Antibiotic Pearls and Pitfalls: Bugs, Drugs, and Stewardship

Chet Cunha, MD, FACP, FIDSA, FSHEA

Medical Director,
Antimicrobial Stewardship Program
Rhode Island Hospital & Miriam Hospital

Associate Professor of Medicine
Alpert Medical School, Brown University

BROWN
Alpert Medical School

Conflict of Interest Disclosure

- I have no financial interest or contractual relationships with any commercial interest to disclose

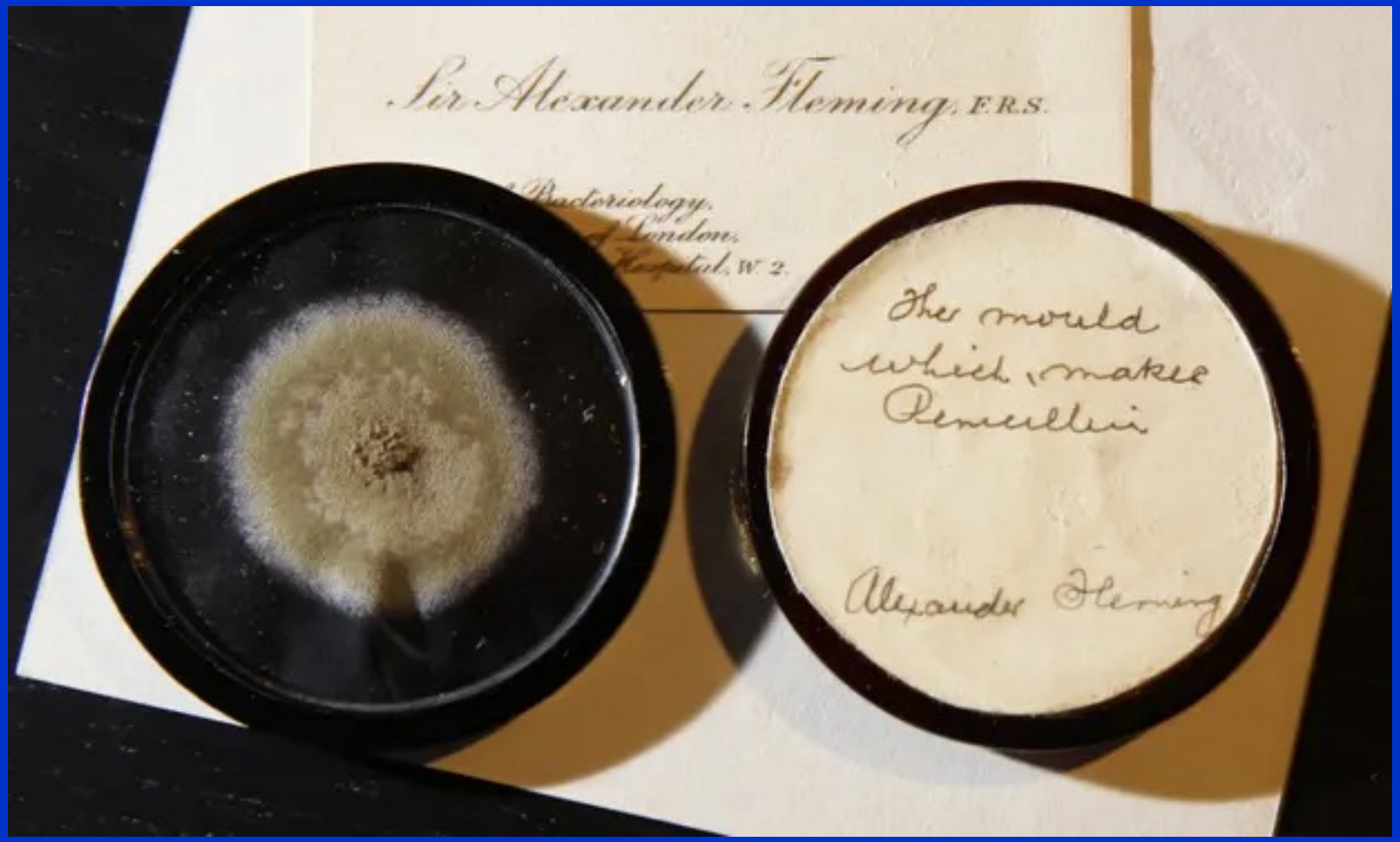
Objectives

- Discuss pearls and pitfalls related to antimicrobial use
- Recognize how a better understanding of antibiotics leads to improved stewardship
- Provide a review of selected antimicrobials

Infectious Diseases and Human History

- Impact of infectious diseases on history cannot be underestimated
- Contributed to the collapse of empires / shaped history
  - Plague of Athens (430- 426 BCE)
  - Antonine (165 – 180 CE) and Justinian (541-549 CE) Plagues
  - Exposure of “New World” to various infectious diseases
  - Smallpox in the American revolution
  - Napoleon in Russia
  - 1918 flu
- Major historical figures killed by infections
  - Alexander
  - Pericles

