Don’t Play It By Ear

APPROPRIATE PRESCRIBING IN ACUTE OTITIS MEDIA

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Disclosures

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I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

Objectives

- Explain the importance of acute otitis media as a focus of outpatient antimicrobial stewardship
- Define best practice management of acute otitis media
- Apply knowledge of pharmacologic and microbiologic principles to everyday clinical practice

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Why acute otitis media?

- Most common indication for antibiotics in pediatrics
- 5 million children are diagnosed annually and account for 10 million antibiotic prescriptions annually
- By 1 year of age, 23% of children have experienced ≥1 episode of AOM. By 3 years of age, 60% of children have experienced ≥1 episode of AOM.

Antimicrobial Stewardship

The right…

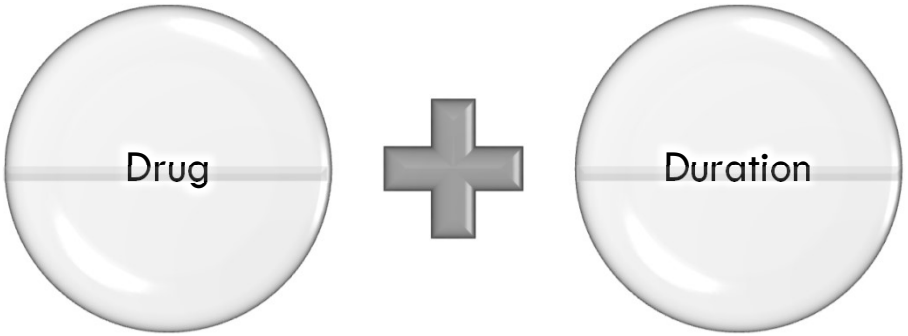
Antimicrobial Stewardship

The right…

Amoxicillin or Augmentin?

Antimicrobial Stewardship

The right…



Antimicrobial Stewardship

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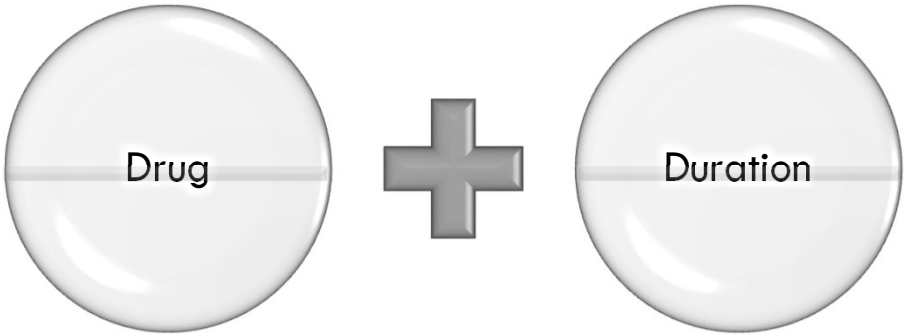

10 days or 5-7 days?

Antimicrobial Stewardship

The right…

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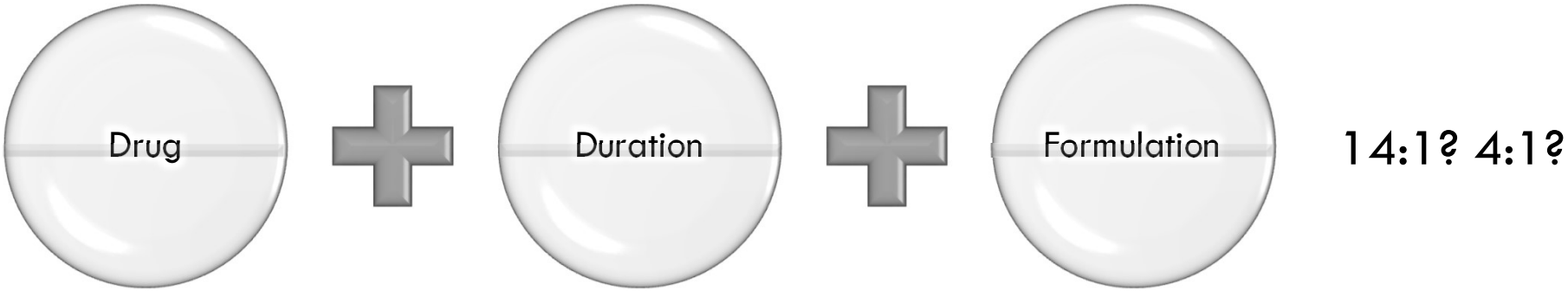
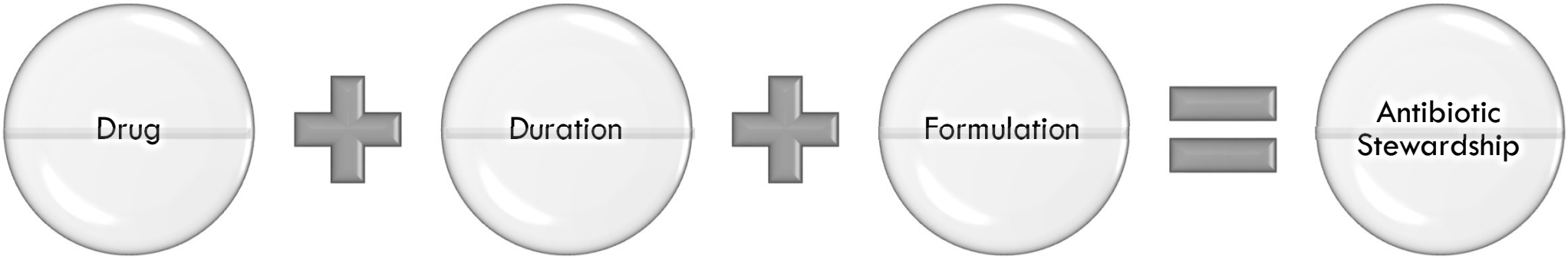


14:1? 4:1?

Antimicrobial Stewardship

The right…



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Who should be diagnosed?

- Moderate to severe bulging of the tympanic membrane (TM) or new onset of otorrhea not due to acute otitis externa
- Mild bulging of the TM and recent (< 48 hours) onset of ear pain (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the TM
- Clinicians should not diagnose AOM in children who do not have middle ear effusion (MEE) (based on pneumatic otoscopy and/or tympanometry).

