

6.6 DIPHTHERIA + TETANUS + ACELLULAR PERTUSSIS (DTPa) VACCINE Infanrix®; GlaxoSmithKline Australia Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested National Immunisation Program (NIP) schedule listing for the combined diphtheria, tetanus and acellular pertussis (DTPa) vaccine at approximately 18 months for the prevention of pertussis.

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
DTPa VACCINE Suspension for injection 0.5 mL glass injection vials or refilled glass injection syringes	1	0	INFANRIX	GlaxoSmithKline
NIP listing Booster dose for infants aged approximately 18 months.				

- 2.1 The listing was requested on the basis that the 18-month DTPa booster was cost-effective compared with the current situation where no 18-month DTPa booster is available.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 DTPa was approved by the TGA in 1996. Until 2003, the treatment schedule for DTPa included a booster dose at approximately 18 months. In 2003, with the introduction of the booster dose for adolescents (15-17 years), the 18-month booster dose was removed. The submission indicates that it voluntarily updated the Australian Product Information (PI) to exclude the 18-month dose to avoid confusion by prescribers. The submission states that it intends to update the PI, and it does not anticipate any delays as a result of the update of the PI.
- 3.2 The Australian Technical Advisory Group on Immunisation (ATAGI) provided pre-PBAC submission and post-PBAC submission advice which indicated that it endorses the re-instatement of a booster dose of DTPa vaccine onto the NIP schedule. ATAGI expects that inclusion of the booster at the 18-month point with the measles, mumps, rubella, and varicella (MMRV) vaccine should be readily implementable.
- 3.3 The DTPa 18-month booster dose was not previously considered by the PBAC.

For more detail on PBAC's view, see section 7 "PBAC outcome"

4 Clinical place for the proposed therapy

- 4.1 Pertussis is a highly infectious disease of the upper respiratory tract, caused by the bacterial organism *Bordetella pertussis*. Currently, there are 5 scheduled childhood doses of pertussis vaccine. The first three occur in infancy at 6 weeks to 2 months, 4 months, and 6 months. Two “booster” shots are given at 4 years (or earlier at 3.5 years) and 15 years.
- 4.2 The submission proposed an additional booster of pertussis vaccine at 18 months. The schedule would otherwise be unaltered.
- 4.3 The ESC noted that ATAGI is of the opinion that consideration of the introduction of a DTPa booster dose at 18 months onto the NIP is necessary from a public health perspective, as an additional measure to improve control of pertussis in Australia. ATAGI noted that while pertussis does not cause severe disease in the majority of the targeted age group (18 months to 4 years of age), this cohort has an important role in overall disease transmission, in particular to vulnerable young infants.
- 4.4 The Australian Immunisation Handbook (10th Edition 2013) (the Handbook) makes the following recommendations about the 18-month booster: “Parents who wish to minimise the likelihood of their child developing pertussis in the 2nd and 3rd years of life (prior to when the booster dose is due at 4 years of age) should be advised that an additional dose of pertussis-containing vaccine can be given in the 2nd year of life (e.g. at 18 months of age). This should also be considered when the child’s mother received a DTPa vaccine during pregnancy, because of the potential for lesser antibody responses following the 3rd infant pertussis dose at 6 months of age. It should be noted that a dose at this age is associated with an increased likelihood of a local adverse event, including extensive limb swelling, in a small percentage of children. DTPa (without other antigens) is currently unavailable in Australia; if an additional dose of a pertussis-containing vaccine is given in the 2nd year of life, any brand of DTPa-IPV may be used. Under these circumstances, the next dose of a DTPa-containing vaccine should not be given until 4 years of age. The additional dose in the 2nd year of life is not included on the NIP schedule.”

For more detail on PBAC’s view, see section 7 “PBAC outcome”

5 Comparator

- 5.1 No booster at 18 months, i.e. current vaccination schedule. This consists of a primary series of vaccine shots at 2, 4 and 6 months, followed by booster doses at 4 and 15 years. The ESC considered this to be the appropriate comparator.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

6 Consideration of the evidence

Sponsor hearing

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6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on seven vaccine effectiveness studies and six trials investigating seroresponse.

