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Scuola
di
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Pneumococcal Disease

Pneumococcal Disease

- S. pneumoniae first isolated by Pasteur in 1881
- Confused with other causes of pneumonia until discovery of Gram stain in 1884
- More than **80 serotypes** described by 1940
- First U.S. vaccine in 1977

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Pneumococcal Disease: A Family's Story

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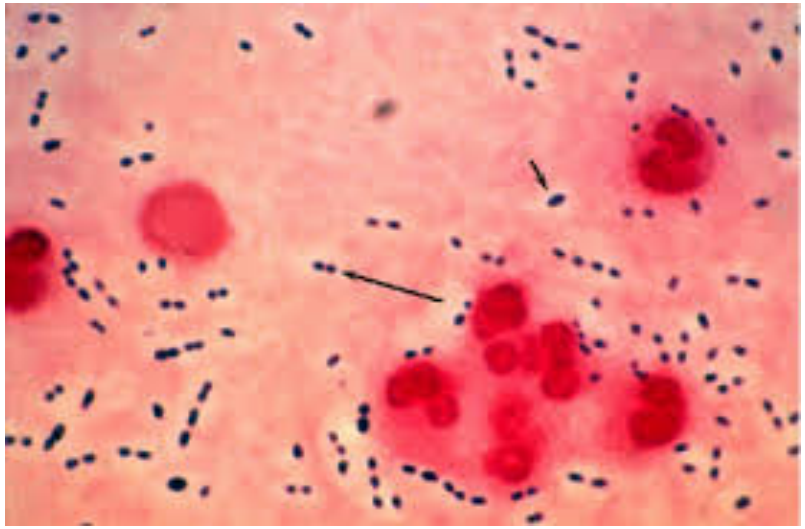
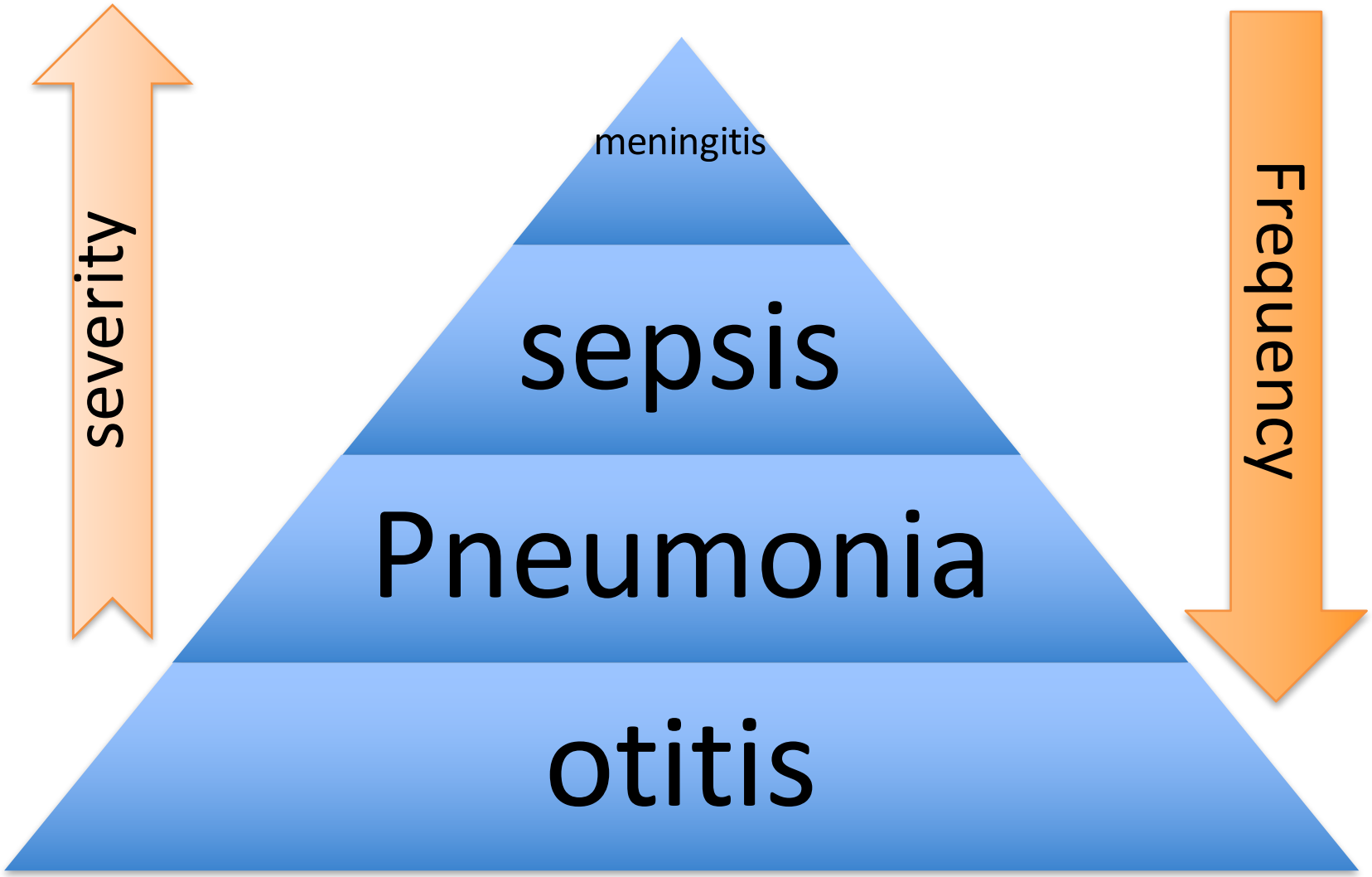
Pneumococcal Infections in Children

