

## **PUBLIC SUMMARY DOCUMENT**

**Product:** Diphtheria-tetanus-acellular pertussis (dTpa) vaccine, 0.5 mL in pre-filled syringe, Boostrix®

**Sponsor:** GlaxoSmithKline Australia Pty Ltd

**Date of PBAC Consideration:** July 2011

### **1. Purpose of Application**

The submission sought an extension of the National Immunisation Program (NIP) for dTpa (Boostrix®) to include active vaccination of both parents of newborn infants, at or around the time of birth of their child, known as a 'cocooning' strategy. It was proposed that parents would be eligible where there is no documented evidence of a dTpa booster having been given in the previous 10 years.

### **2. Background**

This vaccine had not been previously considered by the PBAC for this indication.

Boostrix brand of adolescent/adult (reduced antigen) formulation diphtheria-tetanus-acellular pertussis (dTpa) has been included on the NIP since January 2004. The current NIP indication for dTpa vaccine is for single-dose vaccination of a single age cohort between 15-17 years, according to State and Territory Health Department arrangements.

### **3. Registration Status**

dTpa (Boostrix) was TGA registered on 9 August 2000 for the indication:

- Booster vaccination against diphtheria, tetanus and pertussis of individuals aged ten years and older.

### **4. Listing Requested and PBAC's View**

The submission requested the NIP indication for dTpa be expanded to include both parents of newborn infants, at or around the time of birth of their child, where there is no documented evidence of a dTpa booster having been received in the previous ten years.

No catch up program was proposed.

*For PBAC's view, see Recommendation and Reasons.*

### **5. Clinical Place for the Proposed Therapy**

The submission proposed that the place in therapy of dTpa for the proposed indication is to:

- 1) reduce transmission of pertussis from parents to newborn infants who are too young to have been fully vaccinated against this disease under the infant NIP schedule;
- 2) directly reduce the burden of pertussis illness within the target group of parents; and
- 3) provide recipients of the vaccine with updated immunity against diphtheria and tetanus.

### **6. Comparator**

The submission nominated no parental dTpa vaccination as the main comparator, set against a background of current infant/childhood/adolescent DTPa/dTpa vaccination practice and routine medical management of pertussis disease. The PBAC considered the comparator of no parental dTpa vaccination reasonable.

The submission also presented a comparison of Boostrix to reduced antigen diphtheria and tetanus vaccine (ADT Booster<sup>®</sup>), in terms of protection against diphtheria and tetanus.

## 7. Clinical Trials

The submission and Australian Technical Advisory Group on Immunisation (ATAGI) advice acknowledged the absence of empiric data supporting the effectiveness of a cocooning strategy. Therefore, the submission presented the clinical evidence supporting the proposed dTpa vaccination strategy in two steps. The submission first presented data supporting the efficacy of the dTpa vaccine in preventing pertussis infection in adults. In the second step, the rate of pertussis transmission from infected parents to susceptible infants was then estimated.

To demonstrate the efficacy of the dTpa vaccine in preventing pertussis infection and disease in adults the submission performed an indirect comparison. A meta-analysis was presented of two randomised trials comparing the immunogenicity of the dTpa vaccine with a monovalent acellular pertussis (pa) vaccine only in adult patients to demonstrate equivalence of dTpa and pa vaccine (dTpa-002 and dTpa-003). The submission then presented results from the APERT randomised trial comparing the efficacy of a pa vaccine in preventing pertussis infection and disease compared to an inactive control.

The submission did not provide evidence from randomised controlled trials on the efficacy of dTpa vaccination on the transmission from an infected parent to a susceptible infant.

Details of the published trials presented in the submission are shown below.

