of the PCV vaccination program for older adults[65].

- A study reporting the impact of the pentavalent rotavirus (RV) vaccine demonstrated that the burden of RV gastroenteritis had been reduced significantly since the introduction of RV vaccination[66].

Reduction in the burden of disease in Australia

The Burden of Vaccine-Preventable Diseases in Australia study (BVPD study) estimated the burden of VPD in Australia[67]. The study compared the burden of VPD in 2005 and 2015 and found a substantial reduction in the burden for many diseases – such as chickenpox, hepatitis A, hepatitis B, HPV, meningococcal disease, pneumococcal disease, and rotavirus – where vaccines were included (or vaccine eligibility expanded) in the NIP in the last two decades[68]. The trends suggest that the introduction of vaccines in the NIP helped the overall burden associated with these VPD (Table 4).

Table 4 – Comparison of burden due to selected VPD in Australia in 2005 and 2015

Disease	Year vaccine introduced in NIP	Number of cases			DALY per 100,000 population		
		2005	2015	% change	2005	2015	% change
Chickenpox	2005	95,200	55,300	–42↓	1.7	0.4	–75↓
Hepatitis A	2005	1,200	720	–40↓	0.4	<0.1	–75↓
Hepatitis B	Early 1980s for at-risk groups, 2000 for all infants	580	340	–41↓	2.1	1.2	–44↓
HPV	2007 for girls, 2013 for boys	545,600	291,000	–47↓	48.2	15.8	–67↓
Meningococcal disease	2001 for at-risk infants, 2005 for all infants and those aged 65 and over	1,824	1,576	–14↓	20.4	15.1	–26↓
Pneumococcal disease	2003	369	201	–46↓	6.5	2.7	–58↓
Rotavirus	2007	241,000	47,700	–80↓	1.9	0.3	–85↓

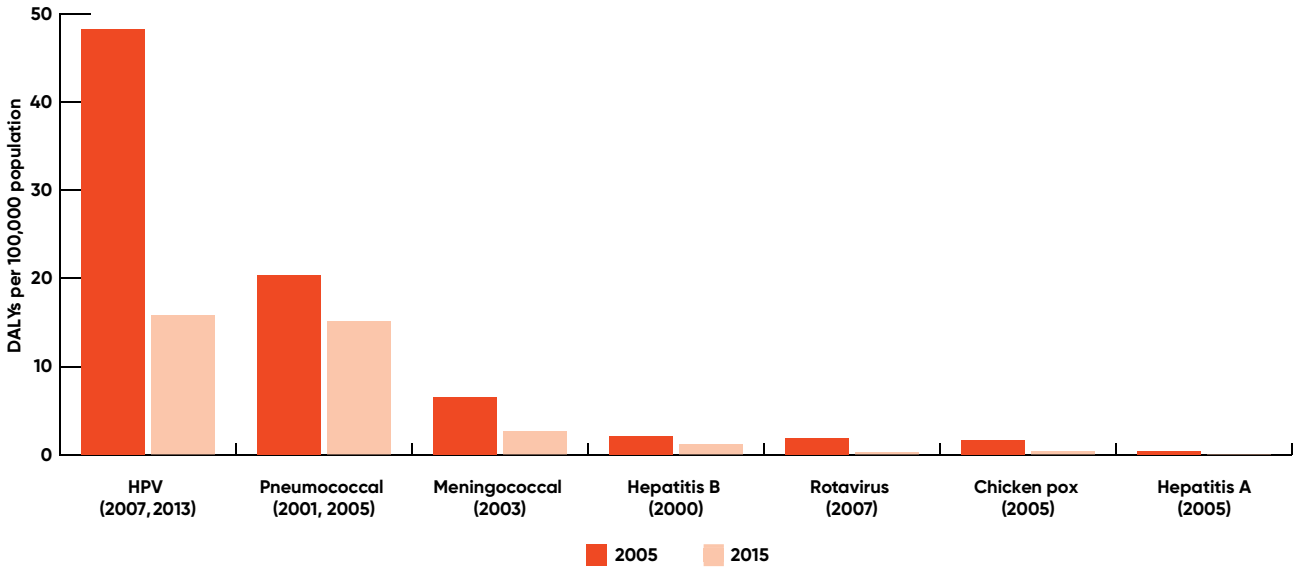
Source: AIHW. 2019. The Burden of Vaccine Preventable Diseases in Australia, November, p. 54, https://www.aihw.gov.au/reports/immunisation/the-burden-of-vaccine-preventable-diseases-in-aust-1/data, accessed 9/4/2021. Rates age-standardised to the 2001 Australian population.

Results provided by the AIHW demonstrate that over the decade to 2015, the numbers of cases of major VPDs have fallen by up to 80% for rotavirus, 47% for human papillomavirus (HPV) and 42% for chickenpox. Similarly, over the same 10-year period significant reductions in DALYs per 100,000 for the Australian population have been seen for major diseases, including 85% reductions for rotavirus, 67% for HPV and 58% for pneumococcal disease.

Consistent with global standards[69], the AIHW measures disease burden through Disability Adjusted Life Years (DALYs). A DALY is a combined measure of the burden of disease that considers years of life lost due to premature death (YLL) and years lived in ill health or with disability (YLD) to measure the burden on the community that results from a disease.

The overall disease burden for a range of VPDs has fallen substantially since the introduction of vaccines for a range of diseases (Figure 4). For example, since the introduction of HPV vaccines in the 2000s to prevent cervical and other cancers, followed by broader HPV vaccines in 2013, the DALY rate in the Australian population for HPV has fallen from 48.2 DALYs per 100,000 of the population in 2005 to 15.8 DALYs per 100,000 by 2015 – a reduction of 67%[70]. Given the previous DALY burden for the population prior to the introduction of HPV vaccines, the sizeable reduction in DALY rate both in percentage terms and overall terms has been substantial over the decade. Other diseases with significant disease burden for Australia – represented by DALYs per 100,000 people – such as pneumococcal disease (26% reduction) and meningococcal disease (58% reduction), have also seen sizeable reductions in disease burden since the introduction of preventative vaccines.

Figure 4 – Burden of Disease Due to Selected Vaccine-Preventable Diseases, Australia, 2005 and 2015



Shawview Consulting Chart. Source: AIHW. 2019. The Burden of Vaccine Preventable Diseases in Australia, November, p. 54, https://www.aihw.gov.au/reports/immunisation/the-burden-of-vaccine-preventable-diseases-in-aust-1/data, accessed 9/4/2021. Number in brackets for each disease is the year vaccination of all children (all indigenous children in high-risk jurisdictions for hepatitis A) was added to the NIP. DALYs is Disability Adjusted Life Years.

The AIHW attributes the major reductions in burden for these diseases to the introduction in vaccines designed to prevent them on the NIP over the time measured. The AIHW notes that the burden from other diseases where vaccines have been widely available for many years, such as diphtheria, measles and rubella is "noticeably small"[71], with measles and rubella being declared eliminated in Australia.

However, other vaccine-preventable diseases (VPDs) have seen their disease burden increase, influenza being a case in point. For example, in 2015 influenza accounted for 5,674 DALYs in total compared to 934 DALYs in 2005, which saw an increase in the DALY per 100,000 population rates for influenza increase from 4.6 up to 21.1 – an increase of 362%[72]. The AIHW explains this increase in the disease burden from influenza being due to increased awareness (both in the medical community and among the public) of the disease and more accessible testing, both contributing to a greater number of notified cases in recent years. This is despite influenza vaccines being available for at-risk groups since 2010. However, a key point here is that NIP coverage of influenza vaccines and community uptake of influenza vaccines for those on the NIP is not high compared to vaccines for other diseases. While groups deemed 'at risk' are covered by the NIP, the working age adult population of Australia is not.

The long view of vaccination: a case study of diphtheria in Australia

A century ago, in 1921, Australia had its highest ever number of deaths due to a major diphtheria outbreak. Diphtheria is an infectious bacterial disease that releases toxins into the body when a person catches it. This toxin infects the upper airways causing a membrane to grow across the windpipe and making it difficult to breathe. If the membrane completely blocks the windpipe this can lead to suffocation and death. The disease can also damage the heart and nervous system.

The first diphtheria vaccines were not introduced into Australia until 1932. The AIHW estimates that 898 Australians died from diphtheria in 1921 which, at a time when the country's population was just under 5.5 million people, meant that the death rate from diphtheria in that year was 16.5 deaths per 100,000 Australian people.

Table 5 — Diphtheria cases, deaths and DALYs in Australian population

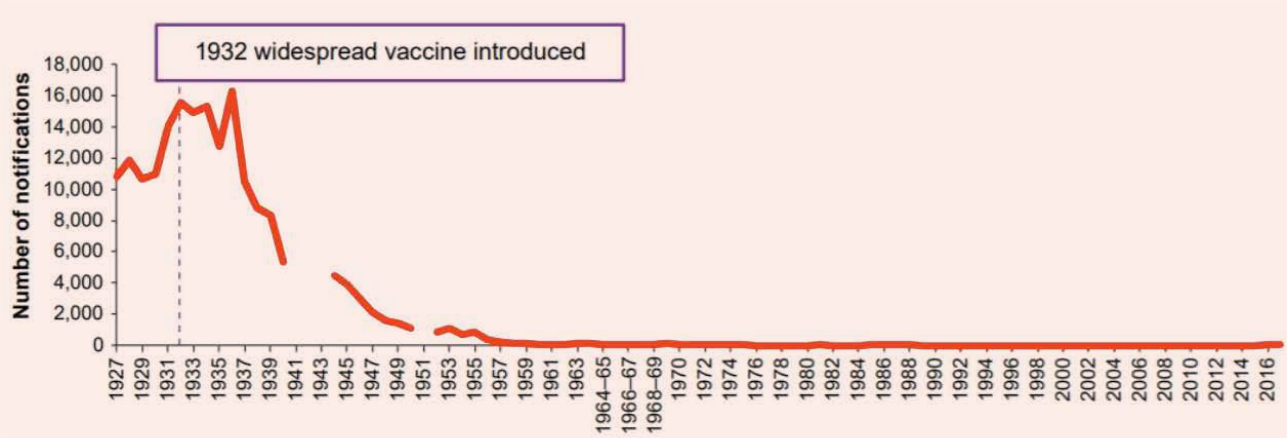
Diphtheria cases, deaths and DALYs in Australian population				
Diphtheria vaccine introduced: 1932	**1921**	**1930**	**2015**	**2021**
Cases		11,894	4	
Deaths	898	403	0.2	
YLL		32,858	14.9	
YLD		43,129	0.02	
Total DALYs		75,987	14.9	
Population	5,455,136	6,462,610	23,815,995	25,693,059
DALYs / 100,000 population		1,176	0.06	
Equivalent cases in today's population			43,832	47,286
Equivalent deaths in today's population			1,485	1,602
Equivalent DALYs in today's population			280,027	302,098

The AIHW has provided a historical comparison of diphtheria rates in Australia between the pre-vaccine period and today. The table above provides a comparison between 1930 and 2015, including years of life lost due to premature death (YLL), years lived in ill health or with disability (YLD) and total disability-adjusted life years (DALYs) as a measure of the burden of disease. Data for Australia's populations at that time has also been included. The table uses data from the AIHW and the ABS.

In 1930, the last full year of data available before diphtheria vaccines were introduced in 1932, Australia recorded 11,894 cases of diphtheria, which included 403 deaths. During that year, Australia suffered a total of 32,858 of years of life lost due to pre-mature deaths plus an additional 43,129 years of disability from diphtheria cases, providing a total burden of disease for Australia from diphtheria in 1930 of 75,987 DALYs, or a rate of 1,176 DALYs per 100,000 of population.

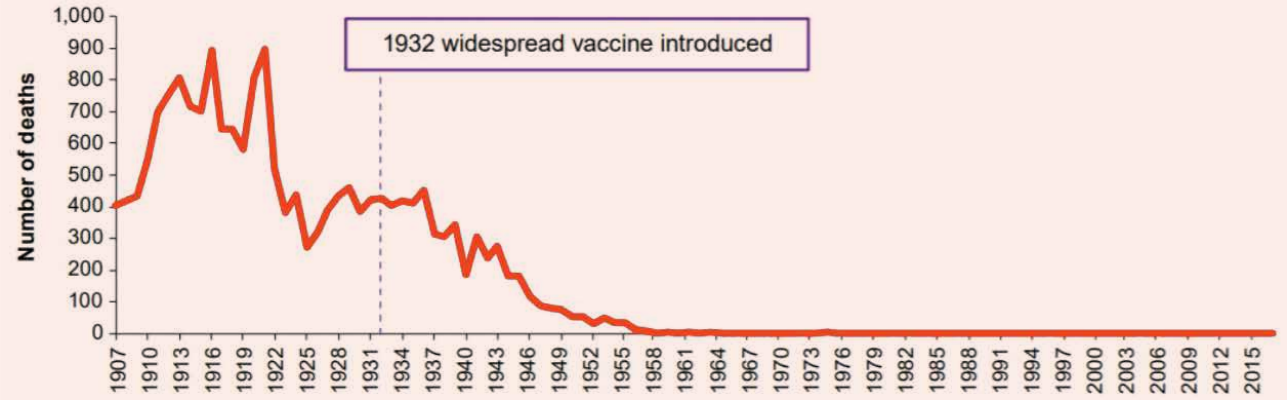
The impact of diphtheria vaccines on the incidence of diphtheria in Australia can clearly be seen in Figure 5 and Figure 6. Australia suffered outbreaks of diphtheria throughout its history until the commencement of vaccination in 1932, where the incidence of diphtheria plummeted substantially soon after their introduction.

Figure 5 – Diphtheria notifications in Australia



Source: AIHW. 2018. Diphtheria in Australia. Fact Sheet. https://www.aihw.gov.au/getmedia/f4c418f9-b4fe-4fb3-84e6-366d5098a8a0/aihw-phe-236_Diphtheria.pdf.aspx, accessed 10/4/2021.

Figure 6 – Deaths from diphtheria in Australia



Source: AIHW. 2018. Diphtheria in Australia. Fact Sheet. https://www.aihw.gov.au/getmedia/f4c418f9-b4fe-4fb3-84e6-366d5098a8a0/aihw-phe-236_Diphtheria.pdf.aspx, accessed 10/4/2021.

One question is: What might be the incidence and disease burden in Australia from diphtheria today if diphtheria vaccines did not exist? While obviously direct comparisons cannot be made due to things like changing demographics and developments in public health systems since the first few decades of the 20th century, indicative comparisons between then and now do demonstrate what the impact of an infectious disease like diphtheria might look like in Australia today.

For example, in Australia in 1930 – prior to the introduction of diphtheria vaccines – there were 403 deaths and a total disease burden of 75,987 DALYs for a population of just under 6.5 million people. Applying those same incidence rates to Australia's population today of 25.7 million people reveal what the equivalent impact would be in terms of today's Australian population.

The results show that were Australia to suffer the same death rate and disease burden from diphtheria today as in 1930, the result would be that diphtheria would account for over 1,600 deaths and a total disease burden of 302,000 DALYs.

To put this into perspective, a disease burden of 302,000 DALYs today would put diphtheria imposing a similar loss of life and disability on the Australian population as currently is imposed by respiratory diseases (357,636 total DALYs in 2015) stemming largely from asthma and chronic obstructive pulmonary disease (COPD), or neurological conditions (346,124 total DALYs in 2015), largely due to dementia.

In effect, the introduction of diphtheria vaccines into Australia in the 1930s would have been the equivalent today of being able to vaccinate away dementia or asthma and COPD.

Taking the comparison one step further, the diphtheria outbreak in 1921 a century ago caused 898 deaths, or 16.5 deaths per 100,000 people. If the same death rate from diphtheria occurred in Australia 100 years later, this would result in 4,229 deaths in 2021. By way of comparison, as of 1 September 2021 there had been 1,006 deaths of COVID-19 in Australia since the beginning of the pandemic in 2020 and prior to the introduction of COVID-19 vaccines.

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Economic modelling of societal, economic and health system impact of the NIP in Australia

In addition to the health benefits for Australians provided by vaccines there have been a range of broader economic and societal benefits stemming from vaccines delivered under the NIP. How these broader societal or non-health economic benefits are assessed and valued in making reimbursement decisions for vaccines is a source of contention (see Section 4).

For this paper, Shawview Consulting commissioned the Victorian Institute of Strategic Economic Studies (VISES) at Victoria University to model the broader economic impacts of several major vaccines listed on Australia's NIP. The results from VISES demonstrate the broader economic effects of several selected vaccines since their introduction on the NIP. The full VISES report with explanation of how the modelling and assumptions is at Appendix F. The summary results are presented in Table 6. Benefit results for vaccines are presented using different discount rate assumptions, however for influenza and rotavirus vaccines, benefits and costs were not modelled using different discount rates on the assumption that the benefits and costs of these vaccines are contained within one calendar year. See Section 4 for more on the economics of discount rates.

The highest benefit-cost ratios are provided by vaccines for HPV, which is consistent with the reductions in disease burden observed in DALYs lost calculated by the AIHW (see previous section). The substantial societal and economic benefits from HPV vaccination come from lives saved, leading to greater production and wages over the course of a person's life for someone who would otherwise die from cervical and other cancers.

Rotavirus vaccines show a similarly high benefit relative to costs, largely due to the inclusion of savings in caregiver costs from parents of children not being required to stay home from work due to their child's illness. Influenza vaccines also have high benefit-cost ratios due to hospital costs avoided for people 65 and older and avoided productivity losses due to young children not being required to be looked after by their working parents when sick. Note that the productivity benefits for influenza vaccines on the NIP do not apply to working age adults because the NIP does not provide free influenza vaccines to all people this population cohort (age 18 - 64 years old)[73]. The NIP provides free influenza vaccines only provided to those Australians aged 64 and under considered at risk, around 2.2 million people.

Another example is meningococcal vaccines which provide significant benefits in the form of productivity benefits from deaths and disability avoided, as well as ongoing medical costs saved. At higher discount rates, meningococcal vaccines outperform rotavirus vaccines in terms of non-health benefits generated for the economy. In net present value terms, meningococcal vaccines provide between $1.9 billion and $5.5 billion per year in economic benefits with benefit-cost ratios between 2.4 and 5.2.

Table 6 — Economic benefits, costs and benefit-cost ratios of top 5 vaccines on NIP

Vaccine		Discount rate (%)		
		5.0	**3.5**	**1.5**
Meningococcal	Benefits ($m NPV)	1,933.8	2,909.6	5,511.6
	Costs ($m NPV)	802.5	903.7	1,069.9
	Benefit-cost ratio	2.4	3.2	5.2
Pneumococcal	Benefits ($m NPV)	1,224	1,432	2,022
	Costs ($m NPV)	939	939	939
	Benefit-cost ratio	1.3	1.5	2.2
Rotavirus	Benefits* ($m NPV)	2,522.3	2,522.3	2,522.3
	Costs ($m NPV)	561.5	561.5	561.5
	Benefit-cost ratio*	4.5	4.5	4.5
HPV	Benefits ($m NPV)	2,884	5,523	13,794
	Costs ($m NPV)	354	392	453
	Benefit-cost ratio	8.2	14.1	30.4
Influenza >65 yrs	Benefits ($m NPV)	5,773.5	5,773.5	5,773.5
	Costs ($m NPV)	1,700.5	1,700.5	1,700.5
	Benefit-cost ratio	3.4	3.4	3.4
Influenza <3 yrs	Benefits ($m NPV)	1,229.1	1,229.1	1,229.1
	Costs ($m NPV)	226.0	226.0	226.0
	Benefit-cost ratio	5.4	5.4	5.4
TOTAL	Benefits ($m NPV)	15,566.7	19,389.5	30,852.5
	Costs ($m NPV)	4,583.5	4,722.7	4,949.9
	Benefit-cost ratio	3.4	4.1	6.2

* Note: Includes savings of care giver costs. If care giver costs are excluded, Benefits $1,186.2m NPV, Costs $561.5m, Benefit-cost ratio: 2.1. Results largely insensitive to discount rate used. Inclusion or otherwise of reductions in care giver costs is key influence on benefit-cost ratio. Source: Shawview Consulting analysis and modelling by VISES. Victorian Institute for Strategic Economic Studies. 2021. Vaccine Study: Benefit Cost Analysis, Report prepared for Shawview Consulting, 16 April (see Appendix F). Note: Modelling impact of different discount rates for influenza and rotavirus vaccines was not conducted as it was assumed that the impact of these vaccines largely lasts within the course of one calendar year or because discounting costs was not feasible.

The table presents VISES modelling for the selected vaccines using different assumptions about discount rates in most cases. Discount rates are essentially the rates used to discount or devalue future benefits and costs in the long-term to bring estimated future benefits and costs into net present value terms in today's dollars (see Section 4). The sensitivity analysis shows that in several cases the assumption made about which discount rate to use has substantial impacts particularly on the broader benefits of NIP vaccines and their benefit-cost ratios. For example, for HPV the use of a 3.5% discount rate currently used by National Institute for Health and Care Excellence (NICE) in the United Kingdom leads to a benefit-cost ratio of 14.1, whereas a discount rate of 5% – the standard used by Australia's PBAC – leads to a benefit-cost ratio of 8.2 and a discount rate of 1.5% delivers a benefit-cost ratio of 30.4, all for essentially the same clinical

outcome. Note that NICE, while historically using a 3.5% discount rate compared to the PBAC's 5%, is proposing to lower its discount rates to 1.5% and already uses 1.5% discount rates in some cases where benefits of a treatment accrue over the long-term.

Finally, the totals for these vaccines can be calculated showing their overall benefits and costs and their benefit-cost ratios. Briefly, the results for these five vaccines shows that for a 5% discount rate the broader benefits provided to the economy are more than $15.6 billion since these vaccines were introduced, for a total cost of $4.6 billion. At a 3.5% discount rate, the total cumulative economic benefit of vaccines for these five diseases was $19.4 billion for a cost of $4.7 billion since their introduction. If a 1.5% discount rate is assumed, the cumulative benefit to the economy of vaccines for these five diseases is $31 billion for a cost to society of $4.9 billion. Similarly, the benefit-cost ratio of the vaccines introduced to prevent these five diseases is 3.4, 4.1 and 6.2 respectively depending on discount rates assumed.

Several points emerge from this analysis. First, overall, the vaccines modelled here by and large generate broader economic benefits to society often several times larger than the costs of those vaccines. In the vaccines modelled here, collectively they provide benefits between three to six times their costs. Second, some vaccines generate much larger benefits to society than others relative to their costs. This will be a function of things such as the risk of serious illness and disease for the population with vaccination compared to non-vaccination, the age of those people avoiding death and disability and the extent of the disease in society. Third, the decision of which discount rate to assume for the calculations of vaccine benefit and cost can have a quite substantial impact on the broader economic benefit-cost ratio and, therefore, the accepted economic value of a vaccine. A discussion of the issues concerning discount rates assumed in Australia compared to other countries is discussed in Section 4.

4 Issues in Australia's vaccine funding process

"In recent years, academics and policymakers have increasingly recognized that the full societal value of vaccination encompasses broad health, economic, and social benefits beyond avoided morbidity and mortality due to infection by the targeted pathogen and limited health care costs. Nevertheless, standard economic evaluations of vaccines continue to focus on a relatively narrow set of health-centric benefits, with consequences for vaccination policies and public investments."

David Bloom, Daniel Cadarette & Maddalena Ferranna, 2021[74]

"The greater problem that might be posed by centralisation is in the longer term if manufacturers fear that R&D into new and improved vaccines will not be rewarded adequately, i.e., if they fear short-sighted opportunistic behaviour by a centralised purchaser unwilling to recognise and pay for the sunk costs of producing vaccines."

Office of Health Economics, The Publicly Funded Vaccines Market in Australia, 2010[75]

Key points

- Not all vaccines recommended by ATAGI for listing on the NIP are funded, in large part because Australia's system of cost-effectiveness evaluation does not fully value vaccines.
- Australia's health technology assessment framework has led to problems in valuing vaccines, particularly with respect to vaccines' incremental cost-effectiveness, broader productivity benefits and longer-term time horizons.
- Australia's system differs from that of many other countries by requiring ATAGI to advise the health technology assessment body, the PBAC, on NIP listings rather than making such recommendations directly to government.
- The centralisation of funding and expenditure of the NIP with the Commonwealth government since 2009 has worked to limit growth in NIP expenditure since that time.
- In recent years the Commonwealth's approach to procurement of NIP vaccines has perhaps focussed too much on managing short-term costs and lacked a strategic preventative plan to develop longer-term supply and business relationships with industry.

Australia's system of evaluating vaccines for public funding has similarities with other high-income countries' systems. Many countries have an expert committee that recommends vaccines for public subsidy on a separate formulary, using some sort of recommendation or assessment process to decide on the most appropriate mix and use of vaccines for their country's population.

While similar to many countries, Australia's system does have several unique characteristics. The requirement that vaccines be assessed by the same HTA agency that assesses medicines – the PBAC – is unusual compared to other countries. In many countries, the assessment and recommendation on whether to purchase a vaccine is made by a separate, dedicated expert committee[76]. This is essentially the system Australia had up until 2005 when ATAGI NIP recommendations were subsumed under the PBAC umbrella and required ATAGI to advise the PBAC rather than advise the Minister directly on NIP funding.

There are several issues that emerge in the evaluation of vaccines for public funding that can potentially affect the number, extent and timing of vaccines on the NIP in Australia. The overlay of the PBAC's HTA framework over the decision making on funding vaccines has presented a number of methodological and health economic issues with policy implications for Australia. While many of the issues may affect medicines more generally as much as vaccines, vaccines can be particularly affected by certain decision frameworks, assumptions and values in the evaluation process. This is due to vaccines' impact on public health, their preventative effects as opposed to treatment or curative effects, broader societal effects and their longer lead time for community protection in ways that can be different from other medicines.

Vaccines recommended by ATAGI but not funded by NIP

Evidence that there are issues in Australia's system of evaluating and funding vaccines starts with the discrepancy between what the Commonwealth funds under the NIP and what vaccination ATAGI recommends for the community. There are a range of vaccine indications that ATAGI has recommended but that are not funded under the NIP (Table 7).

For example, currently the vaccine, Bexsero®, for preventing Meningococcal B (Men B) in the general population is not funded on the NIP despite its recommendation by ATAGI and repeated attempts by the sponsoring companies to have the vaccine listed on the NIP (see Case Study: Bexsero®). A second booster shot for varicella (chicken pox) vaccine in adolescents has also been recommended for some time but not funded. Outstanding recommendations also exist for Meningococcal A, C, W and Y for infants and older adolescents. Bexsero® is a particular case in point, as the sponsor companies for this vaccine made four submissions to PBAC for this to be funded under the NIP for the general non-indigenous Australian population and these have been repeatedly unsuccessful.

Annual influenza vaccination is also recommended for all non-Indigenous Australians aged 6 months or older, however the NIP only funds free vaccination for children aged 6 months to less than 5 years old, those greater than 5 years old with certain medical conditions predisposing them to severe influenza, pregnant women and adults greater than 65 years old. All Aboriginal and Torres Strait Islander people are eligible for free annual influenza immunisation under the NIP.

