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Vaccines, Children, and the Public Health Trust

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Vaccines and the Public Health Trust

Objectives

1. Review the impact of immunizations on the public health over the past 50 years.
2. Childhood Vaccines Now
3. Describe the challenges associated with trying to eliminate “immunizable” diseases.

   Examples: Invasive Pneumoccal Disease

   Neisseria meningitis
4. The Future

Before 1970

- 1949: Smallbox eliminated in the U.S.
- 1950s: Salk and Sabin polio vaccines
- 1963: Measles vaccine
- 1966: Hilleman isolates Jeryl Lynn strain of mumps

Atkinson.Epidemiol Preven Vacc Prev Dis. CDC, 2006

1970s – 1980s

- 1977: Smallpox eliminated from the planet
- 1979: Polio eliminated in the U.S.
- 1985: *H. influenzae* polysaccharide vaccine (PRP)
- 1986: First cancer vaccine (HepB)
- 1987: First polysaccharide conjugate (Hib PRP-D)
- 1989: Measles resurgence in the U.S.

Atkinson.Epidemiol Preven Vacc Prev Dis. CDC, 2006

1990s

- 1991: Polio eliminated in the Western hemisphere
- 1994: Measles eliminated in the U.K.
- 1995: First live-attenuated herpesvirus vaccine (varicella)
- 1996: Acellular pertussis vaccine (DTaP)
- 1998: First live reassortant vaccine (RRV-TV)
- 1999: RRV-TV withdrawn

Atkinson.Epidemiol Preven Vacc Prev Dis. CDC, 2006

2000s

- 2000: Measles eliminated in the U.S.
- 2000: OPV recommendation withdrawn in the U.S.
- 2002: First DTaP-based multivalent combination vaccine (DTaP-HepB-IPV)
- 2003: First intranasal vaccine (LAIV)
- 2004: Rubella eliminated in the U.S.
- 2005: Bird Flu Pandemic
- 2006: Second cancer vaccine (HPV)
- 2009: H1N1 Pandemic

Atkinson.Epidemiol Preven Vacc Prev Dis. CDC, 2006

2010s

- 2012: MERS Outbreak
- 2012: Menigitis B Vaccines Introduced
- 2014: Ebola Outbreak
- 2019: Coronavirus Pandemic

Annual Disease Burden

Disease	Peak		2004-06	
	Cases	Deaths	Cases	Deaths
Diphtheria	30,508	3,075	0	0
Measles	763,094	552	55	0
Mumps	212,932	50	6,584	0
Pertussis	265,269	7,518	15,632	27
Polio	42,033	2,720	0	0
CRS	20,000	2,160	1	0
Smallpox	110,672	2,510	0	0
Tetanus	601	511	41	4

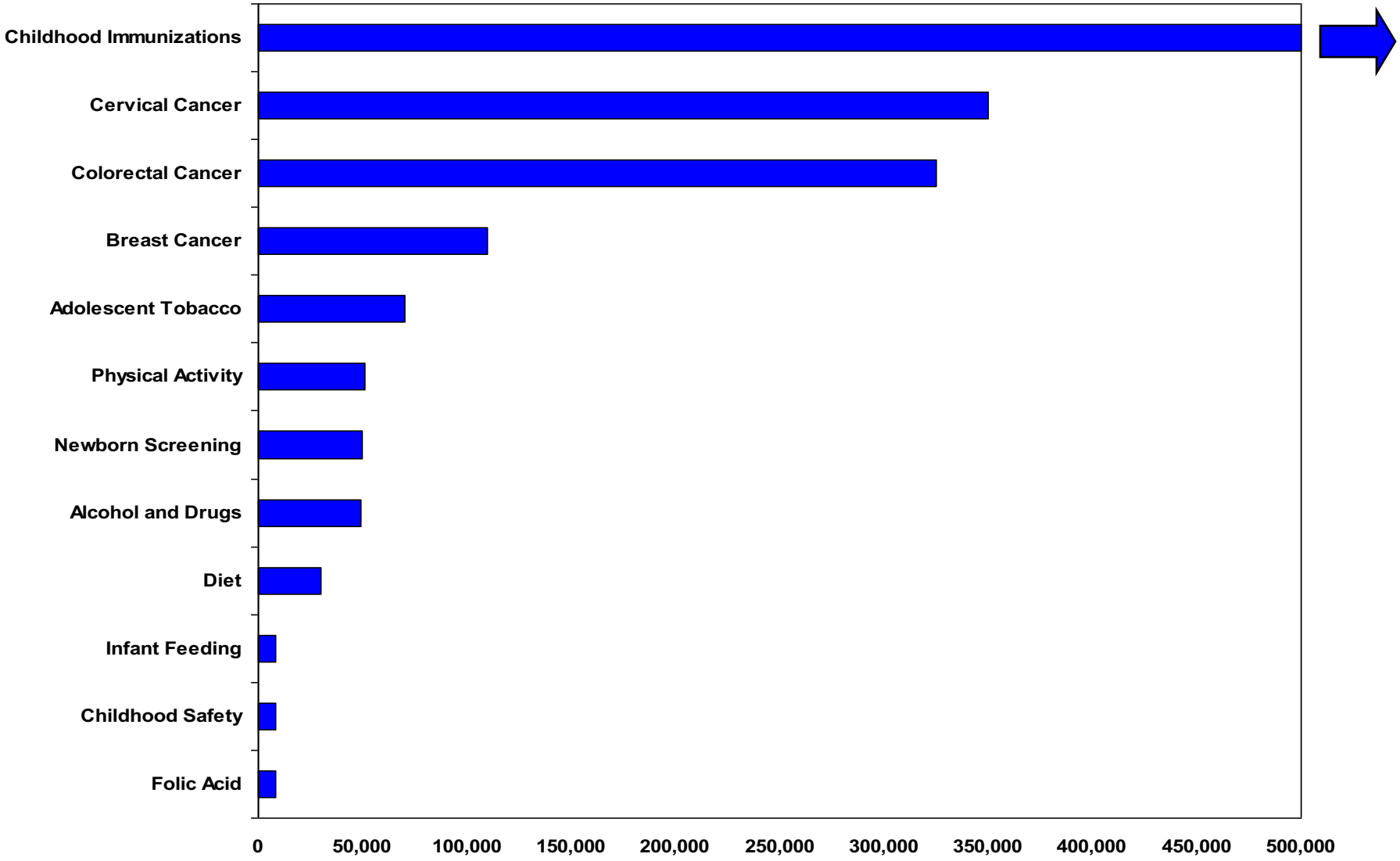
Roush, JAMA 2007; 298:2155 (vaccine programs before 1980)

Annual Disease Burden

Disease	Peak		2004-06	
	Cases	Deaths	Cases	Deaths
Hepatitis A	254,518	298	15,298	18
Hepatitis B	74,361	267	13,169	47
Hib	>20,000	>1,000	<50	<5
IPD	64,400	7,300	41,550	4,850
Varicella	5,358,595	138	612,768	19

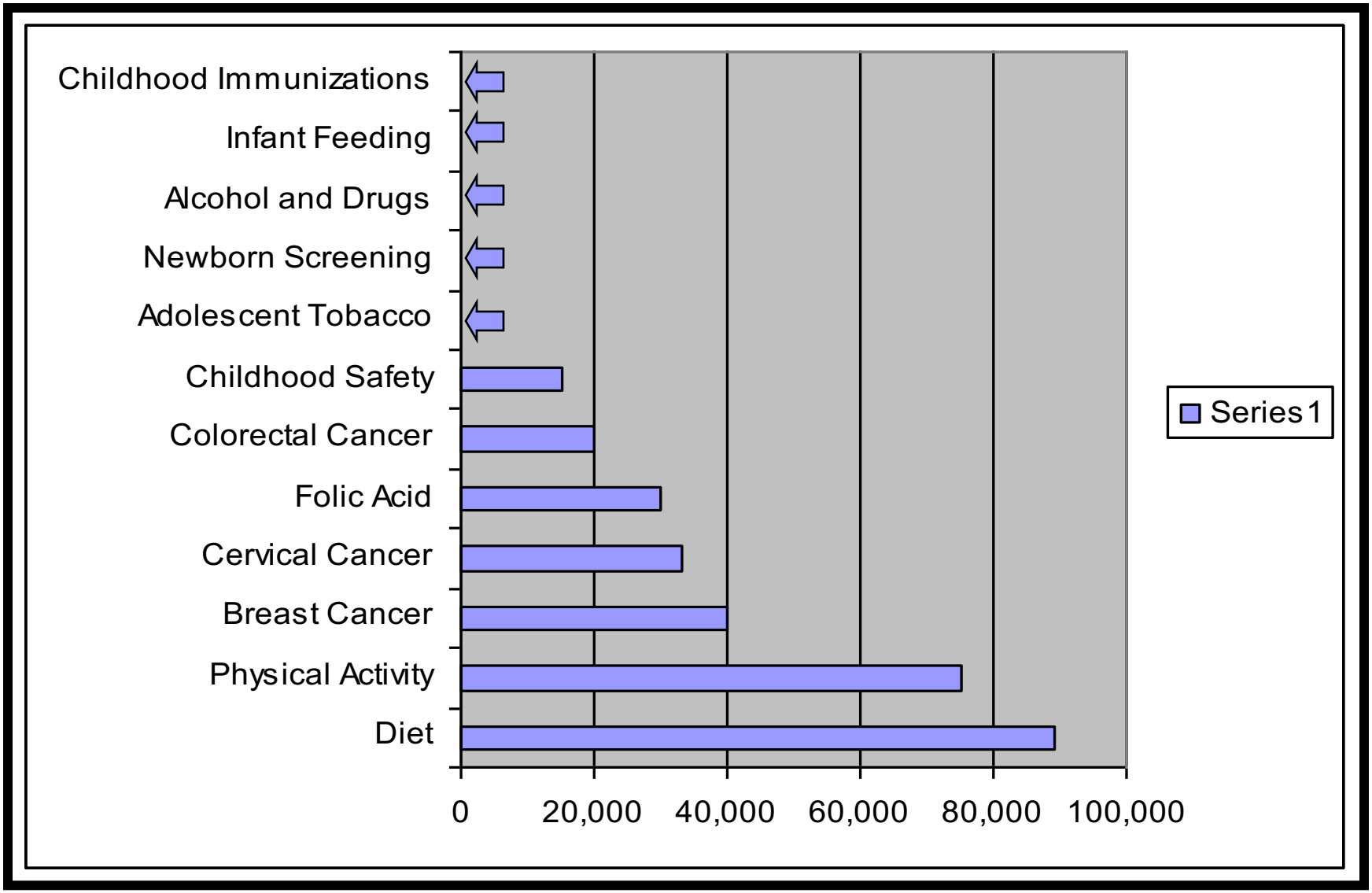
Roush, JAMA 2007; 298:2155 (vaccine programs after 1980)

