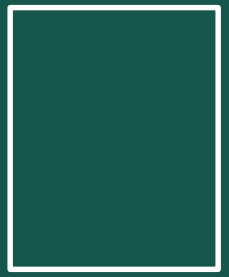
Pediatric Lower Resipiratory Infections



Jesse Papenburg, MD MSc FRCPC
Montreal Children's Hospital
McGill University Health Centre
Montreal, Quebec, Canada

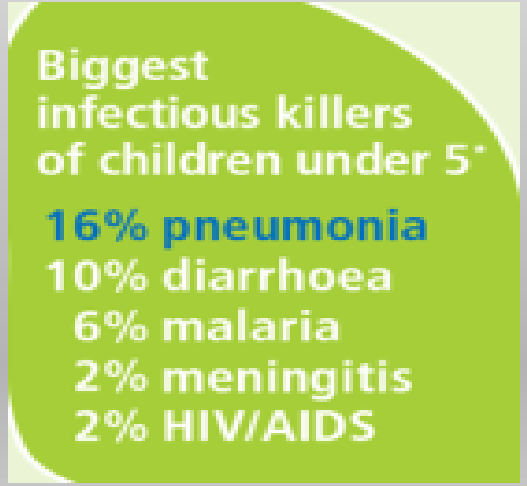
MAC ID Course
August 11, 2019

Outline

- Pneumonia
  - Burden
  - Eiologies
- Bronchiolitis
  - Management / resource utilization

Pneumonia is a leading cause of death in children worldwide

In 2015 alone, more than 900,000 children died from pneumonia, accounting for 16% of all under-5 years old mortality worldwide



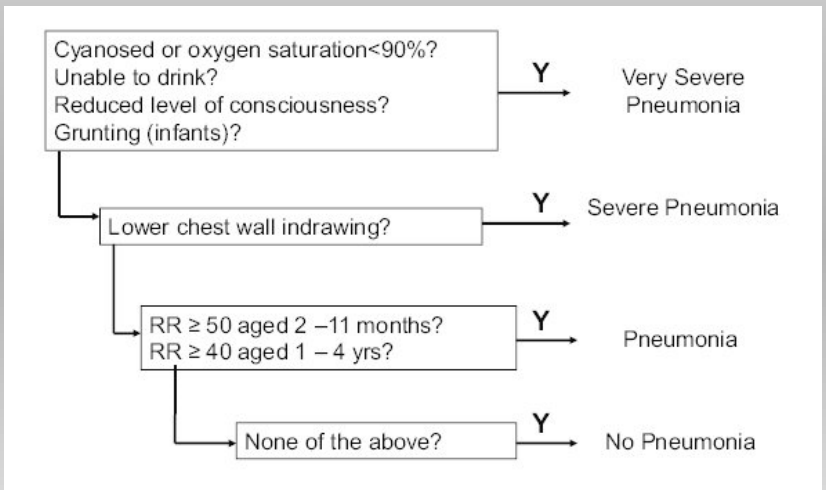
Every 35 seconds a child dies due to pneumonia

WHO World Health Statistics 2015; worldpneumoniaday.org; Liu L, et al. *Lancet* 2016; 388: 3027–35.

Hospitalisation for severe pneumonia presents a huge burden

- Pneumonia sickens ~ 150 million children every year[1]
- Among those, at least 11 million progress to severe disease requiring hospitalisation[2]

Pre-2014 WHO classification of pneumonia (children 1-59 months of age)



1. Rudan et al. *Bull World Health Organ.* 2008; 86: 408-416 2. Nair H, et al. *Lancet*. 2013;381(9875):1380-1390.

Risk factors for developing pneumonia and for severe disease

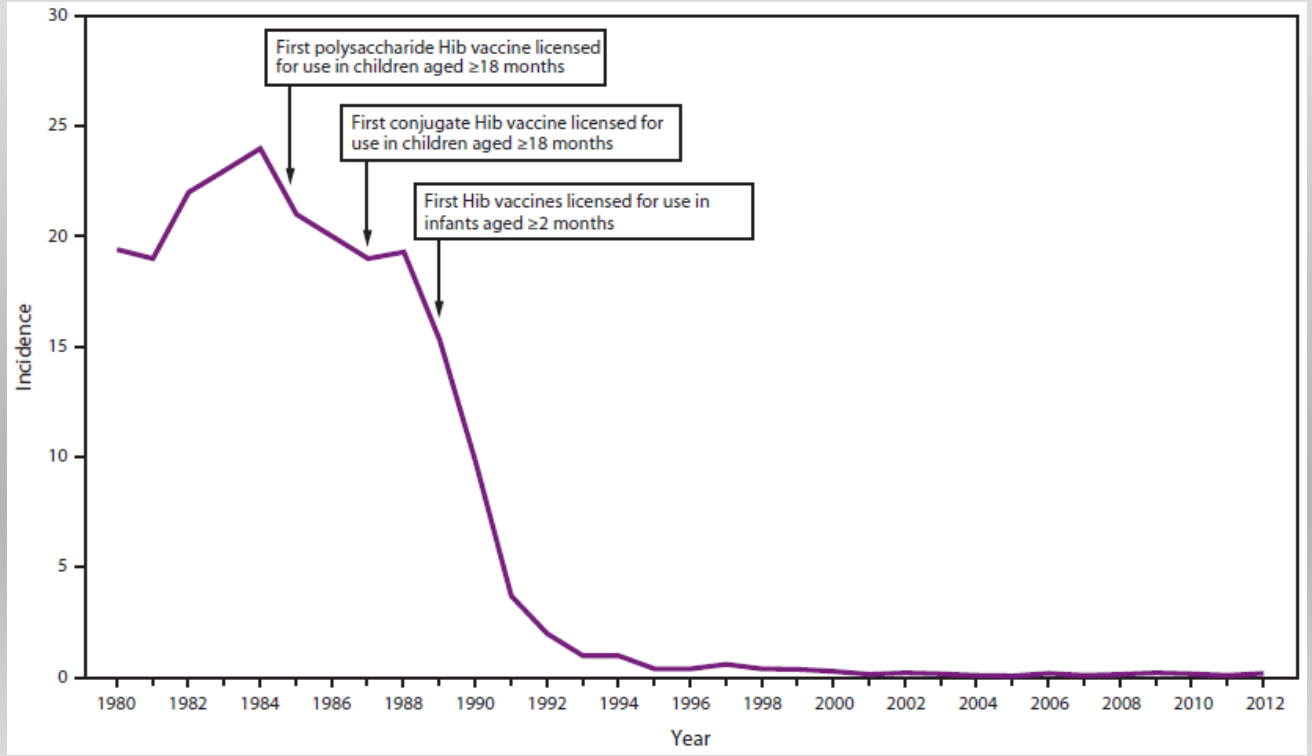
- Malnutrition or undernourishment, especially in infants who are not exclusively breastfed
- Pre-existing illnesses, such as
  - Symptomatic HIV infections
  - Measles
  - Prematurity / SGA infants
  - Cardiopulmonary conditions
  - Immune compromise
- Environmental factors:
  - Indoor air pollution caused by cooking and heating with biomass fuels (such as wood or dung)
  - Living in crowded homes
  - Parental smoking / smoking during pregnancy

Causes of pneumonia: a moving target?

- The main causes of pneumonia today are not the same as they were in past decades, in part due to successful vaccines

- *Streptococcus pneumoniae* – most common cause of bacterial pneumonia in children
- *Haemophilus influenzae* type b (Hib) – second most common cause of bacterial pneumonia
- Respiratory syncytial virus (RSV) – most common viral cause of pneumonia
- *Pneumocystis jiroveci* – responsible for > 25% of pneumonia deaths in HIV-infected infants

