Antibiotic Stewardship in Outpatient Settings

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Oregon Health Authority

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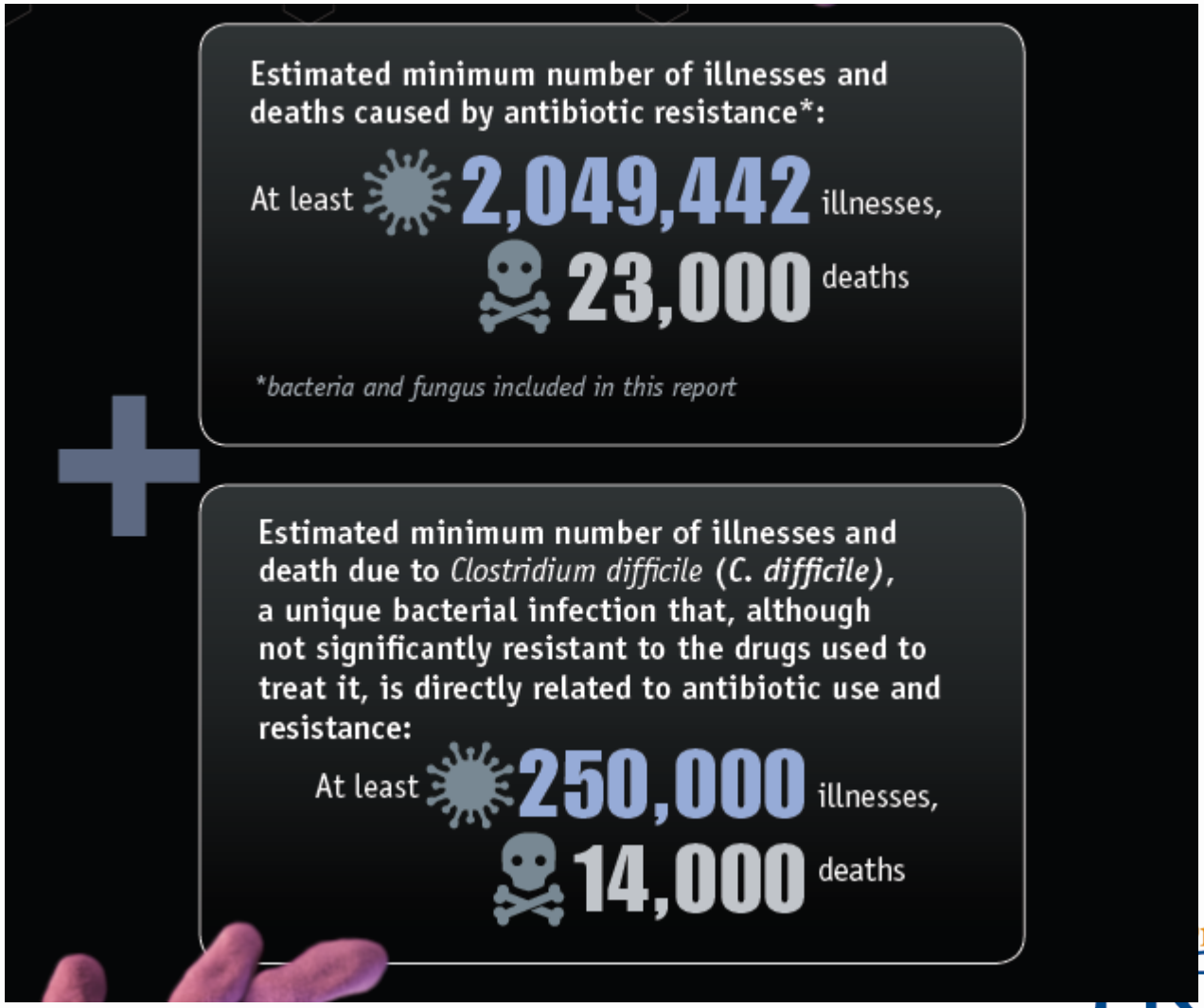
Antibiotic Resistance: should we be concerned?



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HAZARD LEVEL
URGENT

These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridium difficile (C. difficile), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

HAZARD LEVEL
SERIOUS

These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.

Multidrug-resistant *Acinetobacter*, Drug-resistant *Campylobacter*, Fluconazole-resistant *Candida* (a fungus), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs), Vancomycin-resistant *Enterococcus* (VRE), Multidrug-resistant *Pseudomonas aeruginosa*, Drug-resistant Non-typhoidal *Salmonella*, Drug-resistant *Salmonella* Typhi, Drug-resistant *Shigella*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Drug-resistant *Streptococcus pneumonia*, Drug-resistant tuberculosis (MDR and XDR)

HAZARD LEVEL
CONCERNING

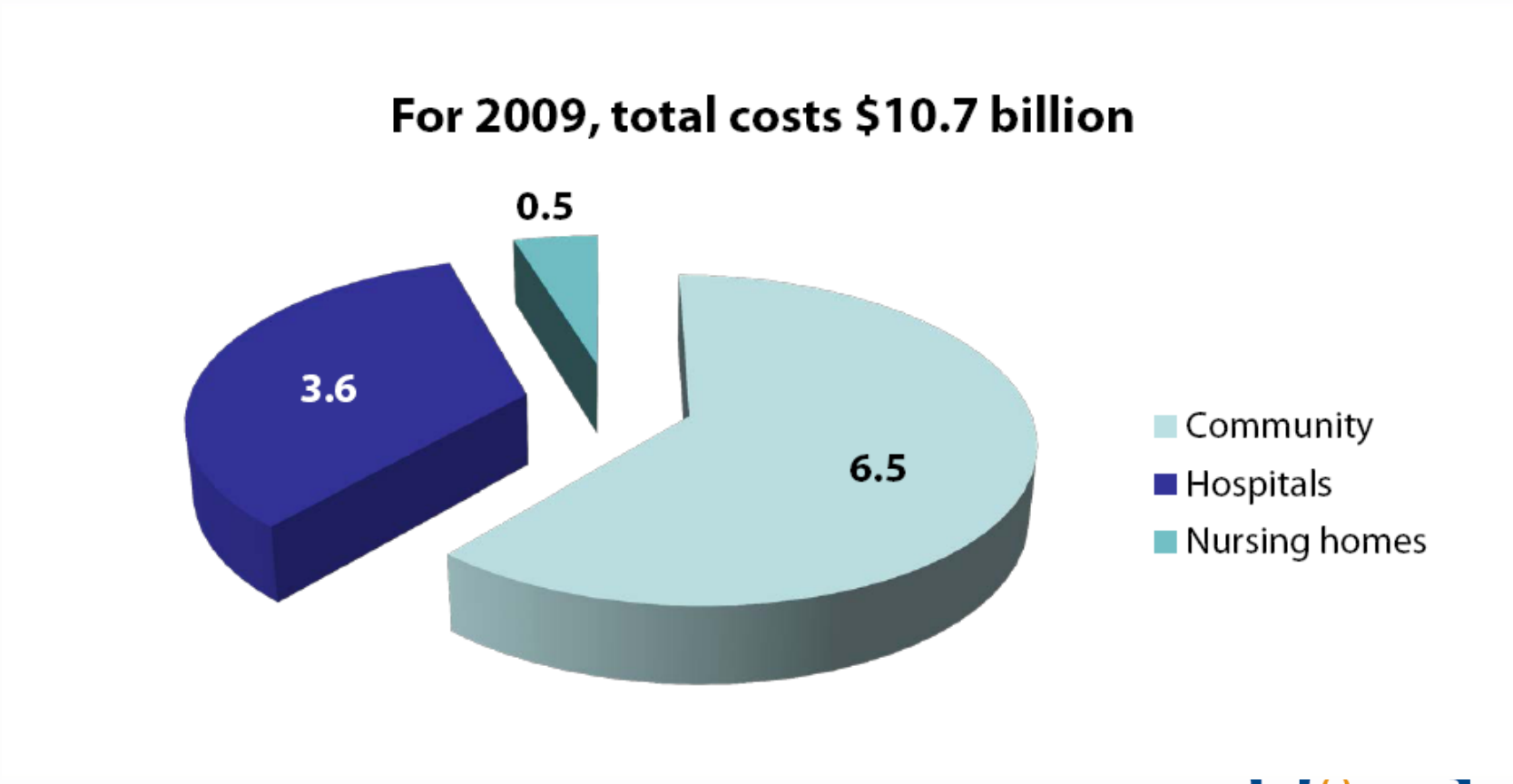
These are bacteria for which the threat of antibiotic resistance is low, and/or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response.

