Introduction to MenB-4C (Bexsero) Interval and Dosing Label Change

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Advisory Committee on Immunization Practices

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MenB-4C (Bexsero) Interval Changes

- Initially licensed by FDA under an accelerated approval process
- New immunogenicity data support changes to dosing schedule
  - No safety concerns
- Full FDA approval: August 19, 2024
- New dosing schedule aligned with MenB-FHbp (Trumenba)

https://www.fda.gov/media/90996/download?attachment
https://wayback.archive-it.org/7993/20190423064853/https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM431447.pdf

Previous Recommendations (Consistent with Label)

MenB-4C (Bexsero): Previous	MenB-FHbp (Trumenba): Existing
Adolescents: **2-dose series (0, ≥1 month)**	Adolescents: **2-dose series (0, 6 month)** *If dose 2 is administered earlier than 6 months, administer 3rd dose at least 4 months after dose 2*
Persistent complement component deficiencies, those with complement inhibitor use, functional or anatomic asplenia, microbiologists routinely exposed to *Neisseria meningitidis*, or persons affected by an outbreak of serogroup B meningococcal disease: **2-dose series (0, ≥1 month)**	Persistent complement component deficiencies, those with complement inhibitor use, functional or anatomic asplenia, microbiologists routinely exposed to *Neisseria meningitidis*, or persons affected by an outbreak of serogroup B meningococcal disease: **3-dose series (0, 1–2, 6 months)**

New MenB-4C (Bexsero) Label

- Two-dose schedule: Administer a dose (0.5 mL) at 0 and 6 months. If the second dose is administered earlier than 6 months after the first dose, a third dose should be administered at least 4 months after the second dose.

- Three-dose schedule: Administer a dose (0.5 mL) at 0, 1–2, and 6 months.

- The choice of dosing schedule may depend on the risk of exposure and the individual's susceptibility to meningococcal serogroup B disease.

Proposed ACIP Recommendations

- Given the recent MenB-4C (Bexsero) label change, ACIP will vote for updated recommendations
- Proposed recommendations will achieve alignment between ACIP recommendations for MenB-4C (Bexsero) and:
  - FDA label
  - ACIP MenB-FHbp (Trumenba) recommendations

Evidence to Recommendations Framework (Abridged) for MenB-4C (Bexsero) Interval and Dosing Change

PICO Questions

PICO 1:

- Among persons aged 16–23 years recommended for MenB vaccination based on shared clinical decision-making, should MenB-4C be administered on a 0, 6 month dosing interval, vs. a 0, ≥1 month dosing interval, for the prevention of invasive meningococcal disease?

PICO 2:

- Among persons with persistent complement component deficiencies, those with complement inhibitor use, functional or anatomic asplenia, microbiologists routinely exposed to *Neisseria meningitidis*, or persons affected by an outbreak of serogroup B meningococcal disease, should MenB-4C be administered on a 0, 1–2, 6 month schedule, vs. a 0, ≥1 month schedule, for the prevention of invasive meningococcal disease?

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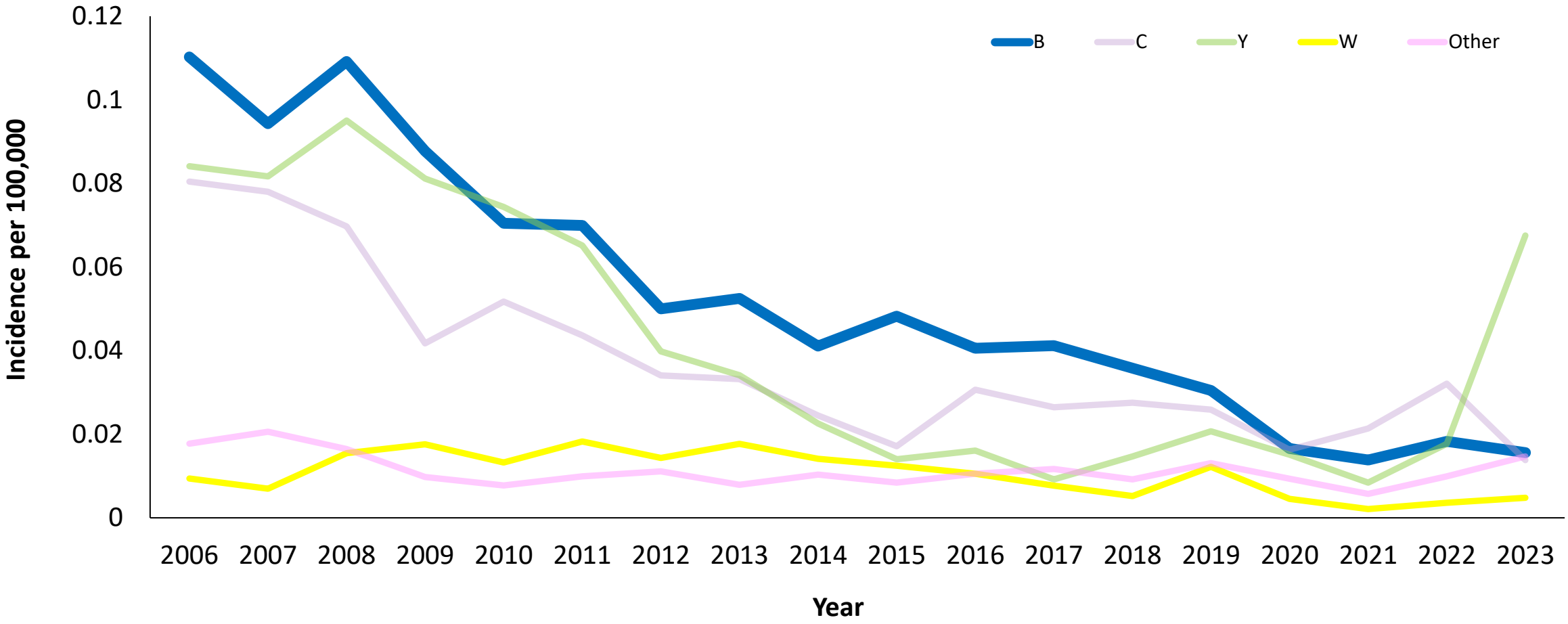
Public health problem

Is invasive meningococcal disease a problem of public health importance?

