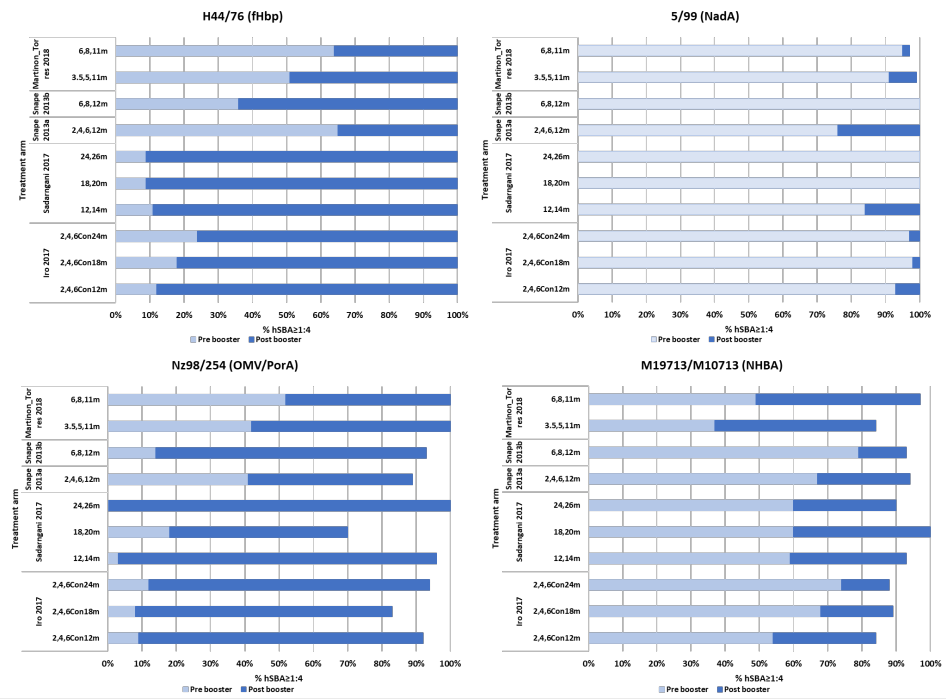
NCIRS is conducting GRADE in support of ATAGI and making results available on the NCIRS website. Please read this material as a supplement to the Australian Immunisation Handbook meningococcal disease chapter

Summary of findings: Bexsero 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: Bexsero booster dose
Comparison: No booster

Outcome № of participants (studies)	Impact	Certainty	Interpretation
Critical outcomes			
Proportion of infant (<2 years) participants with hSBA ≥1:4 (hSBA≥1:4) follow-up: 1 months № of participants: 417^ (5 observational studies[3-5,7,9])		⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of Bexsero on hSBA≥1:4. Bexsero booster may increase the proportion of infants (<2 years) with hSBA≥1:4 but the evidence is very uncertain

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

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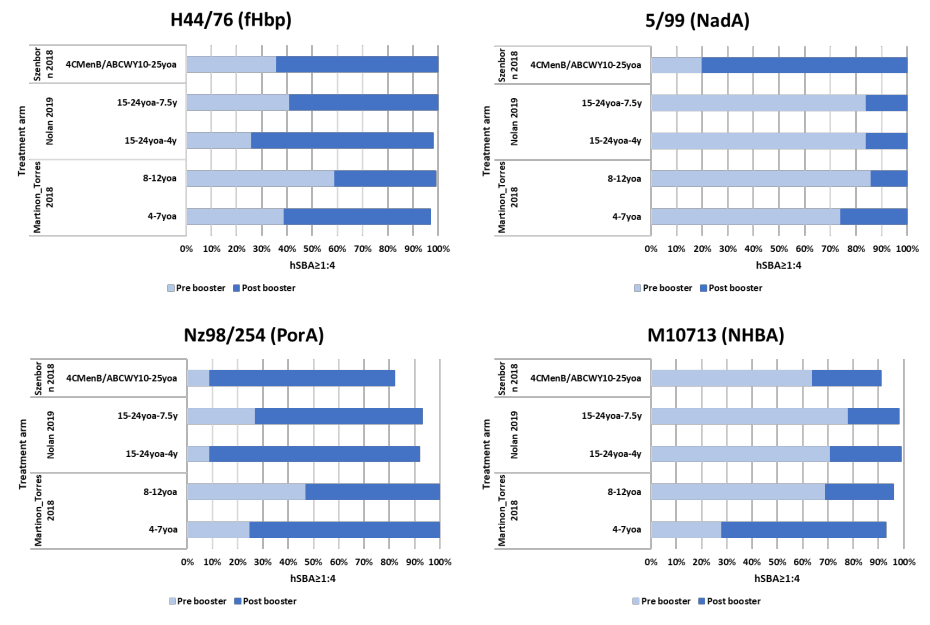
Outcome № of participants (studies)	Impact	Certainty	Interpretation
Proportion of participants aged >2 years with hSBA ≥1:4 (hSBA≥1:4) follow-up: 1 months № of participants: 405^ (3 observational studies[6-8])		⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of Bexsero on hSBA≥1:4. Bexsero booster vaccine may increase the proportion of individuals >2 years of age with hSBA≥1:4 but the evidence is very uncertain

