Community-acquired Pneumonia and the Case for Antimicrobial Stewardship

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Disclosures

- None

Objectives

- Highlight trends in antibiotic use for childhood pneumonia
- Review data on pneumonia etiology
- Highlight opportunities for reducing antibiotic use in the pediatric population

Outline

1. Background / Epidemiology
2. Trends in antibiotic use
   - Special circumstances – macrolides, cefdinir and aspiration pneumonia
3. Antibiotic duration
4. Diagnostic stewardship
   - Blood cultures, nasal MRSA PCR

Background

- Community-acquired pneumonia (CAP) accounts for approx. 2 million outpatient visits annually[1]
- 1 in 500 children with CAP require hospitalization[2]
- Nearly impossible to distinguish viral vs. bacterial CAP in the clinical setting
  - Drives antibiotic prescribing for CAP

1. Kronman et al. *Pediatrics*, 2011
2. McCulloh RJ, Patel K. *Curr Infect Dis Rep*, 2016.

Definition of CAP

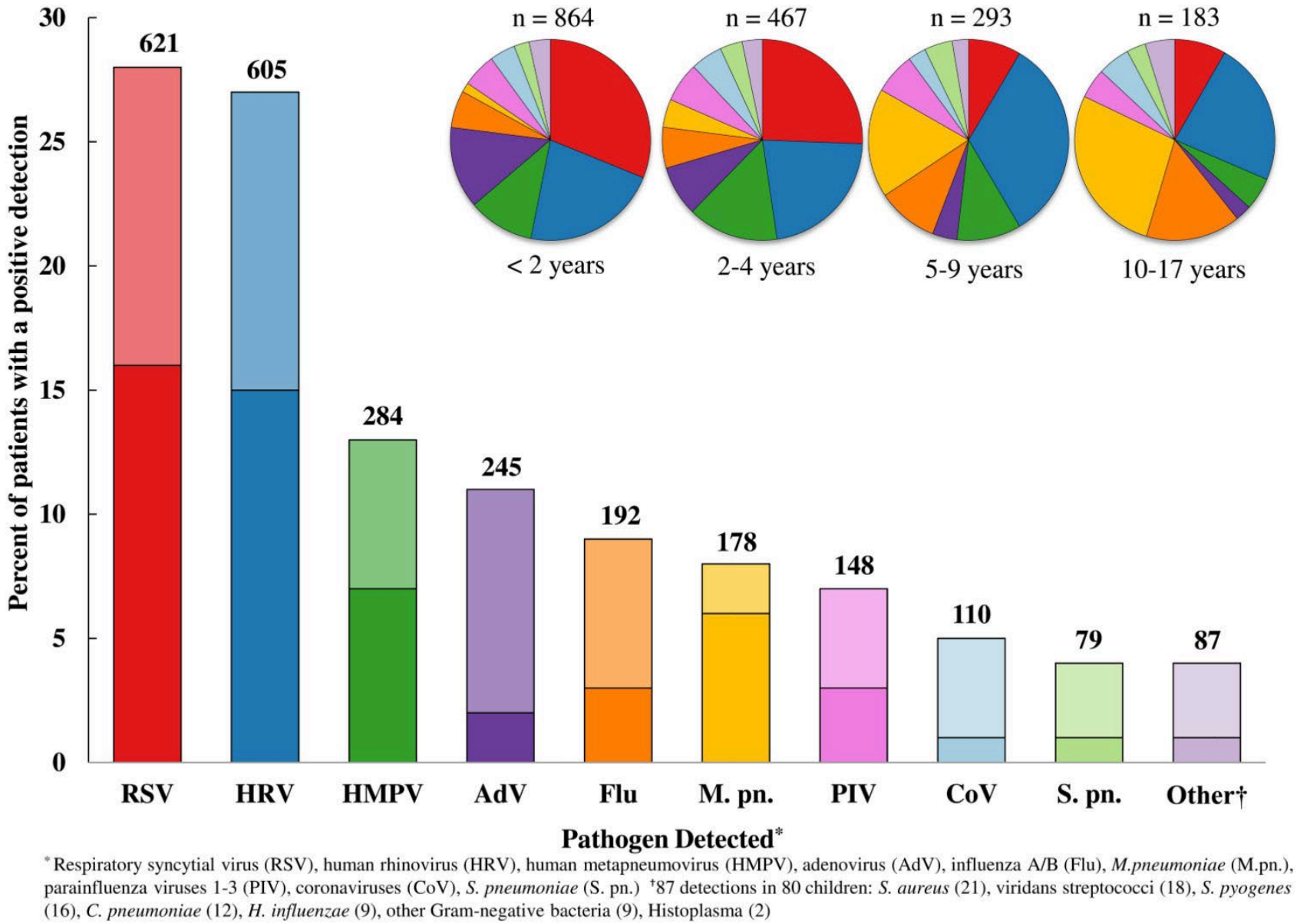
- Acute lower respiratory tract infection acquired in a previously healthy individual
- Associated symptoms: fever, cough, dyspnea, and tachypnea
- Supporting evidence of parenchymal infection and inflammation, diagnosed on physical exam or as a focal opacity on chest x-ray

https://www.faythclinic.com/obesity-in-children-treatment-mumbai-2-2-2/

Epidemiology of CAP

CDC Etiology of Pneumonia in the Community (EPIC) Study

- 2010-2012
- >2,500 children
- Pathogen ID'd in 81%
  - *S. pneumo* 4%

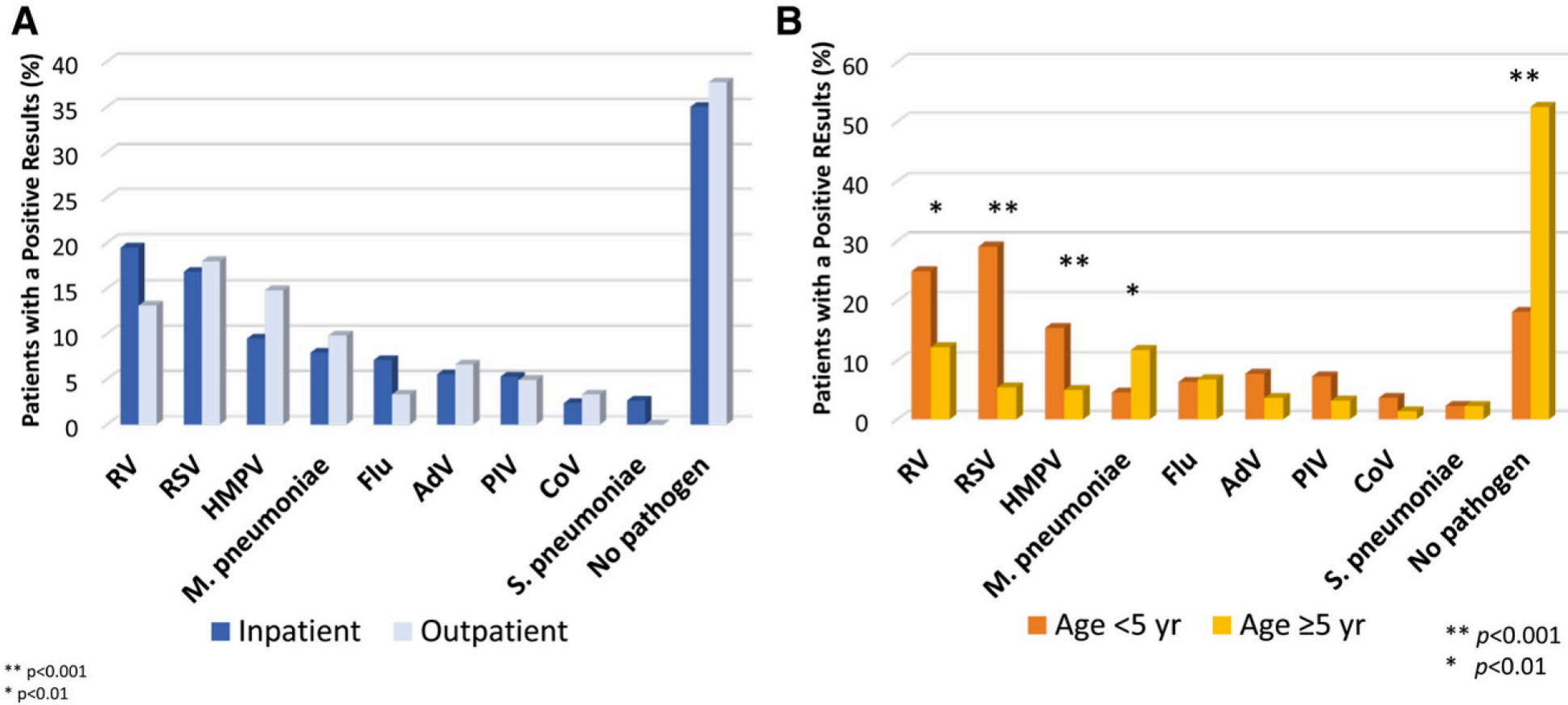


*Respiratory syncytial virus (RSV), human rhinovirus (HRV), human metapneumovirus (HMPV), adenovirus (AdV), influenza A/B (Flu), *M.pneumoniae* (M.pn.), parainfluenza viruses 1-3 (PIV), coronaviruses (CoV), *S. pneumoniae* (S. pn.) †87 detections in 80 children: *S. aureus* (21), viridans streptococci (18), *S. pyogenes* (16), *C. pneumoniae* (12), *H. influenzae* (9), other Gram-negative bacteria (9), Histoplasma (2)

Jain S et al. *NEJM*, 2015

Epidemiology of CAP, 2015-2018

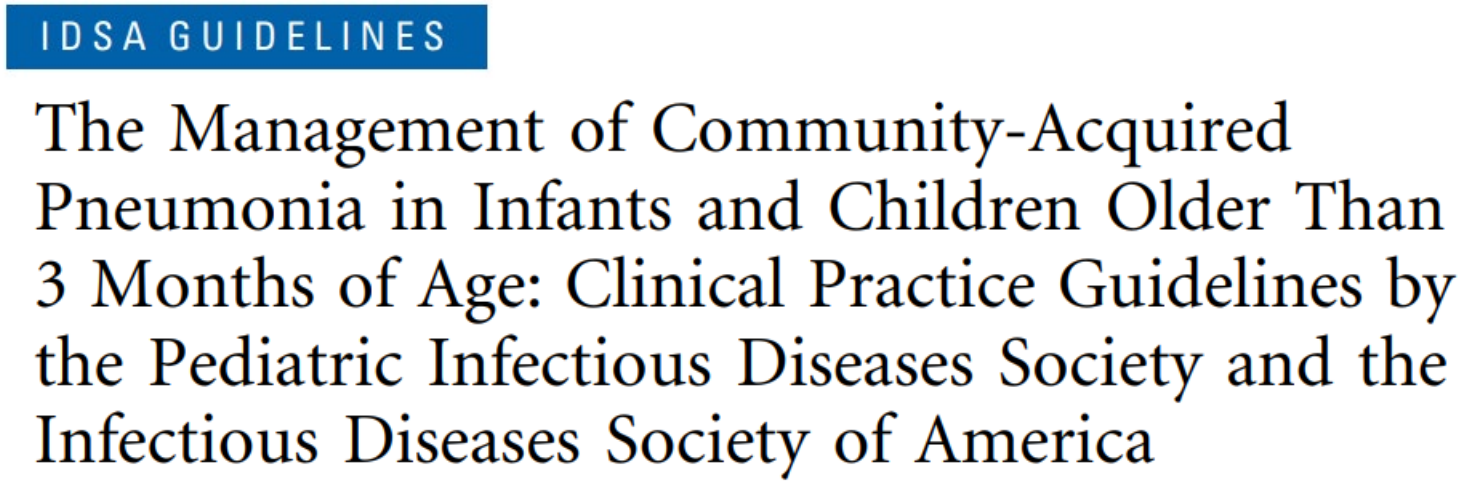
- 441 patients
  - 380 inpatient
  - 61 outpatient)
- Pathogen ID'd in 65%



Yun KW et al. *Pediatric Infect Dis J*, 2022

Antibiotic Treatment

IDSA Guidelines



- Published in 2011 (new version is in process)