Meningococcal Disease

- Most often presents as meningitis or bacteremia
- Progresses rapidly
- 10–15% of cases are fatal (even with appropriate antibiotic therapy)
- ~20% of survivors experience long-term sequelae
  - Cognitive deficits
  - Hearing loss
  - Limb amputations

Trends in Meningococcal Disease Incidence by Serogroup – United States, 2006–2023*



Source: NNDSS data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments
*2023 data are preliminary

Persons at Increased Risk for Serogroup B Meningococcal Disease

	Estimated increased risk	Estimated population size
Persistent complement component deficiency	Up to 10,000-fold	86,000[1]
Complement inhibitor use	2,000-fold	3,000[2]
Anatomic or functional asplenia	Case fatality-rate up to 40-70%	>80,000[3]
Microbiologists routinely exposed to *N. meningitidis*	120-fold	100,000[4]
Persons exposed during an outbreak	Up to 1,400-fold	Up to ~33,000

Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020 | MMWR (cdc.gov)

[1]Estimated prevalence in all ages of 0.03% (Densen R. Clin Exp Immunol. 1991) though many may be undiagnosed.

[2]Preliminary estimate projected from 2017 claims data (Marketscan and Medicaid)

[3]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).

[4]Bureau of Labor Statistics, 2016. Adjusted to estimate personnel with occupational exposure to N. meningitidis. 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

Meningococcal Disease Outbreaks 2022-Present

Outbreak	Outbreak Period	Serogroup	Cases (deaths)
Florida MSM	December 2021 – February 2023	C	46 (9)
New York PEH	February 2022	C	3
Florida College	February – March 2022	B	3
Virginia Statewide	June 2022 – Present	Y	36 (8)*
Iowa Community	November 2022 – July 2023	W	12 (2)
Ohio Amish Community	December 2023 – January 2024	B	6[†]
Colorado PEH	Jan 2024 – Present	Y	6*
Oklahoma Correctional Facility	March 2024 – May 2024	C	2 (1)
Kingdom of Saudi Arabia Travel	April 2024 – Present	W[§]	14*

Abbreviation: MSM, men who have sex with men; PEH, people experiencing homelessness
*Ongoing
[†]5 additional suspect cases
[§]One additional serogroup C case and one additional nongroupable case

Slide provided by Amy Rubis

Public Health Problem

- Is invasive meningococcal disease a problem of public health importance?

	No	Probably no	Probably yes	Yes	Varies	Don't know
PICO 1: Healthy adolescents (0, 6 months)				X		
PICO 2: Persons at increased risk (0, 1–2, 6 months)				X		

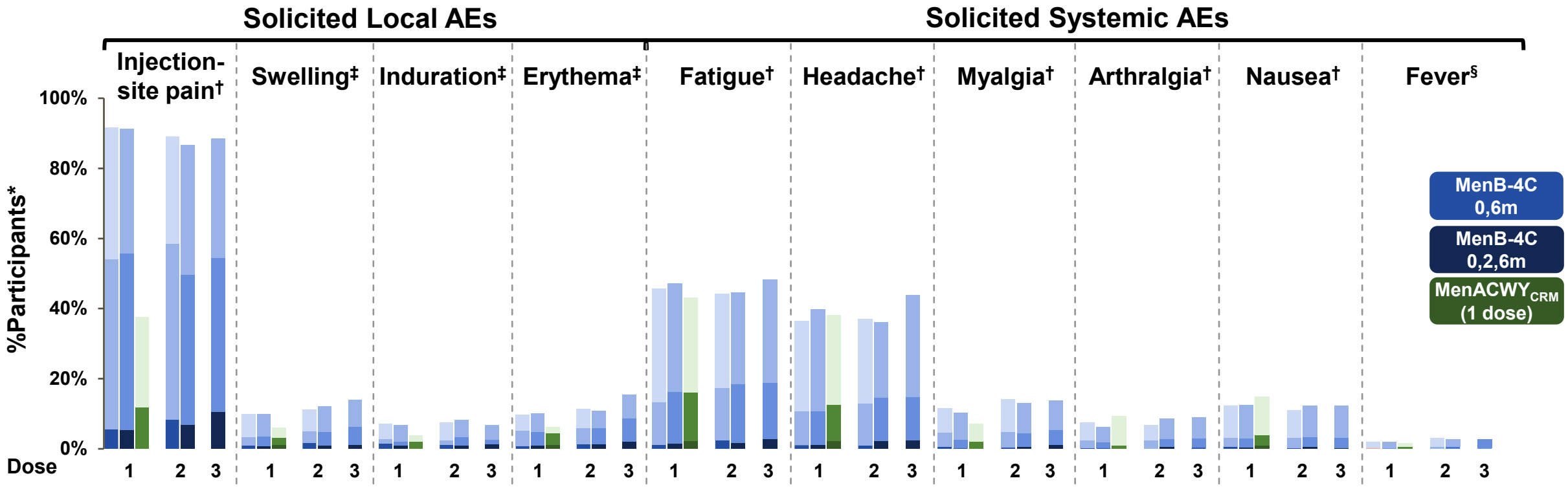
Benefits and harms

- How substantial are the desirable anticipated effects?
- How substantial are the undesirable anticipated effects?
- Do the desirable effects outweigh the undesirable effects?