Summary of findings: Bexsero 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
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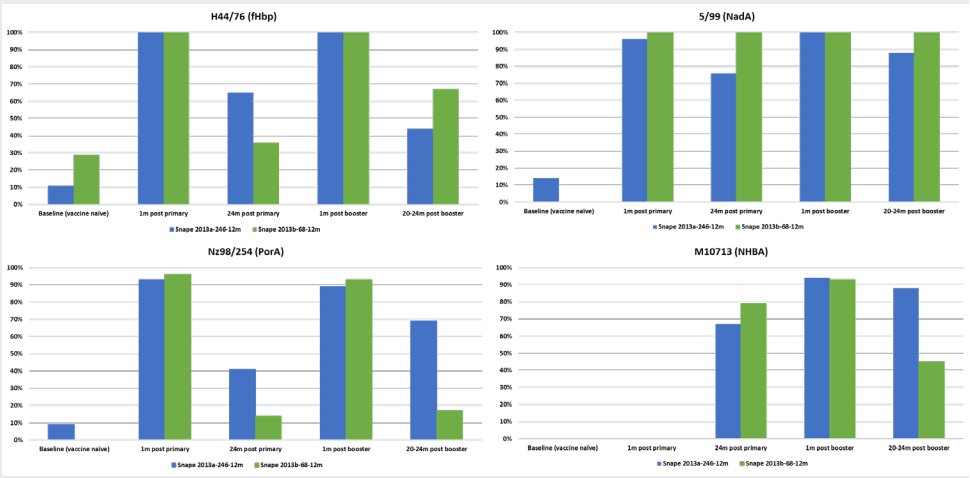
Comparison: No booster

Outcome № of participants (studies)	Impact	Certainty	Interpretation
Persistence: Proportion of infant (<2 years) participants with hSBA ≥1:4 follow-up: 24 months № of participants: 33 (2 observational studies[4,5])		⨁◯◯◯ Very low[a,b,d]	The evidence is very uncertain about the effect of Bexsero booster on hSBA≥1:4 persistence. Bexsero may increase the proportion of infants (<2 years) with hSBA≥1:4 at 24 months post booster vaccine but the evidence is very uncertain
Persistence: Proportion of participants aged >2 years with hSBA ≥1:4 follow-up: 12 months № of participants: 11 (1 observational study[8])		⨁◯◯◯ Very low[a,b,d]	The evidence is very uncertain about the effect of Bexsero booster on hSBA≥1:4 persistence. Bexsero may increase the proportion of individuals >2 years of age with hSBA≥1:4 at 12 months post booster vaccine but the evidence is very uncertain.

Summary of findings: Bexsero 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
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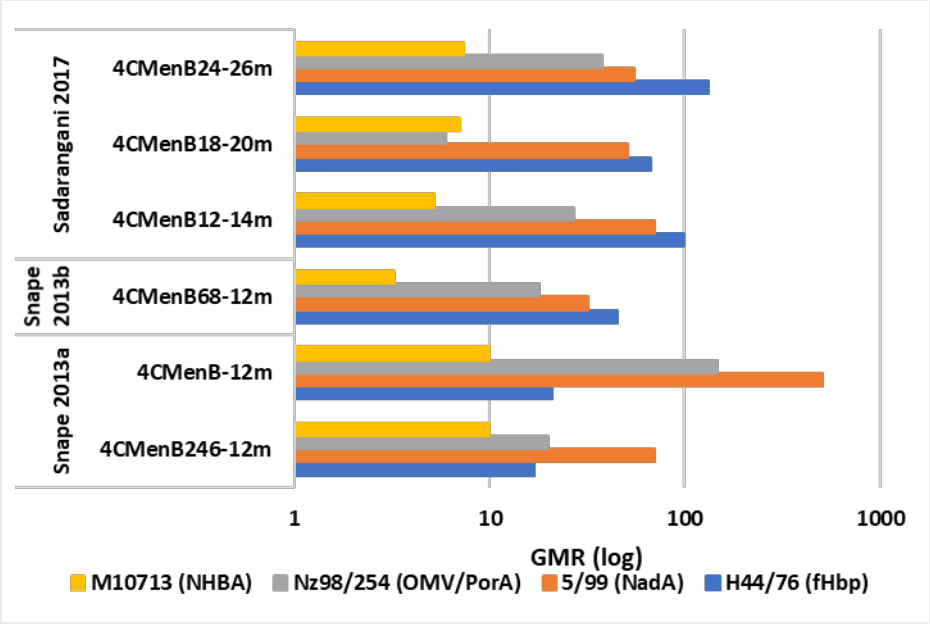
Comparison: No booster