Bradley et al. *Clin Infect Dis*, 2011

IDSA Guidelines - *Outpatients*

IDSA GUIDELINES

- Antibiotics are NOT routinely required for preschool-aged children
  - Viruses = most common cause of pneumonia
  - *Strong recommendation; high-quality evidence*

- **Amoxicillin** is first-line therapy for previously healthy, immunized infants, preschool children and school-aged children
  - Target = *S. pneumoniae*
  - *Strong recommendation, moderate-quality evidence*

Bradley et al. *Clin Infect Dis*, 2011

IDSA Guidelines - *Inpatients*

IDSA GUIDELINES

- **Ampicillin or penicillin** G is first-line therapy for previously healthy, immunized infants, preschool children and school-aged children
  - Target = *S. pneumoniae*
  - *Strong recommendation, moderate-quality evidence*

- **Ceftriaxone** is first-line therapy for children who are not fully immunized, or for children with life-threatening infection, including empyema
  - *Weak recommendation, moderate-quality evidence*

- **Vancomycin or Clindamycin** should be added if characteristics are consistent with *S. aureus*
  - *Strong recommendation, low-quality evidence*

Bradley et al. *Clin Infect Dis*, 2011

Antibiotics – Inpatient Guideline Adoption

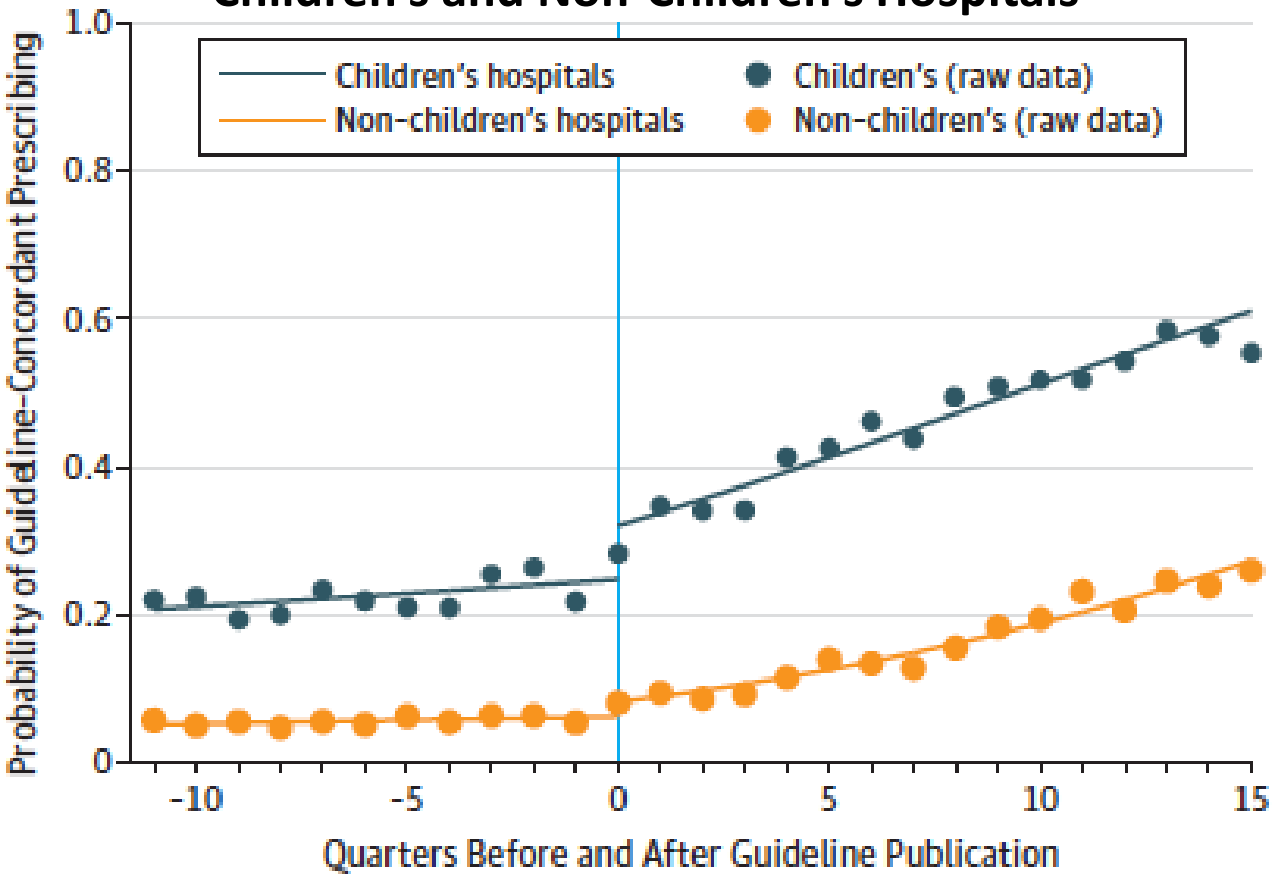
- Hospital billing databases (PHIS vs Premier Perspectives)
- 2009-2015
- 120,238 children

Guideline concordance in 2015:

- Non-children's hospital: 27%
- Children's hospital: 61%

➢ Improvement in guideline-concordant prescribing across the board (but still room to do better)

Guideline-Concordant Prescribing for Pediatric CAP at Children's and Non-Children's Hospitals

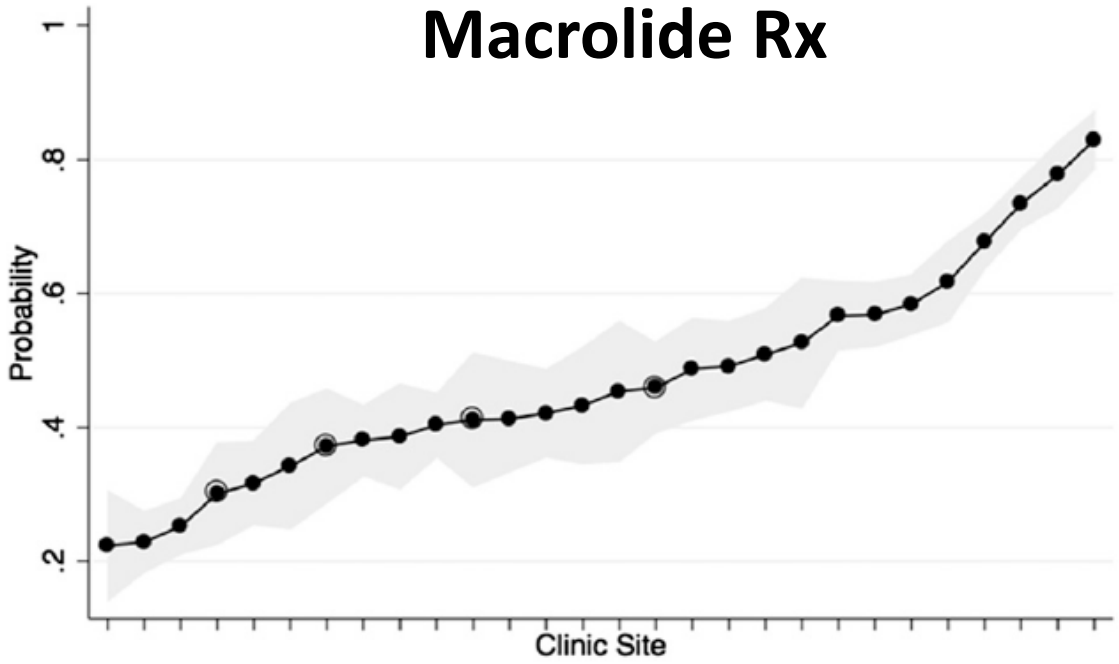


Tribble AC, et al. *JAMA Peds*, 2019

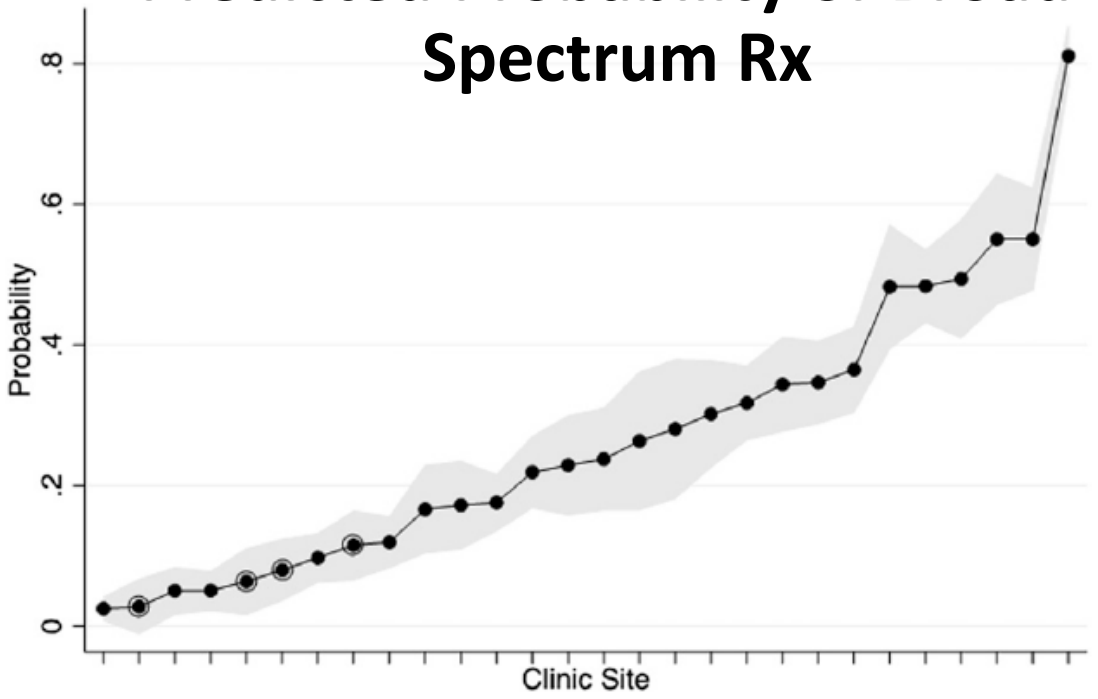
Antibiotics – Outpatient Guideline Adoption

- Retrospective cohort study, pediatric primary care, 2009-2013
- 10,414 children: 41% amoxicillin rx, 43% macrolide rx, 17% broad-spectrum rx