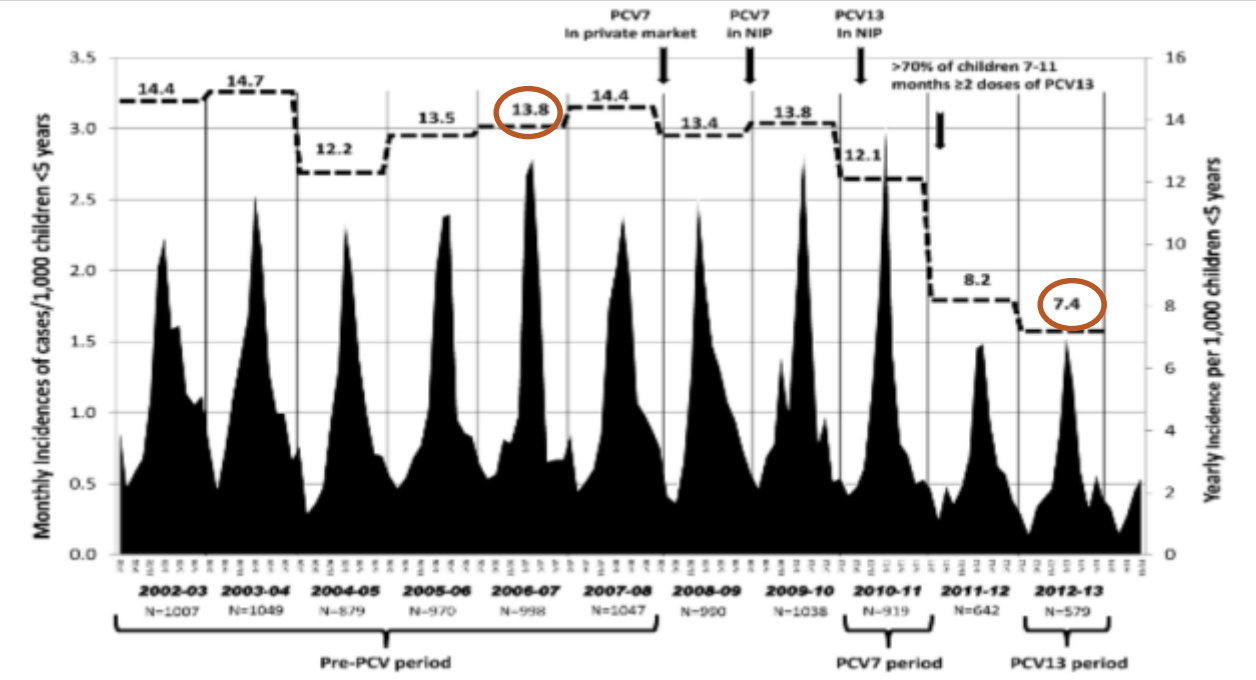
Haemophilus influenzae type b vaccination: tremendous impact



CDC. MMWR: February 28, 2014 / 63(RR01);1-14

Impact of sequential PCV7 and PCV13 vaccines on hospitalization for CAP among children <5 years of age

Monthly Hospital Visits for Alveolar Pneumonia in Children <5 Years, Southern Israel, 2002 to 2013



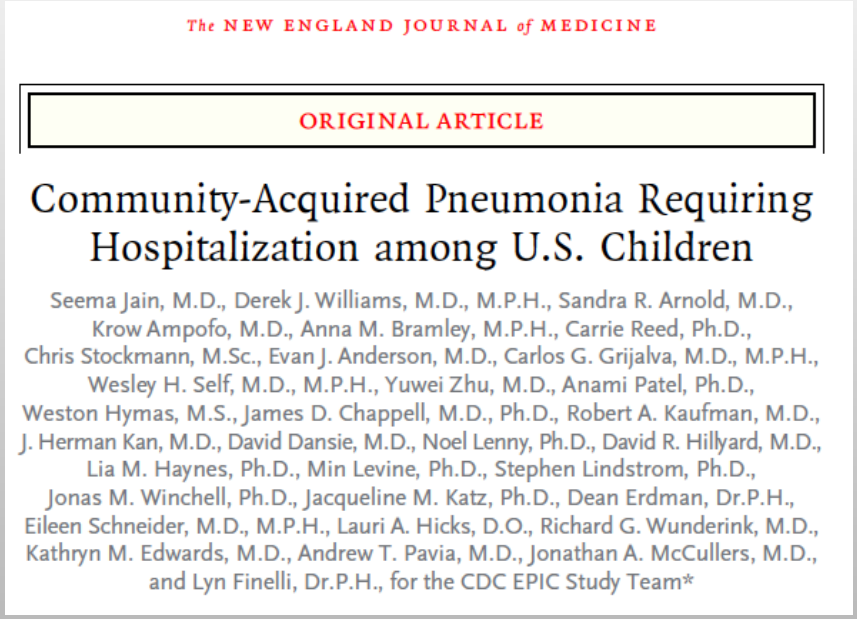
Reduction of CAP incidence of 46%:
from 13.8 to 7.4 per 1,000 children <5yo

Greenberg D. et al. Vaccine. 2015 Aug 26;33(36):4623-9

Pneumonia mortality: some good news

- Estimates of pneumonia deaths in children under 5
  - 1990: 1.7 million deaths
  - 2015: 0.9 million deaths
  - 2017: 0.8 million deaths
- Reflection of
  - Economic development
  - Improved nutrition
  - Reduced household crowding
  - Pneumonia-specific interventions
    - Improved case management— empirical antibiotic treatment
    - Effective vaccines

UPDATED EVIDENCE ON PEDIATRIC PNEUMONIA ETIOLOGY



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

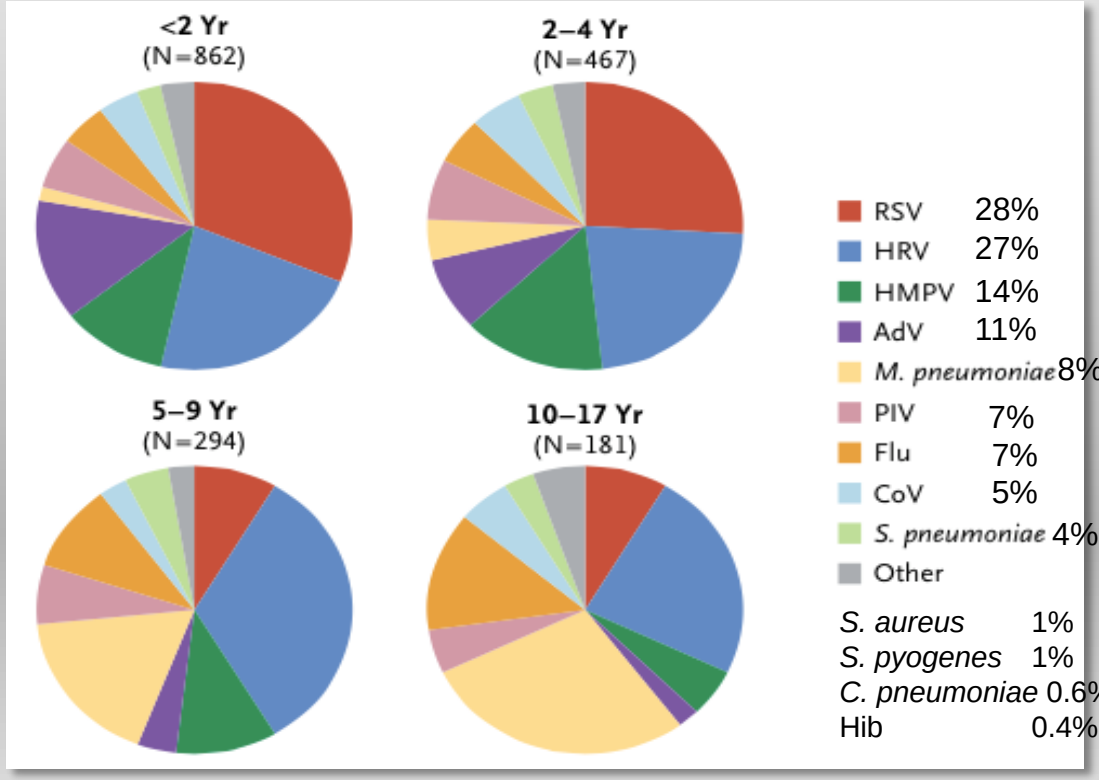
Community-Acquired Pneumonia Requiring Hospitalization among U.S. Children

Seema Jain, M.D., Derek J. Williams, M.D., M.P.H., Sandra R. Arnold, M.D., Krow Ampofo, M.D., Anna M. Bramley, M.P.H., Carrie Reed, Ph.D., Chris Stockmann, M.Sc., Evan J. Anderson, M.D., Carlos G. Grijalva, M.D., M.P.H., Wesley H. Self, M.D., M.P.H., Yuwei Zhu, M.D., Anami Patel, Ph.D., Weston Hymas, M.S., James D. Chappell, M.D., Ph.D., Robert A. Kaufman, M.D., J. Herman Kan, M.D., David Dansie, M.D., Noel Lenny, Ph.D., David R. Hillyard, M.D., Lia M. Haynes, Ph.D., Min Levine, Ph.D., Stephen Lindstrom, Ph.D., Jonas M. Winchell, Ph.D., Jacqueline M. Katz, Ph.D., Dean Erdman, Dr.P.H., Eileen Schneider, M.D., M.P.H., Lauri A. Hicks, D.O., Richard G. Wunderink, M.D., Kathryn M. Edwards, M.D., Andrew T. Pavia, M.D., Jonathan A. McCullers, M.D., and Lyn Finelli, Dr.P.H., for the CDC EPIC Study Team*

