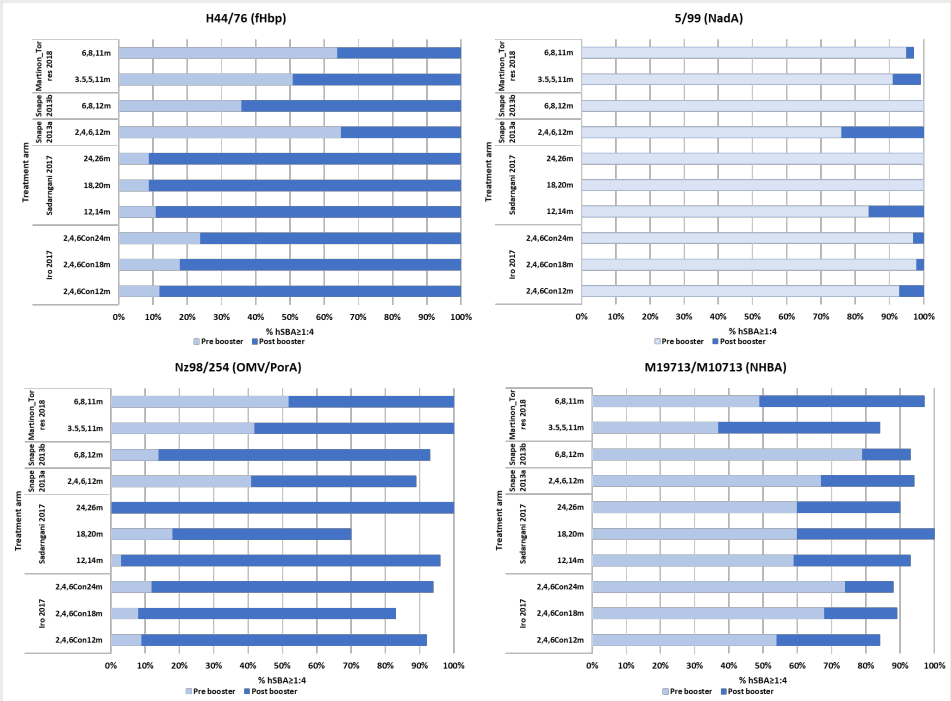
NCIRS is conducting GRADE in support of ATAGI and making results available on the NCIRS website. Please read this material as a supplement to the Australian Immunisation Handbook meningococcal disease chapter

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

Patient or population: Individuals at standard background 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 month № of participants: 417^ (5 observational studies[1,3-5,7])		⨁⨁◯◯ Low[a,b]	Bexsero booster may result in a large increase in proportion of infants (<2 years) with hSBA≥1:4 at 1 month post booster vaccine

