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The Value of Vaccines

Ensuring Australia keeps pace with community values and international practice

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Foreword

By any global standard, Australia has an outstanding system of providing the whole population with vaccines that have immeasurably returned on the investment through highly effective disease control, lives saved and disability prevented. While a number of effective pillars were already in place (e.g. the national immunisation register and a truly national immunisation strategy), the modern era of reform that led to this position began in 1997. The Commonwealth and State and Territory governments of Australia established the National Immunisation Program (NIP) to improve immunisation coverage, by providing vaccines free of charge to eligible infants, children, adolescents and adults. From 2005, the ad hoc vaccine funding advisory mechanism in Australia was changed to bring vaccines into the overall policy framework that had been successfully used for drugs for some years, in the form of the Pharmaceutical Benefits Scheme (PBS), an important pillar (with Medicare and the Medical Benefits Schedule) of Australia's distinctive national health funding model that is founded on the principle of equity of access for all.

The Australian Government's Pharmaceutical Benefits Advisory Committee (PBAC) is responsible for the evaluation and recommendation to the Minister for Health of vaccines that might be funded as part of the NIP, based on a vaccine's estimated cost-effectiveness. Effectively, this mechanism aids the Government's decision-making in purchasing health benefit for Australians through prevention (or at least amelioration) of disease.

The system has to manage the competing demands of a global marketplace, access to valuable products (vaccines) and their reliable supply, transparency of process, and a level playing field amongst others. Various policy elements are built into the overall framework to achieve a rigorous and rational process. However, like all good policy in a changing global environment, continuous improvement and refinement is essential to maintain best practice in the service of public good.

Even in 2005, as Chair of ATAGI at the time, we realized that the methodologic framework for cost-effectiveness analysis of drugs (and other therapeutic interventions) was not ideally-suited to prophylactic vaccines. The notion of a single vaccination, often very early in life, producing health benefit throughout the lifespan (with or without booster vaccinations along the way), was the striking difference compared to, say chronic diseases or cancer in later life. In addition, the 'one-size fits all' framework for diseases of striking contrast (e.g. meningitis with potentially lethal or severe and lifelong disabling consequences). Nonetheless, this mechanism has served the country well and it has resulted in the inclusion on the NIP of several extremely valuable vaccines.

Recently however, Australian State governments have funded some statewide vaccine programs because NIP approval had not been provided (for various reasons), and because citizen opinion was heavily weighted to favour public funding of specific vaccines. This situation shines a light on the current PBAC mechanism for preventative vaccines, and it is timely that there is an objective and rigorous appraisal, and then hopefully a constructive and informed debate on what is needed to maintain Australia's leadership policy position in this area. That debate should involve all relevant parties – government, industry, technical experts in economics and social policy, healthcare professional bodies, and most importantly, consumers.

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06 June 2019

Executive Summary

The value the Australian community places on vaccines and immunisation programs is an important policy question which is not often publicly debated. When determining which vaccines to recommend, experts in our assessment system make a number of judgement calls on behalf of the Australian community. Some of these judgement calls are technical, however some are also value-based judgements that relate to: how our community values extending lives; which treatments or disease areas should be prioritised; and what benefits and costs are meaningful to individuals and society and should therefore be in scope for assessments.

Critically, across a range of issues, preventive interventions like vaccines are undervalued by the current assessment processes when compared to therapeutic medicines. This situation requires increased public engagement and urgent policy updates to ensure the vaccines assessment system meets the needs of the Australian community.

Vaccines are a unique class of medicinal product that provide protection against infectious diseases. Infectious diseases pose significant public health risk—they are often acute in onset, have limited treatment options and can result in death or significant morbidity in otherwise healthy populations. Furthermore, due to the unpredictable incidence and risk of transmission, the cost of disease outbreak and management can be significant. Vaccines are unique in that they often provide benefits not just to the vaccinated individual but also indirect benefits to those who have not received the vaccine, or indeed cannot receive the vaccine due to age or health complications. The value of successful immunisation programs is a reduction in disease transmission benefiting individuals, families, the broader community and the economy.

Over several decades Australia has developed a sophisticated approach to the funding and implementation of vaccination programs on a national scale. This is coordinated through the National Immunisation Program (NIP), a collaborative policy initiative undertaken by agreement between the Commonwealth, State and Territory Governments. The aim of the program is to increase national immunisation coverage and reduce the number of cases of vaccine-preventable diseases through the provision of free vaccines to eligible Australians based on an agreed schedule of vaccines.

The NIP has widespread stakeholder and community support. However, in recent years tensions have arisen regarding the exact composition of the NIP Schedule, resulting in the States and Territories—or indeed parents/ individuals—funding the cost of vaccines not covered by the NIP.

Consistent with most developed universal healthcare systems, the Australian Government determines which new vaccines to fund by conducting a health technology assessment (HTA). In Australia, since 2005 the Pharmaceutical Benefits Advisory Committee (PBAC) is the expert HTA committee that recommends which vaccines the Government should fund under the NIP. In many countries the expert HTA body responsible for vaccines deals solely with vaccines. In Australia, however, the PBAC assesses all medicines funded under the Pharmaceutical Benefits Scheme (PBS) and vaccines funded under the NIP. When determining which treatments should be funded, the PBAC utilises the established principles of HTA, supplemented by detailed guidelines, precedent and context-specific factors.

At present, several aspects of the PBAC's criteria are disadvantageous to vaccines compared to therapeutic medicines, while also being out of step with emerging international best practice and inconsistent with community values. Increasingly, these challenges are emerging as potential barriers to the implementation of clinically appropriate immunisation programs and policy.

Concerns include:

- the high discount rate applied to future costs and benefits, which has the impact of making preventive interventions like vaccines (which often take time for benefits to accrue) appear less cost-effective as compared to therapeutic medicines (which are more likely to provide benefits soon after initiation);
- the narrow healthcare system perspective typically adopted in assessments which limits the scope of review to only the benefits and costs relevant to the individual/patient and to the healthcare system. This approach disregards the broad societal impact of immunisation which occur outside the scope of the health system—for example, benefits to families and carers and benefits to other areas of government expenditure such as the welfare and tax systems; and
- the lower cost-effectiveness threshold (willingness to pay per unit of health gained) applied for preventive interventions like vaccines as compared to therapeutic medicines which has the impact of applying a lower willingness to pay for lives saved through prevention as compared to treatment

While these factors are not unique to vaccines and may apply to some degree to other interventions, the challenge is that when taken together, these issues make the task of demonstrating cost-effectiveness for vaccines very difficult. **This may result in delayed, limited or a lack of access to new vaccines.**

Recommendations

This paper proposes three urgent updates to current practice, all of which are immediately actionable and none of which requires any amendment to legislation or change to current institutions.

Given the broad remit of the PBAC, they are provided with authority and flexibility under the legislation and guidelines to consider a range of issues, including those outlined in this paper. However, to date the PBAC have been reluctant to utilise this flexibility.

This paper, consistent with the principles of the guidelines, urges the PBAC to incorporate these factors directly in their decision-making for vaccines when relevant—not in supplementary analyses, but in the base case.

We urge policymakers and the community to engage appropriately in the PBAC process to outline the value they place on immunisation and to insist that vaccines are not disadvantaged in assessments. Further, we encourage the PBAC to utilise flexibility, consistent with their remit and in line with international practice, when assessing the value of vaccines by:

- **Applying lower discount rates:**
  Discounting reduces the value of events in the future. Adopting a lower discount rate, in line with international practice, will place greater value on lives saved through prevention.
- **Taking a broader perspective, accounting for costs and benefits outside the health system:**
  Consider the broader outcomes from immunisation programs, including at a minimum, the impact on carers and families.
- **Removing the disadvantage applied to prevention through current Incremental Cost-effectiveness Ratio (ICER) ranges:**
  Apply the same 'willingness to pay' thresholds for lives saved through prevention or by therapeutic medicines.

Contents

1. Introduction

Consistent with most developed universal healthcare systems, the Australian Government determines which new healthcare interventions to fund by conducting a health technology assessment (HTA), also termed a health economic evaluation (HEE), of the proposed intervention. This typically involves a form of cost benefit analysis between competing programs. By comparing two or more programs, differences in costs and health outcomes can be estimated to support decision-making on how to spend funds from a finite healthcare budget. It is generally accepted that these decisions should align with country specific healthcare goals and reflect country specific societal values, as the community is ultimately both the patient and the source of funding (as taxpayers).

In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) is the expert HTA committee that recommends which medicines and vaccines the Government should fund. Section 101 (3AA) of *The National Heath Act 1953* specifies that the Australian Government cannot choose to fund an intervention without prior recommendation from the PBAC (NHA 1953). While the process for funding decisions is defined in the legislation, the evaluation criteria that determine whether interventions receive a positive or negative PBAC recommendation are not statutorily defined. The PBAC evaluation criteria are defined and published in the PBAC Guidelines (PBAC 2016). However, due to the expert nature of the PBAC, there is a tendency by Government, policymakers, politicians and the public not to question these criteria or the judgements that inform PBAC recommendations.

Appendix 1 provides a general introduction to the health economic methodologies that government appointed bodies (such as the PBAC) apply when determining what health interventions represent value for money and should be considered for recommendation.

The aim of this paper is to highlight that many aspects of the PBAC criteria relate to value-based judgements, of which the public and elected members of office should be aware and feel empowered to question and discuss. The paper focuses on criteria in our system that disadvantage preventive interventions (such as vaccines) compared to symptomatic interventions (such as medicines for treatment). The paper draws comparisons with alternative approaches in other countries as well as Australia's approach prior to 2005, when the assessment for the funding of vaccines transitioned from the Australian Technical Advisory Group on Immunisation (ATAGI) to the PBAC, with ATAGI maintaining a clinical advisory role.

The paper proposes three key updates to the current PBAC approach that would align Australia with international best practice for vaccine HTA and may better represent community values and expectations. These updates would also ensure that Australia's respected NIP is sustainable for future populations and emerging vaccine technologies.

Importantly, the updates proposed do not require changes to relevant legislation. The PBAC already has the authority and flexibility to implement the proposed changes at any time, particularly when the conditions of a specific evaluation require modification of the criteria to reflect specific community priorities or challenges within a given disease area.

Structurally, the paper is organised as follows:

- An overview of the evolution and methodology of Australia's funding and assessment arrangements for vaccines, including the structure of the NIP and role of the PBAC;
- A critical review of problematic elements of the current decision-making criteria which are particularly relevant to vaccines; and
- Proposed updates to the system we believe will enable the NIP to continue to meet the community's needs and expectations.

2. Overview of arrangements for funding and assessment of vaccines

Over several decades, Australia has developed a sophisticated and bespoke approach to regulation, assessment, funding, procurement, implementation and monitoring of vaccines (**Appendix 2** provides a definition and overview of attributes unique to vaccines). Immunisation programs that were previously managed by the States and Territories have become increasingly centralised in a shift towards a national approach administered through the NIP. Decision-making, while informed primarily by the processes of the PBAC and ATAGI, is ultimately with the Minister for Health.