Outcome № of participants (studies)	Impact	Certainty	Interpretation
Geometric mean ratio (GMR) in infants (<2 years) № of participants: 155^ (3 observational studies[3-5])		⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of Bexsero on GMR. Bexsero booster vaccine may increase in post-booster vs pre-booster titres as measured by GMR in infants (<2 years) but the evidence is very uncertain.

Summary of findings: Bexsero 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
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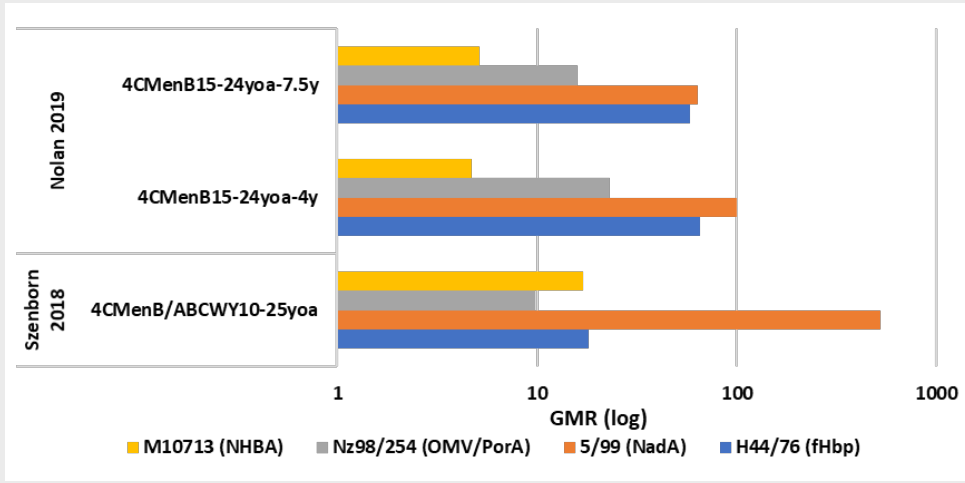
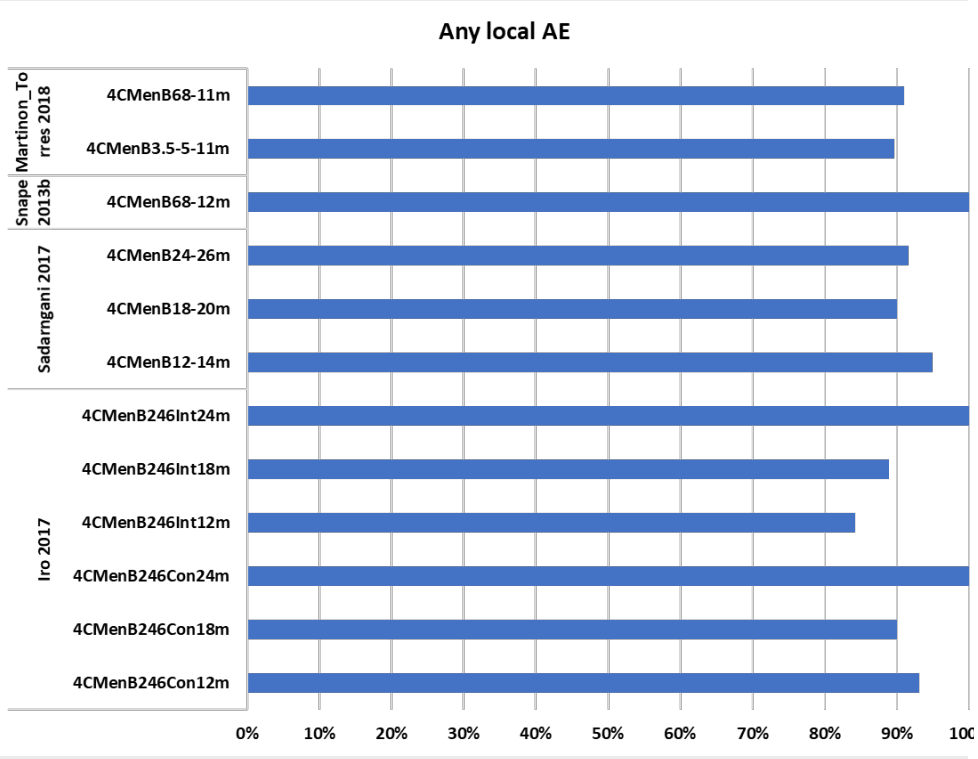
Outcome № of participants (studies)	Impact	Certainty	Interpretation
Geometric mean ratio (GMR) in participants aged >2 years № of participants: 137^ (2 observational studies[6,8])		⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of Bexsero on GMR. Bexsero booster vaccine may increase in post-booster vs pre-booster titres as measured by GMR in individuals >2 years of age but the evidence is very uncertain.
IMPORTANT OUTCOMES			

