Evidence to Recommendations Framework (EtR) and Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Serogroup B Meningococcal (MenB) Vaccine Booster Doses for Persons at increased risk for Serogroup B Meningococcal Disease

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Evidence to Recommendations Framework for MenB Booster Doses

- Background
- Policy question
- Evidence to Recommendations (EtR) Framework:
  - Statement of problem
  - Benefits and harms (including GRADE)
  - Values
  - Acceptability
  - Resource use
  - Feasibility

Background

Meningococcal disease

- Meningococcal disease is a rare, but severe infection.

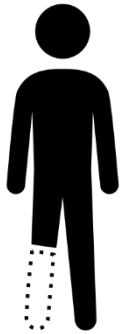
Die despite antibiotics

Survivors left with long-term sequelae:

Hearing loss

Created by Francesca Arena from Noun Project

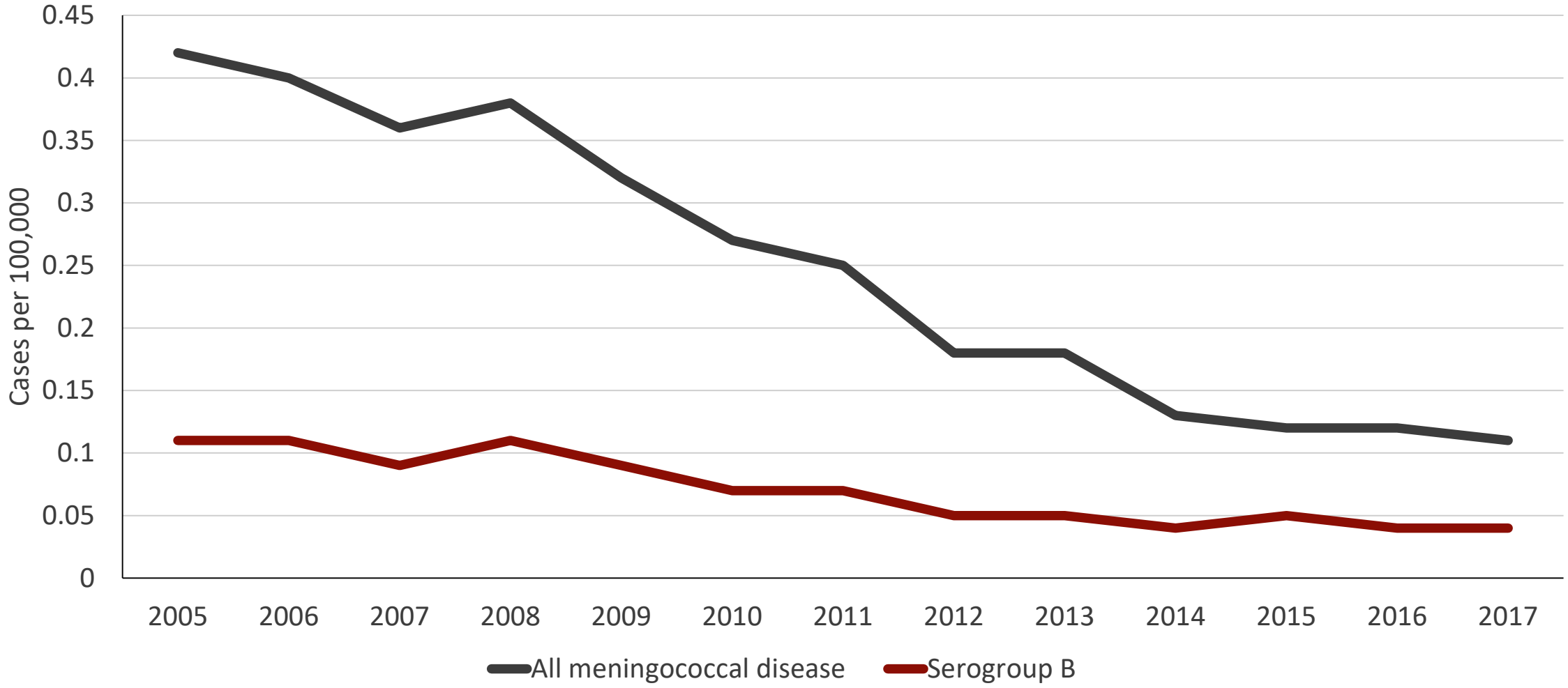
Amputations



Created by Jafri Ali from Noun Project

Cognitive deficits

Incidence of meningococcal disease — United States, 2005 – 2017



Source: National Notifiable Diseases Surveillance System, with additional information on serogroup from state health departments

Serogroup B meningococcal (MenB) vaccination in persons at increased risk for serogroup B meningococcal disease

- ACIP recommends that persons aged ≥10 years at increased risk for serogroup B meningococcal disease receive a MenB primary series.

- Available evidence suggests that antibodies wane in the years following completion of the primary series.
  - MenB booster doses may be necessary to sustain protection.

