5.07 MENINGOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE SEROGROUPS A, C, W-135 and Y Pre-filled syringe, 0.5mL, Nimenrix ®, Pfizer Australia Pty Ltd.

1 Purpose of application

1.1 NIP listing for a meningococcal polysaccharide serogroups A, C, W_{135} and Y tetanus toxoid conjugate (MenACWY-TT) vaccine for the prevention of invasive meningococcal disease (IMD) caused by Neisseria meningitidis serogroups A, C, W_{135}, and Y (MenA, MenC, MenW_{135} and MenY, respectively) in adolescents. The PBAC had not previously considered this vaccine for adolescents, however a PBAC submission for NIP listing of the vaccine for infants was recommended out-of-session in January 2018. If this submission is recommended the NIP Schedule could include two doses of MenACWY-TT vaccine over the lifespan.

1.2 The submission requested the MenACWY-TT vaccine to be listed on a cost-effectiveness basis compared to no vaccination.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adolescents in Year 10 (15-16 years of age) who are meningococcal vaccine naïve. In addition, a catch-up program is proposed for adolescents/young adults aged up to 19 years of age.
Intervention	A single dose of meningococcal polysaccharide serogroups A, C, W_{135} and Y conjugate vaccine (MenACWY-TT)
Comparator	No vaccine
Outcomes	Immunogenicity, persistence
Clinical claim	MenACWY-TT is superior to the current scenario of 'no vaccine' at preventing IMD caused by *Neisseria meningitidis* and inferior to 'no vaccine' in terms of safety.

IMD: Invasive meningococcal disease. Source: Table 1.1.1, p13 of the submission

2 Requested listing

Suggestions and additions proposed by the Secretariat to the requested NIP listing are added in *italics* and suggested deletions are crossed out with ~~strikethrough~~.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Nationally Negotiated Price	Proprietary Name and Manufacturer
MENINGOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE, SEROGROUPS A, C, W-135 AND Y, Pre-filled syringe, 0.5mL	1	0	$[redacted]	Nimenrix Pfizer Australia Pty Ltd

Category/Program:	NIP
NIP indication:	• A single dose of Nimenrix (MenACWY-TT) for *adolescents aged ~~14~~5 to 16 years* ~~Year 10 students~~ administered via a school-based program* *OR* • A single dose of Nimenrix (MenACWY-TT) for adolescents aged up to 19 years administered via a school-based program catch-up program ~~(Year 11 and 12 students)~~ or accessed via the GP (school-leavers).** **for all adolescents in year 10* *** for all adolescents in year 11 and 12 (or school-leavers) who did not receive the vaccination in year 10*

2.1 The submission proposed an ex-manufacturer price of $[redacted].

2.2 The submission suggested a target age for the vaccination program to be Year 10, however the proposed restriction did not specify the age of vaccination. The NIP Schedule lists immunisations for the target age groups under school programs. ATAGI recommended that the preferred target age for an ongoing vaccination program is 14-15 years (p1 of the ATAGI pre-PBAC submission advice, October 2017). The ESC noted that the ATAGI advice recommended vaccination at year 10, starting 14 to 15 years, that State-based programs have been mostly for year 10 students (see Table 2) and school age entry varies. The ESC advised that the age for vaccination would need to include ages 14 to 16 years to cover all students in year 10. The pre-subcommittee response (PSCR) acknowledged the inconsistent target presented in the submission and stated that the sponsor is willing to work with the NIP to support an approach that is practical for the school setting. The proposed changes to the restriction are outlined above.

Table 2: **Details of State-based MenACWY programs (as at November 2017)**

State	Dates	Vaccine	Target group	Providers
ACT	No program implemented*			
NSW	Term 2 2017 and 2018	Meningococcal ACWY (brand unknown)	School years 11-12	Schools and GPs
NT	Mid November 2017	12 months to <24 months: MenACWY-TT (Nimenrix) 2 years to 19 years: MenACWY (Menactra)	Aged 12 months to 19 years in Central Australia, Barkley and Katherine West regions	Community health centres and GPS
QLD	2017 to May 2018	MenACWY (Menveo and Menactra)	Aged 15-19 years	Schools and GPs
South Australia	Ceduna region: 6 March 2017 to 30 June 2017 APY lands: unknown	2 months to 11 months: MenACWY (Menveo) 12+ months: MenACWY-TT (Nimenrix)	Aged 2 months and older in Ceduna region and APY lands	Community health centres
Tasmania	1 August 2017 to 30 April 2018	MenACWY (brand unknown)	Aged 15-19 years	Schools, GPs and community health centres
Victoria	18 April 2017 until 31 December 2017	MenACWY (Menactra)	Aged 15-19 years	Schools, GPs and community health
Western Australia	April 2017 to 2019	MenACWY-TT (Nimenrix)	Aged 15-19 years	Schools and university health centres, GPs, community health centres

*Information as of November 2017. Since that time, the ACT has implemented a program.

2.3 The proposed catch-up program is an ongoing program for adolescents aged up to 19 years who missed school-based vaccination.

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

3 Background

Registration status

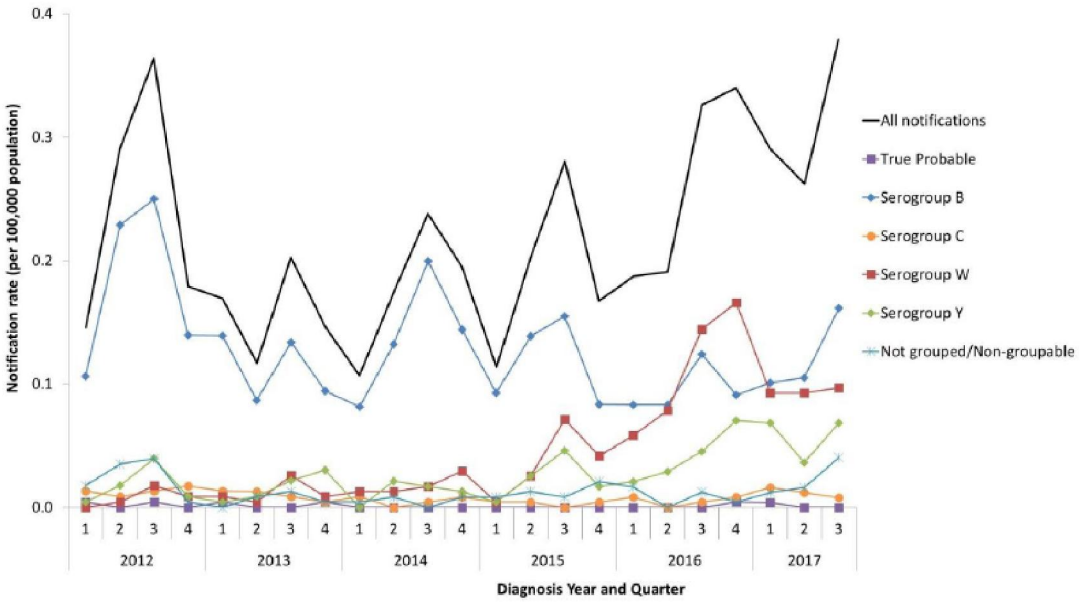
3.1 The MenACWY-TT vaccine was registered on the ARTG on 29 August 2013 for: active immunisation of individuals from the age of 12 months through 55 years against invasive meningococcal diseases caused by *Neisseria meningitidis* serogroups A, C, W_{135} and Y. The ESC noted that ATAGI (Pre-submission advice, p1) had recommended use of the vaccine in several population sub-groups including infants, adolescents and at-risk groups.

4 Population and disease

4.1 IMD is a rare disease caused by the bacterium *Neisseria meningitidis*. IMD can also cause meningitis and sepsis, leading to long-term sequelae including: sensorineural hearing loss, cognitive problems, physical or neurological disability, major amputations, very low IQ, and seizures.[1] About 10 – 30% of survivors of meningococcal disease have permanent sequelae.[2] The case fatality rate for all cases of IMD is around 4.7%[3], however may be higher for MenW.[4]

4.2 There has been an increase in the number of cases caused by MenW and MenY in recent years (see Figures 1 and 2).

Figure 1: Notifications and rates of IMD in Australia (2012 – 2017 by quarter)*, by serogroup

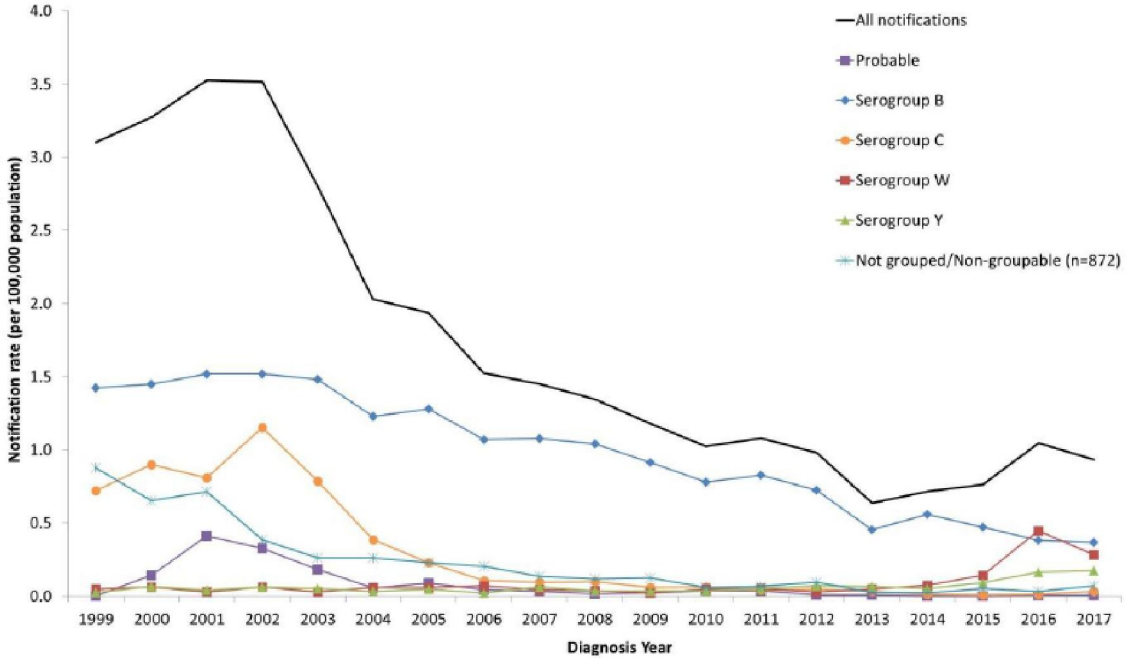


* Data shown is for 1 January 2012 to 11 September 2017. Rates for Q3 2017 were not adjusted for the incomplete observation period of Q3.

Source: NDSS data, access 11 September 2017.

[1] Viner et al (2012). Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study.
[2] Granoff et al (2013). Ch 21 – Meningococcal vaccines. In: Vaccines (6th Edition).
Stoof et al (2015). Disease burden of invasive meningococcal disease in the Netherlands between June 1999 and June 2011: A subjective role for serogroup and clonal complex.
Vyse et al (2013). The burden and impact of severe and long-term sequelae of meningococcal disease.
[3] Australian Government Department of Health (2016) Summary of National Surveillance Data on Vaccine Preventable Diseases in Australia, 2008–2011, Communicable Diseases Intelligence, Volume 40
[4] Australian Government Department of Health (2016) Summary of National Surveillance Data on Vaccine Preventable Diseases in Australia, 2008–2011, Communicable Diseases Intelligence, Volume 40

Figure 2: Notifications and rates of IMD in Australia (1999 - 2017)*, by serogroup



* Data shown is for 1 January 1999 to 11 September 2017. Trends not shown for serogroups A (n=5) and X (n=2). Rates for 2017 are not annualised.