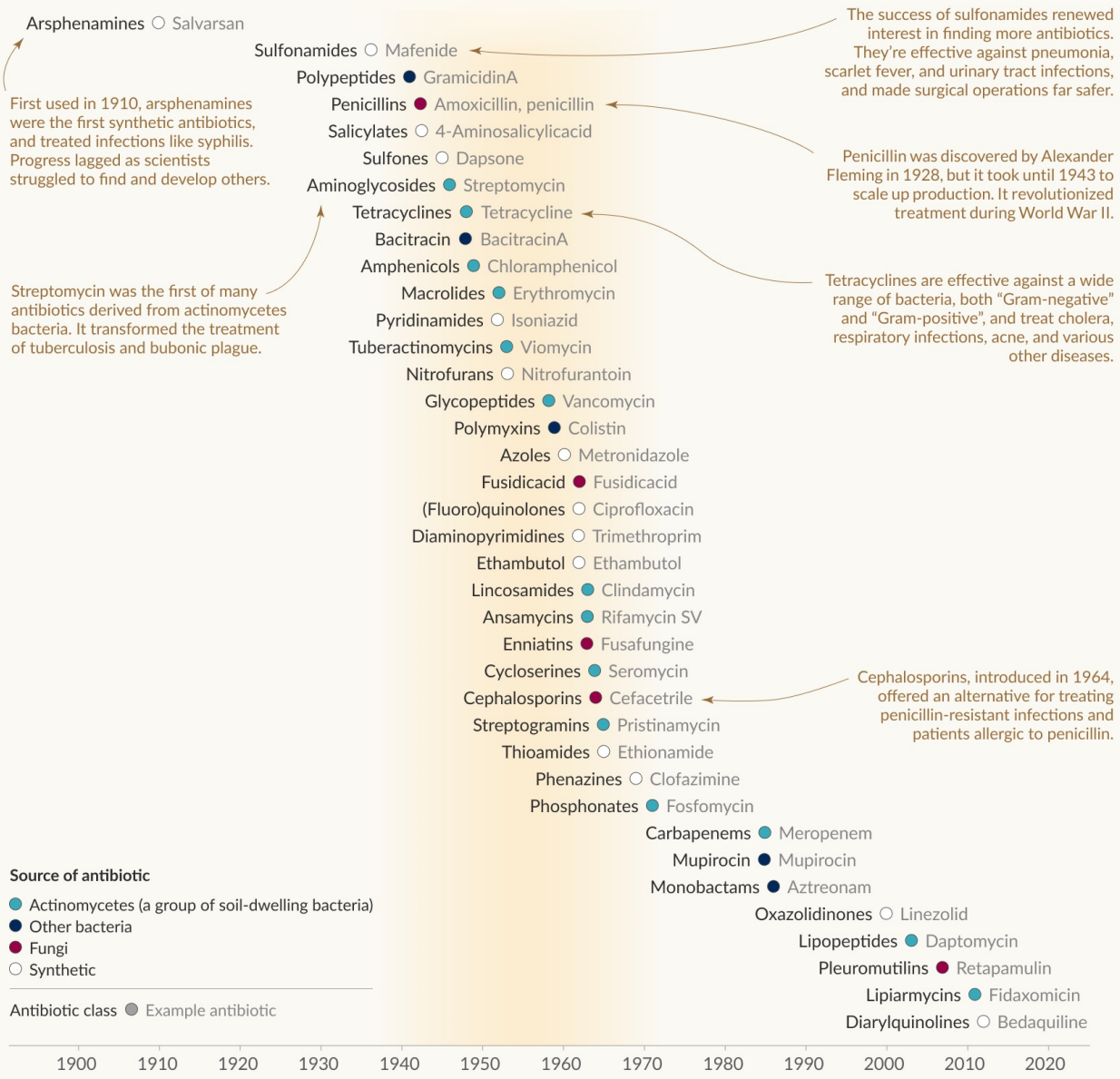
1928 - *Penicillium chrysogenum*



The Golden Age of Antibiotics

Our World in Data

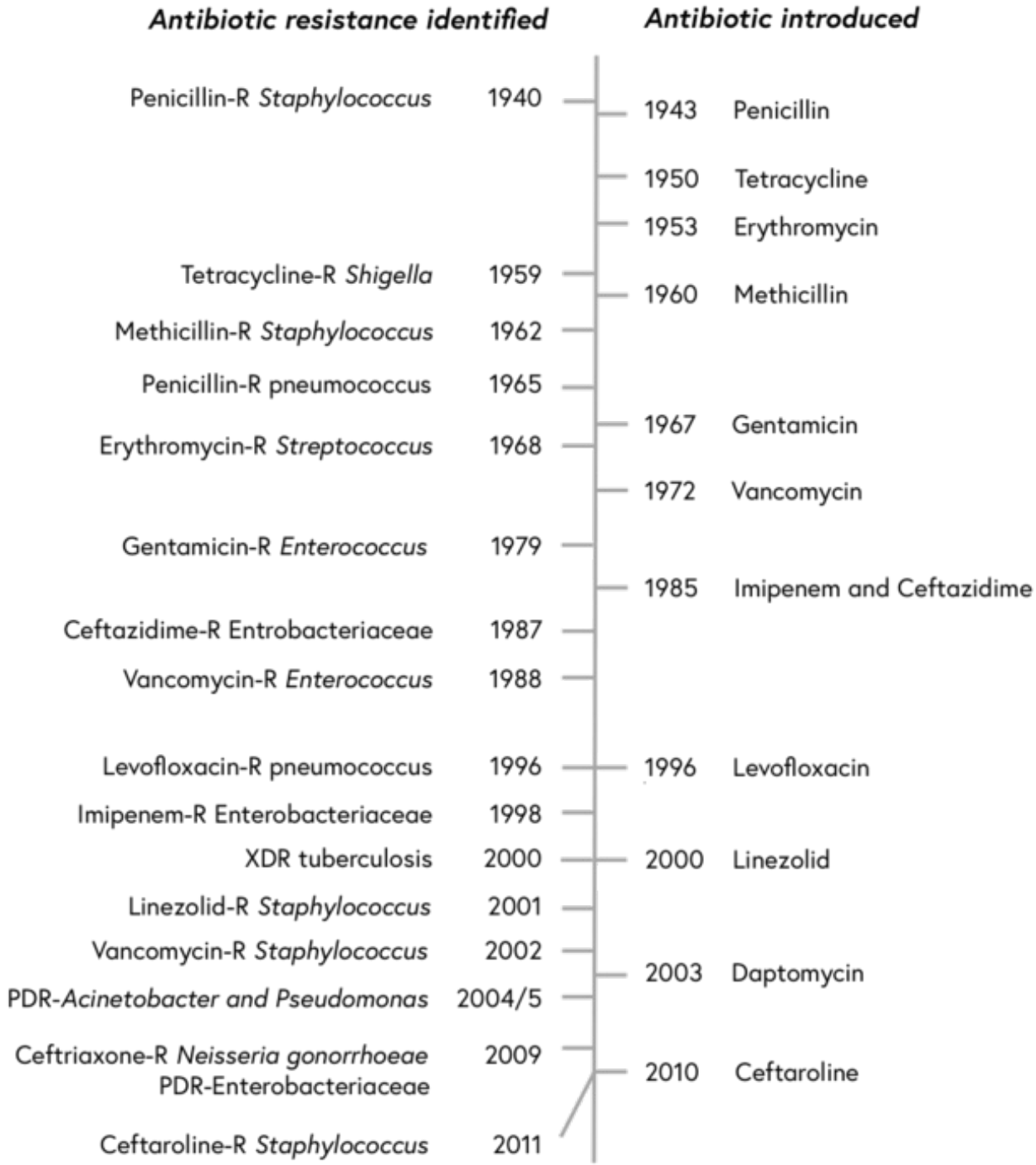
The year when each **antibiotic drug class** was first available for clinical use, along with an **example antibiotic in each drug class**, not necessarily the first.