Clinically Preventable Burden



Coeffield. Am J Prev Med 2001; 21:1

Cost-Utility



Coeffield. Am J Prev Med 2001; 21:1

Benefits of Vaccination

Vaccine Programs	2001 Birth Cohort (N=3,803,295)		
	Cases	Deaths	Total Costs
Without	14,330,376	33,564	$46,557 million
With	708,372	463	$482 million

↑DTaP, Hib, IPV, MMR, HepB, varicella (not included: HepA, PCV-7, ifluenza, MCV-4)

For every dollar spent, vaccine programs saved $5 in direct medical costs and an additional $11 in societal costs

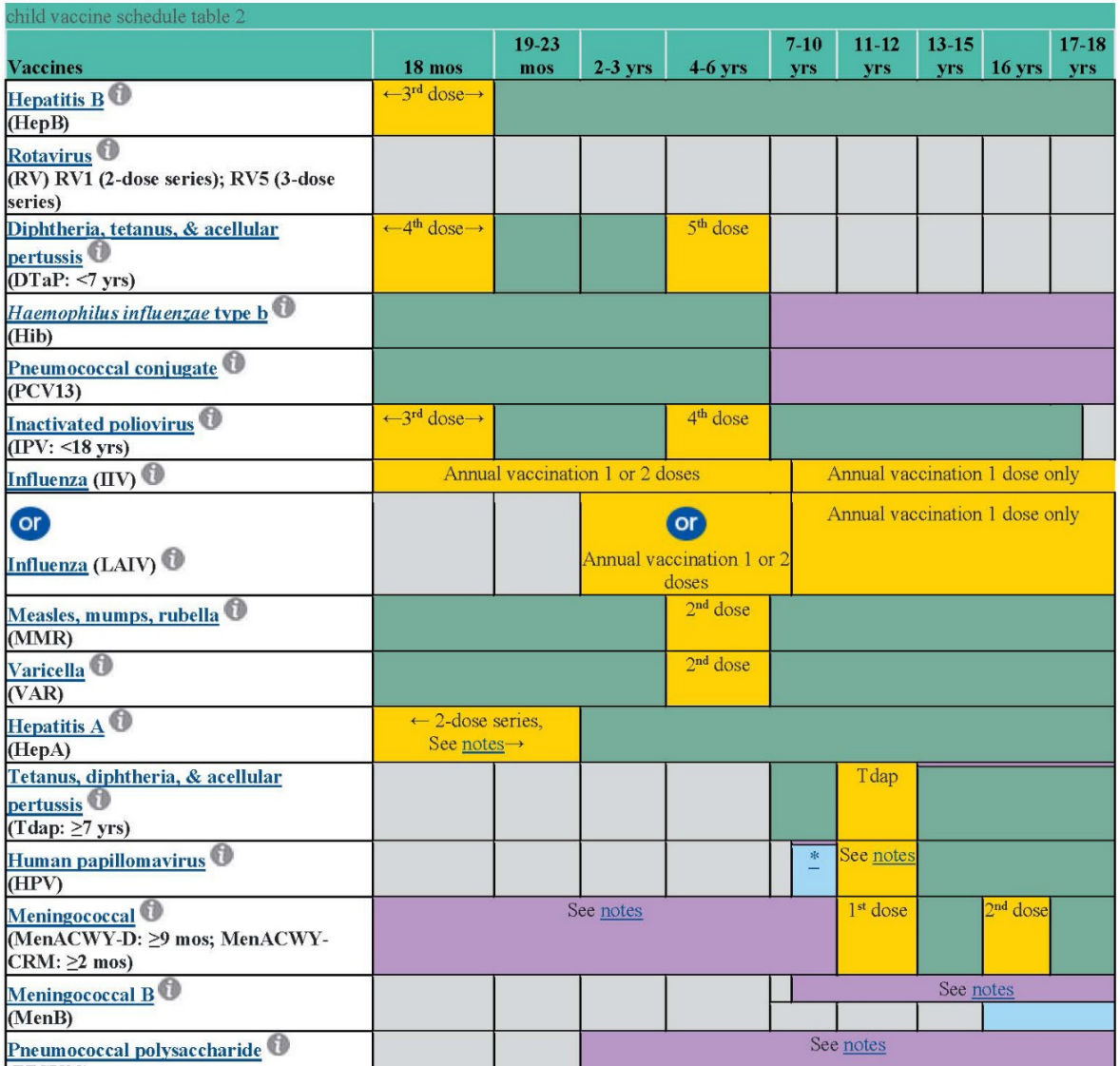
Zhou F et al. Arch Pediatr Adolesc Med 2005; 159: 1136-1144

Birth to 15 Months

child vaccine schedule table 1

Vaccine	Birth	1 mo	2 mos	4 mos	6 mos	9 mos	12 mos	15 mos
Hepatitis B (HepB)	1st dose	2nd dose			←3rd dose→			
Rotavirus (RV) RV1 (2-dose series); RV5 (3-dose series)			1st dose	2nd dose	See notes			
Diphtheria, tetanus, & acellular pertussis (DTaP: <7 yrs)			1st dose	2nd dose	3rd dose			←4th dose→
Haemophilus influenzae type b (Hib)			1st dose	2nd dose	See notes		←3rd or 4th dose, See notes→	
Pneumococcal conjugate (PCV13)			1st dose	2nd dose	3rd dose		←4th dose→	
Inactivated poliovirus (IPV: <18 yrs)			1st dose	2nd dose	←3rd dose→			
Influenza (IIV)					Annual vaccination 1 or 2 doses			
or Influenza (LAIV)								
Measles, mumps, rubella (MMR)					See notes		←1st dose→	
Varicella (VAR)							←1st dose→	
Hepatitis A (HepA)					See notes		←2-dose series, See notes→	
Tetanus, diphtheria, & acellular pertussis (Tdap: ≥7 yrs)								
Human papillomavirus (HPV)								
Meningococcal (MenACWY-D: ≥9 mos; MenACWY-CRM: ≥2 mos)			See notes					
Meningococcal B (MenB)								
Pneumococcal polysaccharide (PPSV23)								

18 Months to 18 Years



child vaccine schedule table 2

Vaccines	18 mos	19-23 mos	2-3 yrs	4-6 yrs	7-10 yrs	11-12 yrs	13-15 yrs	16 yrs	17-18 yrs
Hepatitis B (HepB)	←3rd dose→								
Rotavirus (RV) RV1 (2-dose series); RV5 (3-dose series)									
Diphtheria, tetanus, & acellular pertussis (DTaP: <7 yrs)	←4th dose→			5th dose					
Haemophilus influenzae type b (Hib)									
Pneumococcal conjugate (PCV13)									
Inactivated poliovirus (IPV: <18 yrs)	←3rd dose→			4th dose					
Influenza (IIV)	Annual vaccination 1 or 2 doses				Annual vaccination 1 dose only				
or Influenza (LAIV)			or Annual vaccination 1 or 2 doses		Annual vaccination 1 dose only				
Measles, mumps, rubella (MMR)				2nd dose					
Varicella (VAR)				2nd dose					
Hepatitis A (HepA)	← 2-dose series, See notes→								
Tetanus, diphtheria, & acellular pertussis (Tdap: ≥7 yrs)						Tdap			
Human papillomavirus (HPV)					* –	See notes			
Meningococcal (MenACWY-D: ≥9 mos; MenACWY-CRM: ≥2 mos)	See notes					1st dose		2nd dose	
Meningococcal B (MenB)						See notes			
Pneumococcal polysaccharide			See notes						

Children Age 4 Months through 6 Years

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4	Dose 4 to Dose 5
Hepatitis B	Birth	**4 weeks**	**8 weeks and at least 16 weeks after first dose.** Minimum age for the final dose is 24 weeks.		
Rotavirus	**6 weeks** Maximum age for first dose is 14 weeks, 6 days.	**4 weeks**	**4 weeks** Maximum age for final dose is 8 months, 0 days.		
Diphtheria, tetanus, and acellular pertussis	6 weeks	**4 weeks**	**4 weeks**	**6 months**	**6 months**
Haemophilus influenzae type b	6 weeks	**No further doses needed** if first dose was administered at age 15 months or older. **4 weeks** if first dose was administered before the 1st birthday. **8 weeks (as final dose)** if first dose was administered at age 12 through 14 months.	**No further doses needed** if previous dose was administered at age 15 months or older. **4 weeks** if current age is younger than 12 months ***and*** first dose was administered at younger than age 7 months, ***and*** at least 1 previous dose was PRP-T (ActHib, Pentacel, Hiberix) or unknown. **8 weeks and age 12 through 59 months (as final dose)** if current age is younger than 12 months ***and*** first dose was administered at age 7 through 11 months; OR if current age is 12 through 59 months ***and*** first dose was administered before the 1st birthday, ***and*** second dose administered at younger than 15 months; OR if both doses were PRP-OMP (PedvaxHIB; Comvax) ***and*** were administered before the 1st birthday.	**8 weeks (as final dose)** This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal conjugate	6 weeks	**No further doses needed** for healthy children if first dose was administered at age 24 months or older. **4 weeks** if first dose administered before the 1st birthday. **8 weeks (as final dose for healthy children)** if first dose was administered at the 1st birthday or after.	**No further doses needed** for healthy children if previous dose administered at age 24 months or older. **4 weeks** if current age is younger than 12 months and previous dose given at <7 months old. **8 weeks (as final dose for healthy children)** if previous dose given between 7-11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months.	**8 weeks (as final dose)** This **dose** only necessary for children age 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age.	
Inactivated poliovirus	6 weeks	**4 weeks**	**4 weeks** if current age is <4 years. **6 months** (as final dose) if current age is 4 years or older.	**6 months** (minimum age 4 years for final dose).	
Measles, mumps, rubella	12 months	**4 weeks**			
	12 months	**3 months**			

