Pertussis vaccines: past, present and future in Australia

Proceedings of a workshop held at the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, Royal Alexandra Hospital for Children and University of Sydney, Westmead, New South Wales, 9 August 1997.

Edited by Peter McIntyre[1], Jill Forrest[1], Tim Heath[1], Margaret Burgess[1] and Bronwen Harvey[2]

Abstract

In August 1997, a workshop was convened by the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases to consider current issues in the use of pertussis vaccines and implications for the Australian immunisation schedule. Topics covered included the history, efficacy and reactogenicity of whole-cell and acellular vaccines and vaccine schedules. Acellular pertussis vaccine is preferred by the National Health and Medical Research Council for the primary course as well as the 18 month and 4-5 year old childhood doses. At the time of the workshop, a 3-component acellular vaccine (DTPa) had been approved (licensed) in Australia for all doses in the childhood schedule. It was the first vaccine subject to a cost-effectiveness evaluation under the new vaccine funding arrangements. Issues considered in the evaluation of the cost-effectiveness of the vaccine were discussed. These included comparative efficacy, adverse events and compliance, and the question of community as well as individual benefit from the use of the vaccine. *Comm Dis Intell* 1998;22:125-132

Introduction

Despite the long term availability of an effective vaccine, low vaccination coverage has contributed to the regular outbreaks of Pertussis in Australia over the past 4 years.[1] The recent availability of an acellular pertussis vaccine, and the potential availability of combination vaccines, are expected to lead to improved immunisation coverage. However, the introduction of such vaccines into the Standard Vaccination Schedule requires consideration of a wide range of issues including efficacy, side effect profiles and cost effectiveness. To develop a better understanding of these issues, a two day workshop was convened in August 1997 by the National Centre

ISSN 0725-3141
Volume 22
Number 7
9 July 1998

1. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, Clinical Sciences Building, Royal Alexandra Hospital for Children, PO Box 3515, Parramatta, New South Wales 2124
2. National Centre for Disease Control, Commonwealth Department of Health and Family Services

Contents

for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS). The Centre was established by the Commonwealth Department of Health and Family Services in August 1997 to carry out research to inform policy and planning for immunisation services in Australia.

The meeting brought together a group of Australian experts in infectious diseases, microbiology, immunology and public health to discuss pertussis with Professor James Cherry, a recognised international authority on pertussis and pertussis vaccines. The workshop examined current issues in the use of whole cell and acellular vaccines and implications for the Australian immunisation schedule. Issues relating to the economic evaluation of vaccines were also considered.

Part I - Whole cell and acellular vaccines; the current scene

History

Whole cell vaccines

An overview of whole-cell pertussis vaccine (Pw) in Australia was given by Professor Ian Gust. The first commercial whole-cell vaccines in Australia were made by the then Commonwealth Serum Laboratories (now CSL Limited) in about 1920, but were not used widely until the 1940s. At this time pertussis, diphtheria and tetanus vaccines still had to be given as separate injections, and debate began about whether it was possible to combine antigens. By 1953 the first Australian-made Triple Antigen (DTPw) (diphtheria and tetanus toxoids with whole-cell pertussis) was produced.[2] Although there have been many changes in the surveillance of pertussis in Australia over the past 50 years, a more than tenfold reduction in the incidence of pertussis (from 500-750 per 100,000 to 25-30 per 100,000) and a more than hundredfold reduction in deaths (from 4,000 in the period 1926-1945 to 21 in the period 1976-1995) have occurred during the whole-cell vaccine era. This is impressive evidence of the effectiveness of whole-cell vaccines in Australia.

Acellular vaccines

Professor James Cherry outlined the history of acellular pertussis vaccines (Pa). Japanese investigators accelerated the development of acellular pertussis vaccines in the 1970s. This followed an epidemic of pertussis that occurred after the cessation of whole-cell pertussis immunisation, in early 1971, because of concern about adverse effects.[3] Development of the acellular vaccines became possible once biologically active and extractable components of *Bordetella pertussis* were identified. One or more of the following five components are included in all vaccines developed to date:

- detoxified pertussis toxin (PT);
- the outer membrane protein pertactin (PRN); and
- three surface proteins - filamentous haemagglutinin (FHA) and two agglutinogens (AGGs).

The first acellular vaccines were strongly influenced by the notion that pertussis was a single toxin disease, like diphtheria, and could be prevented by use of a pertussis toxoid. This is incorrect, partly because *Bordetella parapertussis*, which does not produce pertussis toxin, causes an almost identical clinical picture.