- TM immobility
  - Sensitivity: 95%
  - Specificity: 85%
- Cloudiness
  - Sensitivity: 74%
  - Specificity: 93%
- Bulging
  - Sensitivity: 50%
  - Specificity: 97%

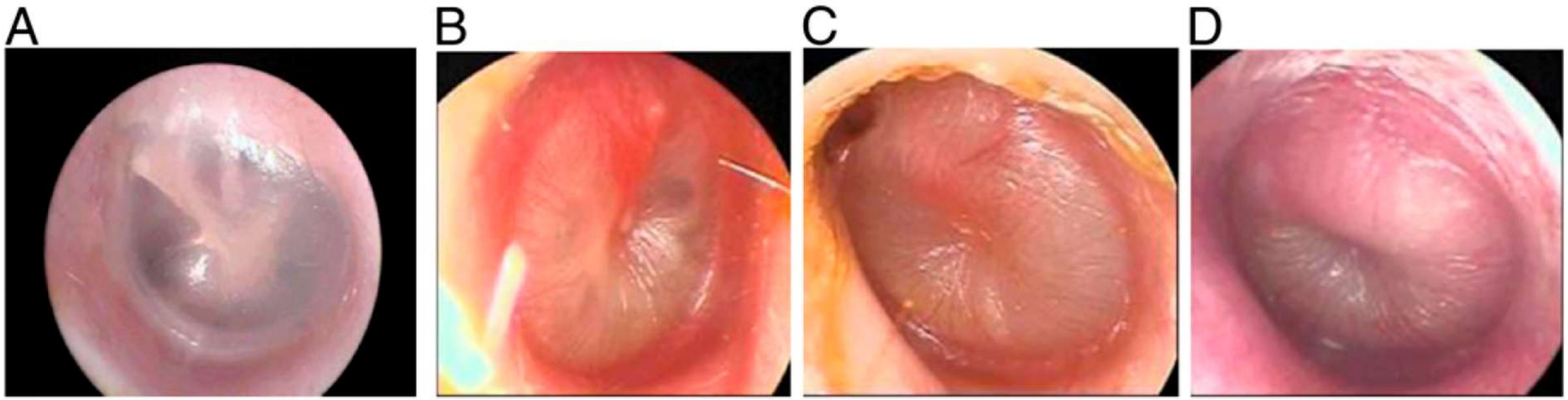

FIGURE 2

A, Normal TM. B, TM with mild bulging. C, TM with moderate bulging. D, TM with severe bulging. Courtesy of Alejandro Hoberman, MD.

The diagnosis and management of Acute Otitis Media. (2021). Pediatric Clinical Practice Guidelines & Policies, 21st Ed, 391–428. https://doi.org/10.1542/9781610025034-part01-the_diagnosis

Who should receive antibiotics?

- **≥6 months** with **severe** signs or symptoms (ie, moderate or severe otalgia or otalgia for at least 48 hours or temperature 39°C [102.2°F] or higher)
- **6 - 23 months** with **bilateral** AOM **without severe** signs or symptoms

Who can be observed with close follow-up?

- **6 - 23 months** with **unilateral** AOM **without severe** signs or symptoms
- **>24 months** with **bilateral <u>OR</u> unilateral without severe** signs or symptoms

What should be prescribed?

- Amoxicillin, when…
  - Not received amoxicillin in the past 30 days
  - Does not have concurrent purulent conjunctivitis
  - Not allergic to penicillin
- Antibiotic with additional β-lactamase coverage, when…
  - Received amoxicillin in the last 30 days
  - Has concurrent purulent conjunctivitis
  - Has history of recurrent AOM unresponsive to amoxicillin

And for how long?

- ≤ 2 years of age
  - 10 days
  - Multiple studies support longer durations in this age group
- 2-5 years of age
  - AAP guidelines – 7 days
  - Some institutional guidelines use 5 days
  - No studies directly comparing 5 days versus 7 days
- 6-12 years of age
  - 5 days

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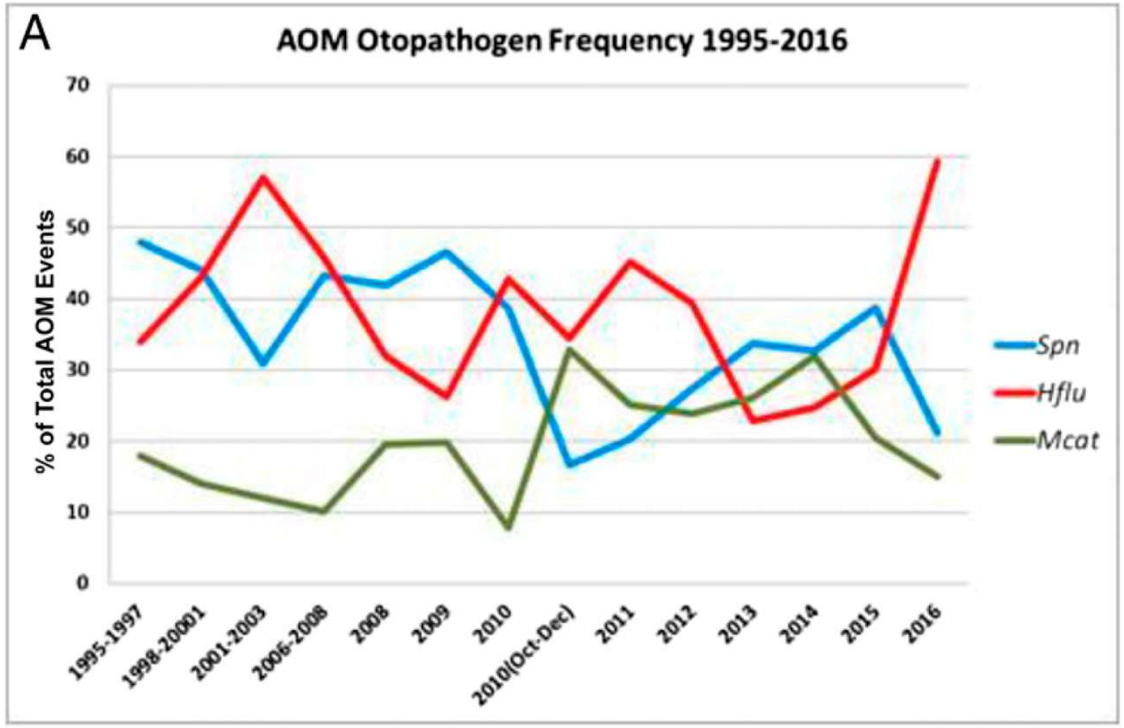
Change in Epidemiology

