"Update on Meningococcal Disease and the Southern California Outbreak among Men Who Have Sex with Men".

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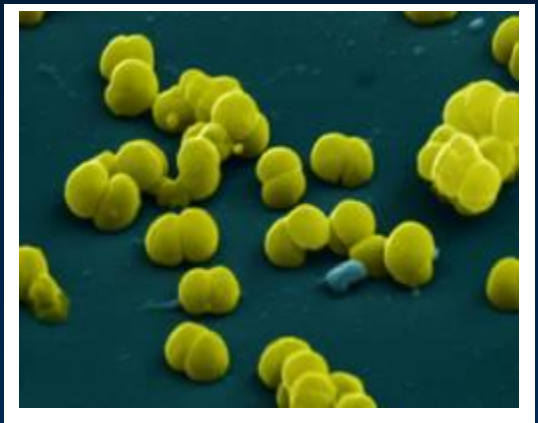
Patient Case #1

- 18 y/o healthy male with ? untreated LTBI, vaccines unknown. 1 day PTA with abrupt fever 102.3, neck pain, pulsatile H/A, followed several hours later by low back pain, abdominal pain, N/V. Also noted to have photophobia and dizziness, as well as “red spots on face”. Brought to ED by girlfriend, where described as alert. WBC 19.6 with 91% polys, crp 16.8 mg/dL, and CSF with 134 wbc, 97% polys, glucose 62, protein 135, gram stain GPC. Rec’d IVF, morphine and abx. Admitted to floor where he is obtunded. Transferred to PICU. Culture + for *N. meningitis* group Z. Rx’d for 7 days and did well.

Neisseria meningitidis



- Gram-negative aerobic diplococcus with polysaccharide capsule
- Typically carried asymptomatically in the nasopharynx
- Transmitted via aerosol, secretions, person-to-person contact
- May penetrate the mucosa to the bloodstream, leading to systemic meningococcal disease
- In nonepidemic periods, ~10% of healthy individuals are colonized
- Up to 34% of college freshmen are colonized

Granoff DM, et al. In: *Vaccines*. 2004: 959; Neal KR, et al. *BMJ.* 2000;320:846.
Photo courtesy of Eye of Science/Photo Researchers, Inc.

Clinically Significant *N. meningitidis* Serogroups

Serogroup	Characteristics
A	• Leading cause of epidemic meningitis worldwide • Most prevalent serogroup in Africa and China • Rare in Europe and the Americas
B	• Major cause of endemic disease in Europe and the Americas • Now vaccine available
C	• Major cause of endemic disease in Europe, North America • Multiple outbreaks in schools/community
Y	• Associated with pneumonia, particularly in the elderly • Increasing problem in the United States
W-135	• Small percentage of infections worldwide • Recent outbreaks associated with Hajj pilgrims

Transmission

- Meningococcal disease is spread from person to person. The bacteria are spread by exchanging respiratory and throat secretions during close or lengthy contact, especially if living in the same household.
- Humans are the only host.
- Asymptomatic nasopharyngeal carriers who are not a close contact of a patient with meningococcal disease do not require prophylaxis.

Most Common Clinical Presentations of Meningococcal Disease

Meningococcemia

- Rash
- Vascular damage
- Disseminated intravascular coagulation
- Multi-organ failure
- Shock
- Death can occur within 24 hours

~5% to 20% of cases

Up to 40% fatality rate

Meningitis

- Fever and headache (flu-like symptoms)
- Stiff neck
- Nausea
- Altered mental status
- Seizures