Table 7 — List of vaccines recommended by ATAGI for non-indigenous Australians but not funded by NIP

Disease/vaccine antigen	Abbreviation	ATAGI recommendation category	Recommendation pertains to a population sub-group
Hepatitis B	HepB	12 months of age	Yes
Diphtheria, tetanus, pertussis	DTPa/dTpa	Adults 65 years	No
		Post-partum	Yes
Measles, mumps, rubella	MMR	Adults	Yes
		Post-partum	Yes
Varicella	VV	4 years of age Adolescent Adults	No Yes
Meningococcal serogroup B	MenB	At birth to 18 months of age 15–19 years of age	No No
Meningococcal serogroup ACWY	MenACWY	2–6 months of age	No
Influenza annual	QIV	All people 5 years to <65 years of age	No
Herpes zoster	HZ	Adults 60 to 69 years of age, adults =<80 years of age	No

DTPa: Diphtheria-tetanus-acellular pertussis vaccine (paediatric formulation); dTpa: Diphtheria-tetanus-acellular pertussis vaccine (reduced antigen formulation); Meningococcal serogroup ACWY conjugate vaccine; MenB: Meningococcal serogroup B vaccine; MenACWY: Meningococcal serogroup ACWY; MMR: Measles-mumps-rubella vaccine; HepB: Hepatitis B vaccine; VV: Varicella vaccine

Description
A booster dose of hepatitis B vaccine is recommended at 12 months of age for infants who were born preterm at <32 weeks gestation or whose birth weight was <2,000 g, unless a blood test 1 month after the final dose of the primary course showed an anti-HBs antibody titre of ≥10 mIU/mL.
dTpa vaccine is recommended for any adult who wishes to reduce their likelihood of becoming ill with pertussis. Adults aged ≥65 years are recommended to receive a dose of dTpa if they have not had one in the past 10 years. Adults aged ≥50 years are recommended to receive a booster dose of tetanus-containing vaccine if their last dose was more than 10 years ago. Adults with tetanus-prone wounds are recommended to receive a booster dose of dT or dTpa if their last dose was more than 5 years ago.
If a mother was not vaccinated during pregnancy, maternal vaccination is recommended as soon as possible after birth and preferably before hospital discharge.
2 doses of MMR are recommended for adults born during or since 1966, unless the individual is documented to be immune. MMR vaccine is strongly recommended for women of child-bearing age who are seronegative for rubella. Vaccinated women should avoid pregnancy for 28 days after vaccination.
2 doses of varicella vaccine are recommended for all adults who are non-immune to varicella. Non-immune women are recommended to receive varicella vaccine before they become pregnant.
A 2nd dose of varicella vaccine is recommended to provide increased protection and minimise the chance of breakthrough varicella in children and adolescents <14 years of age. This could potentially be given at 4 years of age, or at any time up to 14 years of age (at least 4 weeks after the 1st dose). 2 doses of varicella vaccine are recommended for all adults who are non-immune to varicella. Non-immune women are recommended to receive varicella vaccine before they become pregnant.
MenB vaccine is recommended for all people ≥6 weeks of age who wish to reduce the likelihood of becoming ill with meningococcal disease, and is strongly recommended for infants and children aged <2 years and adolescents aged 15–19 years. Bexsero is the only MenB vaccine that can be used in infants and children aged <10 years. The doses required and the schedule depend on the age at which the vaccine course is started and the presence of at-risk medical conditions.
MenACWY vaccine is recommended for all people ≥6 weeks of age who wish to reduce the likelihood of becoming ill with meningococcal disease, and is strongly recommended for infants and children aged <2 years and adolescents aged 15–19 years. The doses required and the schedule depend on the age at which the vaccine course is started, the brand used, and the presence of at-risk medical conditions.
Influenza vaccine is recommended annually for all people ≥6 months of age who wish to reduce the likelihood of becoming ill with influenza. Influenza vaccine is funded under the NIP for all children ≥6 months to 59 months (<5 years) of age, people ≥5 years of age with certain medical conditions predisposing them to severe influenza. For older people aged ≥65 years, the adjuvanted quadrivalent influenza vaccine (aQIV, Fluad Quad®) is funded under the NIP and is preferentially recommended over standard QIV. The QIV is funded under the NIP for adults with a medical condition that predisposes them to severe influenza; pregnant women; non-Indigenous adults aged ≥65 years.
A single dose of herpes zoster vaccine is recommended and funded under the NIP for adults aged 70 years (with a NIP-funded catch-up dose available for adults aged 71–79 until 31 October 2021). A single dose of herpes zoster vaccine is recommended (but not NIP-funded) for adults aged 60–69 years and ≥80 years.

Source: Shawview Consulting analysis based on National Centre for Immunisation Research and Surveillance. 2020. "Immunisation recommendations for Non-Indigenous Australians without risk factors for vaccine-preventable diseases", 1 July, https://ncirs.org.au/sites/default/files/2020-06/NCIRS%20Immunisation%20schedule%20for%20non-Indigenous%20people_1%20July%202020_Final.pdf, accessed 31/5/2021.

These funding gaps have led to circumstances where state governments have decided to go ahead and fund programs where the Commonwealth has not funded them through the NIP. For example, the South Australian state government has funded[77] the full program of Meningococcal B vaccines for all children and adolescents in that state since 2018 and has noted[78] that the Commonwealth does not fund it. Similarly, the Victorian state government notes that it funds several vaccines that are not available through the Commonwealth-funded NIP[79].

In fact, there is a pattern of examples where state and territory governments have funded ATAGI recommended vaccines, sometimes for years, before they are funded by the Commonwealth through the NIP[80]. Examples of these include influenza vaccination in children in most states and territories before NIP funding in 2020, funding of hepatitis A vaccines for Queensland indigenous children by the Queensland state government before NIP funding in 2005 and funding of pneumococcal vaccination for Victorians aged 65 and older by the Victorian state government between 2001 and 2004.

There are also a range of adult vaccinations recommended by ATAGI that are not funded through the NIP, suggesting that there are issues in the acceptance of adult vaccination which are likely to only grow with emerging technologies in adult or whole-of-life vaccination in the future.

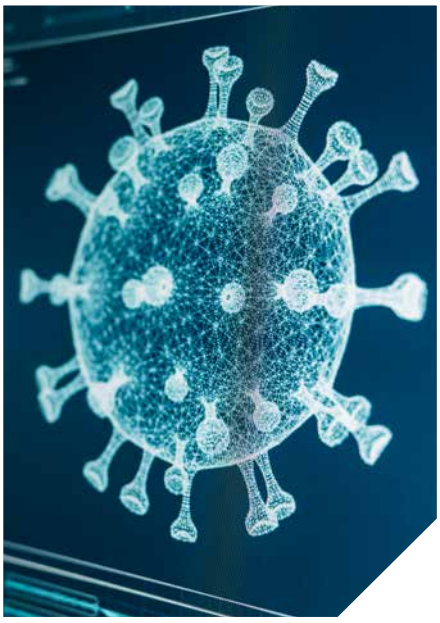
Factors formally considered in Australia's evaluation of vaccines

In making assessments and recommendations on vaccines for funding under the NIP and the PBS, the PBAC takes a range of factors into account. As with medicines intended for the PBS, the PBAC Guidelines provide guidance to companies on applications for listing vaccines on the NIP. The Guidelines contain a dedicated section for vaccines[81] on vaccine-specific issues, together with vaccines being considered under the standard provisions of the PBAC Guidelines[82].

When considering vaccines, as well as medicines more generally, the PBAC endeavours to assess a range of factors raised in the Guidelines including:

- *Narrow health effects* – these are the direct health outcomes affecting an individual patient or person in the community who is immunised. The types of economic measures that can be considered here can include medical events avoided, life-years gained, quality-adjusted life years and so on.

- *Broader community health effects* – relating to health-related outcomes benefits for people other than the patient receiving treatment. This includes things such as the overall burden of disease for society reflecting the overall morbidity and mortality associated with the disease, the impact on the quality of life of carers, decreased carer burden, impact on herd immunity[83] in the community and potential reductions in the transmission of the disease in the community. Importantly, whilst the PBAC says it may accept these analyses in a submission, the onus is on submitting companies to decide whether to provide these outcomes. Companies are advised this data should be presented as supplemental analysis and not to be included in the base-case analysis submitted for consideration.



- *Financial impact, equity and disease resistance* – this includes the projected net financial implications for the NIP over six years, together with any cost offsets for any likely reduction in usage of other medicines. Equity issues and any factors related to disease resistance can be considered. Such equity and ethical issues, including age or socioeconomic and geographical status, may result in targeted coverage of a particular vaccine on the NIP to a subset of the population or disadvantaged socio-economic group.

- *Broader health system economic effects* – Cost offsets to the health care systems may be included in a company's submission and may cover things such as the lower healthcare resource utilisation by an individual person who is immunised against a particular disease and the decline in overall healthcare resource utilisation at the community level due to herd immunity or reduction in outbreaks of infectious disease.

- *Broader societal economic effects* – Companies are permitted in submissions to include analysis of non-health outcomes. This may include things such as productivity gains due to patients gaining or losing working time as a result of improvement in health and consequent work capacity. However, the Guidelines provide relatively limited guidance on how to account for the impact of a vaccine on things like the productivity of carers and overall macroeconomic effects. Importantly, companies are advised to present the non-health outcomes as supplemental analysis, and not to include them in the base-case analysis.

Issues in the practice in the evaluation and funding of vaccines in Australia

While the processes and guidelines for evaluating and funding vaccines in Australia provide an official indication of what *may* be considered in forming recommendations, the extent to which each of these factors will meaningfully influence a decision and recommendation by the PBAC will vary.

In practice, some of these factors, such as individual health outcomes and health system cost offsets, will be given greater importance or weight in a decision than other factors, such as the impact on disease resistance, transmission and broader non-health societal or economic impacts. This higher weighting for some factors over others and the lack of consideration of these factors has been documented elsewhere[84].

While these issues may affect all medicines and therapies, vaccines can be a particular example where the broader health, societal and economic benefits of treatments over the longer-term may disadvantage their appraisal and lead to delays or rejections in funding. These issues are not entirely unexpected. Even the (then) Department of Health and Ageing itself had identified and admitted these emerging problems at the beginning of the 21st century. In its submission to a Productivity Commission inquiry in 2005, the Department reportedly argued to the Commission that vaccine funding was likely to become more difficult:

> *"The Department of Health and Ageing (DoHA, sub. 34) argued that future funding decisions regarding vaccines are likely to become progressively more difficult, observing the trend towards purchasing increasingly expensive vaccines. Unlike older vaccines, which target common diseases and tend to be lower cost, newer vaccines are targeted at individuals with rarer conditions such as meningococcal C"*[85].

The role that traditional HTA frameworks, such as that used by the PBAC, play in undervaluing public health initiatives is particularly demonstrated in the case of vaccines. There are several issues in the HTA framework used by the PBAC which may undervalue and therefore delay the introduction of vaccines to the NIP.

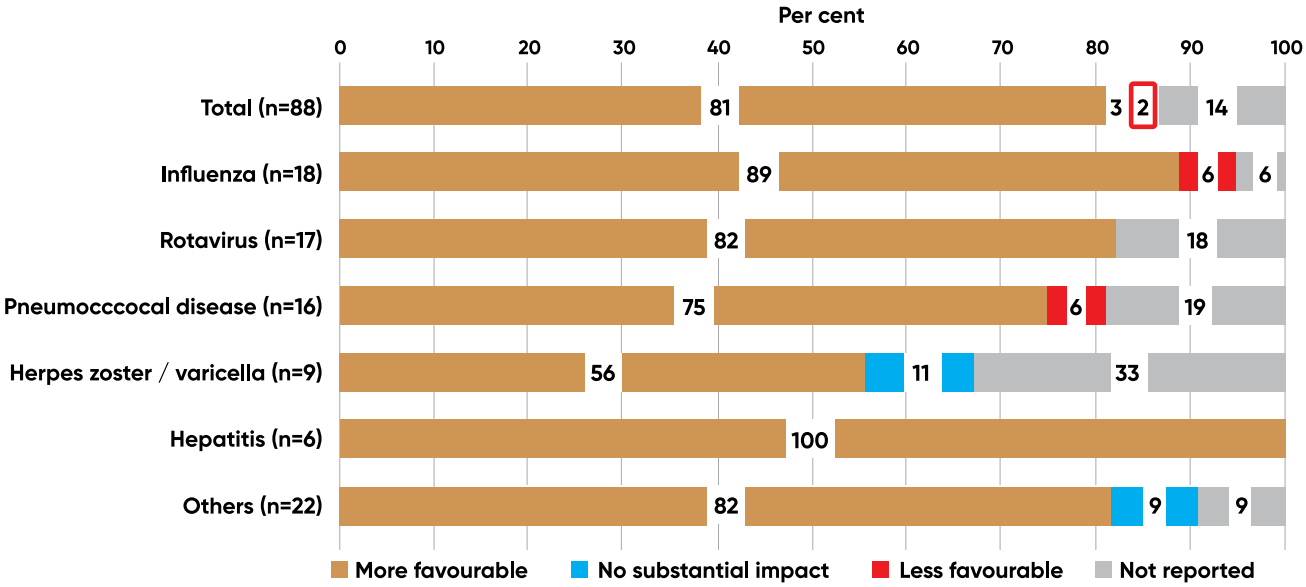
Broader societal benefits of vaccines not sufficiently valued

While in principle the PBAC Guidelines permit the inclusion of broader societal and non-health economic benefits of vaccines in submissions, in practice the PBAC has found it difficult to deal with and accept such claims by companies. The Committee has tended to dismiss or downplay them. The PBAC's insistence over many years that such analyses be included in supplementary evidence of a submission, rather than the base case, is evidence of the difficulty the Committee faces in accepting such evidence. For example, the first submission to the PBAC for a rotavirus vaccine, Rotateq®, in July 2006 was rejected by PBAC because, amongst other reasons, the sponsor company had included in the base case analysis of the vaccine's effect the production gains resulting from parents not needing to look after their sick children. PBAC at the time commented: "The PBAC indicated that non-health gains have not been accepted previously in PBS submissions as base-case analyses for decision making purposes"[86].

There has been international concern expressed that typical, narrower approaches to HTA that do not include broader productivity benefits risk undervaluing vaccines. While declining to give serious consideration to broader productivity benefits can disadvantage a range of treatments, vaccines particularly suffer from such an approach due to the long-term benefit vaccines provide over the course of a person's life and across a broader population. Benefits vaccines provide, such as preventing complications of other diseases stemming from VPDs, generating health and productivity gains for caregivers and generating herd immunity to diseases in the broader community, are examples of vaccine benefits that are under-valued or de-prioritised under a standard HTA framework[87]. Standard QALY-based HTA systems as used by the PBAC have difficulties in incorporating the full benefits of vaccines, like herd immunity, into their assessments[88], which tends to undervalue vaccines.

A study by Yuasa et al[89] demonstrated that incorporating the benefits of avoiding productivity losses through vaccination generally leads to a more favourable ICER for vaccines, making them more cost-effective, while excluding broader productivity benefits from a cost-effectiveness evaluation generally leads to a less favourable ICER for vaccines, making them less cost-effective (Figure 7).

Figure 7 — Impact on ICER on cost-effectiveness of vaccines by including productivity gains



Shawview Consulting chart. Data source: Yuasa, A., Yonemoto, N., LoPresti, N. & Ikeda, S. 2021. "Productivity loss/gain in cost-effectiveness analyses for vaccines: a systematic review", Expert Review of Pharmacoeconomics & Outcomes Research, 21:2, 242, https://doi.org/10.1080/14737167.2021.1881484, accessed 22/4/2021. 'More favourable' means ICER falls/becomes more cost-effective on inclusion of productivity costs, 'No substantial impact' means no substantial impact on ICER, 'Less favourable' means ICER rises/becomes less cost-effective.

The PBAC Guidelines themselves assert that such broader productivity benefits to the economy can be difficult to measure:

> *"If presenting productivity claims associated with a proposed medicine, there are several difficulties in estimating the net present value of production changes. From a societal perspective, the productivity of an individual worker cannot be considered in isolation, but should be considered in the context of a workplace, a workforce and society. The following three underpinning assumptions should be incorporated into all productivity analyses:*
>
> - *For short-term absence, production will be made up on return to work.*
> - *Employers usually have excess capacity in the labour force to cover absenteeism.*
> - *For long-term absence, production will be made up by a replacement worker who would otherwise be unemployed"*[90].

The extent to which PBAC should take 'replacement workers' into account in downplaying productivity benefits was criticised in 2005 by the Productivity Commission which stated that this was "not a robust argument for discounting gains in productive capacity"[91]. While the current PBAC Guidelines are a step forward from earlier versions of the Guidelines which stated that "Such analyses are not likely to be helpful to PBAC in its deliberations"[92], the experience of some vaccines progressing through the PBAC system in that time has demonstrated that such productivity benefits of vaccines are either undervalued or are not well appreciated by the PBAC.

In the Australian context, several submissions have pointed to the PBAC's de-prioritisation of broader indirect productivity benefits as a problem to assessing the full value of vaccines. As a paper on vaccines in Australia commissioned by GSK notes that:

> *"Such costs can currently be included in supplementary analyses, however these analyses do not inform the agreed costs upon which the PBAC recommendation is made. This paper proposes that the PBAC use its appropriate authority and flexibility to include such costs in the base case analyses where relevant to the specifics of the intervention under review"*[93].

Longer term, the same report recommends that the methodologies PBAC use to review vaccines be reconsidered in the context of international developments in options of HTA for vaccines. Similar points have been made by other pharmaceutical companies in Australia[94]. There are examples where vaccines have initially been rejected by PBAC and delayed precisely due to the Committee's policy of not including productivity costs and benefits in the base case.

There has been some debate over the years whether Australia's HTA system can manage these broader societal issues that are particularly relevant to vaccines. For example, in explaining their view of the Australian system, Mitchell et el argue that Australian HTA system through the PBAC can cope with herd immunity effects and that "If data subsequently show that herd immunity exceeds expectations, or even eradicates a disease, there are mechanisms for manufacturers to request an increased vaccine price"[95]. In practice, this is highly unlikely to occur, largely because it is highly unusual for PBAC to award a pharmaceutical company an *increase* in the price of a medicine or vaccine once it has already been listed on the PBS or NIP.

Use of real-world evidence

With developments in data technology and the growth of information-and data-rich health systems, the use of real-world evidence, as opposed to evidence coming out of pre-market clinical trials, has becoming increasingly accepted to evaluate the impact and benefit of medical technologies. Historically, however, the PBAC has tended to downplay the value of such real-world evidence in its evaluations, perhaps due to concerns about the validity of such evidence. There is a need to both upgrade the acceptability of real-world evidence in PBAC decision making and ensure that Australia's health data systems are sufficiently strong to provide this data[96].

For vaccines, this presents issues given the various after-listing effects and benefits of vaccines. Impacts such as broader productivity and workforce benefits for the economy, herd immunity being achieved over time and the elimination of disease in the community require an ability measure these in the population post-trial/post-listing and an acceptance that such real-world, population-level data is valid and robust.

Internationally, the use of real-world evidence in evaluating the effectiveness of vaccines is seen as increasingly important. Recent examples where real-world evidence has been used to evaluate the effectiveness of vaccines include vaccines for influenza, meningococcal disease, vaccines administered to pregnant women and COVID-19 vaccines[97]. However, there have been several examples in Australia where vaccines seeking NIP listing have been rejected in part due to the PBAC's reluctance to accept the use of real-world evidence in assessing vaccines for things like meningococcal B, HPV and influenza (see case studies in Appendix A).

Discount rates in Australia and internationally

The economic evaluation of health technologies applies discounting to reflect the present value of future costs and health effects[98]. The rate at which discounting is applied in an economic evaluation can have significant implications on the final outcomes and resulting decision on whether to fund a medical technology. This becomes particularly important for interventions such as vaccines where large proportions of the health benefits are realised in the distant future rather than in the immediate present[99].

The Productivity Commission's 2005 review of the impact of medical technology on Australia identified that the discount rate used in Australian evaluations may pose a problem for vaccines in the future, particularly with the onset of new types of vaccines emerging:

> *"Vaccines may also pose a challenge for health technology assessment (HTA) processes – as new types of vaccines are expected to primarily deliver benefits in the longer-term, a question arises as to what is the appropriate discount rate to apply to these benefits"*[100].

The Commission had therefore recognised that new vaccine technologies, together with their targeted nature and questions of effectiveness in particular population subgroups, could be affected by the assumptions made about an appropriate discount rate in Australia. For example, in rejecting one submission for MenB vaccine Bexsero®, the PBAC noted that differential discount rates were not to be used to evaluate vaccines and that 5% discount rates were the preferred discount and what should be applied to vaccine submissions[101].

Globally, a typical discount rate of 3% is applied for both cost and outcomes as per the respective guidelines[102]. The current guideline from the 2nd panel on Cost-Effectiveness in Health and Medicine recommends a discount rate of 3% for both costs and health outcomes[103]. International studies generally associate discount rates in health care of 5% to be associated with low-income developing countries[104]. Moreover, the World Health Organization suggests

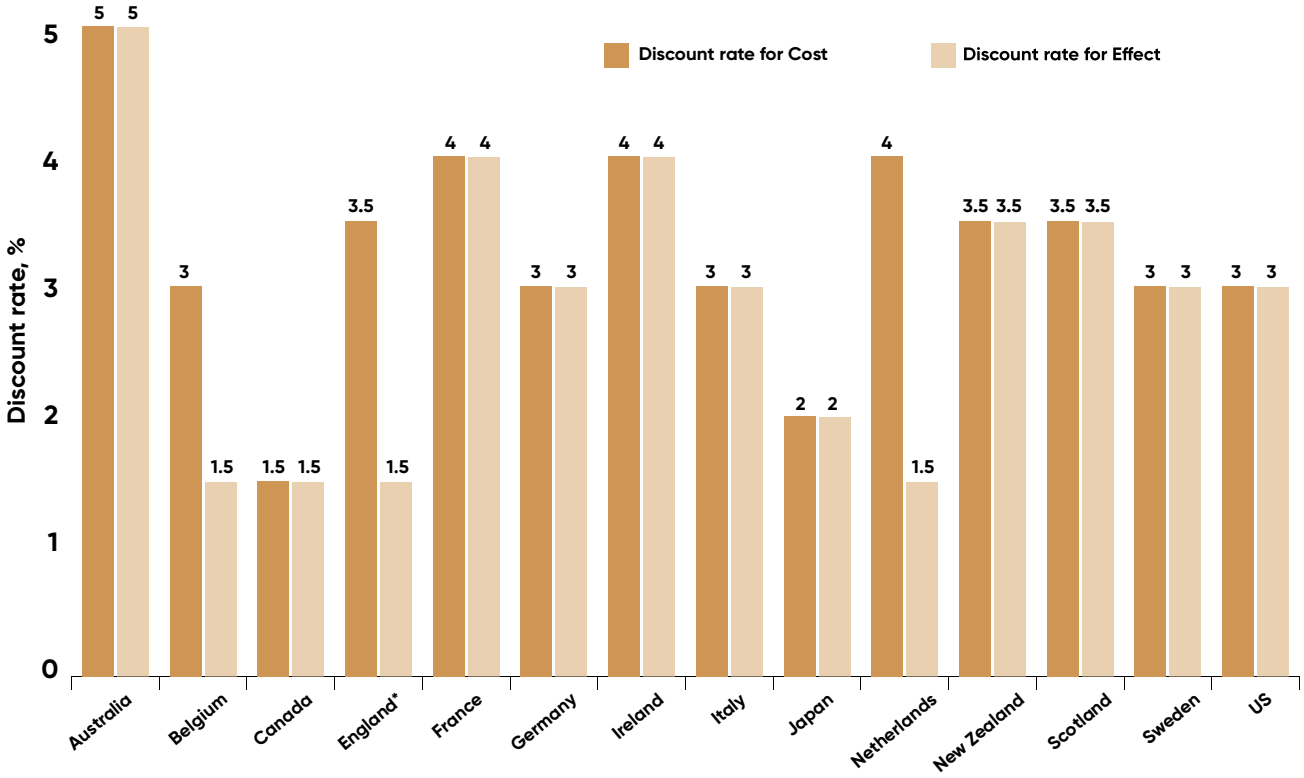
that evaluation agencies should include analyses using discount rates of 3% and 0% when doing economic evaluations of vaccines[105].

The standard discount rate used by the PBAC in Australia is 5% applied equally to both the costs and benefits of treatments[106]. Allowance is made for companies to submit alternative analyses using a 3.5% and 0% discount rate but, again, these are to be included as supplementary analyses and are not permitted to be included in the base case. In practice, the 5% discount rate is the base rate adopted by PBAC to make its recommendations to the Minister for Health whilst companies are permitted to provide supplementary estimates using lower rates to test sensitivity in their economic model[107]. The use by PBAC of this relatively high discount rate of 5% by international standards has not been revised since the publication of the PBAC Guidelines in 1995[108]. It appears that the 1995 Guidelines (including their assumptions about society's expectations and acceptable discount rates of 5% for health care) were drafted in 1990[109]. Moreover, the 1995 Guidelines refer to Chapter 6 of a 'Background Document' to justify why the 5% rate was adopted as the PBAC standard discount rate in 1990, but this document cannot be located[110].

Today, most high-income countries with developed HTA systems apply a lower discount rate than Australia (Figure 8). Moreover, over the years countries such as New Zealand, Canada, and the UK have lowered their discount rates and currently suggest a discount rate of 1.5-3.5% [111]. The European Commission (2018) recommends a discount rate of 3% for the member states, except for the Cohesion Member States for which a discount rate of 5% was recommended based on Social Rate of Time Preference[112]. On the other hand, a discount rate of at least 5% was recommended to be appropriate for the low- and lower middle-income countries[113]. One issue to further consider is whether different discount rates should be applied to the benefits versus the costs of vaccines. This is the subject of some debate in the health economics literature[114]. It is also worth noting that while the NHS in England and Wales currently uses a 3.5% discount rate as a base case with the option of using 1.5% for health interventions with long payback periods such as vaccines, NICE has proposed to adopt a discount rate of 1.5% as its standard discount rate for evaluations for England and Wales[115].

Herd immunity is an example where an unduly high discount rate compounds the problems for the economic assessment of vaccines in Australia. While QALY-based HTA systems such as Australia's already have problems fully accounting for the population value of herd immunity[116] – the broader protective effective to society of a substantial proportion of the population being immunised – a high discount rate further devalues these benefits because herd immunity is something that has a payoff to a society over the longer term[117].

Figure 8 – Discount rate applied in HTA in selected countries with developed HTA system



* UK (England and Wales) uses a discount rate of 1.5% for longer-term health effects accrue for at least 30 years, often used for vaccines.

Shawview Consulting chart. Data source: Attema AE, Brouwer WB, Claxton K. Discounting in economic evaluations. Pharmacoeconomics. 2018 Jul;36(7):745-58; Devlin, N. & Scuffham, P. 2020. "Health Today Versus Health Tomorrow: does Australia Really Care Less About its Future Health than Other Countries Do?", Australian Health Review, 44(3):337-339, https://pubmed.ncbi.nlm.nih.gov/32475385/, accessed 15/9/2021; Consortium YHE. Health Technology Assessment York: York Health Economics Consortium; 2016. Available from: https://yhec.co.uk/glossary/health-technology-assessment.

Australia's relative incremental cost-effectiveness ratio (ICER)

Another issue that may delay the use of vaccines in Australia is the threshold beyond which health interventions like vaccines are judged to not be value for money or cost-effective for purchasing by the Commonwealth government. HTA provides a comprehensive evaluation of clinical effectiveness, cost-effectiveness, and social impact of healthcare technology on the lives of patients and the health care system. Its main aim is to inform health care decision makers on the value of new health care interventions[118]. Cost-effectiveness analyses (CEA) are an integral part of HTA process that compare the costs and outcomes of competing healthcare interventions and this comparison is expressed as the incremental cost-effectiveness ratio (ICER). The ICER is a common metric that is compared with a pre-defined threshold value also known as cost-effectiveness (CE) threshold. The CE threshold can be understood as the maximum cost per health outcome that a health system is willing to pay, or the point beyond which the health system does not see value for money in supporting a health intervention[119,120].

The variation in the approaches used to define a cost-effectiveness (CE) threshold and differences between country specific CE thresholds has been a topic of discussion. The commonly used approaches to define a CE threshold include annual gross domestic product (GDP) per capita based thresholds, benchmarking interventions, and league tables. The recommendation by the World Health Organization's Choosing Interventions that are Cost-

Effective (WHO-CHOICE) project has in the past suggested that a CE threshold value of between 1 to 3 times the national annual GDP per capita is appropriate, where health interventions costing less than this threshold are considered highly cost-effective[121]. However, separately the WHO has said that a simple reliance on a cost-effectiveness threshold set to a benchmark three times GDP per capita has never been recommended by WHO[122].

In the benchmarking interventions approach the CE threshold is established by a retrospective analysis of existing intervention in practice, setting the ICER against previous health intervention decisions[110]. The CE threshold of USD 50,000 used in the US is an example of this approach where this has been benchmarked compared to the estimate of the cost-effectiveness for dialysis for end-stage renal disease. In the league table approach the interventions are ranked according to their ICERs and chosen accordingly to maximize the health impact given a set healthcare budget[110].

Countries that use HTA for decision-making in health care have often been reluctant to establish and publish a definitive CE threshold, with the exception being the UK which does publish an ICER range. For countries like Australia, Canada, and New Zealand that do not publish official ICER ranges, researchers have analysed past decisions by HTA agencies to infer country specific CE thresholds. Public Summary Document reports on Australia's PBAC decisions provides the ranges in which the ICER value falls for particular HTA submissions: AUD 15,000 - 45,000 per QALY; 45,000 -75,000; 75,000-105,000; or 105,000-200,000[123]. Various studies have examined the probability of a medicine being listed on the PBS in Australia as influenced by a submission's cost per QALY ratio. Some studies show that around half of PBS submissions were accepted when the cost per QALY was less than $45,000, whereas this fell to 33% when the cost per QALY ranged between $45,000 and $75,000, and the probability of success falls further to 16% once the cost per QALY goes above $75,000[124].