The first licensed vaccines in Japan contained PT alone or together with FHA. These vaccines were used in the early trials in Sweden, where epidemic pertussis had also followed cessation of immunisation. The vaccines showed low protective efficacy in Sweden (54% for monocomponent and 67% for 2-component vaccine given as 2 doses after 9 months of age)[4] and were not licensed anywhere apart from Japan. In the United States of America, the National Institutes of Health coordinated phase I and II trials of 13 candidate acellular vaccines, selecting the most promising ones to enter randomised controlled trials in Europe.[5]

Efficacy

Whole-cell vaccines

A number of candidate vaccines were examined in trials conducted by the Medical Research Council in the United

Editor's column

We received both compliments and criticisms of our last issue of *CDI*, confirming that people do read and appreciate the journal even if they do not always agree with it. Please continue to send us your feedback as it is only by hearing from our readers that we can make the sorts of improvements that will keep *CDI* relevant and useful.

This issue of *CDI* features a report of the workshop on pertussis vaccines (p 125) convened by the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases in August 1997. As well as providing a summary of the history of pertussis vaccines, the report highlights some of the complexities that face us in making decisions about which vaccines should be incorporated into the Standard Vaccination Schedule. These complexities will increase as the range of diseases for which vaccines are available expands and more combination vaccines come on to the market. The report also discusses some issues in the evaluation of the cost-effectiveness of vaccines used in population programs. Such evaluations are relatively new but likely to be of increasing importance in vaccine scheduling decisions. With the launch of the Measles Control Program this month, the article by *Burgess et al* on adverse events following measles immunisation (p 136) is both timely and reassuring. The slight increase in notifications of meningococcal disease noted in the Communicable Diseases Highlights on page 139 reminds us that we are entering the peak season for meningococcal disease. The short report by *Harvey* (p 134) reviews the 1997 meningococcal disease data and points to the need for increased vigilance to diagnose cases early and commence treatment promptly. There is nothing like claiming that something is a first to provoke correspondence to the Editor. Following reminders of two other reports of infant botulism, we have published (p 133) a clarification of the editorial comment that accompanied last issue's case report.

Table 1. International infant efficacy trials of pertussis vaccines[6,7,11]

Site	Manufacturer (of acellular vaccine)	Composition				Schedule (months)	Efficacy (95%CI) [1]			
		PT	FHA	PRN	FIM		DTPa		DTPw	
Germany	Con (USA)	x	x			2, 4, 6	96	(78-99)[2]	97	(79-100)
Germany	Wyeth	x	x	x	x	2, 4, 6, 15-18	82	(73-87)	91	(85-94)
Sweden	Con (Canada)	x	x	x	x	2, 4, 6	85	(81-89)	48	(37-58)[3]
Sweden	SKB	x	x			2, 4, 6	59	(51-66)	48	(37-58)[3]
Italy	CB	x	x	x		2, 4, 6	84	(76-90)	36	(14-52)[3]
Italy	SKB	x	x	x		2, 4, 6	84	(76-90)	36	(14-52)[3]
Sweden	NAV	x				3, 5, 12	71	(63-78) [2]	Not tested	
Germany	SKB	x	x	x		3, 4, 5	89	(77-95)	97	(83-100)
Africa	PM	x	x			2, 4, 6	86[2]		96	

1. Using WHO definition of 21 days or more cough.
2. These results are likely to be too high due to study methods and observer bias
3. Study used Connaught (Canada) whole-cell vaccine.

Con (USA) = Connaught (USA)
Con (Canada) = Connaught (Canada)
SKB = SmithKlineBeecham
NAV = North American Vaccine
CB = Chiron Biocine
PM = Pasteur Meriux
DTPa = Acellular Diphtheria - Tetanus - Pertussis vaccine
DTPw = Whole-cell Diphtheria - Tetanus - Pertussis vaccine

Kingdom in the 1950s. These trials established a correlation between clinical efficacy and the mouse protection test (Kendrick assay), which has been used ever since to monitor the potency of whole-cell vaccines. Australia has adopted the United Kingdoms' criterion of requiring 4 mouse protection international units (IU), but the United States of America has allowed vaccines to have as low as 2 IU. One of the outcomes of the recent comparative trials has been evidence that whole-cell vaccines may vary significantly in efficacy (Table 1).[6,7] It is suggested that whole-cell vaccines, such as the CSL vaccine, which pass the more stringent mouse protection test (4 IU) are likely to be more protective, but there are limited observational (household contact) data and no trial data estimating the efficacy of the Australian whole-cell vaccine.[2] In general, although waning immunity occurs over time with both, whole-cell vaccines protect better against disease than natural infection. A British study has estimated that waning of immunity is almost complete by 5 years after vaccination.[8] Some experts believe that if the vaccine contains all 3 agglutinogens (1,2,3) it is more likely to be protective against all 3 serotypes of the organism (type 1,2,3; type 1,2; and type 1,3).[2]