Predicted Probability of Macrolide Rx



Predicted Probability of Broad-Spectrum Rx

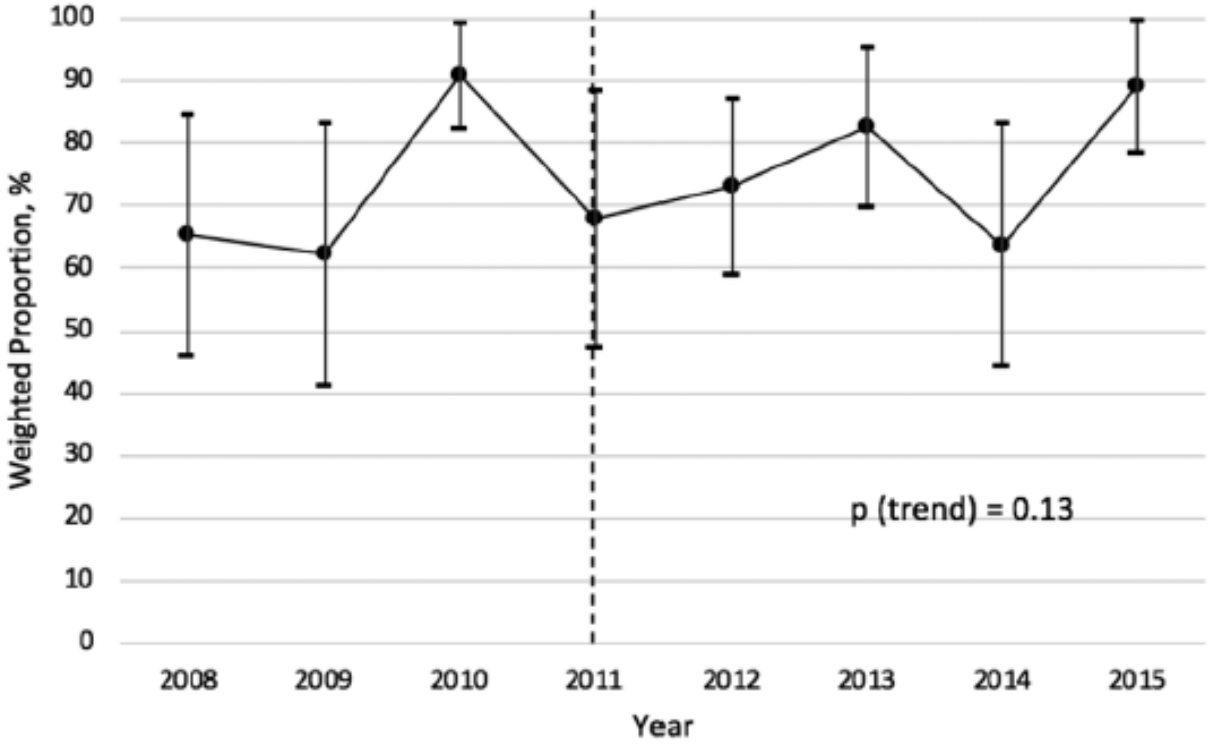


Handy LK, et al. *Pediatrics*, 2017

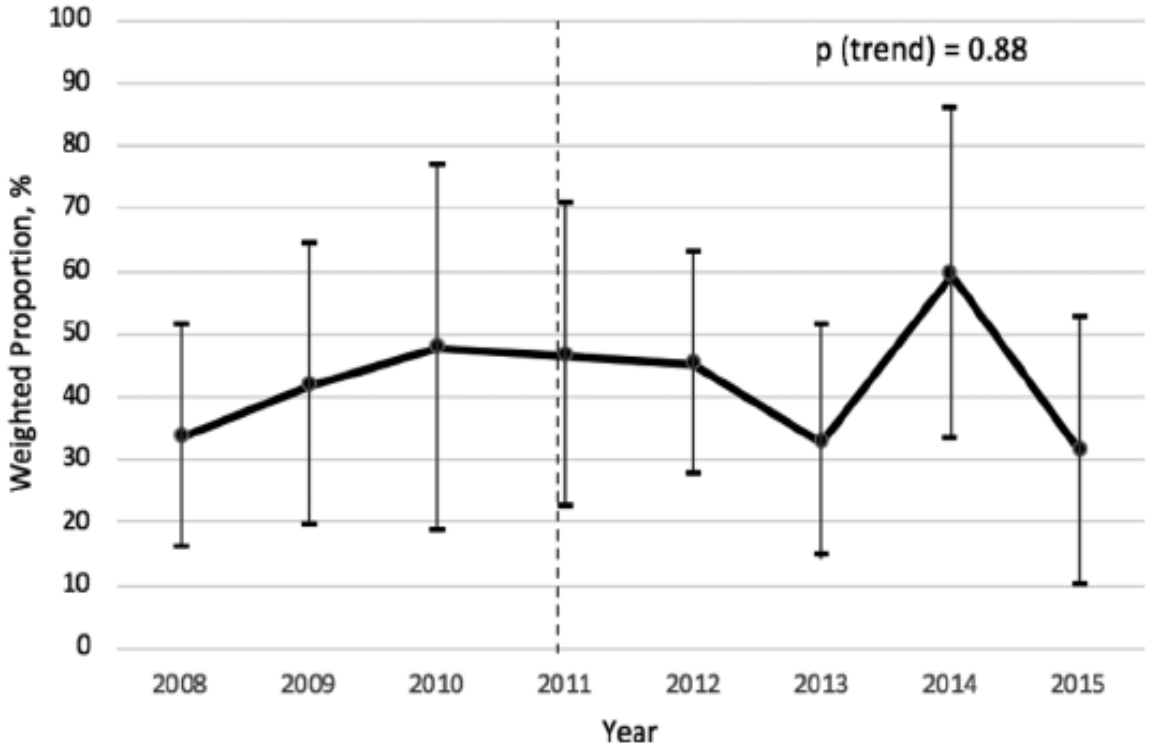
Antibiotics – Outpatient Guideline Adoption

- 2008-2015 retrospective surveys; outpatient clinics & EDs
- 601 children ages 1-6 years (represents estimated 6.3 million visits for CAP)

Any Antibiotics



Narrow-Spectrum Antibiotics



Florin TA, et al. *JPIDS*, 2020

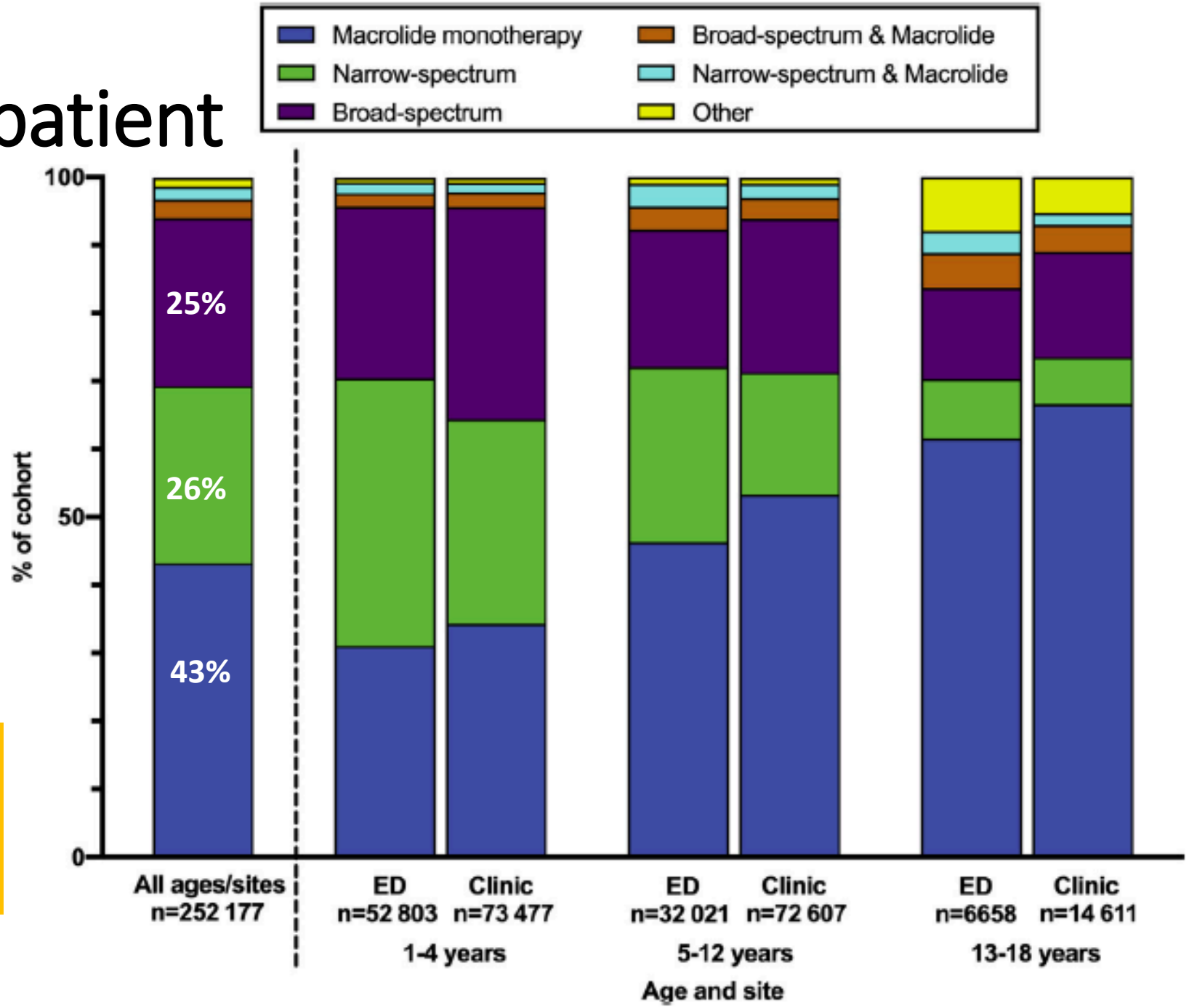
Antibiotics - Outpatient

- Retrospective cohort study, ambulatory Medicaid-enrolled children
- 2010-2016
- 252,177 CAP visits

From EPIC study:

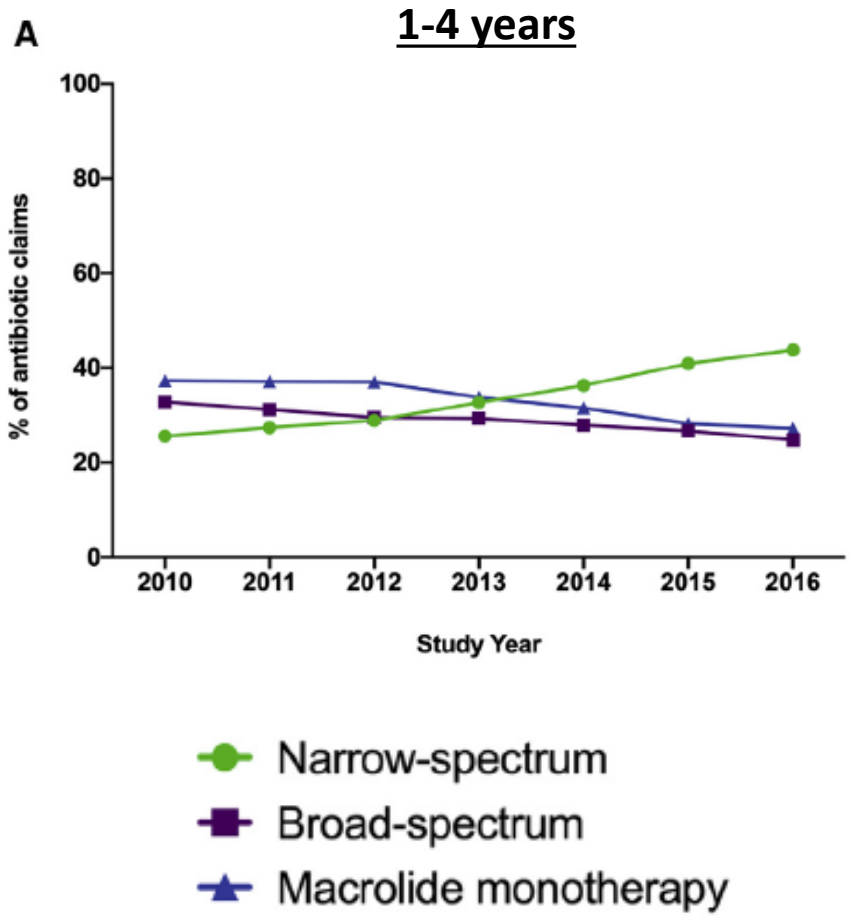
- < 5 years: mostly viral
- 5-17 years: viral + *Mycoplasma* (approx. 15-25%)

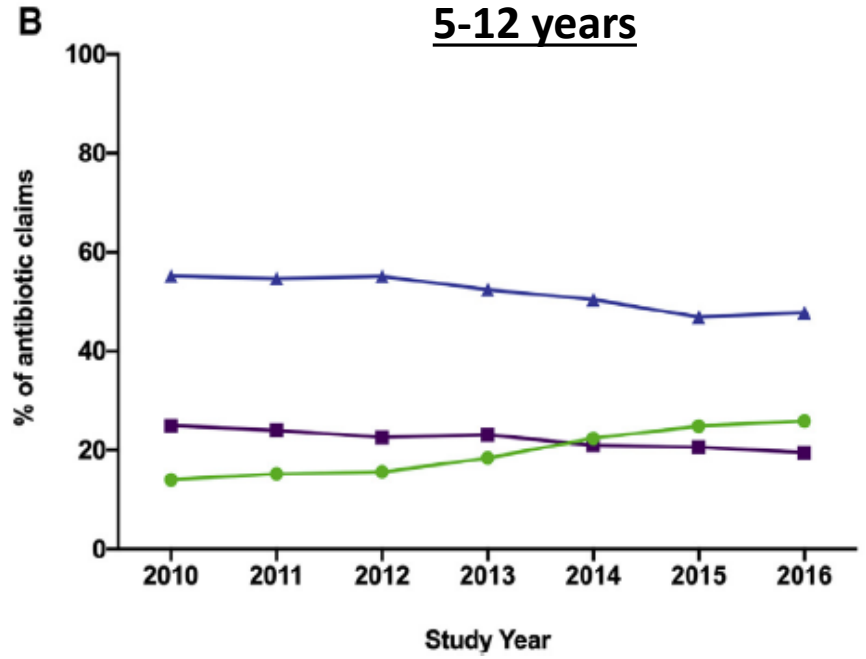
➢ High rates of macrolide rx despite low rates of atypical pneumonia