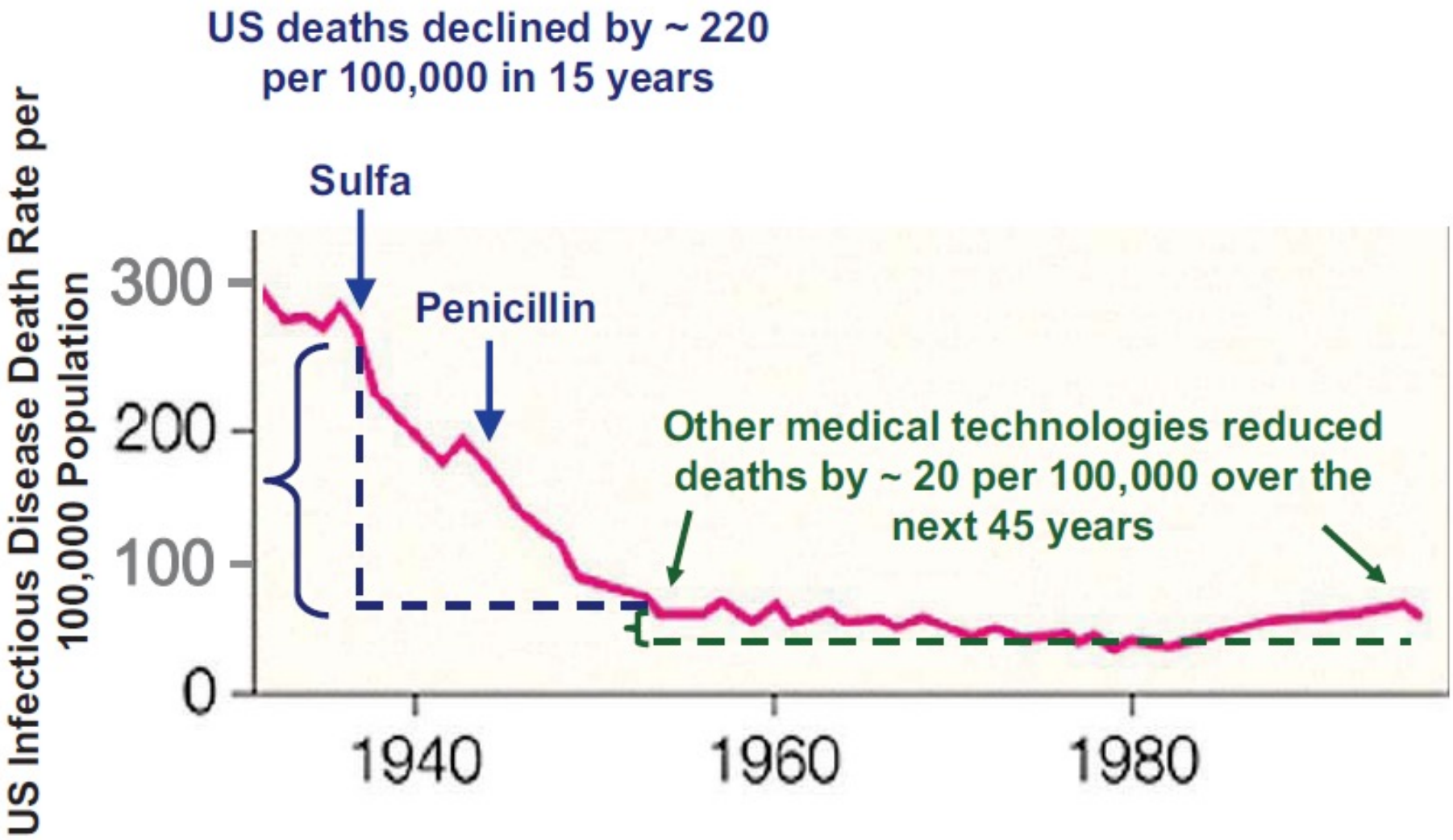
Source: Hutchings, Truman, Wilkinson (2019) Antibiotics: Past, present and future.

Note: As of 2023, no new antibiotic drug classes have become available; see AntibioticDB for further information.

Saloni Dattani (2024) - "What was the Golden Age of Antibiotics, and how can we spark a new one?" Published online at OurWorldinData.org. Retrieved from: 'https://archive.ourworldindata.org/20251125-173858/golden-age-antibiotics.html' [Online Resource] (archived on November 25, 2025).


Antibiotic resistance identified
Antibiotic introduced
Penicillin-R Staphylococcus 1940
1943 Penicillin
1950 Tetracycline
1953 Erythromycin
Tetracycline-R Shigella 1959
1960 Methicillin
Methicillin-R Staphylococcus 1962
Penicillin-R pneumococcus 1965
1967 Gentamicin
Erythromycin-R Streptococcus 1968
1972 Vancomycin
Gentamicin-R Enterococcus 1979
1985 Imipenem and Ceftazidime
Ceftazidime-R Entrobacteriaceae 1987
Vancomycin-R Enterococcus 1988
Levofloxacin-R pneumococcus 1996
1996 Levofloxacin
Imipenem-R Enterobacteriaceae 1998
XDR tuberculosis 2000
2000 Linezolid
Linezolid-R Staphylococcus 2001
Vancomycin-R Staphylococcus 2002
2003 Daptomycin
PDR-Acinetobacter and Pseudomonas 2004/5
Ceftriaxone-R Neisseria gonorrhoeae 2009
PDR-Enterobacteriaceae
2010 Ceftaroline
Ceftaroline-R Staphylococcus 2011

Infectious Disease Mortality in the United States During the 20th Century



Modified from Armstrong, G. L. et al. JAMA 1999;281:61-6.