Acellular vaccines

In contrast to whole-cell vaccines, the Kendrick test does not correlate with efficacy for acellular vaccines, making large trials the only means of evaluating efficacy. Professor Cherry gave a detailed review of the seven large controlled trials now published, all but one in Europe, to evaluate the efficacy of the acellular vaccines (Table 1).[6,7,9] The results of the most recent study (Sweden II) were not published at the time of the meeting but were published subsequently.[10] Professor Cherry emphasised that differences in methodology and case definitions make comparisons between trials difficult.[6,11] In particular, the World Health Organization (WHO) case definition (21 days of cough) detects only typical whooping cough, which is more common in unvaccinated individuals. Using the WHO definition therefore inflates vaccine efficacy estimates compared with case definitions which include milder but still culture positive infections.[6] When mild cases are taken into account, the efficacy of acellular vaccines varies widely. Their efficacy broadly correlates with increasing numbers of components, from around 50% with 1 or 2 components to around 70% with at least 3 components, including PRN, and 80% or more with 5 component vaccines.[6,11] In the second Swedish trial, a 5-component acellular vaccine and the British whole-cell vaccine gave better protection against less severe disease (laboratory confirmed pertussis with or without cough, and whooping cough diagnosed by the child's parents) than a 3-component vaccine (not the 3-component vaccine currently approved in Australia).[10] All three vaccines tested in the second Swedish trial gave similar protection if the WHO case definition was used (laboratory confirmed with cough for 21 or more days).[10]

Reactogenicity

Whole-cell vaccines

Whole-cell vaccines contain inactivated *B. pertussis* organisms and a variable but significant amount of endotoxin, which is probably responsible for the relatively

Table 2. Side effects of Triple Antigen containing whole-cell pertussis vaccine (DTPw) in 591 Australian children[1]

Reaction	Percentage[2]
Systemic	
Fever ≥ 38°C[2]	16
Irritability	90
Crying - intermittent, inconsolable	40
Crying - persistent high-pitched	8
Vomiting	11
Hypotonic-hyporesponsive episode	0
Convulsions	0
Local	
Redness ≥ 2.4 cm	27
Induration ≥ 2.4 cm	30
Swelling	45
Tenderness	46

1. All children were given at least 2 doses of paracetamol around the time of each vaccination.
2. Mean after first three doses at 2, 4 and 6 months of age, to the nearest whole number.

high rate of fever, local reactions, pain and prolonged crying from whole-cell vaccines (Table 2).[12] Endotoxin cannot be exclusively responsible, as these effects also occur, at a lower rate, with DT vaccine. Attempts were made in Australia and elsewhere to eliminate endotoxin from whole cell pertussis vaccines, but this proved difficult and was superseded by development of acellular vaccines.

Whole-cell pertussis vaccine is incorporated into the WHO's Expanded Programme on Immunization (EPI) and is now routine in most countries. However, in some countries the vaccine has been subject to adverse publicity, related to the relatively high rate of minor and moderate side effects and unsubstantiated statements about more serious ones.[13] The only estimates of severe reactions to the Australian vaccine come from a study of two earlier formulations of DTPw, where hypotonic-hyporesponsive episodes (HHE) occurred in 3 out of 1,075 infants.[14]

Acellular vaccines

The much lower incidence of the more common but less severe reactions (such as local swelling, pain and fever) with acellular vaccines was easily established early on. Data concerning uncommon but more severe reactions, such as fits and HHEs were more difficult to accumulate, but the combined results of a number of controlled trials now show that these are also significantly lower than with whole-cell vaccines and do not appear to be related to the number of components or to any one component.[6,9] In the United States of America two products were licensed in 1991 for the fourth and fifth infant doses. Surveillance after this licensure showed that post-vaccination seizures and hospitalisation were reduced by 60%–70% with the acellular product (DTPa).[9] However, none of the trials has been large enough to evaluate the rate of rare serious side effects such as anaphylaxis or encephalopathy in comparison with whole-cell vaccine. What has been established is that HHEs occasionally occur both with acellular pertussis vaccine and with combined diphtheria and tetanus vaccine (without the pertussis component) and that this occurs at about a rate of 1 in 10,000 doses compared to about 1 in 1,000 with the whole-cell vaccine.[6,9] Professor Cherry pointed out that comparing absolute rates of HHEs between trials (different case definitions) and communities (higher rates of reporting in more versus less advantaged) is difficult, but relative comparisons should be valid.

Licensing of acellular vaccines

Status in Australia

One 3-component vaccine (Infanrix, SmithKline Beecham) had been approved for marketing (licensed) in Australia at the time of the meeting. A 5-component vaccine (Tripacel, CSL Vaccines, manufactured by Connaught Laboratories, Canada) has since been licensed. Both vaccines are approved for use for primary and booster doses. In November 1996, the National Health and Medical Research Council recommended that acellular vaccine should be preferred for the booster doses at ages 18 months and 4-5 years.[15] On the advice of its Pertussis Working Party, the National Health and Medical Research Council recommended in June 1997 that acellular vaccines should be preferred for the infant schedule also.