Table 8 lists the explicit and implicit ICER thresholds employed by the selected countries that have a mature HTA system. It is understandable that decision making is not entirely based on the CE considerations and other criteria are also considered. However, traditionally health technologies with a low ICER are more readily recommended for funding than those with a high ICER. Hence, for the interventions that provide a long-term incremental health benefit with a higher ICER, appropriate consideration of the criteria other than ICER become more important.

Table 8 – ICER threshold values used for HTA decision making in selected countries

Country	Assessment agency	Explicit and implicit ICER thresholds	ICER range	ICER in A$
UK	NICE	ICER range set by NICE	£20,000 - £30,000	41,322 - 61,983
The Netherlands	ZIN	Maximum ICER threshold €80000/QALY	€20,000 - €80,000	35,648 - 142,592
Canada	CADTH	No explicit threshold	C$50,000 - C$100,000	59,618 - 119,237
Japan	Central Social Insurance Medical Council	No explicit threshold	¥5,000,000 -¥10,000,000	75,946 - 151,891
Australia	PBAC	No explicit threshold	A$52,400 - A$75,000	52,400 - 75,000
New Zealand	PHARMC	No explicit threshold	NZ$33,306	31,993
Sweden	SBU	No explicit threshold	NA	NA
Norway		No explicit threshold	NA	NA
Korea	HIRA	No explicit threshold	GDP per capita used as a reference value	NA
Belgium	KCE	No explicit threshold	NA	NA

Values reported in respective country currency. Cost converted to 2021 AUD using CCEMG-EPPI-Centre cost converter; Version 1.4. The Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre). 2014. http://eppi.ioe.ac.uk/costconversion/default.aspx.

Source: Kamae I, Thwaites R, Hamada A, Fernandez JL. Health technology assessment in Japan: a work in progress. Journal of medical economics. 2020 Apr 2;23(4):317-22.

ICER threshold used by PBAC for assessing vaccines

The implications of the PBAC's approach to ICERs for the reimbursement of vaccines in Australia is complicated, noting that Australia's PBAC does not publish a specific ICER threshold. Hanley et al note PBAC's repeated assertion that treatments with large opportunity costs – budget impacts that drag funding away from other treatment options – such as population prevention interventions should be at the lower range of acceptable ICER thresholds[125]. This would seem to disadvantage broader population initiatives like vaccines in the PBAC's assessment of value. Reviewing the ICER levels accepted by previous PBAC recommendations for vaccine submissions would tend to support this point that vaccines tend to be acceptable at the lower end of ICER ranges. Indications of what PBAC considers an acceptable ICER for vaccines can be surmised from the following examples of past decisions:

- Gardasil®, November 2006[126] – PBAC initially rejected this HPV vaccine for all programs (primary and catch-up cohorts) where all programs had ICERs more than $15,000/QALY. In so doing, the PBAC noted that "*the cost effectiveness of the vaccine should be compared to other population preventative interventions such as lipid-lowering and anti-hypertensive drugs rather than with treatment of patients with severe symptomatic disease such as late stage cancer*". The decision was subsequently reversed after a request from the Minister for Health and an immediate, brief resubmission by the company with a lower price, although the resulting revised ICER range which proved acceptable to PBAC is not published.

- Truvada®, December 2017[127] – Although an assessment for preventative HIV treatments, the assessments provided guidance on PBAC's approach to ICER thresholds for vaccines. The PBAC commented: "*In July 2017, the PBAC recalled that the threshold of incremental QALYs gained for treatments with large opportunity costs, such as population preventative interventions including lipid-lowering, antihypertensive drugs and vaccines, was at the lower end of the ICER range that PBAC has accepted because these treatments typically have a high opportunity cost.*"

- Shingrix®, November 2018[128] – The vaccine for shingles submitted in 2018 was rejected by PBAC due to high and uncertain cost-effectiveness. In all cases the ICERs were above $15,000/QALY. Again, the PBAC noted that "*The threshold of incremental QALYs gained for treatments with large opportunity costs, such as population preventative interventions including lipid-lowering, anti-hypertensive drugs and vaccines, was at the lower end of the ICER range. The PBAC considered that the ICERs proposed in the submission were highly uncertain and suggested that lower ICERs would be more appropriate.*" As a result, earlier this year the sponsor company decided to launch Shingrix on the private market after being rejected for NIP funding[129].

- Influenza vaccines, November 2007[130] – A submission covering multiple influenza vaccines to extend NIP coverage generally to all Australian adults over the age of 50 was made by the Influenza Specialist Group. In rejecting the submission, the PBAC indicated that one of the reasons for rejecting the submission was the uncertainty in the economic model. In particular, the PBAC was concerned about the uncertainty in mortality and morbidity results driving the cost per QALY in the economic model above the $15,000 per QALY range. The PBAC instead suggested an alternative approach to target coverage to certain adults in the population who were at higher risk.

This would suggest that the PBAC will not recommend a vaccine for listing on the NIP unless it is at the lower end of its acceptable ICER range and has often indicated that the ICER for vaccines needs to be less than $15,000/QALY for a vaccine to be acceptable[131]. Case studies of several vaccines that went through the ATAGI/PBAC/NIP assessment process and the issues in their assessment are at Appendix A.

International experience suggests it is possible to adjust QALY values to acknowledge and accommodate difficulties in assessing the benefits of vaccines through the formal HTA process. For example, in 2016 the United Kingdom's vaccines advisory body, the Joint Committee on Vaccination and Immunisation (JCVI), has previously applied QALY Adjustment Factors to address underestimates of the QALY effects when assessing meningococcal vaccines for funding[132]. Here the JCVI tried to capture QALY losses from not vaccinating the most vulnerable age groups, such as children and adolescents, for meningococcal disease and the insensitivity of the health-related quality of life instruments in assessing the quality of life impact of hearing loss and some neurological sequelae.

Australia's assessment of vaccines in the international context

The methodological and health economic issues being experienced by vaccine submissions in the PBAC context are not unique to Australia. In fact, the appropriateness or otherwise of using an HTA framework for assessing vaccines for universal funding in health systems has been the subject of contentious debate internationally for some time. There are two issues related to the assessment of vaccines in the context of HTA:

1. Whether broader issues concerning productivity benefits, discount rates, ICER ranges, and value placed on public health initiatives that can affect assessment of all therapeutic interventions particularly disadvantage vaccines

2. Whether vaccines should be assessed using the same HTA frameworks used to assess other therapeutic treatments (e.g., cell and gene therapies, statins, cancer medicines, etc).

There has been much discussion in the international academic literature about the suitability or otherwise of traditional HTA methods to capture the full value of vaccination[133]. Typically, these arguments highlight issues discussed in the preceding section about Australia's HTA system. Issues such as insufficient recognition of the societal and population level benefits of vaccines, a lack of value attached to herd immunity, unduly short time horizons, the value attached to prevention as opposed to treatment, insufficient value attached to preventing transmission, insufficient attention given to cost-offsets provided by vaccines and disadvantageous discount rates have all been raised as factors explaining why vaccines may not be sufficiently valued in traditional HTA systems. The suggestions here are that decision making about funding vaccines is adversely affected by undervaluing such factors.

This then leads to the question whether vaccines should be evaluated as part of a broader HTA system for medicines or be evaluated to different criteria. While some have raised the question whether such differences in the treatment and effect of vaccines means they warrant specialist treatment[134], others have argued that such specialised assessment criteria for vaccines over other health interventions could excessively skew the allocation of health resources to vaccines over other treatments[135].

This topic is relevant to the broader question of *how* vaccines are evaluated in different countries. Many countries have developed National Immunisation Technical Advisory Groups (NITAGs) but the extent to which they conduct HTA evaluation does vary. The WHO's Global Vaccine Action Plan (GVAP) recommends for all countries to establish NITAGs[136]. These NITAGs are multidisciplinary groups of national experts tasked with providing independent, evidence-informed advice to the respective countries' policymakers and programme managers on policy issues related to vaccines and immunisation[137]. The WHO recommends using economic evaluation in the decision-making processes by NITAGs; however, a consistent and transparent process is still to be developed in several countries that already have formed a NITAG[138].

Although all NITAGs provide information to their national governments to make evidence-based decisions regarding immunisation and vaccines, several differences between these NITAGs exist. This includes the size and scope of committee membership, the scope of work, role of the Ministry of Health on the committee, the existence of the conflict-of-interest policies, and the ultimate role of the NITAGs in the decision-making process[139].

Australia's NITAG, ATAGI, does have several unique characteristics. One difference is the requirement that the HTA assessment of vaccines be assessed by the same HTA agency that assesses medicines more generally: the PBAC. This is unusual compared to other countries (Table 9). In many countries, the assessment and recommendation on whether to purchase a vaccine is made by a separate, dedicated expert vaccines committee (NITAG). This is essentially the system Australia had up until 2005 when the ATAGI was subsumed under the PBAC umbrella and required to advise the PBAC rather than make recommendations direct to the Minister for Health. While HTA of vaccines is becoming increasingly common, often a country's NITAG itself will be responsible for that HTA evaluation rather than referring it to a separate HTA agency responsible for medicines.

Table 9 – NITAGs and their key characteristics for decision making process

Country	NITAG, Year established	HTA body	Evaluates economic evidence	Reports to HTA body	Reports to department of health
Australia	ATAGI, 1997	PBAC	✓	✓	✓
Austria	-	GÖG	-	-	-
Belgium	NITAG within the Superior Health Council, 1991	KCE	✓	✗	✓
Canada	NACI, 1964	CADTH	✓	✗	✓
Chile	CAVEI, 2011	-	✓	✗	✓
Denmark	Sundhedsstyrelsens vaccinationsudvalg, 1980	Danish Health and Medicines Authority	✓	✗	✓
Estonia	Expert Committee for Immunoprophylaxis, 2006	Centre for HTA, University of Tartu	✓	✗	✓
Finland	KRAR, 2001	THL/Finohta	✓	✗	✓
France	CTV, 1985	HAS	✓	✓	✓
Germany	STIKO, 1972	IQWiG	✓	✗	✓
Greece	National Immunisation Committee, 1991	-	✓	✗	✓
Iceland	Sottvarnarad, 1998	-	✓	✗	✓
Ireland	NIAC, 1996	NCPE	✓	✗	✓
Israel	Advisory Committee on Infectious Diseases and Immunisations, 1974	ICTAHC	✓	✗	✓
Italy	National Vaccination Committee, 2017	AGENAS	✓	✗	✓
Japan	-	Chuikyo	-	-	-
Korea, Rep.	KACIP, 1992	NECA	✓	✗	✓
Latvia	State Immunisation Council, 2000	SAMLV	✓	✗	✓
Lithuania	Board for coordination of National Immunisation Programme, 1999	State Health Care Accreditation Agency	✓	✗	✓
Luxembourg	CSMI, 1963	Ministère de la Sécurité sociale	✓	✗	✓
Netherlands	Committee on the National Immunisation Program (within the Health Council of the Netherlands), 1902	Zorginstituut Nederland	✓	✗	✓
New Zealand	PTAC, 1984	PHARMAC	✓	✓	✓
Norway	Scientific Reference Group for National Immunisation Programs, 2018	NIPH	✓	✓	✓

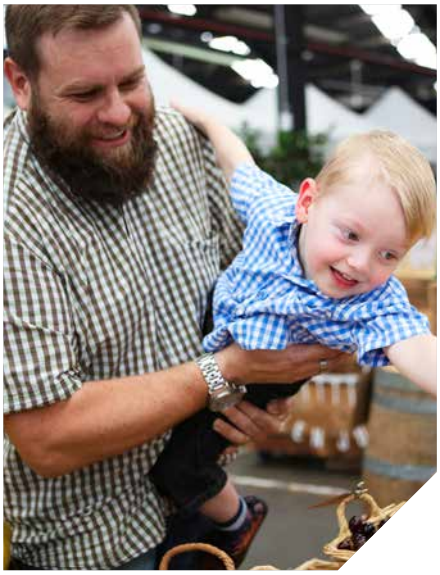
Country	NITAG, Year established	HTA body	Evaluates economic evidence	Reports to HTA body	Reports to department of health
Poland	Sanitary- Epidemiology Advisory Board and Paediatric Group of Experts on Immunisation Program, 2003	AOTMiT	✓	✗	✓
Portugal	CTV, 1997	INFARMED	✓	✗	✓
Slovak Republic	Working Group for Immunisation Issues, 2006	The Working Group for Pharmacoeconomics, Clinical Outcomes and HTA of the Slovak Ministry of Health	✓	✗	✓
Slovenia	PSC, 2011	-	✓	✗	✓
Spain	National Vaccines Committee, 1991	Spanish Network of Agencies for HTA and Services of the National Health System	✓	✗	✓
Sweden	Reference group for national vaccination programmes, 2016	SBU	✓	✗	✓
Switzerland	CFV, 2004	CFPP, CFM, CFAMA	✓	✗	✓
United Kingdom	JCVI	NICE	✓	✗	✓
United States	ACIP	NA	✓	✗	✓

ATAGI: Australian Technical Advisory Group on Immunisation; KCE; Belgian Health Care Knowledge Centre; NACI: National Advisory Committee on Immunisation; CAVEI: Comité asesor en vacunas y estrategias de inmunización; GÖG: Gesundheit Österreich GmbH; TCV: Technical committee on vaccinations; STIKO: Ständige Impfkommission (German Standing Vaccination Committee); NIAC: National Immunisation Advisory Committee; NCPE: National Centre for Pharmacoeconomics; ICTAHC: Israeli Center for Technology Assessment in Health Care; NECA: National Evidence-based Healthcare Collaborating Agency; PTAC: Immunisation Sub-committee of The Pharmacology and Therapeutics Advisory Committee; CTV: Comissão Técnica de Vacinação; PSC: Advisory Committee on Immunisation - Posvetovalna skupina za cepljenje; SBU: Swedish Council on Health Technology Assessment; CFV: Commission Fédérale pour les Vaccinations (Federal Vaccination Commission); CFPP: Federal Commission for general benefits and principles; CFM: Federal Commission drugs; CFAMA: Federal Commission for analysis, means and devices

Sources: World Health Organization. Health Technology Assessment Country profile. 2018 https://www.who.int/health-technology-assessment/country-profile/en/#N accessed 30/4/2021; Global NITAG Network Members. 2021 https://www.nitag-resource.org/network/members accessed 30/4/2021.

Another tool for conducting international comparisons of HTA systems for vaccines has been developed by the Office of Health Economics (OHE), a specialist consulting and research agency in the UK. In a recent study, it reviews the current 'state-of-play' of vaccine assessments in nine higher-income countries (HIC), not including Australia, under a program named Broad Assessment of Value in Vaccines Engagement (BRAVE)[140]. The outcome of the program summarised in its 'BRAVE Narrative' report provides a consolidated framework of factors under which an HTA body can assess the full value generated by vaccines[141, 142, 143, 145, 146]. It assessed the relative balance of factors considered by different HTA agencies in Europe when they evaluate vaccines (See Appendix E).

This framework used by the OHE to evaluate countries' vaccine funding systems uses the following categorised factors:



- Narrow health effects
  - Impact on quality of life of patients
  - Impact on length of life of patients
- Health system economic effects
  - Cost offsets to health care system
- Broad health effects
  - Impact of quality of life of carers
  - Transmission value
  - Value to other interventions
  - AMR prevention value
  - Burden of disease
  - Social equity value
- Societal economic effects
  - Impact on patient productivity
  - Impact on carer productivity
  - Macroeconomic effects

One exercise that Australia could consider undertaking is replicating the OHE evaluation of European countries' vaccine evaluation processes using the BRAVE framework. This could involve an assessment of Australia's vaccines evaluation criteria against the BRAVE framework. This could identify gaps in the current processes and help identify more appropriate value assessments for policy stakeholders and government decision-makers to realise the potential broader benefits of future vaccines.

This is important to consider. If Australia's system of valuing vaccines is consistently and structurally undervaluing vaccines (and other long-term preventative or curative public health interventions for that matter), Australians may increasingly see delays in accessing latest vaccines. For example, one retrospective analysis that looked at the impact of the introduction of rotavirus vaccines in Australia demonstrated that the subsequent benefits to Australia were much broader than pre-implementation models[146]. Similar studies on the impact of HPV vaccines demonstrated that herd immunity had been achieved[147], something difficult for PBAC to accept in its evaluations. This suggests that Australia's pre-implementation evaluation frameworks for vaccines do sometimes underestimate health system benefits, even from a health payer perspective.

Issues in post-PBAC reimbursement – price negotiation and tendering in NIP process

While little attention on vaccines policy in Australia has focussed on the respective roles of PBAC and ATAGI in recommending vaccines for funding under the NIP, even less attention has been directed to the process of tendering, pricing and contract negotiation that occurs after the PBAC makes a recommendation to the Minister for Health to list a vaccine on the NIP. As outlined in Section 2, once the PBAC makes a positive recommendation for funding a vaccine on the NIP, the recommendation together with the NNP is managed by the Population Health Division of the Department of Health. It is here that the vaccine procurement process parts company with the HTA process for assessing medicines under the PBS.

The post-PBAC process to have a vaccine listed and funded on the NIP is complicated and long. It requires a formal tender process, a price negotiation process and creation of legal agreements between the supplying companies and the Commonwealth government through the Department of Health. A substantial amount of planning and administration is required in this process including negotiations with the states and territories, modification of the Australian Immunisation Register, development of a communications strategy, modifications to any legislation if required, development of a Vaccines Safety Monitoring Program, conduct of the tender process and planning for disease surveillance and adverse event reporting. Due to these extended procurement and planning stages the listing of vaccines on the NIP (and the PBS to the extent this still occurs) takes much longer than listing medicines[148].

One issue in the procurement process for vaccines has been the level of engagement and industry collaboration that has changed with the centralisation of purchasing functions with the Commonwealth government. Prior to 1 July 2009, the state and territory governments were responsible for the purchasing of vaccines, receiving funds from the Commonwealth for this purpose. The responsibility for directly purchasing Australia's vaccines has been progressively centralised with the Commonwealth government over the last decade or so. This has been done principally to gain greater efficiencies through a one-purchaser monopsony approach for Australia's entire public vaccine purchase, essentially using a pooled procurement model. Under this model the vaccine requirements of different Australian state and territories are now managed and purchased by the Commonwealth.

This one purchaser approach for vaccines has now increased risk for companies of missing out on supplying the entire Australian market in contrast to the pre-July 2009 arrangements where companies had greater chance of securing at least some part of the Australian market by tendering through the different states and territories[149]. Whereas previously individual state and territory tender processes governed which companies supplied each individual jurisdiction, the Commonwealth now determines company market share through individual national level negotiation.

Centralisation at the federal level has also given the Commonwealth greater control over vaccine spending and avoided the pre-1 July 2009 situation where the Commonwealth was not able to recoup unspent vaccine funds from state and territory governments left over from not completing their vaccination programs. Whilst technically state and territory governments were required to return unspent funds to the Commonwealth, in practice this was difficult to enforce and often those unspent funds were reallocated to other spending priorities. This often led to disputes between the Commonwealth and the states about the return of unspent NIP funds. "The desire by the national Government to retain control of those funds is likely to have been an important motivation for the switch to centralised procurement of vaccines from July 2009"[150]. Under the National Partnership Agreements on Essential Vaccines (NPEVs), the states and territories are required to meet strict performance criteria and at least for a period of time were assessed by the Commonwealth government's Productivity Commission on whether they have achieved their agreed immunisation targets and were eligible for reward payments under the NPEV[151].

The centralisation of purchasing by the Commonwealth may have led to several longer-term issues in procurement. One reason ostensibly raised in favour of centralising purchasing was to avoid sole-supplier arrangements, however with multiple states and territories purchasing through a range of companies prior to 2010 it is difficult to see how centralisation with the Commonwealth would increase the number of vaccine suppliers to Australia when a single purchaser, pooled procurement model was introduced. There are questions whether the shift to Commonwealth responsibility for purchases has increased the priority of short-term savings in purchasing ahead of longer-term strategic relationship and collaboration with vaccine manufacturers.

Arguably, the post-2009 tighter arrangements where the Commonwealth controls purchasing, market share and ultimate market price has not allowed enough suppliers to remain in the Australian market compared to the pre-2009 state-based purchasing arrangements. The drive for short-term efficiency in Australian vaccine purchasing has resulted in the situation today where the Commonwealth evaluates, negotiates, tenders and purchases the vaccines and supplies just enough vaccine stocks to allow states and territories to meet their needs, with little leftover stock for catch up programs or excess stock. While states and territories can take part in the procurement evaluation meetings, it is the Commonwealth that runs the process and makes the decisions.

An issue here is the Commonwealth's focus more on securing the lowest price for vaccines at a moment in time and less on cementing Australia's place in long term supply chains and relationships with the major vaccine companies worldwide. In fact, concerns about the Commonwealth's approach to the long-term viability of Australia's vaccines market were raised back in 2010:

> *"The greater problem that might be posed by centralisation is in the longer term if manufacturers fear that R&D into new and improved vaccines will not be rewarded adequately, i.e., if they fear short-sighted opportunistic behaviour by a centralised purchaser unwilling to recognise and pay for the sunk costs of producing vaccines. Overcoming this problem depends on the centralised purchaser making credible undertakings to pay prices that reflect the total costs of cost-effective (at such prices) new vaccines. This problem may also be attenuated to a greater or lesser degree by the relatively small size of the Australian market in a global context"*[152].

In their 2010 review of the NIP changes, Sussex et al[153] identified several issues that warranted further evaluation as the 2009 changes were implemented:

- The setting of market share by the Commonwealth of competing vaccines which differ in some respects, such as vaccines that protect against different serotypes including a different number of serotypes, and vaccines that may confer additional protection against other diseases.
- Ensuring surety of supply of vaccines and multiple vaccine suppliers in the transition from state and territory to centralised Commonwealth purchasing.
- Whether the shift to a system of centralised monopsony tendering and purchasing at the Commonwealth level has led to lower prices compared to the multi-purchaser competitive purchasing under state- and territory-based arrangements, and
- Whether the Commonwealth-state/territory financial arrangements had been simplified under the new arrangements.

Further evaluation of these and other issues in the Commonwealth's purchasing arrangements would be warranted. Realistically, a better way to redress any of these issues if they occur is not likely to be a return to state-by-state direct purchasing of NIP vaccines, but rather a series of improvements to increase the efficiency, effectiveness and engagement of the Commonwealth's negotiation and purchasing processes. An initial roundtable or collaborative process between industry, distributors, states and territories, and the Commonwealth to review these issues may be a good place to start. Ultimately, this may be achieved by the Commonwealth and industry collaboratively developing a long-term strategy for vaccines and the NIP that develops a collaborative, strategic working relationship between the two and covers issues such as market viability, sufficient incentive supply Australia with the latest vaccines, strategies and metrics to ensure Australia's first tier access to vaccines and developing strong supply chains and manufacturing capability where appropriate.

One option here is to revamp and revitalise Australia's National Immunisation Committee. This is the peak body whose task is to provide advice to the Commonwealth on the NIP[154]. Its membership had originally comprised the state and territory governments responsible for administering NIP vaccines but had been expanded since its creation to include health care professionals, indigenous representatives, and consumers[155]. Unfortunately, it appears this cross-sectoral committee with responsibility for advising the Commonwealth on the NIP appears to have fallen into abeyance – the Department of Health website contains information up to members in 2017 – or has been abolished[156]. One way the Commonwealth could re-engage with the vaccine policy system in Australia and re-establish a strategic approach to the NIP is to reconstitute and revamp this Committee or establish a new replacement committee. The vaccines industry could also be invited to be members to provide industry input and build a strategic relationship between the Commonwealth and the vaccines industry.

Time taken to list new vaccines

The current processes, issues and delays all combine to affect the time it takes to have new vaccines funded in Australia under the NIP.

Shawview Consulting analysed data from the Maestro Database to examine the time taken for vaccines to be funded through the NIP[157]. All submissions for vaccines to be funded under the NIP from 2005 were examined and analysed. Submissions for new vaccines, new indications, and new formulations were analysed.

The analysis found that there were 51 ultimately successful submissions made by companies to have new vaccines, expanded indications or new formulations and strains listed on the NIP. This includes submissions that may have required multiple submissions to achieve a positive PBAC recommendation. Key trends emerging from this analysis were:

- For those vaccine brands that were listed on the NIP and had a listed TGA approval date, it took on an average of 1,375 days to get listed after TGA approval, equivalent to almost four years. There was wide variation around this, ranging from 190 days for Fluad Quad® an influenza vaccine through to 6,400 days for Tripacel®, a booster vaccine for diphtheria, tetanus, and pertussis. This compares with the experience of other medicines seeking PBS listing where the average time taken for cancer medicines, for example, was an average of 730 days between TGA approval and PBS listing[158]. For all PBS medicines, the time taken ranges from 357 to 644 days[159]. While preliminary and indicative, this suggests that vaccines take almost double the time cancer medicines do to achieve public funding in Australia.

- Vaccine brands that were included in NIP took on an average of 506 days to get included in NIP from their first submission to the PBAC until funding on the NIP. These also ranged widely from 46 days for the ADT™ booster for diphtheria and tetanus through to 3,408 days it took for Zostavax® for shingles to be funded on the NIP.

- Of interest also is the time it takes vaccines to be listed on the NIP once the PBAC has made a positive recommendation for their listing, as this gives a measure of the timeliness of the post-PBAC listing process for NIP vaccines. The average time taken for vaccines from a positive recommendation to NIP listing since 2005 is 303 days, ranging from 23 days for the listing of Tet-Tox®, a tetanus vaccine, to 2,070 days for the funding of Priorix-Tetra®, a combined vaccine for measles, mumps, rubella and varicella for infants and children. This average 303 days for the post-PBAC process for vaccines compares with an average of around 213 days for cancer medicines[160] and between 187 and 245 days for all medicines[161] to be listed on the PBS.

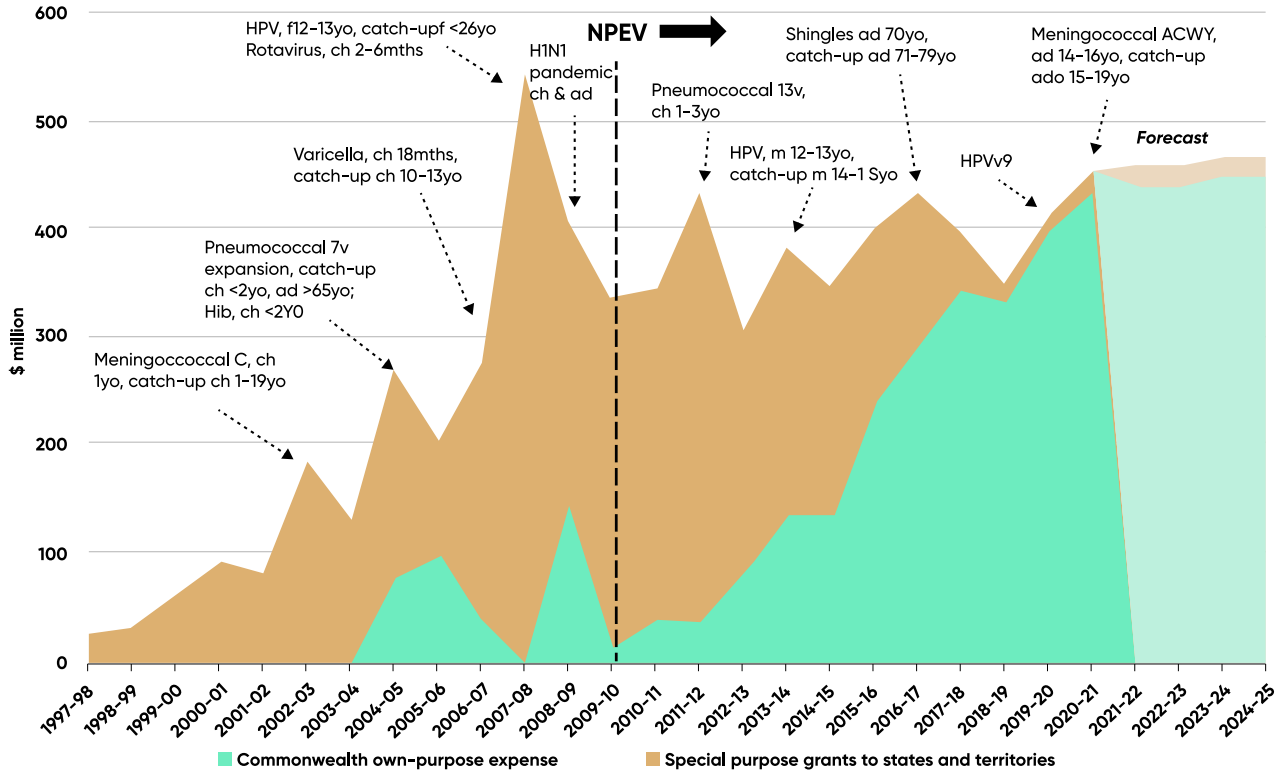
The analysis suggests that overall vaccines take longer to be listed on the NIP than medicines normally take to be listed on the PBS. Overall, vaccines can take twice as long to get listed on the NIP from when first approved for use in Australia. The data suggest that vaccines roughly take on average an extra two years to navigate through the ATAGI, PBAC and NIP tendering, procurement and budgeting process compared with the PBS processes required for medicines.

