MENINGOCOCCAL EPIDEMIOLOGY AND VACCINE RECOMMENDATIONS IN THE UNITED STATES

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Disclosures

Donna Curtis:

- Sanofi-Pasteur provides influenza vaccine and will run one serum test for an investigator-initiated study for which I am the PI.
- No other relevant disclosures

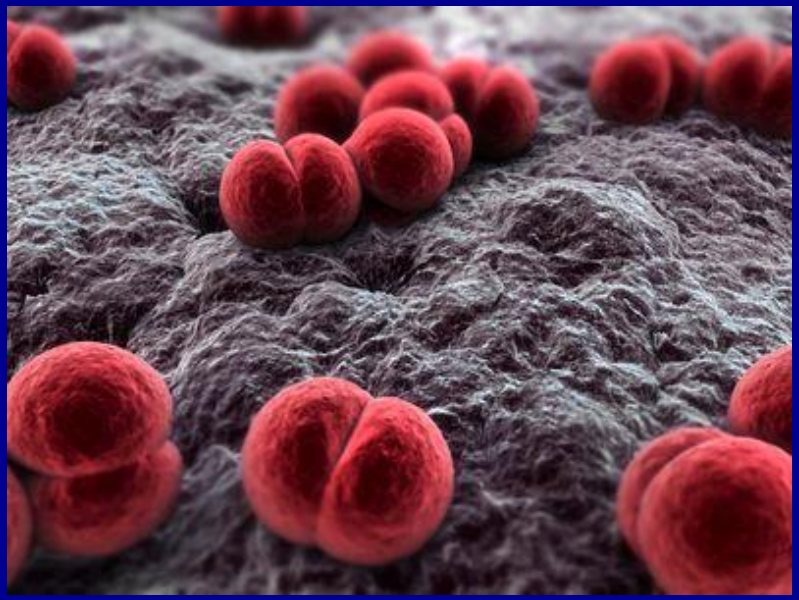
Objectives

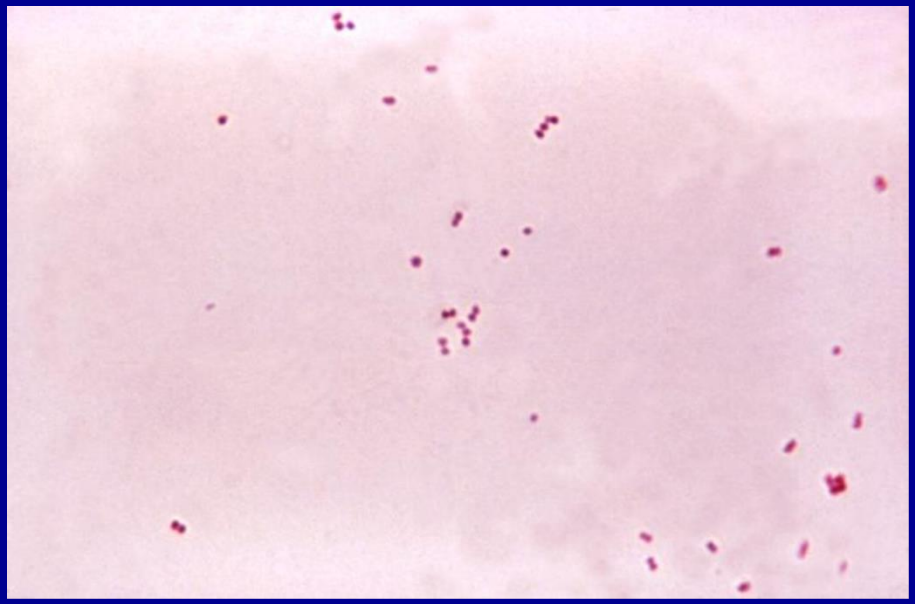
- Describe the epidemiology of meningococcal disease in the United States.
- Describe current CDC vaccine recommendations for meningococcal disease, including recommendations for recently licensed meningococcal-B vaccines.

Outline

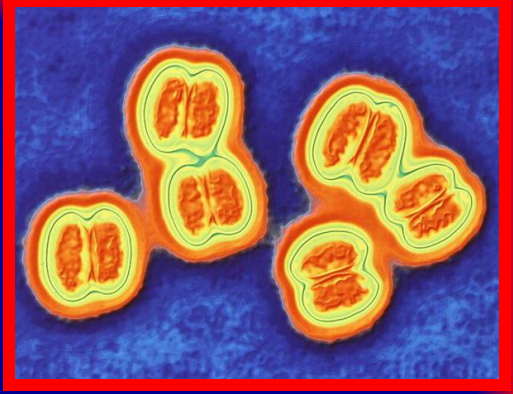
- Meningococcal Epidemiology
- Vaccine recommendations
  - CDC recommended vaccine schedule for A, C, W, Y serogroups
  - Group B vaccines
    - Why they are different
    - Review of safety and immunogenicity of licensed serogroup B meningococcal vaccines
    - ACIP/CDC recommendations for MenB vaccines

Meningococcal Disease and Epidemiology





Neisseria meningitidis



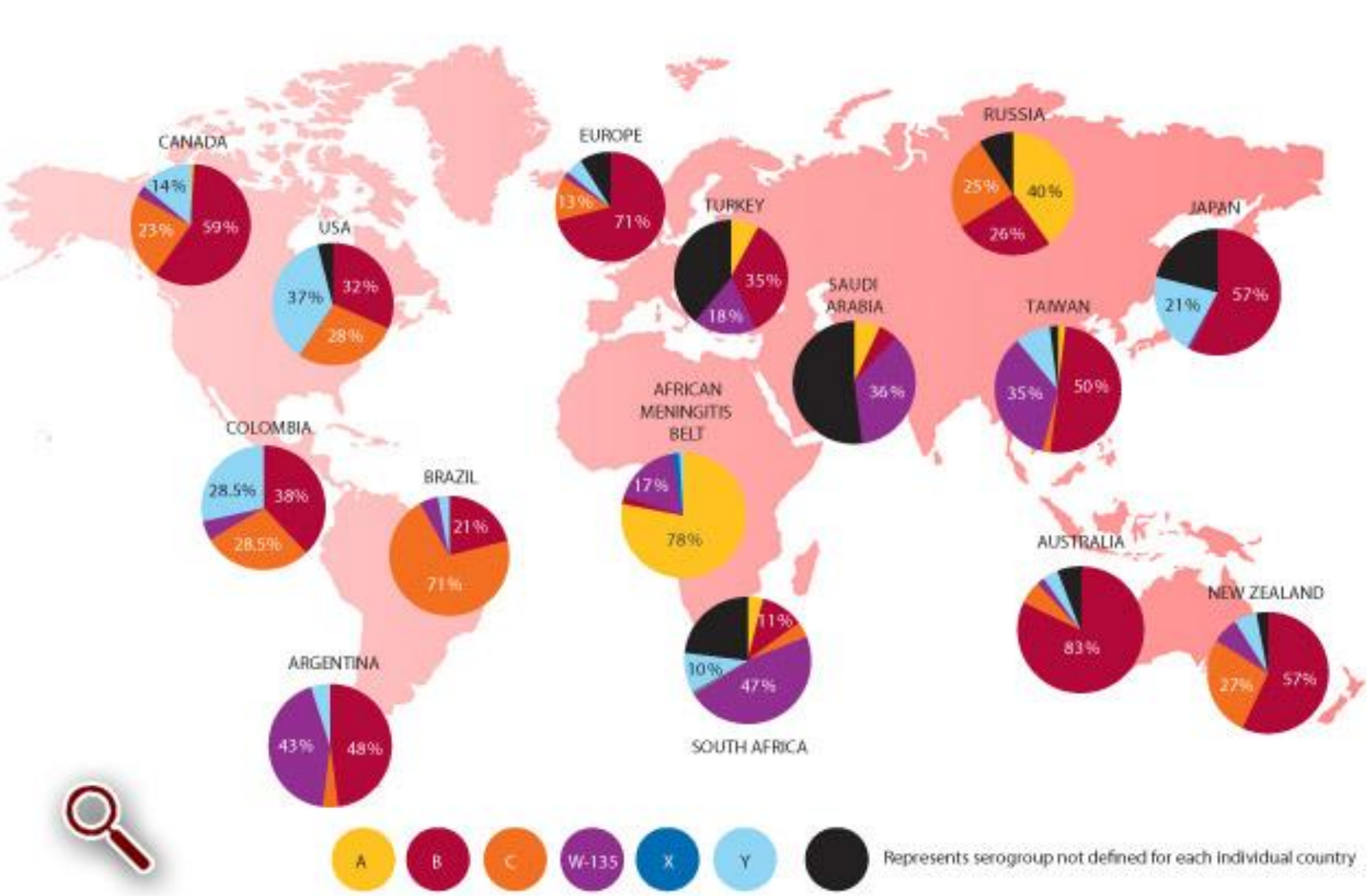
- Gram-negative, aerobic diplococcus polysaccharide capsule
- 5 serogroups cause most disease worldwide – A, B, C, W, and Y
  - B, C, Y cause most disease in the US
- Carried asymptomatically in the nasopharynx of 1 in 10 people
  - Carriage can be as high as 30% in high-risk groups such as adolescents