- Diagnoses:
  - 950 per 1000 children in 1995–1996
  - 634 per 1000 children in 2005–2006
- Prescriptions:
  - 760 per 1000 in 1995–1996
  - 484 per 1000 in 2005–2006



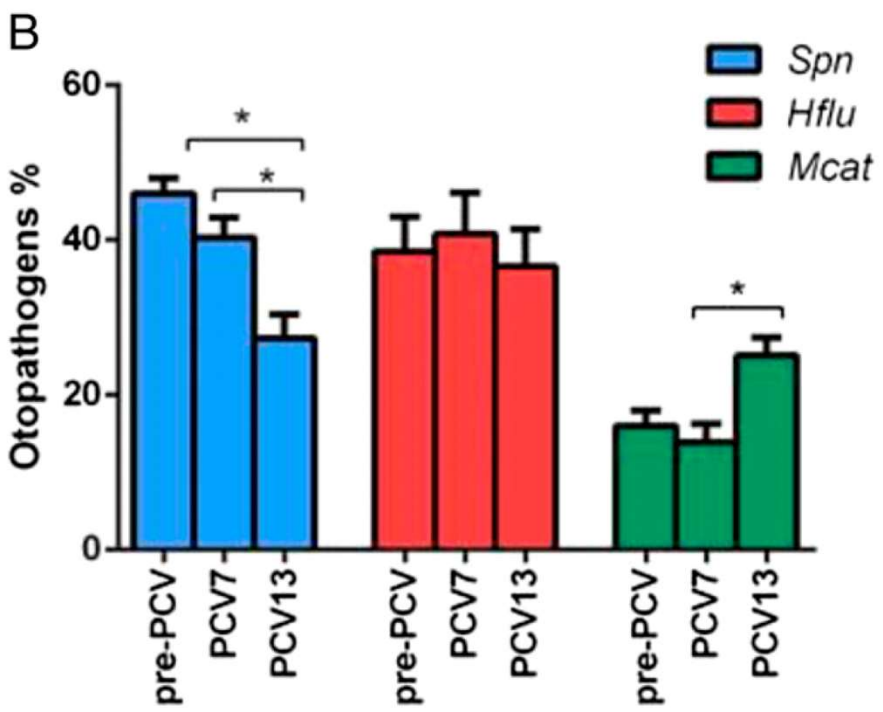


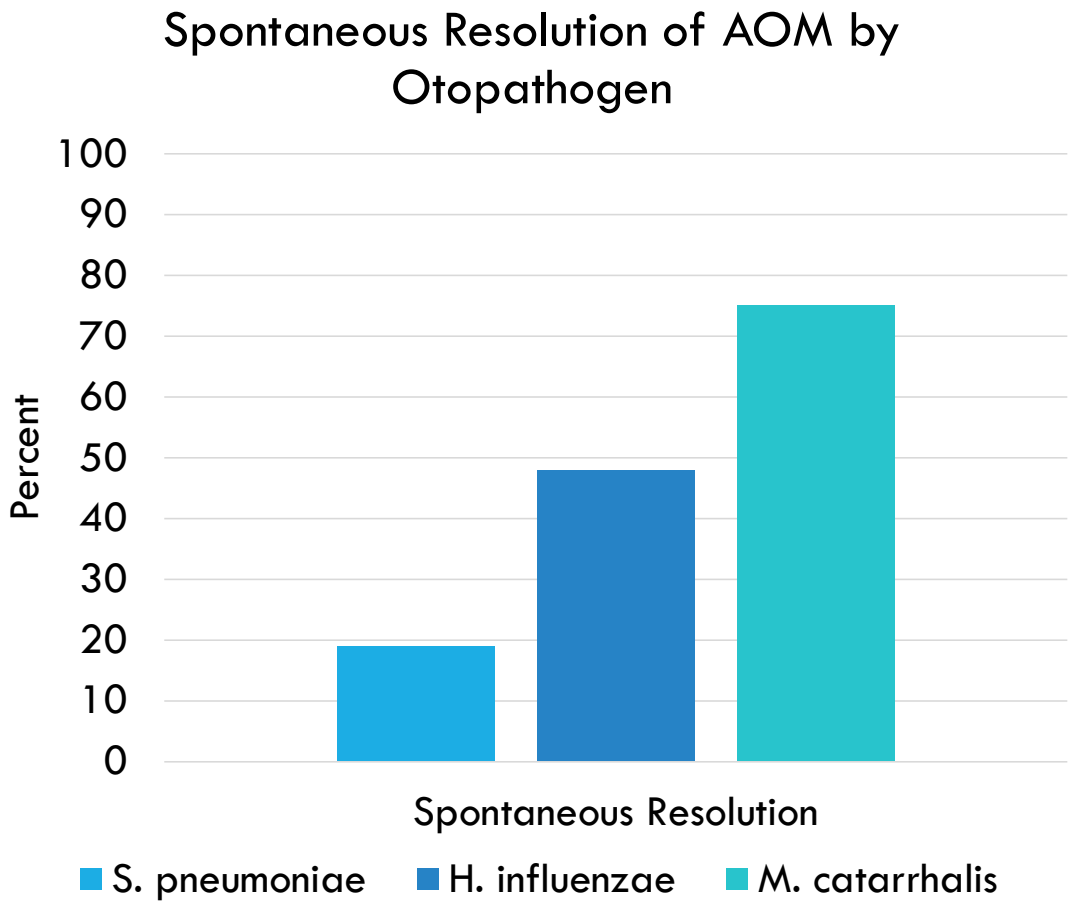
FIGURE 2

(A) The frequency of otopathogens isolated from MEF during AOM from 1995 to 2016. (B) The changes in otopathogen prevalence in different vaccine eras (* $P < .05$). Spn, *S pneumonia*; Hflu, *H influenzae*; and Mcat, *M catarrhalis*.

