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Funding of drugs: do vaccines warrant a different approach?

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Vaccines have features that require special consideration when assessing their cost-effectiveness. These features are related to herd immunity, quality-of-life losses in young children, parental care and work loss, time preference, uncertainty, eradication, macroeconomics, and tiered pricing. Advisory committees on public funding for vaccines, or for pharmaceuticals in general, should be knowledgable about these special features. We discuss key issues and difficulties in decision making for vaccines against rotavirus, human papillomavirus, varicella-zoster virus, influenza virus, and *Streptococcus pneumoniae*. We argue that guidelines for economic evaluation should be reconsidered generally to recommend (1) modelling options for the assessment of interventions against infectious diseases; (2) a wider perspective to account for impacts on third parties, if relevant; (3) a wider scope of costs than health-care system costs alone, if appropriate; and (4) alternative discounting techniques to explore social time preference over long periods.

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Introduction

In many high-income countries, public funding of preventive vaccines is assessed based on the same criteria as the funding of curative pharmaceutical drugs. Such routine drug assessment processes consider evidence on quality, safety, efficacy, and cost-effectiveness. Because of the increase in the number of different vaccines available and advances in the science behind decision making, we have drawn on existing literature and practices to develop the arguments around potential disparities with other pharmaceuticals when assessing vaccines for public funding. These arguments revolve around vaccine-specific features of herd immunity and eradication, which are not evident in pharmaceuticals, and features for which the effects of quality-of-life losses in very young children, parental care and work loss, time preference, macroeconomics, and uncertainty substantially influence cost-effectiveness estimates. Vaccines may increasingly be judged as unacceptable if these features are not acknowledged. We also illustrate these points for five specific vaccines that are currently under consideration for widespread use in high-income countries. We use the term "cost-effectiveness" in a broad sense throughout this article, encompassing cost-utility and cost-benefit analysis, although there are technical differences.[1]

Background

In 1993, Australia was the first country to make evidence on cost-effectiveness a mandatory part of funding decisions of drugs. The Australian Pharmaceutical Benefits Advisory Committee is a rigorous and well-run system for evaluating drugs for acute care, chronic disease, palliation, and more recently vaccines. Many other countries have adopted a similar philosophy towards cost-effectiveness considerations for funding pharmaceuticals (eg, Belgium, Finland, Norway, Canada [Ontario], Portugal, Sweden, Netherlands, UK, and USA [some organisations]), but they deal with preventive public-health measures, such as mass vaccination, in different ways. Some countries have specific advisory groups to make funding recommendations on vaccinations (eg, UK Joint Committee on Vaccination and Immunisation, US Advisory Committee on Immunization Practices). Often, cost-effectiveness evidence for vaccines is assessed in the same manner as for any drug. Nevertheless, as we discuss below, vaccination has special features that make it particularly challenging to assess. Furthermore, vaccination constitutes one of the largest preventive health programmes around the world, and increasing pressures on health-care budgets are as much a challenge for the use of vaccines as for other drugs.

Why vaccination is different

Vaccines provide primary prevention of future morbidity and mortality. Thus, unlike secondary prevention interventions, such as statins for cholesterol lowering, vaccines are targeted before, or in the initial stages of, the recipient's potential risk exposure. Additionally, the recipient may or may not benefit on an individual basis. Vaccination may even harm some recipients through vaccine-associated adverse events (panel); for example, 3–5% of varicella-zoster virus (VZV) vaccine recipients report a localised rash.[2] The individual perception of risks of disease and risks of adverse events drives the demand

***Panel*: Why many vaccines require a different approach**

- Primary prevention in healthy people, but with possibility of adverse events
- Unvaccinated or poorly vaccinated people may experience beneficial or, more rarely, detrimental impact from herd immunity
- Many vaccines prevent short-lived illness in very young children, causing extra family care and work loss, for which evaluation methods lack credibility and acceptability
- The cost-effectiveness of many vaccines is highly sensitive to the choice of discount method
- Some infections are eradicable
- Some emerging infections (eg, SARS, pandemic influenza) would have a major macroeconomic impact that goes beyond lost productivity of sick people

SARS=severe acute respiratory syndrome.

for vaccines, and may dominate the influence of other factors, such as price.[3]

