Coversheet on evidence assessment by ATAGI using the GRADE framework

Summary of key methods and decisions on evidence assessment using GRADE for developing ATAGI recommendations on the use of a meningococcal B booster vaccine

Background

- Meningococcal B (MenB) vaccination was first recommended in April 2014 for individuals at risk of invasive meningococcal disease (IMD).
- While booster recommendations exist in the Handbook for meningococcal ACWY vaccine, there are no current recommendations for MenB.
- There is evidence of waning immunogenicity after vaccination which could necessitate additional boosters in individuals at ongoing risk of IMD.
- The United States Advisory Committee on Immunization Practices recommended MenB booster doses in persons at increased risk of IMD in June 2019
- The need for a MenB booster dose therefore underwent GRADE assessment of the evidence to inform recommendations on MenB booster by The Australian Technical Advisory Group on Immunisation (ATAGI)

Research question

1. Should people previously vaccinated with a meningococcal B vaccine primary series receive a booster Meningococcal B vaccination?

Table 1 PICO 1a and 1b: Bexsero

PICO 1a: Individuals at standard background risk of IMD PICO 1b: Individuals at increased risk of IMD due to complement deficiencies, complement inhibitors e.g. eculizumab use, functional/anatomical asplenia, HIV, haematopoietic stem cell transplant.				
P	**I**	**C**	**O**	**S**
Individuals at standard background risk of IMD • Infants/toddlers: 2 months – 2 years • Adolescents: 15-19 years • Adults	Bexsero booster dose • after standard 2+1 and 3+1 dose age based schedules in infants/toddlers or 2 dose schedules (0m, 2m) in individuals aged ≥12 months Combination vaccines with identical B component to Bexsero also included	Placebo No booster Alternate vaccine 1st dose of vaccine (vaccine naïve control)	Booster dose efficacy/effectiveness, or immunogenicity Immune persistence (immunogenicity over time) Booster dose safety	Meta-analysis, RCT Observational studies
Individuals at increased risk of IMD: • Infants/toddlers: 2 months – 2 years • Adolescents: 15-19 years • Adults	Bexsero booster dose • after standard 2+1 and 3+1 dose age based schedules in infants/toddlers or 2 dose schedules (0m, 2m) in individuals aged ≥12 months	Placebo No booster Alternate vaccine 1st dose of vaccine (vaccine naïve control)	Booster dose efficacy, effectiveness, or immunogenicity Immune persistence (immunogenicity over time) Booster dose safety	Meta-analysis, RCT Observational studies

	Combination vaccines with identical B component to Bexsero also included			
Outcomes (with ranking)				
Booster dose efficacy/effectiveness (Critical) Booster dose immunogenicity / vaccine response (Critical) Booster dose serious adverse events (Critical) Reactogenicity: Local and systemic solicited adverse events (Important) Immune persistence after booster (Important)				
Important potential confounders				
Age Gender Race/Ethnicity Prior vaccination schedule Time since primary vaccination Immunocompromise/immunosuppression Co-administered vaccines				
Exclusion Criteria				
Population	No exclusion.			
Intervention/Comparator	Schedule other than standard 2+1 and 3+1 dose age based schedules in infants or 2 dose schedules (0m, 2m) in individuals aged ≥12 months Investigational pre-licensure preparations of Bexsero/Trumenba with alternate antigens, antigen doses, ingredients, or route of administration			
Study Design	Cross-sectional and ecological studies Non-systematic reviews Reports of passive surveillance data Case series Single case reports Abstracts only with no associated study results Letters/commentaries/editorials In-vitro studies Animal studies			
Language	Language other than English			
Publication	Nil			