Source: NDSS data, access 11 September 2017.

4.3 There were 337 cases of IMD in Australia from January until November 2017 (National Notifiable Diseases Surveillance System, NNDSS), of which around 37 cases were caused by MenACWY in adolescents, of which three died.[5] The ESC noted the increasing number of IMD cases due to serogroup W and that the characteristics of MenW are similar to those of MenC with a relatively high mortality rate.

4.4 The ESC noted the significant reduction in MenC cases since the introduction of the MenC vaccine for infants in 2003 which included a catch-up program in 2006 and 2007 for people aged 1 to 19 years of age (Figure 2). The ESC further noted the low number of vaccine failures which suggests a strong immunogenic response in those vaccinated through mass immunisation programs as well as herd immunity[6]. The ESC noted ATAGI's caution in directly translating outcomes related to MenC, including international data, to other serogroups in Australia (Post-submission advice p6).

[5] Assuming around 38% were MenB, 4% were MenC, 30% were MenW, 19% were MenY, and 8% were other or unknown strains, and 20% of cases were aged 15-24 years old in 2017. Sources: Australian Government Department of Health (2017) Notifications of a selected disease by age group, sex and year, Available: http://www9.health.gov.au/cda/source/rpt_5_sel.cfm. Accessed 16 November 2017.
Australian Government Department of Health (14 August 2017) Invasive Meningococcal disease national surveillance report.

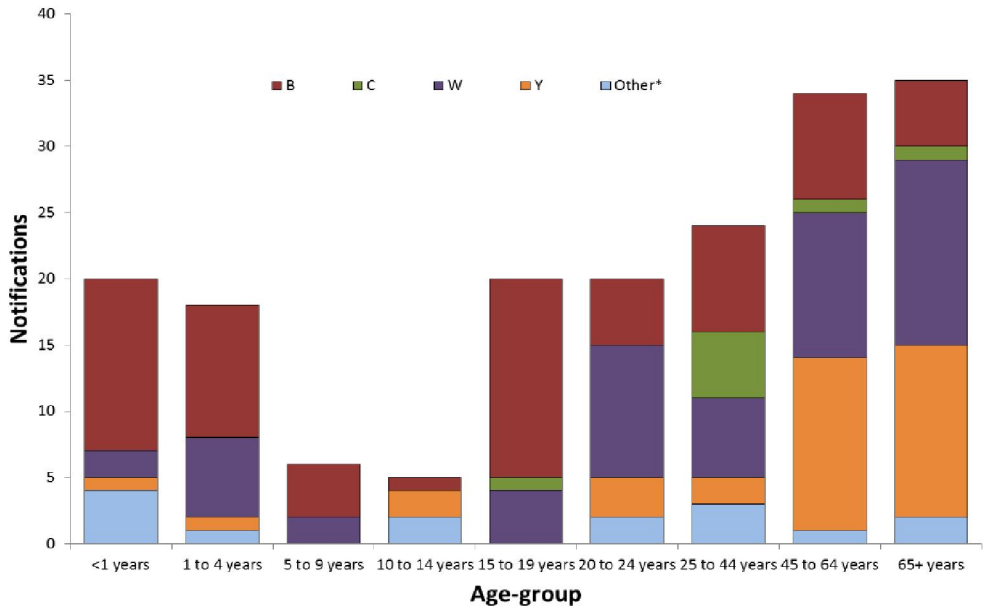
[6] Communicable Diseases Network Australia, *Communicable Diseases Intelligence Supplement: Vaccine Preventable Diseases in Australia, 2005 to 2007, December 2010, Volume 34*

4.5 Overall, the ESC considered that the future incidence of IMD by serogroup without (and with) the MenACWY vaccine was hard to predict.

4.6 The PBAC noted the increase in MenW and Y cases in recent years. The PBAC noted the ESC and ATAGI advice, and specifically the rapid decline in IMD due to MenC post the introduction of the MenC vaccine on to the National Immunisation Program, and the decline of MenB cases in the absence of a national immunisation program. Overall the PBAC noted the variability in the number of meningococcal cases over time and considered that it is difficult to predict future trends.

4.7 The PBAC noted that in the adolescent age group (ages 15-19 years) that the majority of cases of IMD were due to MenB, followed by MenW with very few cases due to MenY and MenC (see Figure 3). In contrast, in the older age groups (45-64 years and 65+ years) a much higher proportion of IMD cases were due to MenW and MenY.

Figure 3: Notifications and rates of IMD in Australia (2017) by age group and serogroup



Source: Invasive Meningococcal Disease National Surveillance Report – with a focus on MenW, Australian Government Department of Health, 30 September 2017

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

5 Comparator

5.1 The submission nominated no vaccine as the main comparator. This was on the basis of there being no national immunisation program for adolescents for the prevention of IMD. However, currently there are several State-based meningococcal programs

for the provision of MenACWY vaccines. The PBAC noted that whilst the State-Based programs are in place, they have varied inclusion criteria and coverage (see Table 2). The ESC and PBAC considered that the nominated comparator was appropriate.

5.2 The submission noted that there are two other quadrivalent meningococcal conjugate (MenACWY) vaccines available in Australia: Menactra and Menveo. The submission argued that these are near-market comparators as they are supplied alongside the MenACWY-TT vaccine in the State-based programs for adolescents (see Table 2) and so a PBAC submission may be lodged for a similar NIP listing. The NIP listing of the MenACWY-TT vaccine may mean that the use of Nimenrix, Menactra and Menveo in the State-based programs would cease. This may impact the supply of non-NIP listed MenACWY-TT vaccines in Australia.

6 Consideration of the evidence

Sponsor hearing

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 single-arm data from ten RCTs and one non-randomised study of the MenACWY-TT vaccine (Nimenrix):

- MenACWY-TT-012 + three extension studies (MenACWY-TT-024 to 26),
- MenACWY-TT-015 + five extension studies (MenACWY-TT-016 to 20),
- MenACWY-TT-021 (non-randomised trial),
- MenACWY-TT-035,
- MenACWY-TT-036 + one extension studies (MenACWY-TT-043),
- MenACWY-TT-037,
- MenACWY-TT-052,
- MenACWY-TT-054,
- MenACWY-TT-084,
- MenACWY-TT-093, and
- MenACWY-TT-098.

6.4 Meta-analyses of immunogenicity data from single-arms of the 11 trials were conducted to estimate the vaccine's response relative to no vaccine.

6.5 The submission did not provide any clinical studies measuring nasopharyngeal meningococcal carriage rates in vaccinated and non-vaccinated recipients, which may indicate the potential herd immunity from the vaccine. The ESC noted that the unpredictable epidemiology around carriage rates and associated invasive disease means that the efficacy of the vaccine at a population level is difficult to quantify, particularly given the absence of studies assessing post vaccination meningococcal carriage. The ESC also noted that it was unclear whether rSBA-Men titres ≥ 1:8 protects against carriage (see below).

6.6 The PBAC agreed with ESC that the carriage rates, and hence impact of herd immunity was uncertain.

6.7 Details of the trials presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
MenACWY-TT-012	104702 (MenACWY-TT-012). A Phase II open (partially double-blind), randomized, controlled, primary vaccination study to assess the immunogenicity, safety and reactogenicity of one intramuscular dose of four different formulations of GlaxoSmithKline (GSK) Biologicals' new generations meningococcal serogroups A, C, W-135, Y-tetanus toxoid conjugate (MenACWY-TT) vaccine versus one subcutaneous dose of MenACWY (Mencevax) in healthy adolescents/young adults aged 15-19 years.	September 2006
	Ostergaard, L., et al. Immunogenicity, reactogenicity and persistence of meningococcal A, C, W-135 and Y-tetanus toxoid candidate conjugate (MenACWY-TT) vaccine formulations in adolescents aged 15-25 years.	*Vaccine* 2009; 27(1):161-8.
MenACWY-TT-015	107386 (MenACWY-TT-015). A phase IIb, open, randomized, controlled primary vaccination study to evaluate the non-inferiority and the persistence of the immune response of GSK Biologicals meningococcal serogroup ACWY conjugate vaccine given intramuscularly versus Mencevax ACWY given subcutaneously to healthy subjects aged 11 to 55 years of age.	April 2009
	Borja-Tabora, C., et al. 2013. Immune response, antibody persistence, and safety of a single dose of the quadrivalent meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine in adolescents and adults: results of an open, randomised, controlled study.	*BMC Infectious Diseases* 2013; 13:116.
MenACWY-TT-021	107408 (MenACWY-TT-021 BST: Mencevax ACWY-004). A phase II, open study to evaluate immunogenicity of GSK Biologicals' MenACWY-TT conjugate vaccine administered intramuscularly to healthy subjects aged 4.5 - 34 years old either previously primed with Mencevax ACWY in GSK Biologicals' study 102394 (Mencevax ACWY-004) or not previously vaccinated with a meningococcal serogroup A, C, W-135, and/or Y vaccine.	September 2009
	Dbaibo, G., et al. 2012a. The tetravalent meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine is immunogenic with a clinically acceptable safety profile in subjects previously vaccinated with a tetravalent polysaccharide vaccine.	*International Journal of Infectious Diseases* 2012; 16(8):e608-15.
MenACWY-TT-035	109067 (MenACWY-TT-035). A phase III, randomized, partially double-blinded, controlled study to demonstrate the lot-to-lot consistency of GSK Biologicals' meningococcal serogroup ACWY conjugate vaccine (GSK134612, MenACWY-TT) and its non-inferiority compared with Mencevax ACWY and to evaluate the co-administration of MenACWY-TT with influenza vaccine in	January 2011

Trial ID	Protocol title/ Publication title	Publication citation
	healthy subjects aged 18 through 55 years of age. Dbaibo G., et al. 2012b. The immunogenicity and safety of an investigational meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (ACWY-TT) compared with a licensed meningococcal tetravalent polysaccharide vaccine: a randomized, controlled non-inferiority study. Aplsaca-De Los Reyes M.R., et al. The investigational meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (ACWY-TT) and the seasonal influenza virus vaccine are immunogenic and well-tolerated when co-administered in adults.	*Human vaccines & Immunotherapeutics* 2012; 8(7): 873 – 80. *Human vaccines & Immunotherapeutics* 2012; 8(7):881-7.
MenACWY-TT-036	109069 (MenACWY-TT-036). A Phase III, randomised, open, controlled, multicenter primary vaccination study to demonstrate the non-inferiority of the immunogenicity of GSK Biologicals' meningococcal serogroup ACWY conjugate vaccine (GSK134612, MenACWY-TT) given intramuscularly versus Mencevax™ ACWY given subcutaneously to healthy subjects aged 11 through 17 years Bermal, N., et al. 2011. Safety and immunogenicity of a tetravalent meningococcal serogroups A, C, W-135 and Y conjugate vaccine in adolescents and adults.	December 2011 *Human Vaccines* 2011; 7(2):239-47.
MenACWY-TT-037	109063 (MenACWY-TT-037). A phase III, randomised, open, controlled, multicentre primary vaccination study to demonstrate the non-inferiority of the immunogenicity of GSK Biologicals' meningococcal serogroup ACWY conjugate vaccine when given as one dose with Twinrix™ versus GSK Biologicals' meningococcal serogroup ACWY conjugate vaccine alone and versus Twinrix™ alone in healthy subjects aged 11 through 17 years Ostergaard, L., et al. 2012. A tetravalent meningococcal serogroups A, C, W-135, and Y tetanus toxoid conjugate vaccine is immunogenic and well-tolerated when co-administered with Twinrix in subjects aged 11-17 years: an open, randomised, controlled trial.	March 2009 *Vaccine* 2012; 30(4):774-83.
MenACWY-TT-052	109377 (MenACWY-TT-052). A Phase II, single-blinded, randomized, controlled, multicenter study to assess the immunogenicity, reactogenicity and safety of one dose of GlaxoSmithKline (GSK) Biologicals' meningococcal serogroups A, C, W-135, Y-tetanus toxoid conjugate (MenACWY-TT) vaccine versus one dose of sanofi-pasteur's meningococcal serogroups A, C, W-135 and Ydiphtheria toxoid conjugate vaccine (Menactra®) in healthy adolescents/adults aged 10-25 years. Baxter, R., et al. Immunogenicity and safety of an investigational quadrivalent meningococcal ACWY tetanus toxoid conjugate vaccine in healthy adolescents and young adults 10 to 25 years of age.	March 2010 *Pediatric Infectious Disease Journal* 2011; 30(3):e41-8.
MenACWY-TT-054	113823 (MenACWY-TT-054). A Phase III, open, randomised, controlled, multicentre study to assess the immunogenicity and reactogenicity of GSK Biologicals' meningococcal serogroups A, C, W-135, Y tetanus toxoid conjugate vaccine (MenACWY-TT) administered alone as compared to MenACWY-TT co-administered with GSK Biologicals' HPV vaccine Cervarix or co-administered with Cervarix and GSK Biologicals' tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Tdap [Boostrix]) in female adolescents and young adults at 9-25 years of age.	May 2017 Clinical Study Report Unpublished
MenACWY-	115524 (MenACWY-TT-084). A phase III, open, controlled study to evaluate	April 2016

