Vaccines to control antimicrobial resistance

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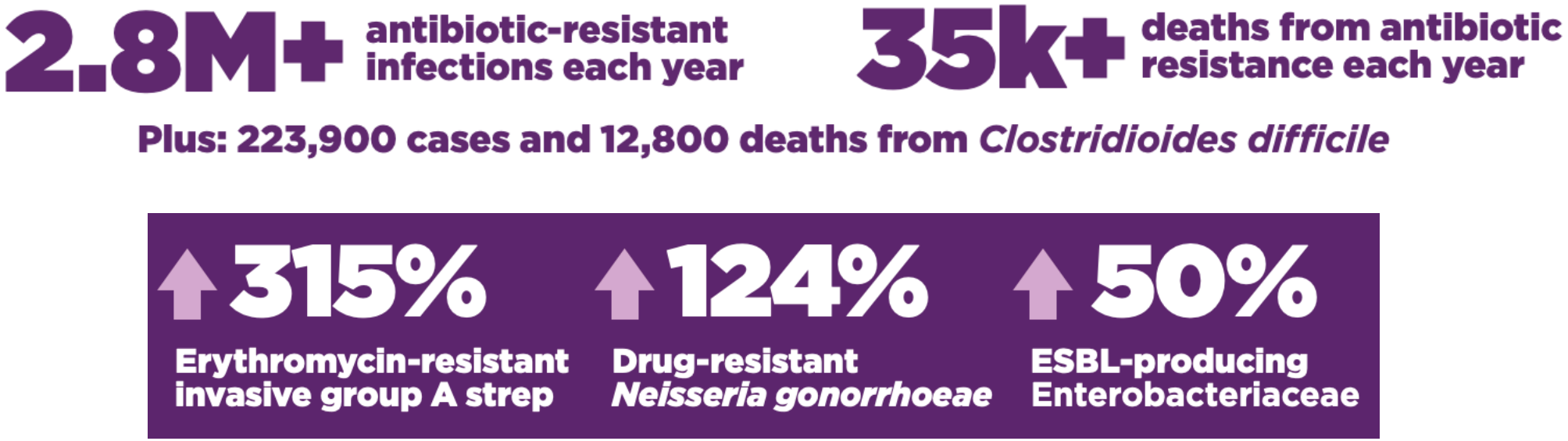
Why do we care about AMR?

KLEBSIELLA PNEUMONIAE

Antibiotic	Interpretation
Amikacin	Resistant
Ampicillin	Resistant
Aztreonam	Resistant
Cefazolin	Resistant
Cefepime	Resistant
Ceftriaxone	Resistant
Ciprofloxacin	Resistant
Ertapenem	Resistant
Gentamicin	Resistant
Imipenem	Resistant
Levofloxacin	Resistant
Meropenem	Resistant
Nitrofurantoin	Resistant
Piperacillin-tazobactam	Resistant
Tetracycline	Intermediate
Trimethoprim/sulfamethoxazole	Resistant

AMR is an urgent threat

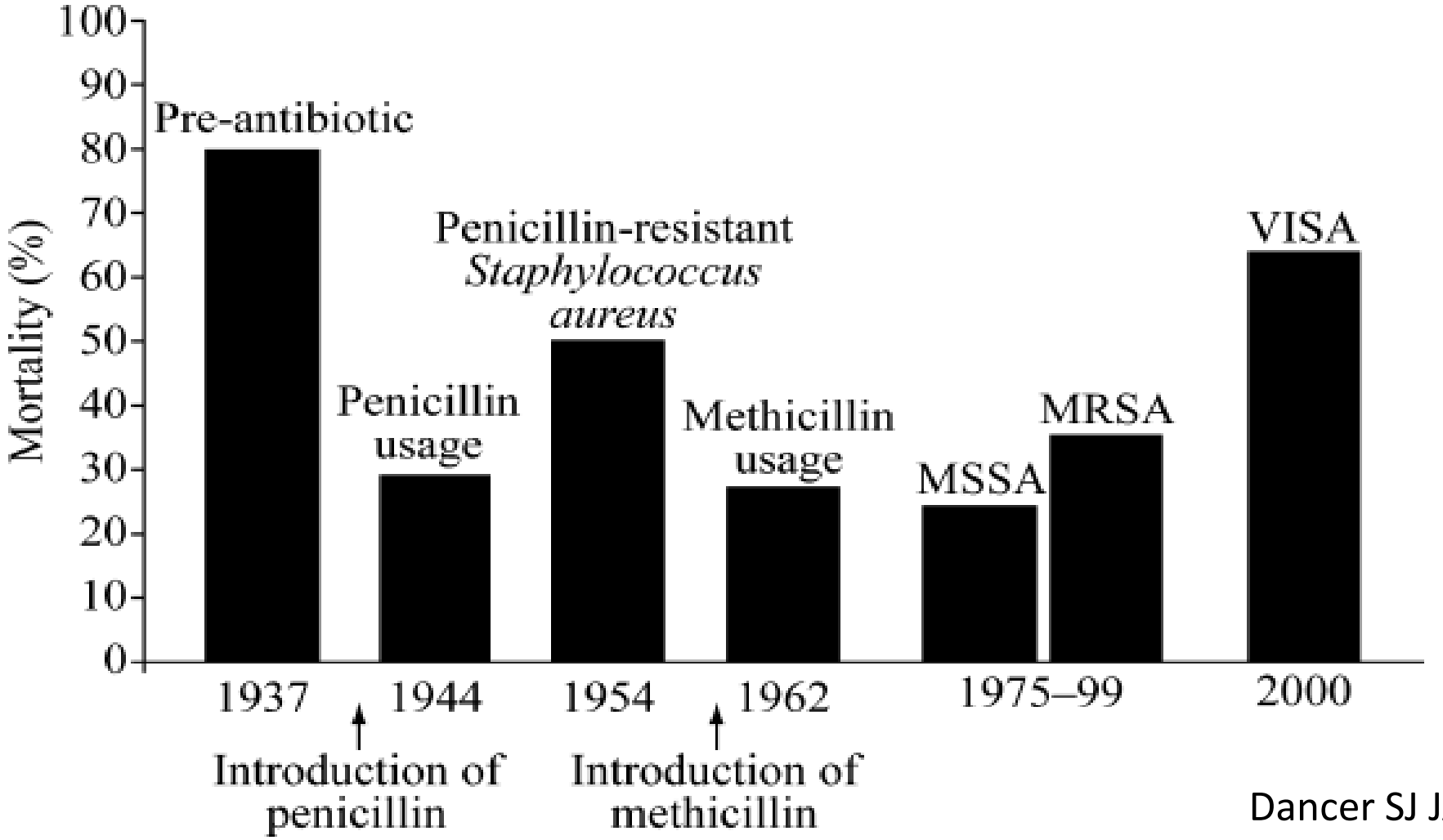


CDC AR Threats, 2019

Why do we care about AMR?

- Increased cost of treatment
- Increased morbidity / mortality from resistant pathogens
- Increased morbidity / mortality from treatment of resistant pathogens

Mortality rates of staphylococcal bacteremia over time



Dancer SJ JAC 2008

Nephrotoxicity Associated with Intravenous Colistin (Colistimethate Sodium) Treatment at a Tertiary Care Medical Center

Joshua D. Hartzell,[1] Robert Neff,[2] Julie Ake,[1] Robin Howard,[3] Stephen Olson,[2] Kristopher Paolino,[1] Mark Vishnepolsky,[2]

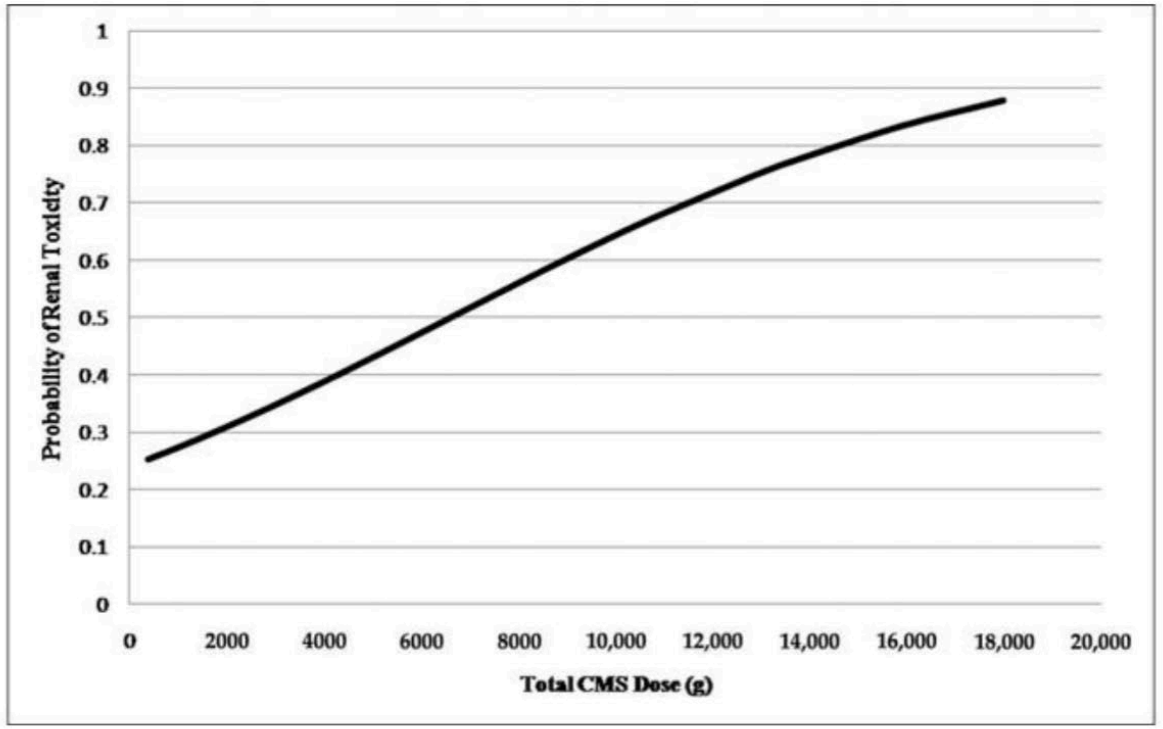
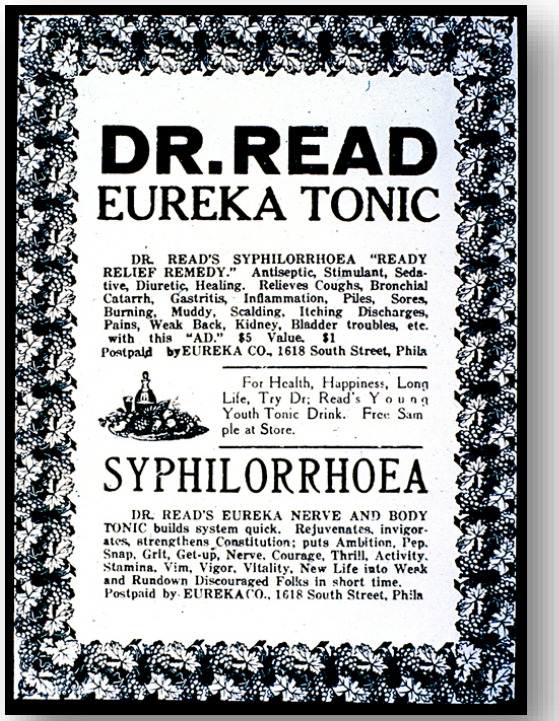


Figure 1. Risk of renal toxicity on the basis of total colistimethate sodium (CMS) dose. Note that renal toxicity was defined by meeting risk, injury, or failure criteria (table 1).

Gonorrhea therapy in the pre-antibiotic era



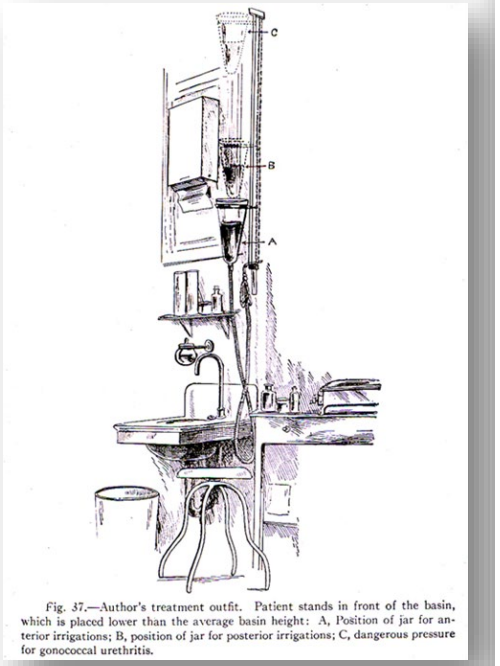


Fig. 37.—Author's treatment outfit. Patient stands in front of the basin, which is placed lower than the average basin height: A, Position of jar for anterior irrigations; B, position of jar for posterior irrigations; C, dangerous pressure for gonococcal urethritis.

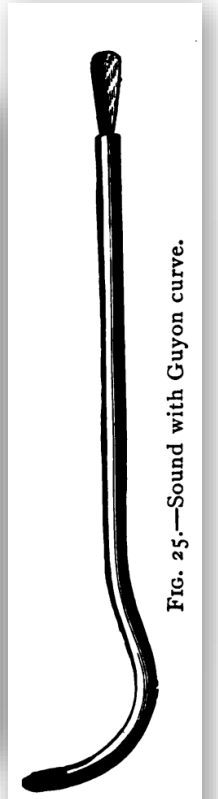


FIG. 25.—Sound with Guyon curve.

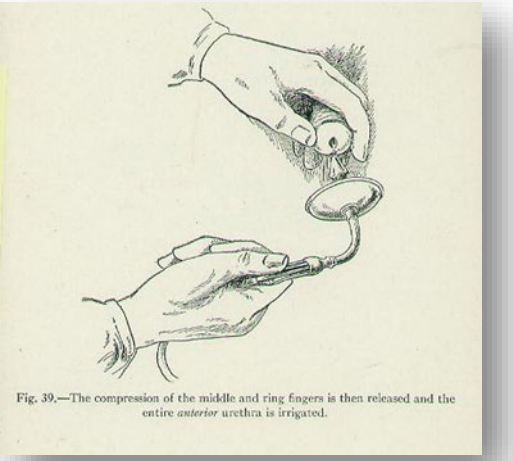


Fig. 39.—The compression of the middle and ring fingers is then released and the entire *anterior* urethra is irrigated.

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FEVER THERAPY FOR GONOCOCCIC INFECTIONS

ARTHUR U. DESJARDINS, M.D.
LOUIS G. STUHLER, M.D.
AND
WALTER C. POPP, M.D.
ROCHESTER, MINN.

For generations, gonococcic urethritis has been treated mainly by irrigating, or by injecting into the urethra various chemical solutions that were thought to have an antiseptic or germicidal effect. The gamut of the so-called urethral germicides has been run from the old standbys potassium permanganate and the "nonirritating" silver proteins argyrol and protargol to another group of miracle workers, the aniline dyes, mercurochrome, gentian violet and acriflavine. Each group and

of gonorrhea in which the urethral discharge had spontaneously disappeared during an attack of pneumonia but recurred after the fever had subsided. Neisser and Scholtz[4] always found it difficult to cultivate the gonococcus in cases in which patients had a fever. Luys[5] in 1917 made a similar observation after a patient of his had had an attack of mumps during which the temperature had attained 40 C. (104 F.). Culver[6] recorded a similar case in 1917 in which the urethral infection was cured after the patient had had a four-day bout of malaria, with a temperature of 40.5 C. (104.9 F.). He claimed that a sudden rise of temperature to 39 C. (102.2 F.) was sufficient to destroy the gonococcus. However, the experience of others, such as Nobl[7] and Nicoll,[8] was different.

