6.01 DIPHTHERIA, TETANUS, & ACELLULAR PERTUSSIS (dTpa) injection, 0.5 mL  
Boostrix®  
GlaxoSmithKline Australia Pty Ltd

1. Purpose of Application
   1. National Immunisation Program (NIP) listing for combined diphtheria, tetanus and acellular pertussis (dTpa) (Boostrix) for immunisation of women in the third trimester of every pregnancy, in order to reduce pertussis disease in the mother and particularly, early onset infant disease.

# Requested listing

* 1. The submission sought the following listing:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Name, Restriction,  Manner of administration and form | Max.  Qty | №.of  Rpts | Dispensed Price for Max. Qty | Proprietary Name and Manufacturer | |
| Combined diphtheria-tetanus-acellular pertussis (dTpa) vaccine  Pre-filled syringe, 0.5 mL | 1 | 0 | $'''''' | Boostrix® | GSK |
| **National Immunisation Program**  Vaccination of pregnant women, during the third trimester of each pregnancy | | | | | |

* 1. Listing was requested based on cost-effectiveness compared with no vaccination.
  2. The ESC noted that the ATAGI post-submission advice stated that “the optimal timing of maternal immunisation is an issue for further consideration, in light of an emerging body of evidence supporting second trimester immunisation. That evidence is under on-going review to inform continuing recommendations for optimal vaccine administration.” The ESC considered that a broader indication, for immunisation of pregnant women during each pregnancy (without the restriction to the third trimester), may be more appropriate due to some ongoing clinical uncertainty about the optimal timing of immunisation during pregnancy.
  3. The ESC noted that the requested price of $''''''' per dose is $''' ''''''''' than the nationally negotiated price (of $''''''') for dTpa for the school program (10-15 year olds) on the NIP Schedule.

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

# Background

* 1. **TGA status at time of PBAC consideration:** dTpa was TGA approved in 2000. '''''''''' '''''''''''''''''''''''''' '''''''''''''' '''''''''' ''' '''''''''' ''''''''''''''''''''''' '''''''''' ''''''''''' ''''''''''''''''''''''''' '''' '''''''''''''''' ''''''' ''''''''' ''''' ''''''' ''''''''''''''''''' '''''''''''''''''''''''''''' ''''''''' '''''''''''''''''''''' ''''''''' '''' '''''''''''''''''''''''' ''''''''''''' '''''' '''''''''''''''''' '''''''''''' '''''' ''''''''''''' ''''''''''''''' ''''''''''''''''''''''''''' '''''''''' ''''' ''''''''''''''''''' ''''''''''''''' ''''''''' '''''''''''''''''''''' ''''''''''''''' '''''''''' '''''' ''''''''' '''''''''''''' '''''''''''''''''''''' ''''''''' ''''''' '''''''''''''''''''''' ''''''''''''''''''''''''''' '''''''''''''''''''' '''''''''''''''' '''''' ''''''''''' ''''''''''''''' '''''''''''''''''''''''''' ''''''''''' '''''''''''''' ''''''''''''''' '''''''''''''''''' ''''''''' ''''''' ''''''''''''''''''' '''''''''''''''''''''''''' ''''''''''''''''''''' '''''''' ''''''''''''''''''' ''''''''''' '''''' ''''''''' ''''''''''''' ''''''''' ''''''''''''' ''''' ''''''' ''''''''''' '''''''''''''''' '''' ''''''' ''''''''''''''' '''' ''''''' '''''''''''''''''''''''''''' ''''''''' ''''''' '''''''''''' ''''''''''''''''''''''' '''''''''''''''''' '''' '''''''' ''''''''''''''' ''''''''''' ''''''' ''''''''''''''''''''' ''''''''' ''''''' '''''''''''''''''''''''' ''''' '''''''' '''''''''''''''''''''' ''''''''''''''''''''' ''''' ''''''' ''''''' '''''''''''''''''' '''''''''''' '''''''''''''''''''''' '''''''' '''''''''''''''''''' '''''''''''''''''''' ''''' '''''''' ''''''''''' '''''''''' '''''''' ''''''''''''''' '''''''''''''''''' '''''' ''''''''''''''''''' '''''' '''''''' '''''''''''''''''''''''' '''''''''''''''''''' '''''''''' '''''' '''''''''''' ''''''''''''' '''''''''''''''''''''''''' '''''''''''' ''''''' '''''''''''''''''''' ''''''''''''''''''''''''''' '''''''''''''''''''' '''''''' ''''''''''''''''''''' '''''''''''' '''''' ''''''' ''''''''''''''''''
  2. The submission noted a further update to the PI, based on ongoing maternal vaccination trials, is anticipated in 2018 or 2019. No detail regarding this further update or the ongoing trials was provided in the submission, the PSCR or the pre‑PBAC response.
  3. The PBAC has not previously considered dTpa for maternal vaccination. In July 2011, the PBAC reviewed a submission for dTpa (Boostrix) for vaccination of both parents of newborn infants, at or around the time of birth of their child (known as a ‘cocooning’ strategy). In November 2011, the PBAC reviewed a submission for dTpa (Adacel) for ‘cocooning’. Both submissions were rejected on the basis of uncertain clinical effectiveness and high and uncertain cost effectiveness.
  4. All states and territories have implemented jurisdictionally-funded antepartum pertussis vaccination programs from late 2013 to June 2015 as a response to ongoing severe disease in young infants. An end date is not specified for any of these programs.
  5. ATAGI advised that dTpa (Boostrix) would be suitable for funding under the NIP for pregnant women in the third trimester of every pregnancy. The ATAGI post‑submission advice further advised that the optimal timing of vaccination is an issue for further consideration (see paragraph 2.3).

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

# Clinical place for the proposed therapy

* 1. Pertussis (or whooping cough) is a highly infectious disease of the upper respiratory tract, caused by the bacterial organism Bordetella pertussis. Currently, childhood doses of pertussis vaccine are scheduled at two, four and six months of age, with booster doses at 18 months, four years and 10-15 years. DTPa (Infanrix, Tripacel) is a child formulation of diphtheria, tetanus and acellular pertussis-containing vaccines. dTpa (Boostrix, Adacel) reduced antigen content formulation, is used in adults, adolescents and children aged ≥10 years.
  2. The submission proposed to include dTpa on the NIP schedule for immunisation of women in the third trimester of every pregnancy.