Trial ID	Protocol title/ Publication title	Publication citation
TT-084	immunogenicity of GSK Biologicals' MenACWY-TT conjugate vaccine administered intramuscularly to at risk subjects from 1 to less than 18 years and to an age-matched control group of healthy subjects.	Clinical Study Report Unpublished
MenACWY-TT-093	114248 (MenACWY-TT-093). A phase III, partially-blinded, multi-centre, controlled study to assess the safety and immunogenicity of GlaxoSmithKline (GSK) Biologicals' meningococcal serogroup ACWY tetanus-toxoid conjugate vaccine (MenACWY-TT) versus one dose of GSK Biologicals' meningococcal polysaccharides A, C, W-135 and Y vaccine, Mencevax™ ACWY and to assess the clinical comparability of two lots of MenACWY-TT administered in healthy subjects aged 18 through 25 years. Lupisan, S., et al. 2013. Meningococcal polysaccharide A O-acetylation levels do not impact the immunogenicity of the quadrivalent meningococcal tetanus toxoid conjugate vaccine: results from a randomized, controlled phase III study of healthy adults aged 18 to 25 years.	October 2011 *Clinical & Vaccine Immunology* 2013; 20(10):1499-507.
MenACWY-TT-098	116705 (MenACWY-TT-098). A Phase III, randomised, partially-blind, controlled, multi-centre, multi-country study to evaluate the immunogenicity, safety and reactogenicity of GSK Biologicals' MenACWY-TT conjugate vaccine co-administered with Boostrix® administered intramuscularly versus MenACWY-TT alone administered intramuscularly, in healthy adolescents and young adults between 11 and 25 years of age.	May 2017 Clinical Study Report Unpublished

Source: Table 2.2.1, p32-35 of the submission.

6.8 The key features of the 11 trials are summarised in the table below.

Table 4: Key features of the included evidence

Study name	N (in arm of interest)	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
MenACWY-TT-012	MenACWY-TT* (Form 3): 24	R, OL 1 month	Moderate	Healthy subjects aged 15 - 19 years	Immunogenicity Safety Reactogenicity Persistence	Not used
MenACWY-TT-015	MenACWY-TT: 374	R, OL 5 years**	Moderate	Healthy subjects aged 11 - 55 years	Immunogenicity Safety Persistence	Not used
MenACWY - TT-021	MenACWY-TT (No MPS): 79	NR, OL 3.5 years**	High	Healthy subjects aged 4.5 - 34 years	Immunogenicity Safety	Not used
MenACWY - TT-035	MenACWY-TT (ACWY_A: 311 ACWY_B: 311 ACWY_C: 313)*	R, OL 1 month	Moderate	Healthy subjects aged 18 - 55 years	Lot-to-lot consistency of three consecutively manufactured lots of MenACWY-TT Immunogenicity Safety	Not used
MenACWY - TT-036	MenACWY-TT: 768	R, OL 5 years**	Moderate	Healthy subjects aged 11 - 17 years	Immunogenicity Safety Persistence	Not used

Study name	N (in arm of interest)	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
MenACWY - TT-037	MenACWY-TT*: 122	R, OL 1 month	Moderate	Healthy subjects aged 11 - 17 years	Immunogenicity Safety	Not used
MenACWY - TT-052	MenACWY-TT: 587	R, SB 1 month	Moderate	Healthy subjects aged 10 - 25 years	Immunogenicity Reactogenicity Safety	Not used
MenACWY - TT-054 Unpublished	MenACWY-TT*: 259	R, OL 1 month	Moderate	Healthy female aged 9 - 25 years	Immunogenicity Safety Reactogenicity	Not used
MenACWY - TT-084 Unpublished	MenACWY-TT (administered to healthy subjects): 43	R, OL 1 month	Moderate	At risk and healthy subjects age matched 1 - 5 years 6 - 10 years 11 - 17 years	Immunogenicity Safety	Not used
MenACWY - TT-093	MenACWY-TT (ACWY_A: 390, ACWY_B: 390)*	R, OL 1 month	Moderate	Healthy subjects aged 18 - 25 years	Immunogenicity Safety	Not used
MenACWY - TT-098 Unpublished	MenACWY-TT (ACWYTap)*: 228	R, OL 1 month	Moderate	Healthy adolescents and young adults 11 - 25 years	Immunogenicity Safety Reactogenicity	Not used
Meta-analysis	Included all 11 trials, excluding pre-specified subgroups that had age groups outside 15-19 years.					Used

DB=double blind; SB=single blind; OL=open label; R=randomised; NR=non-randomised
MenACWY-TT: Meningococcal serogroups ACWY tetanus toxoid vaccine;
*MenACWY-TT-012: contained 4 different formulations of the MenACWY-TT vaccine. The MenACWY-TT vaccine used in the submission is Form 3;
MenACWY-TT-021: noMPS: subjects who were not previously vaccinated with a meningococcal vaccine received one dose of MenACWY-TT;
MenACWY-TT-035: contained 3 different lots, but the same formulation of MenACWY-TT vaccine;
MenACWY-TT-037: one dose of MenACWY-TT vaccine at study Month 0; the comparator group Twinrix is: Hepatitis A inactivated and Hepatitis B (recombinant) vaccine;
MenACWY-TT-054: for the ACWY-TT group, study subjects were vaccinated at Month 0, with MenACWY-TT, at Month 1, 2 and 7 intramuscular injection of HPV (Human papilloma virus vaccine) (Cervarix), information was analysed at the end of Month 0;
MenACWY-TT-093: contained 2 different lots, but the same formulation of MenACWY-TT vaccine;
MenACWY-TT-098: for the ACWYTap (Diphtheria and tetanus toxoids and acellular pertussis) group, study subjects were vaccinated with one dose of MenACWY-TT at Visit 1 (Month 0) and one dose of Boostrix (Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine) at Visit 2 (Month 1), information was analysed at the end of Month 0.
** including extension studies
Source: Compiled during the evaluation from Table 2.3.1, Table 2.3.2, p40-46 of the submission

6.9 During the evaluation the overall risk of bias for the immunogenicity outcomes was considered moderate in the following trials as they were not analysed on an intent-to-treat basis: MenACWY-TT-012, MenACWY-TT-015, MenACWY-TT-035, MenACWY-TT-36, MenACWY-TT-037, MenACWY-TT-052, MenACWY-TT-054, MenACWY-TT-084, MenACWY-TT-093 and MenACWY-TT-098. Furthermore, it was unclear whether

laboratory personnel were blinded in trials MenACWY-TT-015 and MenACWY-TT-36. The risk of bias was considered high in study MenACWY-TT-021 due to being open-label, non-randomised, and the immunogenicity outcomes for some subjects not being available. The ESC agreed with this assessment.

6.10 Most of the trials (except MenACWY-TT-052) were open-label, and the ESC noted this increases the risk of bias in the safety results as the subjects were aware of the vaccines received. This could lead to an over-estimation or under-estimation of the self-reported adverse events.

Comparative effectiveness

6.11 No direct evidence was presented regarding vaccine efficacy against carriage or disease caused by serogroups A, C, W or Y. The submission argued that pre-registration clinical effectiveness studies were not feasible due to the relatively low incidence of meningococcal disease. Consequently, the submission presented immunogenicity results as a surrogate outcome. This increases uncertainty in the results.

6.12 The submission used 'vaccine response' to measure the immunogenicity of the MenACWY-TT vaccine. 'Vaccine response' was defined for each serogroup as:

- Post-vaccination rSBA titre ≥1:32 in initially seronegative subjects at one month after vaccination, or
- A ≥4-fold rise in the pre-vaccination rSBA titre in initially seropositive subjects (rSBA-Men titres ≥ 1:8) at one month after vaccination. The ESC noted that the rSBA titre required for seropositive subjects was more stringent than for seronegative subjects.

6.13 The submission reported the proportion of subjects with rSBA-Men titres ≥ 1:8 as a secondary clinical outcome. The ESC noted this outcome is less stringent than 'vaccine response'.

6.14 The PBAC has previously accepted the use of rSBA titres > 1:8 as a surrogate outcome to estimate vaccine efficacy[7] in its consideration of the combined haemophilus influenzae type B and Meningococcal C (Hib-MenC) vaccine (Menitorix), which used rabbit complement SBA (rSBA) titres > 1:8 to estimate vaccine efficacy. However, there is no established surrogate serological correlate of protection for non-MenC serogroups. This level was based on a study from the 1960s assessing the bactericidal activity of an Army recruit population for susceptibility to meningococcal disease, which found that human complement SBA (hSBA) titres < 1:4

[7] PBAC (*November 2010) Public summary document: Haemophilus influenzae type b and group c meningococcal polysaccharide conjugate vaccine, lyophilised powder for injection, 1 vial with 0.5 mL pre-filled syringe diluent, 10 vials with 10 0.5 mL pre-filled syringe diluent, Menitorix.*

was correlated with the development of MenC.[8] In addition, another study found that hSBA ≥1:4 were correlated with clinical protection against MenA, MenB and MenC.[9] ATAGI noted (Post-submission advice p6) assays which the use rSBA are easier to perform than those using hSBA due to the easy availability of the complement source and the ability to standardise the assay across different laboratories, making the results more directly comparable across studies.

6.15 The ESC advised that the lack of a surrogate serological correlate of protection increases uncertainty regarding the efficacy of the MenACWY-TT vaccine against IMD caused by serogroups A, W and Y.

6.16 ATAGI considered that 'vaccine response' is a reasonable measure to estimate vaccine efficacy in the short term for the economic evaluation. In terms of clinical efficacy, ATAGI accepted that rSBA titre ≥ 1:8 is an appropriate serological correlation of protection against serogroups A, C, W and Y in the short term (p10 of ATAGI pre-submission advice). The PBAC noted that vaccine response was used as a surrogate measure to inform efficacy in the economic model and that a better alternative measure was not available.