CDC; Granoff DM, et al. In: Vaccines, 2004:959;
Neal KR, et al. BMJ 2000;320:846

Clinically Significant Meningococcal Serogroups

Serogroup	Characteristics
A	Primarily Sub-Saharan Africa; uncommon in the Americas and Europe
B	Causes ~50% of US infant disease; Causes substantial percentage of cases in US, Australia, and Europe;
C	Causes a substantial percentage of cases in the US, Australia, and Europe; associated with community and school based outbreaks
W-135	Uncommon worldwide; Outbreaks associated with Hajj pilgrimage, Africa
X	Cause of outbreaks in Sub-Saharan Africa; no vaccine available
Y	Causes a substantial percent of cases in the US and other countries in the Americas

Global distribution of meningococcal disease by serogroup, www.meningitisinfo.com



Neisseria meningitidis transmission and epidemiology

- Transmitted person-to-person:
  - via sharing/exchange of respiratory or throat secretions during close or lengthy contact
- Most cases are sporadic
  - <5% being associated with an outbreak
- Household members have 500-800 times the rate of disease as the general population

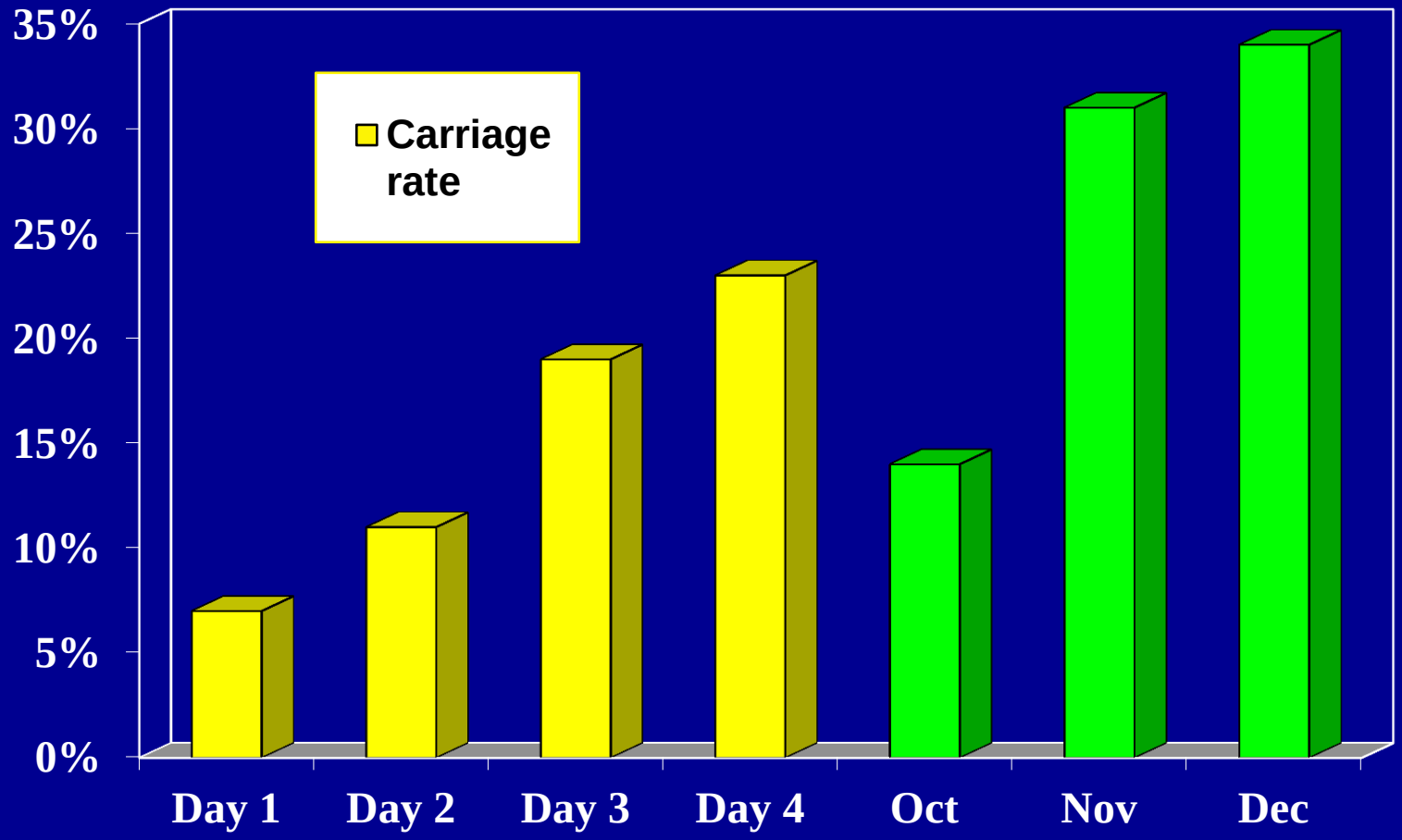
Neisseria meningitidis: Risk factors for invasive disease

- Host factors:
  - Terminal complement pathway deficiency
  - Asplenia
  - Age – infants, adolescents and young adults, adults >65 years at highest risk
- Environmental factors:
  - Contacts:
    - Outbreaks
    - Household or close contact exposure
    - Crowding (Hajj)
    - Travel (meningitis belt in Africa)
  - Concurrent upper respiratory tract infection; smoking (active/passive)

Why increased incidence of meningococcal disease in adolescence and young adulthood?