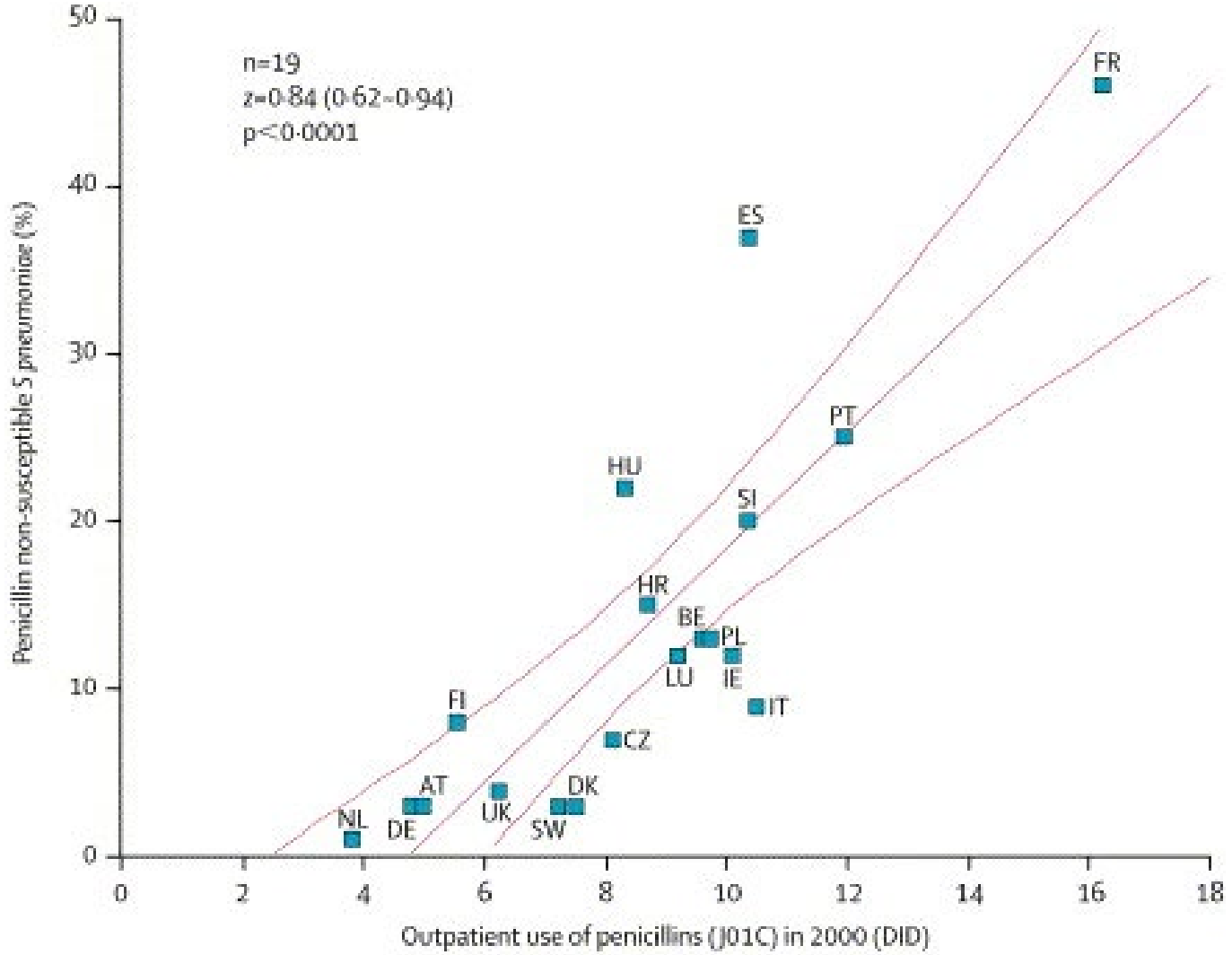
Bacteriologists have long known that Neisseria gonorrhoeae can best be isolated and cultivated at a temperature of 37 C. (98.6 F.), and that the organism does not grow so well at temperatures greater than 38 C. (100.4

Strategies to address antimicrobial resistance

Strategies to address antimicrobial resistance

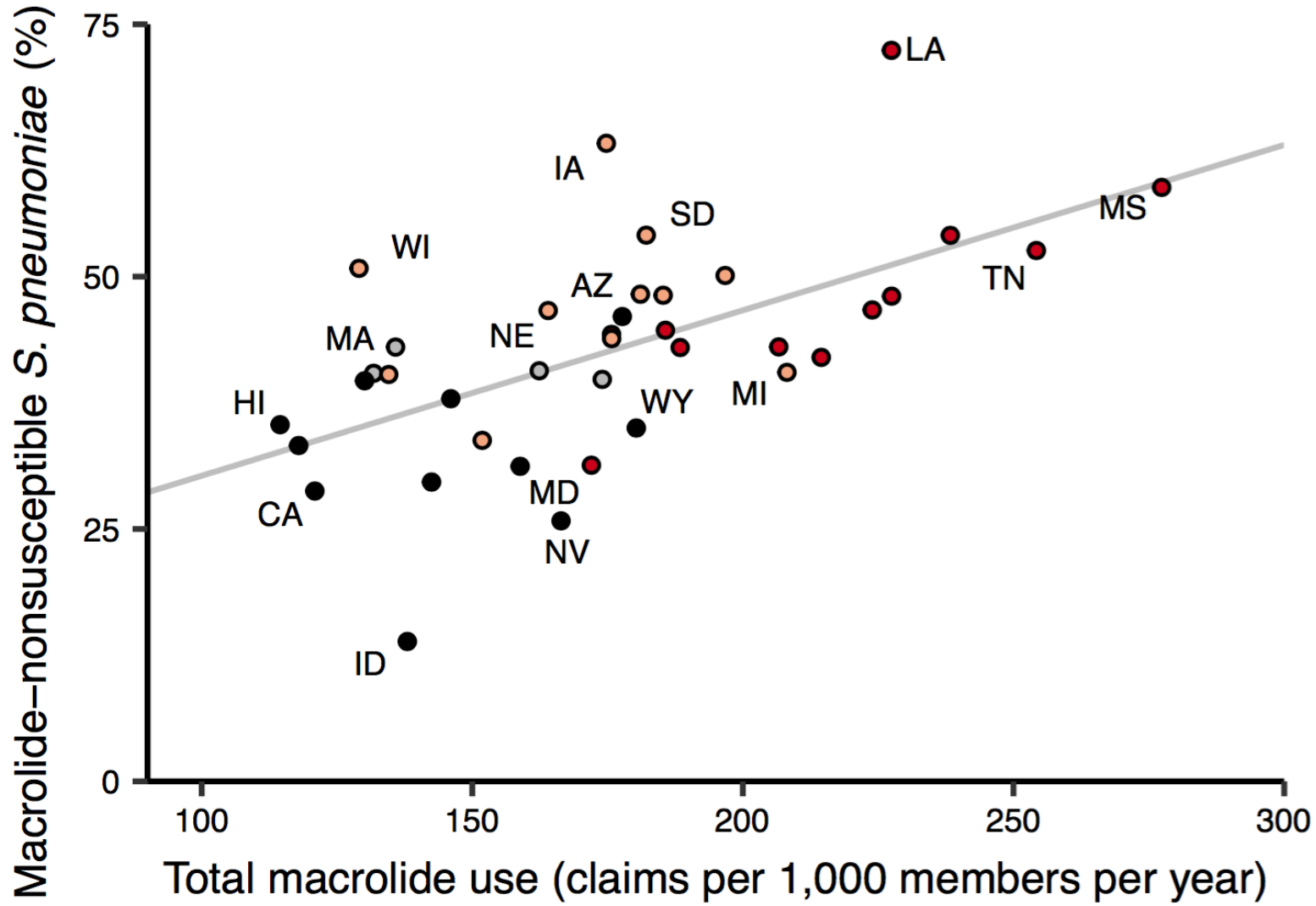
Don’t use antimicrobials

Relationship between antibiotic use and resistance



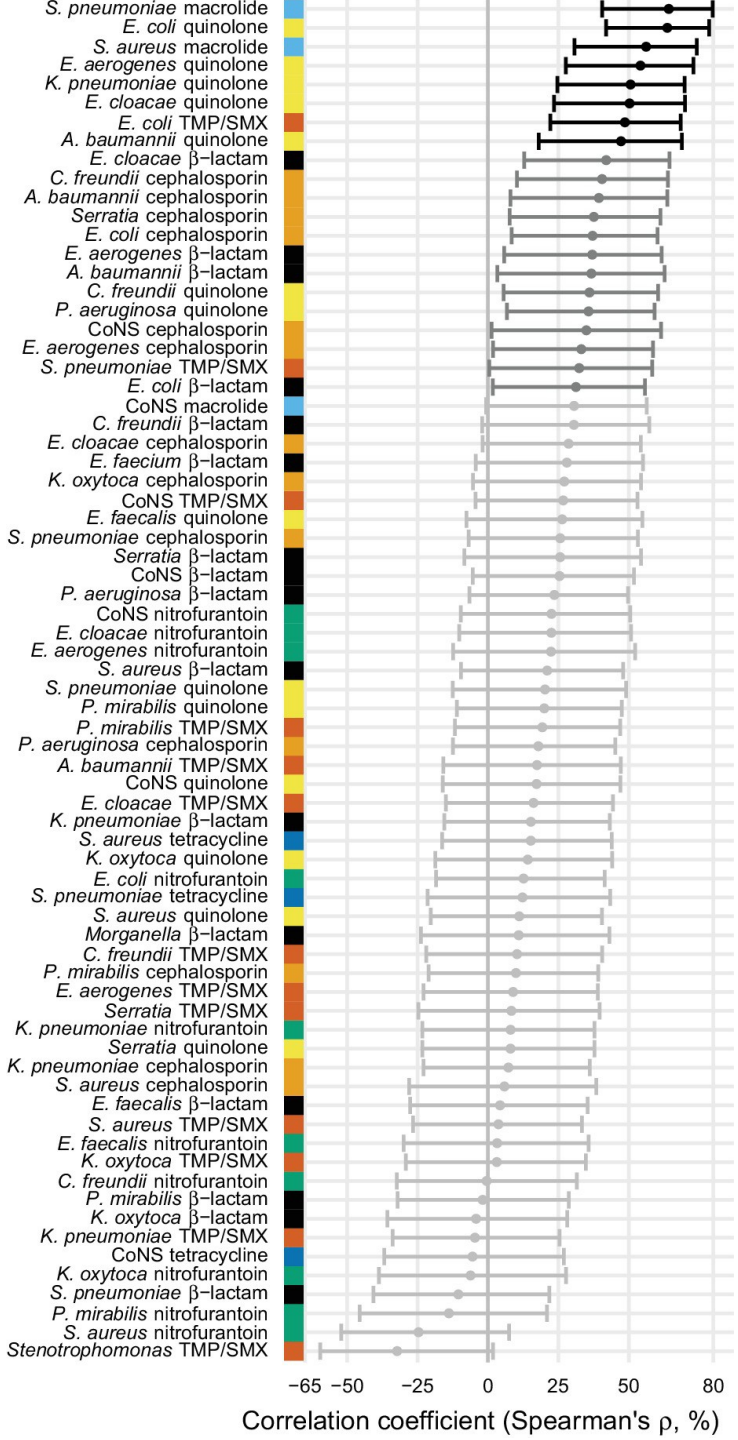
H. Goossens et al., *Lancet* 2005

S. pneumoniae macrolide non-susceptibility in the US, 2014



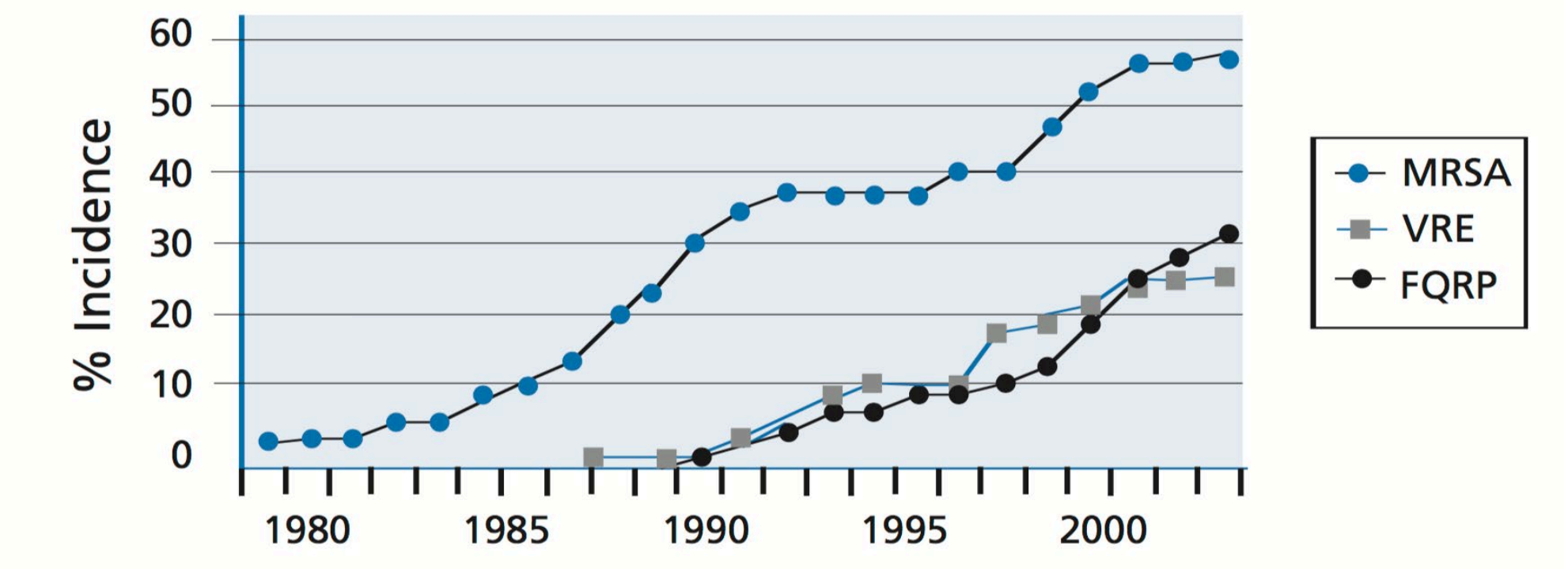
Olesen *et al.*, *eLife* 2018

Across 72 antibiotic-bacteria pairs in the US, most correlations are positive



Olesen *et al.*, *eLife*, 2018

Expectation that resistance increases over time

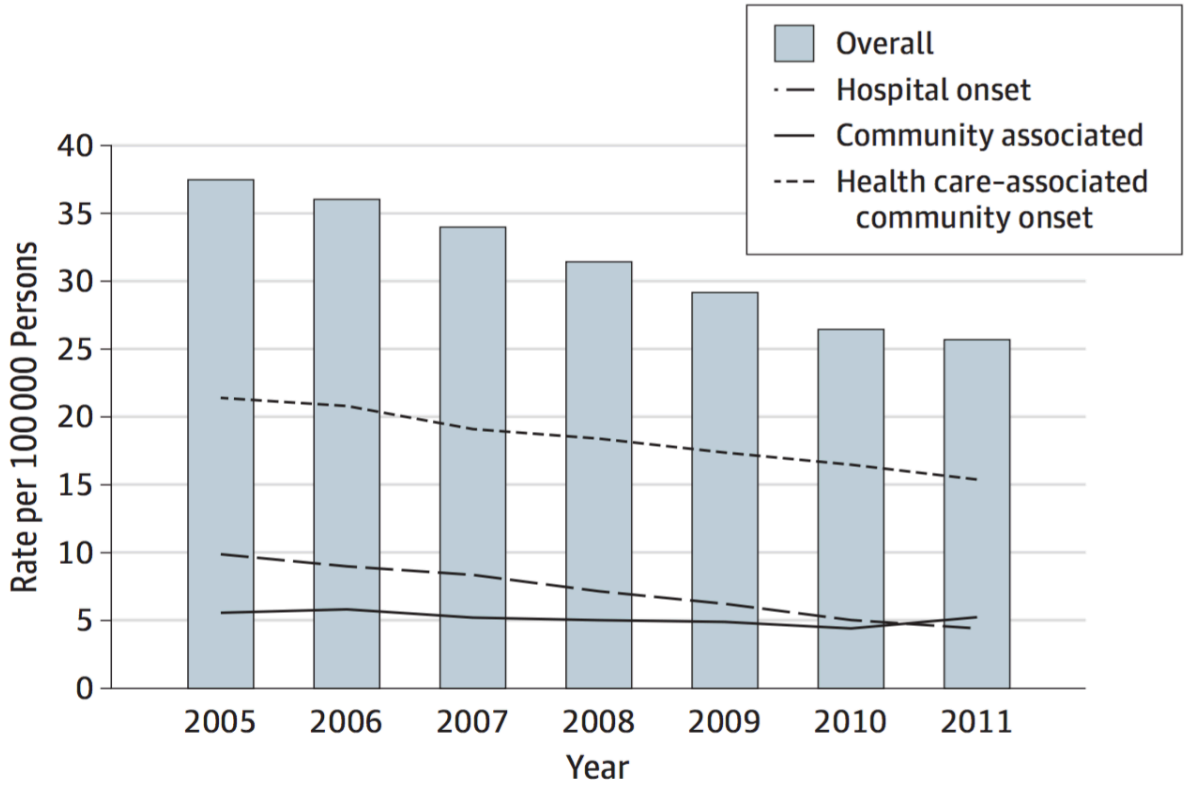


MRSA = methicillin-resistant *Staphylococcus aureus*
VRE = vancomycin-resistant *Enterococcus*
FQRP = fluoroquinolone-resistant *Pseudomonas aeruginosa*

IDSA report, “Bad bugs, no drugs”, 2004

But sometimes resistant lineages decline

Figure 2. National Estimated Incidence Rates of Invasive MRSA Infections, Stratified by Epidemiologic Category[a]



Dantes et al., JAMA Intern Med 2013

Resistant lineages decline across settings

FIGURE 2. Hospital-onset *Staphylococcus aureus* bloodstream and nonbloodstream infection rates,* by methicillin resistance status — 130 Veterans Affairs medical centers, United States, 2005–2017

