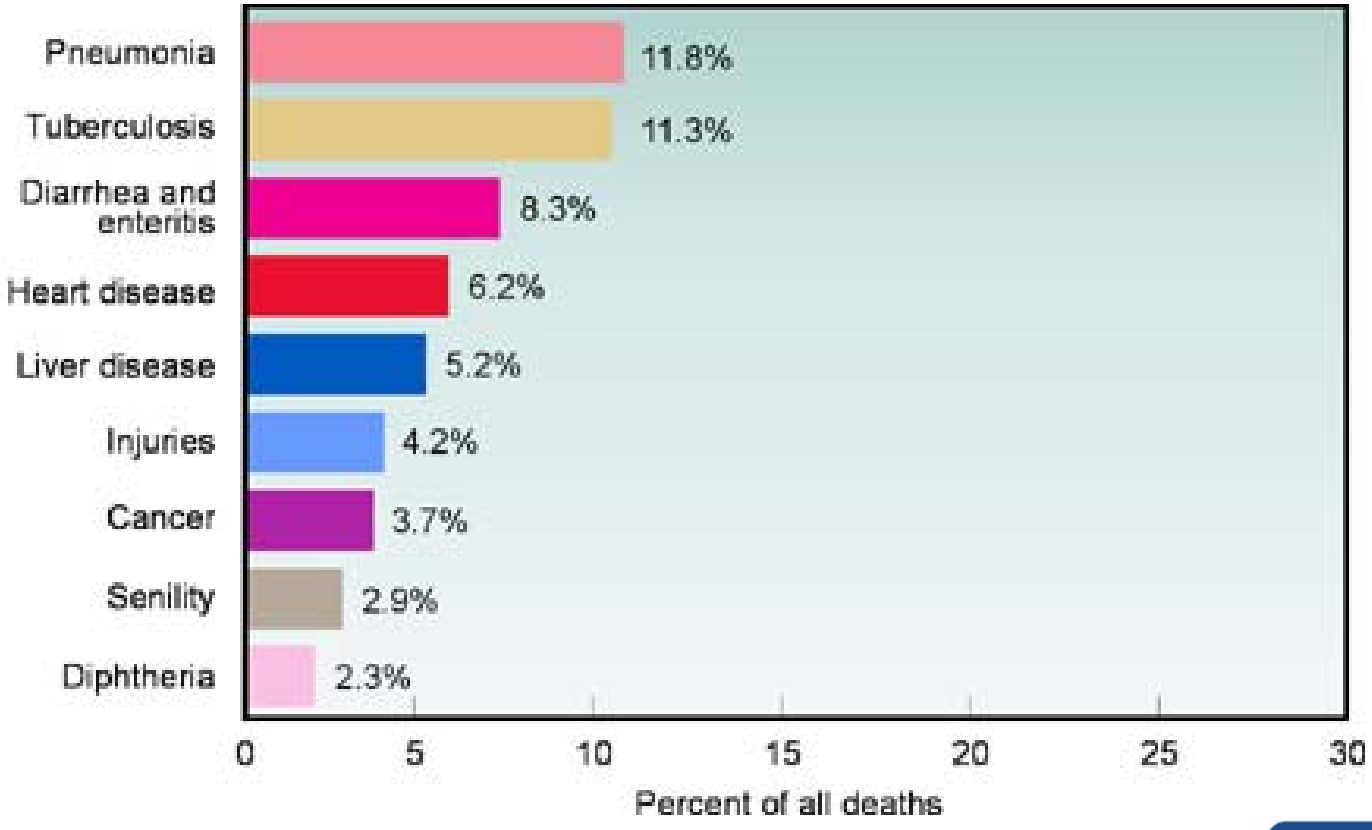
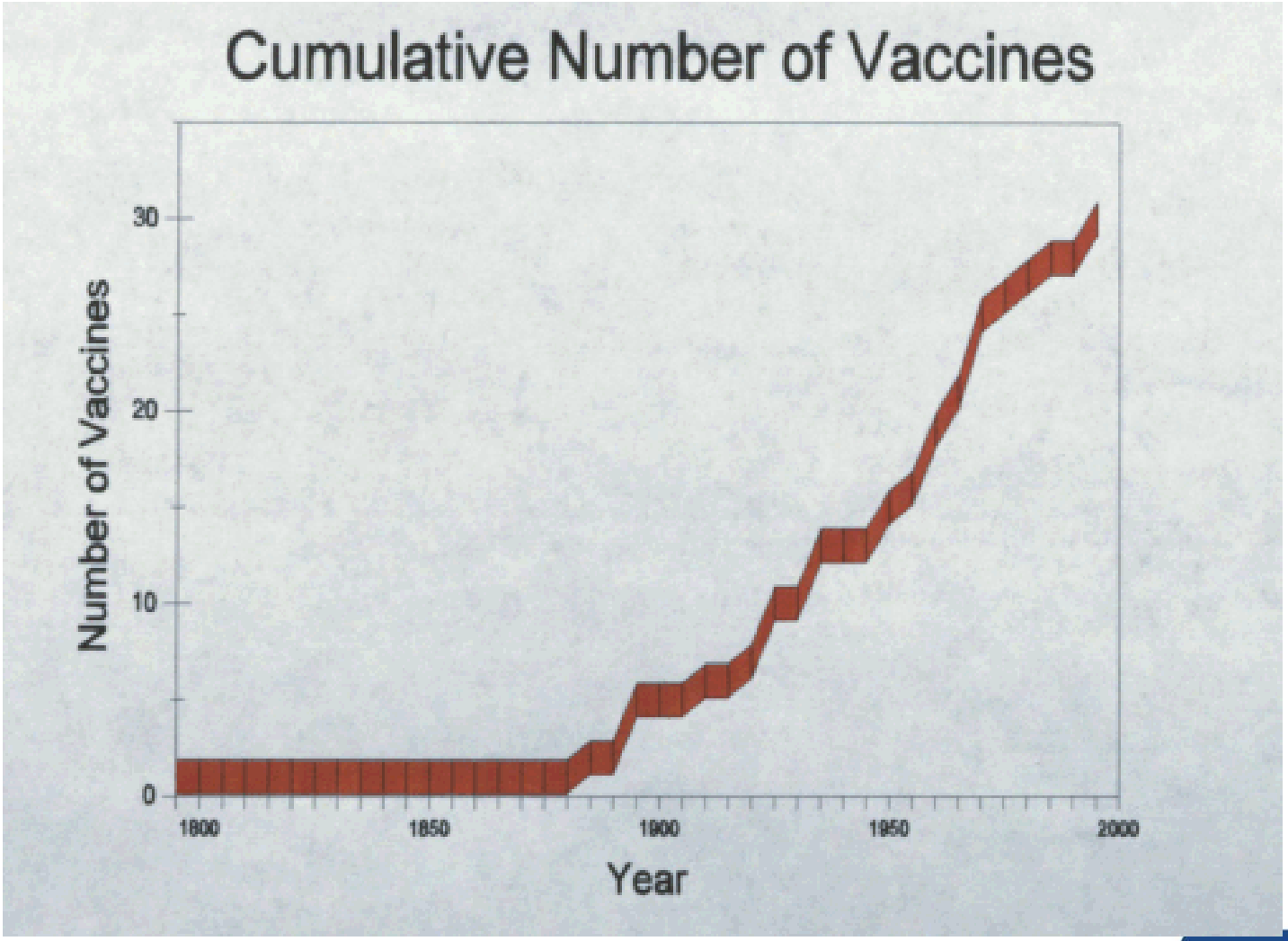
Prevention of Bacterial Meningitis; A 20th Century Triumph