Status in the United Kingdom

Acellular vaccines have not been licensed in the United Kingdom. Here pertussis has been controlled using 3 doses of the British whole-cell vaccine (made by Evans Medeva), administered at 2, 3 and 4 months of age. At present, no boosters are given although preschool boosters with an acellular vaccine are being considered. The incidence of side effects in the infant schedule is low.[10,16]

Acellular pertussis vaccines in adults

Dr Tim Heath reviewed the accumulating literature on the importance of adults in the maintenance of pertussis transmission in the community, much of it emanating from Professor Cherry's research groups in California and Germany.[17] Although it was once thought that clinical whooping cough was followed by life-long immunity, there is evidence that immunity from infection wanes, possibly more than that from immunisation. Very young infants, who are most at risk from serious complications, frequently have contracted pertussis from an adult contact. Acellular pertussis vaccines offer for the first time the possibility of including a pertussis booster with the already recommended tetanus and diphtheria boosters for adults. Trials investigating this are under way in the United States of America and in Australia.

Combination vaccine trials in Australia

Combinations containing whole-cell pertussis vaccine

Associate Professor Terry Nolan discussed the status of multivalent vaccines containing Pw. The motivation for producing such vaccines is the increasing number of antigens being incorporated into the primary schedule. Single injections are likely to be more acceptable to both parents (improving compliance and timeliness) and providers (reduction in material and delivery costs). However, immunological responses to antigens presented in combination cannot be assumed to be equivalent and, in general, responses to Hib in combination have been lower. These problems seem close to resolution now.

Although a number of countries have licensed whole-cell combinations, with either Hib vaccine or hepatitis B and inactivated polio vaccine, Australia is probably unique among industrialised countries in developing a pentavalent combination using a reformulated whole-cell vaccine. Trials of this vaccine, containing DTPw as base, the PRP-OMP♦ Hib vaccine and recombinant hepatitis B in a liquid formulation (produced by CSL Vaccines), have been conducted in Melbourne during the past 5 years. In a controlled trial of this pentavalent vaccine, reactogenicity and immunogenicity has been assessed in about 845 babies after the first 3 doses, and in a smaller number after the fourth dose.[18,19] In contrast to the acellular vaccine combinations, after 3 doses at 2, 4 and 6 months, Hib antibody responses were significantly higher with the whole-cell combination than singly, but there was a lower hepatitis B surface antibody response. The implications of this are uncertain, but preliminary results suggest that hepatitis B responses may be satisfactory with either the

♦ PRP-OMP vaccine (PedvaxHIB) is a conjugated vaccine in which polyribitol ribosyl phosphate (PRP), the purified capsular polysaccharide of Haemophilus influenzae type b, is conjugated to a carrier protein, the meningococcal outer membrane protein (OMP).

addition of monovalent hepatitis B at birth for all babies or the inclusion of hepatitis B vaccine in the combination given at 18 months of age.

Combinations containing acellular pertussis vaccine

Professor Don Roberton discussed multivalent vaccines containing Pa. Comprehensive assessment of combination vaccines has a number of prerequisites as outlined by Edwards and Decker,[20] including blinded and standardised serological assays. To date, most studies of combinations including Hib and acellular pertussis vaccines show reduced Hib responses. Most results are available only in abstract form, but a Finnish study showing significantly reduced Hib responses when given in combination with DTPa and inactivated polio vaccine, has been published.[21] It is not clear why this is occurring, although the most likely explanation is that some adsorption of the PRP antigen is occurring in the combination. The reactogenicity and immunogenicity of a pentavalent vaccine containing acellular pertussis (using the 3-component product currently approved in Australia and manufactured in Europe), diphtheria, tetanus, Hib and hepatitis B is under study in 360 infants in Adelaide and Sydney. The formulation of the Hib component of this vaccine has been changed to overcome adsorption, if present. Enrolment is completed; follow up and evaluation will be completed during 1998. Another group of full-term and preterm infants, immunised with DTPw according to the current schedule, will be evaluated for boosting by the combination vaccine at 18 months.

Pertussis vaccine schedules

Throughout the world various schedules are used. In the United States of America the primary schedule doses are given at 2, 4 and 6 months and most of the European trials have used this schedule. In June 1990, the United Kingdom introduced a 2, 3, 4 months of age schedule with whole-cell vaccine, replacing a 3, 5, 10 months of age schedule. A series of small comparative trials over a number of years has examined the immunogenicity and reactogenicity under the two schedules, using a number of acellular vaccines and the Evans-Medeva whole-cell vaccine. The results of these trials have been summarised recently.[16] These data were reviewed in detail at the workshop by A/Professor Nolan.