~50% of cases

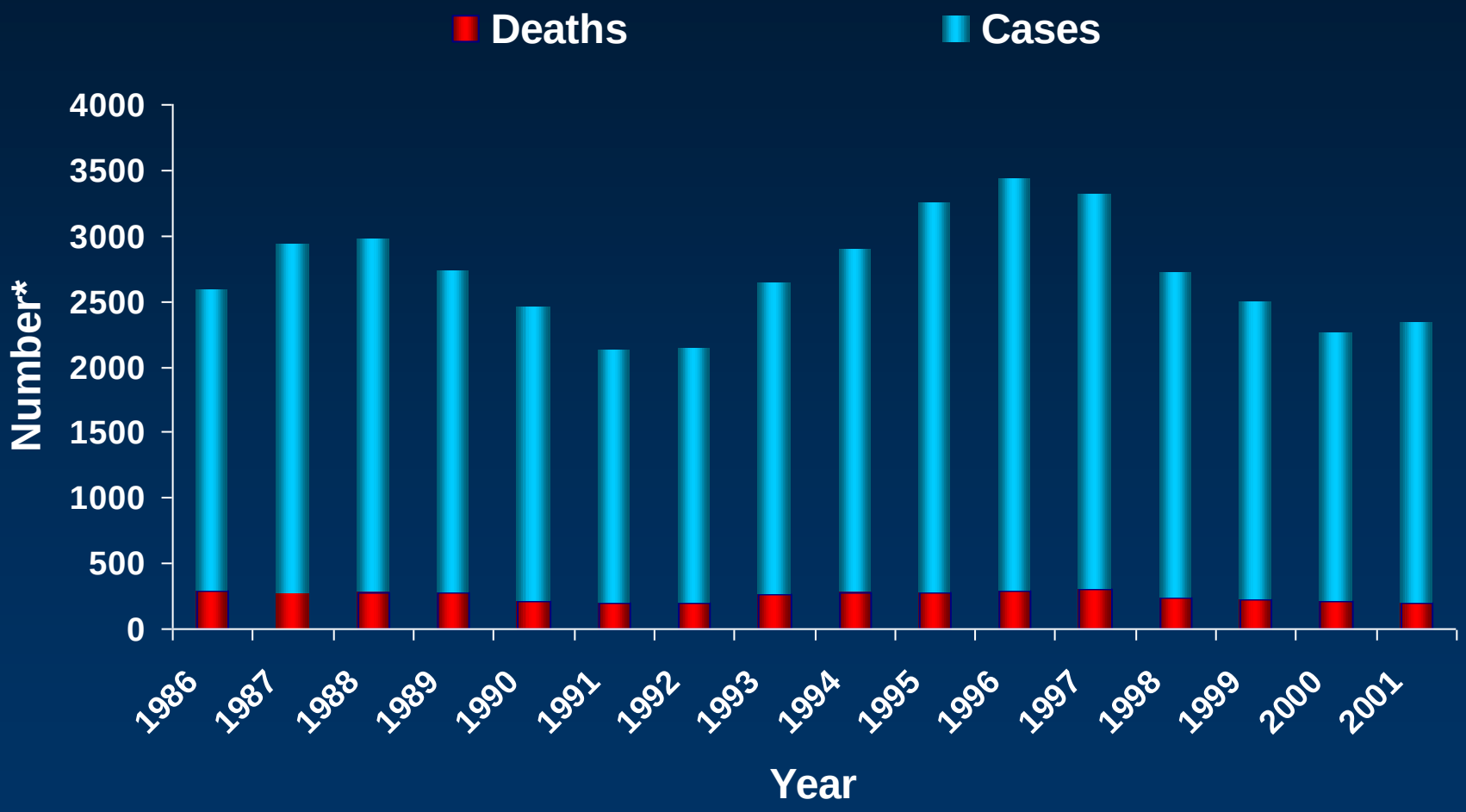
3%–10% fatality rate

Rosenstein NE, et al. *N Engl J Med.* 2001;344:1378.

Diagnosis

- Culture remains the gold standard laboratory test with virtually 100% specificity.
- However, meningococcus has fastidious growth requirements and culture has poor sensitivity in specimens that are not handled properly or who have received antibiotics.
- PCR is a rapid test and has high sensitivity and specificity.
- PCR assays that can detect serogroup are crucial for identifying potential outbreaks and determining appropriate public health responses, such as chemoprophylaxis.
- http://www.cdc.gov/meningococcal/laboratory/pcr-guidance-mening-hflu.html June 2016

Meningococcal Disease Is Endemic and Cyclical in the United States



*All age groups

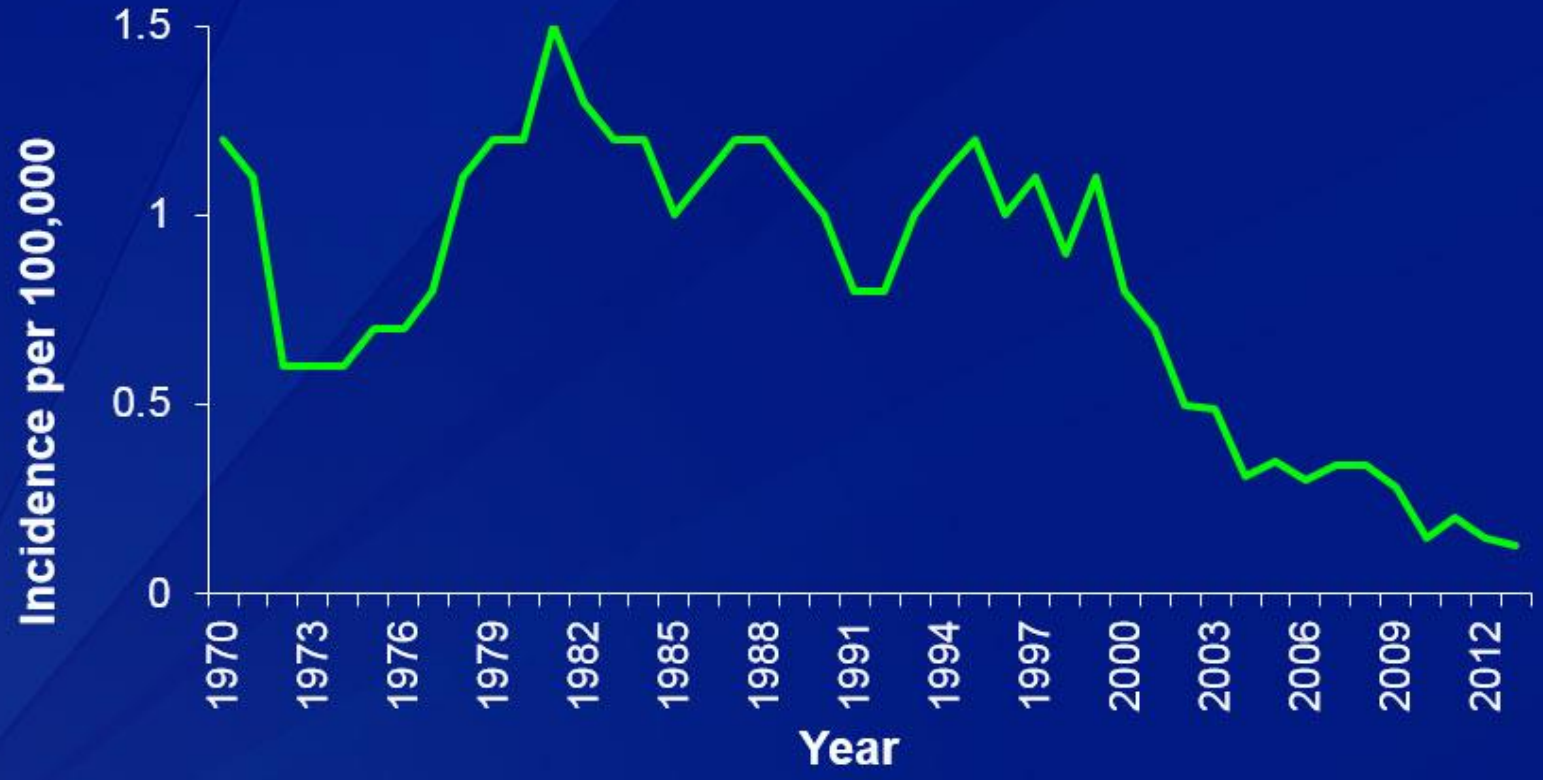
CDC. *MMWR Morb Mortal Wkly Rep*. 2004;51:1; CDC. *MMWR Morb Mortal Wkly Rep*. 1997;45:1; CDC. *National Vital Statistics Reports.* 2003;52:1.