The National Immunisation Program (NIP)

Legally and administratively, the NIP is a collaborative policy initiative undertaken by agreement between the Commonwealth, State and Territory Governments. The stated aim of the program is to increase national immunisation coverage and reduce the number of cases of disease that are preventable by vaccination in Australia. The main mechanism by which this is pursued is free-of-charge provision of an agreed Schedule of recommended vaccines to eligible cohorts according to age and/or medical risk, with special arrangements also in place to provide equitable vaccination opportunities to various disadvantaged and vulnerable populations (DOH 2018). The program encompasses a range of organisations with interdependent responsibilities, as summarised in **Appendix 3**.

Although the NIP is widely supported by stakeholders and the community, tensions sometimes emerge around the exact composition of the Schedule. These are fuelled by a complex interplay of scientific, clinical, practical, commercial, economic, financial, political and emotional considerations. Decision-making has therefore been challenging and sometimes also contentious (Roughead, Gilbert and Vitry 2008); (Parrella, Braunack-Mayer et al. 2016).

During the early 1990s, recommendations regarding the inclusion of vaccines in Australian immunisation programs came from a sub-committee of the National Health and Medical Research Council (NHMRC). These guidelines were communicated to health professionals via the National Immunisation Handbook (NIH) but were not directly connected to government vaccine funding decisions, which were disjointed and fragmented across national, state, territory and local jurisdictions.

In 1997, as part of a broader policy reform package that created the NIP, the Commonwealth Government created the Australian Technical Advisory Group on Immunisation (ATAGI) to assist the Department of Health (DOH) and Minister for Health on issues relevant to the composition and administration of the program and vaccine issues more generally (Nolan 2010). During this time, proposed new immunisation programs (targeting rotavirus, varicella, meningococcal C and pneumococcal disease), as well as new formulations and fixed dose combinations of existing vaccines, quickly gave rise to vigorous debate between the contrasting clinical and public health perspectives of ATAGI and the fiscal imperatives of Government.

In response, in 2005 the Government introduced amendments to the *National Health Act 1953* stipulating that for a vaccine or immunisation program to be included on the NIP Schedule, it had to first be assessed for cost-effectiveness by the PBAC and recommended to the Minister for Health as appropriate for listing in the program. A graphical overview of these arrangements is provided in **Appendix 4**.

The Pharmaceutical Benefits Advisory Committee (PBAC)

The PBAC is an independent statutory body, first established in 1953, which is principally tasked with providing advice to Government on the composition of the Pharmaceutical Benefits Schedule (PBS); (Goddard 2014). The roles, responsibilities

and membership of the PBAC have grown and evolved significantly over time, and its processes and decisions have become increasingly more open and transparent (Biggs 2002). The PBAC ultimately serves the Minister for Health, who retains decision-making authority for final listing decisions and for the policy overlay informing the PBAC system.

The PBAC's role has evolved in line with international development in the field of HTA. In 1987, important amendments were made to the *National Health Act 1953* which required the PBAC to take into account the effectiveness and cost of a medicine compared with other therapies when considering a proposal for the listing of a new medicine on the PBS. This led to the introduction of mandatory HTA for all new PBS medicines from 1993, the establishment of expert Economic and Drug Utilisation Subcommittees (ESC/DUSC) and the subsequent evolution of a highly structured process for considering requests to add or amend PBS product listings (George, Harris and Mitchell 2001) (Lopert 2009).

From a technical perspective, PBAC decision-making is informed by established HTA principles (Drummond, Schwartz et al. 2008), involving a series of questions to the effect of:

- where does the intervention fit into local clinical practice;
- how well does it work in comparison to current standards of care;
- how much does it cost and does this represent good value for money for the local health system; and
- what is the likely net financial impact and is this affordable.

From a practical perspective, the PBAC conducts three formal meetings each year. It reactively considers submissions, mainly from industry sponsors of medicines and medicinal products, but also occasionally from medical bodies, health professionals, patient groups and private individuals. Submissions relate to the inclusion of products or programs on the PBS or NIP and associated eligibility criteria, pricing and administrative requirements. They are required to conform to detailed technical guidelines (PBAC 2016) and these are considered within a structured 17-week evaluation timeline (PBAC 2019).

As described in this paper, many of these questions involve both technical assessment considerations (for example, as described in submission guidelines and published reasons for previous decisions) as well as societal value judgements (for example, whether the Government—and by extension, the community—has the same or different willingness to pay for prevention and treatment).

Since 2005, as part of their broader role in all PBS listings, the PBAC has become arguably the most important arbiter in the composition of the NIP Schedule. While PBAC receives advice from ATAGI on clinical, public health and implementation issues, final recommendations reflect its own bespoke assessment criteria. Moreover, while final listing decisions remain the responsibility of Government, the legislation as it stands does not permit the Minister to include a vaccine on the NIP in the absence of a positive PBAC recommendation (DOH 2018).

Despite this, the Minister and Government of the day have the overarching responsibility and authority, including:

- to ensure the policy settings and societal inputs adopted as part of the assessment system are appropriate and meet community needs and expectations;
- to maintain and update legislation as required to ensure the system is continually modernised to meet future challenges; and
- to work with other branches of government to manage emerging or time-critical issues relating to vaccine-preventable diseases (particularly given the lengthy processes required before permanent changes to the NIP can be made). For example, the States and Territories continue to implement vaccination programs outside of the NIP as required for outbreak control.

To date, vaccine evaluations for the NIP represent only a small fraction of the total number of submissions reviewed by the PBAC and the experience of these has been mixed. Moreover, in most important aspects, decision criteria relating to vaccines and immunisation programs have also been primarily informed by the decision criteria that apply to medicines for the PBS.

An Australian PBAC perspective on the Committee's first four years of assessment of vaccines was published in 2009, when a senior Department of Health official and three then PBAC members co-authored a response to a paper by Beutels et al. entitled "Funding of drugs: do vaccines warrant a different approach?" (Beutels, Scuffham and MacIntyre 2008). The Beutels paper argued that the specifics of immunisation, when taken in totality within a cost-effectiveness framework developed for therapeutic medicines, disadvantage vaccines within the current system (Beutels et al. 2008).

In replying with the then PBAC perspective, Mitchell et al. stated "none of the other features listed by Beutels and colleagues are unique to vaccines. All have applied to drugs in the experience of PBAC, especially the need to manage uncertainty" (Mitchell, Isaacs, Buttery and Viney 2009). However, in rebuttal the original authors Beutels et al. noted "Andrew Mitchell and colleagues misinterpret our viewpoint, since they emphasise that the cost-effectiveness of drugs other than vaccines can also be sensitive to the methodological problems we discussed… However, we argue that the sensitive features we outlined apply more frequently and more widely to vaccines than any other group of drugs. If guidelines were revised as we suggest they would still need to be applied to all drugs, not only vaccines" (Beutels et al. 2008).

While this paper aligns with the view that the challenges facing vaccines in our system may apply to other interventions (and therefore recognises that the recommendations should be relevant to all interventions) we highlight the higher level of disadvantage faced by vaccines because of the cumulative effect of these challenges.

Case history and emerging challenges

Vaccines and programs that were included on the NIP prior to 2005 were effectively grandfathered across to the current version of the Schedule. Most of these have never been subject to any formal economic evaluation, while those that have, were not strictly assessed according to PBAC criteria.

The move to have the PBAC assess proposed immunisation programs has come with some challenges. Although, thus far, the system has grappled with the change in most cases. Since 2005, important new immunisation programs have been evaluated, recommended and implemented including those for rotavirus (RV), human papillomavirus (HPV) and herpes zoster virus (HZV). However, none of these was straightforward: proposals for all three programs were initially rejected by PBAC, mainly based on perceived unacceptable and/or uncertain cost-effectiveness, with approval being granted only following public pressure alongside amendments to the proposed program scope and/or price on the part of the respective sponsors. The RV and HPV programs were commenced promptly, but establishment of the HZV program took several years, initially due to supply issues, then as a result of the PBAC requesting a further evaluation and ultimately a rescoping of the program. Subsequent retrospective evaluations of the RV and HPV programs after 10 years in operation suggest they were undervalued during their initial assessment and that their true value is significantly in excess of their cost (Reyes et al. 2017); (Hall et al. 2019); (Patel et al. 2018)

Various extensions to existing vaccination programs have also been recommended by PBAC since 2005, including: the recent introduction of a new maternal dose of the adult formulation pertussis containing vaccine; reintroduction of the previously deleted 18 month (4th) booster dose of the combined diphtheria, tetanus and pertussis vaccine; expansion of the HPV program to include males as well as females; addition of multiple at risk groups to the annual influenza immunisation program around 2010; and establishment of various targeted immunisation programs for specific at risk subjects. These program extensions have been possible mainly because the vaccines

in question are now older and relatively inexpensive, resulting in the proposals being unambiguously cost-effective (or cost-saving). Various fixed dose combination vaccines have also been recommended by PBAC for inclusion on the NIP, but only based on "sum of the parts" pricing (pricing of the combination vaccine based on earlier pricing for the individual component vaccines) and zero additional program cost.

However, while these examples are frequently cited as evidence that the current assessment system is working well, there are also now several examples where application of PBAC processes and criteria have delayed or even prevented the implementation of clinically appropriate, safe, effective and important changes to the NIP Schedule. These have resulted in significant costs to patient access, public health and community welfare.

Key examples include the ongoing impasse with respect to the slow evolution of the pneumococcal program for elderly subjects to include newer conjugate vaccine formulations, proposed meningococcal B immunisation program, and failure to accommodate improved (intradermal or high dose) vaccines or broader populations (50-65 years) within the influenza program. The likely undervaluation of the RV and HPV programs (noted above) highlights that the system, at least in some cases, is providing suboptimal valuation of vaccines, and therefore suboptimal advice to Government on where to direct resources. For the community this translates to delayed, limited or a lack of access to new vaccines.

Decision criteria for vaccines and immunisation programs

Given the credibility and respect for the NIP locally and internationally, and the possible consequences should the system not remain fit for purpose, it is critical that policymakers, public health experts and the community play an active role in assessing and continually improving the system.

Some principles and criteria the PBAC use in its decision-making on vaccines are not fixed or formally documented. Instead, PBAC processes involve a range of factors including submission guidelines, historical preferences, subjective criteria as documented in the Public Summary Documents of previous decisions, and product/program specific factors conveyed in pre-submission advice provided by the DOH and ATAGI. A vaccines specific appendix was added to Version 4.0 of the PBAC Guidelines (2006) which specified some unique or additional information requirements specific to vaccine products, and this was retained with minor modification in Version 5.0 (2016). However, in most important respects, evidentiary requirements, methodological guidance and decision criteria are identical to and have been primarily informed by those applying to medicines. The key components of these criteria are summarised in **Appendix 5**.