Summary of findings: Bexsero 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: Bexsero booster dose
Comparison: No booster

Outcome № of participants (studies)	Impact	Certainty	Interpretation
Local adverse events (Local AEs) in infants (<2 years) follow-up: 7 days № of participants: 398 (4 observational studies[3,5,7,9])		⨁◯◯◯ Very low[a,b,e]	The evidence is very uncertain about the effect of Bexsero on local AEs. Bexsero booster may increase local AEs in infants (<2 years) but the evidence is very uncertain

Summary of findings: Bexsero 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
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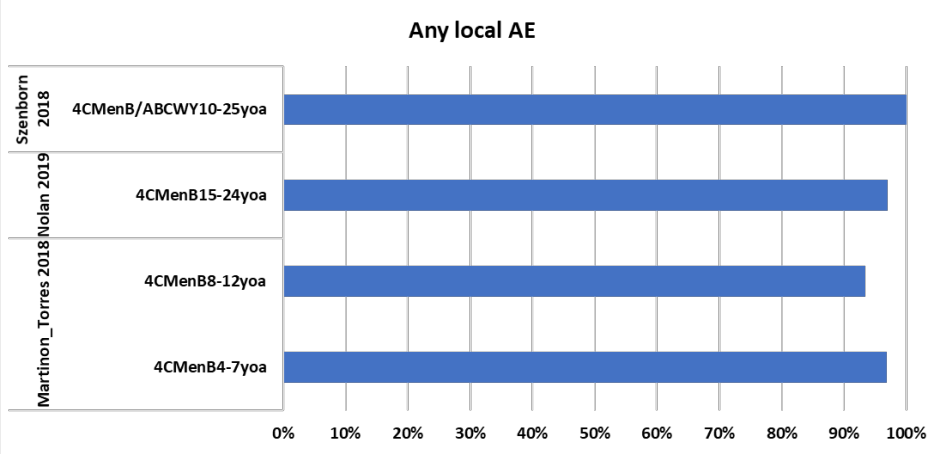
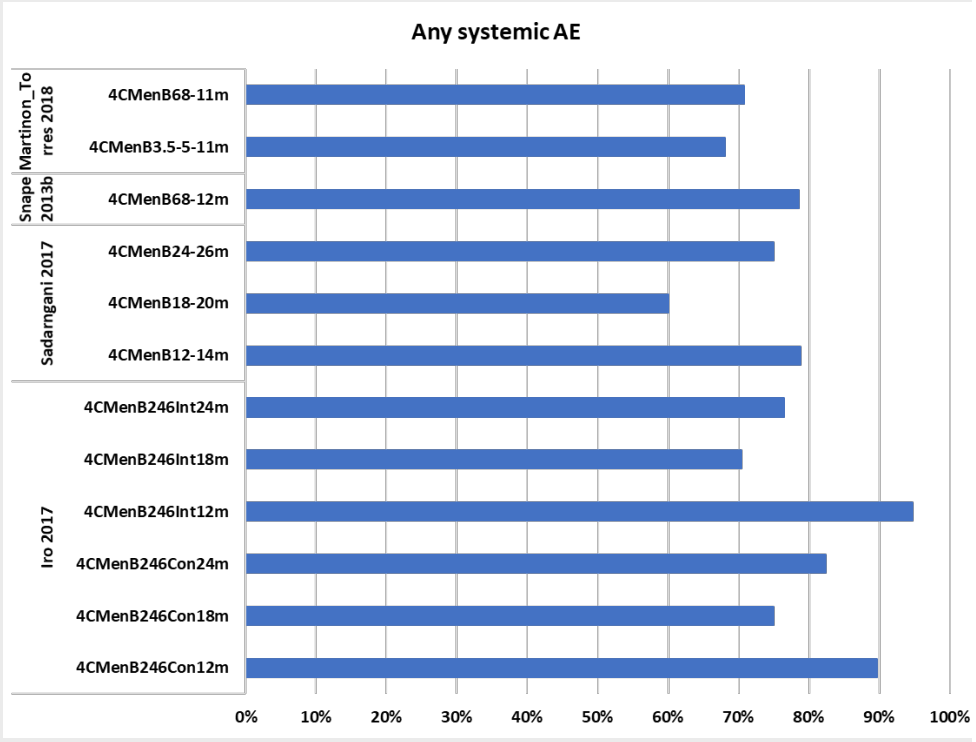
Outcome № of participants (studies)	Impact	Certainty	Interpretation
Local adverse events (Local AEs) in participants aged >2 years follow-up: 7 days № of participants: 405 (3 observational studies[6-8])		⨁◯◯◯ Very low[a,b,e]	The evidence is very uncertain about the effect of Bexsero on local AEs. Bexsero booster may increase local AEs in individuals >2 years of age but the evidence is very uncertain.