Streptococcus pneumonia

- Gram-positive organisms
- **Polysaccharide capsule** important pathogenicity factor
- **92 serotypes** documented as of 2011
- Type-specific antibody is protective





Alberto Baldasseroni, Sara Franchi, Claudia Dellisanti. Dossier. Introduzione universale della vaccinazione contro le patologie causate da *Streptococcus pneumoniae* nei bambini e negli adulti: prove di efficacia. Gruppo per la "Evidence Based Prevention". Agenzia regionale di Sanità Toscana. Anno 2007

Pneumococcal Pneumonia
Clinical Features

- Abrupt onset of fever
- Chills or rigors
- Pleuritic chest pain
- Productive cough
- Dyspnea, tachypnea, hypoxia
- Tachycardia, malaise, weakness

Pneumococcal Pneumonia

- Estimated **400,000 hospitalizations** per year in the United States
- Up to 36% of adult **community-acquired pneumonias**
- Common bacterial **complication of influenza**
- Case-fatality rate 5%–7%, higher in elderly

Microbial aetiology of community-acquired pneumonia and its relation to severity

Cillóniz C et al, Thorax. 2011

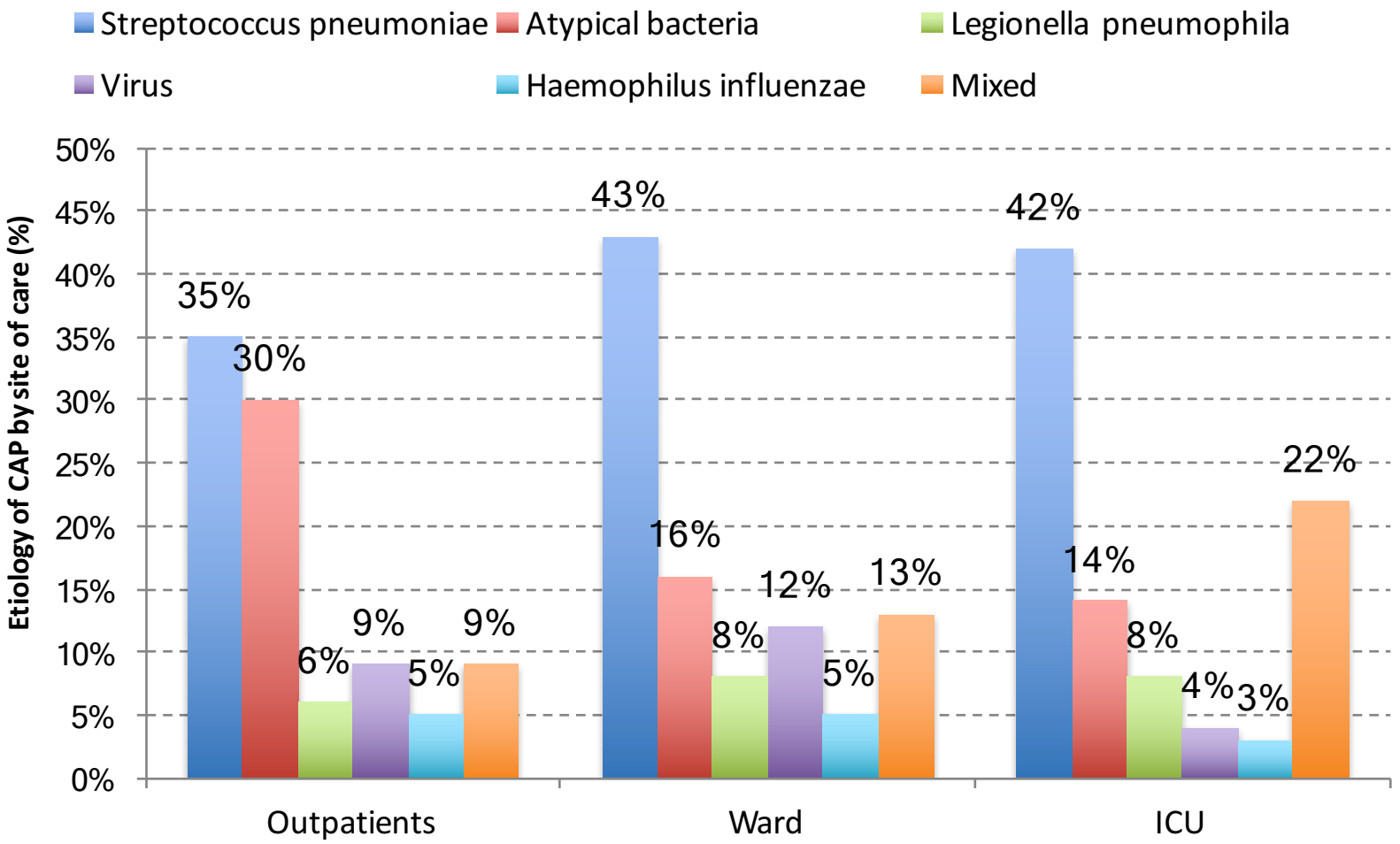
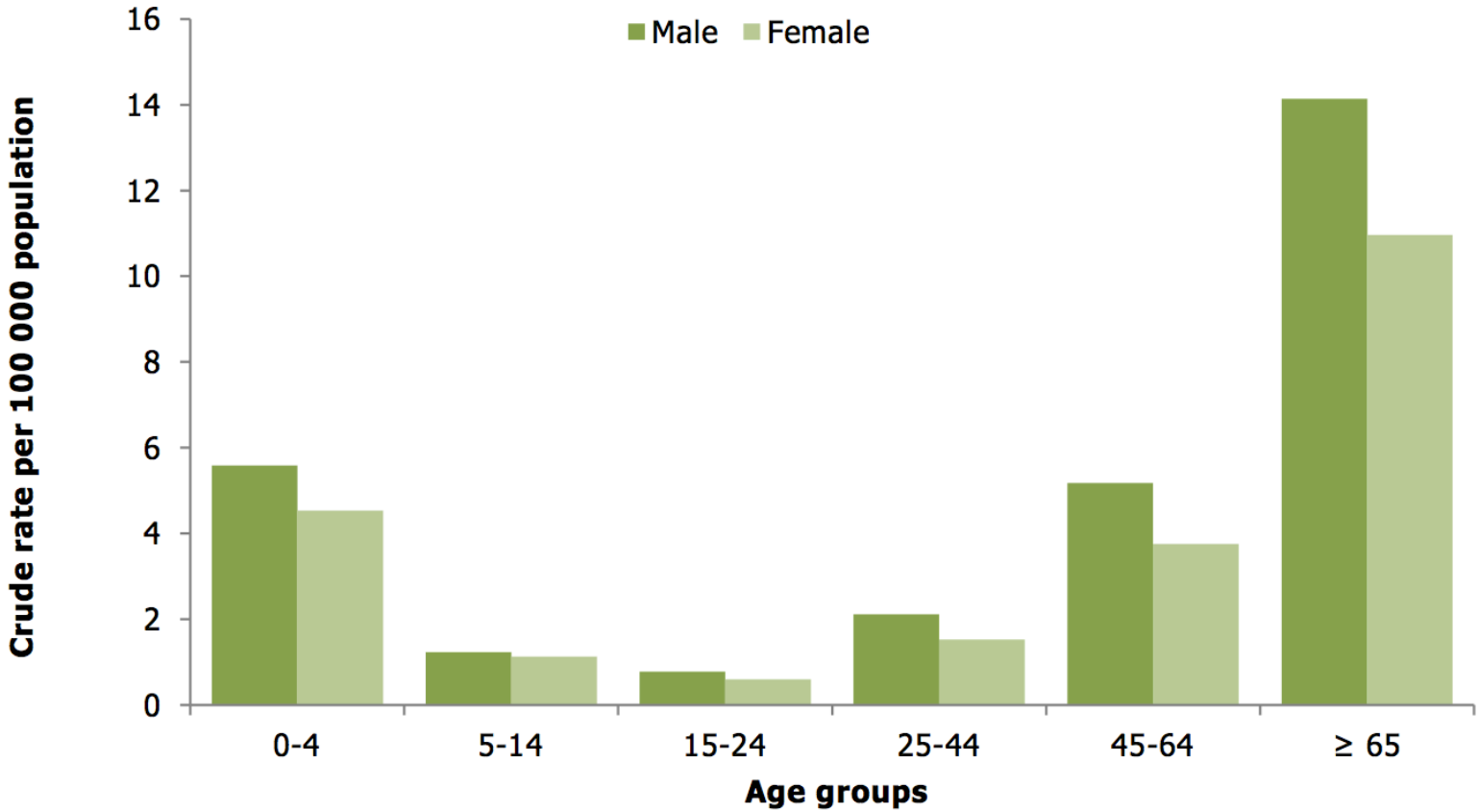


Figure 14. Rates of confirmed invasive pneumococcal disease reported cases by age and gender, EU/EEA, 2012



Source: Country reports from Austria, Czech Republic, Denmark, Estonia, Finland, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Romania, Slovakia, Slovenia, Sweden and United Kingdom.

Among adults, bacteriemic pneumonia accounted around 80% of pneumococcal diseases