There is growing global recognition among health economists, policymakers and international payers that the value assessment of vaccines requires unique considerations (Standaert and Rappuoli 2017). An overview of the unique nature of vaccines provided in **Appendix 2**.

This paper seeks to invigorate debate on the suitability of three key elements of PBAC assessment criteria as they relate to vaccines and immunisation programs: discounting; choice of perspective in relation to costs and benefits; and ICER thresholds. It is argued that current criteria are inappropriate to the evaluation of vaccines, inconsistent with international best practice and potentially societal values and should be updated. Critically, the changes proposed are immediately actionable and do not require either new legislation or substantive structural change to PBAC processes.

3. Problematic elements of current decision criteria

Discounting Overview

An important aspect of the HTA of preventative interventions like vaccines is the question of time preference i.e., how to compare costs and outcomes incurred in the present versus the future. Investing now for benefits in the future means that those resources are no longer available. Future costs and benefits, when valued in monetary terms, are generally discounted, because it is widely held that there is a societal preference to consume in the present and to defer payment. However, this becomes problematic when applied within health where community and policymakers have a stated commitment to valuing prevention.

The choice of discount rate and the way in which it is applied can make a significant difference to whether an intervention is considered cost-effective, especially when costs and benefits accrue at different times and over long periods.

Compared to most other health interventions, vaccination has distinctive features that influence how choices are made over time. Examples include:

- There are often long delays between vaccine administration (when costs are incurred) and disease averted (when benefits are obtained), so benefits are often greatly affected by discounting. By contrast, interventions without long-lasting effects (such as pain medication that provides immediate but short-term relief of symptoms) or that incur costs and benefits at a steady rate (many long-term chronic medications) may be largely insensitive to discounting.
- Some vaccines have positive externalities: they not only reduce disease risk in vaccinated subjects but, in some cases, provide herd or community-level protection to those who cannot be or have not been vaccinated. The externalities are non-linear with respect to coverage: if a single individual is vaccinated, the health gain to others is small, but if most susceptible individuals are vaccinated, there is a substantial health gain to others. Herd protection from vaccination can persist for years and indeed indefinitely in the case of eradication. Hence there can be delays between the earlier cost of vaccination and realisation of herd protection effects.

The PBAC applies a flat discount rate of 5 percent to both costs and outcomes, while guidelines permit consideration of sensitivity analysis. This rate is high by international comparison and renders vaccines, with the same costs and outcomes, less cost-effective under the Australian system than in comparable healthcare systems (UK, New Zealand, France and Canada with lower discount rates, see Table 1 on page 20).

Why discount?

Economists regard present consumption as more valuable than future consumption, because they believe it reflects societal preferences and:

- there is an opportunity cost to consuming now rather than later, since the money spent could have been invested elsewhere to generate some returns; and
- most people simply prefer to consume now rather than later, all other things being equal.

The standard approach to collectively capture these preferences for present over future consumption is by discounting (Krahn and Gafni 1993), which reduces the value of future costs and benefits compared to those in the present (Frederick, Loewenstein and O'Donoghue 2002). Discounting is applied via a negative compounding rate, therefore a small difference in the percentage applied can compound to have large effects over extended periods, for example 20-30 years akin to a mortgage rate, which has a positive compounding factor.

While there is a general consensus that discounting based on the social time preference approach should be applied to costs and benefits valued in monetary terms, the magnitude of discount is more contentious, especially when there are intergenerational or long lag periods to consider (Harrison 2010). Low discount rates are often used in environmental applications, especially when benefits accrue in the distant future. The United States Environmental Protection Agency recommends a discount rate of 2-3 percent (Zhuang, Lin and DeGuzman 2007). A UK government environment report, entitled the Stern Report, used a 1.4 percent rate to discount the benefits from greenhouse gas emission abatement policies (Stern 2007). Debate in this field often relates to the cost of money and government bonds as the theory is based on a monetary assessment of value.

Should discounting be applied to health?

There is no consensus that benefit, when quantified in the non-monetary terms of health (e.g. Quality Adjusted Life Years, or QALYs), should be discounted (Lazaro, Barberan and Rubio 2002). A recent review commissioned by the UK government on the appropriate discount value to apply when discounting health noted 'there is currently no agreement that future increases in health will have a declining value' and have subsequently proposed that the existing UK discount rate of 3.5 percent be reduced to 1.5 percent for health economic evaluation of vaccines, this recommendation has however not yet been ratified (CEMIPP 2016). Indeed existing, albeit limited, research indicates that individuals report a higher positive time preference for health than for money (Lazaro et al. 2002). Such findings are also aligned with a US survey asking future healthcare professionals to choose between different healthcare programs on behalf of society, which found there was a preference to discount cost at a higher rate than health (Brouwer and van Exel 2004).

Given there is no consensus on how technical experts in HTA should apply discount rates, and different theories and value judgements are valid, input from community and policymakers becomes particularly important.

What does discounting mean in practice?

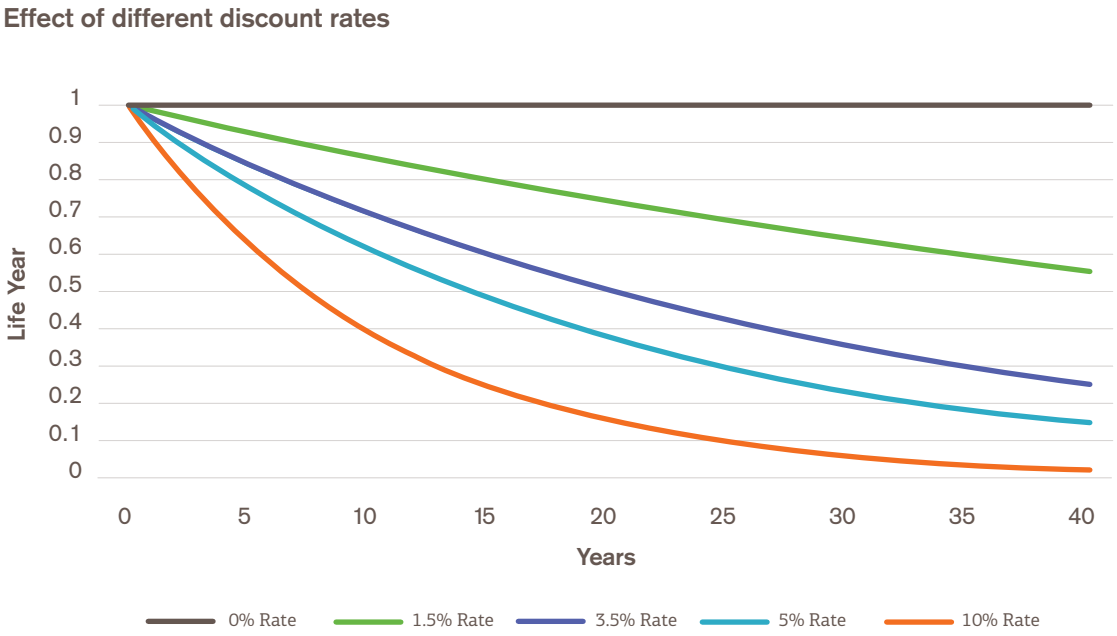
The effect of applying various discount rates to future benefits, is described in Figure 1. For example, a 5 percent discount rate (the rate applied by the PBAC) means that a life year saved 20 years from now is considered to have a present value of 62 percent less than one saved today. This example highlights the difficulty in demonstrating the present value and cost-effectiveness of vaccines which in many cases result in life years saved years or decades into the future, following the original investment in the immunisation program.

Compared to the PBAC's current use of a 5 percent discount rate, the UK current discount rate of 3.5 percent values a life year saved in 20 years as 50 percent less than one saved today. The UK government proposed new discount factor of 1.5 percent will value a life year saved in 20 years as only 26 percent less than one saved today; i.e. a substantially higher valuation of future life year as compared to the PBAC 5 percent rate (CEIMPP 2018).

As noted in the **Appendix 1**, HTA typically involves a detailed comparison of the costs and benefits of a proposed health program with existing and/or feasible alternatives. By comparing programs in this way, differences in costs and health outcomes can be estimated. A typical HTA evaluation quantifies health outcomes in terms of the Quality-Adjusted Life-Years (QALYs) gained. This measurement takes into account both the quality and quantity of life lived in different disease states. HTA bodies often then consider the incremental cost of each added QALY gained. An Incremental Cost-effectiveness Ratio (ICER) can be used to provide a threshold for willingness to pay for added QALYs.

Figure 1: Impact of different discount rates on the expected future value of a life year

- The graph (and corresponding table) below outlines the impact of discounting over time (0-40 years) across a range of relevant discount rates. 5% represents the PBAC rate; 1.5% represents the Canadian rate; and 3.5% represents the New Zealand and UK rate.
- The dashed black line represents a baseline of zero discounting (i.e 100%= 100% at time zero and at 40 years). The coloured lines represent the pace and depth of discounting over time when different rates are applied.
- Due to the compounding nature of the calculation, the effect is not linear but increases significantly when a small change in percentage rates is applied.
- The table below the graph provides the actual value counted when the discounting factor has been applied i.e. the value the payer uses in their decision making. For example, application of 5% discount rate (blue line) at time 10 and 20 years results in 61% (1-39% discount) and 38% (1- 62% discount) of the value being counted, respectively.
- The graph illustrates that for a vaccine providing benefit over 20 years, a 5% discount rate (as applied by the PBAC in Australia) would mean only 38% of the value that vaccine provides after 20 years would be counted. From a real-life perspective, consider that an immunised child who avoids a disease and therefore also avoids 20 years of health and societal complications from that disease, will still be reaping quality of life, health and other benefits 20 years on—yet, with discount rates, only a fraction of those benefits would be valued.



