Brigham and Women's Hospital
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Responsible Use of Antibiotics

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- Clinical focus: Infectious Diseases
- Research focus: HIV

Editor-in-Chief, *Clinical Infectious Diseases*

DISCLOSURES

I have no relevant financial relationships with ineligible companies.

Objectives

At completion of this presentation, learners will:

- Understand the pressures faced by clinicians to prescribe antibiotics
- Select appropriate treatments for commonly encountered infections
- Understand certain antibiotic adverse effects and how to avoid them
- Have a few laughs

"You appear to have caught that bug that's been going around my waiting room."

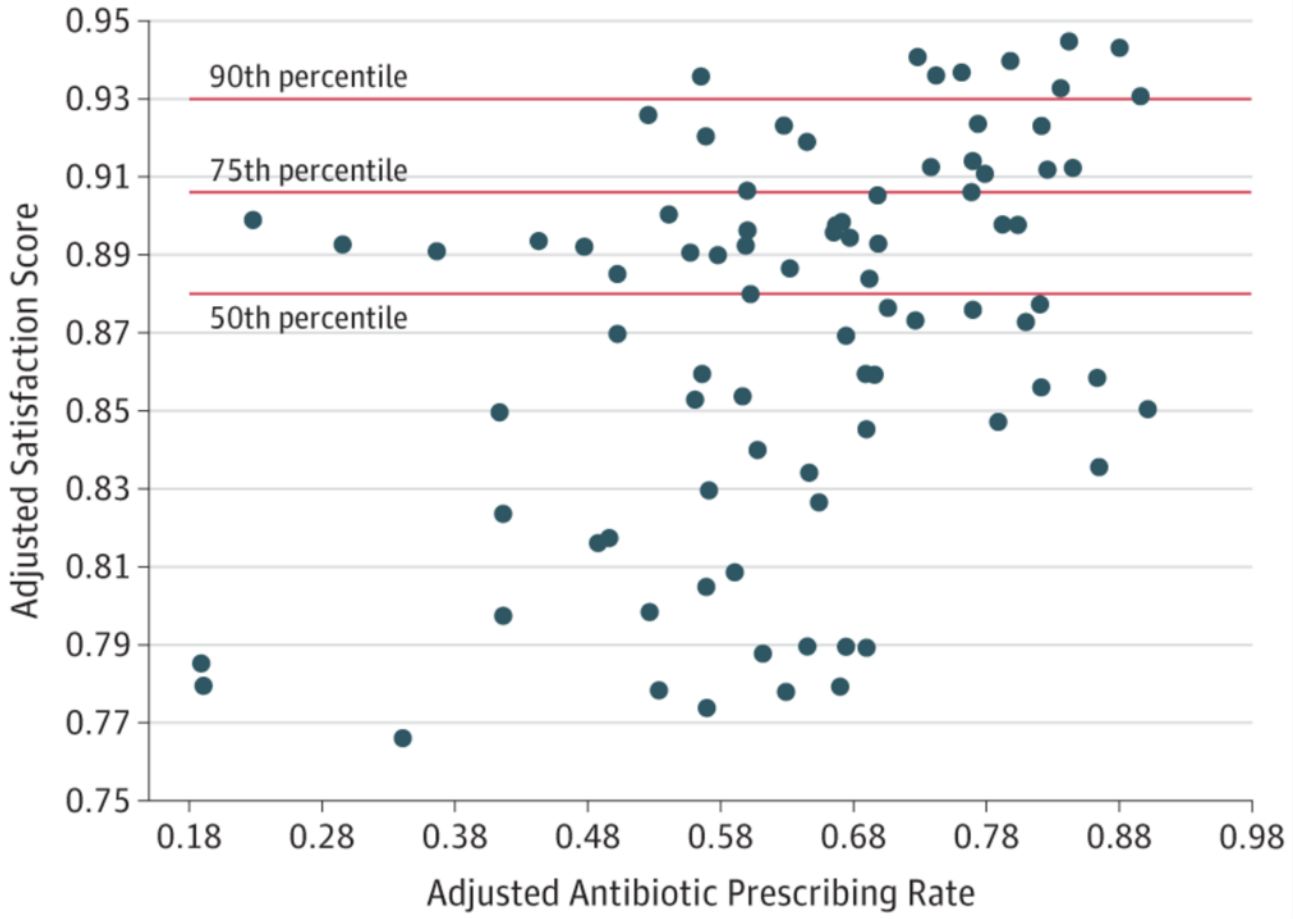
A presentation in two parts

An overview of the problem of antibiotic overuse

Most of the talk: Case-based challenges in outpatient practice

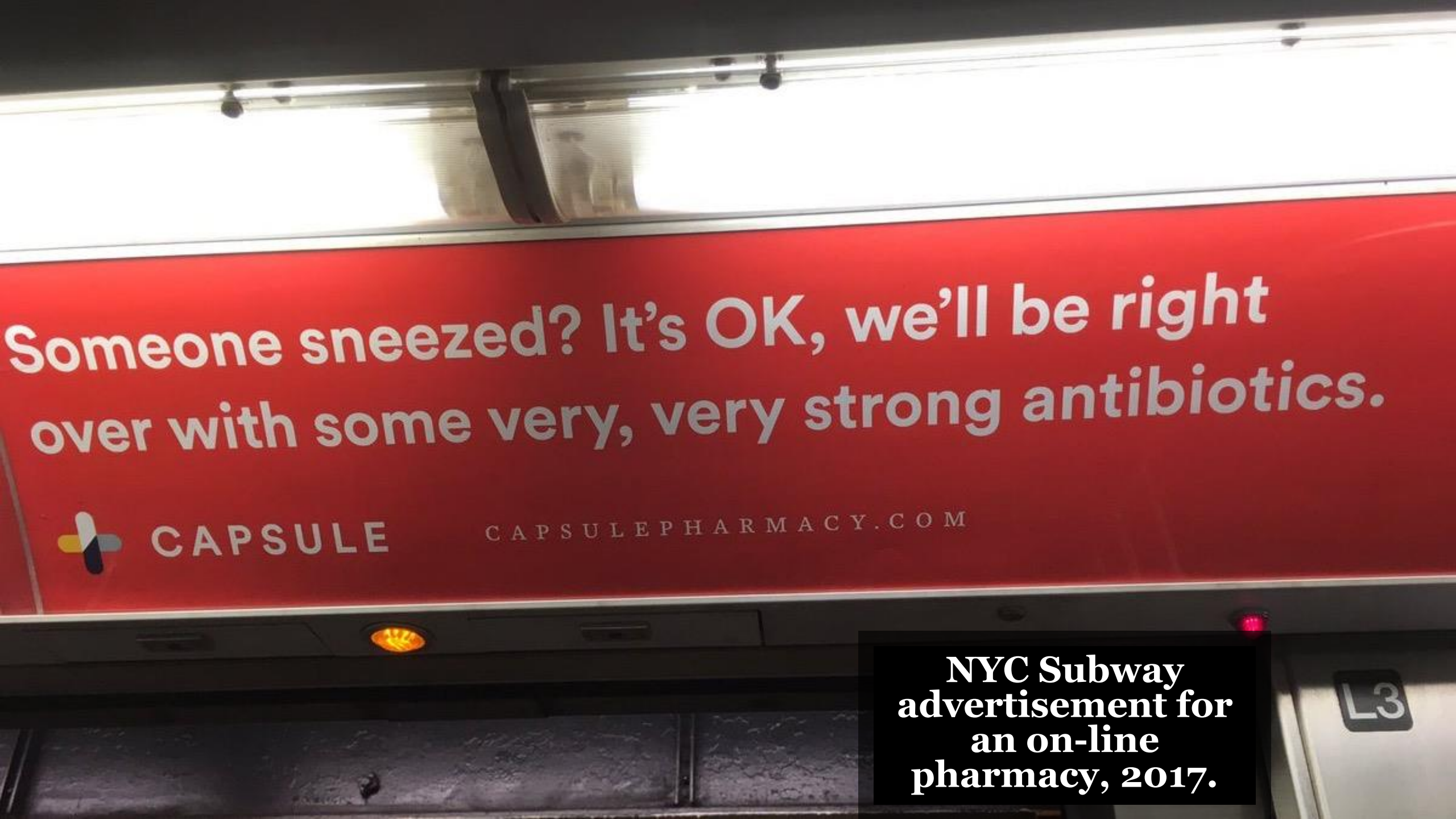
“Don’t forget to take a handful of our complimentary antibiotics on the way out.”