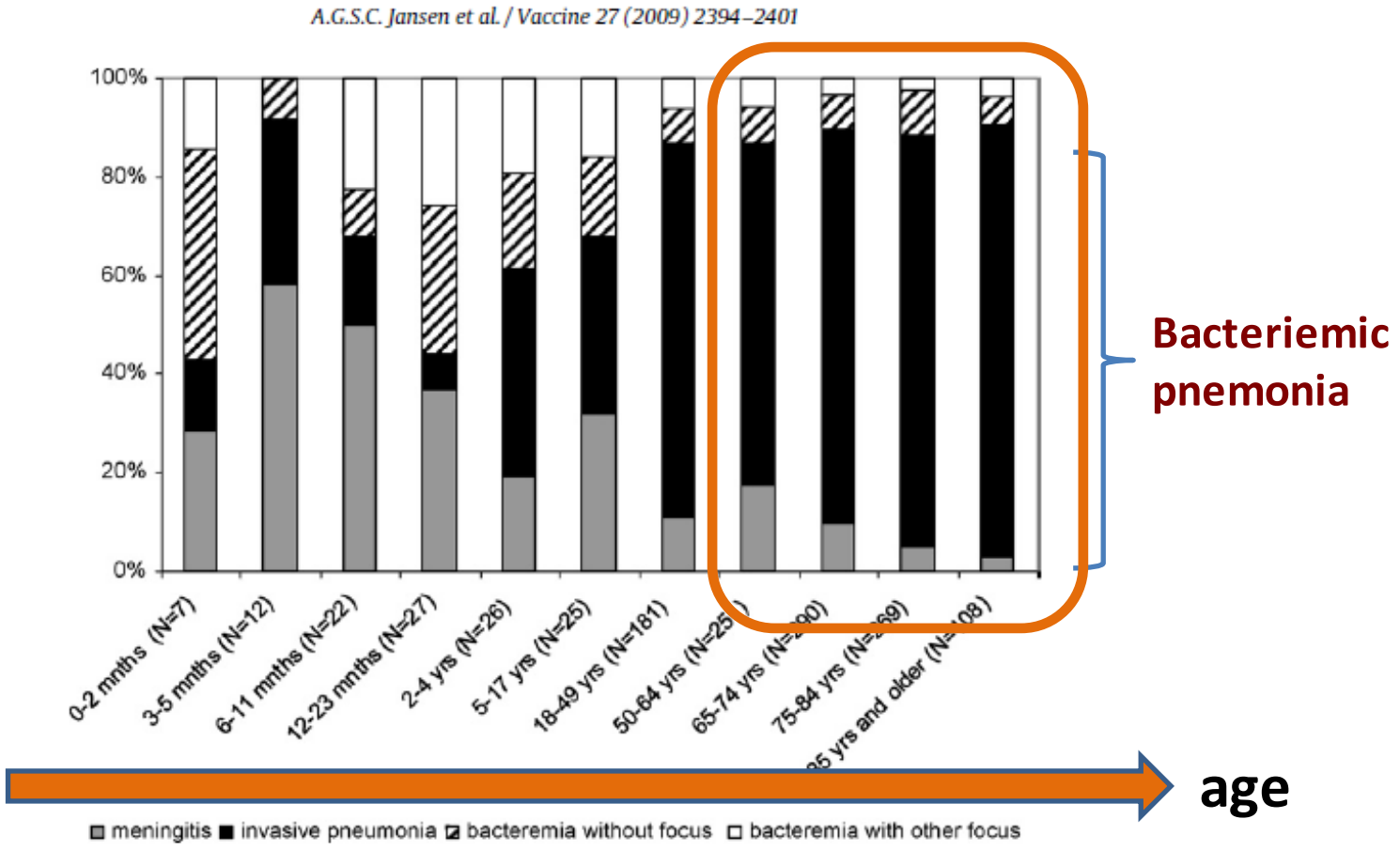


Fig. 3. Distribution of clinical syndromes in invasive pneumococcal disease by age in the Netherlands.

Pneumococcal Bacteremia

- More than 12,000 cases per year in the United States
- Case-fatality rate ~20%; up to 60% among the elderly

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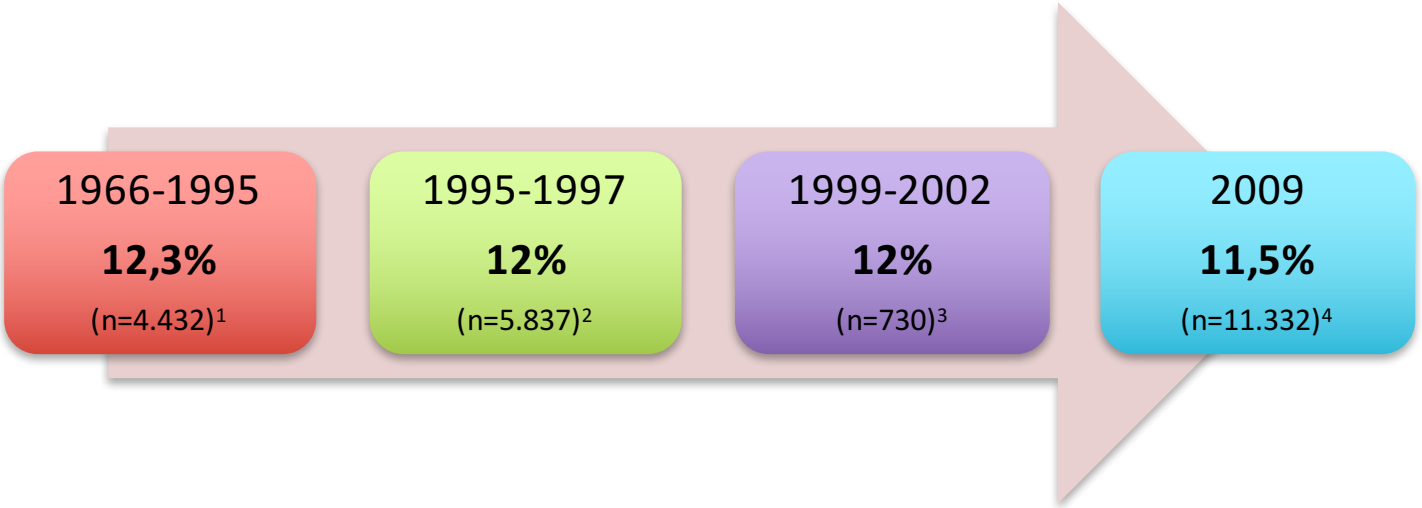
Mortality of patients with CAP