Local erythema and swelling were strikingly reduced under the 2, 3, 4 month schedule, for both Pw (22% to 4%) and Pa (11-21% to 1-5%). Fever greater than a cutoff figure (which differed among studies) was not reduced under the 2, 3, 4 month schedule (11% versus 12%) but was much less common with the acellular vaccines (1-5%). When serological responses under the two schedules were evaluated, there was a significantly reduced geometric mean titre to detoxified pertussis toxin after the third dose with the accelerated schedule, but responses to other antigens were unchanged.

Discussion about the United Kingdoms' experience encompassed a number of issues:

- optimum uptake is the key to control, irrespective of which schedule is used;
- the implications of the known lower antibody responses with earlier immunisation;
- the incidence of fever reported for Pw under both schedules was much lower than expected from experience elsewhere, and similar to that seen with diphtheria-tetanus vaccines;
- will the organism continue to circulate in older children without boosters?
- would this schedule improve uptake in Australia and what would the comparative reactogenicity be under Australian conditions?

Panel discussion on pertussis vaccine schedules in Australia

The discussion was led by Professor Richard Doherty, Professor Don Roberton, Associate Professor David Isaacs, Dr John Carnie and Professor James Cherry.

Multiple injections versus reactogenicity

Professor Cherry was asked to comment on the situation in the United States of America, where, because of compensation legislation, the cost of Pw is much closer to Pa than in Australia. In the United States of America, a Hib/DTPw combination (Tetramune, Wyeth-Lederle) has been available for some time and hepatitis B and inactivated polio vaccine, each given by injection, are now also routinely recommended for infants; a total of 3 injections. Some parents are opting for their children to have the Hib/DTPw combination rather than Hib and DTPa separately, or oral polio vaccine rather than inactivated polio, because of the lesser number of injections, despite the higher potential for side effects with the DTPw. Costs of acellular vaccines and inactivated polio are a significant factor, particularly in health maintenance organisations (HMOs). No data on the prevalence of these approaches were available.

A comparable scenario exists in Australia with the whole-cell multivalent combination likely to be approved some time before acellular combinations. This raises the question of the need to choose between the reactogenicity associated with combinations containing whole-cell vaccine and increased number of injections if the acellular vaccine is chosen. A study commissioned by the Commonwealth Department of Health three years ago (unpublished), indicated that some parents were reluctant to accept multiple injections. No data on attitudes to this issue in representative Australian populations were available at the time of the workshop.

The place of acellular pertussis vaccines in the immunisation schedule

After a discussion about the place of Pa in the immunisation schedule the consensus was that a change to a 2, 3, 4 month schedule was not appropriate in Australia at this time, because of the potential for confusion and the over-riding need to improve compliance with the current schedule.

Professor Gust expressed concern that the economic analysis of acellular versus whole-cell vaccine (see Part II) had not taken sufficient account of the then unpublished results of the Sweden II trial, which suggested superior efficacy for the whole-cell vaccine used in the United Kingdom and a 5-component acellular vaccine over a 3-component vaccine (not the 3-component vaccine currently approved in Australia). On the basis of assumed equivalent efficacy of the Australian and United Kingdom DTPw and the fourfold greater cost of acellular vaccines, he proposed that acellular vaccines should be used only

for the 18-month and 5-year booster doses. Whole-cell vaccine should continue as the routine vaccine for the infant schedule, with acellular vaccine used only for infants with adverse reactions.

In the ensuing discussion, no overall consensus was reached. Some speakers stated that they disagreed with the Pertussis Working Party's conclusion that acellular vaccine should be preferred to whole-cell vaccine for infants, arguing that the vaccines should be equally preferred for the first three doses. Others expressed the view that the Working Party's recommendations should be adopted, and that it would be impractical to restrict the use of acellular vaccine in infants, once it became available for older children.

Professor Cherry considered that a possible difference of 10% in efficacy between acellular and whole-cell vaccines, even if substantiated, was not important if 5 doses were being given, as in the schedules for Australia and the United States of America. The major factor in recommending acellular vaccines in North America was public beliefs about adverse reactions.

Part II - Economic evaluation of acellular pertussis vaccine in Australia

Since the beginning of financial year 1997-1998, decisions on Commonwealth Government funding of new vaccines, recommended by the NHMRC for inclusion in the standard vaccination schedule, may incorporate an evaluation of the cost-effectiveness of the new vaccine by the Pharmaceutical Benefits Advisory Committee (PBAC). The currently approved 3-component DTPa (Infanrix) was the first vaccine evaluated by the PBAC under these new arrangements.♦♦

Dr Suzanne Hill, Discipline of Clinical Pharmacology, University of Newcastle, was on the team which independently appraised the economic analysis of Infanrix for the PBAC. She outlined the nature of the PBAC process in general and highlighted issues involved in the economic evaluation of vaccines.