- Different goals of a booster dose by reason for increased risk:
  - Persons with underlying conditions or microbiologists: Protection for as long as increased risk remains (may be lifelong)
  - Persons at risk during an outbreak: Rapid, short-term protection prioritized

	Policy question: Should persons vaccinated with a MenB primary series who remain at increased risk for serogroup B meningococcal disease receive a MenB booster dose?
Population	Persons aged ≥10 years who have previously completed a MenB-FHbp or MenB-4C primary series who remain at increased risk for serogroup B meningococcal disease due to: • Persistent complement component deficiencies, complement inhibitor use, functional or anatomic asplenia, and microbiologists, *or* • An outbreak of serogroup B meningococcal disease
Intervention	MenB-FHbp or MenB-4C booster dose
Comparison	No MenB-FHbp or MenB-4C booster dose
Outcome	• **MenB booster vaccine effectiveness against serogroup B meningococcal disease** • **Short-term immunogenicity of booster dose** • Persistence of immune response to booster dose • Immune interference due to co-administration of booster dose with other vaccines • **Serious adverse events from booster dose**

Bold font indicates outcomes considered by the WG "Critical" for GRADE analysis

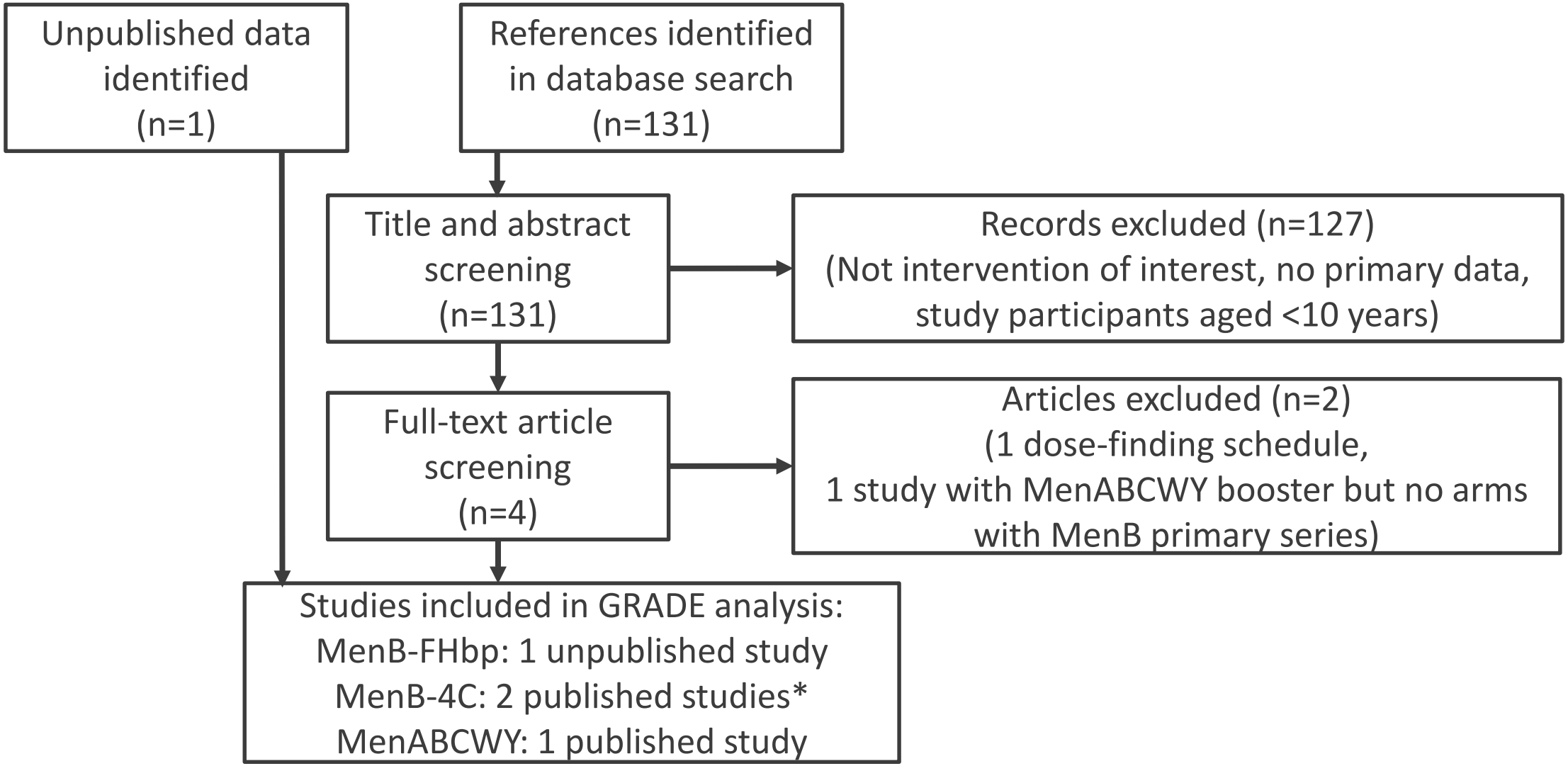
Evidence Retrieval

- Systematic review of studies in any language from PubMed, Medline, Embase, CINAHL, Cochrane, Scopus, and clinicalstrials.gov databases using search string:
  - “booster” AND [“serogroup B meningococcal vaccine” OR “recombinant meningococcal B vaccine” OR “MenB vaccine” OR “Bexsero” OR “MenB-4C” OR “rMenB±OMV NZ” OR “4CMenB” OR “Trumenba” OR “rLP2086” OR “Factor H binding protein vaccine” OR “FHbp”]

- Efforts made to obtain unpublished or other relevant data.

- Included studies that presented primary data on MenB booster doses in subjects who received a licensed MenB primary series at age ≥10 years.
  - Investigational serogroups A, B, C, W, Y meningococcal vaccine (MenABCWY) booster dose used as a proxy for MenB booster dose if MenB vaccine component identical to licensed MenB formulation.

Evidence Retrieval



* Results from two studies were presented in one published article.

