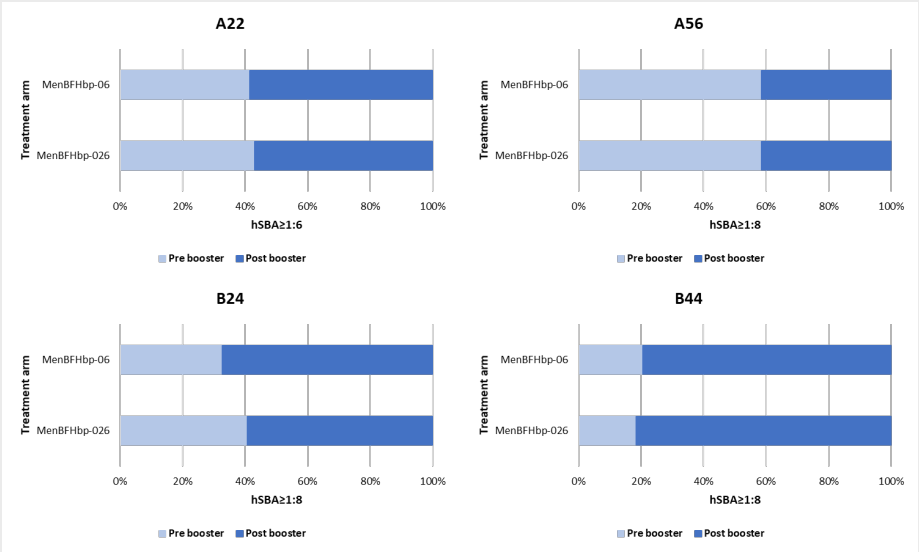
NCIRS is conducting GRADE in support of ATAGI and making results available on the NCIRS website. Please read this material as a supplement to the Australian Immunisation Handbook meningococcal disease chapter

Summary of findings: Trumenba booster dose compared with no booster dose in individuals at increased risk of invasive meningococcal disease (IMD)

Patient or population: Individuals at increased risk of IMD
Intervention: Trumenba booster dose
Comparison: No booster

Outcome № of participants (studies)	Impact	Certainty	Interpretation
Critical outcomes			
Proportion of participants with hSBA ≥1:6/1:8 (hSBA≥1:6/1:8) follow-up: 1 months № of participants: 123^ (1 observational study[1])		⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of Trumenba on hSBA≥1:8/1:6. Trumenba booster vaccine may increase the proportion of participants with hSBA≥1:6/1:8 at 1 month post booster but the evidence is very uncertain.

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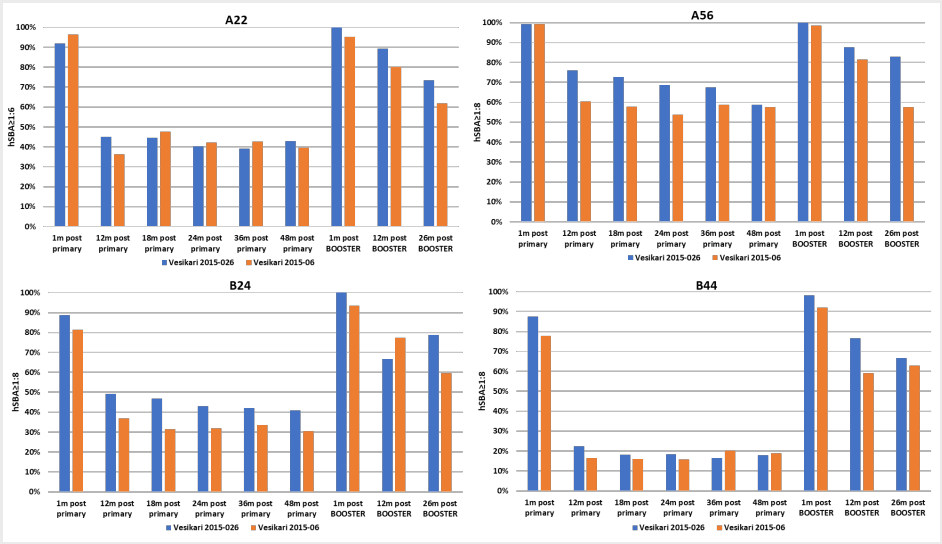
Outcome № of participants (studies)	Impact	Certainty	Interpretation
Persistence: Proportion of participants with hSBA ≥1:6/1:8 follow-up: 26 months № of participants: 123 (1 observational study[1,2])		⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of Trumenba on hSBA≥1:8/1:6 persistence. Trumenba booster vaccine may increase the proportion of participants with hSBA≥1:6/1:8 at 26 months post booster but the evidence is very uncertain.