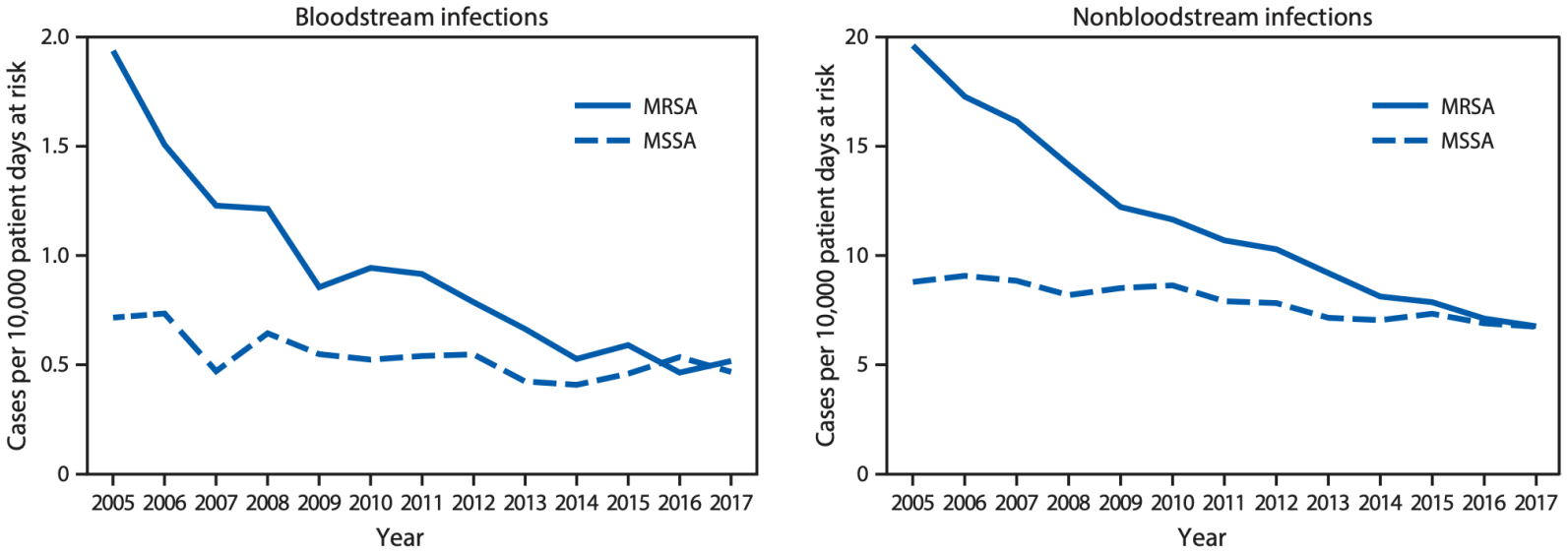
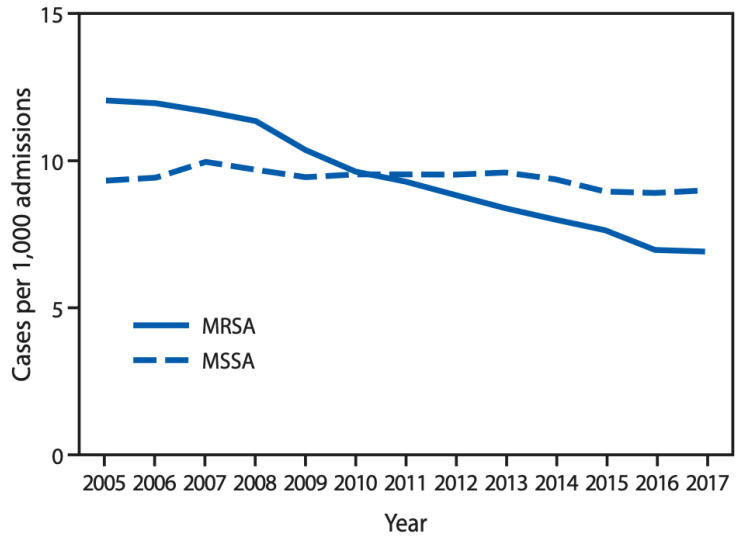


FIGURE 3. Community-onset *Staphylococcus aureus* infection rates,* by methicillin resistance status — 130 Veterans Affairs medical centers, United States, 2005–2017

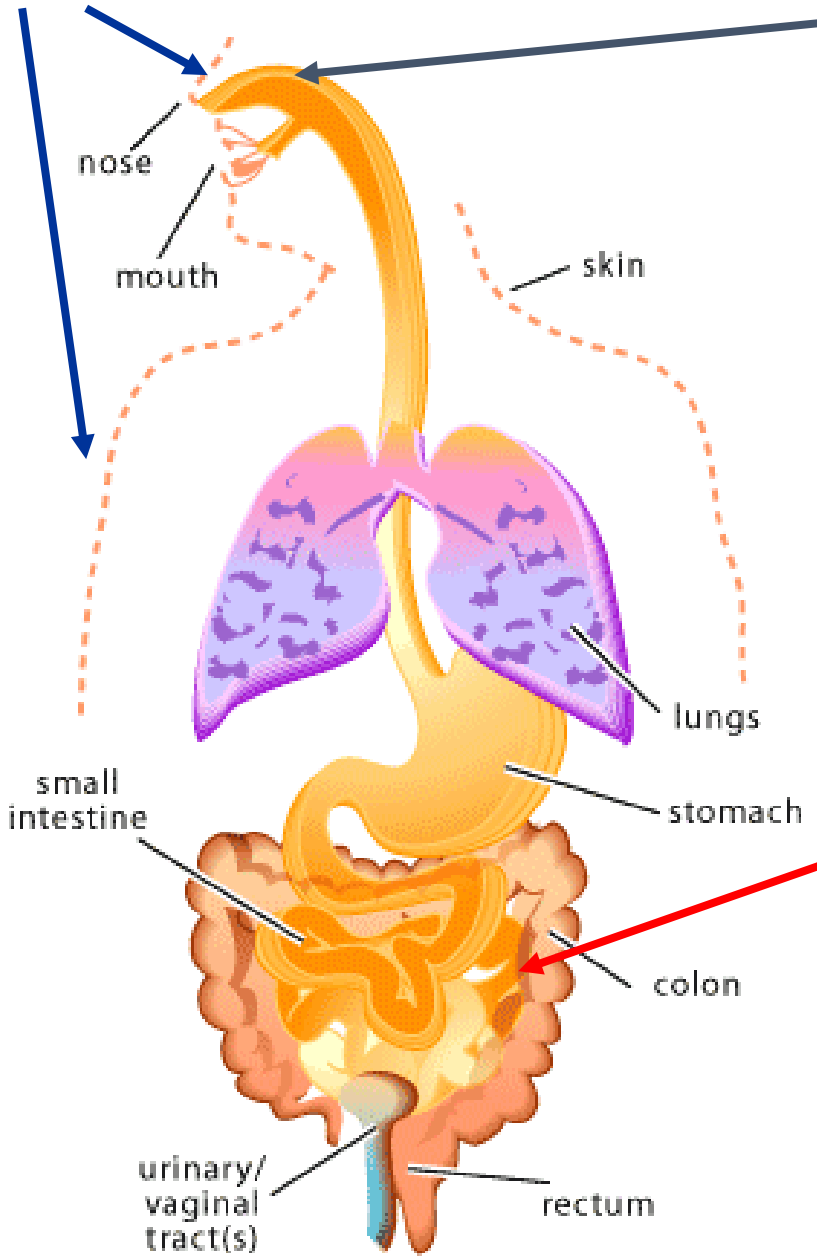


Jones et al., *MMWR* 2019

Antibiotic use and resistance: the importance of bystander selection

S. aureus

S. pneumoniae
H. influenzae
N. meningitidis



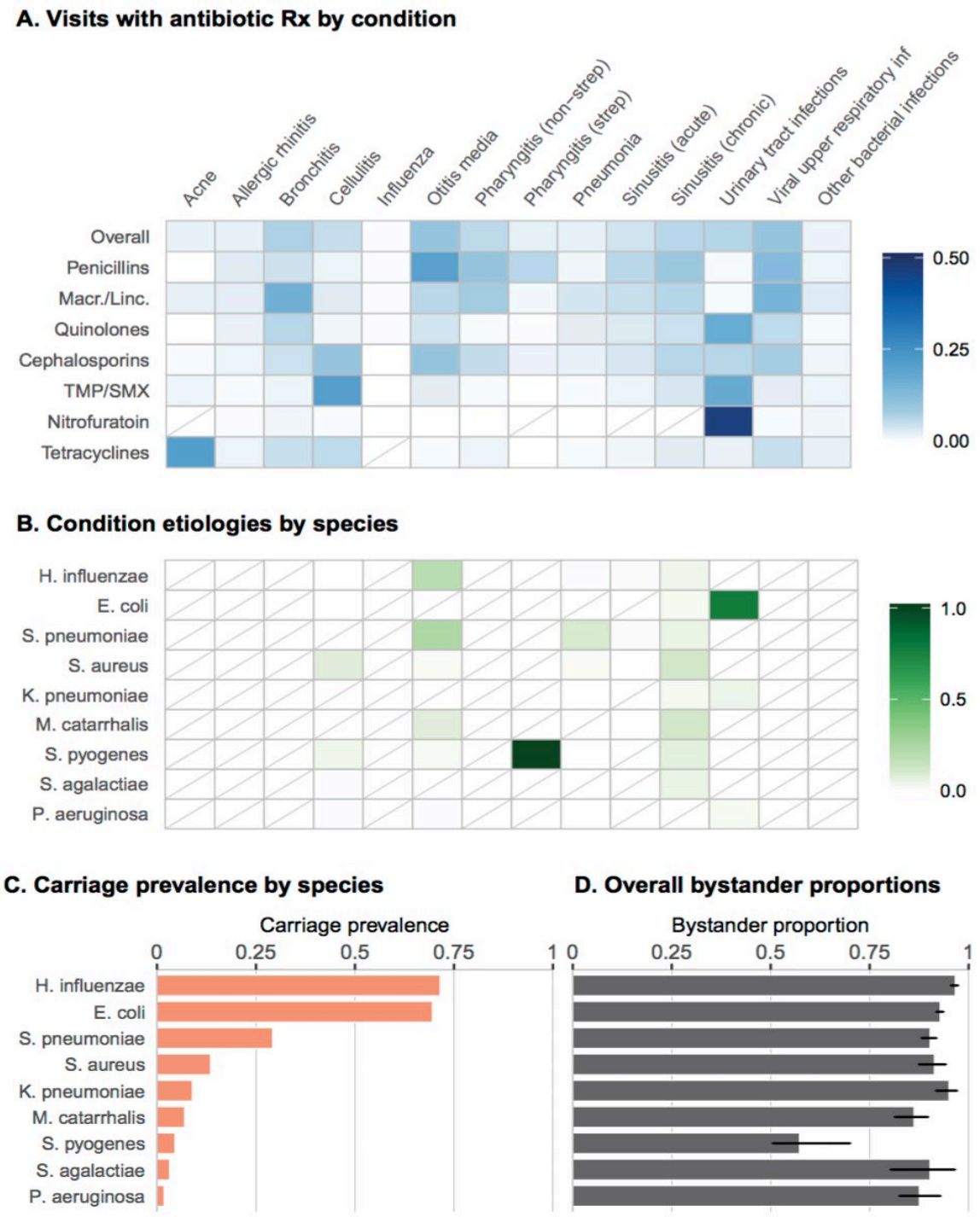
"Normal" Flora

GNR
(*E. coli*,
Klebsiella
Enterobacter)

Enterococcus faecium

Estimating the proportion of bystander selection for AMR in the US

Proportion of antibiotic exposures in a species that are due to treatments they did not trigger



Tedijanto *et al.*, *PNAS* 2019

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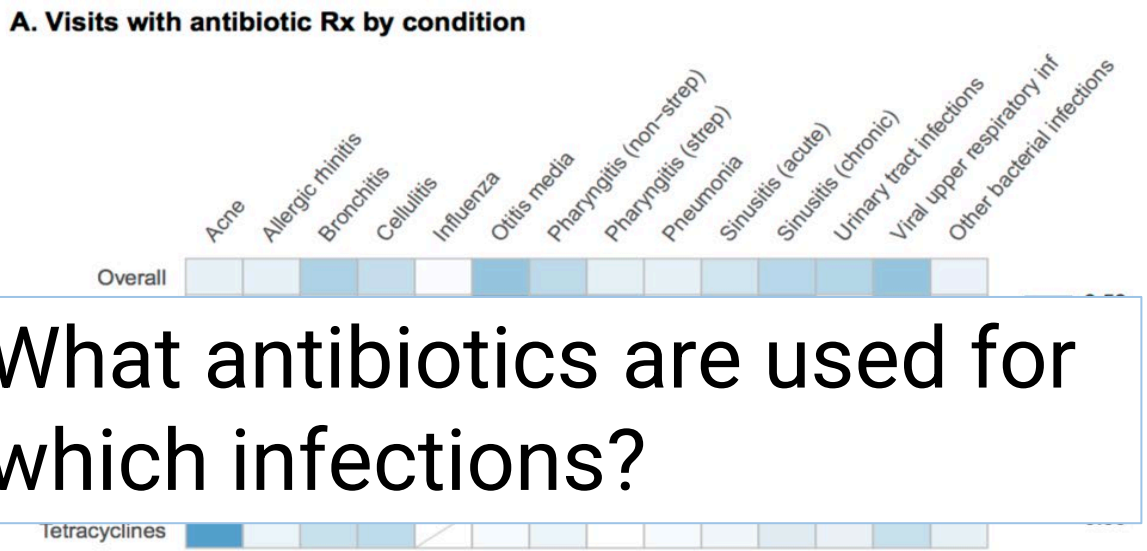
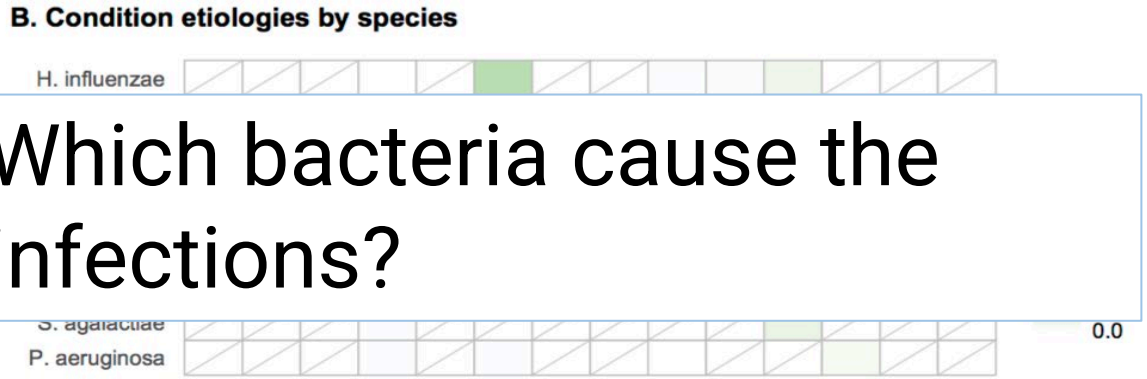
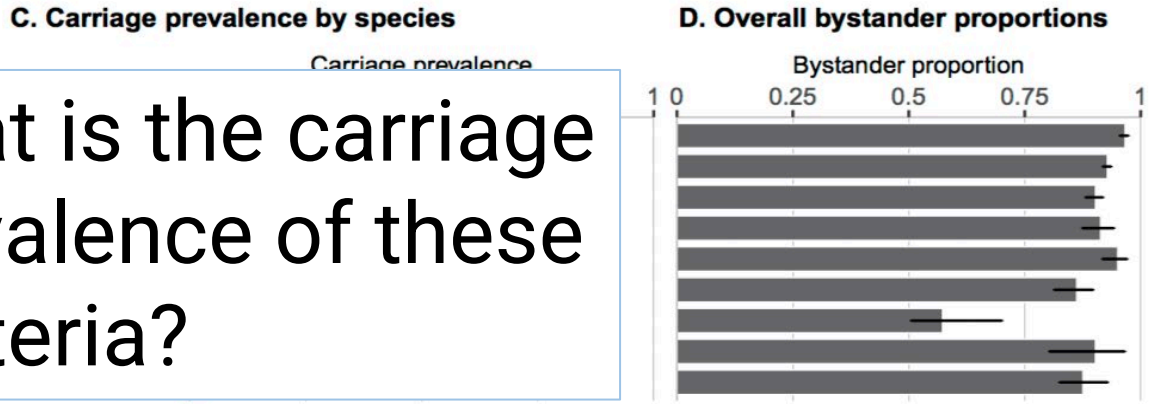


What antibiotics are used for which infections?



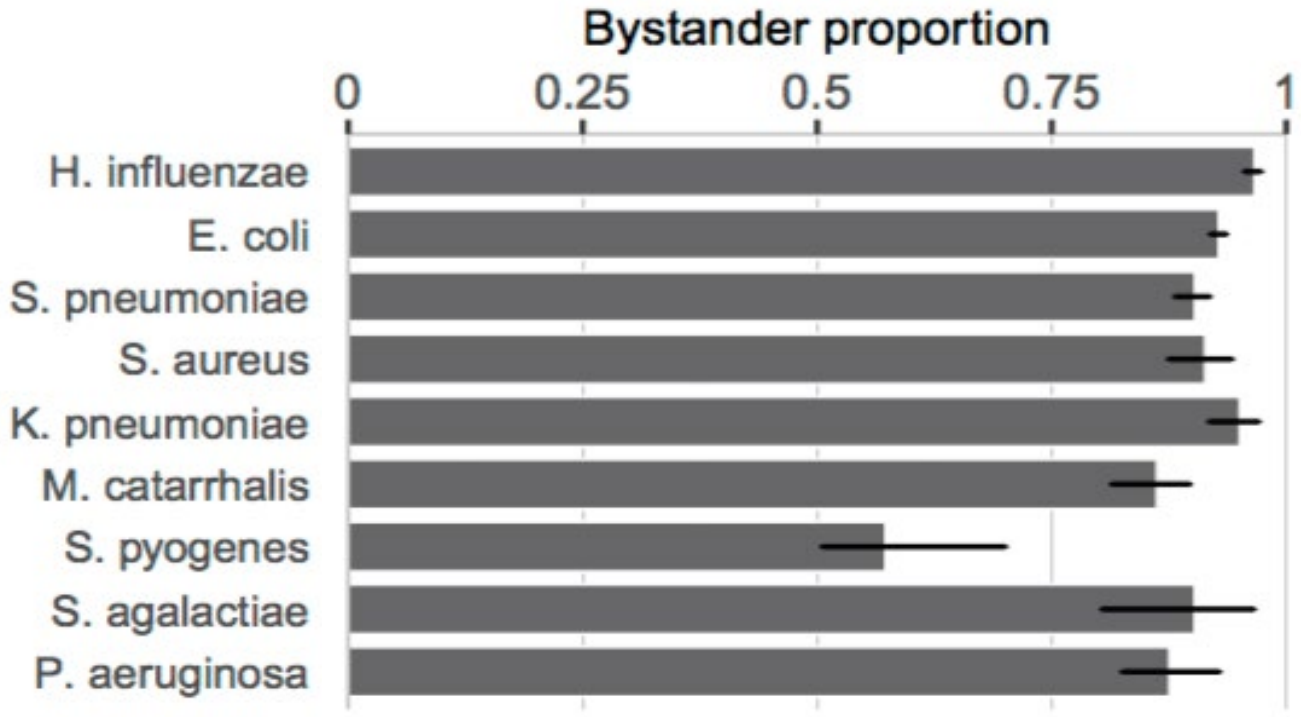
Which bacteria cause the infections?