6.17 Table 5 presents a summary of the vaccine response results across the trials.

[8] *Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. Journal of Experimental Medicine, 1969, 129:1307–1326.*

[9] *Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. II. Development of natural immunity. Journal of Experimental Medicine, 1969, 129:1327–1348.*

Table 5: Total vaccine response rates for rSBA-MenA, rSBA-MenC, rSBA-MenW and rSBA-MenY across trials (ATP immunogenicity cohort)

Trial	Trial Arm	rSBA-MenA		rSBA-MenC		rSBA-MenW		rSBA-MenY	
		n/N (%)	95%CI	n/N (%)	95%CI	n/N (%)	95%CI	n/N (%)	95%CI
MenACWY-TT-012	Form 3	20/23 (87)	(66.4, 97.2)	23/24 (95.8)	(78.9, 99.9)	21/23 (91.3)	(72, 98.9)	19/24 (79.2)	(57.8, 92.9)
MenACWY-TT-015	ACWY-TT	239/289 (82.7)	(77.8, 86.9)	306/324 (94.4)	(91.4, 96.7)	314/326 (96.3)	(93.7, 98.1)	306/329 (93)	(89.7, 95.5)
	ACWY-TT (TVC analysis)	261/319 (81.8)	(77.1, 85.9)	331/355 (93.2)	(90.1, 95.6)	342/356 (96.1)	(93.5, 97.8)	331/360 (91.9)	(88.6, 94.5)
MenACWY-TT-021	noMPS	50/65 (76.9)	(64.8, 86.5)	68/70 (97.1)	(90.1, 99.7)	72/74 (97.3)	(90.6, 99.7)	71/74 (95.9)	(88.6, 99.2)
	noMPS (TVC analysis)	54/69 (78.3)	(66.7, 87.3)	72/74 (97.3)	(90.6, 99.7)	76/78 (97.4)	(91, 99.7)	75/78 (96.2)	(89.2, 99.2)
MenACWY-TT-035	ACWY-TT	595/743 (80.1)	(77, 82.9)	777/849 (91.5)	(89.4, 93.3)	776/860 (90.2)	(88.1, 92.1)	750/862 (87)	(84.6, 89.2)
	ACWY-TT (TVC analysis)	613/769 (79.7)	(76.7, 82.5)	807/880 (91.7)	(89.7, 93.4)	807/892 (90.5)	(88.4, 92.3)	775/894 (86.7)	(84.3, 88.8)
MenACWY-TT-036	ACWY-TT	525/615 (85.4)	(82.3, 88.1)	698/719 (97.1)	(95.6, 98.2)	692/717 (96.5)	(94.9, 97.7)	686/737 (93.1)	(91, 94.8)
MenACWY-TT-037	ACWY-TT	76/84 (90.5)	(82.1, 95.8)	101/112 (90.2)	(83.1, 95)	112/114 (98.2)	(93.8, 99.8)	105/113 (92.9)	(86.5, 96.9)
MenACWY-TT-052	ACWY-TT	428/458 (93.4)	(90.8, 95.5)	454/477 (95.2)	(92.9, 96.9)	491/495 (99.2)	(97.9, 99.8)	476/493 (96.6)	(94.5, 98)
	ACWY-TT (TVC analysis)	467/502 (93)	(90.4, 95.1)	500/530 (94.3)	(92, 96.1)	537/543 (98.9)	(97.6, 99.6)	522/540 (96.7)	(94.8, 98)
MenACWY-TT-054	ACWY-TT	[redacted]							
MenACWY-TT-084	Healthy								
MenACWY-TT-093	ACWY_A	239/302 (79.1)	(74.1, 83.6)	324/346 (93.6)	(90.5, 96)	328/338 (97)	(94.6, 98.6)	334/358 (93.3)	(90.2, 95.7)
	ACWY_B	238/298 (79.9)	(74.9, 84.3)	327/342 (95.6)	(92.9, 97.5)	312/327 (95.4)	(92.5, 97.4)	324/353 (91.8)	(88.4, 94.4)
MenACWY-TT-098	ACWYTdap	[redacted]							

95%CI: exact 95% confidence interval, ATP: According to Protocol Cohort, n: number of subjects with a vaccine response, N: number of subjects with pre and post vaccination results, TVC: Total Vaccinated Cohort; rSBA: serum bactericidal assay using rabbit complement; Vaccine response defined as: For initially seronegative subjects: post-vaccination antibody titre ≥ 1:32 at 30 days post vaccination; for initially seropositive subjects: antibody titre at 30 days post vaccination ≥ 4 fold the pre-vaccination antibody titre.

Source: Table 2.5.1, Table 2.5.2, Table 2.5.3 and Table 2.5.4, p87-p90 of the submission

6.18 Vaccine response was lowest for serogroup A across all trials. There is a low incidence of this serogroup in Australia.

6.19 The ESC noted the proportion of seronegative subjects with a vaccine response was higher than for seropositive subjects.

6.20 Seropositivity (rSBA titres ≥1:8) may be a result of previous vaccination, asymptomatic carriage, infection with *Neisseria meningitidis*, or exposure to other non-pathogenic Neisseria bacteria (e.g. *N. lactamica*) or cross-reacting organisms including *E. coli* (ATAGI Post-submission advice, p2). The ESC noted that the rate of seroprevalence (proportion of seropositive subjects) in the trials was high in comparison to that expected in Australia. The advice from ATAGI (Post-submission advice, P2) stated that the rates of seroprevalence in the Australian adolescent population are negligible and the levels of pre-existing immunity in the studies were not generalisable to the Australian setting. ATAGI added that estimates derived from seronegative study participants may more closely resemble that expected in the Australian population, however ATAGI also noted that seroprevalence may have changed given recent vaccination programs and changing disease epidemiology.

6.21 Overall, the ESC and PBAC noted that if the seroprevalence rates were lower in the Australian setting that the vaccine response rates may be higher than reported in the trials.

6.22 A meta-analysis based on the "All studies" subgroup was performed and the results were used in the economic model to estimate the vaccine efficacy weighted by serogroup prevalence in Australia. The "All studies" subgroup included all 11 trials, excluding pre-specified subgroups that had age groups outside the proposed listing population (15-19 years). The meta-analysis results for vaccine response for the "All studies" subgroup are presented in Table 6.

6.23 The pooled vaccine response rates from "All studies" for rSBA-MenA, rSBA-MenC, rSBA-MenW and rSBA-MenY were 86.8%, 95.1%, 96.5% and 93.5% respectively.

6.24 The heterogeneity across the trials for rSBA-MenA, rSBA-MenW, rSBA-MenY was high with I^2 values of 84%, 50% and 50%, respectively. For rSBA-MenC, the heterogeneity was lower with an I^2 value of 21%.

Table 6: Meta-analyses of vaccine response results for the "All studies" subgroup

Trial ID	Arm of interest	Pre-specified age subgroup	rSBA-MenA		rSBA-MenC		rSBA-MenW		rSBA-MenY	
			n/N(%)	Odds (Random effects,95%CI)	n/N(%)	Odds (Random effects,95%CI)	n/N(%)	Odds (Random effects, 95%CI)	n/N(%)	Odds (Random effects, 95%CI)
MenACWY-TT-012	Form 3		20/23 (87)	6.67 (1.98, 22.43)	23/24 (95.8)	23.00 (3.11, 170.31)	21/23 (91.3)	10.50 (2.46, 44.78)	19/24 (79.2)	3.80 (1.42, 10.18)
MenACWY-TT-015	ACWY-TT		239/289 (82.7)	4.78 (3.52, 6.48)	306/324 (94.4)	17.00 (10.57, 27.35)	314/326 (96.3)	26.17 (14.70, 46.57)	306/329 (93)	13.30 (8.71, 20.33)
MenACWY-TT-021	noMPS	11 - 17 years	11/17 (64.7)	1.83 (0.68, 4.96)	18/19 (94.7)	18.00 (2.41, 134.83)	20/20 (100)	41.00 (2.48, 677.89)	19/20 (95.0)	19.00 (2.54, 141.93)
		18 - 34 years	17/26 (65.4)	1.89 (0.84, 4.24)	25/26 (96.2)	25.00 (3.39, 184.50)	25/27 (92.6)	12.50 (2.96, 52.77)	27/27 (100)	55.00 (3.35, 901.65)
MenACWY-TT-035	ACWY-TT	18 - 25 years	147/177 (83.1)	4.90 (3.31, 7.26)	193/204 (94.6)	17.55 (9.56, 32.21)	193/209 (92.3)	12.06 (7.24, 20.09)	194/213 (91.1)	10.21 (6.37, 16.36)
MenACWY-TT-036	ACWY-TT		525/615 (85.4)	5.83 (4.66, 7.30)	698/719 (97.1)	33.24 (21.53, 51.30)	692/717 (96.5)	27.68 (18.57, 41.25)	686/737 (93.1)	13.45 (10.12, 17.88)
MenACWY-TT-037	ACWY-TT		76/84 (90.5)	9.50 (4.58, 19.68)	101/112 (90.2)	9.18 (4.93, 17.11)	112/114 (98.2)	56.00 (13.83, 226.69)	105/113 (92.9)	13.12 (6.40, 26.93)
MenACWY-TT-052	ACWY-TT		428/458 (93.4)	14.27 (9.85, 20.66)	454/477 (95.2)	19.74 (12.98, 30.01)	491/495 (99.2)	122.75 (45.89, 328.36)	476/493 (96.6)	28.00 (17.26, 45.42)
MenACWY-TT-054	ACWY-TT	15-17 years	[redacted]							
		18 - 25 years								
MenACWY-TT-084	ACWY-TT	11 - 17 years								
MenACWY-TT-093	ACWY-TT		477/600 (79.5)	3.88 (3.18, 4.73)	651/688 (94.6)	17.59 (12.63, 24.50)	640/665 (96.2)	25.60 (17.17, 38.17)	658/711 (92.5)	12.42 (9.38, 16.42)
MenACWY-TT-098	Healthy									
Meta-analysis of overall trial results				6.60 (4.72, 9.22)		19.35 (15.64, 23.93)		27.69 (19.62, 39.06)		14.45 (11.24, 18.57)
Pooled results (%				86.8%		95.1%		96.5%		93.5% (91.8%,

Trial ID	Arm of interest	Pre-specified age subgroup	rSBA-MenA		rSBA-MenC		rSBA-MenW		rSBA-MenY	
			n/N(%)	Odds (Random effects,95%CI)	n/N(%)	Odds (Random effects,95%CI)	n/N(%)	Odds (Random effects, 95%CI)	n/N(%)	Odds (Random effects, 95%CI)
vaccine response)				(82.52%, 90.21%)		(94.0%. 96.0%)		(95.2%, 97.5%)		94.9%)
I^2 with 95% uncertainty interval				I^2 = 84%		I^2 = 21%		I^2 = 50%		I^2 = 50%

95%CI: exact 95% confidence interval, n: number of subjects with a vaccine response, N: number of subjects with pre and post vaccination results; rSBA: serum bactericidal assay using rabbit complement

Vaccine response defined as: For initially seronegative subjects: post-vaccination antibody titre ≥ 1:32 at 30 days post vaccination; For initially seropositive subjects: antibody titre at 30 days post vaccination ≥ 4 fold the pre-vaccination antibody titre.

Source: Table 2.6.1, Table 2.6.2, Table 2.6.3 and Table 2.6.4, p145- 148 of the submission.

6.25 The results for the proportion of subjects with rSBA-Men titres ≥ 1:8 were as follows:

- Serogroup A ranged from 5.0% to 100% pre-vaccination and 99.5% to 100% at one month post-vaccination.
- Serogroup C ranged from 13.3% to 79.2% pre-vaccination and 97.5% to 100% at one month post-vaccination.
- Serogroup W ranged from 7.5% to 86.3% pre-vaccination and 97.5% to 100% at one month post-vaccination.
- Serogroup Y ranged from 20.0% to 94.2% pre-vaccination and 99.1% to 100% at one month post-vaccination.

6.26 The submission reported the results from the persistence studies using the primary outcome of the proportion of subjects with rSBA titres ≥ 1:8. The results are presented in Table 7.

6.27 The persistence studies showed that at least 71.6% of subjects who received the MenACWY-TT vaccine had rSBA ≥1:8 at five years post-vaccination.