Outcomes included in evidence profiles

Type	Outcomes	Importance	Included in evidence profile
Benefits	**MenB booster vaccine effectiveness against serogroup B meningococcal disease**	**Critical**	**No***
	Short-term immunogenicity of booster dose	**Critical**	**Yes**
	Persistence of immune response to booster dose	Important	Yes
Harms	Immune interference due to co-administration of booster dose with other vaccines	Important	No*
	Serious adverse events (SAEs) from booster dose	**Critical**	**Yes**

Bold font indicates outcomes considered by the WG "Critical" for GRADE analysis; *no studies with booster dose reported in persons aged ≥10 years; unable to determine evidence type

Evidence to Recommendations Framework for MenB booster doses

- Given differences in populations and goals of MenB booster dose, EtR completed separately by population at increased risk:
  - Persons with persistent complement deficiency, complement inhibitor use, asplenia, and microbiologists
  - Persons exposed during an outbreak of serogroup B meningococcal disease

- Data reviewed as part of GRADE analysis included as supplementary slides.
  - Evidence included in profiles is the same for both populations at increased risk.

Persons with persistent complement component deficiencies, complement inhibitor use, functional or anatomic asplenia, and microbiologists

Problem

Is the problem of public health importance?

Persons aged ≥10 years at increased risk for serogroup B meningococcal disease	Estimated risk	Estimated population size
Persistent complement component deficiency	Up to 10,000-fold[1]	86,000[2]
Complement inhibitor use (e.g., eculizumab)	2,000-fold[3]	3,000[4]
Anatomic or functional asplenia (e.g. sickle cell disease)	Not quantified; Higher case-fatality rate	80,000[5]
Microbiologists routinely exposed to *N. meningitidis*	120-fold[6]	~100,000[7]
Total		269,000 (<0.1% of US population)

[1] Figueroa JE. Clin Microbiol Rev 1991;4:359–95. [2] Estimated prevalence in all ages of 0.03% (Densen R. Clin Exp Immunol. 1991; 86(Suppl 1): 57-62) though many may be undiagnosed.
[3] Food and Drug Administration. Meeting of the Drug Safety and Risk Management Advisory Committee, Nov 18, 2014. [4] Preliminary estimate projected from 2017 claims data (Marketscan and Medicaid)
[5] Based on estimated 100,000 persons with sickle cell disease (CDC data), minus the ~20,000 children aged <10 years with disease (estimated 1,800-2,000 children identified with sickle cell disease annually through newborn screening, with 95% survival to age 18 years). [6] Sejvar JJ. Journal of Clinical Microbiology. Sept 2005;43(9):4811-14.
[7] Bureau of Labor Statistics, 2016. Adjusted to estimate personnel with occupational exposure to *N. meningiitidis.* https://www.bls.gov/ooh/life-physical-and-social-science/microbiologists.htm#tab-1, https://www.bls.gov/ooh/healthcare/medical-and-clinical-laboratory-technologists-and-technicians.htm

Benefits and Harms of Intervention (MenB Booster dose)

How substantial are the desirable and undesirable anticipated effects?

- No data available on vaccine effectiveness or duration of protection in persons with underlying medical conditions.

- Immunogenicity and antibody persistence of MenB vaccine may differ in persons with underlying conditions:
  - MenB-4C immunogenicity in children and adolescents with asplenia similar to healthy persons, but lower in persons with complement deficiencies (including eculizumab recipients).[1]
  - Meningococcal vaccination may confer little to no protection in persons taking eculizumab.[2,3]

- Evaluations including >69,000 healthy adolescents and adults have demonstrated the safety of MenB-FHbp and MenB-4C primary series.[4-7]
  - Undesirable effects for repeat booster doses or in persons with underlying conditions not assessed.

[1] Martinon-Torres et al., Pediatrics, 2018; [2] McNamara et al., MMWR, 2017; [3] Konar et al., Blood, 2017; [4] Nolan et al., Vaccine, 2015; [5] Perez et al., Expert Review of Vaccines, 2018; [6] Fiorito et al., Pediatric Infectious Disease Journal, 2018; [7] Institut National de Sante Publique du Quebec: https://www.inspq.qc.ca/pdf/publications/1902_SerogroupB_Meningococcal_Vaccine.pdf

Characteristics of included studies for MenB-FHbp booster dose

Study	Type	Population	Intervention	Comparison	Outcomes measured
Unpublished data, Pfizer	Observ-ational*	Healthy persons aged 15–23 years in four European countries	MenB-FHbp booster dose at 48m following either 2- or 3-dose schedule† (n=270)	None	• Immunogenicity • Persistence • SAEs

* Extension study including participants previously enrolled in a phase 2 randomized, single-blinded trial to assess immunogenicity and safety of MenB primary series (ClinicalTrials.gov number NCT01299480).
† 2-dose schedule: 0, 6 months. 3-dose schedule: 0, 2, 6 months.