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

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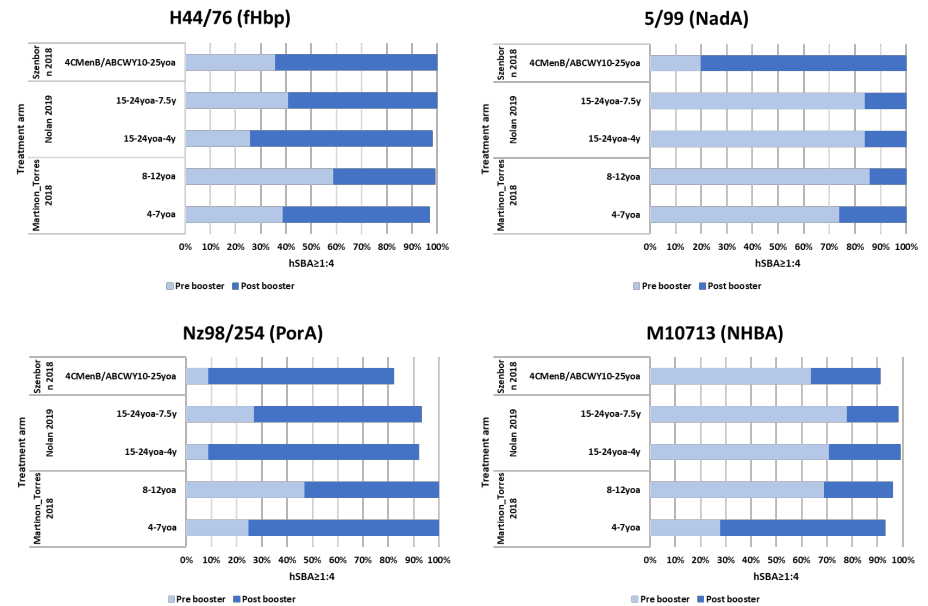
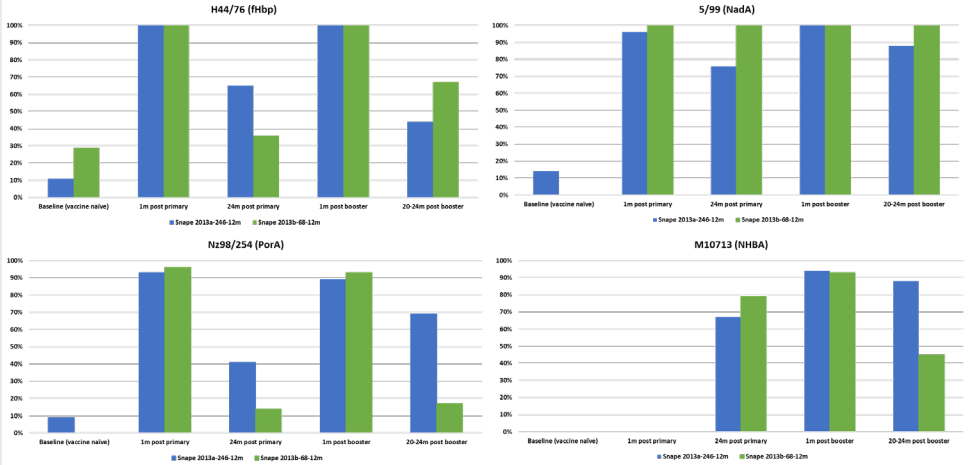
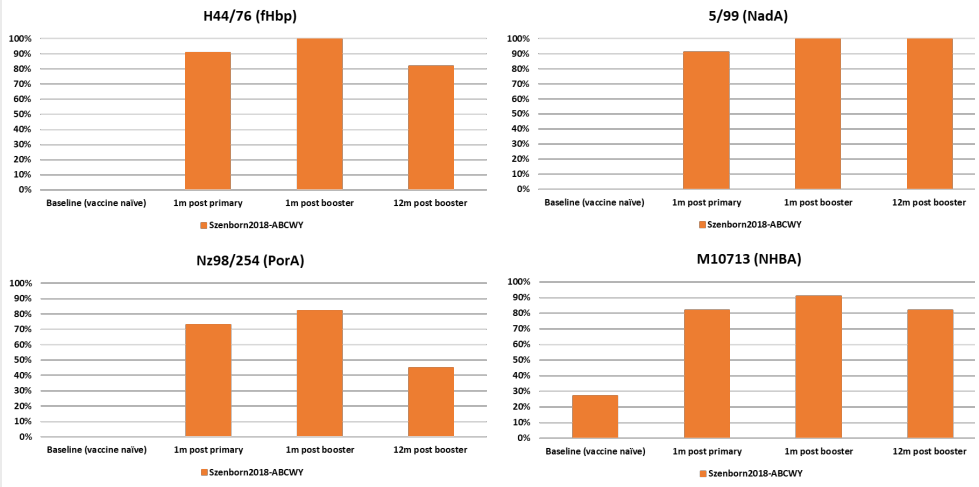
Comparison: No booster

Outcome № of participants (studies)	Impact	Certainty	Interpretation
Proportion of participants aged >2 years with hSBA ≥1:4 (hSBA≥1:4) follow-up: 1 month № of participants: 405^ (3 observational studies[6-8])		⨁⨁◯◯ Low[a,b]	Bexsero booster vaccine may result in an increase in the proportion of individuals >2 years of age with hSBA≥1:4 at 1 month post booster vaccine