Comparators

	0, 6 month schedule	**0, 2, 6 month schedule**
PICO 1 (healthy adolescents)	Dose 2	Dose 2
PICO 2 (persons at increased risk)	--	Dose 3 vs. dose 2

V72_72: Solicited AEs within 7 Days after Vaccination with MenB-4C or MenACWY$_{CRM}$



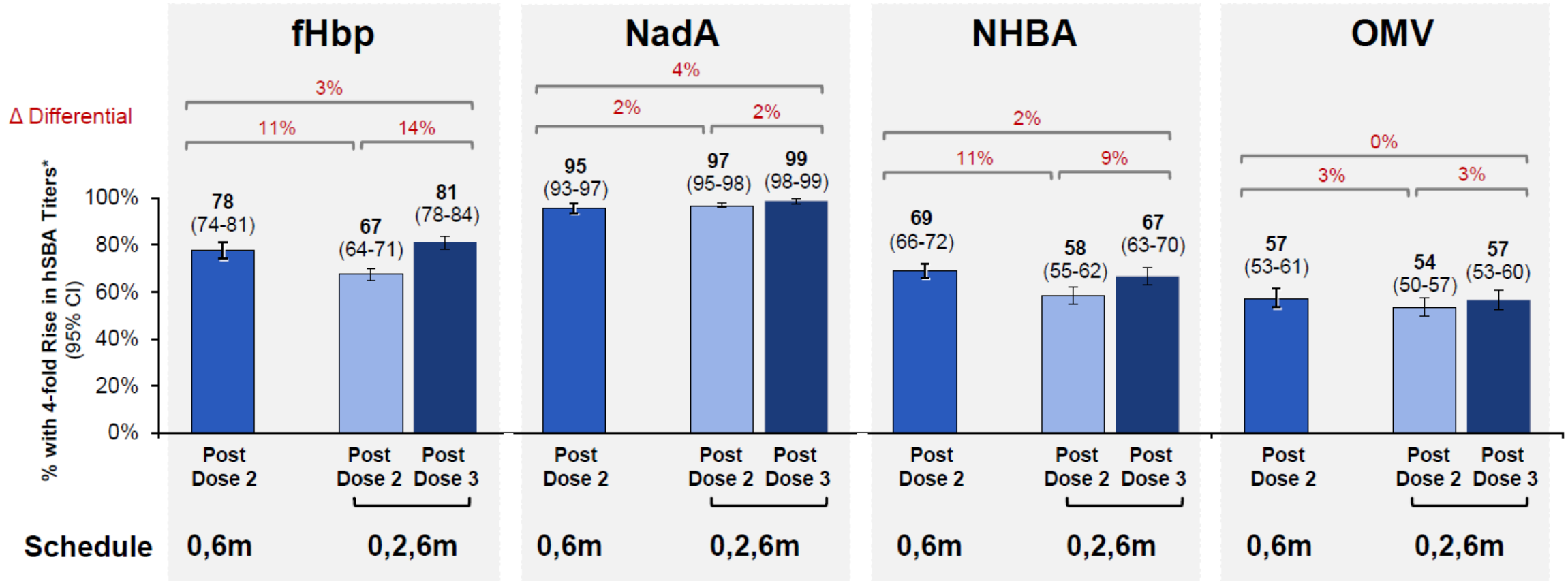
→ Generally **mild-to-moderate** AE were reported following each vaccination

→ Occurred at similar rates after the 1st, 2nd or 3rd dose of MenB-4C, and were higher than after vaccination with MenACWY$_{CRM}$

*Number of participants varies by study vaccination, 823-835 for MenB-4C and 178 for MenACWY.
AE: Adverse Event
GSK, Data on File 2024N555060

†Severity of symptom	‡Size (mm)	§Fever (°C)
Mild – easily tolerated	25–50	38.0–38.9
Moderate – interferes with normal activity	51–100	39.0–39.9
Severe – prevents normal activity	>100	≥ 40.0

V72_72: Seroresponse Against 4 Indicator Strains for Different MenB-4C Schedules



Comparison of the 3 MenB-4C schedules was not part of the statistical analysis plan.

Seroresponses to each indicator strain showed consistent trends across all 3 schedules (54% to 97%, 57% to 95%, and 57% to 99% for 0,2m, 0,6m, and 0,2,6m schedules, respectively).

*At 1 month after 2nd or 3rd MenB-4C vaccination, relative to baseline. 4-fold rise in hSBA titer for each strain was defined as a post-vaccination titer ≥4-fold the LOD or ≥LLOQ, whichever is greater if pre-vaccination titer <LOD, a post-vaccination titer ≥4-fold the LLOQ if pre-vaccination titer ≥LOD and <LLOQ, and a post-vaccination titer ≥4-fold the pre-vaccination titer if pre-vaccination titer ≥LLOQ. LOD: fHbp, 3; NadA, 6; NHBA, 4; OMV, 4. LLOQ: fHbp, 5; NadA, 15; NHBA, 4; OMV, 6.

fHbp, factor H binding protein; hSBA, human serum bactericidal assay; LL, lower limit; LOD, limit of detection; LLOQ, lower limit of quantitation; NadA, *Neisseria* adhesin A; NHBA, Neisserial heparin-binding antigen; OMV, Outer membrane vesicle

