Streptococcus pneumoniae: the perennial pathogen

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Outline

Historic importance
Pathogenesis
Diseases
Antibiotic susceptibility
Treatment
Prevention

Community-acquired pneumonia, pre-antibiotic era (Heffron, 1938)

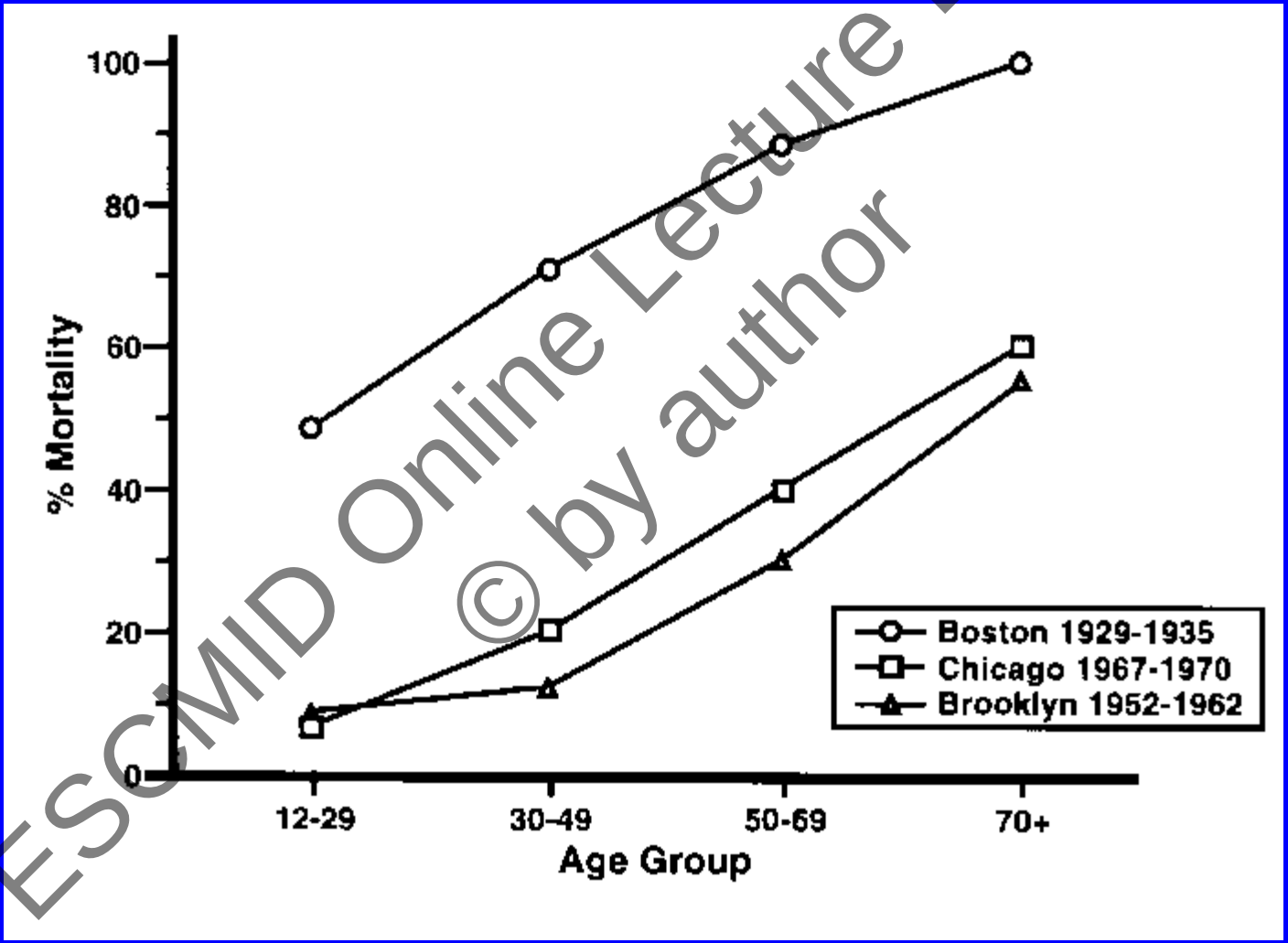
Organism found	*Number of cases*	*Per cent*
Pneumococcus	3,189	96.1
Streptococcus	94	2.8
Friedländer's bacillus	17	0.5
Influenza bacillus	7	0.2
Staphylococcus	6	0.2
Mixed infections	6	0.2
Total	*3,319*	*100.0*

