# ere Pneumonia Children

## In the post pneumococcal conjugate vaccine era

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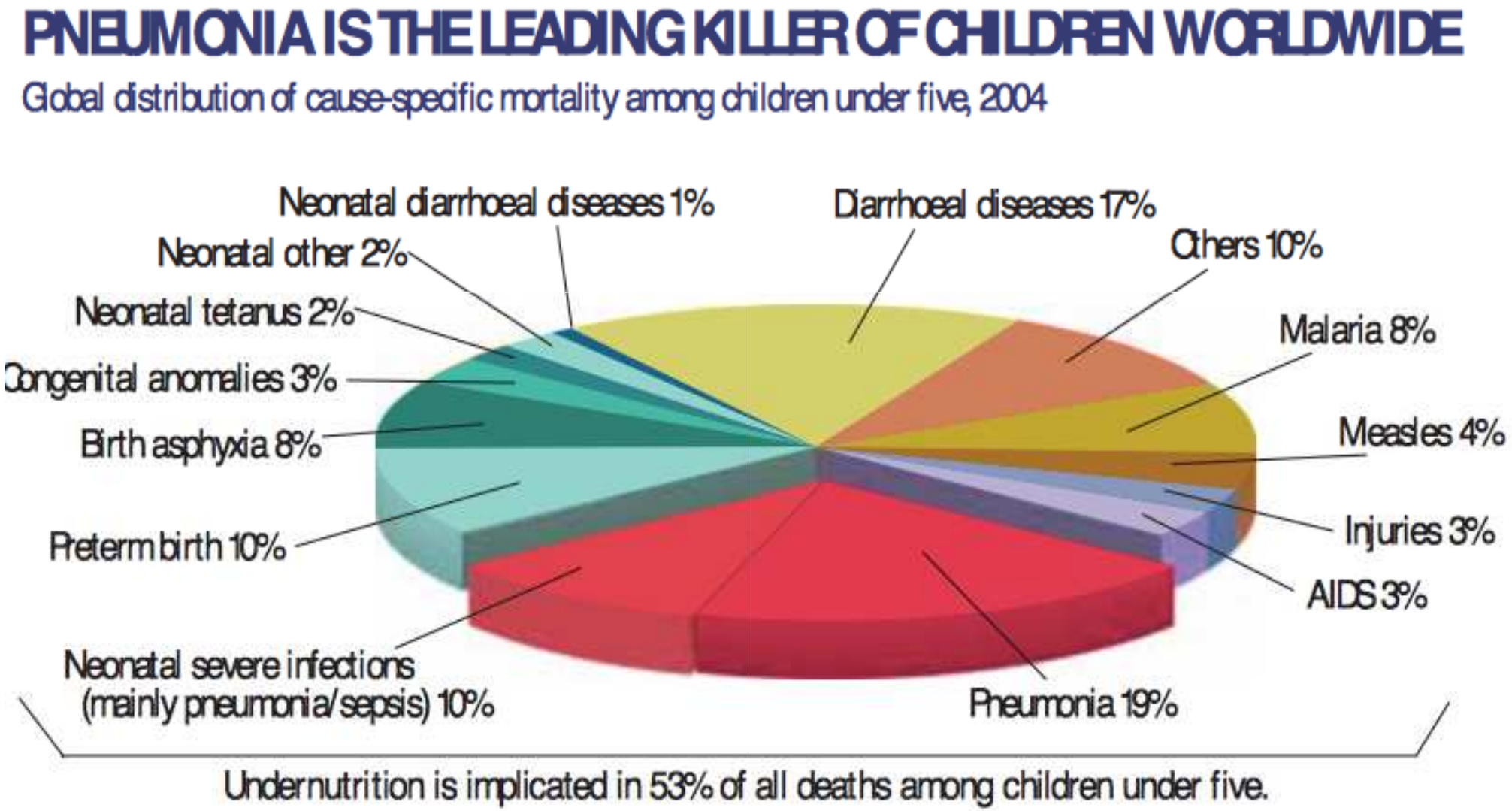
# Overview

- The burden and epidemiology of pneumonia prior to the introduction of PCV
- The impact of PCVs on the disease burden
- Epidemiology of pneumonia and severe pneumonia in the PCV era
- Approaches to treatment of severe pneumonia in children