Antibiotics for URIs and patient satisfaction



"Few physicians achieved even the 50th percentile of satisfaction while maintaining low rates of antibiotic prescribing. **To reach the top quartile, a physician had to prescribe antibiotics at least half the time; almost all physicians above the 90th percentile had a rate of antibiotic prescribing greater than 75%."**

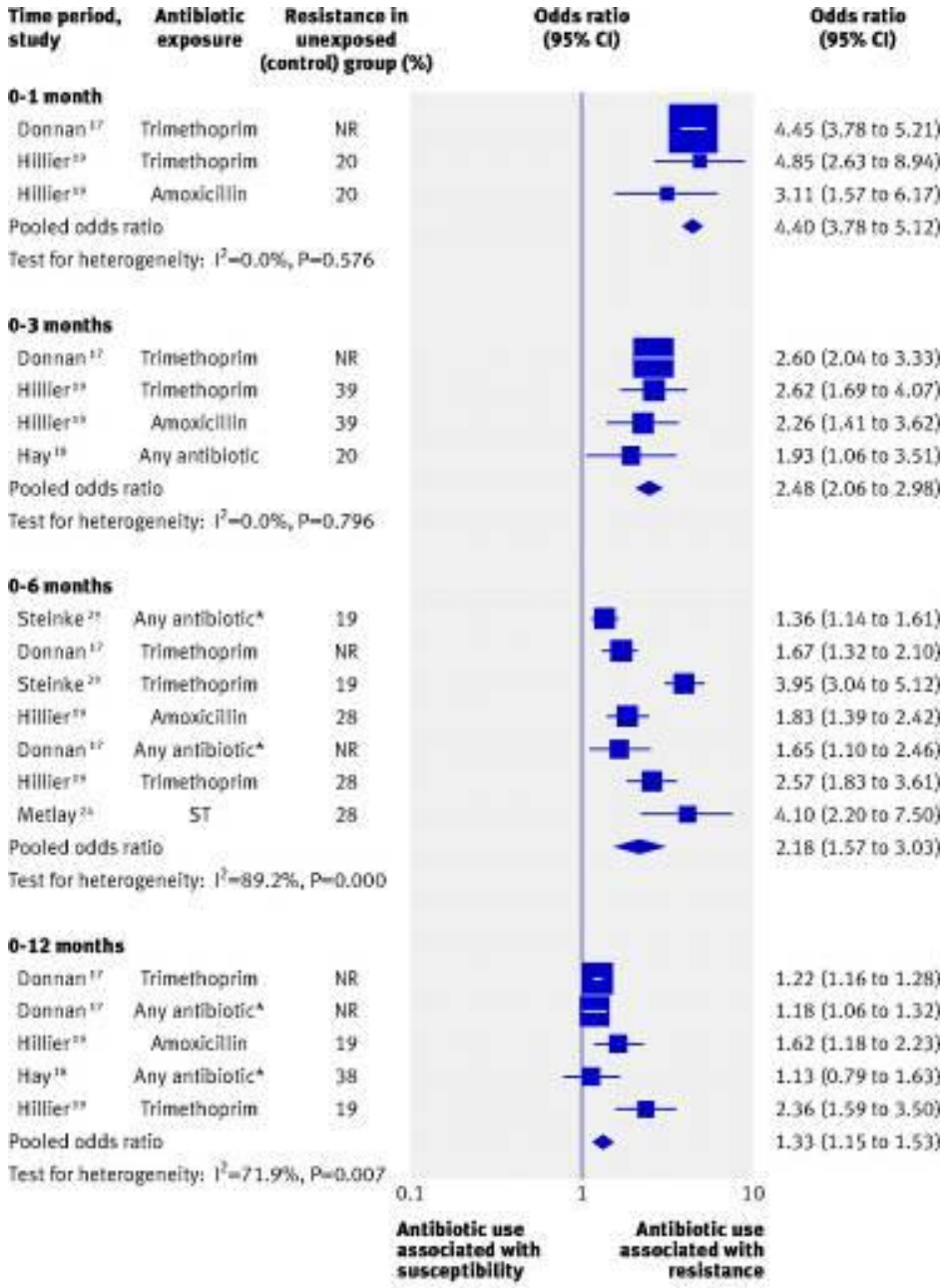
Martinez KA, et al. JAMA Int Med 2018.



NYC Subway advertisement for an on-line pharmacy, 2017.

Systematic review:

Antibiotic use in outpatients increases risk of resistance



Costelloe, C. et al. BMJ 2010;340:c2096

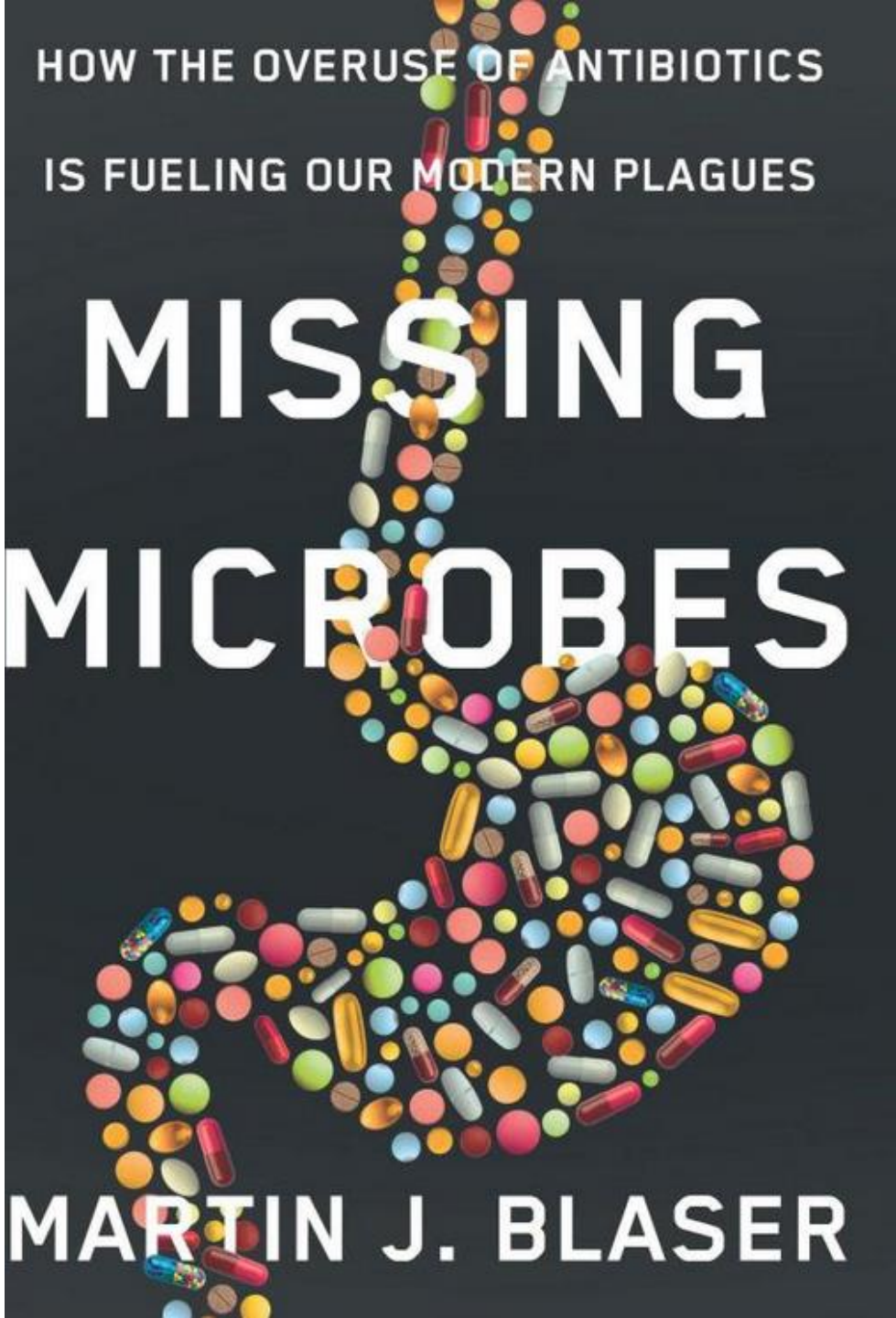
Result 02 Klebsiella species not K. pneumoniae or K. oxytoca
>100 x E6 cfu/L
This organism is phenotypically carbapenemase POSITIVE.
Genotypic confirmation to follow.

Result	K.sp.
Amikacin	R
Amoxicillin/Clavulana	R
Ampicillin	R
Ceftriaxone	R
Cephalexin	R
Ciprofloxacin	R
Ertapenem	R
Gentamicin	R
Meropenem	R
Nitrofurantoin	R
Piperacillin/Taz	R
Tobramycin	R
Trimethoprim/sulfa	R

Beware "Pirate" bacteria!

Selected conditions linked to microbiome alteration

Obesity
Type II diabetes
Asthma
Food allergies
Esophageal reflux
Gluten sensitivity



Question

In your clinical experience, are patients today more or less likely to request antibiotics than when you started practice?

A. More likely
B. Less likely
C. About the same

Case Presentations

24 y.o. female with dysuria, frequency

No systemic symptoms

Two prior UTIs that she can remember – received TMP-SMX once, developed total body rash

PE negative for fever or flank pain

Question

What treatment should you recommend?

A. Amoxicillin-clavulanate
B. Nitrofurantoin
C. Fosfomycin
D. Ciprofloxacin

Question

What treatment should you recommend?

A. Amoxicillin-clavulanate
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D. Ciprofloxacin

Important new UTI definitions

OLD DEFINITION

Uncomplicated UTI:
Acute cystitis in a healthy nonpregnant afebrile women with no diabetes and no urologic abnormalities

Acute Pyelonephritis:

Complicated UTI: Everything else

NEW DEFINITION

Complicated UTI: infection beyond the bladder

- Pyelonephritis
- CAUTI
- Febrile or bacteremic UTI

New recommendation: Seven days of therapy in patients clinically improving

Uncomplicated UTI: Everything else (in women or men)

Standard durations: e.g. Macrobid 5 days, Bactrim 3 days, Cipro 3 days

Images from *Noun Project*; see slide comments for attributions

IDSA Infectious Diseases Society of America

11

Slide: J Lazarus

Preferred initial regimens for UTI: IDSA Guidelines

First-line
Nitrofurantoin 100 mg BID x 5 days
TMP/SMX DS 1 PO BID x 3 days

Second-line:
Fosfomycin 1 gm x 1
Ciprofloxacin 250 mg BID x 3 days
Cephalexin 500 mg BID x 7 days

Effect of 5-Day Nitrofurantoin vs Single-Dose Fosfomycin on Clinical Resolution of Uncomplicated Lower Urinary Tract Infection in Women

Randomized clinical trial of nitrofurantoin 100 mg TID X 5 days vs fosfomycin 3 gm X 1

Primary endpoint: clinical response at day 28

N=513, median age 44

Clinical response to nitrofurantoin (70%) significantly better than fosfomycin (58%); microbiologic response also favored nitrofurantoin

Results raise questions about usefulness of fosfomycin for uncomplicated UTI

Huttner A, et al. JAMA 2018.