Pneumococcus remains common as a cause of community-acquired pneumonia

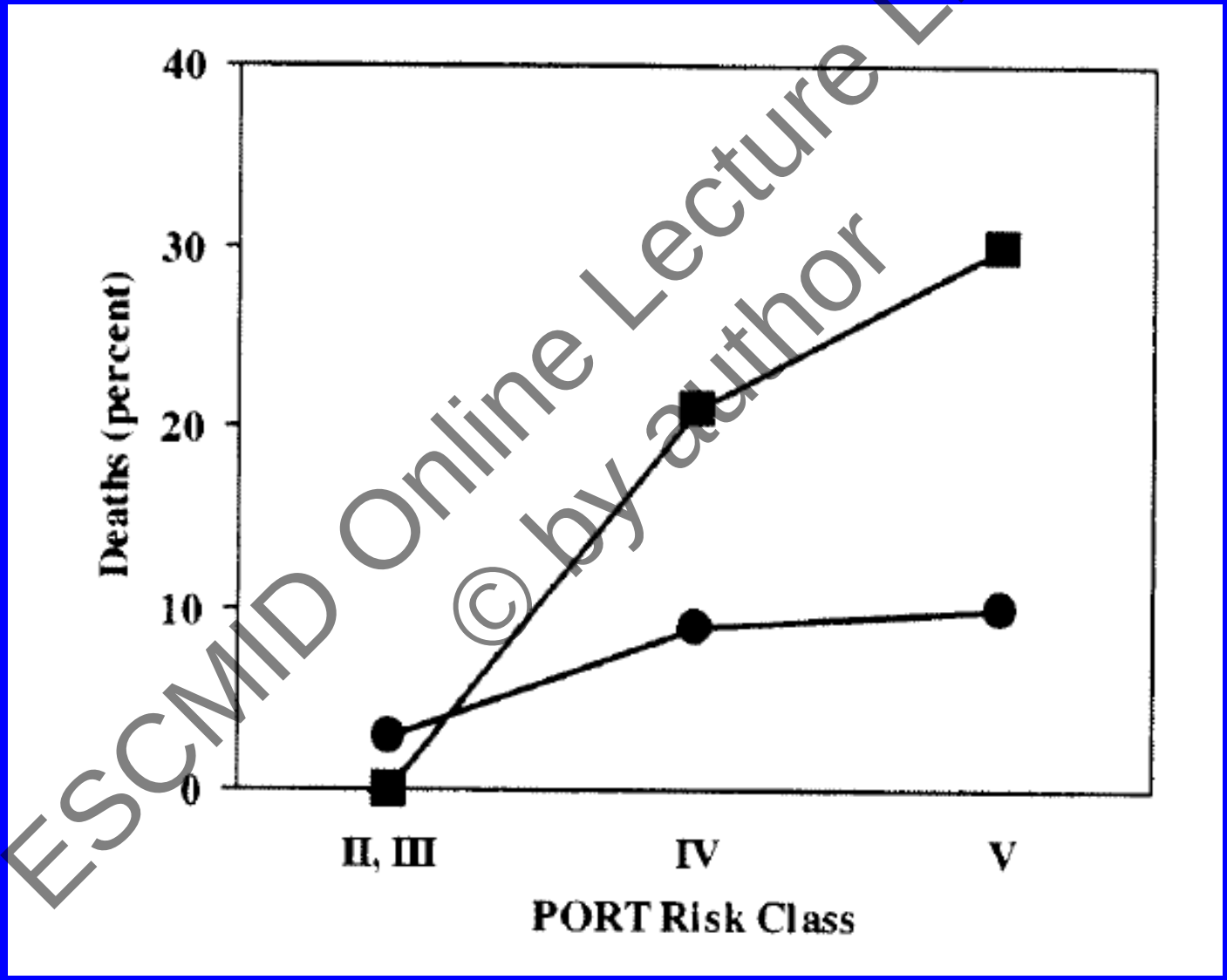
	Holland[1] Snijders	UK[2] Lim, MacFarlane	Sweden[3] Johansson
Str. pneumo	37	48	64
Haemoph	0	7	11
Staph aureus	1	1	1
Gram neg rods	4	1	1
Legionella	4	3	1
Viruses	5	19	29
Mycoplas/Chlamyd	7	18	8
No pathogen	44	25	11