Children and Adolescents Age 7 through 18 Years

Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses		
		Dose 1 to Dose 2	Dose 2 to Dose 3	Dose 3 to Dose 4
Meningococcal ACWY	Not Applicable (N/A)	**8 weeks**		
Tetanus, diphtheria; tetanus, diphtheria, and acellular pertussis	**7 years**	**4 weeks**	**4 weeks** if first dose of DTaP/DT was administered before the 1st birthday. **6 months (as final dose)** if first dose of DTaP/DT or Tdap/Td was administered at or after the 1st birthday.	**6 months** if first dose of DTaP/DT was administered before the 1st birthday.
Human papillomavirus	9 years	**Routine dosing intervals are recommended.**		
Hepatitis A	N/A	**6 months**		
Hepatitis B	N/A	**4 weeks**	**8 weeks *and*** at least 16 weeks after first dose.	
Inactivated poliovirus	N/A	**4 weeks**	**6 months** A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.	A fourth dose of IPV is indicated if all previous doses were administered at <4 years or if the third dose was administered <6 months after the second dose.
Measles, mumps, rubella	N/A	**4 weeks**		
Varicella	N/A	**3 months** if younger than age 13 years. **4 weeks** if age 13 years		

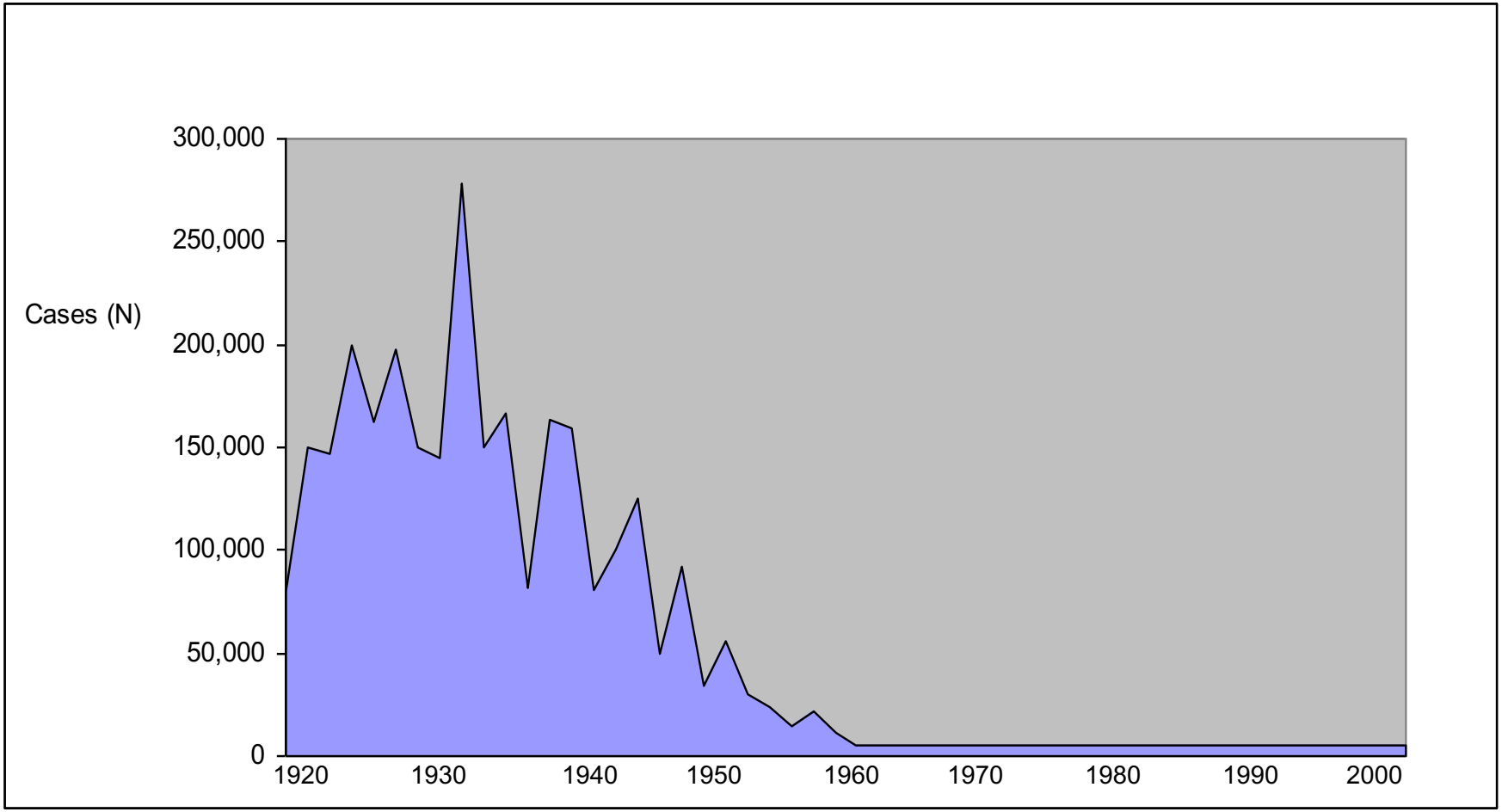
Why the Routine Vaccine Schedule Changes

New Vaccine for old disease	Hib polysaccharide; HepA; varicella; rotavirus; HPV
Old vaccine for new disease	Zoster vaccine
Improved vaccine	Recombinant HepB; DTaP; PCV7;Hib conjugate; MCV4; LAIV
Expansion to new age group	Hib at 2 mo; HepA at 12 mo; Tdap for adolescents and adults
Conversion from targeted to universal program	HepA; HepB; influenza for young children; MCV4 for all adolescents
Change in dosing schedule	Elimination of OPV at 6 mo
New program goal	Second MMR; second varicella; influenza for all children
Altered risk/benefit ratio	All-IPV schedule
Safety issue	Withdrawal of RRV-TV
Eradication	Withdrawal of vaccinia

Immediate Remaining Challenges

- Residual disease
- Delivery
- Cost
- Public confidence
- New target groups

Residual Disease: Pertussis



CDC. Epidemiology and Prevention of Vaccine-Preventable Disease 8th ed. 2004;75

Residual Pertussis

But…

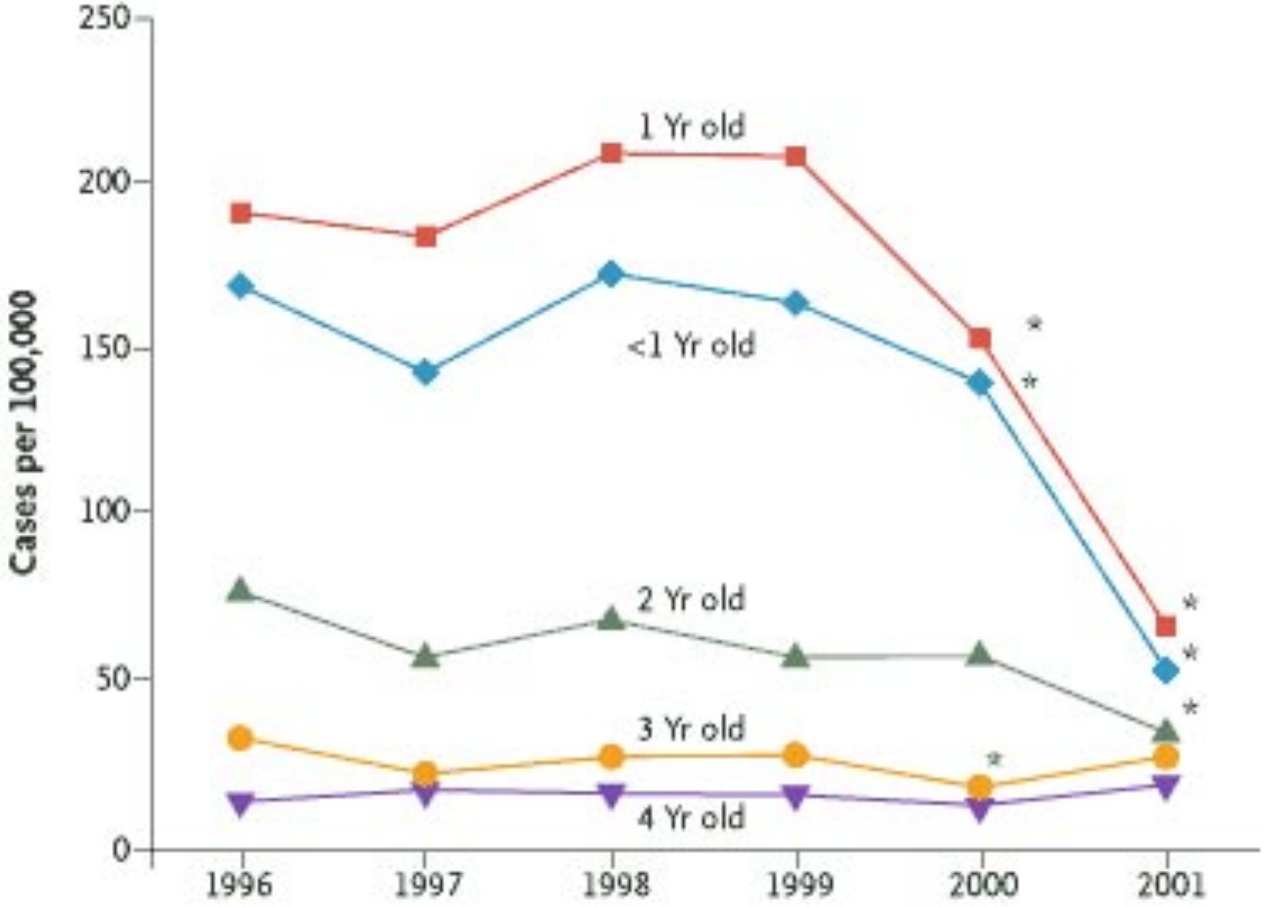
- 25-fold increase in cases since 1976
- Up to 5 million cases per year among individuals ages 15-65 (based on seroconversion rates)