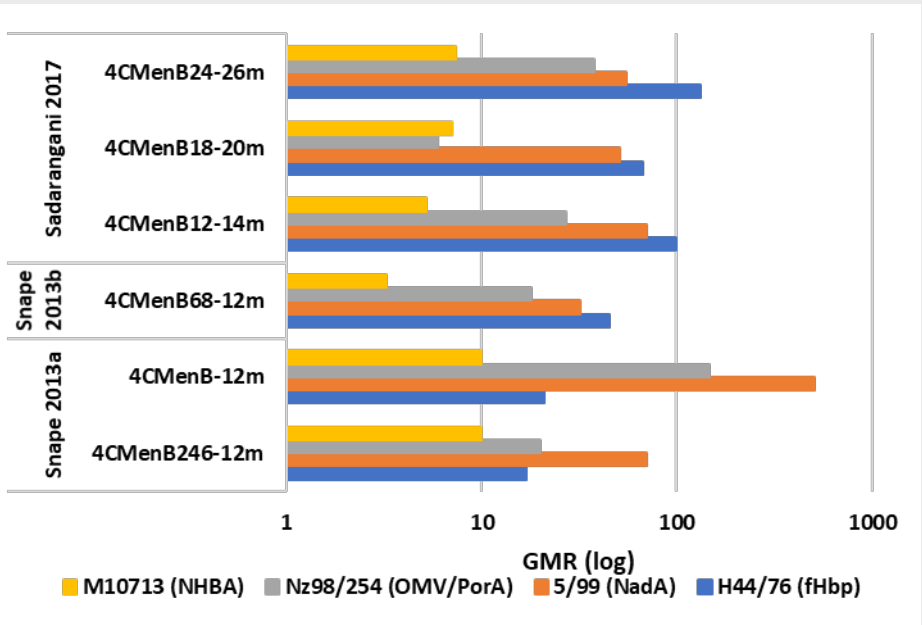
Summary of findings: Bexsero booster dose compared with no booster dose in individuals at standard background risk of invasive meningococcal disease (IMD)

Patient or population: Individuals at standard background risk of IMD
Intervention: Bexsero booster dose
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[1,c]	The evidence is very uncertain about the effect of Bexsero booster on hSBA 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[1,c]	The evidence is very uncertain about the effect of Bexsero booster on hSBA 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.

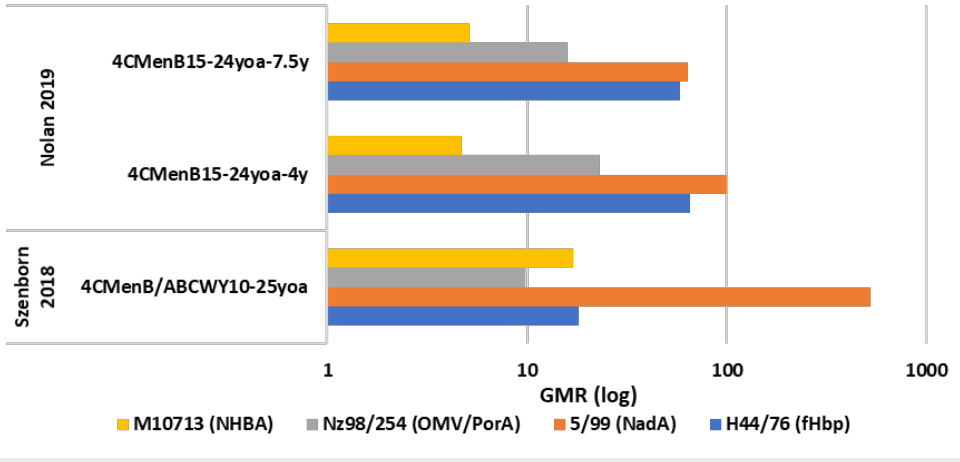
Summary of findings: Bexsero booster dose compared with no booster dose in individuals at standard background risk of invasive meningococcal disease (IMD)

Patient or population: Individuals at standard background risk of IMD
Intervention: Bexsero booster dose
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])		⨁⨁◯◯ Low[a,d]	Bexsero booster vaccine may result in a large increase in post-booster vs pre-booster titres as measured by GMR in infants (<2 years)