6.28 A significant proportion of subjects were lost to follow-up (subjects used in analysis: 58-90% in Year 3, 51-84% in Year 4 and 14-31% of the original cohort) and so the persistence results should be interpreted with caution. The ESC noted persistence of effect out to 5 years although considered the persistence uncertain given the loss to follow-up. Use of single-arms of RCTs does not take into account rates of natural immunity. The ESC noted that the natural history of meningococcal disease remains unpredictable, but it appears that introduction of the MenC vaccine to infants and via an initial catch-up program had a very significant and ongoing impact on the incidence of MenC.

6.29 The PBAC noted the results of the meta-analysis, the persistence data and ATAGI's advice (Pre-Submission Advice, p15) that it is likely that waning occurs in the 5 years post-vaccination and that duration of protection post-vaccination should be assumed to be no longer than 5 years.

Table 7: Persistence of rSBA ≥1:8 reported at each year post-vaccination (ATP & TVC cohort for persistence)

Extension studies	Endpoints reported	Analysis	rSBA-MenA		rSBA-MenC		rSBA-MenW-135		rSBA-MenY	
			n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
Extension of original trial (MenACWY-TT-015)										
MenACWY-TT-016	Year 1	ATP (GSK)	353/354 (99.7)	(98.4, 100)	352/353 (99.7)	(98.4, 100)	355/356 (99.7)	(98.4, 100)	355/355 (100)	(99.0, 100)
MenACWY-TT-017	Year 2	ATP (GSK)	337/338 (99.7)	(99.7, 98.4)	343/345 (99.4)	(97.9, 99.9)	344/346 (99.4)	(97.9, 99.9)	344/345 (99.7)	(98.4, 100)
MenACWY-TT-018	Year 3	ATP (GSK)	322/322 (100)	(98.9, 100)	334/337 (99.1)	(97.4, 99.8)	335/336 (99.7)	(98.4, 100)	337/338 (99.7)	(98.4, 100)
		TVC	328/328 (100)	(98.9, 100)	340/343 (99.1)	(97.5, 99.8)	341/342 (99.7)	(98.4, 100)	343/344 (99.7)	(98.4, 100)
MenACWY-TT-019	Year 4	ATP (PHE)	270/312 (86.5)	(82.2, 90.1)	276/312 (88.5)	(84.4, 91.8)	231/312 (74)	(68.8, 78.8)	256/309 (82.8)	(78.2, 86.9)
MenACWY-TT-020	Year 5	TVC (PHE)	269/299 (90)	(86, 93.1)	237/299 (79.3)	(74.2, 83.7)	214/299 (71.6)	(66.1, 76.6)	252/299 (84.3)	(79.7, 88.2)
Extension of original trial (MenACWY-TT-012)										
MenACWY-TT-024	Year 1.5	ATP	21/21 (100) L11 strain	(83.9, 100)	21/21 (100)	(83.9, 100)	21/21 (100) 3193 strain	(83.9, 100)	21/21 (100)	(83.9, 100)
		TVC	23/23 (100)	(85.2, 100)	23/23 (100)	(85.2, 100)	23/23 (100)	(85.2, 100)	23/23 (100)	(85.2, 100)
MenACWY-TT-025	Year 2.5	ATP	18/18 (100) L10 strain	(81.5, 100)	18/18 (100)	(81.5, 100)	19/19 (100) MP strain	(82.4, 100)	19/19(100)	(82.4, 100)
		TVC	21/21 (100)	(83.9, 100)	21/21 (100)	(83.9, 100)	22/22 (100)	(84.6, 100)	22/22 (100)	(84.6, 100)
MenACWY-TT-026	Year 3.5	ATP	18/18 (100) L11 strain	(81.5, 100) L11 strain	19/19 (100)	(82.4, 100)	19/19 (100) MP strain	(82.4, 100)	19/19 (100)	(82.4, 100)
		TVC	21/21 (100)	(83.9, 100)	22/22 (100)	(84.6, 100)	22/22 (100) MP strain	(84.6, 100)	22/22 (100)	(84.6, 100)
		ATP	17/17 (100) L10 strain	(80.5, 100) L10 strain						
		TVC	20/20 (100)	(83.2, 100)						
Extension of original trial (MenACWY-TT-036)										
MenACWY-TT-043	Year 2	ATP (GSK)	404/405 (99.8)	(98.6, 100)	404/407 (99.3)	(97.9, 99.8)	405/407 (99.5)	(98.2, 99.9)	407/407 (100)	(99.1, 100)
		TVC	476/477 (99.8)	(98.8, 100)	476/480 (99.2)	(97.9, 99.8)	478/480 (99.6)	(98.5, 99.9)	480/480 (100)	(99.2, 100)
	Year 3	ATP (PHE)	417/449 (92.9)	(90.1, 95.1)	409/449 (91.1)	(88.1, 93.6)	368/449 (82.0)	(78.1, 85.4)	418/449 (93.1)	(90.3, 95.3)
	Year 4	ATP (PHE)	353/391 (90.3)	(86.9, 93)	367/390 (94.1)	(91.3, 96.2)	301/390 (77.2)	(72.7, 81.3)	348/389 (89.5)	(86, 92.3)

Extension studies	Endpoints reported	Analysis	rSBA-MenA		rSBA-MenC		rSBA-MenW-135		rSBA-MenY	
			n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI	n/N (%)	95% CI
	Year 5	ATP (PHE)	230/236 (97.5)	(94.5, 99.1)	209/236 (88.6)	(83.8, 92.3)	203/236 (86)	(80.9, 90.2)	228/236 (96.6)	(93.4, 98.5)
		TVC	347/355 (97.7)	(95.6, 99)	324/355 (91.3)	(87.8, 94)	302/355 (85.1)	(80.9, 88.6)	341/355 (96.1)	(93.5, 97.8)

Abbreviations: 95%CI: exact 95% confidence interval, ATP (GSK): According to Protocol Cohort performed at the GSK laboratory, ATP (PHE): According to Protocol Cohort performed at the Public Health of England laboratory, n: number of subjects with titre within the specified range, N: number of subjects with available results, TVC: Total Vaccinated Cohort, TVC(PHE): Total Vaccinated Cohort performed at the Public Health of England laboratory; rSBA: serum bactericidal assay using rabbit complement

Source: Table 2.5.14, p105 of the submission.

Comparative harms

6.30 Table 8 presents a summary of the safety results across the trials.

6.31 Overall, vaccine related adverse events ranged from 40 - 70.7%. Grade 3 adverse events ranged from 0-11.6%. Vaccine related local symptoms (23.3-62.8%) were reported more frequently than general symptoms (15.2-51.4%) (any grade).

6.32 Across all trials, the most common solicited local adverse events were pain (19.4-59%, Grade 3 <3.5%), redness (12.3-33.3%) and swelling (7.9-26%).

6.33 Six trials reported serious adverse events (SAE), of which adverse events from two trials were considered potentially related to the MenACWY-TT vaccine. In trial MenACWY-TT-036, one subject reported experiencing abdominal pain and gastritis. In trial MenACWY-TT-093, one subject became pregnant post-vaccination and it was an anembryonic pregnancy which was considered to be related to the vaccination.

Table 8: Percentage of subjects reporting vaccine related solicited and unsolicited symptoms (regardless of intensity) and grade 3 solicited and unsolicited symptoms reported during the post-vaccination period# (Total Vaccinated cohort)

		Vaccine related solicited and unsolicited symptoms						Grade 3 solicited and unsolicited symptoms					
Trial	**Arm**	**Any symptom***		**General symptoms**		**Local symptoms**		**Any symptom**		**General symptoms**		**Local symptoms**	
		n/N (%)	**95%CI**	**n/N (%)**	**95%CI**	**n/N (%)**	**95%CI**	**n/N (%)**	**95%CI**	**n/N (%)**	**95%CI**	**n/N (%)**	**n/N (%)**
MenACWY-TT-012#*	Form 3	16/24 (66.7)	(44.7, 84.4)	12/24 (50)	(29.1, 70.9)	13/24 (54.2)	(32.8, 74.4)	0/24 (0)	(0, 14.2)	0/24 (0)	(0, 14.2)	0/24 (0)	(0, 14.2)
MenACWY-TT-015	ACWY-TT	174/374 (46.5)	(41.4, 51.7)	57/374 (15.2)	(11.8, 19.3)	162/374 (43.3)	(38.2, 48.5)	12/374 (3.2)	(1.7, 5.5)	5/374 (1.3)	(0.4, 3.1)	9/374 (2.4)	(1.1, 4.5)
MenACWY-TT-21	no MPS	37/79 (46.8)	(35.5, 58.4)	17/79 (21.5)	(13.1, 32.2)	33/79 (41.8)	(30.8, 53.4)	3/79 (3.8)	(0.8, 10.7)	2/79 (2.5)	(0.3, 8.8)	2/79 (2.5)	(0.3, 8.8)
MenACWY-TT-035	ACWY-TT	300/935 (32.1)	(29.1, 35.2)	169/935 (18.1)	(15.7, 20.7)	218/935 (23.3)	(20.6, 26.2)	37/935 (4)	(2.8, 5.4)	22/935 (2.4)	(1.5, 3.5)	18/935 (1.9)	(1.1, 3)
MenACWY-TT-036	ACWY-TT	307/768 (40.0)	(36.5, 43.5)	151/768 (19.7)	(16.9, 22.7)	241/768 (31.4)	(28.1, 34.8)	26/768 (3.4)	(2.2, 4.9)	12/768 (1.6)	(0.8, 2.7)	14/768 (1.8)	(1, 3)
MenACWY-TT-037	ACWY-TT	76/122 (62.3)	(53.1, 70.9)	30/122 (24.6)	(17.2, 33.2)	65/122 (53.3)	(44.0, 62.4)	7/122 (5.7)	(2.3, 11.5)	2/122 (1.6)	(0.2, 5.8)	6/122 (4.9)	(1.8, 10.4)
MenACWY-TT-052#	ACWY-TT (Day 0-3)	390/587 (66.4)	(62.5, 70.3)	227/587 (38.7)	(34.7, 42.7)	339/587 (57.8)	(53.6, 61.8)	42/587 (7.2)	(5.2, 9.5)	21/587 (3.6)	(2.2, 5.4)	23/587 (3.9)	(2.5, 5.8)
MenACWY-TT-052#	ACWY-TT (Day 0-7)	402/587 (68.5)	(64.6, 72.2)	243/587 (41.4)	(37.4, 45.5)	341/587 (58.1)	(54.0, 62.1)	55/587 (9.4)	(7.1, 12.0)	35/587 (6.0)	(4.2, 8.2)	23/587 (3.9)	(2.5, 5.8)
MenACWY-TT-054#	ACWY-TT	[redacted]											
MenACWY-TT-084	Healthy	[redacted]											
MenACWY-TT-093	ACWY-A	271/390 (69.5)	(64.7, 74.0)	176/390 (45.1)	(40.1, 50.2)	231/390 (59.2)	(54.2, 64.1)	15/390 (3.8)	(2.2, 6.3)	6/390 (1.5)	(0.6, 3.3)	10/390 (2.6)	(1.2, 4.7)
	ACWY-B	268/390 (70.3)	(63.9, 73.3)	168/390 (43.1)	(38.1, 48.2)	226/390 (57.9)	(52.9, 62.9)	16/390 (4.1)	(2.4, 6.6)	8/390 (2.1)	(0.9, 4)	8/390 (2.1)	(0.9, 4)
MenACWY-TT-098	ACWYTdap	[redacted]											

95%CI – exact 95% confidence interval, n- number of subjects presenting with symptom, N- number of subjects with at least one documented dose.

Post-vaccination period was 4 days (Day 0-3) in all studies except for MenACWY-TT-012, it was 8 days (Day 0 – 7); for MenACWY-TT-052, 4 days was reported in addition to 8 days (Day 0-7) and for MenCWY-TT-054, it was 7 days (Day 0 – 6).