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

# Comparator

* 1. The submission nominated no vaccination as the main comparator. The ESC noted that states and territories are currently funding antepartum pertussis vaccination programs but considered that no vaccination was the appropriate comparator for PBAC consideration. The ESC noted that the PBAC has not previously assessed such a program for clinical and cost effectiveness. Further, no vaccination would be consistent with the accepted comparator for the July 2011 and November 2011 ‘cocooning’ submissions (which, at that time, was also funded through jurisdictional programs).

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

# Consideration of the evidence

## Sponsor hearing

* 1. There was no hearing for this item.

## Consumer comments

* 1. The PBAC noted and welcomed the input from individuals (132), health care professionals (4) and organisations (1) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of including dTpa on the NIP for vaccination of pregnant women including avoiding infant deaths from pertussis, reduction in morbidity for adults, and improved access, information and certainty of funding associated with a national program (compared with the current state based arrangements). In addition, a small number of comments were not supportive of the requested listing, including concerns regarding a claimed lack of evidence of the efficacy and safety of the vaccine in pregnancy.
  2. The PBAC noted the advice received from Northern Rivers Vaccination Supporters Group which supported the request to list dTpa on the NIP for pregnant women to provide added protection to the infant in the first few weeks of life, until they are able to start their own vaccination schedule at six weeks old. The PBAC specifically noted the advice that listing the vaccine on the NIP will increase awareness of the vaccine with mothers, clinicians and other adults.

## Clinical trials

* 1. No randomised trials were located reporting the clinical effectiveness of maternal dTpa vaccination. The key clinical evidence presented in the submission included:
* Two randomised controlled trials and one cohort controlled clinical study investigating the comparative effect of maternal dTpa vaccination and no active immunisation against pertussis, on immunogenicity and safety outcomes; and
* Two population-level observational studies from the UK assessing the effectiveness of the maternal dTpa vaccination in infants.
  1. Details of the trials presented in the submission are provided in Table 1.

Table 1: Trials and associated reports presented in the submission

| **Trial ID** | **Protocol title/ Publication title** | **Publication citation** |
| --- | --- | --- |
| **Vaccine efficacy in infants – non-randomised studies** | | |
| Amirthalingam 2014 | Amirthalingam G, Andrews N, Campbell H, et al. Effectiveness of maternal pertussis vaccination in England: an observational study. | *Lancet*2014;384 (9953):1521-8. |
| Dabrera 2015 | Dabrera G, Amirthalingam G, Andrews N, et al. A case-control study to estimate the effectiveness of maternal pertussis vaccination in protecting newborn infants in England and Wales, 2012–2013 | *Clin Infect Dis* 2015;60(3):333–7 |
| **Vaccine efficacy in adults - randomised trial** | | |
| Ward 2005  (APERT) | Ward JI, Cherry JD, Chang SJ et al. Efficacy of an acellular pertussis vaccine among adolescents and adults. | *N Engl J Med* 2005; 353(15):1555-1563. |
| **Immunogenicity and safety – Randomised and controlled trials** | | |
| Munoz 2014 | Munoz FM, Bond NH, Maccato M et al. Safety and immunogenicity of tetanus diphtheria and acellular pertussis (dTpa) immunization during pregnancy in mothers and infants: a randomized controlled trial | *JAMA* 2014;311(17): 1760-1769 |
| Maertens 2016 | Maertens K, Caboré RN, Huygen K et al. Pertussis vaccination during pregnancy in Belgium: results of a prospective controlled cohort study | *Vaccine* 2016;34(1): 142-150 |
| Hoang 2016 | Hoang HT, Leuridan E, Maertens K et al. Pertussis vaccination during pregnancy in Vietnam: results of a randomized controlled trial | *Vaccine* 2016;34(1): 151-159 |
| **Vaccine safety – non-randomised studies** | | |
| Vizzotti 2015 | Vizzotti C, Neyro S, Katz N, et al. Maternal immunization in Argentina: A story line from the prospective of a middle income country | *Vaccine* 2015;33: 6413–6419 |
| Donegan 2014 | Donegan K, King B, Bryan P. Safety of pertussis vaccination in pregnant women in UK: observational study | *BMJ* 2014;349: g4219 |
| Kharbanda 2014 | Kharbanda EO, Vazquez-Benitez G, Lipkind GS, et al. Evaluation of the association of maternal pertussis  vaccination with obstetric events and birth outcomes | *JAMA* 2014; 312(18):1897-1904 |
| Sukumaran 2015a | Sukumaran L, McCarthy NL, Kharbanda EO, et al. Association of Tdap vaccination with acute events and adverse birth outcomes among pregnantwomen with prior tetanus-containing immunizations | *JAMA* 2015; 314(15):1581-1587 |
| Sukumaran 2015b | Sukumaran L, McCarthy NL, Kharbanda EO, et al. Safety of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis and Influenza vaccinations in pregnancy | *Obstet Gynecol* 2015;126 (5):1069-74. |
| Walls 2016 | Walls t, Graham P, Petousis-harris H, et al. Infant outcomes after exposure to Tdap vaccine in pregnancy: an observational study. | *BMJ Open.* 2016; 6(1): e009536. |
| Study PIPS | Study report: Pertussis in Pregnancy Safety (PIPS) Study  Studies 2 and 3—Maternal Outcomes Report  With Supplementary Study 3—Infant Outcomes Report | December 2015 |
| Shakib 2013 | Tetanus, diphtheria, acellular pertussis vaccine during pregnancy: pregnancy and infant health outcomes. | *J Pediatr* 2013; 163(5):1422-6 |

Source: Table B-3, p24 of the submission; Table B-23, p48 of the submission

* 1. The key features of the vaccine effectiveness (VE) studies are summarised in Table 2.