6.4 Details of the trials presented in the submission are provided in the following table.

Trials and associated reports presented in the submission

Trial ID	Protocol title/Publication title	Publication citation
Vaccine effectiveness		
Key evidence		
Quinn 2014	Quinn HE, Snelling TL, Macartney KK, et al. Duration of protection after first dose of acellular pertussis vaccine in infants.	Pediatrics 2014; 133: e513-e519
Quinn (2011)	Quinn HE, and McIntyre P. Pertussis vaccine effectiveness in Australia.	NCIRS PowerPoint presentation. August 26, 2011.
Supportive evidence		
Sheridan (2014)	Sheridan SL, McCall B, Davis CA, et al. Acellular pertussis vaccine effectiveness for children during the 2009-2010 pertussis epidemic in Queensland.	MJA; 2014; 6: 334-338.
Rendi-Wagner (2006)	Rendi-Wagner P, Kundi M, Mikolasek A, et al. Hospital-based active surveillance of childhood pertussis in Austria from 1996 to 2003: Estimates of incidence and vaccine effectiveness of whole-cell and acellular vaccine.	Vaccine 2006; 24: 5960-5965.
Bisgard (2005)	Bisgard KM, Rhodes P, Connelly BL, et al. Pertussis vaccine effectiveness among children 6 to 59 months of age in the United States, 1998-2001.	Pediatrics 2005; 116(2): e285-e294.
Lugauer (2002)	Lugauer S, Heininger U, Cherry JD, et al. Long-term clinical effectiveness of an acellular pertussis component vaccine and a whole cell pertussis component vaccine.	Eur J Pediatr 2012; 161: 142-146.
De Serres (2001)	De Serres G, Shadmani R, Boulianne N, et al. Effectiveness of a single dose of acellular pertussis vaccine to prevent pertussis in children primed with pertussis whole cell vaccine.	Vaccine 2011; 19: 3004-3008.
Randomised trials on seroresponse		
Wood (2012)	Wood N, Marshall H, McIntyre P. Waning of pertussis antibodies to 4 years among infants who did and did not receive monovalent acellular pertussis vaccine at birth.	NCIRS. 2012
Nolan (2009)	Nolan T, Ruff TA, Lambert SB, et al. Booster vaccination of toddlers with reduced antigen content diphtheria-tetanus-acellular pertussis vaccine.	Vaccine; 2009; 27: 2410-2413.
213503/046,	Open, randomised phase IIIb, clinical trial to compare the immunogenicity and reactogenicity of GSK Biologicals' DTaP-IP V vaccine (INFANRIX®-IPV), with GSK Biologicals' DTaP (INFANRIX®) and Aventis Pasteur MSD's IPV vaccine (IPOL®) administered separately to healthy children 4 to 6 years of age, previously vaccinated with 4 doses of DTaP and polio vaccine, and coadministered with GSK Biologicals' MMR vaccine (PRIORIX™).	GSK. Study 213503/046 (DTaP-IPV-046). 2009.
Marshall (2006)	Marshall H, Nolan T, Robertson D, et al. A comparison of booster immunisation with a combination DTPa-IPV vaccine or DTPa plus IPV in separate injections when co-administered with MMR, at age 4-6 years.	Vaccine; 2006; 24: 6120-6128.

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Trial ID	Protocol title/Publication title	Publication citation
APV-015B	An open randomized study to evaluate the immunogenicity and reactogenicity of two SmithKline Beecham Biologicals' combined diphtheria, tetanus, acellular pertussis vaccines : a bicomponent (PT 25 µg + FHA 25 µg) and a tricomponent (PT 25 µg + FHA 25 µg + 69 kDa 8 µg), following administration as a booster dose in healthy 15 to 19 months old children previously primed with the same type of vaccine at 3, 4 and 5 months of age.	SmithKline Beecham Biologicals. Synopsis of Study Report APV-015B. 1995.
APV-020B	N/A	SmithKline Beecham Biologicals. Final Study Report APV-020B. 1995.
APV-027B	N/A	SmithKline Beecham Biologicals. Final Study Report APV-027B. 1995.

Source: Table B.4, ppB-26 to B-28 of the submission, N/A = not available

- 6.5 The key features of the vaccine effectiveness studies are summarised in the following table.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Key evidence						
Quinn (2014)	N/A	Case control, Retro Australia 2005-2009	Unclear	No booster DTPa	VE	Used for 'No Booster' arm
Quinn (2011)	N/A	Cross-sectional, Retro Australia 2001-2009	High	18 m Booster, DTPa/w ^a No Booster DTPa	VE	Used for '18 m booster' arm
Supportive evidence						
Lugauer 2012	N/A	Cohort study, Pros Germany 1991-2000	Unclear	15 m booster DTPw 15 m booster DTPa	VE post injection (up to 9 year)	Not used
Rendi-Wagner (2006)	N/A	Cohort study, Pros Austria 1996-2003	Unclear	Yr 2 booster DTPw Yr 2 booster DTPa	VE	Not used
Sheridan (2014)	N/A	Cohort study, Retro Australia, 1999-2010	Unclear	No booster DTPa 18 m Booster DTPa	VE in 2009 ^b	Not used
Bigard (2005)	N/A	Case control, Retro, USA, 1998-2001	Unclear	18-m Booster DTPa	VE for different age categories	Not used
De Serres (2001)	N/A	Case control, Retro, Canada, 1995-1997	Unclear	18 m booster DTPa ^c 18 m booster DTPw	VE after each vaccination	Not used

Source: Table B.4, pp B-26 of the submission

^a Include some patients who received whole cell pertussis vaccine

^b Follow up for children in 18-month booster cohort was 7-12 years, while for the no booster was 1-8 years

^c The primary schedule contained whole cell pertussis vaccine

VE = vaccine effectiveness; Retro = retrospective; Pros = prospective; DTPa = diphtheria, tetanus and acellular pertussis, DTPw = diphtheria, tetanus and whole cell pertussis; m = month

- 6.6 The submission relied on the key evidence from Quinn (2014) and Quinn (2011) for the vaccine effectiveness of the 18-month booster vaccination. Quinn (2014) does not present the vaccine effectiveness of the 18-month booster; rather it presents a case control study on the vaccine effectiveness in Australia when no 18-month booster is available. The submission relied on Quinn (2011) for the effectiveness of

the 18-month booster. Quinn (2011) is a PowerPoint presentation with limited data available, but it appears to be a cross-sectional study. A proportion of the patients received whole cell pertussis vaccine for either the primary vaccination (2, 4, and 6 months) or 18-month booster vaccination.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Comparative effectiveness

- 6.7 The following table presents the vaccine effectiveness results from Quinn (2011) and Quinn (2014).