Fosfomycin

Phosphonic acid, inhibits bacterial cell wall synthesis

- FDA approval *E. coli* and *E. faecalis* uncomplicated cystitis

Susceptibility in urinary isolates:

- ~90.6% of *Enterococci*, 90-94% of *Enterobacteriaceae* (~95% *E. coli*, 90-95% *Klebsiella),* 89.7% PsA susceptible
- Correlates with treatment-response are limited

Response rates 3g dose: 58%-83%

Complicated cystitis: repeat dose every 24-72 hours x 2-4 doses

Barriers/limitations to use:

- Unusual formulation
- Limited data on non-*E. coli* and enterococcal isolates
- Cost – check direct payment pharmacies (e.g. Cost Plus)

Hirsch. *Int J Antimicrob Agents* 2015; 46 :642
Liu. J Microbiol Immunol Infect 2011; 44:364

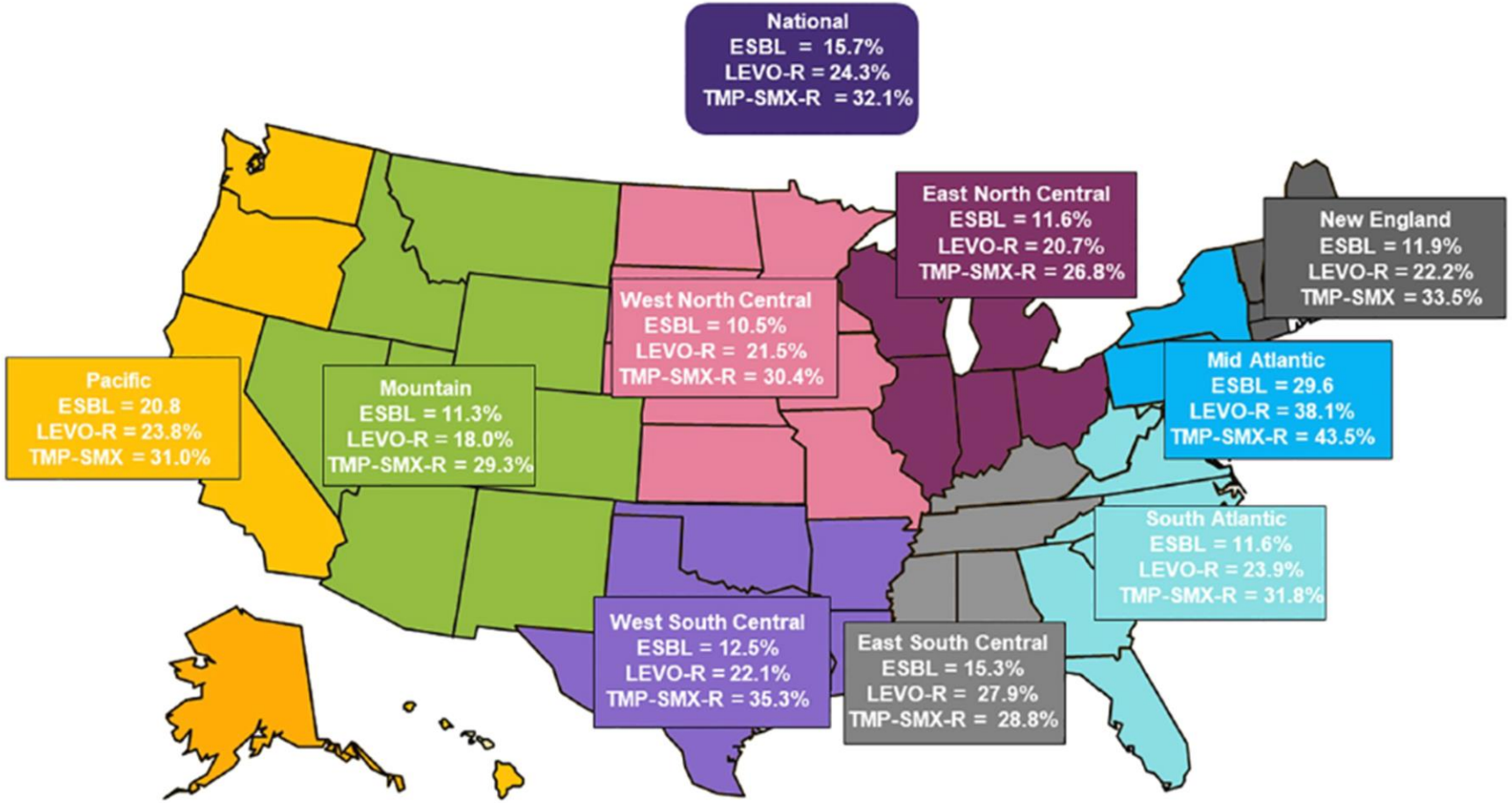

Fig 1. National and regional prevalence of ESBL phenotypes, levofloxacin- and trimethoprim-sulfamethoxazole-resistant phenotypes among 1831 isolates of *E. coli* from UTIs in the USA in 2017. ESBL = extended spectrum β-lactamase, LEVO-R = levofloxacin-resistant, TMP-SMX-R = trimethoprim-sulfamethoxazole-resistant.

Urinary E. coli susceptibilities

Newer agents for uncomplicated UTIs

Pivmecillinam (Pivya), gepotidacin (Blujepa), and sulopenem etzadroxil and probenecid (Orlynvah)

All non-inferior to standard-of-care treatments.

Limited availability in pharmacies – may need special order.

May provide an additional options for people with UTIs resistant to standard treatments.

A Blujepa, in the wild!

Ross JDC et al. The Lancet. 2025

Case Presentations

28 y.o. man with “spider bite”

Noted painful nodules approximately 1 week ago.
Started himself on oral cephalexin left over in his medicine cabinet.
Worried it might be a spider bite – did not actually see a spider.
Two days later, he is no better: T = 100.8; two nodules noted (buttock, inner thigh), largest 5 x 8 cm with surrounding erythema and purulent drainage

Question

In addition to incision and drainage and other local care, how would you manage?

A. Oral trimethoprim-sulfamethoxazole
B. Oral clindamycin
C. Oral linezolid
D. No antibiotics

Question

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Non-prescription antibiotic use is common

Comprehensive survey of published literature including 31 high-quality studies.

Up to two-thirds of those surveyed reported non-prescription antibiotic use

Storage of antibiotics for future use: 14% to 48%
Intention to use antibiotics in the future if "needed": 25%

Risk factors: Easy access through international on-line sources, difficulty with healthcare system

Grigoryan L et al., *Annals Int Med* 2019.

Skin and soft-tissue infections

Most community-acquired cases caused by *Staph aureus*, beta-hemolytic streptococci

- Staph: abscesses
- Strep: cellulitis, lymphangitis, erysipelas

Special cases:

- DM with ulcer: GNR, anaerobes – but also staph, strep
- Bites: *P. multocida*, *Capnocytophaga* spp, mixed flora
- Water: *Aeromonas*, *Vibrio* spp. (esp. with liver disease), *M. marinum*
- Thorns: *Sporothrix schenkii*

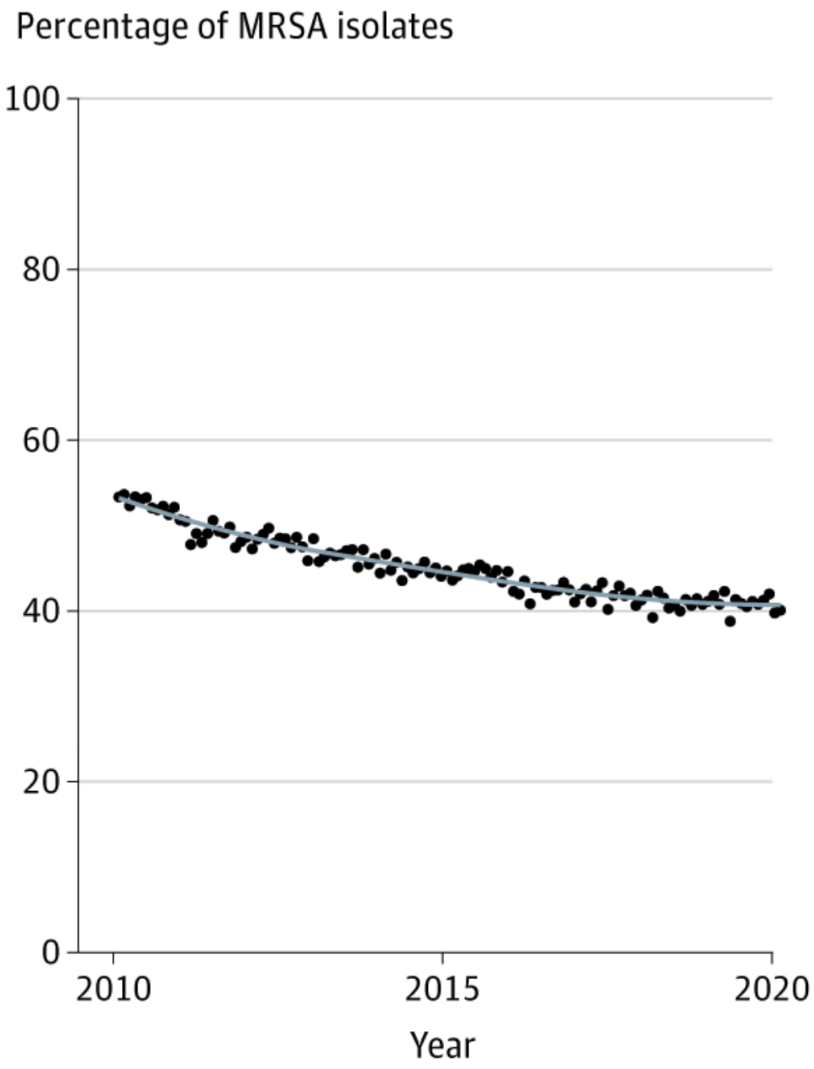
Golan Y. Clin Infect Dis. 2019 Apr 8;68(Suppl 3):S206-S212.