Jain S, et al. *N Engl J Med* 2015; 372:835–45

- The Etiology of Pneumonia in the Community (EPIC) study conducted by the U.S. CDC and three U.S. children's hospitals estimated the burden of community-acquired pneumonia hospitalizations among U.S. children < 18 years old, from January 1, 2010 to June 30, 2012.
  - 2,358 had pneumonia on CXR
  - Annual incidence of **15.7 cases per 10,000** children
    - <2 years of age: 62.2 cases per 10,000 children
  - 21% PICU admission
    - 7% mech. vent.
    - 3 deaths (<1%)

Detection of pathogens according to age group in children with community-acquired pneumonia requiring hospitalisation, USA



- NP/OP swabs
- Paired sera (~44%)
- BAL, ETT, pleural fluid when indicated
- Blood culture
- Whole blood PCR for bacteria

A pathogen was detected in:

- 1802 of 2222 children (81%)
- 1 or more viruses in 1472 (66%)
- 1 or more bacteria in 175 (8%)
- Both bacterial and viral pathogens in 155 (7%)

AdV, adenovirus; CoV, coronavirus; Flu, influenza A or B virus; HMPV, human metapneumovirus; HRV, human rhinovirus; PIV, parainfluenza virus; RSV, respiratory syncytial virus; Hib, *Haemophilus influenzae type b*

Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

*The Pneumonia Etiology Research for Child Health (PERCH) Study Group**

- Multi-site, international case-control study in nine study sites in seven countries: Bangladesh, The Gambia, Kenya, Mali, South Africa, Thailand, and Zambia
- All sites enrolled for 24 months (2011-2014)
- Cases: children aged 1–59 months admitted to hospital with severe pneumonia (WHO def.)
- Controls: age-group-matched children randomly selected from surrounding communities

www.thelancet.com **Published online June 27, 2019** http://dx.doi.org/10.1016/S0140-6736(19)30721-4

Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

*The Pneumonia Etiology Research for Child Health (PERCH) Study Group**

- NP, OP, urine, blood, induced sputum, lung aspirate, pleural fluid, and gastric aspirates were tested with cultures, multiplex PCR, or both.
- Primary analyses restricted to:
  - 1769 cases without HIV infection and with abnormal chest x-ray (WHO def)
  - 5102 community controls without HIV infection
- Bayesian, partial latent class analyses used to estimate probabilities of aetiological agents at the individual and population level, incorporating case and control data

www.thelancet.com **Published online June 27, 2019** http://dx.doi.org/10.1016/S0140-6736(19)30721-4

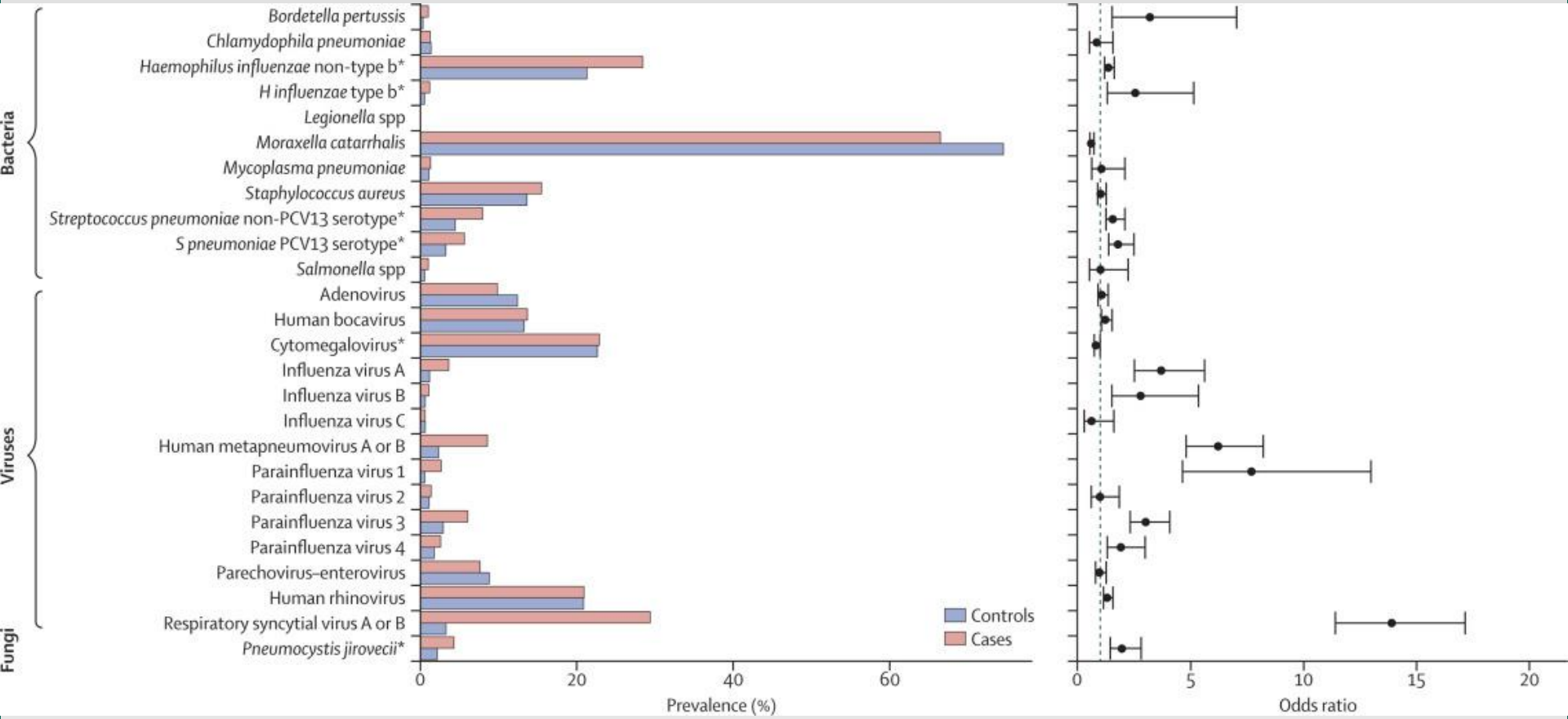
Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

*The Pneumonia Etiology Research for Child Health (PERCH) Study Group**

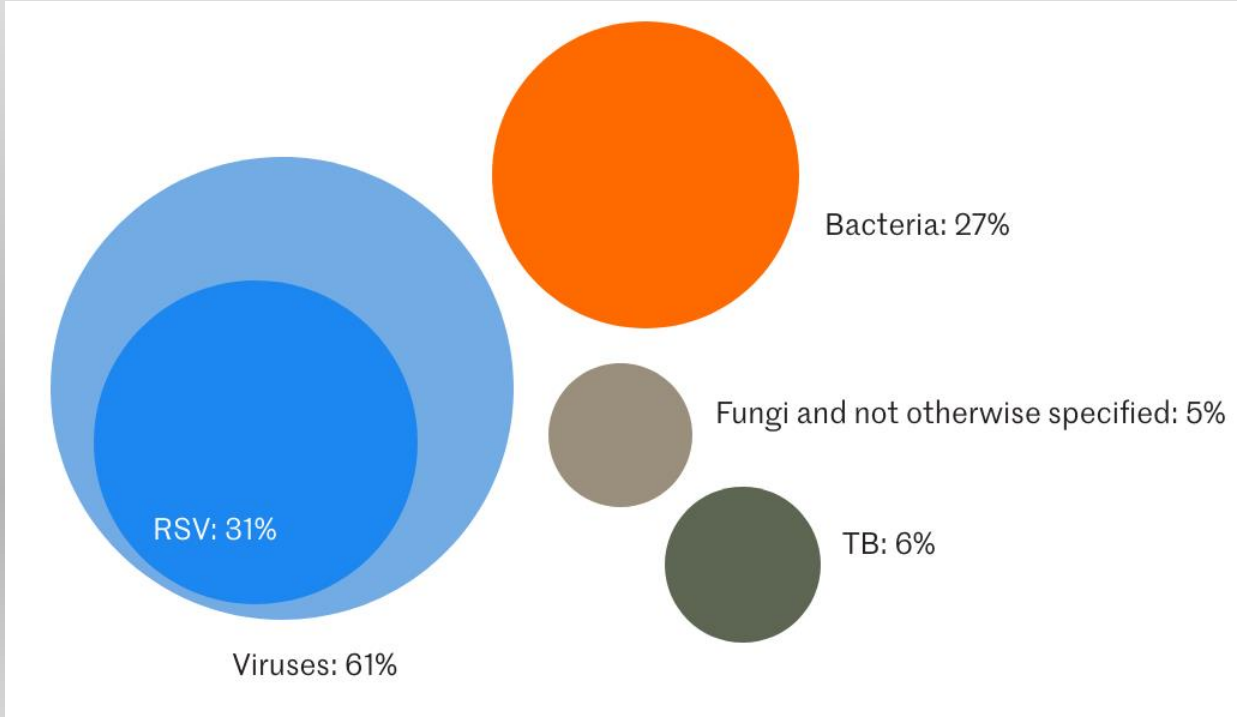
- Wheezing was present in 555 (31·7%) of 1752 cases
- 30-day case-fatality ratio was 6·4% (114 of 1769 cases).
- Blood cultures were positive in 56 (3·2%) of 1749 cases, and *Streptococcus pneumoniae* was the most common bacteria isolated (19 [33·9%] of 56)
- Almost all cases (98·9%) and controls (98·0%) had at least one pathogen detected by PCR in the NP-OP specimen.