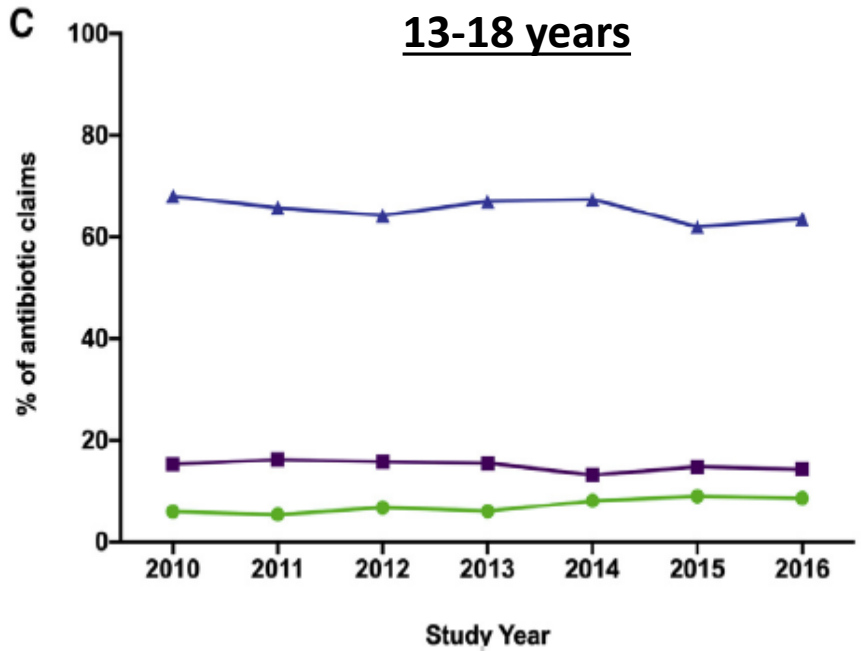


Lipsett SC, et al. *J Peds*, 2021

Antibiotics – Outpatient







- ↑ in narrow-spectrum rx
- ↓ in broad-spectrum and macrolide rx
- Most pronounced for 1-4 years

Lipsett SC, et al. *J Peds*, 2021

Antibiotics - Outpatient

- **1488 (0.69%) hospitalized** in the 2-7 days after their clinic visit
- **117 (0.05%)** developed **severe pneumonia**
- **13,623 (5.4%)** had **change** in antibiotic therapy

Antibiotic groups	Hospitalization	Severe pneumonia	Change in antibiotic therapy
Narrow-spectrum	Referent	Referent	Referent
Narrow-spectrum + macrolide	0.62	0.39	0.47
Broad-spectrum	1.34	1.2	1.15
Broad-spectrum + macrolide	1.43	1.56	0.48
Macrolide only	0.64	0.56	0.97

Color = statistically significant

Lipsett SC, et al. *J Peds*, 2021

Macrolides

Macrolides

IDSA GUIDELINES

- Children with signs and symptoms suspicious for *Mycoplasma pneumoniae* **should be tested to help guide antibiotic selection**
  - *Weak recommendation; moderate-quality of evidence*

- ***Inpatients***: Empiric **combo therapy with a macrolide** should be prescribed in children for whom *M. pneumonaie* and *C. pneumoniae* are **significant considerations**
  - *Weak recommendation; moderate-quality evidence*

- ***Outpatients***: Macrolide antibiotics should be prescribed for treatment of children (**school-aged and adolescents**) with findings compatible with CAP caused by atypical pathogens.
  - *Weak recommendation; moderate-quality evidence*

Antibiogram Data

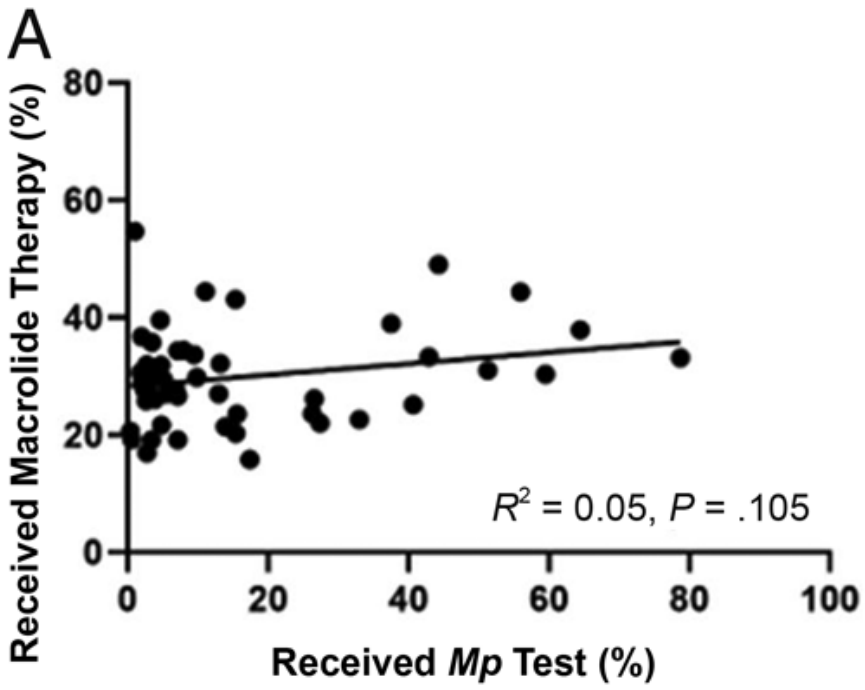
Vanderbilt Children's Hospital Antibiogram

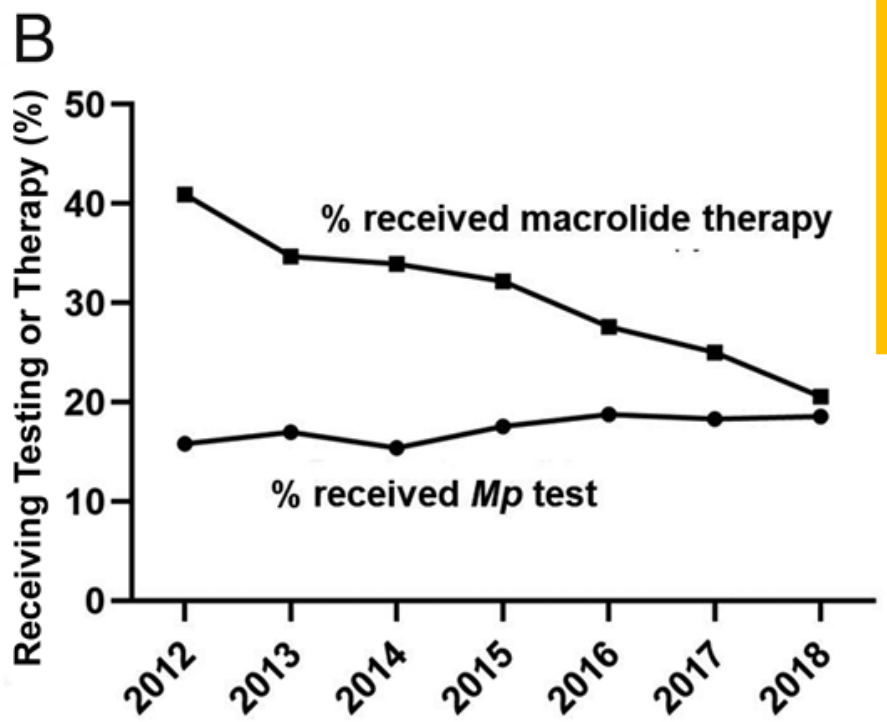
	N	Amoxicillin-clavulanate	Cefepime (meningitis)	Cefepime (non-meningitis)	Cefotaxime (meningitis)	Cefotaxime (non-meningitis)	Ceftriaxone (meningitis)	Ceftriaxone (non-meningitis)	Clindamycin	Erythromycin[1]	Levofloxacin	Meropenem	Moxifloxacin	Penicillin (meningitis)	Penicillin (non-meningitis)
Streptococcus pneumoniae	68	95	71	89	94	98	95	98	86	48	98	73	100	56	94

[1] Predicts activity of azithromycin

Trends in Macrolide Prescriptions

- Hospitalized children (PHIS), 2012-2018
- 103,977 children





- ↑ in *Mycoplasma* testing (15.8% to 18.6%)
- ↓ in macrolide prescribing (40.9% to 20.6%)

Desai S et al. *Hosp Peds*, 2021

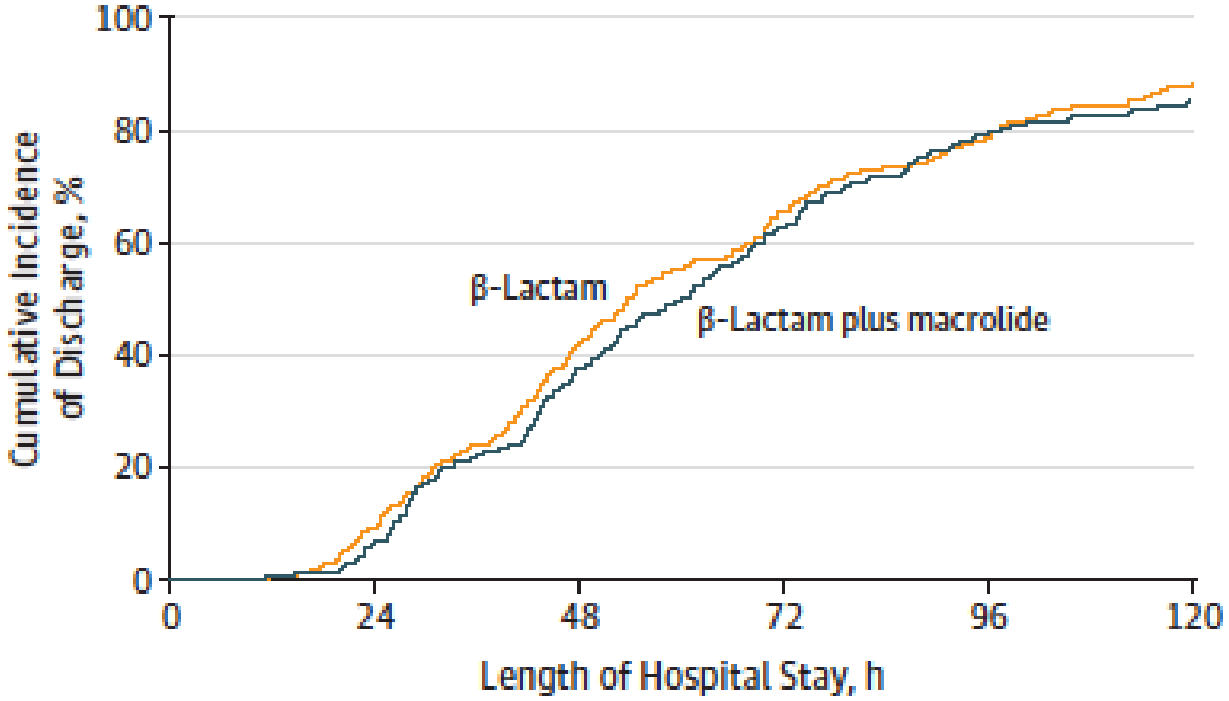
Outcomes with Macrolide Prescribing

- EPIC study data
- Compared beta-lactam + macrolide to beta-lactam only

Results:

