Epidemiology of Meningococcal Disease in the U.S. and Updates on Meningococcal Vaccines

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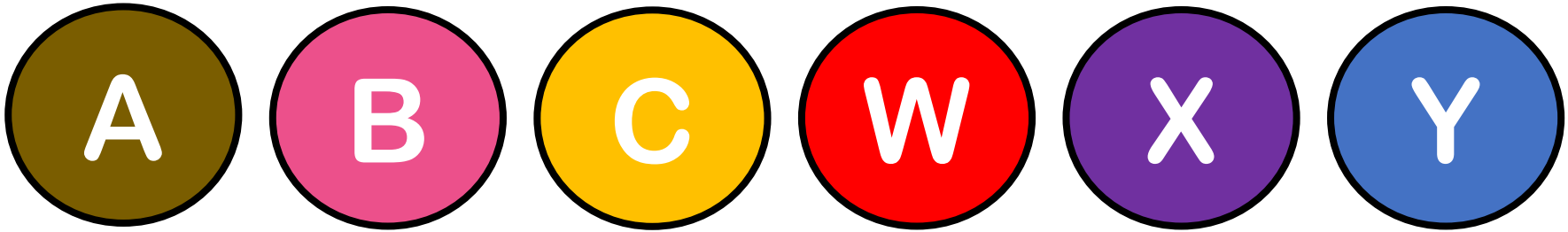
Advisory Commission on Childhood Vaccines
March 8, 2024

Epidemiology

Neisseria meningitidis

- Six serogroups cause almost all meningococcal disease



Neisseria meningitidis

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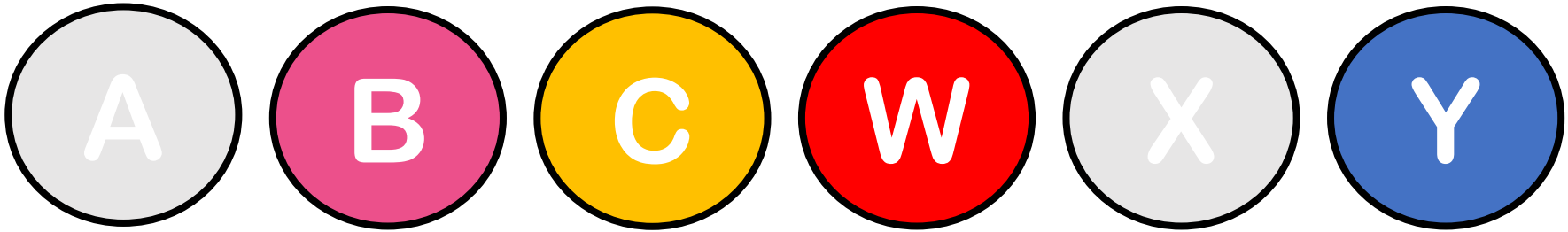
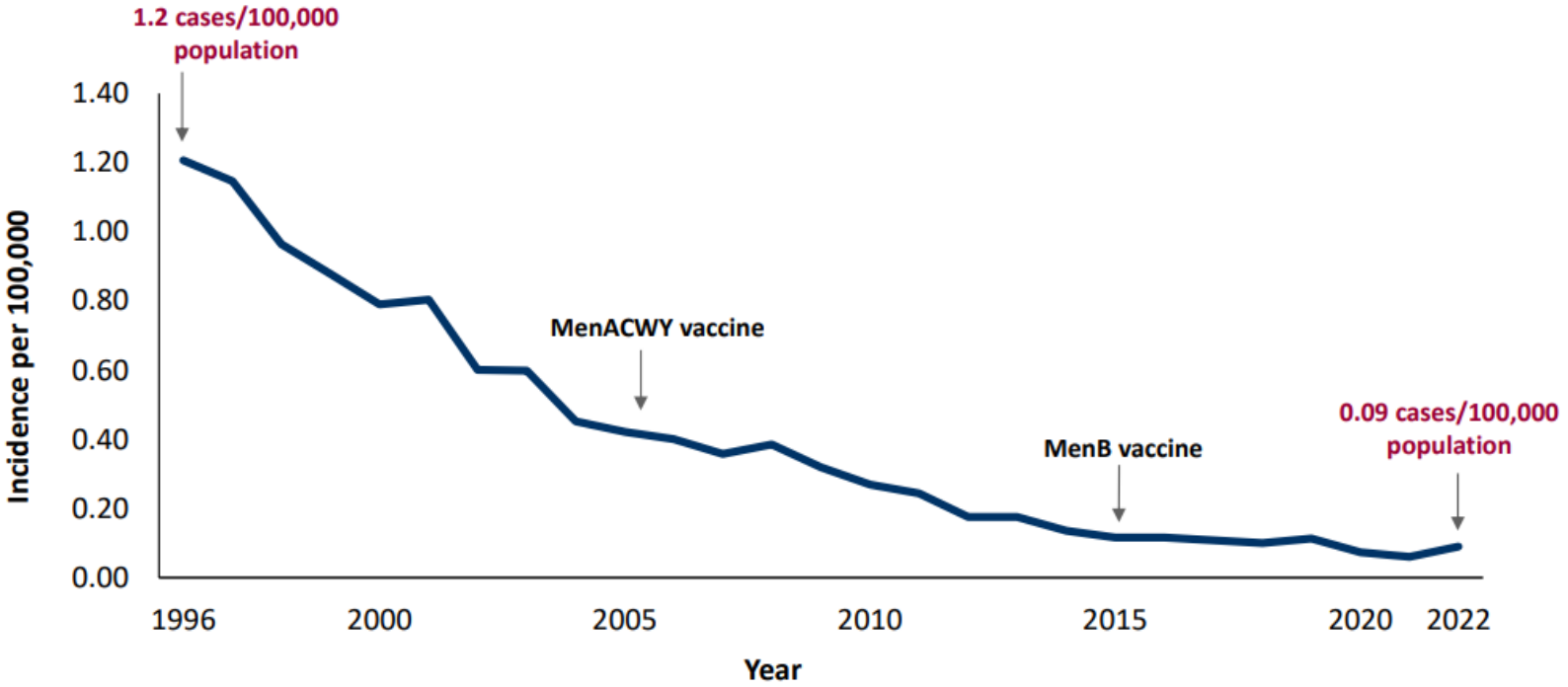


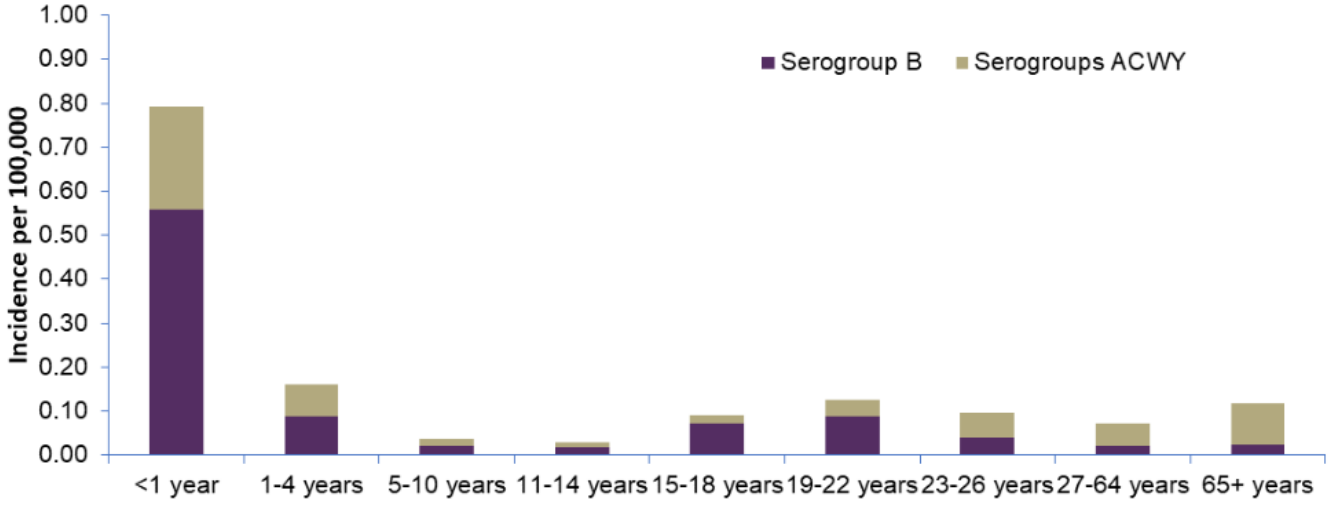
- Four serogroups circulate in the United States

Meningococcal Disease Incidence — United States, 1996-2022*



Abbreviations: MenACWY vaccine = quadrivalent conjugate meningococcal vaccine against serogroups A, C, W, Y; MenB vaccine = serogroup B meningococcal vaccine
Source: 1996–2022 NNDSS Data. *2021–2022 NNDSS data are preliminary.