Vancomycin-resistant *Staphylococcus aureus* (VRSA), Erythromycin-resistant *Streptococcus* Group A, Clindamycin-resistant *Streptococcus* Group B

Why antibiotic resistant infections cost us all more

- Require prolonged and costlier treatments
- Extend hospital stays
- Necessitate additional provider visits and healthcare use
- Result in greater disability and death compared to infections that are easily treatable with antibiotics

Antibiotic prescription costs in billions



Suda, et al. J Antimicrob Chemotherapy 2013;68:715-18

Unintended consequences of antibiotic use: adverse events

- Adverse events range from minor (rash) to severe (systemic allergic reaction, including anaphylaxis)
- Antibiotics are responsible for almost 1 out of every 5 visits to emergency departments for drug-related adverse events
- Antibiotics are the most common cause of drug-related emergency department visits for children

Shehab, et al. Clin Infect Dis. 2008;47(6):735-43

Overuse of Antibiotics

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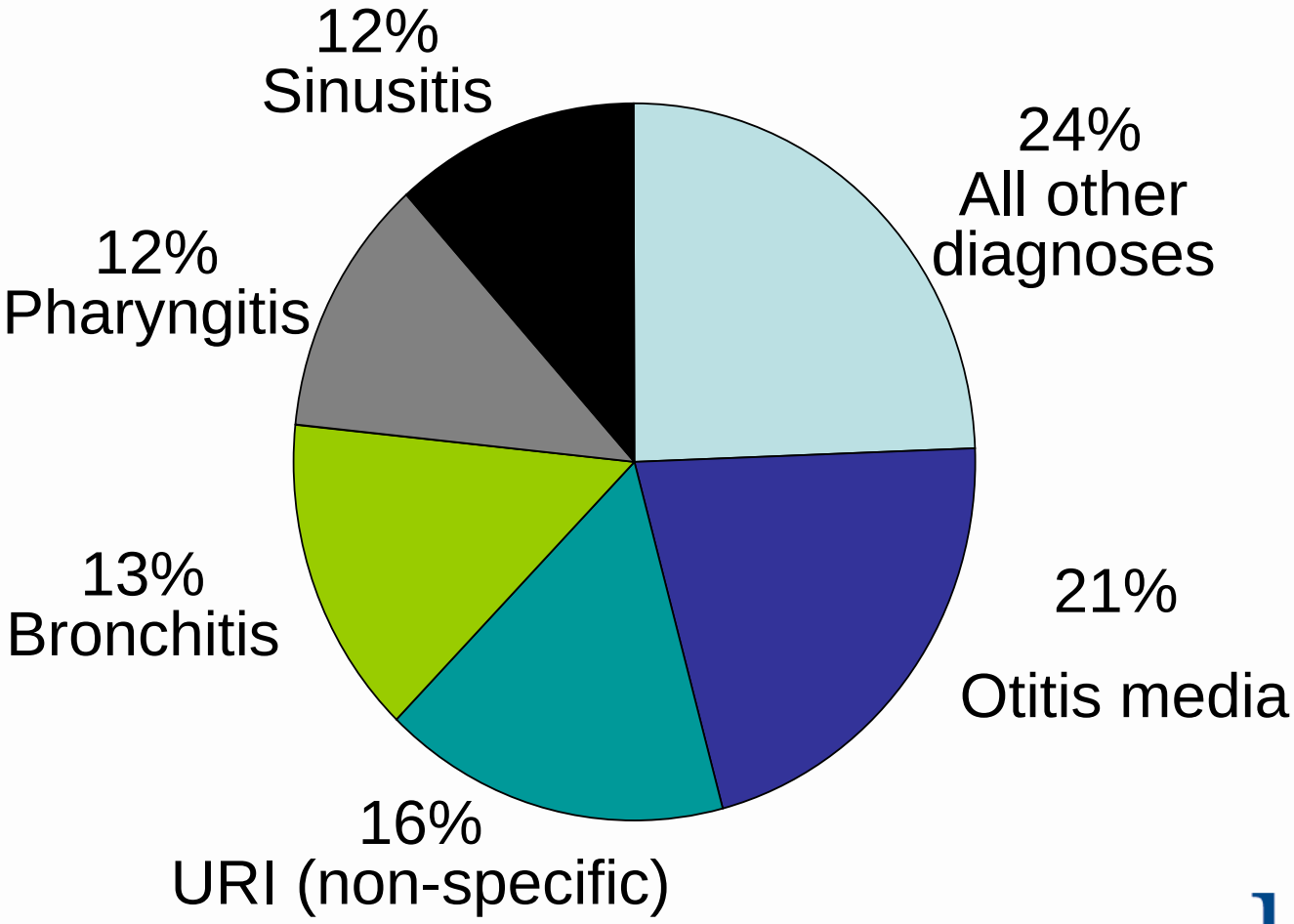
Outpatient Antimicrobial Therapy 1992, US