Community-acquired MRSA

Early 2000s: Increased reports of community outbreaks of skin and soft tissue infections (SSTI) due to MRSA

2010s: Most common cause of microbiologically-confirmed soft tissue infection in the USA

2020s: Rates of MRSA slowly declining – no one knows why



Moran G, et al, NEJM 2006:355:666-74. JAMA 2012;308:50-59. Carrel M, et al. JAMA Netw Open. 2024;7(6):e2417199.

Is it a spider bite?

IF YOU THINK YOU HAVE A SPIDER BITE, IT MIGHT ACTUALLY BE AN INFECTION THAT NEEDS MEDICAL ATTENTION.

When in doubt, check it out.

www.cdc.gov/mrsa

Summary: Approach to skin abscess

Obtain cultures for confirmation

Low threshold for incision and drainage

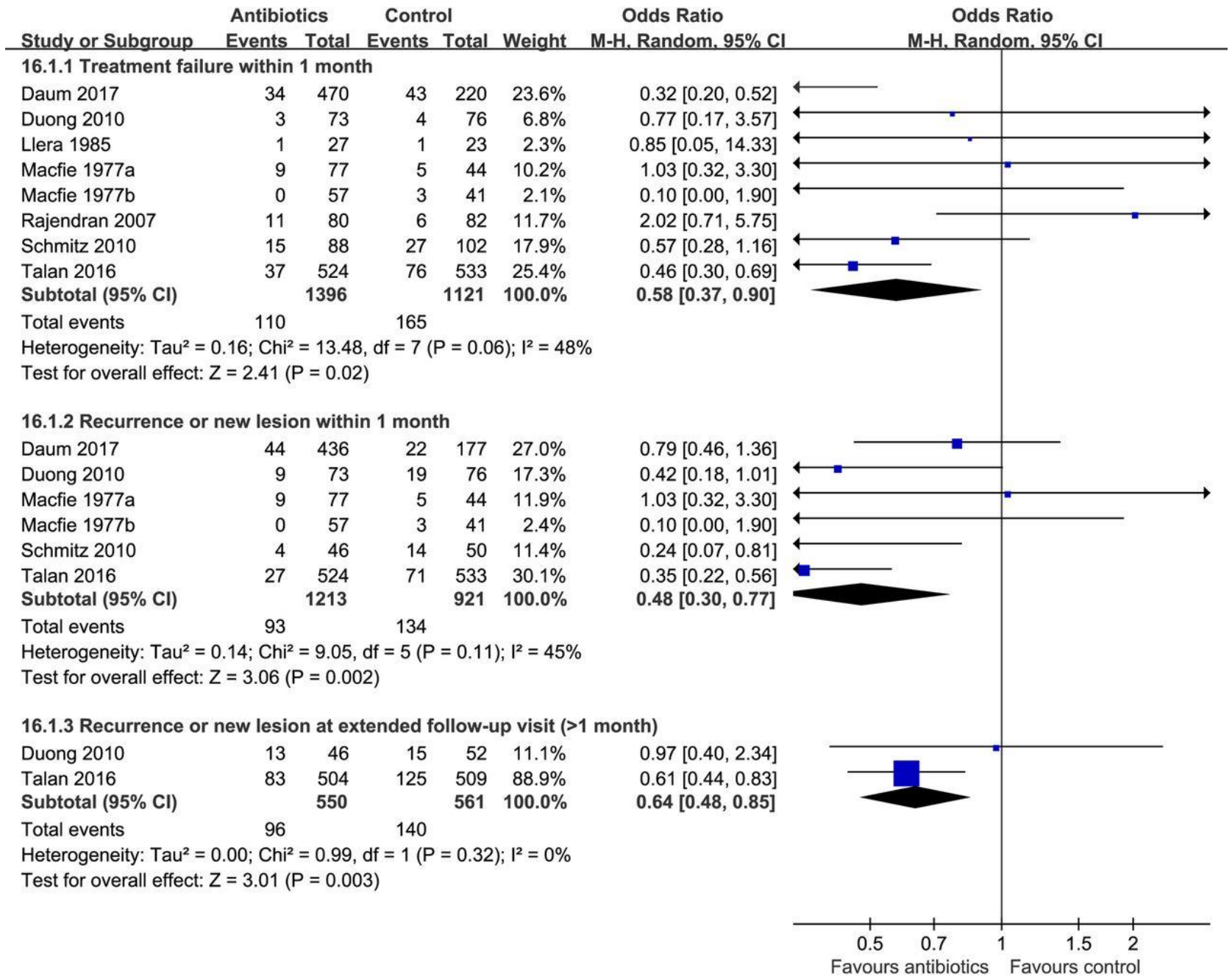
Empiric treatment:

- **TMP-SMX, or doxycycline,** or minocycline, or clindamycin (caveat re: rising resistance – 40%), or linezolid
- IV options include vancomcyin, daptomycin, telavancin, oritavancin, dalbavancin

Antibiotics strongly recommended for large abscesses (5 cm), systemic illness, immunocompromised hosts, diabetes, face/hands/genitalia – maybe for all?

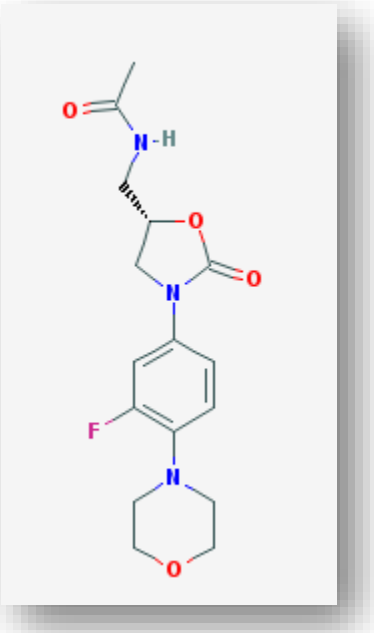
Duration: 5-14 days

NEJM 2008; 359:1063-1067; Liu Clin Infect Diseases 2011; N Engl J Med 2014; 370:1039-1047; Lake JG Clin Infect Dis 2020;71: 661-663.



Wang W, et al. BMJ Open 2018.

Linezolid – An important option for outpatient care



Active against staph (including MRSA) and strep
Excellent oral absorption and tissue penetration
Dose: 600 mg twice daily
Adverse effects – main risk factor is duration of therapy

- Asthenia (the “blahs”)
- Cytopenia
- Neuropathy – peripheral and optic (may be irreversible)

Drug interactions: Potential for serotonin syndrome when coadministered with SSRIs (not an absolute contraindication)
Price down substantially due to generics – usually!

Recurrent MRSA is a very challenging problem!

Very Recurrent MRSA: Strategies for prevention

Topical antibiotics: Mupirocin nasal ointment anterior nares BID

Systemic antibiotics: Bactrim 1 DS BID, +/- rifampin 300 mg PO BID – all for 7-10 days

- Not endorsed in guidelines, but anecdotally useful in some cases

Household contacts (including pets) cultured/treated

Local measures

- COVER WOUNDS
- Bathe for 10 minutes; 1 tsp bleach/gallon of water
- Using a bath sponge, lather armpits, groin, anus, and under the breasts with chlorhexadine topical antiseptic (Hibiclens scrub) after draining bath water
- Shower Hibiclens off

Frequent laundering of towels, sheets, clothing

Daum RS, et al. N Engl J Med 2007;357:380; Liu Clin Infect Dis 2011.

“Never, ever, think outside the box.”

Animal bites: Special considerations

Pasturella multocida

- Early onset (1-3 days) cellulitis following cat (75%) or dog (50%) bites
- *Not* susceptible to cephalexin, dicloxacillin, clindamycin

Capnocytophaga species – can cause overwhelming sepsis in those with asplenia, alcoholism, liver disease

Bartonella ("cat scratch") – lymphadenopathy, fever 7-14 days after cat bite or scratch*

Anaerobes

Empiric therapy

- **Preferred: amoxicillin-clavulanate**
- Alternatives: doxycycline or TMP/SMX or moxifloxacin or cefpodoxime plus metronidazole or clindamycin

*treatment of choice: azithromycin

47 y.o. man with 7 days of cough

Previously-healthy non-smoker, well until 1 week prior when he developed sore throat, rhinorrhea

Now with 3 days of progressive cough, in AM productive of thick sputum, “yellow-green”

Requests “Z-pack”, which he says always works great for him

Exam: normal

Question

How would you manage?

A. Azithromycin
B. Doxycycline
C. Levofloxacin
D. A “delayed” prescription for one of the above
E. No antibiotics

Question

How would you manage?

A. Azithromycin
B. Doxycycline
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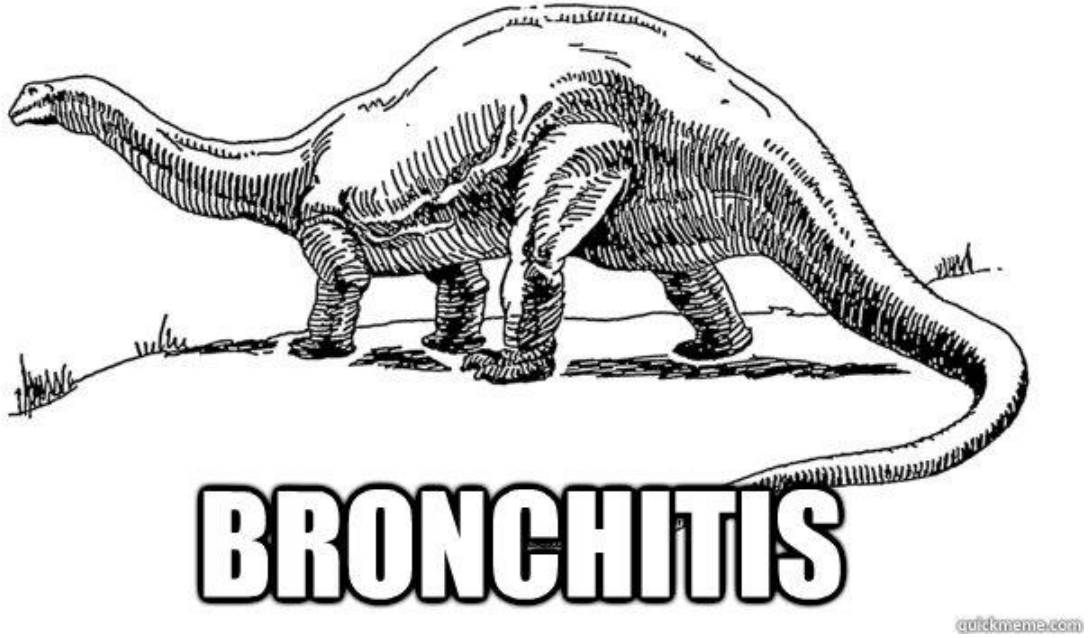
E. No antibiotics

Choose your language carefully!