Kaur, R., Morris, M., & Pichichero, M. E. (2017). Epidemiology of acute otitis media in the postpneumococcal conjugate vaccine era. Pediatrics, 140(3). https://doi.org/10.1542/peds.2017-0181

Changes in Epidemiology

- Streptococcus pneumoniae benefits from antibiotic treatment the most
- Number needed to treat is rising in the post-vaccine era



Penicillin Resistance

- *Streptococcus pneumoniae*
  - Mechanism: Alteration of the penicillin binding protein reducing the beta lactams affinity for this protein
  - Solution? Overwhelm the protein with high-dose Amoxicillin
- *Haemophilus influenzae* and *Moraxella catarrhalis*
  - Mechanism: Production of beta lactamase enzymes
  - Solution? Add a beta-lactamase inhibitor

The Trouble with Amox/Clav…

So many formulations with varying ratios of amoxicillin to clavulanate!

	amoxicillin-clavulanate (AUGMENTIN) suspension 250-62.5...		Oral	2 Times Dail...	$	250-62.5 mg/5 mL
	amoxicillin-clavulanate (AUGMENTIN) suspension 400-57 m...		Oral	2 Times Dail...	$	400-57 mg/5 mL
	amoxicillin-clavulanate (AUGMENTIN) tablet	250 mg of amoxicillin	Oral	3 Times Dail...		
	amoxicillin-clavulanate (AUGMENTIN) tablet 250-125 mg	250 mg of amoxicillin	Oral	3 Times Dail...		250-125 mg
	amoxicillin-clavulanate (AUGMENTIN) tablet 500-125 mg	500 mg of amoxicillin	Oral	3 Times Dail...	$	500-125 mg
	amoxicillin-clavulanate (AUGMENTIN) tablet 875-125 mg	875 mg of amoxicillin	Oral	2 Times Dail...	$	875-125 mg
	amoxicillin-clavulanate (AUGMENTIN-ES) suspension 600-4...		Oral	2 Times Dail...	$	600-42.9 mg/5 mL

The Trouble with Amox/Clav…

- Streptococcus pneumoniae needs more amoxicillin - “high-dose”
  - Increased Amox:Clav ratios are preferred for this
  - The highest is ES suspension at 14:1
- If non-ES formulations are used for “high-dose”, extra clavulanate causes diarrhea
  - Literature proven decreased caregiver quality of life
  - Leads to downstream avoidance of Amox/Clav and increased prescribing of oral 3rd generation cephalosporins

Our Solution

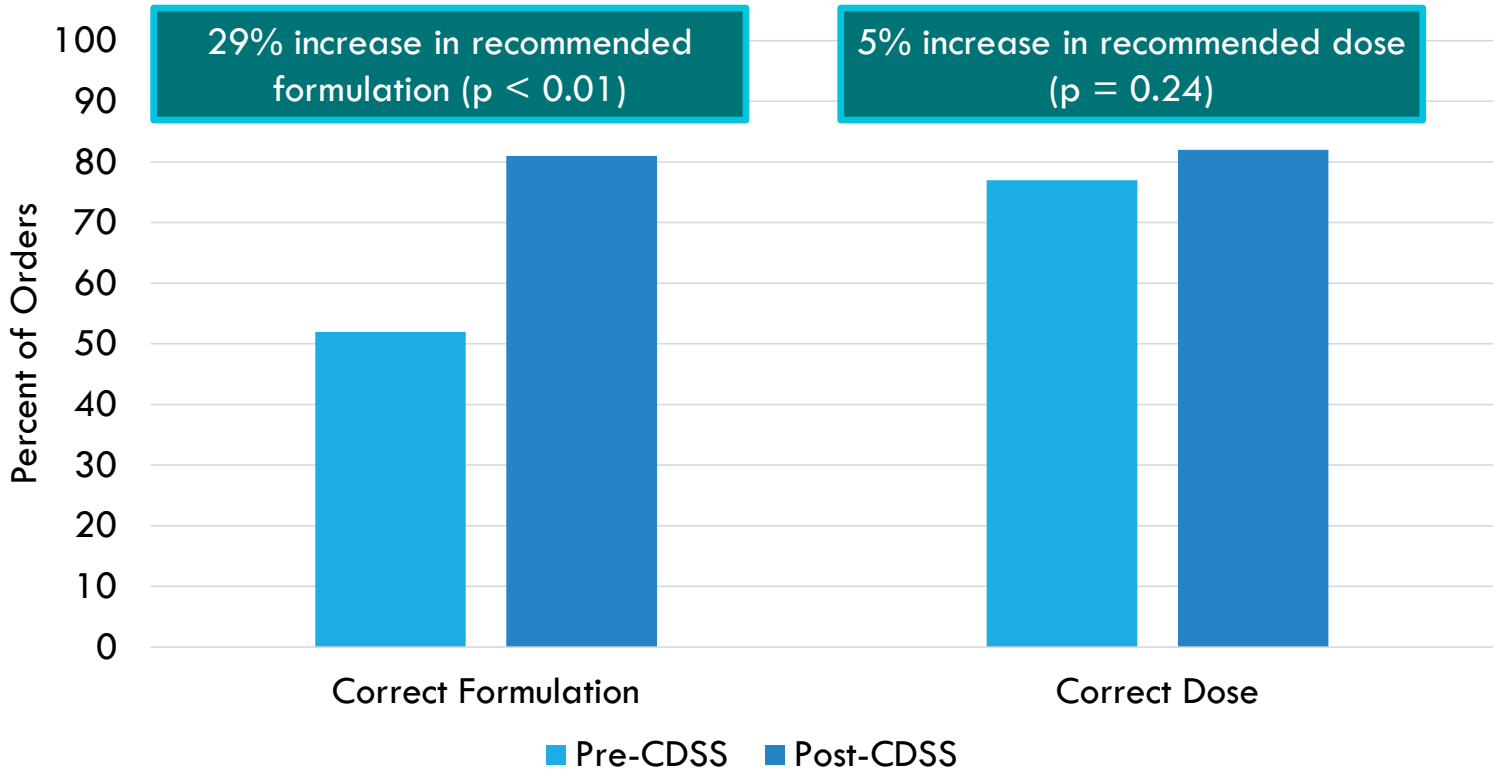
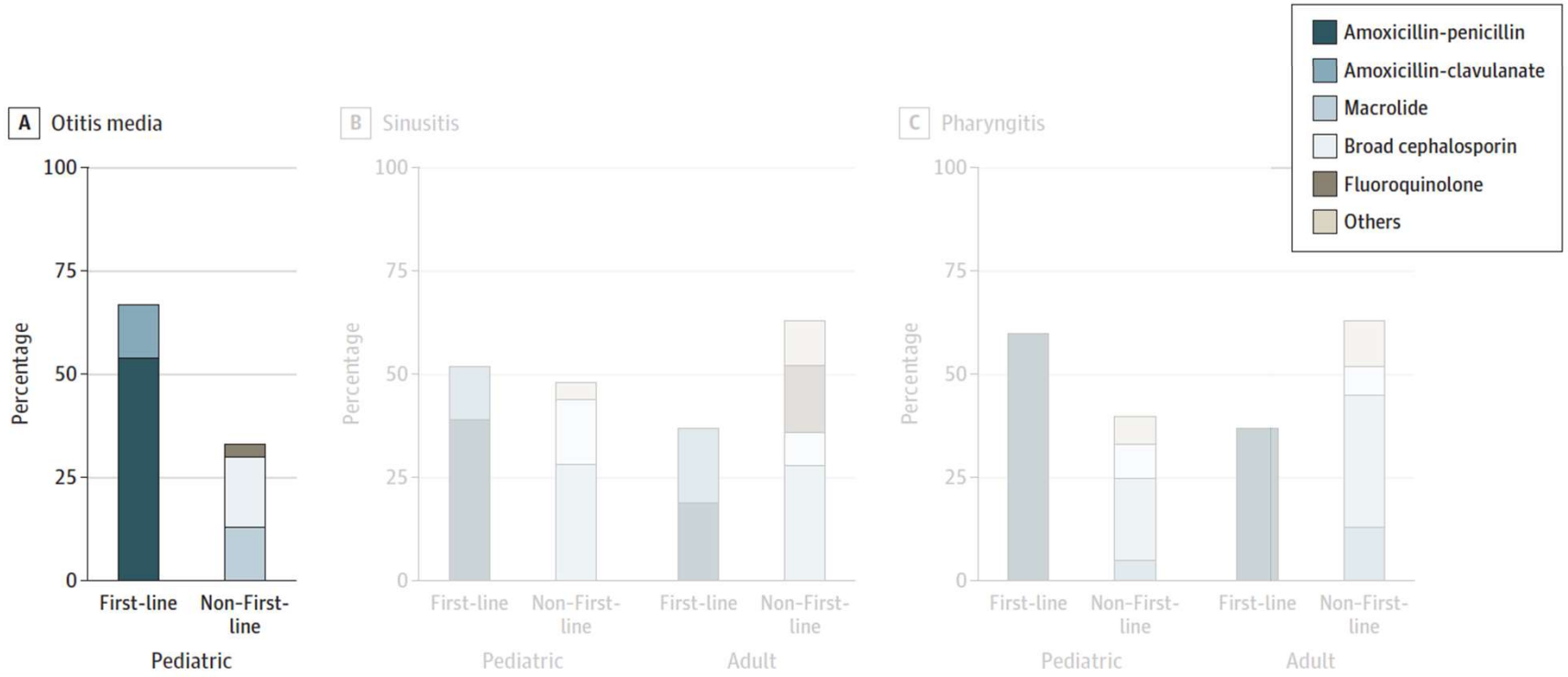