The post-PBAC process is particularly worth reviewing. The fact that it can take an extra 90 to 100 days on average for vaccines to get through this process compared to medicines perhaps reflects the complicated and protracted process used in NIP tendering, procurement and budgeting that vaccines must undergo once the PBAC makes a positive recommendation. The requirement for approval by the Minister for Health for listing on the NIP and approval by federal cabinet for NIP recommendations costing $25 million or more in any one year, with no time limits on this process for the NIP, also has the potential to increase the time taken. Moreover, the inclusion of state and territory governments in this process to varying degrees may well compound administrative timelines. Note, of course, that this analysis includes only successful submissions and not vaccine submissions that were unsuccessful in seeking an NIP listing.

Expenditure on essential vaccines for the NIP

Both the Commonwealth and the state and territory governments have joint responsibility for funding Australia's NIP. Prior to 2009, the states and territories largely purchased vaccines under the NIP relying on federal financial special purpose grants (SPGs) from the Commonwealth to fund these purchases. Today, the states and territories still themselves fund the logistics and rollout of vaccines in their own states. Since 1 July 2009, the NIP transitioned to the Commonwealth continuing to fund Australia's vaccines purchases under the NIP but doing so through direct purchasing itself through own-purpose expenditure rather than funding the states and territories to do this through SPGs. The states and territories retain responsibility for rollout of NIP vaccines in their respective jurisdictions.

Figure 9 – Commonwealth Government expenditure on essential vaccines for NIP, $ million



Shawview Consulting analysis and chart. Data sources:Department of Health,Annual Report, various years, https://www.health.gov.au/about-us/corporate-reporting/annual-reports, https://www.health.gov.au/internet/main/publishing.nsf/Content/publications-Annual%20reports; Department of Health Portfolio Budget Statement, various years, https://www.health.gov.au/about-us/corporate-reporting/budgets; AustraliaGovernment, Budget Paper No. 3 Federal Financial Relations, various years, www.budget.gov.au.; NCIRS, "History of Immunisation in Australia", https://www.ncirs.org.au/health-professionals/history-immunisation-australia.

In financial year 2020-21, the Commonwealth government spent $454 million on essential vaccines for the NIP (Figure 9). Commonwealth government spending on essential vaccines, comprising both its own purpose expenditure and its grants to the states and territories, has averaged around $385 million a year since 2009. Latest Commonwealth Budget forecasts suggest an annual spend of around $464 million year in the coming four years of the forward estimates.

The shift in responsibility for direct purchasing of vaccines for the NIP can be seen in Figure 9. Since the establishment of the NIP in 1997, Commonwealth expenditure on vaccines was largely in the form of SPGs to the state and territory governments for the purchase of vaccines. The exceptions prior to 2009 were Commonwealth direct purchasing of pneumococcal vaccines in 2004-05 and 2005-06 and influenza vaccines for the H1N1 pandemic in 2008-09. These first examples of Commonwealth direct purchasing of vaccines for the NIP were, arguably, precursors to the formal initiation of Commonwealth own-purpose purchase of NIP vaccines from 2009 under the NPEV. The initiation and progression of the shift towards centralised Commonwealth purchasing can be seen from the 2009-10 financial year, such that a decade later in 2019-20 the Commonwealth's own-purpose expenditure on vaccines accounted for essentially all of Australia's vaccine purchases[162].

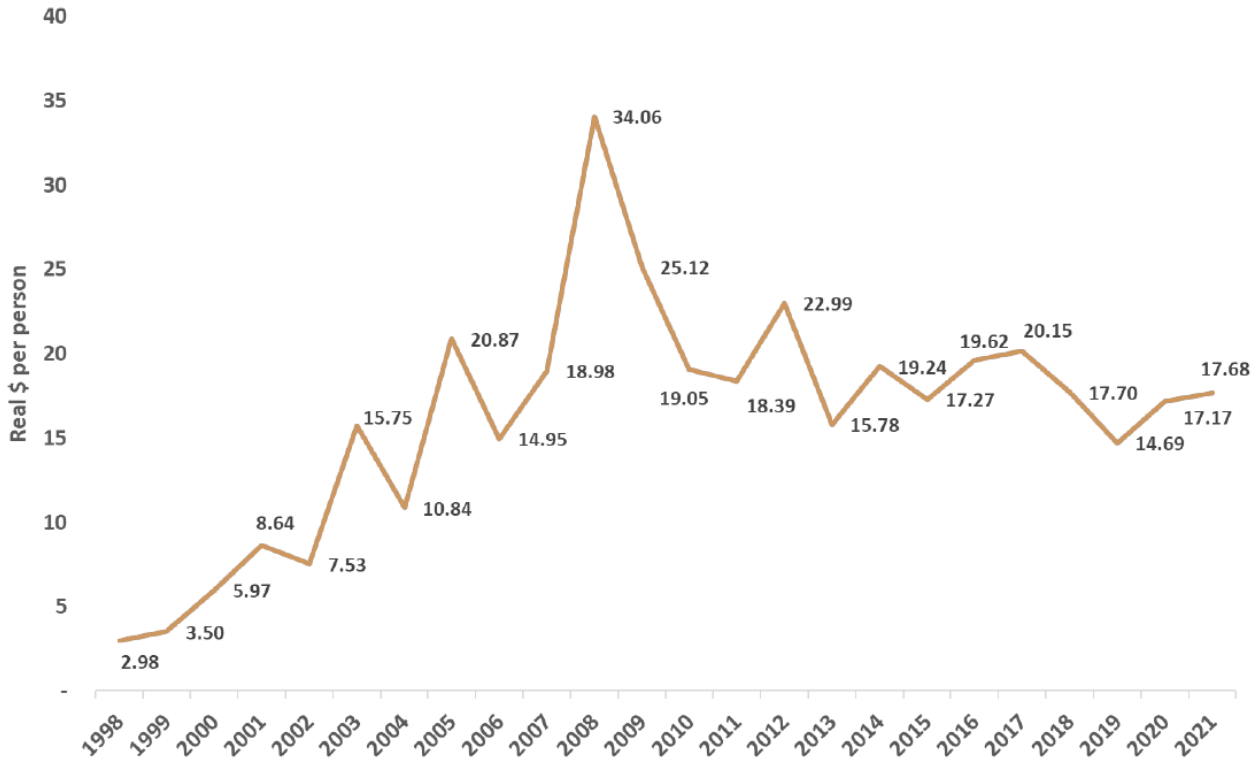
Substantial growth in the level of NIP expenditure on essential vaccines corresponds with the listing of new vaccines on the programs and their initial catch-up programs. For example, the substantial increase in spending in 2002-03 and 2004-05 correspond with funding for new meningococcal and pneumococcal vaccines respectively, while the significant increase in spending in 2007-08 resulted from new listings of HPV and rotavirus vaccines. Similarly, the reduction in 2008-09 is explained somewhat by the post-HPV funding surge. Catch-up programs also have a significant effect, such as the catch-up program for the HPV vaccine for all women in Australia up to the age of 26 when it was first introduced in 2007.

Since the shift to Commonwealth direct purchasing of vaccines and the development of the National Partnership Agreements on Essential Vaccines (NPEVs) growth in NIP vaccine expenditure has slowed. After adjusting for inflation[163], real growth in NIP vaccine spending grew by an average 33% per annum between 1997 and 2009, which coincided with a period when major new patented vaccines were added to the NIP as new vaccine technologies were introduced. By contrast, since 2009 when the Commonwealth started taking responsibility for vaccine purchasing and major new vaccine rollouts and catch-up programs were completed, real average annual NIP vaccine spending was 0.2% per annum and remained around the average $385 million per annum level over the period to 2020-21.

Real per capita spending on the NIP has also plateaued since the scheme was introduced in 1997 (Figure 10). After adjusting for inflation and for growth in the Australian population, per capita Commonwealth spending on the

NIP has varied since 1997. The general trend has been an increase up until the second half of the 2000s, peaking at $34.06 per person in Australia in 2021 price terms, before stabilising at around $20 per person per year. In recent years real per capita Commonwealth spending on NIP vaccines has fallen.

Figure 10 – Real per capita Commonwealth NIP spending ($ per person), 2021 prices



Shawview Consulting analysis and chart. Data sources: Department of Health, Annual Report, various years, https://www.health.gov.au/about-us/corporate-reporting/annual-reports, https://www1.health.gov.au/internet/main/publishling.nsf/Content/publications-Annual%20reports; Department of Health Portfolio Budget Statement, various years, https://www.health.gov.au/about-us/corporate-reporting/budgets; Australia Government, Budget Paper No. 3 Federal Financial Relations, various years, www.budget.gov.au.; ABS, cat. 5206.0 Australian NationalAccounts: National Income, Expenditure and Product, Table 5. Expenditure on Gross Domestic Product (GDP), Implicit price deflators, June 2021, https://www.abs.gov.au/statistics/economy /national-accounts/australian-national-accounts-nationa-income-expenditure-and-product/ jun-2021/5206005_Expenditure_Implicit_Price_Deflators.xls, accessed 1/9/2021;ABS, cat.3101.0, National, state and territory population, Table 1: Population change, https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/dec-2020/310101.xls, accessed 26/8/2021. Prices are 2021 prices.

The slowdown and stabilisation in Commonwealth spending on NIP vaccines with the increasing scrutiny and control being exercised by the Commonwealth since 2009 suggests that its efforts to restrain spending have been successful. More modest average annual real growth in NIP spending can be observed since the introduction of the NPEVs, the introduction of stringent performance targets for states and territories, Commonwealth control over spending decisions and a requirement for positive PBAC recommendations for new vaccine listings suggests all have contributed to restrain expenditure growth in the program over the period.

One issue that should be considered is the likely funding levels needed in the future for NIP vaccines. One study found that compared with high vaccination rates for children, vaccination rates for the *eligible* adult populations in Australia for several diseases such as pneumococcal disease and influenza ranged between 51% and 74% and were as low as 36% in at-risk populations[164].

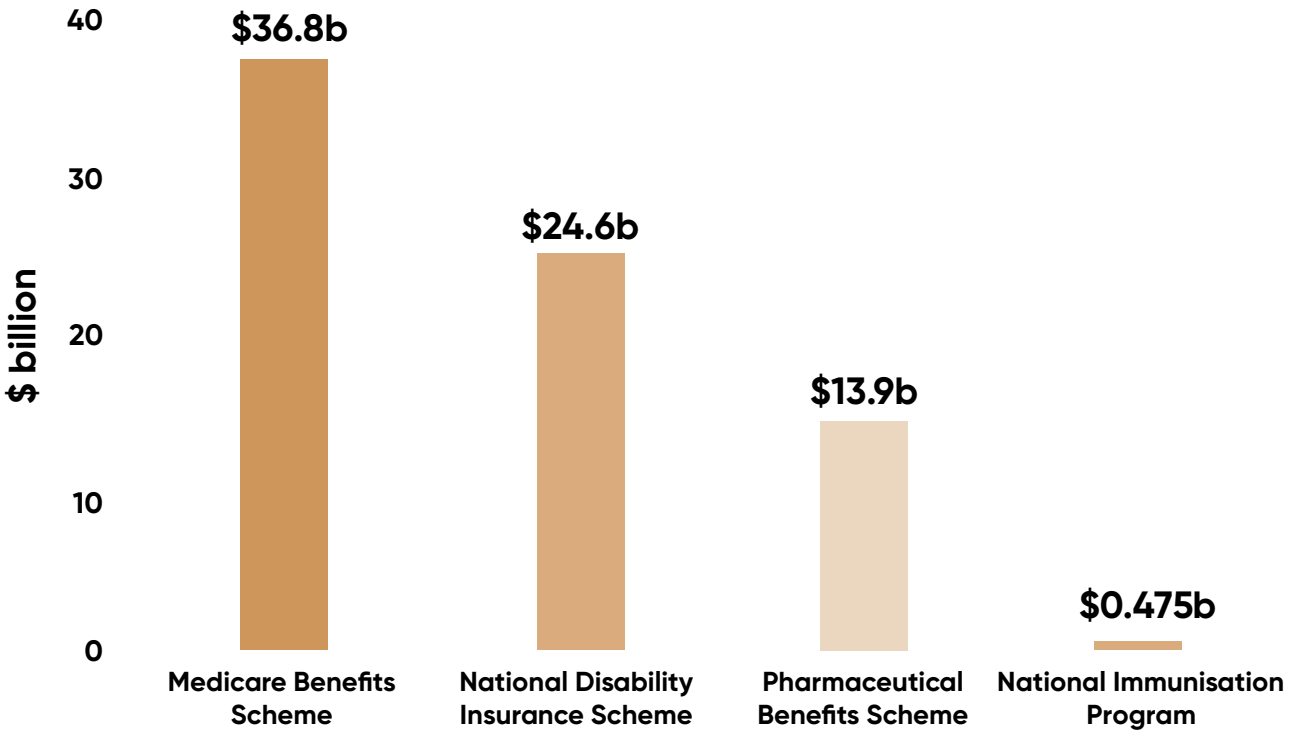
Other studies have shown that Australia's adult vaccination rates are low, with only 41% of eligible pregnant women in Western Australia receiving an influenza vaccine and only 13% of eligible Aboriginal and Torres Strait Islanders receiving a pneumococcal vaccine[165]. Factors such as the existing shortfalls in adult vaccination rates for vaccines already funded under the NIP, funding gaps for vaccines that are not covered by the NIP and the realisation of the value of preventative vaccination following the COVID-19 pandemic all point to a need to reassess whether the current level of funding for a vaccine program like the NIP is appropriate.

Moreover, given the continuing technological development in vaccine technology and the range of new vaccines currently in the development pipeline, the question must be asked whether continued low growth in real terms for the NIP is either realistic or desirable.

In any event, the level of funding provided to vaccines under the NIP is on a substantially smaller scale than other major public health and social programs (Figure 11). The Medicare Benefits Scheme has grown substantially in recent years, the National Disability Insurance Scheme did not exist a decade ago to become a major social program costing $25 billion a year, and the Pharmaceutical Benefits Scheme is a substantial public health program, albeit showing little or no growth over the last decade or so.

All these programs rank in the billions of dollars in expenditure, while the NIP has remained at around $400 million per annum for over a decade. A review of whether the NIP's funding levels are appropriate for the 21st century would seem warranted.

Figure 11 – MBS, NDIS, PBS and NIP, 2020-21, $ billion



Shawview Consulting chart. Data source: Statement 6, 'Expenses and Net Capital Investment', Budget Paper No 1, *Budget Strategy and Outlook. Budget 2021-22*. https://budget.gov.au/2021-22/content/bpl/download/bp l_bs6.docx, accessed 4/6/2021. *Note: PBS does not Include PBS rebates paid to government. NIP includes essential vaccines and Commonwealth funding of supporting services.*

5 Future vaccine technologies and implications for Australia

"Oh, it works. I thought so."

Katalin Kariko, 2020, inventor of mRNA vaccines

"Immunization is a global health and development success story, saving millions of lives every year."

World Health Organization

Key points

- There are over 10,000 clinical trials of new vaccines underway and hundreds of new vaccines being developed worldwide.
- New vaccines in development that could be of importance to Australia in the future include vaccines for cancers, Alzheimer's disease, coronaviruses, multiple sclerosis, respiratory diseases, and allergies.
- New potential vaccine technology platforms in the pipeline of interest include DNA and mRNA technologies, universal vaccines, delivery platforms and longer-acting vaccines.
- Such developments in future vaccine technology could present issues for Australia's NIP and vaccine policies.

According to latest figures released in April 2020, from the global pharmaceutical industry[168], there are 258 vaccines in development by biopharmaceutical companies for the treatment or prevention of disease. These vaccines offer significant hope for the future, with many vaccines in the pipeline utilising new technologies that have the potential to prevent the transmission of the human immunodeficiency virus (HIV) and protect against malaria. While existing vaccines are powerful tools for preventing disease, a new wave of therapeutic vaccines have the potential to treat diseases with therapeutic vaccines for several types of cancer in clinical development. Therapeutic vaccines work by stimulating or restoring the body's immune system to fight infection and disease, such as cancer.

New vaccines technologies under development

Vaccine technology platforms

Traditionally, vaccines use live attenuated viruses, bacterial strains or use inactivated forms of viruses, pieces of bacteria or forms of toxins to provoke an immune response to protect against future infection. Vaccines can also include adjuvants as an 'ingredient' in the vaccine that can help produce a better immune response, in turn reducing the amount of virus needed for production of a vaccine, allowing for more efficient vaccine manufacture. The use of vaccine adjuvants is not a new concept, but developments in this space could have an impact on vaccine production and vaccine uptake.

Vaccines have traditionally been prophylactic in preventing infection. However, advances are leading to vaccines causing immune responses to cure conditions. Some of the major new techniques being explored to create different types of vaccines include live recombinant/sub-unit vaccines and nucleic acid-based (DNA and mRNA) vaccines. These developments are opening new opportunities for vaccination against different classes of diseases, different vaccination schedules and methods of delivery.

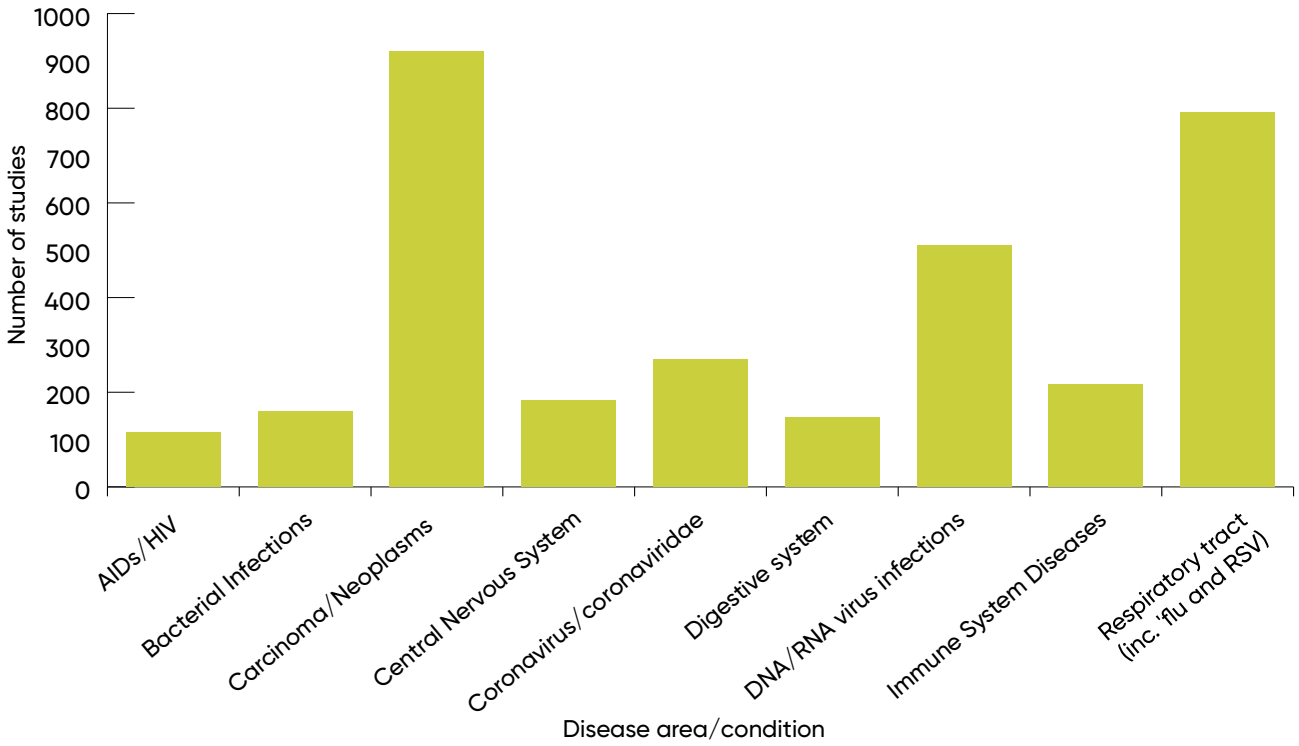
With live recombinant/sub-unit vaccines, attenuated viruses or bacterial strains are introduced as vectors, which are essentially other viruses or bacterium that are used to 'deliver' the attenuated virus of interest into the person being vaccinated. This process can enhance the immune response (depending on the vector material chosen) or it can be used to deliver viruses or bacteria that cannot be attenuated sufficiently to be given as a vaccine (for example HIV).

DNA and mRNA vaccines aim to mimic traditional live, organism-based vaccines to stimulate cell-mediated immunity. These vaccines consist of DNA coding for a particular antigen which is directly injected into the muscle. At this point, the DNA inserts itself into the individual's cells which then produce the (foreign) antigen for the infectious agent, thereby generating an immune response. This approach is relatively straightforward as DNA is easy to produce and is stable. DNA is transcribed into mRNA which is subsequently translated into proteins and these mRNA vaccines are therefore considered to be a form of gene therapy. Two major types of RNA are currently being developed: non-replicating mRNA and virally derived, self-amplifying RNA.

Vaccines under development worldwide

As at September 2021, there were 10,716 clinical trials of vaccines being conducted worldwide. Of these, 2,110 studies were classed as active (e.g. still recruiting patients, enrolling by invitation, or active but not recruiting) covering 1,336 conditions (*Figure 12*). Key developments in the vaccine field are expanding to include non-infectious (non-communicable) diseases and present significant potential opportunities for Australian health care should these vaccines be approved and prove successful.

Figure 12 — Number of active and recruiting vaccine studies around the World, September 2021



Source: Shawview Consulting analysis of www.clinicaltrials.gov as at 15/9/2021. Conditions/diseases included where there were 100 or more clinical trials per category. Note: Double counting is possible due to the keyword filters applied by the website. Search terms used on the clincaltrials.gov website were "vaccine", "vaccination" and "immunization".

Key developments in the global vaccine pipeline that would appear to be particularly relevant to Australia in the future are in:

1. carcinoma
2. degenerative conditions (such as genetic conditions and Alzheimer's disease)
3. coronavirus
4. autoimmune diseases through to vaccinations against allergies ("negative vaccinations")
5. universal vaccines
6. prophylactic/preventative pharmaceuticals, and
7. other (such as new modes of delivery, supply requirements and durability of effect).

Significant developments in these disease areas are likely to have a profound effect on various aspects of the Australian healthcare system. Appendix B outlines the major conditions with vaccines in development across the world and assesses the relevance of these emerging vaccine areas to Australia. While there are high numbers of respiratory tract vaccines being developed, these have not been detailed in length in this report. Successful vaccines for respiratory illnesses (such as influenza and respiratory syncytial virus (RSV)) could have a significant impact on reducing the incidence of these illnesses which would be of great benefit to the health system in reducing emergency department presentations. However, these vaccines are less likely to change how the health system operates in the same order as some of the other developments.

1. Carcinomas

Currently, there are two types of cancer vaccines available: preventive vaccines which protect a person from oncoviruses (viruses that are strongly linked to cancer), while therapeutic vaccines attack cancer cells themselves.

There are currently three preventive vaccines that are approved for use:

- Cervarix® (GlaxoSmithKline), Gardasil® and Gardasil-9® (MSD) – protect against HPV-related cancers of the cervix, anus, throat, head and neck, vulva, vagina and penis (Gardasil-9® has generally replaced Gardasil® because it covers more strains of HPV), and
- Heplisav-B® (Dynamax Technologies) protects against hepatitis B infection and hepatitis B-related liver cancer.

There are currently three vaccines approved to treat cancers:

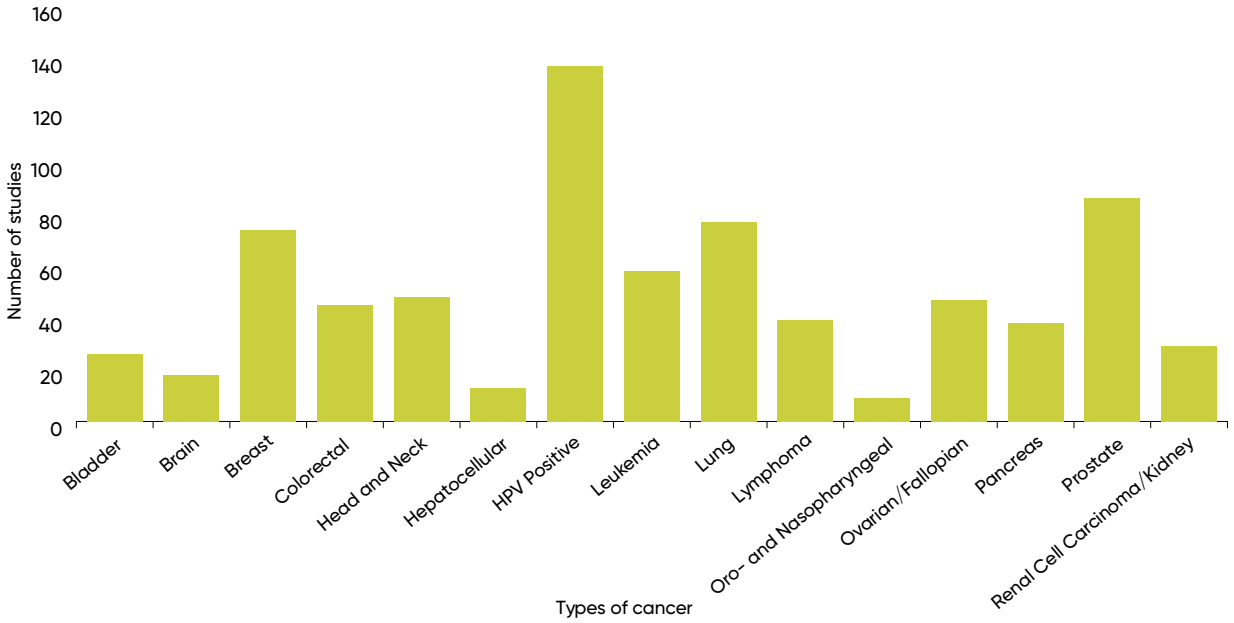
- Provenge® (Sipuleucel-T, Dendreon Pharmaceuticals) for prostate cancer
- Imlygic® (Talimogene Laherparepvec, Amgen) for advanced melanoma, and
- Bacillus Calmette-Guerin vaccine (BCG, MSD) for bladder cancer (note BCG was traditionally developed and approved for use as vaccine against tuberculosis).

There are several new cancer vaccines on the horizon and these generally use neoantigen personalised therapy. These neoantigens are only seen on cancer cells, not on normal healthy cells. The vaccines under development are typically aiming to identify and attack these neoantigens, therefore removing only cancer cells in the body. This should theoretically also eliminate side effects of cancer treatment because the vaccine will not attack healthy cells.

The whole-cell cancer vaccines being explored are either 'autologous' (personalised vaccine made from an individual's own cancer or immune system cells) or 'allogenic' (made from non-self-cancer cells grown in a laboratory). Allogenic vaccines are likely to be cheaper than autologous vaccines to produce. In addition, some vaccines are being explored that use parts of cancer cells; for example, proteins, peptides or DNA associated with tumour antigens that mount an immune response to an existing tumour.

There are a range of vaccines being developed for various types of cancers that are in the pipeline, many of which may come to market in the coming years (Figure 13).

Figure 13 – Number of phase 2 to 4 cancer vaccine studies according to cancer type



Source: Shawview Consulting analysis of www.clinicaltrials.gov as at 15/9/2021. Conditions/diseases included where there were 100 or more clinical trials per category. Note: Double counting is possible due to the keyword filters applied by the website. Search terms used on the clincaltrials.gov website were "Vaccine" and "carcinoma" or "neoplasm"; "Phase 2, 3 or 4"; "Active" and "recruiting" and "completed".

Appendix C lists the cancer vaccines under development which represent significant potential for the Australian healthcare system, given the incidence of breast, colorectal, HPV, lung, ovarian and kidney cancer.