Peter C. Kelly, M.D.

Bureau of Public Health
Emergency Preparedness

1900

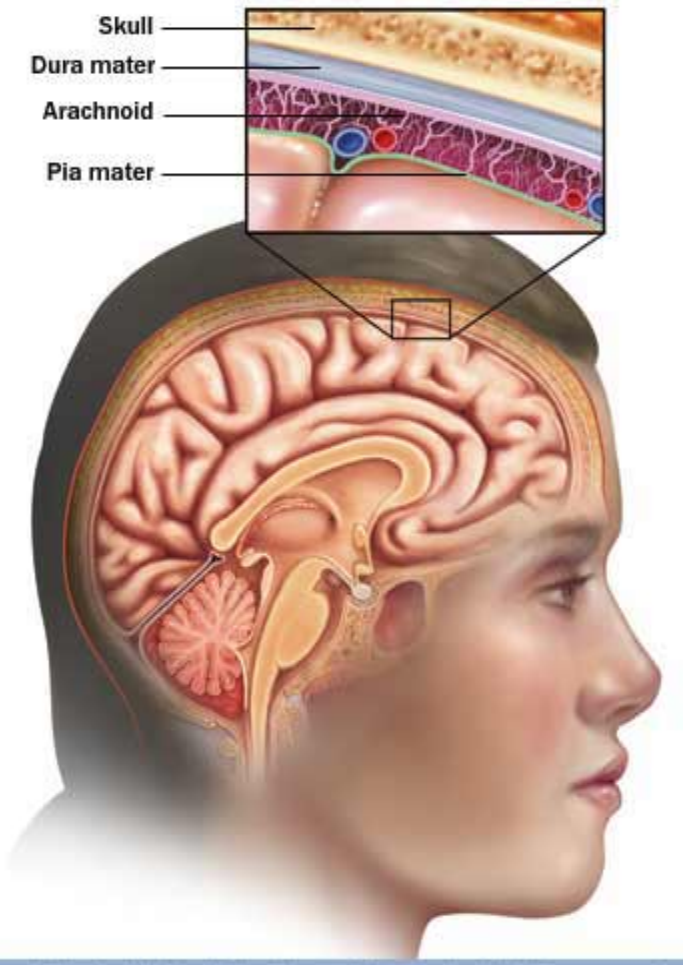

Pneumonia
11.8%
Tuberculosis
11.3%
Diarrhea and enteritis
8.3%
Heart disease
6.2%
Liver disease
5.2%
Injuries
4.2%
Cancer
3.7%
Senility
2.9%
Diphtheria
2.3%
0
5
10
15
20
25
30
Percent of all deaths


Cumulative Number of Vaccines
Number of Vaccines
0
10
20
30
1800
1850
1900
1950
2000
Year

- Characters
  - *H. influenza,* 6 serotypes
  - *S. pneumoniae*, 90 serotypes
  - *N. meningitidis*, 13 serogroups
- Villain: fatal meningitis
- Time line ~ 100 years
  - 1900-1935 basic science
  - 1935-present antibiotic Rx
  - 1965-present vaccine