[1] 2010: Intense micro; exclude COPD ; [2] 2001 Intense micro + urine antigen
[3] 2010 Intense micro + PCR (nearly all specimens)

Pneumococcal pneumonia is a potentially lethal infection



Pneumococcal pneumonia as a serious disease (1990-2000)



What features of pneumococcus make it such a common and important pathogen for humans?

- Readily adheres to respiratory epithelium
- Replicates in the nasopharynx to large numbers (especially in infants and small children)
- Persists weeks to months
- Transmissible by human-to-human contact; transmission facilitated by respiratory viruses

Immunity to pneumococcus

- Adherence via TLR 2,4, enables ingestion by dendritic cells and macrophages
- With replication, the bacteria may overwhelm innate immunity
- PMNs do not ingest pneumococci in the absence of antibody to capsule
- Type-specific anticapsular antibody develops with colonization (Musher et al, CID, 1997)
- But many serotypes, and antibody to polysaccharides is relatively short-lived

Two basic mechanisms for causing disease: I. Local proliferation

In the respiratory tract, pneumococci are carried to spaces where they do not belong (middle ear, sinuses, bronchi, alveoli)
Normally cleared, but clearance mechanisms may fail, often as a result of concurrent inflammation and/or obstruction
Organisms replicate, overwhelm innate immunity
Stimulate vigorous inflammatory response
In absence of antibody, PMNs are unable to ingest organisms
Inflammatory response = disease

Two basic mechanisms for causing disease: II. Systemic

- Direct invasion across mucosal barriers, either at site of colonization (uncommon, but certainly occurs) or at a site of infection (pneumonia, otitis, sinusitis)
- Leads to spread along lymphatics, bacteremia
- Spread results in meningitis or hematogenous disease

Diseases caused by pneumococcus

I. Direct extension and proliferation

A. Respiratory tract:

otitis media (mastoiditis), sinusitis (periorbital cellulitis, facial), acute exacerbation of chronic bronchitis, pneumonia

B. Other:

cellulitis, salpingitis, peritonitis, appendicitis

II. Invasion and direct penetration of lymphatics:

meningitis

III. Hematogenous spread:

primary bacteremia, meningitis, septic arthritis, osteomyelitis, spontaneous bacterial peritonitis (with preexisting peritoneal disease), endocarditis, pericarditis, cellulitis, endophthalmitis

(Entirely different mechanism: Hemolytic-uremic syndrome)

Pneumococcal disease outside the respiratory tract in adults *

Outside respiratory tract	
Bacteremic pneumonia¶	85%
Bacteremia, no focus	5%
Meningitis	4%
Spontaneous peritonitis‡	2%
Endocarditis	1%
Osteomyelitis	1%
Spinal epidural abscess	1%

* Rueda, Musher et al, Medicine, 2011

¶ Empyema in 3% of cases

‡ See Dugi, Musher et al Medicine 80:236, 2001

How susceptible is pneumococcus (Spn) to antibiotics?

At beginning of antibiotic era, Spn was fully susceptible to each drug as it came along; MIC reported as ≤.06 ug/ml penicillin

Laboratories did not even test Spn

Rare reports of resistant isolates in 1960's

South Africa, 1977-8, outbreaks that failed standard treatment; penicillin MIC 0.1-2 ug/ml

Also resistant to other drugs such as chlorampenicol, tetracycline (Appelbaum, Jacobs, Koornhof, Lancet and NEJM, 1977, 1978).