Neisseria meningitidis Epidemiology

- Incidence falling since 2000 (before licensure of MCV4)
- Incidence of all serogroups falling, including serogroup B which is not in MCV4
- 426 cases reported in 2014 in US

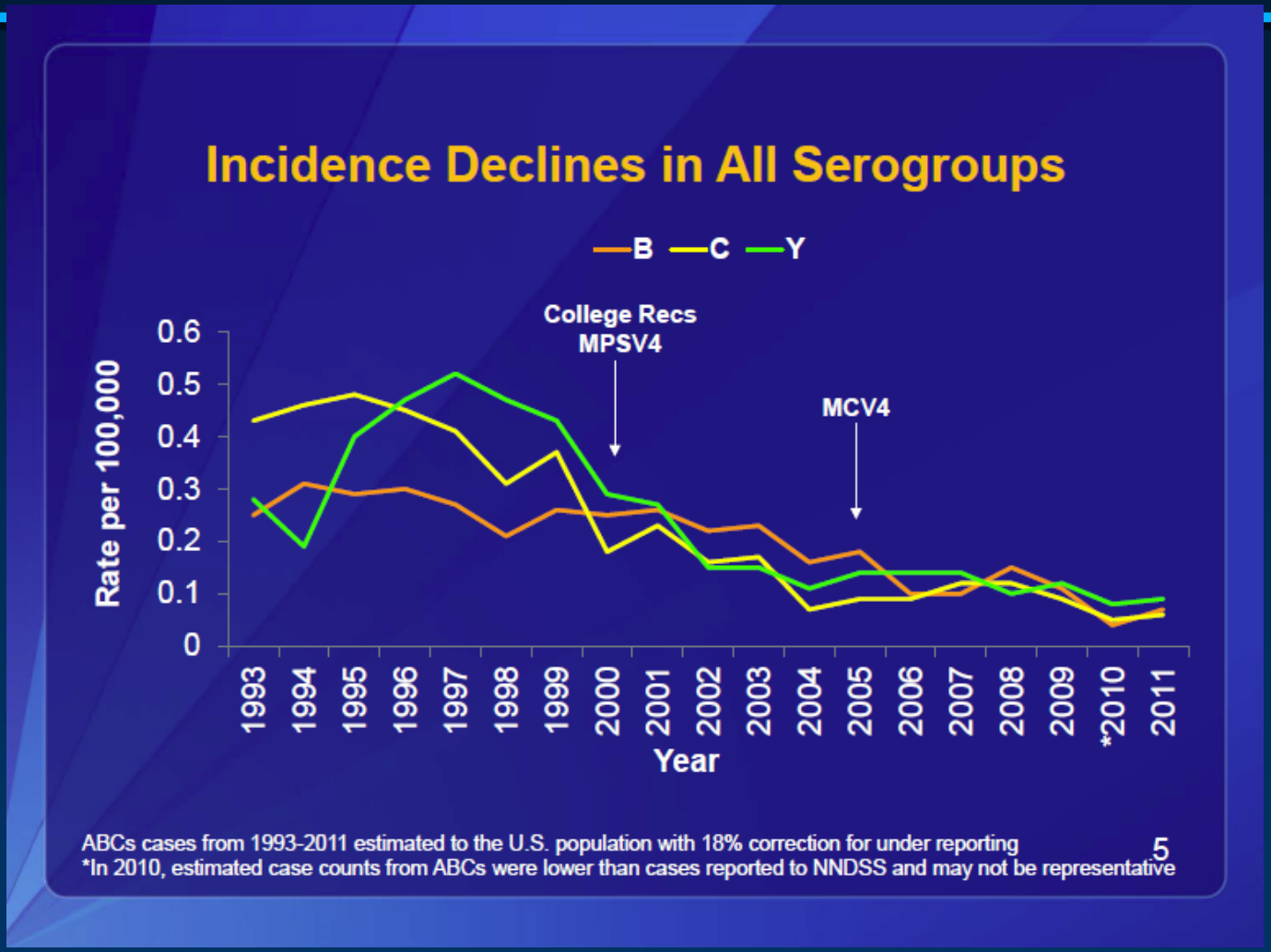
CDC data

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

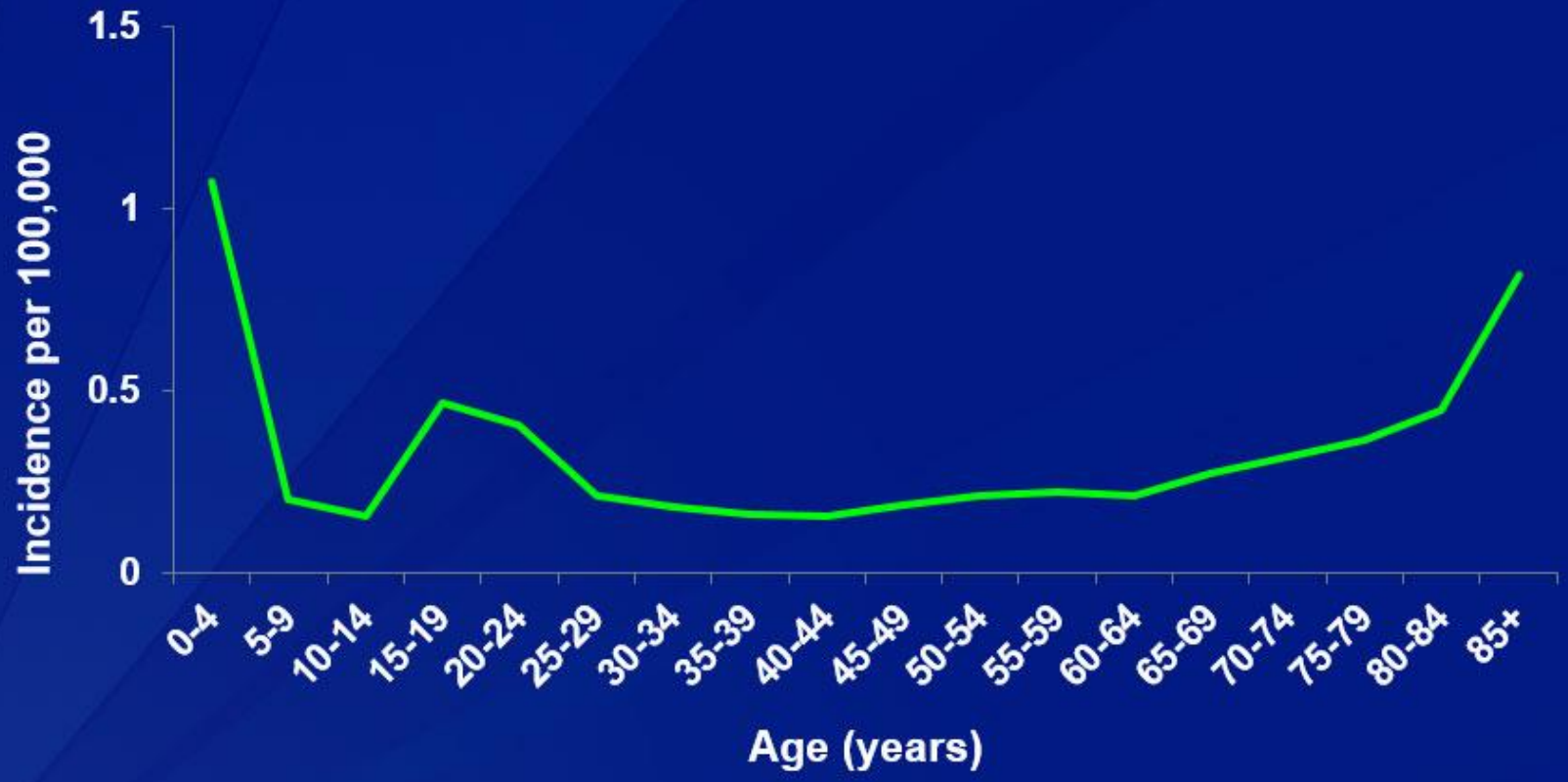