What is the carriage prevalence of these bacteria?

Tedijanto *et al.*, *PNAS* 2019

Estimating the proportion of bystander selection for AMR in the US

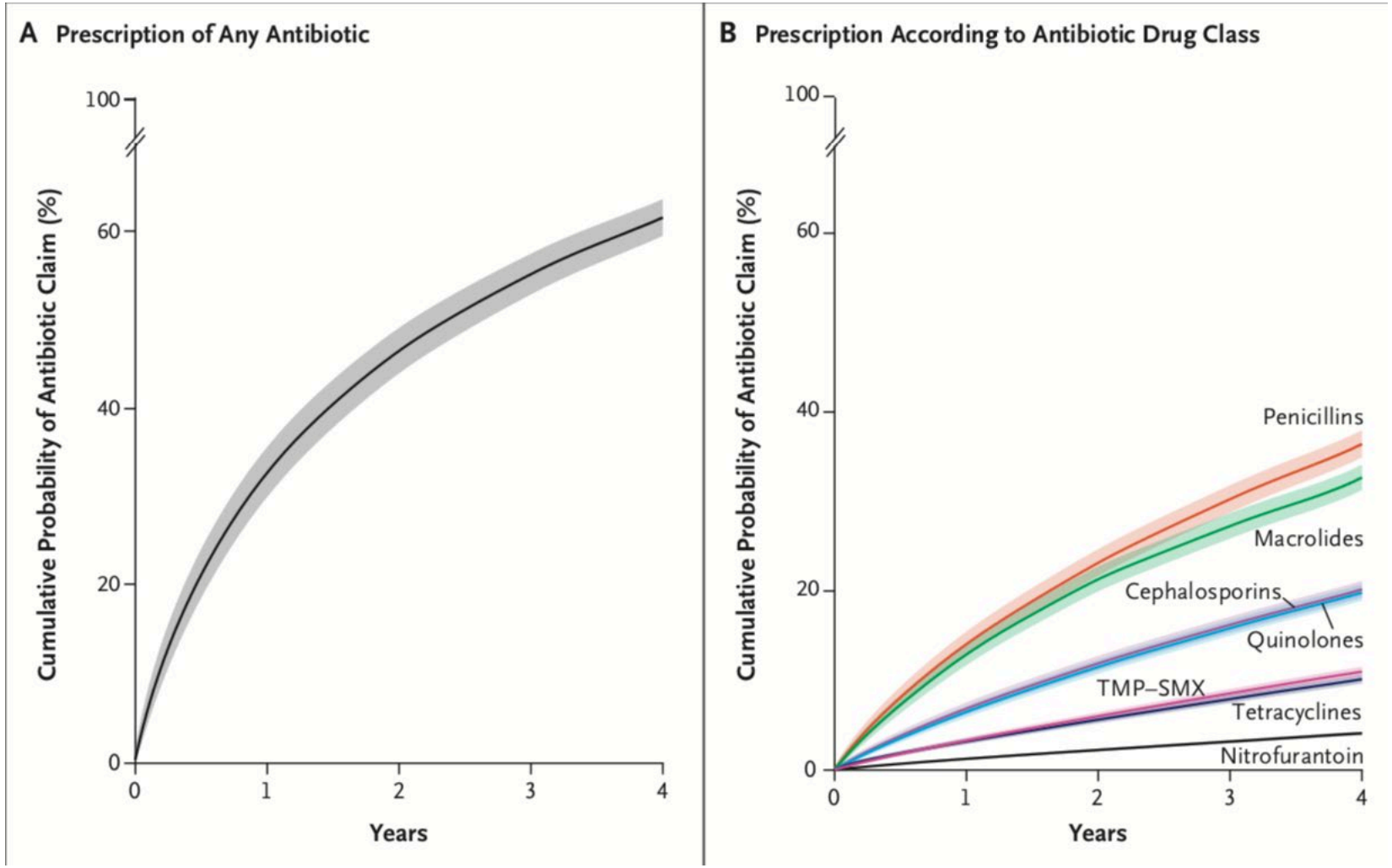


Tedijanto *et al*., *PNAS* 2019

What’s your antibiotic use?

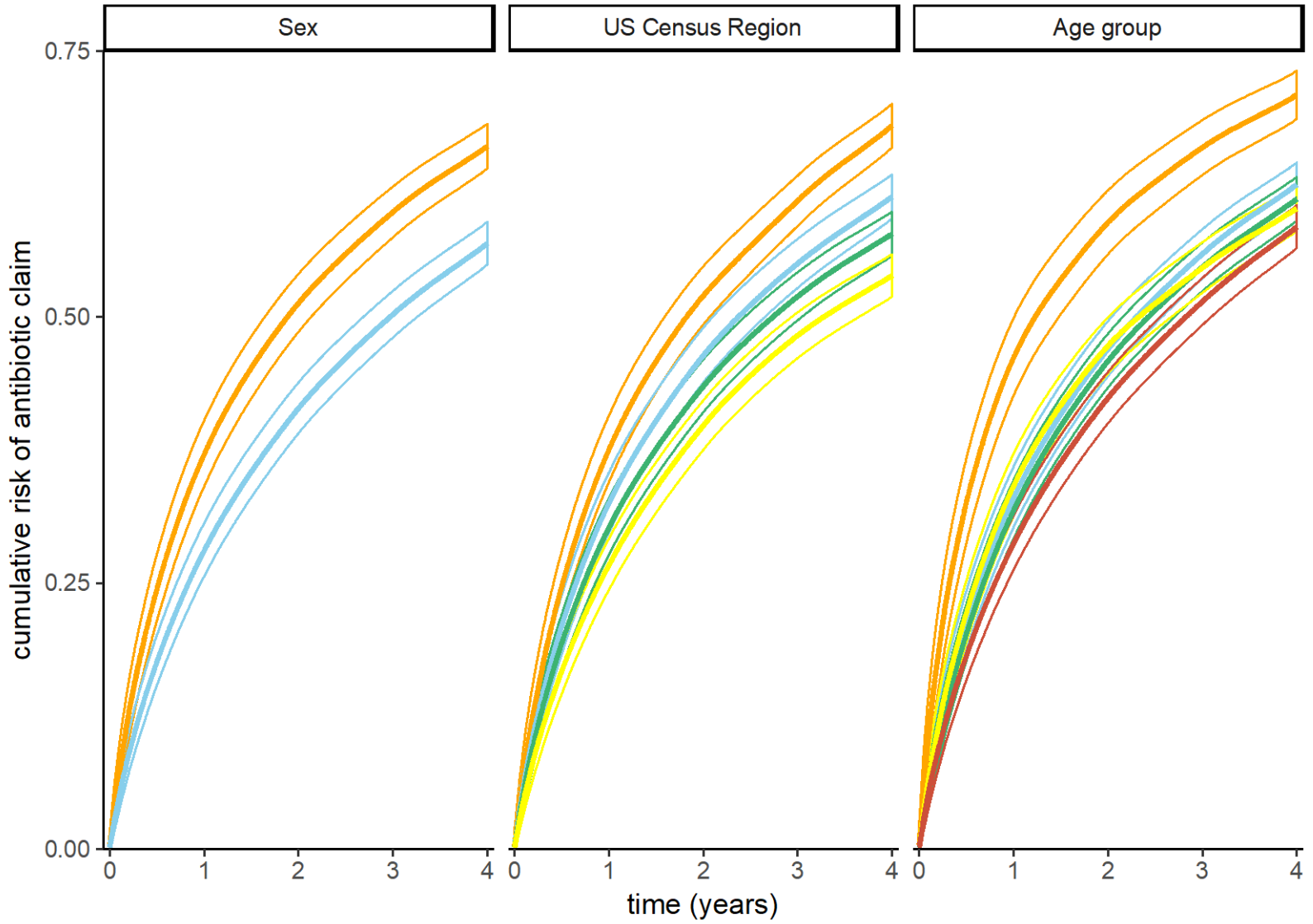
Olesen, MacFadden, Grad, *NEJM* 2019

What's your antibiotic use?

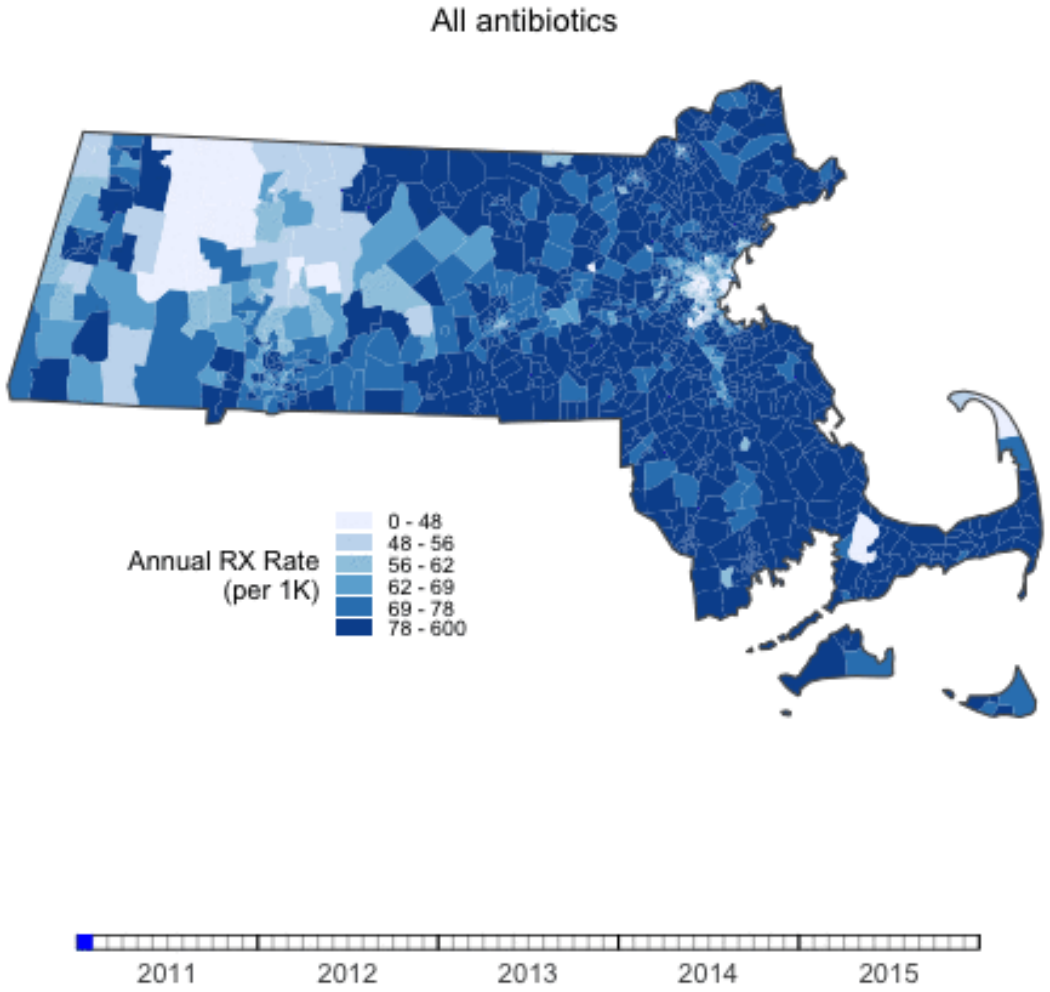


Olesen, MacFadden, Grad, *NEJM* 2019

What's your antibiotic use?

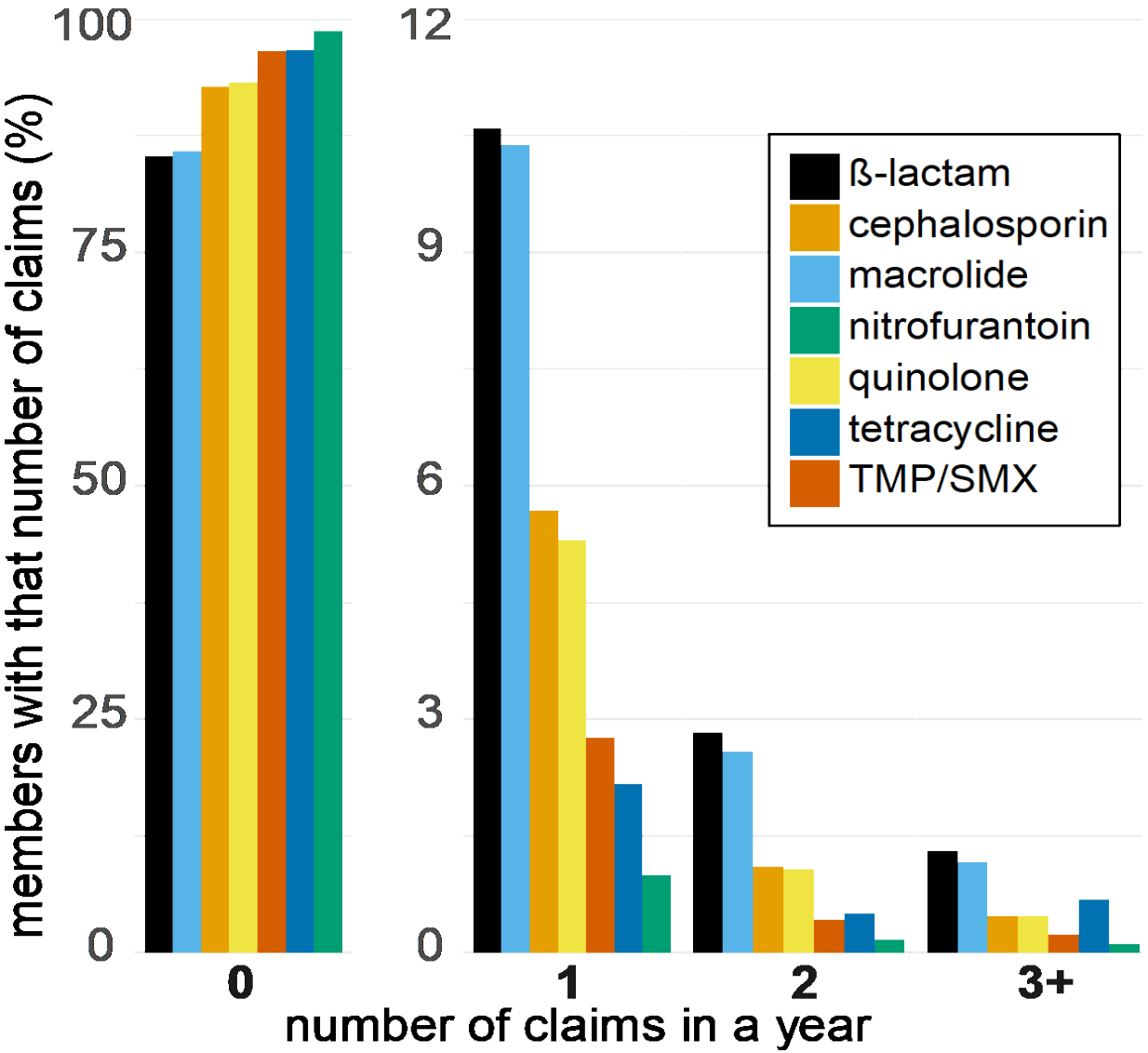


Prescribing varies geographically and temporally



Kissler *et al.*, *CID* 2020

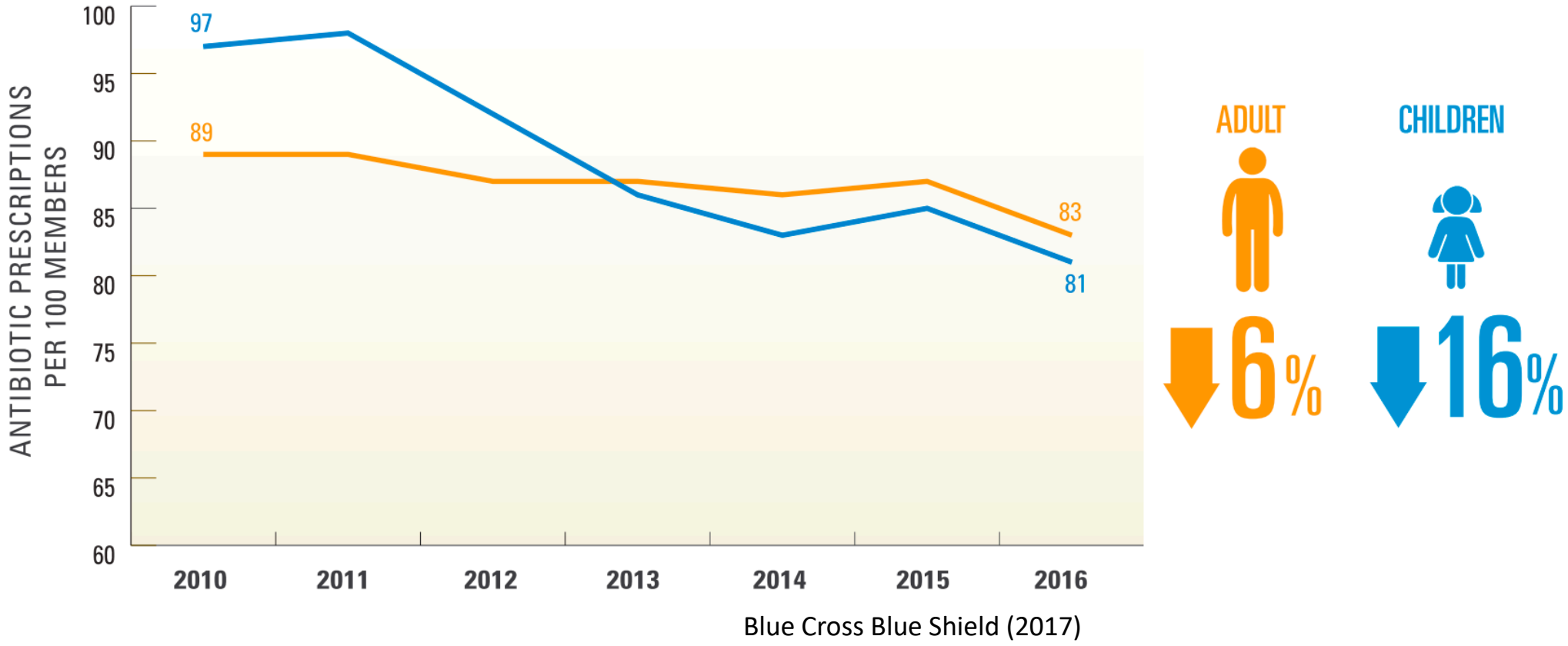
What is the distribution of outpatient antibiotic use?