<b>Trial ID / First author</b>	<b>Protocol title / Publication title</b>	<b>Publication citation</b>
<b>Common reference pa</b>		
<b>dTpa vaccine vs. pa and dT components</b>		
dTpa-002	Single-blind, randomised clinical study of the immunogenicity and reactogenicity of dTpa, pa vaccines and a dT vaccine in adults, aged ≥18 years.	
Turnbull et al.	A randomised trial of two acellular pertussis vaccines (dTpa and pa) and a licensed diphtheria-tetanus vaccine (dT) in adults.	<i>Vaccine</i> 2000; 19(2001):628-636
dTpa-003	Blinded, randomised, comparative clinical study of the immunogenicity, reactogenicity and safety of a single booster dose of dTpa and pa vaccines and licensed Td vaccine in adults aged ≥18 years.	
Van der Wielen et al.	A randomised controlled trial with a diphtheria-tetanus-acellular pertussis (dTpa) vaccine in adults.	<i>Vaccine</i> 2000; 18(2000):2075-2082
<b>No dTpa vaccine vs. pa only vaccine</b>		
APERT	Multicentre double blind, randomised trial comparing the efficacy of an acellular pertussis vaccine against a hepatitis A vaccine in preventing	

Le et al.	infection with pertussis. Immune responses and antibody decay after immunisation of adolescents and adults with an acellular pertussis vaccine: The APERT study.	<i>The Journal of Infectious Diseases</i> 2004; 190:535-544
Ward et al. (2005)	Efficacy of an acellular pertussis vaccine among adolescents and adults.	<i>The New England Journal of Medicine</i> 2005; 353(15):1555-1563
Ward et al. (2006)	Bordetella Pertussis infections in vaccinated and unvaccinated adolescents and adults, as assessed in a national prospective randomised acellular pertussis vaccine trial (APERT).	<i>Clinical Infectious Diseases</i> 2006; 43:151-157
<b>Additional Studies</b>		
dTpa-039	Observational study assessing seroconversion and safety of a decennial booster dose of dTpa.	
Booy et al.	A decennial booster dose of reduced antigen content diphtheria, tetanus, acellular pertussis vaccine (Boostrix) is immunogenic and well tolerated in adults.	<i>Vaccine</i> 2010;29(1):45-50
dTpa-040	Observational study assessing seroconversion and safety of a decennial booster dose of dTpa.	
Mertsola et al.	Decennial administration of a reduced antigen content diphtheria and tetanus toxoids and acellular pertussis vaccine in young adults.	<i>Clinical Infectious Diseases</i> 2010; 51(6):656-662

dTpa = diphtheria-tetanus-acellular pertussis; pa = acellular pertussis

## 8. Results of Trials

The PBAC considered the meta-analysis presented in the submission of trials dTpa-002 and dTpa-003 provided sufficient evidence of non-inferiority of dTpa vaccine compared with monovalent acellular pertussis (pa) vaccine in eliciting an immune response to the pertussis antigens pertussis toxin, filamentous haemagglutinin and pertactin in adults. Results of the trials dTpa-002 and dTpa-003 are shown in the tables below:

### Vaccine response to PT 30 days after vaccination

Study	dTpa			pa			Weight %	Risk Ratio [95% CI]
	n	N	%	n	N	%		
dTpa-002	400	427	93.7	92	99	92.9	59.0	1.01 (0.95, 1.07)
dTpa-003	89	95	93.7	87	92	94.6	41.0	0.99 (0.92, 1.06)
Total	489	522	93.7	179	191	93.7	100	1.00 (0.96, 1.05)
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.13, df = 1 (P = 0.71); I <sup>2</sup> = 0%								
Test for overall effect: Z = 0.04 (P = 0.97)								

PT = pertussis toxin; dTpa = diphtheria-tetanus-acellular pertussis; pa = acellular pertussis; n = number analysed; N = total number vaccinated

### Vaccine response to FHA 30 days after vaccination

Study	dTpa			pa			Weight %	Risk Ratio [95% CI]
	n	N	%	n	N	%		
dTpa-002	414	426	97.2	98	99	98.9	77.6	0.98 (0.96, 1.01)
dTpa-003	90	94	95.7	91	92	98.9	22.4	0.97 (0.92, 1.02)

Total	504	520	96.9	189	191	98.9	100	0.98 (0.96, 1.00)
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.29, do = 1 (P = 0.59); I <sup>2</sup> = 0%								
Test for overall effect: Z = 1.87 (P = 0.06)								