Meningococcal Disease – CDC data



Rates of Disease

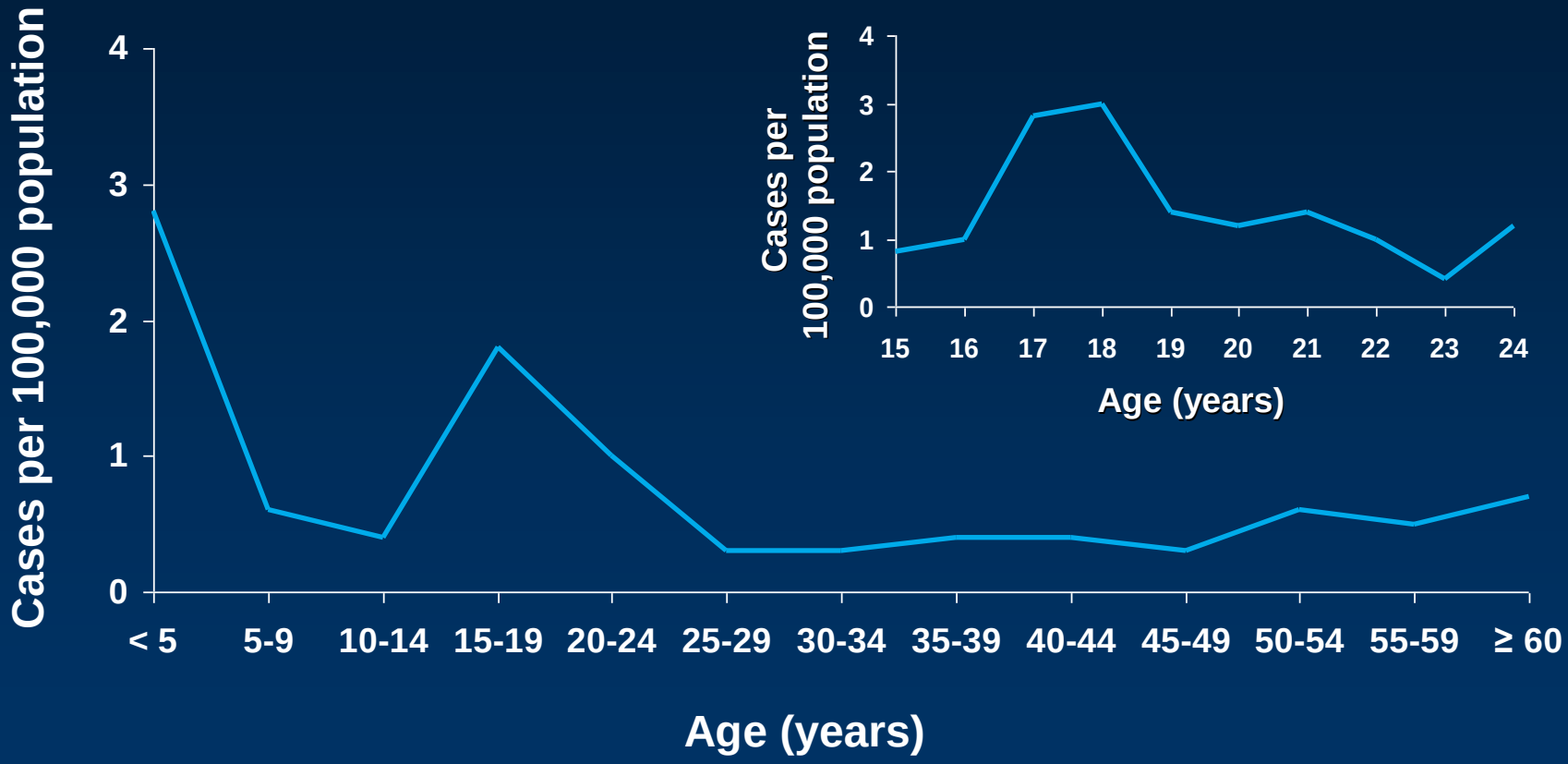
- Rates of disease are highest in children younger than 1 year old.
- This is followed by a second peak in adolescence.
- Among adolescents and young adults, those 16 through 23 years old have the highest rates of meningococcal disease.