Table 2 PICO 2a and 2b: Trumenba

PICO 2a: Immunocompetent individuals PICO 1b: Individuals at increased risk of IMD due to complement deficiencies, complement inhibitors e.g. eculizumab use, functional/anatomical asplenia, HIV, haematopoietic stem cell transplant.				
P	**I**	**C**	**O**	**S**
Individuals at standard background risk of IMD • Adolescents: 15-19 years • Adults	Trumenba booster dose • after standard 2 or 3 dose primary schedule	Placebo No booster Alternate vaccine 1st dose of vaccine (vaccine naïve control)	Booster dose efficacy/effectiveness, or immunogenicity Immune persistence (immunogenicity over time) Booster dose safety	Meta-analysis, RCT Observational studies
Individuals at increased risk of IMD: • Adolescents: 15-19 years • Adults	Trumenba booster dose • after standard 2 or 3 dose primary schedule	Placebo No booster Alternate vaccine	Booster dose efficacy/effectiveness, or immunogenicity Immune persistence (immunogenicity over time)	Meta-analysis, RCT Observational studies

		1st dose of vaccine (vaccine naïve control)	Booster dose safety	
Outcomes (with ranking)				
Booster dose efficacy/effectiveness (Critical) Booster dose immunogenicity / vaccine response (Critical) Booster dose serious adverse events (Critical) Reactogenicity: Local and systemic solicited adverse events (Important) Immune persistence after booster (Important)				
Important potential confounders				
Age Gender Race/Ethnicity Prior vaccination schedule Time since primary vaccination Immunocompromise/immunosuppression Co-administered vaccines				
Exclusion Criteria				
Population	Significant medical conditions other than those associated increased risk of IMD.			
Intervention/Comparator	Schedule other than standard 2 or 3 dose Investigational pre-licensure preparations of Trumenba with alternate antigens, antigen doses, ingredients, or route of administration			
Study Design	Cross-sectional and ecological studies Non-systematic reviews Reports of passive surveillance data Case series Single case reports Abstracts only with no associated study results Letters/commentaries/editorials In-vitro studies Animal studies			
Language	Language other than English			
Publication	Nil			

Literature search

A systematic review of the literature was carried out on 4 June 2021 to identify all trials on a booster dose of Meningococcal B vaccines. Details of the literature search and search terms are presented in Appendix A. The citations were included for review if they met the following criteria:

- Study type: randomised controlled trial, observational study, meta-analysis
- Population: individuals at standard background risk of IMD and individuals at increased risk of IMD
- Intervention: Meningococcal B vaccines - Bexsero or Trumenba booster dose after age-appropriate primary schedule
- Outcomes: Effectiveness, efficacy, immunogenicity, safety

The review was not limited by population.

The published literature search retrieved a total of 1098 unique citations, of which eight citations met the pre-defined inclusion criteria. All studies were non-randomised, observational immunogenicity studies of Bexsero (n=7)[1-7] or Trumenba (n=1)[8]; each study included one or more age cohorts: healthy infants (n=5)[1,2,4-6], children (n=1)[2] and adolescents or adults (n=3)[3,7,8]. There were no identified booster studies in individuals at increased risk of IMD. There were no identified effectiveness studies in meningococcal B booster vaccines.