Table 2: Key features of the included evidence

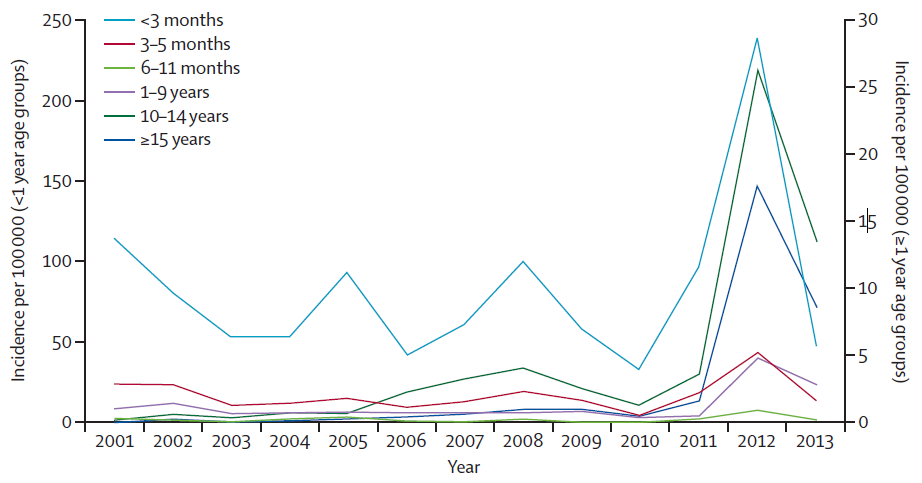
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| --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **N (Cases/**  **control)** | **Design/ Case identification period** | **Risk of bias** | **Patient population** | **Outcome** | **Use in modelled evaluation** |
| Amirthalingam 2014 | 82/NA | Retro, Screening Method (case-coverage study), January 2008 and September 2013 | High | Population level maternal dTpa-IPV vaccination program in the UK | VE | VE for infants |
| Dabrera 2015 | 58/55 | Retro, Case-control study, October 2012 and July 2013 | High | VE | Not used |

Source: Compiled during the evaluation

VE = vaccine effectiveness; Retro = retrospective; dTpa = diphtheria toxoid, tetanus toxoid and three purified antigens of Bordetella pertussis [pertussis toxoid (PT), pertussis filamentous haemagglutinin (FHA) and pertactin (PRN)]; IPV = inactivated poliovirus

* 1. In the absence of formal clinical trial data assessing vaccine efficacy, VE estimates were sourced from two observational studies (Amirthalingam 2014 and Dabrera 2015). The risk of bias with these estimates is high due to the observational design of the studies. Amirthalingam 2014 used the screening method to estimate VE. The evaluation noted that the screening method is considered a useful tool for monitoring VE but not a reliable method for precise VE estimates[[1]](#footnote-1). Dabrera 2015 used a case control method. A matched analysis was originally planned but due to a lack of controls an unmatched analysis was undertaken. The PSCR noted that “the screening method used to estimate vaccine effectiveness in Amirthalingam 2014 is certainly dependent upon the accuracy of the external estimate of vaccination coverage employed. However, where this assumption holds, the screening method is considered the most appropriate methodology for assessing vaccine effectiveness”. The PSCR further noted that the different approaches in Amirthalingam 2014 and Dabrera 2015 yielded almost identical estimates of vaccine effectiveness.
  2. The ESC noted the ATAGI pre-submission advice which considered that, in the absence of formal clinical trial data assessing vaccine efficacy, the Amirthalingam 2014 and Dabrera 2015 results are “very high level evidence for the effectiveness of a routine antepartum vaccination strategy”.
  3. The studies were conducted in the UK during a national pertussis outbreak when the incidence of pertussis was relatively high (see Figure 1) and it is unknown if the results are directly applicable to non-epidemic periods in Australia. Since the overall level of pertussis varies, effect size of interventions to prevent may also vary. The PSCR argued that the relative effectiveness of pertussis vaccination appears to be at least reasonably constant across epidemic and non‑epidemic conditions.

##### **Figure 1: Annual incidence of laboratory-confirmed cases of pertussis by age group (Amirthalingam 2014)**

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Source: Figure B-1, p50 of the submission

* 1. In these observational studies the immunisation status of people in contact with the infants, other than the mother, is unknown. It is therefore unknown if the incidence of pertussis has been impacted by the immunisation of people other than the mother. The PSCR argued that it is unlikely that the incidence of pertussis observed in the observational studies was confounded by changes in the immunisation status of anyone other than the mother on the basis of public health guidelines in England and that cocoon vaccination strategies have not been funded or recommended. The ESC noted that it is inherently difficult to link changes in the incidence to changes in the vaccine schedule (i.e. it is unknown how high notifications would have been without the additional immunisation). The ESC further noted that private vaccination is significant and social media plays an unquantifiable role in immunisation promotion and testing rates.
  2. The ESC considered the evidence presented from Amirthalingam 2014 and Dabrera 2015. In the absence of a randomised control trial data assessing vaccine efficacy, the ESC considered that maternal vaccination is likely to be effective in preventing pertussis in infants. The ESC considered that data on the impact of the Australian jurisdictional maternal vaccination programs on the incidence of pertussis would be informative. However, the ESC noted that, as with the UK data, it would be difficult to link changes in the overall incidence of pertussis to changes in the Australian vaccine schedule.
  3. The vaccine used in the UK at the time the studies were conducted was Repevax (marketed in Australia as Adacel Polio) which includes the same components as Adacel with the addition of inactivated poliovirus. The PBAC has previously concluded that a single booster dose of Adacel is as effective as a single dose of Boostrix although it was noted that the data for diphtheria and tetanus are more convincing than for pertussis because protective antibody levels have been established for these diseases (Adacel Public Summary Document (PSD) March 2006). The ATAGI post‑submission advice noted that it is reasonable to assume comparable efficacy for Boostrix and Repevax on the basis of bridging immunogenicity data.

## Comparative effectiveness

* 1. The estimates for VE in preventing pertussis in infants are presented below. The VE against pertussis in mothers was not measured in the presented clinical studies. In the economic model, VE for mothers is sourced from a RCT conducted in the general population (APERT). The results from this study are also presented in Table 3.

Table 3: Summary of VE results of pertussis vaccines

| **Infant age/vaccination timing** | **dTpa-IPV Vaccinated cases n/N (%)** | **Matched coverage (%) /**  **Vaccinated controls n/N (%)** | **VE: % (95% CI)** |
| --- | --- | --- | --- |
| **Amirthalingam 2014: Screening Method** | | | |
| Infants <3 months | | | |
| ≥ 7 days before birth (primary) | 12/82 (15%) | 62% | 91% (84, 95) |
| ≥ 7 days before birth, reduce coverage by 20% | 12/82 (15%) | 49% | 84% (71, 93) |
| ≥ 28 days before birth | 10/69 (14%) | 63% | 91% (83, 95) |
| 7-27 days before birth | 2/72 (3%) | 19% | 91% (70; 96) |
| < 7 days before birth | 2/68 (3%) | 5% | 38% (-95, 80) |
| Infants <2 months | | | |
| ≥ 7 days before birth | 11/71 (15%) | 61% | 90% (82, 95) |
| ≥ 7 days before birth, reduce coverage by 20% | 11/71 (15%) | 49% | 82% (67, 90) |
| **Debrera 2015: Case-Control Study** | | | |
| Infants < 8 weeks | 10/58 (17%) | 39/55 (71%) | 91% (77, 97) |
| 93% (81, 97)a |
| **APERT: randomised trial** | **pa3V**  **(N=1391; 2421 person-yr)** | **Hepatitis A vaccine**  **(N=1390; 2444 person-yr)** | **VE: % (95% CI)** |
| Adult | 1 case of pertussis | 9 cases of pertussis | 89% (19-99) |
| 92% (32, 99)b |