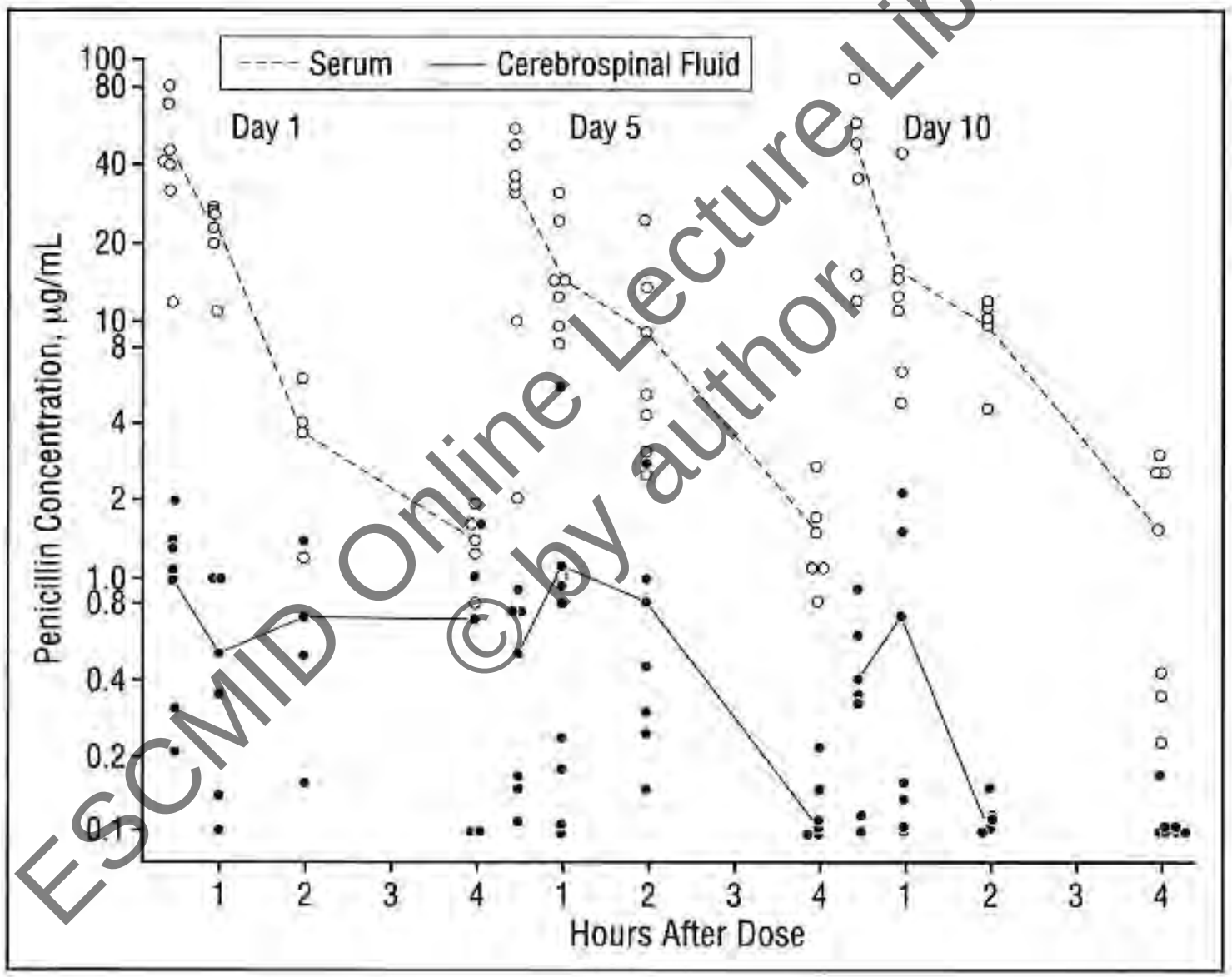
Led to a definition of penicillin susceptibility

MIC ≤0.06 = susceptible

MIC 0.12 to 1 = intermediate susceptibility

MIC ≥2 = resistant

A fresh look at the definition of Spn to beta-lactam antibiotics Musher, Arch Intern Med 2001 (from Hieber. Nelson, NEJM 1977)



Led to a redefinition of beta-lactam susceptibility based on site of disease

Non-CNS disease

- MIC ≤2 ug/ml= susceptible
- MIC 4 ug/ml = intermediate susceptibility
- MIC ≥8 ug/ml = resistant

CNS disease

- MIC ≤0.06 = susceptible
- MIC 0.1 to 1 = intermediate susceptibility
- MIC ≥2 = resistant

General rates of resistance of pneumococci to other antibitiocs

Varies with geographic location, age of patient, source of isolate; also affected by widespread use of conjugate vaccine.