- 1019 (72%) beta-lactam monotx vs. 399 (28%) beta-lactam + macrolide
- No difference in length of stay (55 vs. 59 hours)
- No difference in ICU admission, rehospitalization or self-reported recovery at follow-up

Cumulative Incidence of Discharge According to Antibiotic Treatment



No. at risk						
β-Lactam	280	254	162	96	59	33
β-Lactam plus macrolide	280	261	174	104	57	41

Williams DJ, et al. *JAMA Peds*, 2017

Cefdinir

Cefdinir

IDSA GUIDELINES

The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America

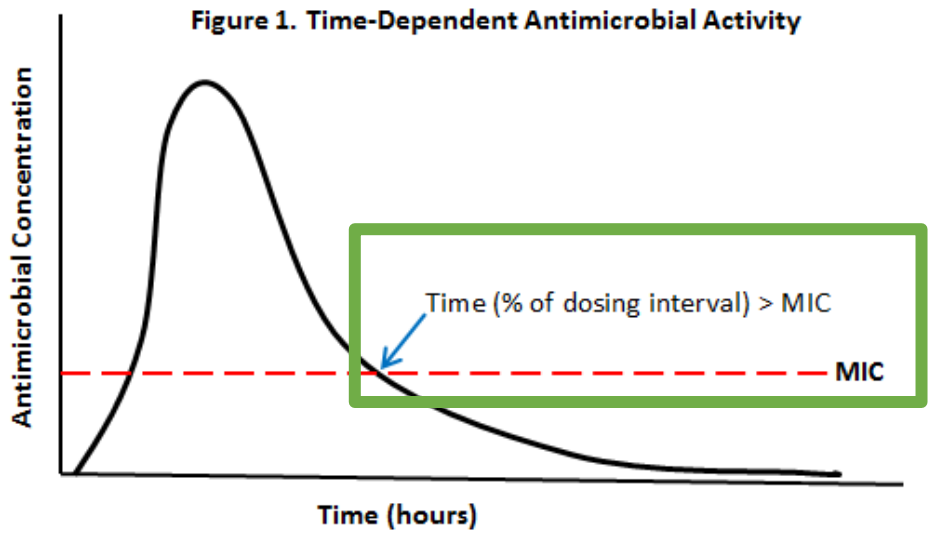
No oral cephalosporin at doses studied in children provides activity at the site of infection that equals high-dose amoxicillin. Most second- or third-generation oral cephalosporins provide adequate activity against only 60%–70% of currently isolated strains of pneumococcus. Clindamycin provides in vitro activity

Bradley (*CID* 2011)

Cefdinir

- Pharmacokinetics
  - Poorly absorbed
  - Highly protein bound (only unbound drug is active!)
  - Limited accumulation in tissues [tissues] ≤ [serum]
  - Metabolized quickly (short half-lives)

- Pharmacodynamics
  - Target: Time/MIC
    - Outpatient: 30-40% of the day
    - Inpatients: 60-80% of the day
    - Immunocompromised: ≥90% of the day



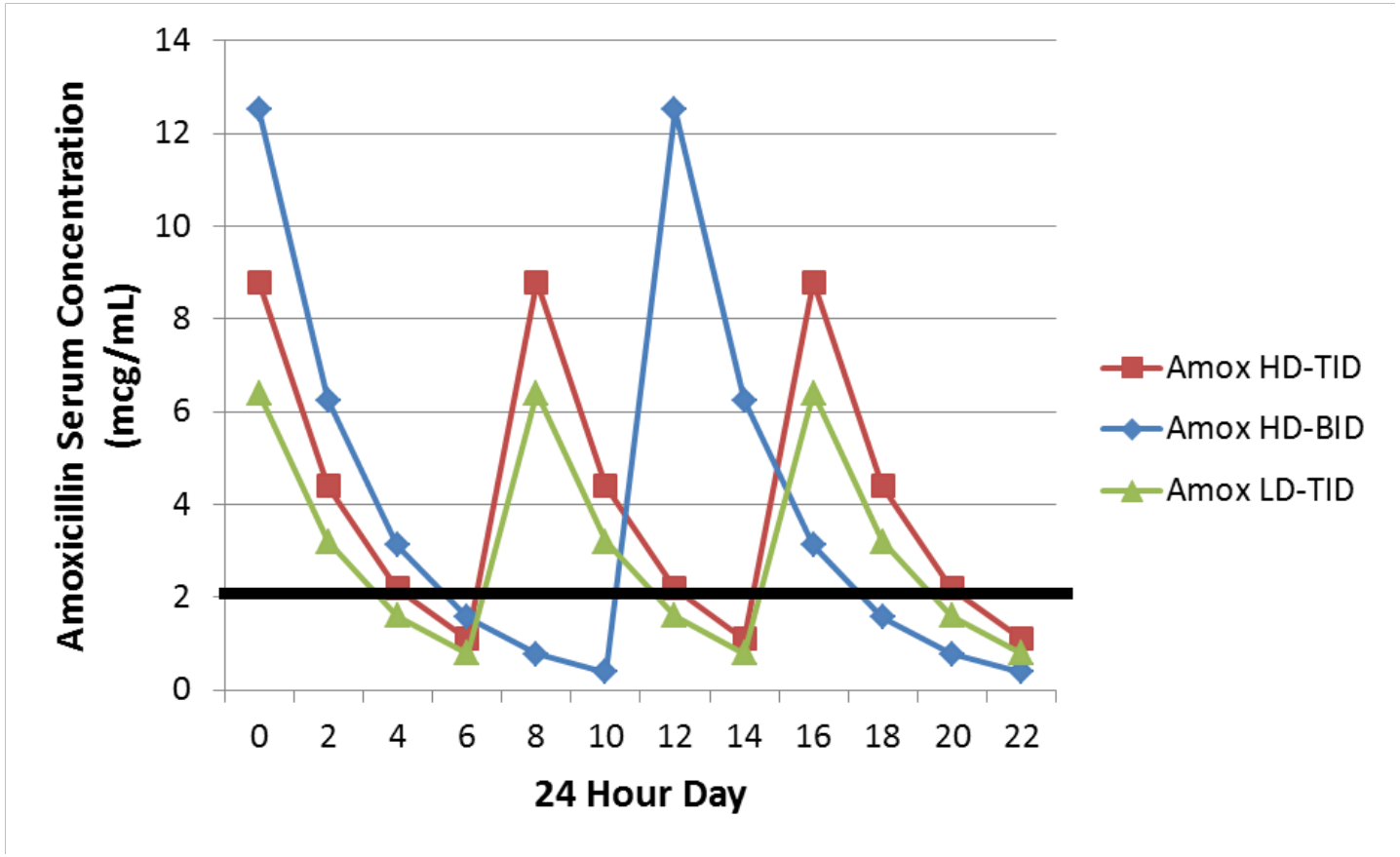
https://labmedicineblog.com/2016/10/20/minimal-inhibitory-concentrations-and-antimicrobial-dosing-how-are-they-related/

Parker S et al. *Peds in Rev*, 2013
Slides courtesy of Amanda Hurst, Pharm D

Amoxicillin for *S. pneumoniae*

PK Quick Stats – Amoxicillin
Absorption = 89%
Protein Binding = 20%
Half-life (hours) = 1.2-2

- **Sensitive *S. pneumoniae* Isolate (MIC of 2 mcg/mL)**



Time/MIC = 62.5% (15hrs)
Time/MIC = 50% (12hrs)
Time/MIC = 37.5% (9hrs)

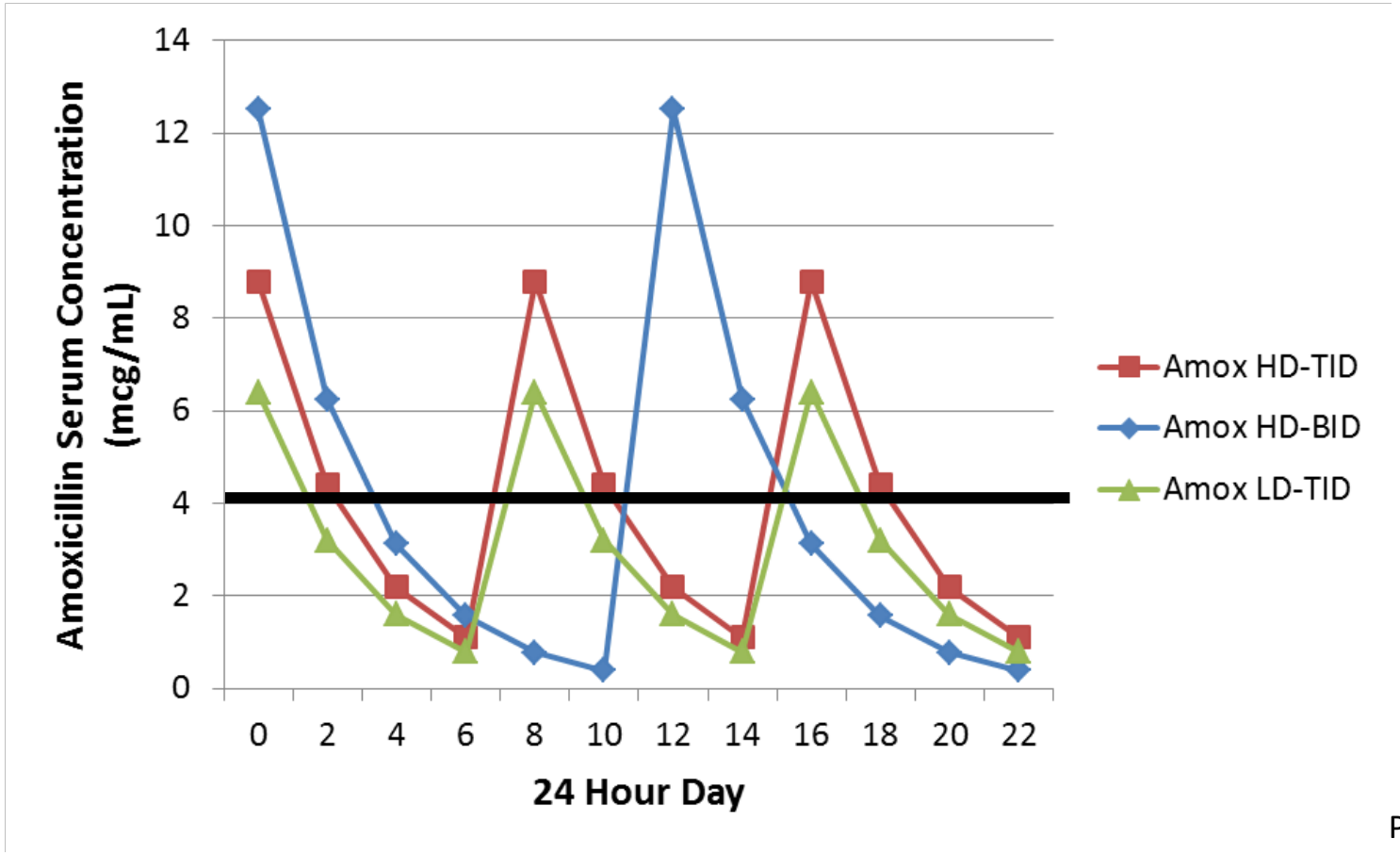
From prior slide- Target: Time/MIC
- Outpatient: 30-40% of the day
- Inpatients: 60-80% of the day

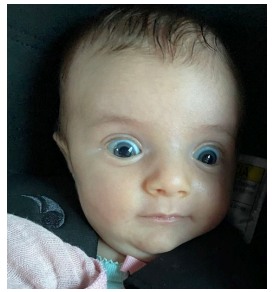
Parker S et al. *Peds in Rev*, 2013
Slides courtesy of Amanda Hurst, Pharm D

Amoxicillin for *S. pneumoniae*

PK Quick Stats – Amoxicillin
Absorption = 89%
Protein Binding = 20%
Half-life (hours) = 1.2-2

- **Intermediate *S. pneumoniae* Isolate (MIC of 4 mcg/mL)**





Time/MIC = 37.5% (9hrs)

Time/MIC = 25% (6hrs)

Time/MIC = 12.5% (3hrs)