Clin infect Dis 43:151 (2006)

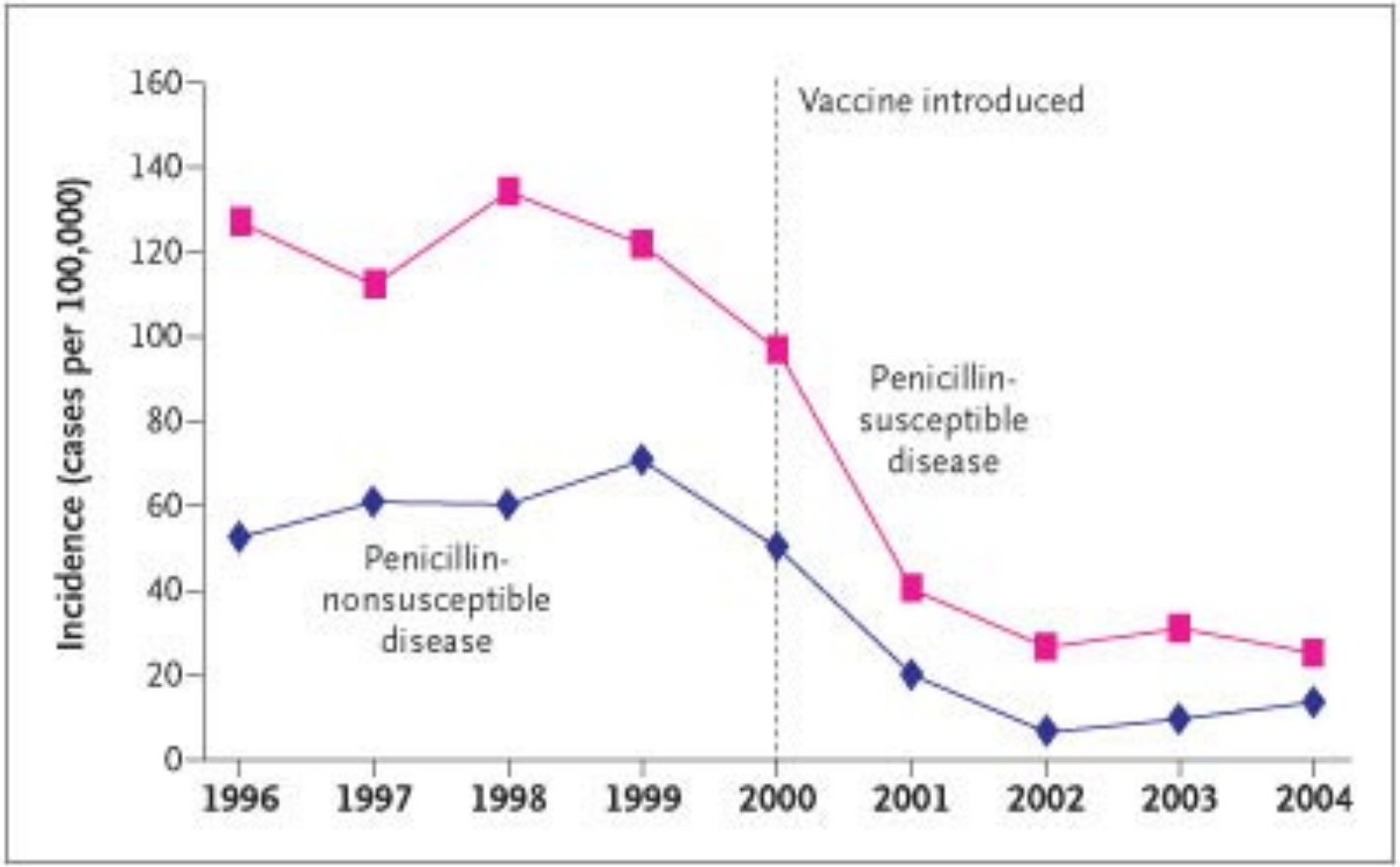
Recommendation; Tdap booster at age 11-12 (approved 10-64)

Invasive Pneumococcal Disease

Rates of Invasive Pneumococcal Disease among Children under Five Years Old, According to Age and Year



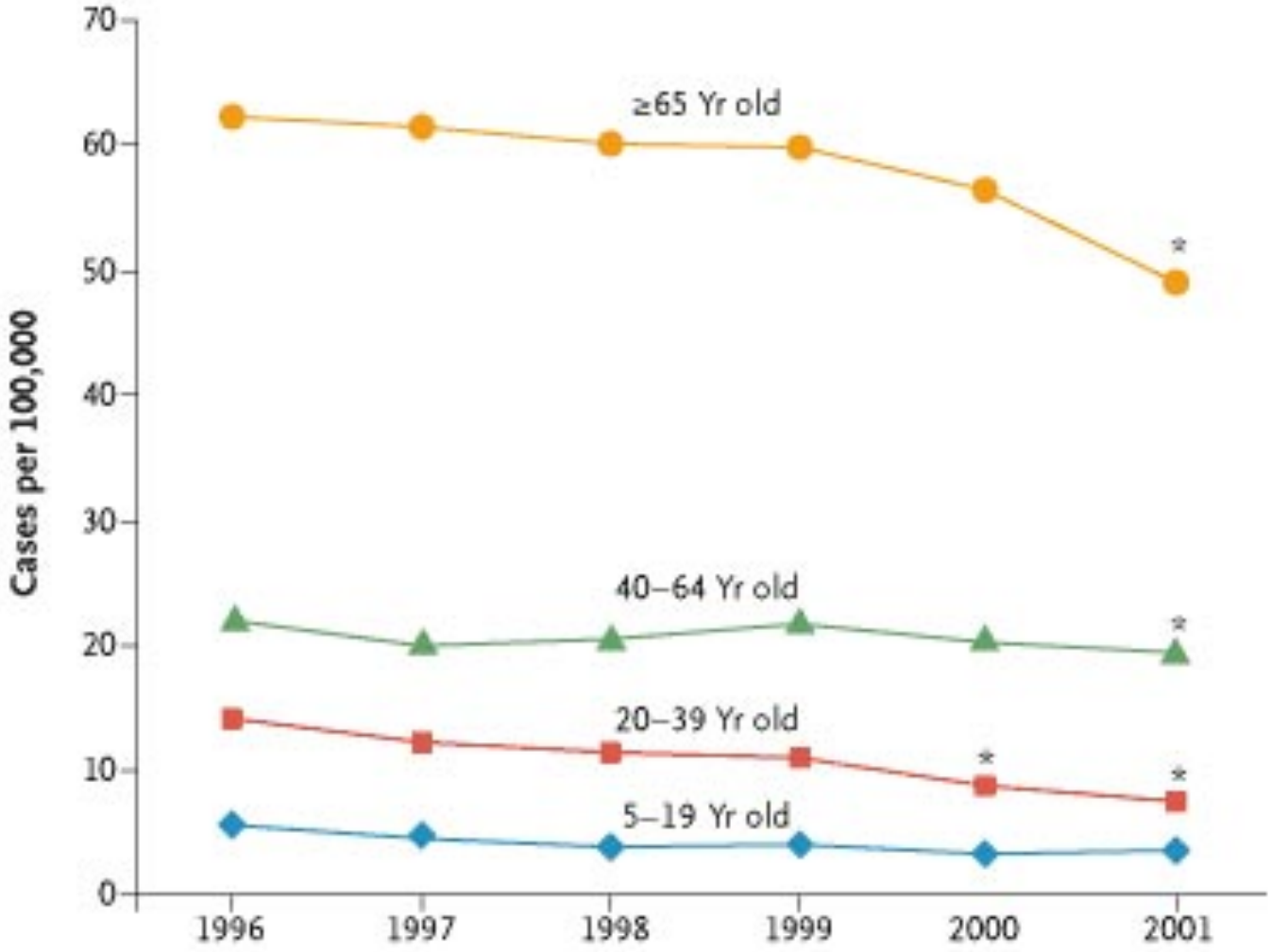
Annual Incidence of Invasive Disease Caused by Penicillin-Susceptible and Penicillin-Nonsusceptible Pneumococci among Children under Two Years of Age, 1996 to 2004