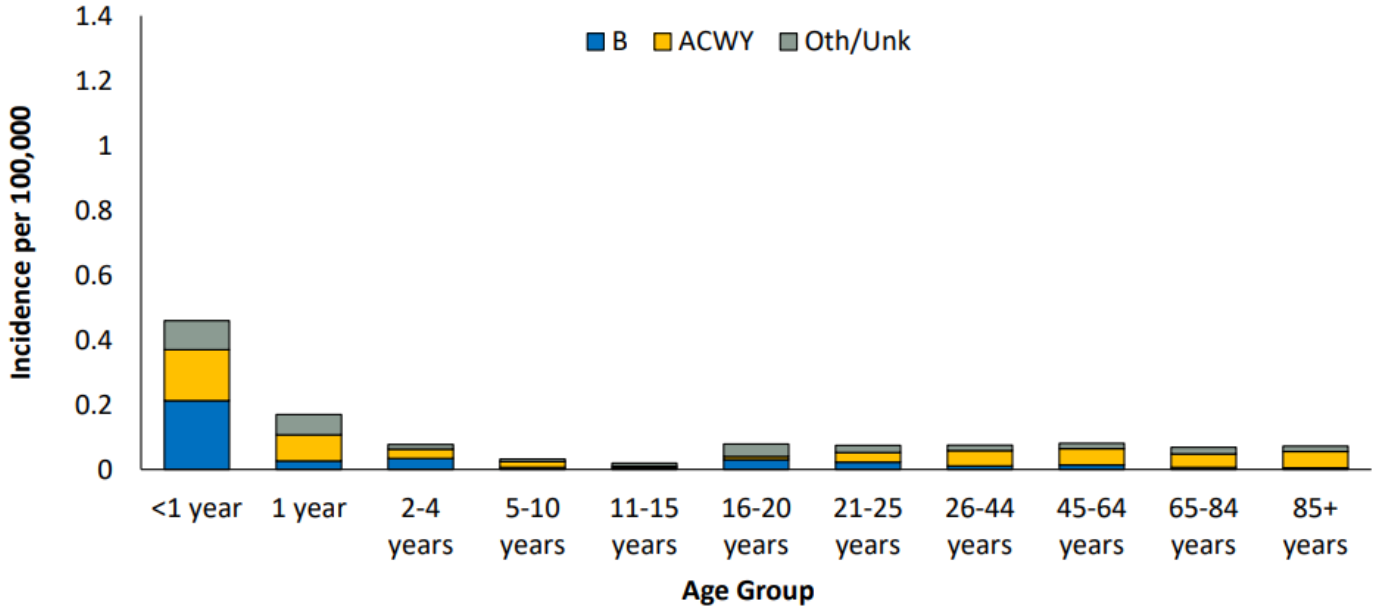
Average Annual Meningococcal Disease Incidence by Age-Group and Serogroup — United States, 2012-2021*



* Unknown serogroup (12%) and other serogroups (9%) excluded

SOURCE: CDC; National Notifiable Diseases Surveillance System with additional serogroup data from Active Bacterial Core surveillance and state health departments

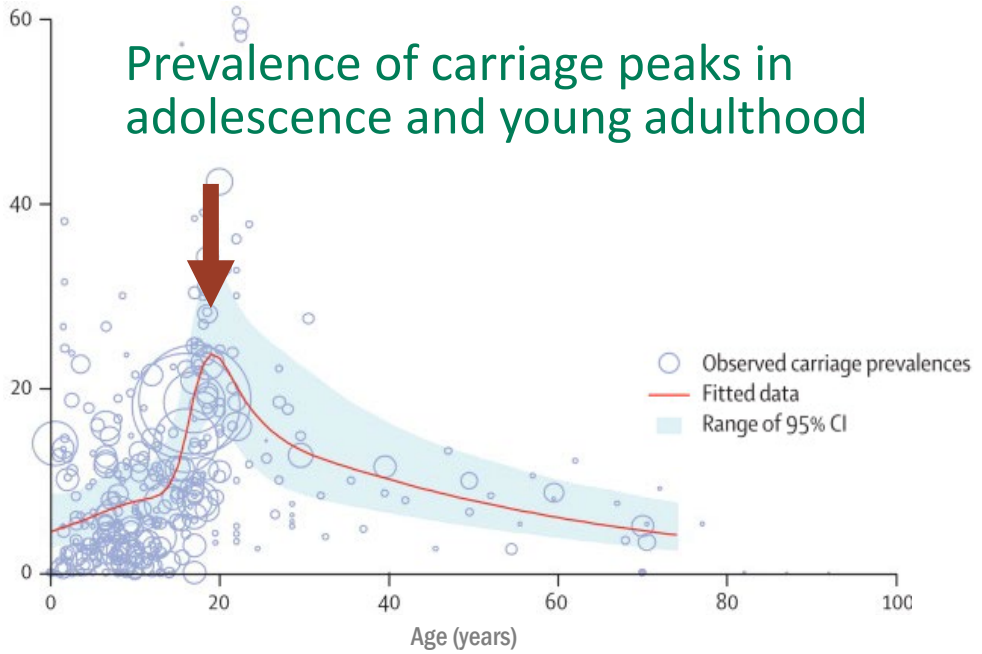
Average Annual Meningococcal Disease Incidence by Age-Group and Serogroup — United States, 2020-2022*



Source: NNDSS data with additional serogroup data from ABCs and state health departments
*2021 and 2022 data are preliminary

N. meningitidis is Carried Asymptomatically in the Nasopharynx

- Carriage can range from weeks to months
- 5-10% of the population are carriers
- <1% of people who acquire the bacteria develop disease



Source: https://www.sciencedirect.com/science/article/pii/S1473309910702516?via%3Dihub

Meningococcal Disease Outbreaks in the United States

5%

of cases are in outbreaks

An outbreak is defined as

2-3 cases,

or above baseline, in 3 months

Students
MSM
Homeless

Meningococcal Vaccines

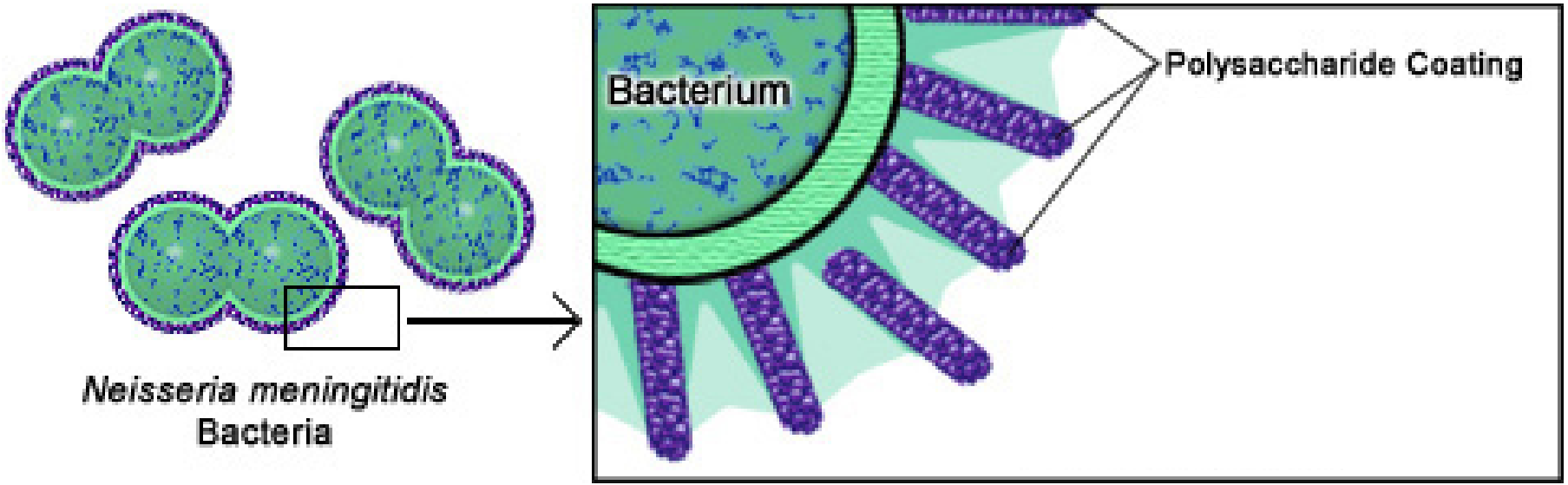
Meningococcal Vaccine Products

Vaccine Product	Trade Name	Licensed Age Group*
Quadrivalent meningococcal conjugate vaccines (MenACWY)		
~~MenACWY-D~~	~~Menactra®~~	~~9 months–55 years~~
MenACWY-CRM	Menveo®	2 months–55 years 10–55 years (single vial)
MenACWY-TT	MenQuadfi®	≥2 years
Serogroup B meningococcal vaccines (MenB)		
MenB-FHbp	Trumenba®	10–25 years
MenB-4C	Bexsero®	10–25 years
Pentavalent meningococcal vaccine (MenABCWY)		
MenACWY-TT/MenB-FHbp	Penbraya™	10–25 years

*ACIP recommends off-label use of some vaccine products outside of the licensed age group

Information from: https://www.cdc.gov/vaccines/pubs/pinkbook/mening.html and https://www.cdc.gov/vaccines/vpd/mening/hcp/about-vaccine.html

MenACWY Vaccines have Evolved from Polysaccharide to Conjugate



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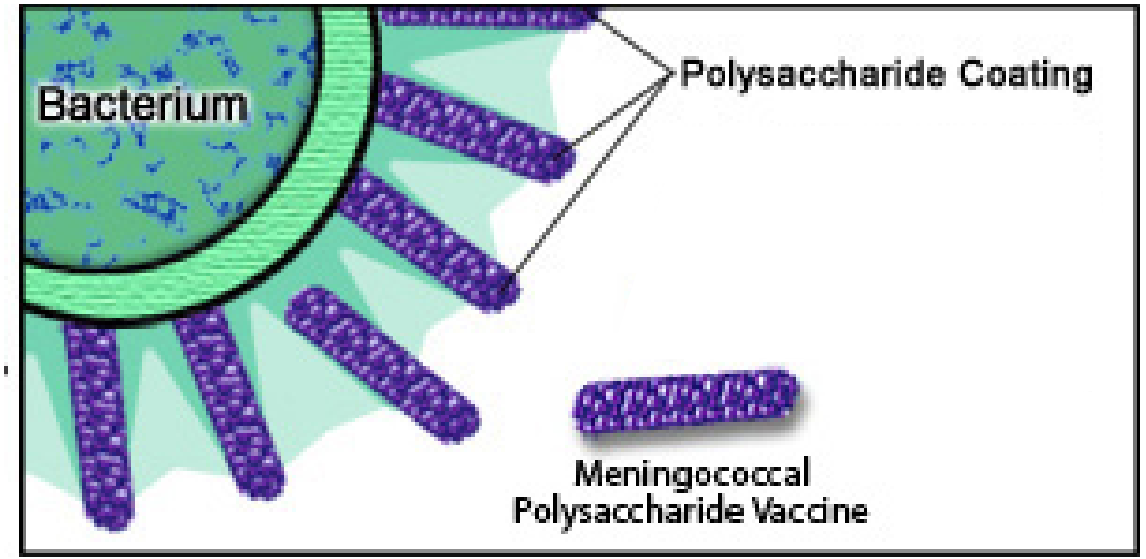
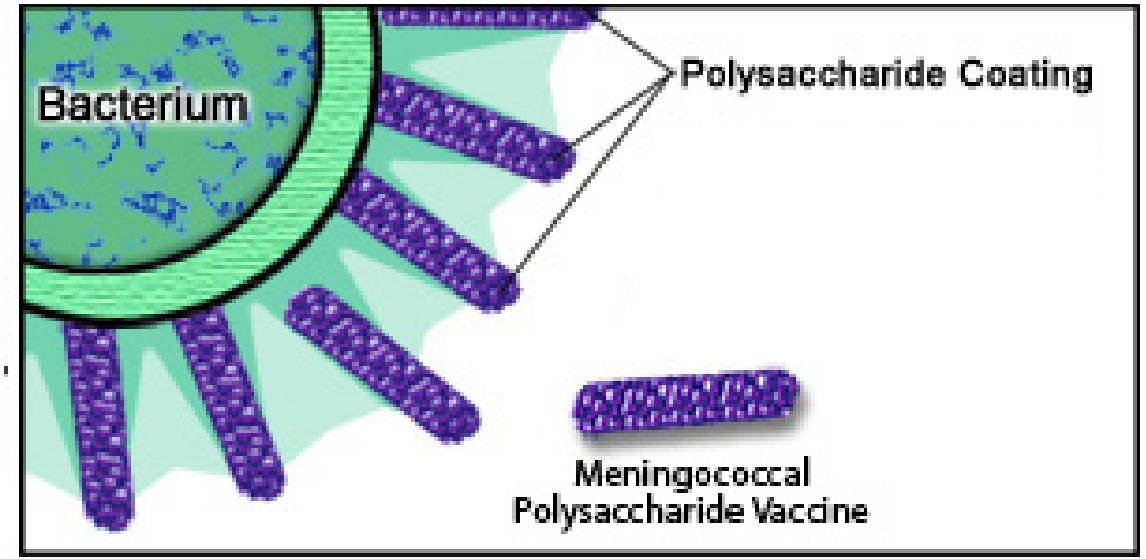