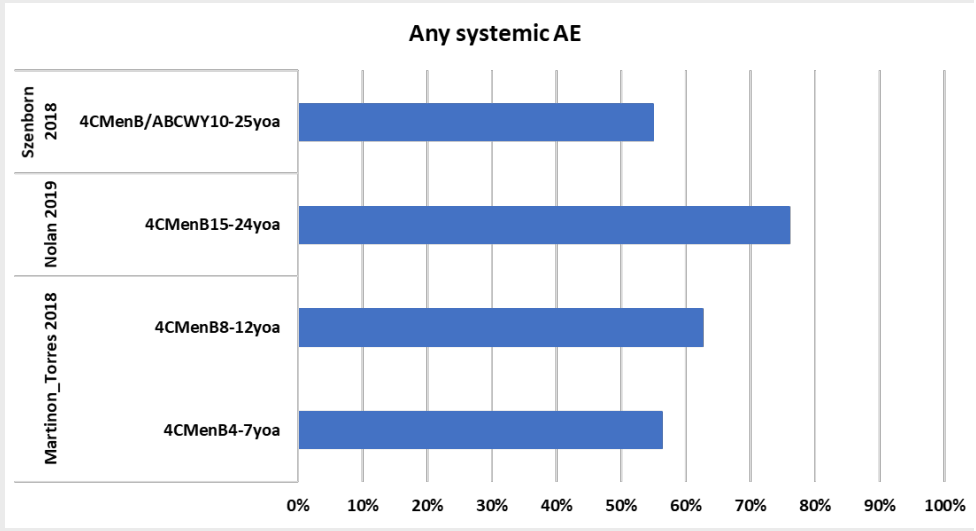
Summary of findings: Bexsero booster dose compared with no booster dose in individuals at increased risk of invasive meningococcal disease (IMD)

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

Outcome № of participants (studies)	Impact	Certainty	Interpretation
Systemic adverse events (Systemic AEs) in infants (<2 years) follow-up: 7 days № of participants: 398 (4 observational studies[3,5,7,9])		⨁◯◯◯ Very low[a,b,e]	The evidence is very uncertain about the effect of Bexsero on systemic AEs. Bexsero booster may increase systemic AEs in infants (<2 years) but the evidence is very uncertain.

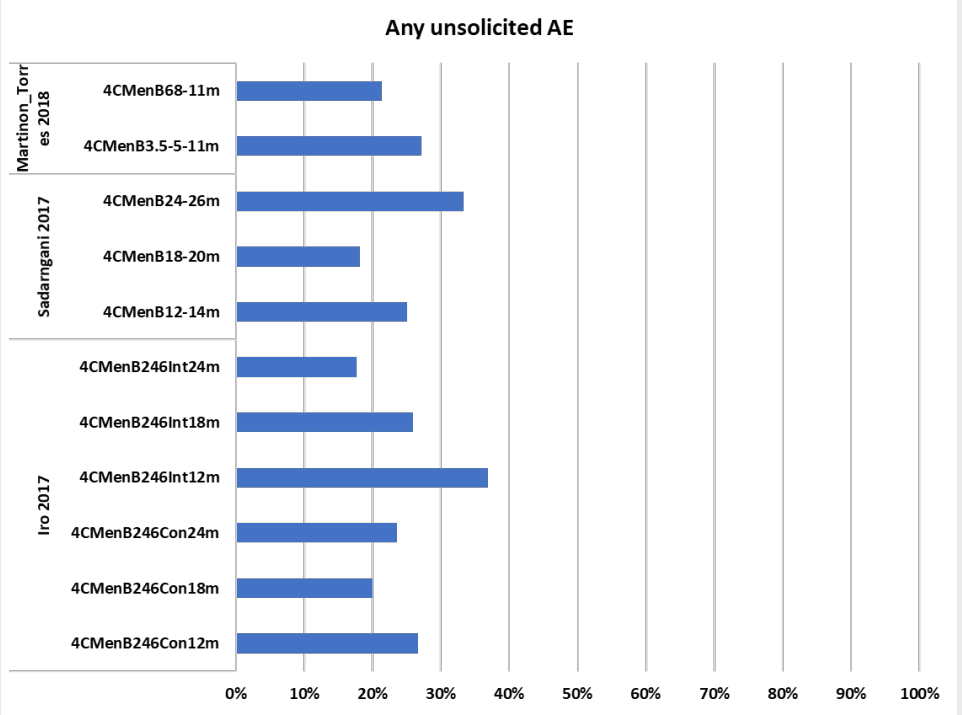
Summary of findings: Bexsero booster dose compared with no booster dose in individuals at increased risk of invasive meningococcal disease (IMD)