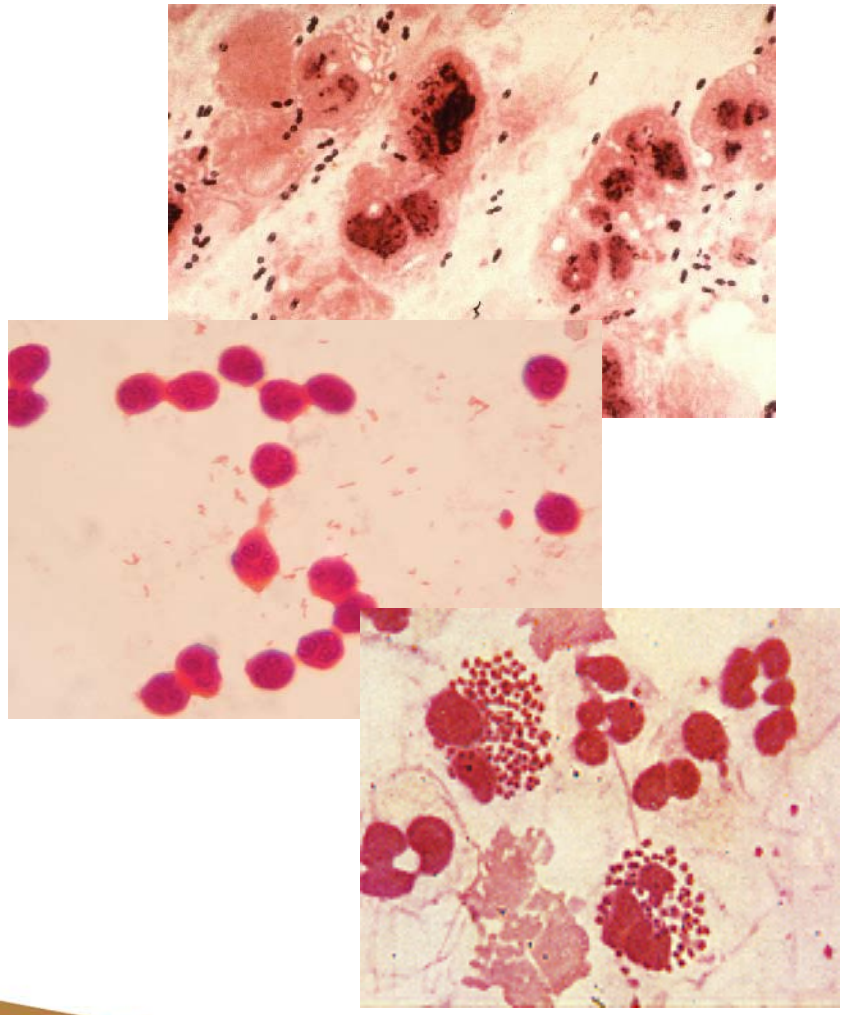
Bacterial Meningitis

- Organisms infect meningies
- Via blood stream or extension form ears, sinuses
- Intense inflammatory response
- Brain swelling, sepsis
- Death



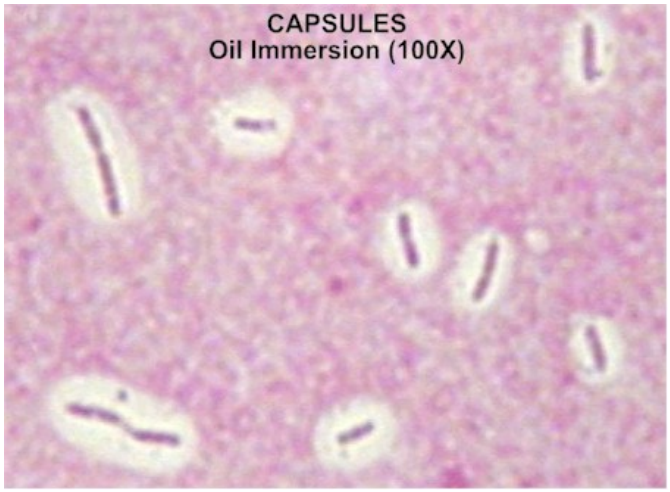
The Organisms

- Each identified in late 19th century
- Known to cause a fatal meningitis
- Each has a capsule



Capsules

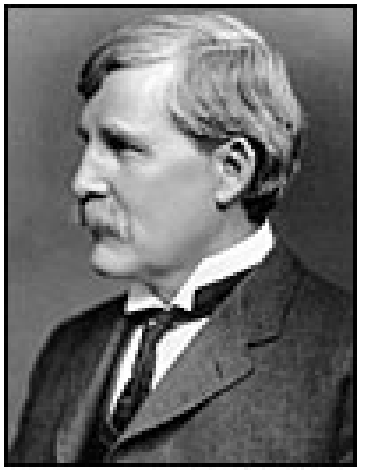
- Outer most part of the 3 organisms
- Polysaccharide
- Capsules are antigenic



Rockefeller

- 1901 Rockefeller Institute
- Medical research
- Pneumonia, #1
- *S. pneumoniae*