Meningococcal Disease Incidence by Age, United States, 2005-2013



SOURCE: CDC. National Notifiable Diseases Surveillance System

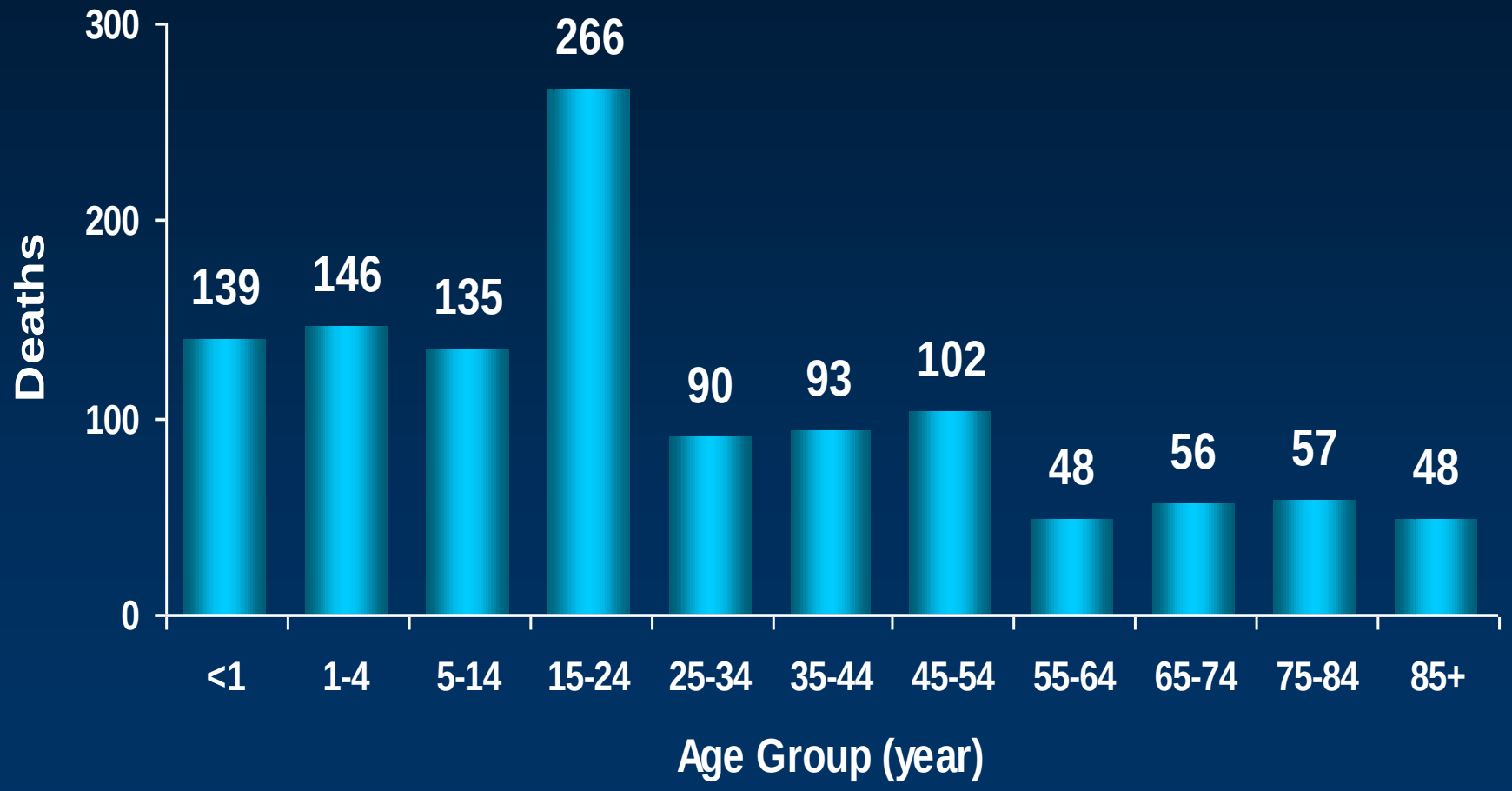
A Peak of Meningococcal Disease Incidence Occurs in 15- to 19-Year-Olds*