Antibiotics: Powerful Tools

Disease	Pre-Antibiotic Death Rate	Death with Antibiotics	Change in Death
Community Acquired Pneumonia[1]	~ 35%	~ 10%	-25%
Nosocomial Pneumonia[2]	~ 60%	~ 30%	-30%
Cardiac Infection[3]	~ 100%	~ 25%	-75%
Brain Infection[4]	~ 80%	~ 20%	-60%
Skin / Soft Tissue Infection[5]	11%	< 0.5%	- 10%
MI treatment with ASA / thrombolytics[6]			~3%

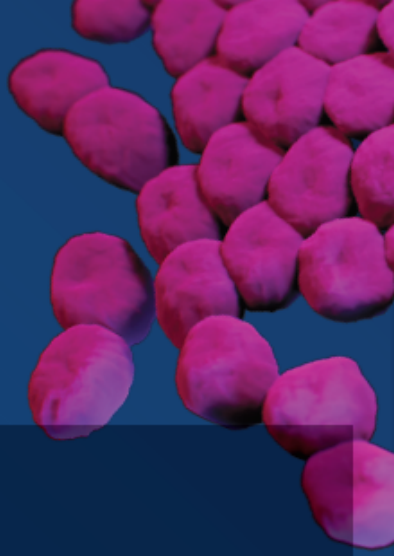
[1]IDSA Position Paper '08 Clin Infect Dis 47(S3):S249-65; [2]IDSA/ACCP/ATS/SCCM Position Paper '10 Clin Infect Dis In Press; [3]Kerr AJ. Subacute Bacterial Endocarditis. Springfield IL: Charles C. Thomas, 1955 & Lancet 1935 226:383-4; [4]Lancet '38 231:733-4 & Waring et al. '48 Am J Med 5:402-18; [5]Spellberg et al. '09 Clin Infect Dis 49:383-91 & Madsen '73 Infection 1:76-81; [6]'88 Lancet 2:349-60

Antibiotics
A Double Edged Sword

Disadvantages

- **Antibiotic side effects**
  - Phlebitis
  - Hepatotoxity
  - Nephrotoxicity
  - Diarrhea (non-*C. difficile* & *C. difficile*)
  - Drug fever
  - Drug rash
  - Seizures
- **Antibiotic *drug-drug interactions***
- **Acquired antibiotic resistance (MDROs)**

The Threat of Antibiotic Resistance in the United States



Antibiotic resistance—when germs (bacteria, fungi) develop the ability to defeat the antibiotics designed to kill them—is one of the greatest global health challenges of modern time.

New National Estimate*

Each year, antibiotic-resistant bacteria and fungi cause at least an estimated:

2,868,700 infections

35,900 deaths

+

Clostridioides difficile **is related to antibiotic use and antibiotic resistance:**

223,900 cases

12,800 deaths

New Antibiotic Resistance Threats List

Updated urgent, serious, and concerning threats—totaling 18

Comparison of different antibiotics and the risk for community-associated *Clostridioides difficile* infect A case-control study

Miller et al., 2023 | *Open Forum Infectious Diseases*

IDSA
Infectious Diseases Society of America

Study Population

Matched case-control study of patients with and without *Clostridioides difficile* infection (CDI), using a large database of commerical insurance claims.

Methods

Bayesian analysis used to estimate CDI risk associated with exposure to 27 different types of antibiotics within 30 days of infection. Comparison of time periods to capture antibiotic exposure (e.g., 90 days).

Results

Differentiated and ordered individual antibiotics in terms of their level of associated risk for CDI. Risk estimates varied across antibiotic types, classes and exposure windows.

CDI risk varies widely within and between classes of antibiotics; the individual type of antibiotic is important to consider for informing antibiotic stewardship tradeoffs with regard to CDI risk.

Open Forum Infectious Diseases https://doi.org/10.1093/ofid/ofad413

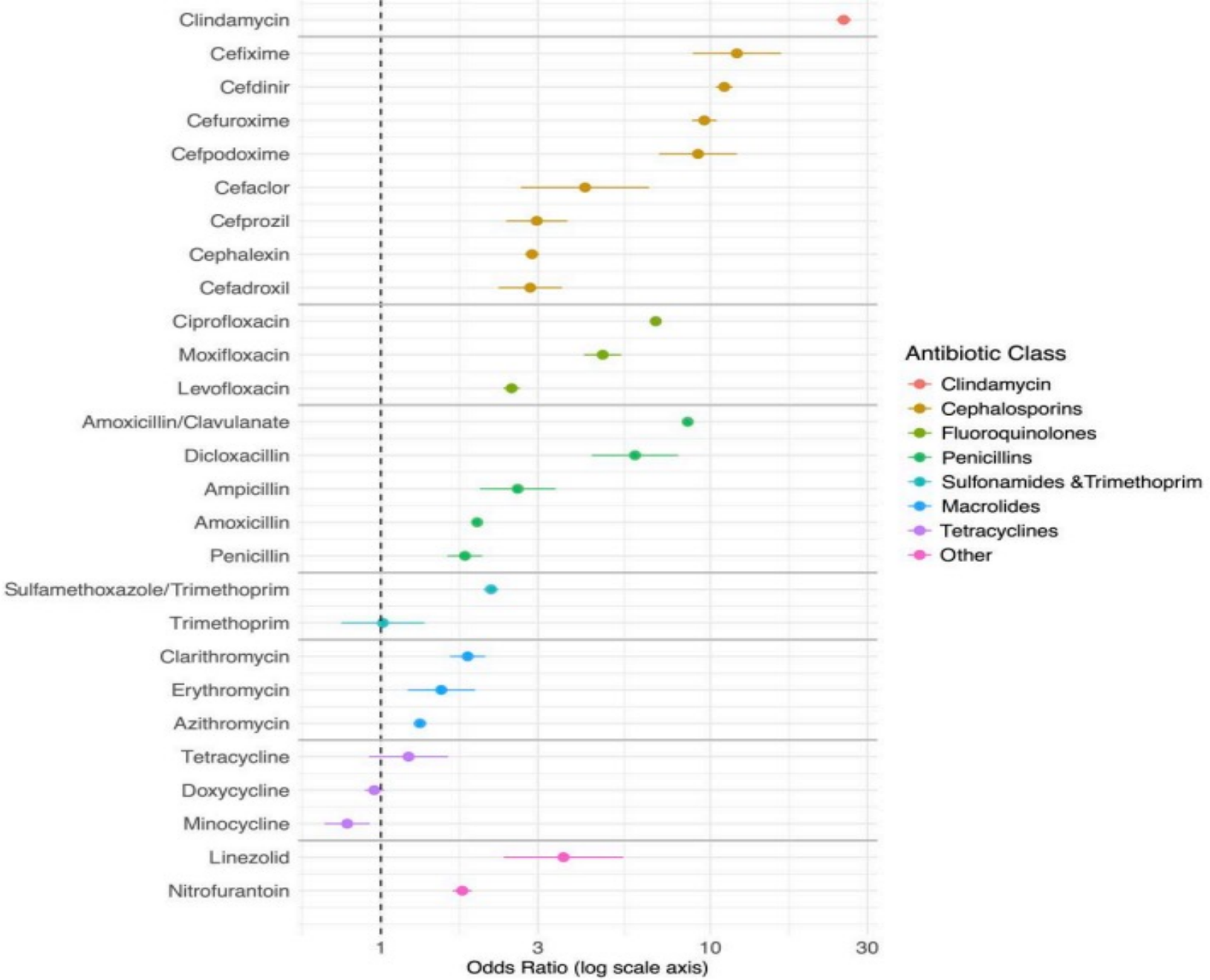


Figure 1. Visual comparison of effect estimates across antibiotic types, grouped by antibiotic class. Point estimates are depicted by the circle and 95% credible intervals by the line segments. Exact values can be found in Table 2.