FHA = filamentous haemagglutinin; dTpa = diphtheria-tetanus-acellular pertussis; pa = acellular pertussis; n = number analysed; N = total number vaccinated

#### Vaccine response to PRN 30 days after vaccination

Study	dTpa			pa			Weight %	Risk Ratio [95% CI]
	n	N	%	n	N	%		
dTpa-002	420	427	98.4	97	100	97	57.3	1.01 (0.98, 1.05)
dTpa-003	93	95	97.9	90	92	97.8	42.7	1.00 (0.96, 1.04)
Total	513	522	98.3	187	192	97.4	100	1.01 (0.98, 1.04)
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 0.22, df = 1 (P = 0.64); I <sup>2</sup> = 0%								
Test for overall effect: Z = 0.59 (P = 0.56)								

PRN = pertactin; dTpa = diphtheria-tetanus-acellular pertussis; pa = acellular pertussis; n = number analysed; N = total number vaccinated

The table immediately below presents the pa vaccine efficacy in the APERT trial against the inactive control (in this case Hepatitis A Vaccine).

#### Pa vaccine efficacy - APERT trial

pertussis case definition	pa n	HAV n	Vaccine efficacy Unadjusted % (95%CI)	Vaccine efficacy Adjusted <sup>a</sup> % (95%CI)
N	1,391	1,390		
Person-years of follow-up	2,421	2,444		
Primary				
- Culture or PCR positive	0	5	100 (NC)	100 (NC)
- Positive culture, PCR & Serology (clinical case definition)	1	9	89 (19, 99)	92 (32, 99)
Secondary <sup>b</sup>	0	0	89 (19, 99)	92 (32, 99)
Tertiary <sup>c</sup>	4	10	60 (-40, 91)	67 (-9, 90)
Quaternary <sup>d</sup>	5	11	54 (-42, 88)	63 (-11, 87)
Post-hoc analysis				
Sub-clinical cases <sup>e</sup>	10	49	79 (60, 89)	NR
Calculated during evaluation <sup>f</sup>	9	40	78 (55, 89)	NC

PCR = polymerase-chain-reaction; HAV = hepatitis A vaccine; CI = confidence interval; NC = not calculable; NR = not reported; n = number; N = number of subjects vaccinated

<sup>a</sup> analyses were adjusted for duration of illness

<sup>b</sup> Cough lasting >5 days, negative culture and PCR assay, positive primary serologic criteria within 6 months before onset of illness.

<sup>c</sup> Cough lasting >5 days, negative culture and PCR assay, negative primary serologic criteria, positive to any pertussis antibody rise within 5-15 days after onset of illness.

<sup>d</sup> Cough lasting >5 days, negative culture and PCR assay, negative primary serologic criteria, positive to any pertussis antibody rise within 6 months before onset of illness.

<sup>e</sup> Defined at the number of subjects with any IgA or IgG pertussis toxin antibody rise between one month and 12 months after vaccination.

<sup>f</sup> Excluding cases already used in the vaccine efficacy against clinical cases

Vaccination with pa reduced the primary cases of pertussis compared to hepatitis A vaccination (HAV). Adjusted vaccine efficacy of 92% (95% CI: 32% to 99%) was calculated as 1 minus the relative risk using the primary case definition including the serologic criteria. Vaccine efficacy calculations were based on the detection of ten primary pertussis cases in a clinical trial.

The meta-analyses of specific antibody responses to the vaccine were appropriate.

Using data from a later publication based on the APERT trial (Ward, Cherry et al 2006) the submission conducted a post-hoc analysis to estimate the vaccine's efficacy in preventing infection with pertussis (as opposed to pertussis illness calculated above) identified with serologic criteria. Ten cases in the vaccinated group and 49 cases in the unvaccinated group were identified, producing a vaccine efficacy of 79.5% (95% CI: 60.2% to 89.4%). In its advice, ATAGI made no reference to the efficacy of the vaccine in preventing subclinical infection.