Actual values once discounting has been applied, relating to graph above

Year	0%	1.5%	3.5%	5%	10%
0	100%	100%	100%	100%	100%
10	100%	86%	71%	61%	39%
20	100%	74%	50%	38%	15%
30	100%	64%	36%	23%	6%
40	100%	55%	25%	14%	2%

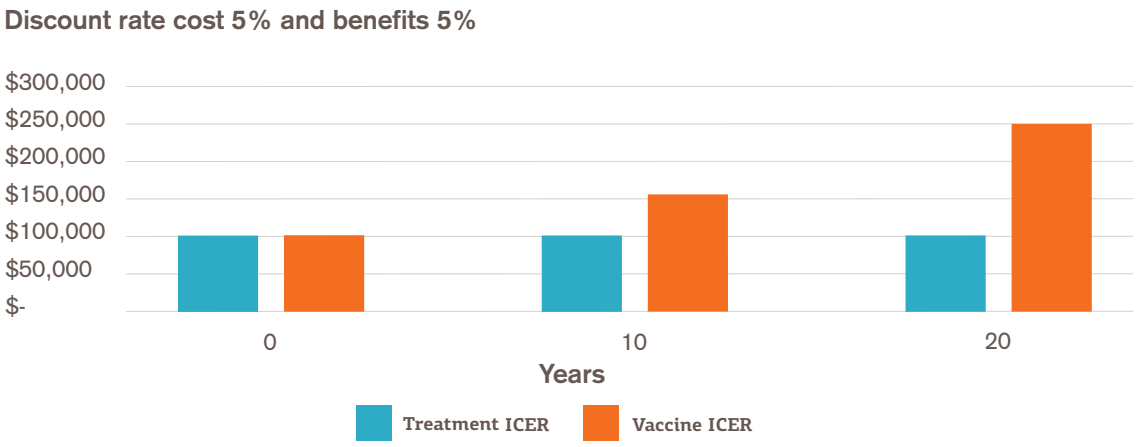
Comparing how the impact of discount rates can differ between vaccines and therapeutic medicines

To demonstrate the impact of discount rates on vaccines as compared to most other health interventions, the following theoretical example is helpful:

- Consider two interventions; a vaccine and a therapeutic medicine.
- Both have equal costs ($1m) and equal health benefits (10 QALYs) but they differ regarding the rate of accrual of benefit and cost over time.
- For the vaccine, assume 100% of cost upfront and test for cost-effectiveness results when 100% of benefit accrues at time 0, 10 or 20 years.
- For the medicine, assume a constant rate of accrual of benefit and costs. The differences in the respective ICERs are presented in Figure 2.
- As the costs and benefits for the medicines accrue at a steady rate, the effect of discounting over time has negligible impact.
- In contrast, the ICER for the vaccine in this example is dramatically altered depending on the assumed time for the accrual of benefit.
- Note that the lower the ICER value, the more cost-effective an intervention is considered.

Figure 2: Simplified illustration of the impact of discount rates vaccines vs. therapeutic medicines due to time differences in the accrual of cost and benefit

- The graph below illustrates the impact on ICERs/ measure of cost-effectiveness for a theoretical therapeutic medicine (treatment ICER) and a vaccine (vaccine ICER) when costs and benefits accrue at different time periods with the PBAC's 5% discount rate.
- The three scenarios illustrate what happens when both interventions cost the same amount ($1m) and provide equal benefits (10 QALYs). For the therapeutic medicine, we assume that costs and benefits accrue at a steady rate (as may be likely for a treatment for a chronic respiratory condition like asthma). On the other hand, for the vaccine we assume all the cost is incurred upfront, but the time for accrual of benefit is: immediate (0 years), 10 years, or 20 years.
- The bars illustrate the magnitude of the ICERs. The lower the ICER value, the more cost- effective an intervention is considered. We can see that when we assume the benefit of the vaccine is delayed until 10 or 20 years, the ICER increases approximately 50% ($150K at 10 years vs $100K at 0 years) and 150% ($250K at 10 years vs. $100K at 0 years), respectively. In contrast the ICER remains $100K for the therapeutic medicine as it assumed there is no difference in the timing of the accrual of cost and benefit i.e. the cost and benefit above and below the line are reduced at an equal rate over time resulting in the same ICER ratio.



[1] Actual values =ICER $155,133 (QALY difference 6.14/ Cost difference $952,381) at 10 years vs. $100K (QALY difference 10/ Cost difference $1,000,000) at 0 years.

[2] Actual values =ICER $252,695 (QALY difference 3.77/ Cost difference $952,381) at 10 years vs. $100K (QALY difference 10/ Cost difference $1,000,000) at 0 years.

To further demonstrate the sensitivity of cost-effectiveness of vaccines to discounting, it is worth considering analyses of the cost-effectiveness of HPV vaccination in the Netherlands, in which nine different discounting approaches and rates were evaluated. Other things being equal, the ICERs ranged between £7,600/QALY gained and £165,400/QALY gained (Westra et al. 2012). This demonstrates the impact different discount rates can have—with some acting as a barrier for the demonstration of cost-effectiveness, and therefore a barrier for funding by government.

Is there a consensus on what discount rate and methodology to use?

There is no consensus on the most appropriate discount rates. However, most comparable developed HTA markets use discount rates lower than the 5 percent applied by PBAC, as summarised in Table 1.

Selecting an appropriate discount rate is subjective, and there is therefore a need for this to be informed by societal preferences, particularly given the large impact discount rates can have on the demonstration of cost-effectiveness for preventative interventions, where benefits accrue over a longer period of time.

Several key markets have recently or are currently reviewing discount rates (UK, Canada, New Zealand); (Rafferty, Gagnon, Farag and Waldner 2017). The World Health Organisation (WHO) has published advice on discounting which is lower (3 percent) than the PBAC's current position (5%), and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has recently issued updated advice on alternative approaches to standard HTA for vaccines and areas where further research is required. However, they have not recommended a specific value for discounting, deferring instead to country specific preferences (Mauskopf et al. 2018).

In addition to differing views on the most appropriate discount rate, there is also no consensus on discount rate methodology (for example, application of a uniform or variable rate over time). Due to the compounding nature of the discount rate, over time, it quickly accrues such that a significant proportion of the effects post 20-30 years are substantially reduced or near negligible depending on the magnitude of the discount factor employed. In France, the first 30 years are discounted with a uniform rate of 4 percent, and years thereafter at 2 percent. This "slow" discounting procedure is also recommended by WHO if the effects of vaccination begin only long after the intervention (WHO 2008).

The WHO further recommend that a discount rate of 3 percent, consistent with earlier recommendations made by WHO-CHOICE and the Second Edition of Disease Control Priorities in Developing Countries (DCP2) be tested, in addition to the country specific discount rates, when assessing the value of future immunisation programs (WHO 2008).

The ongoing Cost-Effectiveness Methodology for Vaccination Programmes and Procurement (CEMIPP) review in the UK has also acknowledged the UK Treasury Green Book advice on broad economic evaluation, whereby post 30-year discount rates should be revised downwards. Although the CEMIPP does not make specific recommendation about lowering the discount rate post 30 years, it does recognise the challenges inherent in assessing value post compounding discounting over such a long period (CEIMPP 2016).

Table 1: Discount rates applied by international HTA agencies

Parameter	Canada	Belgium	Germany	New Zealand	UK	France	Netherlands	Australia
Discount rate costs	1.5%[2]	3%	3%	3.5%	3.5%[1]	4%	4%	5%
Lower discount rate for health	No	Yes. 1.5%	No	No	No	No	Yes. 1.5%	No
Variable discount rate over time	No	No	No	No	No	Yes, 2% from 30 years[3]	No	No

Note These countries were chosen as they are considered comparable developed HTA markets.
[1] However current recommendation is to reduce this to 1.5% (CEMIPP 2016);
[2] Source: https://www.cadth.ca/dv/guidelines-economic-evaluation-health-technologies-canada-4th-edition
[3] Source: http://www.crest.uts.edu.au/pdfs/FactSheet_Discounting.pdf
Source: Ultsch, Damm et al. 2016

The Australian PBAC perspective from the Mitchell et al. paper published in 2009 also addressed discounting. The Mitchell response argued that discounting affects non-vaccine related interventions including chronic treatments, and further argued that discounting accounts for uncertainty (Mitchell et al. 2009).

This paper agrees that discounting affects non-vaccine related treatments. As explained in Beutels' rebuttal to the Mitchell paper, "the lag between intervention and infection (which precedes the lag between infection and clinical disease) is relevant for the evaluation of infection prevention, but not for treating chronic infections"; that is discounting is most relevant when the treatment relates to prevention be it via a vaccine or another intervention.

This paper further contests the Mitchell et al view that "discounting is critical in allowing for the uncertainty about future benefits and costs" (Mitchell et al. 2009). Discounting relates to time related preference, it does not relate to uncertainty. Uncertainty is captured and addressed via sensitivity analyses around the ICER. Reflecting uncertainty via a high discount rate would be in contravention of health economic theory and would represent double counting. Furthermore the "slow" discounting approach which Mitchell et al found unreasonable, is current position of the WHO as outlined in this paper.

What change is recommended?

The theoretical basis for discounting costs and outcomes in health economic evaluation is still debated and there is no consensus around either the rate to be applied or the methodology for applying them (Zhao et al. 2018); (Jit and Mibei 2015).

The PBAC applies a rigid, common and constant 5 percent compound annual rate for both costs and outcomes, with ranges outside this bound considered in supplementary analyses. This rate is at the upper end of international recommendations and possibly inconsistent with contemporary social time preferences. A review of this approach during the 2016 update of the PBAC Guidelines (v.5.0) was brief, technical and not accessible for the community to be involved. Greater flexibility is required around application of current PBAC Guidelines to interventions with particularly long horizons of benefit, including many paediatric vaccines. This could include applying discount rates consistent with current cost of capital, consideration of different discount rates for costs and outcomes reflecting societal unwillingness to discount health and/or application of discount factors that vary over time to reflect various intergenerational equity.

Healthcare perspective Overview

The perspective or viewpoint adopted by a HTA body determines which elements of a proposed intervention are included in the base case economic evaluation and which elements, although arguably economically relevant, should be omitted. Adoption of a healthcare perspective generally includes consideration of the costs and benefits relating to the patient and the healthcare sector should the new intervention be adopted. However, some payers choose to adopt a broader societal perspective including consideration of costs and benefits beyond the patient and the healthcare sector—for example, whether and how much a new intervention may reduce costs in the welfare system or reduce the demands placed on caregivers. The choice of perspective by a HTA body can have a significant impact on the value and thus likelihood of a positive or negative funding decision for an intervention.

The PBAC base case cost assessment is limited to the healthcare perspective. There are many types of benefits from medicines that are typically excluded from consideration. The PBAC does not generally assess broader societal benefits from medicines such as productivity gains in the workforce and avoidance of welfare transfers which would be considered only if a broader perspective (such as a societal perspective) is adopted. Likewise, the PBAC does not typically apply a broader, societal assessment of benefits, for example the quality of life improvements that might benefit families and caregivers. As with the choice of the most appropriate discount rate, the choice of perspective is an important value judgement that should be informed by the community and policymakers for the technical experts of the PBAC to then apply.

How does the choice of perspective impact the scope of costs and benefits considered?

The choice of perspective or viewpoint determines the scope of the costs and benefits included in an evaluation, therefore a position must be adopted as to which costs and benefits are considered applicable to the medicine or vaccine under review. Broadly speaking, perspectives are categorised as follows:

1. Direct costs and outcomes: evaluation includes direct costs borne by the healthcare system (e.g. drug cost, cost of hospitalisation) and direct outcomes (quality of life impact) on the patient
2. Indirect costs: evaluation includes productivity loss of the patient due to illness in addition to the costs borne by the healthcare system (e.g. drug cost, cost of hospitalisation)
3. Indirect outcomes: evaluation includes indirect outcomes (quality of life impact) on those affected by caring for an ill patient (e.g. carers, parents)
4. Indirect costs and outcomes: combination of item #2 and #3
5. Inclusion of indirect effects is termed a societal perspective, whereas exclusion of indirect effects is termed the payer perspective

It has been argued that indirect costs and outcomes are difficult to measure and, in any case, may be provided as supplementary analyses in PBAC submissions (Mitchell et al. 2009). However, as in other areas of Government expenditure, more comprehensive information on cost-effectiveness allows Government to make better informed decisions. When indirect costs and outcomes can be appropriately estimated in reference to the proposed new intervention (whether it be a new vaccine or a new therapeutic medicine), this is relevant context for Government decision-making and should be factored in PBAC assessments in the base case.