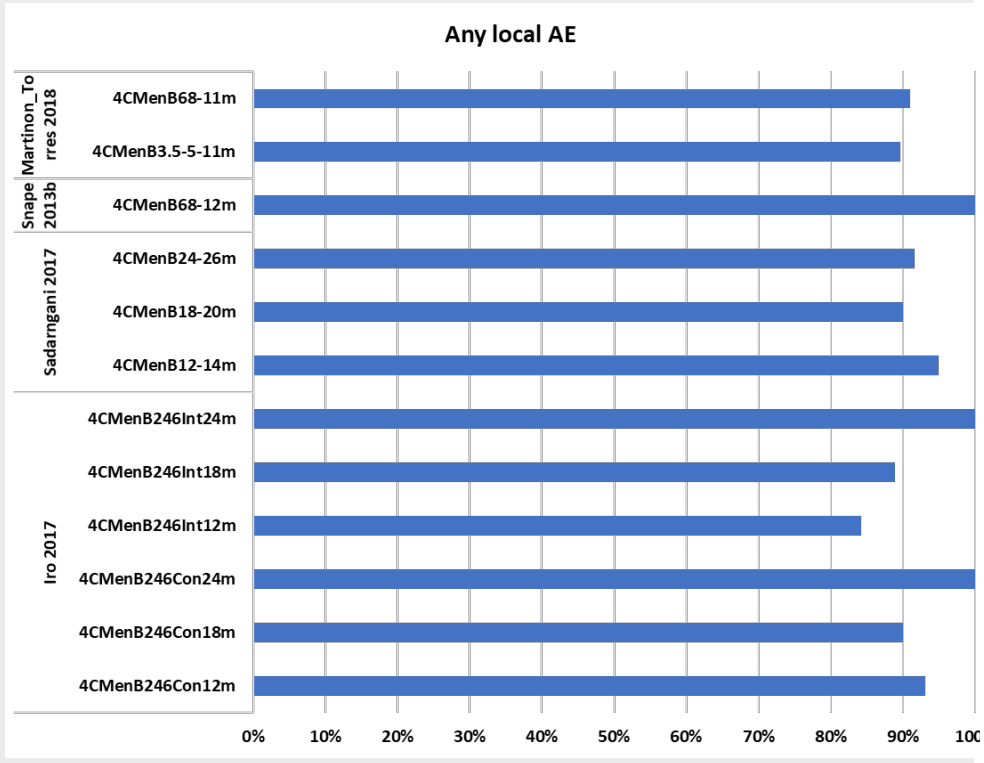
Summary of findings: Bexsero booster dose compared with no booster dose in individuals at standard background risk of invasive meningococcal disease (IMD)

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

Outcome № of participants (studies)	Impact	Certainty	Interpretation
Geometric mean ratio (GMR) in participants aged >2 years № of participants: 137^ (2 observational studies[6,8])		⨁⨁◯◯ Low[a,d]	Bexsero booster vaccine may result in a large increase in post-booster vs pre-booster titres as measured by GMR in individuals >2 years of age
important outcomes			

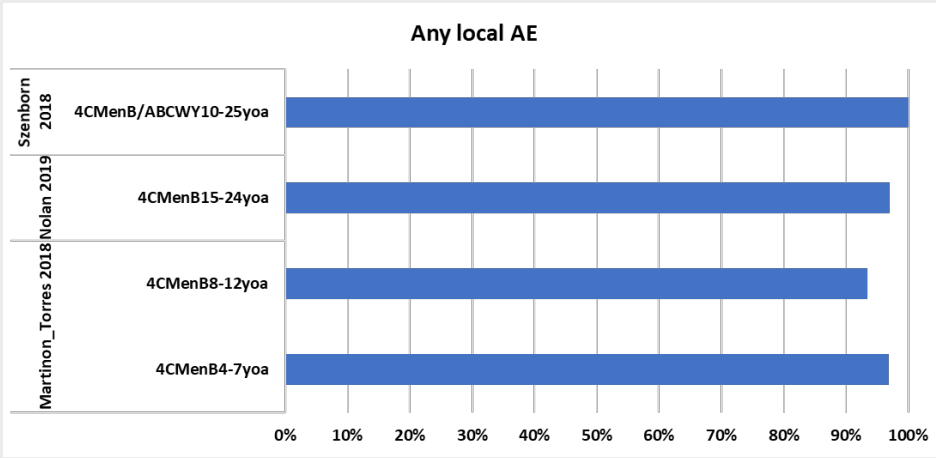
Summary of findings: Bexsero booster dose compared with no booster dose in individuals at standard background risk of invasive meningococcal disease (IMD)

Patient or population: Individuals at standard background 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[1,3,5,7])		⨁⨁◯◯ Low[a,b]	Bexsero booster may result in a large increase in local AEs in infants (<2 years)