Antibiotics may be misused

- Given when they are not needed
- Continued when they are no longer necessary
- Given at the wrong dose
- Broad spectrum used to treat very susceptible bacteria (depending on the agent)
- The wrong antibiotic is given to treat an infection
  - Inappropriate for site, nonsusceptible at site, tissue penetration problem

NEW CDC DATA

MORE THAN HALF OF ANTIBIOTIC PRESCRIBING FOR SELECTED EVENTS IN HOSPITALS WAS NOT CONSISTENT WITH RECOMMENDED PRESCRIBING PRACTICES

ANTIBIOTIC PRESCRIBING WAS NOT SUPPORTED IN:

- **79%** OF PATIENTS with community-acquired pneumonia
- **77%** OF PATIENTS with urinary tract infections
- **47%** OF PATIENTS prescribed fluoroquinolone treatment
- **27%** OF PATIENTS prescribed intravenous vancomycin antibiotic

HOSPITAL PRESCRIBERS & PHARMACISTS CAN IMPROVE PRESCRIBING:

- Optimize antibiotic selection
- Re-assess antibiotic treatment when the results of diagnostic testing are available
- Use the shortest effective duration of therapy

FIND RESOURCES ON HOW TO IMPROVE HOSPITAL ANTIBIOTIC USE AND HELP FIGHT ANTIBIOTIC RESISTANCE:

https://bit.ly/HospitalCoreElements

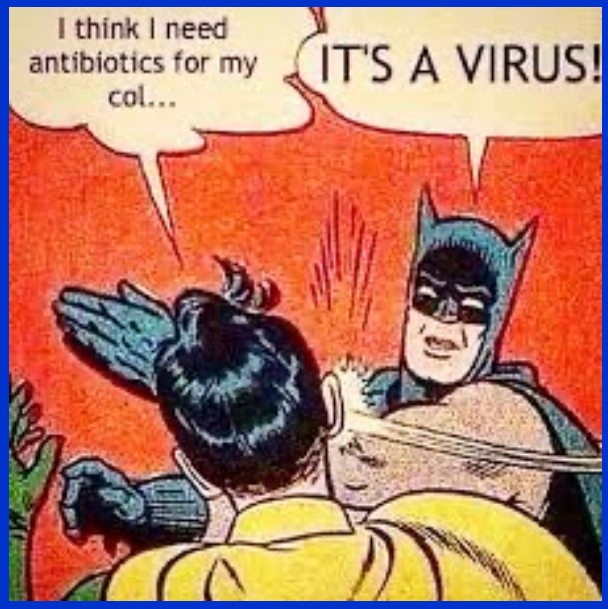
Avoid Antibiotics for Inappropriate Indications

- Viral respiratory tract infections

  - COVID-19, "Colds", acute bronchitis, non-streptococcal pharyngitis

- Early or mild sinusitis

- Asymptomatic bacteriuria (ASB)
  - Except in specific patient populations



Little or no potential benefits which are significantly outweighed by potential harms!

Why do we misuse antibiotics so much?

- Personal experience
- Fear of lawsuits
- Lack of knowledge about antibiotics
- Safety Blanket
- TRADITION / ?Addiction?

ASP – Not Just an Inpatient Issue

- Inpatient is important and is typically the most developed / has most resources
- Long term-care facilities
- ESRD Facilities