2. Central nervous system

The studies in this category which may be profound and system-changing for the Australian healthcare system are developments concerning vaccines for dementia, including:

- ACI-35.030 (AC Immune SA) recently announced positive phase Ib/IIa results with a significant antigen-specific antibody response against phosphorylated tau (pTau) in 100% of older patients with early Alzheimer's disease. The vaccine candidate is now being developed further in collaboration with Janssen Pharmaceutical.
- UB-311 (United NeuroSciences) is beginning phase IIb studies after promising phase IIa results with 96% of the 42 patients with early Alzheimer's showing improvements in cognition and lower levels of beta-amyloid. A phase III study will be undertaken pending the phase IIb results.
- ABvac40 (Araclon Biotech) is an investigational vaccine targeting the C terminus of Aβ40, a beta-amyloid peptide found to contribute to the development of Alzheimer's disease. It is being studied in a phase II trial in Europe (n=135) and as at June 2020, 124 participants had received at least one dose with the trial expected to finish in February 2022.
- BCG (MSD) where in studies of BCG's effect on bladder cancer, a protective effect for Alzheimer's disease was noted. This is now being formally tested in a phase II study of 50 participants and is due to finish in December 2021.

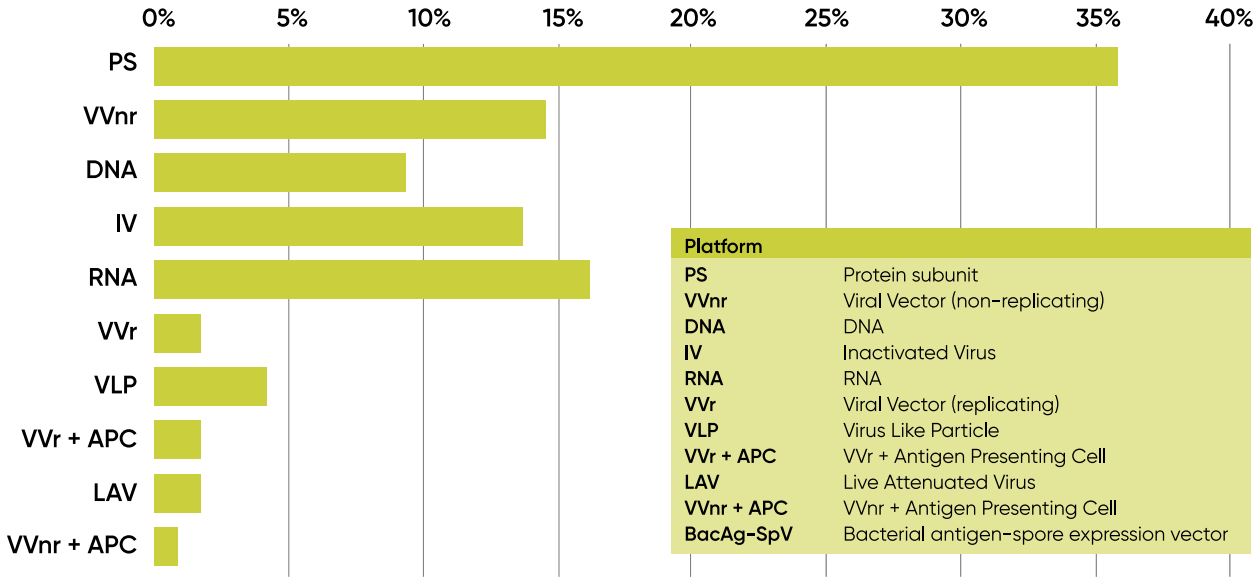
Dementia is a major disease in Australia that is taking on increased prevalence with Australia's population[169].

3. Coronavirus

As at August 2021, there are 7 coronavirus vaccines that have already obtained emergency use authorisation in several countries with another 13 awaiting assessment[170]. By mid-September 2021, according to the World Health Organization (WHO), there are a total of 117 coronavirus vaccines in clinical development and another 185 coronavirus vaccines that are in pre-clinical development[171].

According to WHO data, the majority of vaccines in development are given over two shots (63%) and as intramuscular injections (77%). Most of the coronavirus vaccines being developed are protein subunits (PS), however viral vectors (where other viruses are used to 'host' the vaccine material), DNA and RNA vaccines are all being studied. The more traditional live and attenuated virus types of vaccine are also being studied.

Figure 14 – Coronavirus vaccines in development according to mechanism of action, September 2021



Source: World Health Organization. 2021. "Draft landscape and tracker of COVID-19 candidate vaccines", https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines, accessed 15/9/2021.

4. Immune system disorders

Many of the clinical studies in for immune system disorders pertain to testing of existing vaccines in populations with compromised immune systems (for example people with HIV). As such, these developments are unlikely to have a profound effect on the Australian healthcare system and will not be explored in further detail in this report. There are, however, a small number of ongoing studies that are examples of vaccines with the potential for great impact in Australia, such as:

- Type 1 diabetes – several vaccines including PIpepTolDC and BCG are in early phase trials to vaccinate against Type 1 diabetes.
- Multiple Sclerosis – BioNTech is using its mRNA vaccine technology to trial a vaccine for preventing MS, and
- Allergies – several vaccines are being trialled for allergies including peanut allergies.

While early in trials, new vaccines for preventing things like Type 1 diabetes and multiple sclerosis could provide substantial health benefit and have major impacts on Australia's vaccination and broader health systems. Further details on these vaccines and their progress are at Appendix D.

5. Universal vaccines

The concept of a 'universal vaccine' is becoming more commonly discussed, with many media reports of the potential for a universal vaccine for all variants of influenza or for coronavirus. Universal vaccines, if they can be developed, are essentially effective against many or all strains of a disease and could therefore be able to deal with mutating disease strains in the community as they occur. Work towards universal vaccines for viruses like influenza and coronavirus is possible due to advances in artificial intelligence and knowledge from research such as the transformative Human Genome Project[172].

6. Prophylactic/preventative pharmaceuticals

A related emerging area is the growing range of prophylactic/preventative pharmaceuticals that have been available for many years (such as antibiotics given to prevent recurrent infections). This is an area of great development, such as the use of monoclonal antibodies (mAbs). Monoclonal antibodies are immune system proteins that are created in a laboratory. Like human antibodies, mAbs recognise specific targets (such as bacteria and viruses) and are used most commonly to treat cancer and inflammatory conditions (such as arthritis and ulcerative colitis). Several monoclonal antibody technologies have been developed recently including phage display, single B cell culture, single cell amplification and single plasma cell interrogation.

Recent examples of mAbs that are being used prophylactically include nirsevimab, which was reported to result in fewer medically attended RSV-associated lower respiratory tract infections and hospitalisations than placebo throughout RSV season in healthy pre-term infants[173]. Another example is the recent FDA emergency use authorisation of REGEN-COV (casirivimab and imdevimab together) as post-exposure prophylaxis for COVID-19 in adults and children at high-risk of progression to severe COVID-19. The FDA do note that the authorisation is not for pre-exposure usage and should not be considered as a substitute to a licensed COVID-19 vaccine.

7. Other areas of development

New modes of delivery, reduced dependency on cold chains for storage and vaccines that last longer with reduced requirements for booster vaccinations will likely have an impact on Australia's national immunisation approach and, potentially, the NIP.

Delivery techniques

Traditionally, nearly all vaccines currently available are administered by injection either subcutaneously or intramuscularly. New and different modes of delivery are being investigated which could prove more effective, more convenient, preferred by patients, or easier to deliver such as in remote settings where trained clinicians may not be present. Examples of such advances include inhaled nasal sprays for influenza or vaccine patch technology where a matrix of tiny needles deliver a vaccine without the use of a syringe[174].

Cold chain dependency

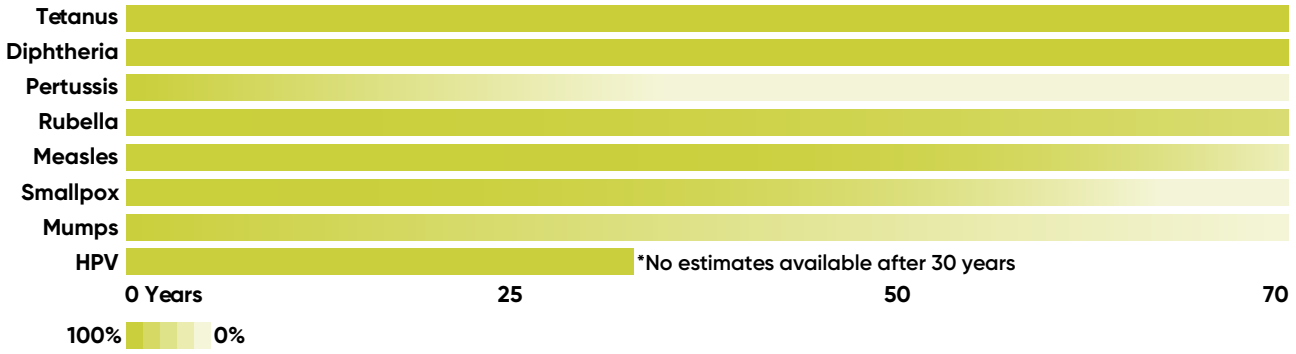
Many vaccines require refrigerated storage in cool to cold temperatures to remain viable. Temperature-controlled storage is unavailable in some parts of Australia, particularly rural and remote locations which particularly affects indigenous communities. Requirements for cold storage can also cause issues with supply, for example if air traffic cannot occur as expected due to supply disruptions, such as volcanic eruptions as happened in Iceland in 2010. Developments in cold-chain technology include the introduction of small filter-like membranes coated with glass to 'protect' the active virus particles during storage until required

and stabilisation techniques such as using a 'holder' for the live virus to allow the person administering the vaccine to manage the vaccine material onsite.

Longer acting vaccines

Recent studies show that the effectiveness of vaccines varies compared with official recommendations. For example, vaccines for mumps, pertussis, meningococcal disease and yellow fever lose their effectiveness faster than official immunisation recommendations suggest. However, vaccines for diphtheria and tetanus appear to last longer than recommendations for boosters (*Figure 15)*.

Figure 15 – Vaccine durability



Most vaccine durability estimates are based on tested antibody levels. The HPV estimates is based on a model of the Cervarix vaccine. Waning pertussis immunity is estimated from outbreak cases per year following a fifth dose of vaccine and before a subsequent booster. The smallpox estimate draws on data from six ourbreaks a century ago and assesses protection from disease, not infection.

Source: N. Desai, Science Cancer Med,11,2723, 2017 in Cohen. J. 2019. "How Long do Vaccines Last? The Surprising Answers May Help Protect People Longer", *Nature*, 18 April, https://www.sciencemag.org/news/2019/04/how-long-do-vaccines-last-surprising-answers-may-help-protect-people-longer, accessed 31/5/2021.

Research into the duration of effect of vaccines is growing. To date, immunologic memory has not been systematically measured. With more research in this area, the potential is there to make all vaccines work better than currently is the case[175].

Conclusion

Vaccines for diseases and conditions such as cancer, Alzheimer's disease, Type 1 diabetes and allergies could have profound effects on the Australian health care system. Such vaccines, should they prove successful and brought to market, could lead to major paradigm shifts in how diseases are prevented, screened, diagnosed and treated. This could ultimately lead to changes in the financing of the whole health care system and the Australian reimbursement system should be prepared for these changes.

Possibly less profound, but likely to create challenges for the Australian reimbursement system, are more subtle innovations, such as in the delivery systems of vaccines. Where there are innovative developments that are deemed more convenient or palatable by the public, perhaps providing minimal increases in efficacy but at extra cost, these developments may face barriers to reimbursement because such innovation is something that has often faced difficulty being valued and assessed by the PBAC[176]. Developments in cold-chain storage independence (i.e. a decreased reliance on cold storage facilities when transporting and administering vaccines) and optimisation of use of vaccines in marginalised populations may also have implications for both rural and remote Australia and Australia's Aboriginal and Torres Strait Islander people. Developments in vaccine patch technology may be another example where innovation in delivery systems may find the HTA -based framework used by PBAC to evaluate vaccines a challenge.

6 COVID-19 vaccines and lessons for Australia

"A safe and effective vaccine, available globally, will dramatically improve health outcomes and societal wellbeing and facilitate economic recovery."

Australian Government, Australian COVID-19 Vaccination Policy, November 2020[177]

"The successful development of COVID-19 vaccines has improved the medium-term outlook for global growth."

Reserve Bank of Australia, Statement on Monetary Policy, February 2021[178]

"On the downside, without widespread vaccination, the economy is vulnerable to a sizeable outbreak and accompanying restrictions, and delays to skilled immigration could crimp growth."

OECD, "Australia", Economic Outlook, May 2021[179]

Key points

- The COVID-19 pandemic has provided a timely reminder on the value of vaccines and health care to Australia and the world.
- Australia's management of the NIP and broader vaccines policy should learn from the COVID-19 pandemic, such as opportunities for faster decision making and processes.
- The pandemic has graphically demonstrated the importance of appropriately valuing the economic benefit of vaccines and the economic case for investing more to provide vaccines to Australians.
- The pandemic has illustrated the importance for government of developing long-term, strategic collaborative relationships with manufacturers, ensuring robust high-priority supply chains and considering domestic manufacturing capability.

The COVID-19 pandemic has been an instructional masterclass for Australia on the importance of appreciating the social and economic value of vaccines.

While many of the issues in Australia's vaccines policy have been there for many years, the pandemic illustrated with searing clarity just how important the development, supply and broader economic valuation of vaccines are to Australia.

At the time of writing, Australia is managing COVID-19 outbreaks of the Delta variant and enduring further stringent lockdowns to contain the virus. This has come at a time when issues in the speed of Australia's COVID-19 vaccine rollout, delays in securing sufficient supply of vaccines, issues in the logistics of the rollout and lingering vaccine hesitancy and complacency in the community mean the risk of further outbreaks is still present. Australia's COVID-19 vaccine rollout has triggered much debate in the community about Australia's approach to evaluating and purchasing vaccines. At the time of writing, it appears after substantial initial delays compared with other OECD countries that Australia is now securing sufficient supplies of COVID-19 vaccines and community vaccination rates are quickly accelerating.

As already discussed in previous sections, issues in Australia's vaccine policies are not new. Things such as the timeliness of approvals and funding, the extent to which evaluation systems recognise the economic value of vaccines, the relative balance between clinical need for new vaccines versus managing their fiscal budgets, the relative priority put on the longer-term economic benefits of vaccines to society versus their shorter-term cost, constructive understanding of and engagement with vaccines industry by governments, Australia's relative priority in the global vaccines market, the speed of uptake of new vaccines, logistical and supply chain issues and the level of Commonwealth-state cooperation are all ongoing issues in Australian vaccine policy.

Such issues have been present for years and managed to varying degrees of success, but the COVID-19 pandemic has revealed to everyone in Australia just how important these issues are for the success of vaccines policy, the economic strength of the country and the health of the Australian community.

Australia's vaccine response to COVID-19 has, however, been materially different to how Australia normally values, assesses, funds and supplies vaccines for the Australian community. The scale of the pandemic's impact, the speed with which the virus spreads and the relative newness of both the disease and the vaccines to prevent it have meant that policy and funding responses have evolved in real time and are materially different from Australia's more routine – almost day-to-day – management of vaccines for all other diseases through the NIP.

Given that the average time for the Commonwealth to fund a vaccine after TGA approval is 1,375 days – almost four years – under normal circumstances, it is hardly likely the Australian community were going to tolerate waiting this long for COVID-19 vaccines to be funded and provided to them.

Australia's response to the COVID-19 pandemic therefore provides an opportunity to reflect on how Australia has approached the assessment, procurement and use of vaccines in this situation and the lessons that might be learned for Australia's vaccines policy more generally.

Regulatory and reimbursement arrangements for COVID-19 vaccines

One key difference with the pandemic is that to date the assessment, procurement and supply of COVID-19 vaccines has not been conducted through the NIP or its supporting policy and assessment processes in the way that other vaccines normally would. This is different approach from how the 2009 H1N1 pandemic was managed, where H1N1 influenza vaccines were purchased directly by the Commonwealth through the NIP.

According to the Commonwealth government's Australian COVID-19 Vaccination Strategy released in August 2020, the government will "draw from the strengths of the NIP – including the reliance on robust regulatory pathways, timely application of expert scientific and medical advice, and effective cross-jurisdictional coordination and delivery mechanisms – while adopting sufficient flexibility to ensure the safe, efficient, effective and transparent delivery of a pandemic-context vaccination program over an acceptable time period"[180].

This is effectively an admission that Australia's normal assessment and funding processes for vaccines are not sufficiently timely. Due to the speed and timeliness in decision making required for securing COVID-19 vaccines for the Australian community during the pandemic, many of the normal NIP valuation processes had to be sidestepped altogether. While ATAGI has provided clinical advice to the Commonwealth, the PBAC has not yet evaluated any COVID-19 vaccines. The normal tender processes were not used, and the Commonwealth used different procurement processes through advance purchase agreements – often before vaccine development was finalised and the vaccines were even approved – to secure sufficient supplies for Australia. That said, the Commonwealth has already been advising companies that once the pandemic has finished, COVID-19 vaccines will be assessed through the PBAC process the same as other vaccines for listing on the NIP.

During the pandemic, the Commonwealth Government has instead developed a structure to negotiate and purchase COVID-19 vaccines that included:

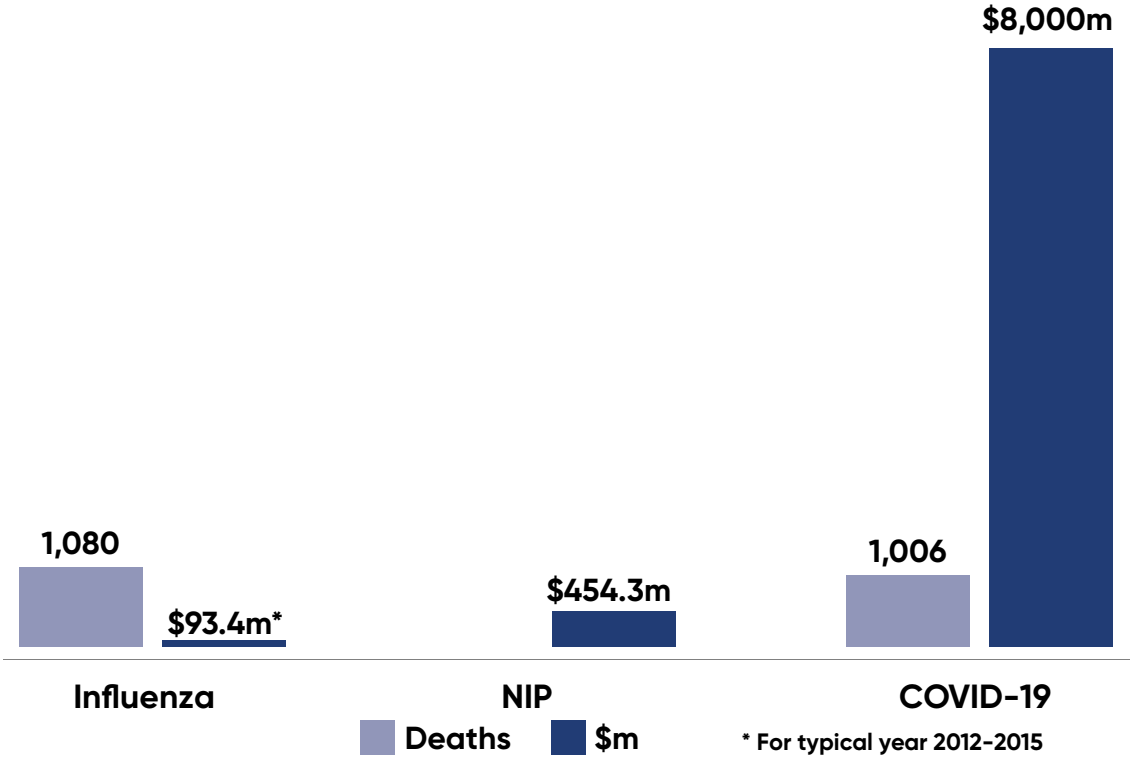
- A COVID-19 Vaccines Taskforce to advise the Commonwealth on purchasing and supplying vaccines.
- Formal and informal approaches to market by directly contracting companies that were known to be developing COVID-19 vaccines, and
- Providing $66 million in coronavirus related research for vaccines and treatments[181], including an effort to develop a COVID-19 vaccine through the University of Queensland, a trial which was later discontinued.

Economic impact of COVID-19 and the economic benefit of vaccines

Given the difficulties the processes used for evaluation NIP vaccines have in assessing the long-term broader economic vaccines in normal times, an important question is whether such systems would have even coped with evaluating the COVID-19 vaccines where a key factor was their economic benefit to the Australian community.

The assumptions and policy approach for valuing and funding COVID-19 vaccines has been materially different compared to the approach normally used by Australia to assess and fund vaccines under the NIP. For example, as at 1 September 2021 the Commonwealth government had committed at least $8 billion towards the purchasing and rollout of COVID-19 vaccines for Australia during the 2020-21 period at time when there had been 1,006 deaths from COVID-19 over the 18 months since COVID-19 emerged in Australia (Figure 16). In the last year before the pandemic started, 2019, 1,080 Australians died directly from influenza[182] while the average annual spend on influenza vaccines in Australia was around $93.4 million and spending on the total NIP in 2020-21 was $454.3 million.

Figure 16 – Influenza (2019) vs NIP (2020-21) vs COVID-19 (as at 1 Sept 2021) – deaths and vaccine spend, Australia



Source: ABS. "Causes of Death, Australia, 23 October 2020, https://www.abs.gov.au/statistics/health/causes-death/causes-death-australia/latest-release, accessed 27/5/2021; Department of Health. "Coronavirus (COVID-19) case numbers and statistics", 1 September 2021, https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-case-numbers-and-statistics#covid19-summary-statistics, accessed 1/9/2021 Department of Health. 2021. "Australia's vaccine agreements", https://www.health.gov.au/initatives-and-programs/covid-19-vaccines/covid-19-vaccine-government-response/australias-vaccine-agreements, accessed 1/9/2021; VISES. 2021. *Vaccine Study: Benefit-Cost Analysis*, Report to Shawview Consulting, Victoria University, 16 April. Note: costs for inluenza derived from typical year 2012 - 2015. COVID deaths as at 1 September 2021; Commonwealth of Australia 2021. *Budget 2021-22: Budget Paper No. 1 and Budget Paper No. 3*, https://budget.gov.au/2021-22/content/bp1/index.htm, accessed 20/9/2021.

This is not to downplay the importance of securing sufficient COVID-19 vaccines for the Australian population. The vaccine strategy is a critical factor in Australia's protection and recovery from the pandemic. Rather, the spend Australia is prepared to devote to protecting itself from COVID-19 compared with what it normally spends to protect itself from a disease like influenza is substantially more. Influenza kills hundreds of Australians each year and thousands of Australians in bad outbreak years. Australia's preparedness to invest billions of dollars in COVID-19 vaccines should raise questions about how Australia values vaccines that treat other infectious diseases in more 'normal' times.

The economic impact of the COVID-19 pandemic and the potential for COVID-19 vaccines to prevent severe disease and death has been a major factor in the response to the pandemic by Australia and just about every other country in the world. In Australia, various macroeconomic scenarios, strategies and Budget projections of Australia's economic recovery prepared by Commonwealth government agencies like the Treasury and the Reserve Bank of Australia hinge on the successful and timely rollout of COVID-19 vaccines[183].

The cost of the COVID-19 pandemic to the economy has been substantial. For example, the total cost of the Commonwealth government's economic support response to the pandemic, comprising assistance to individuals, households and businesses, is $291 billion or 14.7% of GDP[184]. This means that the impact of the pandemic through an infectious disease has been to cost almost 15% of the national economy. This has been a significant cost for the government, the economy and society, let alone the longer term economic and social damage brought on by the COVID-19 pandemic.

There has also been a belated recognition in Australia that the country's economic performance is influenced by the health of Australians and health systems. The Governor of the Reserve Bank, for example, has said that "As is increasingly clear from experience both here and overseas, the health of the population and the health of the economy are inextricably linked"[185]. The Australian Government's 2020 Budget also recognised that "The challenges for the Australian economy from the virus remain significant. Further outbreaks of the virus are likely until a vaccine is developed and widely available"[186]. Similarly, international organisations like the IMF, World Bank and OECD have all shown that a key factor in the successful post-pandemic recovery of the global economy hinges on successfully developing and rolling out COVID-19 vaccines[187].

The pandemic and government responses to it have also triggered a broader reflection on the value of human life and the costs that society is willing to bear to save lives. More than one commentator has noted that the costs to the Commonwealth of beating the COVID-19 pandemic infer a value of life higher than that used more normally in health care decision making[188]. This begs the question whether the Government's level of expenditure and response to COVID-19 is wrong or whether, in fact, cost-effectiveness and value of life assumptions used in more normal health economic evaluations for programs like the NIP are consistent with modern community standards.

Time from regulatory approval to subsidised access

The COVID-19 pandemic has provided a valuable lesson in how quickly the Commonwealth government can assess and purchase vaccines for the Australian population. The time between regulatory approval by the TGA and commencement of publicly funded access for the Pfizer-BioNTech, the AstraZeneca/Oxford COVID-19 and Moderna vaccines took between 4 to 6 weeks (Table 10).

Table 10 – Time between regulatory approval and publicly-funded access to COVID-19 vaccines in Australia

	TGA registration date	Vaccination program began	Time TGA approval to availability	HTA assessment
Pfizer-BioNTech vaccine	25 Jan 2021	21 Feb 2021	4 weeks	No
AstraZeneca/Oxford vaccine	16 Feb 2021	22 Mar 2021	6 weeks	No
Moderna vaccine	9 Aug 2021	20 Sep 2021	6 weeks	No

Source: Department of Health. "Australia's Vaccine Agreements", https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/covid-19-vaccine-government-response/australias-vaccine-agreements, accessed 16/9/2021; Belot, H. 2021. "Another 1 Million Moderna COVID 19 Vaccine Doses Coming to Australia after EU deal", *ABC News*, 12 September, https://www.abc.net.au/news/2021-09-12/one-million-moderna-vaccines-secured-from-eu-scott-morrison/100455502, accessed 16/9/2021.

The very short time taken to make COVID-19 vaccines available stands in stark contrast to the normal timelines seen for other vaccines to be listed on the NIP. Typically, it takes years for a vaccine to obtain subsidy under the NIP compared with the 4 to 6 weeks seen for COVID-19 vaccines. While obviously the pandemic conditions of COVID-19 required substantially more program and administrative resourcing than the normal operation of the NIP listing process, this does raise the valid question whether improvements in the timeliness of the NIP listing process could be realistically achieved in a post-COVID world. This is worthy of further consideration.

Manufacturing, advance purchase agreements and supply chain issues

The COVID-19 pandemic has also highlighted issues for Australia in developing, manufacturing, purchasing and securing vaccines for the Australian population. Purchase and manufacturing are key areas identified in Australia's COVID-19 Vaccine and Treatment Strategy[189] so that Australians will have access to safe and effective vaccines. This is done through direct procurement from overseas or through manufacturing under license in Australia. This is being progressed through:

- advance purchase agreements to secure direct purchase of vaccine or treatment doses, once they are available.
- agreements to use Australian manufacturers for vaccine production and expand their capability and capacity.
- international and multilateral agreements to support and facilitate access for Australia and its region, and
- procurement contracts to buy the goods, materials and services needed to distribute and administer vaccines and treatments.

The government is also collecting information on Australia's COVID-19 vaccine and treatment manufacturing capability and capacity. This includes an audit identifying opportunities to expand, modify or repurpose local industry's capability and capacity.

The Commonwealth government has entered into five separate agreements for the supply of 280 million doses of COVID-19 vaccines in total. The Commonwealth estimates that these five supply agreements will cost more than $8 billion[190]. The current five agreements are with:

- Pfizer-BioNTech – an mRNA-based vaccine which received provisional TGA approval on 25 January 2021.
- Astra-Zeneca/Oxford (to be largely manufactured under licence by CSL in Australia) – a viral vector vaccine which received TGA approval on 16 February 2021.
- Moderna – an mRNA vaccine which received provisional TGA approval on 9 August 2021.
- Novavax – a protein vaccine undergoing TGA evaluation at the time of writing, and
- COVAX Facility – the Australian Government has made two financial commitments to GAVI's COVAX Facility for the supply of safe and effective COVID-19 vaccines:
    - An upfront payment of $123.2 million to allow the purchase of over 25 million doses of COVID-19 vaccines for the Australian population. This would be sufficient for 50% of the population to receive a two-dose regimen, and
    - An initial investment announced on 26 August 2020 for $80 million to support vaccine access for up to 94 lower-income countries through the Facility's Advanced Market Commitment (AMC), with an additional investment of $50 million announced on 3 June 2021, taking the Commonwealth government's total commitment to the COVAX AMC to $130 million.

Through its advance purchase agreements, the Commonwealth government has reached agreements with vaccine companies to purchase just over 280 million doses of COVID-19 vaccines (Table 11).