The need to show protective efficacy beyond the typical duration of clinical trials generally affects the assessment of vaccines more than therapeutic pharmaceuticals, primarily because the endpoints may not be immediate. In fact, the clinical endpoints might not show clinical efficacy at the time of trial reporting because the numbers required can be extremely large. Clinical endpoints of mortality or hospital admissions might require follow-up of thousands to millions of participants over as long as several decades. As such, some vaccines have been funded on the basis of immunogenicity data or intermediate endpoints alone (eg, meningococcal C conjugate vaccine[4] and human papillomavirus [HPV] vaccine in several countries).[5,6]

Vaccination not only protects vaccine recipients, but reduces exposure of unvaccinated people to infection through herd immunity.[7] Herd immunity, in addition to lowering the incidence of infection in the unvaccinated, is well known to lead to an increased average age at infection.[7] Vaccination is therefore not always entirely beneficial to public health because some childhood infections are more severe if contracted in adolescence or adulthood. Furthermore, vaccination itself may modify vaccine effectiveness over time because of factors such as strain replacement and cross reactivity. Some of these indirect effects improve the cost-effectiveness (eg, non-exposure of most of the unvaccinated, cross reactivity), whereas others may reduce the cost-effectiveness (eg, shift in the average age of infection, serotype replacement). For most vaccination programmes, the sum of these effects substantially improves cost-effectiveness, but sometimes the reverse may be true.[8,9]

Convincing evidence for the extent of herd immunity, and the duration of immunity, may only come from widespread use in another country, not from clinical trials. For example, the population impact of vaccinations against VZV and *Streptococcus pneumoniae* in the USA are of major interest to other countries.[10] Appropriately parameterised dynamic transmission models could also provide credible estimates of herd-immunity effects. Lieu and colleagues[11] were the first to estimate the cost-effectiveness of a vaccine based on dynamic model simulations.[12] Such models, which take into account the above indirect effects, are gradually becoming more widespread, but are not yet part of the traditional toolbox of epidemiologists or health economists. All these features add to the uncertainty under which vaccine funding decisions are made, as opposed to those of other drugs.

For whatever the reason some people decline vaccination for their child, they may trade the uncertain value of direct protection for the certainty of avoiding the risk of vaccine-associated adverse events and the cost of vaccination, while potentially counting on a "free ride" from herd immunity induced by others being vaccinated. The risk perceptions driving this trade-off are distorted as a result of imperfect information. Reductions in vaccine-preventable disease make people believe that their child's risk of disease has decreased. However, their risk is highly dependent on historical and future rates of exposure and vaccination in the rest of the population and can quickly rebound when uptake declines.[13,14] Therefore, government intervention in the form of subsidies or public funding is required to ensure that vaccine uptake remains high enough to guarantee beneficial herd immunity.[15] The UK's recent struggle with the measles, mumps, and rubella vaccine uptake illustrates this point.[16] For other pharmaceuticals, this kind of trade-off is not even conceivable.

Potential global eradication is another feature that sets some vaccines apart. For example, polio has been eliminated in high-income and middle-income countries. The risk of acquiring paralytic polio from the live oral polio vaccine is thus particularly sensitive to public scrutiny. However, replacing the oral vaccine with the risk-free inactivated polio vaccine is far more expensive, and would be judged unacceptable if cost-effectiveness were the only criterion under consideration.[17] Nevertheless, until polio is eradicated globally, vaccination must continue or polio will again become endemic, as shown by occasional outbreaks in unvaccinated communities.[18] Although not usually quantified in cost-effectiveness analysis,[14,19] the prospect of eradication and concerns over the public's perception about the entire vaccination programme has led to the replacement of oral vaccine by inactivated vaccine in nearly all high-income countries.[20]

Some infections have the capacity to affect not only patients and their direct contacts (ie, their family, health-care provider, employer) in terms of economic costs and medical effects, but they may also affect health-care use, and expectations and behaviour of consumers and investors. For instance, pandemic influenza is likely to lead to capacity problems within the health-care system, affecting the timely treatment of patients with influenza in addition to those with unrelated illnesses. Additionally, it would have a macroeconomic impact that goes beyond lost productivity to employers of sick patients, because virtually everyone—employers, consumers, and investors—would adapt their intentions under its perceived threat.[21,22] The latter was also shown in countries affected by the 2003 outbreak of severe acute respiratory syndrome.[23]