What is the overall certainty of evidence for critical outcomes? GRADE Summary of Evidence table: MenB-FHbp booster dose

Outcome	Design (# studies)	Initial Evidence Type	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Final Evidence Type
Benefits								
Short-term immunogenicity	Observational (1)	3	Serious*	N/A†	Serious‡	Not Serious	N/A†	4
Persistence of immune response	Observational (1)	3	Serious*	N/A†	Serious‡	Serious§	N/A†	4
Harms								
Serious adverse events	Observational (1)	3	Serious*	N/A†	Serious‡	Serious¶	N/A†	4

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† N/A: Not applicable, as only one study has available data.
‡ Data were available for healthy persons, but not for persons with certain underlying medical conditions.
§ Wide confidence intervals due to small number of subjects
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Serious adverse events	Observational (1)	3	Serious*	N/A†	Serious‡	Serious¶	N/A†	4

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Characteristics of included studies for MenB-4C booster dose

Study	Type	Population	Intervention	Comparison	Outcomes measured
Nolan, 2019	Observ-ational*	Healthy persons aged 15–21y in Australia, Canada	MenB-4C booster at 4y (n=145)	1st MenB-4C dose (n=105)	• Immunogenicity • SAEs
Nolan, 2019	Observ-ational†	Healthy persons aged 17–24y in Chile	MenB-4C booster at 7.5y (n=131)	1st MenB-4C dose (n=150)	• Immunogenicity • SAEs
Szenborn, 2018	RCT	Healthy persons aged 12–27y in United States and Poland	MenABCWY booster at 2y (n=11)	1st MenB-containing (MenABCWY) dose (n=21)	• Immunogenicity • Persistence • SAEs

* Extension study including participants previously enrolled in a phase 3 observer-blind randomized controlled trial to assess lot consistency, immunogenicity, and safety of MenB-4C series (ClinicalTrials.gov number NCT01423084).

† Extension study including participants previously enrolled in a phase 2b/3 randomized, observer-blind, placebo-controlled trial to assess immunogenicity and safety of MenB-4C primary series (ClinicalTrials.gov number NCT00661713).

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What is the overall certainty of evidence for critical outcomes? GRADE Summary of Evidence table: MenB-4C booster dose

Outcome	Design (# studies)	Initial Evidence Type	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Final Evidence Type
Benefits								
Short-term immunogenicity	Observational (2)	3	Serious*	Not serious	Serious‡	Not Serious	None	4
	RCT (1)	1	Not Serious	N/A†	Very Serious‡§	Serious¶	N/A†	4
Persistence of immune response	RCT (1)	1	Not Serious	N/A†	Very Serious‡§	Serious¶	N/A†	4
Harms								
Serious adverse events	Observational (1)	3	Serious*	N/A†	Serious‡	Serious**	N/A†	4
	RCT (1)	1	Not Serious	N/A†	Very Serious‡§	Serious**	N/A†	4

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† N/A: Not applicable, as only one study has available data.
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§ Investigational MenABCWY vaccine used as a proxy for MenB-4C booster in one study.
¶ Wide confidence intervals due to small number of subjects
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What is the overall certainty of evidence for critical outcomes? GRADE Summary of Evidence table: MenB-4C booster dose

Outcome	Design (# studies)	Initial Evidence Type	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Final Evidence Type
Benefits								
Short-term immunogenicity	Observational (2)	3	Serious*	Not serious	Serious‡	Not Serious	None	4
	RCT (1)	1	Not Serious	N/A†	Very Serious‡§	Serious¶	N/A†	4
Persistence of immune response	RCT (1)	1	Not Serious	N/A†	Very Serious‡§	Serious¶	N/A†	4
Harms								
Serious adverse events	Observational (1)	3	Serious*	N/A†	Serious‡	Serious**	N/A†	4
	RCT (1)	1	Not Serious	N/A†	Very Serious‡§	Serious**	N/A†	4

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What is the overall certainty of evidence for critical outcomes? GRADE Summary of Evidence table: MenB-4C booster dose

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Values, Acceptability, Resource Use, and Feasibility

Does the target population feel that the desirable effects are large relative to undesirable effects?

- 8% of persons with complement deficiency, complement inhibitor use, asplenia, or sickle cell disease received ≥1 MenB dose from October 2014 to July 2018.
  - Compared to 26% for ≥1 dose MenACWY

- Low MenB uptake in this group may reflect that they or their providers:
  - Do not value the intervention
  - Are unaware of the need for MenB vaccination
  - Do not feel MenB vaccination is programmatically or financially acceptable
  - Encounter barriers that limit feasibility

[1] CDC unpublished analysis; persons with continuous health plan using IBM Marketscan Treatment Pathways commercial claims data

Is the intervention acceptable to key stakeholders?

- 81% of pediatricians and 56% of family physicians recommend MenB vaccine for children aged ≥10 years at increased risk of serogroup B meningococcal disease.[1]
  - May reflect level of acceptance, awareness, or feasibility of MenB vaccination.

[1] Kempe et al., Pediatrics, 2018

Is the intervention a reasonable and efficient allocation of resources?

- No published cost-effectiveness analysis on the use of a MenB primary series or booster dose in this population.

Is the intervention feasible to implement?

- Data presented on MenB vaccine coverage and provider practices may signal feasibility challenges in implementing the MenB primary series recommendation.
  - Feasibility challenges may be encountered for booster doses as well.

Balance of consequences

Should persons aged ≥10 years at increased risk for serogroup B meningococcal disease due to persistent complement component deficiencies, complement inhibitor use, functional or anatomic asplenia, and microbiologists receive a MenB booster dose following completion of the MenB primary series?