Vaccines effectiveness by age from the key clinical evidence

VE (95% CI)	Quinn 2011		Quinn 2014
	Cross-sectional		Case control
	18-month booster	No booster	No booster
1 year	NR	NR	79.2% (75.0, 82.8)
2 year	88% (81.6, 92.1)	78% (73.0, 81.6)	70.7% (64.5, 75.8)
3 year	89% (85.0, 92.1)	72% (66.4, 76.7)	59.2% (51.0, 66.0)
4 year	87% (82.0, 91.2)	86% (82.9, 88.2)	NR

Source: Table B.17 and B.18, ppB-48 to B-49 of the submission

VE = vaccine effectiveness; CI = confidence interval; NR = not reported; **bold** = values used in the economic model

- 6.8 Quinn (2014) reported vaccine effectiveness without the 18-month booster dose. Quinn (2014) notes a reduction in vaccine effectiveness from 1 to 3 years; however, hospitalisation cases for the target population (2-3 year) were not reported. Quinn (2014) does not provide effectiveness of the 18-month booster, and therefore could be seen as providing evidence for the comparator arm only.
- 6.9 Given the limited information available from Quinn (2011), the methodology by which vaccine effectiveness was calculated has not been made clear, and the reporting of the results is minimal to verify whether the vaccine effectiveness values are reasonable. While Quinn (2011) did not provide statistical analyses to compare the vaccine effectiveness with and without booster, the point estimates at 2 and 3 years differ, with no overlapping 95% confidence intervals. This suggests that the 18-month booster may improve vaccine effectiveness. Quinn (2011) reported that DTPw (including whole cell pertussis) may be more effective against pertussis than DTPa. DTPw was substituted for DTPa for all five schedule doses in 1999, near the time the 18-month booster was removed (2003). This represents a possible confounding variable for the key comparison from Quinn (2011). Vaccine effectiveness for children who received an 18-month booster that included DTPw was higher than when children only received DTPa (acellular pertussis), with vaccine effectiveness of 91% (95% CI: 85.23 to 94.1) compared to 87% (95% CI: 83.8 to 89.6), respectively. However, it is unclear at what time point the vaccine effectiveness was measured.
- 6.10 The ESC accepted that rates of pertussis infection had increased and noted the clinical need for the ‘18-month booster’ but considered that the vaccine effectiveness of the ‘18-month booster’ compared with ‘no booster’ was difficult to quantify due, in part, to the following reasons:
- Increasing notifications of pertussis coincided with the introduction of the more sensitive Polymerase Chain Reaction (PCR) diagnostic test.

- Increasing hospitalisation rates due to pertussis infection mirrors notification rates.
- Under reporting of cases is likely to be significant.
- Delay in infectious patients seeking medical attention.
- The vaccine effectiveness for ‘no booster’ is derived from a case-control study (Quinn 2014). The vaccine effectiveness for ‘no booster’ from the cross-sectional data from Quinn (2011) demonstrated higher effectiveness than that presented in Quinn (2014). Using the vaccine effectiveness for ‘no booster’ from Quinn (2014) may overestimate the vaccine effectiveness of ‘18-month booster’ compared to ‘no booster’.
- The ATAGI post-submission advice noted that while pertussis does not cause severe disease in the majority of the targeted age group (18 months to 4 years of age), this cohort has an important role in overall disease transmission, in particular to vulnerable young infants.

6.11 The Pre-Sub-Committee Response (PSCR) argues that the vaccine effectiveness for the ‘no booster’ scenario sourced from Quinn (2014) is the best available evidence. The response notes that Quinn (2014) is referenced in the ATAGI pre-submission advice as the primary reference for the vaccine effectiveness and associated waning of the current Australian DTPa schedule and that the model is relatively insensitive to this assumption in any case. The ESC considered that while Quinn (2014) may be the primary reference for vaccine effectiveness and associated waning, it would have been preferable to use comparable data from the same study.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Comparative harms

6.12 The vaccine effectiveness studies did not report adverse events. Localised adverse events associated with the DTPa booster included pain, redness, and swelling. Systemic reactions included fever, drowsiness, fussiness or irritability, loss of appetite, related rash, and respiratory tract infection. The Handbook notes that these reactions may be more likely with an 18-month booster compared to the primary course.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Benefits/harms

6.13 A summary of the comparative benefits and harms for 18-month DTPa booster vaccination and the no booster scenarios is presented in the following tables. The data were extracted during evaluation from the revised economic model. The submission did not include any discussion of changes in local adverse events following the 4 year preschool DTPa booster if an 18 month booster is reintroduced.

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Summary of comparative benefits (pertussis cases) for 18 months DTPa booster vs. no booster for the whole Australian population (23,129,218) – derived from the revised base-case (ESC) economic model

Pertussis cases	18 m booster	No booster	RR (95% CI)	Event rate/100,000 patients/year		RD (95% CI)	NNT (95% CI)
				18-m booster	No booster		
Non-notified	606,423	667,082	0.91 (0.91, 0.91)	2,622	2,884	-0.26% (-0.27, -0.25)	381 (368, 396)
Notified	3,586	5,243	0.68 (0.66, 0.71)	15.5	22.7	-0.007% (-0.008, -0.006)	13,958 (12,563, 15,704)
Hospitalised	273	355	0.77 (0.66, 0.90)	1.2	1.5	-0.000 (-0.001, -0.000)	282,064 (176,367, 704,225)

Source: Compiled during the evaluation using the outputs from the economic model, using the consistent inclusion of pertussis cases.