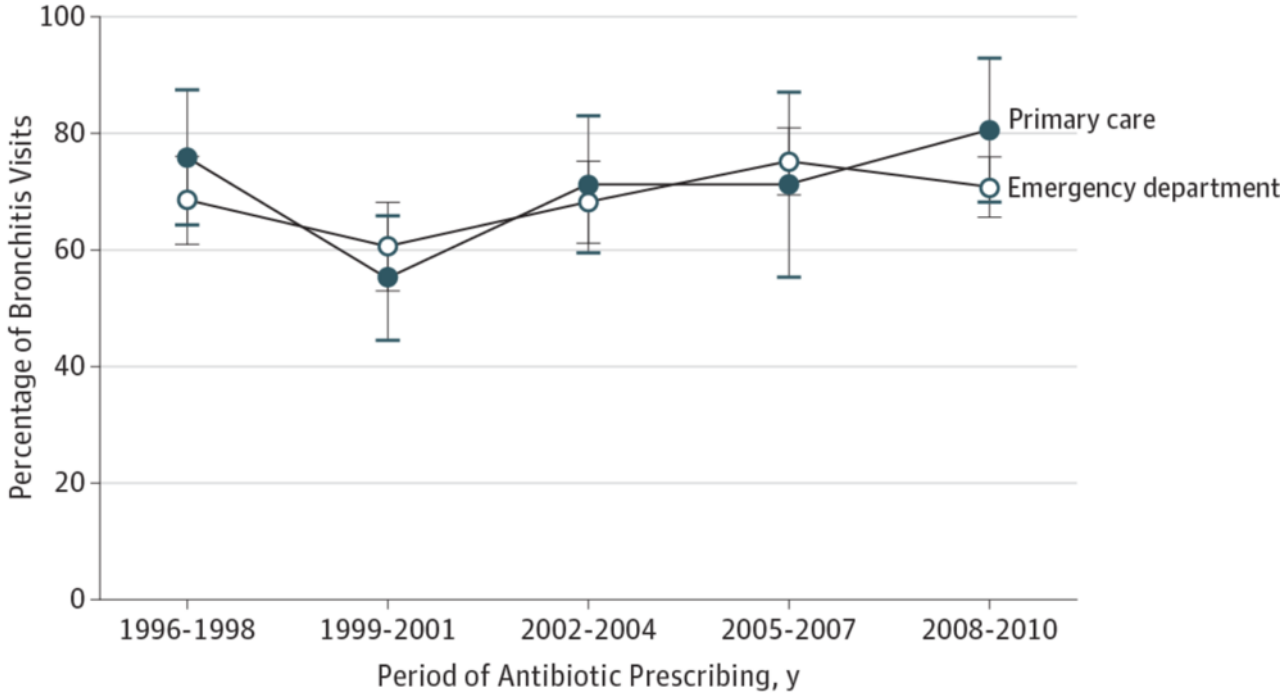


Survey of 459 patients regarding **treatment dissatisfaction** if no antibiotic given for “cough with grey phlegm for 1 week”, and illness called:

- “Bronchitis” 26%
- “Viral illness” 17%
- “Cold” 13%

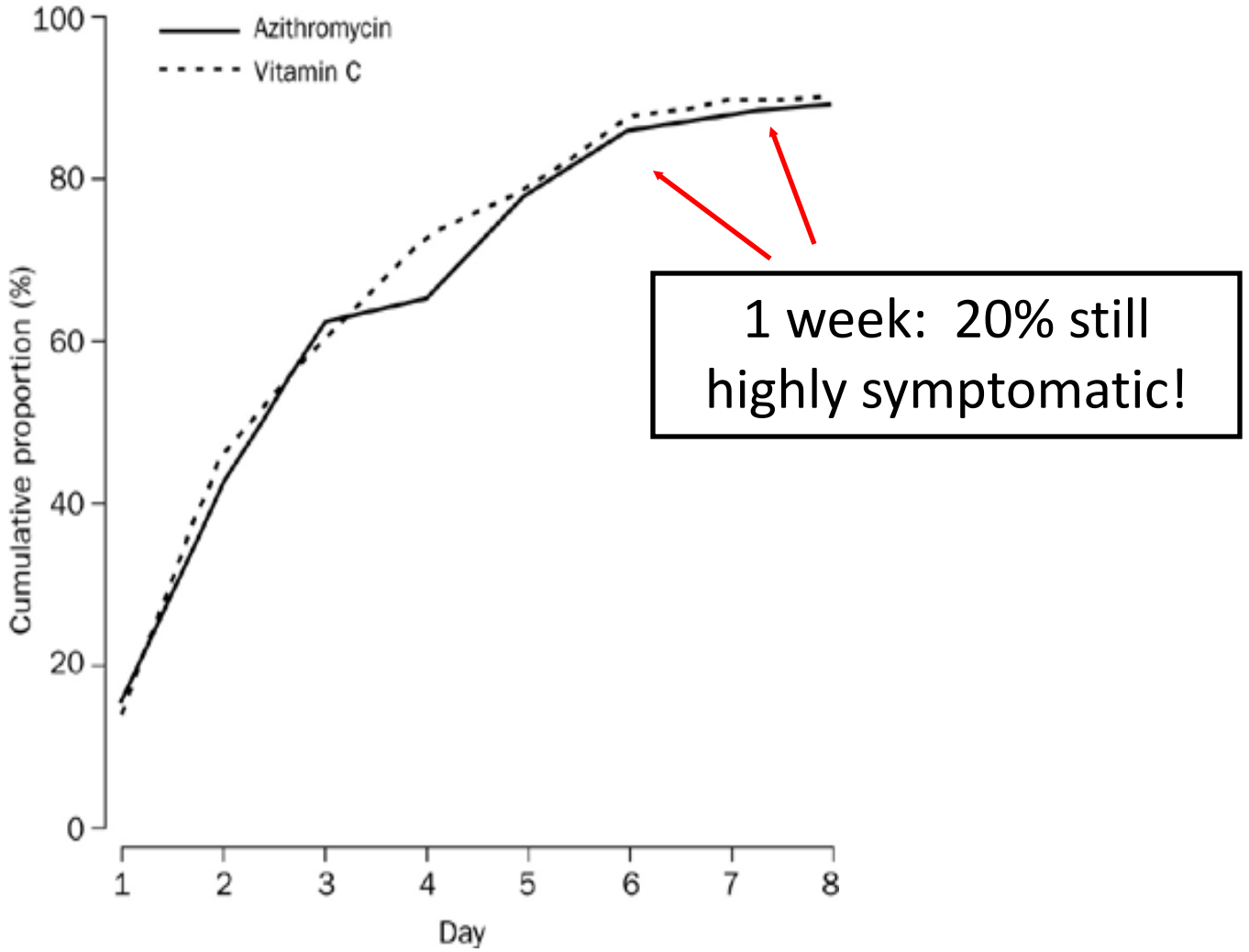
J Am Board Fam Pract. 2005 Nov-Dec;18(6):459-63.

Antibiotic prescribing for bronchitis is common



No. of sampled visits					
Primary care	168	167	185	217	234
Emergency department	293	401	499	462	527

JAMA. 2014;311(19):2020-2022.



Proportion of pts who had returned to their usual daily activities.

Evans T, Lancet 2002;359:1648.

Taking an Antibiotic or Not?

ACUTE RESPIRATORY TRACT INFECTIONS (ARI)

Diagnostic Decision Support Tool

STEPS 1 and 2: Complete the Diagnostic Decision Support Tool according to your patient's ARI to estimate his/her probability of bacterial infection.
STEP 3: Share your estimate of probability with your patient.
STEP 4: Communicate the therapeutics options regarding the use of antibiotics (taking or not taking) and the benefits and risks associated with each option.
STEP 5 : Clarify the values and preferences of your patient regarding each option.
STEP 6: Evaluate the decisional comfort of your patient regarding his/her decision.

ACUTE RHINOSINUSITIS

To differentiate patients with an ACUTE RHINOSINUSITIS due to a bacteria from those whose ACUTE RHINOSINUSITIS is due to a virus

STEP 1

Tick all the key symptoms and signs identified in your patient with symptoms of rhinosinusitis

INITIAL QUESTION
Duration of symptoms
☐ < 10 days ☐ ≥ 10 days

ADDITIONAL QUESTIONS
☐ Double sickening (worsening after improving)
☐ Colored nasal discharge
☐ Facial/sinus pain
☐ Maxillary tooth pain
☐ No response to decongestants

ADDITIONAL SIGNS
☐ Purulent discharge in nasal cavity (middle meatus) and/or throat
☐ Sinus pain on **one side**
☐ Abnormal transillumination (**one side**)

ALERTS

- Persistent high fever
- Severely ill
- Orbital swelling or erythema
- Diplopia, proptosis or other neurologic signs

STEP 2

Encircle the clinical probability (%) of a bacterial acute rhinosinusitis according to signs and symptoms of patients assuming a prevalence of 15%

Additional symptoms/signs	<10 days	>10 days*
4+	30%	95%
3	15%	75%
2	5%	50%
1	2%	25%
0	1%	5%

*Adults 7-10 days; children 10-14days

STEP 3 to 6 on the Shared Decision Making Support Tools

Legare F, et al CMAJ 2012 (online appendix).