Criteria	Question	Work Group Interpretation
Problem	• Is the problem of public health importance?	Yes
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects? • What is the overall certainty of the evidence for the critical outcomes?	Varies Minimal Favors intervention Very low
Values and preferences	• Does the target population feel that the desirable effects are large relative to undesirable effects? • Is there important uncertainty about or variability in how much people value the main outcomes?	Uncertain Yes
Acceptability	• Is the intervention acceptable to key stakeholders?	Probably yes
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?	Uncertain
Feasibility	• Is the intervention feasible to implement?	Uncertain

Type of recommendation

Group	Work Group Interpretation
Persons with persistent complement component deficiencies, complement inhibitor use, functional or anatomic asplenia, and microbiologists	We recommend the intervention

Persons at increased risk during a serogroup B meningococcal disease outbreak

Problem

Serogroup B meningococcal disease outbreaks

- 7% of all serogroup B cases in the United States are outbreak-associated.[1]
- The majority of organization-based serogroup B outbreaks are college-based. [1]
  - 11 reported outbreaks (41 cases and 2 deaths) during 2013–2018[2]
- College students are the primary group at risk for serogroup B outbreaks
  - May have received a MenB primary series as healthy adolescents

[1] Mbaeyi et al., Clinical Infectious Diseases, 2018; [2] Soeters et al., EID, 2019 and CDC unpublished data.

Benefits and Harms of Intervention (MenB Booster dose)

How substantial are the desirable and undesirable anticipated effects?

- No data available on vaccine effectiveness or duration of protection in U.S. adolescents or adults.
  - In the 4 years following mass MenB-4C vaccination of persons aged <20 years during a regional outbreak in Canada, vaccine effectiveness was 79% (95% CI: -231 to 99%).[1]

- No consistent evidence to-date that MenB vaccines reduce or prevent serogroup B meningococcal carriage; thus, herd immunity unlikely.[2,3]

- Evaluations following mass vaccination campaigns during outbreaks at U.S. universities have demonstrated the safety of MenB primary series. [2,3,4]

[1] Institut National de Sante Publique du Quebec https://www.inspq.qc.ca/sites/default/files/publications/2491_impact_vaccination_meningocoque_serogroupe_b.pdf;
[2] Soeters et al., CID, 2017; [3] McNamara et al., JID, 2017; [4] Fiorito et al., Pediatric Infectious Diseases Journal, 2018

Characteristics of included studies for MenB-FHbp booster dose

Study	Type	Population	Intervention	Comparison	Outcomes measured
Unpublished data, Pfizer	Observ-ational*	Healthy persons aged 15–23 years in four European countries	MenB-FHbp booster dose at 48m following either 2- or 3-dose schedule† (n=270)	None	• Immunogenicity • Persistence • SAEs

* Extension study including participants previously enrolled in a phase 2 randomized, single-blinded trial to assess immunogenicity and safety of MenB primary series (ClinicalTrials.gov number NCT01299480).
† 2-dose schedule: 0, 6 months. 3-dose schedule: 0, 2, 6 months.

What is the overall certainty of evidence for critical outcomes? GRADE Summary of Evidence table: MenB-FHbp booster dose

Outcome	Design (# studies)	Initial Evidence Type	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Final Evidence Type
Benefits								
Short-term immunogenicity	Observational (1)	3	Serious*	N/A†	Not Serious	Not Serious	N/A†	4
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Serious adverse events	Observational (1)	3	Serious*	N/A†	Not Serious	Serious§	N/A†	4

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Characteristics of included studies for MenB-4C booster dose

Study	Type	Population	Intervention	Comparison	Outcomes measured
Nolan, 2019	Observ-ational*	Healthy persons aged 15–21y in Australia, Canada	MenB-4C booster at 4y (n=145)	1st MenB-4C dose (n=105)	• Immunogenicity • SAEs
Nolan, 2019	Observ-ational†	Healthy persons aged 17–24y in Chile	MenB-4C booster at 7.5y (n=131)	1st MenB-4C dose (n=150)	• Immunogenicity • SAEs
Szenborn, 2018	RCT	Healthy persons aged 12–27y in United States and Poland	MenABCWY booster at 2y (n=11)	1st MenB-containing (MenABCWY) dose (n=21)	• Immunogenicity • Persistence • SAEs

* Extension study including participants previously enrolled in a phase 3 observer-blind randomized controlled trial to assess lot consistency, immunogenicity, and safety of MenB-4C series (ClinicalTrials.gov number NCT01423084).

† Extension study including participants previously enrolled in a phase 2b/3 randomized, observer-blind, placebo-controlled trial to assess immunogenicity and safety of MenB-4C primary series (ClinicalTrials.gov number NCT00661713).

Characteristics of included studies for MenB-4C booster dose

Study	Type	Population	Intervention	Comparison	Outcomes measured
Nolan, 2019	Observ-ational*	Healthy persons aged 15–21y in Australia, Canada	MenB-4C booster at 4y (n=145)	1st MenB-4C dose (n=105)	• Immunogenicity • SAEs
Nolan, 2019	Observ-ational†	Healthy persons aged 17–24y in Chile	MenB-4C booster at 7.5y (n=131)	1st MenB-4C dose (n=150)	• Immunogenicity • SAEs
Szenborn, 2018	RCT	Healthy persons aged 12–27y in United States and Poland	MenABCWY booster at 2y (n=11)	1st MenB-containing (MenABCWY) dose (n=21)	• Immunogenicity • Persistence • SAEs

* Extension study including participants previously enrolled in a phase 3 observer-blind randomized controlled trial to assess lot consistency, immunogenicity, and safety of MenB-4C series (ClinicalTrials.gov number NCT01423084).

† Extension study including participants previously enrolled in a phase 2b/3 randomized, observer-blind, placebo-controlled trial to assess immunogenicity and safety of MenB-4C primary series (ClinicalTrials.gov number NCT00661713).