ROCKEFELLER ARCHIVE CENTER


THE NEW YORK HISTORICAL SOCIETY

Simon Flexner

- First director of Rockefeller Institute
- C. Dopter, serotypes of *N. mening*.
- Develops anti serum against *N. mening* for treatment of meningitis

Pneumococcal Work

- Pneumococci antigenic in rabbits
- Serum (antibody) protects non immune animal from infection with same strain
- Multiple different “types” of pneumococci
- “Specific soluble substance”
- Capsular polysaccharide
- Capsular polysaccharide antibody protective

Applications of Research

- Type specific antibody raised in horses can treat pneumococcal pneumonia and meningitis

- Capsular polysaccharide can vaccinate and protect humans against pneumococcal infections

Oswald Avery

Library of Congress

Margaret Pittman
H. influenzae

- Early 1930s at Rockefeller Institute
- Capsule types
- Serotype b, bld &CSF
- Antibody to capsule protects rabbits

Fothergill and Wright

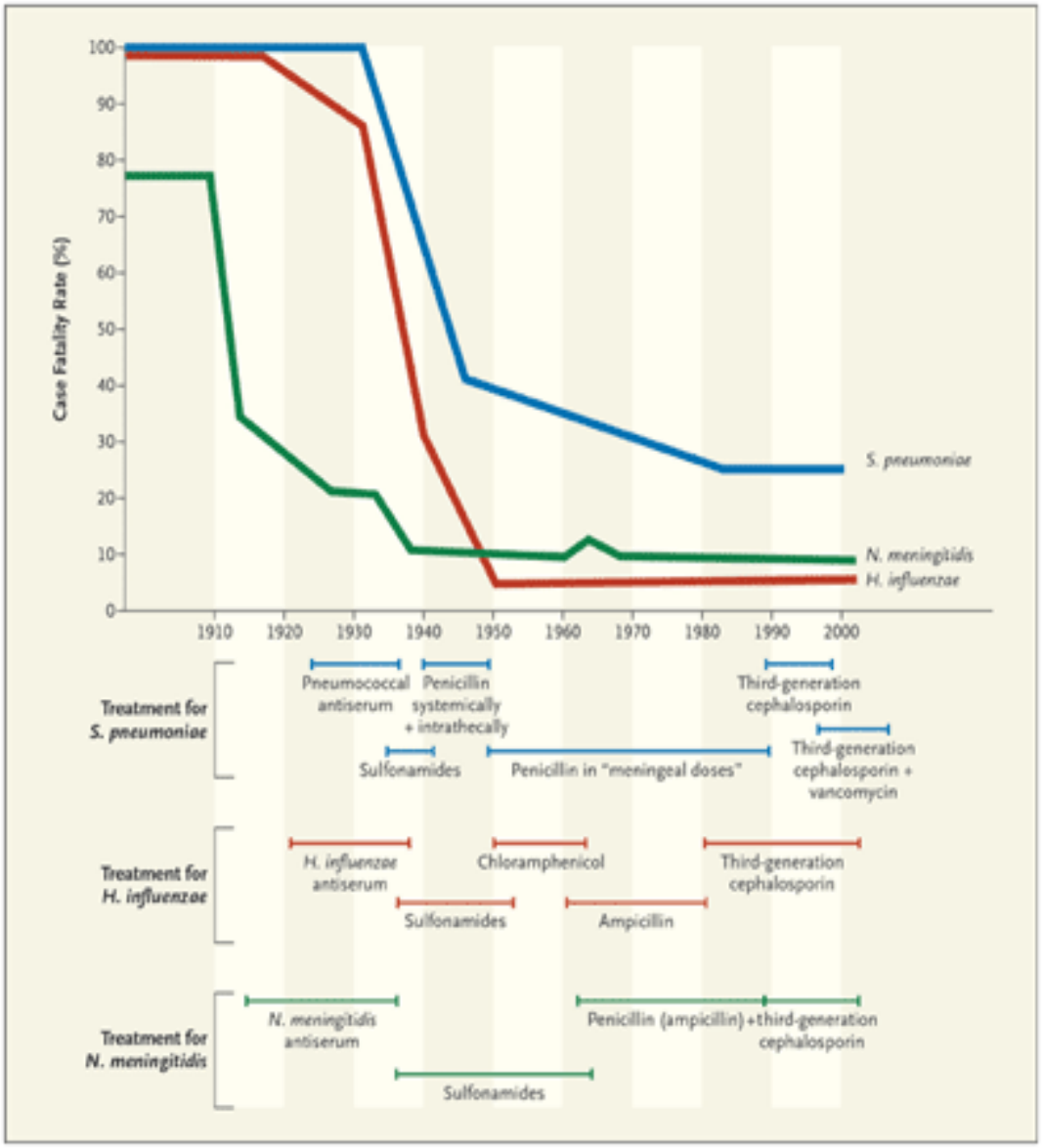
(J Immunol 1933;24: 273-84.)

- *H. influenza* meningitis occurs in children without bactericidal antibody to Hib

- Age related acquisition of antibody decrease in *Hi* meningitis.

Bacterial Meningitis-A View of the Past 90 Years

(Swartz. NEJM 2004;35: 1826-28.)