McCaig JAMA 1995;273:214

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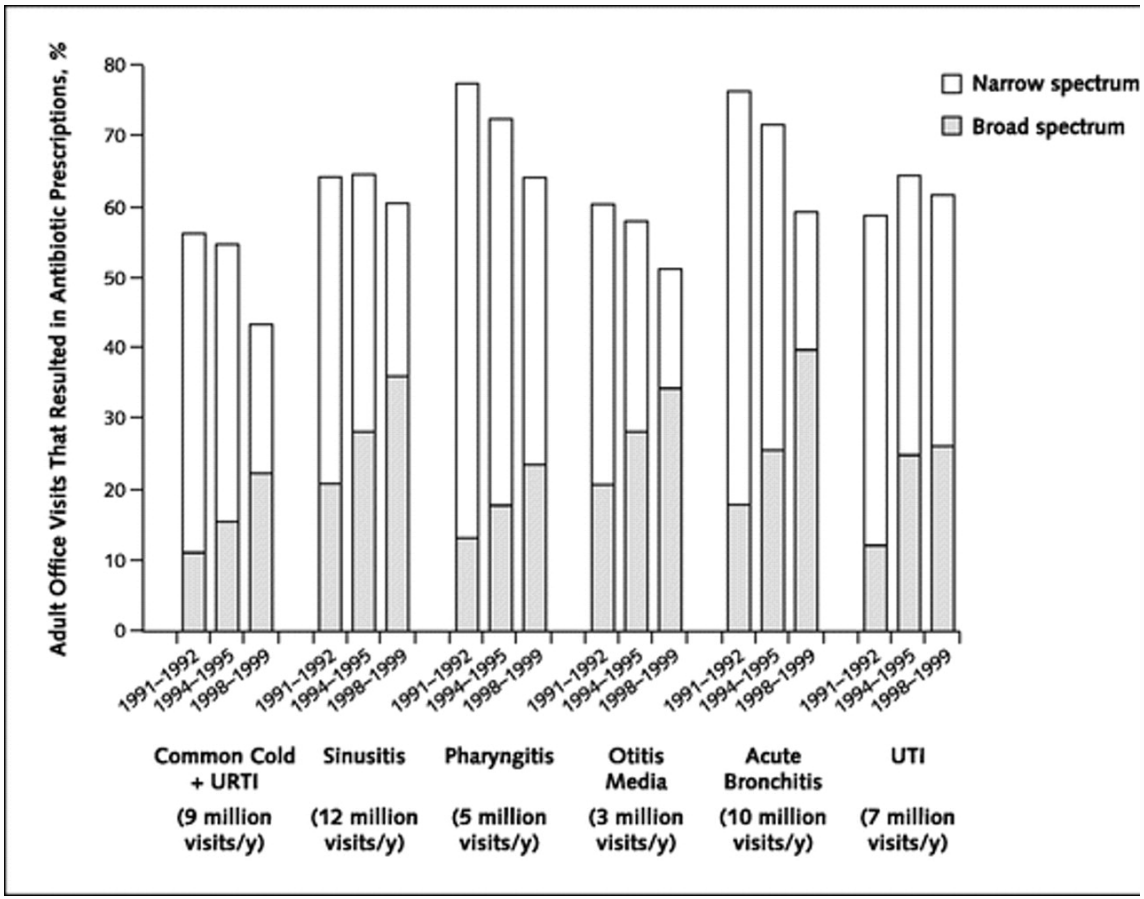
Antibiotic Prescribing among Adults US, 1991-1992 and 1998-1999



Steinman, M. A. et. al. Ann Intern Med 2003;138:525-533

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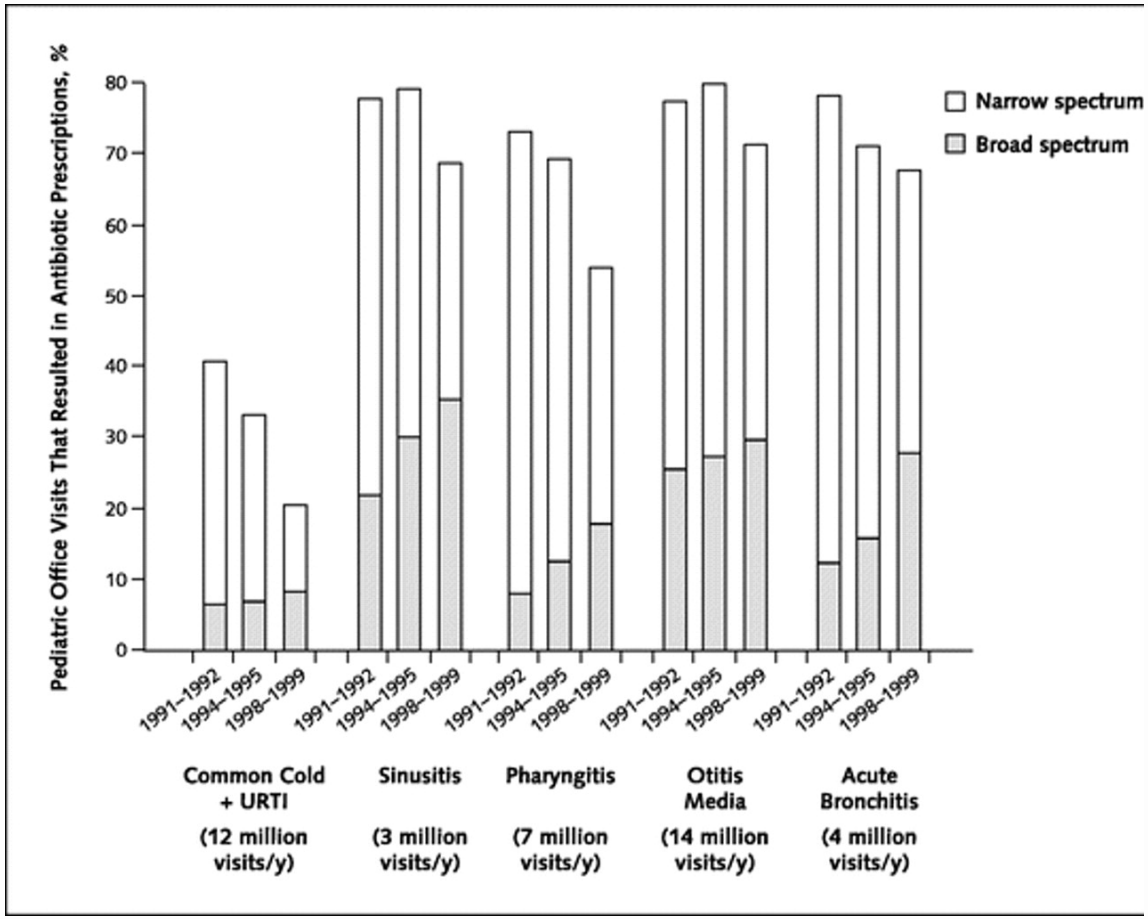
Antibiotic Prescribing among Children US, 1991-1992 and 1998-1999



Steinman, M. A. et. al. Ann Intern Med 2003;138:525-533

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Antibiotic-Prescribing by Condition, Adults, US, 2007-9

Condition	Treated with Abx	% Receiving Broad-spectrum Abx
Respiratory	38%	74%
Abx indicated	65%	65%
Abx not indicated	51%	80%
Other respiratory	23%	76%
Other	7%	52%
Skin	13%	38%
UTI	60%	69%
GI	10%	77%

Shapiro, et al. J Antimicrob Chemother doi:10.1093/jac/dkt301

Antibiotic-Prescribing by Condition, Children < 18, US, 2006-8

Condition	Treated with Abx	% Receiving Broad-spectrum Abx
Respiratory	48%	53%
Abx indicated	72%	48%
Abx not indicated	30%	63%
Other respiratory	28%	65%
Other	8%	42%
Skin	19%	38%
UTI	59%	39%
GI	6%	54%