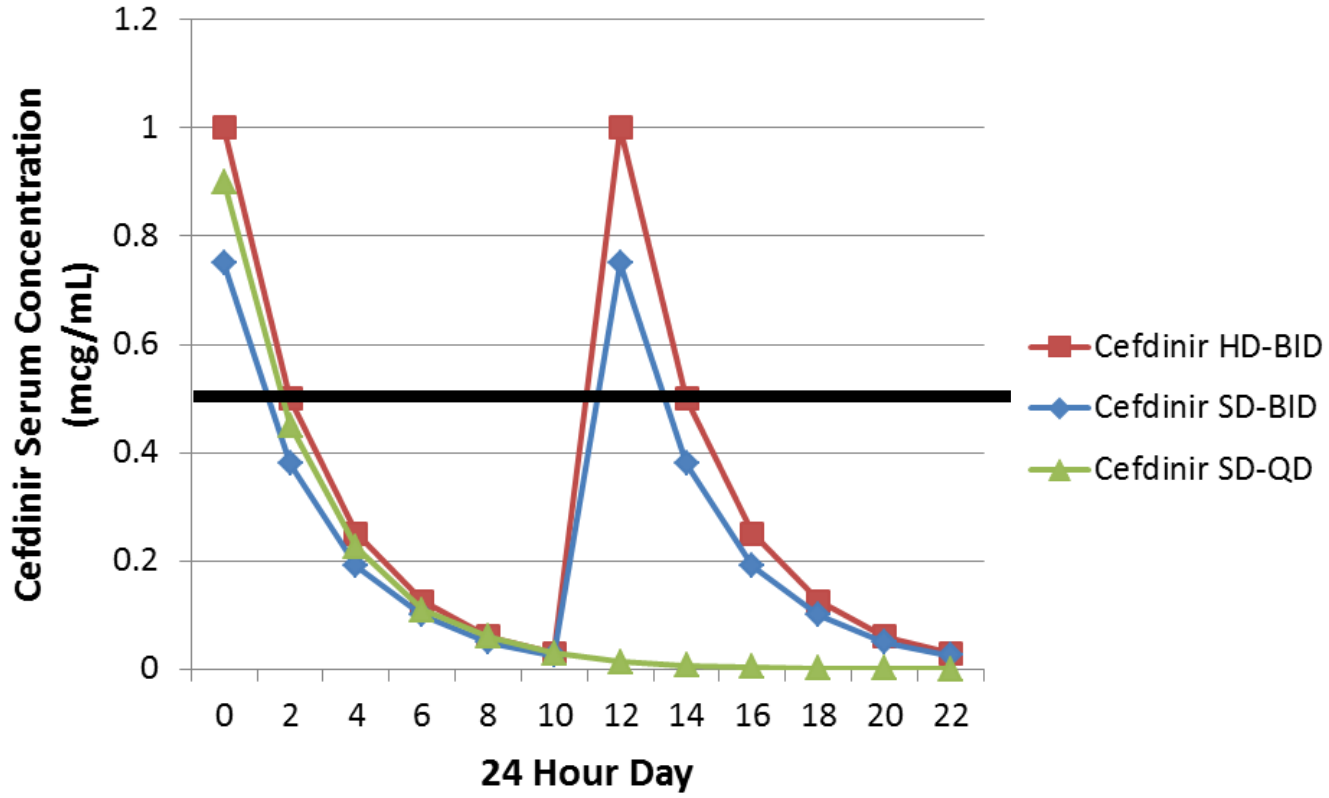
From prior slide- Target: Time/MIC
- Outpatient: 30-40% of the day
- Inpatients: 60-80% of the day

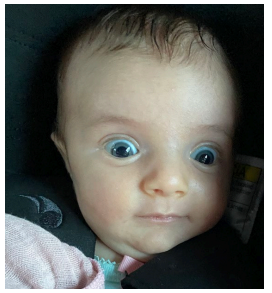
Parker S et al. *Peds in Rev*, 2013
Slides courtesy of Amanda Hurst, Pharm D

Cefdinir for *S. pneumoniae*

PK Quick Stats – Cefdinir
Absorption = 16-25%
Protein Binding = 73%
Half-life (hours) = 1.4-1.8

- **Sensitive *S. pneumoniae* Isolate (MIC of 0.5 mcg/mL)**





Time/MIC = 21% (5hrs)
Time/MIC = 12.5% (3hrs)
Time/MIC = 8% (2hrs)

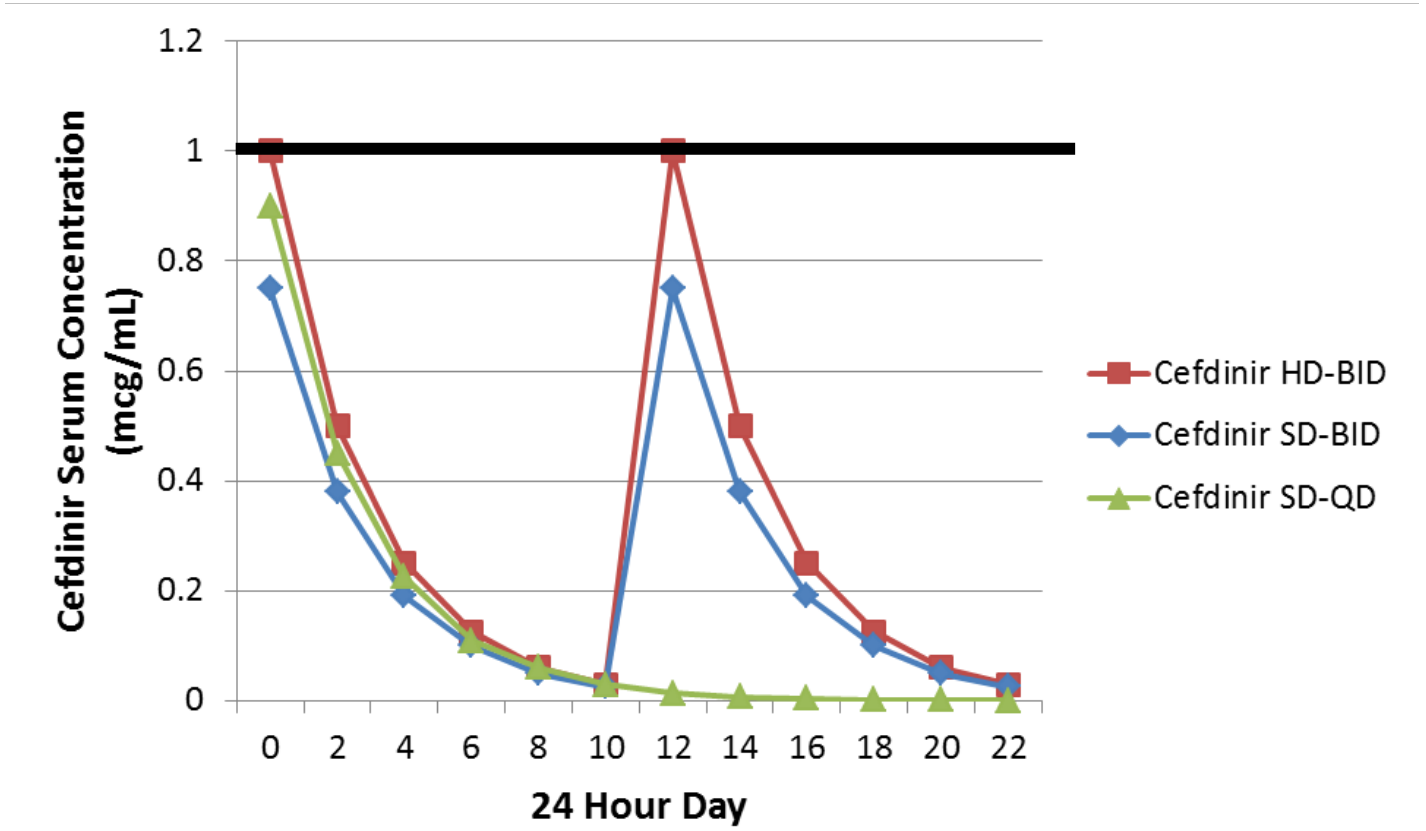
From prior slide- Target: Time/MIC
- Outpatient: 30-40% of the day
- Inpatients: 60-80% of the day

Parker S et al. *Peds in Rev*, 2013
Slides courtesy of Amanda Hurst, Pharm D

Cefdinir for *S. pneumoniae*

PK Quick Stats – Cefdinir
Absorption = 16-25%
Protein Binding = 73%
Half-life (hours) = 1.4-1.8

- **Intermediate *S. pneumoniae* Isolate (MIC of 1 mcg/mL)**

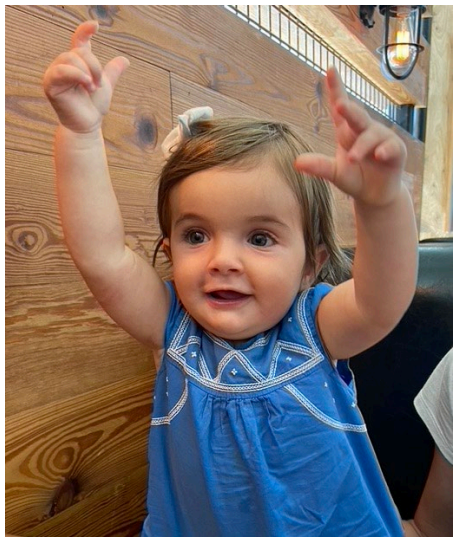


Time/MIC = 0% (0hrs)
Time/MIC = 0% (0hrs)
Time/MIC = 0% (0hrs)

Parker S et al. *Peds in Rev*, 2013
Slides courtesy of Amanda Hurst, Pharm D

Take Home Points – Cefdinir

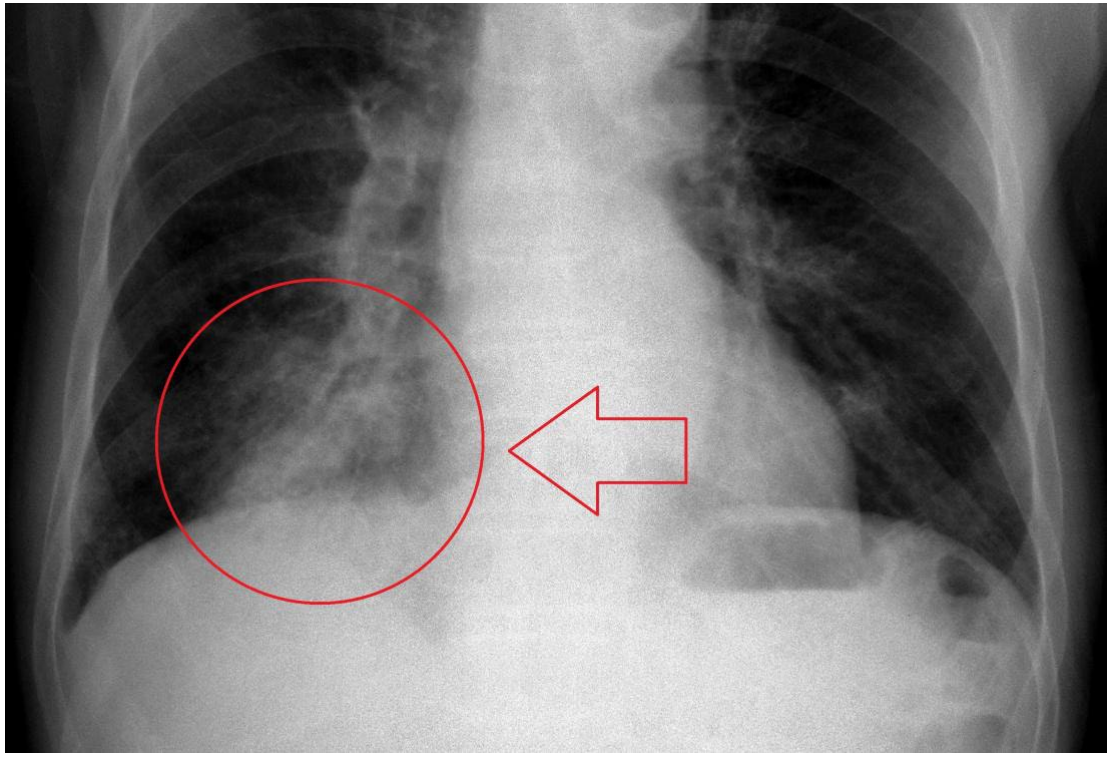
- The PK/PD profile of cefdinir is why amoxicillin / amox-clav are preferred agents for treating respiratory tract infections
  - If concern for resistance / lack of improvement on first-line agents, would recommend ceftriaxone or cefixime