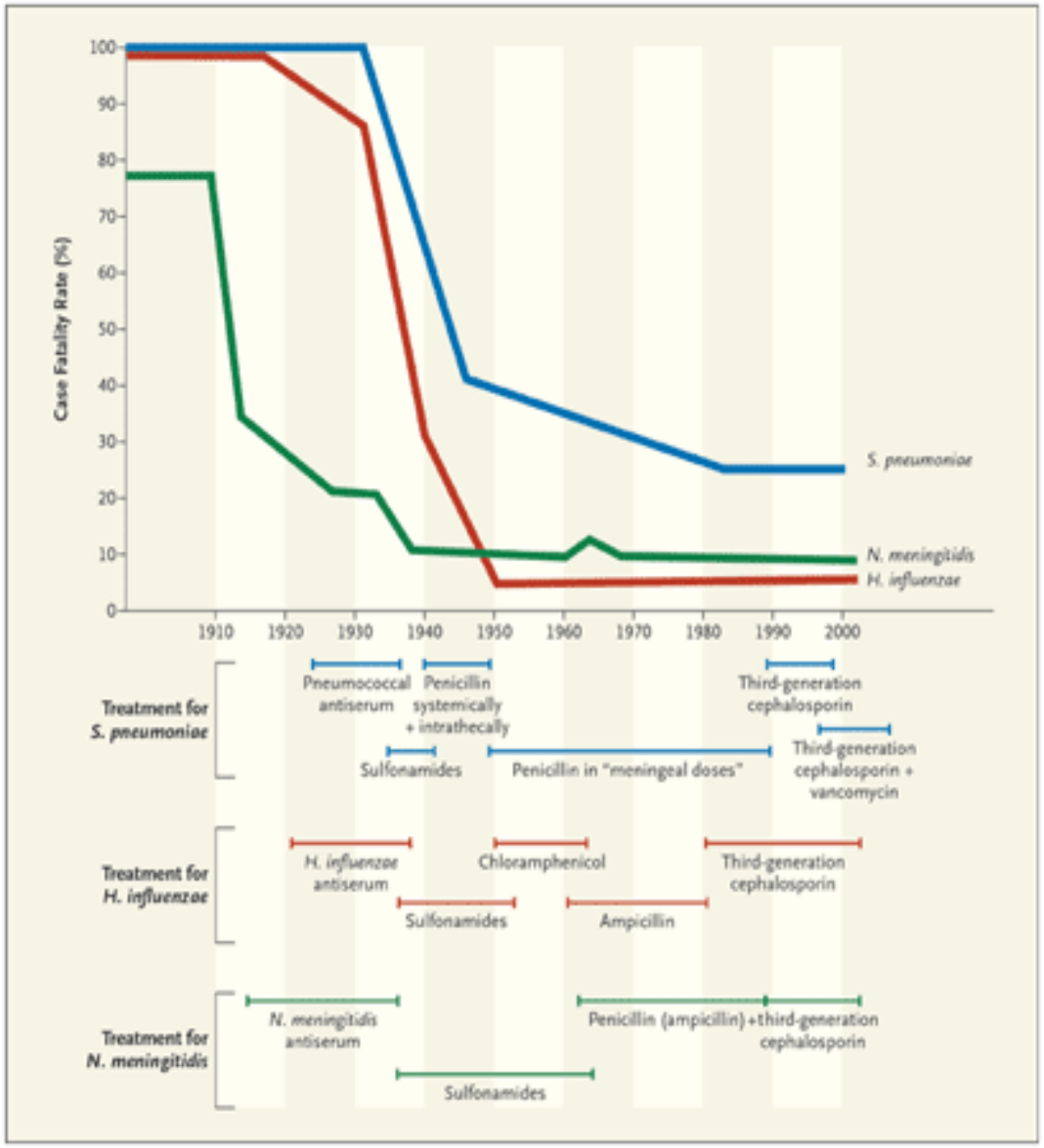


Antibiotic Era, 1935 to Present

- Dramatic decrease in meningitis mortality
- Large number of cases continues
- Antibiotic resistance develops

Bacterial Meningitis-A View of the Past 90 Years

(Swartz. NEJM 2004;35: 1826-28.)