Inclusion criteria and rationale

Table 3 Rationale for PICO and inclusion criteria

	Rationale
Study type:	RCT, observational studies, meta-analysis. It was expected that there would be limited evidence on booster doses therefore PICO was not limited by study design. Only observational studies were identified
Population	Infants, children, adolescents and young adults - separated out by individuals at standard background risk of IMD and individuals at increased risk of IMD
	Individuals at standard background risk of IMD included immunocompetent individuals who do not have occupational risk to IMD. Individuals at increased risk of IMD include individuals at increased medical risk and/or occupational risks. Conditions associated with increased medical risk include: • defects in, or deficiency of, complement components, including factor H, factor D or properdin deficiency • current or future treatment with eculizumab (a monoclonal antibody directed against complement component C5) • functional or anatomical asplenia, including sickle cell disease or other haemoglobinopathies, and congenital or acquired asplenia • HIV, regardless of disease stage or CD4+ cell count • haematopoietic stem cell transplant
	Bexsero is available for individuals aged ≥6 months Trumenba is available for individuals aged ≥10 years
Intervention	A booster dose of a MenB vaccine – Bexero or Trumenba
	Defined as: a dose received after an Australian age-appropriate primary schedule was completed. An age-appropriate Bexsero schedule was considered to be a 3 or 4 dose schedule in those receiving the first dose less than 12 months of age with the last dose at ≥12 months of age (with a minimum 2 dose interval between doses), and 2 doses (minimum 2 month interval) in those receiving the first dose aged 12 months or older. Data were not utilised from treatment arms that were not an age-appropriate primary schedule.
Comparator	Placebo, no booster dose, alternative vaccine or 1st dose of vaccine (vaccine naïve control)
	There were no studies identified that compared MenB boosters to placebo. All studies were single arm trials assessing outcomes before and after booster dose. For the immunogenicity outcomes the results from participants prior to receiving the booster dose were used as the comparator. For safety outcomes the comparison was no booster (i.e. no adverse event)
Outcomes	Included outcomes as stated above in Table 1 and Table 2. Included iteratively according to outcomes found in the studies.
	Ranking of importance discussed in many iterations with portfolio leads / ATAGI full panel.
	Critical • Efficacy/Effectiveness of booster dose • Immunogenicity: hSBA ≥ 1:4 (Bexsero) and hSBA ≥ LLOQ (Trumenba) for test strains pre/post booster • Immunogenicity: Geometric mean ratio of post/pre hSBA titres Important • Local solicited adverse events • General/systemic solicited adverse events • Fever • Unsolicited adverse events • Serious adverse events Note: some outcomes may be missing in GRADE projects due to no data from available studies. Extra outcomes added due to relevance.
	No studies with efficacy or effectiveness outcomes of a booster dose were identified. The GRADE assessment evaluated only the available immunogenicity and safety outcomes

Abbreviations: ATAGI, Australian Technical Advisory Group on Immunisation; AE, adverse event; hSBA, human serum bactericidal activity assay; IMD, invasive meningococcal disease; LLOQ< lower limit of quantitation; MenB, meningococcal B vaccine

Risk of bias assessment

Risk of bias (RoB) assessment was carried out on all included studies by two assessors using ROBINS-I[9] for comparative observational studies. Refer to Appendix B for RoB rating of included studies.

Appendix A

A series of literature searches were conducted to locate literature on Meningococcal B vaccine immune persistence, effectiveness, safety and booster doses.

Searches were conducted on 04.06.21 in OVID Medline (1946 to 4 June 2021), OVID Embase (1974 to 3 June 2021), Cochrane Library Database of Systematic Reviews, Issue 6 of 12, 2021 and Cochrane Library Central Register of Controlled Trials, Issue 6 of 12, 2021. Key thesaurus terms used in Medline and the Cochrane Library included ‘Neisseria meningitidis’, ‘Meningococcal Infections’, ‘Meningococcal Vaccines’, ‘Antibodies, Bacterial’, ‘Antibody Formation’, ‘Immunogenicity, Vaccine’, ‘Treatment Outcome’, ‘Safety’, ‘Safety-Based Drug Withdrawals’, ‘Product Surveillance, Postmarketing’, ‘Drug Evaluation’, ‘Population Surveillance’, ‘Adverse Drug Reaction Reporting Systems’, ‘Time Factors’ and ‘Immunization, Secondary’. Relevant textword terms were also extensively used. Corresponding thesaurus terms were used in Embase, with the same relevant textwords. The searches were limited to items published from 2008 onwards. No language limits were applied.

Appendix B

Table 4 Risk of Bias assessment for comparative, observational studies using ROBINS-I