As noted by Beutels et al. (2009), “since vaccine development is based largely on private enterprise, we should strive to value vaccine correctly. All costs and benefits

should be included, if they are relevant for the chosen perspective of the analysis. We do not want an inside track for vaccines; we want national drug policy committees to adopt a consistent social perspective, and to also consider relevant effectiveness claims when these can only be estimated by modelling."

What do differing perspectives mean in practice?

Omitting important costs and benefits in an economic evaluation will lead to an inefficient allocation of resources. The impact of this can mean that cost-effective medicines will not be reimbursed and incentives for innovation will be adversely affected (Jonsson 2009). The above categories considered by healthcare payers are arguably narrow in their perspective and do not accommodate the full breadth of the impact of an intervention even under the apparent societal perspectives. Arguably a more informed societal economic analysis would include effects in the healthcare sector and beyond it into the private healthcare sector and non-health sectors (housing, education, treasury) public or private. Only when the societal approach is adopted can decision-makers be provided with a full information set of the costs and consequences of alternative actions. Anything less comprehensive will necessarily be subject to omitted variable bias of unknown sign and size causing over- or under-investment in both old and new technologies (Siegel, Weinstein, Russell and Gold 1996).

The question of perspective is particularly important for vaccines, which have distinctive broader societal impacts compared to many other health interventions. Examples include:

- In many cases, vaccine benefit is observed at the population level, because it includes externalities such as herd protection and the reduction in antimicrobial resistance which are additional benefits for people other than the at-risk group targeted for vaccination (i.e., caregivers, employers, payers), and the overall economic and welfare improvement resulting from a permanently healthier population who may therefore be more active and productive (Standaert and Rappuoli 2017).
- Vaccines in some cases avoid disease events that normally do not receive medical attention but may nonetheless cause important productivity losses for non-professional caregivers. This occurs especially for disease episodes among children (parents) and the elderly (family members). The vaccination impact can also be substantial at the level of overall disease management in the healthcare sector; for example, improvement in hospital quality of care after the introduction of the rotavirus vaccine in Europe (Standaert and Rappuoli 2017); (Standaert, Alwan, Strens, Raes and Postma 2015)

Is there a consensus on which healthcare perspective to adopt?

As with discounting, the determination of the healthcare perspective varies from country to country. According to the WHO, analyses should include the perspective of society and include all effects and all related costs, regardless of who benefits from or pays for them. However, it is recommended the costs should be separated where feasible by providers (e.g. donors and governments, patients and their families) to allow judgements to be made from the viewpoints of various decision-makers (WHO 2008). Selected additional viewpoints on the topic, from key opinion leaders and non-governmental organisations, as summarised in a review conducted for the UK Department for International Development, are outlined in Table 2. Additional views are provided in the relevant publications.

Table 2: Key opinion leader and organisational views on healthcare perspective

Source	Position
Sanders 2016	Recommends both a societal and a healthcare system perspective.
Drummond 2015	Recommends a multi-sectoral perspective because, although it may not embrace all costs and consequences in the economy, it might identify trade-offs of consequence.
Wilkinson 2016	Like Drummond et al. (2015), a disaggregated societal perspective should be used to capture relevant non-health effects and costs
IPF 2006 20	The choice of perspective must be derived from the research question. The societal-economic perspective is the most comprehensive approach, but other perspectives are possible, e.g. the health system, social insurance, other service providers (hospitals).
ISPOR 2017	The primary perspective uses costs that fall on the decision-maker and QALYs as measures of the expected population health impacts including direct effects, herd effects, and serotype replacement. A secondary and broader societal perspective includes costs and effects both inside and outside the healthcare sector, possibly including educational attainment, productivity, household financial risk, and tourism impact.
WHO 2008	Resource use and health effects should be identified and valued from the societal perspective.

Abbreviations: ISPOR = International Society for Pharmacoeconomics and Outcomes Research; IPF = Institut für Pharmaökonomische Forschung; WHO = World Health Organization; Source: (Culyer et al. 2018)

Like discount rates, international payers vary in their judgement as to what approach to adopt (Table 3). The PBAC typically adopts the narrow approach of considering direct health costs and outcomes only, in contrast to payers in Belgium, the Netherlands and in relevant circumstances, the UK, where payers consider the quality of life impact beyond the patient, for example, carers and parents. The Dutch system further considers productivity loss costs.

Table 3: International payer healthcare perspectives*

Parameter	Canada	Belgium	New Zealand	UK	France	Netherlands	Australia	Germany
Direct health costs and outcomes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Indirect costs	No	No	No	No#	No	Yes	No	Yes
Indirect outcomes	No	Yes	No	Generally no but guidelines permit inclusion in base-case when relevant	No	Yes	No	Yes

* Relate to guideline defined base-case not supplementary or sensitivity analyses
# However, clause added in 2004, to consider broader costs when requested by the Department of Health
Note: These countries were chosen as these are considered comparable developed HTA markets.
Sources: (Culyer, Chalkidou, Teerawattananon and Santatiwongchai 2018; Angelis Lange and Kanavos 2018; PHARMAC 2017)

What change is recommended?

The direct healthcare perspective adopted by the PBAC for both costs and outcomes is at the more conservative end of approaches applied by international payers. Given the unique, broad and indirect nature of vaccine benefit across a population, it is appropriate to question whether for vaccines the exclusion of effects beyond the patient and impact on sectors beyond healthcare is the more appropriate or more useful in making funding decisions. At a minimum, we propose the PBAC include indirect benefits to carers and parents for vaccines when relevant in the base-case economic evaluation. Although still a conservative position, it would align the PBAC with the UK payer perspective on indirect benefit. This proposal is consistent with the PBAC's current remit and scope of flexibility, as the PBAC may in some circumstances allow inclusion of indirect benefits to carers and families in situations where it is considered of relevance. We believe it would be appropriate and relevant to include these indirect benefits in the assessment of vaccines, in particular paediatric vaccines where benefits may include the parent's quality of life when a child's disability or death is avoided.

As noted in the Mitchell et al 2009 paper reflecting the then PBAC view of indirect costs, "indirect costs may apply to drugs as well as vaccines, and PBAC accepts these as supplemental analyses if they can be measured validly". This paper agrees 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.

In the longer term, there may also be merit in reconsidering whether the reductive incremental Cost Utility Analysis (CUA) methodology (see **Appendix 1**) applied by PBAC remains the most appropriate for vaccines in the Australian setting. This question has been recently and extensively considered in international circles: (CEMIPP 2016); (Jit and Hutubessy 2016); (Luyten and Beutels 2016); (Lasseter, Al-Janabi, Trotter, Carroll and Christensen 2018). Various alternative and more flexible multi-criteria approaches have been suggested, specified and demonstrated in the literature (Mauskopf et al. 2018); (Bloom, Brenzel, Cadarette and Sullivan 2017) and these may ultimately be more appropriate and reflective of the characteristics of vaccines and the preferences of Australian community.

ICER Thresholds Overview

Cost-effectiveness analysis is the assessment of two or more alternative courses of action in terms of costs and benefits (quantified in health gains). These are separately quantified, then summarised using an incremental ratio, the ICER. When these analyses are being used to inform an allocative decision-making process, the ICER is usually compared with a threshold value to establish whether the technology represents an efficient and acceptable use of limited resources (McCabe, Claxton and Culyer 2008). Threshold values are inherently subjective and specific to a given treatment setting and decision-maker (Griffiths, Hendrich, Stoddart and Walsh 2015).

The PBAC has never explicitly specified a fixed or formal willingness to pay threshold for additional health outcomes (Wang, Gum and Merlin 2018). However, summary analyses of recommendations made over many years provide some insight into the implicit thresholds that might apply (Harris, Hill, Chin, Li and Walkom 2008); (George et al. 2001). The text of some individual recommendations also provides further insight into the PBAC's perspectives on value and acceptable cost-effectiveness.

Why are thresholds required and where do they come from?

Because it is difficult to capture the costs and effects of a healthcare intervention in a single common unit of measurement, methods of health economic evaluation have traditionally used the concept of an ICER; i.e. the additional cost per extra unit of "effect" in terms of a given outcome (e.g. QALYs) for an intervention compared with an appropriate comparator (Black 1990).

Despite extensive use of ICERs in HTA, it is not always straightforward to give a meaning to ICERs or to use them in a decision-making context. There is a difference between representing efficient use of resources and being worthwhile. ICERs only help in answering the efficiency question (See **Appendix 1**), but decision-makers must decide whether an intervention is worthwhile, considering broader societal considerations. This is where the concept of a threshold value becomes critical to determine whether an intervention is considered to be an acceptable investment (Cleemput, Neyt, Thiry, Da Laet and Leys 2011).

There is considerable diversity of opinion around questions of how ICER thresholds should be derived, whether they should be explicitly or implicitly stated, whether they should be fixed or flexible in relation to time and circumstances, and what they currently are or ideally should be in given settings (Eichler, Kong, Gerth, Mavros and Jonsson 2004); (McCabe et al. 2008); (Cleemput et al. 2001); (Basu 2013).

Three broad approaches have been proposed as to how thresholds should be set: by inference to previous decisions; to determine the optimal healthcare budget; or to exhaust an exogenously determined budget. However there is an emerging consensus that the value of the threshold in a given setting should be empirically defined using the marginal productivity of expenditure within the relevant health system (Edney, Haji Ali Afzali et al. 2018); (Claxton et al. 2015).

What do ICER thresholds mean in practice?

The absence of an explicit ICER threshold for PBAC decision-making means that all Committee recommendations are inherently subjective; i.e. the PBAC can decide on a case-by-case basis whether a given ICER for a specified intervention is acceptably cost-effective or not. For vaccines, this challenge is magnified by the PBAC's repeated view that the ICER threshold for treatments with large opportunity costs, such as population preventive interventions, should be at the lower end of the range (See public summary documents: Truvada PrEP, Nov 2017; Gardasil, Nov 2006; Shingrix, Nov 2018).

Is there a consensus on ICER thresholds for prevention and/or treatment?

There is no international consensus as to specific ICER thresholds that should apply to either preventive or therapeutic interventions, or even what values are currently being used (Gafni and Birch 2006); (Cleemput, Thiry, De Laet and Leys 2008); (Griffiths et al. 2015). The PBAC is relatively unique in its explicit application of a lower ICER threshold for prevention (requiring it to be more cost-effective) compared to therapeutic medicines.