MenACWY Vaccines have Evolved from Polysaccharide to Conjugate

T-cell independent
response generating
IgM antibodies



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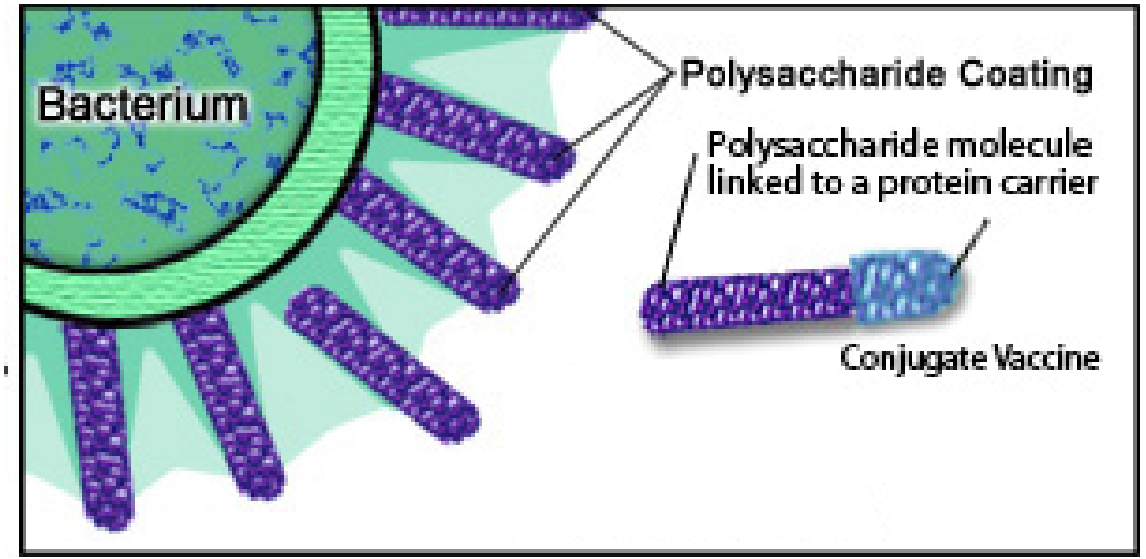
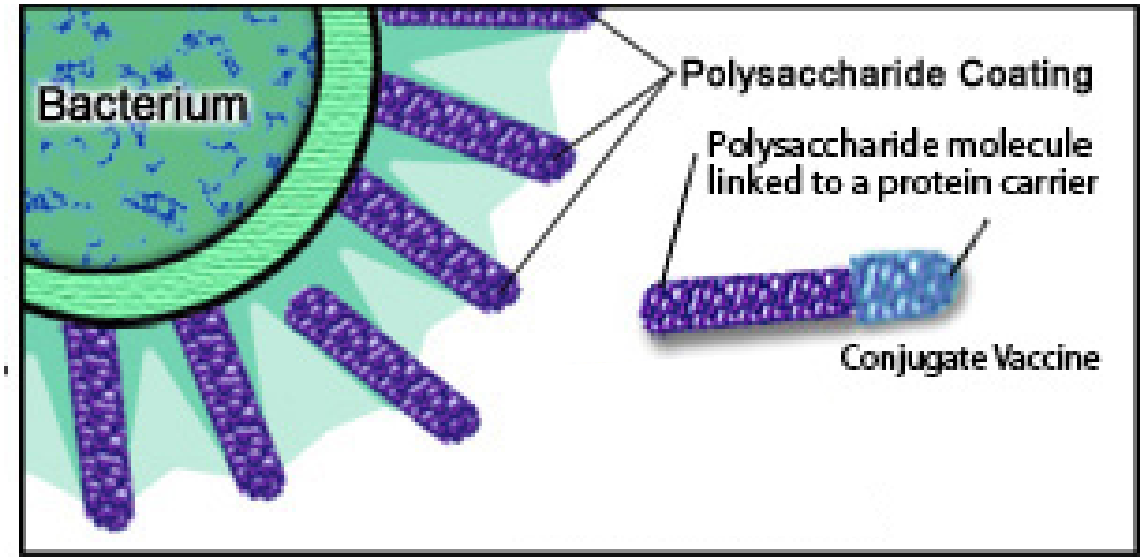
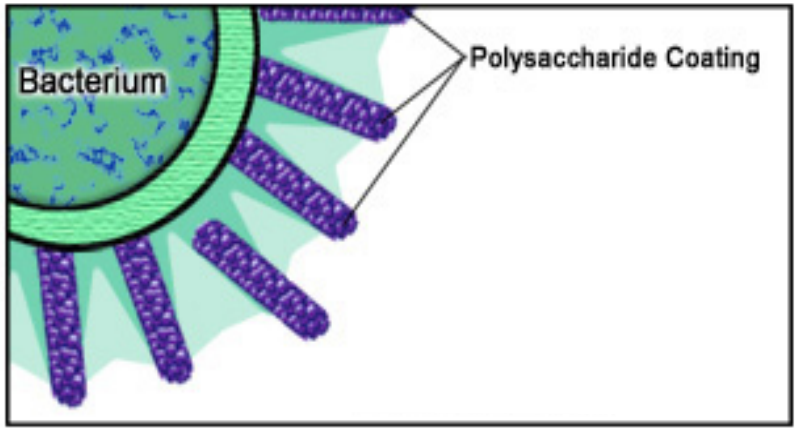


MenACWY Vaccines have Evolved from Polysaccharide to Conjugate

T-cell dependent response generating an **IgG response**



MenB Vaccine Development was Challenging



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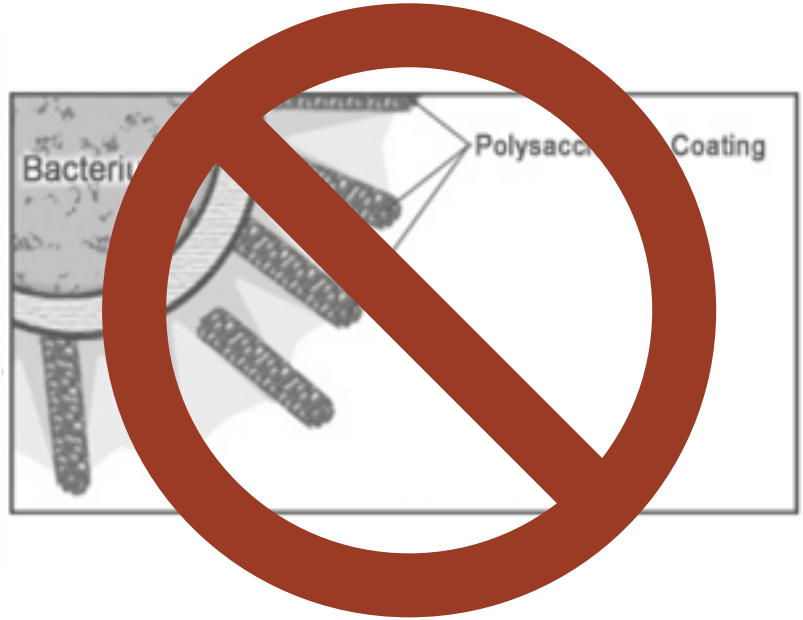
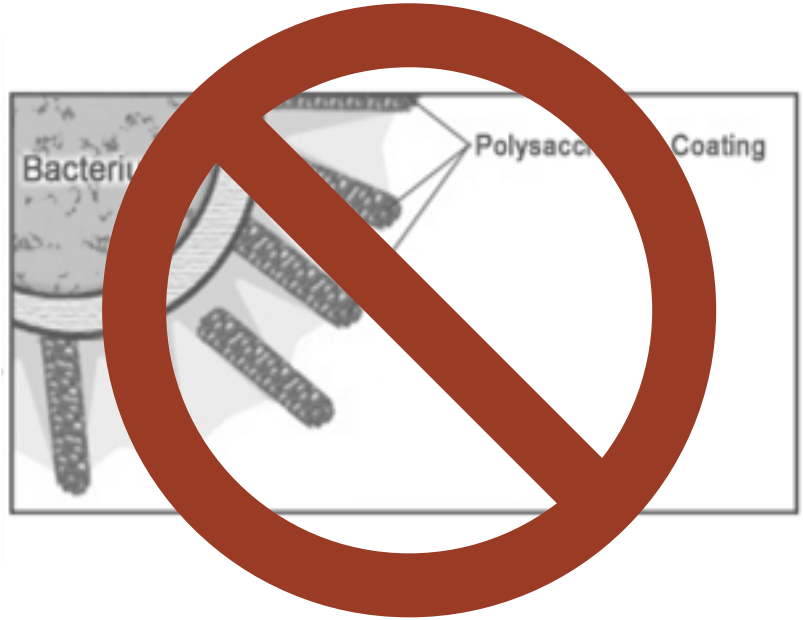


Serogroup B capsule is poorly immunogenic

MenB Vaccine Development was Challenging



Serogroup B capsule is poorly immunogenic

Protein antigen must provide protection against diverse strains

MenB Vaccines Target Outer Membrane Proteins

MenB-4C (Bexsero®, GSK)