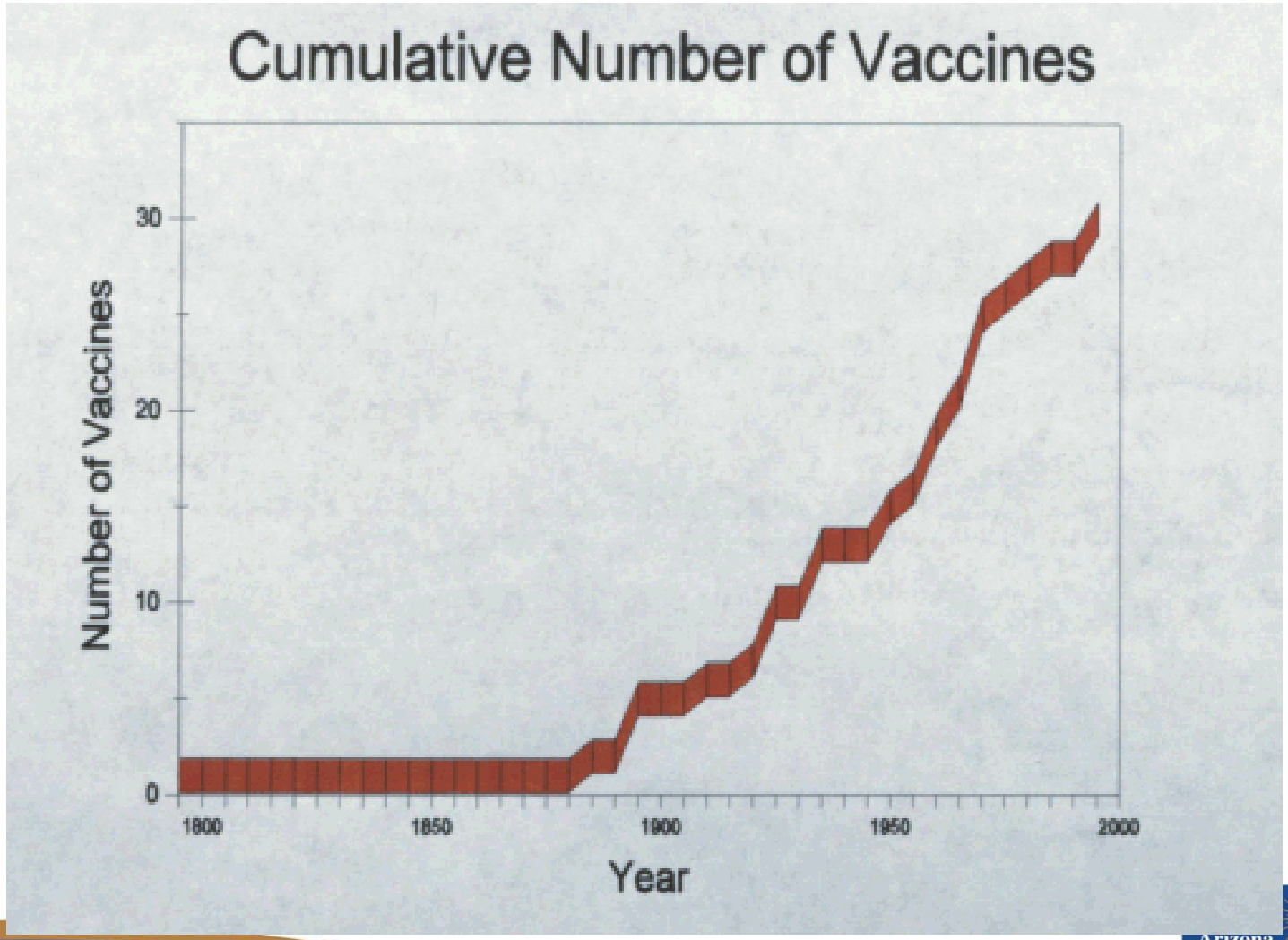


Bacterial Meningitis in US, 1978 -'81

(Schlech. JAMA1985;253:1749-54)

- 13,974 cases from 27 states
- *Hi*b 48.3%, 6% CFR
- *N menig* 19.6%, 10.3% CFR
- *S. pneum* 13.3%, 26.3% CFR
- Young children most frequently infected
  - *Hi*b 85% , <2 yrs.
  - *N mening*, 42%
  - *S pneumo*, 38%

Vaccine Era


Cumulative Number of Vaccines
Number of Vaccines
30
20
10
0
1800
1850
1900
1950
2000
Year

Vaccines- Back to the Future

- Hib capsule polysaccharide is poly-ribitol phosphate (PRP)
- PRP induces antibody in humans
- PRP vaccine developed
- 1974 trial in Finland partial success
  - incomplete protection
  - No antibody in infants

Conjugated Hib Vaccine

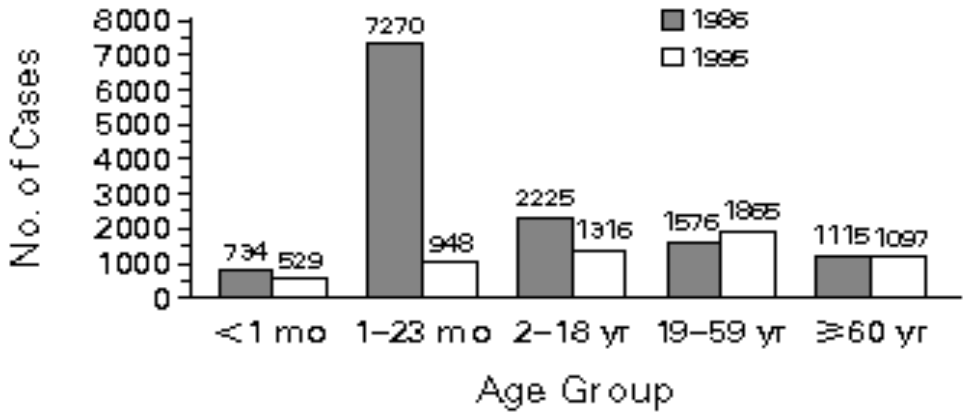
- Oswald Avery observed a better antibody response with polysacc protein pairs
- PRP covalently bonded to proteins produced a robust response. Works by recruiting T cells to augment antibody production
- Clinical trials successful

*Hi*b Vaccine Lasker Award

Bacterial Meningitis in the US in 1995

(Schuchat et al. NEJM1997;337:970-76.)