Study	Outcome	Confounding	Selection	Intervention classification	Deviations from intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall bias
Iro 2017	hSBA	Serious	Serious	Low	Low	Low	Low	Low	Serious
	GMT	Serious	Serious	Low	Low	Low	Low	Low	Serious
	Safety	Serious	Serious	Low	Low	Low	Serious	Low	Serious
Sadarangani 2017	hSBA	Serious	Serious	Low	Low	Low	Low	Low	Serious
	GMT	Serious	Serious	Low	Low	Low	Low	Low	Serious
	Safety	Serious	Serious	Low	Low	Low	Serious	Low	Serious
Snape 2013a	hSBA	Serious	Serious	Low	Low	Low	Low	Low	Serious
	GMT	Serious	Serious	Low	Low	Low	Low	Low	Serious
	Safety	Serious	Serious	Low	Low	Serious	Serious	Low	Serious
Snape 2013b	hSBA	Serious	Serious	Low	Low	Low	Low	Low	Serious
	GMT	Serious	Serious	Low	Low	Low	Low	Low	Serious
	Safety	Serious	Serious	Low	Low	Low	Serious	Low	Serious
Martinon-Torres 2018	hSBA	Serious	Serious	Low	Low	Moderate	Low	Low	Serious

	GMT	Serious	Serious	Low	Low	Moderate	Low	Low	Serious
	Safety	Serious	Serious	Low	Low	Moderate	Serious	Low	Serious
Nolan 2019	hSBA	Serious	Serious	Low	Low	Low	Low	Low	Serious
	GMT	Serious	Serious	Low	Low	Low	Low	Low	Serious
	Safety	Serious	Serious	Low	Low	Low	Serious	Low	Serious
Szenborn 2018	hSBA	Serious	Serious	Low	Low	Low	Low	Low	Serious
	GMT	Serious	Serious	Low	Low	Low	Low	Low	Serious
	Safety	Serious	Serious	Low	Low	Low	Serious	Low	Serious
Vesikari 2015	hSBA	Serious	Serious	Low	Low	Low	Low	Low	Serious
	GMT	Serious	Serious	Low	Low	Low	Low	Low	Serious
	Safety	Serious	Serious	Low	Low	Low	Serious	Low	Serious

References

1. Iro MA, Snape MD, Voysey M, et al. Persistence of bactericidal antibodies following booster vaccination with 4CMenB at 12, 18 or 24months and immunogenicity of a fifth dose administered at 4years of age-a phase 3 extension to a randomised controlled trial. *Vaccine* 2017;35:395-402.
2. Martinon-Torres F, Carmona Martinez A, Simko R, et al. Antibody persistence and booster responses 24-36 months after different 4CMenB vaccination schedules in infants and children: A randomised trial. *J Infect* 2018;76:258-69.
3. Nolan T, Santolaya ME, de Looze F, et al. Antibody persistence and booster response in adolescents and young adults 4 and 7.5 years after immunization with 4CMenB vaccine. *Vaccine* 2019;37:1209-18.
4. Sadarangani M, Sell T, Iro MA, et al. Persistence of immunity after vaccination with a capsular group B meningococcal vaccine in 3 different toddler schedules. *CMAJ* 2017;189:E1276-E85.
5. Snape MD, Philip J, John TM, et al. Bactericidal antibody persistence 2 years after immunization with 2 investigational serogroup B meningococcal vaccines at 6, 8 and 12 months and immunogenicity of preschool booster doses: a follow-on study to a randomized clinical trial. *Pediatr Infect Dis J* 2013;32:1116-21.
6. Snape MD, Saroey P, John TM, et al. Persistence of bactericidal antibodies following early infant vaccination with a serogroup B meningococcal vaccine and immunogenicity of a preschool booster dose. *CMAJ* 2013;185:E715-24.
7. Szenborn L, Block SL, Jackowska T, et al. Immune Responses to Booster Vaccination With Meningococcal ABCWY Vaccine After Primary Vaccination With Either Investigational or Licensed Vaccines: A Phase 2 Randomized Study. *Pediatr Infect Dis J* 2018;37:475-82.
8. Vesikari T, Østergaard L, Beeslaar J, et al. Persistence and 4-year boosting of the bactericidal response elicited by two- and three-dose schedules of MenB-FHbp: A phase 3 extension study in adolescents. *Vaccine* 2019;37:1710-9.
9. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
10. Archer BN, Chiu CK, Jayasinghe SH, et al. Epidemiology of invasive meningococcal B disease in Australia, 1999-2015: priority populations for vaccination. *Med J Aust* 2017;207:382-7.
11. Deng L, Barton B, Lorenzo J, et al. Longer term outcomes following serogroup B invasive meningococcal disease. *J Paediatr Child Health* 2021;57:894-902.
12. Martin NV, Ong KS, Howden BP, et al. Rise in invasive serogroup W meningococcal disease in Australia 2013-2015. *Commun Dis Intell Q Rep* 2016;40:E454-e9.
13. Lahra MM, Enriquez R. Australian Meningococcal Surveillance Programme annual report, 2016. *Commun Dis Intell Q Rep* 2017;41:E369-e82.
14. Lahra MM, Enriquez RP, George CRR. Australian Meningococcal Surveillance Programme annual report, 2017. *Commun Dis Intell (2018)* 2019;43.
15. Lahra MM, Enriquez RP, Hogan TP. Australian Meningococcal Surveillance Programme annual report, 2018. *Commun Dis Intell (2018)* 2020;44.
16. Lahra MM, George CRR, Shoushtari M, Hogan TR. Australian Meningococcal Surveillance Programme Annual Report, 2020. *Commun Dis Intell (2018)* 2021;45.
17. Lahra MM, Hogan TR. Australian Meningococcal Surveillance Programme annual report, 2019. *Commun Dis Intell (2018)* 2020;44.
18. Ladhani SN, Andrews N, Parikh SR, et al. Vaccination of Infants with Meningococcal Group B Vaccine (4CMenB) in England. *N Engl J Med* 2020;382:309-17.
19. Deceuninck G, Lefebvre B, Tsang R, et al. Impact of a mass vaccination campaign against Serogroup B meningococcal disease in the Saguenay-Lac-Saint-Jean region of Quebec four years after its launch. *Vaccine* 2019;37:4243-5.
20. Martinon-Torres F, Banzhoff A, Azzari C, et al. Recent advances in meningococcal B disease prevention: real-world evidence from 4CMenB vaccination. *J Infect* 2021;83:17-26.
21. Read RC, Dull P, Bai X, et al. A phase III observer-blind randomized, controlled study to evaluate the immune response and the correlation with nasopharyngeal carriage after immunization of university students with a quadrivalent meningococcal ACWY glycoconjugate or serogroup B meningococcal vaccine. *Vaccine* 2017;35:427-34.