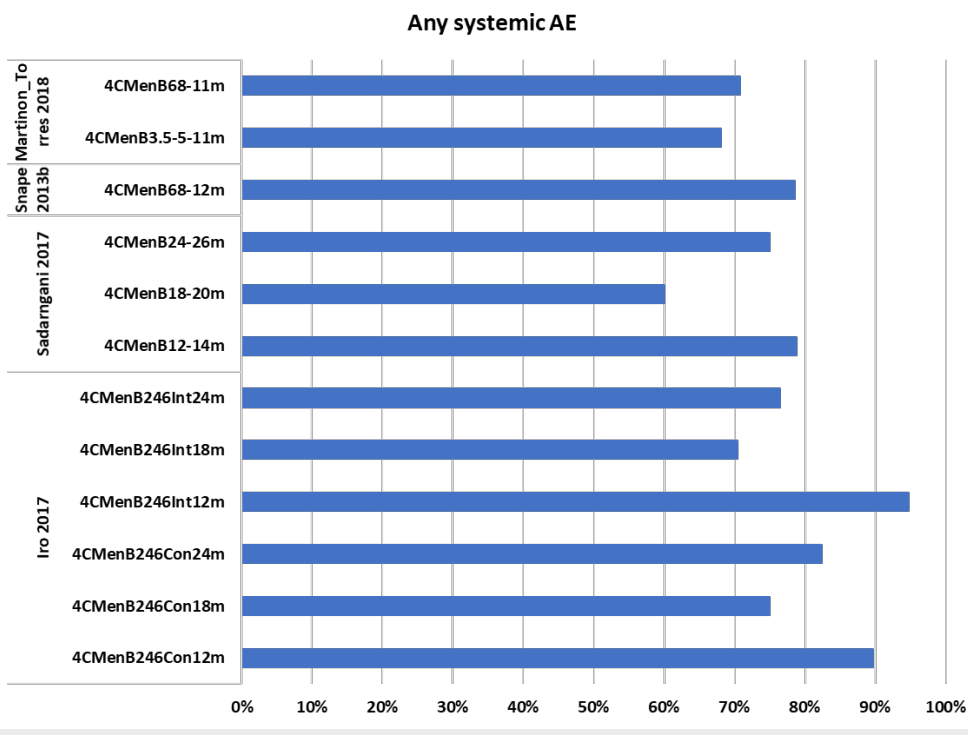
Summary of findings: Bexsero booster dose compared with no booster dose in individuals at standard background risk of invasive meningococcal disease (IMD)

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

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])		⨁⨁◯◯ Low[a,b]	Bexsero booster may result in a large increase in local AEs in individuals >2 years of age

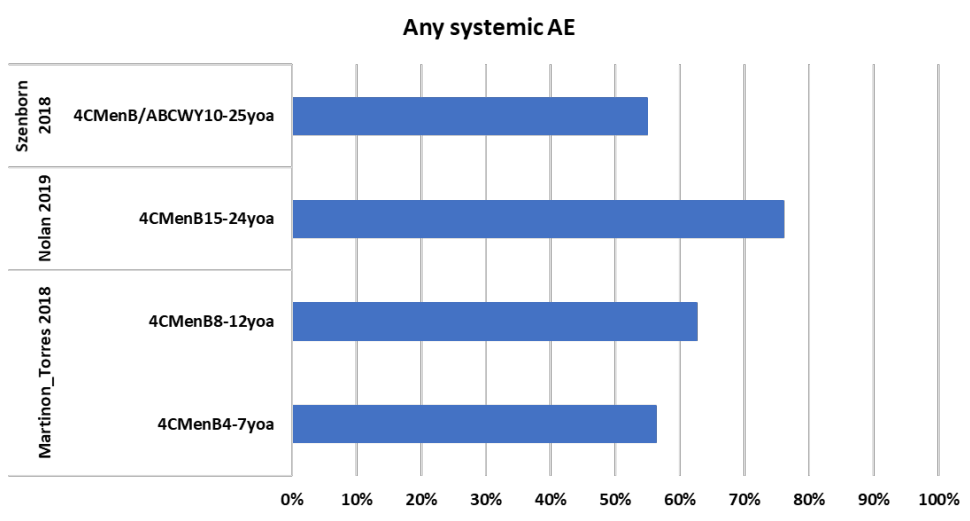
Summary of findings: Bexsero booster dose compared with no booster dose in individuals at standard background risk of invasive meningococcal disease (IMD)

Patient or population: Individuals at standard background 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[1,3,5,7])		⨁⨁◯◯ Low[a,b]	Bexsero booster may result in a large increase in systemic AEs in infants (<2 years)