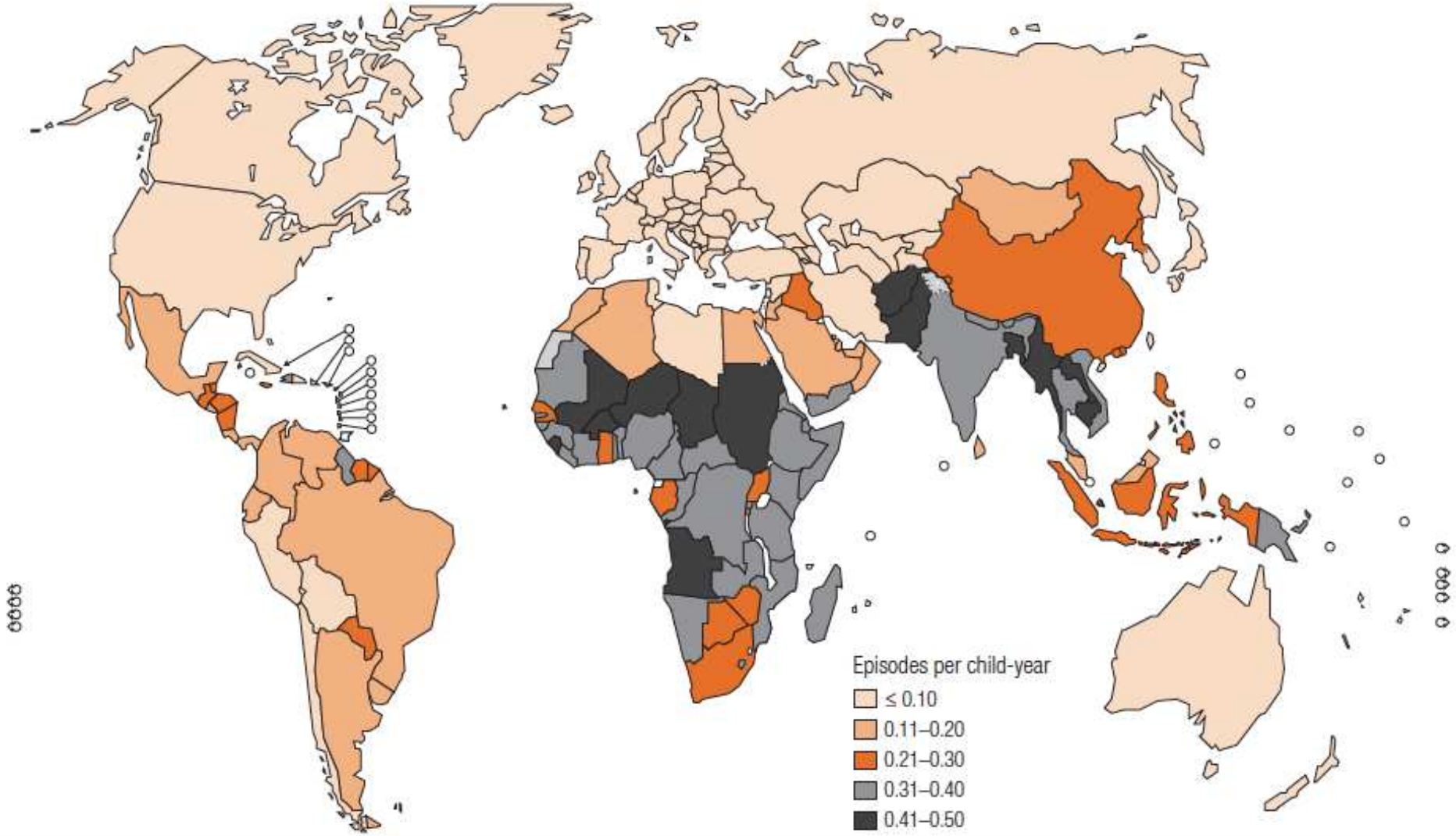
# The burden of pneumonia prior to PCV

## WHO 2006



# Global Incidence of Pneumonia by Country

Fig. 1. **Incidence of childhood clinical pneumonia at the country level**




Bulletin of the World Health Organization 2008;86:408–416.

# What was causing these infections prior to PCV?

**ETIOLOGY OF COMMUNITY-ACQUIRED PNEUMONIA IN THE NON-IMMUNOSUPPRESSED HOST REQUIRING HOSPITALIZATION**

| Etiology | Patients n (%) | Pathogens n (%) | Pathogens Definite/ Presumptive n |
|---|---|---|---|
| *Streptococcus pneumoniae* | 39 (21) | 65 (29) | 30/35 |
| *Legionella pneumophila* | 14 (8) | 17 (8) | 17 |
| Atypical bacterial agents | 26 (14) | 41 (18) | 41 |
| *Chlamydia pneumoniae* | 9 (5) | 15 (7) | |
| *Chlamydia psittaci* | 2 (1) | 2 (1) | |
| *Mycoplasma pneumoniae* | 9 (5) | 13 (6) | |
| *Coxiella burnetti* | 6 (3) | 11 (5) | |
| Atypical viral agents | 26 (14) | 39 (17) | 39 |
| Influenza virus A | 10 (6) | 16 (17) | |
| Influenza virus B | 6 (3) | 7 (8) | |
| Parainfluenza virus 1 | 2 (1) | 4 (2) | |
| Parainfluenza virus 2 | 2 (1) | 2 (1) | |
| Parainfluenza virus 3 | 3 (2) | 3 (1) | |
| Adenovirus | 2 (1) | 2 (1) | |
| Respiratory syncytial virus | 1 (1) | 5 (2) | |
| Nonpneumococcal, nonatypical agents | 19 (10) | 39 (17) | 15/24 |
| *Haemophilus influenzae* | 11 (6) | 25 (11) | 6/19 |
| *Moraxella catarrhalis* | 2 (1) | 4 (2) | 1/3 |
| *Staphylococcus aureus* | 5 (3) | 7 (3) | 5/2 |
| *Streptococcus viridans* | — | 1 (1) | 1/0 |
| *Streptococcus mitis* | 1 (1) | 1 (1) | 1/0 |
| *Enterococcus faecalis* | — | 1 (1) | 1/0 |