* MenACWY-TT-012: did not report on vaccine related solicited and unsolicited symptoms, only reported all solicited and unsolicited symptoms during the post-vaccination period

Source: Table 2.5.19, Table 2.5.20 and Table 2.5.21, p116 -118 of the submission.

Benefits/harms

6.34 A summary of the comparative benefits and harms for the MenACWY-TT vaccine versus no vaccine is presented in Table 9 below. The comparative harms were based on the clinical trials. The comparative benefits were derived from the economic model, which converted the estimated immunogenicity results from the clinical trials into the number of IMD cases and deaths avoided. Concerns regarding quantification of the number of IMD cases and deaths avoided based on the immunogenicity results are discussed in the Economic section below.

Table 9: Summary of comparative benefits and harms for the MenACWY-TT versus no vaccination

Trial	MenACWY-TT	No vaccination	Difference	Event rate/100 vaccinations		RD (95% CI)	NNT**
				MenACWY-TT	No vaccination		
Benefits							
IMD cases (based on economic model)*							
Over 85 years	6,316	7,980	-1,664	NA	NA	NA	2,838
IMD Deaths (based on economic model)*							
Over 85 years	508	646	-139	NA	NA	NA	34,092
Harms							
	MenACWY-TT n/N	**No vaccination n/N**	**RR (95% CI)**	**Event rate/100 vaccinations**		**RD (95% CI)**	**NNH##**
				MenACWY-TT	**No vaccination**		
Grade 3 solicited and unsolicited symptoms							
MenACWY-TT-012#	0/24	NA	NA	0.0%	NA	NA	NA
MenACWY-TT-015	12/374	NA	NA	3.2%	NA	NA	31.25
MenACWY-TT-21	3/79	NA	NA	3.8%	NA	NA	26.32
MenACWY-TT-035	37/935	NA	NA	4.0%	NA	NA	25.00
MenACWY-TT-036	26/768	NA	NA	3.4%	NA	NA	29.41
MenACWY-TT-037	7/122	NA	NA	5.7%	NA	NA	17.54
MenACWY-TT-052#	42/587	NA	NA	7.2%	NA	NA	13.89
MenACWY-TT-052#	55/587	NA	NA	9.4%	NA	NA	10.64
MenACWY-TT-054#	[redacted]						
MenACWY-TT-084	[redacted]						
MenACWY-TT-093	[redacted]						
MenACWY-TT-098	[redacted]						

NA: not available; RD: risk difference; RR: relative risk

* The results from the economic model were presented as they are more clinically relevant than the immunogenicity results reported by the clinical trials. See Comparative effectiveness for a summary of the immunogenicity results.

** Number needed to vaccinate to avoid one case = 4,722,130 vaccinated / cases or deaths avoided (calculated from Nimenrix Economic Model_Section 3)

Post-vaccination period was 4 days (Day 0-3) in all studies except for MenACWY-TT-012, it was 8 days (Day 0 – 7); for MenACWY-TT-052, 4 days was reported in addition to 8 days (Day 0-7) and for MenACWY-TT-054, it was 7 days (Day 0 – 6).

Number needed to harm = 1/event rate

Source: Table 2.5.21, p118 of the submission.

6.35 On the basis of the results of the economic model presented by the submission:

- Approximately 1,664 IMD cases would be avoided over 85 years if 80% of adolescents in the school-based program and 22% of adolescents in the out-of-school program are vaccinated. Approximately 2,838 individuals would need to be vaccinated with the MenACWY-TT vaccine to avoid one IMD case.
- Approximately 139 deaths would be avoided over 85 years if 80% of adolescents in the school-based program and 22% of adolescents in the out-of-school program are vaccinated. Approximately, 34,092 individuals would need to be vaccinated with the MenACWY-TT vaccine to avoid one death.

6.36 The ESC noted these estimates are based on modelling and not actual observed patterns as direct data are not available. The number of cases of meningococcal disease and deaths prevented by adolescent immunisation could be higher or lower that these estimates.

6.37 On the basis of single arm studies presented by the submission, for every 100 subjects vaccinated with the MenACWY-TT vaccine, approximately six additional subjects would experience Grade 3 solicited (pain, redness and swelling) or unsolicited symptoms (infections, infestation, otitis externa and scarlet fever). Approximately one Grade 3 solicited or unsolicited symptoms would occur in every 17 vaccinations.

Clinical claim

6.38 The submission described the MenACWY-TT vaccine as superior in terms of efficacy and inferior in terms of safety compared to no vaccine.

6.39 Regarding the efficacy claim it should be noted that:

- There were no placebo controlled RCTs of the MenACWY-TT vaccine and hence the submission was based on single-arm data from ten RCTs and one non-randomised trial of the MenACWY-TT vaccine.
- There is no established surrogate serological correlate of protection for non-MenC serogroups.
- The PBAC has not previously considered the measure of vaccine response.
- For all trials, most of the subjects were seropositive prior to vaccination, which may lead to the vaccine response being non-generalisable to the Australian setting.
- Most of the trials were open-label, which increases the risk of bias for the safety outcomes as the subjects were aware of the vaccines received.

- The submission did not provide any clinical studies measuring nasopharyngeal meningococcal carriage rates in vaccinated and non-vaccinated recipients, which may indicate the potential herd immunity from the vaccine.

6.40 The ESC and PBAC noted ATAGI's advice that the harms were relatively minor and manageable.

6.41 The PBAC considered that the claim of superior comparative effectiveness compared with no vaccine was reasonable based on the immunogenicity results.

6.42 The PBAC considered that the claim of inferior comparative safety was reasonable; although noted MenACWY-TT appears to have an acceptable safety profile in adolescents.

Economic analysis

6.43 The submission presented a cost-effectiveness (cost per life year saved) and cost-utility (cost per quality adjusted life year (QALY) saved) analysis of vaccinating adolescents as part of a combined school based program and an on-going catch-up program. Health benefits were estimated directly for vaccinated cohorts until 84 years, and indirectly for all 0-84-year-old Australians through herd immunity, compared to a scenario of no immunisation. A summary of the model structure is presented in the table below.

Table 10: Summary of model structure and rationale

Component	Summary
Time horizon	Follow-up of Australians currently aged 0-84 years until age 85 years. Hence a maximum time horizon of 85 years and minimum time horizon of 1 year
Outcomes	Non-fatal and fatal IMD events prevented, years of life saved and QALYs saved.
Methods used to generate results	Decision analysis. Markov state-transition modelling. Cohort expected value analysis.
Health states	1. 'Alive without prior IMD' 2. 'Alive post IMD and without long-term complications' 3. 'Alive post IMD and with long-term complications' 4. 'Dead'
Utilities	Alive and no previous IMD, and Alive post IMD without long term complications: Australian population norms (AQoL) from Hawthorne 2013. Alive post IMD with long-term complications: Tu (2014) and Wang et al (2014). A weighting of 80.5% for major complications (and 19.5% for minor complications) was relatively high compared to previous published economic evaluations.
Cycle length	1 year
Transition probabilities	Background incident IMD. Background incident rates of IMD were based on a single year of incidence data (2016-2017) and were assumed to be constant over the 85-year projection in the model. Case-fatality ratios were taken from ATAGI pre submission advice. This is reasonable, however uncertain as the future dynamics of the incidence of IMD caused by MenY and MenW is unknown. Likelihood of long-term complications among survivors of IMD: ATAGI advice (October 2017) (Wang et al 2014). The evidence base is limited, although ATAGI supported the use of this dataset (p20 of the ATAGI pre-submission advice). Background mortality: Australian Bureau of Statistics, 2016 data. This is appropriate. Relative increase in risk of mortality among survivors of IMD with long-term complications: published sources (Roed et al 2015). This is reasonable. Vaccine efficacy: Pooled vaccine response from clinical trials presented in Section 2, weighted by serogroup prevalence in Australia. Vaccine waning: assumed to wane by 5% per year until Year 5, and 50% per year thereafter. Herd immunity: a linear reduction was assumed from Year 2 to Year 10, so baseline IMD incidence reduced by 67% in Year 10 (based on data from the MenC program in the UK). The reduction was sustained until Year 17, then diminished, so by Year 27 no relative risk reduction was apparent.

ATAGI: Australian Technical Advisory Group on Immunisation, IMD: invasive meningococcal disease, MenY: Neisseria meningitidis serogroup Y, MenW: Neisseria meningitidis serogroup W, rSBA: rabbit serum bactericidal assay; QALY: Quality Adjusted Life Year.
Source: Table 67, p139 of the submission and compiled during the evaluation.

6.44 A summary of the key drivers of the model is presented in the table below.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Model structure	The economic model represents the costs and effects of vaccination on the current Australian population, i.e. not allowing for vaccination of newborns at birth nor in adolescence. A more realistic model may have defined a set time horizon (e.g. 50 years, at the end of which period, discounting negates any cost and outcome differences) and allowed for newborns to reflect the vaccination of newborns over the time horizon.	Moderate. Favours the MenACWY-TT vaccine
Background incidence of IMD in absence of vaccination.	Background incident rates of IMD were based on a single year of incidence data (2016-2017) and were assumed to be constant over the 85-year projection in the model. Over the previous 5-years (2012-2017) the average incidence of IMD was lower (less than half) than in 2016-2017. The future dynamics of the incidence of IMD caused by MenY and MenW without vaccination is unknown. ATAGI advised that IMD incidence is increasing in younger age groups, and is higher in the older age groups (≥65 years) compared with adolescents (15-19 years). The ESC also noted the background incident rates of IMD may not adequately capture the impact of the infant vaccination program.	Uncertain
Herd immunity assumption	Herd immunity was assumed, based on data from the MenC program in the UK. In the model, 0 to 18 year olds are vaccinated over an 18-year time horizon. Due to waning, the full population of 0 to 18 year olds are not all protected at the same time. The model accounts for delayed vaccination by assuming a linear increase in herd immunity to reach 67% by 10 years, which is maintained for 8 years and then decreases linearly to zero after 27 years, i.e. herd immunity effects are assumed for 27 years, 11 years after school-based vaccination ceases (in the model). In contrast to the UK data, the economic model applies the same herd immunity effect to all ages, and on top of a direct vaccination effect but the estimate from the UK data (67%) incorporates both a direct vaccination effect as well as the herd immunity effect. Herd immunity was responsible for 70% of the included health benefits underpinning ICER results.	High. Favours the MenACWY-TT vaccine
Waning	The submission assumed vaccine efficacy will wane by 5% per year until Year 5, and 50% per year thereafter. The approach is generally consistent with the advice from ATAGI, though ATAGI recommend a sensitivity analysis in which a 5-year vaccination effect is assumed. The ICER is not overly sensitive to these parameters due to the benefits of vaccination being largely driven by herd immunity.	Minor. Favour the MenACWY-TT vaccine
Costs for long term management of IMD complications.	Constant annual costs of IMD were based on a Canadian study of costs for children with medical complexity, the relevance of which to the costs of IMD is uncertain, especially as patients move into adulthood.	Moderate. Favours the MenACWY-TT vaccine

ICER: incremental cost effectiveness ratio, IMD: invasive meningococcal disease, MenY: Neisseria meningitidis serogroup Y, MenW: Neisseria meningitidis serogroup W, QALY: Quality Adjusted Life Year
Source: Compiled during the evaluation.