Finally, affluent countries pay much higher prices than poorer countries.[24] This system of tiered pricing is not unique to vaccines, but might be most relevant for new vaccines (eg, rotavirus, pneumococcal, and HPV) and medications (eg, highly active antiretroviral therapy) with great lifesaving potential in poor countries. Some economists argue that market prices set for high-income countries need to be much higher to sufficiently stimulate

innovation through market mechanisms, rather than rely on publicly funded research.[25] Conversely, if a vaccine is added to a low-income country's national programme, it is likely to become cheaper for high-income countries through price discrimination mechanisms.[26] Clearly, decision making becomes more complex if such moral or opportunistic considerations are thought to be important.

Standard methodological choices and vaccination

There are some methodological aspects to which the cost-effectiveness of vaccines is particularly sensitive. First, the definition of the analytical viewpoint is crucial. Guidelines for economic evaluation, as used by most advisory committees, generally focus on direct health-care costs and do not consider indirect costs to society (eg, the value of lost productive and leisure time from illness or caregiving). These indirect costs can be very large for infectious diseases that affect virtually the entire population, even for generally benign illness. For example, the cost-effectiveness of childhood VZV vaccination is unlikely to be thought acceptable from the health-care budget perspective, but is possibly cost-saving from a societal perspective.[8,11,27]

Second, the use of quality-adjusted life-years is widely advocated as the best measure currently available for valuing health states. However, standardised quality-of-life estimates for short-term diseases in young children are virtually non-existent, and the appropriate methods to measure them are subject to debate.[28–30] Additionally, the impact of a child's illness on the quality of life of caregivers can be substantial, just as it is for life-threatening and severe chronic diseases in adults (eg, cancer).[31] However, such indirect quality-of-life losses are typically not accounted for. These impacts have the potential to change decisions, for instance on rotavirus vaccine.[32] Finally, the peace of mind offered through the reassurance of vaccine protection is a quality-of-life improvement of prevention programmes that is routinely ignored in economic evaluation.[33]

A third issue is the impact that discounting has in accounting for time preference. Discounting is a technique that aims to put costs and benefits occurring at different timepoints on the same basis of comparison. Discounting scales down future events, such that, the further into the future they occur or the higher the discount rate, the less important they are to a decision maker in the present. In health economics, there is continued debate about whether the discount rate for health outcomes should be lower than or equal to that for costs.[34,35] For curative therapies, most benefits accrue immediately or shortly after the intervention is initiated, and the cost-effectiveness of these interventions is therefore largely independent of these methodological disagreements on discounting. Conversely, the cost-effectiveness of most prevention programmes is highly sensitive to discounting because of the long time spans over which benefits accrue. A slight decrease in discount rate—eg, from 5% to 3%—could change the cost-effectiveness of vaccination from unacceptable to attractive. Country-specific recommendations on discount rates vary to the extent that a vaccine could be deemed cost effective in one country and cost-ineffective in another for this reason alone (table 1).

	Year	Costs	Health outcomes	Comments
USA[36]	1996	3%	3%	The listed and widely used US rates were recommended by an influential panel of US health economists, and the official, annually revised rates from the US Office of Management and Budget currently tend to be slightly lower at, for example, 2·8% in 2008[42]
Australia[37]	2002	5%	5%	..
UK[38]	2004	3·5%	3·5%	In the period 2001–04, these rates were 6% for costs and 1·5% for health outcomes[35,43]*
Netherlands[39]	2006	4%	1·5%	In the period 1999–2006, these rates were 4% for both costs and health outcomes[34]*
Canada[40]	2006	5%	5%	..
New Zealand[41]	2007	3·5%	3·5%	In the period 2005–07 these rates were 8% for both costs and health outcomes[44] (and 10% in 1999–2005)[45]*

*These changes from previous recommendations illustrate the difference and volatility of opinions on this matter both within and between countries.