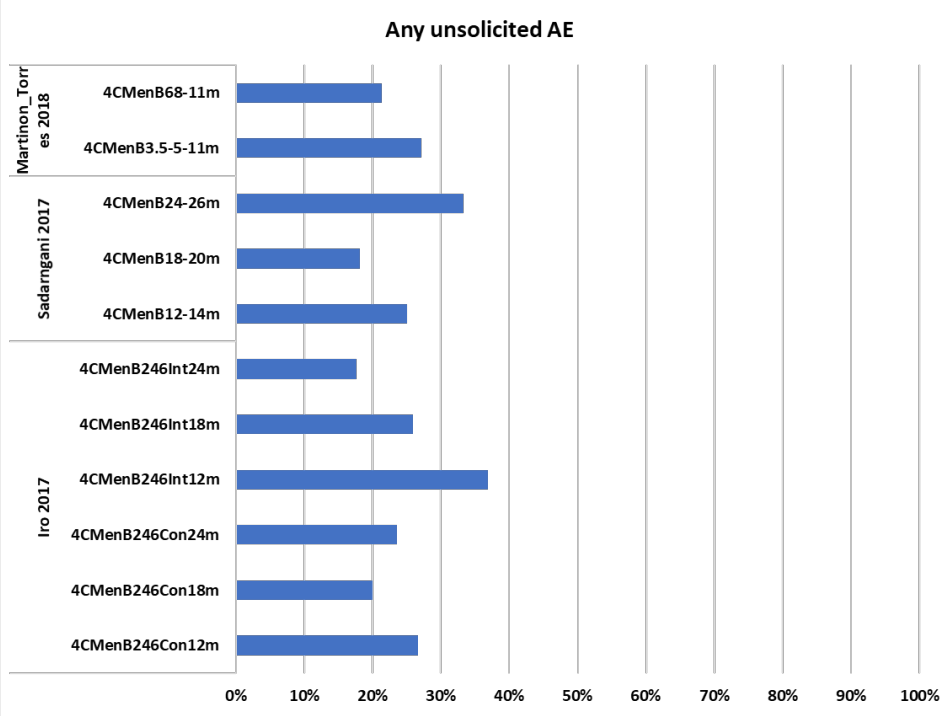
Summary of findings: Bexsero booster dose compared with no booster dose in individuals at standard background risk of invasive meningococcal disease (IMD)

Patient or population: Individuals at standard background 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])		⨁⨁◯◯ Low[a,b]	Bexsero booster may result in an increase in systemic AEs in individuals >2 years of age

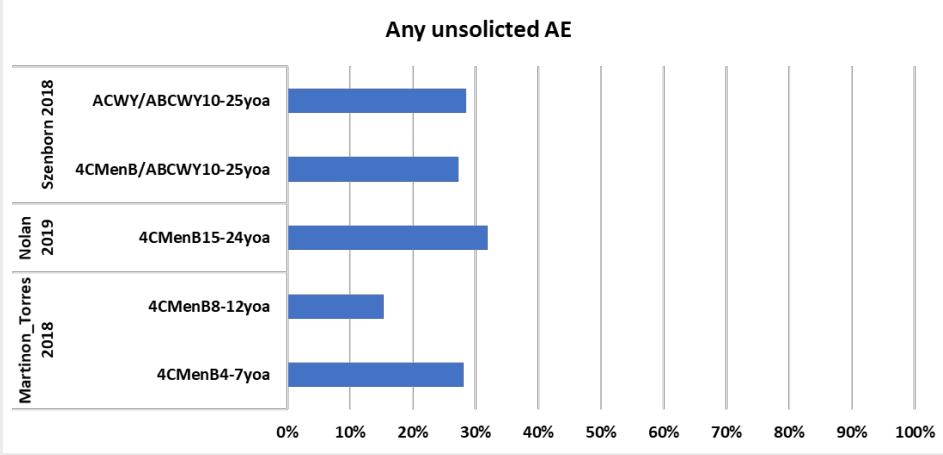
Summary of findings: Bexsero booster dose compared with no booster dose in individuals at standard background risk of invasive meningococcal disease (IMD)

Patient or population: Individuals at standard background 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[1,3,7])		⨁⨁◯◯ Low[a,b]	Bexsero booster may result in a slight increase in unsolicited AEs in infants (<2 years)