29% increase in recommended formulation (p < 0.01)
5% increase in recommended dose (p = 0.24)
Percent of Orders
100
90
80
70
60
50
40
30
20
10
0
Correct Formulation
Correct Dose
Pre-CDSS
Post-CDSS

Figure. Percentage of Visits in Which Antibiotics Were Prescribed That Are First-line and Non–First-line for Otitis Media, 2010-2011



A, Otitis media. First-line: amoxicillin or amoxicillin-clavulanate. B, Sinusitis. First-line: amoxicillin or amoxicillin-clavulanate. C, Pharyngitis. Amoxicillin or penicillin. Estimates were based on 1705 sampled visits for otitis media, 463 for pediatric sinusitis, 1223 for adult sinusitis, 1006 for pediatric pharyngitis and 830 for adult pharyngitis. Broad cephalosporin includes second- and third-generation agents. Pediatric patients were defined as those 19 years or younger.

Hersh, A. L., Fleming-Dutra, K. E., Shapiro, D. J., Hyun, D. Y., & Hicks, L. A. (2016). Frequency of First-line Antibiotic Selection Among US Ambulatory Care Visits for Otitis Media, Sinusitis, and Pharyngitis. *JAMA Internal Medicine*, *176*(12), 1870. https://doi.org/10.1001/jamainternmed.2016.6625

Third Generation Cephalosporins

- Cefdinir
  - Favored for its once-a-day dosing and palatability
  - Marketing strategies that emphasize positive aspects of non-inferiority trials
- Problem?
  - Poor absorption, short half-lives, increased protein binding
  - Pneumococcal Serotype 19A has particularly high levels of resistance
  - High rates of community acquired *Clostridium difficile* infections when compared to first-line agents

Table 1. **Compiled Cephem and Comparative Penicillin Agent Pharmacokinetic and Pharmacodynamic Data**

Antibiotic (Year Approved)	Absorption, %/Protein Binding, %/Half-life, h	Recommended maximum adult dose (mg/d)/pediatric dose (mg/kg/d)	Dose evaluated	Peak Dose, μg/mL (Total dose is bound and unbound)	Time That the Antibiotic Plasma Concentration (Active, Unbound Drug) for a Single Dose Remains Above a Certain MIC, h[a]				
					Time Above an MIC of 0.5 μg/mL	Time Above an MIC of 1.0 μg/mL	Time Above an MIC of 2.0 μg/mL	Time Above an MIC of 4.0 μg/mL	Time Above an MIC of 8.0 μg/mL
Comparative Oral Penicillin									
Amoxicillin[b] (1970s)	89/20/1.2–2	4,000/90 given 2 to 3 times daily	500 mg	9.0	6	4.5	2.5	1	–
			875 mg	11.6	6.5	5	3.5	2	–
			15 mg/kg	7.9	5.5	4	2.5	1	–
			25 mg/kg	10.6	6	4.5	3	1.5	–
			45 mg/kg	15.7	7	5.5	4	2.5	1

Parker, S., Mitchell, M., & Child, J. (2013). Cephem Antibiotics: Wise Use Today Preserves Cure for Tomorrow. *Pediatrics in Review*, *34*(11), 510–524. https://doi.org/10.1542/pir.34-11-510