10% of the population uses 57% of the antibiotics

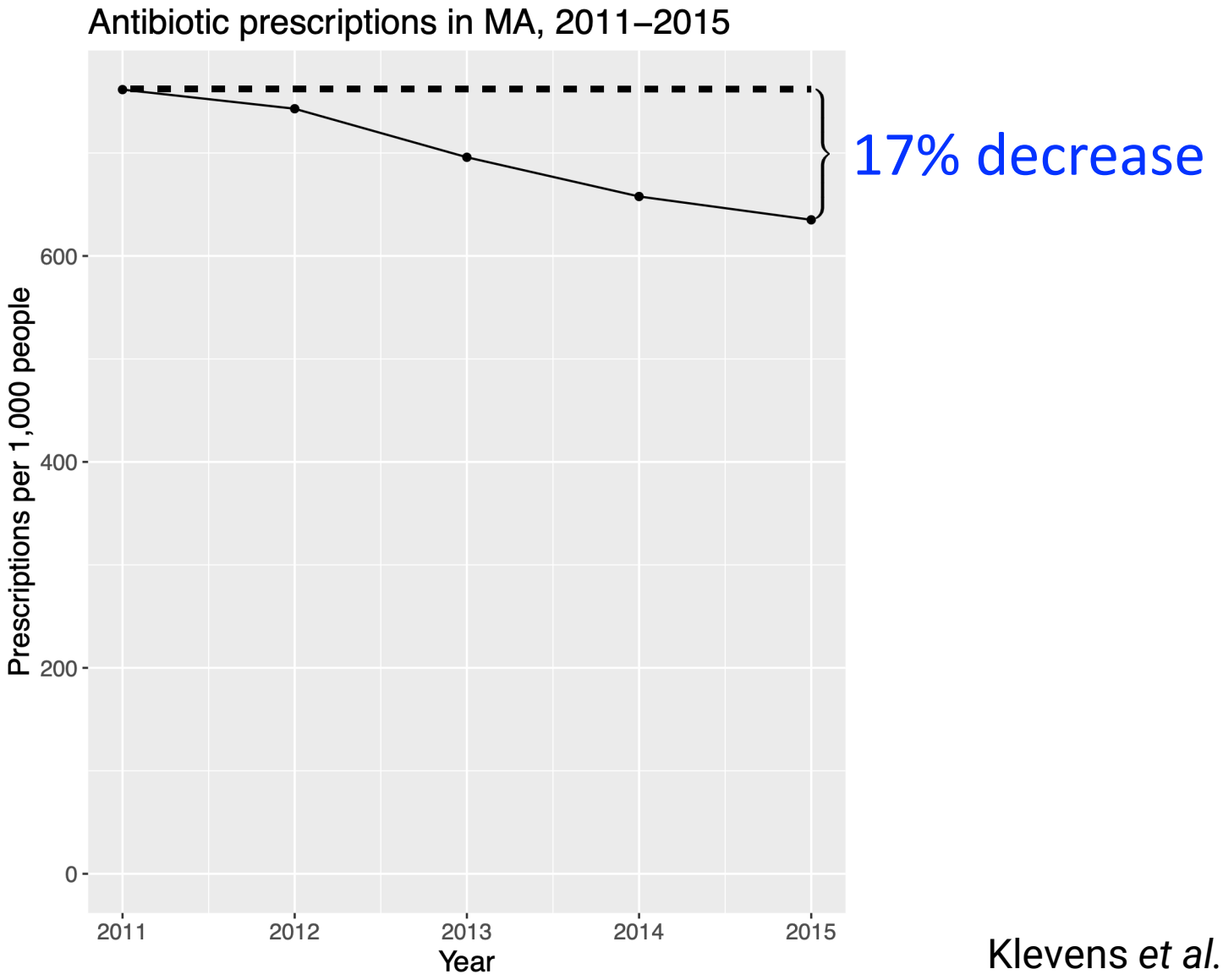
Olesen *et al.*, *eLife*, 2018

Antibiotic use has been declining across the US



Blue Cross Blue Shield (2017)

Antibiotic use has been declining in Massachusetts, too

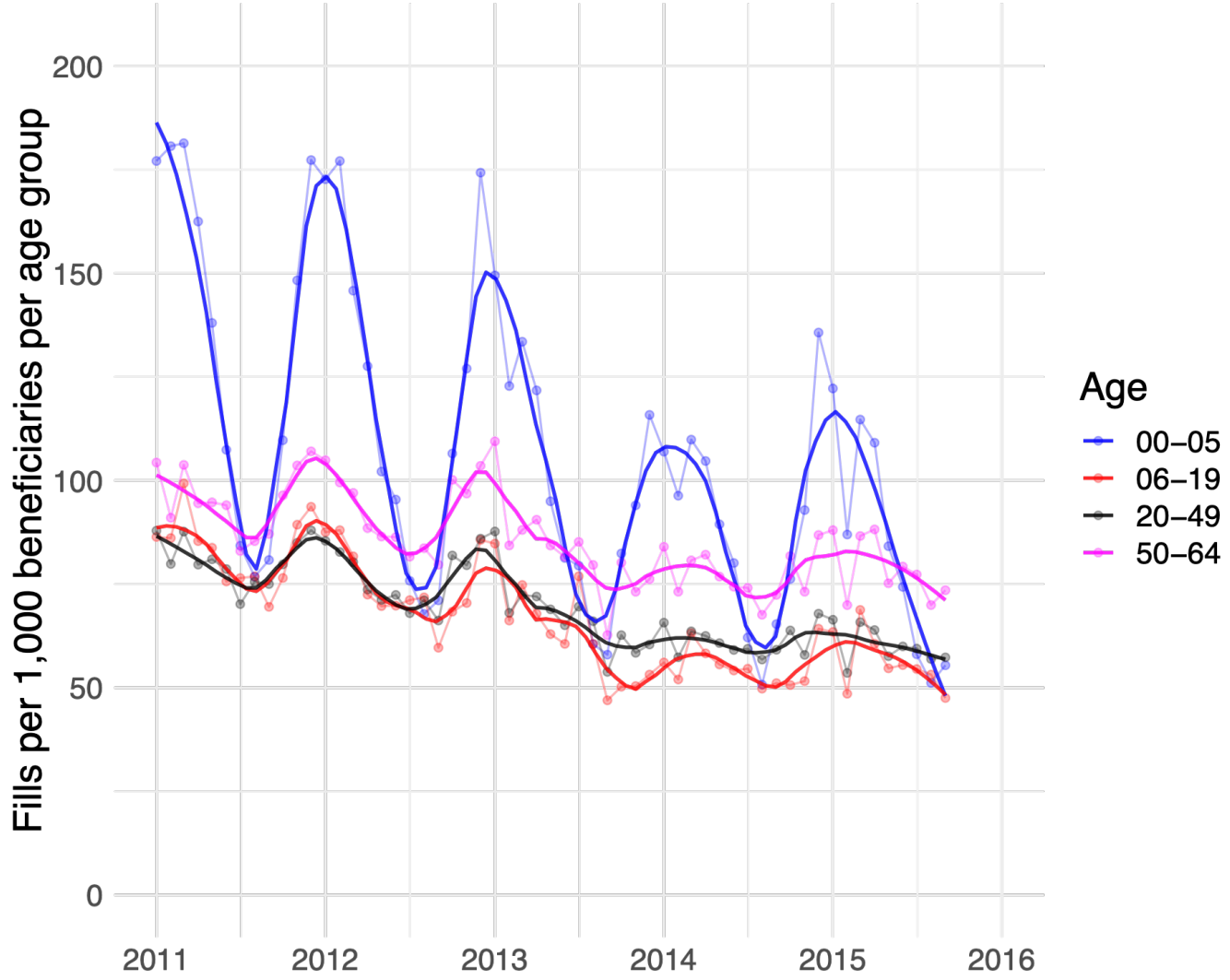


Klevens *et al.*, *OFID* 2019

What’s driving the decline in prescribing?

Kissler, *et al*., *Clinical Infectious Diseases* 2020

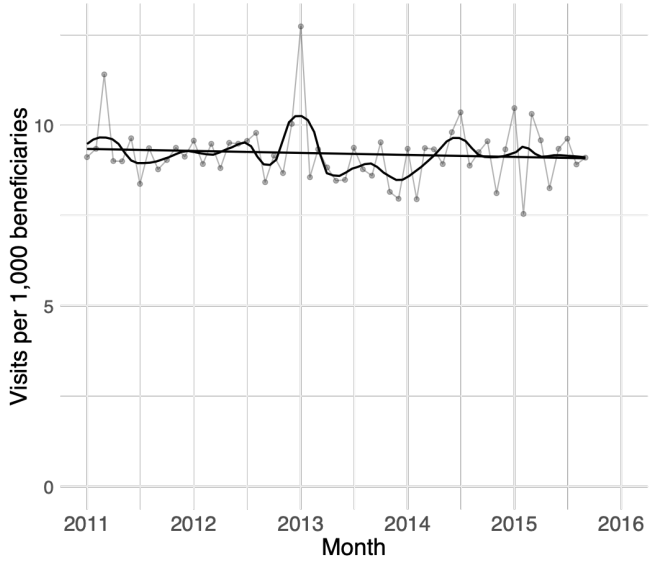
Most of the decline is in wintertime pediatric prescribing



Kissler *et al.*, *CID* 2020

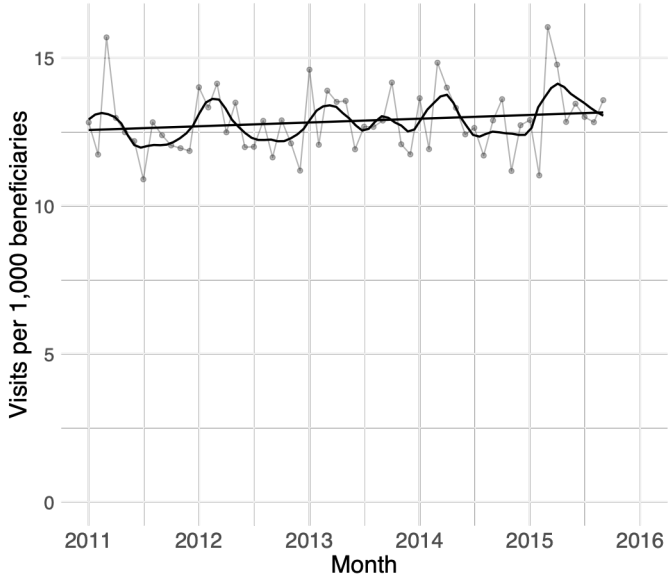
Misc. bacterial infections

No significant change
(p = 0.49; 95% CI: (−11.5%, 6.8%))



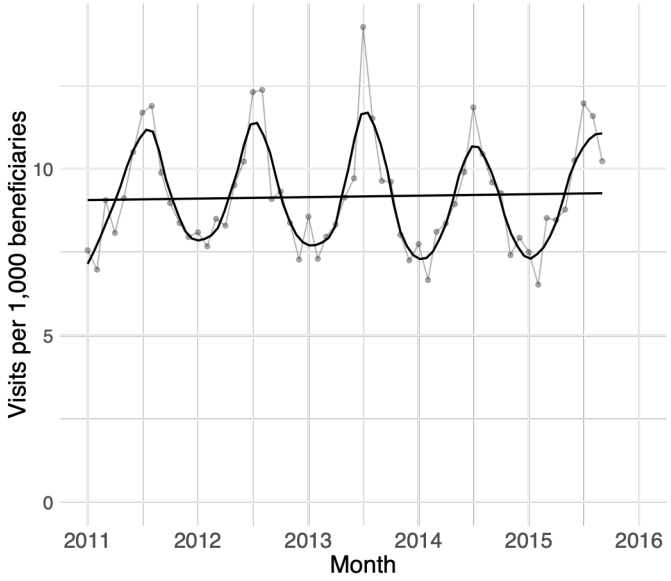
Gastrointestinal infections

No significant change
(p = 0.23; 95% CI: (−4.1%, 14.5%))



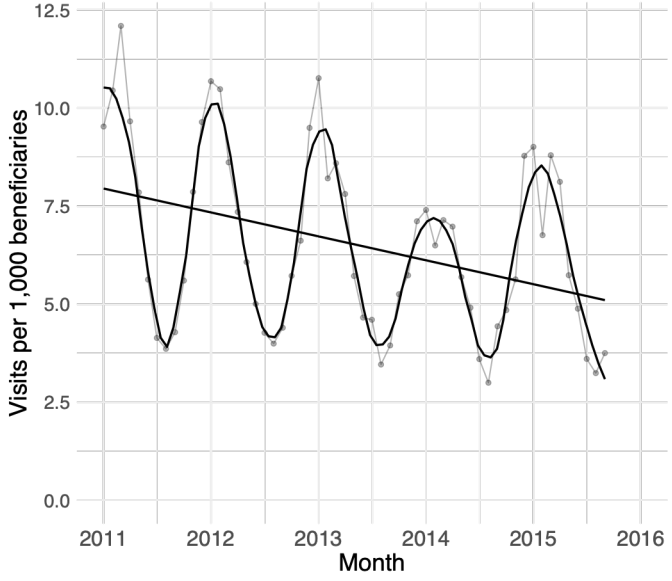
Skin, cutaneous and mucosal infections

No significant change
(p = 0.78; 95% CI: (−15.4%, 23.7%))



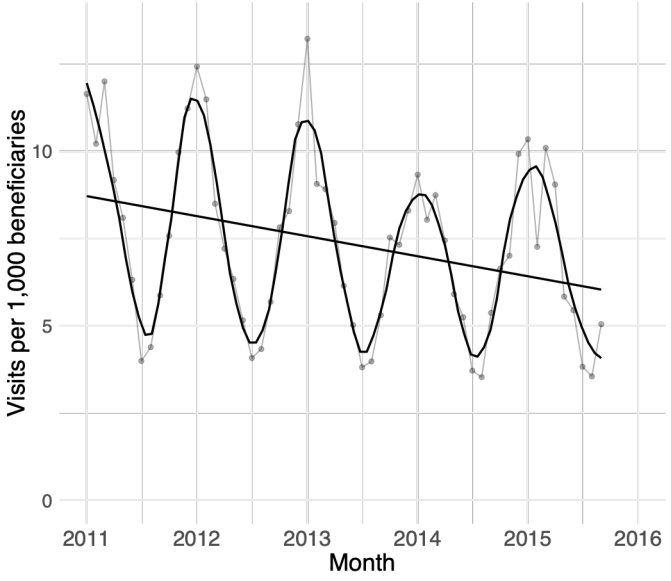
Suppurative otitis media

Change of −35.8%
(p = 0.0053; 95% CI: (−56.4%, −8.3%))



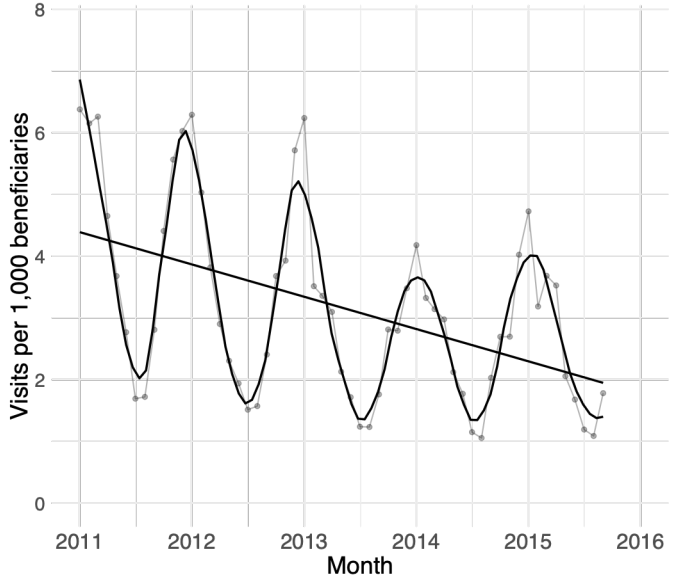
Sinusitis

Change of −30.8%
(p = 0.019; 95% CI: (−52.6%, −1.4%))



Bronchitis/bronchiolitis

Change of −55.6%
(p = 0.00025; 95% CI: (−76.1%, −27.1%))