Access to drugs and vaccines in Australia

Two processes contribute to making drugs and vaccines accessible in Australia:

- the marketing approval (licensing) process, through the Therapeutic Goods Administration (TGA), which considers the quality, safety and efficacy of pharmaceutical products; and
- the process for subsidising the cost of drugs through inclusion on the national Pharmaceutical Benefits Scheme (PBS), for which the data required are comparative efficacy and comparative cost-effectiveness.

The PBS was established in 1953 and has been a remarkably robust political policy, the aim of which is to provide access to essential drugs. Drugs are evaluated for listing on the PBS by the PBAC, which is a powerful advisory committee; the Minister cannot make a decision to list a drug unless the PBAC has recommended that (s)he do so.

Requirement for the PBAC to consider comparative cost-effectiveness

An amendment to the *National Health Act* in 1989 established the requirement for the PBAC to consider comparative cost-effectiveness in making recommendations to the Minister. The PBAC guidelines for comparative cost-effectiveness, first developed in 1990-1991, are now in their second edition and consist of two major parts:

- establishing the relative clinical benefit of any new product, and
- evaluating that benefit.

This is a very clinical and epidemiological approach, and has been one of the points of contention about the guidelines. It is somewhat different to the approach to economic evaluation adopted in Canada and in some of the health maintenance organisations (HMOs) in the United States of America, where the emphasis has been much more on an economic model rather than starting with assessment of the relative clinical benefit.

In looking at clinical benefit, the first question is choice of comparator. The company is asked to conduct a mini-systematic review to identify the best data that are available to support its drug's performance against this comparator. The Committee has expressed a definite preference for randomised controlled trials, where the trial arms compare the two treatments directly, if at all possible. Companies are asked to estimate the relative effect size, and they have two options - equivalence to the comparator or a claim for superiority. The company is then asked to conduct what has become known as a 'trial-based economic evaluation', where it provides an estimate of the costs and benefits around the outcome that is measured in the trial. In the evaluation of benefit it is asked to adopt a societal perspective. It is then asked to provide an estimate of the incremental cost-effectiveness ratio, that is, the incremental cost per outcome. Finally, companies estimate the total financial implications to both the PBS and the government of the potential listing of the drug.

To date the Committee has considered over 350 applications, and it is clear that establishing equivalence to a comparator is easier than establishing superiority. Decisions are not based solely on the cost-effectiveness ratio; a number of other factors are considered, including the total financial implications. If it is estimated that the cost to the Commonwealth of a new drug may be more than $10 million, the Cabinet, as well as the Minister, must take the decision to approve the listing. The Committee is required to take into account the perception of clinical or community need for a drug, the question of equity of access, and what might be called 'the rule of rescue', where the assessment tends to err on the side of positive rather than negative assessment.

Cost-effectiveness evaluation for vaccines

Vaccines have been required to be approved for marketing through the TGA, but have not generally been subject to evaluation of comparative efficacy and cost-effectiveness, either because they were PBS listed for individual use prior to the introduction of current guidelines or because funding for population use (as for NHMRC schedule vaccines) has

♦♦ Evaluations for funding vaccines in the NHMRC Standard Vaccination Schedule are undertaken by the PBAC as an expert advisory body to the Department of Health and Family Services. They are separate from the PBS listing process and do not result in recommendation for PBS listing.

been provided under separate processes. Infanrix was the first vaccine subjected to an economic evaluation and presented a number of new issues to the PBAC.

Although vaccines are used for prophylaxis rather than treatment, they are not alone in that, drugs for osteoporosis and hypertension, for example, are also prophylactic. Probably of more difficulty for evaluating vaccines is the question of community as well as individual benefit, which is not usually part of a drug evaluation.

Issues in evaluating cost-effectiveness of vaccines

One of the immediate issues for the first evaluation of a vaccine by the PBAC was the availability of comparative efficacy data. The obvious comparator was the CSL Triple Antigen (DTPw). For Infanrix, the assessment of comparative efficacy was relatively straightforward because of the existence of good quality randomised trial data with clearly defined outcomes such as protective efficacy and side effects.

Other issues were:

- compliance with vaccine schedules and what actually drives it; and
- data to support the assumption that adverse effects are the major factor in determining compliance.

A key assumption was that a decrease in side effects would lead to an increase in vaccination rates, translating into an improvement in coverage and completion rates, a change to which the model was extremely sensitive. An added difficulty in assessing this assumption was the relative impact of other initiatives to increase immunisation rates, such as financial incentives for parents and providers, the new Australian Childhood Immunisation Register and mandatory review of vaccination status at school entry.

The estimates presented for Infanrix (under $3,000 per infection averted, and under $25,000 per life year gained) can be considered in the context of previous decisions about other drugs. A league table of estimated cost per quality adjusted life year (QALY) for various drugs presented to the PBS since 1990 suggests that estimates of $20,000–$30,000 per QALY are acceptable and estimates of more than $100,000 are unacceptable. The estimates for Infanrix were well within the boundaries considered by PBAC when evaluating drugs.