www.thelancet.com Published online June 27, 2019 http://dx.doi.org/10.1016/S0140-6736(19)30721-4

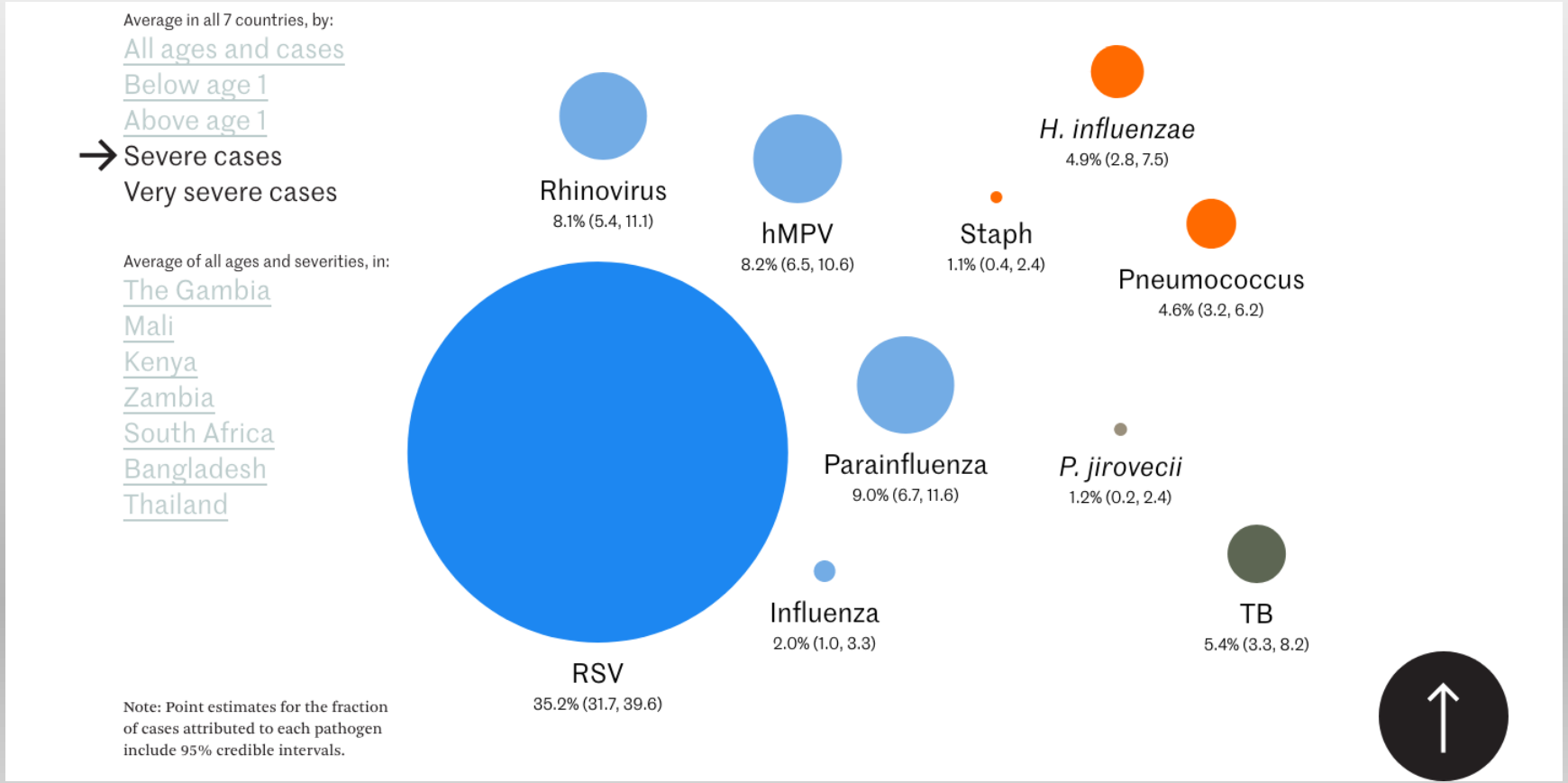
Detection in NP/OP swabs: cases vs controls