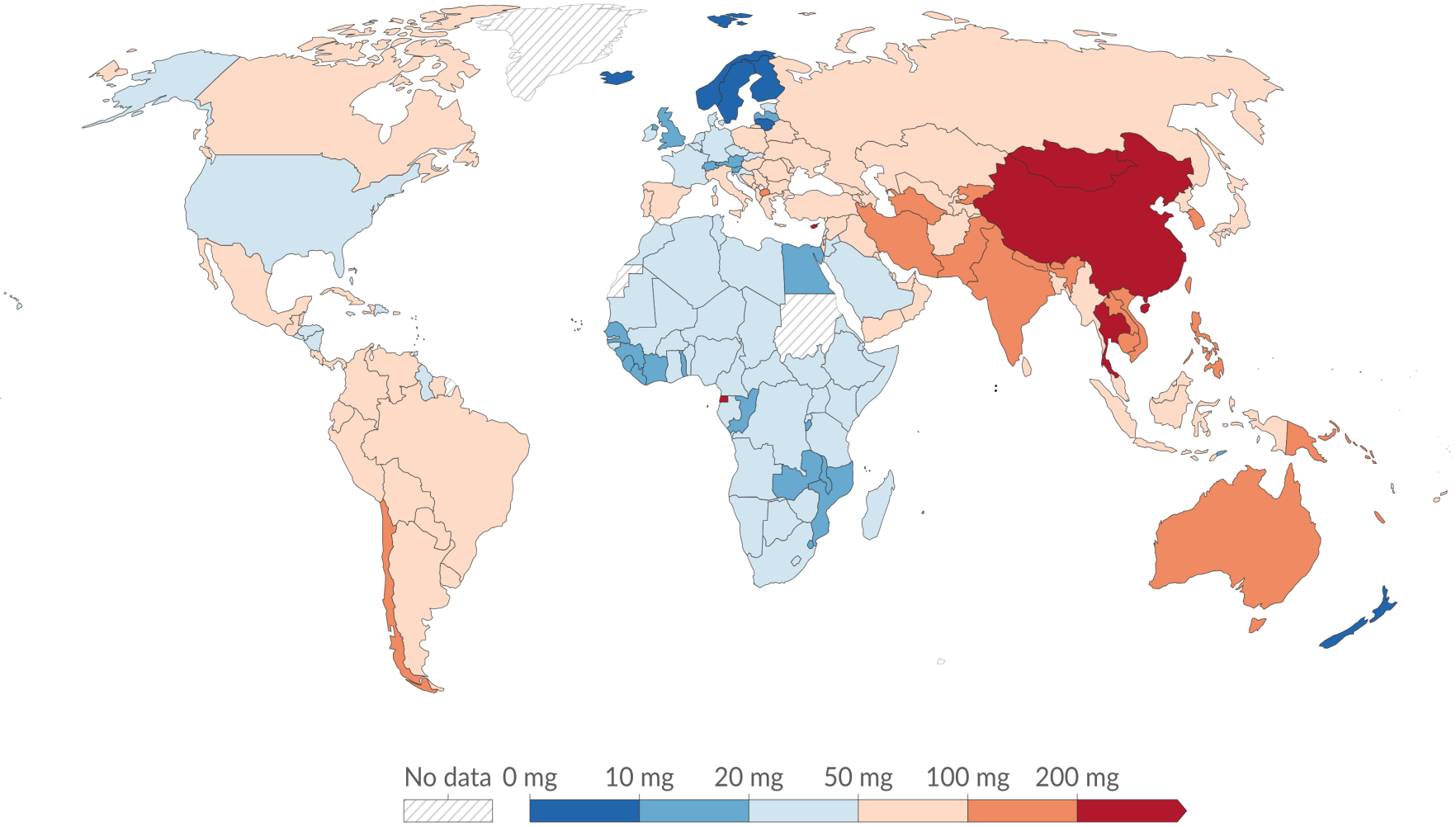
ASP – Not Just an Inpatient Issue

- Outpatient settings:
  - Dental practices
  - Emergency departments
  - Walk-in clinics/Urgent care centers
  - Ambulatory Surgery Centers (ASCs)
  - Physician offices
  - Outpatient pharmacies
- Non-human antibiotic use (livestock, etc.)
  - ~70% globally

Antibiotic usage in livestock per kilogram of meat 2020

Our World in Data

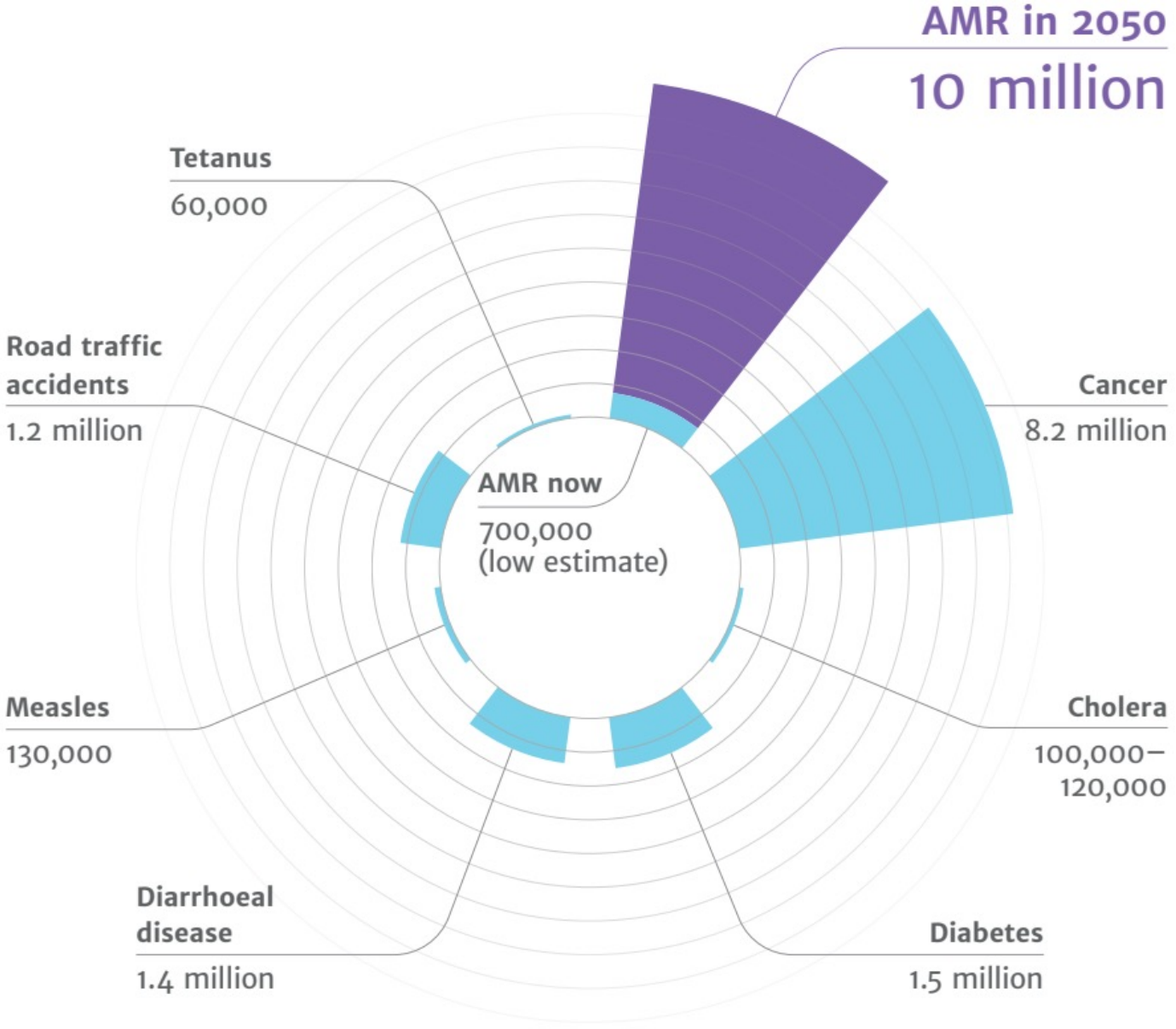
Milligrams of antibiotic use per kilogram of livestock. This is adjusted for differences in livestock numbers and species by standardizing to a population-corrected unit (PCU).



Data source: Mulchandani et al. (2023)

OurWorldinData.org/antibiotics | CC BY

Note: Researchers working on antimicrobial resistance have proposed a threshold of 50mg per PCU, which is shown as a threshold here.