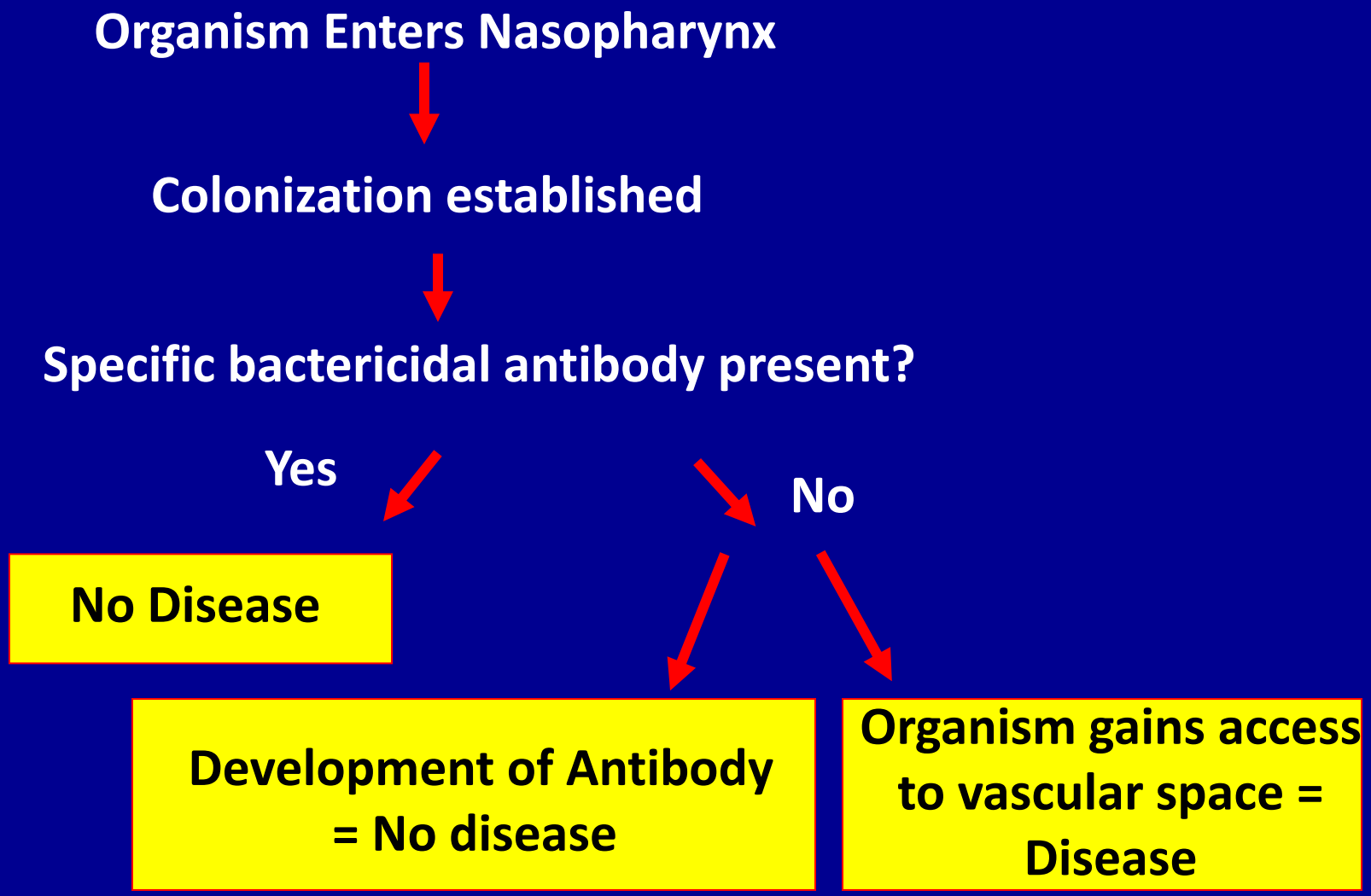
- Increased person to person transmission due to crowded living conditions and behaviors
  - Living in dormitories
  - Going to bars and parties
  - More than one kissing partner
  - Sharing cups, beverages
  - Sports teams
  - Smoking

Carriage Rate Of Meningococcus in College Students



BMJ 2000;320:846–9

Pathophysiology of invasive disease



Meningococcal disease

- With the success of vaccination against *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitidis* are now the leading causes of bacterial meningitis in the U.S
  - ≥50% of meningococcal disease presents as meningitis
  - ~20% presents as sepsis (meningococcemia)
- Also causes:
  - pneumonia, arthritis, and rarely other localized infections
- Case fatality rate for invasive disease: 10-15%

CDC

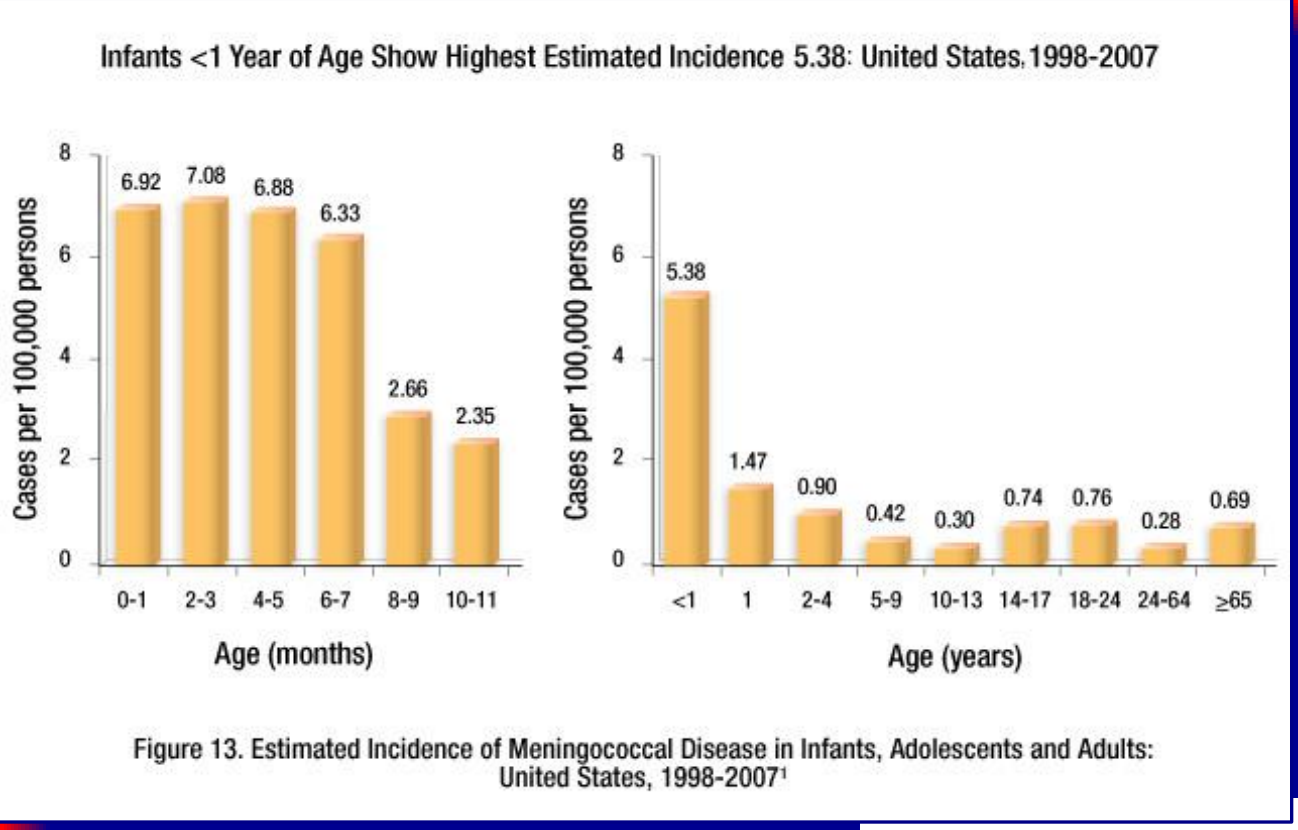


Figure 13. Estimated Incidence of Meningococcal Disease in Infants, Adolescents and Adults: United States, 1998-2007[1]

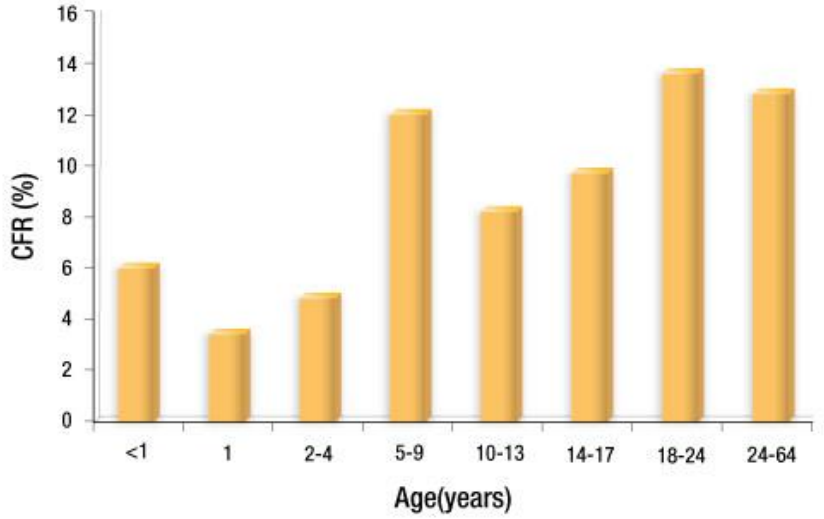


Figure 16. Case-fatality rate for meningococcal disease in the United States by age group, 1998–2007[7]

Clin Infect Dis. 2010;50(2):184-191.;
www.meningitisinfo.com

Estimated Average Annual Cases, Deaths, and Sequelae by Age Group and Serogroup, 2009–2013

	Age Group	Cases[1]	Deaths[2]	Sequelae[3]
Serogroup B	<5 years	74–94	7-14	7-19
	11-24 years	54–67	5-10	5-13
	All ages	203–260	20-39	20-52
Serogroups C & Y	<5 years	34–43	3-6	3-9
	11-24 years	62–77	6-12	6-15
	All ages	307–393	31-59	31-79

- The majority (~80%) of serogroup B cases that occur in 11–24 year olds occur in older adolescents and young adults aged 16–24 years

[1]Range in estimated cases: Low=NNDSS data supplemented with additional serogroup data from ABCs and state health departments, High= NNDSS data supplemented with additional serogroup data from ABCs and state health departments + proportion serogroup B or serogroup C & Y applied to cases with unknown serogroup.