1. Fine MJ, et al. JAMA. 1996;275:134-141. 2. Feikin DR, et al. Am J Pub Health. 2000;90:223-229. 3. Restrepo MI, et al. Chest. 2008;133:610-617.4. Klausen HH et al. Respir Med. 2012;106:1778-87. 5. Torres A, Persistent burden of pneumococcal disease in adults. ECCMID 2015

Pneumococcal Meningitis

- Estimated 3,000–6,000 cases per year in the United States
- Case-fatality rate 8% among children
- Case-fatality rate 22% among adults
- Neurologic sequelae common among survivors

Conditions That Increase Risk for Invasive Pneumococcal Disease

- Decreased immune function — including hematologic cancer and HIV infection
- **Asplenia** (functional or anatomic)
- Chronic heart, pulmonary (including asthma in adults), liver or renal disease
- **Cigarette smoking** (in adults)
- Cerebrospinal fluid (CSF) leak
- Cochlear implant

Pneumococcal Disease in Children

- **Bacteremia without known site of infection** most common clinical presentation
- *S. pneumoniae* leading cause of **bacterial meningitis** among children younger than 5 years of age
- Common cause of **acute otitis media**

Burden of Pneumococcal Disease in Children- USA*

Syndrome	Case
Bacteriemia	13,000
Meningitis	700
Death	200
Otitis media	5,000,000

**Prior to routine use of pneumococcal conjugate vaccine*

Children at Increased Risk of Invasive Pneumococcal Disease

- Functional or anatomic asplenia, particularly sickle cell disease
- Immune compromise, including HIV infection
- Alaska Native, African American, American Indian (Navajo and White Mountain Apache)
- Child care attendance
- Cochlear implant

Laboratory Diagnosis

- isolation of the organism from **blood** or other normally **sterile body sites** (CSF)
  - PCR
  - Culture
- On sputum:
  - more than 25 white blood cells
  - fewer than 10 epithelial cells per high-power field
  - predominance of gram-positive diplococci
- urinary antigen

Pneumococcal Disease Epidemiology

Reservoir	Human carriers
Transmission	Respiratory and Autoinoculation
Temporal pattern	Winter and early spring
Communicability	Unknown (Probably as long as organism appears in respiratory secretions)

Pneumococcal Vaccines

Year	Vaccine
1977	14-valent polysaccharide vaccine licensed
1983	23-valent polysaccharide vaccine licensed (PPSV23)
2000	7-valent polysaccharide conjugate vaccine licensed (PCV7)
2010	13-valent PCV licensed

Pneumococcal Polysaccharide Vaccine

- Purified capsular polysaccharide antigen from 23 types of pneumococcus
- Account for 60% –76% of bacteremic pneumococcal disease

Pneumococcal Polysaccharide Vaccine

- Purified pneumococcal polysaccharide (23 types)
- Not effective in children younger than 2 years
- 60%–70% effective against invasive disease
- Less effective in preventing pneumococcal pneumonia

Pneumococcal Conjugate Vaccine

- Purified capsular polysaccharide from 13 types of pneumococcus **conjugated to nontoxic diphtheria toxin** (CRM197)
- In 2008 vaccine serotypes contained in PCV13 accounted for **61% of invasive pneumococcal disease cases** among children younger than 5 years

Pneumococcal Conjugate Vaccine

- More than **90% effective** against invasive disease caused by vaccine serotypes in children
- 45% effective against vaccine-type non-bacteremic pneumococcal pneumonia in adults older than 65 years
- **75% effective against vaccine-type invasive disease** in adults older than 65 years

Pneumococcal Conjugate Vaccine Recommendations

- **Routine vaccination of children 2 through 59 months of age**
- Vaccine schedule:
  - USA: doses at 2, 4, 6, months of age, booster dose at 12–15 months of age
  - Italy: doses at 3, 5/6, 11/12 months of age
- First dose as early as 6 weeks
- Unvaccinated children 7 months of age or older require fewer doses
- Adults 65 years old and older (1 dose)

Pneumococcal Conjugate Vaccine Schedule for Unvaccinated Older Children-Primary Series

Age at first dose	Numner of doses	booster
7—11 months	2 doses	Yes
12-23 months	2 doses	No
24-59 months	1 dose	NO

Subjects >24/71 months of age, affected by:

- chronic heart
- lung disease
- diabetes
- CSF leak
- cochlear implant
- sickle-cell disease
- other hemoglobinopathies
- functional or anatomic asplenia
- HIV infection
- immunocompromising conditions

Required 2 doses of vaccine and a booster after 5 years

Pneumococcal Conjugate Vaccine High-risk Schedule — Children 6 years through 18 years

- Anatomic asplenia (including sickle-cell disease)
- Immunocompromising conditions (e.g. HIV infection)
- Cochlear implant
- Cerebrospinal fluid leak

Single dose if no dose of PCV13 received previously

Pneumococcal Conjugate Vaccine for Persons 65 Years Old and Older

- For those who have not received PCV13 previously, administer a dose of PCV13
- A dose of PPSV23 should be administered 6-12 months after the dose of PCV13
- Do not administer the two vaccines simultaneously
- **Adults who previously received a dose of PPSV23 should receive PCV13 no earlier than 1 year after the dose of PPSV23**