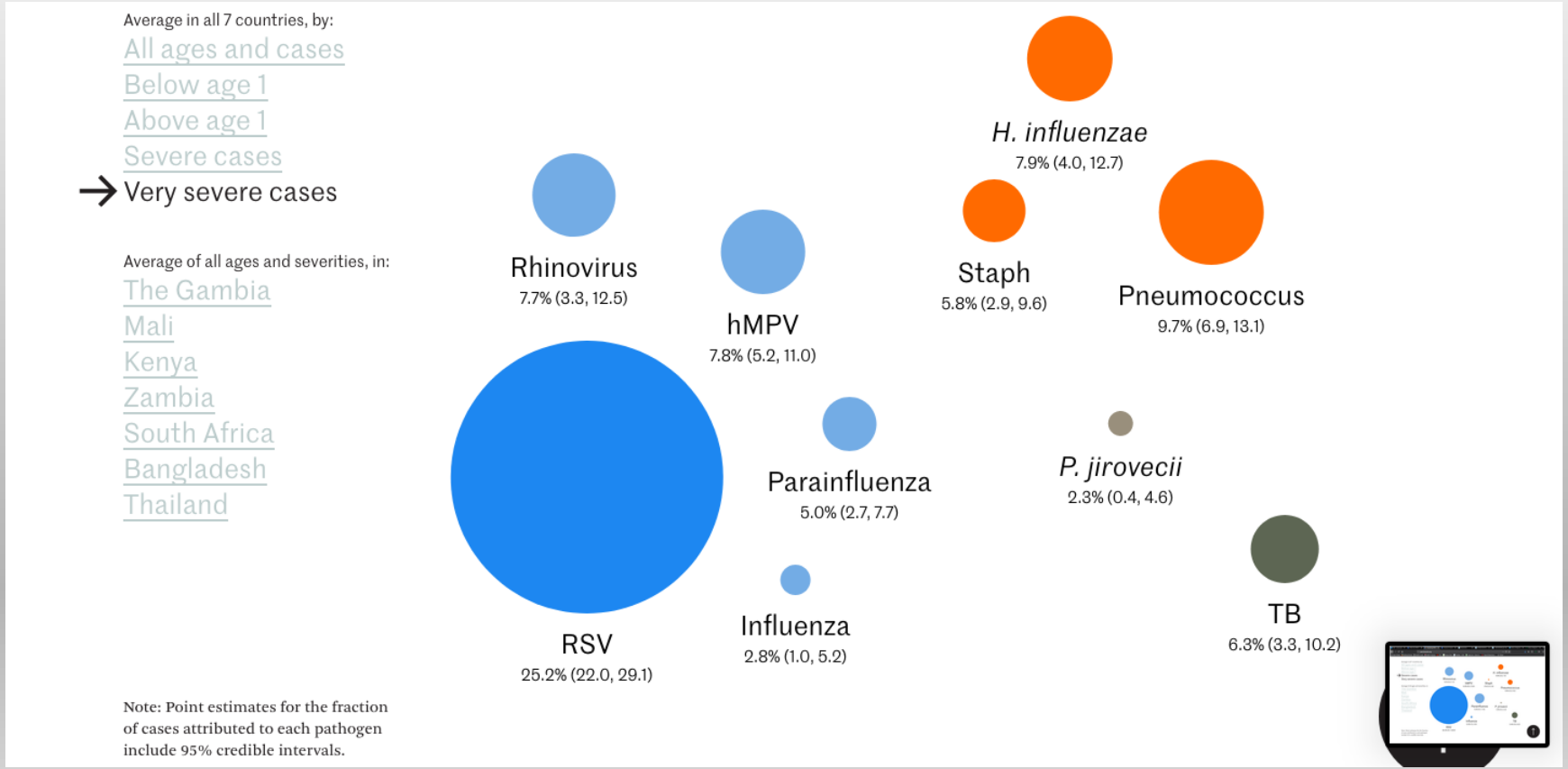
Attributable fractions



http://perchresults.org/



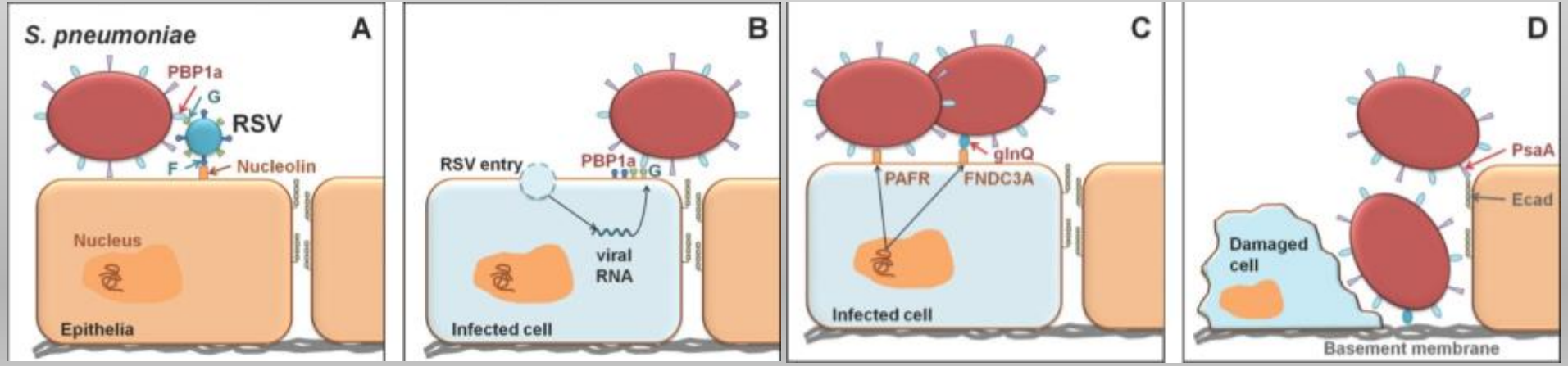
http://perchresults.org/



http://perchresults.org/

Mechanisms of virus-mediated bacterial adherence to the upper respiratory epithelium

- *Streptococcus pneumoniae* and RSV as an example

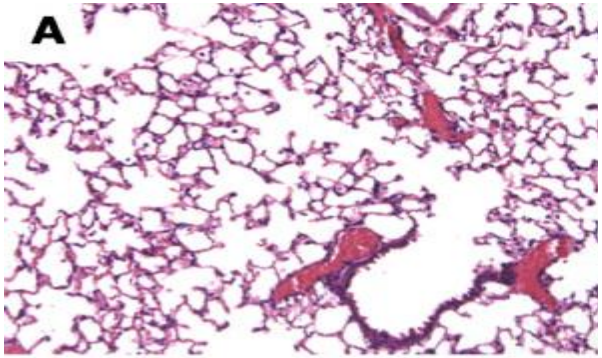


From: Viral bacterial co-infection of the respiratory tract during early childhood. FEMS Microbiol Lett. 2015;362(10). doi:10.1093/femsle/fnv062.

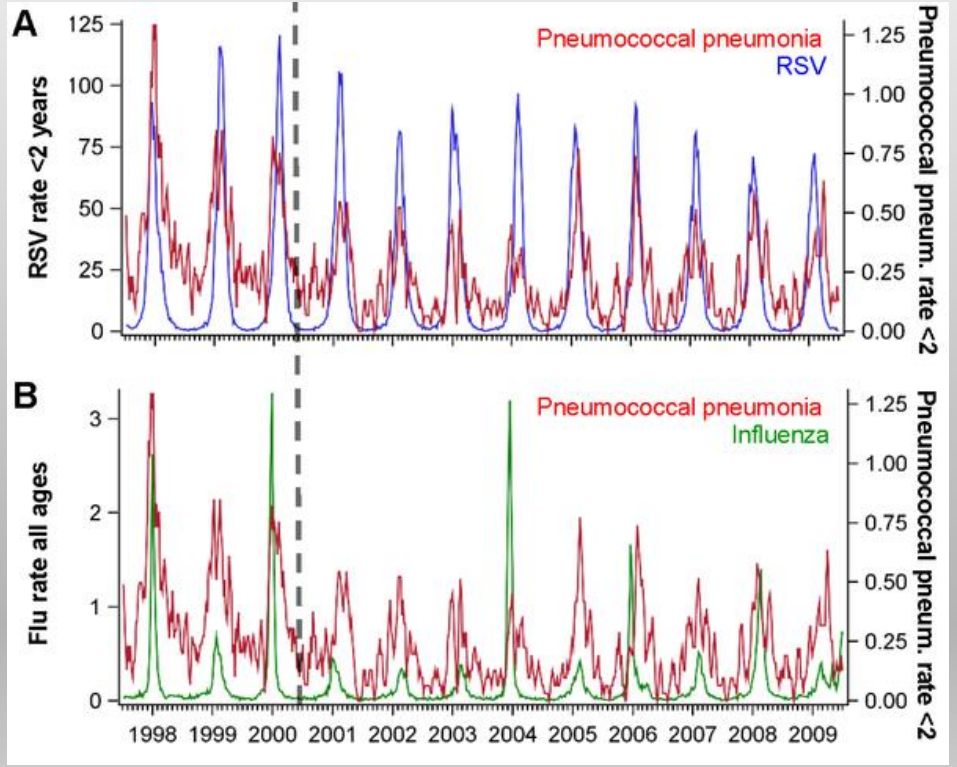
Histopathology of RSV-*S. pneumoniae* sequential infection in BALB/cJ mice

BALB/cJ mice exposed to RSV or control media from uninfected cells on day 0 then challenged with StPn or PBS 7 days later

Control-PBS



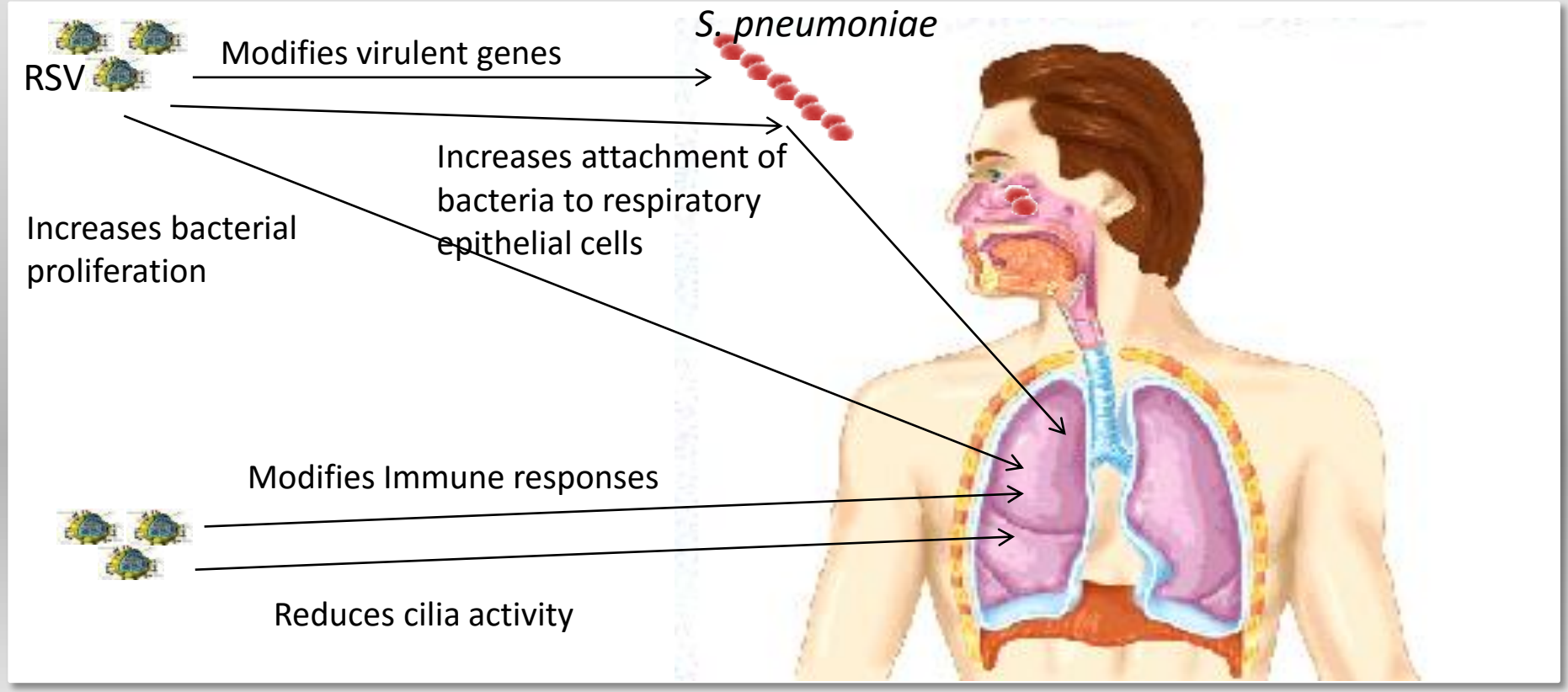
Stark JM, et al. J Med Virol 2006; 78:829–38