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

Outcome № of participants (studies)	Impact	Certainty	Interpretation
Systemic adverse events (Systemic AEs) in participants aged >2 years follow-up: 7 days № of participants: 405 (3 observational studies[6-8])		⨁◯◯◯ Very low[a,b,e]	The evidence is very uncertain about the effect of Bexsero on systemic AEs. Bexsero booster may increase systemic AEs in individuals >2 years of age but the evidence is very uncertain.

Summary of findings: Bexsero 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: Bexsero booster dose
Comparison: No booster

Outcome № of participants (studies)	Impact	Certainty	Interpretation
Unsolicited adverse events (Unsolicited AEs) in infants (<2 years) follow-up: 7 days № of participants: 384 (3 observational studies[3,7,9])		⨁◯◯◯ Very low[a,b,e]	The evidence is very uncertain about the effect of Bexsero on unsolicited AEs. Bexsero booster may increase unsolicited AEs in infants (<2 years) but the evidence is very uncertain

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

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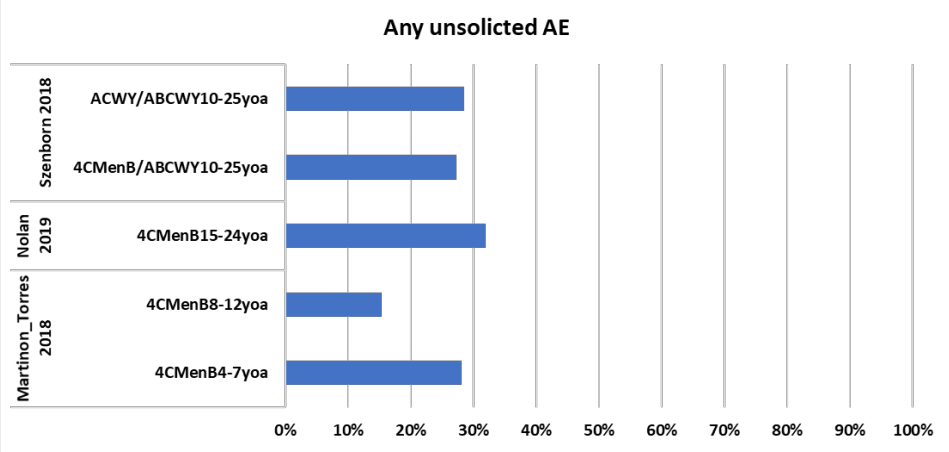
Outcome № of participants (studies)	Impact	Certainty	Interpretation
Unsolicited adverse events (Unsolicited AEs) in participants aged >2 years follow-up: 7 days № of participants: 405 (3 observational studies[6-8])		⨁◯◯◯ Very low[a,b,e]	The evidence is very uncertain about the effect of Bexsero on unsolicited AEs. Bexsero booster may increase unsolicited AEs in individuals >2 years of age but the evidence is very uncertain