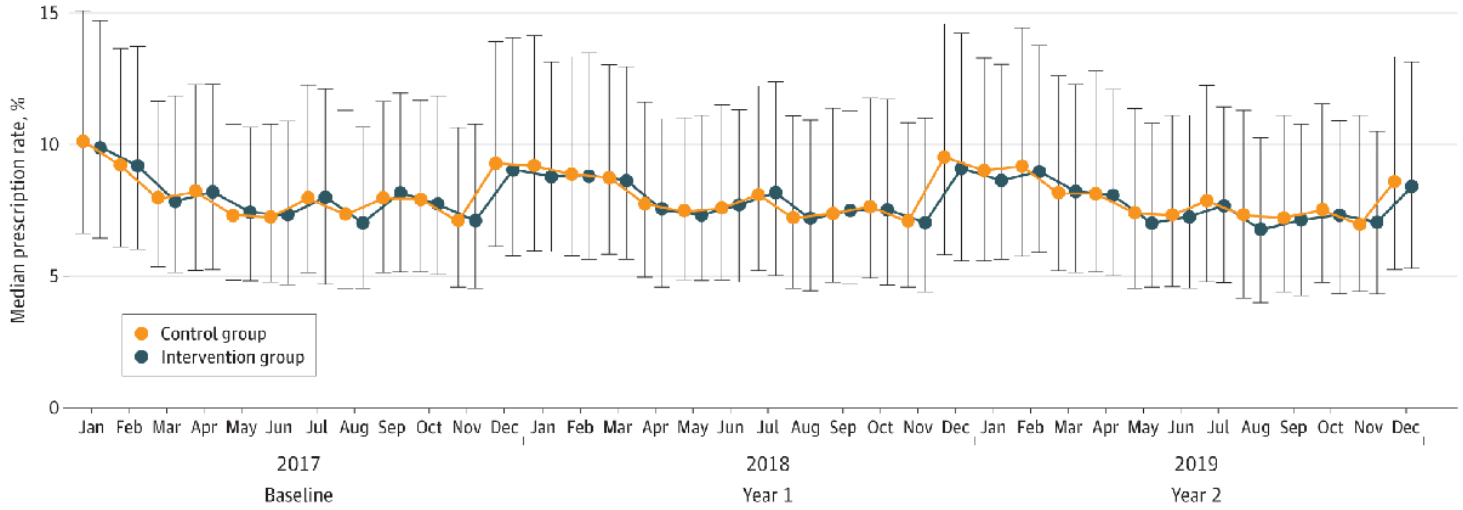
What about provider feedback?

Does *automated* quarterly antibiotic prescribing feedback with peer benchmarking reduce antibiotic among primary care physicians?

Randomized trial of 3426 PCPs over 2-year period, with special focus on top 75% prescribers of antibiotics

Results – no significant effect

- Feedback group: 8.2 Rx/100 visits
- Control: 8.4 Rx/100 visits



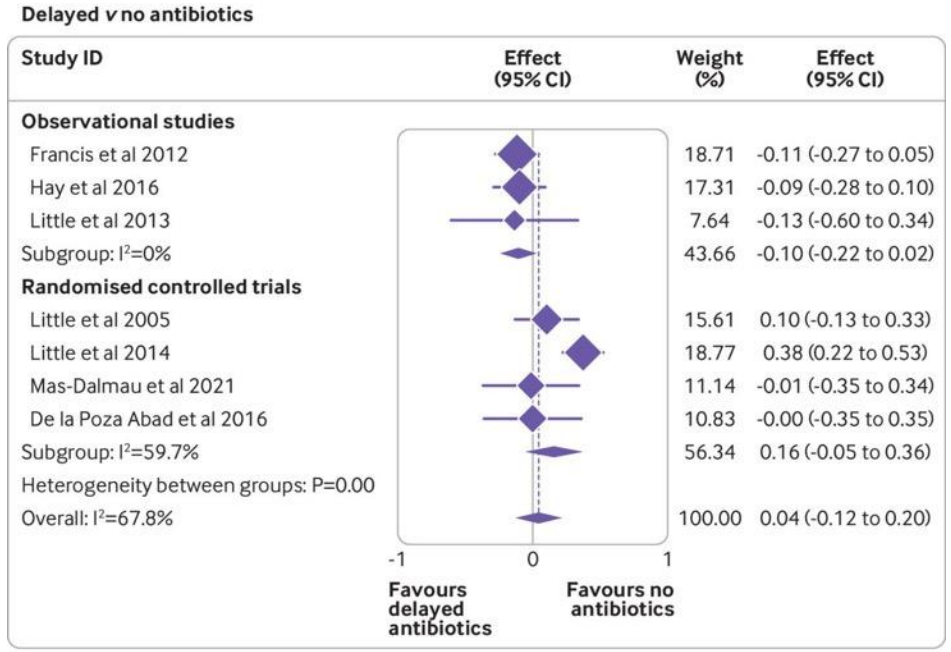
Aghlmandi S, et al. JAMA Intern Med 2023;183(3):213-220.

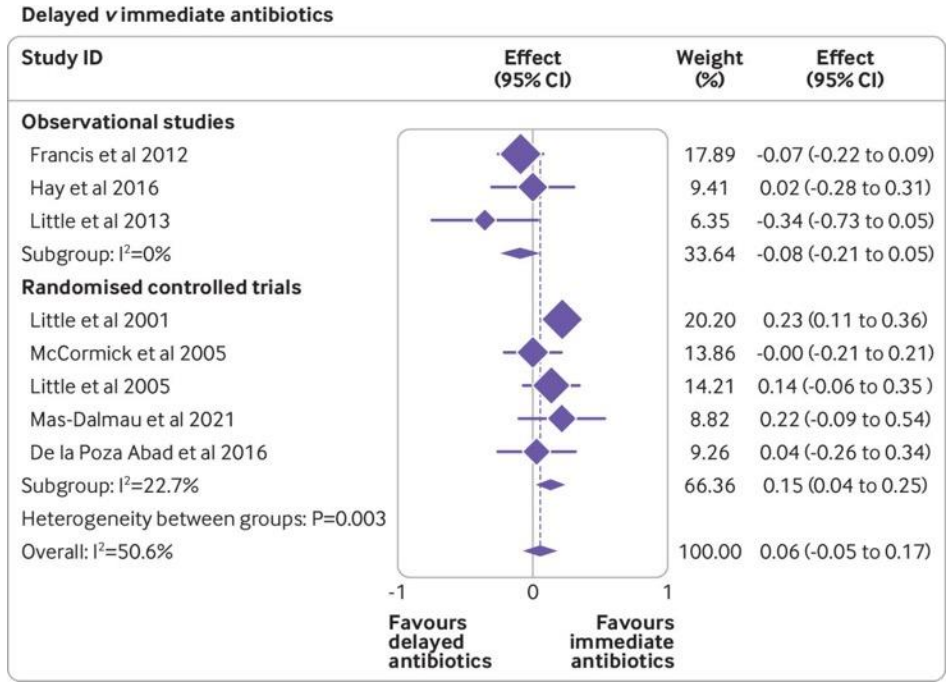
Delayed Antibiotic Prescribing

Strategy: Prescribe an antibiotic but advise not to start unless their condition deteriorates or fails to improve after a set period

Systematic review of clinical trials and cohorts

- No adverse clinical outcomes (figure)
- Compared with immediate antibiotics – reduces antibiotic exposure
- Compared with no antibiotics – reduces subsequent visits, increases patient satisfaction





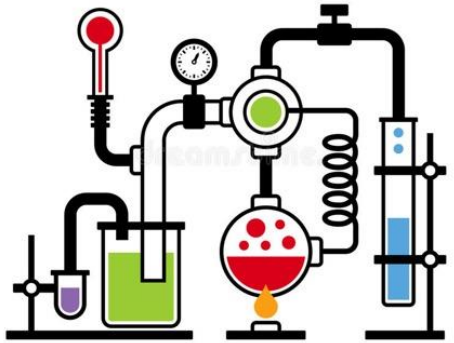
Stuart B, et al. BMJ 2021;373:bmj.n808

Can lab tests help?

C-reactive protein – non-specific marker of inflammation, rises more with bacterial infections

Procalcitonin

Rapid viral diagnostic tests – increasingly available



Some support the use of these tests in reducing antibiotic exposure – but point-of-care availability and rapid turnaround are critical for implementation

Cals JW et al. Ann Fam Med 2010; Rhee C et al OFID 2016; Keske S, et al Eur J Clin Microbiol Infect Dis. 2018.

58 y.o. woman with fever, cough, pleuritic pain

Also experiences a shaking chill

PMHx: Diabetes, obesity, HTN, CHF

PE: T 101.8, decreased breath sounds on right; CXR: dense RLL infiltrate

Patient requests “Z-pack”, which she says always works great for her

Question

How would you manage?

A. Amoxicillin-clavulanate
B. Azithromycin
C. Ciprofloxacin
D. Levofloxacin

Question

How would you manage?