Table 11 — Australia's COVID-19 vaccine advance purchase agreements

Company	Doses purchased	Place of manufacture
Pfizer-BioNTech	126 million[191] - 10 million announced Nov 2021 - 10 million announced Feb 2021, - 20 million announced Apr 2021, due Q4 2021 - 85 million booster shots announced Jul 2021, due 2022 and 2023 - 1 million announced August 2021 (via purchase from Poland)	Manufactured offshore
Astra-Zeneca/Oxford	53.8 million	3.8 m doses manufactured offshore 50 million doses manufactured by CSL in Melbourne, Australia
Novavax	51 million (most doses likely available 2022[192])	Manufactured in several locations across Europe
Moderna	25 million – announced 13 May 2021 - 10 million late 2021 - 15 million for variants first half 2022	Manufactured offshore
COVAX	25 million	Likely to be manufactured offshore

Source: Department of Health. "Australia's vaccine agreements", https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/covid-19-vaccine-government-response/australias-vaccine-agreements, accessed 16/9/2021.

The Commonwealth government also initially supported the University of Queensland's development of a COVID-19 vaccine. However, the development of this vaccine was abandoned after it was revealed a side effect of the vaccine was the creation of false positive tests for HIV for some test participants[193].

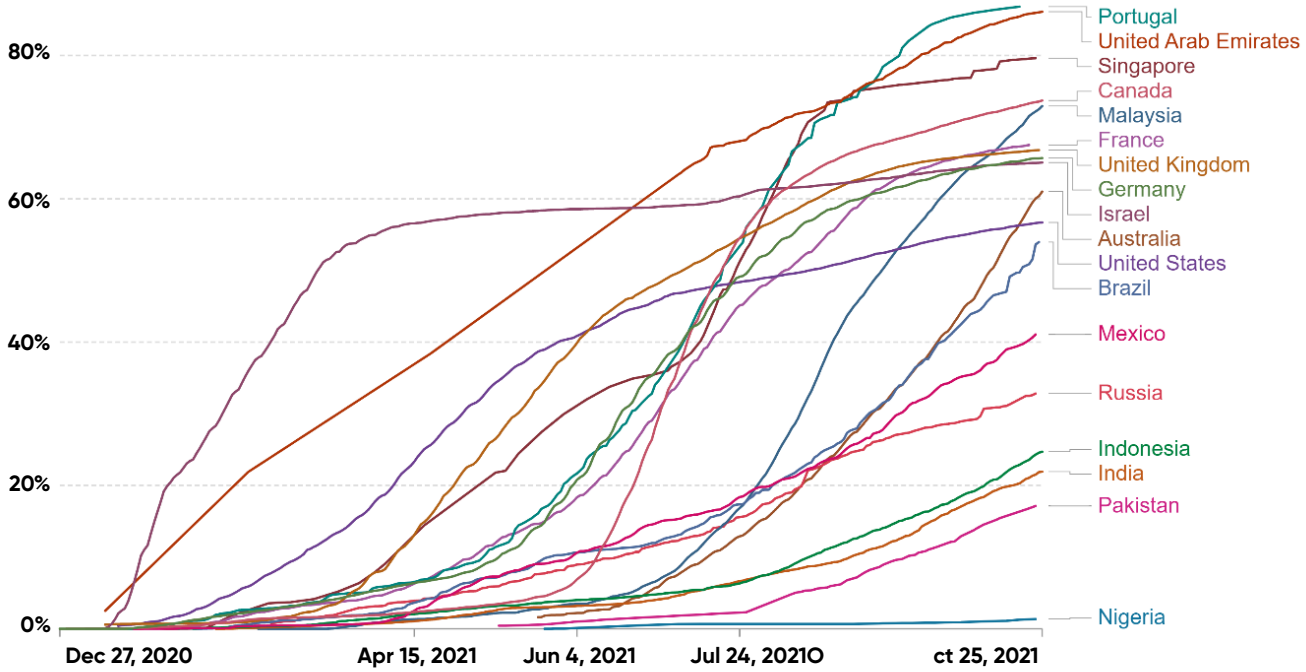
Issues in providing COVID-19 vaccines to Australians

Australia has experienced several issues in executing securing and supplying COVID-19 vaccines for the community which provide some lessons for longer-term supply of vaccines more generally.

Australia's rollout and supply of COVID-19 vaccinations to its population started slower than many other industrialised countries, although progress is starting to ramp up (Figure 17). As at 26 October 2021, after a slow start Australia's rate of full vaccination in the population had ramped up significantly, pulling away from India and Indonesia, had overtaken the United States and was approaching the same full vaccination rates as Germany and the United Kingdom.

Moreover, for a long time the Commonwealth's original target for all Australians to be vaccinated by October 2021 looked like it was not going to be met due to supply delays, however given the most recent extra spending on vaccines, more deals belatedly being done with manufacturers and vaccine 'swaps' with countries such as Poland, Singapore and the United Kingdom, will significantly speed up the vaccine rollout[194]. However, since the beginning of 2021, the original October 2021 deadline was set aside, and subsequent revised targets were frequently not met to the point where the Commonwealth has abandoned an official target for when all Australians would be vaccinated.

Figure 17 – Population shares fully vaccinated with COVID-19 vaccine, by country, as at 26 Oct 2021



Source: Our World in Data. "Coronavirus (COVID-19) Vaccinations", Global Change Data Lab, University of Oxford, https://ourworldindata.org/covid-vaccinations, accessed 27/10/2021. Note: Alternative definitions of a full vaccination, e.g. having been infected with SARS-CoV-2 and having 1 dose of a 2-dose protocol, are ignored to maximize comparability between countries. OurWorldInData.org/coronavirus • CC BY

The reasons for this are many and varied. Since the pandemic initially started in early 2020, the Commonwealth was criticised for not initiating its advance purchase agreements early enough compared to other countries[195] and global supply issues have played a key part in slowing down Australia's vaccine rollout[196]. The reasons for this might have been an early reluctance by the Commonwealth to commit large investments of public funds upfront into emerging technologies, an over-reliance on existing Australian research options, and suggestions that there was a lack of priority and strategic communication by the Department of Health in engaging with global vaccine companies[197]. These problems may have been compounded by the Commonwealth's lack of connection to emerging vaccine technology trends, pharmaceutical industry business strategy and global supply chains. Ultimately the Commonwealth now has five advance purchase agreements for vaccines[198], the supply of vaccines has increased due to greater priority being applied to securing supply, and the vaccine rollout now appears to be on track to reach revised milestones perhaps by the end of 2021.

When supplies of vaccines were available there were initial issues in the timetable and methods used for the rollout of the vaccines. The Commonwealth opted to undertake the COVID-19 vaccine rollout using different strategies and structures from the more normal distribution channels for vaccines supplied through the NIP. A selective delivery general practitioner (GP) model was adopted, whereby initially 4,000 of the 10,000 GP clinics in Australia were invited to participate in the rollout, specialist contracts for wholesale distribution were given to different companies separate from the standard full line wholesale distribution system, and pharmacists were not initially used to support the COVID-19 vaccine rollout in the same way they are usually used for delivering influenza vaccine rollouts each year[199]. The Government's timetable for starting initially with around 1,000 GPs to deliver the vaccine against available supply[200] was criticised as being too slow[201]. Subsequently, more GP clinics were added to the rollout and pharmacists were finally added to the rollout later in 2021[202].

Investment in manufacturing

Given emerging international supply chain issues in vaccines, the Commonwealth government has been keen to expand vaccine manufacturing capability in Australia. In 2020, the Commonwealth announced[203] the investment of $1 billion in a joint venture with Seqirus (a subsidiary of biotech company CSL), which itself will contribute $800 million to build the largest flu vaccine manufacturing plant in the southern hemisphere. The plant will be based in Melbourne and is expected to be operational by 2026.

The Commonwealth's objective is to ensure that Australia has stockpiles of critical vaccines and antivenoms in the future. While much of Australia's existing flu vaccine capability is based on chicken egg-based technology, this new plant will use cell-based technology for the manufacture of vaccines, making it the only cell-based influenza vaccines facility in the Southern Hemisphere. The facility aims to future-proof Australia's access to coronavirus vaccines and provide support for a range of vaccines including pandemic flu, seasonal flu, antivenoms and Q fever.

The Commonwealth has also recently issued an invitation to market for the development of mRNA vaccine manufacturing capabilities in Australia[204]. The Victorian state government has also offered to contribute $50 million to the development of an mRNA manufacturing facility in its state[205], and there are proposals for similar such plants in South Australia[206]. Currently Australia does not have sovereign capability in mRNA vaccine manufacturing.

The subject of Australia's manufacturing capability, or lack thereof, in medicines and vaccines has resurfaced in the light of the COVID-19 pandemic and the subsequent supply chain issues in securing COVID-19 vaccines. For example, the Australian Academy of Science has called on the Commonwealth government to develop additional onshore vaccine nucleic acid manufacturing capability in its 2021-22 Pre-Budget submission:

> *"The Australian Academy of Science believes that despite our one-hundred-year-old investment in CSL, there are gaps in our ability to produce vaccines onshore. Without the ability to produce vaccines onshore, Australia and the region remain vulnerable to supply shocks and outbreaks of 'vaccine nationalism'"*[207].

For example, while Australia can currently manufacture entire recombinant protein-based vaccines, for the mRNA technology Australia cannot mass produce the nucleic acid-based or lipid nanoparticle technology part of the vaccine, although it can produce adjuvants and complete the formulation, fill and finish capability. Nor does Australia have manufacturing capability in other vaccine technologies, such as conjugated vaccines or live attenuated vaccines. One result of this is that Australia is dependent on Europe and North America for supply of such vaccines rather than having the technology platform to manufacture domestically.

The revealed gaps in Australia's vaccine manufacturing capability are symptomatic of a broader issue in Australia's domestic manufacturing capability in life sciences. Despite an excellent medical science and technology base and strong research capabilities, the country has struggled to capitalise on this in a commercial sense, in part due to vacillating priority in policy support over many decades and varying investment interest from the private sector. This has occurred particularly in the global shift of economic and investment activity and other countries securing more investment in pharmaceutical and vaccine manufacturing capability[208].

What are the key reflections from COVID-19?

While a unique set of circumstances, there are several reflections for vaccines policy coming out of the COVID-19 pandemic that provide some guidance for vaccines policy more generally in Australia:

- the response to the pandemic and prioritisation put on urgent access to COVID-19 vaccines by the Commonwealth and state and territory governments demonstrates their recognition of the link between health and economic wealth.
- the effect of health on the economy is clearly demonstrated through the impacts of the pandemic on GDP, productivity, unemployment and investment, all factors which do not normally feature in the HTA decision making for other vaccines in Australia.
- the imperative to have COVID-19 vaccines available for the Australian community has shown that the existing processes for assessing and funding vaccines are slow and could be dramatically improved.
- governments are approaching procurement of these vaccines for COVID-19 with an early investment mindset and a similar approach to obtaining other vaccines for other diseases could be adopted in Australia.
- the need for strong global supply chain arrangements and long-term strategic relationships with suppliers has been demonstrated, given that most of Australia's vaccines are imported.
- Australia should build greater manufacturing capability with a comprehensive strategy to ensure Australia's potential opportunities in vaccine manufacturing, science, clinical trials are fully exploited, and
- Australia should develop a pandemic vaccine plan and consider how this can be consistent with and work in tandem with Australia's normal vaccine funding policies.

7 Conclusions

Key points

- At a broad historical level, Australia's immunisation policies have been successful in achieving broad coverage and uptake in funded programs; however, there are several issues which could impede continued success in suppressing disease and improving health outcomes in the future.
- Australia's system differs from that of many other countries by requiring ATAGI to advise the health technology assessment body, the PBAC, on NIP listings rather than making such recommendations directly to government.
- At around $450 million a year, the level of investment in the National Immunisation Program (NIP) is relatively low in comparison to other federally funded health and social programs and may not be sufficient to meet the needs of Australia's future requirements given the pipeline of new vaccines in development.
- Challenges caused by delays to access to new and innovative vaccines, problems with the current evaluation system and its ability to appropriately assess and value emerging future vaccine technologies, inadequate funding levels, all of which have been highlighted by the COVID-19 pandemic, point to a need to reform Australia's vaccine policies.
- How Australia values and funds vaccines must be reformed and enhanced to ensure that Australians can continue to access innovative and best in class vaccines now and in the future.
- A suggested four-point plan to reform Australia's vaccine policies is presented in the report.

Key findings

Australia's vaccines policies are at a crossroads

As a major piece of Australia's public health policy, the NIP has by and large served Australians well since its creation in 1997. Australia now has a coordinated, national immunisation scheme that ensures particularly children are fully immunised for most vaccines recommended by expert advice, albeit not always with the latest and most effective vaccines. In fact, Australia recently reached the key milestone of 95% vaccination rates for children – a long-held ambition. In the scheme of things, for a mere $450 million a year the NIP protects the Australian population from severe disability and death stemming from a range of diseases that once were a scourge for Australian society. At a broad historical level, as a result of these achievements, Australia an enviable position internationally for its successful health outcomes.

However, there are several issues with the way that Australia values and funds vaccines through the NIP. Many of these have been developing for some time, while the recent COVID-19 pandemic has thrown some of these longer-term issues into stark relief.

How Australia assesses the value of vaccines

The processes Australia uses to evaluate and value vaccines are out of step with international standards. On several levels, the NIP and how it is administered is different from the practice of other countries and recommendations of the WHO. This Australian experience leaves open the possibility that Australians are not, and will not, gain full access to vaccines in a timely fashion, or at all, particularly given evolving changes in vaccine technology.

The system today where ATAGI, reports to the PBAC and it is the PBAC that is responsible for assessing and recommending vaccines for funding to the Minister for Health is somewhat unique. In our analysis, we have found relatively few examples where a country's NITAG reports to the medicines HTA evaluation committee rather than directly to the government. In most other countries, the NITAG will report directly to the health department or the minister and, in many cases, will undertake its own health economic evaluation of vaccines. In Australia, this is not the case. This raises questions whether vaccines can be appropriately valued by the standard HTA framework used by the PBAC. There have been claims internationally that such HTA frameworks frequently under-value vaccines because of vaccines' unique evidence requirements, the health economic assumptions made and questions about the ability to assess of evidence of vaccines' broader economic and social benefits.

There are examples in Australia of vaccines that have been delayed or never funded due to the PBAC's framework for decision-making. Vaccines for meningococcal B, for example, are still not funded for the general population today under the NIP, despite repeated submissions and recommendations from ATAGI and one company has chosen to take its shingles vaccine to the private market after not being able to get an NIP listing. In the past, submissions to fund other vaccines from cervical cancer to rotavirus were delayed in part due to the PBAC's HTA framework. Moreover, there are several vaccines recommended for funding by ATAGI on clinical grounds that are still not funded, such as a second booster shot for chickenpox and the adult vaccine shot for diphtheria, tetanus, and pertussis. In addition, despite the impact of influenza on society and the economy, influenza immunisation has largely been privatised for Australia's working-age population, with only the elderly and very young able to receive free flu shots through the NIP.

The fact is there are several issues with how the PBAC applies health economic evaluation to vaccines in Australia:

- The general imposition of a maximum ICER of $15,000 per QALY seems destined to delay the listing of vaccines and raises questions about the priority attached to public health programs like vaccination compared with other treatments for disease.

- Australia's use of a 5% discount rate to evaluate the costs and benefits of vaccines (and all other medicines for that matter) is an historical anachronism and is out of step with international best practice. The majority of other high-income countries consistently use discount rates in the range of 1% to 3%. Despite the many economic arguments why it should be a lot lower, Australia's 5% discount rate disadvantages all medical interventions that have high up-front cost and significant benefits over the long-term. Vaccines are a key example of this and are therefore front and centre one of the key medical interventions disadvantaged by the current high discount rate.

- The usual rejection by PBAC in its vaccine evaluations of broader non-health economic and productivity benefits to society is problematic. While perhaps done for reasons of lack of certainty or methodological difficulty, it is not good enough to ignore such benefits because they look too hard. Modelling done for this study has shown that the broader economic benefits to society from just five individual vaccines funded in the NIP are substantially larger than their upfront costs. Other studies demonstrate this as well. Such benefits should be considered in evaluating the worth of vaccines for the Australian population.

There is also the question of whether the Australian experience of moving ATAGI under the purview of the PBAC has worked from an administrative and policy sense. As per the recommendations of the WHO, Australia has a NITAG responsible for prioritising vaccination policy and making recommendations on vaccines in the form of ATAGI. Yet, it operates as a sub-committee of the committee responsible for medicines, the PBAC. The question is, has this worked? There are questions about whether either ATAGI *or* the PBAC have the requisite expertise, depth, and priority to undertake comprehensive health economic assessments of vaccines. While there may have been issues in the past in relation to ATAGI not making recommendations to the Commonwealth government cognisant of funding constraints, it is unclear whether moving ATAGI under the PBAC umbrella and giving the PBAC the job of recommending vaccines has worked either.

The Commonwealth's administrative processes could be more efficiently and effectively delivered. Vaccines undergo a four-step process of evaluation, being assessed by the TGA, then ATAGI, then the PBAC and then a substantial and somewhat opaque tender process at the Commonwealth level. Aside from the fact that the industry funds much of this process, this process could be more efficient or effective. All this administrative process takes time and is costly for industry and government.

Vaccine funding and purchasing

At around $450 million a year, the NIP, compared to other programs like the Medical Benefits Scheme, the National Disability Insurance Scheme and even the Pharmaceutical Benefits Scheme, is a relatively low-budget program. Yet the NIP prevents a range of diseases that, if they were as prevalent as they once were, would have substantial impacts on Australian health, society and the economy.

The question is whether $450 million a year is sufficient to ensure Australia can access current vaccines and further vaccine development. Since the move to centralise purchasing of NIP

vaccines with the Commonwealth in 2009, the scheme has seen no real growth in spending since that time. Compared with other parts of the health portfolio, funding for vaccines under the NIP has been the same for a decade.

The preparedness of the Commonwealth government to fund COVID-19 vaccines to the tune of $8 billion when funding for all other vaccines in Australia is $450 million a year only serves to illustrate the disparity in funding between vaccines for a disease that has demonstrably visible economic impacts versus those vaccines for diseases where the economic impact – while substantial – is perhaps less immediately obvious.

For example, in 2019 over 1,000 Australians died from influenza, yet the funding levels attached to Australia's annual influenza campaign are nothing like the same scale applied to COVID-19. This is not to devalue the importance of the COVID-19 vaccine rollout – it is a critical program for the country – rather to highlight that other vaccination programs could perhaps benefit from a similarly broad view of their societal and economy-wide benefit.

There are questions about whether the shift to Commonwealth responsibility for vaccine purchasing has resulted in a better strategic relationship with the vaccine industry. The Commonwealth's typically 'transactional' approach to tendering and purchasing, while perhaps efficient in the short-term, may not help instil a longer-term 'strategic' relationship with vaccines manufacturers. It appears that in recent years the Department of Health has let slip the important task of developing and maintaining a strategic working relationship and understanding with the vaccines industry, something that came to light during the COVID-19 pandemic.

Future priorities

The range of new vaccines currently being developed offer the potential promise of preventing a range of illnesses that currently cannot be vaccinated against. Vaccines for the prevention of conditions such as everything from respiratory diseases, cancer, Alzheimer's disease, Type 1 diabetes, multiple sclerosis, and even peanut allergies offer the prospect of substantial health for the community and economic gains to Australia in the future. As history shows, vaccines have the potential to eliminate diseases quietly, unobtrusively and comprehensively in Australian society, so ensuring that our funding and evaluation systems are up to scratch is important. In addition, better embedding a system of horizon scanning into the NIP processes to better prepare the program for future vaccine technologies should be considered.

In contrast to childhood vaccination, Australia's track record in adult vaccination is not good. Given that a sizeable portion of Australia's population are missing out on vaccinations they are already entitled to receive for free, and more adult vaccinations being developed, it suggests that more work needs to be done. Universal vaccines, new technological platforms, and delivery through channels like cold-chain technologies all point to a need to ensure Australia's systems are fit-for-purpose.

Lessons from COVID-19 pandemic

Australia's experience in using vaccination during the COVID-19 pandemic only serves to illustrate the importance of a timely and effective vaccine program. By necessity, the Commonwealth government was forced by the pandemic to recognise the major potential economic impact of an infectious disease in COVID-19 and up-front commit major funding to develop and acquire vaccines to address this economic impact. The fact is such issues are present in any vaccination program, with the economic and societal effects of infection varying from disease to disease. As well as revealing what can be achieved in vaccine technological development when prioritised, the pandemic showed the economic importance of investing in preventive health care and vaccines, and in having long-term, constructive relations with and

understanding of the vaccines industry. In the aftermath of the pandemic, it will be important for Australia to understand and reflect on these lessons and apply them to future policy.

A four-point-plan for Australia's future vaccines policy

Considering the findings of this report, all stakeholders should work together to upgrade the way Australia's vaccines policies value and fund vaccines for Australians, supported by an appropriate level of investment. The post-COVID environment provides a unique opportunity for governments, industry, patients, health care professionals, vaccine experts and others to work together collaboratively to enhance Australia's NIP and vaccines funding policies for the long-term future benefit of the Australian community. The following four-point-plan provides key recommendations that should be implemented.

A four-point-plan for Australia's future vaccines policy

1. Long-term strategic plan for vaccines.
2. Reform Australia's vaccine health technology assessment methodology.
3. Reform the post-HTA procurement process for NIP vaccines.
4. Create a framework to develop a pandemic vaccination plan and ensure it remains operationally ready in the face of rapidly evolving risk.

1. Long-term strategic plan for vaccines

The Commonwealth along with a broad range of industry stakeholders should develop a long-term strategy for vaccines and the NIP. This strategic plan should complement the existing National Immunisation Strategy and preventative health strategies by covering gaps such as overarching principles and objectives, mechanisms to enhance government-industry dialogue and information exchange, horizon scanning, measures to maintain and improve the long-term viability of the Australian vaccines market, manufacturing and supply chain integrity and strategic procurement relations. The development of the plan should be supported by collaboration with patient groups, clinical and public health experts and others. This could be achieved by reconstituting and revamping Australia's National Immunisation Committee or creating a new strategic consultative committee on Australia's vaccination policies. Any committee should include vaccine industry representation and delivery channels for vaccine distribution on the Committee.

2. Reform Australia's vaccine health technology assessment methodology

Introduce changes to Australia's health technology assessment (HTA) methodology for evaluating vaccines to ensure that the full value of vaccines is appropriately assessed and considered when deciding on funding vaccines in Australia. These changes could be implemented to support the new Commonwealth government and Medicines Australia Strategic Agreement, the government's upcoming HTA Review and the current review of the National Medicines Policy. Changes that the Commonwealth government should make include:

- Consolidate, streamline, and strengthen the HTA evaluation of vaccines to remove duplication, improve administrative efficiency, reduce the time to listing and increase recognition of the value of vaccines. This could be achieved either through a more efficient and integrated evaluation system involving ATAGI and PBAC, or by adopting a model similar to many countries where ATAGI makes the HTA recommendation direct to the Minister for Health.

- Reduce the 5% discount rate used by the PBAC to be consistent with rates used in other high-income countries, in order to properly assess/value the future economic and social benefits of vaccines. Ensure that considerations specific to vaccines are included in the review of discount rates announced as part of the new Strategic Agreement.

- Require PBAC to consider the broader economic and productivity benefits of vaccines in the base case of vaccine submissions where appropriate rather than consigning them to supplementary analyses and consider the appropriate use of real-world evidence and local evidence generation to address concerns regarding uncertainty in valuing the full benefits to Australian society which accrue beyond the directly vaccinated cohort, such as herd immunity.

- Increase Australia's incremental cost-effectiveness ratio (ICER) implicit threshold for vaccines to not disadvantage vaccines against other medical technologies, and

- Benchmark Australia's HTA evaluation of vaccines against international best practice, in consultation with industry, patient groups and other health stakeholders.

3. Reform the post-HTA procurement process for NIP vaccines

Reform the objectives and approach of the post-PBAC NIP price negotiation process to remove duplicative processes and to shift procurement from a 'transactional' to 'strategic' approach with industry. This will help to ensure long-term market and supply chain viability is given equal weight to short-term cost-saving priorities. Greater priority should be given to ensuring that developing, manufacturing and supplying the latest vaccines in Australia is commercially attractive to companies and ensures Australia is sufficiently prioritised in international markets by the vaccines industry.

4. Create a framework to develop a pandemic vaccination plan and ensure it remains operationally ready in the face of a rapidly evolving risk

The Commonwealth should work with stakeholders, including industry, delivery channels and other stakeholders to collaboratively develop a pandemic vaccination plan to complement existing pandemic plans and better operate in tandem with the more normal NIP processes of regular community vaccination. While providing many instructive lessons for Australia's broader more routine vaccination programs, the COVID-19 pandemic and the government's vaccine response to it have demonstrated the need to develop a pandemic vaccination plan for future pandemics. The pandemic vaccination plan should complement existing plans such as the Emergency Response Plan for Communicable Disease Incidents of National Significance and the Australian Health Management Plan for Pandemic Influenza and look at overseas models of vaccine-based pandemic responses, including a Centre for Disease Control. This pandemic vaccination plan should be reviewed in close collaboration with industry to ensure Australia is able to develop, manufacture and purchase vaccines for future pandemics in a timely manner.

A final word

Australia's vaccination policies and the NIP have served Australians well over many years. They have protected Australians from disease, prevented many deaths and provided enormous benefits to the Australian economy and society. However, how Australia values vaccines and how the NIP operates to ensure Australians have access to vaccines in the future needs to be improved. This report has shown several areas and examples where Australians have either not been provided access to vaccines or where the processes to provide vaccines have not performed well. It is imperative in a post-COVID world that we invest in best practice vaccine valuation and funding systems to ensure Australians have access to the emerging new vaccine technologies of the future. Having a robust and best-in-class NIP is key to a future health system that Australians deserve.

8 Appendices

A: Case studies of vaccines going through NIP assessment process and issues

B: Global clinical studies of vaccines by disease/condition

C: Selected cancer vaccines in development according to cancer type

D: Selected vaccines in development according to type of immune system disorder

E: BRAVE Framework for value elements considered by European country

F: Victorian Institute of Strategic Economic Studies Vaccines Study: Benefit-Cost Analysis

APPENDIX A: Case studies of vaccines going through NIP assessment process and issues

Case Study: Gardasil®

Background to vaccine and disease

The world's first[209] human papillomavirus (HPV) vaccine, Gardasil®, to immunise against cervical cancer was first developed by Professor Ian Frazer at the University of Queensland and subsequently developed and commercialised first by CSL and then licensed to Merck Sharp & Dohme (MSD) worldwide. This made Gardasil® unique in that it was an Australian-developed vaccine to help prevent cervical cancer[210].

The initial vaccine worked by immunising patients for HPV serotypes 6, 11, 16 and 18, which at the time, accounted for at least 70% of cervical cancers and pre-cancerous cervical lesions[211]. Since the introduction of Gardasil®, the HPV rate amongst women aged 18 to 24 years has dropped from 22.7% to 1.1% between 2005 to 2015[212], with the prospect that Australia could now become the first country in the world to eliminate cervical cancer within the next 20 years[213].

Registration

Gardasil® was registered by the TGA in June 2006 for use in females aged 9 to 26 years for the prevention of cervical, vulvar and vaginal cancer, precancerous or dysplastic lesions, genital warts and infection caused by human papillomavirus (HPV) types 6, 11, 16 and 18 (which are included in the vaccine), and males aged 9 to 15 years for the prevention of infection caused by human papillomavirus (HPV) types 6, 11, 16 and 18 (which are included in the vaccine).

Reimbursement and NIP listing

As per the relatively new NIP listing process that had just been introduced the previous year in 2005, Gardasil was submitted to the November 2006 PBAC meeting. The first submission to PBAC for listing for Gardasil® on the National Immunisation Program (NIP) for the prevention of HPV infection in an ongoing group of 12 year old girls and for a catch-up program for all girls and women aged 13 to 26 years.

After consideration at its November 2006 meeting, the PBAC rejected the listing of Gardasil® on the NIP "based on unacceptable and uncertain cost effectiveness at the price requested". The PBAC based its rejection on its views that:

- the magnitude of the per patient clinical benefit for this vaccine was judged to be small across the vaccinated population overall and the PBAC believed that in most cases, the overall benefits for cervical cancer prevention would take a long time to be realised.
- whether the inclusion of herd immunity would have sufficient favourable impact.
- the proposed utility gains were viewed as overstated.
- the existing National Cervical Screening Program could be more efficient and effective than vaccination.
- the costs of the vaccination program and associated education programs were large, and that for already sexually active women a better use of resources might be pap smear programs.

The initial rejection of Gardasil® by the PBAC caused a substantial debate and backlash against the PBAC, with various media reports and politicians commenting on the matter[214].