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

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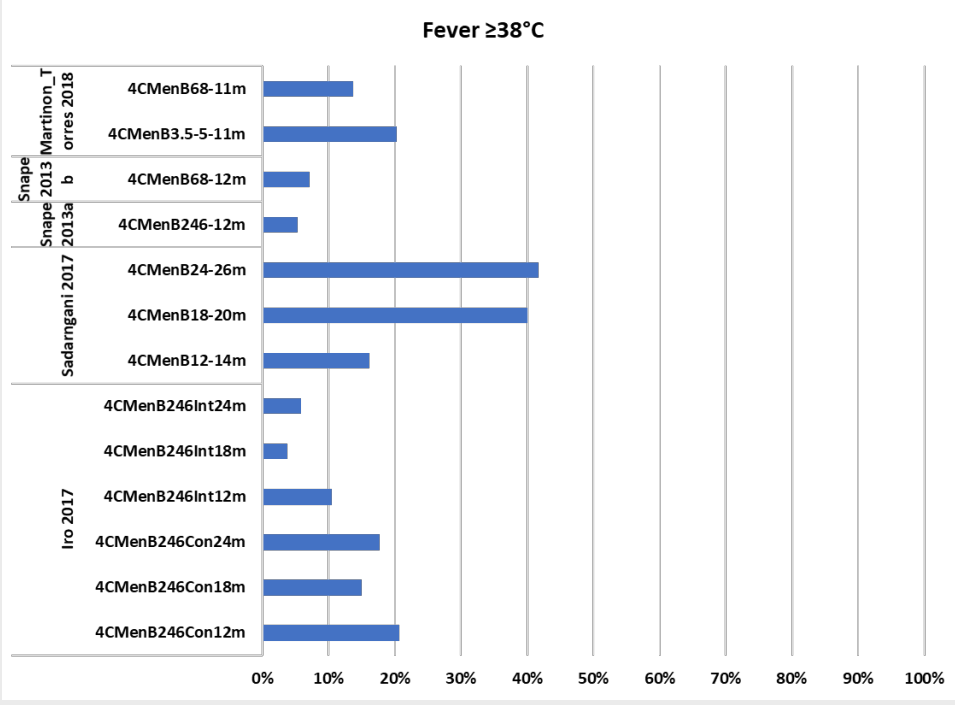
Outcome № of participants (studies)	Impact	Certainty	Interpretation
Fever ≥38°C (Fever) in infants (<2 years) follow-up: 7 days № of participants: 417 (5 observational studies[3-5,7,9])		⨁◯◯◯ Very low[a,b,e]	The evidence is very uncertain about the effect of Bexsero on fever. Bexsero booster may increase fever≥38°C in infants (<2 years) but the evidence is very uncertain.

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

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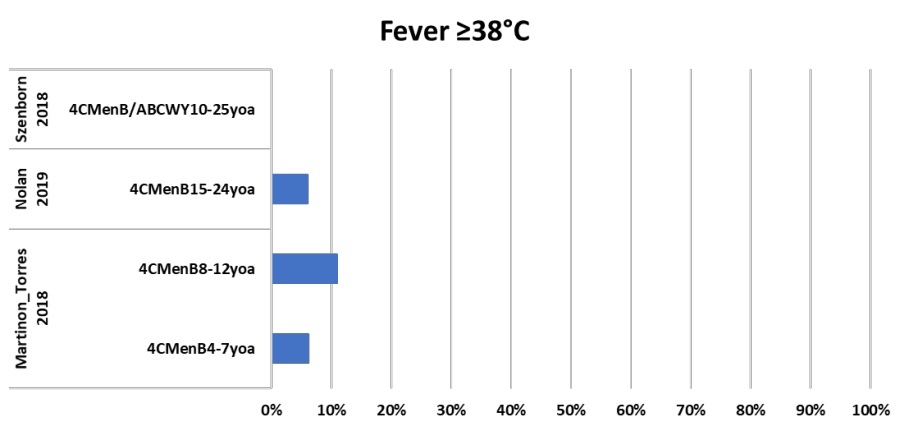
Outcome № of participants (studies)	Impact	Certainty	Interpretation
Fever ≥38°C (Fever) in participants aged >2 years follow-up: 7 days № of participants: 405 (3 observational studies[6-8])		⨁◯◯◯ Very low[a,b,e]	The evidence is very uncertain about the effect of Bexsero on fever. Bexsero booster may have little to no effect on fever≥38°C in individuals >2 years of age but the evidence is very uncertain.