Important outcomes

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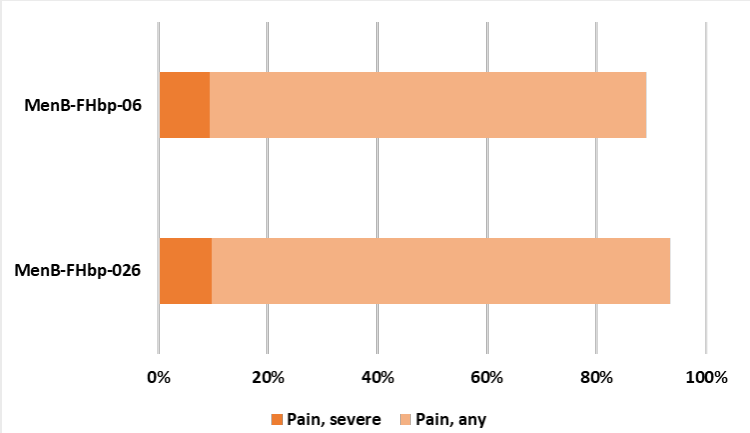
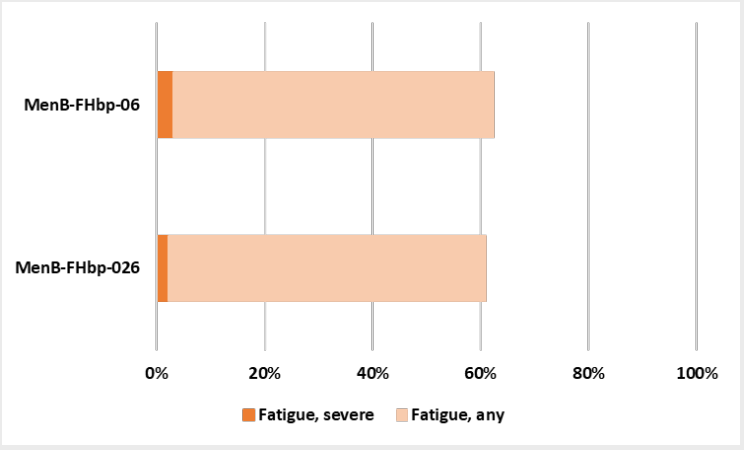
Outcome № of participants (studies)	Impact	Certainty	Interpretation
Pain* (any and severe) follow-up: 7 days № of participants: 123 (1 observational study[1])		⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of Trumenba on pain. Trumenba booster vaccine may increase pain but the evidence is very uncertain.
Fatigue* (any and severe) follow-up: 7 days № of participants: 123 (1 observational study[1])		⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of Trumenba on fatigue. Trumenba booster vaccine may increase fatigue but the evidence is very uncertain.

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GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

* Pain and fatigue were commonest reported local and systemic adverse events respectively and were used as a proxy for local adverse events and systemic adverse rates
a. Single arm comparison, assessed as serious risk of bias using ROBINS-I
b. The population included in the studies are healthy participants without an increased risk of IMD
c. Low number of events (<300) from a single study
^number of participants includes those in the 'post booster' analysis and does not double count the 'pre booster' participants

Evidence profile: Trumenba booster dose compared with no booster dose for individuals at increased risk of IMD

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Proportion of participants with hSBA ≥1:4 (follow-up: 1 months)									
1	observational studies	serious[a]	NA[b]	serious[c]	very serious[d]	none	Proportion of participants with hSBA≥1:4 at 1 month post booster vaccine ranged from 92-100%	⨁◯◯◯ Very low	CRITICAL
Proportion of participants with hSBA ≥1:4 (persistence) (follow-up: 26 months)									
1	observational studies	serious[a]	NA[b]	serious[c]	very serious[d]	none	Proportion of participants with hSBA≥1:4 at 26 months post booster vaccine ranged from 58-83%	⨁◯◯◯ Very low	CRITICAL
Pain* (any and severe) (follow-up: 7 days)									
1	observational studies	serious[a]	NA[b]	serious[c]	very serious[d]	none	Pain, any, ranged from 89-94% and severe pain ranged from 9-10%	⨁◯◯◯ Very low	IMPORTANT
Fatigue* (any and severe) (follow-up: 7 days)									
1	observational studies	serious[a]	NA[b]	serious[c]	very serious[d]	none	Fatigue, any, ranged from 61-63% and severe fatigue ranged from 2-3%	⨁◯◯◯ Very low	IMPORTANT
Serious AE (follow-up: 7 days)									
1	observational studies	serious[a]	NA[b]	serious[c]	very serious[d]	none	There was 1 (3%) serious AE in the treatment arm that received primary vaccination at 0, 2, 6 months and no serious AEs in the treatment arm that received primary vaccination at 0 and 6 months.	⨁◯◯◯ Very low	IMPORTANT