Prescribing Information for Bexsero

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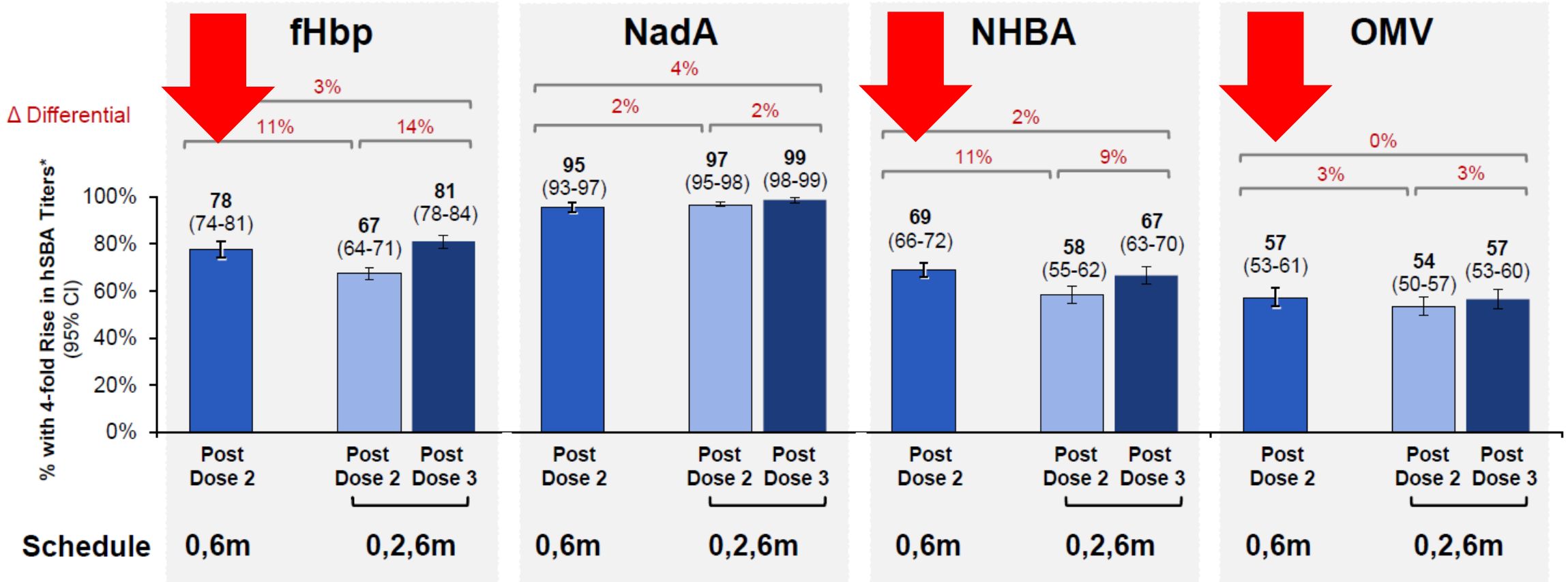

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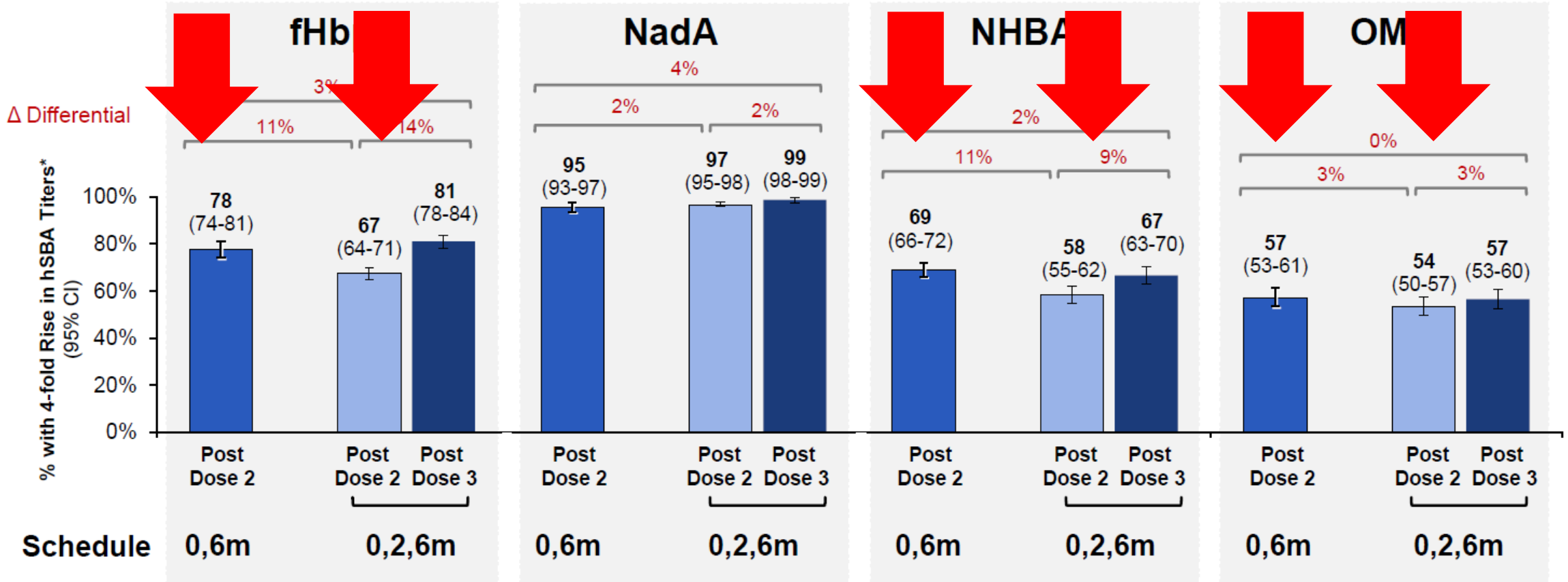