Source: Table B-24, p50 of the submission and publications

dTpa = diphtheria toxoid, tetanus toxoid and three purified antigens of Bordetella pertussis [pertussis toxoid (PT), pertussis filamentous haemagglutinin (FHA) and pertactin (PRN)]; IPV = inactivated poliovirus; pa3v = three component acellular pertussis

a analysis was adjusted for sex, geographical region, and birth period

b analysis was adjusted for duration of illness

* 1. The VE estimate for infants less than 3 months from Amirthalingam 2014 (which used the screening method) was 91% (95% CI: 84%, 95%) when the mother is vaccinated at least 7 days before birth. Using the screening method, the VE estimate is sensitive to the estimated vaccination coverage. A sensitivity analysis was presented in Amirthalingam 2014 in which the population vaccine coverage was reduced by 20%. The VE reduced to 82% (95% CI: 67%, 90%) and 84% (95% CI: 71%, 93%) in infants less than two and three months respectively.
  2. The unadjusted VE estimate from Debrera 2015 using a case-control design was 91% (95% CI: 77%, 97%), which was consistent with the estimate from Amirthalingam 2014.
  3. The ESC noted that “12 deaths have been reported in young babies with confirmed pertussis who were born after the introduction of [pertussis vaccination in] pregnancy programme [in the UK] on 1 October 2012, as at end June 2015. Eleven of these 12 babies were born to mothers who had not been vaccinated against pertussis, all of the 12 babies were too young to be fully protected by vaccination themselves and only one had received their first dose of pertussis-containing vaccine.”[[2]](#footnote-2) Maternal coverage during this period was approximately 50-60%. Accordingly, the ESC considered that it was likely that pertussis vaccination in pregnancy has prevented some deaths in infants in the UK.
  4. The number of pertussis events in the APERT trial was low and hence the 95% CI for the estimate of VE is wide (32% to 99% for the adjusted analysis and 19% to 99% for the unadjusted analysis). The applicability of the results from APERT, which was conducted in the general population, to pregnant women is unknown. The ATAGI post-submission advice stated that it was reasonable to assume that vaccine efficacy in pregnant women will be equivalent to that in non‑pregnant women on the basis of a comparison of immunogenicity data. The ATAGI advice provided a comparison of vaccine efficacy of influenza vaccine among pregnant women compared with that of healthy adults, concluding that vaccine efficacy is comparable in the two groups and suggested that in the absence of evidence to the contrary, it is reasonable to assume the same for the pertussis vaccine.
  5. The immunogenicity RCTs (Munoz 2014, Hoang 2016) and cohort controlled study (Maertens 2016) demonstrate that maternal vaccination with dTpa induces an immune response to pertussis antigens, among both mothers and their infants. The submission acknowledged the absence of established immunological correlates of protection against pertussis disease. The evidence further suggests potential interference of maternal pertussis vaccination with the infant immune response to pertussis vaccination, namely ‘blunting’. ATAGI considers the clinical importance of this is uncertain and notes that the recently introduced 18-month DTPa booster dose in infants may reduce any impact of ‘blunting’ (ATAGI pre-submission advice p12).

## Comparative harms

* 1. Three immunogenicity trials and seven non-randomised studies provided safety data for maternal dTpa vaccination. Local reactions are the most commonly reported adverse events in dTpa vaccinated pregnant women and pain is the most commonly reported local reaction. dTpa vaccination during pregnancy has not been associated with an increased risk of maternal or infant events, such as still birth, maternal or neonatal death, preterm delivery, pre-eclampsia, post-partum haemorrhage or low birth weight.

## Benefits/harms

* 1. A summary of the comparative benefits and harms for maternal dTpa vaccination versus no maternal vaccination is presented in the following table.

Table 4: Summary of comparative benefits and harms for maternal dTpa vaccination and no vaccination (based on the non-randomised evidence)

| **Benefits** | | |
| --- | --- | --- |
| **Vaccine effectiveness (VE) % (95% CI)** | | |
|  | **Amirthalingam 2014** | **Debrera 2015** |
| Infants < 3 months | 91% (84, 95) | NA |
| Infants < 8 weeks | 90% (82, 95) | 91% (77, 97) |
| **Harms** | | |
|  | **dTpa** | **Placebo** |
| **Munoz 2014**  Injection site reactions  - Pain  - Redness  - Swelling | N=33 Antepartum  26 (78.8%)  25 (75.8%)  3 (9.1%)  3 (9.1%) | N=15 Antepartum  3 (20%)  2 (13.3%)  1 (6.7%)  0 |
| **PIPS**  -Mild pain  -Moderate pain  -Severe pain | N=793  347 (43.8%)  279 (35.2%)  21 (2.6%) | NA |

Source: Table B-24, p50 of the submission and publications

* 1. Based on the non-randomised observational data, maternal vaccination is estimated to reduce the number of cases of pertussis in infants aged less than 3 months by 91%. In 2014 there were 106 cases of pertussis in Australia in infants less than 3 months of age. If all pregnant women in Australia were vaccinated, 96 cases of pertussis would be prevented. If 70% of pregnant women were vaccinated, as was assumed in the economic model and suggested by ATAGI (pre‑submission advice), 67 cases of pertussis would be prevented.
  2. Pain is the most commonly reported injection site reaction.

## Clinical claim

* 1. The submission described dTpa vaccination during the third trimester of pregnancy as superior in terms of comparative effectiveness in preventing pertussis in infants and mothers, and inferior in terms of comparative safety, over no vaccination. The ESC considered that these claims were appropriate and that the vaccine effectiveness for dTpa for prevention of pertussis in infants was likely to be high. However, the submission did not provide clinical evidence on the effectiveness of dTpa in preventing pertussis in mothers. Although dTpa elicits a significant immunogenic response in mothers, there is no clear evidence supporting the correlation of immunogenicity outcomes and protection from pertussis. In the economic model it is assumed that the effectiveness of dTpa in the general population is directly applicable to pregnant women.
  2. The PBAC considered that the claim of superior comparative effectiveness in preventing pertussis disease in infants and mothers was reasonable.
  3. The PBAC considered that the claim of inferior comparative safety was reasonable.