The UK's CEMIPP review of cost-effectiveness methodology for vaccines addresses several issues including discounting, in addition to ICER thresholds. As compared to the PBAC's practice of applying a lower cost-effectiveness threshold for prevention, in the course of the review the CEIMPP working group has stated "the working group considered whether there is any theoretical and/or empirical evidence to suggest that a different cost-effectiveness threshold should be applied to immunisation programmes compared to other areas of healthcare. No theoretical or empirical evidence could be identified to support such a case. Indeed, it was felt that even if data were available to inform an immunisation-specific cost-effectiveness threshold, it is likely to result in sub-optimal levels of population health" (CEIMPP 2016). More broadly, in the UK there is an overall recommendation that ICER thresholds be lowered for both medicines and vaccines, however, this remains contentious and has not been implemented.

The CEMIPP review was requested by the Joint Committee on Vaccination and Immunisation (JCVI), to effectively ask Government whether the processes and rules by which it makes its recommendations, including the ICER threshold, remain appropriate and relevant to current circumstances. The review has involved a comprehensive technical report (CEMIPP 2016), while an extensive consultation process is now underway to elicit views from relevant organisations and committees within the health and care sector as well as specialists with an interest in health economics, including academics, public health practitioners, epidemiologists, charities and patient groups, clinicians and vaccine industry professionals (CEMIPP 2018).

The review generally aligns with broader international reassessments of the methods and criteria by which the cost-effectiveness of vaccines and immunisation programs should ideally be assessed (Mauskopf et al. 2018); (Ultsch et al. 2016); (Standaert and Rappuoli 2017). Other influential HTA markets, such as Canada and New Zealand are in the process or have recently revised specific guidelines for the evaluation of vaccines and immunisation programs (Rafferty et al. 2017); (Chit et al. 2016).

One of the key drivers of these reviews is a view that vaccines are somewhat undervalued by HTA agencies; i.e. that the ICER threshold applied is too low or that conventional evaluation methods and standards do not permit valuation of sufficient benefit to enable vaccines ICER to meet expected ICER value thresholds (Bloom 2011); (Standaert and Rappuoli 2017); (Barnighausen, Bloom, Cafiero-Fonseca and O'Brien 2014); (Timmis, Rigat and Rappuoli 2017). Most research in this area has focussed on elements of the potential economic value of immunisation programs that are largely ignored within conventional cost-effectiveness analysis, including indirect health, behavioural, productivity, ecological and equity effects (Bloom et al. 2017). Less emphasis has been placed around equally important questions as to the relative value placed on different attributes of these programs by the communities they are supposed to represent.

Studies that have been conducted, in Australia and internationally, suggest societal values and preferences around the costs and benefits of preventive health programs

are far more nuanced than purist cost-effectiveness analysis, informed by principles of health maximisation, would admit. Surveys conducted in a range of settings have consistently shown that respondents place greater value around interventions targeted towards prevention, younger and/or lower socioeconomic status subjects, severe conditions which are not lifestyle related, and which have the potential for large individual health gains (Gu, Lancsar, Ghijben, Butler and Donaldson 2015); (Nord and Johansen 2014). A recent Australian study designed to test the hypothesised preference for greater expenditure on more severe health states also found that respondents unanimously selected more than a utility-maximising level of insurance for protection against such states, indicating a preference for greater spending on prevention of severe health states than would occur in conventional cost-effectiveness analysis (Richardson, Iezzi and Maxwell 2018).

Consistent findings emerged from an earlier immunisation-specific discrete choice experiment study conducted among Australian adolescents, which observed significantly stronger preferences for vaccination in the case of a life-threatening illness (Wang et al. 2017). Meanwhile, a more targeted willingness to pay study for meningococcal B vaccine, which was conducted among Australian adult and adolescent subjects in 2013, suggests that valuation of this vaccine is significantly higher within the target population than determined by PBAC using conventional methods of cost-effectiveness analysis (Marshall, Chen, Clarke and Ratcliffe 2016).

These findings are further borne out in the real world willingness of state and territory governments (Rowe et al. 2018) and/or employer organisations (QLD_Health 2019) to institute immunisation programs for diseases/populations which have been deemed insufficiently cost-effective for the NIP, and also in strong private market uptake of vaccines for rare but serious conditions.

What change is recommended?

The rationale and evidentiary basis for the PBAC's apparently higher willingness to pay for curative, chronic and palliative treatments over preventive interventions have never been adequately described. This preference is inconsistent with most international HTA practice, misaligned with principles of health maximisation, and even further at odds with recent research suggesting greater societal preferences for avoidance of rare but serious/catastrophic risks in young and healthy populations and stated/observed willingness to pay for vaccines and immunisation programs.

Recent emphasis and commentary on the need to further reduce ICER thresholds where budgetary impacts and opportunity costs are large represents a potential further hardening of this bias against preventive interventions, where this is typically the case. In the absence of clear justification, this bias should be overturned, and similar thresholds applied across all health technologies.

4. Conclusion and Recommendations

The NIP is a locally acclaimed and internationally regarded public health program, which provides free and equitable access to a wide range of life-saving, health improving and cost-effective vaccines to a variety of target populations. It has achieved relatively high rates of uptake within these populations and in many cases has delivered optimal control of challenging infectious diseases.

These outcomes have been achieved at a relatively modest cost of around $420 million per annum to the Australian Government, with additional contributions from the States and Territories. This contrasts with a budget for the PBS of more than $11 billion, total government healthcare expenditure of around $120 billion and overall health spending of more than $170 billion per annum. At the same time, the program has thus far been able to accommodate most relevant advances in vaccine development and practice and procure new products at internationally competitive and highly cost-effective prices.

However, there are some weaknesses beginning to appear in the evaluation system which threaten the continued sustainability of the program. These mainly centre on the need for greater community and policymaker input into how the value placed on prevention is applied within the assessment system which currently applies a restrictive and conservative estimation of the value of vaccines. These issues have already presented a significant delay or barrier to the establishment of clinically important new immunisation programs for HZV, meningococcal disease and influenza.

Against this background, it is timely for Australia to reflect upon recent international reconsideration of the criteria by which vaccines and immunisation programs are assessed and valued. The role of the PBAC as an internationally respected HTA body remains essential within the NIP setting. It ensures an appropriate level and allocation of public investment, identifies the most efficient target populations and strategies for specific vaccines, compensates for various sources of market failure, and delivers a program which meets the complex needs, expectations and values of the broader community. However, the specific methodologies and criteria currently applied by PBAC in relation to discounting, choice of perspective and ICER thresholds require urgent review and updating.

A key question is whether current PBAC methods, guidelines and decisions around vaccines are consistent with the objectives of the NIP, values of the broader Australian community and international best practice within immunisation policy. Greater attention to, and discussion of, the implicit and explicit preferences applied within the evaluation system for vaccines are required. This is a debate of principles more than technical methodology and rightly belongs in a community and policymaker sphere, to provide a policy overlay to and inform the technical assessment process.

Recommendations

This paper proposes three urgent updates to current practice, all of which are immediately actionable and none of which requires any amendment to legislation or change to current institutions.

Given the broad remit of the PBAC, they are provided with authority and flexibility under the legislation and guidelines to consider a range of issues, including those outlined in this paper. However, to date the PBAC have been reluctant to utilise this flexibility.

This paper, consistent with the principles of the guidelines, urges the PBAC to incorporate these factors directly in their decision-making for vaccines when relevant—not in supplementary analyses, but in the base case.

We urge policymakers and the community to engage appropriately in the PBAC process to outline the value they place on immunisation and to insist that vaccines are not disadvantaged in assessments. Further, we encourage the PBAC to utilise flexibility, consistent with their remit and in line with international practice, when assessing the value of vaccines by:

- **Applying lower discount rates:**
  Discounting reduces the value of events in the future. Adopting a lower discount rate, in line with international practice, will place greater value on lives saved through prevention.
- **Taking a broader perspective, accounting for costs and benefits outside the health system:**
  Consider the broader outcomes from immunisation programs, including at a minimum, the impact on carers and families.
- **Removing the disadvantage applied to prevention through current Incremental Cost-effectiveness Ratio (ICER) ranges:**
  Apply the same 'willingness to pay' thresholds for lives saved through prevention or by therapeutic medicines

5. Appendix 1 – Overview of health economic evaluation

Definition

Economics is the study of the optimal allocation of limited resources for the production of benefit to society (Samuelson 1998). Health economics is a sub-discipline of economics applied to the topic of healthcare. Broadly defined, health economics uses economic concepts and methods to understand and explain how people make decisions regarding their health behaviours and use of healthcare. It also provides a framework for thinking about how society should allocate its limited health resources to meet people's demand/need for healthcare services, health promotion and prevention (MSGPH 2019).

Decision criteria

There is no exact science as to how best to allocate resources; i.e. to determine what should or should not be funded within a healthcare system. The established literature notes that the following key considerations should be incorporated in health economic funding decisions:

- **Technical efficiency:** Technical efficiency is about how best to achieve an objective. This relates to efficient use of resource in achieving an outcome i.e. which population to immunise when seeking to control an infectious disease. For example, for Human papillomavirus (HPV), the most efficient choice was to immunise the population pre-sexual maturity (Lowy and Schiller 2006).
- **Allocative efficiency:** With allocative efficiency, all objectives compete for implementation. For example, "should we allocate more resources to the prevention of childhood injury or improve clinics for children with chronic disease such as asthma?" is a question of allocative efficiency. Allocative efficiency is about whether to do something (Shiell, Donaldson, Mitton and Currie 2002). This occurs where the ratio of marginal benefits to marginal costs is equal across all healthcare programs in the system; i.e. when one dollar spent is equal to one unit of generic health and the decision is therefore where best to allocate the respective health spend. Allocative efficiency relates to opportunity costs and public health priorities.
- **Equity:** Equity is about fairness. It is often confused with equality, or "the state of being equal". Fairness and being equal are not necessarily the same things. Inequality can be fair if there are differences in need/ contribution/ risk etc. The reason health economists are interested in equity is the same as for efficiency; i.e. scarcity. If resources were not scarce, it would be fair for people to consume as much as they want or need of any commodity, including healthcare. However, because of scarcity, society must judge what a fair allocation might be (Shiell et al. 2002). In healthcare, there are two general equity concepts to consider:
    - **Horizontal equity:** This refers to the "equal treatment of equals", which is embodied in healthcare objectives such as "equal access for equal need" (Mooney 1992).
    - **Vertical equity:** This refers to the "unequal treatment of unequals" (Mooney 1996) and can be justified on the basis of morally relevant factors. However, what determines a morally relevant factor and who is the decision-maker for a respective society remains contentious.

Of these three criteria, arguably only the first, technical efficiency, relates to technical expertise, with the latter in regard to allocative efficiency and equity related to public health priority settings aligned with ethical agreements and distributive justice (Ferraz 2015).

Methods and approaches

Health economic evaluation compares the costs and outcomes of at least two alternatives, one of which may be doing nothing; i.e. no intervention or no vaccine (WHO 2008). There are several common methods of HEE employed in practice: cost-minimisation analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA). These different evaluation techniques all estimate costs in a similar fashion but measure the outcomes or consequences of a health program differently. All methods of HEE are subtly different from financial or budget impact analysis which considers only the monetary aspects of a program or proposal.