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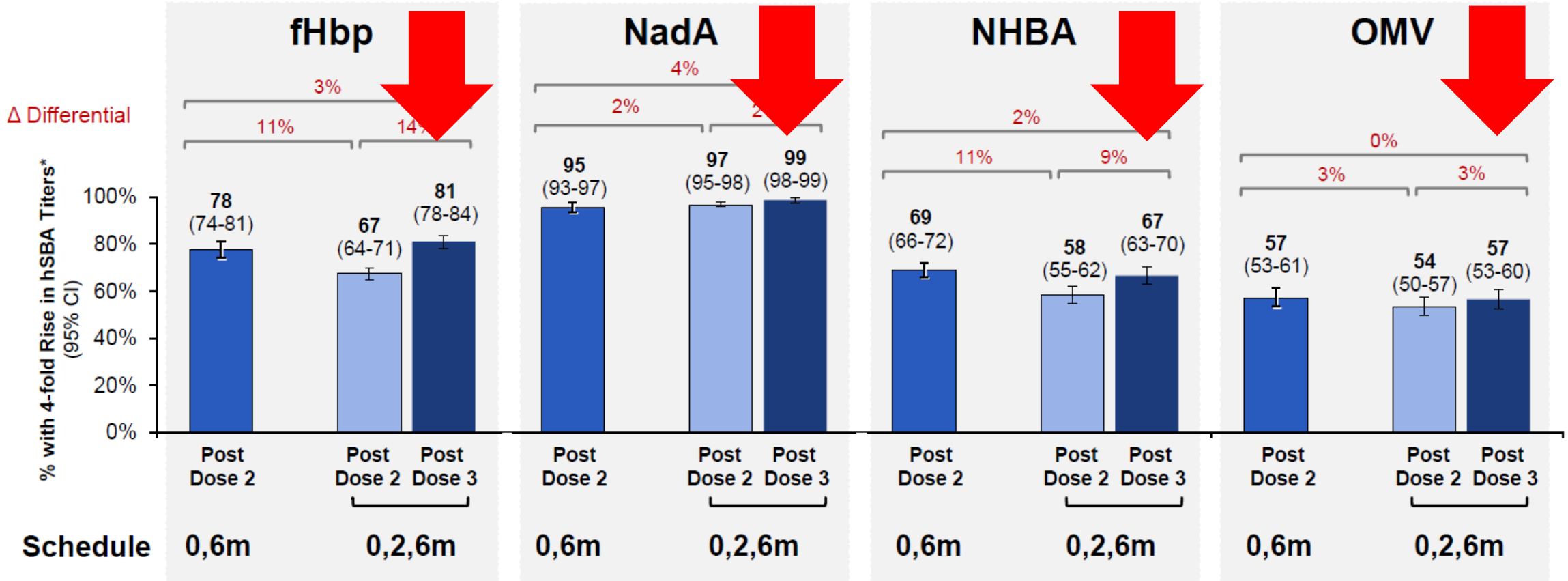

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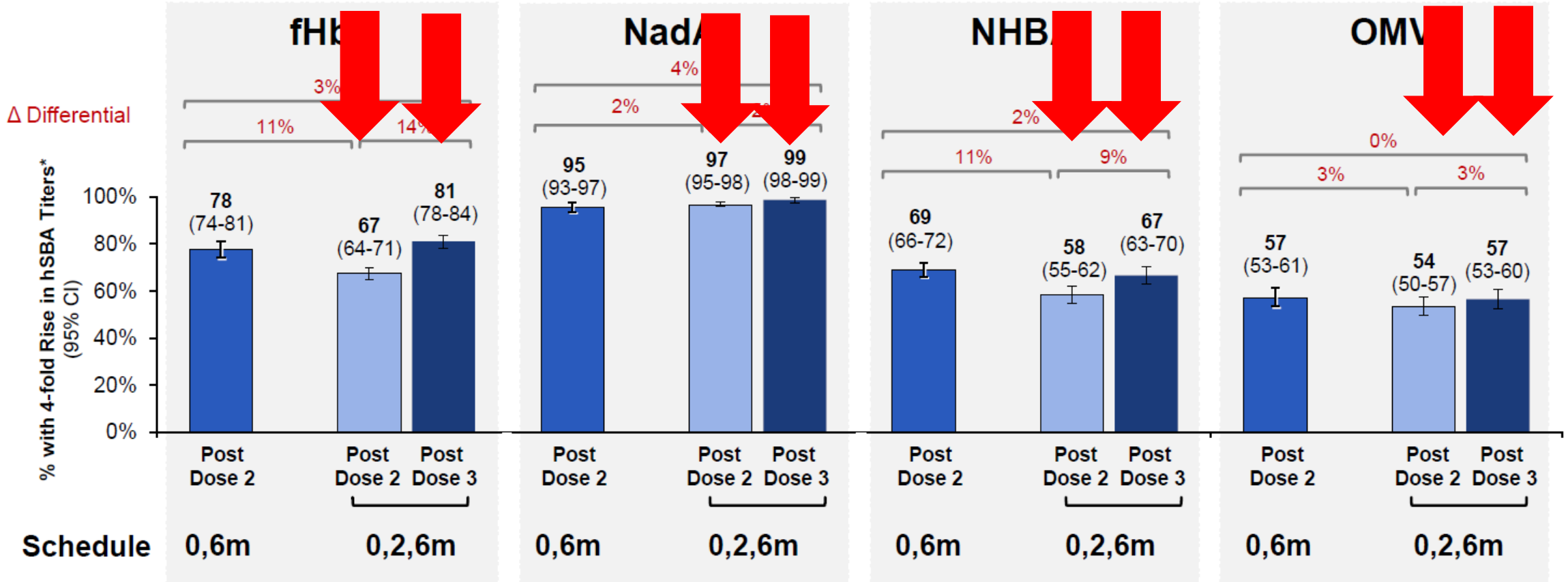