FHbp subfamily B/v1

NhbA

NadA

OMVs containing Por A 1.4

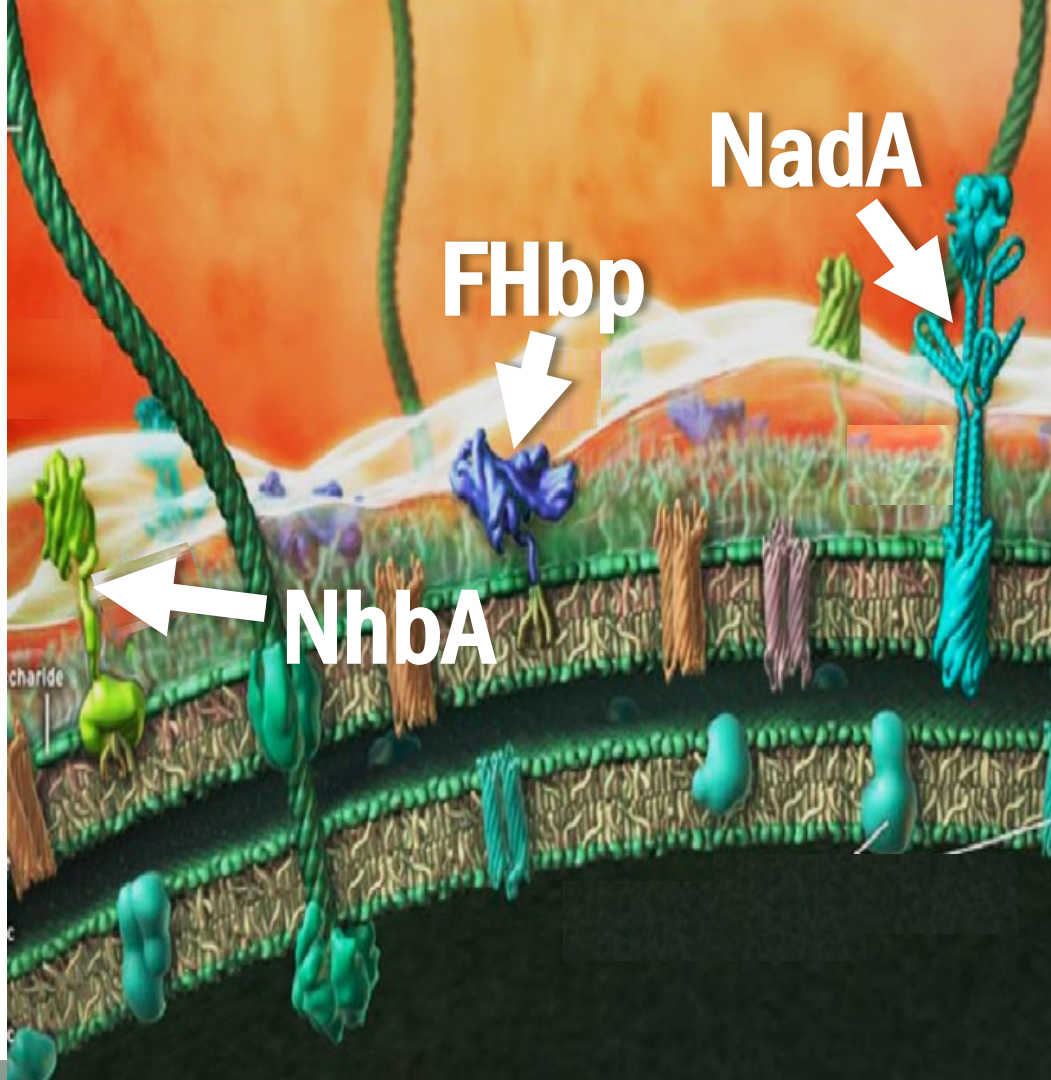
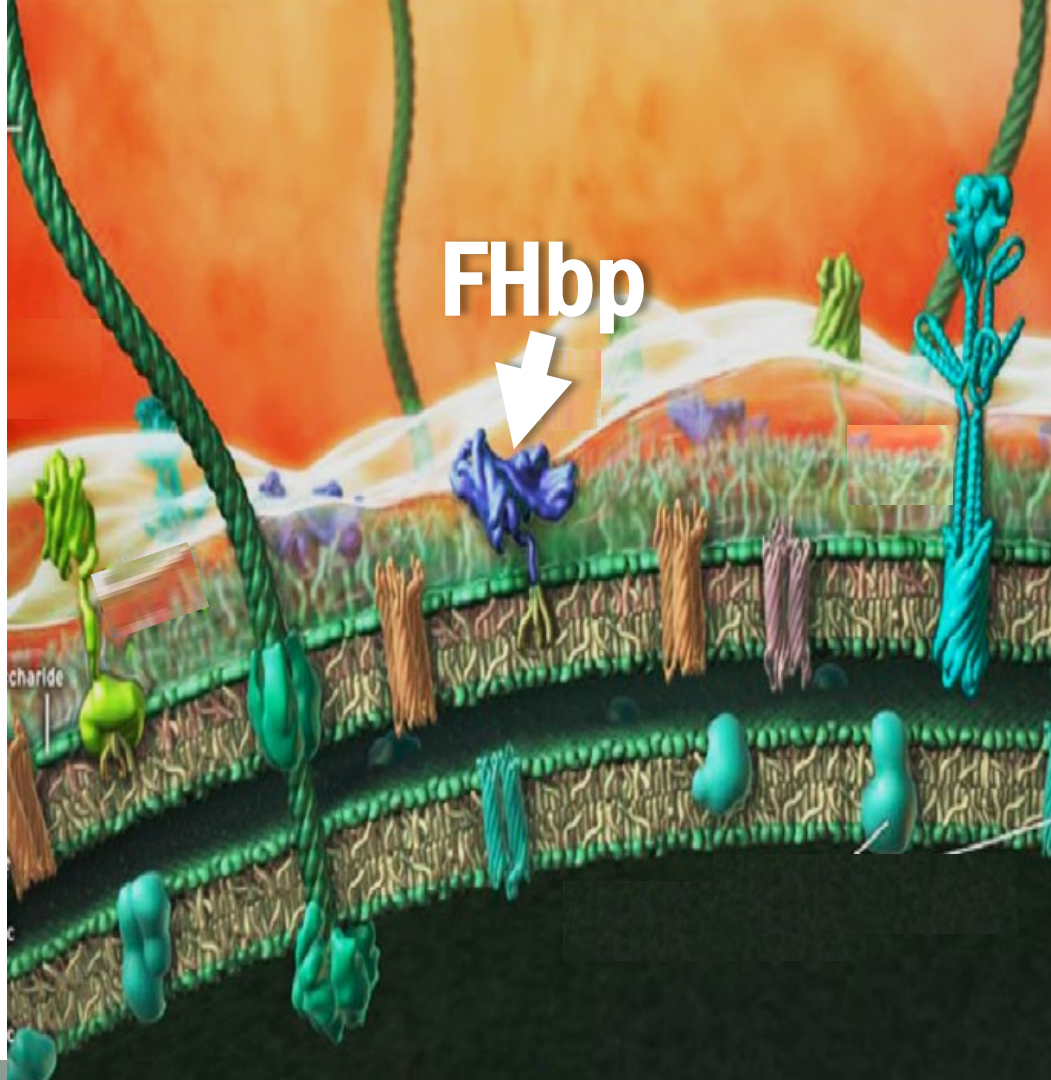


Image modified from Serruto et al. Vaccine 30S:B87,2012

MenB Vaccines Target Outer Membrane Proteins

MenB-FHbp (Trumenba®, Pfizer)

FHbp subfamilies A/v2,3 and B/v1



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MenB Vaccines Target Outer Membrane Proteins

- MenB vaccines do not protect against every serogroup B strain
- Potential for cross-protection against non-serogroup B *N. meningitidis*