Kyaw M et al. N Engl J Med 2006;354:1455-1463

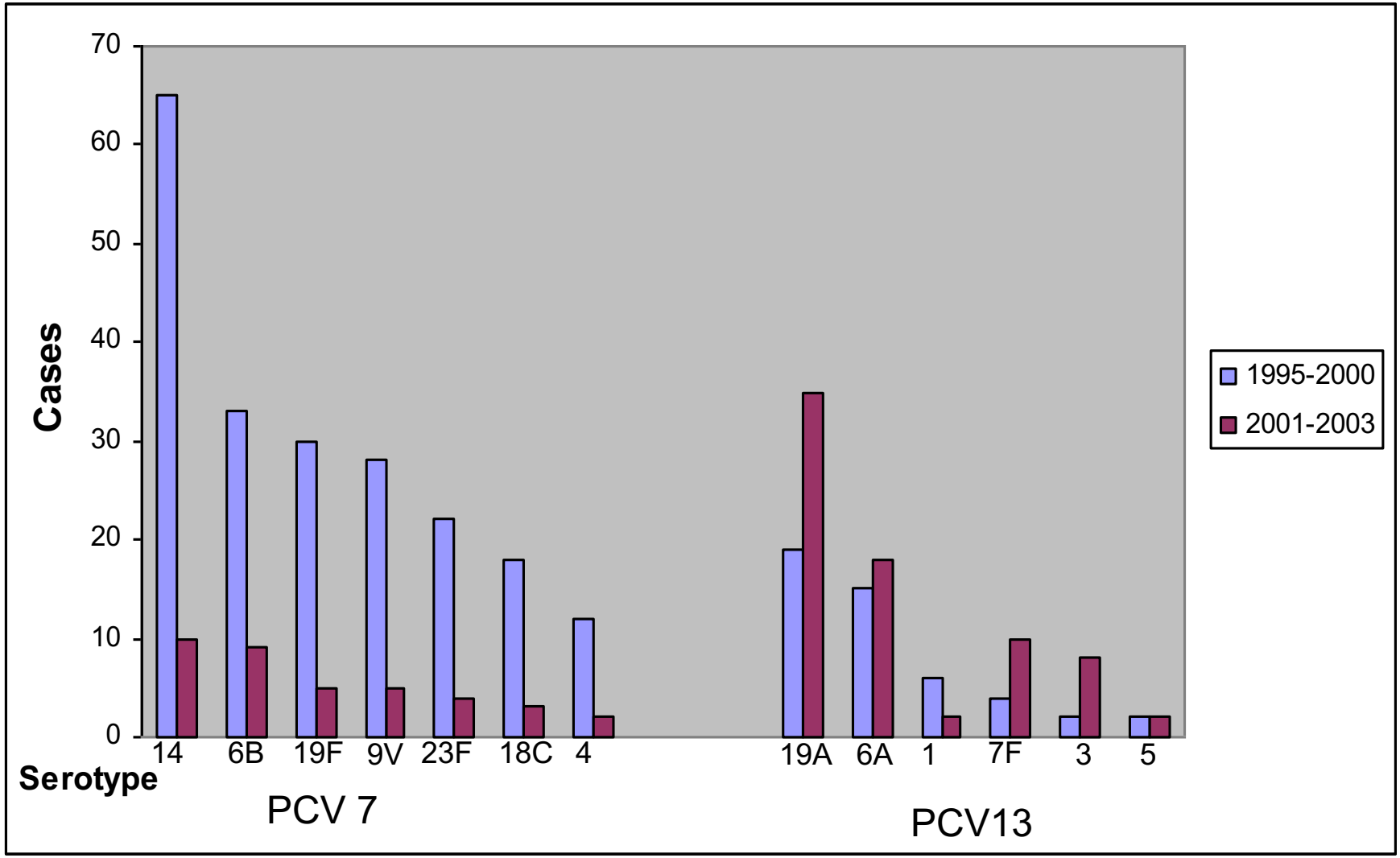
The NEW ENGLAND JOURNAL of MEDICINE

Rates of Invasive Pneumococcal Disease among Persons at Least Five Years Old, According to Age Group and Year



Whitney C et al. N Engl J Med 2003;348:1737-1746

The “Replacement Effect”
Increase in Invasive Disease by Non-Vaccine Serotypes



JAMA 297(16): 1784 (2007)

Invasive Pneumococcal Disease (IPD) 10 U.S. Sites (2007)

Age (mos)	All IPD	PCV Serotypes	Serotype 19A
< 12	155	104	60
12-23	124	73	57
24-35	71	43	32
36-47	48	34	20
48-59	29	20	11
All < 60	427	274	180

MMWR 59: 253 (2010)