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Prescribing Information for Bexsero

Benefits and Harms

- How substantial are the desirable anticipated effects?

	Minimal	Small	Moderate	Large	Varies	Don't know
PICO 1: Healthy adolescents (0, 6 months)		X				
PICO 2: Persons at increased risk (0, 1–2, 6 months)		X	X			

Benefits and Harms

- How substantial are the undesirable anticipated effects?

	Minimal	Small	Moderate	Large	Varies	Don't know
PICO 1: Healthy adolescents (0, 6 months)	X	X				
PICO 2: Persons at increased risk (0, 1–2, 6 months)	X	X				

Benefits and Harms

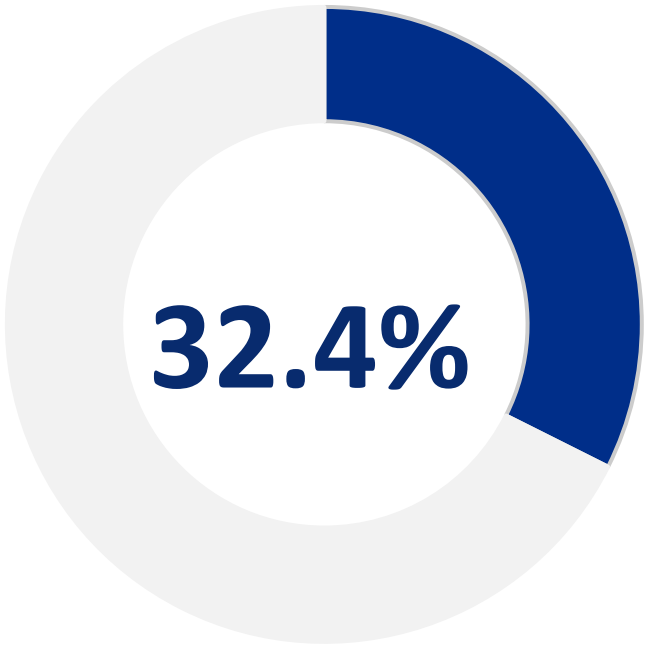
- Do the desirable effects outweigh the undesirable effects?

	Favors new dosing schedule	Favors previous dosing schedule	Favors both	Favors neither	Varies	Don't know
PICO 1: Healthy adolescents (0, 6 months)	X		X			
PICO 2: Persons at increased risk (0, 1–2, 6 months)	X					

Values

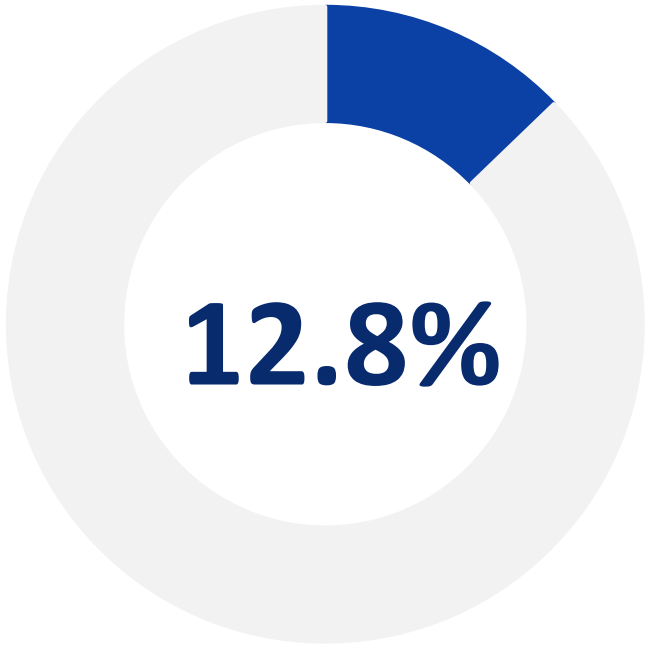
- Does the target population feel that the desirable effects are large relative to the undesirable effects?
- Is there important uncertainty about or variability in how much people value the main outcome?

MenB Coverage among Adolescents (2023)



≥ 1 dose

among 17 yr olds



≥ 2 doses

among 17 yr olds

Pingali C et al. MMWR Morb Mortal Wkly Rep 2024.

Values

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

	No	Probably no	Probably yes	Yes	Varies	Don't know
PICO 1: Healthy adolescents (0, 6 months)						X
PICO 2: Persons at increased risk (0, 1–2, 6 months)			X			X

Values

- Is there important uncertainty about or variability in how much people value the main outcome?

	Important uncertainty or variability	Probably important uncertainty or variability	Probably not important uncertainty or variability	No important uncertainty or variability	No known undesirable outcomes
PICO 1: Healthy adolescents (0, 6 months)			X		
PICO 2: Persons at increased risk (0, 1–2, 6 months)			X		

Acceptability

- Is the intervention acceptable to key stakeholders?