Aspiration Pneumonia

Aspiration Pneumonia

- Often self-resolving pneumonitis
- Etiology: *S. pneumoniae* + oral anaerobes



https://www.medicalnewstoday.com/articles/322091#what-is-aspiration-pneumonia

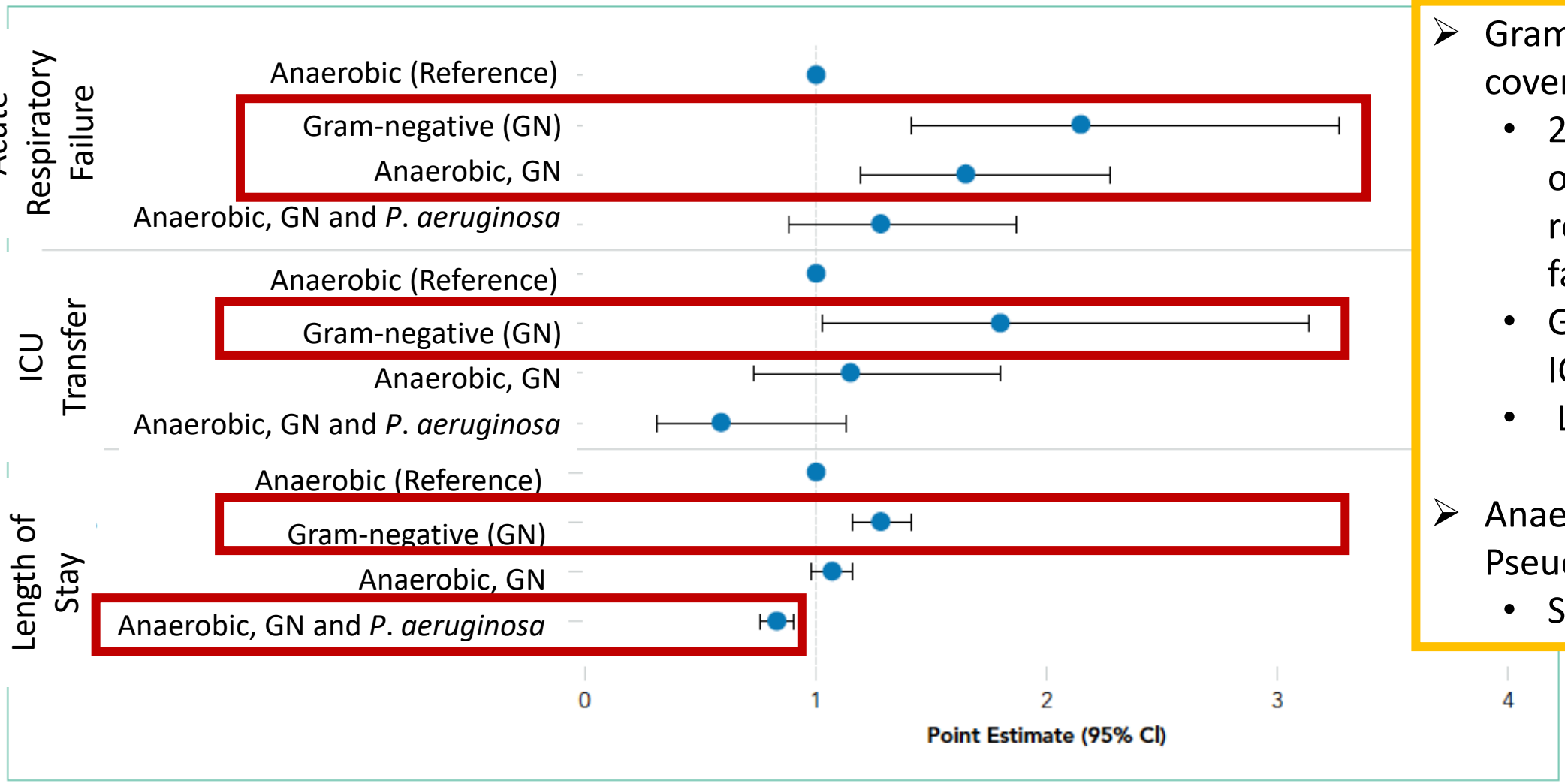
Thomson J et al. *J Hosp Med*, 2019

Aspiration Pneumonia – Anaerobic Coverage

- Single-center RCT, comparing IV PCN G to IV clindamycin
- 42 children (ages 6 mo to 18 years)
- No difference in:
  - Time to hospital discharge (4.9 vs 3.4 days, *p*=0.66)
  - Total hospitalization (8.5 vs 6.7 days, *p*=0.37)
  - Re-admissions within 2-weeks (6 vs. 6, *p*=0.99)

Jacobson SJ et al. *Arch Pediatr Adolesc Med*, 1997

Antibiotics: Aspiration Pneumonia (Neurologic Impairment)



- Gram-negative coverage alone:
  - 2-fold greater odds of respiratory failure
  - Greater odds of ICU transfer
  - Longer LOS
- Anaerobic, GN and Pseudomonas:
  - Shorter LOS

Thomson J et al. *J Hosp Med*, 2019

Antibiotic Duration

CAP-IT RCT

- Multicenter, RCT in the UK and Ireland, Feb 2017-April 2019

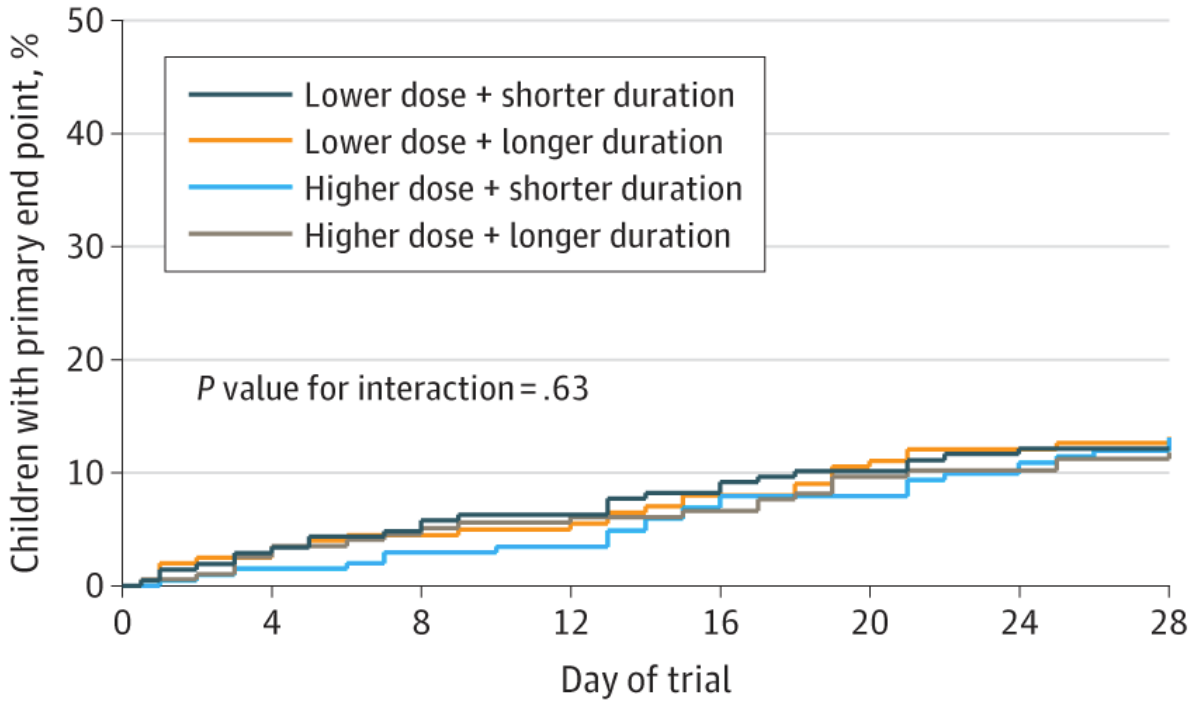
- Randomized to:
  - Dose
    - Lower dose amox (35-50mg/kg/day; n=410)
    - Higher dose amox (70-90mg/kg/day; n=404)
  - Duration
    - Shorter duration (3 days; n=413)
    - Longer duration (7 days; n=401)

- **Primary Outcome**: Antibiotic retreatment within 28 days

Bielicki JA et al. *JAMA*, 2021

Antibiotic Dose and Duration – CAP-IT RCT

A Comparisons for all groups



No. at risk								
Lower dose + shorter duration	208	202	196	193	189	185	180	166
Lower dose + longer duration	202	196	191	189	181	176	173	154
Higher dose + shorter duration	205	202	198	196	187	185	177	157
Higher dose + longer duration	199	193	187	185	182	176	171	154

- No difference in outcomes!

Bielicki JA et al. *JAMA*, 2021

SAFER RCT

- Non-inferiority, randomized controlled trial
- Outpatient children ages 6 months to 10 years with CAP
- 5-days vs. 10-days of high-dose amox
- **Primary Outcome**: Clinical cure at 14-21 days

- Clinical cure observed in:
  - 101/114 (88.6%) intervention group
  - 99/109 (90.8%) control group

Conclusion:
5 days is just as good as 10 days for uncomplicated outpatient CAP

Pernica JM et al. *JAMA Peds*, 2021

SCOUT-CAP RCT

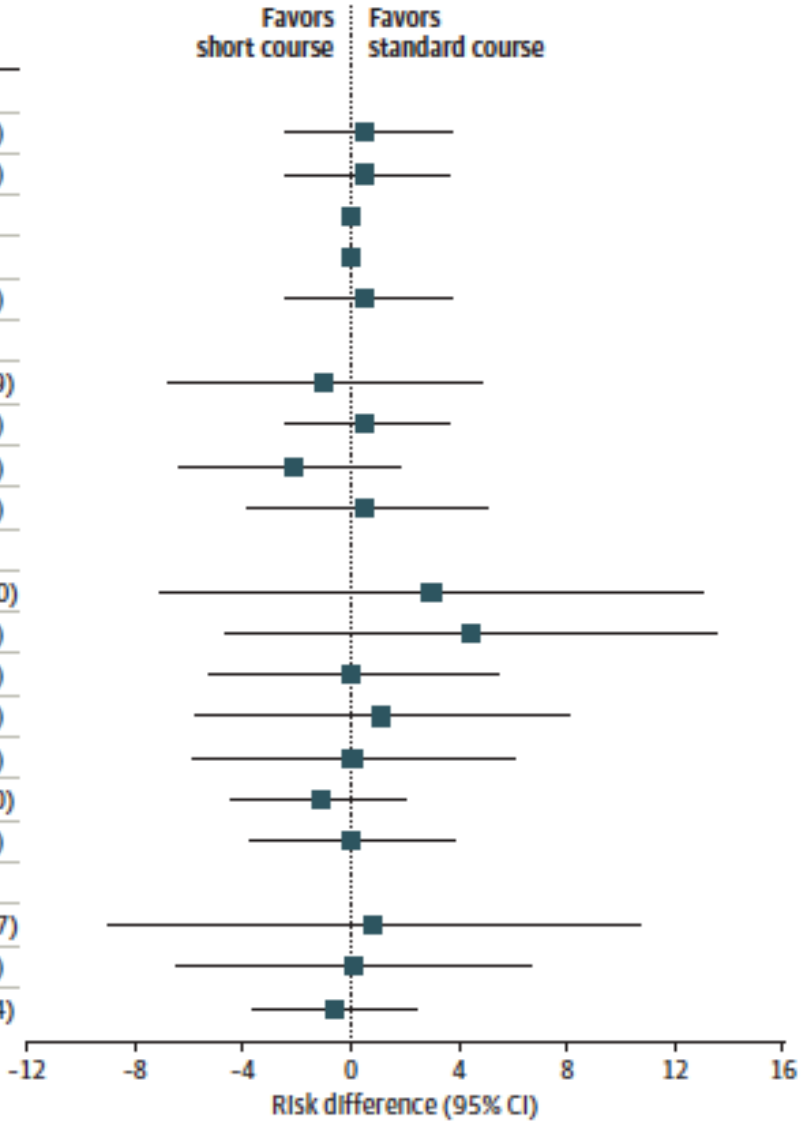
- Non-inferiority, randomized controlled trial
- Outpatient children ages 6 months to 71 months with CAP demonstrating early clinical improvement
- Interventions:
  - 5-days vs. 10-days of high-dose amox (randomized on day 3-6)
  - Outcome: composite of clinical response, resolution of symptoms and antibiotic-associated adverse effects
  - Throat swabs to quantify antibiotic resistance genes in oropharyngeal flora in a subset of patients