Table 1: **Recommended discount rates for evaluation of health interventions in selected countries**

In the standard discount procedure, as recommended in all guidelines known to us, the discount rate is constant, implying that preferences between outcomes are held constant through time and depend only on the length of the time interval between them. One can argue that discounting at a constant rate exaggerates the importance we give for the present over the future.[46–48] This assertion is backed by psychological empirical evidence, which suggests that the difference between equidistant outcomes is thought less important the further into the future the outcomes occur.[47] So-called "slow" discounting procedures could be used for cases in which the discount rate decreases and falls close to zero for the more distant future (eg, 3·5% for years 0–10, 1·5% for years 11–20, 0% thereafter), thus yielding a higher present value of benefits.[49,50] Additionally, time preference may exist only to the time until risk exposure, and not the time until health consequences from risk exposure arise (eg, cervical cancer is the health consequence of a much earlier exposure to HPV).[51] Adjustment of the discount procedure to account for these aspects is not current practice, but would substantially improve the estimated cost-effectiveness of prevention versus cure.[49,50] Currently, policy makers are presented with very wide cost-effectiveness ranges for preventive public-health actions when sensitivity to discounting is illustrated to them. In 1968, Baumol[52] noted the "sorry spectacle" that economists provided through their diverging understandings on this subject, and his assertion that "little help is provided to the decision maker who is confronted with such an enormous range of

estimates" rings through 40 years of subsequent vaccination research.

Finally, the equity impact of vaccination is far less predictable than for most drugs. Generally, the less healthy or less wealthy are those least likely to be vaccinated, and thus more likely to experience the effect of herd immunity from other people receiving vaccination. As shown for measles in Bangladesh,[53] this effect is often equitable, but the reverse may also occur for poorly executed vaccination programmes.[54] The redistribution effects on health and wealth are thus less straightforward in the prediction of decisions on vaccination compared with those used for therapeutic medicines.

Decision making for vaccines is getting tougher

The first generation of vaccines, such as measles, pertussis, and polio vaccines, were against serious childhood diseases that were common worldwide. Little analysis was done before their introduction because their benefits were obvious and their costs were low in an era when there was less pressure on the health-care budget. New vaccines are much more expensive and often aimed at less common or less serious diseases, particularly in wealthy countries. Thus, whether these vaccines are worth introducing is less clear. We will explain key aspects of the cost-effectiveness of current vaccines, while focusing on high-income countries.

Rotavirus

Rotavirus is the commonest cause of dehydrating gastroenteritis in the world and accounts for most gastroenteritis hospital admissions in children under 4 years of age. Deaths are infrequent because of good medical care in high-income countries (eg, about three deaths per year in the UK).[55] A challenge to the evaluation of both current oral rotavirus vaccines is the estimation of the part of the gastroenteritis disease burden specifically attributable to rotavirus, as well as assessing the extent to which these vaccines would invoke herd immunity. In high-income countries, the main benefit of rotavirus vaccines is the prevention of parental care and productivity losses in virtually all households with infants or toddlers. However, as we have outlined, gains in quality-adjusted life-years in such young children and their parents, as well as parental care and work loss, are not standard features in cost-effectiveness analyses. Given the current price setting (€80–120 per fully vaccinated child) and the recommended schedule for these vaccines (two doses Rotarix [GlaxoSmithKline]; three doses Rotateq [Merck]), they are unlikely to be judged as cost effective unless these so-called "soft" benefits are also included.[32,56–58] But if they are, why should they not also be considered for all other health-care interventions, thus potentially reshuffling the comparison between all health-care programmes (including the other vaccines discussed here)? Table 2 describes potential consequences of including soft costs and benefits at various levels of government decision making.

Human papillomavirus

HPV vaccines are effective against the two HPV serotypes associated with most cervical cancers, and one of these vaccines also protects against two of the serotypes that cause genital warts. Effectiveness against cervical cancer would have to be modelled based on the premise that HPV infection is a necessary condition for cervical cancer to develop, although often only decades later. The cost-