## Economic analysis

* 1. The economic evaluation is a cost-utility analysis. The submission presented a decision tree model.

Table 5: Summary of model structure and rationale

| Time horizon | The number of cases of pertussis occurring in one year is reported.   * For infants there is a benefit of maternal vaccination for up to 7 months (after which the infant is covered by the primary DTPa doses). * For mothers dTpa is assumed to be effective for up to 5 years. The median follow‑up in the clinical trial (APERT) was 22 months. * For deaths (which occur in infants <6 months of age) the life years lost are calculated using a life time horizon. |
| --- | --- |
| Outcomes | Number of cases of pertussis, number of hospitalisations due to pertussis, deaths due to pertussis, QALYs |
| Methods used to generate results | Static population based decision tree. The number of cases of pertussis with and without maternal vaccination is calculated. Costs and QALY losses are applied to each case. |
| Incidence of pertussis without maternal dTpa | Reported: based on NNDSS data  Unreported: assumed proportional increase compared with reported cases, with proportion differing across age groups |
| Incidence of pertussis with maternal dTpa | Number of cases multiplied by the VE and coverage |
| Outcomes for each event | Reported: Costs for hospitalisation or ambulatory care, QALY loss, death  Unreported: QALY loss |
| Discount rate | 5% annually to costs and QALYs |
| Software package | Excel |

Source: constructed during the evaluation

* 1. The key model drivers are summarised in the Table 6 below.

Table 6: Key drivers of the model

| **Description** | **Method/Value** | **Impact** |
| --- | --- | --- |
| The number of unreported cases of pertussis | Underreporting factor of 2 assumed for infants (i.e. 50% cases are unreported); Underreporting factor of 20 assumed for mothers (i.e. 95% of cases are unreported). It is not stated in the submission how the underreporting factors were calculated. | High |
| Disutility applied to unreported cases | Infant: 0.15; Mother 0.08-0.11  The disutilities applied are 50% of the disutilities for reported cases. Supporting literature is not provided for the 50% reduction. | High |
| Duration of disease | The duration of pertussis is assumed to be between 62 and 80 days. This was inadequately justified in the submission. | High, favours dTpa |
| Baseline incidence of pertussis | NNDSS data for 1999-2008 for infants. NNDSS data for 1999-2014 for mothers (revised in the PSCR from 2008-2014 in the submission). The incidence is more representative of an epidemic year than a non-epidemic year. | Moderate, favours dTpa |
| VE for mothers | 91% sourced from an RCT in the general population. VE assumed to wane over 5 years. | Moderate |
| Vaccine administration cost | No cost assumed | Moderate, favours dTpa |
| Discount rate | 5% annually for costs and benefits | Moderate |

Source: compiled during the evaluation

* 1. The results of the economic evaluation (using a revised base case) in which 224,510 mothers are vaccinated (equivalent to 70% of Australian mothers vaccinated during pregnancy based on 2013 population data) are provided in Table 7. The number of cases prevented is influenced by the uptake rate. The ICER is not sensitive to this because the average costs and benefits are the same for each mother/infant. The base case presented in the submission estimated an incremental cost per QALY gained due to avoided cases of pertussis of $15,000 - $45,000. The following issues identified in the evaluation were addressed in the PSCR and the ESC considered they should be incorporated into a revised base case (referred to as the ‘ESC base case’) which resulted in an ICER of $15,000 - $45,000 per QALY gained.
     + The evaluation considered that the model may have overestimated the average number of deaths due to pertussis and hence the number of deaths prevented with maternal dTpa. From 1993 to 2014 there was an average of 1.45 infant pertussis deaths per year reported to the National Notifiable Diseases Surveillance System (NNDSS) (ATAGI pre-submission advice, p4). ATAGI estimated that there are 2 deaths per year in infants aged <4 months in epidemic years but none in non‑epidemic years. Without maternal vaccination the model estimated that there are 2 deaths per year in infants <6 months of age, and maternal dTpa is estimated to prevent 1 of these deaths. The PSCR and the ESC agreed that the number of infant deaths prevented should be halved in the base case.
     + The model’s baseline incidence of pertussis in adults was based on data for 2008‑2014 which were primarily epidemic years. The PSCR provided an alternative set of estimates for baseline incidence of pertussis for adults, based on data spanning 1999-2014 and a revised ICER of $15,000 - $45,000 incorporating these revised estimates (but not including the above change to mortality). The ATAGI post-submission advice considered that it would be preferable to use the same time period as a basis for estimation of cases across the age spectrum. Accordingly, the ESC considered this revised incidence data should be incorporated into a revised base case. However, despite providing the revised incidence data and ICER in the PSCR, the pre-PBAC response stated that the revised adult incidence estimates should not be incorporated without additional adjustment to other parameters in the model. The PBAC accepted the use of the more recent 2008-2014 incidence data on the basis that the overall incidence of pertussis appears to be increasing over time.
  2. Protection due to a herd effect was not included in the analysis. ATAGI considered that maternal vaccination would have limited impact on overall herd immunity given that pregnant women represent only 1.3% of the total population (ATAGI pre‑submission advice). The ESC considered this was appropriate, noting that any estimate of an effect on herd immunity would be small and subject to considerable uncertainty. The ESC noted another conservative assumption which may have a small and uncertain impact on the results was that the model did not include any benefits related to the additional prevention of diphtheria and tetanus.

Table 7: Results of the economic evaluation (ESC base case)

|  |  |  |  |
| --- | --- | --- | --- |
| **Component** | **Maternal vaccination vs No maternal vaccination** | **Current strategy vs No maternal vaccination** | **Increment** |
| Incremental costs | $''''''''''''''''''''''''''''' | $'''''''''''''''''''''''''' | $''''''''''''''''''''''''' |
| QALYs gained due to avoided cases | ''''''''''''''' | ''''''''''''' | '''''''''''''''' |
| **Incremental cost/extra QALY gained** | | | **$'''''''''''''** |

Source: Table D-14, p99, of the submission.

The redacted table shows an incremental cost/extra QALY gained in the range of $15,000 - $45,000.