The PBAC was subsequently asked to reconsider the application at an extraordinary meeting a matter of weeks later after intervention from the then Prime Minister[215]. At this extraordinary meeting, the PBAC recommended Gardasil® for the NIP after the sponsor company, CSL, offered a price reduction[216] and met some of the PBAC's concerns on the costs of a possible booster shot if required.

In its response[217] to the November 2006 PBAC recommendation, while welcoming a recommendation for listing based on its resubmission the sponsoring company CSL said: *"CSL does not agree with the PBAC decision to reject the initial application for funding based on unacceptable and uncertain cost-effectiveness at the price requested, particularly related to the non-acceptance of quality of life offsets for cervical cancer and precancer, and the non-acceptance of herd immunity benefits. CSL also has concerns that the PBAC position to not consider a lower discount rate and to require a lower cost-effectiveness threshold for preventative vaccination programs, has the potential to disadvantage such programs compared to pharmaceuticals. CSL will continue to work with the PBAC and Government on these issues."*

Since the development and listing of HPV vaccines like Gardasil®, various studies in Australia and internationally have demonstrated the overwhelming broader economic value of HPV vaccination, indicating the broad success of such vaccination in reducing the incidence of cervical cancer and pre-cancerous lesions as well as generating broader social and economic well-being for society[218].

Issues highlighted by the Gardasil case study

Aside from the political debate after the PBAC's initial rejection of Gardasil®, the issues that led the PBAC its rejection were principally around the value, price and cost-effectiveness of the vaccine as viewed by the PBAC. Whilst some have defended the evaluation process and lamented the resulting political furore over the PBAC's rejection, the reasons the PBAC rejected Gardasil® reflect several of the fundamental economic valuation and process issues of concern about how PBAC assesses the value of vaccines.

The PBAC's relative lack of value attributed to herd immunity, reluctance or inability to assess the long-term societal and non-health economic benefits – let alone the long-term health benefits – of immunisation and its relatively high discount rate which de-valued the long-term value attributed to immunisation all helped to lead the PBAC to initially reject Gardasil®. Subsequent studies in the years since the introduction of Gardasil® have shown substantial reductions in the incidence of cervical and associated cancers, to the point where there is now active contemplation of eliminating HPV from Australia altogether. Moreover, the vaccine appears to have driven herd immunity in the community against HPV, something the PBAC found uncertain and under-valued at the time of consideration. The subsequent real-world evidence from multiple countries showing the benefits of the vaccine after introduction, suggests that greater recognition, comfort with and acceptance of broader benefits by PBAC would be advantageous.

Case Study: Fluzone High Dose

Background

Influenza is an acute viral infection of the respiratory tract. Beyond the acute symptoms, influenza is also associated with complications including (but not limited to) acute bronchitis, pneumonia (both primary viral and secondary bacterial pneumonia), exacerbations of underlying conditions such as diabetes and cardiovascular complications including myocarditis and pericarditis. There are four types of influenza viruses: influenza A, B, C, and D but only influenza A and B viruses cause clinically important human disease and seasonal epidemics.

The trivalent influenza vaccine high dose (TIV-HD) vaccine, Fluzone High-Dose, was TGA registered on 20 December 2017 for active immunisation against influenza disease caused by influenza virus types A and B contained in the vaccine for use in persons 65 years of age and older.

1st submission

The company first provided a cost-effectiveness submission for listing on the National Immunisation Program (NIP) schedule from the 2019 influenza season onwards, for people aged ≥65 years, at the July 2018 PBAC meeting. The comparator was the current standard of care, the QIV-SD.

The submission utilised randomised clinical trials of efficacy against influenza infection and non-specific outcomes, which represented the highest level of scientific evidence for medicines and vaccines.

The PBAC considered ATAGI's pre-submission advice that in most years the potential additional disease burden due to the alternative B lineage not included in the TIV-HD is likely to be offset by the potential additional protection provided by the TIV-HD against the common strains, due to the superior protection afforded by the vaccine against the A/H3 strain, relative to the standard dose (TIV-SD). However, the PBAC considered that the extent to which the benefits of TIV-HD outweighed the potential loss of protection against the mismatched B strain in QIVSD compared to TIV-SD remained uncertain given year to year variability in influenza strains and severity of the season.

The PBAC rejected the submission on the basis of the high financial implications of the proposed price, the uncertainty around the loss of protection against the alternative B lineage and the incremental benefit of the strains matched with the comparator vaccine, and the associated uncertainty in assessing the incremental cost-effectiveness of the vaccine.

The PBAC considered that any future resubmission would need to be a major submission. The PBAC considered that the provision of further data and modelling comparing TIV-HD to QIV-SD under a range of scenarios using longer-term Australian data to address the uncertainties around the loss of the alternate B strain and the incremental benefit of TIV-HD to QIV-SD directly would be required.

2nd submission

The resubmission to the November 2019 PBAC meeting proposed TIV-HD as an alternative to a TIV for the 2020 season. The resubmission suggested that TIV-HD could be the standard of care for influenza immunisation in people aged ≥ 65 years in the 2020 influenza season. It proposed a stepped approach to adoption where TIV-HD could be provided for an aged care facilities cohort initially (2020) with consideration to broaden access to the full cohort in the future. The NIP does not currently delineate eligibility for people living in aged care facilities in the ≥65 years and older cohort. The resubmission did not analyse this sub-cohort in the economic model or the financial model.

Use of real-world evidence

The resubmission used Izurieta to inform the comparison of TIV-HD to aTIV. Izurieta is an observational study comparing cell-cultured QIV and egg-based QIV-SD, TIV-HD, aTIV and TIV-SD in approximately 13 million adults aged ≥65 years in the US within the 2017-18 influenza season.

The ESC considered that although Izurieta presented real-world data, the extent of benefit as reported in this study was uncertain due to:

- The moderate to high risk of bias associated with the study;
- The IPTW analysis resulted in a large change in the estimated rVE (from 0.4% (95% CI:-1.8, 2.6) before IPTW to 9.0% (95% CI: 7.2, 10.6) after IPTW for TIV-HD vs QIV-SD);
- There may be additional confounders not accounted for in the analysis;
- Results for office visit are generally considered to be unreliable;
- The study only covered one influenza season, and egg-adaption potentially affected the results; and
- The exclusion of the aged care facility resident population for which the resubmission indicated is the highest need sub-group population.

The resubmission also included strain distribution data over 15 seasons (2002 to 2016). These were divided into seasons where the prevalence of A strain was high, moderate, or low (approximately five seasons of each), and the matching of the B strain to the TIV vaccine was high, moderate or low (approximately five seasons of each). Taken together, these data allowed for nine possible scenarios over which to assess the value of TIV-HD relative to QIV-SD.

PBAC Outcome

The PBAC recommended an increase in the price of inactivated trivalent influenza vaccine (Fluzone High-Dose, TIV-HD), on the *National Health (Immunisation Program – Designated Vaccines) Determination 2014 (No.1)* (the Determination), for active immunisation against influenza in adults aged ≥65 years, but it considered that a claim of superiority vs aQIV could not be adequately supported by the clinical evidence presented and therefore a cost-minimisation approach in which TIV-HD was the same price as aQIV would be appropriate.

Outcome

The sponsor has been unable to take this vaccine forward for NIP listing, because price based on a cost-minimisation devalues the benefit of this vaccine, and there is no avenue for addressing any uncertainty around the claim of superiority, through the collection of real-world evidence. Nor does Australia's data collection infrastructure enable effective real-world evidence collection. A country such as Estonia, for example, has a fully digitised health system where patient data can be linked and the true medical costs of infectious diseases can be calculated (hospital and community care interventions), as well as calculate the broader societal and economic impact. Australia lacks such systems which makes it challenging to provide accurate numbers of disease burden and cost to satisfy the PBAC criteria.

Many of the benefits of a vaccine such as Fluzone cannot be demonstrated until a vaccination program is in place, such as herd immunity, and the presence of seasonal variations speaks to the need to better utilise real-world evidence.

Other countries' approach to Fluzone HD

Evidence from the usage of Fluzone overseas is demonstrating its superiority:

- Fluzone HD has been assessed as the only influenza vaccine that has clearly demonstrated superior efficacy and effectiveness against influenza disease compared to unadjuvanted standard dose vaccines in people aged >=65 years, by the only two GRADE reviews published to date - by the National Advisory Committee on Immunization (Canada) and the European Centre for Disease Control.

- Fluzone HD is the majority or only vaccine recommended and/or funded for the elderly in the US, Germany, France and Canada as at the 2021/22 season. HD is preferentially recommended in Germany (population level), Canada (individual patients' level) and France (for aged care setting only). From last winter, HD has been funded for all nursing homes in Canada for two years at least. HD is the most popular vaccine in older Americans.

In all these settings the price paid is substantially higher than what the PBAC has been willing to approve to date.

Issues highlighted by this case study:

- differences in clinical opinion between ATAGI and the PBAC
- requirement for unique Australian data
- use of real-world evidence dismissed
- patients in other countries having access where Australian patients do not
- the NIP does not accommodate access being considered by cohort e.g. Aged care residents

Case study: Meningococcal disease vaccines

Background to vaccine and disease

Invasive meningococcal disease (IMD) is a serious bacterial infection caused by Neisseria meningitidis (N. meningitidis). Globally, most cases of meningococcal disease are caused by serogroups A, B, C, W and Y. Currently, even with antibiotic treatment, the mortality rate for meningococcal disease is around 7-13% globally, and 5-11% in Australia. About 10-30% of children and adolescents who survive the disease develop permanent complications such as limb deformity, skin scarring, deafness and neurological deficits[225].

Infection often causes septicaemia and/or meningitis and is most common in children aged <2 years and adolescents aged 15-19 years. Rates of nasopharyngeal carriage of the bacteria are highest in older adolescents and young adults.

Currently, meningococcal serogroups B and W cause most meningococcal disease in Australia. Meningococcal serogroup B (MenB) disease remains the most common cause of IMD in children, adolescents and young adults. Meningococcal disease caused by serogroups W and Y occurs over a more diverse age range and may present with less typical clinical manifestations than disease due to other serogroups.

There is no single vaccine that offers protection against all serogroups that cause meningococcal disease. There are three types of meningococcal vaccines registered in Australia, which cover different serogroups:

1. quadrivalent (A, C, W, Y) meningococcal (MenACWY) conjugate vaccines: Menactra®, Menveo®, Nimenrix®
2. recombinant meningococcal B (MenB) vaccines: Bexsero®, Trumenba®

meningococcal C (MenC) conjugate vaccines: Menitorix® (combination formulation with the Haemophilus influenzae type b vaccine), NeisVac-C® (monovalent meningococcal C vaccine)

MenACWY vaccines available for use in Australia are:

- Menactra® (Sanofi Pasteur) for ages ≥9 months
- Menveo® (GlaxoSmithKline) for ages ≥6 weeks
- Nimenrix® (Pfizer) for ages ≥6 weeks

Registration

Nimenrix® was registered on the ARTG on 29 August 2013 for active immunisation of individuals from the age of 12 months through 55 years against invasive meningococcal diseases caused by *Neisseria meningitidis* serogroups A, C, W[135] and Y.

MenQuadfi® was registered on the ARTG on 29 October 2020 for active immunisation for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W and Y.

Menveo® was registered on the ARTG on 20 May 2010 for active immunisation of infants and children (from 2 months of age), adolescents and adults to prevent invasive disease caused by Neisseria meningitidis serogroups A, C, W-135 and Y.

Reimbursement and NIP Listing

Nimenrix®

At its March 2018 meeting, the PBAC recalled that for vaccination programs a cost per quality adjusted life year (QALY) of $15,000 or less is generally considered acceptable. The PBAC considered the cost of the MenACWY-TT vaccine should be reduced such that the cost per QALY gained was less than $15,000.

The sponsor submitted a revised pricing proposal in August 2018. The sponsor proposed the same price for adolescents as agreed for its use in the infant vaccination program. The PBAC advised that a cost/QALY gained of $15,000/QALY - $45,000/QALY or less would be acceptable in this instance. The PBAC's advice was given in the context of the relatively small cost of the primary program and that the financial impact of the catch-up program may have been overstated in the submission, as students who have been vaccinated through the current statebased programs were not excluded from the estimates.

Nimenrix® is funded through the National Immunisation Program (NIP) at 12 months of age and in adolescents aged 14-19 years. The other two vaccines are not available through the NIP but are available through private prescription. It was funded through the NIP in 2018 for children 12 months old. In 2019, the NIP was expanded to adolescents aged 14-19 years, replacing the temporary state and territory programs. The PBAC noted that since the introduction of the national vaccination program, the cases of IMD, particularly those caused by MenW and MenY, have declined.

MenQuadfi®

Considered at the Nov 2020 PBAC meeting.

ATAGI noted that as MenQuadfi® is a fully liquid preparation, its preparation may be simpler for providers as there is no requirement to mix a powdered vaccine and diluent, as is the case for Nimenrix®. This was particularly relevant outside of primary health care facilities, such as in schools or within a meningococcal outbreak vaccination program.

The submission stated that the sponsor would match the revealed NNP of Nimenrix® if MenQuadfi® was recommended for listing on the NIP. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of MenQuadfi® would be acceptable if it were cost-minimised against the nominated comparator, Nimenrix®.

Menveo®

Considered at the July 2018 PBAC meeting.

The Pre-Subcommittee Response and Pre-PBAC Response acknowledged the state-based programs may cease with an NIP listing, and claimed that the availability of two MenACWY vaccines through the NIP would improve surety of supply. The ESC noted the value of having more than one vaccine available for NIP listing on the designated vaccines list.

The PBAC recalled it recommended Nimenrix® be listed on the NIP for adolescents in March 2018. The PBAC further recalled that it recommended Nimenrix® on a cost-effectiveness basis, subject to a reduction in the requested price such that the cost per QALY gained was less than $15,000. At its meeting on 17 August 2018, the PBAC considered a revised pricing proposal from the sponsor which was sent to the Department on 15 August 2018.

The PBAC recalled that the sponsor chose not to present a cost-effectiveness analysis compared with 'no vaccine' (placebo) in the July 2018 submission and that the basis of the recommendation for adolescents is cost-minimisation with Nimenrix® for the same population.

The PBAC considered that the revised price offer did not provide a basis for the Committee to change its advice from the July 2018 meeting.

Issues highlighted by this case study

- Low prices have prevented the listing of two other vaccines as alternatives to Nimenrix®, despite ESC noting the value of having more than one vaccine available on the NIP.

The sponsor company of Menveo® stated in its Pre-Subcommittee Response that the PBAC should be aware the low vaccine prices could impact supply where there is international competition or limited doses, which may reduce confidence in the NIP. The Pre-PBAC Response stated that a low recommended price may impact the sponsor's ability to progress listing and requested that "the PBAC consider the limitations on vaccine supply due to complex manufacturing processes and associated long lead times, and existing issues with supply constraints of multiple brands of MenACWY vaccine due to high global demand."

- The QALY associated with vaccines is $15,000 or less.
- There is no value placed on preparation of vaccines being simpler for providers.

Case Study: Multicomponent Meningococcal Group B vaccine (4CMenB) (Bexsero®)

Background

Invasive meningococcal B disease is a rare disease caused by the bacterium *Neisseria meningitidis*. Meningococcal B is the single leading cause of bacterial meningitis and sepsis in Australian infants and teenagers, accounting for approximately 85% of all meningococcal disease cases. The disease is easily misdiagnosed in its early stages and can develop rapidly, frequently leading to death or permanent disability within 24 hours of onset of symptoms.

The 4CMenB vaccine contains four antigenic components. It is intended to stimulate the production of bactericidal antibodies that recognise these antigens, and protect against a broad range of disease-causing meningococcal group B strains.

The PBAC[226] considered that the vaccine was an important advance in vaccinology, using new technology to address issues specific to meningococcal B. While there are conjugate based and polysaccharide capsule-based vaccines currently available for other meningococcal groups, similar approaches for meningococcal B vaccines have failed because the meningococcal B polysaccharide capsule is poorly immunogenic. 4CMenB was created using an innovative approach to vaccine development known as reverse vaccinology. This process employs genomic mining to identify multiple surface-exposed antigens that are important virulence factors and that are believed to be highly conserved across most isolates.

PBAC journey

The 4CMenB vaccine was registered in August 2013. The November 2019 resubmission represented the 4th submission for this vaccine. Previous submissions for 4CMenB included a major submission in November 2013, major resubmission in July 2014 and a minor resubmission in July 2015.

This resubmission requested listing on the National Immunisation Program (NIP) for multicomponent meningococcal group B vaccine (4CMenB) for active immunisation against invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* group B strains, in individuals from 2 months of age and older; adolescents in Year 10, plus a time-limited catch-up program for infant and toddlers; Aboriginal and Torres Strait Islander people (under 20 years of age) and all people with medical conditions known to increase the risk of IMD.

The PBAC recommended the listing of multicomponent meningococcal group B vaccine (4CMenB, Bexsero®), on the NIP for only one of the indications sought - the prevention of invasive meningococcal disease (IMD) caused by Neisseria meningitidis group B strain in Aboriginal and Torres Strait Islander children, as the incidence of IMD caused by the group B strain was more than 6 times higher in Aboriginal and Torres Strait Islander children under 5 years of age compared with non-Indigenous children

PBAC views on managed entry (coverage with evidence development)

In the 2013 submission, the PBAC considered whether a managed entry approach would be appropriate for the 4CMenB vaccine to accommodate these research proposals. Co-implementation with the sponsor of such a scheme would likely address the extent and persistence of vaccine effectiveness, the extent of the reduction of nasopharyngeal carriage leading to extent of herd immunity, the surveillance for reactogenicity and the requirement of an additional booster dose at age of 4 or in early adulthood.

However, the PBAC held grave concerns that if NIP listing was implemented in the context of a managed entry scheme, and the research subsequently showed that the expected benefits were not realised, there would be great difficulty associated with disinvestment and removal of the vaccine from the NIP, and such an event may undermine public confidence in immunisation in general.

Use of real-world evidence

The 2019 resubmission presented four real-world evidence studies to support the clinical claim of superior effectiveness compared to no vaccination. The main study was the UK Public Health England Vaccination Program that vaccinated infants against IMD caused by Men B. Three other studies, the Quebec Regional Vaccination Program, the Portugal PT-BEST study and the 'South Australia B part of it' were also presented as supporting evidence. These studies had not previously been considered by the PBAC.

The resubmission also presented three real-world evidence studies to support the clinical claim of superior effectiveness compared to no vaccination against *Neisseria gonorrhoea* in adolescents.

While the evaluation considered that the risk of bias in the RWE studies as low to medium, the PBAC did not agree. It "*noted that evidence from observational studies is generally associated with a high risk of bias compared to evidence from randomised controlled trials. Specifically, the observational studies are at high risk of confounding due to underlying differences between vaccinated and unvaccinated children, and due to temporal changes in the incidence of disease unrelated to the vaccination program*"[227].

The PBAC considered the real-world evidence provided in the resubmission supported the benefit of vaccinating infants with 4CMenB in the short-term, although noted there is still uncertainty about the size of the benefit and the duration of protection.

Discount rate

The resubmission assumed a 3.5% discount rate. Based on the PBAC guidelines, lower discount rates can be considered in a sensitivity analysis rather than the base case. The sponsor considered the 5% compounding rate too high and that this disproportionally disadvantages preventive treatments such as vaccines, particularly those such as 4CMenB that realise the majority of the utility benefit and cost offsets in the longer term but incur the cost of the vaccine immediately. The ESC considered it was appropriate to apply a 5% discount rate in the base case analysis and use a lower discount rate in a sensitivity analysis. The ESC noted the ICER was highly sensitive to the discount rate.

Broader societal benefits

The PBAC guidelines state that changes in productivity should not be included in the base case but can be included in supplementary (sensitivity) analyses.

The base case incremental cost effectiveness ratio (ICER) as presented in the resubmission for the routine vaccination of infants and adolescents was $15,000/QALY - $45,000/QALY in the general population and less than $15,000/QALY in the Aboriginal and Torres Strait Islander population. The PBAC noted the base case ICERs incorporated a broader perspective than is usually considered by the PBAC (by inclusion of outcomes and costs beyond the patient and the health system), a Quality Adjustment Factor (QAF) (which, it said, is not appropriate in the context of PBAC decision making) and a lower discount rate than recommended in the PBAC Guidelines.

The PBAC considered that, given the high and uncertain ICER, the lack of herd protective effects, the lack of data on the duration of clinical protection, and the absence of data on clinical effectiveness for adolescent vaccination, circumstances that could enhance the acceptability of the cost-effectiveness would include arrangements resulting in a reduction in effective price and a sharing of the cost of delivery of an adolescent program for the general population

Company comment

GSK noted that significant real-world evidence has been generated since the previous submission which GSK believed addressed most of the key clinical uncertainties upon which the prior three rejections were based. From a clinical and public health perspective, the Australian Technical Advisory Group on Immunisation (ATAGI) considered that inclusion of meningococcal B (MenB) vaccines in the NIP was warranted for the requested populations included in the submission.

GSK argued the PBAC's current decision-making framework and criteria is prohibitive to obtaining public subsidy for this clinically recommended vaccine in all infants and adolescents for the prevention of a rare and unpredictable life-threatening disease, with devastating impact in children, adolescents and their families. Consequently, GSK cannot see a path forward to enable this vaccine to be widely available on the NIP beyond the current PBAC recommendation.

Issues highlighted by this case study:

- PBAC acceptance of real-world evidence
- issues around managed entry/coverage with evidence development
- impact of excessively high discount rate
- broader societal benefits

APPENDIX B: Global clinical studies of vaccines by disease/condition

Condition/Disease Category	Vaccine studies	Relevance to Australian health system
Carcinoma/Neoplasms	921	Given the substantial prevalence of cancer in Australian society, vaccines that can potentially prevent and/or treat cancer could make a major contribution to reducing the burden of disease in Australia. See Appendix C.
Respiratory Tract infections and diseases (including influenza and RSV)	791	This category includes infectious respiratory conditions that are already within the Australian vaccination schedule (including influenza, whooping cough (pertussis), TB and some COVID-19 studies). As such, the developments in this area are less likely to have profound effects on the Australian healthcare system, instead small expansions of current immunisation schedules, save for RSV (which is notifiable in Australia as of July 2021) and the COVID-19/Coronavirus vaccines (See below).
DNA/RNA Virus Infections	511	Given current immunisation schedules and living conditions, developments in vaccines for viral infections will primarily affect low- and middle-income countries and less so countries like Australia. Developments in administration and storage may be of interest (detailed below).
Immune system diseases	216	This category of studies primarily looks at the efficacy and effectiveness of existing vaccines in populations who are potentially immunocompromised or who have not been studied (e.g. frail elderly, pregnancy). As such the developments in this area will not have profound effects on the Australian healthcare system (rather small expansions of current immunisation schedules). There are some studies of vaccines for allergies which are expanded below.
Bacterial infections	160	Given current immunisation schedules and living conditions, developments in vaccines for bacterial infections will primarily affect low- and middle-income countries rather than Australia. Developments in administration and storage may be of interest (see below)
Digestive system diseases	147	This category of studies primarily explores optimisation of existing vaccines (for example those given for rotavirus, hepatitis B) and expansion to some previously unstudied populations. As such the developments in this area will not have profound effects on the Australian healthcare system (rather small expansions of current immunisation schedules).
Central Nervous System diseases	183	This is of (limited) relevance to Australia (see below)
Coronavirus	269	This is of relevance to Australia (see below)
Acquired Immunodeficiency syndrome (HIV/AIDS)	115	There are almost 30,000 Australians living with HIV, with less than 1000 new infections per year – vaccine would have relatively low resource implications in Australia.

Source: Shawview Consulting analysis of www.clinicaltrials.gov as at 15/9/2021. Conditions/diseases included where there were 100 or more clinical trials per category. Note: Double counting is possible due to the keyword filters applied by the website. Search terms used on the clincaltrials.gov website were "vaccine", "vaccination" and "immunization".

APPENDIX C: Selected cancer vaccines in development according to cancer type

Condition	Vaccines in Development	Comments
Breast Cancer	NeuVax (Galena Biopharma)	NeuVax has been studied at phase III and has been granted a special protocol assessment by the FDA. Follow up results from this study (PRESENT) are pending.
Colorectal Cancer	OncoVax (Vaccinogen)	OncoVax has been studied at Phase IIIa, however these studies were either completed or have not been updated since 2015. No regulatory approval has been granted.
"HPV Positive"; cervix, anus, throat, head and neck, vulva, vagina, penis	Number of vaccines already available	Studies in this category are primarily focused on optimising the currently available vaccines
Lung Cancer	Tedopi (OSE Immunotherapeutics)	Vaccine has been tested in an early phase III study for non-small cell lung cancer, results were reported as "promising" but more studies are planned. It is also going to be studied for pancreatic and ovarian cancer.
Lung Cancer	CIMAvax (Center of Molecular Immunology, Havana, Cuba)	Vaccine is reportedly available in Cuba and entering phase III studies in the US
Multiple Myeloma	PVX-410 (OncoPep)	Open label phase 1b clinical trial has started recruitment (n=20) in the US. It is also being studied for triple-negative breast cancer.
Ovarian/fallopian Cancer	OPT-821 (OBI pharma)	OPT-821 was studied in phase 3 studies, but was not found to prolong progression-free or overall survival. It is now being studied in phase I/II trials for neuroblastoma. Most other studies are still early phase (I/II), although they are all relatively recent (2018 onwards). Various experimental vaccines are being studied given in combination with chemotherapies and/or immunotherapies already approved for the treatment of ovarian and/or fallopian cancer.
Renal cell carcinoma/Kidney Cancer	TroVax (Oxford BioMedica)	TroVax has been studies in phase 3 trials, however this was in 2006 and no regulatory approval has been granted
Renal cell carcinoma/Kidney Cancer	IMA901 (Immatics Biotechnologies)	IMA901 has been tested in phase 3 trials, however this was in 2016 and no regulatory approval has been sought or granted
Renal cell carcinoma/Kidney Cancer	Oncophage (Vitespen, Antigenics Inc)	Oncophage was approved for use in Russia and designated orphan status in Europe. However, the application for European Medicines Agency approval was withdrawn by the company.

Source: Shawview Consulting analysis of www.clinicaltrials.gov as at 15/9/2021. Conditions/diseases included where there were 100 or more clinical trials per category. Note: Double counting is possible due to the keyword filters applied by the website. Search terms used on the clincaltrials.gov website were "vaccine", "vaccination" and "immunization".

The potential opportunities from the development of new cancer vaccines currently undergoing clinical trials come from the prevalence of cancer in Australian society today:

- Apart from non-melanoma skin cancer, breast cancer is the most common cancer in women in Australia and the second most common cancer to cause death in women. It is estimated that 19,807 women and 167 men will be diagnosed with breast cancer in 2020; the 5-year survival rate is now 91% (thanks to screening and advances in treatment).

- Colorectal (bowel) cancer is the third most common cancer in both men and women in Australia. It is estimated that 15,494 cases of colorectal cancer will be diagnosed in 2020; the 5-year survival rate is 70%.

- Lung cancer is the fifth most common cancer but is the leading cause of cancer death in Australia. It is estimated that there would be 3,258 new cases of lung cancer diagnosed in Australia in 2020; the 5-year survival rate is just 19%.

- Ovarian cancer is the eighth most common cancer affecting women in Australia. In 2018 there were 968 deaths caused by ovarian cancer in Australia and the 5-year survival rate is 45.7%.

- Kidney cancer (the most common type being renal cell carcinoma, accounting for about 90% of cases) has a 5-year survival rate of 79%. It was estimated that 4,193 people in Australia would be diagnosed with kidney cancer in 2020, and

- Regarding HPV positive cervical cancer, a systemic review published in the Lancet in 2019 demonstrated that there has been a significant reduction in the rates of HPV infection by 92% and in precancerous lesions by 50-70% since the introduction of the Gardasil vaccine. It is anticipated this will have a significant impact on the rates of cervical cancer in the coming years in Australia.