Penicillin, amoxicillin 5%
Ceftriaxone 5%
Macrolides 15-20%
Doxcycycline 15-20%
TM/SMX 25%
Quinolones 1-2%
Vancomycin 0%

Prevention of pneumococcal infection by vaccination

Landmark scientific evidence on protective effect of antibody to CPS

1890's, Klemperers, experiments in rabbits, show basis for humoral immunity, type specificity

1912-21, Wright and Lister administered killed pneumococci as vaccines in miners, showing protection (later critique by Orenstein [S Afr J Med Sci] questions findings)

1920's Avery shows that humoral protection results specifically from antibody to capsule

1930's Felton isolates capsule for use as vaccine

Landmark scientific evidence on protective effect of antibody to CPS

Many, many studies, different kinds: here are just three with range of results:

1940's, US Army trials show significant reduction in pneumococcal pneumonia in military recruits

1986 VA study (Simberkoff) shows no efficacy of PN14 in older veterans with comorbid conditions

1991 case control study in Connecticut (Shapiro) shows vaccine is effective for >5 years in most adults, but less effective in elderly, and more rapid decline of effectiveness after 3 years

Is 23-valent pneumococcal polysaccharide vaccine (PPV23) effective? Meta-analyses

Moberley (2008): For pneumococcal pneumonia with bacteremia), find 74% ↓ due to all types; 92% ↓ vaccine-specific types. For nonbacteremic pneumococcal pneumonia (NBPP), 53% ↓ all types; 73% ↓ vaccine-specific types (this study often misquoted)

Huss (2009) reanalyzed data based on statistical criteria leaving 4-5 studies. Principal ones (Koivula, Ortqvist) were elegantly designed but diagnosis of NBPP was problematic. This metaanalysis shows no benefit

So you can cite a recent metaanalysis to defend any position you want to take. No solution but to read the literature for yourself

Conclusions from all the studies of pneumococcal polysaccharide vaccine

Even the most ardent proponents of pneumococcal vaccination would agree that:

a. protection is far from complete

b. efficacy declines in those most at risk

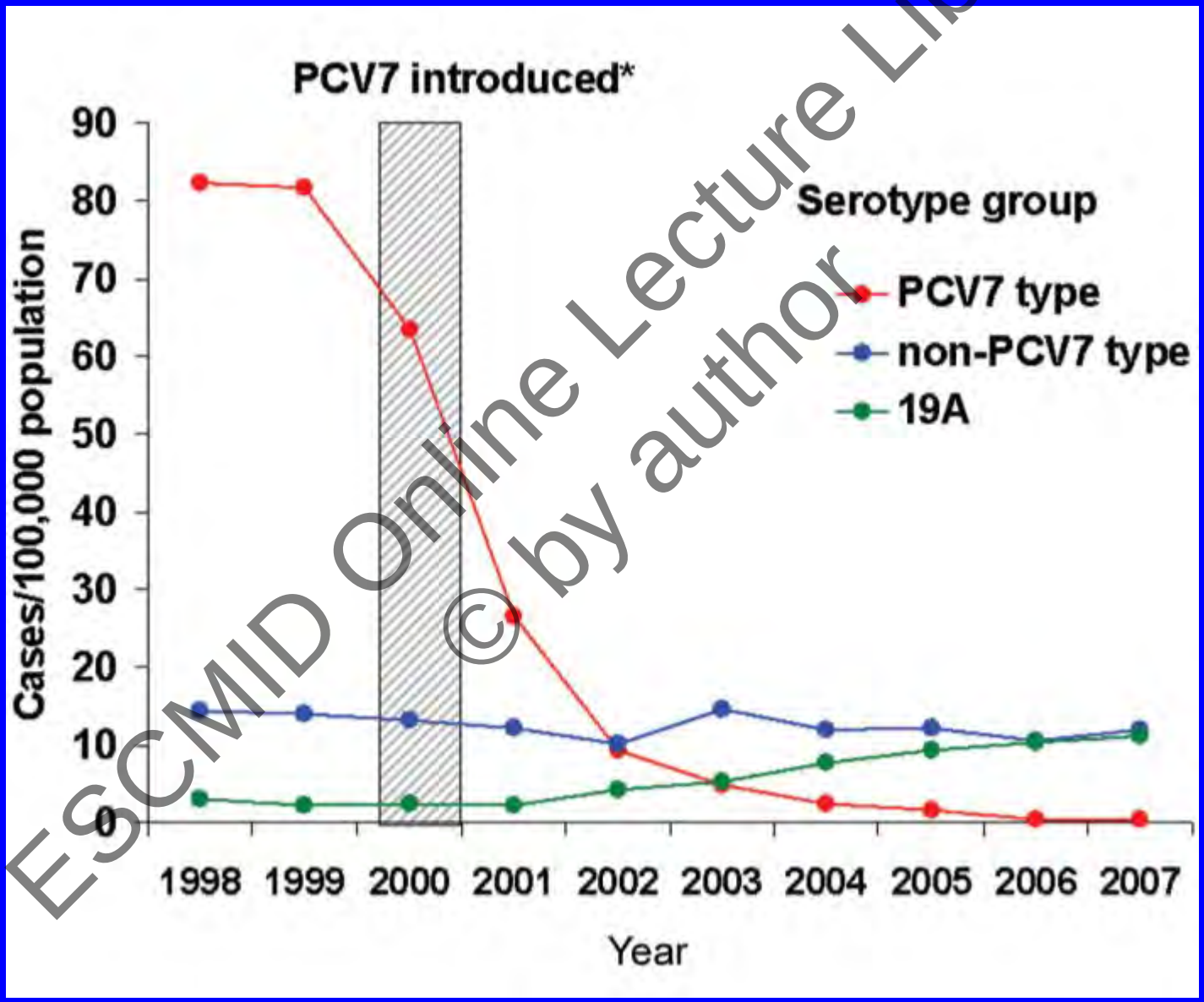
c. a better vaccine or a better vaccine strategy is needed