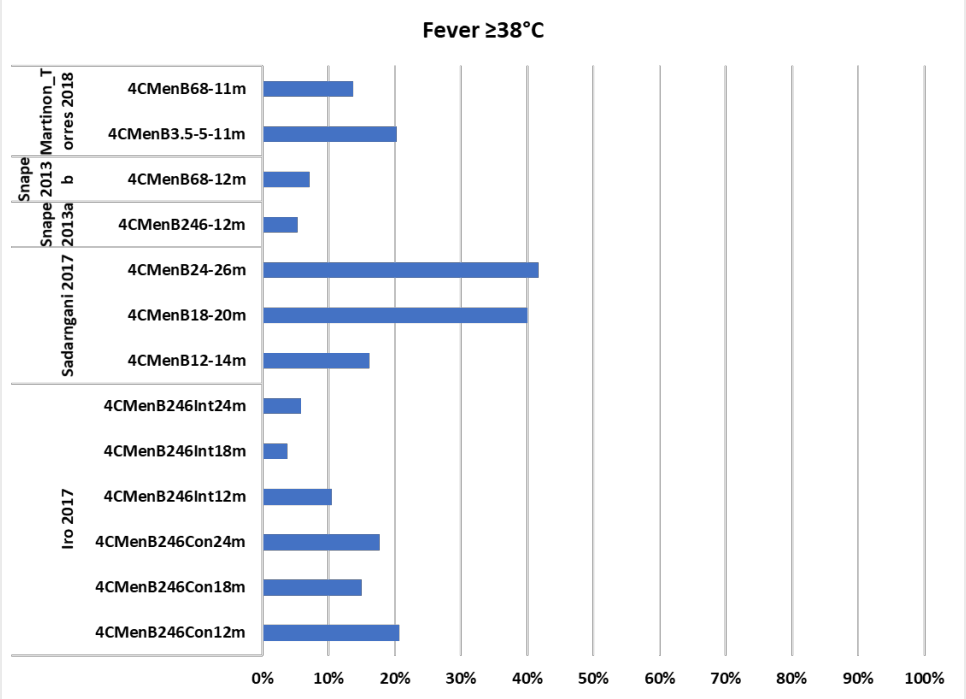
Summary of findings: Bexsero booster dose compared with no booster dose in individuals at standard background risk of invasive meningococcal disease (IMD)

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

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])		⨁⨁◯◯ Low[a,b]	Bexsero booster may result in a slight increase in unsolicited AEs in individuals >2 years of age

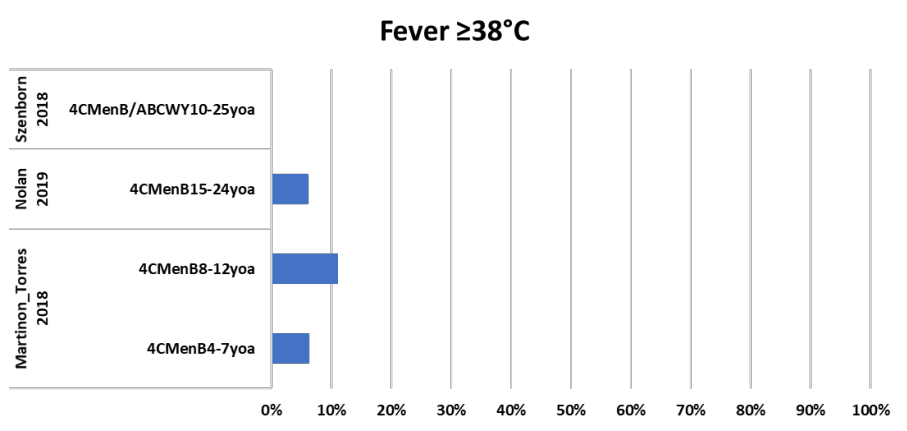
Summary of findings: Bexsero booster dose compared with no booster dose in individuals at standard background risk of invasive meningococcal disease (IMD)

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

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[1,3-5,7])		⨁⨁◯◯ Low[a,b]	Bexsero booster may result in a slight increase in fever≥38°C in infants (<2 years)

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

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

Outcome № of participants (studies)	Impact	Certainty	Interpretation
Fever ≥38°C (Fever) in participants >2 years follow-up: 7 days № of participants: 405 (3 observational studies[6-8])		⨁⨁◯◯ Low[a,b]	Bexsero booster may result in little to no effect on fever≥38°C in individuals >2 years of age