- Active surveillance 5 years after Hib conjugated vaccine in use
- 94% decrease in *Hi* meningitis
-



Pneumococcal Vaccine

- A vaccine developed in 1945 and was efficacious in trials
- No further development until the 1970s
- Robert Austrian championed the development of a 14 polysaccharide vaccine for pneumonia. Not conjugated.
- Later expanded to 23 serotypes
- Target was adults

1978 Lasker Awards for Pneumococcal Vaccine

Robert Austrian
Department of Research Medicine
University of Pennsylvania
School of Medicine

Michael Heidelberger
Columbia University

Burden of Pneumococcal Infection

- Post Hib vaccine *S. pneumoniae* most common cause of meningitis in children and adults
- In children pneumococcal otitis media a significant cause of illness and source of meningitis
- Cost of pneumococcal OM estimate $1-3 billion

Pneumococcal Conjugated Vaccine

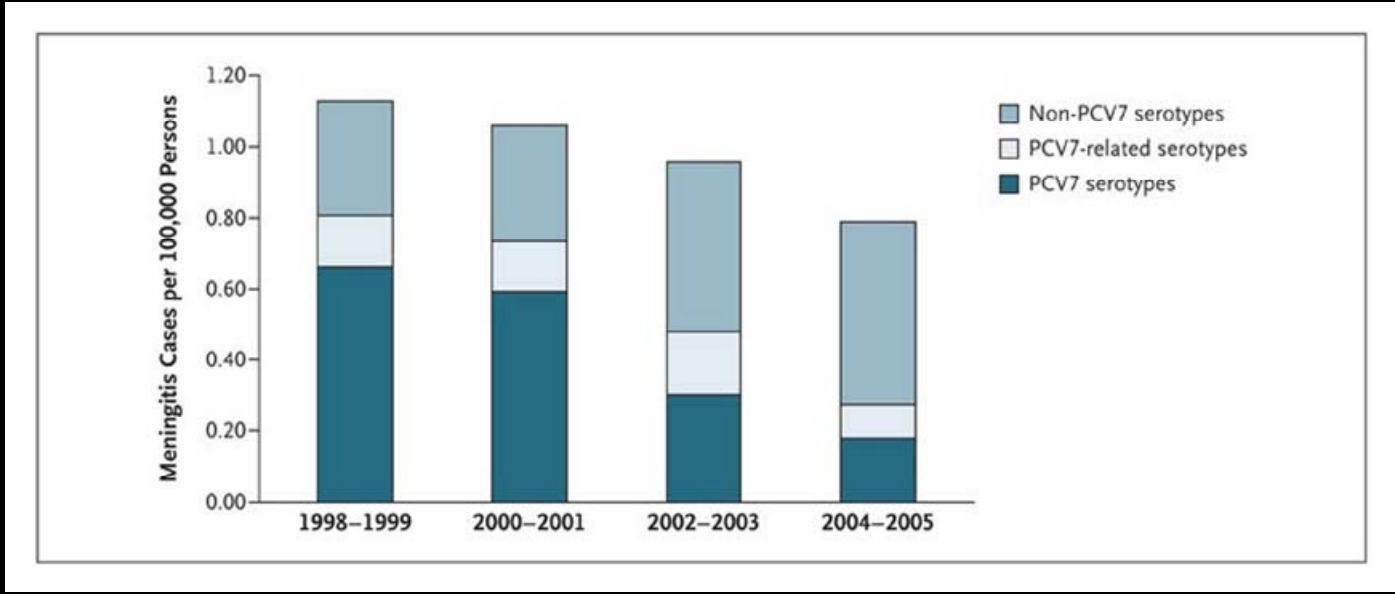
- Target is children
- Fewer serotypes (7 vs 23) in vaccine because of fewer types in children
- Conjugated vaccine developed. Trials successful for invasive disease (~70-94%)
- Less effective against otitis media
- Licensed in US in 2000.

Effect of Pneumococcal Conjugate Vaccine on Pneumococcal Meningitis

(Hsu. NEJM2009;360;244-56)

- Decreased pneumococcal vaccine serotype meningitis by 73.3% All ages.
- But non vaccine serotype disease increased by 60.5%
- Total pneumococcal meningitis rates decreased 30.1%
- In adults (not vaccinated) pneumococcal bacteremia decreased 57%

Mean Annual Incidence of Pneumococcal Meningitis, According to Serotype Group and Time Period



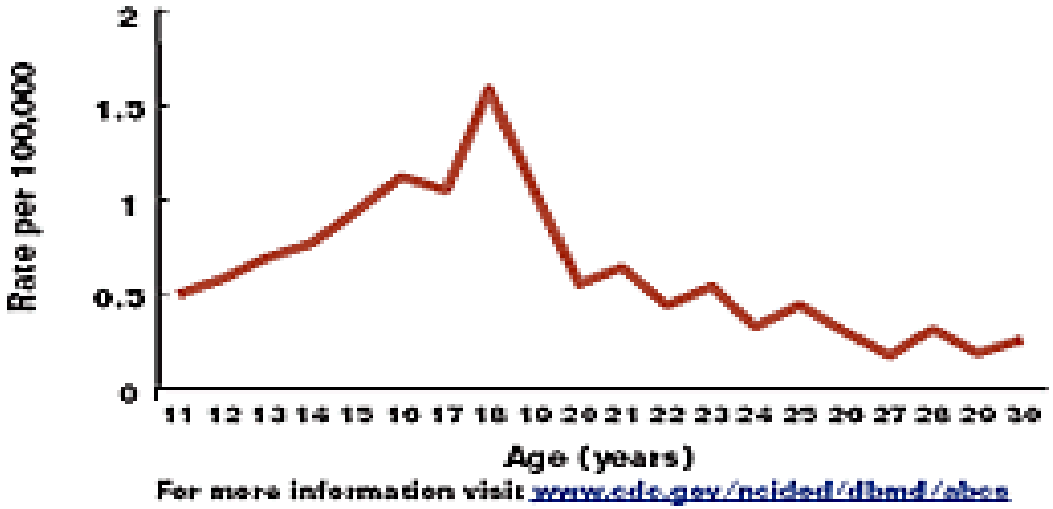
Hsu H et al. N Engl J Med 2009;360:244-256