Ruiz, Ewig, Marcos et al: CAP in Barcelona AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE 19

# Pediatric Pneumonia 1999

IMPACT OF SEVERITY OF PNEUMONIA ON MICROBIAL ETIOLOGY

| Microbial Etiology | Number of Patients/ Proportion of Patients with Corresponding Etiology (%) | Odds Ratio | 95% Confidence Interval | p Valu |
|---|---|---|---|---|
| Severe pneumonia (ICU admission) | 64 | | | |
| Univariate | | | | |
| *Streptococcus pneumoniae* | 18/65 (28) | 2.4 | 1.3–4.4 | 0.00 |
| Bacteremic *Streptococcus pneumoniae* | 8/22 (36) | 3.2 | 1.3–8.1 | 0.00 |
| Gram-negative enteric bacilli + | | | | |
| *Pseudomonas aeruginosa* | 7/24 (29) | 2.3 | 0.8–6.1 | 0.09 |
| Mixed infections | 12/41 (29) | 2.4 | 1.1–5.3 | 0.02 |
| Bacteremia | 11/34 (33) | 2.8 | 1.2–6.4 | 0.00 |
| Multivariate | | | | |
| *Streptococcus pneumoniae* | — | 2.5 | 1.3–4.7 | 0.00 |
| Gram-negative enteric bacilli + | | | | |
| *Pseudomonas aeruginosa* | — | 2.5 | 0.99–6.5 | 0.05 |

*Definition of abbreviations*: ICU = Intensive care unit.