Pneumococcal Conjugate Vaccine High-risk Schedule – Adults 19 and older

- Anatomic asplenia (including sickle-cell disease)
- Immunocompromising conditions (e.g. HIV infection)
- Cochlear implant
- Cerebrospinal fluid leak

PCV13 administered first followed by a dose of PPSV23 8 weeks later

Pneumococcal Polysaccharide Vaccine Recommendations

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

Pneumococcal Polysaccharide Vaccine Revaccination — High-risk Immunocompetent Persons

- Routine revaccination of immunocompetent persons is not recommended
- Revaccination recommended for immunocompetent persons 2 through 64 years of age who are at high risk of serious pneumococcal infection chronic heart disease
  - pulmonary disease (including asthma, 19 years and older)
  - liver disease
  - alcoholism
  - CSF leaks
  - cochlear implants
  - those who smoke cigarettes (19 years and older)
- Single revaccination dose at least 5 years after the first dose and after the 65th birthday

Pneumococcal Polysaccharide Vaccine Revaccination — Highest-risk Persons

- Persons 2 years of age or older with: functional or anatomic asplenia
  - immunosuppression
  - transplant
  - chronic renal failure
  - nephrotic syndrome
- A revaccination dose 5 years after the first dose
- For those who receive 2nd dose prior to the 65th birthday, a third dose is recommended after the 65th birthday (and at least 5 years from the second dose)

Pneumococcal Vaccines
Contraindications and Precautions

- Severe allergic reaction to vaccine component or following prior dose of vaccine
- Moderate or severe acute illness

Pneumococcal Conjugate Vaccine Adverse Events

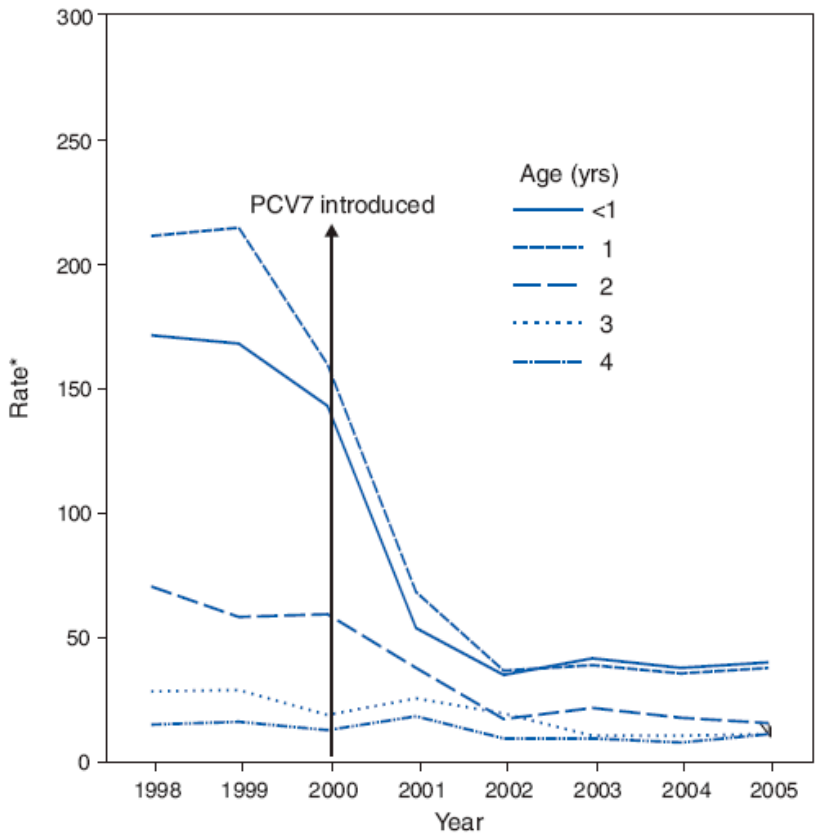
Events reported after PCV7 include apnea

- hypersensitivity reactions
- dyspnea
- bronchospasm
- anaphylactic/anaphylactoid reactions
- angioneurotic edema
- erythema multiforme
- injection site reactions

Pneumococcal Vaccines Adverse Reactions

- **Local reactions**
  - polysaccharide 30%–50%
  - conjugate 5%–49%
- **Fever, myalgia**
  - polysaccharide <1%
  - conjugate 24%–35%
- **Febrile seizures**
  - conjugate 1.2–13.7/100,000
  - conjugate (with TIV) 4–44.9/100,000
- **Severe adverse reactions**
  - polysaccharide rare
  - conjugate 8%

Impact of PCV7 on IPD burden - USA



*Per 100,000 population.
†California (one county); the state of Connecticut; Georgia (20 counties); Maryland (six counties); Minnesota (seven counties); New York (seven counties); Oregon (three counties); and Tennessee (four counties).