Because of the concern about the assumption of increased coverage and the sensitivity of the overall model to that assumption, the intermediate outcome of cost per averted side effect was considered in the evaluation. The effect of the vaccine in the community on other parts of the immunisation process were also considered.

Finally we come to the 'willingness to pay' factor. It is clear that some people have been willing to pay quite a lot for this vaccine, which raises the difficult issue of the need to trade off the costs of a vaccine, for example, against the costs of something else.

The evaluation process is part of a consistent move to evidence-based decisions. For pharmaceuticals, the clinical evidence is often much better than for other health technology interventions. For pertussis vaccine the data were complex. The important question of how the impact of the introduction of acellular vaccines will be evaluated must be considered immediately.

Economic evaluation of Infanrix versus whole-cell vaccine

Ms Michelle Burke, health economist with SmithKline Beecham (SKB), led the team that conducted the economic analysis of the vaccine (Infanrix) which was submitted to the PBAC. She presented the methodology and summary findings of the economic analysis, but was unable to present detailed data because of commercial confidentiality issues.

The team working on the analysis developed a model with several key assumptions:

- the efficacy of Infanrix (DTPa) and the CSL whole-cell vaccine (DTPw) was equivalent;
- the better tolerability of Infanrix would result in improved coverage rates; and
- increased coverage would lead to fewer cases and deaths from pertussis.

The model developed was complex. It included changes over time in both the probability of infection, to account for cyclical epidemics, and coverage rates. It also included consideration of children of differing ages and immunisation histories. No empirical data were available for a number of variables in the model (for example, improvement in coverage from use of Infanrix) and values for these variables were derived from the consensus opinion of an expert panel. Sensitivity analysis was used to examine the changes that occurred in the model estimates when different values, within the plausible range of values, were substituted for the value selected as baseline for the model.

The model estimated that the cost per pertussis infection prevented was less than $3,000, and the cost per life year gained was less than $25,000. These estimates were sensitive to changes in the following three factors: baseline coverage rates, coverage with Infanrix, and the probability of pertussis infection. Where less favourable estimates were obtained with sensitivity analysis, estimated costs did not increase to unacceptable levels.

As submissions on cost-effectiveness for the PBAC are protected under secrecy provisions of the *National Health Act*, Dr Hill congratulated SKB on their willingness to have their data discussed.

References

1. Andrews R, Herceg A, Roberts C. Pertussis notifications in Australia, 1991 to 1997.*Comm Dis Intell* 1997;21:145-148.
2. Burgess M, Forrest J. Pertussis and the acellular vaccines. *Comm Dis Intell* 1996;20:192-196.
3. Cherry JD, Brunell PA, Golden GS, Karzon DT. Report of the task force on pertussis and pertussis immunisation - 1988. *Pediatrics* 1988;81(Supplement):939-984.
4. Ad Hoc Group for the Study of Pertussis Vaccines. Placebo-controlled trial of two acellular pertussis vaccines in Sweden - protective efficacy and adverse events. *Lancet* 1988;1:955-960.
5. Decker MD, Edwards KM. Editors. Report of the nationwide multicenter acellular pertussis trial. *Pediatrics* 1995;96(Supplement):547-603.
6. Cherry JD. Comparative efficacy of acellular pertussis vaccines: an analysis of recent trials. *Pediatr Infect Dis J* 1997;16:S90-S96.
7. Hewlett EL. Pertussis: current concepts of pathogenesis and prevention. *Pediatr Infect Dis J* 1997;16:S78-S84.