Although the PBAC considered that the evidence presented in the submission demonstrated that dTpa causes a rise in antibody titre and the vaccine reduces symptomatic pertussis in adults, the key source of uncertainty was to what extent a reduction in symptomatic pertussis in the parents of newborns leads to a reduction in pertussis in infants. The submission did not provide clinical evidence on the relationship between vaccine efficacy in adults and transmissibility to infants and did not provide data to show to what extent subclinical pertussis infection in a parent is transmissible to infants (or others). In addition, no data had been presented on whether duration of illness affects transmission to susceptible infants.

The PBAC considered there were a number of sources of uncertainty in the assumptions made in the submission in deriving a transmission propensity of pertussis infection from adults to infants. The PBAC considered that the assumption that subclinical infection is 90 % as infectious as clinical infection is implausible. The PBAC considered that the pertussis case fatality rate estimation used in the submission of 1.8 % of severe hospitalised pertussis cases in infants less than three months of age derived from US Centres for Disease Control and Prevention (CDC) data is an overestimation of the incidence in Australia, even when taking into account under-reporting. The PBAC also considered the duration of dTpa vaccine efficacy to be uncertain.

dTpa vaccination was frequently associated with mild injection site reactions such as pain, redness and swelling and general reactions such as headache and fever. Serious adverse events were generally rare and their relationship to vaccination was uncertain. Findings from the additional studies supplied did not provide further cause for concern with dTpa vaccine safety. Although adverse events were common, they were mild, and these were most frequent in vaccines containing the diphtheria-tetanus toxoids. The dTpa vaccine was associated with a higher rate of adverse events than the monovalent pa vaccine. The dT component of the vaccine was the suspected cause of the more frequent adverse events.

## **9. Clinical Claim**

Step one – efficacy of vaccination in adults

The submission described the dTpa vaccine as superior in terms of comparative effectiveness and inferior in terms of comparative safety over no vaccine in preventing pertussis in adults. The submission used the vaccine efficacy estimate from the APERT trial in the modelled economic evaluation.

Step two – transmission from infected parent to susceptible infants

The submission did not provide clinical evidence on the comparative efficacy in preventing pertussis in susceptible infants when the vaccine is provided to parents shortly after birth.

The PBAC considered the evidence presented in the submission supported the claim of superior comparative effectiveness and inferior safety of dTpa vaccine to no vaccine in adults.

However, the PBAC considered the clinical effectiveness of the intent of the requested program to reduce the transmission of pertussis from parents to infants was uncertain as no evidence was presented on the relationship between vaccine efficacy in adults and transmission to infants.

## **10. Economic Analysis**

A modelled economic evaluation was presented through a cost utility analysis. The PBAC noted the model assumed that only one child is born every five years. The PBAC considered it is likely that one or more additional children are likely to be born in the five year time horizon of the model in a significant number of households and hence that the model was not entirely representative of the population for whom PBS listing was sought.

The model compared the vaccination of both parents with the dTpa vaccine at or around the time of the birth of their child with no parental dTpa vaccination. Current infant DTPa vaccination and usual clinical practice for the treatment of pertussis disease formed a common background to both strategies.

The model was a discrete event simulation model and was described by the submission as a “linked unit” model. The model simulated 500,000 hypothetical family units consisting of a mother, father and newborn infant. Family units were linked at an individual level, with the probability of infection and disease for each infant at any point in time dependent on its age and the disease status of the parents. Parents entered the model as either receiving the vaccine (with adverse event disutility) or not in cycle zero. They then faced a monthly risk of acquiring pertussis infection (clinical or subclinical) for the five year duration of the model. Parents and infants could only be infected once in the model. Infants either experienced mild, moderate or severe pertussis, with case fatality a risk only in severe cases. Counts of resource items used, their associated costs and quality of life were recorded on a monthly basis for both parents and infants. Vaccine costs were the most significant cost driver in the model, and infant morbidity and mortality in the first three months of life contributed most to QALY gains in the model. The model also assumed no replacement of parental transmission risk (i.e. infection from external sources), which was not reasonable.