Hersh, et al. Pediatrics 2011;128:1053-1061

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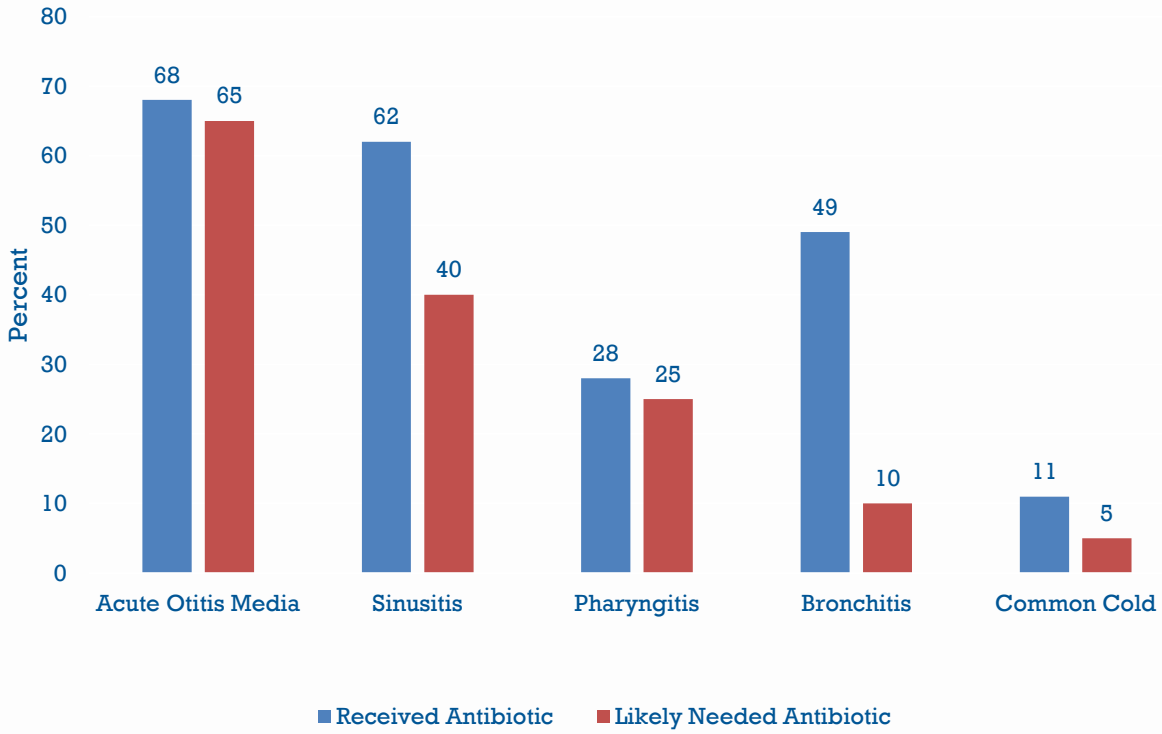
Proportion of patients filling antibiotic prescriptions vs proportion needing antibiotics, Oregon, 2013



Gonzales CID 2001;33:757-62; Oregon APAC data, 2013

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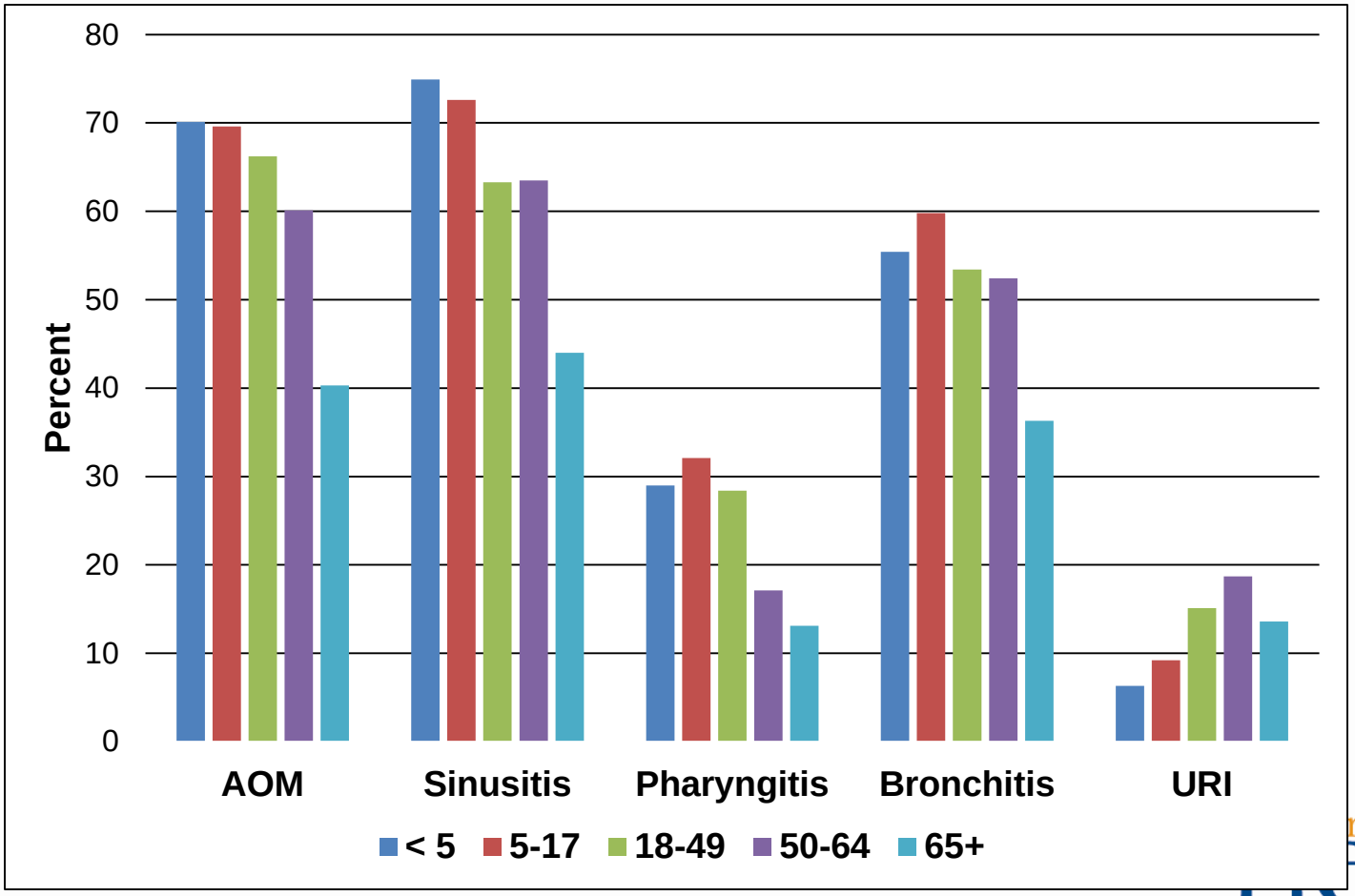
Proportion of patients filling antibiotic prescriptions, by age group and syndrome, Oregon, 2013