RD = risk difference; RR = relative risk; CI = confidence interval; NNT = number needed to treat.

Summary of comparative harms for 18 months DTPa booster vs. no booster for the 18-month infant population (307,934) – derived from the revised base-case (ESC) economic model

Adverse events	18 m booster	No booster	RR (95% CI)	Event rate/100,000 patients/year		RD (95% CI)	NNT (95% CI)
				18-m booster	No booster		
Local reaction	15,335	0	NC	4,980	0	4.98% (4.9, 5.06)	20.1 (19.8, 20.4)
Systemic reaction	15,335	0	NC	4,980	0	4.98% (4.9, 5.06)	20.1 (19.8, 20.4)

Source: Compiled during the evaluation using the outputs from the economic model, using the consistent inclusion of pertussis cases.

RD = risk difference; RR = relative risk; CI = confidence interval; NNT = number needed to treat; NC = not calculable.

6.14 On the basis of a dynamic transmission model, which uses the whole Australian population, for every 100,000 persons vaccinated, if the 18-month DTPa booster vaccination is included in the immunisation schedule in comparison to ‘no booster’ (the current schedule) per year:

- Approximately 262 fewer persons would have a non-notified case of pertussis.
- Approximately 7 fewer persons would have a notified case of pertussis.
- Approximately 0.4 fewer persons would be hospitalised due to pertussis.
- Approximately 4,980 additional 18-month old infants would have a local reaction due to vaccination.

Clinical claim

6.15 The submission described the 18-month DTPa booster as superior in terms of comparative effectiveness and inferior in terms of comparative safety over the status quo of care.

6.16 The PBAC considered that the claim of superior comparative effectiveness was reasonable, though agreed with the ESC that the extent of the comparative effectiveness was unclear.

6.17 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

6.18 The economic evaluation is a cost-utility analysis. The submission presented the model in two parts. The first was a compartmental transmission model using Matlab, and the second was a static decision tree model using Excel. The former describes the evolution of the disease, while the latter calculates the effects of the infection on individuals and the health care system. A dynamic transmission model was used to estimate the evolution of the disease in both the ‘no booster’ and ‘18-month booster’ scenarios. The model then assigned reporting and hospitalisation rates to each age category, after which costs and QALYs are calculated. It should be noted the submission did not calculate absolute QALYs, but rather the QALY loss for non-notified and notified pertussis cases, hospitalisation due to pertussis, and adverse events due to vaccination.

Summary of model structure and rationale

Component	Summary
Time horizon	100 years in the model
Outcomes	QALYs
Methods used to generate results	A dynamic transmission model to estimate the discounted number of symptomatic cases over 100 year of pertussis and the percentage of these cases who would be notified. These values are then incorporated in an economic model.
Health states	<p>11 health states:</p> <ul style="list-style-type: none"> • Protected by maternal antibodies (available to a fraction of newborns) • Primary susceptible (never exposed to pertussis infection, never vaccinated, never born with maternal antibodies, or have had maternal protection wane) • Primary infection (infected with pertussis while primary susceptible) • Full protection (immune after being infected naturally, not by vaccine) • Partial protection (immunity has waned from Full protection, vulnerable only to asymptomatic infection) • Recidive susceptible (susceptible again after being exposed to pertussis either by previous infection, or vaccination, and having immunity wane) • Recidive infection (infected with pertussis while recidive susceptible) • Full protection after vaccination (immune after being vaccinated by primary vaccine) • Partial protection after vaccination (immunity has waned from Full protection after vaccination, vulnerable only to asymptomatic infection) • Asymptomatic infection (No utility loss, no cost, but symptomatic disease is transmissible to others) • Partial protection after booster vaccination (vulnerable only to asymptomatic infection)
Cycle length	1 year
Rates of change	<ul style="list-style-type: none"> • Recovery rates from infected health states were taken from De Vries (2010) • Waning of immunity after natural infection, maternal protection, or primary vaccination was taken from De Vries (2010) • Waning of partial immunity after primary vaccination was taken from Quinn (2014) • Waning of partial immunity after booster vaccination was taken from Klein (2012) • Force of infection (tendency for susceptible people to become infected) was determined from model calibration of infectiousness parameters informed by de Vries (2010), Mossong (2008), and Campbell (2012).