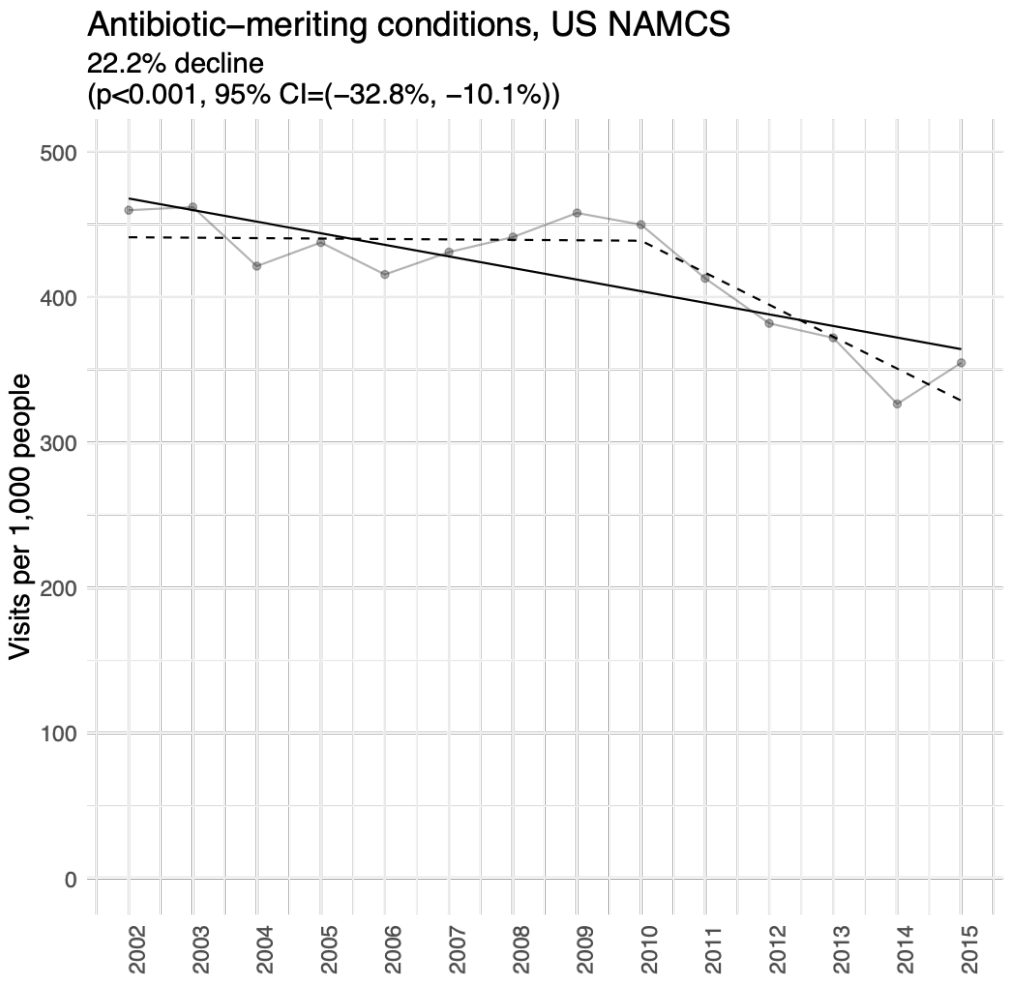
Comparing improved stewardship *vs.* reduced observed disease

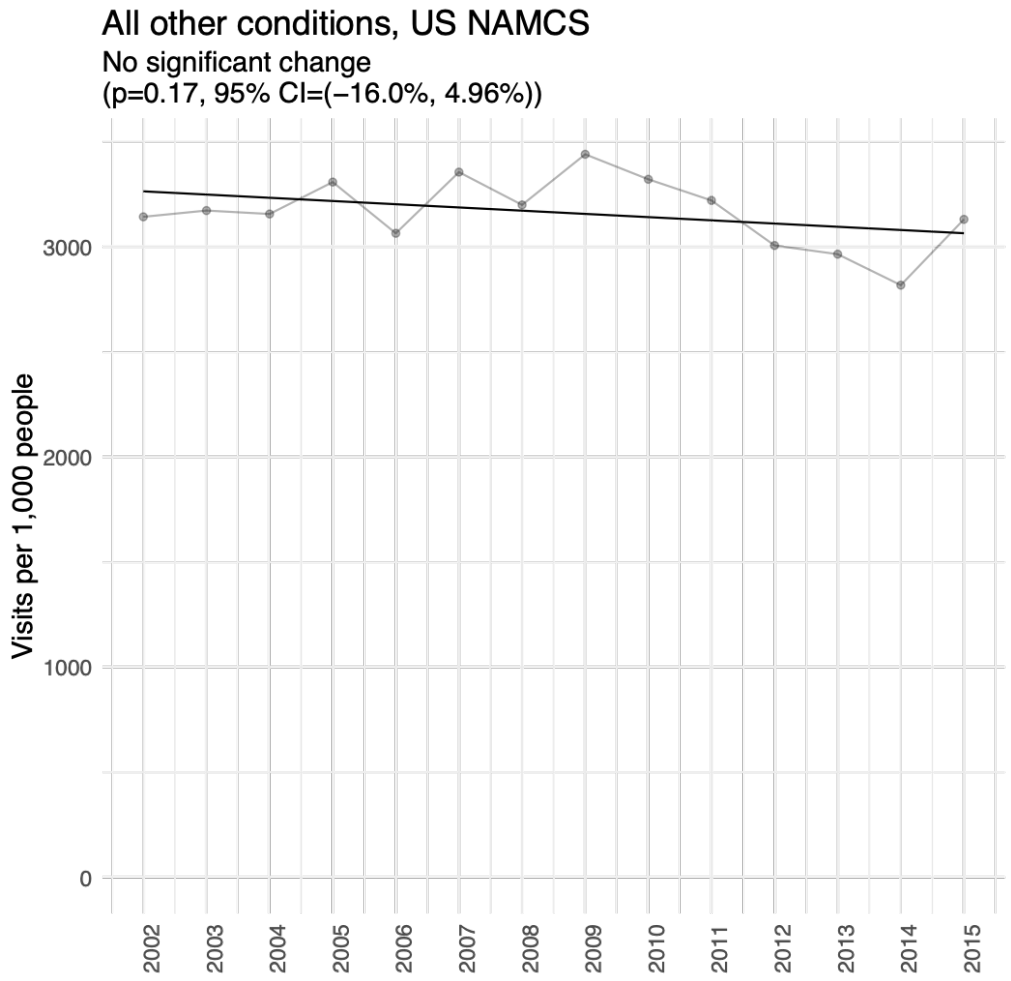
Table 1. Number of Antibiotic Prescriptions per 1000 Individuals Filled for 20 Medical Conditions Between January 2011 and September 2015 and Number of Prescriptions per 1000 Individuals Avoided Through Reductions in Observed Disease and Reductions in Antibiotic-prescribing Rate per Outpatient Visit

		Rx/1000 Avoided (95% CI)	
Condition	Rx/1000 Individuals	Disease	Prescribing
Sinusitis	248	52.0 (34.0, 69.9)	19.4 (15.5, 23.4)
Pharyngitis	242	36.2 (23.8, 48.7)	24.1 (19.1, 29.0)
Suppurative otitis media	226	53.1 (35.4, 70.9)	8.67 (5.76, 11.6)
Bronchitis/bronchiolitis	52.4	19.4 (14.7, 24.2)	11.9 (10.8, 13.0)
Viral upper respiratory infection	84.8	11.6 (4.97, 18.3)	12.7 (10.9, 14.4)
Pneumonia	52.7	15.3 (10.2, 20.4)	1.86 (.984, 2.73)

Kissler et al., CID 2020

Rates of infectious disease in the US declined starting around 2010





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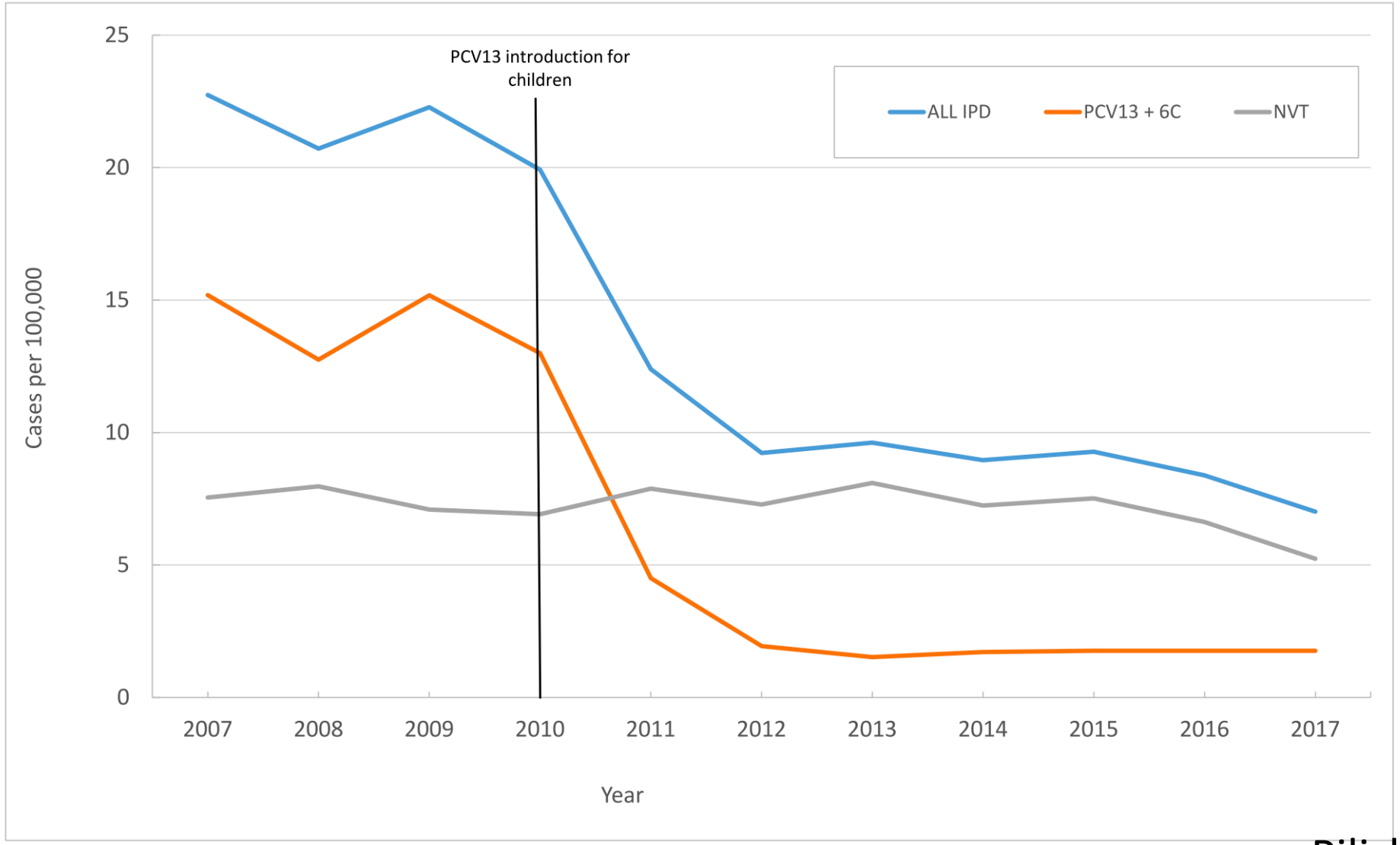


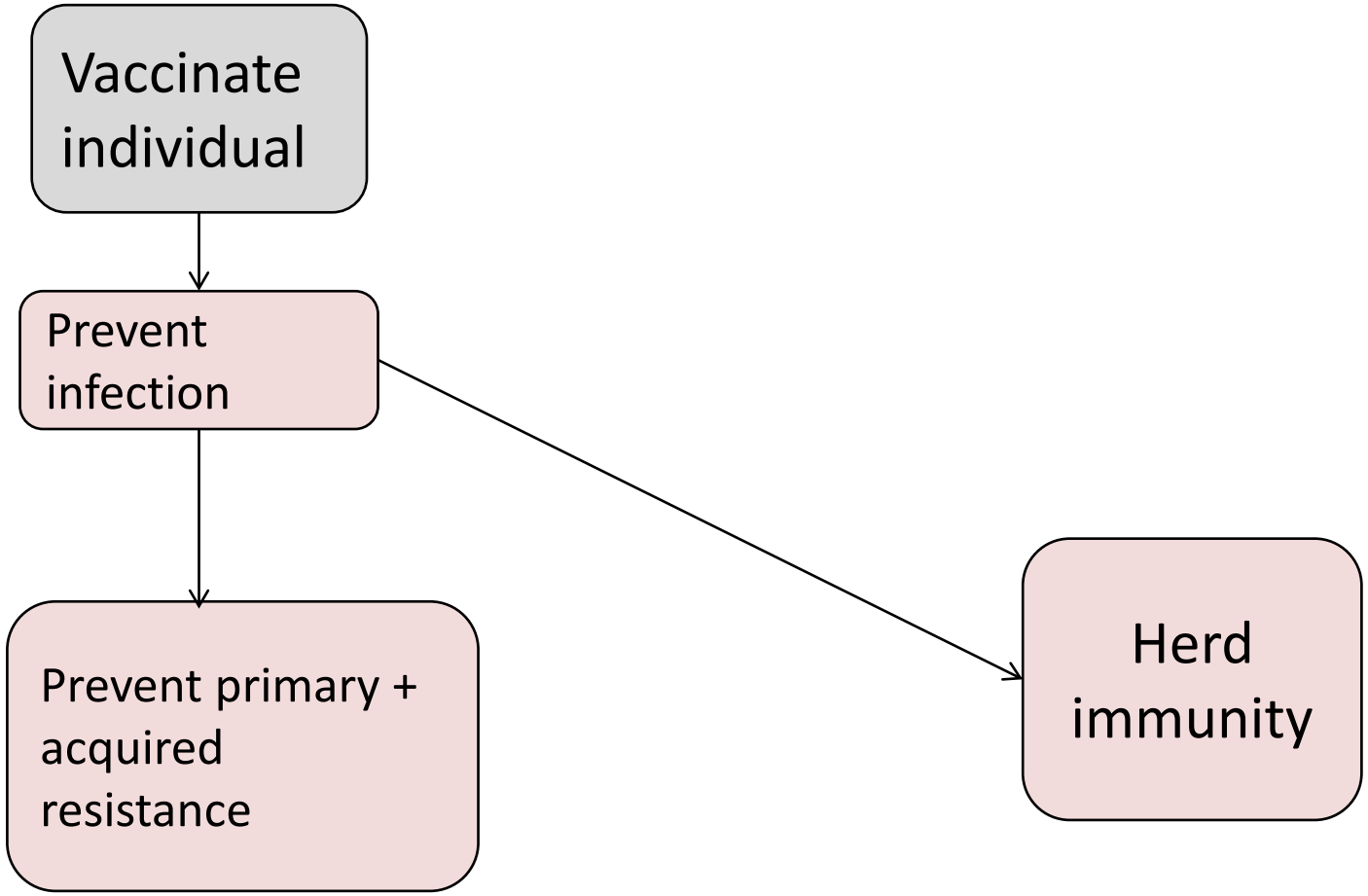
Pilishvili 2018

Strategies to reduce antibiotic use

- Address inappropriate use
  - Accurate (ideally cheap) diagnostics
  - Antibiotic stewardship

- Disease prevention
  - Access to clean water and sanitation (e.g., typhoid, cholera)
  - Vaccination