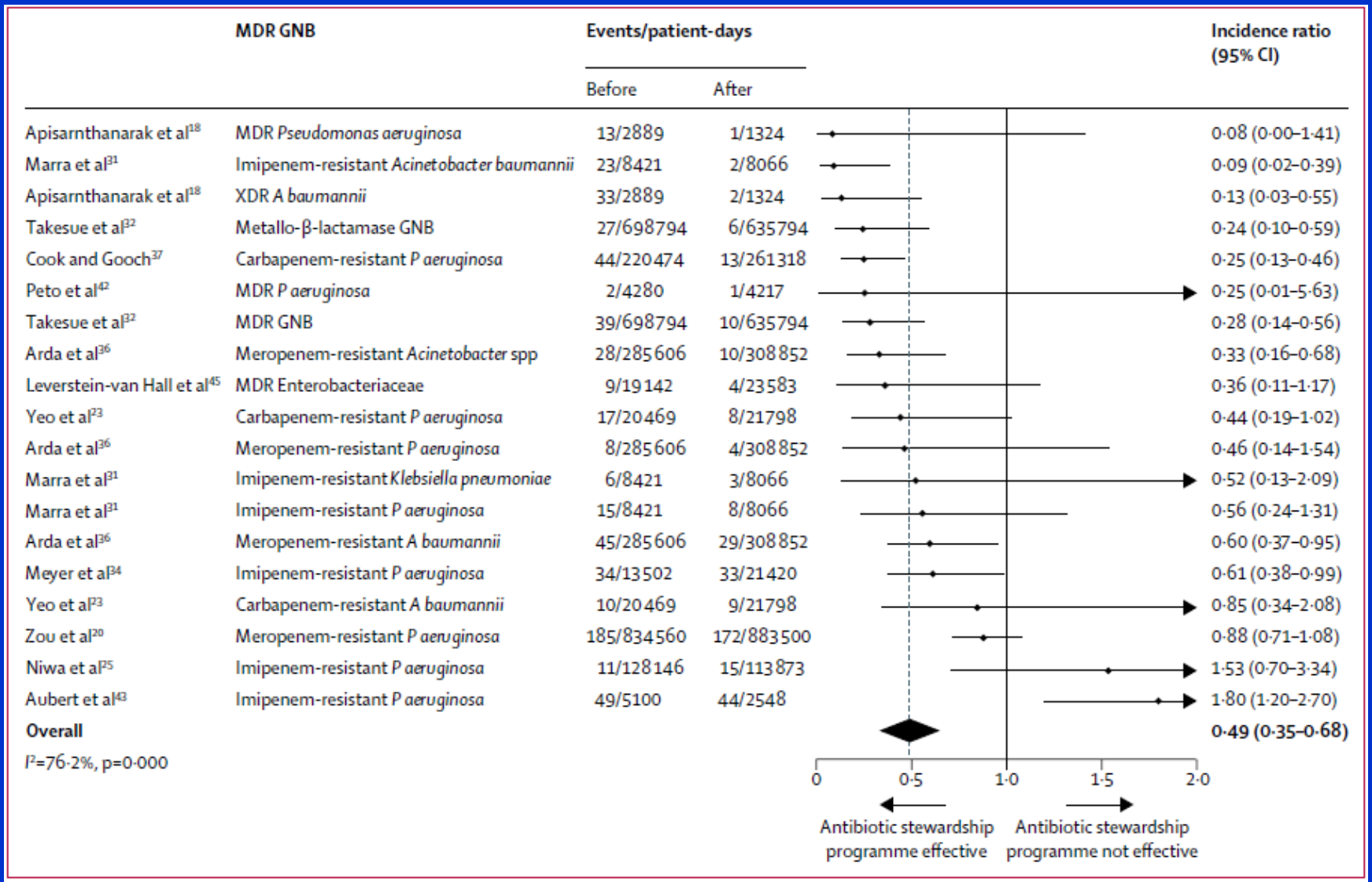


https://www.fdiworlddental.org/sites/default/files/2020-11/abr_white_paper_english.pdf

Does Stewardship Work?

- Improve quality of patient care
- Decreased:
  - Length of stay
  - Antimicrobial resistance
  - *C. difficile* infections
  - IV antimicrobial use
  - Other complication of antimicrobials

Effect of Antibiotic Stewardship on Antibiotic Resistance



	MDR GNB	Events/patient-days		Incidence ratio (95% CI)
		Before	After	
Apisarnthanarak et al[18]	MDR *Pseudomonas aeruginosa*	13/2889	1/1324	0·08 (0·00–1·41)
Marra et al[31]	Imipenem-resistant *Acinetobacter baumannii*	23/8421	2/8066	0·09 (0·02–0·39)
Apisarnthanarak et al[18]	XDR *A baumannii*	33/2889	2/1324	0·13 (0·03–0·55)
Takesue et al[32]	Metallo-β-lactamase GNB	27/698794	6/635794	0·24 (0·10–0·59)
Cook and Gooch[37]	Carbapenem-resistant *P aeruginosa*	44/220474	13/261318	0·25 (0·13–0·46)
Peto et al[42]	MDR *P aeruginosa*	2/4280	1/4217	0·25 (0·01–5·63)
Takesue et al[32]	MDR GNB	39/698794	10/635794	0·28 (0·14–0·56)
Arda et al[36]	Meropenem-resistant *Acinetobacter* spp	28/285606	10/308852	0·33 (0·16–0·68)
Leverstein-van Hall et al[45]	MDR Enterobacteriaceae	9/19142	4/23583	0·36 (0·11–1·17)
Yeo et al[23]	Carbapenem-resistant *P aeruginosa*	17/20469	8/21798	0·44 (0·19–1·02)
Arda et al[36]	Meropenem-resistant *P aeruginosa*	8/285606	4/308852	0·46 (0·14–1·54)
Marra et al[31]	Imipenem-resistant *Klebsiella pneumoniae*	6/8421	3/8066	0·52 (0·13–2·09)
Marra et al[31]	Imipenem-resistant *P aeruginosa*	15/8421	8/8066	0·56 (0·24–1·31)
Arda et al[36]	Meropenem-resistant *A baumannii*	45/285606	29/308852	0·60 (0·37–0·95)
Meyer et al[34]	Imipenem-resistant *P aeruginosa*	34/13502	33/21420	0·61 (0·38–0·99)
Yeo et al[23]	Carbapenem-resistant *A baumannii*	10/20469	9/21798	0·85 (0·34–2·08)
Zou et al[20]	Meropenem-resistant *P aeruginosa*	185/834560	172/883500	0·88 (0·71–1·08)
Niwa et al[25]	Imipenem-resistant *P aeruginosa*	11/128146	15/113873	1·53 (0·70–3·34)
Aubert et al[43]	Imipenem-resistant *P aeruginosa*	49/5100	44/2548	1·80 (1·20–2·70)
Overall				**0·49 (0·35–0·68)**
I^2=76·2%, p=0·000				

Figure 2: **Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of MDR GNB**
GNB=Gram-negative bacteria. MDR=multidrug-resistant. XDR=extensively drug-resistant.