Williams DJ et al. *JAMA Peds*, 2022

SCOUT-CAP RCT Outcomes

- Non-inferior:
  - Clinical Response
  - Persistent Symptoms
  - Antibiotic-associated adverse effects
- Composite outcome:
  - 69% probability of a more desirable outcome

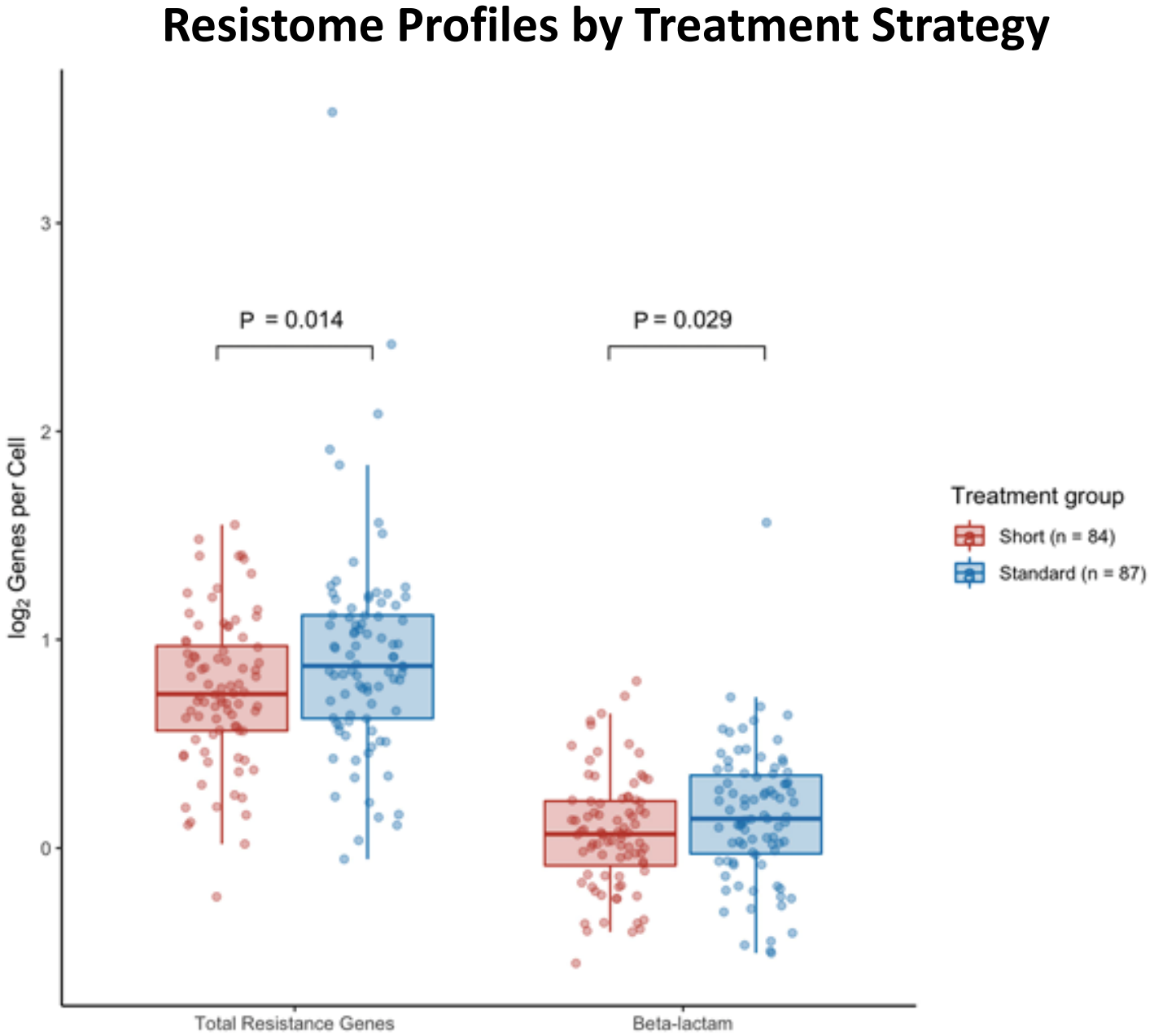
Source	Short course (n = 189) n (%)	Standard course (n = 191) n (%)	Risk difference (95% CI)
Inadequate clinical response			
Any	2 (1)	1 (<1)	0.5 (-2.4 to 3.7)
ED or clinic visit	2 (1)	1 (<1)	0.5 (-2.4 to 3.7)
Hospitalization	0	0	NA
Surgical procedure	0	0	NA
Receipt of nonstudy antibiotic	2 (1)	1 (<1)	0.5 (-2.4 to 3.7)
Persistent symptoms			
Any	13 (7)	15 (8)	-1.0 (-6.8 to 4.9)
Fever	2 (1)	1 (<1)	0.5 (-2.4 to 3.7)
Elevated respiratory rate	3 (2)	7 (4)	2.1 (-6.3 to 1.9)
Cough	7 (4)	6 (3)	0.6 (-3.8 to 5.1)
Antibiotic-associated adverse effects			
Any	75 (40)	70 (37)	3.0 (-7.0 to 13.0)
Irritability	53 (28)	45 (24)	4.5 (-4.7 to 3.6)
Vomiting	11 (6)	11 (6)	0.1 (-5.3 to 5.4)
Diarrhea	23 (12)	21 (11)	1.2 (-5.7 to 8.1)
Allergic reaction	15 (8)	15 (8)	0.1 (-5.9 to 6.1)
Stomatitis	1 (<1)	3 (2)	-1.0 (-4.4 to 2.0)
Candidiasis	4 (2)	4 (2)	0.0 (-3.8 to 3.9)
Severity of antibiotic adverse effects			
Mild	66 (35)	65 (34)	0.9 (-9.0 to 10.7)
Moderate	19 (10)	19 (10)	0.1 (-6.4 to 6.7)
Severe	1 (<1)	2 (1)	-0.5 (-3.6 to 2.4)



Williams DJ et al. *JAMA Peds*, 2022

SCOUT-CAP RCT Resistome Profiles

- Significantly lower levels of resistant bacteria in short-course group



Williams DJ et al. *JAMA Peds*, 2022

Diagnostic Stewardship

Blood Cultures

IDSA GUIDELINES

Outpatient

- Blood cultures should not be routinely performed in nontoxic, fully immunized children
  - *Strong recommendation; moderate-quality evidence*
- Blood cultures should be obtained in children who fail to demonstrate clinical improvement after starting antibiotics
  - *Strong recommendation; moderate-quality evidence*

Inpatient

- Blood cultures should be obtained in children requiring hospitalization for presumed bacterial CAP that is moderate to severe, particularly those with complicated pneumonia
  - *Strong recommendation, low-quality evidence*

Blood Cultures - Inpatient

- Cross-sectional study of children hospitalized with CAP in 6 children's hospitals, 2007-2011

- 7509 children in study (excluded children with complex chronic conditions and those in ICU)

- **Objective**: Determine the prevalence of bacteremia and characterize the microbiology and penicillin-susceptibility patterns of positive blood culture results

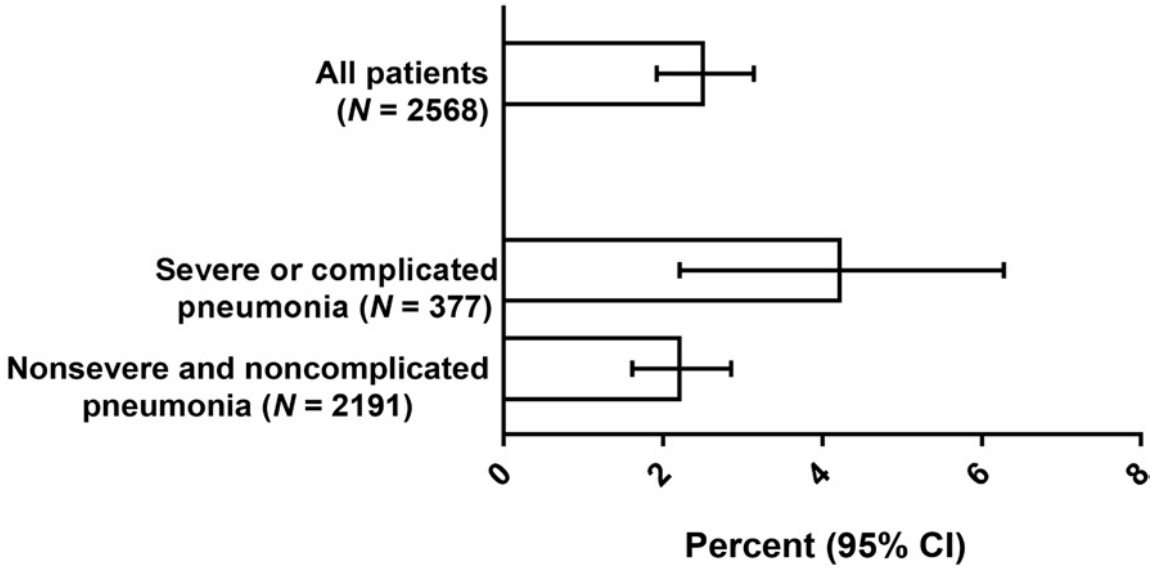
Neuman MI et al. *Pediatrics*, 2017

Blood Cultures - Inpatient

Overall Yield of Blood Cultures

	N	% of Cohort (N=7509)	% of All Blood Cultures Performed (n=2568)
Cohort	7509	--	--
Blood culture performed	2568	34.2	--
Pathogen	65	0.87	2.53
Penicillin-nonsusceptible organism	11	0.15	0.43

Percentage of Patients with Bacteremia Because of a Pathogen



- Low rates of bacteremia and high rates of penicillin-susceptible organisms
- Blood cultures may not be needed for most children hospitalized with CAP

Neuman MI et al. *Pediatrics*, 2017

Nasal MRSA PCR

IDSA GUIDELINES

- ADULT pneumonia guidelines: Recommend nasal PCR to determine need for MRSA antibiotic coverage[1]

- 435 adult patients with confirmed pneumonia + nasal swab MRSA PCR test + culture specimen obtained[2]

	Positive for MRSA on Culture	Negative for MRSA on Culture	Total Swabs
Positive MRSA PCR	22	40	62 (14%)
Negative MRSA PCR	3	370	373 (86%)
Total Cultures	25 (6%)	410 (94%)	435

Sensitivity	88%
Specificity	90%
Positive Predictive Value	35%
Negative Predictive Value	**99.2%**

➢ High negative predictive value

1. Metlay JP et al. *Am J of Resp and Crit Care Med*, 2019
2. Dangerfield B et al. *Antimicrob Agents and Chemo*, 2014

Take Home Points

1. Guideline-concordant antibiotic prescribing for CAP has improved since the IDSA guidelines were published in 2011, but there is room for improvement

2. The most common etiology of pneumonia in all ages is viral

3. A 5-day course of antibiotics is safe for children with uncomplicated CAP (and may be superior to longer courses)

4. Blood cultures are not needed in children with uncomplicated CAP

5. Nasal MRSA PCR can help to de-escalate antibiotic therapy in hospitalized children with CAP

Thank you!

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