Weinberger DM, Klugman KP, Steiner CA, Simonsen L, Viboud C (2015) Association between Respiratory Syncytial Virus Activity and Pneumococcal Disease in Infants: A Time Series Analysis of US Hospitalization Data. *PLOS Medicine* 12(1) https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001776

PLOS | MEDICINE

Direct effect of RSV on *S. pneumoniae* and the respiratory system



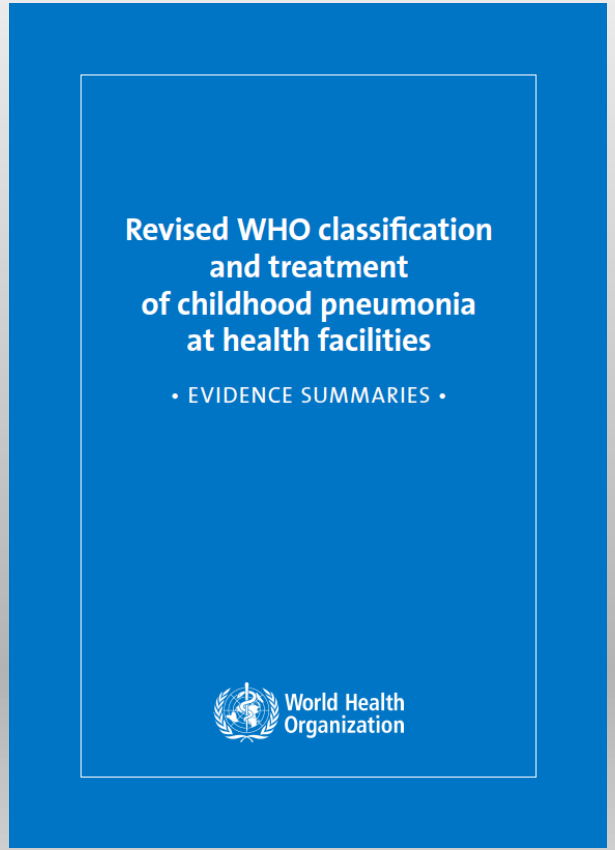
Marieb EN, Wilhelm PB, Mallatt JB. Human Anatomy, 7th Edition; Published by Pearson

CAP TREATMENT

IDSA Guidelines: Empiric Therapy for CAP

	Presumed bacterial pneumonia	Presumed atypical pneumonia	Presumed influenza pneumonia
Outpatient <5 y o	Amoxicillin	Azithromycin Alt: clarithromycin or erythromycin	Oseltamvir
Inpatient, fully immunized	Ampicillin or penicillin G	Azithromycin	Oseltamivir or zanamivir for ≥7yo
	Alt: ceftriaxone or cefotaxime	Alt: clarithromycin or erythromycin; doxycycline if >7yo	Alt: peramivir, oseltamivir and zanamivir (all IV, under investigation)
Inpatient, not fully immunized	Ceftriaxone or cefotaxime	Azithromycin	
	Alt: levofloxacin	Alt: clarithromycin or erythromycin; doxycycline if >7yo	

Bradley JS et al. *Clinical Infectious Diseases*, Volume 53, Issue 7, 1 October 2011, Pages e25–e76,



Recommendation 1

Children with fast breathing pneumonia with no chest indrawing or general danger sign should be treated with oral amoxicillin: at least 40mg/kg/dose twice daily (80mg/kg/day) for five days. In areas with low HIV prevalence, give amoxicillin for three days.

Children with fast-breathing pneumonia who fail on first-line treatment with amoxicillin should have the option of referral to a facility where there is appropriate second-line treatment.

Recommendation 2

Children age 2–59 months with chest indrawing pneumonia should be treated with oral amoxicillin: at least 40mg/kg/dose twice daily for five days.

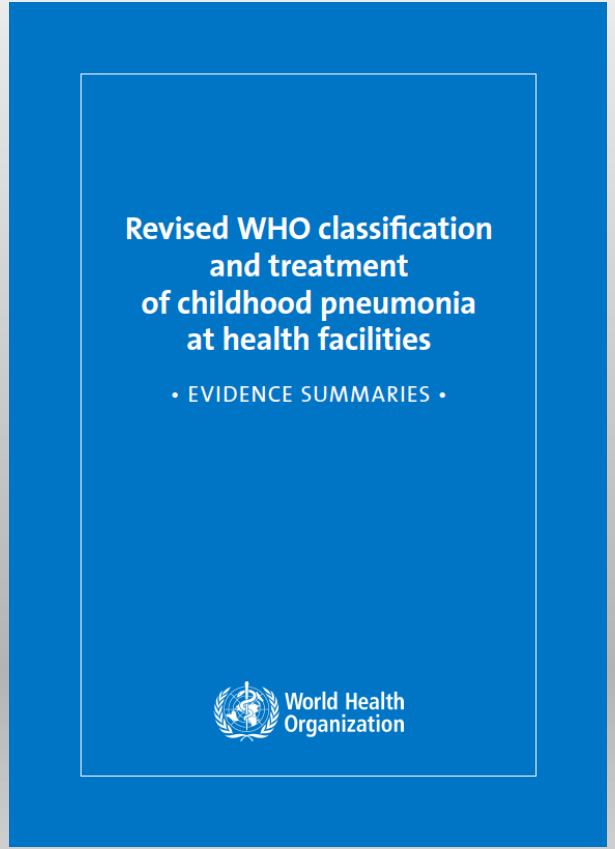
Recommendation 3

Children aged 2–59 months with severe pneumonia should be treated with parenteral ampicillin (or penicillin) and gentamicin as a first-line treatment.

— Ampicillin: 50 mg/kg, or benzyl penicillin: 50 000 units per kg IM/IV every 6 hours for at least five days
— Gentamicin: 7.5 mg/kg IM/IV once a day for at least five days

Ceftriaxone should be used as a second-line treatment in children with severe pneumonia having failed on the first-line treatment.

https://apps.who.int/iris/bitstream/handle/10665/137319/9789241507813_eng.pdf?sequence=1



Recommendation 4

Ampicillin (or penicillin when ampicillin is not available) plus gentamicin or ceftriaxone are recommended as a first-line antibiotic regimen for HIV-infected and -exposed infants and for children under 5 years of age with chest indrawing pneumonia or severe pneumonia.

For HIV-infected and -exposed infants and for children with chest indrawing pneumonia or severe pneumonia, who do not respond to treatment with ampicillin or penicillin plus gentamicin, ceftriaxone alone is recommended for use as second-line treatment.

Recommendation 5

Empiric cotrimoxazole treatment for suspected *Pneumocystis jirovecii* (previously *Pneumocystis carinii*) pneumonia (PCP) is recommended as an additional treatment for HIV-infected and -exposed infants aged from 2 months up to 1 year with chest indrawing or severe pneumonia.

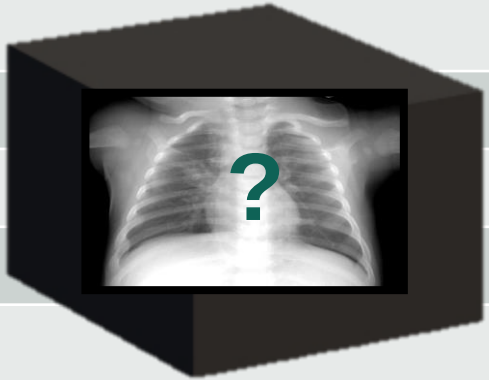
Empirical cotrimoxazole treatment for *Pneumocystis jirovecii* pneumonia (PCP) is not recommended for HIV-infected and -exposed children over 1 year of age with chest indrawing or severe pneumonia.

https://apps.who.int/iris/bitstream/handle/10665/137319/9789241507813_eng.pdf?sequence=1

CAP PREVENTION

Adequate vaccination and immunoprophylaxis for CAP – today and the future

Currently available	Future need for
***S. pneumoniae* PCV: 7, 10, 13** →	Higher valency vaccines
Palivizumab →	RSV vaccine?
Influenza vaccine →	Better responses and stability?
HIB vaccine →	Non-type b *H. influenzae* vaccine?
Pertussis vaccine →	Better protection in <2mo old infants
	Human metapneumovirus vaccines?
	Coronavirus vaccines?
	Parainfluenza virus 1-3 vaccines?
	Mycoplasma pneumoniae vaccines?
	Adenovirus vaccines?