Harmonized Schedules

- Harmonized dosing schedules for MenB-4C (Bexsero) and MenB-FHbp (Trumenba) would likely be viewed favorably by providers

Extended Dosing Intervals

- Doses administered at shorter-than-recommended intervals can result in a sub-optimal immune response
  - However, extended intervals prolong the time until one achieves protection
- May be challenging for patients needing to complete vaccine series prior to complement inhibitor therapy initiation
  - Persons using complement inhibitors should complete or update vaccination at least 2 weeks before complement inhibitor initiation unless the risks for delaying treatment outweigh the risks for developing meningococcal disease

General Best Practice Guidelines for Immunization. https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html
Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020 | MMWR (cdc.gov)

Persons Taking Complement Inhibitors

- Among unvaccinated persons for whom complement inhibitor therapy cannot be delayed, antimicrobial prophylaxis should be administered alongside meningococcal vaccination and continued for 2 weeks after vaccine administration
- Persons taking complement inhibitors likely remain at substantially increased risk for meningococcal disease, even if vaccinated and/or taking prophylaxis
- Providers could consider continued antimicrobial prophylaxis for the duration of complement inhibitor treatment
  - Clinical judgement indicated

MMWR - Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020 (cdc.gov)

Acceptability

- Is the new dosing schedule acceptable to key stakeholders?

	No	Probably no	Probably yes	Yes	Varies	Don't know
PICO 1: Healthy adolescents (0, 6 months)			X			
PICO 2: Persons at increased risk (0, 1–2, 6 months)			X			

Resource use

- Is the intervention a reasonable and efficient allocation of resources?

Number of Doses

- Number of doses remains the same for most healthy adolescents
  - Unless 2nd dose administered earlier than 6 months after 1st dose
- Additional dose required for at-risk populations

Dose Price

- Harmonization with MenB-FHbp (Trumenba) dosing schedule could increase pricing competition

Price per Dose	
Bexsero (MenB-4C)	Trumenba (MenB-FHbp)
Private: $223.746	Private: $190.26
Public pediatric: $150.026 Public adult: $128.352	Public pediatric: $135.97 Public adult: $111.90

Current CDC Vaccine Price List | VFC Program | CDC

Resource Use

- Is the new dosing schedule a reasonable and efficient allocation of resources?

	No	Probably no	Probably yes	Yes	Varies	Don't know
PICO 1: Healthy adolescents (0, 6 months)			X			
PICO 2: Persons at increased risk (0, 1–2, 6 months)			X			

Equity

- What would be the impact on health equity?

Equity

- Schedules that require extended intervals or additional visits could disproportionately affect populations with lower access to health care
  - Unknown to what extent this would occur

Proportion Completing Series by Age 17 Years: NIS-TEEN (2022)

	%
Non-VFC eligible	
MenB-4C (Bexsero)	49.6%
MenB-FHbp (Trumenba)	35.5%
VFC-eligible	
MenB-4C (Bexsero)	51.4%
MenB-FHbp (Trumenba)	16.2%

Proportion Completing Series by Age 19 Years: Commercial Claims (2017-2023)

	%
Continuously-enrolled	
MenB-4C (Bexsero)	67%
MenB-FHbp (Trumenba)	60%

Equity

- What would be the impact on health equity

	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
PICO 1: Healthy adolescents (0, 6 months)		X	X				
PICO 2: Persons at increased risk (0, 1–2, 6 months)			X				

Feasibility

- Is the intervention feasible to implement?

Feasibility

- Providers may need to make adjustments to their practices (e.g., reminder/recall systems)
  - Especially for providers who administer MenB vaccine just prior to college matriculation
- Different manufacturers' MenB vaccine products remain not interchangeable

Feasibility

- Is the new dosing schedule feasible to implement?

	No	Probably no	Probably yes	Yes	Varies	Don't know
PICO 1: Healthy adolescents (0, 6 months)				X		
PICO 2: Persons at increased risk (0, 1–2, 6 months)				X		

Summary

EtR Domain	Question	PICO 1: WG Determination	PICO 2: WG Determination
Public health problem	Is IMD a problem of public health importance?	Yes	Yes
Benefits and harms	How substantial are the desirable anticipated effects?	Small	Small/moderate
	How substantial are the undesirable anticipated effects	Minimal/small	Minimal/small
	Do the desirable anticipated effects outweigh the undesirable effects?	Favors new schedule/favors both	Favors new schedule
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	Don't know	Don't know/ probably yes
	Is there important variability in how patients value the outcome?	Probably not	Probably not
Acceptability	Is the intervention acceptable to key stakeholders?	Probably yes	Probably yes
Resource use	Is the intervention a reasonable allocation of resources?	Probably yes	Probably yes
Equity	What would be the impact of the intervention on health equity?	Probably reduced/probably no impact	Probably no impact
Feasibility	Is the intervention feasible to implement?	Yes	Yes

Balance of Consequences

	Undesirable consequences ***clearly outweigh*** desirable consequences in most settings	Undesirable consequences ***probably outweigh*** desirable consequences in most settings	The balance between desirable and undesirable consequences is ***closely balanced or uncertain***	Desirable consequences ***probably outweigh*** undesirable consequences in most settings	Desirable consequences ***clearly outweigh*** undesirable consequences in most settings	There is ***insufficient evidence*** to determine the balance of consequences
PICO 1: Healthy adolescents (0, 6 months)			X	X	X	
PICO 2: Persons at increased risk (0, 1–2, 6 months)				X	X	

Work Group Interpretation

- Is there sufficient information to move forward with a recommendation?