The main differences between the two arms of the evaluation were the vaccine related costs and adverse events, and the associated reduction in pertussis incidence (clinical and subclinical) in adults. The magnitude of this reduction in incidence (a function of starting incidence estimates and vaccine efficacy at reducing incidence) were the main drivers of the model.

The table below presents the number of parents needed to be vaccinated to prevent a single case of pertussis in parents and infants.

**Numbers of parents needed to treat to prevent pertussis illness and infant death**

NNT	Parents		Infants			
	Clinical	sub-clinical	Mild	Moderate	Severe	Death
Base case <sup>a</sup>	60	25	372	204	596	83,333
Re-specified base case <sup>a</sup>	112	47	1,129	621	1,804	262,388

Source: Calculated using estimates from the economic model.

<sup>a</sup> Assumes equal vaccination coverage of mothers and fathers

Using the assumptions from the submission the number of parents needed to treat to prevent one infant death was 83,333, compared to 262,388 in the re-specified base case where lower incidence rates were assumed.

The submission claimed the strategy costs between \$45,000 and \$75,000 per additional QALY gained, with this value being the median of ten sets of model simulations to demonstrate the stability of the model results. This was subject to uncertainty as a result of inappropriate parameter estimates and model instability.

During the evaluation, 50 simulations were performed and the median ICER from these simulations was between \$45,000 and \$75,000/QALY. Half of the simulation results generated an ICER over \$50,000/QALY (compared to 10% of submission presented simulations). Results ranged from a value in the range of \$15,000 - \$45,000/QALY to a value in the range of \$75,000 - \$105,000/QALY. The variation in outcomes was driven primarily by the occurrence or absence of case fatalities in infants.

During the evaluation, a number of parameters were tested in sensitivity analyses. The model was most sensitive to estimates of vaccine efficacy, incidence of pertussis in adults, transmission propensity from parents to infants and infant case fatality rate. The ICER was lower when the vaccine was given only to mothers (\$15,000 - \$45,000/QALY using the submission's base case, however using the evaluation's respecified base case, the 'mothers only' strategy remained unlikely to be cost-effective \$105,000 - \$200,000/QALY).

The PBAC considered the assumption in the submission, that there would be no cost involved with dTpa vaccine administration to mothers and for 70% of fathers, was an underestimation, considering that there may be a cost involved with administration of vaccination in some hospitals and that the proportion of administration of dTpa vaccine in the general practitioner setting is likely to be higher, especially for fathers.

Based on further advice provided by ATAGI to PBAC, key model parameters were modified and new ICERs calculated.

The reduction in the childhood incidence of pertussis resulted in a drop in the number of childhood deaths due to pertussis predicted by the model. However, the rate of hospitalisations still exceeded the recommended rate from ATAGI of 16 per 100,000 in children aged 1-4. Adjustments were made to reduce the number of severe cases to the rate recommended by ATAGI while also maintaining the suggested number of fatalities (4.5 per year in the Australian population) with the new case fatality rates.

Applying revised proportions of disease severity in children produced an incidence of severe hospitalised pertussis in children aged <12 months of 160 per 100,000 and 16 per

100,000 in children aged 1-4, with overall incidence in children aged 0-4 of approximately 50 cases per 100,000. These rates also resulted in a fatality rate of around 4.5 deaths per year. Over 10 iterations, the median ICER was in the range of \$105,000 - \$200,000 per QALY gained, which corresponded to incremental QALYs of 197.

The ratio for the ‘mothers only’ strategy was substantially lower than for vaccination of both parents because the reduction in costs associated with vaccination of fathers outweighed the loss of clinical benefit:

- Vaccine administration costs for fathers (in addition to the cost of the vaccine) constituted a significant proportion of costs in the model;
- Vaccine related adverse events for the father were avoided; and
- The numbers of pertussis cases in infants aged 0-4 increased from 220 per 100,000 to 290 per 100,000 when excluding fathers from the vaccination strategy. This compared to the no-vaccine base case of around 400 per 100,000.