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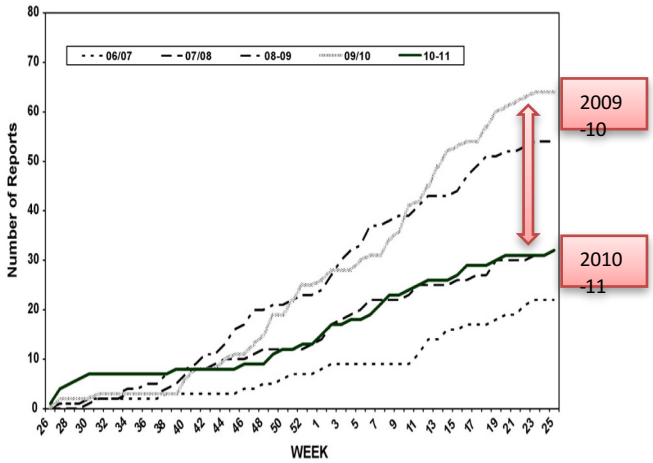
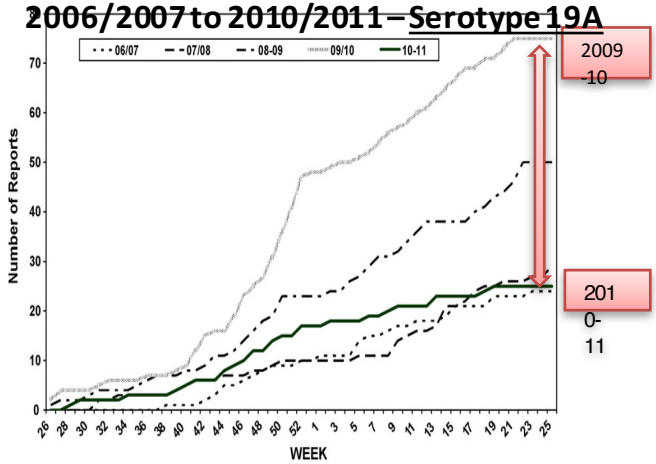
Impact of PCV13 on IPD burden – England and Wales

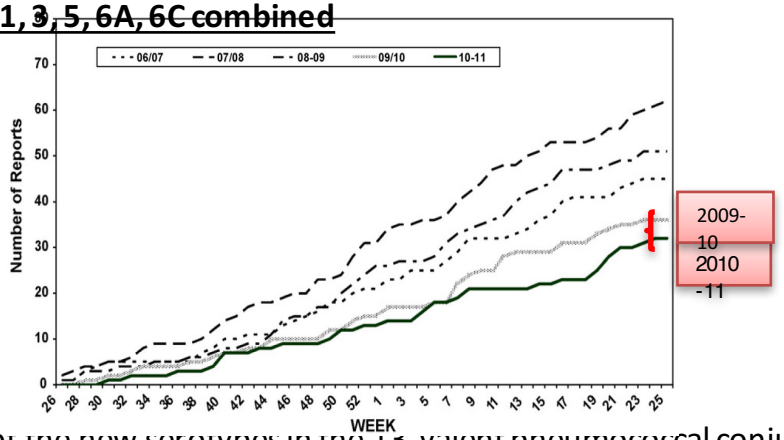
Cumulative number of cases of IPD in children <2 years of age by serotype and epidemiological year July to June



Cumulative number of cases of IPD in children <2 years of age by serotype and epidemiological year July to June 2006/2007 to 2010/2011 – Serotype 19A



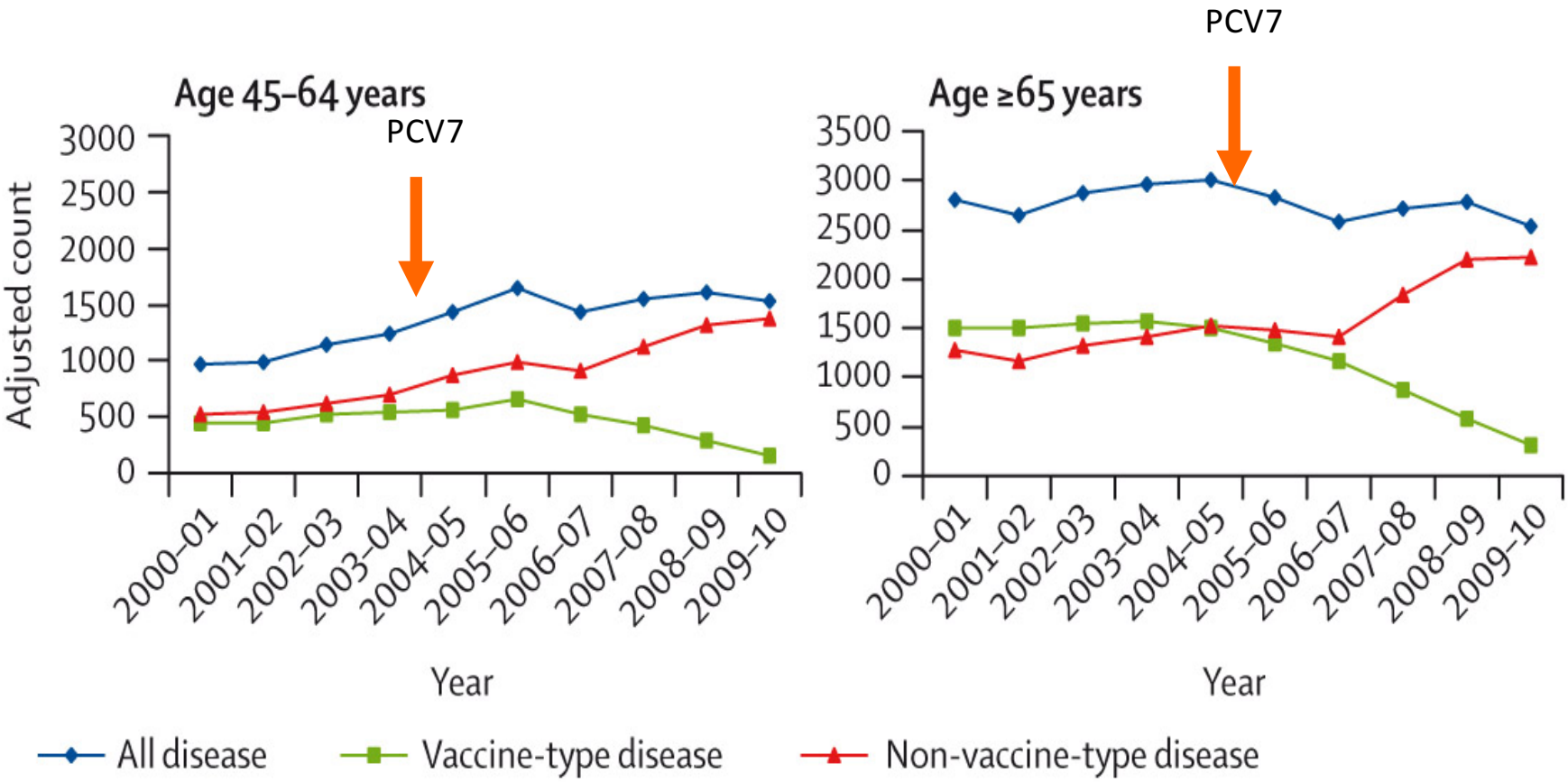
Cumulative number of cases of IPD in children <2 years of age by serotype and epidemiological year July to June 2006/2007 to 2010/2011 – Serotypes 1, 3, 5, 6A, 6C combined