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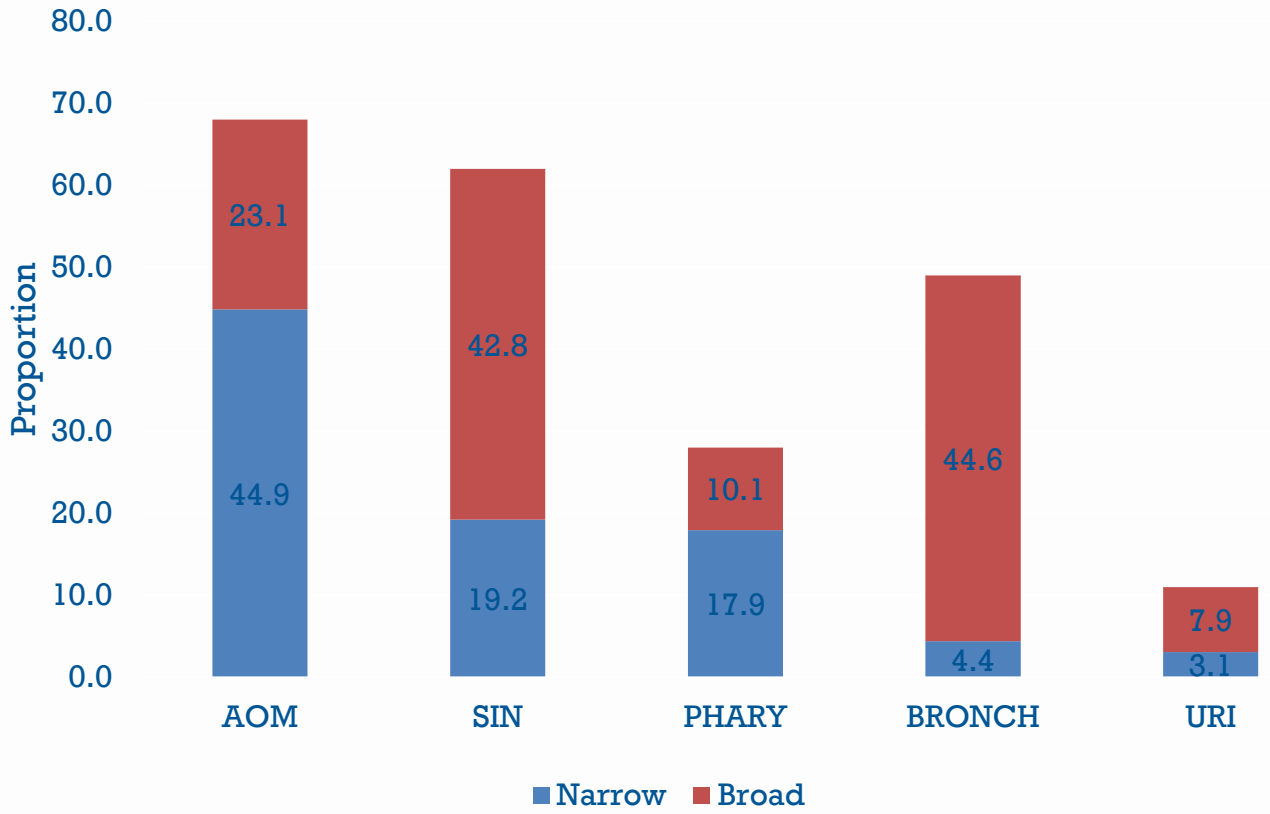
Proportion of patients receiving broad and narrow spectrum antibiotics, by syndrome, Oregon, 2011-12



Includes penicillin, ampicillin, amoxicillin, and first generation cephalosporins

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Class of antibiotics used for respiratory infections, Oregon, 2013

Antibiotic Class	AOM (n=64,291)	Sinusitis (n=57,935)	Pharyngitis (n=38,656)	Bronchitis (n=41,722)	URI (n=20,281)
Narrow spectrum beta lactams[#]	66.5%	31.4%	64.2%	9.2%	28.3%
Amoxicillin-clavulanate	11.3%	26.0%	7.2%	5.7%	8.7%
Azithromycin	12.0%	25.2%	21.1%	69.4%	48.8%
Fluoroquinolones	0.5%	3.0%	0.9%	4.5%	2.7%
2nd generation and above cephalosporins	7.6%	6.0%	2.5%	1.9%	3.4%
All other broad spectrum	2.1%	8.4%	4.1%	9.4%	8.1%

Review of Upper Respiratory Tract Pathogens and Trends in Resistance

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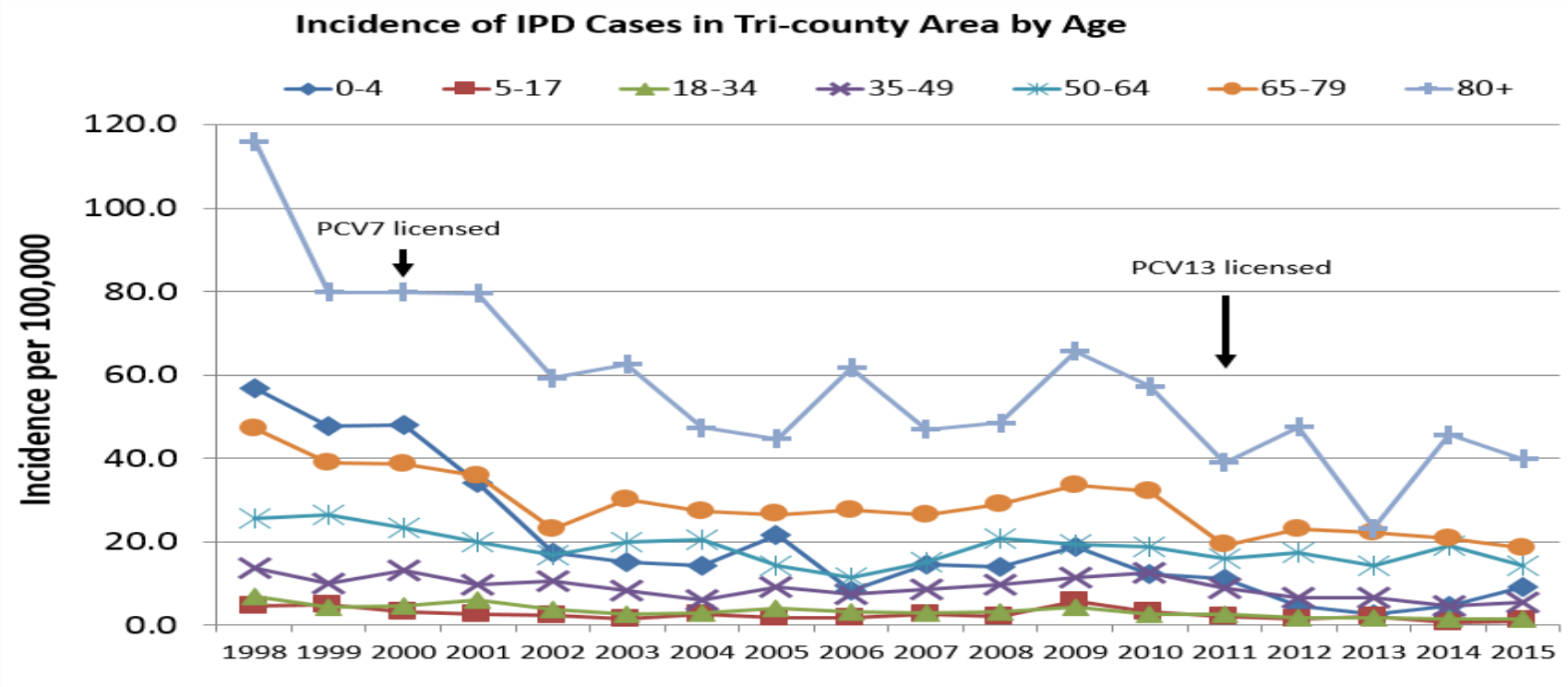
Streptococcus pneumoniae (SP)

- Leading cause of bacterial meningitis, CAP, and AOM
- 2nd leading cause of bacteremia