8. Jenkinson D. Duration of effectiveness of pertussis vaccine: evidence from a 10 year community study. *BMJ* 1988;296:612-614.
9. Committee on Infectious Diseases, 1995 to 1996, American Academy of Pediatrics. Acellular pertussis vaccine: recommendations for use as the initial series in infants and children. *Pediatrics* 1997;99:282-288.
10. Olin P, Rasmussen F, Gustafsson L, Hallander HO et al. Randomised controlled trial of two-component, three-component and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. *Lancet* 1997;350:1569-1577.
11. Olin P. Commentary: the best acellular pertussis vaccines are multicomponent. *Pediatr Infect Dis J* 1997;16:517-519.
12. Harris G, Nolan T, Hartman L. Clinical signs associated with Triple Antigen (DTP) vaccination in infants. *J Paediatr Child Health* 1995;31:228-232.
13. Gangarosa EJ, Galazka AM, Wolfe CR, et al. Impact of anti-vaccine movements on pertussis control: the untold story. *Lancet* 1998;351:356-361.
14. Feery B, Finger WK, Kortus Z, Jones GA. The incidence and type of reactions to plain and adsorbed DTP vaccines. *Aust Paediatr J* 1985;21:91-95.
15. NHMRC. *The Australian Immunisation Handbook*. 6th Edition,. Canberra: AGPS, 1997. ISBN 0644475781.
16. Miller E, Ashworth LAE, Redhead K, et al. Effect of schedule on reactogenicity and antibody persistence of acellular and whole-cell pertussis vaccines: value of laboratory tests as predictors of clinical performance. *Vaccine* 1997;15:51-60.
17. Cherry JD. The epidemiology of *Bordetella pertussis*: implications for the use of acellular vaccines. Proceedings of the First International Pediatric Infectious Disease Conference. *Vaccine Bulletin* 1996;10-15.
18. Nolan T, Hogg G, Darcy MA, et al. Controlled trial of a pentavalent (DTPw-Hib-HepB) vaccine: immunogenicity and reactogenicity. Proceedings of the 42nd Annual Scientific Meeting, Australian College of Paediatrics, August 1997. *J Paediatr Child Health* 1997;33:A18.
19. Nolan T, Hogg G, Darcy MA, et al. Primary course immunogenicity and reactogenicity of a new diphtheria-tetanus-whole cell pertussis vaccine (DTPw). *J Paediatr Child Health* 1997;33(5):413-417.
20. Edwards KM, Decker MD. Combination vaccines consisting of acellular pertussis vaccines. *Pediatr Infect Dis J* 1997;16:S97-102.
21. Eskola J, Olander RM, Hovi T, Litmanen L, Kayhty H. Randomised trial of the effect of co-administration with acellular pertussis DTP vaccine on immunogenicity of *Haemophilus influenzae* type b conjugate vaccine. *Lancet* 1996;348:1688-1692.

Speakers

Professor James Cherry, Professor of Paediatrics and Chief, Paediatric Infectious Diseases, School of Medicine, University of California, Los Angeles, United States of America

Professor Ian Gust, Director of Research and Development, CSL Limited

Associate Professor Terry Nolan, Head, Clinical Epidemiology and Biostatistics Unit, Department of Paediatrics, University of Melbourne and the Royal Childrens Hospital, Melbourne, and Member of the Pertussis Working Party of the NHMRC

Professor Don Roberton, Head, Department of Paediatrics and Paediatric Immunology, University of Adelaide and Member of the Pertussis Working Party of the NHMRC

Dr Tim Heath, Research Fellow, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, The New Children's Hospital (Royal Alexandra Hospital for Children), Sydney

Ms Michelle Burke, Health Economist**,** SmithKline Beecham

Dr Suzanne Hill, Discipline of Clinical Pharmacology, Faculty of Medicine, University of Newcastle

Panel members

Professor Richard Doherty, Head, Department of Paediatrics, Monash University, Melbourne, and Chair of the Pertussis Working Party of the NHMRC

Associate Professor Terry Nolan, as above

Associate Professor David Isaacs, Head, Department of Immunology and Infectious Diseases, The New Children's Hospital (Royal Alexandra Hospital for Children), Sydney and Member of the Pertussis Working Party of the NHMRC

Dr John Carnie, Director, Communicable Diseases Section, Department of Human Services, Victoria and Member of the Pertussis Working Party of the NHMRC

Dr Cathy Mead, Head, National Centre for Disease Control, Commonwealth Department of Health and Family Services

Editorial note

Since the workshop, Commonwealth funding has been made available to all States and Territories for DTPa vaccine to be provided free for the booster doses at 18 months and 4-5 years of age and for primary course doses in infants who have had reactions to DTPw. The South Australian and Northern Territory Governments have made additional funds available to provide DTPa vaccine free for all primary course and booster doses for children who live in their jurisdictions.

The funding of vaccines is a complex issue and requires consideration of the context in which they are recommended for use. Where vaccines are recommended for limited use on the basis of individual medical need, it is appropriate that they be evaluated by the PBAC for funding under the PBS. Where vaccines have been recommended by the NHMRC for inclusion on the Standard Vaccination Schedule, funding through the PBS is not the most cost effective mechanism. Using PBAC processes for the evaluation of vaccines enables evidence-based decisions to be made in determining the funding of these vaccines through alternative mechanisms.

For a number of reasons, several alternative mechanisms have developed and vaccine funding currently occurs through three separate streams. To ensure that future vaccine funding arrangements are simpler and more transparent, the Commonwealth Government recently announced that, from the 1999-2000 financial year, all childhood vaccines will be funded through one stream under the Public Health Outcome Funding Agreements (http:www.health.gov.au/pubs/budget98/fact/hfact1.htm)**.** Also announced in the Budget was an increased threshold for Ministerial approval of essential vaccine funding. This will ensure that, as new vaccines become available through advances in vaccine technology, there will be timely provision of funds to purchase them.