Pneumococcal Vaccine Serotypes

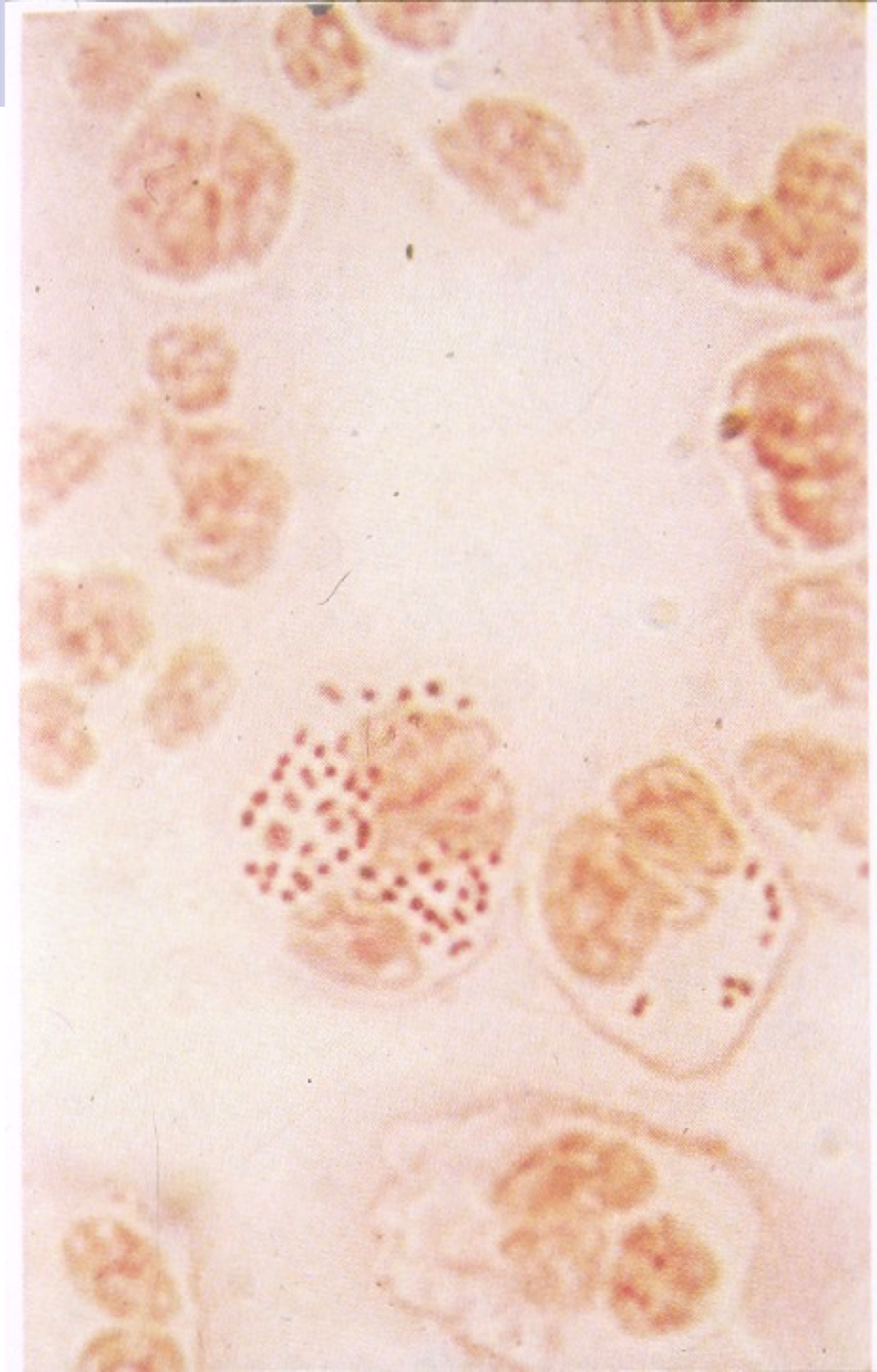
PCV 7: 4, 6B, 9V, 14, 18C, 19F, 23F

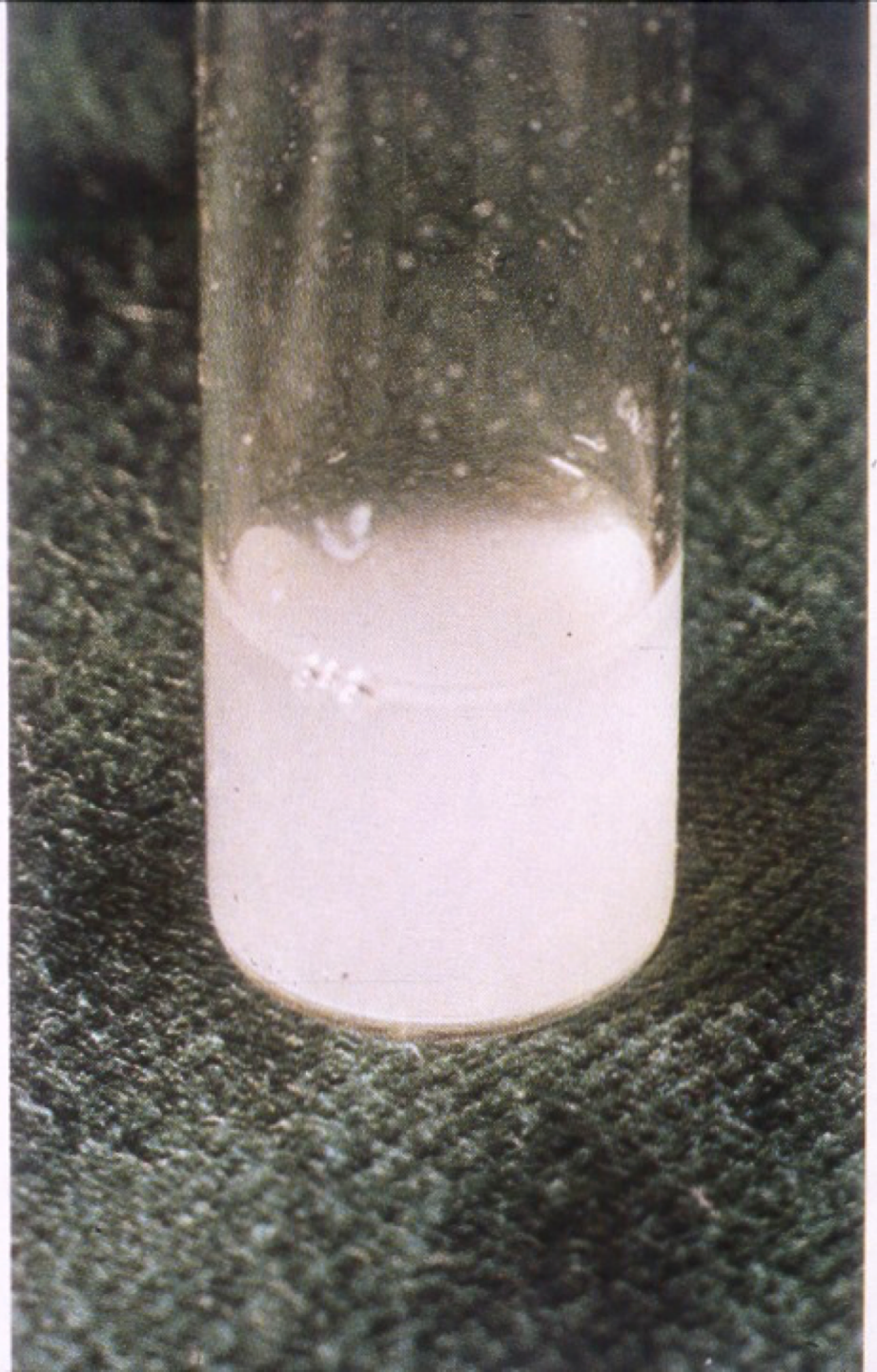
PCV 13: PCV7 + 1, 3, 5, 6A, 7F, **19A**

New: 22F, 33F, others

Case

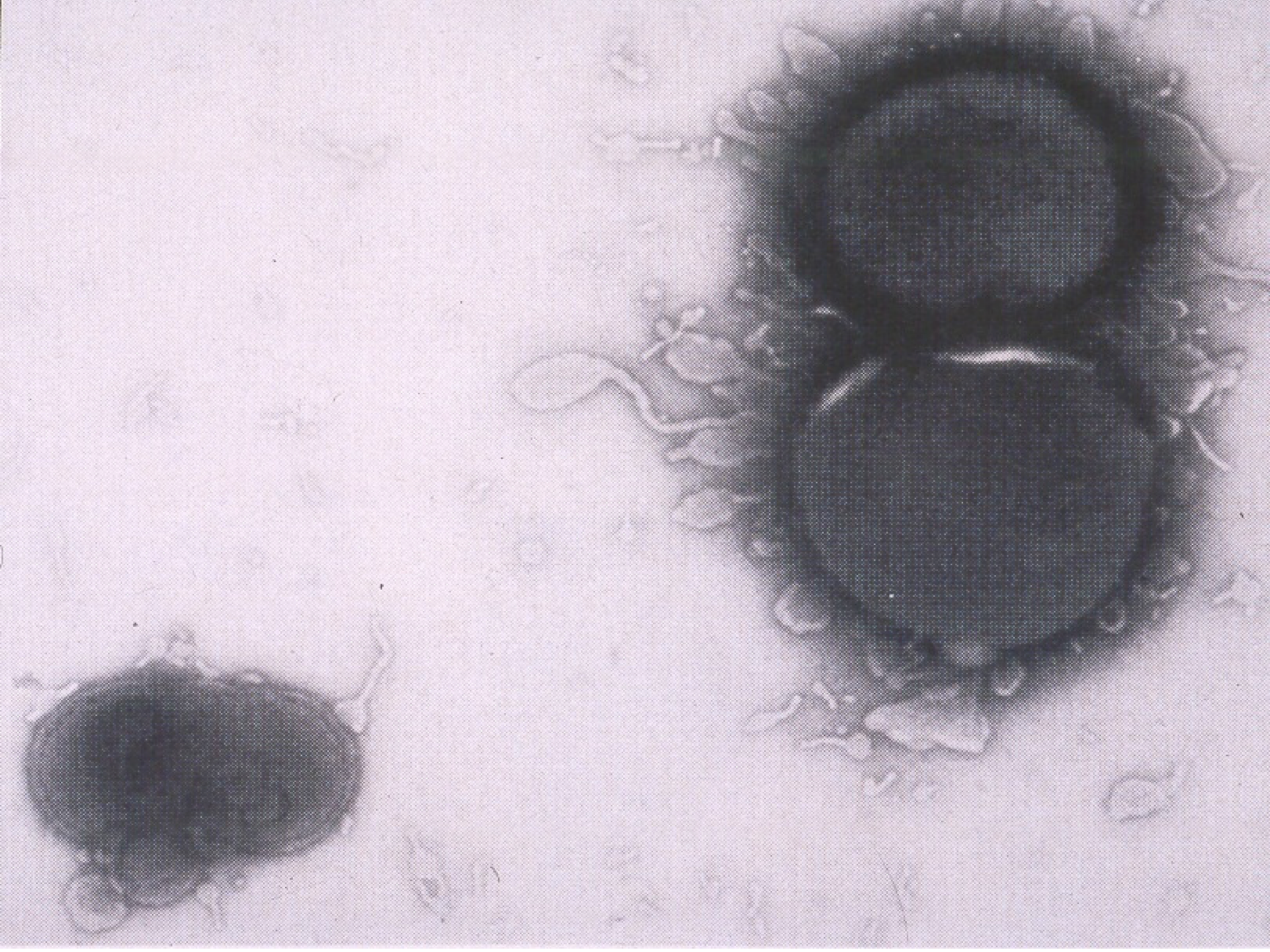
- An 18-year-old male is admitted through the emergency room with a 12-hour history of fever, rigors, stiffneck and headache. He noted a rash 3-4 hours before going to the ER.
- He is a freshman at the University of the Arts, but lives off campus with a new girlfriend.





Neisseria meningitidis

- Gram-negative diplococcus
- Polysaccharide capsule determines serogroup (13 serogroups)
- Nasophayngeal carriage is an immunizing state
- Transmission via respiratory route
- Invasive disease occurs in newly infected



N. meningitidis Disease

- Leading cause of bacterial meningitis in children and young adults
- Cases are sporadic (95-97%) or via outbreaks (increasing)
- Case fatality rate: 10-13%
- Morbidity (11-19%): neurologic, limb loss, hearing loss

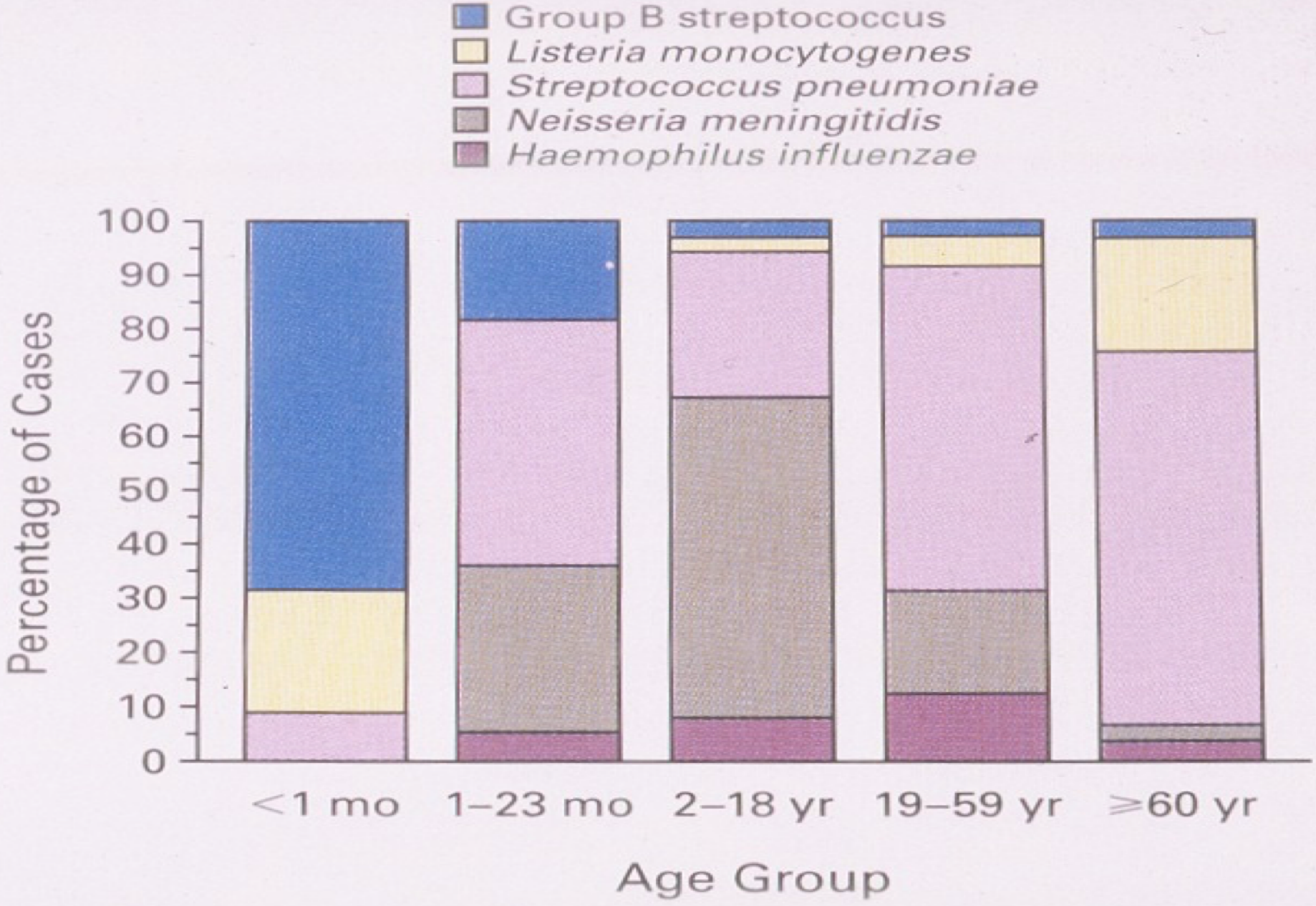


Figure 1. Pathogenic Agents of Bacterial Meningitis According to Age Group.