* 1. The ESC base case model predicted 6,060 cases of pertussis will be prevented per year:
* 277 cases in infants <1 year of age (138 reported and 138 unreported cases); and
* 5,783 cases in mothers (289 reported and 5,494 unreported cases).
  1. The submission stated that the prevention of pertussis in very young infants is the motivating factor behind maternal dTpa; however, the ESC noted that the majority of cases of pertussis prevented in the model due to the vaccine accrued to the mothers (95% of prevented cases). Excluding the benefit in mothers increased the ICER to $105,000 - $200,000/QALY (using the ESC base case). The ESC considered that it was reasonable to consider the benefit to the mothers from the proposed vaccination but reiterated that there was no evidence to support the disutilities applied to unreported cases. The ESC further noted that the cost per life year saved in the ESC base case was more than $200,000.
  2. In the model, the incidence of pertussis reported by the NNDSS was inflated to account for unreported cases. The submission stated that estimating the extent of underreporting of pertussis in Australia is inherently challenging as data are limited, rates are different across age groups, and rates vary over time, geographic region and due to different background vaccination practices. The model assumed an underreporting factor of 2 for infants (i.e. 50% cases are unreported) and 20 for mothers (i.e. 95% of cases are unreported). Of the prevented cases, 5,633 (93%) were unreported cases. Excluding the unreported cases increased the ICER to $105,000 - $200,000/QALY gained in the ESC base case. The PSCR argued that the assumptions used in the submission were conservative and consistent with available seroepidemiology survey data. The ATAGI post‑submission advice stated that “it is reasonable to assume that fewer cases are under-reported in the very young than in the adult population, given evidence of asymptomatic or very mild infection with increasing age. In the absence of detailed data in the Australian context, the estimates provided are within broadly plausible bounds but are recognised to be unavoidably uncertain”. The ESC considered that estimating the rate of under-reporting is inherently difficult and that the estimates are broadly plausible. Given the lack of more reliable data, the ESC accepted the use of the under‑reporting rates in the base case in this instance but considered that sensitivity analyses examining the impact of the underreporting rates were informative.
  3. The ESC base case model predicted there will be '''''''''' undiscounted QALYs gained as a result of the pertussis cases avoided in one year. Of these, '''''' are in infants less than 1 year of age (''' for reported cases, ''' for unreported cases and '''''' for the death prevented). In mothers, ''''''' QALYs are gained ('''' for reported cases and ''''''' for unreported cases). Of the undiscounted QALYs gained, 53% were due to preventing unreported cases in the mothers and 32% were due to preventing infant deaths.
  4. The model assumed the disutilities for unreported cases are half that for a reported case (0.15 for 80 days for infants and 0.08 to 0.11 for 68 days for mothers). Supporting literature was not provided in the submission for this assumption either in terms of magnitude or duration of disutility and the direction of bias is unknown. The same assumption was included in the November 2014 Infanrix submission. The ESC previously considered that the assumption of a 50% utility reduction in unreported cases compared with reported cases was not supported by evidence from the literature (DTPa PSD, November 2014, paragraph 6.21). The PSCR argued that it would be inappropriate to apply a utility reduction of 0% for symptomatic non-notified cases compared with reported cases and that the submission conservatively assumed non‑notified symptomatic cases incur no cost. The ESC agreed that applying a utility decrement of zero to symptomatic non-notified cases would be inappropriate but considered it was reasonable to assume that unreported cases are generally milder than reported cases which involve some disutility. However, the ESC reiterated that there is no evidence to suggest that a 50% reduction in disutility is a reasonable estimate. In this regard, the ESC noted that if the disutility for unreported cases were a quarter of that for a reported case, the ESC base case ICER would increase to $45,000 - $75,000/QALY gained. The ESC agreed with the PSCR that assuming no costs for the symptomatic non-notified cases was a conservative assumption which may have had a small impact on the ICER favouring no vaccination.
  5. The model’s baseline incidence of pertussis (without maternal dTpa) in infants was more consistent with an epidemic than a non-epidemic year. The baseline incidence in infants aged <4 months was 407 cases per year (all of which are assumed to be hospitalised). This compared with ATAGI’s estimates of 536 hospital admissions due to pertussis in an epidemic year and 96 in a non-epidemic year. The PSCR argued that the baseline incidence of pertussis in infants was estimated using data from 1999 to 2008 which encompassed both epidemic and non-epidemic years. The ESC agreed with the evaluation that this incidence was more reflective of an epidemic year and may favour the vaccination strategy.
  6. The results were sensitive to the VE estimate for mothers and the assumed duration of VE (decline over 5 years).
     + VE was sourced from APERT and, although a randomised trial, the number of pertussis events was small and hence the confidence intervals for the estimate are wide. The ICER (using the ESC base case) ranged from $15,000 - $45,000/QALY to $75,000 -$105,000/QALY using the upper and lower 95% confidence limits for the VE. The PSCR argued that this sensitivity analysis was meaningless as the 95% confidence intervals for maternal VE reflect the very low background incidence of cases observed in the APERT study and it is implausible that the true efficacy of adult booster dTpa vaccination is anything like the lower confidence interval (of 32%).
     + For mothers who have a second child within 5 years, the benefits of the first maternal vaccination would be superseded by a second vaccination and thus assuming 5 years of benefit for each vaccination overestimated the benefit. With VE waning over 3 years the ICER increased to $45,000 - $75,000/QALY (using the ESC base case). The PSCR and pre-PBAC response recognised this issue but argued that accounting for this would require considerably more complex modelling techniques and the model was already conservative. Specifically, the VE estimate reported in APERT was an average observed over almost two years of follow-up but the model conservatively applied this estimate as the maximum VE obtained immediately after vaccination with linear waning to zero at the end of five years (despite published literature suggesting antibody persistence following vaccination of at least 10 years).
  7. Costs for administering the vaccine were not included in the model. Assuming a cost of $7 for administering the vaccine increased the ESC base case ICER to $$45,000 - $75,000/QALY. The PSCR stated that vaccination can occur alongside routine prenatal care, so would not incur extra costs. The ESC agreed that the vaccine could be provided at standard appointments through antenatal clinics, midwifery programs or GP practices. However, the ESC considered that it was unreasonable to assume no additional cost for administering the vaccine, noting the time taken to record information and marginal increases in consultation times.
  8. The results were sensitive to the discount rate ($15,000 - $45,000/QALY with no discounting; $45,000 - $75,000/QALY with costs and benefits discounted at 10% using the ESC base case). This is because the life years gained for the deaths prevented were substantially reduced when discounted (46.95 years when undiscounted versus 10.43 years when discounted at 5% and 5.18 when discounted at 10%).
  9. The durations of illness used in the model (62-82 days) were sourced from economic analyses (Lee 2007 and Lee 2008) which did not contain information regarding how the duration of illness was estimated. Accordingly, the ESC considered that the durations of illness were insufficiently justified. The Centres for Disease Control and Prevention (CDC) describe three stages of pertussis with accompanying durations: catarrhal (7‑10 days), paroxysmal (1-6 weeks) and convalescent (7‑10 days)[[3]](#footnote-3). If a duration of illness of 41 days for adults 20 years and above was assumed (based on the sum of the midpoints of the three stages) the ESC base case ICER increased to $45,000 - $75,000/QALY. The pre-PBAC response argued that the ESC cited the CDC report somewhat selectively and that it is the mean duration of disease that is critical rather than the midpoint. In this regard, the pre-PBAC response noted that “the mean duration of cough in a cohort of 664 cases in Canada was 10 weeks in adolescents and 12 weeks in adults” which the response noted were longer than the durations used in the model.
  10. The duration of illness assumed in the model included the convalescence and catarrhal phases. The ESC considered that the utility weights derived from Lee 2005 are most representative of the paroxysmal phase of pertussis (based on the description of pertussis in the vignettes used in the time-trade off study) and therefore may overestimate the disutility for the whole duration of illness.