Source: compiled during the evaluation

6.19 The following table provides the key drivers of the dynamic transmission model.

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Key drivers of the model

Description	Method/Value	Impact
Utility loss for cases	<ul style="list-style-type: none"> Least conservative, most uncertain utility values used to represent pertussis effects Asymptomatic non-notified cases incurred no disutility 50% disutility loss for symptomatic non-notified cases compared to notified cases 	High
Contact matrix	Set of numbers indicating rate of social contact between different age groups	Cannot be tested, but likely to be high
Model structure (consistent vs. inconsistent inclusion of cases)	The submission uses a different approach to include the cases	Low
Cohort size	Base case is whole population	High
Efficacy in no booster arm	Based on Quinn (2014)	Cannot be tested, but likely to be medium to high
Calibration method to determine infectiousness	Based on Campbell (2012), and contact matrix	Cannot be tested, but likely to be medium to high

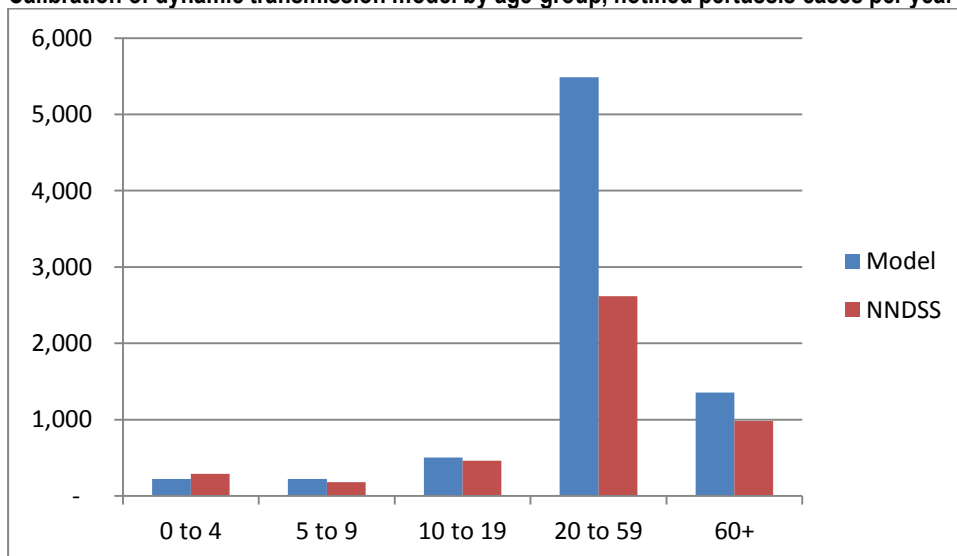
Source: compiled during the evaluation

- 6.20 The ICER is sensitive to the utility decrements applied to unreported cases. The number of unreported cases is calibrated to seroprevalence data, for which source documents imply that only 20 to 25% are symptomatic.
- 6.21 For symptomatic non-notified cases, the submission applies a disutility which is 50% of the notified cases (e.g. for 1-3 year old children with notified pertussis a disutility of 0.28 is applied for 62 days vs. 0.14 for non-notified pertussis cases). This assumption is not supported by the literature and has a large impact on the cost-effectiveness. The PSCR argued that it would be inappropriate to apply a utility decrement of 0% compared with notified cases and that the submission conservatively assumes that non-notified symptomatic cases incur no costs. The ESC agreed that applying a utility decrement of zero to symptomatic non-notified would be inappropriate (as non-notified symptomatic pertussis cases may have some disutility) and that the costs associated with non-notified symptomatic cases were underestimated in the model. That said, the specific assumption of a 50% utility reduction (compared to reported cases) is not supported by evidence from the literature. The pre-PBAC response reiterated that the submission assumes that non-notified symptomatic cases incur no cost and 50% less disutility than notified cases and noted that the published analyses of pertussis vaccination have adopted a higher utility decrement for non-notified symptomatic cases than that utilised in the submission.
- 6.22 The model assumes that 100% of primary and recidive cases during the first year are reported, falling to 2% for primary and 0% for recidive cases after the first birthday (and rising to 100% again at greater than 65 years of age). The ESC noted the biological implausibility of this assumption and the implication that the model is unable to replicate the observed epidemiology of disease by age. ATAGI noted in its post-submission advice (p6) that this “inability of the model to replicate the observed epidemiology of disease by age means that herd effects during the first year of life cannot be estimated with confidence and will underestimate the impact of toddler vaccination on infants”.
- 6.23 The contact matrix describing the degree of social interaction between people of different ages is an important part of the model. The data used was based on

average daily interactions between random volunteers, which may not provide an accurate picture for people ill with pertussis. This is especially true for school aged children, who are likely to stay home from school, thereby limiting their interactions with peers. The PSCR (p3) argued that the “use of the Mossong (2008) United Kingdom general population contact matrix is considered appropriate. The pathogenesis and World Health Organisation (WHO) recommended diagnosis of pertussis (requires a minimum of 21 days of paroxysmal cough) is such that a patient is unlikely to be diagnosed until post the most infectious period (Catarrhal phase). Therefore patients are likely to behave as per the general population during the infectious period (Kerr, 2000).” The ESC agreed that diagnosis of pertussis usually follows the end of the most infectious period while noting that contacts would likely be reduced from the onset of symptoms, as opposed to diagnosis. The ESC considered that the contact matrix for 0 to 4 years olds used in the model could have been more precise.

- 6.24 During evaluation, notified cases of pertussis from the ‘no booster’ arm of the model were compared to actual notified cases from the National Notifiable Diseases Surveillance System (NNDSS). There was a significant discrepancy, particularly in the broad age group 20-59. This was due to the model applying the mean reporting rate within each broad age group, rather than using age-year specific reporting rates.