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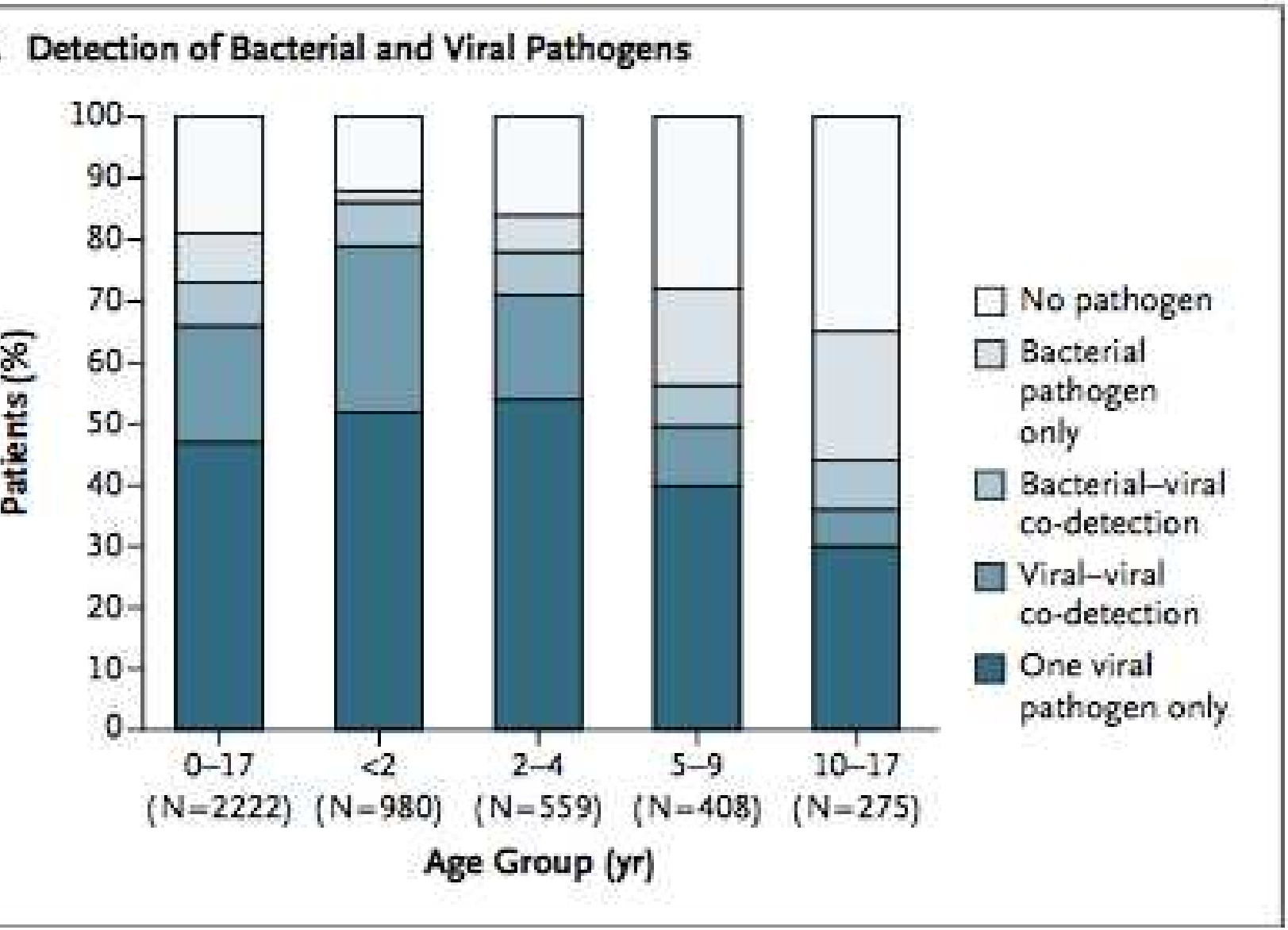
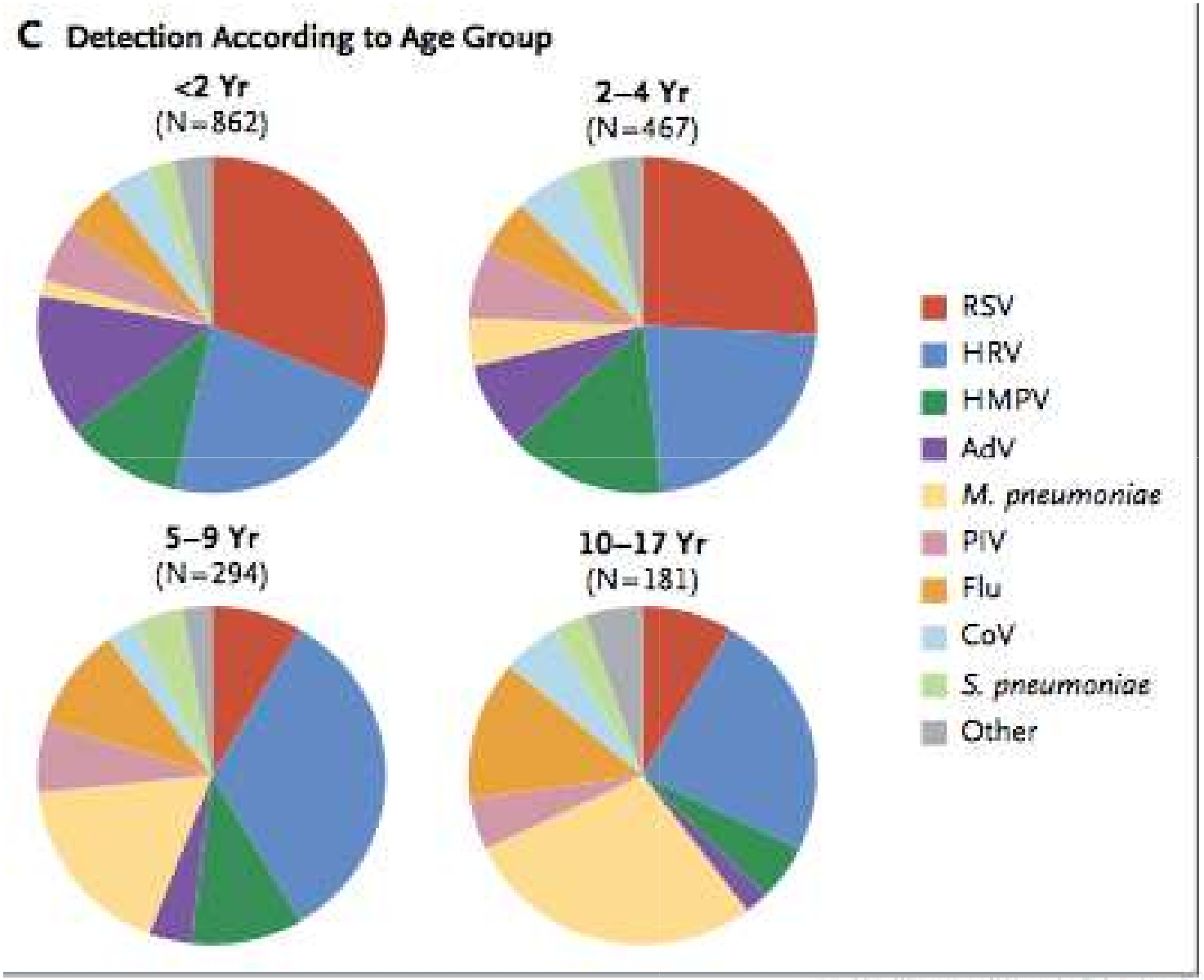
# ter PCV: CAP requiring hospitalization in US ildren 2015

| racteristic | Children with Radiographic Evidence of Pneumonia (N=2358) |
|---|---|
| group — no. (%) | |
| <2 yr | 1055 (45) |
| 2–4 yr | 595 (25) |
| 5–9 yr | 422 (18) |
| 10–17 yr | 286 (12) |
| ptom — no. (%) | |
| Cough | 2230 (95) |
| Fever or feverish feeling | 2155 (91) |
| Anorexia | 1766 (75) |
| Dyspnea | 1657 (70) |
| underlying condition — no. (%)* | 1197 (51) |
| Asthma or reactive airway disease — no. (%) | 779 (33) |
| Preterm birth among children <2 yr — no./total no. (%) | 218/1055 (21) |
| Radiographic finding — no. (%)† | |
| Consolidation | 1376 (58) |
| Alveolar or interstitial infiltrate | 1195 (51) |
| Pleural effusion | 314 (13) |
| Hospitalization | |
| Length of stay — days | |
| Median | 3 |
| Interquartile range | 2–5 |
| Intensive care unit admission — no. (%) | 497 (21) |
| Invasive mechanical ventilation — no. (%) | 166 (7) |
| Death in the hospital — no. (%) | 3 (<1) |