[2]10-15% case fatality ratio

[3]10-20% cases with long term sequelae

McNeil J, CDC, ACIP Presentation, June 2015

Meningococcal disease sequelae, US

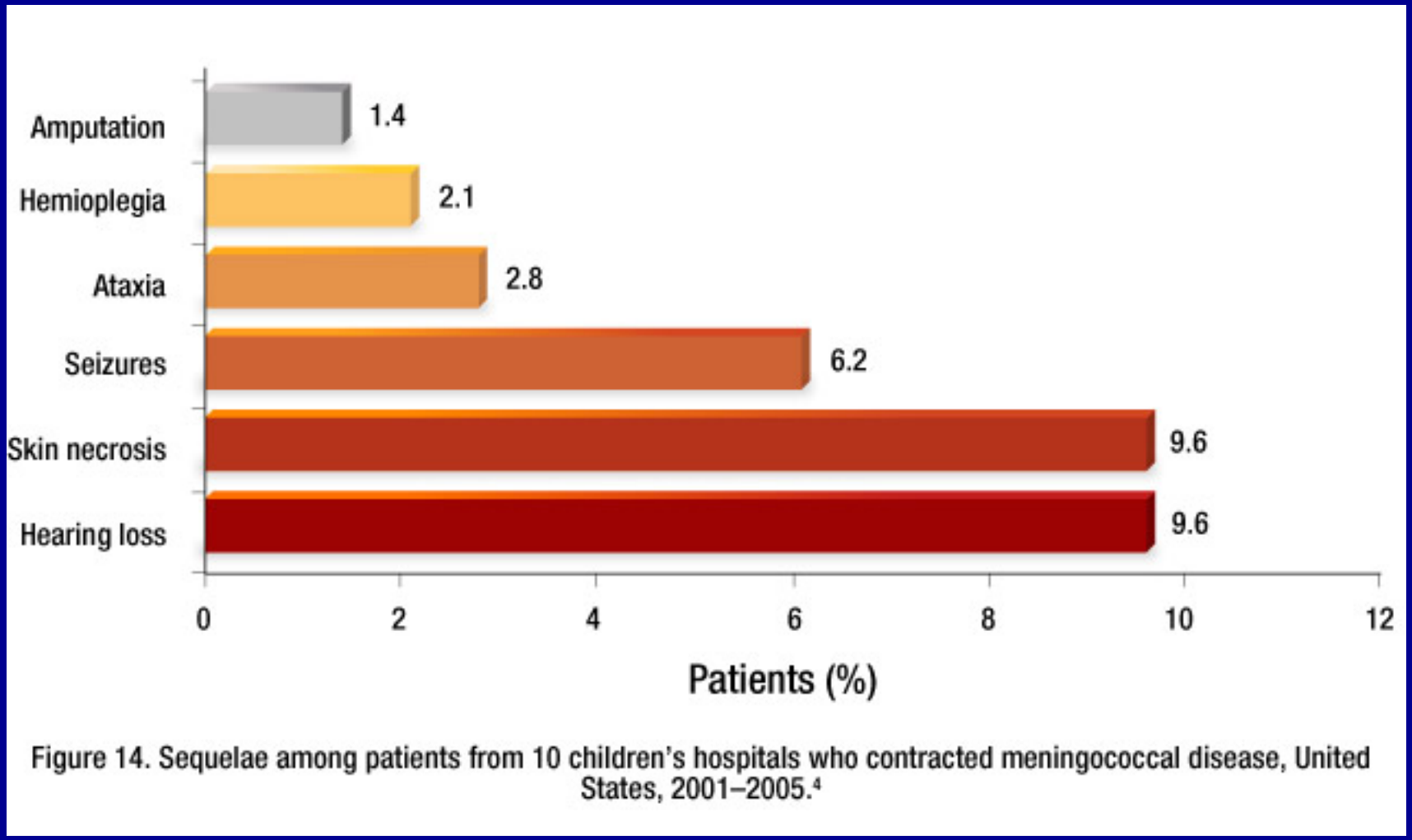
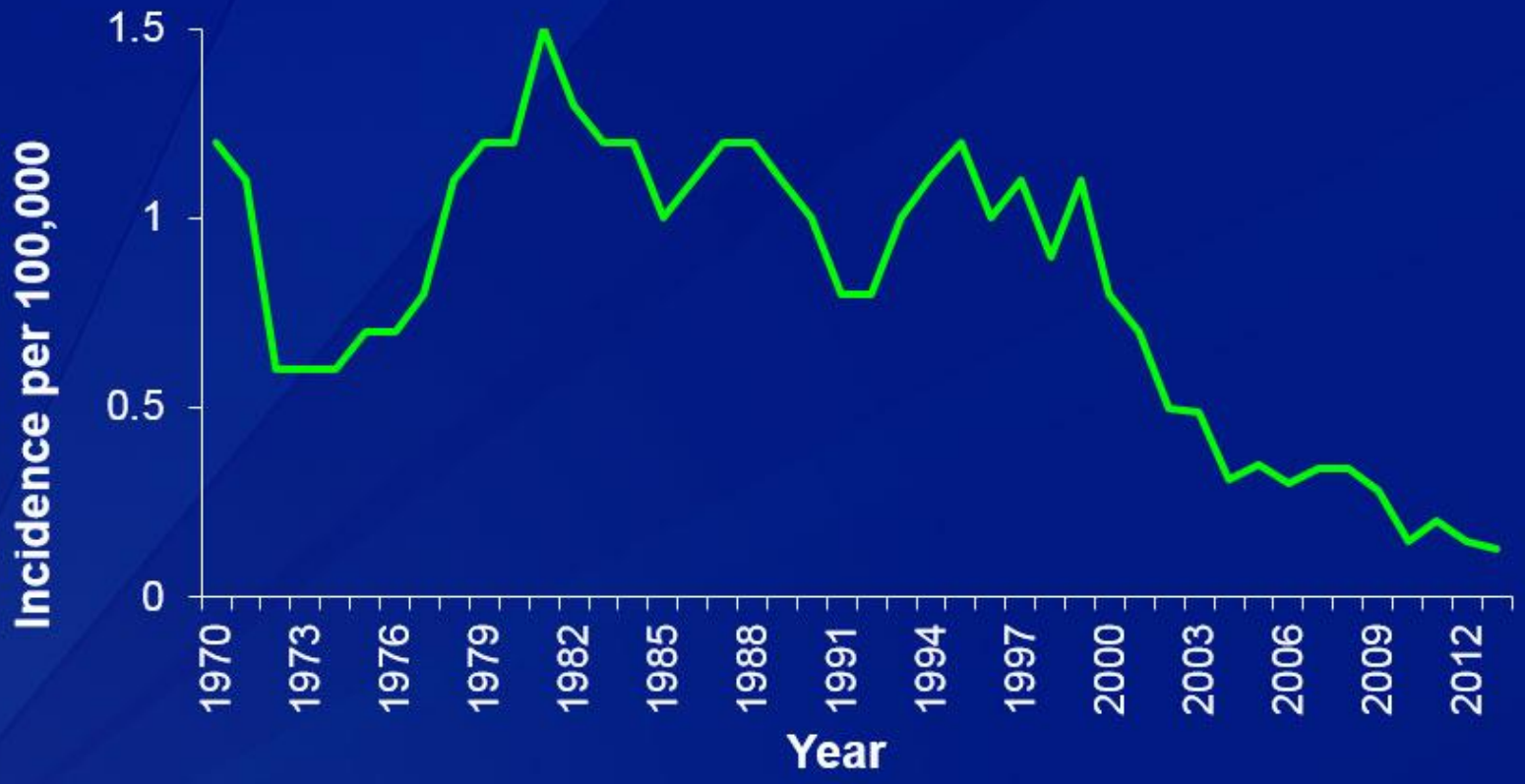