Table 1. (Continued)

Antibiotic (Year Approved)	Absorption, %/Protein Binding, %/Half-life, h	Recommended maximum adult dose (mg/d)/pediatric dose (mg/kg/d)	Dose evaluated	Peak Dose, μg/mL (Total dose is bound and unbound)	Time That the Antibiotic Plasma Concentration (Active, Unbound Drug) for a Single Dose Remains Above a Certain MIC, h[a]				
					Time Above an MIC of 0.5 μg/mL	Time Above an MIC of 1.0 μg/mL	Time Above an MIC of 2.0 μg/mL	Time Above an MIC of 4.0 μg/mL	Time Above an MIC of 8.0 μg/mL
Cefpodoxime (1992)	50/14–24/ 2.09–2.84	400/10 given 2 times daily	200 mg	2.3	4.5	2	–	–	–
			400 mg	3.9	6.5	4	1.5	–	–
			5 mg/kg	2.1	4	1.5	–	–	–
			10 mg/kg	5.3	7.5	5	2.5	–	–
Ceftibuten (1995)	80/65/2–2.4	400/9 given once daily	9 mg/kg	13.4	6	4	1.5	–	–
			400 mg	15	6.5	4.5	2	–	–
Cefdinir (1997)	16–25/73/ 1.4–1.8	600/25 given 1–2 times daily	300 mg	1.6	–	–	–	–	–
			600 mg	2.87	1	–	–	–	–
			7 mg/kg	2.3–2.56	–	–	–	–	–
			14 mg/kg	2.07–3.86	1	–	–	–	–
			25 mg/kg	4.42	2	–	–	–	–

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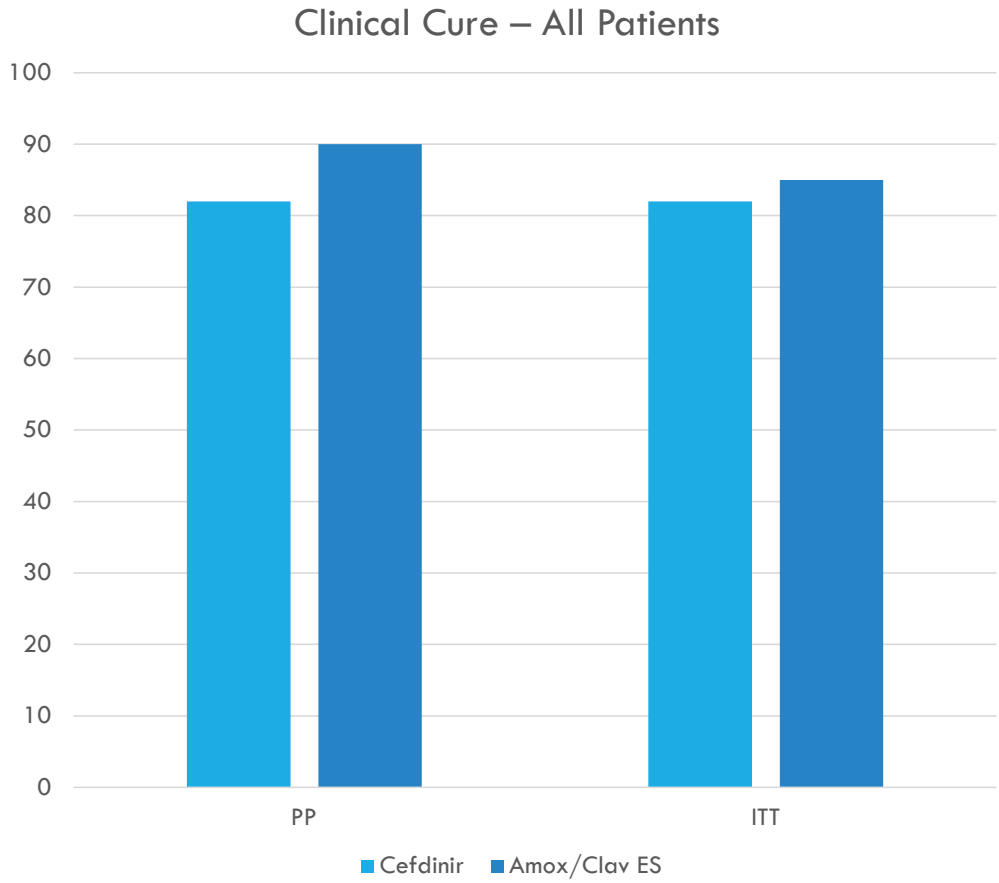
Streptococcus pneumoniae Susceptibilities

- *Streptococcus pneumoniae* antibiotic susceptibilities to beta-lactams can be tested directly or extrapolated from penicillin testing
- Example of extrapolation
  - Amoxicillin is extrapolated from a penicillin MIC ≤ 2
  - Cefdinir is extrapolated from a penicillin MIC of ≤ 0.06
- Example of direct testing
  - Ceftriaxone is predicted to be susceptible with an MIC of ≤ 1
  - Cefdinir is predicted to be susceptible with an MIC of ≤ 0.5

Drug	MIC Determination	CHNO Susceptibilities
Amoxicillin	Penicillin MIC ≤ 2	94%
Cefdinir	Penicillin MIC ≤ 0.06	44%
Ceftriaxone	MIC ≤ 1	99%