Incidence of Invasive Pneumococcal Disease by Age, Portland, Oregon EIP

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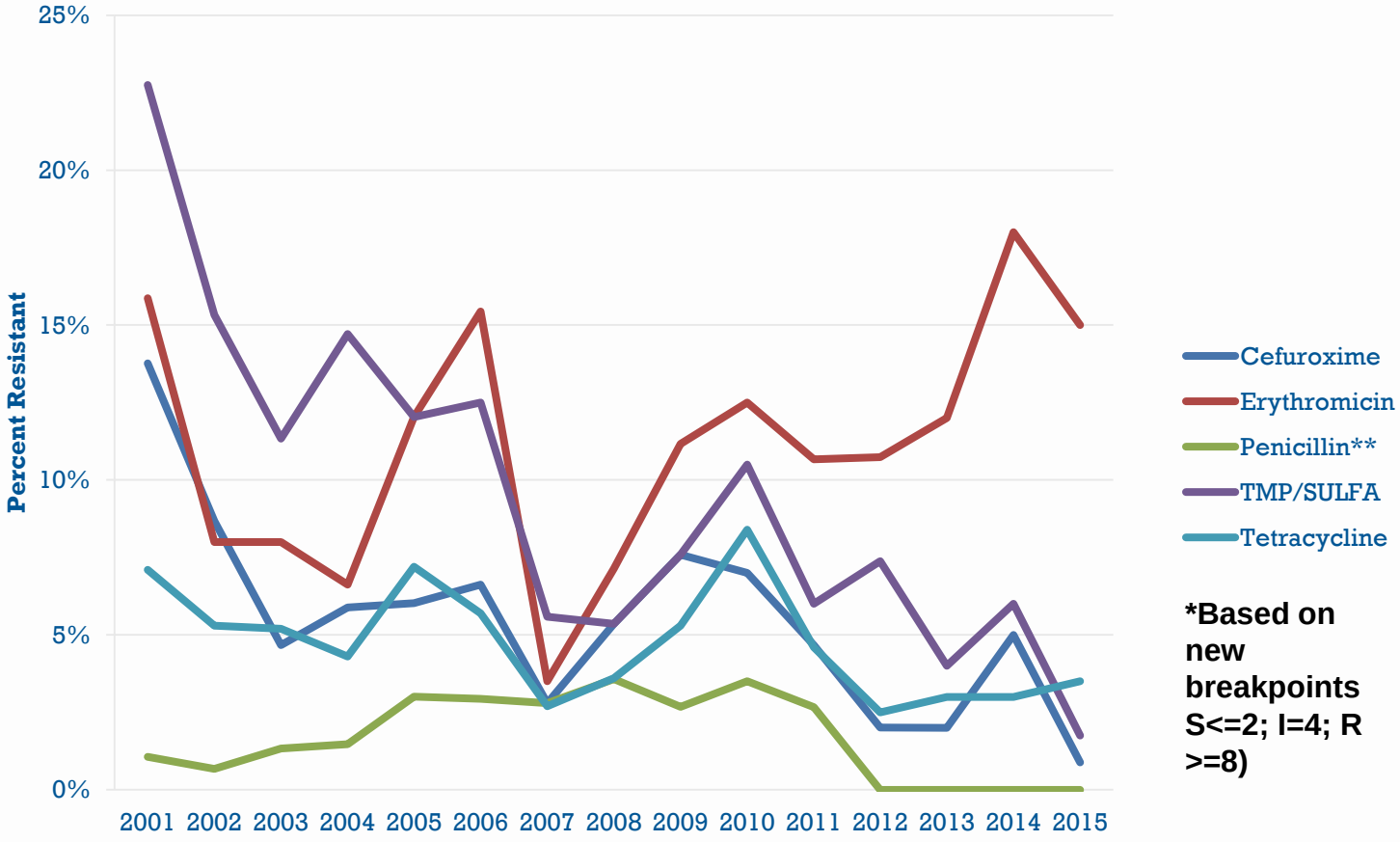
Risk Factors for Acquisition of DRSP

- Recent antibiotic use, especially macrolides
- Age < 2 years or > 65 years
- Daycare attendance
- Exposure to young children
- Immunodeficiencies and underlying diseases
- Recent hospitalization

Lynch Seminars Resp Crit Care Med 2009;30:189-209
Campbell Clin Infect Dis 1998;26:1188-95

Proportion of Pneumococcal Isolates Resistant to Commonly Used Antibiotics Portland, 2001–2015



***Based on new breakpoints S<=2; I=4; R >=8)**

Oregon Emerging Infections Program ABCs data

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Mechanism of Resistance: *S. pneumoniae*

- Alterations in alterations in penicillin-binding proteins
- Can overcome by increasing dose
- Rationale for use of high dose amoxicillin

Haemophilus influenzae (HI)

- Prior to vaccine introduction, type B leading cause of bacterial meningitis in children, as well as epiglottitis, pneumonia, septic arthritis, cellulitis, osteomyelitis, and bacteremia (especially in kids)
- Type B now very rare, only 1-2 cases per year in Oregon
- Mechanism of resistance: 25%-45% produce β-lactamase, can't be treated with higher dose

Brook J of Med Micro 2006;55:943-6;
Harrison J Antimicrob Chemotherapy 2009;63:511-9

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Moraxella catarrhalis

- After SP and HI, 3rd leading cause of AOM in children (15%-20% of cases), also causes pneumonia in adults, especially in elderly, and sinusitis

- 90% produce β-lactamase

Harrison J Antimicrob Chemotherapy 2009;63:511-9

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Group A beta-hemolytic streptococcus (GAS)

- Most frequent clinical manifestations are pharyngitis and pyoderma, less commonly erysipelas, cellulitis, necrotizing fasciitis (known as “flesh-eating virus” in the tabloids), myositis, myonecrosis, and streptococcal shock syndrome

- GAS accounts for 20%-30% of pediatric cases of pharyngitis, 10% in adults

Nonsusceptibility of Invasive GAS Isolates Portland Tri-County area, 2014

Antibiotic	Intermediate	Fully Resistant
Vancomycin	0%	0%
Cefotaxime	0%	0%
Penicillin	0%	0%
Clindamycin	0%	1%
Erythromycin	0%	10%
Tetracycline	0%	30%

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Basic Strategy

- Don’t give antibiotics unless indicated
  - Wait and see option
- When giving antibiotics:
  - Narrowest spectrum possible
  - Optimal dosage, timing (high dose, short course)
  - Macrolides not good choice for pneumococcus or *H. influenzae*
    - mostly useful for pertussis, some cases of community-acquired pneumonia

Diagnostic Criteria for AOM

Patients with MEE (lack of mobility of TM with insufflation or presence of air-fluid interface), plus one of the following:

- Moderate to severe bulging of the TM; *or*
- New onset of otorrhea not due to otitis externa; *or*
- Mild bulging of the TM and recent (< 48 hours) onse of ear pain or intense erythema of the TM

AAP Pediatrics 2013;131:e964-e999

Treatment of AOM: Observation Option

	6 mo – 2 yr	≥ 2 yr
Otorrhea + AOM	**Antibiotics**	**Antibiotics**
Severe* Sx (bi- or unilateral)	**Antibiotics**	**Antibiotics**
Bilateral, no otorrhea	**Antibiotics**	**Antibiotics** *or observation*
Unilateral, no otorrhea	**Antibiotics** *or observation*	**Antibiotics** *or observation*

***Persistent otalgia > 48 hours, temperature ≥ 39°, or follow-up uncertain**

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Treatment of Acute OM

Observation:

- Defer antibiotics for 48-72 hours
- Involve caretaker in decision
- Treat pain, acetaminophen or ibuprofen preferred, longer-lasting than topical
- Only if follow-up can be assured and pt > 6 mos

AAP Pediatrics 2013;131:e964-e999

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Treatment of Acute OM

Antibiotic choice:

- Amoxicillin benefits:
  - Narrow spectrum, good safety profile, tastes great
  - Little resistance to penicillin/amoxicillin in OR
  - 45 mg/kg/day X 10 days if < 2 yrs, 5-7 days if older