Meningococcal Meningitis

- Currently 2nd most common cause of meningitis in US.
  - 25% of total, 3-10% CFR
- Sporadic but clusters occur
  - Military training camps
  - Dormitory
- Military outbreaks stimulated vaccine development

Meningococcal Disease Rates, USA

Projected Rates of Meningococcal Disease (A/C/Y/W-135) by Age, United States, Active Bacterial Core Surveillance System, 1991–2002



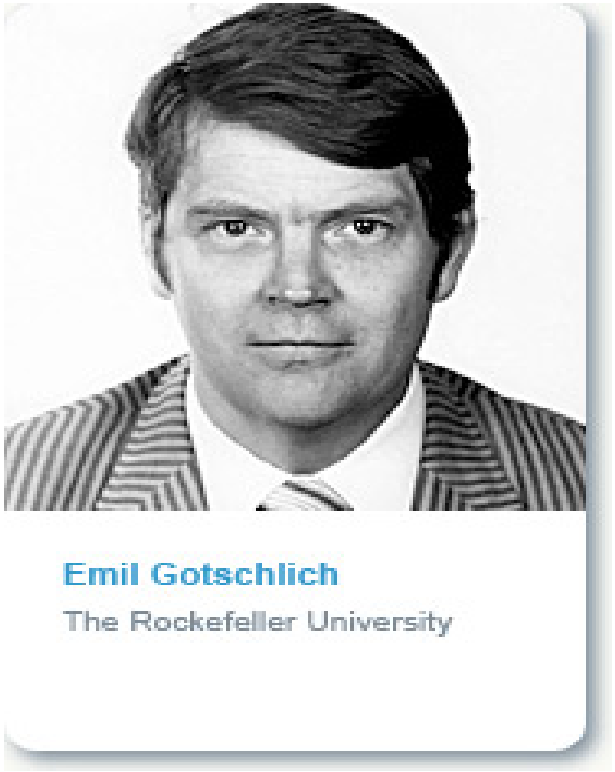
For more information visit www.cdc.gov/ncidod/dbmd/abcs

Current Serogroups, USA

- Group B 21%, Group C 42%, Group Y 21%
- 75% of cases >11years, caused by C, Y, W-135
- Children <1 year, > 50% cases caused by Grp B
- MMWR 2005;54 RR-7

Meningococcal Vaccine

- Late 1960s meningococcal polysaccharides (A and C) purified at Walter Reed Medical Center
- Shown to be immunogenic and safe
- Trial of Grp C vaccine in Army recruits showed an 87% reduction in disease.



Conjugated Vaccine, Grp C England

- 1999 monovalent conjugated vaccine

- 2000-2001 88-98% effectiveness with ~85% coverage

Current Meningococcal Vaccines

- MPSV4: Polysaccharide, 4 serogroups(A,C,Y,W-135)

- MCV4: conjugated polysaccharide, 4 serogroups

Summary

- Early 20th century science set the stage
- 1960-’70 purified polysaccharide vaccines developed
- Vaccines have reduced the burden of bacterial meningitis, especially in children

Pneumococcal Polysaccharide Vaccine Recommendations

- Adults 65 years of age or older
- Persons 2 years of age or older with
  - chronic illness
  - anatomic or functional asplenia
  - immunocompromised (disease, chemotherapy, steroids)
  - HIV infection
  - environments or settings with increased risk
  - cochlear implant

Pneumococcal Conjugate Vaccine

- Routine vaccination of children age <24 months and children 24-59 months with a high-risk medical condition
- Doses at 2, 4, 6, months of age, booster dose at 12-15 months of age
- Unvaccinated children ≥7 months of age require fewer doses

Pneumococcal Conjugate Vaccine

- Children aged 24-59 months at high risk and previously vaccinated with PPV23 should receive 2 doses of PCV7
- Children at high risk who previously received PCV7 should receive PPV23 at age ≥2 years

Meningococcal Vaccines

- MCV4: Single dose IM
  - 11-12 year olds
  - High school entry
  - Higher risk groups: college freshmen in dorms, lab workers, military recruits, travel to endemic zones, asplenia,comp def.

Meningococcal Vaccines

- MPSV4: Single dose, subcutaneous
- Elevated risk age 2-10 and >55yrs old
- Substitute if MCV4 not available 11-55 years

Chemoprophylaxis

- Administration of antibiotic to close contacts of mening cases to prevent meningitis
- Antibiotics; rifampin for 2 days, single dose po cipro, single dose IM ceftriaxone
- Key: close contacts (house hold level or closer)
- Be quick