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

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 sample size (<400 participants). Confidence intervals overlap within some strains
d. Very low sample size (<50 participants)
e. Low number of events (<300 events)
^number of participants includes those included in the analysis post booster dose and does not double count the 'pre booster' participants

Evidence profile: Bexsero 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)									
5	observational studies	serious[a]	not serious	serious[b]	serious[d]	none	Proportion of participants with hSBA≥1:4 at 1 month post booster vaccine ranged from 70-100% in infants (<2 years)	⨁◯◯◯ Very low	CRITICAL
3	observational studies	serious[a]	not serious	serious[b]	serious[d]	none	Proportion of participants with hSBA≥1:4 at 1 month post booster vaccine ranged from 82-100% in participants aged >2 years	⨁◯◯◯ Very low	CRITICAL
Proportion of participants with hSBA ≥1:4 (persistence) (follow-up: 24 months)									
2	observational studies	serious[a]	not serious	serious[b]	very serious[d]	none	Proportion of participants with hSBA≥1:4 at 24 months post booster vaccine ranged from 17-100% in infants (<2 years)	⨁◯◯◯ Very low	CRITICAL
1	observational studies	serious[a]	NA*	serious[b]	very serious[d]	none	Proportion of participants with hSBA≥1:4 at 12 months post booster vaccine ranged from 45-100%	⨁◯◯◯ Very low	CRITICAL
Geometric mean ratio									
3	observational studies	serious[a]	not serious	serious[b]	serious[c]	none	The GMR in infants (<2 years) before and after booster vaccination ranged from 3.25-509	⨁◯◯◯ Very low	CRITICAL
2	observational studies	serious[a]	not serious	serious[b]	serious[c]	none	The GMR in participants aged >2 years before and after booster vaccination ranged from 4.69-525	⨁◯◯◯ Very low	CRITICAL
Local adverse events (follow-up: 7 days)									
4	observational studies	serious[a]	not serious	serious[b]	serious[d]	none	Local AEs ranged from 84-100% in infants (<2 years)	⨁◯◯◯ Very low	IMPORTANT
3	observational studies	serious[a]	not serious	serious[b]	serious[d]	none	Local AEs ranged from 93-100% in participants aged >2 years	⨁◯◯◯ Very low	IMPORTANT
Systemic adverse events (follow-up: 7 days)									
4	observational studies	serious[a]	not serious	serious[b]	serious[d]	none	Systemic AEs ranged from 60-95% infants (<2 years)	⨁◯◯◯ Very low	IMPORTANT
3	observational studies	serious[a]	not serious	serious[b]	serious[d]	none	Systemic AEs ranged from 55-76% in participants aged >2 years	⨁◯◯◯ Very low	IMPORTANT
Unsolicited adverse events (follow-up: 7 days)									
3	observational studies	serious[a]	not serious	serious[b]	serious[d]	none	Unsolicited AEs ranged from 18-37% infants (<2 years)	⨁◯◯◯ Very low	IMPORTANT
3	observational studies	serious[a]	not serious	serious[b]	serious[d]	none	Unsolicited AEs ranged from 15-32% in participants aged >2 years	⨁⨁◯◯ Low	IMPORTANT
Fever ≥38°C (follow-up: 7 days)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
5	observational studies	serious[a]	not serious	serious[b]	serious[d]	none	Fever ≥38°C ranged from 4-42% infants (<2 years)	⨁◯◯◯ Very low	IMPORTANT
3	observational studies	serious[a]	not serious	serious[b]	serious[d]	none	Fever ≥38°C ranged from 0-11% in participants aged >2 years	⨁◯◯◯ Very low	IMPORTANT

Explanations

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 sample size (<400 participants). Confidence intervals overlap within some strains
d. Very low sample size (<50 participants)
e. Low number of events (<300 events)

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 Bexsero (recombinant multicomponent meningococcal group B vaccine)
Comparison	No booster
Main outcomes	Efficacy/Effectiveness of booster dose Immunogenicity: hSBA≥1:4 / 1:5 (Bexsero) 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	US, Canada, Europe, Australia, United Kingdom, Chile
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%.[10-12]
- Survivors of infection are often left with permanent sequelae including limb / digit amputations, deafness and neurological deficits.[11]
- 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.[13]

Desirable effects
How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- All evidence is derived from booster studies in healthy individuals.
- There is evidence of a moderate effect from a booster dose of Bexsero, based on immunogenicity data only, which increases the proportion with hSBA≥1:4 or 1:5 (the 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 is of very low certainty and immunogenicity data is limited to ≤2 years following the booster. The rate of waning appears to vary by strain after booster and may be similar to or 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. Rates are similar to those seen after primary vaccination in vaccine-naïve cohorts within the booster studies.
- There were no vaccine related serious adverse events due to the vaccine in the included booster studies.

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 specifically in populations at increased medical risk of IMD, small study sizes, non-randomised observational studies, 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 Bexsero in healthy individuals at standard background risk of IMD (PICO 1a).
- 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 is likely to outweigh the additional frequency of non-serious adverse events/reactogenicity compared to no booster, particularly where the baseline risk of IMD is high.
- 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.[14] Meningococcal B vaccine which is not funded has low coverage nationally (only 1.65% of adolescents in 2019)[15], 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.

References

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