N. meningitidis Disease

- 2400-3000 cases/year (0.8-1.3 cases/100,000)
- Highest rate in infants < 1 year old
- 3% of cases (1998-1999) in college students
- Individuals 18-23 yo have a higher rate (1.4 cases/100,000)
- College freshman living in dorms have a much higher rate (4.6 cases/100,000)

FIGURE 1. Incidence of meningococcal disease, by age group — selected U.S. areas, 1989–1991

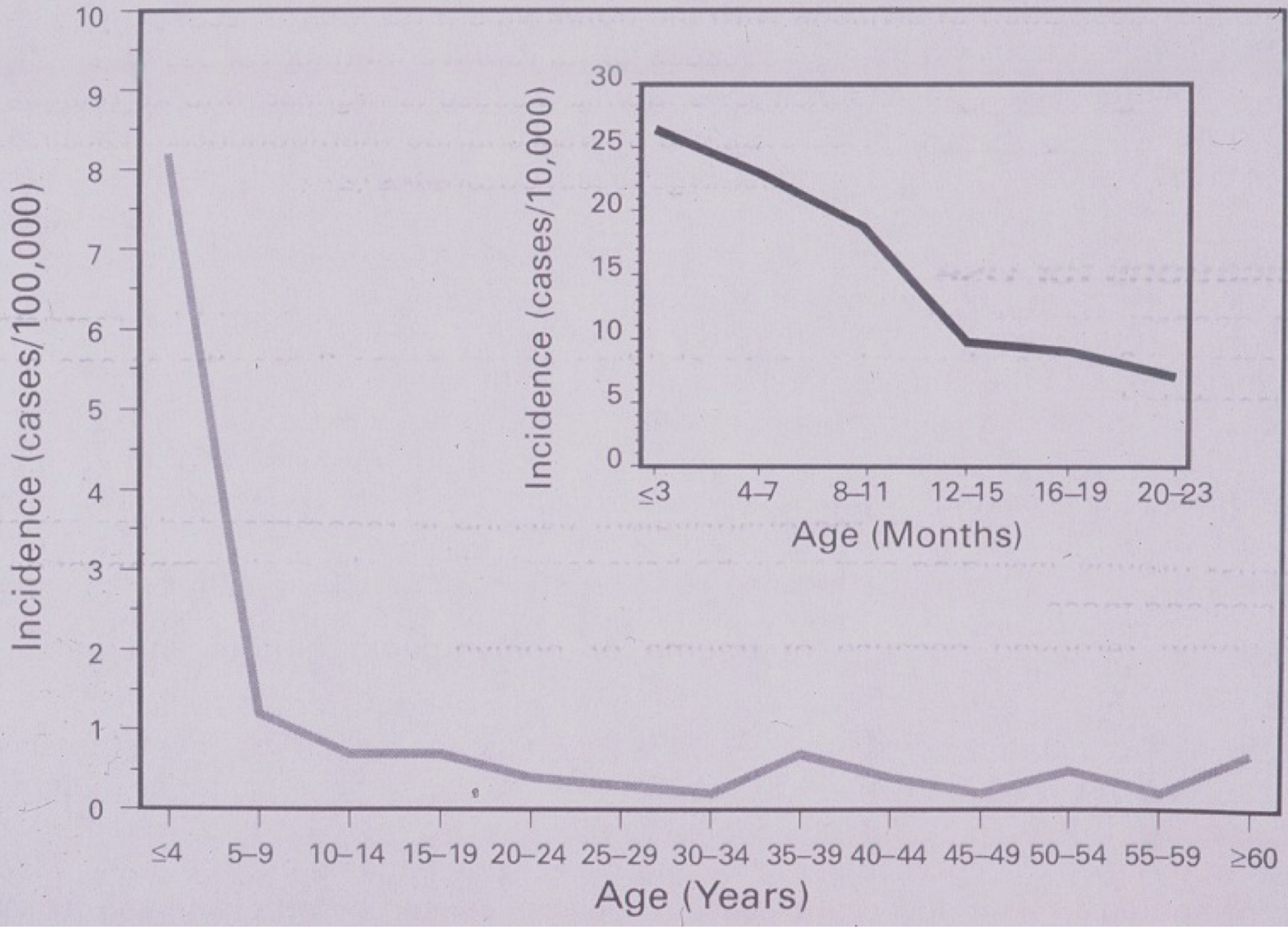
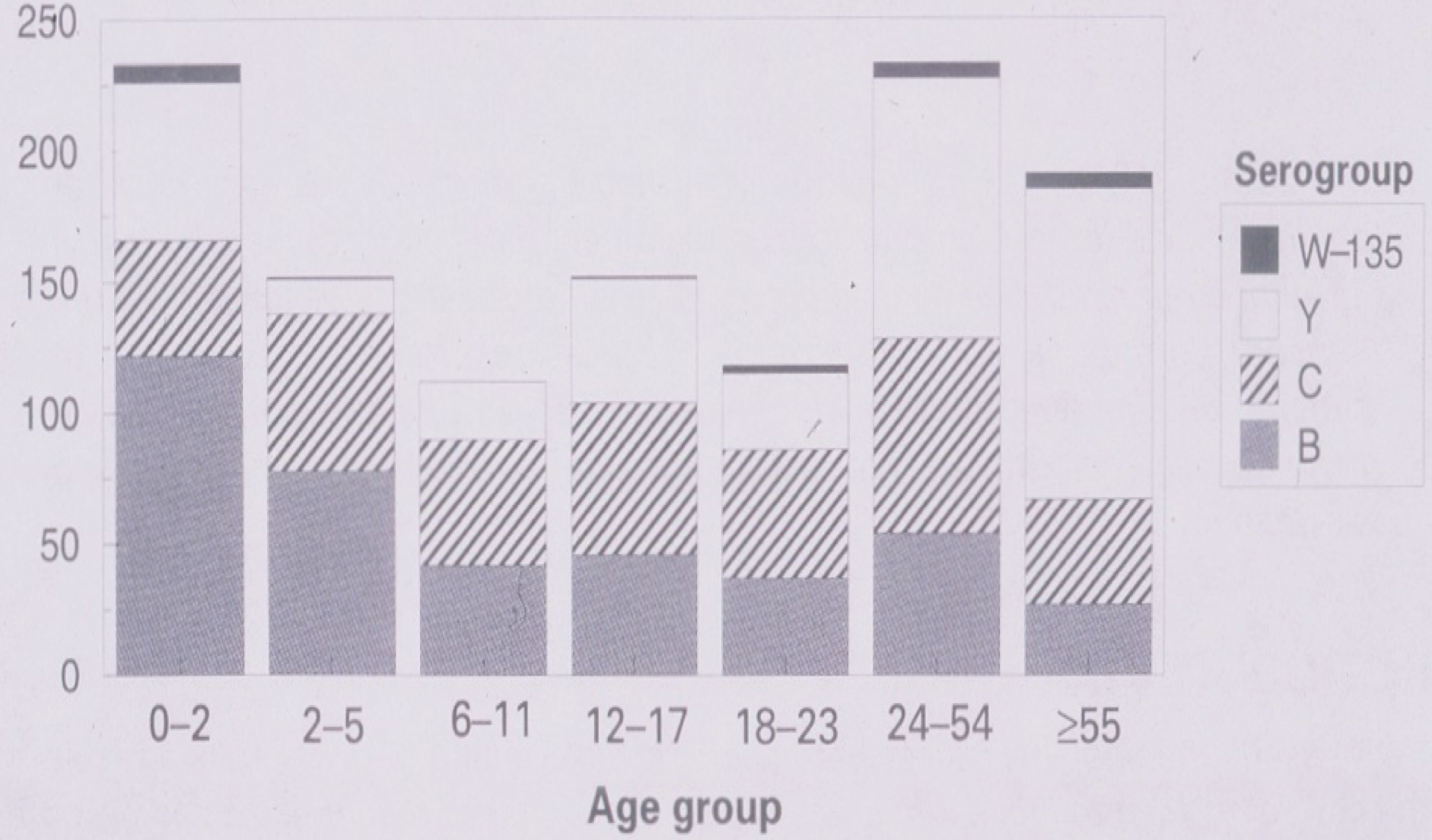


FIGURE 1. Serogroup distribution of meningococcal disease cases, by age group—United States, 1994–1998