Figure 14. Sequelae among patients from 10 children's hospitals who contracted meningococcal disease, United States, 2001–2005.[4]

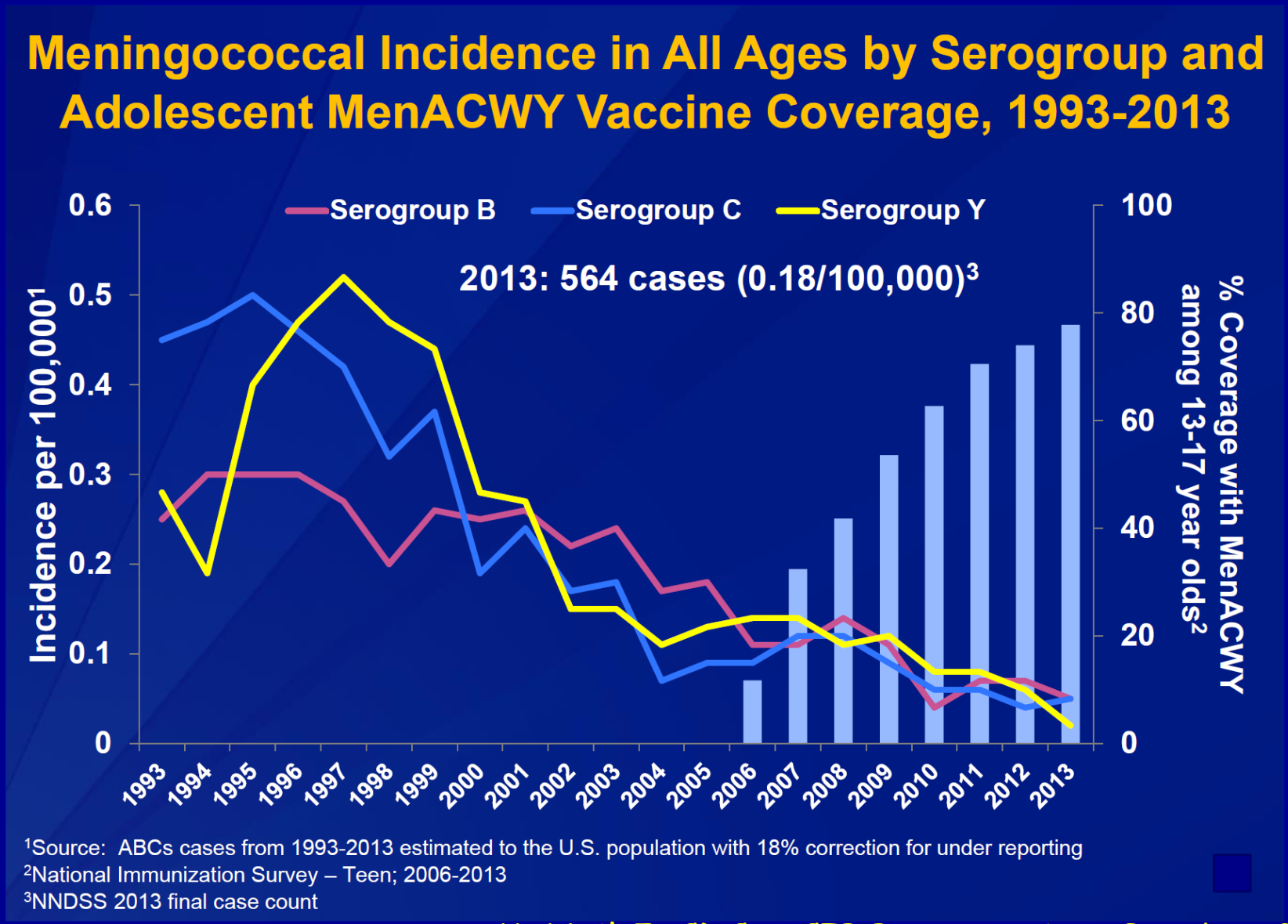
www.meningitisinfo.com; Kaplan SL, Schutze GE, Leake JA, et al. Multicenter surveillance of invasive meningococcal infections in children. *Pediatrics.* 2006;118(4):e979-984

Meningococcal Disease Incidence, United States, 1970-2013



SOURCE: CDC. 1970-1996 National Notifiable Diseases Surveillance System, 1997-2013 Active Bacterial Core surveillance estimated to U.S. population