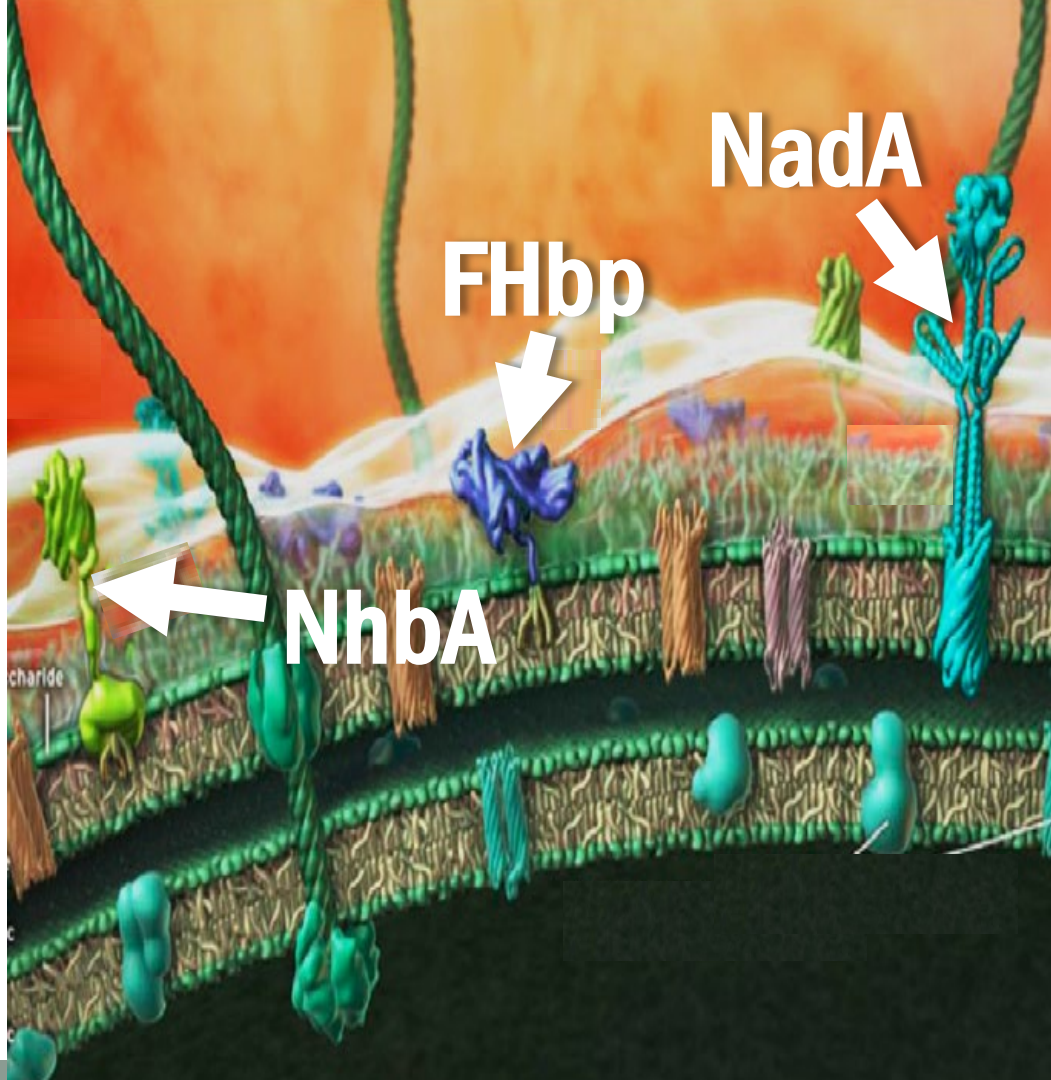

Image modified from Serruto et al. Vaccine 30S:B87,2012

Duration of Vaccine-Induced Protection for MenACWY and MenB

- Vaccine effectiveness difficult to evaluate due to small number of cases
- MenACWY
  - Protection wanes 3 to <8 years postvaccination
    - <1 year: 79%
    - 1—<3 years: 69%
    - 3—<8 years: 61%
  - Among those primed 3-10 years previously, ≥94% of subjects achieved seroprotective titers
- MenB
  - Protection wanes 1-2 years following primary vaccination

Mbaeyi et al, MMWR Recomm Rep 2020; Stephens et al, Meningococcal Vaccines Directed at Capsular Group B in Plotkin's Vaccines 8th edit; Dretler et al, Human Vaccines & Immunotherapeutics 2018; Cohn et al., Pediatrics 2017

Vaccination Schedule

Current ACIP MenACWY Vaccine Recommendations

Adolescents

- Dose 1 at 11-12 yrs
- Booster dose at age 16 yrs

Current ACIP MenACWY Vaccine Recommendations

Adolescents

- Dose 1 at 11-12 yrs
- Booster dose at age 16 yrs

People ≥2mo old at increased risk

- Complement deficiency, asplenia, HIV
- Microbiologists, college freshmen*, military recruits
- People who travel to/reside in hyperendemic or epidemic countries

*Highest risk for those living on campus at 4-year colleges

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People ≥2mo old at increased risk

- Complement deficiency, asplenia, HIV
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- People who travel to/reside in hyperendemic or epidemic countries

People at increased risk during an outbreak

*Highest risk for those living on campus at 4-year colleges

Current ACIP MenB Vaccine Recommendations

People ≥10 yrs old at increased risk

- Complement deficiency, asplenia
- Microbiologists
- During an outbreak

Current ACIP MenACWY Vaccine Recommendations

People ≥10 yrs old at increased risk

- Complement deficiency, asplenia
- Microbiologists
- During an outbreak

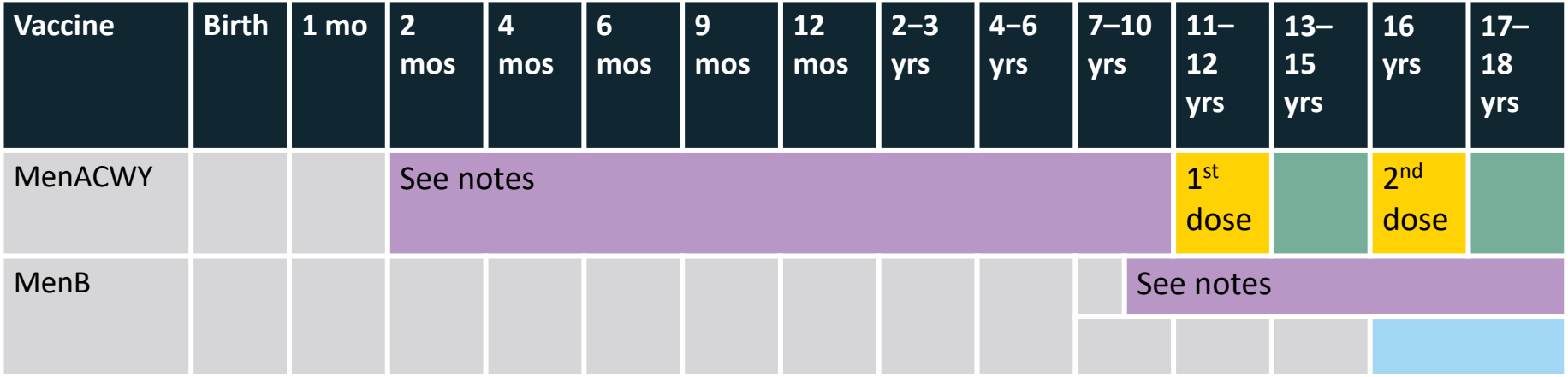
Adolescents

At age 16-23 yrs

(preferably at 16-18 yrs)

based on shared clinical decision-making

Meningococcal Vaccine Recommendations: Children/Adolescents



Range of recommended ages for all children

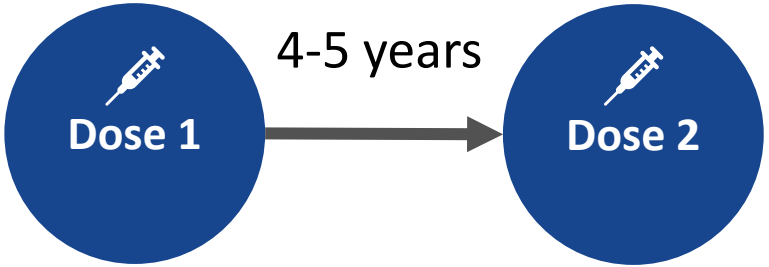
Range of recommended ages for catch-up vaccination

Range of recommended ages for certain high-risk groups

Recommended vaccination based on shared clinical decision-making

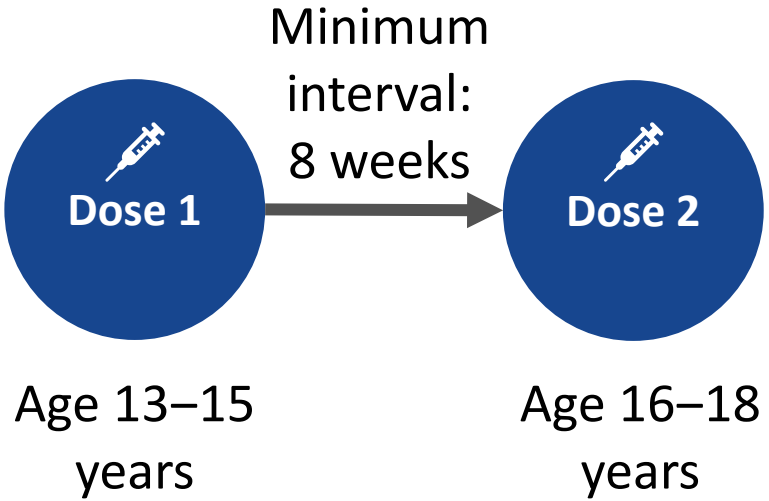
Information from www.cdc.gov/vaccines/schedules/hcp/imz/child-adolescent.html

MenACWY Recommendations for Healthy Children/Adolescents: Routine Vaccination



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

MenACWY Recommendations for Healthy Children/Adolescents: Catch-up Vaccination



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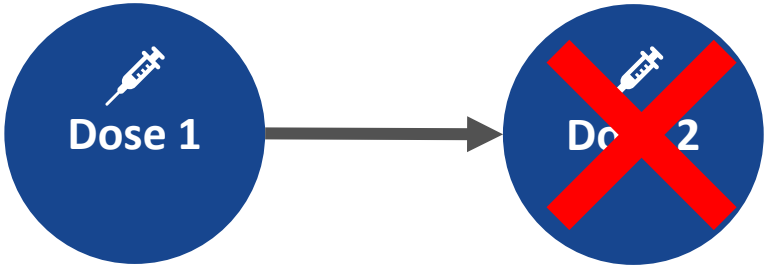


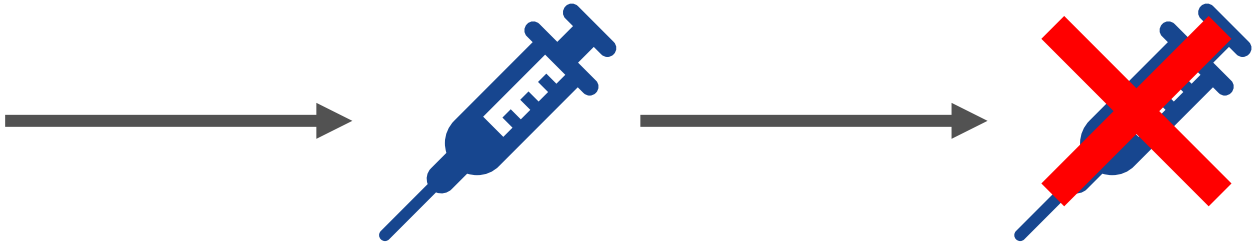
No booster dose

Age 16+ years

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

MenACWY Recommendations for Healthy Children/Adolescents: Catch-up Vaccination

If NO dose was given after the 16th birthday



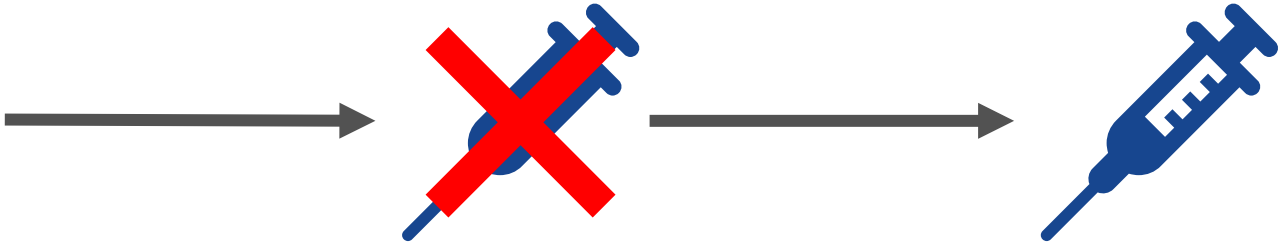
MenACWY may be given to persons age 19–21 years