6.45 The results of the economic evaluation are presented in the table below.

Table 12: Results of the economic evaluation

Costs			Health outcomes				ICER
MenACWY-TT vaccine	No vaccine	Incremental	Outcome	MenACWY-TT vaccine	No vaccine	Incremental	
$[redacted]	$[redacted]	$[redacted]	LYs	393,738,769	393,737,638	1,131	$[redacted]
			QALYs	351,696,621	351,694,474	2,147	$[redacted]

LYs: Life years; QALYs: quality adjusted life years. ICER: incremental cost-effectiveness ratio.
Source: p139 of the submission

6.46 Regarding the model structure, the ESC noted ATAGI (Pre-submission advice, p16) considered the dynamic model validated in the UK for the MenC program could be adapted to the proposed Men ACWY program in the Australian context. The submission's justification for presenting a static model was "In the interests of the current public health concerns with respect to the emerging nationwide outbreak of IMD driven by serogroup W, it was considered more appropriate to lodge the PBAC submission with a 'static' Markov model than delay the submission to develop a dynamic model de novo". The ESC considered a dynamic model would be more appropriate for assessing the cost-effectiveness of the MenACWY vaccine. In the absence of such a model, the ESC considered that conservative assumptions regarding the background incidence of IMD and herd immunity are appropriate.

6.47 The sponsor's Pre-PBAC Response stated that a dynamic model would not resolve the uncertainty around unknown future incidence of IMD, and reiterated that the incidence data used in the modelling was based on latest available data and a highly conservative assumption that background incidence remained the same over the time horizon when in reality it is likely to increase. The Pre-PBAC Response noted that a dynamic model requires robust data inputs that are not available for IMD in Australia. The PBAC considered that a dynamic model would be able to address, at least in part, some of the structural concerns regarding the model presented, however acknowledged the limited data available to inform such a model.

6.48 Background incident rates of IMD were based on a single year of incidence data (2016-2017) and were assumed to be constant over the 85-year projection in the model. ESC noted that IMD incidence is increasing in younger age groups, and is higher in the older age groups (≥65 years) compared with adolescents (15-19 years) (ATAGI Pre-submission advice, p5). The PSCR and Pre-PBAC response noted that incidence is increasing in younger groups, and stated that the assumed rates were conservative as IMD incidence is likely to increase. The Pre-PBAC response noted more recent data showed a further increase in MenW and MenY cases from September 2017 (as included in the submission) to December 2017 (National Surveillance Reports). Overall, the incidence of IMD was 1.6 per 100,000 in 2017 compared to 1.1 per 100,000 in 2016 and notifications of MenW continued to increase year on year, from 17 in 2014 to 140 in 2017. Similarly notifications of MenY increased from 12 in 2014 to 75 in 2017.

6.49 The ESC considered that the future incidence of IMD was hard to predict. The ESC also noted the background incidence rates of IMD may not adequately capture the

impact of the infant vaccination program. The Pre-PBAC Response confirmed that the modelled economic evaluation focused on the proposed adolescent MenACWY vaccination program, and it did not directly or indirectly assess the impact of an infant MenACWY vaccination program. The sponsor considered the impact of the infant MenC vaccination program was captured by the background incidence of IMD applied in the model which used the latest Australian age-specific notification rates by serogroup categories. The PBAC considered that as the national infant vaccination program has not yet commenced that its impact may not be adequately captured in the background IMD rates applied in model. However, overall, the PBAC considered that the future incidence of IMD is hard to predict.

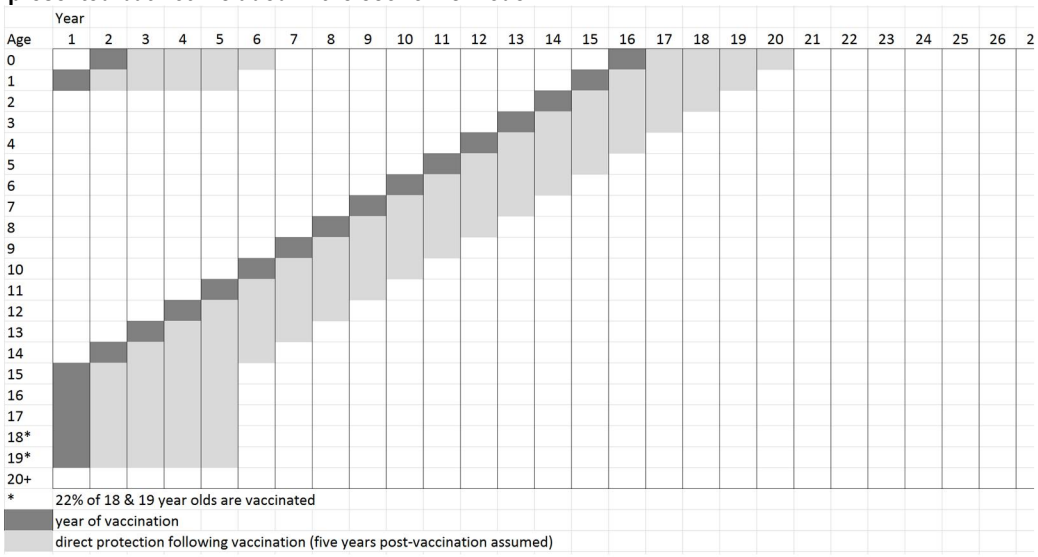
6.50 The PBAC has not previously considered the outcome of 'vaccine response'. ATAGI considered it reasonable to assume that immunogenicity results (measured as 'vaccine response' in adolescents) directly correlate with expected vaccine efficacy in the short term for the purpose of economic assessment (p23 of the ATAGI pre-submission advice 2017). The ESC noted 'vaccine response' is a more conservative estimate of vaccine efficacy than the proportion of subjects with rSBA titres ≥1:8.

6.51 The submission assumed vaccine efficacy in vaccinated individuals will wane by 5% per year until Year 5, and 50% per year thereafter. The ESC noted this approach was generally consistent with the advice from ATAGI, though ATAGI recommended a sensitivity analysis in which a 5-year vaccination effect is assumed. The ESC noted that the base case results were not sensitive to this change because waning had no relation to the assumed herd immunity effect, which is the key driver of cost-effectiveness.

6.52 Herd immunity was based on data from the MenC program in the UK. ATAGI considered that estimates of the indirect herd protection benefit from existing MenC vaccination programs, both in Australia and overseas, could not be directly extrapolated to the proposed MenACWY-TT program (p15 of the ATAGI pre-submission advice). The ESC noted a number of issues, as outlined below, with the translation of UK data to the Australian setting and application of herd immunity in the model.

6.53 The vaccination program in the UK differed from that represented in the economic model. In the UK program over 80% of those aged 0-18 were vaccinated in 1 year. Figure 4 represents the vaccination and direct vaccine effect profile that is represented in the economic model for adolescents, assuming five-year protection post-vaccination. With the proposed vaccination program it will take 16 years before 80% of 0-17 year olds are vaccinated and due to waning there is limited overlap in protection. The figure also includes the vaccination of infants (which was not included in the model) assuming five-year protection post-vaccination, although the duration of protection for infants is uncertain.

Figure 4: Assumed vaccine coverage in the economic model for adolescents. Assumed vaccine coverage for infants is also presented but not included in the economic model



Source: Prepared for ESC advice

6.54 Based on the UK program a 67% reduction in IMD was applied in the model to all age groups to reflect the impact of herd immunity. The ESC noted the 67% reduction was observed in the age groups targeted for catch-up vaccination in the UK (everyone under 18 years) but that a smaller reduction (35%) was observed in adults not eligible for vaccination[10]. The PSCR stated that herd immunity was not varied according to age because it was not known what the age-differential was, if any. The ESC considered a lower herd immunity effect should be applied to adults.

6.55 The ESC noted in the model the herd immunity benefit was applied on top of the direct vaccination effect in those covered. However, the 67% reduction in IMD applied for the herd immunity effect (see above) incorporates both a direct vaccination effect as well as the herd immunity effect. The ESC considered the model should exclude vaccine effects in vaccinated individuals to avoid double counting with the assumed herd immunity effect. The Pre-PBAC Response disagreed with this statement, stating that it implied that no direct benefit of vaccination is conferred, however, it also noted that if the direct vaccine effectiveness was excluded altogether that the cost per LY gained increased from $75,000 - $105,000 to $105,000 - $200,000 and the cost per QALY gained increased from $45,000 – $75,000/QALY to $45,000 – $75,000/ QALY. The PBAC noted that the assumed herd immunity effect (67% reduction in IMD) also incorporated the direct effect of the vaccine; however it also considered the approach in the Pre-PBAC Response of removing the direct vaccine effect from the model was inconsistent with the data and structure used in the model in which the direct effect and herd immunity effect

[10] Ramsay M, Andrews N, Trotter C, Kaczmarski E, Miller E. Herd immunity from meningococcal serogroup C conjugate vaccination in England: database analysis. *BMJ 2003;* 326:365

were separately calculated.

6.56 The model accounts for delayed vaccination coverage by assuming a linear increase in herd immunity to reach 67% by 10 years. The ESC noted this is over a shorter period than the 16 years for which it will take for 80% of 0-17 year olds to be vaccinated. This level of coverage is assumed to be maintained for 8 years and then decreases linearly to zero after 27 years. The ESC noted the herd immunity effects are assumed for 27 years, 11 years after school-based vaccination ceases (in the model).

6.57 The PSCR (p2) stated that the assumptions made regarding herd immunity were conservative when compared with the MenC experience in Australia, noting that notification rates for IMD due to serogroup C declined by over 10-fold from 2002 to 2007.

6.58 The Pre-PBAC Response noted that ATAGI considered the introduction of a MenACWY-TT program for adolescents is warranted due to anticipated direct benefits to the vaccinated group and herd protection for other age groups. The sponsor also noted ATAGI's advice that vaccinating adolescents would be most likely to interrupt transmission of MenW and MenY given that adolescents have the highest rates of acquiring nasopharyngeal carriage.

6.59 The likelihood of long-term complications among survivors of IMD was based on a South Australian study in which 41 of 109 patients experienced long-term complications[11] [12]. In this study, 6 participants (14.6%) had a single minor complication, 2 (4.9%) had multiple minor complications, 11 (26.8%) had a single major complication, and 22 (53.7%) had multiple major complications. The most commonly reported major complications were classified as 'neurology' or 'skin necrosis/scarring/grafts'. A weighted annual cost of $15,069 was applied for the management of chronic IMD complications based on an economic evaluation of MenB vaccination in Canada (Tu et al 2014). Because of an absence of long-term costs for permanent sequelae of invasive MenB disease, Tu et al 2014 sourced healthcare costs for children with medical complexity from Cohen et al. 2012. The reported costs could not be identified in the Cohen paper. The ESC considered the relevance of these costs to be uncertain, especially as patients move into adulthood.

6.60 Cost information from the Cohen study was provided with the Pre-PBAC response. The sponsor acknowledged the uncertainty regarding long-term costs of managing subjects with permanent complications of IMD however considered that best estimates were used. The sponsor also noted that as subjects affected by permanent IMD complications move into adulthood, their healthcare costs would

[11] Wang B, Haji Ali Afzali H, Marshall H. The inpatient costs and hospital service use associated with invasive meningococcal disease in South Australian children. *Vaccine* 2014;32:4791-8.

[12] Wang B, Clarke M, Thomas N, et al. The clinical burden and predictors of sequelae following invasive meningococcal disease in Australian children. *Pediatr Infect Dis J* 2014;33:316-8.

likely increase, however the model had conservatively assumed costs remained the same.

6.61 Table 13 presents the results of the key univariate sensitivity analyses conducted by the submission and during the evaluation.