Miller E, et al. Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine. Vaccine 2011; 29(49): 9127-31

Trend of IPD among adults– England and Wales, 2000-10

Health Protection Agency (HPA) National Surveillance



Miller E, et al. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. Lancet Infect Dis 2011; 11: 760–68

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Burden of pneumococcal diseases

Worldwide burden of disease: *Streptococcus pneumoniae* and *Haemophilus influenza* type b in children less than 5 years old

It has been estimated that, despite available preventive measures, *Streptococcus pneumoniae* kills up to a million children around the world each year, and *Haemophilus influenzae* type b up to 400 000. Much attention, research and funding has centred on HIV infection, malaria and tuberculosis, but country-specific estimates funded by the GAVI (Global Alliance for Vaccines and Immunisation) Alliance and the Vaccine Fund have now shown that child mortality from *S pneumoniae* and *H influenzae* type b infections is just as great (Katherine L O'Brien and colleagues. *Lancet* 2009;**374**:893–902; James P Watt and colleagues. Ibid: 903–11; see also Comment, ibid: 854–6).

Using data from vaccine trials, national data where available and a systematic literature review, estimates of disease burden in 2000 were obtained. Pneumococcal disease was estimated to have caused about 14.5 million (11.1–18.0 million) severe episodes. There were approximately 826 000 deaths from pneumococcal disease in children under the age of 5 years, of which 91 000 were in HIV-positive children. The greatest burden was in sub-Saharan Africa and Asia. Pneumococcal deaths were from pneumonia (90%), meningitis (7%) and non-pneumonia, non-meningitis syndromes (3%). *S pneumoniae* in HIV-negative children caused about 11% of all deaths among children aged 1–59 months. Of the total number of cases of pneumococcal disease, fatal and non-fatal, 27% were in India, 12% in China, 5% in Nigeria and 5% in Pakistan. Almost all were cases of pneumonia, with only 0.7% having meningitis. The risk of death from pneumococcal disease in childhood in countries not using routine pneumococcal conjugate vaccination is almost 40 times that in countries using the vaccine. Financial support for pneumococcal vaccination is available via GAVI; Rwanda was the first country to take up this offer, starting vaccination in April 2009.

The accompanying study of *H influenzae* type b disease (Hib) gave an estimate of 8.13 million (7.3–13.2 million) serious cases worldwide, and 371 000 deaths, in children under the age of 5 years in 2000. Of these deaths, 363 000 were of HIV-negative children. The greatest numbers of cases and deaths were in southeast Asia, followed by Africa, the western Pacific and the eastern Mediterranean. It is estimated that, without vaccination, Hib causes around 31 cases of meningitis and 1304 cases of pneumonia per 100 000 children under the age of 5 years. Hib disease is responsible for 5.6% of all post-neonatal child deaths. Almost all of these deaths could be prevented by vaccination. The cost of vaccines has fallen and financial assistance is available to low-income countries through GAVI.

Provenance and peer review Not commissioned; internally peer reviewed.

Arch Dis Child 2010;**95**:973. doi:10.1136/adc.2010.202382

Despite mass vaccination programs, carried out in several countries, according to WHO statistics every year 1,6 milion persons died for pneumococcal diseases; of these, 1 milion is aged <5 years

nber 2010 Vol 95 No 12

Arch Dis Child 2010;95:973

World Health Organization. Pneumococcal conjugate vaccine for childhood immunization – WHO position paper. Wkly Epidemiol Rep 2007;12:93-104