Table 8: Results of the economic evaluation and sensitivity analyses using the ESC base case

| **Scenario** | **Incremental number of pertussis deaths avoided** | **Incremental costs** | **Incremental effectiveness (QALYs gained)** | **Incremental cost-effectiveness (per QALY)** |
| --- | --- | --- | --- | --- |
| Submission base case | ''''''''''' | $''''''''''''''''''''''' | ''''''''''''''' | $'''''''''''''''' |
| ESC base case (uses mortality 0.4% and 1999‑2014 baseline incidence of pertussis in adults) | '''''''''' | $''''''''''''''''''''''''' | '''''''''''''''''' | $''''''''''''''' |
| Pre-PBAC response base case (uses mortality 0.4%) | '''''''''' | $''''''''''''''''''''''''' | ''''''''''''''''' | $'''''''''''''''' |
| ***Sensitivity analyses using the ESC base case*** | | | | |
| Administration cost ($7 per dose) included | ''''''''''' | $''''''''''''''''''''''''' | ''''''''''''''' | $''''''''''''''' |
| Unreported cases excluded | '''''''''' | $'''''''''''''''''''''''' | '''''''''''''' | $''''''''''''''''' |
| Maternal benefit excluded (VE=0 for mothers) | '''''''''''' | $'''''''''''''''''''''''''' | '''''''''''''' | $''''''''''''''''''' |
| Utility weights for unreported cases 25% of reported cases (base case 50%) | ''''''''''' | $''''''''''''''''''''''''' | '''''''''''' | $''''''''''''''' |
| Adult VE lower 95% CI: 32% (base case 92%) | ''''''''''' | $'''''''''''''''''''''''''' | '''''''''''' | $'''''''''''''''' |
| Adult VE upper 95% CI: 99% (base case 92%) | ''''''''''' | $''''''''''''''''''''''' | ''''''''''''''' | $'''''''''''''''' |
| Duration of disease 41 days in mothers 20+ years (base case 68 days) | ''''''''''' | $''''''''''''''''''''''''' | ''''''''''''''' | $''''''''''''''' |
| Duration of VE 3 years (base case 5 years) | ''''''''''' | $''''''''''''''''''''' | '''''''''''''' | $'''''''''''''''' |
| Discount rate 0% (base case 5%) | ''''''''''' | $''''''''''''''''''''''''' | ''''''''''''''' | $''''''''''''''' |
| Discount rate 10% (base case 5%) | ''''''''''' | $''''''''''''''''''''''' | '''''''''''''' | $''''''''''''''' |

Source: Compiled during the preparation of the ESC Advice.

The redacted table shows ICERs in the range of $15,000 - $45,000/QALY, $45,000 - $75,000/QALY, $75,000 - $105,000/QALY and $105,000 - $200,000/QALY.

* 1. The ATAGI post-submission advice noted that data on Australian pertussis-related paediatric intensive care unit admissions in infants for the period 1997-2013[[4]](#footnote-4) were offered to the sponsor but were not referenced in the submission. Accordingly, ATAGI considered that the substantive burden of disease demonstrated in this publication was not captured in the submission.
  2. The PBAC considered that there were factors which would have underestimated the ICER (such as not including administration costs or accounting for reduced effectiveness in mothers receiving multiple shots within a 5 year period) and factors which would have overestimated the ICER (such as not including costs for unreported cases and conservative use of the APERT VE estimate). The impact on the ICER of other factors such as the rate of, and disutility applied to, unreported cases was unknown. On balance, the PBAC considered the ‘pre-PBAC response base case’ (with an ICER of $15,000 - $45,000 per QALY) was the most informative estimate for decision making, while noting some uncertainty around this estimate.

## Drug cost/patient/dose: $''''''

* 1. The dTpa cost per dose in the submission was $''''''. The nationally negotiated price of dTpa for the adolescent program at the time of the submission was $''''''.

## Estimated PBS usage & financial implications

* 1. This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the net financial impact of including maternal dTpa vaccination on the NIP. The NIP cost was calculated based on the number of pregnant women (assumed to be the same as the number of births), the assumed uptake of dTpa (70%) and the dTpa cost ($'''''').

Table 9: Estimated use and financial implications

|  | **Year 1** | **Year 2** | **Year 3** | **Year 4** | **Year 5** |
| --- | --- | --- | --- | --- | --- |
| Eligible women | '''''''''''''''''''''' | ''''''''''''''''' | ''''''''''''''''''' | '''''''''''''''''' | '''''''''''''''''''' |
| Vaccinated women (70%)/ number of dTpa doses | '''''''''''''''''' | '''''''''''''''''''' | '''''''''''''''''' | ''''''''''''''''' | '''''''''''''''''' |
| Total NIP cost  (vaccinated women x $'''''') | $''''''''''''''''''''''''' | $'''''''''''''''''''''' | $''''''''''''''''''''''' | $''''''''''''''''''''''''' | $''''''''''''''''''''''' |

Source: Table E-2, p106, of the submission.

* 1. At year 5, the estimated number of patients was over 200,000 and the net cost to the NIP would be less than $10 million.
  2. The ESC noted that the financial estimates were sensitive to the assumed uptake. ATAGI estimated 70% uptake and the associated cost over 5 years is $20 - $30 million. Reducing the uptake to 50% reduced the cost to $10 - 20 million. Increasing the uptake to 90% increased the cost to $30 - 60 million.