A. Amoxicillin-clavulanate
B. Azithromycin
C. Ciprofloxacin
D. Levofloxacin

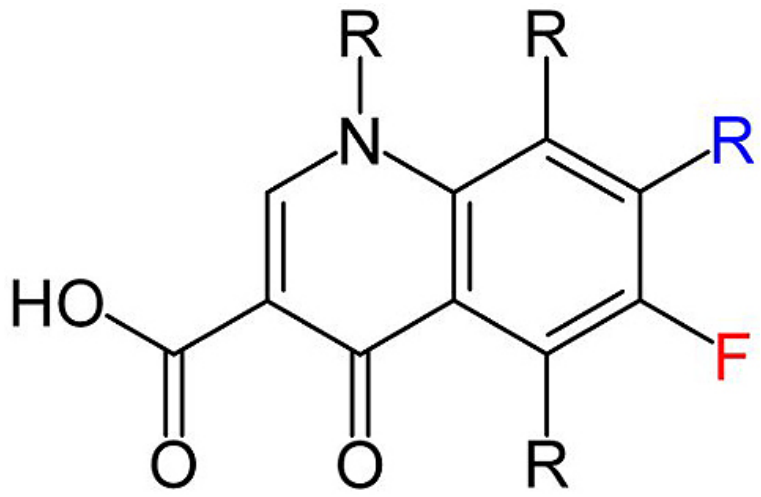
Ambulatory treatment of pneumonia – Patients with comorbidities

Combination therapy:

- amoxicillin-clavulanate or cephalosporin *AND*
- azithromycin or doxycycline

OR

Monotherapy with a respiratory fluoroquinolone (levofloxacin or moxifloxacin)



Metlay JP, et al. AJRCCM 2019.

New: Diagnosis and Management of Community-acquired Pneumonia

Should lung ultrasound be considered a reasonable alternative to chest x-ray for diagnosis in adults with suspected community-acquired pneumonia?

Should adults with community-acquired pneumonia who test positive for a respiratory virus be treated with empiric antibacterial therapy?

Should adults with community-acquired pneumonia who reach clinical stability be treated with less than 5 days of antibiotics?

Should adults who are hospitalized with community-acquired pneumonia be treated with corticosteroids?

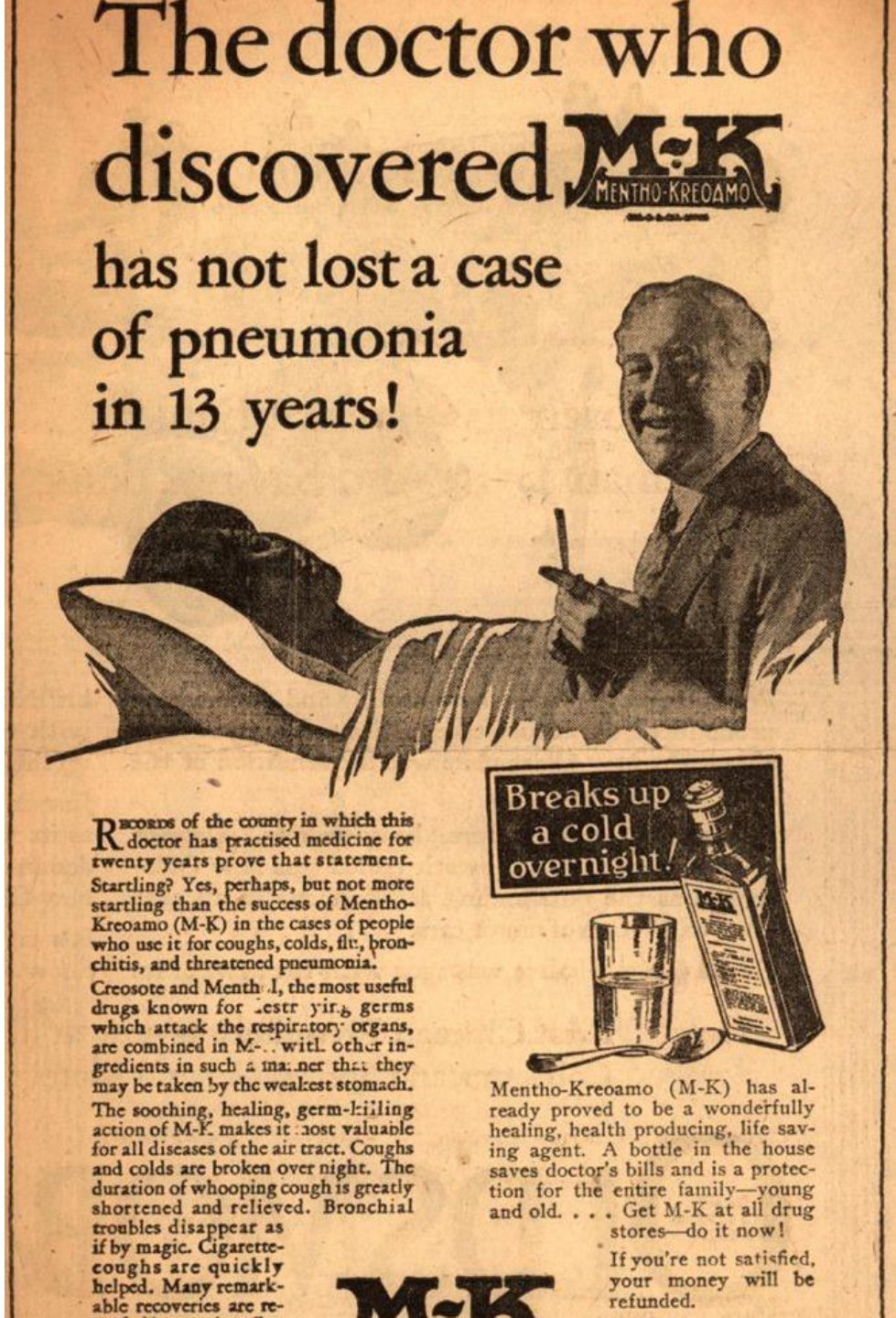
Not addressed: Antibiotic selection

Jones BE, et al. AJRCCM 2025.

“Respiratory” fluoroquinolones

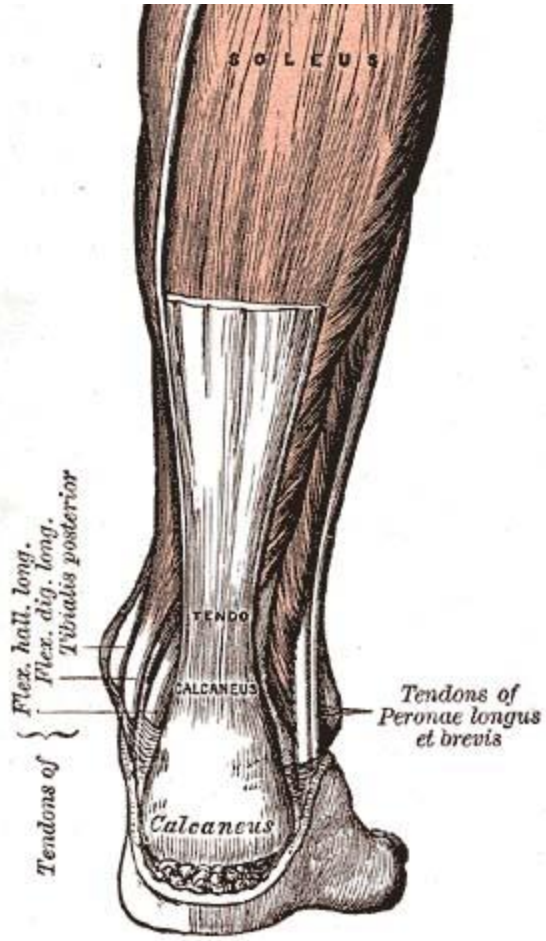
Levofloxacin and moxifloxacin – not ciprofloxacin (poor *Strep pneumo* activity and lung penetration)
Antibacterial spectrum ideally suited to treatment of community-acquired pneumonia

- *S. pneumoniae*
- *H. influenzae*
- Pathogens of “atypical” pneumonia: *Mycoplasma pneumoniae, Legionella pneumophila, Chlamydia pneumoniae*



Quinolones: Notable adverse effects

Tendinitis/tendonopathy, tendon rupture
QT prolongation
C difficile
Neuropsychiatric reactions, neuropathy
Allergic reactions, including urticaria, anaphylaxis
Photosensitivity
Drug interaction: Mg, Fe, Ca, Al: decrease FQ absorption
“Fluoroquinolone toxicity syndrome”



PERSONAL HEALTH | SEPTEMBER 10, 2012, 12:01 AM | 511 Comments

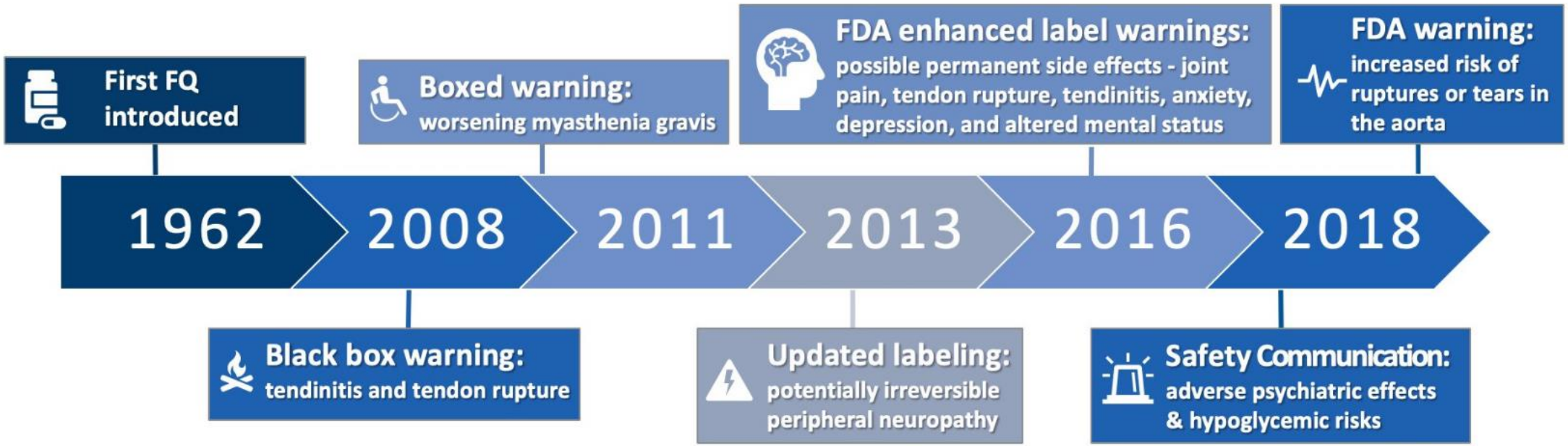
Popular Antibiotics May Carry Serious Side Effects