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

Evidence profile: Bexsero booster dose compared with no booster dose for individuals at standard background 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	not serious	serious[b]	none	Proportion of participants with hSBA≥1:4 at 1 month post booster vaccine ranged from 70-100% in infants (<2 years)	⨁⨁◯◯ Low	CRITICAL
3	observational studies	serious[a]	not serious	not serious	serious[b]	none	Proportion of participants with hSBA≥1:4 at 1 month post booster vaccine ranged from 82-100% in participants aged >2 years	⨁⨁◯◯ Low	CRITICAL
Persistence: Proportion of participants with hSBA ≥1:4 (follow-up: 24 months)									
2	observational studies	serious[a]	not serious	not serious	very serious[c]	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*	not serious	very serious[c]	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	not serious	serious[d]	none	The GMR in infants (<2 years) before and after booster vaccination ranged from 3.25-509	⨁⨁◯◯ Low	CRITICAL
2	observational studies	serious[a]	not serious	not serious	serious[d]	none	The GMR in participants aged >2 years before and after booster vaccination ranged from 4.69-525	⨁⨁◯◯ Low	CRITICAL
Local adverse events (follow-up: 7 days)									
4	observational studies	serious[a]	not serious	not serious	serious[b]	none	Local AEs ranged from 84-100% in infants (<2 years)	⨁⨁◯◯ Low	IMPORTANT
3	observational studies	serious[a]	not serious	not serious	serious[b]	none	Local AEs ranged from 93-100% in participants aged >2 years	⨁⨁◯◯ Low	IMPORTANT
Systemic adverse events (follow-up: 7 days)									
4	observational studies	serious[a]	not serious	not serious	serious[b]	none	Systemic AEs ranged from 60-95% infants (<2 years)	⨁⨁◯◯ Low	IMPORTANT
3	observational studies	serious[a]	not serious	not serious	serious[b]	none	Systemic AEs ranged from 55-76% in participants aged >2 years	⨁⨁◯◯ Low	IMPORTANT
Unsolicited adverse events (follow-up: 7 days)									
3	observational studies	serious[a]	not serious	not serious	serious[b]	none	Unsolicited AEs ranged from 18-37% infants (<2 years)	⨁⨁◯◯ Low	IMPORTANT
3	observational studies	serious[a]	not serious	not serious	serious[b]	none	Unsolicited AEs ranged from 15-32% in participants aged >2 years	⨁⨁◯◯ Low	IMPORTANT
Fever ≥38°C (follow-up: 7 days)									
5	observational studies	serious[a]	not serious	not serious	serious[c]	none	Fever ≥38°C ranged from 4-42% infants (<2 years)	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
3	observational studies	serious[a]	not serious	not serious	serious[c]	none	Fever ≥38°C ranged from 0-11% in participants aged >2 years	⨁⨁◯◯ Low	IMPORTANT

Explanations

a. Single arm comparison, assessed as serious risk of bias using ROBINS-I
b. Low number of events (<300 events)
c. Very low sample size (<50 participants)
d. Low sample size (<400 participants). Confidence intervals overlap within some strains
*inconsistency not assessed as only 1 study included

Evidence to Decision Framework: Individual perspective

Should people at standard background risk of invasive meningococcal disease, who are previously vaccinated with a meningococcal B vaccine primary series receive a booster Meningococcal B vaccination?	
Population	Healthy infants, children, adolescents/young adults
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%.[9-11]
- Survivors of infection are often left with permanent sequelae including limb / digit amputations, deafness and neurological deficits.[10]
- Epidemiology suggests the peak period of risk for Meningococcal B is in those aged 0-12 months, followed by those aged 1 - <5 years, with a subsequent peak in adolescents and young adults aged 15-19 years with relatively lower rates outside of these age ranges.[9]

Desirable effects
How substantial are the desirable anticipated effects?

Don't know	Varies	Large	Moderate	Small	Trivial

- 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 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 low due to small study sizes, non-randomised observational studies, and evaluation of single arm data.
- 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.
- Possibly important uncertainty in those at standard risk due to lack of clinical outcome data after boosters and relative rarity of MenB disease.

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.[12] Meningococcal B vaccine which is not funded has low coverage nationally (only 1.65% of adolescents in 2019)[13], 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 overall uptake nationally remains low.

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