What is the overall certainty of evidence for critical outcomes? GRADE Summary of Evidence table: MenB-4C booster dose

Outcome	Design (# studies)	Initial Evidence Type	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Final Evidence Type
Benefits								
Short-term immunogenicity	Observational (2)	3	Serious*	Not Serious	Not Serious	Not Serious	None	4
	RCT (1)	1	Not Serious	N/A†	Serious‡	Serious§	N/A†	3
Persistence of immune response	RCT (1)	1	Not Serious	N/A†	Serious‡	Serious§	N/A†	3
Harms								
Serious adverse events	Observational (1)	3	Serious*	N/A†	Not Serious	Serious¶	N/A†	4
	RCT (1)	1	Not Serious	N/A†	Serious‡	Serious¶	N/A†	3

* Concern of selection bias from parent study to extension study
† N/A: Not applicable, as only one study has available data.
‡ Investigational MenABCWY vaccine used as a proxy for MenB-4C booster in one study.
§ Wide confidence intervals due to small number of subjects
¶ Small number of subjects may not be able to detect rare serious adverse events.

What is the overall certainty of evidence for critical outcomes? GRADE Summary of Evidence table: MenB-4C booster dose

Outcome	Design (# studies)	Initial Evidence Type	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Final Evidence Type
Benefits								
Short-term immunogenicity	Observational (2)	3	Serious*	Not Serious	Not Serious	Not Serious	None	4
	RCT (1)	1	Not Serious	N/A†	Serious‡	Serious§	N/A†	3
Persistence of immune response	RCT (1)	1	Not Serious	N/A†	Serious‡	Serious§	N/A†	3
Harms								
Serious adverse events	Observational (1)	3	Serious*	N/A†	Not Serious	Serious¶	N/A†	4
	RCT (1)	1	Not Serious	N/A†	Serious‡	Serious¶	N/A†	3

* Concern of selection bias from parent study to extension study
† N/A: Not applicable, as only one study has available data.
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What is the overall certainty of evidence for critical outcomes? GRADE Summary of Evidence table: MenB-4C booster dose

Outcome	Design (# studies)	Initial Evidence Type	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Final Evidence Type
Benefits								
Short-term immunogenicity	Observational (2)	3	Serious*	Not Serious	Not Serious	Not Serious	None	4
	RCT (1)	1	Not Serious	N/A†	Serious‡	Serious§	N/A†	3
Persistence of immune response	RCT (1)	1	Not Serious	N/A†	Serious‡	Serious§	N/A†	3
Harms								
Serious adverse events	Observational (1)	3	Serious*	N/A†	Not Serious	Serious¶	N/A†	4
	RCT (1)	1	Not Serious	N/A†	Serious‡	Serious¶	N/A†	3

* Concern of selection bias from parent study to extension study
† N/A: Not applicable, as only one study has available data.
‡ Investigational MenABCWY vaccine used as a proxy for MenB-4C booster in one study.
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¶ Small number of subjects may not be able to detect rare serious adverse events.

What is the overall certainty of evidence for critical outcomes? GRADE Summary of Evidence table: MenB-4C booster dose

Outcome	Design (# studies)	Initial Evidence Type	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other	Final Evidence Type
Benefits								
Short-term immunogenicity	Observational (2)	3	Serious*	Not Serious	Not Serious	Not Serious	None	4
	RCT (1)	1	Not Serious	N/A†	Serious‡	Serious§	N/A†	3
Persistence of immune response	RCT (1)	1	Not Serious	N/A†	Serious‡	Serious§	N/A†	3
Harms								
Serious adverse events	Observational (1)	3	Serious*	N/A†	Not Serious	Serious¶	N/A†	4
	RCT (1)	1	Not Serious	N/A†	Serious‡	Serious¶	N/A†	3

* Concern of selection bias from parent study to extension study
† N/A: Not applicable, as only one study has available data.
‡ Investigational MenABCWY vaccine used as a proxy for MenB-4C booster in one study.
§ Wide confidence intervals due to small number of subjects
¶ Small number of subjects may not be able to detect rare serious adverse events.

Values, Acceptability, Resource Use, and Feasibility

Is the intervention valued by the target population and accepted by key stakeholders?

- All 11 universities that experienced an outbreak during 2013–2018 implemented MenB primary series vaccination, demonstrating acceptability of MenB vaccination[1]

- First-dose MenB vaccination coverage varied from 14–98% and may reflect:
  - Target population's value and acceptability of MenB vaccines
  - Parents' acceptability and encouragement for their children to receive MenB vaccine[2,3,4]
  - Feasibility concerns (e.g., logistical, financial), especially at large universities[2,5]
  - Differences in student population, campus culture, perceived risk of disease[2,3]

[1] Soeters et al., EID, 2019; [2] Fisher et al., J Adol Health, 2018; [3] Capitano et al., Hum Vacc and Imm, 2018; [4] Breakwell et al., J Adol Health, 2016; [5] Fiorito et al., J Am Coll Health, 2017

Is the intervention a reasonable and efficient allocation of resources?

- MenB mass vaccination during outbreaks requires substantial resources.[1,2]
  - At one large university, total costs of vaccination were $1.7 million dollars (projected: $7.7 million for 100% primary series coverage).[1]

- Strategy of MenB mass vaccination for outbreak response estimated to be more cost-effective than universal vaccination of all students at college entry.[3]

- High costs incurred by universities may reflect the belief that campaigns for MenB primary series were a reasonable and efficient allocation of resources.
  - MenB booster doses are anticipated to be reasonable and efficient use of resources.