Meningococcal Incidence and Vaccine Coverage, 1993-2013

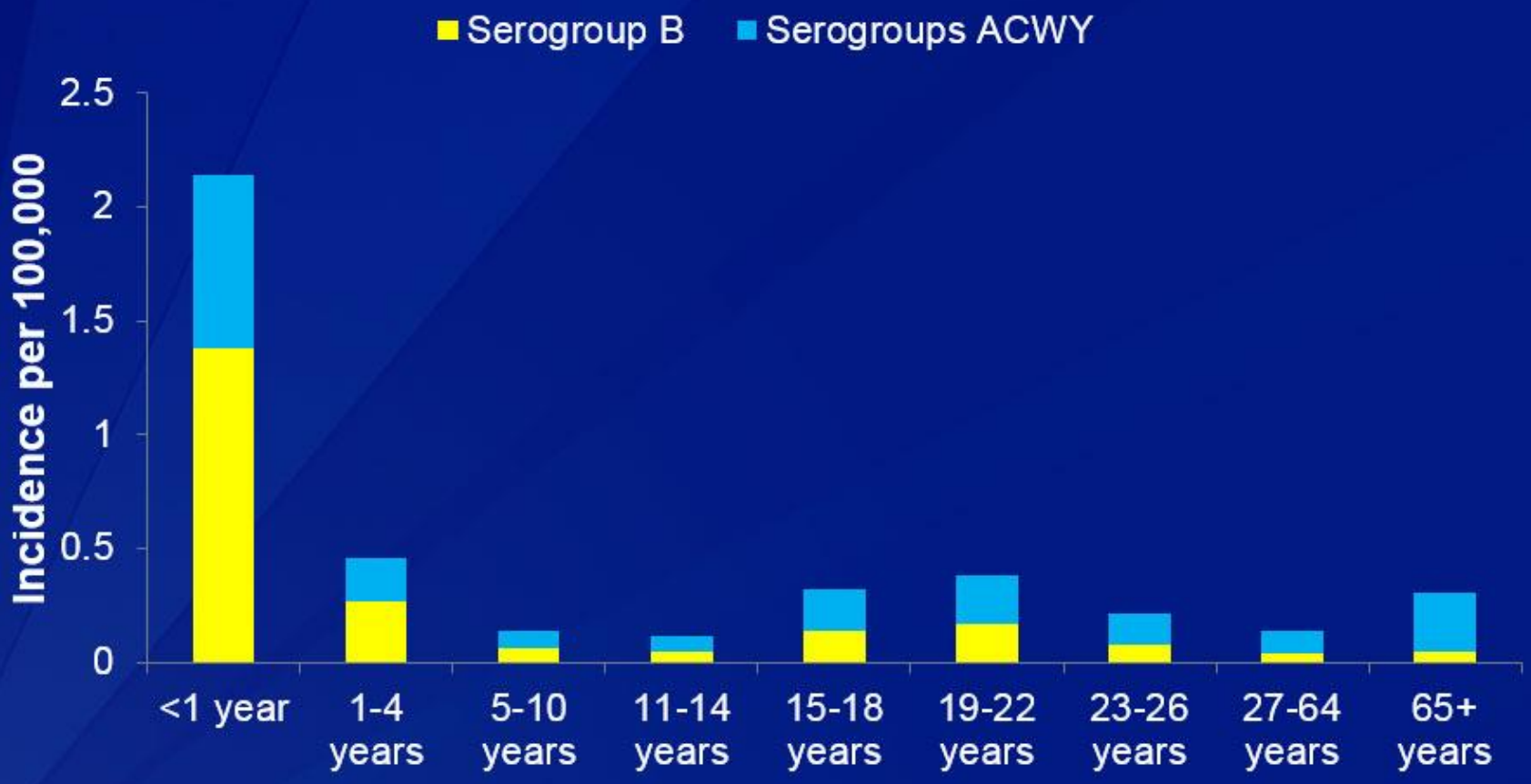


McNeil J, CDC, ACIP Presentation, October 2014

Epidemiology of Serogroup B Meningococcal Disease

- With changing background epidemiology and widespread use of meningococcal ACWY conjugate vaccines (MenACWY) in adolescents and young adults
  - Serogroup B now causes 40% of all meningococcal disease cases in 11-24 year olds
  - Approximately 50-70% of cases of serogroup B disease in 18-23 year olds occur in college students

Meningococcal Incidence by Serogroup and Age-Group, United States, 2005-2013



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

Unknown serogroup (25%) and other serogroups (8%) excluded

DESCRIPTION OF THE OUTBREAK THAT PRECEDED LICENSURE OF MENB VACCINES

Princeton University Outbreak

- March 2013, Princeton student developed serogroup B meningococcal disease while on spring break with her family in another state
- Several weeks later, a prospective student developed serogroup B meningococcal disease—cases were not recognized as connected
- A few weeks later, a second Princeton student was diagnosed with mening B
- New Jersey Health Dept recognized there were 3 cases related to Princeton
  - Widespread education/hygiene campaign began at Princeton on ways to reduce transmission

Addressing the Challenges of Serogroup B Meningococcal Disease Outbreaks on Campuses, NFID, May 2014

Princeton Outbreak

- 4th case was identified and genetic testing showed all isolates identical
  - Outbreak was declared
- End of the school year (2013) approaching
  - Estimated 20,000 people coming to campus for graduation activities and a reunion
  - No new cases at end of semester
- June 2013, 5th case occurred in a Princeton student traveling with other students in Greece

Princeton Outbreak

- July 2013, Princeton and CDC discussed obtaining IND for meningococcal serogroup B vaccine (MenB) to interrupt outbreak
- Fall classes started
  - Hygiene and education campaign continued
  - 3 more cases occurred (#6-8)
- IND approved in late November, just prior to 8th case
  - Vaccine clinics organized—1st one occurred in early Dec; 2nd dose clinics started in Feb
  - By May 14, 2014, 94.9% of the target population had received at least 1 dose of the vaccine and 89.1% had received both doses

Addressing the Challenges of Serogroup B Meningococcal Disease Outbreaks on Campuses, NFID, May 2014

Princeton Outbreak

- March 2014 a Drexel University student died of invasive mening B (same strain) after contact with a group of students from Princeton who traveled to Drexel for a social event (#9)
  - Most of the Princeton students had received 2 doses of vaccine
- Princeton began offering serogroup B mening vaccine to incoming freshman in fall 2014
- No students receiving the 2 dose vaccine developed meningococcal disease

Addressing the Challenges of Serogroup B Meningococcal Disease Outbreaks on Campuses, NFID, May 2014; McNamara LA. Pediatrics 135(5);798-804, 2015

Use of Serogroup B Vaccine

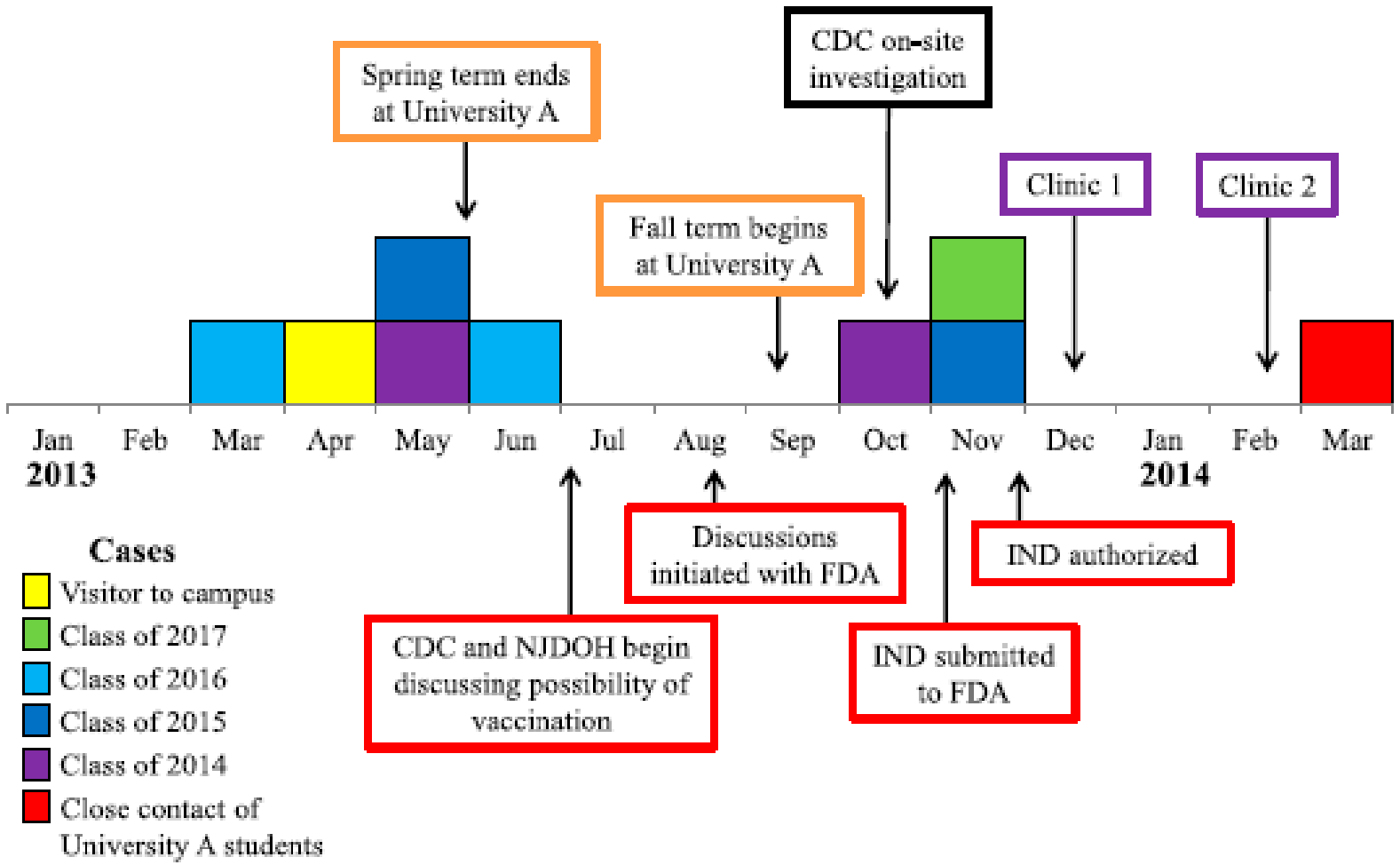


FIGURE 1

Timeline of outbreak cases and response activities.

McNamara LA. Pediatrics 135(5);798-804, 2015

Princeton Outbreak

- No cases in students receiving 1 or more doses of MenB suggests the vaccine was effective in protecting against disease in vaccinees

- 9th Case in the Drexel student after vaccine campaigns suggests
  - Strain was still circulating
  - Carriage not completely eliminated by vaccination

CDC Recommendations for A, C, Y, W Meningococcal Vaccines

Licensed vaccines against A, C, W, Y

Type of vaccine	Name	Serogroups included	Minimum age of approval*
Conjugate	MenACWY-D (Menactra)	A, C, W, Y	9 mos
Conjugate	MenACWY-CRM (Menveo)	A, C, W, Y	2 mos
Conjugate	Hib-MenCY (MenHibrix)	A, C + Hib	6 weeks
Polysaccharide	MPSV4 (Menomune)	A, C, W, Y	2 years

* This is the youngest age for which the vaccine is approved. This age does not necessarily correlate with ACIP/CDC recommendations.