	Question posed	Likely effect of including soft costs and benefits*	
		Vaccines only	All decisions†
Government	How much of the government's budget should be spent on health generally, as opposed to the other government sectors (eg, defence, education, etc)?	Investments in vaccines, and preventive health sector as a whole, become more cost effective in relation to other sectors	Interventions with beneficial impacts on typically ignored externalities (eg, environmental pollution, herd immunity) would gain in relative importance, and those with adverse impacts would lose importance
Health sector	What proportion of the health budget should be spent on vaccination programmes as opposed to other health-care or public-health interventions?	Most vaccines become more cost effective in relation to other health interventions	Interventions that prevent and cure disease, with a proportionately larger aggregate impact on the quality of life and/or productivity of patients and their families, become more cost effective compared with other interventions
Vaccination programmes	Which vaccinations should be given priority (eg, rotavirus, HPV, or pneumococcal conjugate vaccines)? Which schedules and formulations should be chosen (eg, Rotarix‡ or RotaTeq§ for rotavirus; Gardasil§ or Cervarix‡ for HPV, three or four doses of Prevenar¶ for *S pneumoniae*)?	Programmes that prevent disease, with a proportionately larger aggregated impact on the quality of life and productivity of patients and/or their families, become more cost effective compared with other vaccination programmes	..

HPV=human papillomavirus. *Costs and benefits arising to parties generally not considered relevant in guidelines for economic evaluation of pharmaceuticals for which public funding is sought. These third parties can consist of people not receiving the intervention, parents of patients, employers of patients, and employers in general. †Cost-benefit analyses do not routinely inform other sector decisions in many countries (eg, education, transport infrastructure, military, etc.). Politics may dominate rational decision rules in other sectors more than in health care. ‡Produced by GlaxoSmithKline. §Produced by Merck. ¶Produced by Wyeth.

Table 2: **Levels of decision making and potential consequences of considering soft costs and benefits**

effectiveness of HPV vaccines depends heavily on the choice of the discounting approach used.[59,60] Furthermore, mathematical models for HPV vaccination ideally have to build in complexities related to herd-immunity effects from vaccinating cohorts of girls only and boys additionally, the optimum frequency of cervical cancer screening, and type-specific progressive infection and replacement, all over long time periods, which makes this a very complex programme to assess properly.[59,61] However, a more simple approach, based on static models, could give insights on the basic question: should we vaccinate girls before their sexual debut?[60] Such models would underestimate the benefits of HPV vaccination, and therefore would only be helpful for policy if they resulted in favourable cost-effectiveness ratios. The static models that have been published so far have tended to be favourable.[59,60,62] Policy makers could therefore quickly decide about vaccinating a limited number of cohorts before their sexual debut, and have reasonably confident cost-effectiveness evidence to support this decision. However, they cannot rely on such analyses to decide on more complicated aspects of the programme, such as the breadth of the programme in girls and boys. In view of the high costs of this programme (€250–350 per fully vaccinated individual), the uncertainty surrounding these more complicated decisions could unnecessarily postpone policy on the more basic issue.

Varicella-zoster virus

VZV childhood vaccination prevents chickenpox in vaccinated children and is likely to protect these vaccinees against shingles later in life. Since chickenpox infects virtually all children by age 12 years, the accumulated societal savings, including avoided parental care and productivity losses, are likely to be greater than the costs of vaccination at a price of €15–50 per fully vaccinated person. However, childhood VZV vaccination increases the occurrence of shingles in adults and this may be such that it counteracts these societal savings and leads to adverse health effects.[63] A further complication is that with single-dose infant vaccination many teenage breakthrough cases can still be expected, but the addition of a second dose to prevent this would make it a much less cost-effective programme. Modified VZV vaccine in adults was recently shown to prevent shingles, and was shown by static models to be cost effective.[64,65]

Finally, vaccination of susceptible pre-adolescents is an alternative strategy that has consistently been shown to be cost effective to the health-care budget, and is thus independent of the wider societal perspective.[66] However, it is not advocated by public-health specialists, because it would only prevent a small part of all chickenpox disease, albeit the most severe proportion.[8,11,27] Clearly, the simultaneous modelling of all these strategies and considerations requires complex models and data from various sources to establish effectiveness. Empirical studies alone cannot answer all these questions.

Infant influenza

Infant influenza vaccination may be a cost-effective way of preventing seasonal influenza and pneumonia in young children directly and the elderly indirectly through herd immunity.[67,68] However, vaccinating a child partially to save a grandparent from experiencing serious illness does not only raise concerns over intergenerational equity, but also the effectiveness of such an approach could only be shown if put into practice on a large scale, or by applying an appropriately parameterised model.[69] Seasonal variations in incidence, severity of disease, and vaccine efficacy are complicating factors that contribute to uncertainty. Furthermore, preparing for pandemic influenza demands very large investments, and this can only be shown to be worthwhile by modelling.[70] A policy-relevant approach to modelling the cost-effectiveness of pandemic influenza vaccination would entail considering macroeconomic impacts across sectors and across countries.[21] Clearly, deciding on the best options to prevent and control influenza requires an analytical framework and applied modelling work that substantially digresses from usual drug assessments.