APPENDIX D: Selected vaccines in development according to type of immune system disorder

Condition	Vaccines in Development	Comments
Allergies (peanut)	Palforzia (Aimmune Therapeutics)	Palforzia is the first vaccine approved for use against allergies; it was granted FDA approval on 31st January 2020, available under the Risk Evaluation and Mitigation Strategy (due to the risk of anaphylaxis).
Allergies (peanut)	ASP0892 (Astellas Pharmaceuticals)	ASP0892 has been studied in phase I (study completed in 2019) and a second phase I study was terminated in June 2021 .ASP0892 had FDA "fast-track" designation
Allergies (non specified)	BCG (Merck)	Phase III study of BCG given in the first 12 months of life to assess effects on allergy and infection. There are other (early phase) studies of vaccines for allergies to dust mites, grass and pollen but these have completed nearly 10 years ago with no follow up.
Autoimmune Type 1 Diabetes	PIpepTolDC (City of Hope)	Phase I study of vaccine that uses the patients own immune cells to treat Type 1 diabetes. The study is estimated to complete in October 2022. There are other phase I studies of potential vaccines for diabetes but these were all completed by 2018 and no further studies were identified.
Autoimmune Type 1 Diabetes	BCG (Merck)	Phase II study to see if repeat BCG vaccinations can infer an immune and metabolic effect on Type 1 Diabetes. Study completion is expected in July 2027 (with primary outcomes anticipated by July 2025)
Multiple Sclerosis	BioNTech – mRNA vaccine	Very early phase (initial mouse, pre-clinical studies) with "promising results" announced January 2021. More studies are expected (not yet identified in clinicaltrials.gov)

Source: Shawview Consulting analysis of www.clinicaltrials.gov as at 15/9/2021. Conditions/diseases included where there were 100 or more clinical trials per category. Note: Double counting is possible due to the keyword filters applied by the website. Search terms used on the clincaltrials.gov website were "vaccine", "vaccination" and "immunization".

Allergies have a major impact on Australians and the Australian health system. For example:

- According to the Australasian Society of Clinical Immunology and Allergy (www.allergy.org.au), peanuts are one of the most common foods to trigger anaphylaxis and up to 3% of children in Australia have a peanut allergy. Allergic reactions can range from mild to severe and can have a huge impact on patient quality of life.

- According to Diabetes Australia (www.diabetesaustralia.com.au), Type 1 diabetes accounts for 10% of all diabetes in Australia, meaning that more than 10,000 Australians are diagnosed with Type 1 diabetes every year. In addition, diabetes is the fastest growing chronic condition in Australia; increasing at a faster rate than heart disease and cancer. Having diabetes can lead to serious complications such as blindness, amputations, heart and kidney disease.

- According to Multiple Sclerosis (MS) Australia (www.msaustralia.org.au), MS affects over 25,600 people in Australia and most people are diagnosed between the ages of 20 and 40. There is currently no known cure for MS and it is associated with reduced quality of life and life expectancy.

APPENDIX E: BRAVE Framework for value elements considered by European country

Broad framework	Value elements	Belgium	Canada	France	Germany	Italy	Japan	Sweden	UK	US
Narrow health effects	Disease impact on length of life									
	Disease impact on QoL of patients									
Broad health effects	Disease impact on QoL of carers									
	Burden of disease									
	Value to other interventions									
	Transmission value									
	Prevent the development of AMR									
	Social equity									
Societal economic effects (broad)	Productivity of patients									
	Productivity of carers									
	Macroeconomic effects									
Health system economic effects	Costs-offset to healthcare system									

Formally considered	Commonly and informally considered	Uncommonly and informally considered	Not considered	Unknown

Source: Bell, E., Neri, M. and Steuten, L., 2020. *The BRAVE Narrative for Broad Recognition of Value in Vaccines Engagement*. OHE Research Paper, London: Office of Health Economics, p. 6,. https://www.ohe.org/publications/brave-initiative-brave-narrative-broad-recognition-value-vaccines-engagement, accessed 10/6/2021.

APPENDIX F: Victorian Institute of Strategic Economic Studies Vaccine Study: Benefit-Costs Analysis

VACCINE STUDY: Benefit Cost Analysis

Report to Shawview Consulting

Bruce Rasmussen and Kim Sweeny
June 2021

CONFIDENTIAL

VICTORIA UNIVERSITY | VISES VICTORIA INSTITUTE OF STRATEGIC ECONOMIC STUDIES

SHAW VIEW CONSULTING VISES VACCINE STUDY

- Project purpose
  - Generate BCRs for vaccines issued under the National Immunisation Program
- Presentation outlines the results for two vaccines to treat:
  - Meningococcal disease (invasive) IMD
  - Pneumococcal disease (invasive) IPD
  - Rotavirus
  - Human papilloma virus
  - Influenza

2

MENIGICOCCAL DISEASE (IMD): Characteristics

- IMD is a rare, but serious, unpredictable, and life-threatening infectious disease. It mostly occurs in children less than five years of age and during late adolescence (15–19 years) (Si et al. 2019)
- IMD cause meningitis and sepsis leading to death in 3–8% of cases depending on age, and complications in almost 38% of cases (Si et al. 2019)
- More than 50% of those with complications are serious and multiple (Si et al. 2019)
- Long-term sequelae include limb amputations, hearing loss and neurodevelopment disabilities
- There are multiple serogroups. However A,B,C,W, X and Y cause almost all cases of IMD
- A conjugate vaccine Nimenrix addresses serogroups A,C,Y,W. Two does are given to children under 12 months and one dose over 12 moths, to teenagers aged 14-16 in a school program (GSX 2014)

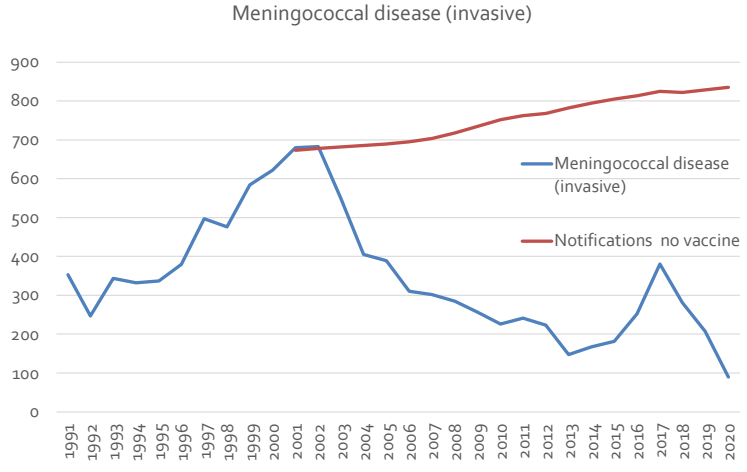
3

IMD VACCINE: Methodology overview

The model estimates the impact of the vaccine by the difference in deaths and disabilities of two scenarios – one with and the other without the vaccine.

The one without is based on a continuation of the age-based notification rate prior to the introduction of the vaccine.

The scenario with the vaccine is based on actual notifications post introduction of the vaccine.



4

IMD VACCINE: Methodology

Benefits

- Productivity increase from saved lives and reduced morbidity from time of entering the work force until retirement
- Hospital costs avoided from acute treatment
- On going medical costs avoided from sequelae groups

Costs

- Vaccination costs for the two age groups, under 12 months and 14–16

IMD VACCINE: Assumptions

Hospitalisation costs

Input	Value	Source
Cost of hosp. acute (death/complicated)	*$24,453*	Si et al. 2019
IMD with complications	0.376	Si et al. 2019
% major complications	0.805	Si et al. 2019
Assume acute (death/comp)	0.30268	
Cost of hosp. acute (non-complicated)	*$7,432*	Si et al. 2019
IMD with no complications	0.624	Si et al. 2019

On going medical and hospital costs, long-term cost per annum

Complication	%	$	Source
Minor, single	14.6	$1,512	Si et al. 2019 (sourced from Tu et al. 2014)
Minor, multiple	4.9	$3,753	Si et al. 2019 (sourced from Tu et al. 2014)
Major, single	26.8	$10,742	Si et al. 2019 (sourced from Tu et al. 2014)
Major, multiple	53.7	$18,176	Si et al. 2019 (sourced from Tu et al. 2014)
Weighted average ongoing cost		$13044	

Vaccination costs $56 per shot

Age group	No. of shots	Coverage	Source
0-4	2	0.95	GSX 2014
15-19	1	0.51	GSX 2014; Si et al. 2019

Productivity benefits

Variable	Source
Population	ABS
Case fatality rates	Si et al. 2019, Appendix
IMD incidence	Si et al. 2019, Appendix
Death rates	ABS
Utility decrement wtd average (see table below)	Based on Si et al. 2019
Notifications	NNDSS 2021
Economic variables (labour force participation rates, employment, GDP)	ABS

Utility decrement

Complication	Weights	%	Source
Minor, single	0.06	14.6	Si et al. 2019
Minor, multiple	0.12	4.9	Si et al. 2019
Major, single	0.14	26.8	Si et al. 2019
Major, multiple	0.39	53.7	Si et al. 2019
Decrement wtd average		0.26159	

IMD VACCINE:
Results

Meningococcal vaccine, current period from 2003

	Discount rate			Period
Discount rate	**3.50%**	**5.0%**	**1.50%**	
	NPV $m	**NPV $m**	**NPV $m**	
Productivity benefits	$2,147.2	$1,407.3	$4,120.7	To retirement
Hospital costs saved	$57.0	$49.9	$68.8	2003-19
Ongoing medical cost saved	$705.4	$476.6	$1,322.2	To retirement
Total benefits	$2,909.6	$1,933.8	$5,511.6	
Vaccination costs	$903.7	$802.5	$1,069.9	2003–19
BCR	3.2	2.4	5.2	

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PNEUMOCOCCAL DISEASE (IPD):
Characteristics

- IPD is a respiratory tract infection which is one of the major causes of meningitis and acute otitis media (AOM) mainly in children, and septicaemia and pneumonia largely among the elderly (Melegaro and Edmunds 2004)
- The case fatality rate for those with IPD rises from about 2% in infancy to 17% over 65 (Newall et al. 2011)
- The most serious long-term sequelae are for those who contract meningitis (13%) who suffer limb amputations, hearing loss and neurodevelopment disabilities. Other long-term sequelae are for those who suffer permanent hearing damage from otitis media
- Australia introduced the 7-valent pneumococcal conjugate vaccine (7vPCV) on the universal infant National Immunisation Program (NIP) in 2005 and replaced it with the 13-valent pneumococcal conjugate vaccine (13vPCV) in 2011, both under a 3 + 0 schedule. The schedule is now 2+1. (Perdizet et al. 2021)

8

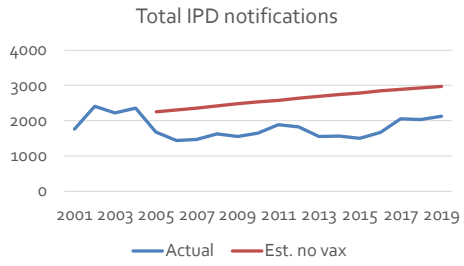
IPD VACCINE: Methodology Overview

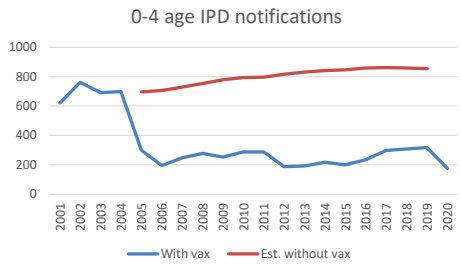
The model estimates the impact of the vaccine by the difference in deaths and disabilities of two scenarios – one with and the other without the vaccine.

The one without is based on a continuation of the age based notifications prior to the introduction of the vaccine.

The scenario with the vaccine is based on actual notifications post introduction of the vaccine.

The effect of the vaccine has been most noticeable for those aged 0-4 as shown below





9

IMD VACCINE: Methodology

Benefits

- Productivity increase from saved lives and reduced morbidity from entering the work force until retirement
- Medical and hospital costs avoided from acute treatment (IPD, pneumonia, otitis media)

Costs

- Vaccination costs for two doses for infants under 12 months with booster at 4 years for high risk children

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IPD VACCINE:
Assumptions

Productivity benefits

Variable	Source
Population	ABS
Case fatality rates	Newall et al. 2011
IPD incidence	Perdrizet et al 2021
Death rates	ABS
Utility decrement wtd average (see table below)	Based on Perdrizet et al. 2021; Melegaro & Edmunds 2004
Notifications	NNDSS 2021
Economic variables (labour force participation rates, employment, GDP)	ABS

Utility decrement (based on hearing loss due to meningitis)

Variable	Value	Source
Meningitis % notifications	13%	Perdrizet et al 2021
% Severe bilateral hearing loss	14%	Melegro & Edmunds 2004
QALY loss	0.2	
Av utility decrement per notification	0.00364	

Hospital and medical costs saved

Condition	Cost saved per notification	Source
IPD	$21,285	Perdrizet et al. 2021, NNDSS 2021
Pneumonia	$11,634	Perdrizet et al. 2021, NNDSS 2021
Otis media	$30,810	Perdrizet et al. 2021, NNDSS 2021

Vaccination costs

Vaccination cost/dose ($)	81	Perdrizet et al. 2021
No. of doses	3	NNDSS 2021
No. vaccinated	3.87m	Perdrizet et al. 2021

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IPD VACCINE:
Results

Pneumococcal vaccine, current period from 2005

	Discount rate			Period
	3.50%	5.0%	1.50%	
	NPV $m	NPV $m	NPV $m	
Productivity benefits	$552	$343	$1,141	To retirement
Direct costs saved (1)	$881	$881	$881	2005–19
Total benefits	$1,432	$1,224	$2,022	
Vaccination costs(1)	$939	$939	$939	2005–19
BCR	1.5	1.3	2.2	

(1) No discount applied by source Pedrizet, J., Lai, Y.S., Williams, S., et al. 2021

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ROTAVIRUS: Characteristics

- Rotavirus is the most frequent cause of severe dehydrating diarrhoea in young children worldwide resulting in substantial health care utilisation, quality of life impact, and productivity loss in caregivers (Reyes et al. 2017).
- Death however is rare. Just two lives estimated to be saved in the period 2007–12 (Reyes et al. 2017).
- Severe cases of the disease require hospitalisation costing $2350 per case. Other costs include GP visits and emergency department presentations.
- Caregiver working days lost is considered a significant cost of the disease (Bilcke et al. 2009).
- Two oral live attenuated rotavirus vaccines were included on the NIP in 2007. They are Rotarix®, a human monovalent vaccine (given in a 2-dose schedule at 2 and 4 months of age), and RotaTeq®, a pentavalent human bovine reassortant vaccine (given in a 3-dose schedule at 2, 4 and 6 months of age) (NCIRS 2020 Rotavirus Fact Sheet).

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ROTAVIRUS VACCINE: Methodology overview

There are three sets of factors in determining the BCR outcome:

1. Hospitalisation and medical costs from
   - Coded rotavirius hospitalisations
   - Unspecified acute gastroenteritis hospitalisations
   - Emergency dept presentations
   - GP consultations

   Costs are modelled based on average costs and case numbers
2. Vaccination costs
   - Two vaccines have been used. The cheaper RotaTeq requires 3 doses compared with the more expensive Rotarix requiring only 2 doses. The total cost of each is about the same ($105).
3. Caregiver costs depend on assumptions about days lost. A detailed study by Bilcke et al. 2009 suggests 5 days for hospital cases and 3 for those requiring GP consultations. The proportion of caregivers losing income has been assumed to be 33% derived from a survey of rotavirus carers (Bilcke et al 2009).

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ROTAVIRUS VACCINE: Methodology

Benefits

- Medical and hospital costs avoided from treatment for acute gastroenteritis
- Productivity increase from carers working days lost avoided

Costs

- Vaccination costs for two doses of Rotarix and three doses of RotaTeq for infants under 12 months

The costs and benefits are similarly sequenced so the BCR is largely invariant to the discount rate. The larger issue is the inclusion of caregiver costs.

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ROTAVIUS VACCINE: Assumptions

Hospitalisation costs (Reyes et al. 2017)

	Total prevented cases	Base costs, $	Total prevented cases	Base costs, $
	2007–2012 (program period)		**2013–2022 (program period)**	
0–4 year olds				
Deaths (coded RV)	2.62		5.45	
Hospitalisations (coded RV)	16,549	2,351	34,447	2351
Hospitalisations (unspecified AGE)	59,938	2,351	128,140	2351
ED presentations	26,024	436	43,961	436
GP consultations	317,843	43	567,199	43
5–14 year olds (additional benefit)				
Hospitalisations (coded RV)	336	2,351	270	2351
Hospitalisations (unspecified AGE)	5,152	2,351	7,684	2351
ED presentations	21,485	436	61,044	436
GP consultations	82,867	43	215,143	43

Vaccination costs

	Vaccine cost per dose (incl. admin)	Doses	Total cost	Source
RotaTeq	35.17	3	105.51	Reyes et al. 2017, NCIRS 2013
Rotarix	52.43	2	104.86	Reyes et al. 2017, NCIRS 2013
Average cost	43.8		105.185	

Caregiver benefits

Variable	Days	Source
Caregiver days lost hospital per case	5	Bilcke et al. 2007
Caregiver days lost GP per case	3	Bilcke et al. 2007
Average weekly earnings		ABS
Employment rates		ABS

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ROTAVIRUS VACCINE:
Results

	W/O caregiver, $m	With caregiver, $m
Costs saved		
Hospital and medical costs		
2007-12	$384.3	$384.3
2013-22	$801.9	$801.9
Total hospital and medical costs	$1186.2	$1186.2
Caregiver costs		
2007-12		$445.7
2013-22		$890.5
Total caregiver costs		$1336.2
Total cost saved	$1186.2	$2522.3
Vaccination costs		
2007-12	$221.7	$221.7
2013-22	$339.7	$339.7
Total vaccination costs	$561.5	$561.5
BCR	2.1	4.5

Note: Discount rate 5% as used by Reyes et al. 2017.

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HUMAN PAPILLOMA VIRUS VACCINE

- Infection with the human papilloma virus(HPV) is very common. In a small minority of people, HPV infection will contribute to the development of cancer and genital warts. There are over 170 different types of HPV. More than 40 types are typically transmitted through sexual contact and infect the anogenital region (anus and genitals). Several of these are high-risk HPV types, which can contribute to the development of cancer, the most common of which is cervical cancer.
- There are 3 types of vaccines against HPV. The 2-valent and 4-valent forms protect against 70% of cervical cancer and the 9-valent against 90%.

- In April 2007 a 3-dose schedule of 4vHPV was funded under the NIP for females aged 12–13 years, delivered through a school-based program, followed in February 2013, for males aged 12–13 years
- Vaccination is recommended for girls and boys before sexual debut.

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HUMAN PAPILLOMA VIRUS VACCINE
Methodology

- This analysis calculates the benefits and costs arising from cervical cancer deaths averted associated with the period from introduction of the vaccine for girls in 2007 through to 2020.
- The methodology follows that used in previous studies (Sheehan et al. 2017; Rasmussen et al. 2019).
- We assume that the target group for the vaccine is girls aged and population estimates of their numbers over the period was sourced from ABS.
- Coverage rates for the vaccine in each year of the period were sourced from the CW Department of Health website and were typically 75-80% (https://www.health.gov.au/resources/publications/national-hpv-3-dose-vaccination-coverage-for-all-adolescents-turning-15-years-of-age-from-year-of-program-commencement https://www.health.gov.au/resources/publications/historical-human-papillomavirus-hpv-immunisation-coverage-rates)
- Combined with the population estimates, this enabled the calculation of how many girls were vaccinated in each year of the period.

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HUMAN PAPILLOMA VIRUS
Methodology (cont)

- Australian cervical cancer death rates by 5-year age group for the period 1990 to 2019 were sourced from the Global Burden of Disease website (IHME 2021).
- These death rates were extrapolated into the future based on trends over the past 5 years.
- Combining these death rates with the estimates of the number of girls produces estimates of the number of cervical cancer deaths in the future as these girls get older, if there was no vaccination.
- Assuming that the vaccine prevents 70% of cervical cancer we can calculated the number of cervical deaths avoided in the future.

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HUMAN PAPILLOMA VIRUS
Methodology (cont)

- The cost of the vaccine was obtained from a recent HPV cost-effectiveness study in Australia (Mahumud et al. 2019) which quotes the total cost of vaccination per fully immunised girl as between $310 and $339
- Assuming a value of $340 and combing this with the estimates of the number of girls vaccinated gives a total cost of the vaccination program for each year from 2007 to 2020.
- The economic benefits were calculated as in previous studies using projections of death rates from the ABS, projections of labor force participation rates from the ILO and assuming an annual growth in productivity per person in the labor force of 0.7% in line with long -term trends.
- Benefit-cost ratios were calculated with benefits and cost expressed in net present value terms using a range of discount rates

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HUMAN PAPILLOMA VIRUS:
Results

	Discount rate		
	1.5%	**3.5%**	**5.0%**
GDP (NPV, AUD million)	13,794	5,523	2,884
Cost (NPV, AUD million)	453	392	354
BCR	30.4	14.1	8.2

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INFLUENZA

- Influenza is an infectious disease caused by influenza viruses. Symptoms typically begin 1–4 days after exposure to the virus and last for about 2–8 days. Influenza is typically characterized by seasonal epidemics and sporadic pandemics.
- In a typical year, 5–15% of the population contracts influenza. Deaths most commonly occur in high risk groups, including young children, the elderly, and people with chronic health conditions.
- In general, there are no long-term sequelae of influenza so the analysis only considers one year.
- The severity and infectiveness can vary significantly from year to year depending on the strains of the virus.

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INFLUENZA

- This analysis therefore concentrates on benefits and costs occurring in a "typical" year of influenza and is similar to a cost-benefit analysis of a national influenza vaccination program in preventing hospitalisation costs in Australian adults aged 50–64 years old (Raj et al. 2019). They found a BCR of 1.4.
- Influenza vaccine has been funded under NIP for adults aged ≥65 years since 1999, and children aged 6 months to <5 years since 2018.

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INFLUENZA

Dey et al. (2019) present surveillance and other data for the period 2012 to 2015 during which there were no pandemics or other unusual events. We take some of these metrics as a "typical" year.

Influenza notifications, hospitalisations and deaths, Australia, 2012 to 2015, by age group

Age	Notifications	Hospitalisations	LOS	Deaths
<1	5,400	2,988	2	1–3
1–4	23,954	4,545	2	15
5–14	42,998	3,194	2	9
15–24	24,295	2,857	2	Not given
25–49	72,637	10,657	2	61
50–64	33,907	8,462	4	115
≥65	37,922	21,496	5	834
All ages	241,177	54,199	3	1045

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INFLUENZA

- The main difficulty with modelling influenza is that the number of cases in a year is many times the number notified to NIDSS (Li-Kim-Moy et al. 2016).
- Somes et al. (2018) undertook a systematic review of 32 randomised controlled trials that reported on influenza and estimated the attack rate (incidence) of symptomatic influenza as shown below.

Age	%
Under 3 years	13.5
3–17 years	11.8
18–64 years	4.4
65 years and over	7.2

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INFLUENZA

- The efficacy of the influenza is assumed to be 50% based on the range of 40% to 60% quoted on the DoH website.
- The vaccination rate in 2019 is estimated (Hull et al. 2020; Dyda et al. 2019) to be as shown below.

Age	%
Under 3 years	42.0
3–17 years	20.0
18–64 years	5.0
65 years and over	72.6

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INFLUENZA

- In the following analysis we compare two scenarios. The first is with the vaccination rates given above. The second is with no vaccination, i.e. 0%.
- Using population data from the ABS for 2019, we can estimate the numbers effectively vaccinated by age and the vulnerable (i.e. unvaccinated and ineffectively vaccinated)
- Applying the attack rates to the vulnerable gives and estimate of the numbers of symptomatic cases of influenza in 2019 by age.
- Using the hospitalisation data given earlier, we can estimate the number of hospitalisations associated with these cases.

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INFLUENZA

- The average length of stay in hospital is assumed to be 5 days for 65 years and over, and 2 days for the other age groups. The cost per day is assumed to be $6,418. With the number of hospitalisations, these can be used to calculate the hospitalisation costs for each age group.
- For the age groups <3 years and 3-17 years, we assume that each case requires a parent to care for the child and the average duration of influenza is 7 days or 5 working days.
- For the age group 18 to 64 years, we assume that each case will result in 5 working days lost for those in the labor force.
- We assume no productivity loss for the age group 65 years and over.
- The average GDP per worker per day is $580 or $2,838 per influenza case and the labor force participation rate is 66.1%
- The cost per vaccinated person is estimated to be $30.

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INFLUENZA

Combining these estimate gives the hospitalisation costs and GDP loss averted by vaccination as shown below, as well as costs of the vaccination program and benefit-cost ratios.

	Under 3	3 to 17	18 to 64	65 and over
Hospitalisation costs avoided, $	14,211,165	9,440,659	7,150,271	296,377,091
Productivity loss avoided, $	48,920,791	103,869,850	32,426,595	0
Cost of vaccination, $	11,589,858	28,153,080	23,570,408	87,266,808
BCR	5.4	4.0	1.7	3.4

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    1. an increase in vaccination coverage rates for 60–<63 month old relative to the baseline
    2. an increase in the vaccination coverage rates for Aboriginal and Torres Strait Islander people in at least two of the following three age cohorts: 12–<15 months; 24–<27 months; and 60–<63 months, relative to the baseline
    3. an increase in the vaccination coverage rate for both adolescent boys and adolescent girls for HPV, relative to the baseline
    4. an increase in vaccination coverage rates for 60–<63 month olds in four of the ten lowest vaccination coverage SA3 geographical areas, relative to the baseline
    5. an annual decrease in the wastage and leakage rate for agreed vaccines, relative to the baseline.

    A performance milestone of "provision of annual schools HPV immunisation data for the previous school year by 30 April each year" is also specified in the Agreement. For the second year of the Agreement, all states and territories achieved this milestone.

    In relation to the 5 benchmarks assessed for the period 1 April 2018 to 31 March 2019:
    • New South Wales met 4 benchmarks, with benchmark 5 not being met

- Victoria met all 5 benchmarks
- Queensland met all 5 benchmarks
- Western Australia met all 5 benchmarks
- South Australia met 4 benchmarks, with benchmark 5 not being met
- Tasmania met 4 benchmarks, with benchmark 5 not being met
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43. In the evaluation of the price the Department of Health may, at its sole and absolute discretion, consider and, if necessary, adjust prices for the purpose of evaluation. Such adjustments may include but are not limited to:
    - consideration of normalised and discounted cash flow;
    - any assumptions or other caveats attaching to the price;
    - net present value analysis;
    - analysis of risks related to a Tender; and
    - other costs, if any, or financial impacts on the Department of Health and purchasers that may arise from appointing a particular Tenderer.

    Health may also undertake a sensitivity analysis including scenario modelling in evaluating Prices. Discounted cash flow may be used to estimate the net present value of amounts in future years of the Term of the Vaccine Agreement/s, with all assumptions on costs, interest rates and related factors to be determined in the sole and absolute discretion of Health. RFT-Health/1920/00502 – Supply of seasonal influence vaccines for the National Immunisation Program, p.33.
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114. One issue debated in the health economics literature is the validity or otherwise of using different discount rates for the costs and benefits of health interventions like vaccines. The rate and approach (similar or differential discounting) at which discounting is applied in a health economic evaluation greatly influences the cost-effectiveness ratio. The impact of discounting depends on the timing of costs and health outcomes realisations and therefore a longer delay in the health outcome results in a lower net present value. This becomes important for health technologies that accrue health benefits over time such as preventive treatment, cancer screening, or vaccination. Moreover, discounting both costs and health gains at the same rate introduces a systematic bias against healthcare technologies that might have, sometimes large, upfront costs but large health effects that accrue over a long time horizon. Health economists have also argued in support of differential discounting rates with a lower (0.3-1.5% lower) discounting rate applied for the health outcomes compared to costs. To account for expected increase in the value of health effects over time, countries such as Belgium, the Netherlands and the UK (for longer-term health effects) recommend differential discounting, with a lower discount rate applied to health effects than costs. Although a larger consensus is still to be reached on the use of differential discounting approach, in the current context, for the health technologies that have long-term effect a differential discounting approach can be tried.

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• Dementia is the second leading cause of death in Australia and Alzheimer's disease accounts for about 70% of all cases of dementia.
• In 2021 there are an estimated 472,000 Australians living with dementia (predicted to increase to 590,000 by 2028), with an estimated 1.6 million people involved in the care of people with dementia
• An estimated 250 people are diagnosed with dementia in Australia every day, and
• In 2018, dementia was believed to cost the Australian health system $15 billion.

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1. Understanding the rules and components of immunity, and
2. Creating Artificial Intelligence models of immunity.
In its first three years, the Project has:
- Open sourced the first sequencing of the human immune system
- Used machine learning to predict who will and will not respond to certain types of vaccines, and
- Established one of the world's leading scientific consortia across industry, government and academia.

In the next five years, the Project aims to:
- Finish the initial genetic sequencing of the human immune system
- Determine the initial rules by which the immune system fights disease, and
- Develop the first artificial intelligence model of the human immune system.

Priority areas for the project include:
- Immunotherapies for cancer, for all cancers, in all cancer patients
- Vaccines being effective for life and in all populations
- Alzheimer's Disease being preventable, and
- Avoiding the next flu pandemic, or other emerging threats.

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