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

# PBAC Outcome

* 1. The PBAC recommended a change to the circumstances under which dTpa is made available as a designated vaccine for the NIP to include vaccination of women during each pregnancy to reduce pertussis disease in infants (prior to being vaccinated) and in mothers on the basis of cost-effectiveness compared with no vaccination.
  2. The PBAC noted the optimal timing of vaccination during pregnancy is an issue for further consideration in light of an emerging body of evidence supporting second trimester immunisation. Accordingly, the PBAC recommendation is for vaccination during each pregnancy, without the requested restriction to the third trimester. The PBAC considered the optimal timing of vaccination during pregnancy should be based on clinical evidence and informed by ATAGI.
  3. The PBAC noted that the states and territories currently fund dTpa vaccination during pregnancy in line with the Australian Immunisation Handbook recommendation (section 4.12.7). ATAGI advised that there is a need to adopt a new strategy for protection in early infancy given the persistent high notification rates in siblings and other infant contacts which underpin the ongoing risk of exposure to pertussis disease for young infants (pre-submission advice). Accordingly, the PBAC considered that the introduction of dTpa for pregnant women on the NIP is warranted from a public health perspective as an additional measure to directly target the group with the highest burden of disease (i.e. infants). The PBAC noted that the recently introduced pertussis vaccination in infants aged 18 months was also partly aimed at preventing disease in vulnerable infants and with the maternal vaccination there would, in effect, be a total of seven pertussis vaccinations on the NIP.
  4. The PBAC accepted the comparator nominated in the submission of ‘no vaccination’.
  5. The PBAC noted that the consumer comments in support of the vaccine indicated that there is variation in information and provision of the vaccine for pregnant women across jurisdictions. The PBAC considered that the implementation of a national program for dTpa vaccination during pregnancy may assist to address these concerns.
  6. The PBAC noted the key clinical evidence presented was two population-level observational studies from the UK assessing the effectiveness of a maternal dTpa vaccination program in infants, using two different methods (the screening method and case control). The PBAC considered that the results of these studies likely overestimated the precision of vaccine effectiveness (that is, the confidence intervals are likely to be wider than indicated). However, the PBAC considered that in the absence of formal clinical trial data assessing vaccine efficacy, the observational studies provided acceptable evidence for the effectiveness of maternal vaccination. The PBAC noted that based on the non-randomised observational data, maternal vaccination is estimated to reduce the number of cases of pertussis in infants aged less than three months by 91%.
  7. The PBAC noted number of pertussis events in the APERT trial, which was used to inform vaccine efficacy in the mother, was low and resulted in a wide confidence interval for the estimated efficacy. The PBAC further noted that the majority of the modelled benefits were due to a reduction in the number of non‑notified cases of pertussis in the mother. The PBAC agreed with the claim of superior comparative effectiveness in terms of prevention of pertussis disease in mothers and considered that the results of the APERT trial were applied conservatively in the model with respect to duration of benefit.
  8. The PBAC agreed with the submission and the ESC that the vaccine would result in additional localised adverse events at the time of vaccination and was therefore inferior in safety compared with no maternal vaccination. However, the PBAC noted that dTpa vaccination during pregnancy has not been associated with an increased risk of maternal or infant events, such as still birth, maternal or neonatal death, preterm delivery, pre-eclampsia, post-partum haemorrhage or low birth weight.
  9. The PBAC considered that some assumptions included in the model presented in the submission were likely to have overestimated the cost-effectiveness of maternal dTpa vaccination whereas others may have underestimated the cost-effectiveness. However, on balance and in the context of the public health imperative, the PBAC accepted the ICER presented in the pre-PBAC response. The PBAC considered that it would be valuable to examine the pertussis vaccination schedule in its entirety rather than limit the assessment to cost-effectiveness of each individual vaccination. In this regard, the PBAC noted that one of the primary aims of pertussis containing vaccines on the NIP is to prevent disease in vulnerable infants. Given that maternal vaccination provides direct protection to infants in the first few months of life, the PBAC considered that targeted dTpa vaccination of pregnant women was likely to be reasonably cost-effective. However, the PBAC requested advice from ATAGI on the clinical place and effectiveness of the vaccines currently listed on the NIP schedule aimed at preventing pertussis disease, particularly in light of the inclusion of dTpa vaccination of pregnant women and the recent inclusion of an 18 month dose, with a view to potentially informing a review of the cost effectiveness of these vaccines.
  10. The PBAC noted that estimates of utilisation and cost to the Government were subject to uncertainty about uptake rates of the vaccine but accepted the submission estimates which based on an uptake rate of 70%.
  11. The PBAC noted that this submission is not eligible for an Independent Review as the PBAC has made a positive recommendation.

**Outcome:**

Recommended

# Recommended listing

* 1. Add new indication as follows:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Name, Restriction,  Manner of administration and form | Max.  Qty | №.of  Rpts |  | Proprietary Name and Manufacturer | |
| Combined diphtheria-tetanus-acellular pertussis (dTpa) vaccine  Pre-filled syringe, 0.5 mL | 1 | 0 |  | Boostrix® | GSK |
| **National Immunisation Program**  Vaccination of pregnant women during each pregnancy | | | | | |

# 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.

# Sponsor’s Comment

GlaxoSmithKline welcomes the PBAC’s recommendation to list Boostrix® on the NIP for the vaccination of pregnant women.

1. [Observational methods in epidemiologic assessment of vaccine effectiveness](http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-pubs-cdi-2002-cdi2603-htm-cdi2603o.htm), *Communicable Diseases Intelligence,* Volume 26, No 3, September 2002; accessed 12 December 2014. [↑](#footnote-ref-1)
2. *Public Health England,* [*HPR volume 9 issue 30: news (28 August)*](https://www.gov.uk/government/publications/health-protection-report-volume-9-2015/hpr-volume-9-issue-30-news-28-august)*, Laboratory confirmed pertussis in England: data to end-June 2015. Updated 29 December 2015* [↑](#footnote-ref-2)
3. CDC, [Pertussis (whooping cough), clinical features](http://www.cdc.gov/pertussis/clinical/features.html). Page last updated 8 September 2015. [↑](#footnote-ref-3)
4. Kaczmarek MC, Ware RS, McEniery JA, et al. Epidemiology of pertussis-related intensive care unit (ICU) admissions in Australia, 1997-2013: an observational study. BMJ Open. 2016;6:e010386. [↑](#footnote-ref-4)