Not recommended after age 21 years

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

MenACWY use in Healthy Children Before Age 11 years

Vaccinated **at** age 10 years



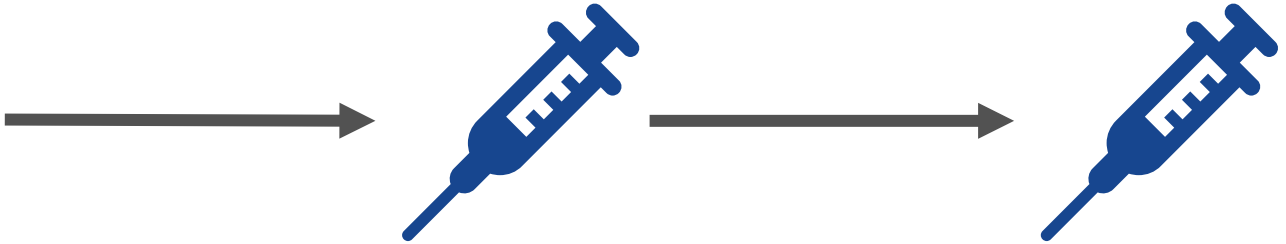
Do **NOT** give a dose at age 11 or 12 years

DO give a dose at age 16 years

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

MenACWY use in Healthy Children Before Age 11 years

Vaccinated **before** age 10 years



DO give a dose at age 11 or 12 years

DO give a dose at age 16 years

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

MenB Recommendations for Healthy Children/Adolescents

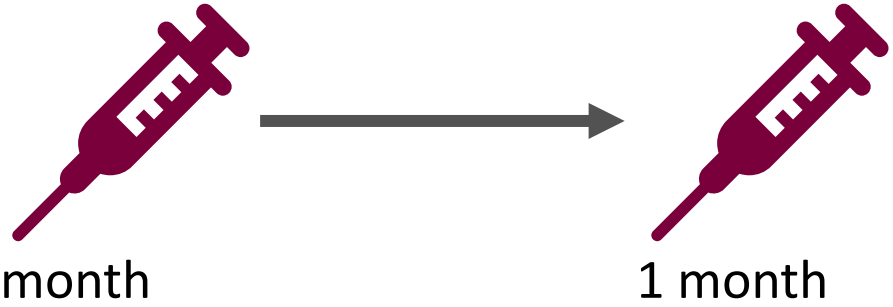
- Not routinely recommended for ALL adolescents
- Primary vaccination: 2 doses at ages 16–23 years based on shared clinical decision-making (preferred age 16–18 years)
- Booster vaccination: NOT recommended

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

MenB Recommendations for Healthy Children/Adolescents

MenB-FHbp (Trumenba)

MenB-4C (Bexsero)



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

MenB Recommendations for Healthy Children/Adolescents

MenB-FHbp (Trumenba)

0 month

Earlier than 6 months

4 months after dose 2

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

Meningococcal Vaccine Recommendations for Adults

Vaccine	19–26 years	27–49 years	50–64 years	≥64 years
MenACWY	1 or 2 doses depending on indication, see notes for booster recommendations			
MenB	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations			
	19–23 years			

Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

Recommended vaccination based on shared clinical decision-making

Meningococcal Vaccination for Persons at Increased Risk

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	2–3 yrs	4–6 yrs	7–10 yrs	11–12 yrs	13–15 yrs	16 yrs	17–18 yrs
MenACWY			See notes								1st dose		2nd dose	
MenB										See notes				

Vaccine	19–26 years	27–49 years	50–64 years	≥64 years
MenACWY	1 or 2 doses depending on indication, see notes for booster recommendations			
MenB	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations			
	19–23 years			

Meningococcal Vaccination for Persons at Increased Risk

Risk group	MenACWY	MenB
Persons with complement component deficiency (including patients using a complement inhibitor)	Age ≥2 months	Age ≥10 years
Persons with functional or anatomic asplenia (including sickle cell disease)	Age ≥2 months	Age ≥10 years
Persons with HIV infection	Age ≥2 months	No recommendation
Microbiologists routinely exposed to *Neisseria meningitidis*	Age appropriate*	Age appropriate†
Persons exposed during an outbreak of meningococcal disease due to a vaccine-preventable serogroup	Age ≥2 months	Age ≥10 years
Persons who travel to or live in countries where meningococcal disease is hyperendemic or epidemic	Age ≥2 months	No recommendation
College freshmen living in residence halls	Age appropriate*	No recommendation
Military recruits	Age appropriate*	No recommendation

*Persons aged ≥2 months in these risk groups are recommended to receive MenACWY vaccination
†Persons aged ≥10 years in this risk group are recommended to receive MenB vaccination.
Includes off-label recommendations

MenACWY and MenB Vaccine Schedules for Persons at Increased Risk

- Number of doses and intervals vary based on:
  - Risk condition
  - Vaccine product
  - Age of patient
- For complete information, refer to:
  - Immunization Schedules Immunization Schedules | CDC
  - MMWR MMWR - Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020 (cdc.gov)

Booster Recommendations for Persons at Increased Risk

- MenACWY: For persons who remain at increased risk and completed the primary vaccination at age:
  - < 7 years:
    - —1 dose 3 years after primary series; boosters every 5 years
  - ≥7 years:
    - —1 dose 5 years after primary series; boosters every 5 years
- MenB: For persons who remain at increased risk:
  - Booster dose 1 year* since primary series; repeat every 2-3 years as long as risk remains.

*During an outbreak, may be administered at least 6 months after series if recommended by public health authorities

Interchangeability of Meningococcal Vaccine Products

MenACWY vaccines ARE interchangeable

- Same vaccine product is **recommended**, but **not required**, for all doses

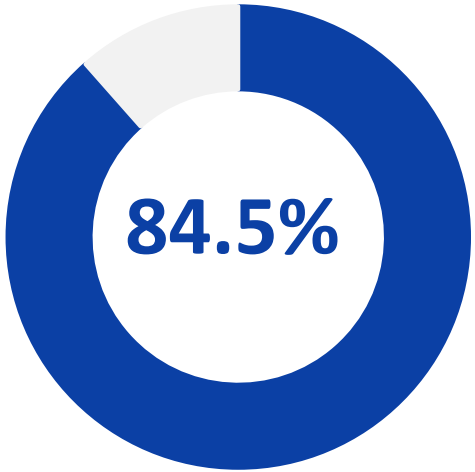
MenB vaccines are <u>NOT</u> interchangeable by manufacturer

Penbraya (MenACWY-TT/MenB-FHbp)

- Pfizer's MenABCWY vaccine (MenACWY-TT/MenB-FHbp) may be used when both MenACWY and MenB are indicated at the same visit.*
  - Use of MenACWY-TT/MenB-FHbp should not supersede discussion of whether to administer MenB under shared clinical decision-making.
  - If MenACWY-TT/MenB-FHbp is inadvertently given in lieu of MenACWY or MenB when only one was indicated, the dose can be considered valid if it would otherwise have been a valid dose of MenACWY or MenB

*1) Healthy individuals aged 16–23 years (routine schedule) when shared clinical decision-making favors administration of MenB vaccination, 2) individuals aged 10 years and older at increased risk of meningococcal disease (e.g., due to persistent complement deficiencies, complement inhibitor use, or functional or anatomic asplenia) due for both vaccines

MenACWY Coverage among Adolescents (2022)



≥ 1 dose

among 13 yr olds

Pingali et al., MMWR Morb Mortal Wkly Rep 2023. DOI: http://dx.doi.org/10.15585/mmwr.mm7234a3

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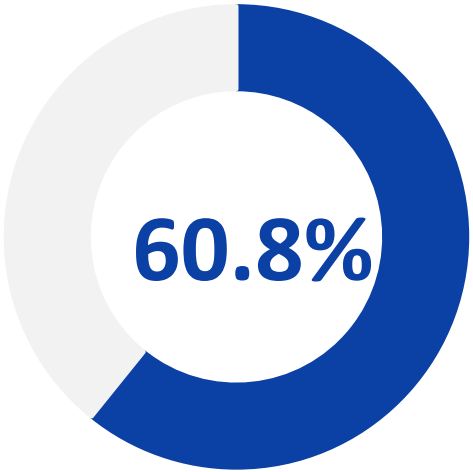
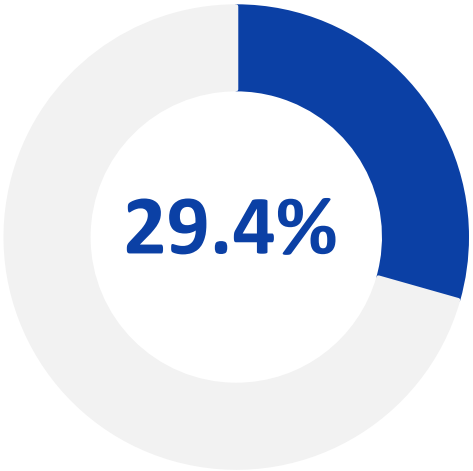


≥ 2 doses

among 17 yr olds

Pingali et al., MMWR Morb Mortal Wkly Rep 2023. DOI: http://dx.doi.org/10.15585/mmwr.mm7234a3

MenB Coverage among Adolescents (2022)



≥ 1 dose

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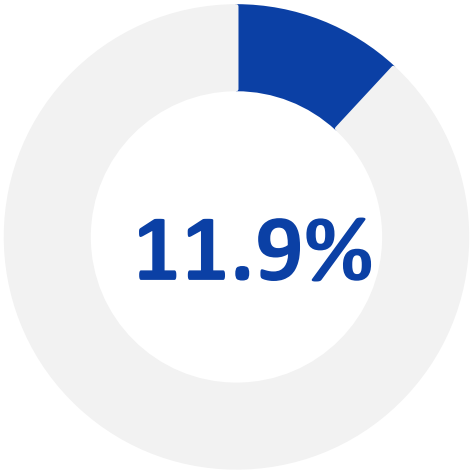

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Vaccine Safety

Meningococcal ACWY Vaccine Products

Ingredient	Menveo	MenQuadfi
Adjuvant	No	No
Antibiotic	No	No
Preservative	No	No
Thimerosal	No	No
Yeast	Used in manufacturing	No
Formaldehyde	Yes	Yes
Latex	No	No