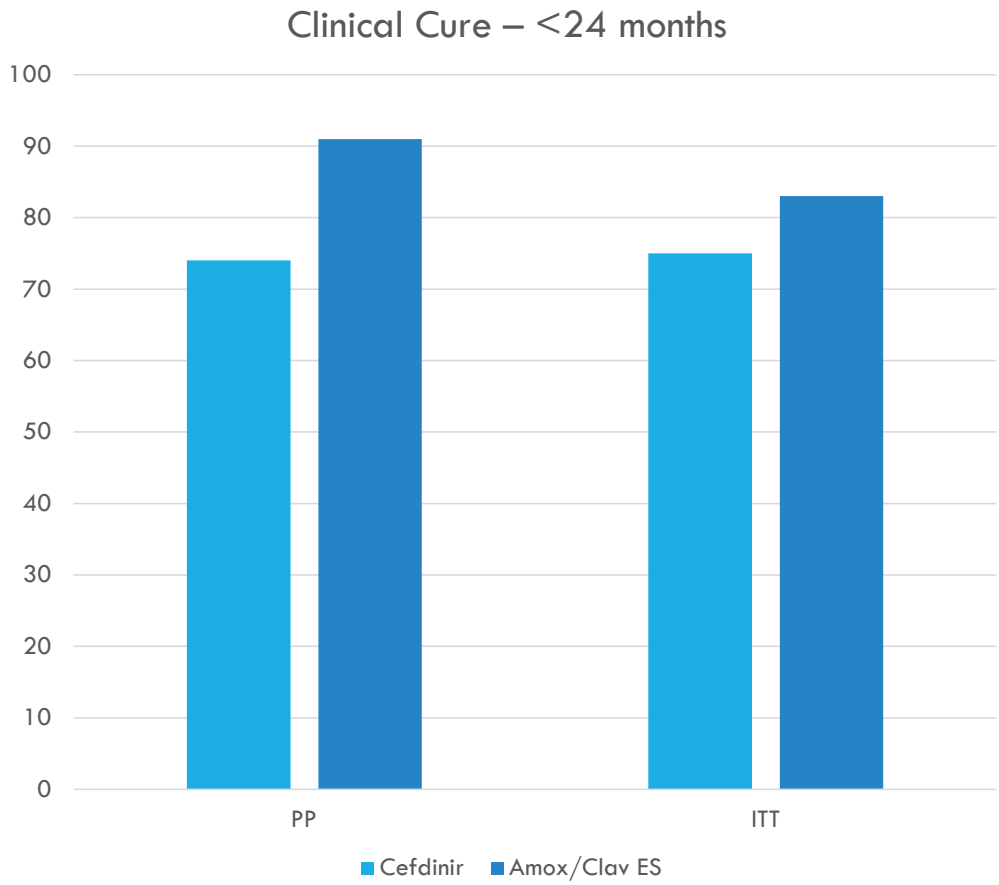
Comparing Cefdinir vs. Amox/Clav

- Multicenter, investigator blinded study of 6 month – 6-year-olds with AOM
- Cefdinir worse than Amox/Clav ES in PP (p=0.045)



Comparing Cefdinir vs. Amox/Clav

- Cefdinir worse than Amox/Clav ES in those <24 months in PP (p=0.039)



Antimicrobial Stewardship

- Inpatient
  - Prospective audit and feedback
  - “Hand-shake” rounds
  - Formulary restrictions
- Outpatient
  - What is feasible in the outpatient setting?

CDC Core Elements of Outpatient Antibiotic Stewardship

- 2016 Report published by the CDC
- 4 Core Elements

Joint Commission R3 Report

Antimicrobial Stewardship in Ambulatory Health Care

Effective January 1, 2020, new antimicrobial stewardship requirements will be applicable to Joint Commission-accredited ambulatory health care organizations that routinely prescribe antimicrobial medications. These include organizations providing medical or dental services, episodic care, occupational/worksite health, urgent/immediate care, or convenient care. The requirements are not applicable to ambulatory surgery centers or the office-based surgery program.

This project is a continuation of The Joint Commission's initiative to promote antimicrobial stewardship in the hospital, critical access hospital, and nursing care center programs (see R3 Report Issue 8, October 19, 2016).

The inappropriate use of antimicrobial medications contributes to antibiotic resistance and adverse drug events, and improving antimicrobial prescribing practices is a patient safety priority. As a result, The Joint Commission has developed a new standard in the Medication Management (MM) chapter (Standard MM.09.01.03) with 5 new elements of performance (EPs) addressing antimicrobial stewardship in the ambulatory setting.

The new EPs align with current recommendations from scientific and professional organizations and address the following concepts:

- Identifying an antimicrobial stewardship leader.
- Establishing an annual antimicrobial stewardship goal.
- Implementing evidence-based practice guidelines related to the antimicrobial stewardship goal.
- Providing clinical staff with educational resources related to the antimicrobial stewardship goal.
- Collecting, analyzing, and reporting data related to the antimicrobial stewardship goal.

UPPER RESPIRATORY TRACT INFECTION Manage User Versions

- Group A Streptococcus Pharyngitis
- Acute Bacterial Sinusitis
  - First-line — Click for more
  - Penicillin Allergy — Click for more
- Acute Otitis Media
  - First-line
    - ○ Non-recurrent, no conjunctivitis, and no amoxicillin within 30 days
    - ◉ Recurrent, conjunctivitis present, or receipt of amoxicillin within 30 days
      - ◉ amoxicillin-clavulanate (AUGMENTIN-ES) 600-42.9 mg/5 mL suspension
        - Take 2.6 mLs every 12 (twelve) hours by mouth for 10 days
        - Normal, Disp-52 mL, R-0
  - Penicillin Allergy
    - ◉ Non-severe
      - ◉ cefdinir (OMNICEF) 250 mg/5 mL suspension
        - Take 1.9 mLs daily by mouth for 10 days
        - Normal, Disp-19 mL, R-0
    - ○ Severe