22. Vesikari T, Prymula R, Merrall E, et al. Meningococcal serogroup B vaccine (4CMenB): Booster dose in previously vaccinated infants and primary vaccination in toddlers and two-year-old children. *Vaccine* 2015;33:3850-8.
23. Tozer SJ, Smith HV, Whiley DM, et al. High coverage of diverse invasive meningococcal serogroup B strains by the 4-component vaccine 4CMenB in Australia, 2007-2011: Concordant predictions between MATS and genetic MATS. *Hum Vaccin Immunother* 2021;17:3230-8.
24. Findlow J, Lucidarme J, Taha MK, Burman C, Balmer P. Correlates of protection for meningococcal surface protein vaccines: lessons from the past. *Expert Rev Vaccines* 2021:1-13.
25. Holst J, Feiring B, Fuglesang JE, et al. Serum bactericidal activity correlates with the vaccine efficacy of outer membrane vesicle vaccines against Neisseria meningitidis serogroup B disease. *Vaccine* 2003;21:734-7.
26. McNeil LK, Donald RGK, Gribenko A, et al. Predicting the Susceptibility of Meningococcal Serogroup B Isolates to Bactericidal Antibodies Elicited by Bivalent rLP2086, a Novel Prophylactic Vaccine. *mBio* 2018;9.
27. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. *Clinical microbiology reviews* 1991;4:359-95.
28. Martinón-Torres F, Bernatowska E, Shcherbina A, et al. Meningococcal B Vaccine Immunogenicity in Children With Defects in Complement and Splenic Function. *Pediatrics* 2018;142.
29. van den Broek B, van Els C, Kuipers B, et al. Multi-component meningococcal serogroup B (MenB)-4C vaccine induces effective opsonophagocytic killing in children with a complement deficiency. *Clin Exp Immunol* 2019;198:381-9.