Cost-minimisation analysis involves the assessment of two or more interventions that have identical outcomes to see which the cheapest way is of delivering the same outcome. This is generally employed by payers such as the PBAC when determining whether to fund a second version of an existing treatment, i.e. a competitor with the same indication. Therefore cost-minimisation is generally not employed when determining whether to fund new vaccine indications.

Cost-effectiveness analysis measures the outcomes of approaches in terms of natural units. For example, if the outcome of interest was a reduction in childhood pneumonia, CEA might compare vaccines against Haemophilus influenzae type b (Hib) and pneumococcal diseases to determine which averted a case of pneumonia most cheaply. The outcome is therefore the cost per case of pneumonia avoided.

Cost-utility analysis is a special case of CEA, in which the health outcome is quantified as a generic unit of health termed a QALY, a quality adjusted life year. A QALY is one year of perfect health. The QALY is widely used in health economic evaluations as it allows comparisons of health gains across therapeutic areas thereby informing the decision criteria of allocative efficiency. A QALY has the further benefit of incorporating patient and societal preferences, as the method of elicitation and valuation relies on societal and individual values of health states (Whitehead and Ali 2010).

In either CEA or CUA, results are presented as an estimated incremental cost-effectiveness ratio (ICER); i.e. the estimated incremental costs of a program or intervention divided by its incremental benefits. This is usually a ratio of additional costs over positive health benefits, with lower ratios representing more cost effective alternatives, although other outcomes are not uncommon and careful interpretation is sometimes required (Klok and Postma 2004).

Cost-benefit analysis expresses health outcomes in terms of monetary units and usually presents results in the form of a positive or negative net monetary benefit (NMB). This type of analysis enables comparisons between vaccines or other interventions in the health sector or in other sectors, such as education, to identify which generates the greatest return on investment. However, the need to measure outcomes in monetary units limits the use of this type of analysis in determining health policy and as such it is generally not used by health economic payer such as the PBAC.

Budget impact analysis captures only the likely financial impact of a program or intervention, usually from the viewpoint of a particular fundholder (e.g. hospital, health system, or level of government) over specified interval of time (e.g. episode of care, annual budget, or 5-year forecast period). The emphasis of such an analysis is usually on affordability, more than effectiveness or efficiency. This contrasts sharply with all methods of HEE, which consider both costs and effects of an intervention compared with current practice to provide an estimate of technical efficiency and value.

Important elements of economic evaluation

Across all forms of HEE and budget impact analysis, the question of **perspective** is critical; i.e. what range of costs and effects should be included in the analysis? Clearly, it is impossible to consider all costs and effects of complex healthcare interventions, such as a vaccination program. However, when considering resource allocation decisions at a societal level, the geographical/ institutional/ sectoral scope of relevant costs and benefits must be considered. In universal healthcare systems, this scope is typically national, and encompasses all healthcare costs and health related outcomes; however, even this approach can ignore important non-health societal benefits, such as increased individual and population productivity, economic activity, tax revenue, and social amenity, which may be impacted by a proposed program.

Equally important is the question of time preference; i.e. how to compare and balance costs incurred, and outcomes obtained in current and future periods. Investing now for benefits in the future means that those resources are not available for an alternative present consumption. Allowances are often made to **discount** future costs and benefits, because it is widely held that there is a preference to consume in the present and to defer payment. This alleged preference for the present leads to any economic good being accorded higher value in the present than at some time in the future, or alternatively a lower or discounted value in the future than if it were available in the present. While discounting is common practice in HEE, there is ongoing debate about both the validity of the approach and the most appropriate methodology and rates to apply (West, McNabb, Thompson, Sheldon and Grimley Evans 2003).

Finally, where results of a CEA or CUA are being used to guide societal decisions on resource allocation, it is necessary to establish a reference standard or **threshold** against which to compare an estimated ICER. Usually interventions which both reduce costs and improve outcomes compared to alternatives are considered to be dominant and acceptable by definition, while those that increase costs and lead to poorer outcomes are said to be dominated and unacceptable in any circumstances (Black 1990). However, scenarios in which an intervention leads to increased costs and benefits are inherently more subjective, while those in which both costs and benefits are reduced can be even more challenging (Klok and Postma 2004); (O'Brien, Gertsen, Willan and Faulkner 2002). Debate regarding both the theoretical basis from which ICER thresholds might be constructed and what these might be in different healthcare settings is ongoing (Eichler et al. 2004); (Edney, Haji Ali Afzali, Cheng and Karnon 2018).

While each of these critical elements of HEE and related decision-making are widely assumed to be technical issues, they require societal judgements and a community and/or policymaker overall for experts to then apply in decision-making.

6. Appendix 2 – Definition and attributes of prophylactic vaccines

Definition

Prophylactic vaccines are highly specialised medicinal products containing antigenic substances that induce specific, active and protective host immunity against infective agents or toxins, thereby providing protection against serious disease (CDC 2019); (WHO 2004). Vaccines represent one of the most important scientific developments in human history and their systemic implementation in structured immunisation programs is perhaps the most significant public health achievement of the last century (Plotkin 2014); (Walton, Orenstein and Pickering 2015).

Attributes

Prophylactic vaccines have historically been viewed as a unique class of medicinal product, with distinct pharmacological properties, development pathways, regulatory requirements, distribution methods, funding sources, ethical issues and social contexts (Milstien 2004); (Pulendran and Ahmed 2011); (Timmis, Black and Rappuoli 2017); (Luyten and Beutels 2016); (Beutels et al. 2008); (Einsiedel 2011).

The elements of this uniqueness and reasons for functional separation are complex and interrelated:

- Prophylactic vaccines are administered to subjects without signs, symptoms, or pathologic evidence of disease, to prevent it, which contrasts with both therapeutic interventions aimed at curing, managing or relieving the symptoms of established disease and secondary/tertiary prevention measures designed to modify or attenuate the course of a disease once it has begun;
- Most such vaccines target infectious diseases characterised by an acute onset, life threatening symptoms, potentially catastrophic long-term consequences, limited available/effective treatment options, high costs for acute/chronic management, and random/unpredictable incidence within otherwise young/healthy populations, thus addressing an urgent and otherwise unmet clinical need;
- Vaccines are also typically most effective when used widely within a target population over an extended period of time, frequently disrupting patterns of infection and transmission, in some cases enabling effective elimination from the population, and even where this is not the case, modifying wider healthcare system requirements in terms of delivery of care (Naevdal 2012).

Particular vaccines are furthermore associated with a range of important positive externalities that extend beyond the subject receiving them, and sometimes even the health system, such as:

- Reducing the potential emergence of antimicrobial resistance by restricting challenge opportunities, (Ginsburg and Klugman 2017);
- Reducing unpredictable high cost outbreak scenarios and resulting temporary capacity constraints across the health system and/or affected communities for example schools, remote at-risk communities etc (Singh et al. 2017);
- Reducing the time, cost, productivity and quality of life burden imposed on the parents and carers of otherwise affected patients (Marlow, Finn and Trotter 2015);
- Creating broader benefits in the form of individual productivity, economic activity, taxation revenue and less tangible but equally important impacts on tourism and/or the attractiveness of a country for potential immigrants and new business (Standaert and Rappuoli 2017); and

- Generating broader country level social benefits arising from infectious disease control or elimination, and societal peace of mind and reassurance that the unpredictable risk of frequently serious and untreatable infectious diseases have been mitigated (Mirelman, Ozawa and Grewal 2014).

Benefits

By preventing infection, attenuating the effects, halting the spread, and in some cases even eliminating diseases that have plagued humanity for centuries, vaccines and the immunisation programs that employ them, have saved countless millions of lives, prevented untold morbidity, and underpinned major advances in economic and social development (van Panhuis et al. 2013); (Deogaonkar, Hutubessy, van der Putten, Evers and Jit 2012); (Bloom 2011). Since the first introduction of routine vaccination for children in Australia in 1932, it is estimated that deaths from vaccine-preventable diseases have fallen by 99 percent, despite a threefold increase in the population over that period (DOH 2019), while globally it is estimated that immunisation programs continue to prevent 2-3 million deaths each year (WHO 2019).

7. Appendix 3 – Structural overview of the NIP

The National Immunisation Program (NIP) is a collaborative policy initiative undertaken through long-term agreement by the Commonwealth, State and Territory Governments.

The complex architecture of the NIP is coordinated by the Office of Health Protection (OHP), specifically the Immunisation Branch (IB) within the Australian Government Department of Health (DOH).

A National Immunisation Committee (NIC) drawn from a cross section of relevant stakeholders' strategic direction and leads policy development, evaluation and implementation activities.

Epidemiological, medical and practical advice is provided by the Australian Technical Advisory Group on Immunisation (ATAGI) which also compiles the Australian Immunisation Handbook (AIH).

Assessment of the cost-effectiveness of vaccines and immunisation programs and advice on their implementation in the NIP is provided by the Pharmaceutical Benefits Advisory Committee (PBAC).

Responsibility for regulation and monitoring of the efficacy, safety and quality of vaccines lies with the Therapeutic Goods Administration (TGA) and the Advisory Committee on Vaccines (ACV).

The NIP Schedule is specified by the National Health (Immunisation Program – Designated Vaccines) Determination, which is maintained by the Minister for Health, subject to TGA and PBAC advice.

The National Health and Medical Research Council (NHMRC) provides funding for various vaccine related research initiatives and also approves and publishes the AIH.

The National Centre for Immunisation Research and Surveillance (NCIRS) provides additional independent advice on all aspects of immunisation to inform policy and service planning.

Individual States and Territories have their own institutional arrangements for implementation and delivery of the NIP in practice, often in collaboration with local government agencies.

Financial arrangements and the various roles and responsibilities of different levels of government are stipulated in the National Partnership on Essential Vaccines (NPEV) agreement.

Procurement of vaccines under the NPEV is performed centrally by the Australian Government Department of Health (DOH) subject to Commonwealth Procurement Rules (CPRs).

Immediate and long-term directions for the program are outlined in the National Immunisation Strategy (NIS) a five-year rolling plan built around eight agreed strategic policy areas.

8. Appendix 4 – Summary of the NIP Listing Process

Figure 3: Immunisation Program vaccine listing process

In order for a vaccine to be supplied through the NIP, the following regaltory steps must occur

1. TGA Registration

- All vaccines must be registered by the Therapeutic Goods Administration (TGA) as clinically safe and effective for use in Australia.
- A positive TGA delegate's overview must be provided in order for the Pharmaceutical Benefits Advisory Committee (PBAC) to consider recommending a submission (refer Step 2).
- Full TGA registration is required before Government approval can be sought to fund a vaccine for a particular cohort through the NIP (refer Step 4).