Pneumococcus

The currently available seven-valent pneumococcal conjugate vaccine (PCV7), which costs about €100–150 per vaccinated child, is effective against invasive and non-invasive disease caused by seven serotypes of *S pneumoniae*. Because of its high price, in the short term the cost-effectiveness of PCV7 depends in most high-income countries on the inclusion of positive herd-immunity effects in adults, which were observed after 1 year of widespread use in the USA.[71] If the long-term effect of its widespread use, consisting of a mix of herd immunity, serotype replacement, antibiotic resistance, and cross reactivity, remains beneficial and if the cheaper three-dose schedule confers near-equivalent protection to the original four-dose schedule, PCV7 vaccination programmes are judged to be cost effective in high-income countries.[71] To budget for this vaccine, European policy makers should accept imputations from herd-immunity effects observed in other countries in the short term as well as uncertainties with both positive and negative impacts of the programme in the longer term.

Conclusions

Advisory processes on drug funding can be generally effective at selecting which pharmaceuticals, and which subgroups of patients, should be subsidised to make the most of scarce health-care resources. Vaccines are different and more complex than most drugs assessed by such processes for the reasons we have outlined. This implies that such processes should be more flexible in accepting the best available quantified evidence of the unique features of vaccination programmes, and that decision makers and their advisers should be aware of these features if they cannot be quantified. The best

available evidence depends on the type of infection and vaccine, and the time of its consideration.

Guidelines for economic assessment of pharmaceuticals dictate the approach to use to make such analyses acceptable for a country's decision makers. Since economic evaluation is not an exact science, such guidelines are made on the basis of compromises between the people designing them and therefore can be changed (table 1).

Economic evaluation requires quantification of the effects of interventions, as well as valuing these effects. In terms of quantifying the effects of vaccination, governments should adapt their guidelines to specify modelling options for the assessment of interventions against infectious diseases. This should enable submitters and drug-reimbursement committees to better understand which models are acceptable (or unacceptable) under which circumstances. Crucially, drug-reimbursement committees must be represented by the required expertise to properly understand and evaluate complex vaccine models.

In terms of valuing the effects of vaccination, we do not plead for a special case, but for a level playing field. That is, we argue that not all aspects of ill health and time preference are currently captured by recommended techniques for economic evaluation, and that this may disadvantage the cost-effectiveness of interventions against diseases in children relative to interventions against diseases in adults, and prevention relative to cure. Therefore, guidelines should also be adapted in general terms to allow for (1) a wider perspective to account for effects on third parties, if these are affected substantially by specific interventions (eg, parents experiencing a quality-of-life impact through the illness of their child); (2) a wider scope of costs to be included, if appropriate, than health-care system costs alone (eg, irrecoverable losses caused by modified behaviour when faced with a large public-health threat); and (3) alternative discounting techniques to deal with social time preference over long time periods.

Large uncertainties about the value and distribution of particular variables imply that timely vaccine decisions may need to be taken with more uncertainty than decisions on other drugs. This should not deter the widespread use of new safe and efficacious vaccines, if—all things considered—these are unlikely to be judged cost-ineffective relative to other interventions. Furthermore, other criteria, including the programme's acceptability, feasibility, budget, and equity impact, are also important. A WHO guide for the standardisation of economic evaluations of immunisation programmes, which will become shortly available for public use, could be used as a starting point for governments to adapt their guidelines with respect to some of the issues mentioned here.[72]

Conflicts of interest

PB has no conflicts of interest to declare. CRM has received funding from GlaxoSmithKline and CSL Biotherapies in 2007 and 2008 for investigator-driven research, and has done industry clinical trials for Merck in 2007. PRS received consulting fees in 2007 from a consortium partly funded by GlaxoSmithKline, Sanofi-Aventis, and CSL Biotherapies, and was a director of an evaluation group for the Australian Pharmaceutical Benefits Advisory Committee in 2004–06.

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