Given the model’s complexity and based on the parameter values suggested by ATAGI, a simplified approach was adopted during the evaluation in estimating cost-effectiveness of the proposed “cocooning” strategy using the following assumptions, noting that these were still considered to favour the vaccine:

- Infant pertussis incidence (based on ATAGI feedback): 375/100,000;
- Infant pertussis mortality (based on ATAGI feedback): 1.5/100,000;
- Cases due to parental infection (based on submission): 55%;
- Vaccine efficacy (based on submission): 92%;
- Cost per immunisation (both parents, ignoring administration, AEs and pertussis treatment costs);
- QALY loss per non-fatal case (based on submission); and
- QALY loss per fatal case (based on submission)

The cost per QALY gained was in the range of greater than \$200,000.

*For PBAC’s view, see Recommendations and Reasons.*

## **11. Estimated PBS Usage and Financial Implications**

The submission estimated a total net cost to the NIP of less than \$10 million in year 5.

The submission included a cost offset of 300,000 fewer doses of the vaccine delivered by State and Territory governments if the cocooning strategy is funded through the NIP rather than through State and Territory vaccination programs.

## **12. Recommendation and Reasons**

The PBAC considered the comparator of no parental dTpa vaccination reasonable.

The PBAC considered the meta-analysis presented in the submission of trials dTpa-002 and dTpa-003 provided sufficient evidence of non-inferiority of dTpa vaccine compared with monovalent acellular pertussis (pa) vaccine in eliciting an immune response to the pertussis antigens pertussis toxin, filamentous haemagglutinin and pertactin in adults. The submission then presented the results of the APERT trial as evidence of the efficacy of pa vaccine in preventing pertussis infection and disease compared to hepatitis A vaccine as the inactive control. The PBAC considered the evidence presented in the

submission supported the claim of superior comparative effectiveness and inferior safety of dTpa vaccine to no vaccine in adults.

However, the PBAC considered the clinical effectiveness of the intent of the requested program to reduce the transmission of pertussis from parents to infants was uncertain as no evidence was presented on the relationship between vaccine efficacy in adults and transmission to infants.

The PBAC considered there were a number of sources of uncertainty in the assumptions made in the submission in deriving a transmission propensity of pertussis infection from adults to infants. The PBAC considered that the assumption that subclinical infection is 90 % as infectious as clinical infection to be implausible. The PBAC considered that the pertussis case fatality rate estimation used in the submission of 1.8 % of severe hospitalised pertussis cases in infants less than three months of age derived from US Centres for Disease Control and Prevention (CDC) data to be an overestimation of incidence in Australia, even when taking into account under-reporting. The PBAC also considered the duration of dTpa vaccine efficacy to be uncertain.

The PBAC considered the assumption in the submission that there would be no cost involved with dTpa vaccine administration to mothers and for 70 % of fathers an underestimation, considering that there may be a cost involved with administration of vaccination in some hospitals and that the proportion of administration of dTpa vaccine in the general practitioner setting is likely to be higher, especially for fathers.

The submission presented a cost utility analysis. The PBAC noted the model assumed that only one child is born every five years. The PBAC considered it is likely that one or more additional children are likely to be born in the five year time horizon of the model in a significant number of households and hence that the model is not entirely representative of the population for whom PBS listing was sought.

The PBAC noted that the results of the economic evaluation were highly variable, with the base case incremental cost effectiveness ratio ranging from a value in between \$15,000 - \$45,000 per QALY to a value in between \$75,000 - \$105,000 per QALY when simulations of the model were performed during the evaluation. The PBAC hence considered the submission's base case of a value in between \$45,000 - \$75,000 per QALY to be highly uncertain. The PBAC noted that the cost per QALY gained, using parameter values based on the advice of the ATAGI was greater than \$200,000. The PBAC also noted that the number of infant deaths is the largest contributor to QALY gains in the model and that even when the incidence of pertussis in children is set to the upper limit of the range suggested by the ATAGI (of 500 per 100,000) the ICER using this re-specified base case is greater than \$100,000 per QALY gained.

The PBAC hence rejected the submission on the basis of uncertain clinical effectiveness and high and highly uncertain cost effectiveness.

***Recommendation:***

**Reject**

**13. Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**14. Sponsor's Comment**

The sponsor has no comment.