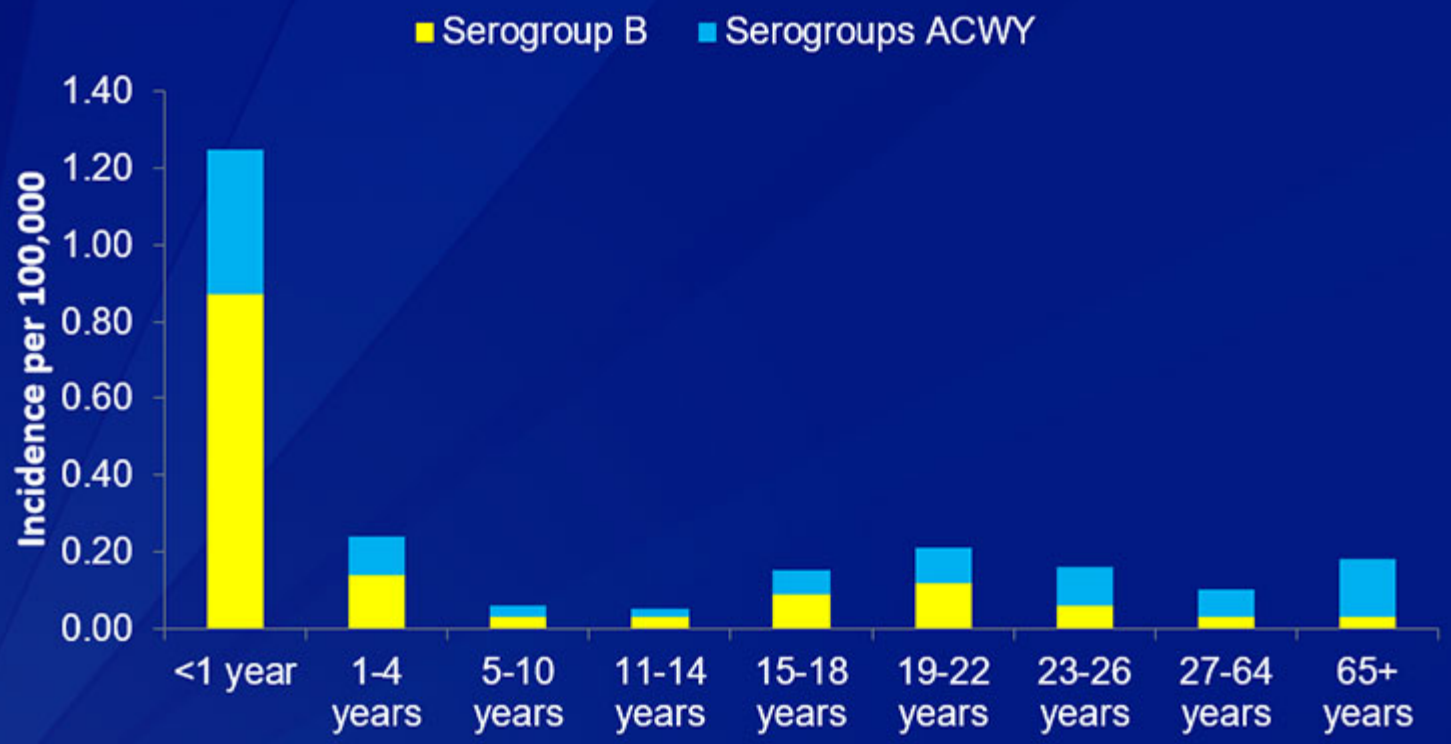
Meningococcal Conjugate Vaccines

- Recommended for adolescents aged 11-18 years and others at increased risk for meningococcal disease
  - MCV4-D (Sanofi) licensed for persons 2-55 years
  - MenACWY-CRM_{197} (Novartis) licensed 2/19/2010 for persons aged 11-55 years.
- Infant vaccines in late-stage development
  - HibMenCY (GSK): 2,4,6, and 12-15 months*
  - MenACWY-CRM_{197}: 2,4,6 and 12-15 months
  - MCV4-D: 9 and 12 months

Why no vaccine against serogroup B?

- Meningococci differentiated by capsular type
- Vaccines are conjugated capsular polysaccharide-protein complexes
- Serogroup B polysaccharide capsule has structural homology with neural cell adhesion molecule
- Fear of inducing autoimmune response
- Development of a vaccine against serogroup B focusing on outer membrane proteins

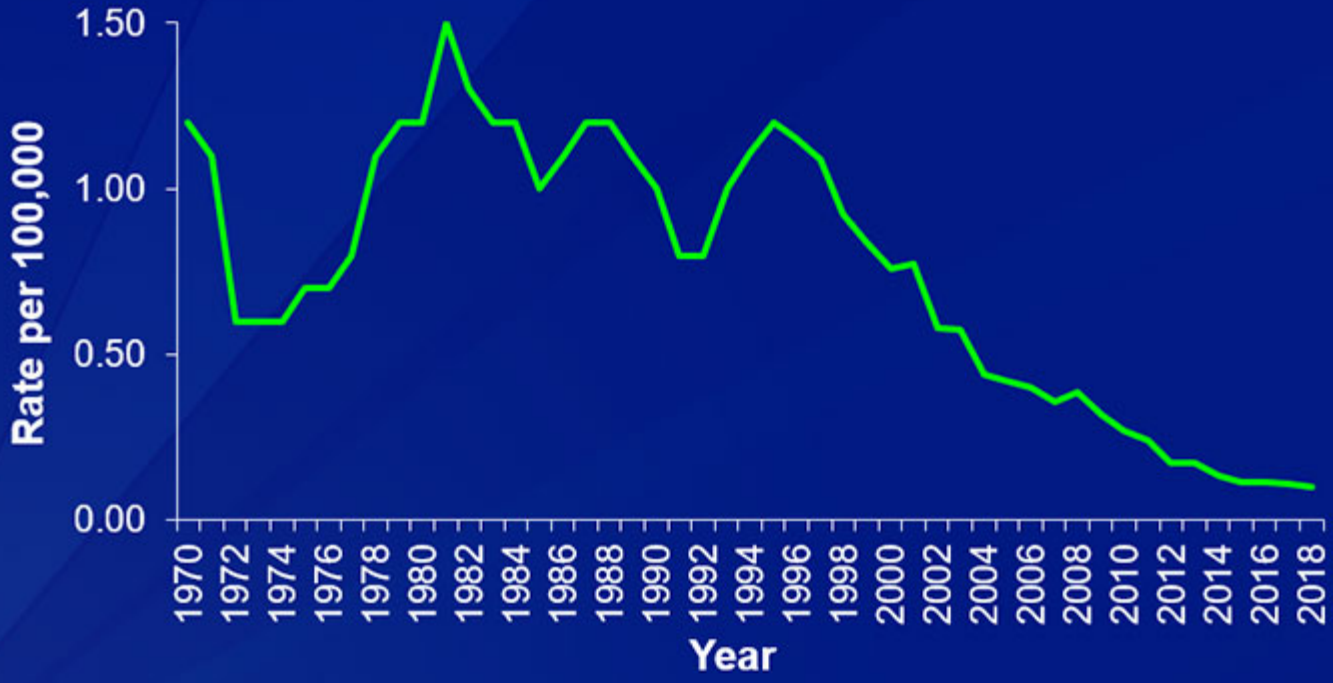
Meningococcal Incidence by Serogroup* and Age-Group, 2009-2018



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

Unknown serogroup (16%) and other serogroups (6%) excluded

Meningococcal Disease Incidence, United States, 1970-2018



SOURCE: CDC; National Notifiable Diseases Surveillance System

Meningococcal Disease Cases and Incidence by Serogroup and College Attendance*

	B No. (Incidence†)	C No. (Incidence†)	W No. (Incidence†)	Y No. (Incidence†)	Nongroupable No. (Incidence†)	Total** No. (Incidence†)
Attending college‡	11 (0.10)	0 (0.00)	0 (0.00)	0 (0.00)	6 (0.05)	**18 (0.16)**
Not attending college‡	9 (0.05)	5 (0.03)	0 (0.00)	0 (0.00)	1 (0.01)	**16 (0.08)**

*Among cases 18-24 years. **Includes 1 case with unknown serogroup and 1 serogroup E case. †Cases per 100,000 population; and ‡assumes 38.3% of 18–24 year olds attending college [1]

Vaccination Status among cases 18-24 years

MenACWY* vaccine receipt:

College students: 100% (18/18) had information on MenACWY receipt; of those 94.4% received MenACWY.

Persons not attending college: 50.0% (8/16) had information on MenACWY receipt; of those 75.0% received MenACWY.

MenB** vaccine receipt:

College students: 77.8% (14/18) had information on MenB receipt; of those 14.3% received MenB.

Persons not attending college: 50.0% (8/16) had information on MenB receipt; of those 0 received MenB.

*MenACWY = meningococcal conjugate vaccine, **MenB = serogroup B meningococcal vaccine.

Public Concerns About Vaccines

Concern	Proposed Mechanism	Implicated Vaccines
Encephalopathy	Toxins	DTP
Allergy	Hygeine Hypothesis	All
Autoimmunity	Molecular mimicry	Many
SIDS	Toxins	DTP, HepB
Mad Cow Disease	Prions	Many
AIDS	SIV contamination	OPV
Cancer	SV40 contamination	OPV
Neurological damage	Thimerosal	Many
Autism	Bowel inflammation	MMR

The Future:

New technology for coronavirus vaccines

- mRNA codes for spike protein
  - Moderna
  - Pfizer/BioNTech
- DNA Plasmid
  - Inovio
- Intranasal recombinant adenovirus + CoV-2 protein
  - J & J/Janssen
- DNA inserted into bacteria to produce spike protein
  - Sanofi/GSK (adjuvant)

Vaccines: Conclusions

1. Vaccinating at-risk populations is our single most important medical intervention
2. The risks of not vaccinating far outweigh the risks of vaccinating.
3. Physicians need to be ready with scientific data when confronting parents who decline recommended immunizations.
4. Science rules! We will have a covid-19 vaccine.