Prevention of RSV Hospitalisation: RCT evidence for Palivizumab

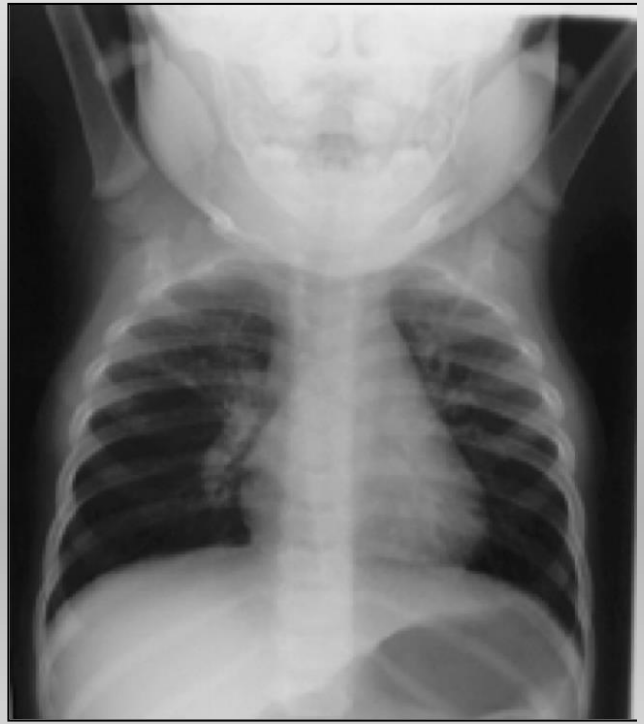
Study	Population	Reduction in RSV Hospitalisation (95% CI)
IMpact	- Infants born **<36 weeks GA** - **With or without CLD** - <6 mo at start of RSV season	**55% (38-72)**
IMpact	- Infants born **<36 weeks GA** - **No CLD** - <6 mo at start of RSV season	**82% (45-94)**
IMpact	- Children born **<36 weeks GA** - **With CLD** - <24 mo at start of RSV season	**38% (5-60)**
Feltes et al.	- Children with **hemodynamically significant CHD** - <24 mo at start of RSV season	**45% (18-63)**

1. The IMpact-RSV Study Group. Pediatrics. 1998;102(3):531-7
2. Feltes TF et al. J Pediatr. 2003;143:532–40.

BRONCHIOLITIS

Bronchiolitis

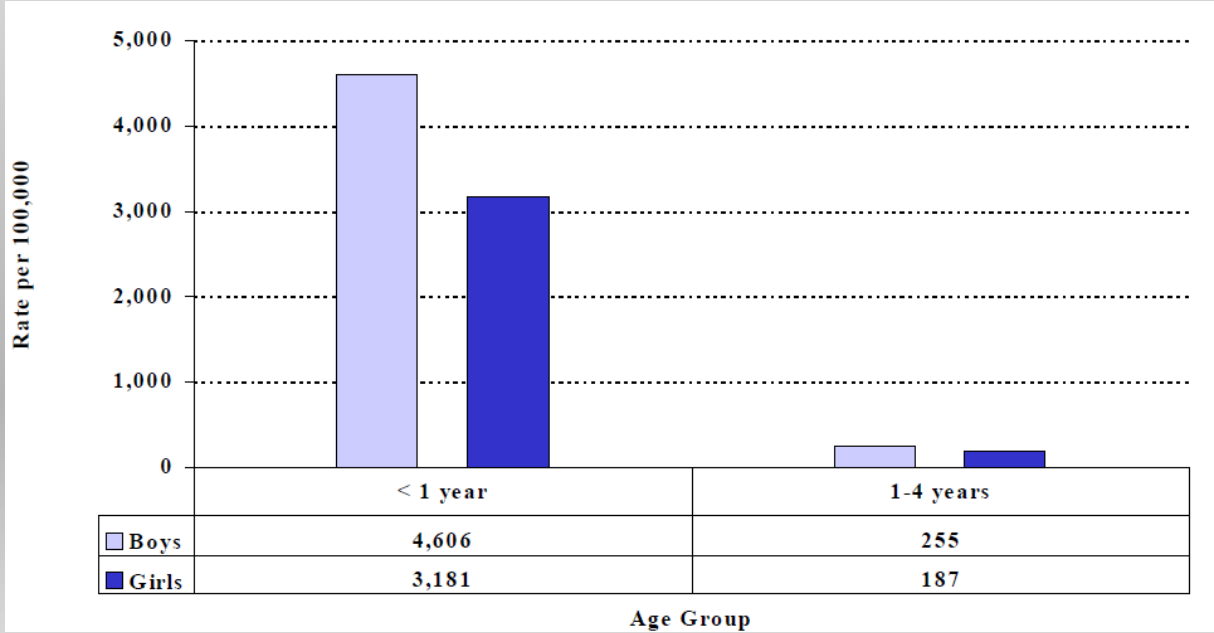
- Common disease of the lower respiratory tract in infants and young children due to inflammatory obstruction of the small airways (the bronchioles)
  - Severe disease most common in infants
- An acute viral infection
  - RSV responsible for 50-80%
- Seasonal
  - November to April



Nelson Textbook of Pediatrics, 19th ed. 2011.

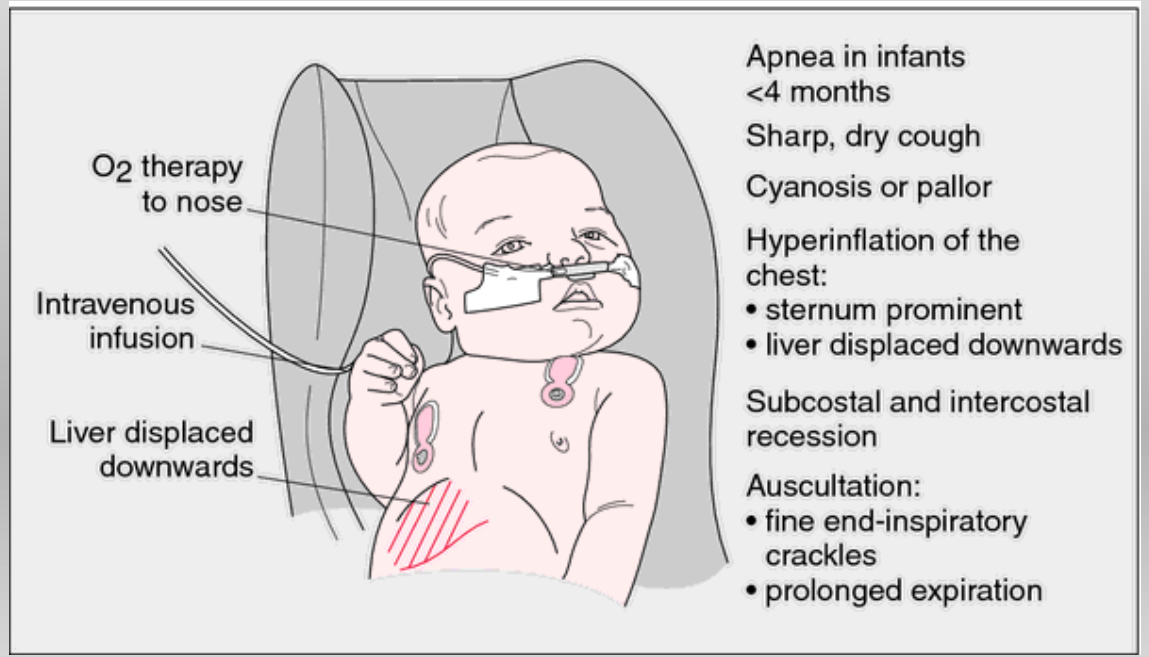
Bronchiolitis-associated hospitalizations

- > 50% occur in children <6 months
- > 81 % occur in those <1 year[1]



1. Shay et al. Bronchiolitis-associated hospitalizations among US children, 1980-1996. JAMA 1999.
2. CIHI. Respiratory disease in Canada. 2001.