Calibration of dynamic transmission model by age-group, notified pertussis cases per year



Source: Constructed during evaluation
NNDSS = National Notified Diseases Surveillance System

- 6.25 In its base case, the submission took an inconsistent approach to counting cases in the two treatment arms of the model.
- The dynamic transmission model was first run for 100 years without vaccination to allow the epidemic to approach a steady state, but results of these pertussis cases were not directly used to inform the economic model in the submission. Instead, for years 96 to 100, incidence of primary and recidive infection (per 100,000) was recorded for each of six broad age classes (<1 year, 1-3, 4-9, 10-19, 20-59, 60-75). The submission then took the average for these five years, for each age group and infection type. This creates 12 numbers representing incidence/100,000 for each infection-type/age-category. The model assumes that for 100 years, each

of these 12 numbers will be the same. Thus the undiscounted 100 year model of ‘no booster’ treatment arm was created.

- The model then introduced the 18-month booster at year 100, and allowed it to run for a further 100 years. For each of these 100 years, the model recorded incidence of primary and recidive infection for each of the 6 age groups. This creates 12 numbers every year for 100 years and these numbers in general vary from year to year. Thus the undiscounted 100 year model of ‘18-month booster’ was created.

6.26 After correcting for this inconsistent approach and grouping reported cases after using age-year specific reporting rates, rather than grouping of ages together in broad age groups and then applying average reporting rates, a revised base case was independently run. The model presented in the submission provided only the discounted pertussis cases. During evaluation, the data was extracted to be able to present the number of cases over 100 years. The PSCR (p4-5) accepted the appropriateness of this respecified base case, termed base case (ESC). The revised base case in the commentary included a coding error to extract the number of cases for ‘18-month booster’, which resulted in the number of recidive pertussis cases being overestimated. For the revised base case (ESC), this error was corrected. The following table presents the cases, discounted costs and discounted QALYs for non-notified cases, notified cases, hospitalized cases, vaccination and adverse events due to vaccination.

Results of the economic evaluation – Revised base case (ESC) – 100 year model duration, Australian population^a

Step and component	18-month booster	No booster	Increment
Cases (undiscounted)			
Non-notified cases			
Notified (non-hospitalised) cases			
Hospitalisation cases			
Local AE due to vaccination			
Systemic AE due to vaccination			
Costs			
Non-notified cases			
Notified (non-hospitalised) cases			
Hospitalisation cases			
Vaccine costs			
Total Costs			
Discounted QALY^b			
Non-notified cases			
Notified (non-hospitalised) cases			
Hospitalisation cases			
Adverse events due to vaccination			
Total discounted QALY			

Source: Table D.21, pp E-150 of the submission, and independent evaluation.

^a In the submission’s base case, the pertussis cases included was inconsistently done for the two treatment options. During evaluation the inclusion of cases was performed for both treatment options, using the submission’s approach for ‘no booster’. The data was extracted for each year up to the age of four. Additionally, age-year specific reporting rates are used, and then reported cases are grouped, rather than grouping of ages together in broad age groups and then apply average reporting rates. Further, the error (in the commentary base case) to estimate the number of recidive cases has been corrected.

^b The Discounted QALYs reflect the reduction in QALYs due to pertussis cases (non-notified, notified or hospitalised) or adverse events due to vaccinations. Positive QALYs represent a health gain.

AE = adverse event; QALY = quality adjusted life year; ICER = incremental cost effectiveness ratio

- 6.27 The following table presents a summary of the submission’s base case and the revised base case.

Costs and QALYs in the economic evaluation (submission’s base case vs revised base case)

Step and component	18-month booster	No booster	Increment
Submission’s modelled evaluation (base case)			
Costs			
Discounted QALY ^b			
Incremental cost/ QALY			
Revised base case (ESC)^a			
Costs			
Discounted QALY ^b			
Incremental cost/ QALY			

Source: Table D.21, pp E-150 of the submission, and independent evaluation.

^a In the submission’s base case, the pertussis cases included was inconsistently done for the two treatment options. During evaluation the inclusion of cases was performed for both treatment options, using the submission’s approach for ‘no booster’. The data was extracted for each year up to the age of four. Additionally, age-year specific reporting rates are used, and then reported cases are grouped, rather than grouping of ages together in broad age groups and then apply average reporting rates. Further, the error (in the commentary base case) to estimate the number of recidive cases has been corrected.

^b The Discounted QALYs reflect the reduction in QALYs due to pertussis cases (non-notified, notified or hospitalised) or adverse events due to vaccinations. Positive QALYs represent a health gain.
QALY = quality adjusted life year; ICER = incremental cost effectiveness ratio

- 6.28 The evaluation corrected the inconsistencies in the model by extracting the model outputs from both the ‘no booster’ and ‘18-month booster’ groups from the point at which the model is in a steady state. As noted, however, the steady state is not reflective of pertussis epidemiology, and it may be more appropriate to use model outputs over the whole 100-year time horizon, over which period incidence increases and decreases.
- 6.29 An alternative re-specification of the model would use the non-steady state model outputs for both booster and non-booster (i.e. the results over the 100 years that it takes the model to become stable).
- 6.30 The ESC considered that the model may underestimate the cost savings of the ‘18-month booster’ scenario. For instance, the addition of the 18-month booster and expected reduction in transmission may impact on GP behavior such as increased testing rates and antibiotic use during outbreaks. In addition, the assumption of no resource costs for non-notified symptomatic infection was considered to be conservative for the following reasons:
- patients may wait several weeks before seeking treatment for a cough, at which point a general practitioner may be unlikely to order serology as the test is not sensitive; and
 - general practitioners may treat suspected pertussis cases without reporting.
- 6.31 The base case ICER presented in the submission is less than \$15,000/QALY, and using consistent inclusion of pertussis cases for the two treatment options and grouping reported cases using age-year specific reported rates, less than \$15,000/QALY. While uncertainties regarding the model’s external and internal validity cast doubt on both ICERs, the ESC considered that the revised base case is more robust than that presented in the submission, exhibiting reduced sensitivity to changes in assumptions. The key sensitivity analyses are presented in the table below.