d. and, of course, polysaccharide vaccine does not immunize infants, toddlers

Now, let's address protein-conjugate pneumococcal polysaccharide vaccine

- Chemical linking of polysaccharide to a protein (conjugation) yields an antigen that effectively immunizes infants and young children
- Pneumococcal vaccine containing 7 capsular polysaccharides conjugated to proteins – Prevnar7® (PCV7) – was developed
- Brilliantly successful in preventing meningitis and invasive disease in randomized study of 38,000 infants (Black, Ped Infect Dis J 19;187-195, 2000)

Invasive pneumococcal disease in US children ≤5 yrs of age (Pilishvili, J Infect Dis Jan, 2010)



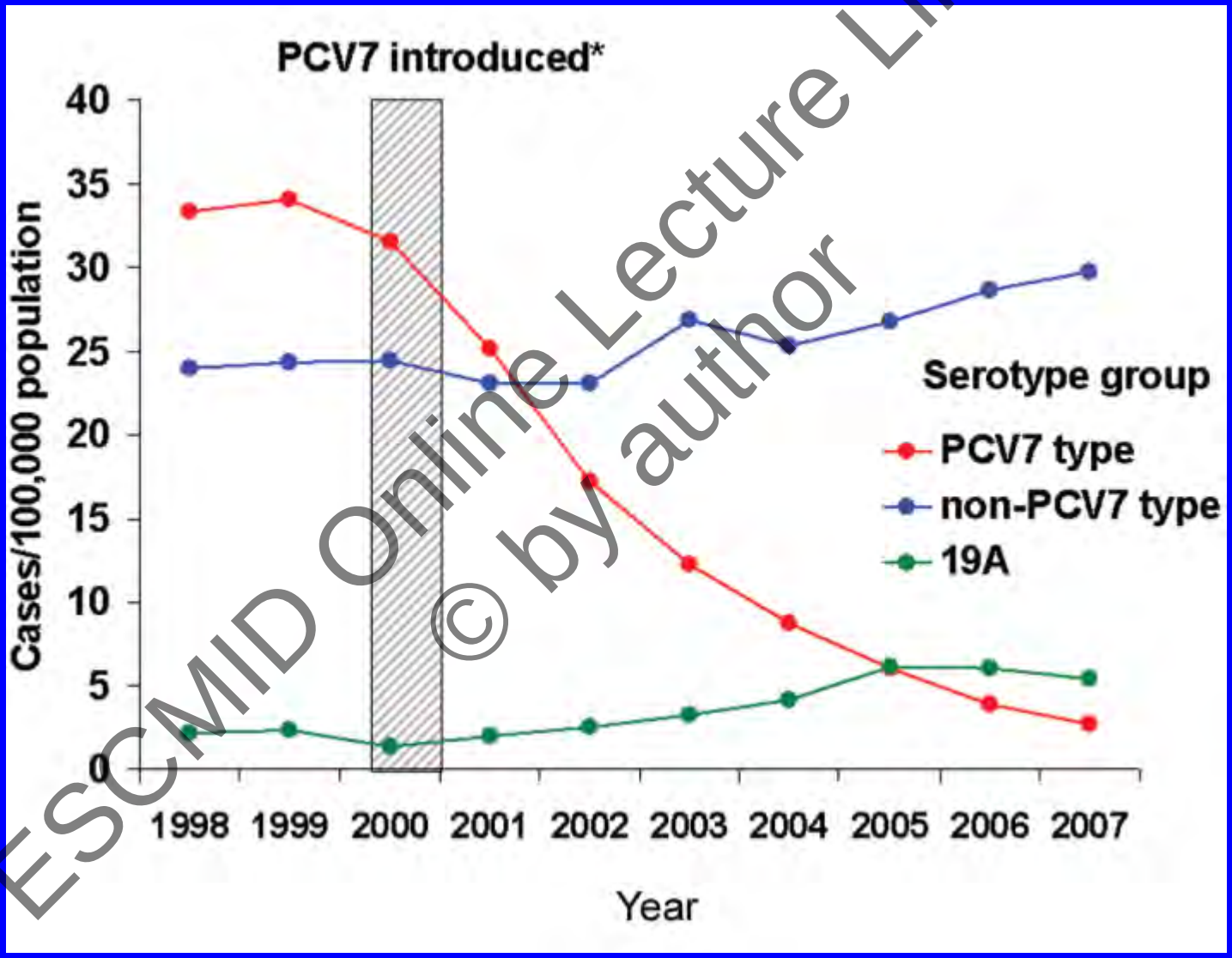
Further effects of conjugate vaccine

In addition to protecting against infection, PCV protects against colonization of the nasopharynx, which the polysaccharide vaccine does not do

That means that the prevalence of vaccine-type pneumococci in the population is greatly reduced

That leads to **HERD PROTECTION;** infection caused by vaccine serotypes is greatly reduced in nonvaccinated children and in adults

Invasive pneumococcal disease in older US children and adults (Pilishvili, J Infect Dis Jan, 2010)



A major problem with PCV7: replacement strains

- "Replacement strains," not included in PCV7 (19A, 6A, 7F, and others) have greatly increased as colonizers in kids
- Adults acquire pneumococci from exposure to kids
- Therefore, ↑ non-vaccine types as cause of pneumococcal disease in adults
- The most common cause of pneumonia in older adults in US 2008-2010 was replacement strain type 19A

The new PCV (PCV13)

- PCV13 includes types 1, 3 and 5, which are the major epidemic strains in developing countries and 3 important 'replacement strains' (including 19A)
- A PCV15 is currently under development
- But once these in widespread use in children, expect other replacement strains to emerge

PCV13 vs PPV23 in adults

- Because of its immunologic properties, is conjugate vaccine a better vaccine than PPV23 in adults? Probably not (Musher CID, 2011)
- Widespread use of PCV13 in toddlers will vastly reduce its potential effectiveness in adults
- New replacement strains will become prevalent; will they be PPV23 strains??
- Netherlands PCV13 study in progress
- We need to develop an entirely new approach – e.g. a vaccine based on conserved pneumococcal proteins

Summary

- Long-standing importance as a cause of serious disease
- Pathogenesis: direct spread vs hematog
- Range of diseases – predicted by pathogenesis
- Susceptibility to antibiotics
- Prevention by vaccine: is PPV23 is a good vaccine in adults? Will conjugate vaccine have a role in adults?
- Need to develop a better vaccine