Vaccines to control AMR



A case prevented is a case that can't fail treatment

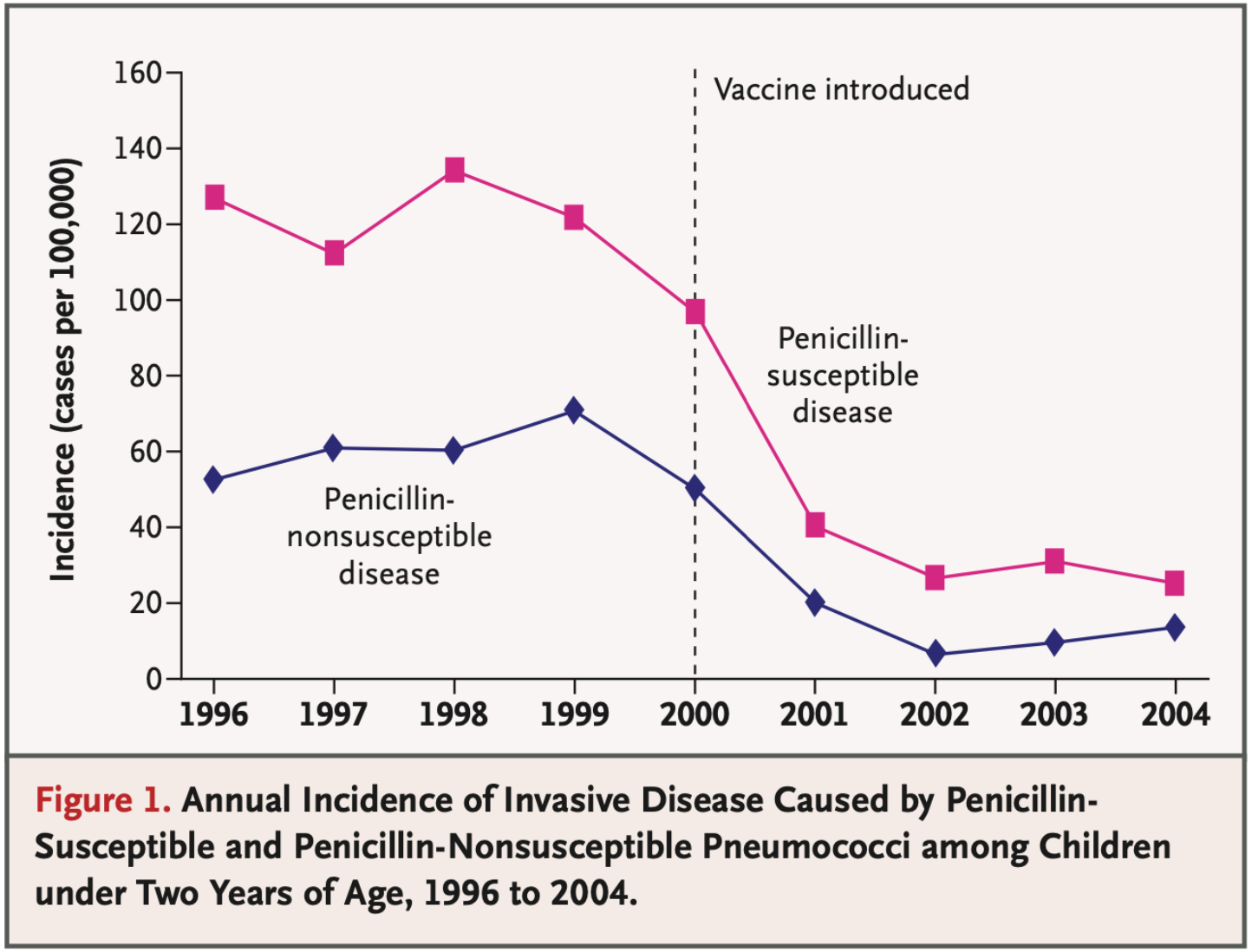
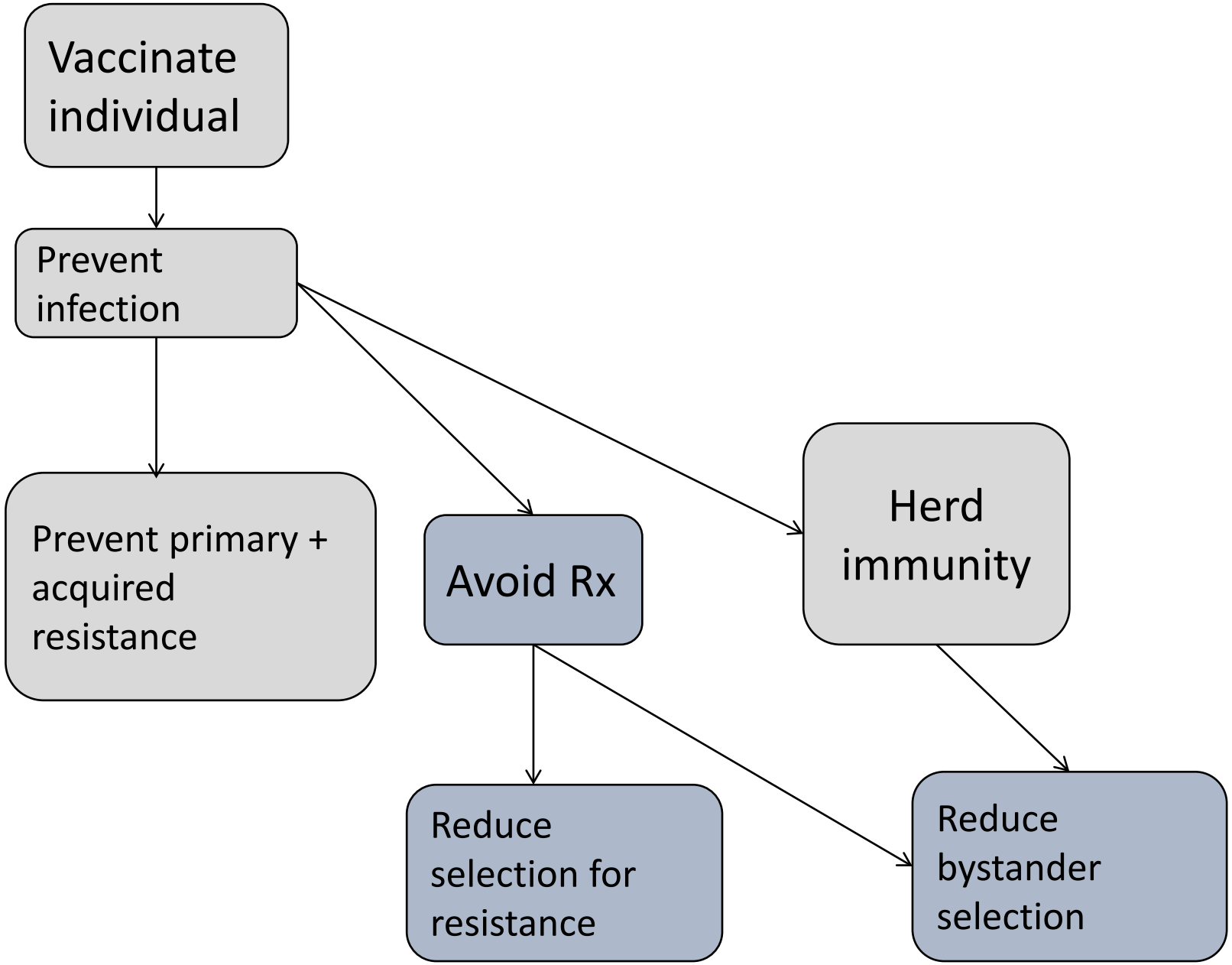


Figure 1. Annual Incidence of Invasive Disease Caused by Penicillin-Susceptible and Penicillin-Nonsusceptible Pneumococci among Children under Two Years of Age, 1996 to 2004.

Kyaw et al. 2006 *NEJM*

Vaccines to control AMR

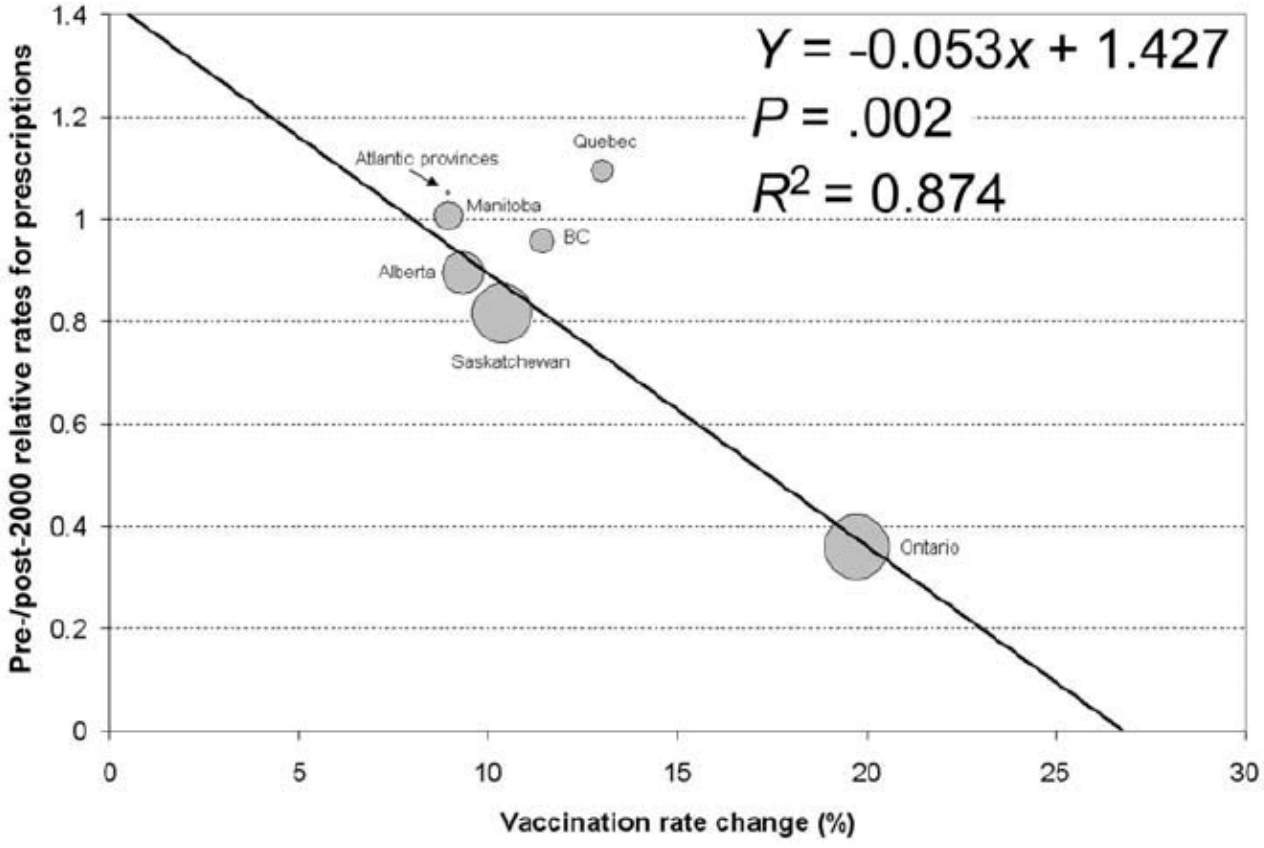


Vaccines prevent need for treatment

- Both appropriate (bacterial infection) and inappropriate (viral infection) treatment
- Impact on both…
  1. target organism (vaccines for bacteria), and
  2. bystander organisms (nearly all vaccines, bacterial and viral)

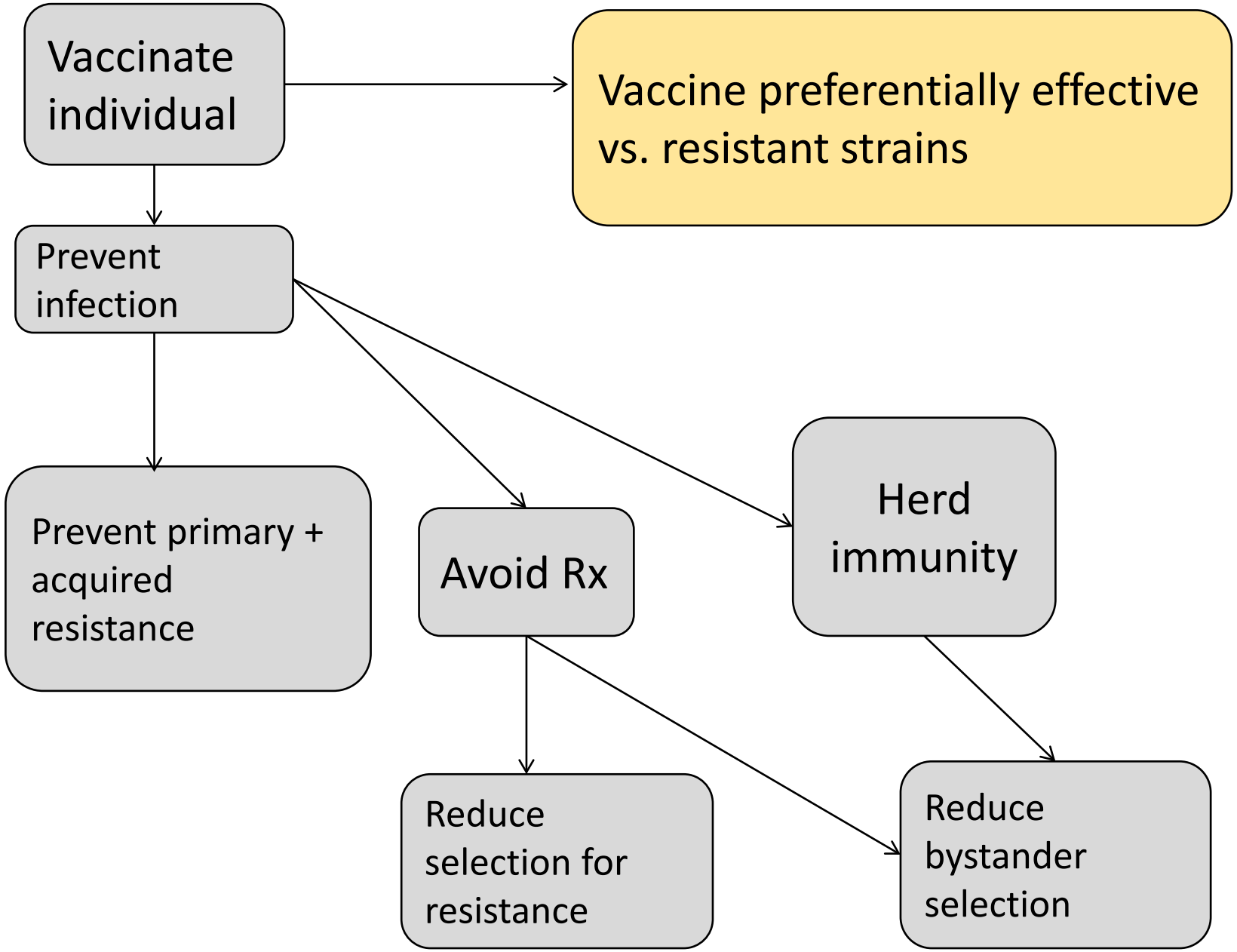
Flu vaccine: prevent (mostly) inappropriate prescribing

Increasing influenza vaccine coverage in Ontario associated with disproportionate decline in antibiotic prescriptions



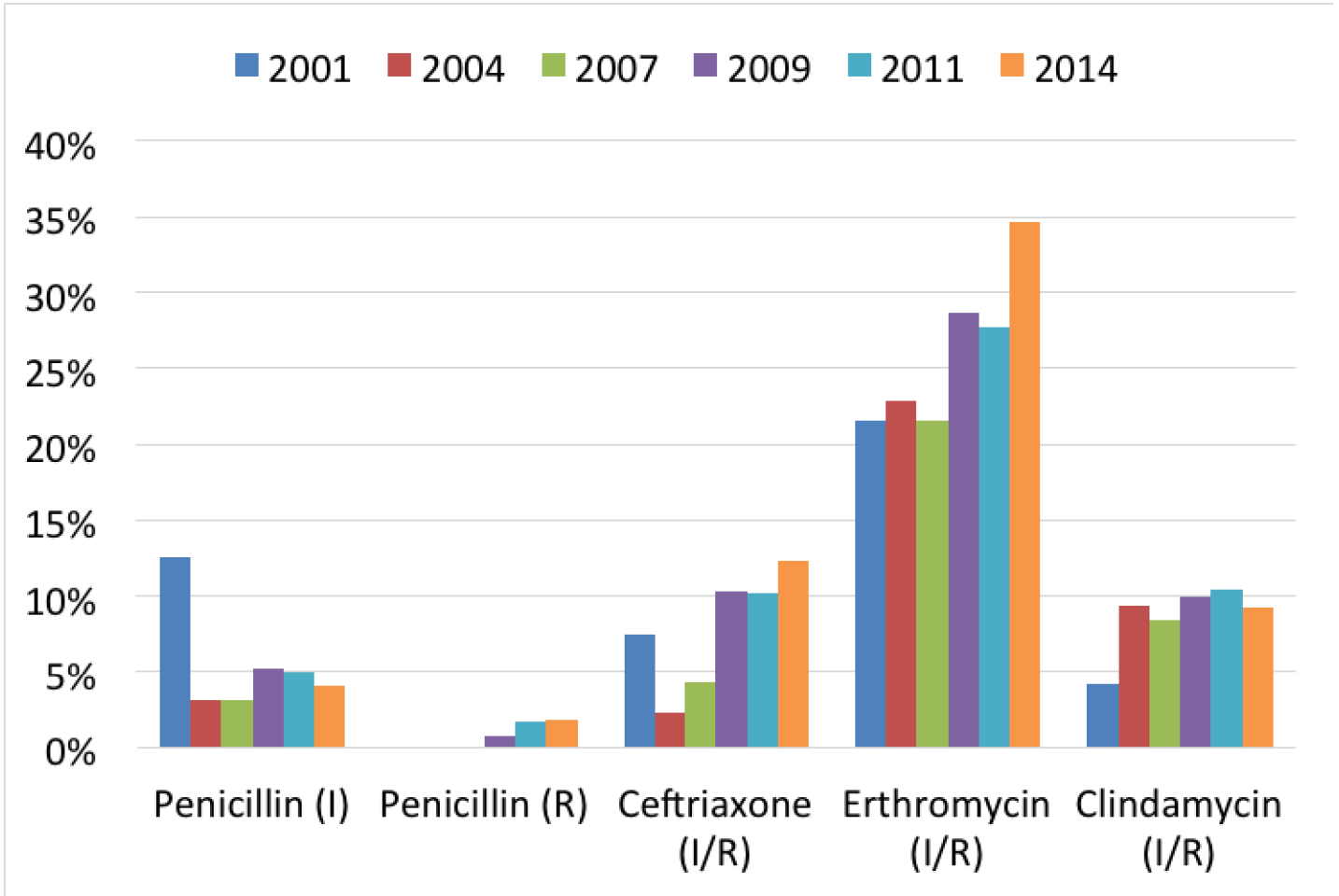
Kwong et al. *CID* 2009

Vaccines to control AMR



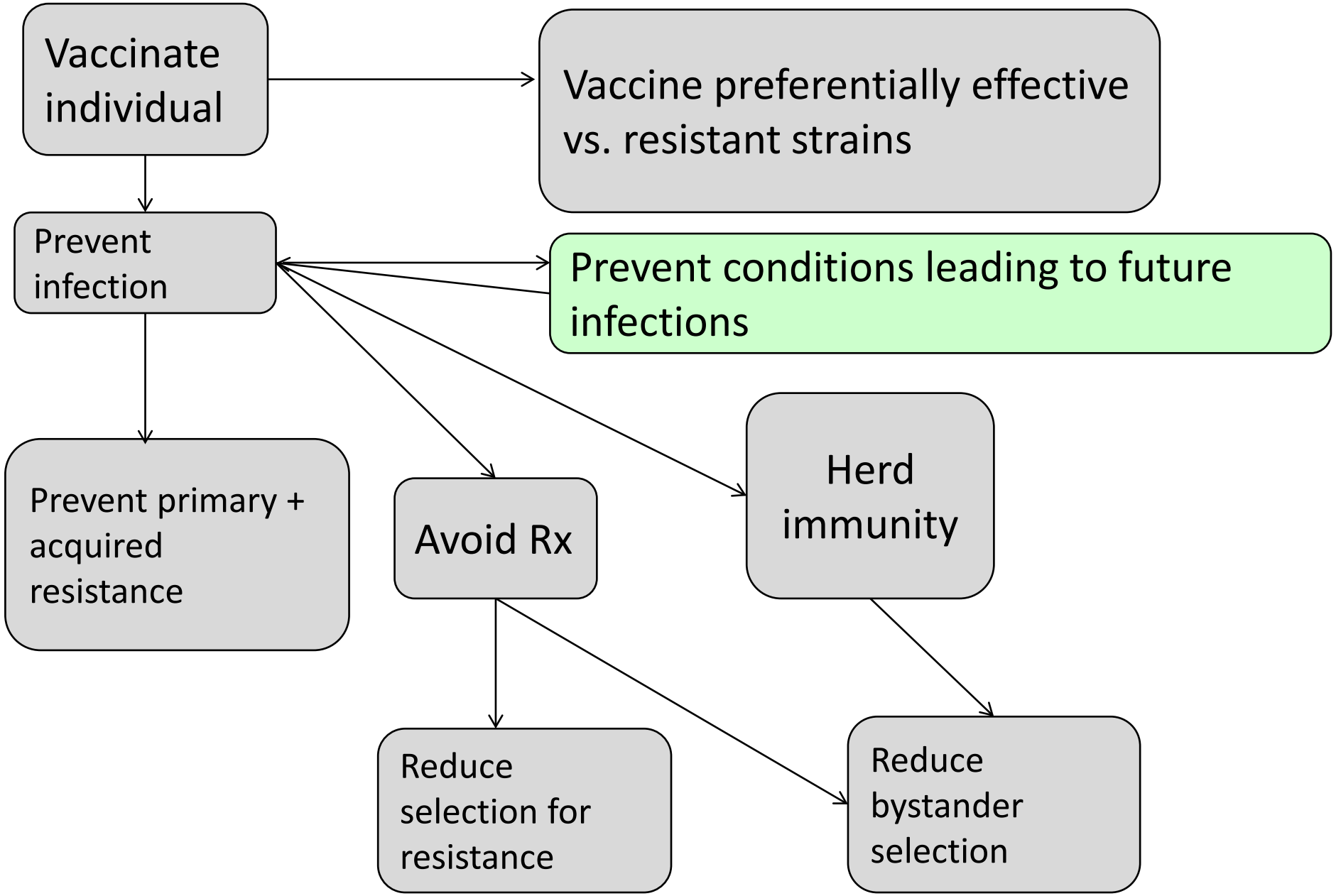
PCV temporarily reduced penicillin/cephalosporin resistance