Explanations

* Pain and fatigue were commonest reported local and systemic adverse events respectively and were used as a proxy for local adverse events and systemic adverse rates

a. Single arm comparison, assessed as serious risk of bias using ROBINS-I

b. Inconsistency cannot be assessed as only 1 study included

c. The population included in the studies are healthy participants without an increased risk of IMD

d. Low number of events (<300) from a single study

Evidence to Decision Framework: Individual perspective

Should people at increased risk of IMD previously vaccinated with a meningococcal B vaccine primary series receive a booster Meningococcal B vaccination?	
Population	Infants, children, adolescents/young adults at increased medical/occupational risk of invasive meningococcal B
Intervention	Booster dose of Trumenba (recombinant factor-H-binding-protein-based Meningococcal group B vaccine)
Comparison	No booster
Main outcomes	Efficacy/Effectiveness of booster dose Immunogenicity: hSBA ≥ lower limit of quantitation [LLOQ] (Trumenba) for test strains pre/post booster Immunogenicity: Geometric mean ratio of post/pre hSBA titres Local Solicited Adverse Events General/systemic solicited AEs Fever Unsolicited adverse events Serious Adverse Events
Setting	Czech Republic, Denmark, Germany, Sweden
Perspective	Individual

ASSESSMENT

Problem
Is the problem a priority?

Don't know	Varies	No	Probably No	Probably Yes	Yes

- Invasive meningococcal disease (IMD) is a life-threatening infection with high rates of morbidity and mortality. Even with antibiotic treatment, the mortality rate for B strain in Australia is approximately 4%.[3-5]
- Survivors of infection are often left with permanent sequelae including limb / digit amputations, deafness and neurological deficits.[4]
- Risk of meningococcal disease is substantially increased in certain medical conditions including asplenia, complement deficiency and treatment with eculizumab. This can be up to 10,000 times higher than the general population in people with genetic deficiencies of the complement pathway.[6]

Desirable effects
How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Evidence is derived from a single booster study in healthy individuals.
- There is evidence of a moderate effect from a booster dose of Trumenba, based on immunogenicity data only, which increases the proportion with hSBA≥1:8 or 1:16 (lower limit of quantitation, but higher than the 1:4 proposed correlate of protection) but the increase varies in size dependent on test strain and on the degree of waning prior to the booster dose.
- Evidence of persistence after a booster dose is of very low certainty, and immunogenicity data is limited to approximately 2 years following the booster; the rate of waning may be slower than after primary vaccination.

- There is no evidence available on clinical outcomes after booster doses.

Undesirable Effects
How substantial are the undesirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- Undesirable effects include frequent rates of local adverse events and systemic adverse events which are mostly of mild to moderate severity.
- There were no vaccine-related serious adverse events in the included booster study.

Certainty of evidence
What is the overall certainty of the evidence of effects?

No Included Studies	Very Low	Low	Moderate	High

- The certainty of evidence is very low due to absence of studies of boosters in populations at increased risk of IMD, small study size, non-randomised observational study design, and evaluation of single arm data.
- The certainty of evidence for risks and benefits for individuals who are healthy but at increased occupational / exposure risk would be low, similar to that for Trumenba in healthy individuals at standard background risk of IMD (PICO 2a).
- There is additional uncertainty in how immunogenicity findings correlate to clinical benefit against serogroup B meningococcal disease. However, inferring efficacy from immunogenicity has generally been accepted due to the rarity of the disease.

Values
I*s there important uncertainty about or variability in how much people value the main outcomes?*

Important uncertainty	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability

- Unlikely to be important uncertainty in how people value protection against invasive meningococcal disease.
- Individuals at increased risk of IMD are likely to still consider protection based on immunogenicity evidence as worthwhile.

Balance of effects
Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Don't Know	Varies	Favours comparison	Probably favours comparison	Does not favour either comparison or intervention	Probably favours intervention	Favours intervention

- The overall improvement and likely prolongation of protection from a booster dose probably outweighs the additional frequency of non-serious adverse events/reactogenicity compared to no booster.
- Undesirable effects are minor

Acceptability
Is the intervention acceptable to key stakeholders?

Don't know	Varies	No	Probably No	Probably Yes	Yes

- Vaccination to prevent meningococcal disease appears to be acceptable in the Australian setting. There is high uptake of the MenACWY NIP-funded vaccine with 93.6% coverage by 2 years of age.[7] Meningocccal B vaccine which is not funded has low coverage nationally (only 1.65% of adolescents in 2019)[8], but is likely to be higher in South Australia where it is freely available under state funding. In a large state-wide South Australian study of the impact of vaccination with Bexsero on nasopharyngeal carriage of N. meningitidis in adolescents ('B Part of It'), 99.5% of those enrolled received 1 dose and 97% received 2 doses.

Feasibility
Is the intervention feasible to implement?

Don't know	Varies	No	Probably No	Probably Yes	Yes

- Vaccine delivery system already exists. Small numbers as the population at increased risk of IMD is low and uptake nationally is low.

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