- Risks for DRSP: < 2 years, recent use of Abx or hospitalization, daycare, immunocompromise
  ⟹ high dose amoxicillin for DRSP
- AOM with conjunctivitis or amoxicillin in past 30 days
  ⟹ use amoxicillin-clavulanate for *H. influenza*

Alternative Regimens for Treatment of Acute OM

- **For treatment failure:**

- amoxicillin/clavulanate 80-90mg/kg/day bid or tid

  or

- cefdinir, cefpodoxime, or cefixime (consider ceftriaxone 50 mg/kg IM qd X 3 if vomiting)

- **For penicillin-allergic patients:**

- Mild: cefdinir, cefpodoxime, or cefixime

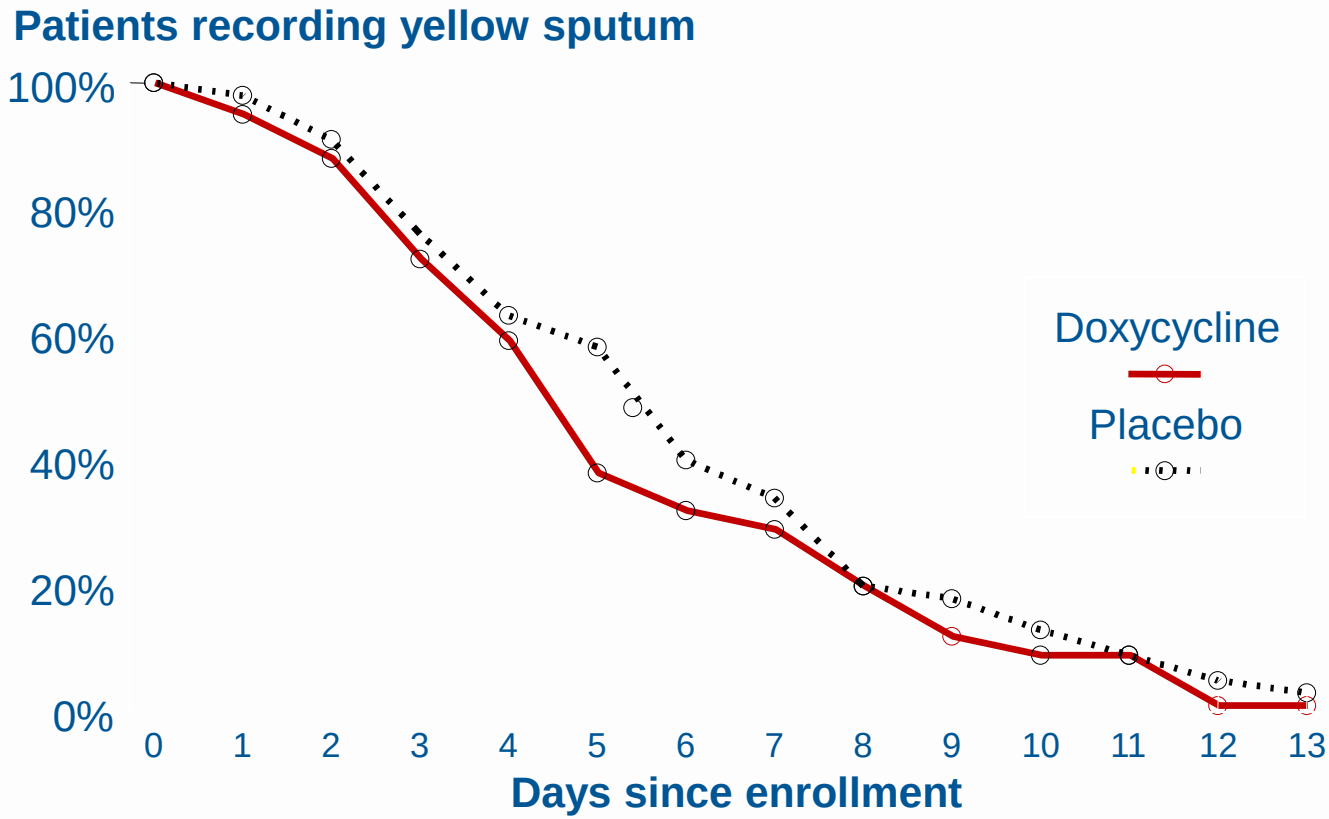
- Severe (hives or anaphylaxis): levofloxacin, clindamycin, consider ENT consultation and tympanocentesis

Cough Illness/Bronchitis

- Bronchitis is a self-limited inflammation of the bronchial respiratory mucosa, viruses account for 90%
- Although bacteria can be found in sputum, bronchial biopsies have not shown bacterial invasion
- Consider pertussis, particularly if disease present in community
- Purulent sputum usually indicates presence of sloughed tracheobronchial epithelium and WBCs

Wenzel NEJM 2006;355:2125-30; Albert Am Family Physician 2010;82:1345-50

Antibiotics for The Common Cold Benefit on Day 5 ?



Stott BMJ 1976;2:556

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Diagnosis and Management: Adults

Duration < 3 weeks

- If no fever, chest exam is clear and VS are normal, pneumonia is highly unlikely
- Recommend: avoid cigarette smoke,
- bronchodilators,
- hydration, steam to loosen secretions

Duration > 3 weeks

- Obtain CXR
- Most likely: postnasal drip, asthma/RAD, secondhand smoke, GER, ACE-inhibitor cough, environmental exposures, chronic bronchitis, bronchectasis,
- malignancy

- Infectious: consider *B. pertussis, M. pneumoniae, C. pneumoniae*
- Treat COPD exacerbation amoxicillin, TMP/SMX or doxycycline and 7-10d course of oral corticosteroids

Diagnosis and Management: Children

Duration < 4 weeks

- If no fever, chest exam is clear and VS are normal, pneumonia is highly unlikely
- Recommend: avoid cigarette smoke, drink plenty of liquids, nasal saline washes, topical vapor rubs,
- acetaminophen or ibuprofen for fever/pain, rest

Duration > 4 weeks

- Obtain CXR and spirometry (> 3-6 yrs)
- Most likely: postnasal drip, allergies, habit cough, sinusitis, CF, foreign body aspiration, asthma/RAD,
- secondhand smoke,
- GER, congenital malformations
- Infectious: consider *B. pertussis, M. pneumoniae, C. pneumoniae*
- Treat with macrolide or if > 8 yrs, doxycycline