Information from: https://www.cdc.gov/vaccines/pubs/pinkbook/html and Package Inserts Vaccines Licensed for Use in the United States | FDA

Meningococcal B Vaccine Products

Ingredient	Trumenba	Bexsero
Adjuvant	Aluminum	Aluminum
Antibiotic	No	Kanamycin
Polysorbate 80 (stabilizer)	Yes	No
Thimerosal	No	No
Yeast	No	No
Formaldehyde	No	No
Latex	No	Some

Information from: https://www.cdc.gov/vaccines/pubs/pinkbook/html and Package Inserts Vaccines Licensed for Use in the United States | FDA

Meningococcal ABCWY Vaccine Product

Ingredient	Penbraya
Adjuvant	Aluminum
Antibiotic	No
Polysorbate 80 (stabilizer)	Yes
Thimerosal	No
Yeast	Used in manufacturing
Formaldehyde	No
Latex	No

Information from: https://www.cdc.gov/vaccines/pubs/pinkbook/html and Package Inserts Vaccines Licensed for Use in the United States | FDA

Contraindications: MenACWY Vaccines

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose
- Severe allergic reaction (e.g., anaphylaxis) to a vaccine component (including yeast) and also including:
  - For MenACWY-CRM only: severe allergic reaction to any diphtheria toxoid– or CRM197 containing vaccine
  - For MenACWY-TT only: severe allergic reaction to a tetanus toxoid-containing vaccine

ACIP Contraindications Guidelines for Immunization | CDC

Precautions: MenACWY Vaccines

- Moderate or severe acute illness with or without fever

- For MenACWY-CRM only: Preterm birth if less than age 9 months
  - Concern about apnea

ACIP Contraindications Guidelines for Immunization | CDC

Common Adverse Reactions: MenACWY Vaccines

Injection site reactions: pain and erythema

Fever

Irritability

Fatigue, drowsiness

Headache

Myalgia

Malaise

https://www.cdc.gov/vaccines/pubs/pinkbook/mening.html#Safety

Contraindications: MenB Vaccines

- Severe allergic reaction (e.g., anaphylaxis) after a previous dose
- Severe allergic reaction (e.g., anaphylaxis) to a vaccine component

ACIP Contraindications Guidelines for Immunization | CDC

Precautions: MenB Vaccines

- Moderate or severe acute illness with or without fever
- Pregnancy
- Latex sensitivity (some Bexsero only)

ACIP Contraindications Guidelines for Immunization | CDC

Common Adverse Reactions: MenB Vaccines

Injection site reactions: pain, induration, erythema

Fever

Fatigue

Headache

Myalgia

Arthralgia

https://www.cdc.gov/vaccines/pubs/pinkbook/mening.html#Safety

Vaccine Safety Considerations: MenACWY Vaccines

- History of Guillain-Barré syndrome (GBS) previously a precaution for vaccination with any MenACWY vaccine
  - ACIP removed this precaution in 2010

- Increased risk for Bell's Palsy observed in adolescents within 84 days following vaccination, when MenACWY-CRM co-administered with other vaccines
  - Increased risk not observed when MenACWY-CRM administered alone

- Administration errors reported for MenACWY-CRM
  - Related to failure to reconstitute vaccine

MMWR - Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020 (cdc.gov); ACIP Contraindications Guidelines for Immunization | CDC

Vaccine Safety Considerations: MenB Vaccines

- Theoretical risk exists for development of factor H autoantibodies following MenB-FHbp vaccination
  - Vaccine contains factor H binding protein
  - Proportion with a newly diagnosed autoimmune disease cases during trial and within 6 months low and similar to unvaccinated controls
- Transient decreased mobility of the arm was disproportionately reported for MenB-4C compared with other vaccines.
- Four cases of likely idiopathic nephrotic syndrome identified in young children within 1 year following MenB-4C vaccination
  - Clinical significance uncertain; post-marketing surveillance has not identified increased risk

MMWR - Meningococcal Vaccination: Recommendations of the Advisory Committee on Immunization Practices, United States, 2020 (cdc.gov); ACIP Contraindications Guidelines for Immunization | CDC; Perez-Vilar, Vaccine 2022

MenACWY and MenB Vaccination during Pregnancy

- MenACWY: No concerning events identified
  - Recommended if otherwise indicated
- MenB: Data are limited
  - Generally defer vaccination

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

Vaccination-Related Syncope

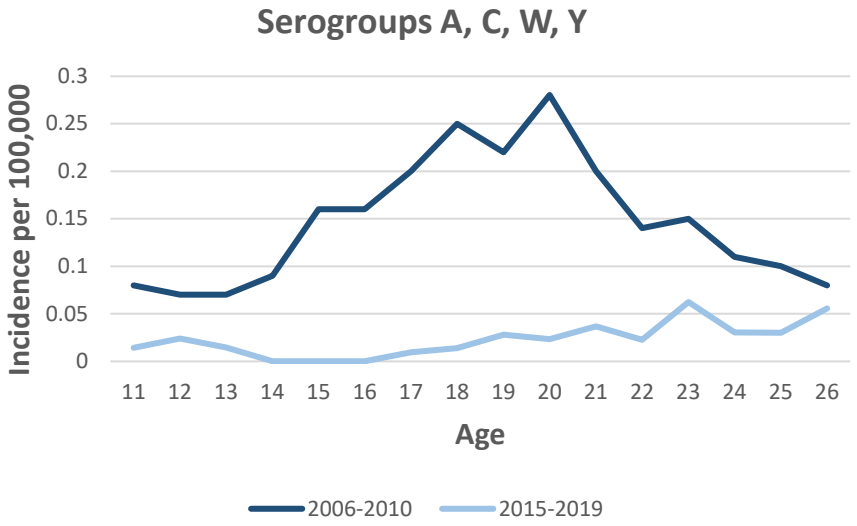
- Can be common in adolescents
  - 62% of VAERS syncope reports occurred among adolescents 11-18 years of age
- Syncope-related falls can cause injury, e.g., head injury
- During MenB vaccination campaign, 0.88 syncopal events occurred per 1,000 vaccinated persons
- Consider observing patients for 15 minutes after vaccination (especially adolescents)
  - Patients should be seated or lying down
- Reducing number of injections (e.g., via combined MenACWY and MenB vaccines) may reduce potential for syncope associated with vaccination among adolescents

Advisory Committee on Immunization Practices (ACIP) General Best Guidance for Immunization (cdc.gov); Syncope After Vaccination --- United States, January 2005--July 2007 (cdc.gov)

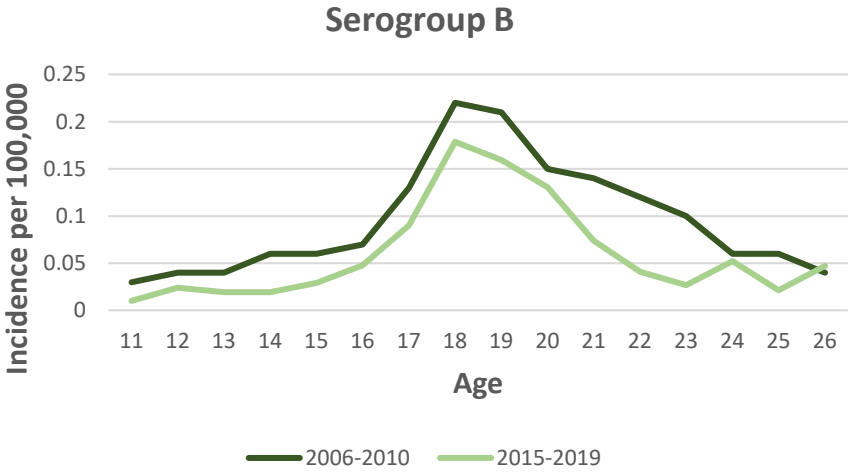
Vaccine Impact

Incidence of Meningococcal Disease by Serogroups Following MenACWY Vaccine Implementation

ACWY disease incidence substantially **decreased** in **adolescents**



B disease incidence was **similar** in **adolescents** over time



Source: National Notifiable Diseases Surveillance System (NNDSS) data with additional serogroup data from Active Bacterial Core surveillance (ABCs) and state health departments

Cases Averted Due to Quadrivalent Vaccination

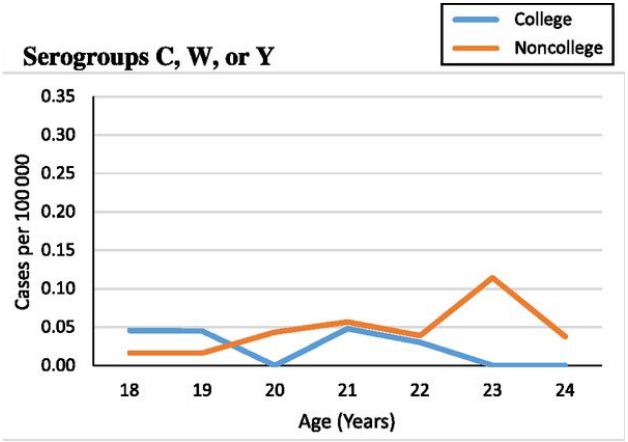
- Incidence of meningococcal disease declined prior to introduction of vaccine
- Among adolescents 11-15 years old, incidence decreased:
  - 16.3% (12.1%-20.3%) during prevaccine period
  - 27.8% (20.6%-34.4%) during post-primary dose period
- Among adolescents 16-22 years old, incidence decreased:
  - 10.6% (6.8%-14.3%) in post primary dose period
  - 35.6% (29.3%-41.0%) in post-booster dose period
- Estimated 222 cases of serogroup C,W,Y disease averted through vaccination of adolescents during 2006-2017

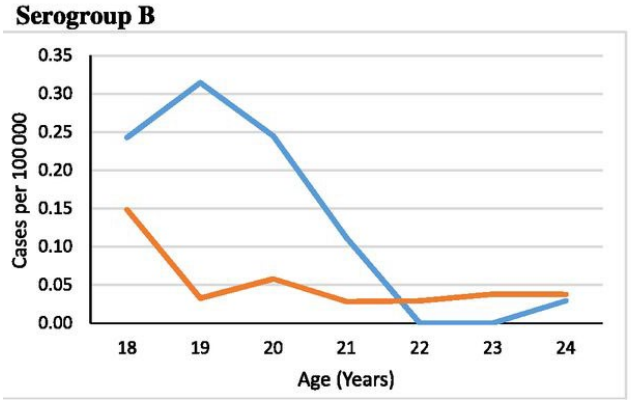
Mbaeyi et al, JAMA Pediatr. 2020;174(9).