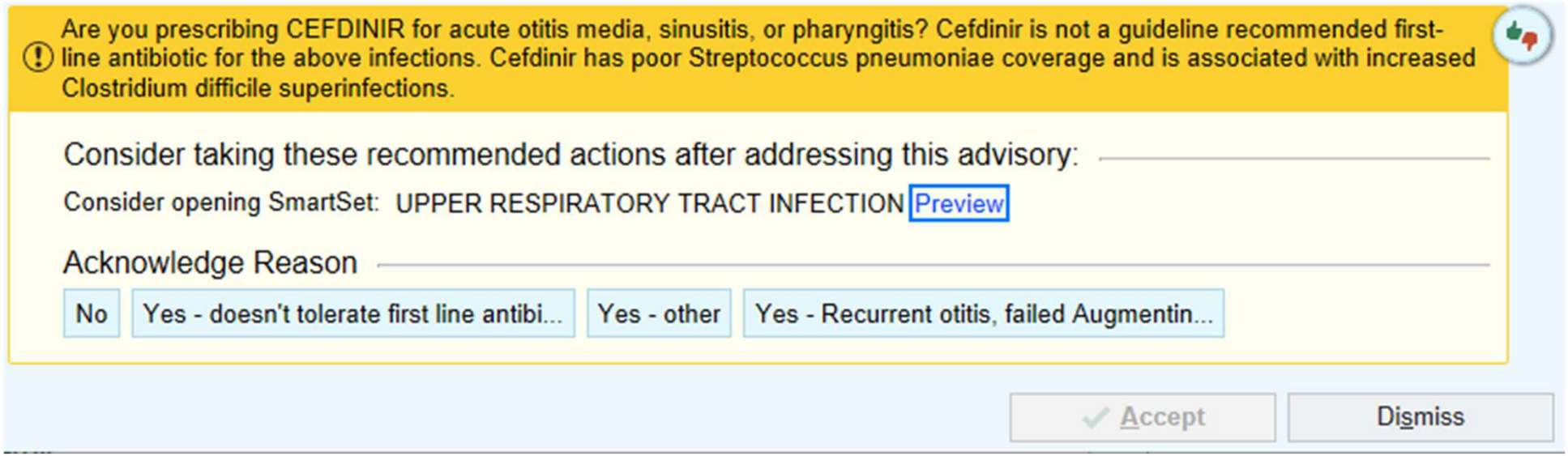
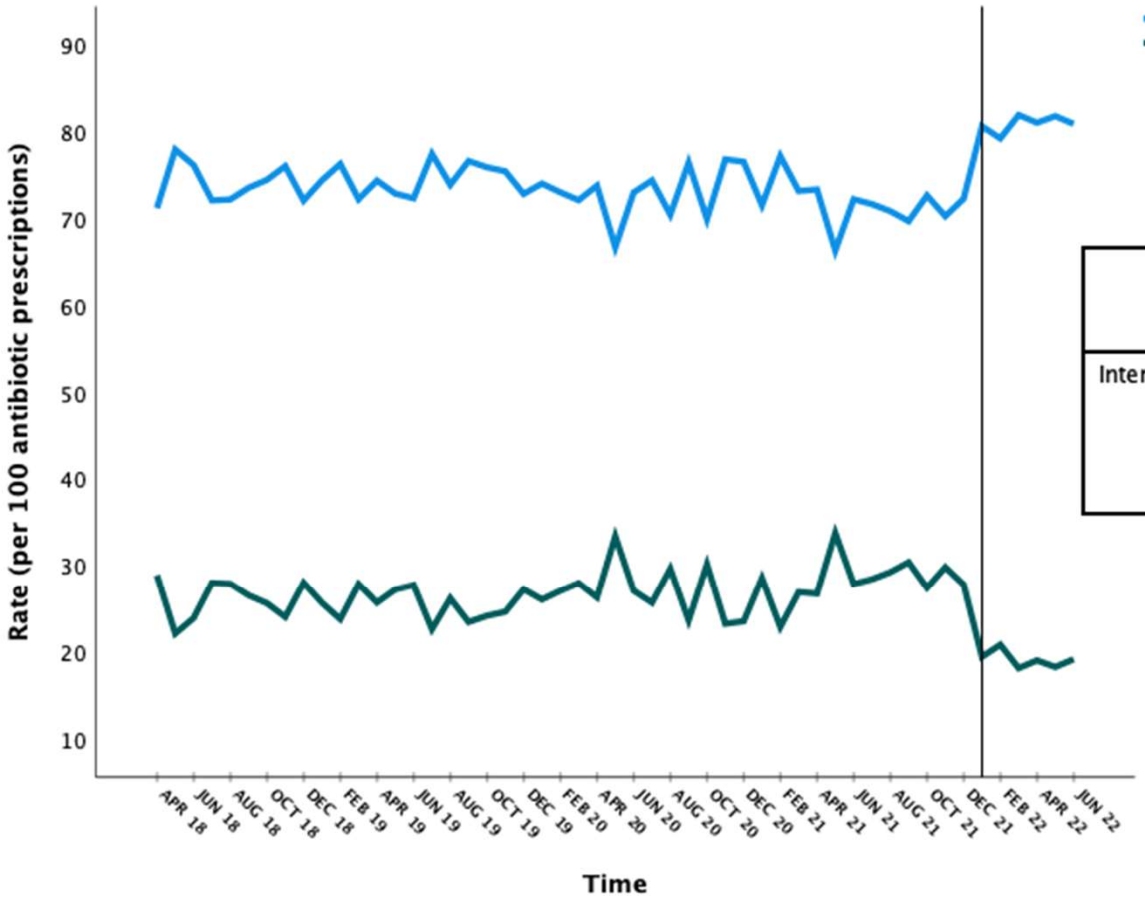

Are you prescribing CEFDINIR for acute otitis media, sinusitis, or pharyngitis? Cefdinir is not a guideline recommended first-line antibiotic for the above infections. Cefdinir has poor Streptococcus pneumoniae coverage and is associated with increased Clostridium difficile superinfections.
Consider taking these recommended actions after addressing this advisory:
Consider opening SmartSet: UPPER RESPIRATORY TRACT INFECTION Preview
Acknowledge Reason
No
Yes - doesn't tolerate first line antibi...
Yes - other
Yes - Recurrent otitis, failed Augmentin...
Accept
Dismiss

Figure 1: Rate of prescrbing of first-line and non-first-line antibiotis pre- and post-intervention



Comparison of Pre- and Post- Intervention Groups

			Antibiotics		
			First-line	Non-first-line	Total
Intervention	Pre	Count	26895	9683	36578
		%	73.5%	26.5%	100.0%
	Post	Count	4137	973	5110
		%	81.0%	19.0%	100.0%

P = <0.001

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- ✓ Explain the importance of acute otitis media as a focus of outpatient antimicrobial stewardship
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Take Home Points

- As the most common indication for antibiotics in pediatrics, acute otitis media is an excellent target for improving prescribing practices.
- With high incidence of viral pathogens and decreasing prevalence of *Streptococcus pneumoniae* in the post-vaccine era, the number needed to treat for acute otitis media is rising.
- We cannot extrapolate Cefdinir susceptibility from Ceftriaxone susceptibility. Cefdinir's role should be limited to use in penicillin-allergic patients.

References

Block, S. L., Schmier, J. K., Notario, G. F., Akinlade, B. K., Busman, T. A., MacKinnon, G. E., Halpern, M. T., & Nilius, A. M. (2006). Efficacy, tolerability, and parent reported outcomes for Cefdinir vs. high-dose amoxicillin/clavulanate oral suspension for acute otitis media in young children. Current Medical Research and Opinion, 22(9), 1839–1847. https://doi.org/10.1185/030079906x132406

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Thanks for listening!