CDC vaccine recommendations for children

- Routine recommendations, quadrivalent conjugated vaccines (MCV4 = MenACWY-D or MenACWY-CRM):
  - One dose at 11-12 years
  - One dose at 16 years of age (booster)

- Special groups – refer to most updated CDC vaccine schedule for full details:
  - HIV-positive: give 2 doses as primary vaccine
  - Anatomic or functional asplenia
  - Children with persistent complement component deficiency includes:
    - persons with inherited or chronic deficiencies in C3, C5-9, properidin, factor D, factor H, or taking eculizumab (Soliriis®
  - Travel to country where meningococcal disease is hyperendemic or epidemic (i.e. African meningitis belt or Hajj)
  - Community outbreaks with a vaccine serogroup

CDC vaccine recs for adults

High-risk adult groups:

- Complement component deficiency (same as kids)
- Functional or anatomic asplenia
- Profession with routine exposure to *Neisseria meningitidis*
- Traveling or residing in countries in which the disease is common
- At increased risk for a serogroup A, C, W or Y meningococcal disease outbreak
- First-year college student living in a residence hall
- Military recruits

CDC vaccine recs for adults

Vaccines:

- MCV4 should be used through age 55
- Only the polysaccharide vaccine (MPSV4, Menomune) is approved for adults ≥65 yrs
- Adults at increased risk because of complement component deficiencies and persons with functional or anatomic asplenia should receive a two-dose primary series 2 months apart and then get a booster dose every 5 years.

Serogroup B Meningococcal Vaccines

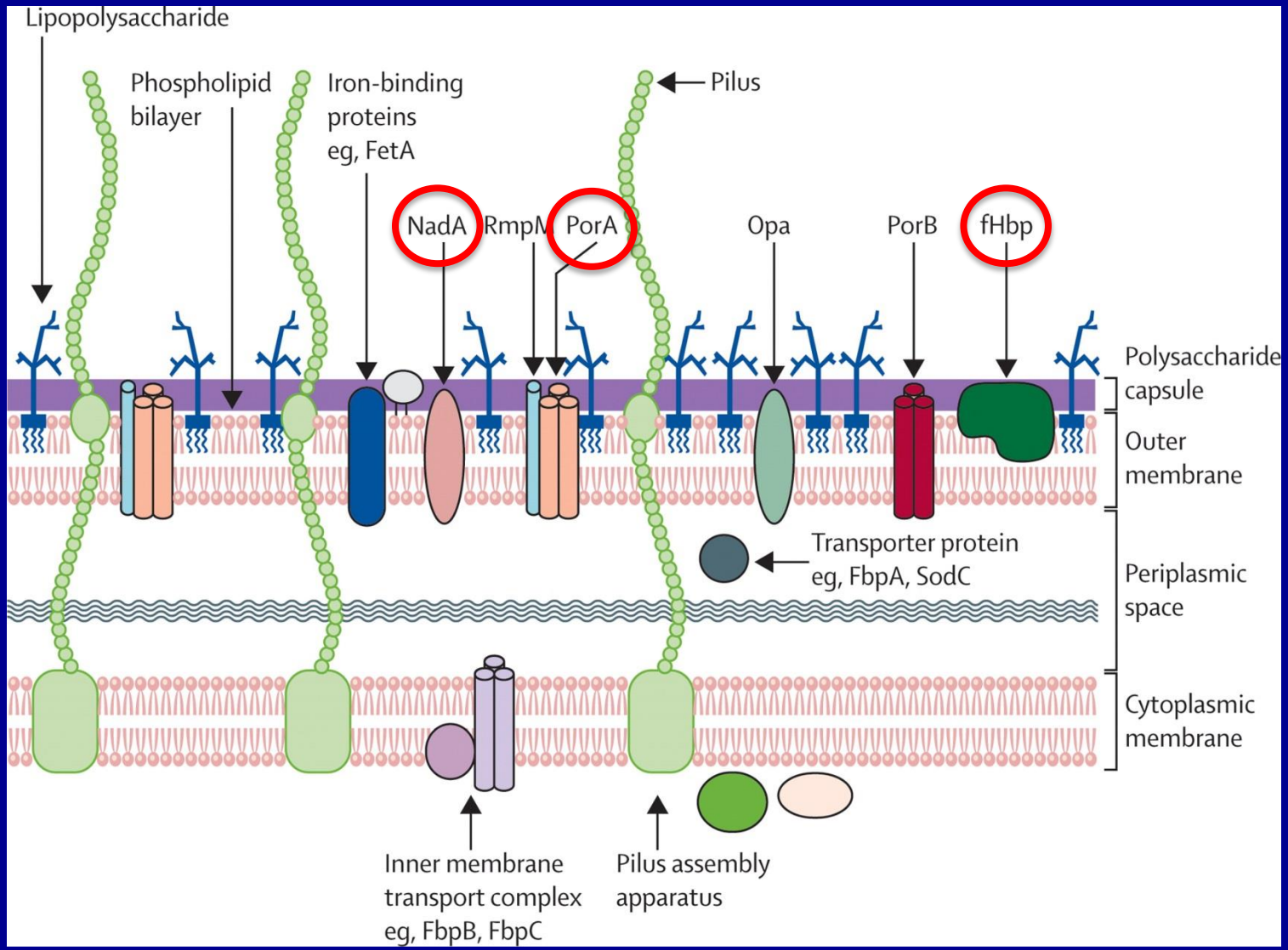
Challenges with Meningococcal Serogroup B Vaccines

- Polysialic acid is present in the polysaccharide capsule of Serogroup B
  - Antigenically similar to human neuronal tissue
  - Seen as a “self” antigen
  - Poorly immunogenic
  - Potential to induce autoimmune response
- Current vaccine development focuses on
  - Use of subcapsular antigens which are
    - Surface exposed
    - Conserved
    - Induce bactericidal activity

Outer Membrane Antigens

- Factor H Binding Proteins (FHbp)
  - Allows bacteria to evade complement mediated lysis
- NadA
  - Allows bacteria to adhere and invade epithelial cells
- Neisseria Heparin Binding Antigen (NHBA)
  - Promotes bacterial survival in the blood
- Outer membrane vesicles (OMV)
  - Buds from the cell membrane
  - Important in protein trafficking and secretion
  - Porin protein, PorA, elicits strong serum bactericidal antibody in children and adults

Figure 1



The Lancet Infectious Diseases 2010 10, 112-124DOI: (10.1016/S1473-3099(09)70324-X)

Meningococcal B Vaccines Approved in the U.S.