Table 13: Results of univariate and scenario sensitivity analyses

Scenario	$/LY saved	$/QALY
Base-case	**$**	**$**
Annual discount rate = 3.5% (base case=5%)	$	$
Annual discount rate = 7% (base case=5%)	$	$
Vaccine coverage (15-17 year olds) = 86% (base case 80%)	$	$
Vaccine coverage rate (18 year olds) = 36.6% (base case 22%)	$	$
Base MenY and MenW IMD per 100,000 assumed to be 41% of 2016-2017 notifications (base case 100%)	$	$
10% increase in IMD incident rate in Year 2- Year 5, then plateau (base case 0%)	$	$
25% increase in IMD incident rate in Year 2- Year 5, then plateau (base case 0%)	$	$
50% increase in IMD incident rate in Year 2- Year 5, then plateau (base case 0%)	$	$
10% decrease in IMD incident rate in Year 2- Year 5, then plateau (base case 0%)	$	$
25% decrease in IMD incident rate in Year 2- Year 5, then plateau (base case 0%)	$	$
50% decrease in IMD incident rate in Year 2- Year 5, then plateau (base case 0%)	$	$
Vaccine response at baseline = 94.14% (base case 95.59%)	$	$
Vaccine response at baseline = 96.69% (base case 95.59%)	$	$
Vaccine response at baseline = 60% (base case 95.59%)	$	$
Waning vaccine effectiveness: 50% per year in Year 2 – Year 5; zero from Year 6 (base case 5% per year until year 5 and 50% per year thereafter)	$	$
No herd immunity from adolescent program (base case 67% reduction in IMD by Year 10)	$	$
Herd immunity: 12.6% reduction in IMD by Year 10 (base case 67% reduction in IMD by Year 10)	$	$
Herd immunity: 50% reduction in IMD by Year 10 (base case 67% reduction in IMD by Year 10)	$	$
Herd immunity: 67% reduction in IMD by Year 5 (and 5-year wane) (base case 67% reduction in IMD by Year 10)	$	$
Annual costs of long-term complications = $23,454 (De Wals 2007) (base case $15,069)	$	$
Annual costs of long-term complications = $5,026 (De Wals 2007) (base case $15,069)	$	$
Annual costs of long-term complications = 0 (Included to gauge model results) (base case $15,069)	$	$

GP: General practitioner; IMD: invasive meningococcal disease; LY: life years; QALYs: quality adjusted life years; RR: Relative risk.
Source: Table 3.9.2, p. 197 of the submission and calculated during evaluation)

6.62 Overall, the ICER was most sensitive to herd immunity assumptions, discount rate, assumed background IMD incidence attributable to vaccine preventable serogroups and annual costs of long term complications.

6.63 Herd immunity had a substantial impact on the estimated ICER. A reduction of 12.6% on carriage acquisition (herd immunity) (as per the 2015 submission for the 4CMenB program, which was based on nasopharyngeal carriage prevalence of MenB in a RCT

of the 4CMenB vaccine in young adults (Study V72_29, 1,958 university students) [13]) increased the ICER to $105,000/QALY - $200,000/QALY gained. This is because all non-vaccinated individuals received the same herd immunity benefit (67% reduction in IMD). This assumption does not account for differential mixing and contract rates between age-classes. These indirect benefits were far more substantial than those estimated for the vaccinated proportion of the population. Consequently, the estimated ICER was not overly sensitive to changes in vaccine efficacy, coverage, vaccine persistence and cost of delivery.

Drug cost/patient/course

6.64 $[redacted], assuming a single dose per patient.

Estimated PBS usage & financial implications

6.65 This submission was not considered by DUSC. The submission used a population-based approach to estimate the MenACWY-TT vaccine usage and financial implication for the primary and catch-up program.

6.66 Key data sources were ABS population projections, ABS summary table of full-time equivalent students (by level and year of education, 2016), ABS audit of proportion of school leavers aged 17-19 years, average uptake rate of HPV vaccine and MenC vaccine in NSW, and Lawrence et al.'s (2016) [14] publication on the uptake rate of catch-up programs via schools and GPs.

6.67 Estimated use and financial implications of the primary and catch-up vaccination programs are presented in Table 14.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of the MenACWY-TT vaccines used in the primary program[a] (80% uptake)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of the MenACWY-TT vaccines used in the catch-up program[a] (22% uptake)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of the primary program (Year 10 adolescents vaccination program)						
Cost to NIP	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$0	$0	$0	$0	$0	$0
Estimated financial implications of the catch-up program						

[13] PBAC (November 2013) Public summary document: multicomponent meningococcal group B vaccine, 0.5mL, injection, prefilled syringe, Bexsero and PBAC (July 2015) Public summary document: multicomponent meningococcal group B vaccine, injection, 0.5mL, Bexsero.

[14] Lawrence GL, Wang H, Lahra M, Booy R and McIntyre P. Meningococcal disease epidemiology in Australia 10 years after implementation of a national conjugate meningococcal C immunization programme. Epidemiol Infect. 2016; 1-10

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Cost to NIP	$	$	$	$	$	$
Cost to MBS [b]	$	$	$	$	$	$
Copayments	$0	$0	$0	$0	$0	$0
Net financial implications						
Net cost to NIP	$	$	$	$	$	$
Net cost to the Australian Government health budget	$	$	$	$	$	$

NIP: National Immunisation Program, GP: general practitioner

[a] Assuming a single dose per patient.

[b] In the catch-up program, adolescents might receive the vaccination through their GP.

Source: Table 4.2.1, p208 in the submission, Table 4.2.2, p210 in the submission, Table 4.2.3, p211 in the submission, Table 4.2.4, p212 in the submission.

The redacted table shows that at year 6, the estimated number of patients was over 200,000 per year and the net cost to the Government would be $10 – $20 million in year 6.

6.68 The submission estimated a total use of [redacted] MenACWY-TT vaccines ([redacted] in the primary program and [redacted] in the catch-up program) over six years.

6.69 The submission estimated that the cost of the primary and catch-up program to the Australian Government health budget is $10 – $20 million over six years.

6.70 There are some uncertainties in the estimates of vaccine usage and financial implications:

- The uptake rates are uncertain, and the submission did not exclude students who have received a MenACWY vaccine through the State-based programs. Therefore the financial implications for the catch-up program may be over-estimated. The PSCR stated that the uptake rates were informed by previous similar school-based vaccination programs, were considered reasonable by the state immunisation coordinators and were within the uptake limits recommended by ATAGI. It was also noted that uptake numbers for the State-based programs were not available.
- The submission applied MBS item number 23 for GP visits. The evaluators considered this to be too high and that a lower value (Level A consultation price of $16.95) should be applied. The ESC acknowledged that a nurse may administer the vaccine but advised that, unless administered as part of a vaccine clinic, a level B consultation item was more likely to be used in practice.

Quality Use of Medicines

6.71 The submission assumed that appropriate activities would be undertaken as part of the implementation of a new vaccine program if the MenACWY-TT vaccine is listed on the NIP.

6.72 ATAGI noted that considerable health professional and consumer education is required given that this is a new vaccine to be listed on the NIP. Additionally, significant public communication strategies would be required to make adolescents who have left school or otherwise missed the school dose aware of the need for and availability of vaccination in order to achieve good coverage (p19 of the ATAGI pre-PBAC Advice 2017).

6.73 Concerns which should be addressed via health professional and parent education include:

- Difference between the current MenC vaccine and the MenACWY-TT vaccine;
- Lack of need to vaccinate adolescents already vaccinated with a MenACWY vaccine (i.e. received through State-based programs or via the catch-up program to those who received the vaccine in year 10); and
- Targeted education programs for Aboriginal and Torres Strait Islander populations - including health workers, health professionals, community elders and community members.

6.74 The PSCR noted that meningococcal infections are notifiable and as a consequence there will be ongoing surveillance of the efficacy of the MenACWY-TT vaccine.

6.75 The PBAC agreed with the need for quality use of medicine activities and a review of the MenACWY vaccination program after five years.

Financial Management – Risk Sharing Arrangements

6.76 None proposed.

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

7 PBAC Outcome

7.1 The PBAC recommended that meningococcal polysaccharide serogroups A, C, W_{135} and Y conjugate vaccine (MenACWY-TT) be a designated vaccine for the purposes of the National Health Act 1953 for the prevention of invasive meningococcal disease (IMD) caused by *Neisseria meningitidis* serogroups A, C, W_{135}, and Y (MenA, MenC, MenW_{135} and MenY, respectively) in adolescents as part of a school based immunisation program for year 10 students (aged 14-16) and via a catch-up program for adolescents aged up to 19 years old. The PBAC's recommendation was based on, among other matters, its assessment that the cost effectiveness of the MenACWY-TT vaccine could be brought into an acceptable range contingent upon a reduced price.

7.2 The PBAC considered that there was a clinical need for the vaccination of the adolescent age group to both provide direct protection and to provide indirect protection to other age groups through herd immunity.

7.3 The PBAC considered the proposed comparator of no vaccine to be appropriate, noting that there are other MenACWY-TT vaccines available, distributed through State-based programs, which are relevant near market comparators.

7.4 The PBAC noted the limitations of the available clinical evidence including the use of single-arms of randomised trials which do not take into account rates of natural immunity, as well as the lack of studies measuring nasopharyngeal meningococcal carriage rates to assess the potential for herd immunity.

7.5 The PBAC considered that the clinical claim of superior efficacy compared with no vaccine was reasonable. However, the PBAC noted the impact of vaccination on the population incidence of IMD was highly uncertain.

7.6 The PBAC considered that overall, the MenACWY-TT vaccine had a reasonable safety profile and whilst inferior to the comparator of no vaccine, the adverse events were generally mild or moderate.

7.7 The PBAC noted ESC's advice that a dynamic model would be more appropriate for assessing the cost-effectiveness of the MenACWY vaccine. The PBAC considered that although a dynamic model may be useful, it may not provide further certainty regarding the cost-effectiveness of the MenACWY vaccine given that it would not be possible to resolve the key uncertainties regarding the impact of the vaccine on carriage rates and hence likely extent of herd immunity.

7.8 The PBAC noted the background rates of IMD were based on a single year of incidence data (2016-2017) and were assumed to be constant over the 85-year projection in the model. The PBAC noted the sponsor's arguments regarding the possibility of the incidence increasing over time. Overall, the PBAC considered the future incidence was hard to predict but that the rates used in the model were potentially conservative.

7.9 The PBAC noted the lack of a surrogate serological correlate of protection for the efficacy of the MenACWY-TT vaccine against IMD caused by serogroups A, W and Y. The PBAC noted ATAGI's advice that 'vaccine response' is a reasonable measure of vaccine efficacy in the short term. The PBAC noted that vaccine response was used as a surrogate measure to inform efficacy in the economic model and that a better alternative measure was not available.

7.10 The PBAC noted that in the economic model herd immunity was based on data from the MenC program in the United Kingdom (UK). The PBAC noted the issues regarding translation of the UK data to the Australian setting, as outlined by ESC, including that the proposed vaccination schedule differs to that implemented in the UK.

7.11 The PBAC noted based on the UK program a 67% reduction in IMD was applied in the model to all age groups to reflect the impact of herd immunity. The PBAC noted ESC's advice that in the UK a smaller reduction was observed in adults not eligible for vaccination and considered that the herd immunity effect among older individuals may have been overestimated.

7.12 The PBAC noted the costs applied in the economic model for the long-term management of IMD were uncertain and had a moderate impact on the cost-effectiveness of the vaccine. The PBAC considered the costs associated with treating the permanent sequelae of IMD were largely unknown.

7.13 The PBAC recalled that for vaccination programs a cost per quality adjusted life year (QALY) of $15,000 or less is generally considered acceptable. The PBAC considered the cost of the MenACWY-TT vaccine should be reduced such that the cost per QALY gained was less than $15,000.

7.14 The PBAC noted the financial impact associated with the listing of the MenACWY-TT vaccine would be reduced compared with the estimates presented in the submission as a result of the price reduction required for MenACWY-TT to be considered cost-effective. The PBAC also noted the financial impact of the catch-up program may be overstated in the submission as students who have been vaccinated through the State-based programs were not excluded.

7.15 The PBAC noted that ATAGI recommended a review of this drug five years after implementation and that activities to support quality use of this medicine were suggested.

7.16 The PBAC noted that this submission is not eligible for independent review as independent review is only relevant to PBS listing.

Outcome:
Recommended

8 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.

9 Sponsor's Comment

The sponsor had no comment.