2. PBAC recommendation

- All new vaccines and extended cohorts for existing NIP vaccines must be recommended by the PBAC as clinically and cost-effective for the NIP.
- Clinical advice from ATAGI must accompany all vaccine submissions to the PBAC and submissions must address all matters raised in the ATAGI advice where appropriate (refer to information on ATAGI pre-submission advice below). For further information regarding the PBAC process please refer to the PBAC Guidelines.

3. Price agreement

- Following a positive PBAC recommendation, a price must be agreed between the Department and the pharmaceutical company.
- There will be opportunity for further price negotiations as part of the NIP vaccine procurement process (refer Step 6).

4. Government approval

- Following full TGA registration and a positive PBAC recommendation, the Department must seek Government approval to fund a new vaccine for a particular cohort through the NIP.
- Actual purchasing arrangements are subject to the outcomes of a NIP vaccine procurement process - no vaccine is guaranteed to be purchased for supply on the NIP (refer Step 6).

5. Listing on Determination

- Following Government approval, a vaccine must be listed on the National Health (Immunisation Program - Designated Vaccines) Determination 2014 (No. 1) (the Determination).
- All amendments to the Determination are registered on the Federal Register of Legislation.

6. Vaccine Procurement

- Following a positive PBAC recommendation, a company is eligible to participate in a procurement process to have that vaccine purchased by the Government for supply through the NIP.
- A vaccine must be approved by Government and listed on the Determination before any contract for supply can be executed

Source: (DOH 2019)

9. Appendix 5 – Summary of the PBAC considerations in assessment and recommendation of vaccines

Element	Detail
Contextual	
Population	This is usually (but not always strictly) bound by the TGA registered indication and recommendations. Within these boundaries, a narrower target population can be specified based on considerations of clinical appropriateness. There are examples of cases where target populations have been narrowed based on considerations of cost-effectiveness or affordability, however this is not PBAC's usual preference. Additional criteria around provision of a broader community benefit are required to justify the establishment of a new NIP program and/or catch up component thereof.
Intervention	The intervention of interest is the completely specified change to current treatment practice, inclusive of any differences in administration or concomitant use of other healthcare resources. In the case of vaccines for the NIP, this is usually a broad immunisation program, including various considerations of subject eligibility, timing and location of delivery, consequent changes to other elements of the Schedule and any changes healthcare resource use due to expected uptake/effectiveness/safety.
Comparator	The comparator should be the therapy that prescribers would most replace with the proposed medicine, with emphasis on what is most likely to (rather than what should) happen in the real-world environment. For most vaccines, where an alternative is available on (or recommended for) the NIP, this will usually be the comparator. Where the proposed program is for a disease or population not covered by an existing vaccine, the comparator will usually be standard medical management of that disease.
Clinical	
Evidence base	The PBAC strongly prefers clinical and economic evaluations that are based on high quality direct (head to head) randomised controlled trials and/or meta-analyses. However, it is recognised that such evidence is not always available, and guidelines therefore provide a framework for considering indirect comparisons of randomised trials and nonrandomised studies. For these, simple adjusted frequentist methods are preferred to more complex Bayesian or Matched Adjusted approaches. Evidentiary standards applied to vaccines are largely identical to any other product class.
Clinical outcomes	Emphasis is placed on the primary endpoints of the included trial(s), any patient relevant clinical outcomes, and directly assessed measures of Health Related Quality of Life. Outcomes supporting clinical claims are expected to be statistically significant and clinically important according to pre-specified criteria. Extremely high hurdles exist for establishing the clinical importance of surrogate outcome measures. For vaccines, unless there are internationally accepted standards, the criteria developed to support any claims of superiority based on immunogenicity surrogates or correlates must be prespecified and justified, and their limitations addressed.
Comparative harms	A conservative approach is recommended in relation to comparative safety, with greater emphasis placed on the possibility of long-term harm than of benefit. For vaccines, it is required that the assessment of comparative harms extends beyond those temporally associated with the administration of the vaccine to those that might emerge long after the vaccine course is completed, specifically including the consequences of possibly delaying, rather than preventing, disease.
Generalisability	Significant emphasis is also placed on differences in the populations, disease or condition, and circumstances or treatments as conducted in the trial(s), as compared to expected clinical practice, which may result in a difference in (absolute or relative) treatment effects, adverse events or patient management. For vaccines against infectious diseases, where epidemiological and socioeconomic factors can vary significantly across geographic settings, this can be a very important consideration.
Clinical conclusions	Clinical conclusions are usually bluntly categorical (superior, non-inferior or inferior) and any uncertainty relating to the quality, applicability, significance, importance or relevance of the available evidence will typically result in a categorical downgrading. Claims of superiority based on indirectly comparative evidence and/or surrogate outcomes are rarely supported, while the absence of evidence for a difference in effectiveness is generally considered insufficient to support a claim of non-inferiority.

Element	Detail
Economic	
Perspective	The preferred healthcare system perspective includes health and health-related resource use (costs and cost offsets), and health-related outcomes. Costs include those incurred by the patient, and the public or private healthcare provider; outcomes are those associated with the patient. Broader societal perspectives, incorporating considerations beyond the patient and the healthcare system are considered only as supplementary evidence. These may be considered informative where the proposed intervention has important societal implications extending beyond the health outcomes of the patient receiving the medicine, and/or the healthcare system; which is frequently relevant (but not unique) to immunisation programs.
Type of analysis	For non-inferiority claims: A cost minimisation (or cost) analysis is preferred, to which a range of complex and opaque rules apply. For superiority or inferiority: A cost-effectiveness (utility) analysis is preferred, with a strong preference for valuing outcomes in Quality Adjusted Life Years (QALYs) in most circumstances. Cost-consequences analyses are usually considered only as supplementary evidence in circumstances where the intervention has a different profile of effects that are not adequately captured by a single outcome measure. Cost-benefit analyses are not recommended and unlikely to support a claim of cost-effectiveness in the absence of a complementary cost-utility analysis. Specific guidance regarding appropriate presentation of supplementary cost benefit analyses for vaccines and immunisation programs, which was included in Version 4.0 of the PBAC Guidelines, was removed from Version 5.0.
Input data	The PBAC strongly prefers economic evaluations based directly upon the evidence included in the clinical evaluation, in relation to both absolute and relative risks. For vaccine products, alternative sources of epidemiological evidence for estimating baseline risks include routine surveillance data, seroprevalence studies and surveys.
Time horizon	The general principle is to ensure that the time horizon should capture all important differences in costs and outcomes between the intervention and comparator but not extend unnecessarily beyond this. However, in practice, as time horizons extend, in both absolute terms and relative to available data, they are associated with increasing uncertainty and the PBAC is highly sceptical of economic claims based on models with very extended time horizons and predominantly extrapolated benefits. Specific advice for vaccine products requires that the duration of a model extend to the point where the estimate of cost-effectiveness is stable, to adequately support any herd immunity effects included, and to consider any possible waning of immunity.
Discount rate	Any costs and outcomes that occur or extend beyond one year are required to be discounted at a uniform, annual (compounding) rate of 5 percent per year in the base case. Fixed common discount rates of 3.5 percent, and 0 percent per year are requested as sensitivity analysis. If relevant, supplementary analyses using other discounting methodologies may be presented (with adequate justification). In practice, the PBAC rarely considers anything other than the 5 percent base case discount rate for decision-making.
Outcomes considered	Consistent with the clinical evaluation, outcomes are expected to be both statistically significant and clinically important according to pre-specified criteria to inform an economic claim. For the purposes of conducting a (preferred) cost utility analysis, claimed associations between surrogate and final outcomes must be quantified and all outcomes expressed as a composite of survival and quality of life (QALYs).
Costs considered	Consistent with the PBAC's preferred perspective, only direct healthcare costs incurred by the patient, and/or public/private healthcare providers are usually considered. Item costs are expected to be estimated based on a series of reimbursed/scheduled prices and/or historical data collections, as specified in a technical manual, which do not always reflect the true cost of service provision. Consideration of broader societal and productivity costs, which are often impacted by immunisation programs, is actively discouraged both in guidelines and practice.

Element	Detail
Economic	
Modelling methods	The general principle for economic models (for any product class) supports selection of the least complicated modelling technique for which it is feasible to implement the specified model structure. Significant emphasis is placed on transparency, particularly within the relationship between trial based and modelled outcomes. A formal "stepped" approach, in which trial-based outcomes are gradually extrapolated with respect to time and outcomes is usually recommended. Individual-level modelling approaches are recommended only when the required structure cannot be feasibly implemented as a cohort-based model. However, specific guidance is provided around the use of dynamic models for immunisation programs where herd immunity, other changes in the force of infection, and/or age shift factors may be relevant.
ICER threshold	There is no fixed or formal incremental cost-effectiveness ratio (ICER) threshold below which PBAC considers proposed interventions to be acceptably cost-effective and in practice this is influenced by multiple additional criteria, including therapeutic area, target population, extent of clinical need, magnitude and concentration of clinical benefit, budget impact, historical and international pricing references, and precedent. Typically, immunisation programs (along with other preventive interventions) have been considered acceptably cost-effective by PBAC at lower ICER thresholds than curative, chronic or palliative treatments (≈$30,000/QALY vs. ≈$50,000/QALY). However, there is significant variability within these ranges and generalised downwards pressure on ICERs for all types of intervention being considered.
Uncertainty tolerance	The PBAC has a heightened awareness of and low tolerance for clinical and economic uncertainty. Both submission guidelines and historical precedent demonstrate a strong preference for Type II over Type I error, and decisions are frequently based on the lower bounds of confidence intervals for clinical impact and/or cost-effectiveness.
Financial	
Perspective	Financial analyses are generally required to adopt a limited Australian Government perspective, excluding potential implications for State, Territory or Local Government operated hospitals, facilities and programs. An exception applies to submissions for immunisation programs, which are specifically requested to estimate administration related costs to other government budgets, including those beyond the health sector.
Costs	Costs are required to be estimated using constant prices, with no allowance for inflation or other anticipated changes, and no discounting.
Uncertainty	It is requested that any financial uncertainty be quantified in sensitivity analysis. Tolerance for uncertainty around utilisation and cost is typically greater than that effectiveness and value, as this can often be managed via risk sharing arrangement.
Other Factors	
Equity and access	Diverse aspects of equity, ethics and access to healthcare are often considered as supplementary considerations in PBAC decision-making, but do not substitute or supplant key criteria of appropriateness, clinical/cost-effectiveness and affordability. Common considerations include the age and/or socioeconomic characteristics of the target population and geographic elements of service delivery.
Non-health outcomes	Non-health outcomes, most often indirect financial, time or quality of life benefits to family members or carers of the target patients/subjects for an intervention are sometimes also considered as supplementary evidence.
Antimicrobial agents	Specific guidance is provided requiring consideration of prudent use principles for antimicrobial agents, which can be highly relevant to vaccines for infectious diseases.
Rule of rescue	Detailed rule of rescue criteria is defined which supplement, rather than substitute evidence-based considerations of comparative cost-effectiveness. However, these are not deemed to apply to preventive immunisation programs, even where there are no other viable treatment options and the consequences of infection are routinely fatal.

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