*Average annual incidence rate by age in Maryland, 1992–1999

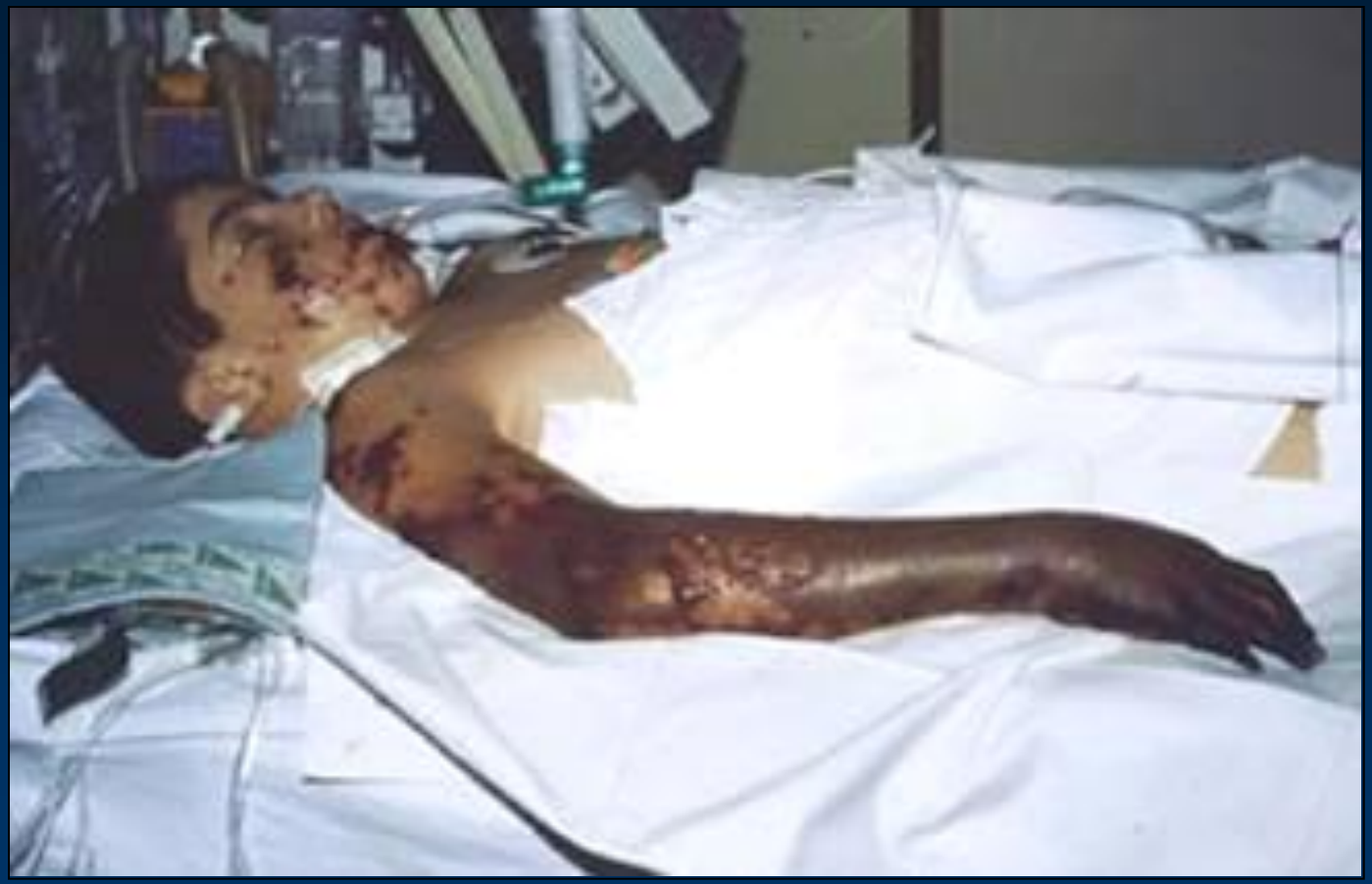
Harrison LH, et al. *JAMA.* 2001;286:694.

Age-Specific Fatalities From Meningococcal Disease in the US, 1997–2001



CDC. *National Vital Statistics Reports.* 2003;52:30.