By JANE E. BRODY

Yvetta Fedorova

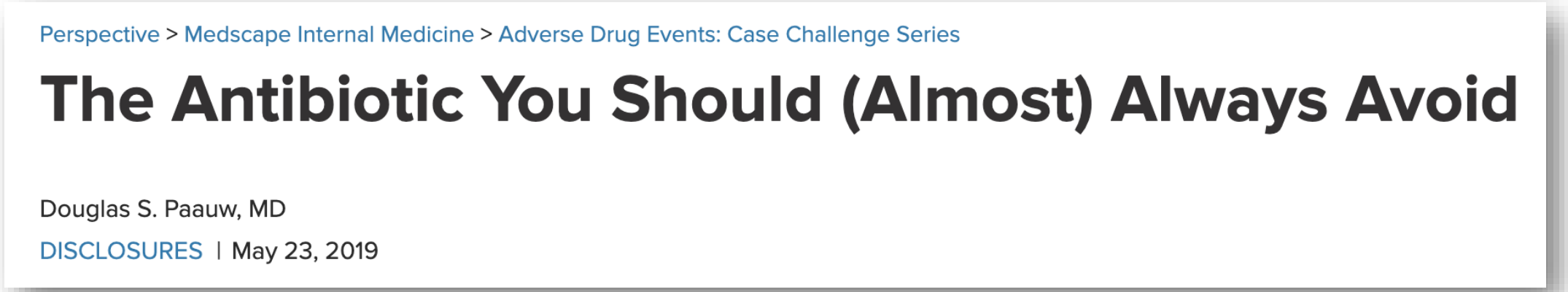
New York Times, Sept 10, 2012

Safety concerns with fluoroquinolones



MedWatch FDA Safety Report, Updated Dec 20 2018.
Graphic courtesy Travis Jones, PharmD.

Have we overreacted to the potential toxicity of quinolones?



Perspective > Medscape Internal Medicine > Adverse Drug Events: Case Challenge Series

The Antibiotic You Should (Almost) Always Avoid

Douglas S. Paauw, MD

DISCLOSURES | May 23, 2019

Medscape.com, May 23, 2019.

Which fluoroquinolone?

	GNR	GPC	Anaerobes	Metabolism	Comments
Ciprofloxacin	***	*	*	Renal	Preferred for GU infections; poor *Strep pneumo* coverage
Levofloxacin	**	**	*	Renal	Preferred for respiratory tract infections
Moxifloxacin	*	***	**	Hepatic	No activity vs. *Pseudomonas*

GNR = gram negative rods; GPC = gram positive cocci; relative activity denoted by number of *

Efficacy of Doxycycline for Mild-to-Moderate Community-Acquired Pneumonia in Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Get access ›

Systematic review of prospective clinical trials

6 deemed evaluable, including 834 patients, with comparators macrolides or fluoroquinolones

Doxycycline comparable to both approaches

Should it be added to treatment guidelines?

Doxycycline

Choi S, et al. Clin Infect Dis 2023;76:683-91.

Some comments about antibiotic therapy duration

"I understood why I needed to complete the full course, of course. What I didn't understand was why a full course took precisely seven days. Why not six, eight or nine and a half? Did the number seven correspond to some biological fact about the human digestive tract or the life cycle of bacteria?"

Professor Daniel Gilbert, "Magic by Numbers," New York Times, Oct 16, 2010

http://www.nytimes.com/2010/10/17/opinion/17gilbert.html?_r=2&scp=1&sq=numbers+antibiotic&st=nyt

The Reality: Only ID Doctors Know the Optimal Length of Antibiotic Therapy

… but now I'll share the secret formula

Mystery Solved!
How to Determine the Duration of Antibiotic Therapy

1. Choose a multiple of 5 (fingers of hand) or 7 (days of week).
2. Is the problem relatively mild or improving rapidly? Then choose 5 or 7.
3. Is it REALLY mild, so that it would get better on its own if you did nothing? Then break the rule, and go with 3.
4. Is it a serious problem? 10-14 days minimum.
5. Patient not doing better after initial course? Extend treatment, again using multiples of 5 or 7.
6. Bone or heart valve? Four weeks (28 days) or 6 weeks (42 days) – but never 5 weeks, because the 5's and 7s would cancel each other.
7. Avoid these lengths of therapy: 4, 9, 11, 13, 3.14159265 …

JOURNAL ARTICLE

Short-course Antibiotic Therapy—Replacing Constantine Units With "Shorter Is Better" FREE

Noah Wald-Dickler, Brad Spellberg

Clinical Infectious Diseases, Volume 69, Issue 9, 1 November 2019, Pages 1476–1479,
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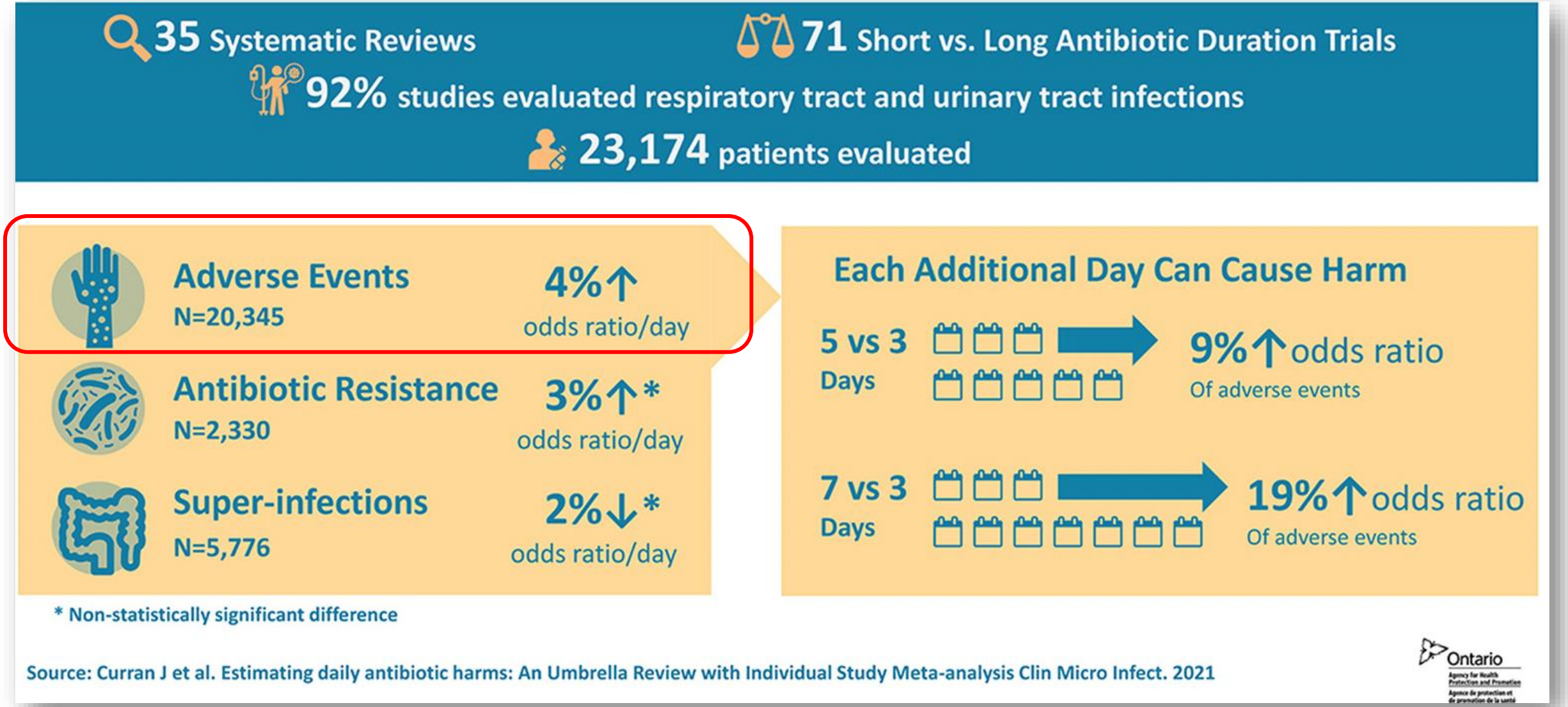
Clinical Infect Dis 2019.


35 Systematic Reviews
71 Short vs. Long Antibiotic Duration Trials
92% studies evaluated respiratory tract and urinary tract infections
23,174 patients evaluated
Adverse Events
N=20,345
4%↑
odds ratio/day
Antibiotic Resistance
N=2,330
3%↑*
odds ratio/day
Super-infections
N=5,776
2%↓*
odds ratio/day
Each Additional Day Can Cause Harm
5 vs 3
Days
9%↑odds ratio
Of adverse events
7 vs 3
Days
19%↑odds ratio
Of adverse events
* Non-statistically significant difference
Source: Curran J et al. Estimating daily antibiotic harms: An Umbrella Review with Individual Study Meta-analysis Clin Micro Infect. 2021
Ontario

Antibiotics: Take-home points

Growing data support the importance of limiting antibiotic use

- Resistance
- Alteration in the microbiome

Strategies to reduce use in clinical practice include shared decision making and delayed antibiotic prescribing

Linezolid access and use should increase with reduced cost

Fluoroquinolones may rarely cause severe side effects, but still useful

Duration of therapy – shorter usually better!

Thank you!