- 6.32 The ESC noted that the utility weights in the submission were derived from Lee (2005). The ESC considered that the use of the short-term time trade-off (TTO) utilities from Lee (2005) (based on health states described as lasting for 8 weeks for an infant, adolescent or adult) was a non-conservative approach. Use of the long-term time trade-off utilities (based on health states described as lasting for the lifetime of the infant, adolescent or adult) increased the ICER to less than \$15,000/QALY. The pre-PBAC response noted that these short-term TTO utilities have been applied in publications of the cost-effectiveness of the pertussis vaccine.
- 6.33 The ESC noted that the model was not sensitive to the inclusion of maternal immunity to pertussis at a value between 0% and 34%.

Selected sensitivity analyses performed during evaluation

	Whole population			0-3 year old population		
	Δ Cost	Δ QALY ^a	ICER	Δ Cost	Δ QALY ^a	ICER
Base case submission	■	■	■	■	■	■
Revised (corrected) base case ^b	■	■	■	■	■	■
Revised base case (ESC) ^c	■	■	■	■	■	■
Disutility for non-notified pertussis cases (base case 50% of notified pertussis cases)						
25% ^d	■	■	■	■	■	■
Source of disutilities (base case: short-term TTO from Lee (2005))						
long-term TTO	■	■	■	■	■	■
Maternal immunity (base case: 34% of new-borns have maternal immunity)						
0% new-borns	■	■	■	■	■	■
Duration waning booster (base case 5 years partial immunity)						
8 years partial	■	■	■	■	■	■
Vaccine administration cost (base case \$0)						
\$7	■	■	■	■	■	■
Extraction of cases from the dynamic transmission model (Revised base case ESC: last 5 years for both arms)						
Use 100 year of model duration	■	■	■	■	■	■
Multivariate analysis						
25% disutility + long term TTO	■	■	■	■	■	■

Source: Calculated during evaluation

^a The Discounted QALYs reflect the reduction in QALYs due to pertussis cases (non-notified, notified or hospitalised) or adverse events due to vaccinations. Positive QALYs represent a health gain.

^b In the submission's base case, the pertussis cases included was inconsistently done for the two treatment options. During evaluation the inclusion of cases was performed for both treatment options, using the submission's approach for 'no booster'. Additionally, the data was extracted for each year up to the age of four. These values have been updated compared to the base case presented in the commentary to include the correct number of recidive cases in the '18-month booster' arm.

^c The Updated base case (ESC) includes the changes from the updated base case (Commentary) and age-year specific reporting rates are used, and then reported cases are grouped, rather than grouping of ages together in broad age groups and then apply average reporting rates. Additionally, the error (in the commentary base case) to estimate the number of recidive cases has been corrected.

^d The base cases assumes that non-notified pertussis cases have a disutility which equates to 50% of the notified cases. For this sensitivity analysis, the assumption is made that the disutility is 25% of the disutility of notified cases, e.g. for 1 year old, notified cases disutility of 0.28, non-notified cases in base case disutility of 0.14, in sensitivity analysis disutility of 0.07. QALY = quality adjusted life year; ICER = incremental cost effectiveness ratio; CI = confidence interval; TTO = time trade-off.

- 6.34 Some key aspects of the model could not be tested, e.g. monthly cycles for the first year of life, changes in the contact matrix to better reflect persons with pertussis and the differences in contact in the younger age category (0-4 years was one category in

the matrix used in the submission), and the primary vaccination schedule effectiveness without the 18-month booster.

- 6.35 The PBAC accepted ESC’s respecified base case, which corrected, amongst other inputs, for the inconsistent approach to counting cases in the two treatment arms in the model and grouping reported cases after using age-year specific reporting rates. The committee noted the respecified base case resulted in an ICER of less than \$15,000/QALY (for the whole population). The PBAC further agreed with the ESC that the revised model is more robust and noted that the ICER for the whole population remained under \$20,000 per QALY under all scenarios tested.
- 6.36 The PBAC considered that the cost-effectiveness of the 18-month booster may be underestimated, given that the magnitude of the clinical effectiveness of adding the 18-month booster is unknown and the model, particularly in the 0-3 year old population, is sensitive to the source of the disutilities and the application of disutility for non-notified pertussis cases as well as other uncertain assumptions and methodologies highlighted by the ESC. The PBAC considered that while the booster is likely to be cost-effective, the extent of uncertainty may be ameliorated via a reduction in the proposed price per booster dose.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Drug cost/patient: \$■

- 6.37 The proposed treatment consists of a single additional booster dose of DTPa at 18 months, with a cost of \$■.