	Yes	No
PICO 1: Healthy adolescents (0, 6 months)	X	
PICO 2: Persons at increased risk (0, 1–2, 6 months)	X	

Work Group Interpretation

PICO 1:

- Should MenB-4C be administered on a 0, 6 month dosing interval, vs. a 0, ≥1 month dosing interval, for the prevention of invasive meningococcal disease for persons aged 16–23 years recommended for MenB vaccination based on shared clinical decision-making?

We ***do not*** recommend the intervention	We ***do*** recommend the intervention
	X

Work Group Interpretation

PICO 2:

- Should MenB-4C be administered on a 0, 1–2, 6 month schedule, vs. a 0, ≥1 month schedule, for the prevention of invasive meningococcal disease among persons with persistent complement component deficiencies, those with complement inhibitor use, functional or anatomic asplenia, microbiologists routinely exposed to *Neisseria meningitidis*, or persons affected by an outbreak of serogroup B meningococcal disease?

We ***do not*** recommend the intervention	We ***do*** recommend the intervention
	X

Proposal Language

- ACIP recommends MenB-4C (Bexsero) be administered as a 2-dose series at 0 and 6 months when given to healthy adolescents and young adults aged 16–23 years based on shared clinical decision-making for the prevention of serogroup B meningococcal disease
- ACIP recommends MenB-4C (Bexsero) be administered as a 3-dose series at 0, 1–2, and 6 months when given to persons aged ≥10 years at increased risk for serogroup B meningococcal disease (i.e., persons with anatomic or functional asplenia, complement component deficiencies, or complement inhibitor use; microbiologists routinely exposed to *N. meningitidis* isolates; and persons at increased risk during an outbreak)

Summary and Work Group Considerations Regarding MenB-4C (Bexsero) Interval and Dosing Change

Summary

- Proposed recommendations will align with updated FDA label for MenB-4C (Bexsero)
  - Harmonized with existing recommendations for MenB-FHbp (Trumenba)

- **Pros:**
  - New dosing schedules associated with increased immunogenicity compared to previous schedule
  - Harmonization between MenB-4C (Bexsero) and MenB-FHbp (Trumenba) dosing intervals and schedules likely to be viewed favorably by providers (although vaccines from different manufacturers remain not interchangeable)

- **Cons:**
  - Longer interval between doses increases the time to achieve vaccine-induced protection and delays series completion
  - Persons receiving complement inhibitor therapy may need prolonged antimicrobial prophylaxis due to extended time for vaccine series completion

Proposed MenB-4C (Bexsero) Recommendations

- Healthy adolescents and young adults (based on shared clinical decision-making):
  - 2-dose series at 0 and 6 months

- Persons aged ≥10 years at increased risk for serogroup B meningococcal disease (i.e., persons with anatomic or functional asplenia, complement component deficiencies, or complement inhibitor use; microbiologists routinely exposed to *N. meningitidis* isolates; and persons at increased risk during an outbreak):
  - 3-dose series at 0, 1–2, and 6 months

Proposal Language

- ACIP recommends MenB-4C (Bexsero) be administered as a 2-dose series at 0 and 6 months when given to healthy adolescents and young adults aged 16–23 years based on shared clinical decision-making for the prevention of serogroup B meningococcal disease
- ACIP recommends MenB-4C (Bexsero) be administered as a 3-dose series at 0, 1–2, and 6 months when given to persons aged ≥10 years at increased risk for serogroup B meningococcal disease (i.e., persons with anatomic or functional asplenia, complement component deficiencies, or complement inhibitor use; microbiologists routinely exposed to *N. meningitidis* isolates; and persons at increased risk during an outbreak)

Proposed CDC Clinical Considerations

- No recommendation to recall persons previously vaccinated at 0, ≥1 month
  - Healthy adolescents
  - Persons at increased risk

- Persons should continue with booster vaccination as previously recommended

Proposed CDC Clinical Considerations, cont.

- The 3-dose series (doses administered at 0, 1–2, 6 months) may be used to optimize rapid protection for those who initiate the vaccine series less than 6 months prior to period of increased risk
  - e.g., when series initiation occurs within 6 months of college matriculation
- Would apply to MenB-4C (Bexsero) and MenB-FHbp (Trumenba)

CDC Clinical Considerations

(currently recommended for MenB-FHbp [Trumenba])

- When administering the 2-dose series (e.g., for healthy adolescents):
  - If the second dose is administered <6 months after the first dose, a third dose should be administered ≥4 months after the second dose (as per label)
  - A second dose administered ≥6 months following the first dose is valid and does not need to be repeated
- When administering the 3-dose series (e.g., for persons at increased risk):
  - A third dose is not needed if the second dose was administered ≥6 months after the first dose
  - If the third dose is administered <4 months after the second dose and <6 months after the first dose, the dose should be repeated ≥4 months after the last dose

Clinical Considerations, cont. (Unchanged)

- MenB vaccines from different manufacturers are not interchangeable
  - All doses in a series, as well as booster doses, should be from the same manufacturer.
  - If doses from both manufacturers have been administered to the same patient, the patient should receive a complete series of either manufacturers' product without counting doses of the other manufacturer as valid.

- MenB-4C (Bexsero) may be administered simultaneously with other vaccines
  - MenB vaccine should be administered in a separate limb from other vaccines administered on the same clinic day, if feasible.

- Contraindications: Severe allergy to prior dose or component of vaccine
- Precautions: Pregnancy, moderate or severe acute illness

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