# CAP requiring hospitalization in US children 2015



# CAP requiring hospitalization in US children 2015



# Mortality due to Pneumonia in Children in 2010

| | Aged 0–11 months | | Aged 12–59 months | | Aged 0–59 months | |
|---|---|---|---|---|---|---|
| | Studies | CFR (%) | Studies | CFR (%) | Studies | CFR (%) |
| Africa | 9 | 3·8% (2·4–5·9) | 8 | 1·9% (1·2–3·2) | 11 | 3·9% (2·7–5·5) |
| Americas | 10 | 1·6% (1·1–2·4) | 10 | 0·6% (0·2–1·3) | 11 | 1·3% (0·8–1·9) |
| Eastern Mediterranean | 1 | 9·9% (8·6–11·5) | .. | .. | 2 | 7·6% (4·1–13·9) |
| Europe | .. | .. | .. | .. | 1 | 0·4% (0·3–0·5) |
| Southeast Asia | 6 | 2·6% (1·4–4·7) | 4 | 0·3% (0·1–0·9) | 9 | 2·1% (1·1–4) |
| Western Pacific | 1 | 2·4% (1·3–4·3) | .. | .. | 3 | 2·3% (1·7–3·2) |
| Developing | 26 | 2·4% (1·7–3·6) | 21 | 0·8% (0·4–1·3) | 34 | 2·3% (1·6–3·4) |
| Industrialised | 1 | 0·8% (0·7–0·9) | 1 | 0·3% (0·2–0·5) | 3 | 0·6% (0·4–0·8) |
| Global | 27 | 2·3% (1·5–3·4) | 22 | 0·7% (0·4–1·2) | 37 | 2·1% (1·4–3·1) |

Data in parentheses are 95% CI. CFR=case-fatality ratio.

***Table 2*: Case-fatality ratio due to severe acute lower respiratory infections in children younger than 5 years who were admitted, by region**

**Nair, Shabi Madhi, Angela Gentile et al:**
**and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010**

# Pneumonia incidence and disease burden in Latin American Children in 2010

| Age | Severe ARLI Estimated number of cases/yr | Incidence Severe ALRI (per 1000/yr) | Very Severe ALRI Estimated number of cases/yr | Incidence Very Severe ALRI (per 1000/yr) |
|---|---|---|---|---|
| Age < 1 years | 693,000 | 46 | 130,000 | 8.6 |
| | | | | |
| Age < 5 years | 1,525,000 | 19.8 | 179,000 | 3.0 |

Nair, Shabi Madhi, Angela Gentile et al: Global and regional burden of hospital admissions for severe acute lower respiratory infections n in 2010

# Pneumonia etiology in Ecuadorian children

Pneumonia etiology by age category.

| | | Age Group N (%) | | Total (N = |
|---|---|---|---|---|
| thogens | | < 1 year (n = 238) | 1 to 5 years (n = 168) | |
| rus | | 35 (14.7%) | 27 (16.1%) | 62 (15. |
| a | | | | 40 (9.9 |
| | Type A | 16 (6.7%) | 13 (7.7%) | 29 (7.1 |
| | Type B | 7 (2.9%) | 4 (2.4%) | 11 (2.7 |
| uenza | | | | 57 (14. |
| | Type 1 | 10 (4.2%) | 5 (3.0%) | 15 (3.7 |
| | Type 2 | 3 (1.3%) | 4 (2.4%) | 7 (1.7 |
| | Type 3 | 27 (11.3%) | 8 (4.8%) | 35 (8.6 |
| metapneumovirus | | 40 (16.8%) | 31 (18.5%) | 71 (17. |
| ory syncytial virus | | 105 (44.1%) | 54 (32.1%) | 159 (39 |
| l Pathogens | | | | |
| *occus pneumoniae* (n = 403) | | 20 (8.5%) | 17 (10.1%) | 37 (9.2 |
| *sma pneumoniae* | | 0 (0%) | 3 (1.8%) | 3 (0.74 |

ology of severe pneumonia in Ecuadorian children. PLoS ONE 12(2): e0171687. doi:10.1371/ journal.pone.0171687

# Impact of PCV in Latin America: The COMPAS Trial

- Efficacy against 25.7% (95% CI: 8.4%, 39.6%) against World Health Organization–defined consolidated CAP.
- Efficacy against Invasive Pneumococcal Disease due to vaccine serotypes: 100% (95% CI: 74.3%, 100%)
- Efficacy against any IPD  was 65.0% (95% CI: 11.1%, 86.2%)
- Serotypes in PCV13 and PCV-10 were selected because they caused the most disease in children. BUT
- In the COMPAS trial with most patients coming from Argentina, **35% of pneumococcal IPD remained.**
- Therefore we can not forget about the pneumococcus yet !