- MenB-FHbp (Trumenba, Pfizer) for ages 10-25 years
  - 3 dose series at 0, 2, 6 months
  - Component: factor H binding proteins, subfamily A/v2,3 and B/v1 (bivalent)
  - Licensed in US October 29, 2014

- MenB-4C (Bexsero, Novartis) for ages 10-25 years
  - 2 dose series at 0, ≥1 month
  - 4 component vaccine (-4C): fHbp subfamily B/v1, NhbA, NadA, PorA1.4
  - Licensed in US January 23, 2015
  - Licensed in >37 countries for persons ≥2 mos of age

Safety

Licensed Meningococcal B Vaccines*

	MenB-4C (Bexsero)	MenB-FHbp (Trumenba)
Indicated ages	10-25 years	10-25 years
Schedule	2 doses; 0, 1-6 mo	3 doses; 0, 2, 6 mo apart
Most Common Reported Adverse Reactions after dose 1	Injection site pain 90% Erythema 50% Induration 32% Fever >38°C 1% Headache 33% Fatigue 37% Muscle Pain 49% Arthralgia 13%	Injection site pain 93% Erythema 20% Induration 22% Fever >38°C 6% Headache 55% Fatigue 62% Chills 29% Muscle Pain 42% Arthralgia 22%

*Package insert information for MenB-4C and MenB-FHbp, 2015

Safety Data Outside Clinical Trials

- MenB-4C
  - 17,000 persons vaccinated under IND for University outbreaks
  - 40,000 vaccinated in Quebec in response to outbreak (2 mo-20 years of age)
  - >37 countries have licensed the vaccine
- MenB-FHBP
  - Safety data collected during recent outbreak responses at Providence college, University of Oregon

Safety Monitoring

- **Vaccine Adverse Event Reporting System (VAERS)**
  - Few reports received as of 10/05/2015
    - MenB-FHbp n=65
    - MenB-4C n=21
  - No safety signals detected to date
- **Vaccine Safety Datalink (VSD)**
  - Few doses administered in the VSD population to date
  - Safety assessment can begin when a larger number of doses have accumulated

Rubin L, ACIP meeting presentation, Oct 21, 2015

MenB-4C: Evidence of Harms
Post Vaccination Campaign SAEs Data

- **59,091 participants received at least one dose of MenB-4C**
  - 60 SAEs were reported
    - 3 SAEs* determined to be related to the vaccine
    - 1 death** reported - unrelated to vaccine

* Rhabdomyolysis, anaphylaxis and fever
**Cause of death was drowning

Folaranmi T, ACIP Presentation, June 2015

MenB-FHbp: Evidence of Harms

- **11,338 participants received at least one dose of MenB-FHbp**
  - 190 SAEs were reported in the vaccine group
    - 7 SAEs* determined to be related to vaccine
    - 1 death** reported - unrelated to vaccine

* Pyrexia, vomiting, vertigo, chills, headache, anaphylaxis and neutropenia
**Death due to road accident

Folaranmi T, ACIP Presentation, June 2015

Licensed MenB Vaccines-Safety

- Majority of local and systemic reactions are mild to moderate and transient
  - Pain at the injection site is the most common adverse event reported
  - Local reactions more common in adolescents than other vaccines used in this age group
- SAEs rare and similar to other vaccines
  - Anaphylaxis reported in 2 cases (1 each MenB-4C and 1 MenB-FHbp)
  - Low disease burden should be considered
- No concerning pattern of AEs yet identified

MacNeil J, ACIP meeting presentation, June 2015

Immunogenicity

Immunogenicity

- Studies starting in the late 1960s showing protection in infants from maternal antibody and then efficacy studies from the polysaccharide vaccine (MPSV4) have given us immune correlates of protection

- For the FDA licensing endpoints, immunogenicity is measured by serum bactericidal antibodies as an immune correlate of protection against a small number of serogroup B strains
  - Use a functional assay called serum bactericidal activity

Immunogenicity

- Immunogenicity assessed by the
  - Proportion of subjects who achieved ≥4 fold increase in hSBA titer for each strain tested and
    - hSBA indicates that human serum was used in the assay as a source of the complement
  - Proportion of subjects who achieved a titer ≥LLOQ (lower limit of quantitation) of the assay for all strains (composite response)

Short-term immunogenicity

- MenB-4C (Bexsero)
  - At 1 mo following vaccination, composite response to 3 strains tested:
    - 90-94% of Chilean adolescents
    - 88% of university students in the UK (95% CI 82-93%)
    - 63% of adolescents in Australia and Canada
- MenB-FHbp (Trumenba)
  - At 1 mo following vaccination, composite response to 4 strains tested:
    - 81-83% of adolescents in the US
    - Similar results in European adolescents

Patel M, Presented ACIP Meeting, October 2014; Folaranmi T, ACIP Presentation, June 2015; MMWR Oct 23, 2015

Antibody Persistence Data

- MenB-4C
  - 11-mo follow-up (UK university students)
    - 66% had protective antibody after 2 doses (95% CI 58-72%)
  - 18-24 mo follow-up (Chilean adolescents)
    - 77%-94% had protective AB against the 3 antigens tested (fHBP, NAD, OMV) after 2 doses
- MenB-FHbp
  - 48 mo follow-up
    - >50% of vaccinees have hSBA and titers >LLOQ against 3 reference strains amongs adolescents in Australia, Spain and Poland

Folaranmi T, ACIP Presentation, June 2015 ; Santolaya M. Human Vaccines and Immunotherapeutics, 9(11):2304-2310, 2013; MMWR Octover 23, 2015

Concomitant Vaccine Administration

- 4MenB-4C (Bexsero)
  - Studies with concomitant vaccines in infants and children outside the US – no clinically significant interaction
  - No adolescent data
- MenB-FHbp (Trumenba)
  - 3 adolescent trials evaluating concomitant administration with HPV-4, MCV, Tdap, IPV
    - No immunologic interference with HPV 6,11,16, MenACWY, Tdap, IPV antigens observed
    - Possible decrease in HPV18
  - Reassuring for non-inferiority

CDC, MMWR Oct 23, 2015; Bhuyan P, ID Week; October 8–12, 2014; Philadelphia, PA; Vesikari T, Presented at 32nd ESPID, 2014; Dublin, Ireland.

CDC, MMWR October 23, 2015

Potential cases and deaths prevented by different strategies for MenB vaccination of adolescents and young adults by age – United States

Age at MenB series	Cases Prevented	Deaths Prevented	NNV to prevent case	NNV to prevent death
11 yrs	15	2	203,000	1,512,000
16 yrs	28	5	107,000	788,000
18 yrs	29	5	102,000	638,000
College student	9	1	368,000	2,297,000

Abbreviations: MenB = meningococcal B vaccine; NNV = number needed to vaccinate; QALY = quality-adjusted life years

Sources: Unpublished data, ACIP meeting June 2015. Key model assumptions were presented at the June 2015 ACIP meeting. Methods described in Shepard CW, Ortega-Sanchez IR, Scott RD 2nd, Rosenstein NE. Cost-effectiveness of conjugate meningococcal vaccination strategies in the United States. Pediatrics 2005;115:1220-32.

What we know

- The vaccines appear safe and immunogenic.
- There is some effectiveness data from outbreak situations (Canada, Princeton)
- The vaccines received accelerated approval
  - Approval based on safety, immunogenicity
  - Serum bactericidal activity does have a correlate of protection
    - The serum bactericidal antibody (SBA) for licensure was done against representative strains of Serogroup B *Neisseria meningitides*

Rubin L, ACIP meeting presentation, Oct 21, 2015; CDC/ACIP

What is still unknown

- We do not know how effective the vaccines will be against all the circulating strains
  - Not all strains have the proteins in the vaccines
  - Variable expression of the proteins
  - Will they mutate?
- We do not know the duration of antibody persistence
  - Current data suggests it is short-term
- We do not know the impact on carriage
- We do not know the potential impact on circulating strains
- There are no studies comparing the two vaccines

Rubin L, ACIP meeting presentation, Oct 21, 2015; CDC/ACIP

ACIP RECOMMENDATIONS FOR MENB VACCINES

ACIP recommendations for serogroup B meningococcal vaccines

- 2 Serogroup B meningococcal vaccines are licensed for persons 10-25 years of age
- Given the safety, immunogenicity and effectiveness data but also knowing the limitations of the data, recommendations are category B, permissive recommendations
  - Category A = for all persons in an age- or risk-factor gorup
  - Category B = for individual clinical decision-making

CDC/ACIP

CDC recs on MenB vaccines

Clinical discretion:

- "Young adults aged 16 through 23 years (preferred age range is 16 through 18 years) may be vaccinated with either a 2-dose series of Bexsero or a 3-dose series of Trumenba vaccine to provide short-term protection against most strains of serogroup B meningococcal disease. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses."

CDC recs on MenB vaccines

For high-risk groups:

- "Persons 10 years or older who have not received a complete series. Administer a 2-dose series of Bexsero, at least 1 month apart. Or a 3-dose series of Trumenba, with the second dose at least 2 months after the first and the third dose at least 6 months after the first. The two MenB vaccines are not interchangeable; the same vaccine product must be used for all doses."

QUESTIONS?