[1] Fisher et al., J Adol Health, 2018; [2] La et al., Hum Vacc and Imm, in press; [3] Leeds et al., Am J Prev Med, 2018;

Is the intervention feasible to implement?

- Outbreaks require intensive coordination, significant human resources, and action among multiple stakeholders to efficiently respond within a short time.[1-4]

- As MenB vaccines are not interchangeable, determining whether a MenB primary series was completed, the vaccine product, date of last dose, and ensuring availability of both MenB vaccines may impact feasibility during an outbreak.

- Universities have demonstrated the feasibility of conducting mass vaccination campaigns for the primary series under challenging circumstances.
  - Administering MenB booster doses is anticipated to be feasible as well.

[1] Capitano et al., Hum Vacc and Imm, 2018; [2] Ritscher et al., J Am Coll Health, 2018; [3] Fiorito et al., J Am Coll Health, 2017; [4] Fisher et al., J Adol Health, 2018; [5] CDC unpublished data

Balance of consequences

Should persons aged ≥10 years at increased risk for serogroup B meningococcal disease due to an outbreak receive a MenB booster dose following completion of the MenB primary series?

Criteria	Question	Work Group Interpretation
Problem	• Is the problem of public health importance?	Yes
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects? • What is the overall certainty of the evidence for the critical outcomes?	Large Minimal Favors intervention Very low
Values and preferences	• Does the target population feel that the desirable effects are large relative to undesirable effects? • Is there important uncertainty about or variability in how much people value the main outcomes?	Yes Probably yes
Acceptability	• Is the intervention acceptable to key stakeholders?	Yes
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?	Yes
Feasibility	• Is the intervention feasible to implement?	Yes

Type of recommendation

Group	Work Group Interpretation
Persons at risk during a serogroup B outbreak	We recommend the intervention

Conclusion

Work Group conclusion for GRADE and EtR

Group	Work Group Interpretation
Persons with persistent complement component deficiencies, complement inhibitor use, functional or anatomic asplenia, and microbiologists	We recommend the intervention
Persons at risk during a serogroup B outbreak	We recommend the intervention

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For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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Supplemental slides

Short-term immunogenicity of MenB-FHbp booster dose

Time point after booster	Primary series schedule	No. of subjects*	% of subjects with hSBA† titer ≥1:4 (95% Confidence Interval)				
			Test strain				
			A22	A56	B24	B44	Composite‡
1m	2-dose (0, 6m)	62–64	**96.8** (88.8, 99.6)	**98.4** (91.6, 100)	**96.9** (89.2, 99.6)	**93.7** (84.5, 98.2)	**91.8** (81.9, 97.3)
	3-dose (0, 2, 6m)	57–59	**100** (93.9, 100)	**100** (93.7, 100)	**100** (93.8, 100)	**100** (93.9, 100)	**100** (93.6, 100)
	3-dose (0, 2, 6m)	31–32	**96.9** (83.8, 99.9)	**100** (88.8, 100)	**96.9** (83.8, 99.9)	**100** (89.1, 100)	Not available

* Number of subjects who received the booster vaccination and who had at least one valid and determinate assay result
† Human complement serum bactericidal antibody assay
‡ hSBA titer ≥1:8 (1:16 for A22) for all 4 primary strains

Persistence of immune response to MenB-FHbp booster dose

Time point after booster	Primary series schedule	No. of subjects*	% of subjects with hSBA titer ≥1:4 (95% Confidence Interval)				
			Test strain				
			A22	A56	B24	B44	Composite†
12m	2-dose (0, 6m)	61–64	**82.3** (70.5, 99.6)	**82.0** (70.0, 90.6)	**78.1** (66.0, 87.5)	**61.9** (48.8, 73.9)	**62.7** (49.1, 75.0)
	3-dose (0, 2, 6m)	54–56	**78.2** (65.0, 88.2)	**91.4** (80.4, 97.0)	**72.7** (59.0, 83.9)	**79.6** (66.5, 89.4)	**63.3** (48.3, 76.6)
	3-dose (0, 2, 6m)	21–27	**93.1** (77.2, 99.2)	**87.5** (67.6, 97.3)	**74.2** (55.4, 88.1)	**83.9** (66.3, 94.5)	Not available
26m	2-dose (0, 6m)	42–45	**65.9** (50.1, 79.5)	**66.7** (50.5, 80.4)	**59.1** (43.2, 73.7)	**62.2** (46.5, 76.2)	**42.1** (26.3, 59.2)
	3-dose (0, 2, 6m)	30–35	**74.3** (56.7, 87.5)	**90.0** (73.5, 97.9)	**76.5** (58.8, 89.3)	**70.6** (52.5, 84.9)	**46.4** (27.5, 66.1)

* Number of subjects who received the booster vaccination and who had at least one valid and determinate assay result

† hSBA titer ≥1:8 (1:16 for A22) for all 4 primary strains

Persistence of immune response to MenB-FHbp booster dose

Time point after booster	Primary series schedule	No. of subjects*	% of subjects with hSBA titer ≥1:4 (95% Confidence Interval)				
			Test strain				
			A22	A56	B24	B44	Composite†
12m	2-dose (0, 6m)	61–64	**82.3** (70.5, 99.6)	**82.0** (70.0, 90.6)	**78.1** (66.0, 87.5)	**61.9** (48.8, 73.9)	**62.7** (49.1, 75.0)
	3-dose (0, 2, 6m)	54–56	**78.2** (65.0, 88.2)	**91.4** (80.4, 97.0)	**72.7** (59.0, 83.9)	**79.6** (66.5, 89.4)	**63.3** (48.3, 76.6)
	3-dose (0, 2, 6m)	21–27	**93.1** (77.2, 99.2)	**87.5** (67.6, 97.3)	**74.2** (55.4, 88.1)	**83.9** (66.3, 94.5)	Not available
26m	2-dose (0, 6m)	42–45	**65.9** (50.1, 79.5)	**66.7** (50.5, 80.4)	**59.1** (43.2, 73.7)	**62.2** (46.5, 76.2)	**42.1** (26.3, 59.2)
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* Number of subjects who received the booster vaccination and who had at least one valid and determinate assay result