PLOS-ONE: http://dx.doi.org/10.1371/journal.pmed.1001657

# Pleural Effusion follow PCV 13

| ex | Age on Admission (years) | PCV13 Immunization History | Previous PCV7/PCV10 Immunization | Chest Tube Placement | Fibrinolys Performe |
|---|---|---|---|---|---|
| | 2½ | 2 doses: 21 and 25 months | No | Yes | Yes |
| | 3½ | 1 dose: 27 months | No | Yes | Yes |
| | 3½ | 1 dose: 24 months | PCV7, 3 doses | Yes | Yes |
| | 4 | 1 dose: 32 months | No | Yes | Yes |
| | 6 | 1 dose: 54 months | PCV7, 3 doses | Yes | No |

The Pediatric Infectious Disease Journal • Volume 33, Number 1, January 2014

# Antibiotic Resistant Pneumococcus

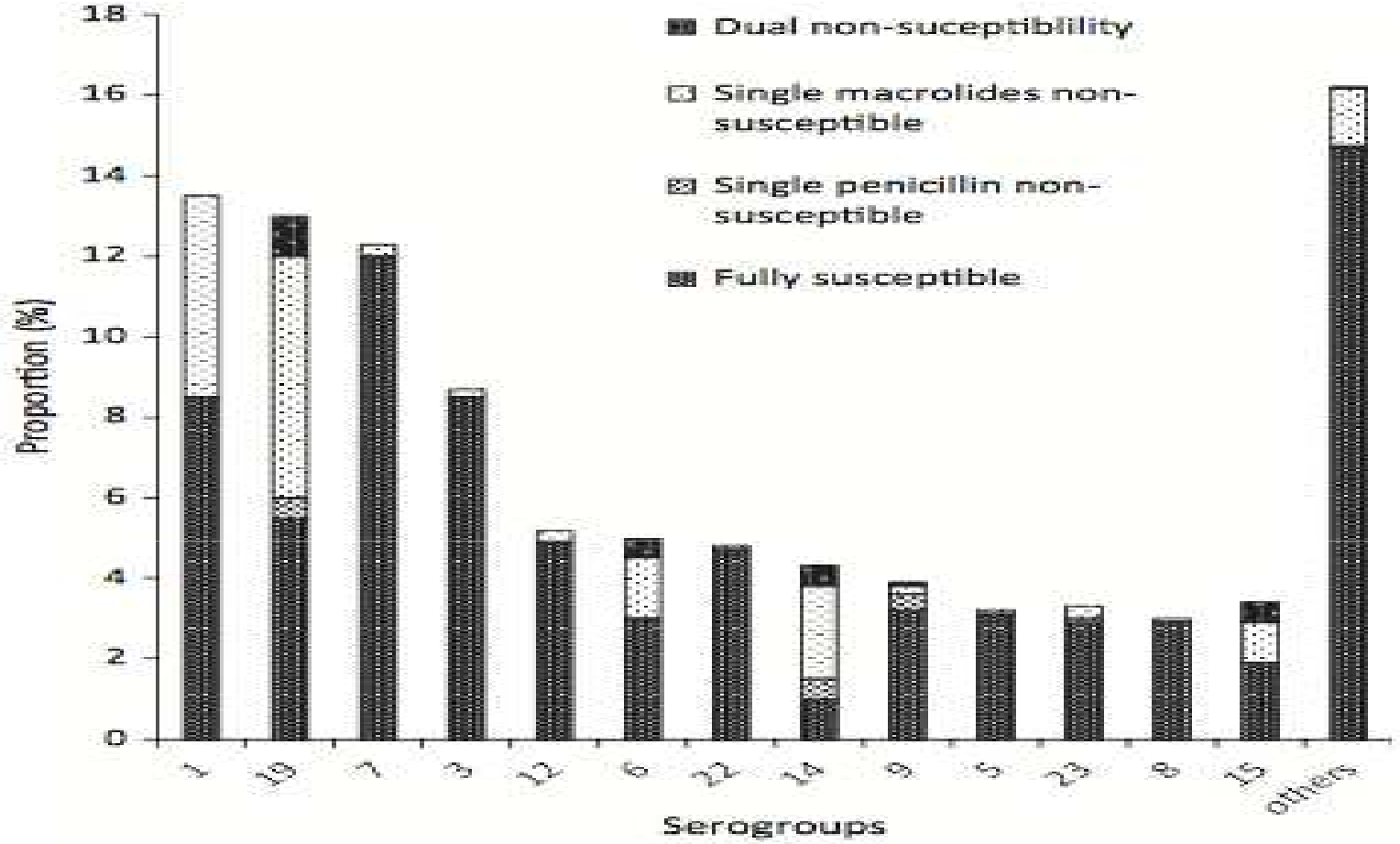
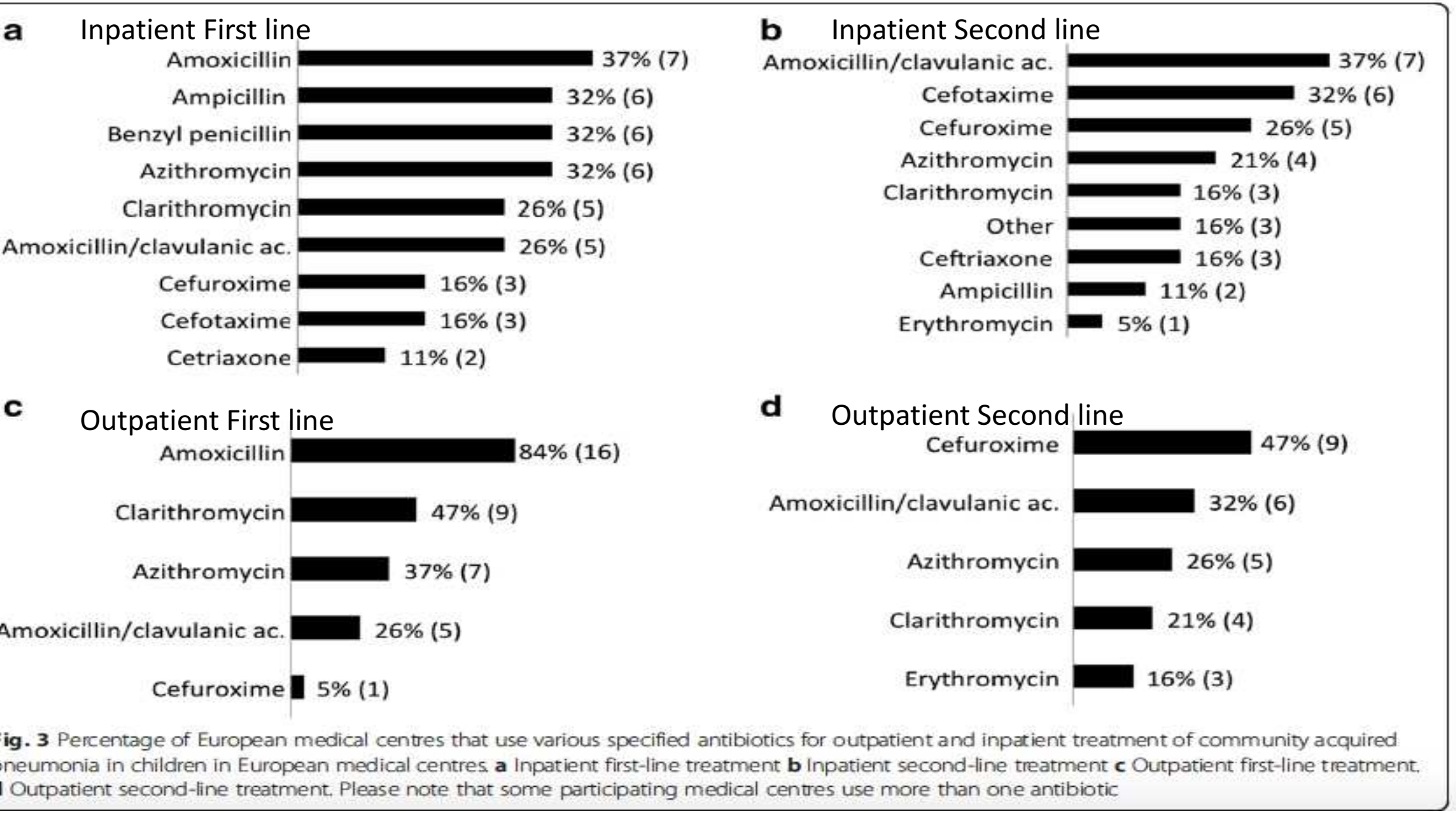