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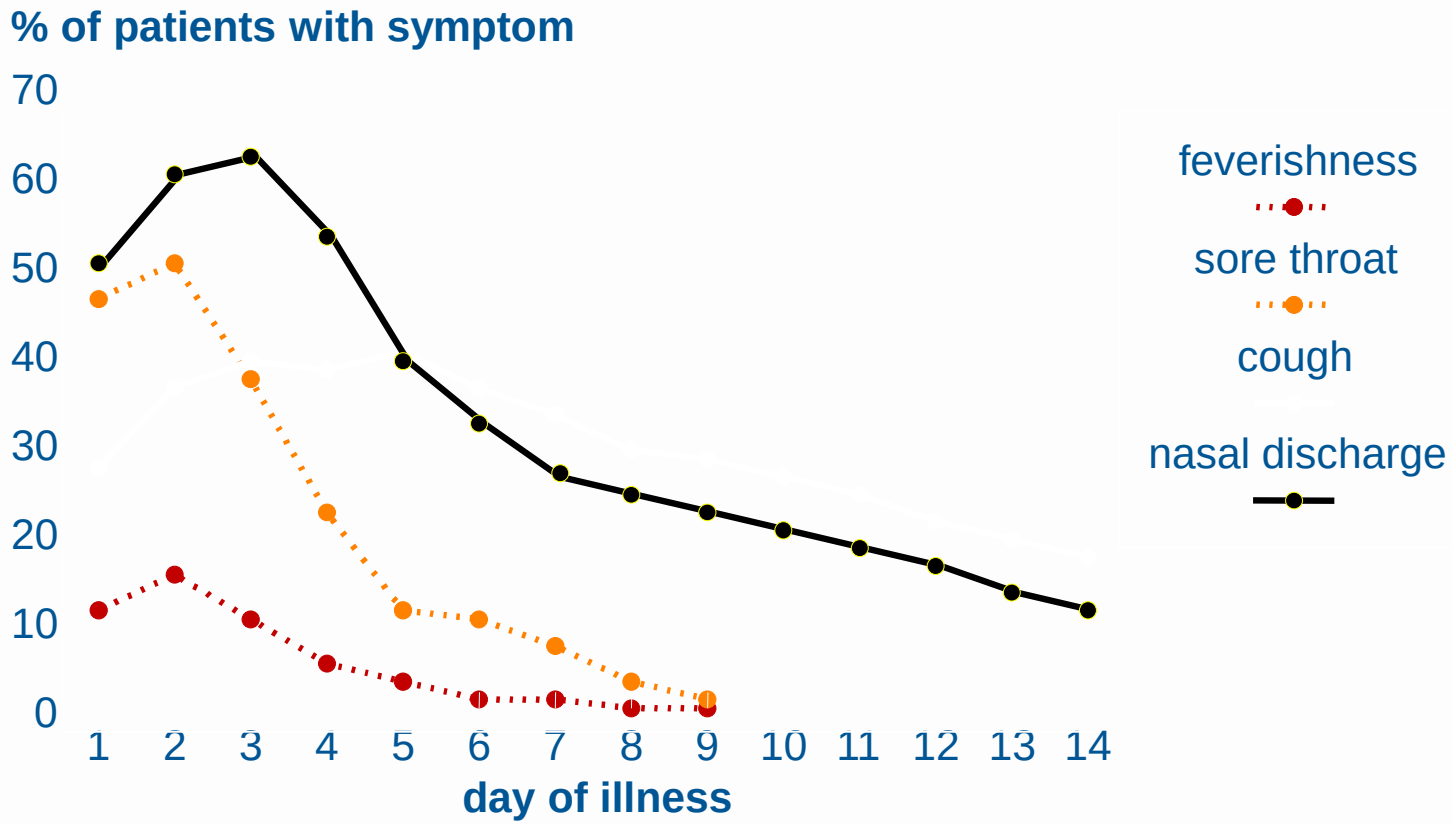
Sinusitis

- Antimicrobial treatment should be limited to:
  - prolonged nonspecific upper respiratory signs and symptoms (i.e. rhinorrhea and cough without improvement) for > 10 days, *or*
  - onset with severe symptoms or signs of fever > 39.0 C, and nasal discharge or facial pain, lasting at least 3-4 days, *or*
  - worsening signs/symptoms (new onset of fever, HA, or increased nasal discharge) following a URI of 5-6 days

IDSA (Chow) Clin Inf Dis 2012;54:e72-e112

Duration of Symptoms in 139 Rhinovirus Colds



Gwaltney JAMA 1967;202:158

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Treatment of Acute Sinusitis: Adults

Initial choice:

amoxicillin 1 gm po bid X 5-7 days

High dose amoxicillin?

severe infection, daycare exposure, age>65, recent hospitalization, abx use in past 3 months,

immunocompromised

Treatment Failure:

High dose amoxicillin-clavulanate

Beta-lactam allergy:

FQ or doxycycline

Adjunctive measures:

Nasal corticosteroid spray

Sinus irrigation

IDSA (Chow) Clin Inf Dis 2012;54:e72-e112

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Treatment of Acute Sinusitis: Children

Initial choice:

amoxicillin 45-50 mg/kg/day X 7-10 days

High dose Amoxicillin?

Severe infection, daycare, age <2, recent hospitalization, abx use in past 3 months,

immunocompromised

Treatment failure:

High dose amoxicillin-clavulanate

Beta-lactam allergy

Mild (no hives or anaphylaxis): cefixime, cefdinir, or cefpodoxime

If hives or anaphylaxis: FQ or if > 8 yrs, doxycycline

IDSA (Chow) Clin Inf Dis 2012;54:e72-e112

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Treatment of Acute Sinusitis: Other Considerations

- Duration:
  - Adults, 5-7 days
  - Children, 10-14 days
- Age: doxycycline > 8 years
- Macrolides and TMP/SMX not recommended
- For pts who worsen despite 72 hours of Rx or don't improve in 3-5 days: evaluate for resistant pathogens, inadequate dosing, a non-infectious cause (allergy, structural abnormality)

Pharyngitis

- Sore throat accounts for 1%-2% of all pt visits to primary care offices and EDs
- Most caused by viruses
- GAS only common bacterial etiology requiring treatment

	Adults	Children
% of sore throats caused by GAS	10%	15%-30% in cooler months, rare under age 3

Alcaide, Bisno Infect Dis Clin N Am 2007;21:449-69

Rationale for Treating GAS Pharyngitis

- Relative benefit of antibiotics low:
  - Rheumatic fever now rare in US, number needed to treat=3,000-4,000
  - Doesn't prevent acute glomerulonephritis
  - Strep due to groups C and G don't lead to rheumatic fever and don't need Rx

- Main benefit: antibiotics started within 2-3 days of onset shortens duration of symptoms by 1-2 days

Del Mar Cochrane Database Syst Review 2006; Cooper Ann Intern Med 2001;134:509-17

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Signs and Symptoms of GAS Pharyngitis

1) tonsillar exudate; 2) tender anterior cervical lymph nodes; 3) no cough; 4) fever

If 2-4 present, obtain rapid antigen test and treat if positive

If < 2 are present, supportive care only

Centor Med Decis Making 1981;1:239-246; IDSA Clin Infect Dis 2012;55:e86-102

Treatment of Acute GAS Pharyngitis

- **Adults:**
  - single dose benzathine penicillin 1.2 m.u. IM *or* penicillin V 500 mg po bid X 10 days or amoxicillin 775 mg po qd (FDA-approved)
- **Children <12 years:**
  - amoxicillin or penicillin V 45 mg/kg/day X 10 days (not FDA-approved, but Sanford guide recommends amoxicillin qd in kids)
- **For penicillin-allergic patients:**
  - Cephalexin or cefadroxil or clindamycin

IDSA Clin Infect Dis 2012;55:e86-102; Wessels NEJM 2011;364:648-5

Other considerations

- Must treat for at least 24 hours before return to daycare/school
- Routine testing of asymptomatic contacts not recommended
- Post-therapy culturing not recommended
- Recurrent episodes of culture-confirmed GAS may be recurrent viral episodes in chronic carrier (20% of school children)
  - Carriers unlikely to spread and are at low risk for complications themselves

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- Clinicians
  - Consensus guidelines
  - Printed materials to give patients
  - Motivational interviewing seminars
- General public
  - Mass media
  - Training of students in health professions
  - Development of curriculum for school children, K-6, HS

www.healthoregon.org./antibiotics

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