† hSBA titer ≥1:8 (1:16 for A22) for all 4 primary strains

Serious adverse events from MenB-FHbp booster dose

Primary series schedule	No. of subjects	No. of reported SAEs	No. of reported deaths
2-dose (0, 6m)	116	0	0
3-dose (0, 2, 6m)	114	0	0
3-dose (0, 2, 6m)	40	0	0

Short-term immunogenicity of MenB-4C or MenABCWY booster dose

Time point	Site	Intervention	No. of subjects*	% of subjects with hSBA titer ≥1:4† (95% Confidence Interval)			
				Antigen			
				FHbp	NadA	NHBA	PorA
1m	Australia, Canada	MenB-4C booster	134–144	**98.0** (93.9, 99.6)	**100** (97.1, 100)	**99.0** (96.1, 99.9)	**94.0** (89.2, 97.5)
		1st MenB-4C dose	100–105	**81.0** (71.9, 87.8)	**87.0** (78.2, 92.7)	**84.0** (76.0, 90.0)	**41.0** (31.2, 50.9)
	Chile	MenB-4C booster	120–131	**100** (97.1, 100)	**100** (96.4, 100)	**99.0** (95.7, 99.9)	**93.0** (87.3, 97.1)
		1st MenB-4C dose	139–150	**81.0** (73.3, 86.6)	**84.0** (76.7, 89.7)	**93.0** (87.2, 96.3)	**62.0** (53.8, 70.0)
	US, Poland	MenABCWY booster	11	**100** (71.5, 100)	**100** (71.5, 100)	**91.0** (58.7, 99.8)	**82.0** (48.2, 97.7)
		1st MenB-containing (MenABCWY) dose	20–21	**35.0** (15.4, 59.2)	**25.0** (8.7, 49.1)	**33.0** (14.6, 57.0)	**19.0** (5.4, 41.9)

* Number of subjects who received the booster vaccination and who had at least one valid and determinate assay result; †1:5 in MenABCWY study

Short-term immunogenicity of MenB-4C or MenABCWY booster dose

Time point	Site	Intervention	No. of subjects*	% of subjects with hSBA titer ≥1:4† (95% Confidence Interval)			
				Antigen			
				FHbp	NadA	NHBA	PorA
1m	Australia, Canada	MenB-4C booster	134–144	**98.0** (93.9, 99.6)	**100** (97.1, 100)	**99.0** (96.1, 99.9)	**94.0** (89.2, 97.5)
		1st MenB-4C dose	100–105	**81.0** (71.9, 87.8)	**87.0** (78.2, 92.7)	**84.0** (76.0, 90.0)	**41.0** (31.2, 50.9)
	Chile	MenB-4C booster	120–131	**100** (97.1, 100)	**100** (96.4, 100)	**99.0** (95.7, 99.9)	**93.0** (87.3, 97.1)
		1st MenB-4C dose	139–150	**81.0** (73.3, 86.6)	**84.0** (76.7, 89.7)	**93.0** (87.2, 96.3)	**62.0** (53.8, 70.0)
	US, Poland	MenABCWY booster	11	**100** (71.5, 100)	**100** (71.5, 100)	**91.0** (58.7, 99.8)	**82.0** (48.2, 97.7)
		1st MenB-containing (MenABCWY) dose	20–21	**35.0** (15.4, 59.2)	**25.0** (8.7, 49.1)	**33.0** (14.6, 57.0)	**19.0** (5.4, 41.9)

* Number of subjects who received the booster vaccination and who had at least one valid and determinate assay result; †1:5 in MenABCWY study

Persistence of immune response to MenABCWY booster dose

Time point	Site	Intervention	No. of subjects*	% of subjects with hSBA titer ≥1:5 (95% Confidence Interval)			
				Antigen			
				FHbp	NadA	NHBA	PorA
12m	US, Poland	MenABCWY booster	11	**82.0** (48.2, 97.7)	**100** (71.5, 100)	**82.0** (48.2, 97.7)	**45.0** (16.7, 76.6)
		1st MenB-containing (MenABCWY) dose	20–21	**14.0** (3.0, 36.3)	**15.0** (3.2, 37.9)	**29.0** (11.3, 52.2)	**19.0** (5.4, 41.9)

* Number of subjects who received the booster vaccination and who had at least one valid and determinate assay result

Serious adverse events from MenB-4C or MenABCWY booster dose

Booster dose (Site)	Primary series received	Length of monitoring period post-booster	No. of subjects†	No. of reported serious adverse events	No. of reported deaths
MenB-4C					
(Australia, Canada, Chile*)	MenB-4C	30 days	266	0	0
MenABCWY					
(United States and Poland)	MenB-4C	1 year	11	0	0

* Participants from the Australia/Canada and Chile studies were analyzed as one study for safety outcomes, as per the vaccine manufacturer.
† Single dose in the primed group and any of the two vaccine doses in the naïve group