Hot Topics in Meningococcal Disease Prevention

Serogroup B Disease Risk is Higher among College Students

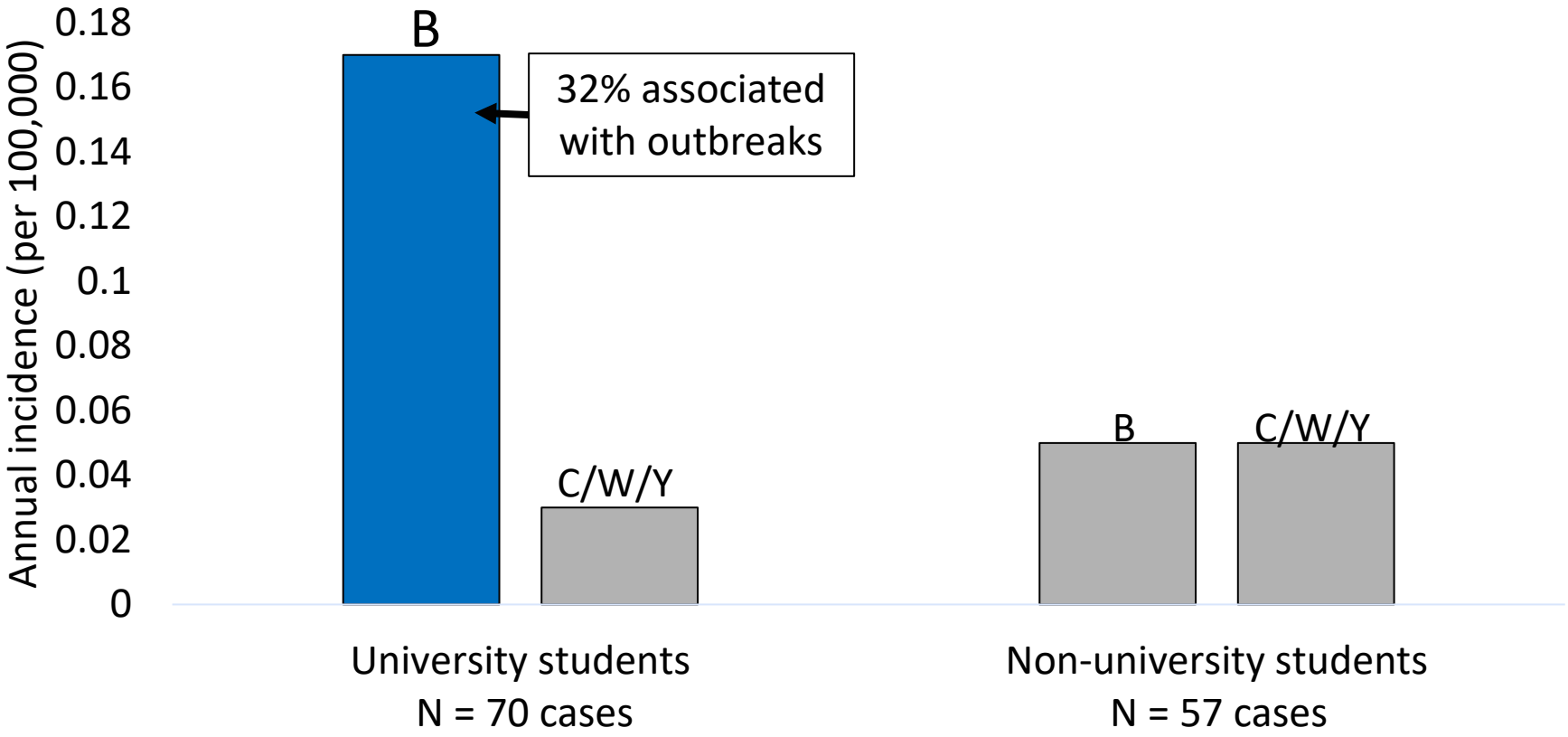
- College students have a 3.54-fold (95% CI: 2.21-5.41) higher risk of serogroup B disease than non-college students
- Serogroup B incidence is highest among 18-19 year college students





https://publications.aap.org/pediatrics/article/143/1/e20182130/76851/Meningococcal-Disease-Among-College-Aged-Young?autologincheck=redirected

Meningococcal Disease in People aged 18-24 years – United States, 2014-2016



Additional Factors Associated with Increased Risk among College Students

- 4-year college students had a **5.2**-fold (95% CI: 3.6-7.7) higher risk of serogroup B disease than non-undergraduates aged 18-24 years
  - Risk among 2-year college students was comparable to non-undergraduates (RR 1.0, 95% CI 0.4-2.1)
- First-year students were at **3.8**-fold (95% CI: 2.4-6.0) higher risk of serogroup B disease than non-first-year students
- On-campus residents at **2.9**-fold (95% CI: 1.8-4.6) higher risk of serogroup B disease than off-campus residents
- Students participating in Greek life were at **9.8**-fold (95% CI: 4.6-21.2) higher risk of serogroup B disease than other students during outbreaks

Adapted from slide prepared by L. McNamara

Effectiveness of Bexsero against Gonorrhea

- *N. meningitidis* and *N. gonorrhoeae* closely genetically related
  - ~80 to 90% sequence homology
- Potential for outer membrane vesicle (OMV)-containing MenB vaccines (e.g., Bexsero) to provide protection against *N. gonorrhoeae*

Effectiveness of Bexsero against Gonorrhea, cont.

- Case control study in New Zealand
  - 31% effectiveness
  - Waning of vaccine effectiveness (VE) noted, although decrease in VE was not significant between 2004-2009 and 2010-2014
- Observational cohort study in Australia
  - 32.7% effectiveness (2 dose)
- Retrospective observational study in New York and Philadelphia
  - 40% effectiveness (2 dose); 26% effectiveness (1 dose)
- Matched cohort study in California
  - 46% reduction in Gonorrhea cases

Petousis-Harris H, et al. Lancet 2017; Wang B, et al. Lancet 2022; Abara W, et al. Lancet 2022; Bruxvoort K, et al. CID 2023

Summary

- Meningococcal disease incidence declining overall, although uptick observed in recent years
  - Some persons remain at higher risk
- Potential changes to vaccination policy will consider:
  - Changing epidemiology for meningococcal disease
  - Duration of vaccine-induced protection
  - Newly available pentavalent vaccine(s)
  - Gonorrhea protection with MenB outer membrane vesicle vaccines

Acknowledgements

- Lucy McNamara
- Jennifer Collins
- Elisha Hall

Additional Slides

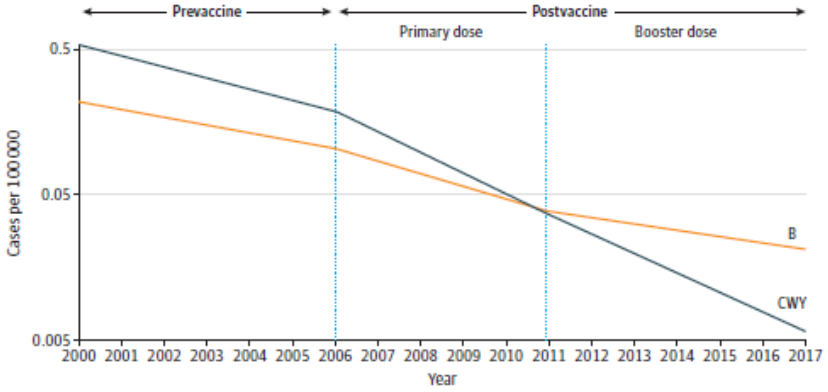
History of Guillain-Barré syndrome (GBS)

- History of Guillain-Barré syndrome (GBS) previously a precaution for vaccination with any MenACWY vaccine
  - ACIP removed this precaution in 2010
- Retrospective study among 5 U.S. health plans
  - 99 cases GBS during 18,322,800 person-years
- MCV4 vaccination saves 2397 quality-adjusted life years (QALYs)
  - Vaccine-attributable GBS could result in 5 QALYs lost
- None (of 5 cases representing signal) represented true new-onset GBS during observation window

Cho et al., Vaccine 2010; Velentgas et al. Pharmacoepidemiol Drug Saf 2012, Yih et al., Pediatrics 2011

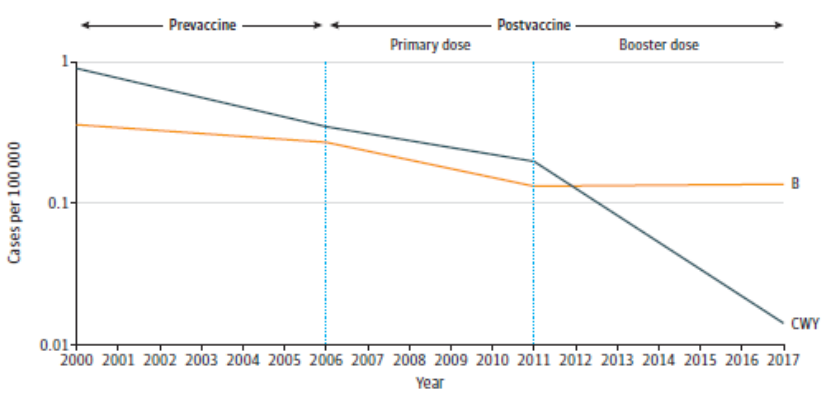
Estimated Log Annual Incidence and Annual Percentage Change in Meningococcal Disease Incidence in Adolescents — United States, 2000-2017

11-15 year-olds



Period	Serogroup	
	CWY % (95% CI)	B % (95% CI)
2000-2005	-16.3 (-20.3 to -12.1)	-11.8 (-18.6 to -4.4)
2006-2010	-27.8 (-34.4 to -20.6)	-18.0 (-26.2 to -8.9)
2011-2017	-26.5 (-39.0 to -11.4)	-9.5 (-20.8 to 3.4)

16-22 year-olds



Period	Serogroup	
	CWY % (95% CI)	B % (95% CI)
2000-2005	-14.6 (-17.0 to -12.1)	-4.7 (-8.4 to -0.9)
2006-2010	-10.6 (-14.3 to -6.8)	-13.3 (-17.4 to -9.0)
2011-2017	-35.6 (-41.0 to -29.3)	0.5 (-4.4 to 5.8)

Mbaeyi et al, JAMA Pediatr. 2020;174(9).