**Figure 1** Proportion of susceptible pneumococcal isolates in Europe by serogroups. Data from the Annual Report of the European Antimicrobial Resistance Surveillance Network (16).

Need to consider other treatments besides penicillin in a toxic child

Some have recommended high dose amoxicillin others agents such as Ceftriaxone, Clindamycin or Teicoplanin (Galli Acta Pediatrica 2013)

# eatment of Childhood Pneumonia in Europe




**ig. 3** Percentage of European medical centres that use various specified antibiotics for outpatient and inpatient treatment of community acquired neumonia in children in European medical centres. **a** Inpatient first-line treatment **b** Inpatient second-line treatment **c** Outpatient first-line treatment. Outpatient second-line treatment. Please note that some participating medical centres use more than one antibiotic

Usonis et al. Pneumonia (2016) 8:5

# ntibiotic Treatment of Severe Pneumonia in Childre

| | |
|---|---|
| e<br>nonia | **Either ceftriaxone 100 mg/kg per day in 2 divided doses (MAX 4 g/day), OR cefotaxime 150 mg/kg per day in 4 divided doses (MAX 10 g/day)**<br>**PLUS one of the following:**<br>**•Azithromycin 10 mg/kg once per day for two days (MAX 500 mg/day); transition to or therapy at 5 mg/kg per day as soon as clinically appropriate, OR**<br>**•Erythromycin¥ 20 mg/kg per day in 4 divided doses (MAX 4 g/day), OR**<br>**•Doxycycline** 4 mg/kg per day in 2 divided doses (MAX 200 mg/day); transition to or therapy as soon as clinically appropriate** |
| e<br>nonia | **Vancomycin 60 mg/kg per day in 4 divided doses (MAX 4 g/day) PLUS either**<br>**Ceftriaxone 100 mg/kg per day in 2 divided doses (MAX 4 g/day) OR cefotaxime 150 mg/kg per day divided doses (MAX 10 g/day)**<br>**PLUS**<br>**Azithromycin 10 mg/kg once per day for two days (MAX 500 mg/day); transition to oral therapy at mg/kg per day as soon as clinically appropriate**<br>**PLUS (if necessary)**<br>**NafcillinΔΔ 150 mg/kg per day in 4 or 6 divided doses (MAX 12 g/day)**<br>**PLUS (if indicated)**<br>**Antiviral treatment for influenza** |
| tal<br>red<br>nonia | **Either gentamicin†† 7.5 mg/kg per day divided in 3 doses for children <5 years; 6 to 7.5 mg/kg per divided in 3 doses for children ≥5 years OR amikacin 15 to 22.5 mg/kg per day divided in 3 doses, P one of the following:**<br>**•Piperacillin-tazobactam 300 mg/kg per day in 4 divided doses (MAX 16 g/day), OR**<br>**•Meropenem 60 mg/kg per day in 3 divided doses (MAX 3 g/day), OR**<br>**•Ceftazidime 125 to 150 mg/kg per day in 3 divided doses (MAX 6 g/day), OR**<br>**•Cefepime 150 mg/kg per day in 3 divided doses (MAX 4 g/day), OR**<br>**•Clindamycin 30 to 40 mg/kg per day in 3 or 4 divided doses (MAX 3.6 g/day)** |

# eatment of CAP in the era of antibiotic resistanc

Antibiotics used in drug-resistant community-acquired pneumonia

| ics | Dose | Route | Adverse effects | Comments | Species |
|---|---|---|---|---|---|
| mycin | 15 mg/kg every 6–8 h | IV | Nephrotoxicity, ototoxicity, 'red man' syndrome | Slowly bactericidal. Therapeutic levels to be monitored | *Streptococc pneumon Staphyloc aureus* |
| anin | 10 mg/kg every 12 h for three doses then 10 mg/kg/day | IV/IM | Nephrotoxicity, ototoxicity, thrombocytopenia | Bactericidal. Therapeutic levels to be monitored | *S. pneumo S. aureu* |
| id | 10 mg/kg (max 600 mg) every 8 <12 years; every 12 h >12 years | IV/PO | Lactic acidosis, myelosuppression, peripheral and optic neuropathy | Bacteriostatic. Inhibit toxin synthesis Treatment duration <28 days | *S. pneumo S. aureu* |
| nycin | 6–10 mg/kg (max 1.2 g) every 6 h | IV/PO | Diarrhoea, *C. difficile* colitis | Bacteriostatic. Inhibit toxin synthesis | *S. pneumo S. aureu* |
| icin | 10 mg/kg (max 600 mg) every 12 h | IV/PO | Hepatotoxicity, anaphylaxis agranulocytosis | Bactericidal. Colours biological fluids red. Rapid development of resistance in monotherapy | *S. aureus* |
| ncin | 10 mg/kg/day | IV | Nausea, vomiting, taste sense disorders, nephrotoxicity | Bactericidal. Not approved for children | *S. pneumo S. aureu* |
| line | 600 mg every 12 h | IV | Rash | Bactericidal. Not approved for children | *S. pneumo S. aureu* |
| line | 2 mg/kg stat, then 1 mg/kg | IV | Diarrhoea, nausea, vomiting, headache, raised ALT/AST, pancreatitis | Bacteriostatic. Not approved for children | *S. pneumo S. aureu* |
| dine | 1–2 mg/kg (max 200 mg) every 12 h | PO/IV | Diarrhoea, Hepatotoxicity, tooth discolouration in children | Bacteriostatic. Not recommended <8 years | *Mycoplasm pneumon* |
| cline | 4 mg/kg stat (max 200 mg) then 2 mg/kg (max 100 mg) | PO | Dizziness, headache, hepatotoxicity, diarrhoea, tooth discolouration in children | Bacteriostatic. Not recommended <8 years | *M. pneumo* |
| oxacin | 10–15 mg/kg every 12 h PO, every 8–12 h IV | IV/PO | Rupture of tendon. Cartilage damage reported in animals | Bactericidal. Not recommended for children | *S. pneumo M. pneu* |
| xacin | 8 mg/kg (max 500 mg) every 12 h | IV/PO | Rupture of tendon. Cartilage damage reported in animals | Bactericidal. Not recommended for children | *S. pneumo M. pneu* |
| xacin | 10 mg/kg/day (max 400 mg) | IV/PO | Rupture of tendon. Cartilage damage reported in animals | Bactericidal. Not recommended for children | *S. pneumo M. pneu* |

alli: Acta Pediatrica 2015

# Summary

- There are multiple causes of severe pneumonia and pneumonia with effusion in children – viruses not only bacteria play a key role.
- It is important to make a clinical assessment of severity early, obtain cultures as well as PCR testing.
  Genomic testing will provide sensitivity and etiology rapidly soon
- Don't forget
  - Pneumococcus is down but not out.
  - TB
  - Co-infection with viruses and bacteria
- Important to reevaluate your therapy frequently to assess response