Estimated PBS usage & financial implications

- 6.38 This submission was not considered by DUSC.
- 6.39 The submission assumed that all 18-month old children are eligible for vaccination and that the uptake will be similar to current MMRV vaccination, i.e. 94.1%. Therefore, the submission expected that there will be no additional administration costs. The ESC considered that this assumption may not be reasonable. If a GP is administering the vaccine the consultation would be expected to take at least 5 minutes longer and may therefore result in a greater cost to the MBS. The pre-PBAC response argued that there unlikely to be an increase in the cost of administration of vaccine.

Estimated costs and financial implications of 18-month booster of DTPa for NIP and PBS/RPBS

Description	2015	2016	2017	2018	2019
Number of children treated	■	■	■	■	■
prescriptions	■	■	■	■	■
Net cost NIP	■	■	■	■	■
Net saving PBS/RPBS	■	■	■	■	■
Cost to Government for MBS	■	■	■	■	■
Cost to State/Territory Government	■	■	■	■	■
Overall Net cost	■	■	■	■	■
Net cost NIP and PBS/RPBS	■	■	■	■	■

Source: Table E.4, p166 and Table E.20, pE-175 of the submission

The redacted table above shows that at Year 5, the estimated number of children treated to be over 200,000 and the net cost to NIP and PBS/RPBS to be less than \$10 million.

- 6.40 The estimated cost to the Government over the first five years of listing is \$[REDACTED]. This is subject to uncertainty about uptake rates of the vaccine and its effectiveness to reduce the number of pertussis cases for the five year period. Additionally, the submission did not include any costs for the treatment of adverse injection reactions or administration costs which will underestimate the financial implications of implementing the 18-month booster.

For more detail on PBAC's view, see section 7 "PBAC outcome"

7 PBAC Outcome

- 7.1 The PBAC recommended including an 18-month booster dose of the DTPa vaccine on the NIP for the prevention of pertussis on the basis of cost-effectiveness compared with the current schedule without the booster.
- 7.2 The PBAC recalled that the NIP previously included a booster dose of DTPa at approximately 18 months until 2003, when it was removed with the introduction of the booster dose for adolescents (15-17 years). The PBAC considered the removal of the 18-month dose may have contributed to resurgence in pertussis notifications between 2008 and 2012.
- 7.3 The PBAC agreed with the ATAGI that the reintroduction of an 18-month DTPa booster onto the NIP is necessary from a public health perspective, as an additional measure to improve control of pertussis in Australia. The PBAC further noted advice from the ATAGI that while pertussis does not cause severe disease in the majority of the targeted age group (18 months to less than 4 years), children in this age group have an important role in overall disease transmission, in particular to vulnerable young infants.
- 7.4 The PBAC accepted the comparator nominated in the submission, the current vaccination schedule with no 18-month DTPa booster.
- 7.5 The PBAC noted the limitations of the evidence of vaccine effectiveness for the 18-month booster treatment arm, which was derived from a cross-sectional study presented as a PowerPoint presentation (Quinn 2011). This study was considered to have a high risk of bias due to confounding factors such as the change from DTPw to DTPa and the subsequent introduction of the more sensitive PCR diagnostic test. However, the committee noted the limited information available and that the magnitude of the burden of disease was difficult to quantify.
- 7.6 The PBAC considered that while the magnitude of effectiveness is unclear, it is reasonable to assume that the introduction of the 18-month DTPa booster would result in superior comparative effectiveness compared with the current immunisation schedule. The PBAC noted that the majority of benefits in the model were due to a reduction in the number of non-notified cases of pertussis.

- 7.7 The PBAC agreed with the submission and the ESC that the introduction of the 18-month booster would result in additional localised adverse events at the time of vaccination and was therefore inferior in safety compared with the current immunisation schedule. The PBAC noted that the submission did not consider implications of the introduction of the 18-month DTPa booster on adverse reactions at the 4 year old vaccine schedule point.
- 7.8 The PBAC agreed with the ESC that the base model presented in the submission included some inconsistent and inappropriate methodologies. The PBAC accepted the ESC's respecified base case, which corrected, amongst other inputs, for the inconsistent approach to counting cases in the two treatment arms in the model and grouping reported cases after using age-year specific reporting rates.
- 7.9 The PBAC noted that the ESC's respecified base case reduced the ICER for the whole population to less than \$15,000/QALY and that the model exhibited reduced sensitivity to changes in assumptions, compared with the base case presented in the submission. In this regard, the PBAC noted that the ICER for the whole population remained under \$20,000 per QALY under all scenarios tested.
- 7.10 The PBAC considered that estimates of utilisation and cost to the Government were subject to uncertainty about uptake rates of the vaccine and its effectiveness to reduce the number of pertussis cases for the five year period. Additionally, the submission does not include any costs for the treatment of adverse injection reactions which will underestimate the financial implications of implementing the 18-month booster. As noted by the ESC, however, the model may also underestimate the cost savings of the '18-month booster' scenario. In the context of these uncertainties, the PBAC considered that the estimates were reasonable.

Outcome:

Recommended

8 Recommended listing

- 8.1 List DTPa vaccine on the NIP for infants aged approximately 18 months.

9 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.

10 Sponsor's Comment

Public Summary Document – November 2014 PBAC Meeting

GlaxoSmithKline welcomes the PBAC's recommendation to include an 18 month booster of Infanrix® (DTPa vaccine) for the prevention of pertussis in the National Immunisation Program.