Severe bronchiolitis: management is supportive



http://medical-dictionary.thefreedictionary.com/Bronchiolitis

American Academy of Pediatrics: Guidance for Diagnosis and Management of Bronchiolitis

Treatment		
Bronchodilator therapy	Not recommended	Randomized trials have not shown a consistent beneficial effect on disease resolution, need for hospitalization, or length of stay
Epinephrine	Not recommended	Large, multicenter, randomized trials have not shown improvement in outcome among outpatients with bronchiolitis or hospitalized children
Glucocorticoid therapy	Not recommended	Large, multicenter, randomized trials provide clear evidence of lack of benefit
Nebulized hypertonic saline	May be considered	Nebulized 3% saline may improve symptoms of mild-to-moderate bronchiolitis if length of stay is >3 days (most hospitalizations are <72 hr)
Supplemental oxygen	Routine use not recommended if oxyhemoglobin saturation is >90% in the absence of acidosis	Transient episodes of hypoxemia are not associated with complications; such episodes occur commonly in healthy children
Pulse oximetry	Not recommended for patients who do not require supplemental oxygen or if oxygen saturation is >90%	Oxygen saturation is a poor predictor of respiratory distress; routine use correlates with prolonged stays in the emergency department and hospital
Chest physiotherapy	Not recommended	Deep suctioning is associated with a prolonged hospital stay; removal of obstructive secretions by suctioning the nasopharynx may provide temporary relief
Antimicrobial therapy	Not recommended for routine use	Risk of serious bacterial infection is low; routine screening is not warranted, especially among infants 30 to 90 days of age
Nutrition and hydration	Hospitalization for observation of hydration and nutritional status may be needed for infants with respiratory distress	Intravenous or nasogastric hydration may be used

Julie R. Ingelfinger, M.D., Editor Viral Bronchiolitis in Children; Meissner. *N Engl J Med* 2016;374:62-72.

Chest radiography in bronchiolitis

Society of Hospital Medicine – **Pediatric Hospital Medicine**

Released February 21, 2013

DOWNLOAD PDF

1

Don't order chest radiographs in children with uncomplicated asthma or bronchiolitis.

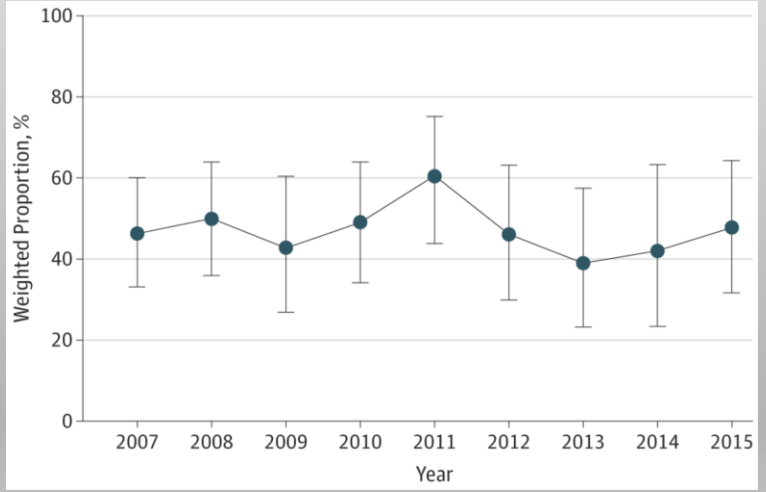
National guidelines articulate a reliance on physical examination and patient history for diagnosis of asthma and bronchiolitis in the pediatric population. Multiple studies have established limited clinical utility of chest radiographs for patients with asthma or bronchiolitis. Omission of the use of chest radiography will reduce costs, but not compromise diagnostic accuracy and care.

http://www.choosingwisely.org/societies/society-of-hospital-

Use of Radiography in Patients Diagnosed as Having Acute Bronchiolitis in US Emergency Departments, 2007-2015

Brett Burstein, MDCM, PhD, MPH[1]; Amy C. Plint, MD, MSc[2]; Jesse Papenburg, MDCM, MSc[3]

- Data from the National Hospital Ambulatory Medical Care Survey (NHAMCS), 2007 to 2015
- Mean CXR use: 46%
  - No diff. admit /non-admit
    - 45% vs. 46% (*P* = .83)
- Higher rates of imaging associated with
  - Non-pediatric hospital
    - aOR 3.06 (1.75-5.34)
  - Race other than black or white
    - aOR 3.08 (1.13-8.43)



Weighted Proportion of Children Undergoing Radiography in US Emergency Departments for Acute Bronchiolitis by Year. Error bars indicate 95% CIs.

Mean value for 2007-2015, 46% (95% CI, 40%-53%)

P for trend =.87

JAMA. 2018;320(15):1598-1600

Consequence of chest radiography on antibiotic use in ED for severe bronchiolitis: Montreal Children's Hospital, 2014-16

	Model 1	Model 2
	aOR (95% CI)	aOR (95% CI)
Age (months)		
>1-<3	**0.17 (0.06-0.49)**	**0.15 (0.05-0.47)**
3-<12	0.67 (0.37-1.23)	0.70 (0.35-1.38)
12-<24	Ref.	Ref.
Low oxygen saturation (<94%) at presentation	1.42 (0.79-2.52)	1.35 (0.71-2.57)
Fever at presentation (T ≥39.0°C)	**2.58 (1.28-5.19)**	**2.64 (1.19-5.88)**
> 3 days of symptoms	**2.38 (1.19-4.75)**	2.03 (0.94-4.40)
Acute otitis media	**8.21 (3.31-20.34)**	**15.34 (5.47-43.03)**
ED chest radiography	**3.46 (1.73-6.94)**	-
ED radiography findings		
No radiography	-	Ref.
Normal	-	0.22 (0.03-1.34)
Pneumonia only	-	**28.27 (8.56-93.26)**
Pneumonia with bronchiolitis	-	**7.50 (3.06-18.36)**
Bronchiolitis only	-	1.99 (0.86-4.60)

Model 1: CXR use, dichotomous (yes/no)
Model 2: CXR findings, vs. no CXR

Inappropriate Antibiotic Prescribing for Acute Bronchiolitis in US Emergency Departments, 2007–2015

Jesse Papenburg,[1,2] Patricia S. Fontela,[1,3] Raphael R. Freitas,[4] and Brett Burstein[4]

[1]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada; and [2]Division of Pediatric Infectious Diseases, Departments of Pediatrics and Microbiology, [3]Division of Pediatric Critical Care Medicine, Department of Pediatrics, and [4]Division of Pediatric Emergency Medicine, Department of Pediatrics, Montreal Children's Hospital, McGill University Health Centre, Montreal, Quebec, Canada

One-fourth of patients with bronchiolitis seen in US emergency departments between 2007 and 2015 received antibiotics; 70% of them had no documented bacterial coinfection. Macrolides were prescribed in 38% of the cases. Antibiotic use did not decrease after national recommendations against routine prescribing. Efforts are needed to reduce unnecessary and inappropriate antibiotic use for bronchiolitis.

J Pediatric Infect Dis Soc. 2019 Jan 17.

Table 2. Multivariable Logistic Regression Model of Factors Associated with ED Antibiotic Prescribing Among Children With a Diagnosis of Bronchiolitis and Without a Concomitant Bacterial Infection[a]

Factors	aOR for Antibiotic Use (95% CI)
Age group	
<3 mo	Ref
≥3 to <12 mo	1.62 (0.70–3.73)
≥12 to <24 mo	2.64 (1.06–6.59)
Sex	
Male	1.39 (0.73–2.64)
Race	
Black	Ref
White	0.80 (0.38–1.68)
Other	0.49 (0.11–2.10)
Type of institution: teaching hospital	
Nonteaching	3.03 (1.04–9.77)
Type of institution: pediatric hospital	
Non-pediatric hospital	3.32 (1.07–11.36)
Patient disposition	
Admitted	0.83 (0.30–2.32)
Radiography use	
Radiography performed	3.37 (1.55–7.32)
Triage acuity level	
Nonurgent	Ref
Semiurgent	1.78 (0.38–8.38)
Urgent	0.90 (0.21–3.89)
Immediate/emergent	2.03 (0.34–12.16)
Unknown/unavailable	0.98 (0.21–4.56)
Insurance provider	
Self-pay	Ref
Private	1.11 (0.30–4.13)
Medicare/Medicaid	2.16 (0.68–6.84)
Other/unknown	1.47 (0.30–7.27)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ED, emergency department; Ref, reference category.

Summary

- Despite efforts to improve prevention and management, pediatric CAP causes a huge burden
- Determining the causative agent of CAP in children is challenging, both at the individual and population levels
- New vaccines for the viral agents of pediatric CAP could greatly improve child health
- Antibiotics are overused in pediatric CAP and bronchiolitis
  - Further LRTI research is needed on how to distinguish children that would benefit from antibiotics from those in whom antibiotic therapy can be safely witheld