Nonsusceptibility in carriage isolates of S. pneumoniae, <7year olds, MA, USA

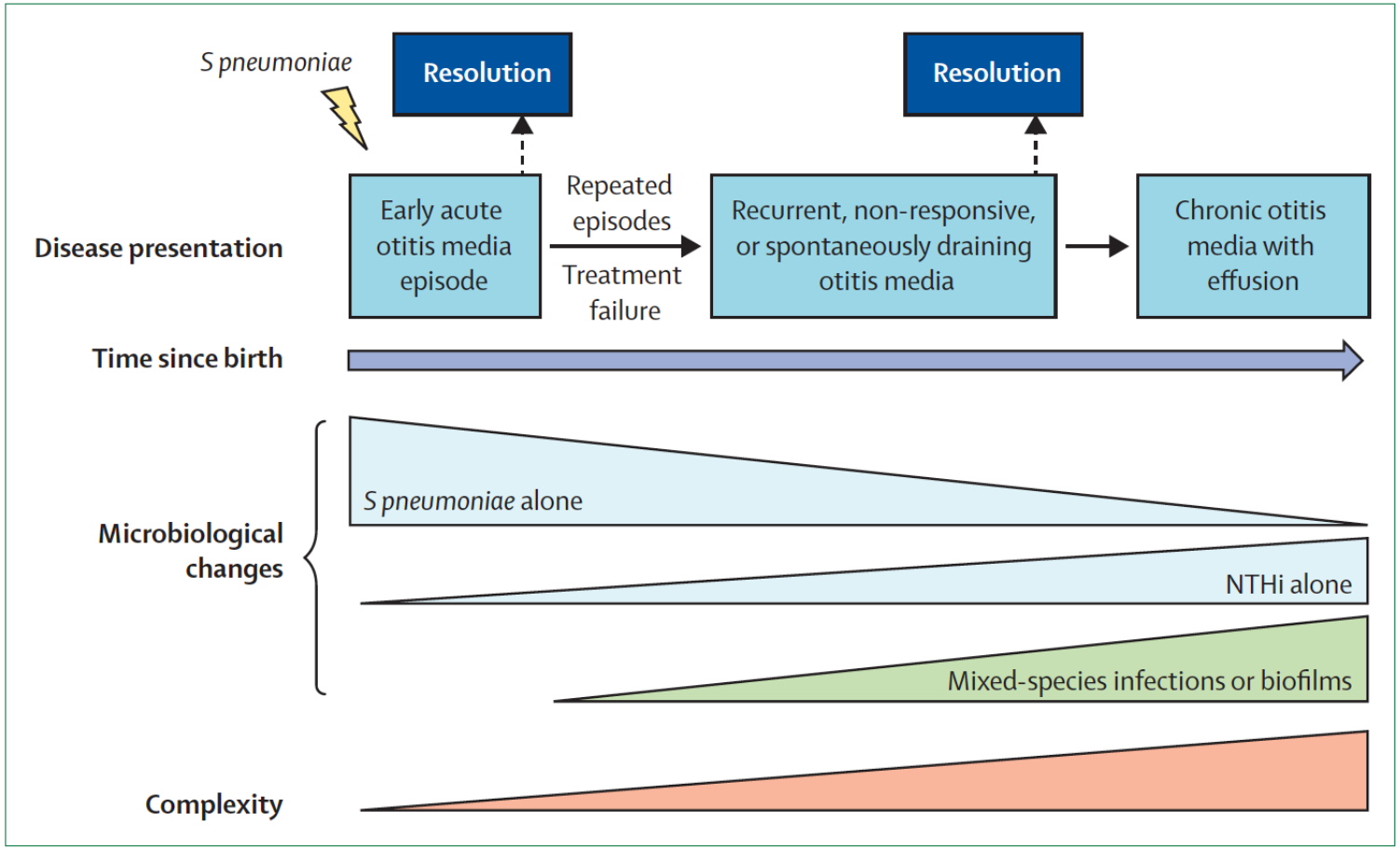


Lee et al. *Pediatrics* 2017

Vaccines to control AMR



Hypothesis: early pneumococcal otitis media predisposes to future otitis media from multiple species



Dagan et al. *Lancet ID* 2016

Pneumococcal conjugate vaccination associated with reduced nonpneumococcal otitis media

Episode by Pathogen	Pre-PCV[a] Mean Annual Incidence[b] (±SD)	PCV7[a] Mean Annual Incidence[b] (±SD)	IRR (95% CI) PCV7 vs Pre-PCV	PCV13[a] Mean Annual Incidence[b] (±SD)	IRR (95% CI) PCV13 vs PCV7	IRR (95% CI) PCV13 vs Pre-PCV
Pneumococcal VT7 + 6A serotypes	4.1 ± 0.3 (n = 718)	1.5 ± 0.4 (n = 134)	**0.35 (.29–.42)**	0.1 ± 0.0 (n = 9)	**0.06 (.03–.12)**	**0.02 (.01–.04)**
Pneumococcal VT5 serotypes	1.5 ± 0.1 (n = 261)	1.6 ± 0.5 (n = 148)	1.07 (.87–1.31)	0.2 ± 0.0 (n = 19)	**0.12 (.07–.19)**	**0.12 (.08–.20)**
Pneumococcal non-VT13 serotypes	1.1 ± 0.2 (n = 193)	1.6 ± 0.4 (n = 152)	**1.48 (1.20–1.84)**	0.9 ± 0.3 (n = 92)	**0.55 (.42–.71)**	0.82 (.64–1.05)
All pneumococcal serotypes	6.8 ± 0.5 (n = 1178)	4.7 ± 0.5 (n = 436)	**0.70 (.63–.78)**	1.2 ± 0.3 (n = 122)	**0.25 (.21–.31)**	**0.18 (.15–.21)**
NTHi + *Streptococcus pneumoniae*	2.7 ± 0.3 (n = 461)	2.1 ± 0.2 (n = 196)	**0.80 (.68–.95)**	0.5 ± 0.2 (n = 48)	**0.22 (.16–.31)**	**0.18 (.13–.24)**
NTHi single culture	4.9 ± 0.5 (n = 853)	4.6 ± 0.5 (n = 422)	0.93 (.83–1.05)	1.5 ± 0.2 (n = 148)	**0.32 (.26–.38)**	**0.30 (.25–.35)**
All NTHi	7.9 ± 0.7 (n = 1370)	7.2 ± 0.8 (n = 664)	**0.91 (.83–1.00)**	2.0 ± 0.4 (n = 203)	**0.28 (.24–.33)**	**0.25 (.22–.29)**
Single *Moraxella catarrhalis*	0.3 ± 0.1 (n = 54)	0.3 ± 0.1 (n = 30)	1.05 (.67–1.64)	0.1 ± 0.0 (n = 6)	**0.18 (.08–.44)**	**0.19 (.08–.44)**
Single *Streptococcus pyogenes*	0.6 ± 0.0 (n = 109)	0.7 ± 0.2 (n = 63)	1.09 (.80–1.49)	0.2 ± 0.0 (n = 24)	**0.35 (.22–.55)**	**0.38 (.24–.59)**
Culture negative	6.7 ± 1.6 (n = 1159)	5.8 ± 0.2 (n = 535)	**0.87 (.79–.96)**	3.2 ± 0.2 (n = 329)	**0.56 (.49–.64)**	**0.49 (.43–.55)**
All-cause otitis media	19.6 ± 2.5 (n = 3411)	16.6 ± 1.5 (n = 1532)	**0.85 (.80–.90)**	6.3 ± 0.3 (n = 636)	**0.38 (.34–.41)**	**0.32 (.29–.35)**

Each study year is 1 July through 30 June.

Bold type represents numbers which are Statistically significant ($P < .05$)

Ben-Shimol et al. *CID* 2016

Recent vaccines that may help address AMR

- RSV vaccines
- Typhoid vaccines
- Malaria vaccines: RTS,S and R21/Matrix-M

New vaccines on the horizon that may help address AMR

- Improved influenza vaccines
- Nosocomial infection vaccines:
  - *S. aureus*
  - *C. difficile*
  - *P. aeruginosa*
  - *Candida*
- Others
  - *Shigella*, non-typeable *H. influenzae*
  - *N. gonorrhoeae*
  - Recurrent UTIs

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ORIGINAL ARTICLE

Sublingual MV140 for Prevention of Recurrent Urinary Tract Infections

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Vaccines to control AMR: Pros

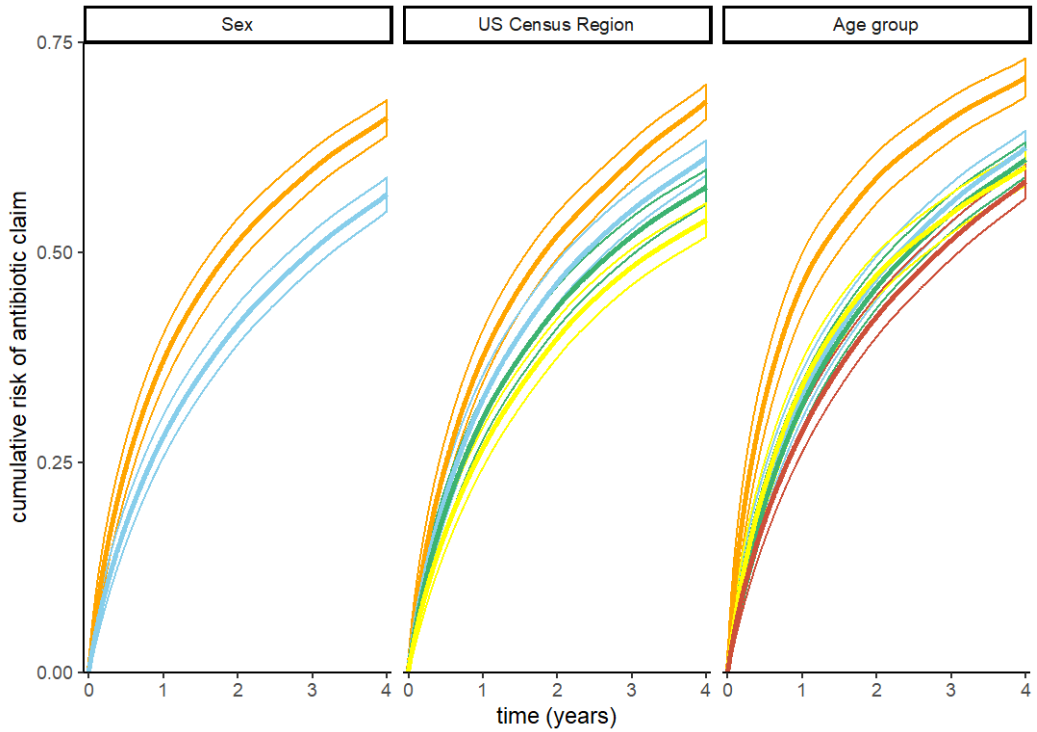
- Alignment of incentives
  - Public health: Prevent disease, prevent resistant disease, reduce antibiotic use
  - Economic: Selling a good and a service, rather than restricting (stewardship)
- Herd immunity: amplify protection beyond the recipients
- Evidence for morbidity/mortality benefits of vaccines are clearer than evidence for stewardship
- Scaleup of stewardship is challenging
- Vaccines usually more “resistance-proof” than antibiotics
- Vaccines lower R&D barrier than new antibiotics?

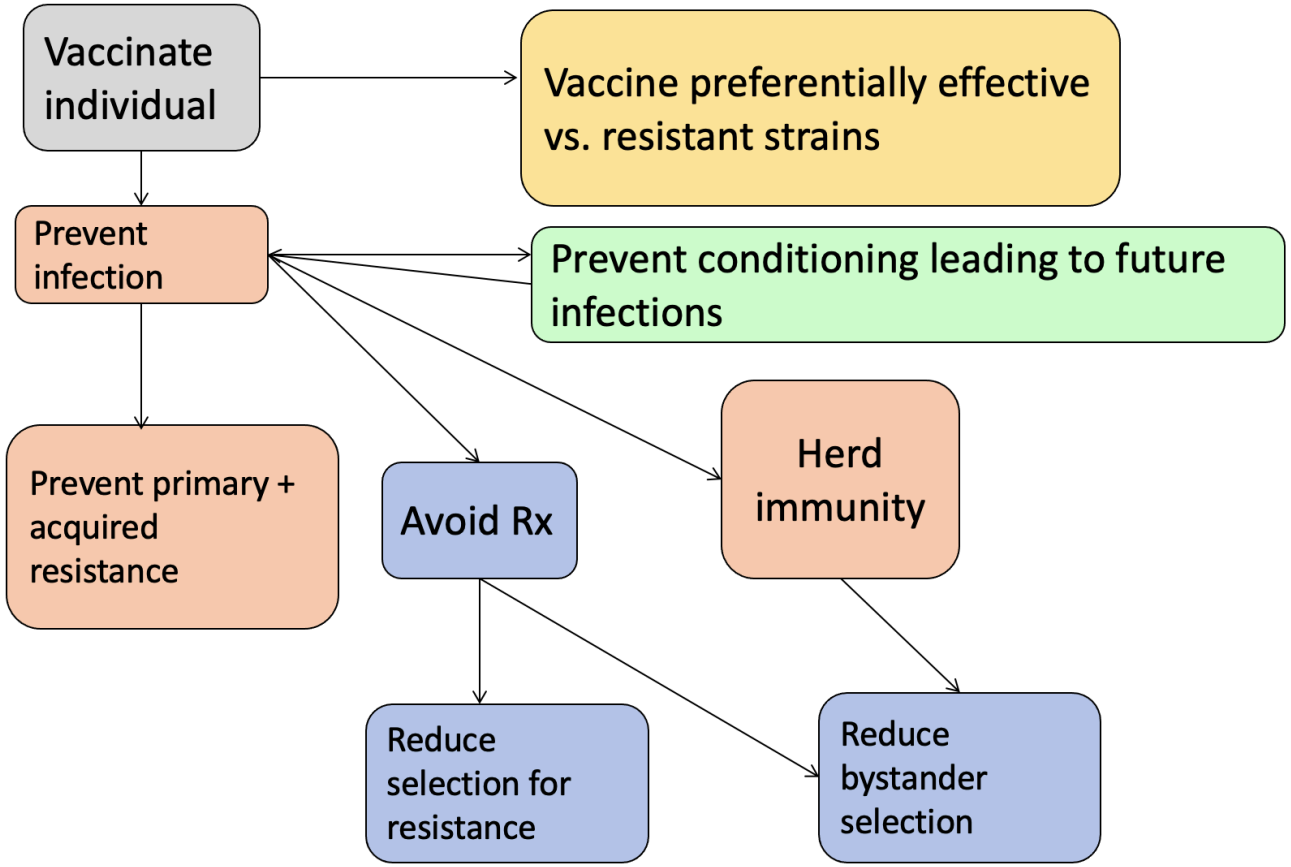
J Sevilla et al. *PNAS* 2018

Vaccines to control AMR: Cons

- Cost of vaccines and distribution vs. potential savings from stewardship
- Challenging regulatory path for vaccines against highly resistant pathogens which are rare and infect very sick, hospitalized patients
- Stewardship and innovation in antibiotic development can affect many pathogens vs. single-pathogen vaccines
- Relatedly, we will always need innovative antibiotics to treat infections not prevented by vaccines
- Vaccines could fuel compensatory risk behavior (worse hygiene, postponing sanitation innovations, risky sexual behavior) that could spread other infections
- Quantifying AMR effects of vaccines difficult
  - But similar challenges for stewardship and innovation!

J Sevilla et al. *PNAS* 2018


Sex
US Census Region
Age group
cumulative risk of antibiotic claim
0.75
0.50
0.25
0.00
0
1
2
3
4
time (years)


Vaccinate individual
Vaccine preferentially effective vs. resistant strains
Prevent infection
Prevent conditioning leading to future infections
Prevent primary + acquired resistance
Avoid Rx
Herd immunity
Reduce selection for resistance
Reduce bystander selection

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Thank you!

NIH National Institute of Allergy and Infectious Diseases

CDC Centers for Disease Control and Prevention

wellcome

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