Severe Late-Stage Meningococcal Infection in a 15-Year-Old Boy

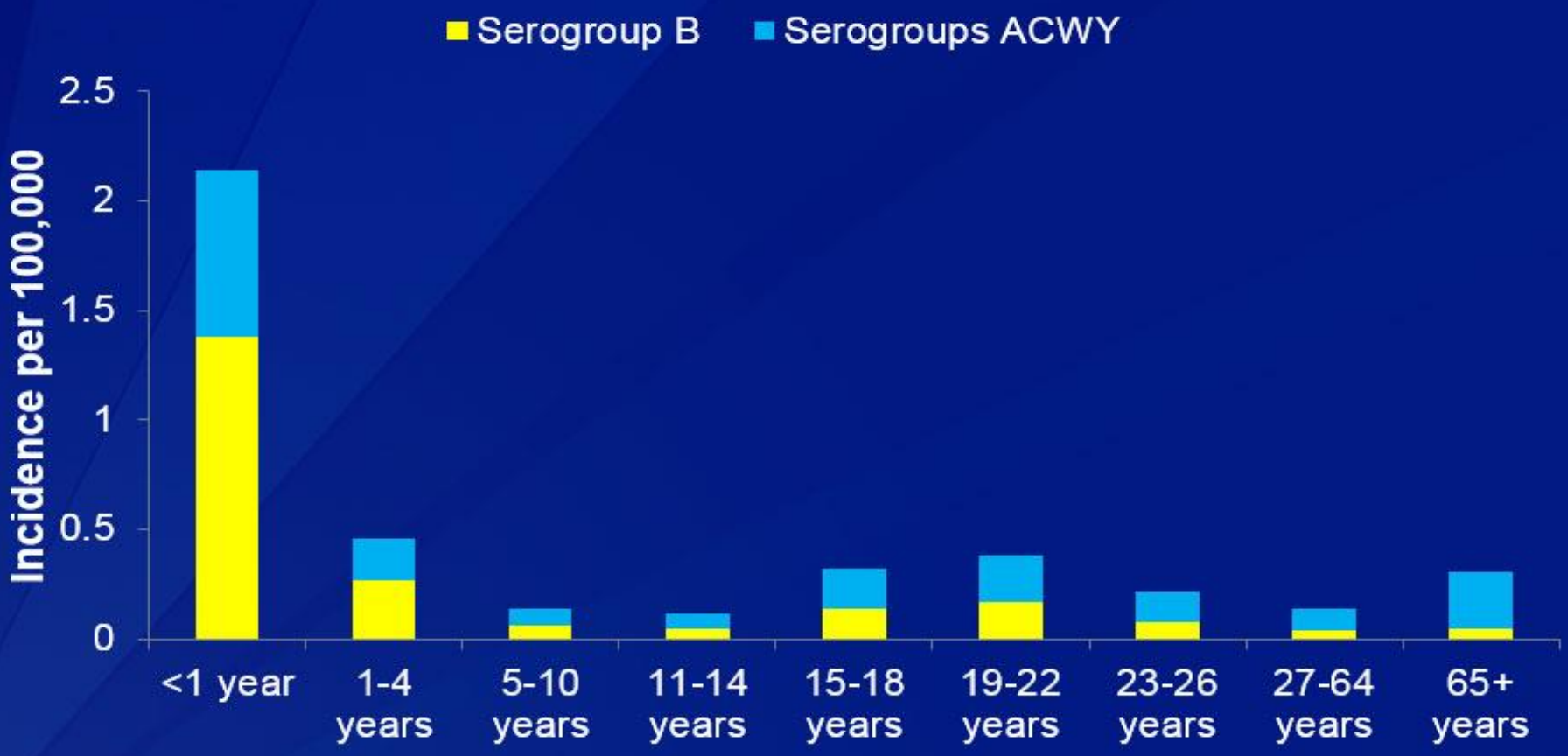


Reprinted with permission from Schoeller T, Schmutzhard E. *N Engl J Med.* 2001;34:1372.

Serogroup Distribution by Age

- The proportion of cases caused by each serogroup varies by age group.
- Serogroup B causes approximately 60% of cases among children less than 5 years old.
- Serogroups C, Y, or W, which are covered by meningococcal conjugate vaccines, cause approximately two out of three cases of meningococcal disease among persons 11 years old and older

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

Groups at Increased Risk for Meningococcal Disease

- High-risk medical conditions: persistent complement component deficiencies
- Functional or anatomic asplenia
- Certain microbiologists
- Populations at risk during an outbreak
- Men B disease - NOT at increased risk: international travelers, first year college students

CDC unpublished data

Outbreaks of Meningococcal Disease

- Meningococcal outbreaks are rare, historically causing ~2-3% of US cases
- Five serogroup B meningococcal disease clusters/outbreaks on college campuses Princeton: 1,400 fold increased risk; 5,800 recommended vaccine
- UCSB: 200 fold increased risk; 20,000 recommended vaccine

National Notifiable Diseases Surveillance System

High Risk Contacts

- Living in same household with a case (increases risk by 500-800x).
- Sharing drinks, cigarettes
- Sharing multiple meals
- Childcare center and nursery contacts
- Healthcare workers directly exposed to patient's oral secretions
- School or college contacts during outbreak
- Index patient if treated with penicillin

Rationale for Meningococcal Immunization

- Meningococcal disease can be a serious, rapidly progressive infection that leaves little time for diagnosis and treatment
- Early meningococcal disease can present with symptoms similar to common viral illness, making diagnosis difficult
- *N. meningitidis* is now the most prevalent etiologic agent of bacterial meningitis among children and adolescents 2 to 18 years of age in the US

Granoff DM, et al. In: Plotkin SA, ed. *Vaccines*. 4th ed. Philadelphia: W.B. Saunders Co; 2004; Rosenstein NE, et al. *N Engl J.* 2001;344:1378; Schuchat A, et al. *N Engl J Med.* 1997;337:970; Whitney CG, et al. *N Engl J Med.* 2003;348:1737

Meningococcal Vaccines

- Vaccines are now available that help protect against all three serogroups (B, C, and Y) of meningococcal disease that are commonly seen in the United States:
- Meningococcal conjugate vaccines (Menactra®, Menveo®, and MenHibrix®)
- Serogroup B meningococcal vaccines (Bexsero® and Trumenba®)
- Meningococcal polysaccharide vaccine (Menomune®)

Serogroup B Vaccines

- Problem - group B polysaccharide capsule is a homopolymer of human tissue sialic acid found in the developing fetal brain; Identified as self-antigen even after conjugation to carrier protein, therefore non-immunogenic.
- Surface proteins such as OMP and LPS candidates.
  - However, high antigenic diversity among OMP's without cross-reactivity. May have limited use where a single serosubtype of group B predominates.
- Outbreaks at Princeton and UCSB led to use of candidate 4 component vaccine

Meningococcal Serogroup B Vaccines

- rLP2086 (Trumenba, Pfizer) 2 fHbp (factor H-binding protein) subvariants (B/v1 and A/v2-3)

- 4CMenB (Bexsero, Novartis) –Single subvariant of fHbp (B/v1)
  - –NadA (Neisserial adhesin A)
  - –NhbA (Neisserial heparin binding antigen)
  - –Outer membrane vesicles of the New Zealand epidemic strain (OMV - NZ)

Meningococcal Serogroup B Vaccines

- rLP2086 (Trumenba, Pfizer)
  - Licensed by FDA on October 29, 2014
  - Approved for 10 through 25 years of age
  - 3 dose series (0, 2, 6 months)
  - 2 dose series (0, 6 months)

- 4CMenB (Bexsero, Novartis)
  - Licensed by FDA on January 23, 2015
  - Approved for 10 through 25 years of age
  - 2 dose series (0, 1 months)

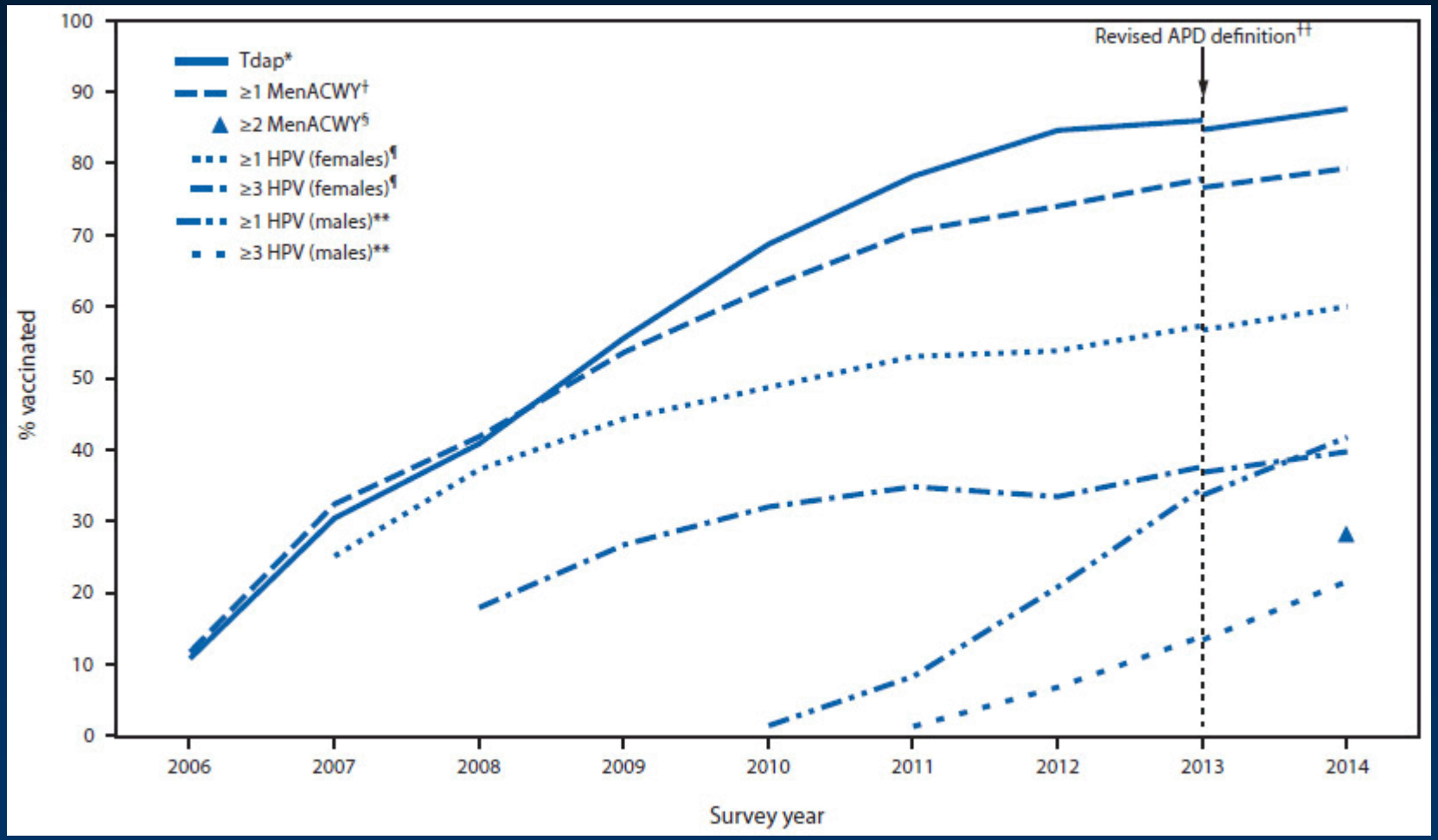
ACIP Recommendations – MCV4

- Routine vaccination of adolescents with conjugated vaccine beginning at age 11-12
- Booster dose to be given at age 16
- Anatomical or functional asplenia, including sickle cell disease and complement component deficiency
- Unvaccinated or incompletely vaccinated first-year college students living in residence halls
- Military recruits
- Microbiologists routinely exposed
- Travelers to countries in which meningococcal disease is hyperendemic or epidemic
- Persons at risk due to a community outbreak attributable to a vaccine serogroup

ACIP Recommendations – Men B Vaccine

- A serogroup B meningococcal (MenB) vaccine series may be administered to adolescents and young adults 16 through 23 years of age to provide short term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16 through 18 years of age. □Category B recommendation□No product preference indicated
- Persons aged ≥10 years at increased risk for meningococcal disease (persistent complement component deficiencies,anatomic or functional asplenia, microbiologists routinely exposed, increased risk because of a serogroup B meningococcal disease outbreak

National Immunization Survey – Teen, 2006-2014



Global Disease

- Serogroups B and C together account for a large majority of cases in Europe and the Americas.
- Major African epidemics are associated with Neisseria meningitidis serogroup A, which is usually the cause of meningococcal disease in Asia.
- There is increasing evidence of serogroup W being associated with outbreaks of considerable size. In 2000 and 2001 several hundred pilgrims attending the Hajj in Saudi Arabia were infected with Neisseria meningitidis W.

Disease in Africa

- Epidemic meningococcal disease has been present on the African continent for about 100 years, prevalent in the sub-Saharan “meningitis belt”.
- Epidemics there occur in the dry season (December to June)
- Epidemics usually take place in irregular cycles every 5-12 years
- •Serogroup A meningococci account for about 80-85% of all cases
- •In 2002 there was a major outbreak of meningococcal disease in Burkina Faso with about 80% of cases due to serogroup W

Information for Health-Care Professionals

NNII (www.immunizationinfo.org)

VEC (www.vaccine.chop.edu)

IAC (www.immunize.org)

CDC/NIP (www.cdc.gov/nip)

AAP (www.aap.org)

AAFP (www.aafp.org/)

IVS (www.vaccinesafety.edu)

Vaccine Page (www.vaccines.org)

Every Child by Two (www.ecbt.org)