Baur D, Gladstone BP, Burkert F, Carrara E, Foschi F, Döbele S, Tacconelli E. Effect of antibiotic stewardship on the incidence of infection and colonisation with antibiotic-resistant bacteria and Clostridium difficile infection: a systematic review and meta-analysis. Lancet Infect Dis. 2017 Sep;17(9):990-1001. doi: 10.1016/S1473-3099(17)30325-0. Epub 2017 Jun 16. PMID: 28629876.

Effect of Antibiotic Stewardship on *C. difficile*

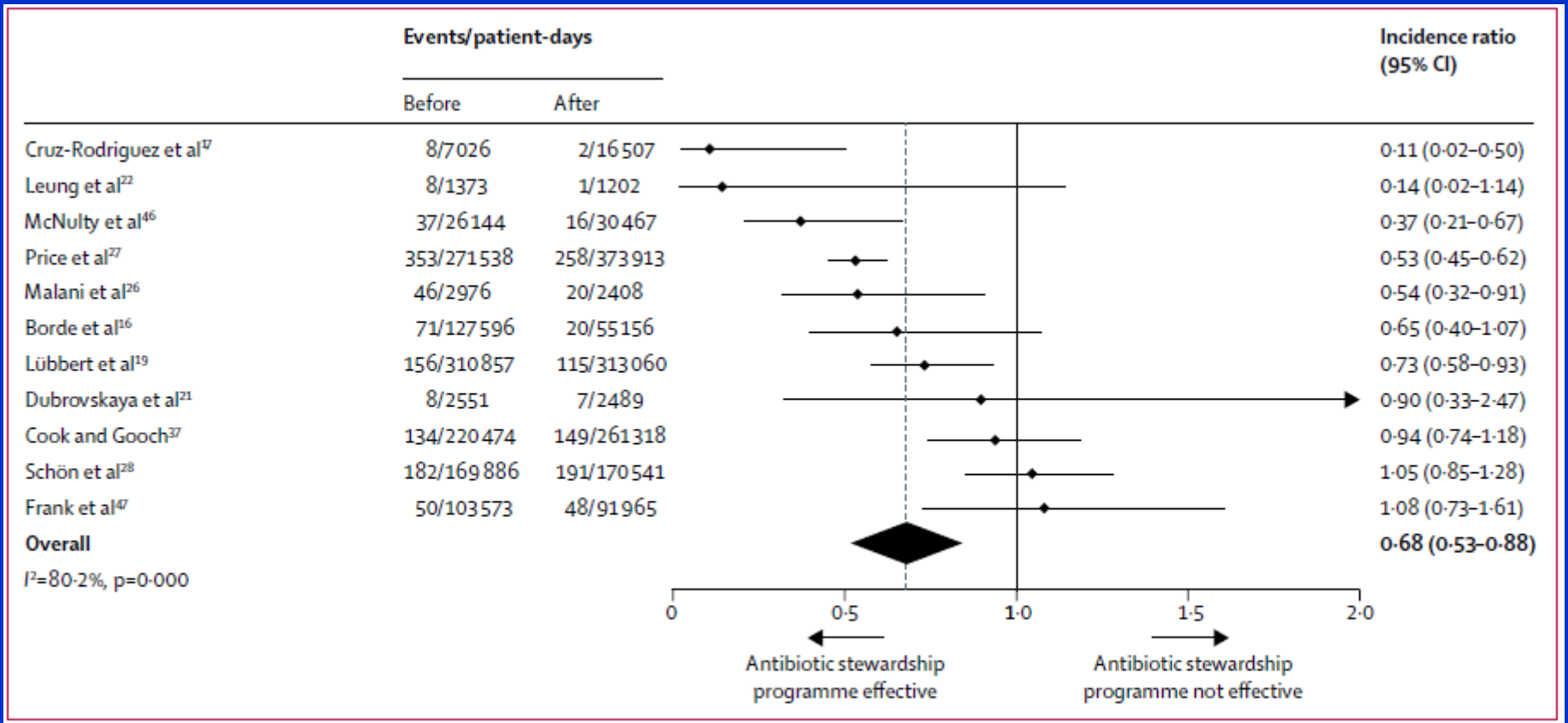


Figure 4: Forest plot of the incidence ratios for studies of the effect of antibiotic stewardship on the incidence of *Clostridium difficile* infections

How can I be a good steward?

- Make sure you have the correct diagnosis
  - Make sure that diagnosis needs antibiotics!
  - Target your therapy using the diagnostics you have
- Optimize the route of antibiotic administration (PO)
- Treat only as long as you need (shorter is better)
- Help dispel false PCN allergies

Factors in Antibiotic Selection

Key Factors

- **Appropriate Spectrum** (*based coverage of usual body site* flora)
- **Tissue Penetration** (*must achieve therapeutic concentration at site of infection*)
- "**Low Resistance Potential"** (*first do no harm*!)
- **Side Effect Profile** (*avoid antibiotics with high C. difficile potential*)

Unimportant Factors

- **Bactericidal vs. bacteriostatic**
- **Synergy** (*rarely important and applicable to very few organisms*)

Antibiotic Resistance Potential

"High resistance potential" antibiotics → *antibiotics to avoid*

- **Ciprofloxacin**
  (*S. pneumoniae, P. aeruginosa*, ↑ MRSA)
- **TMP-SMX**
  (*S. pneumoniae, E. coli*)
- **Imipenem**
  (*P. aeruginosa*, ↑ MRSA)
- **Gentamicin/tobramycin**
  (*P. aeruginosa*)
- **Ceftazidime**
  (*P. aeruginosa*, ↑ MRSA)
- **Macrolides**
  (*S. pneumoniae*)

"Low resistance potential" antibiotics

IV

- Meropenem
- Ceftriaxone
- Piperacillin/tazobactam
- Aztreonam
- Cefepime
- Colistin/Polymyxin B
- Tigecycline

PO

- Doxycycline
- Minocycline
- Levofloxacin/Moxifloxacin
- Linezolid
- Fosfomycin
- Nitrofurantoin

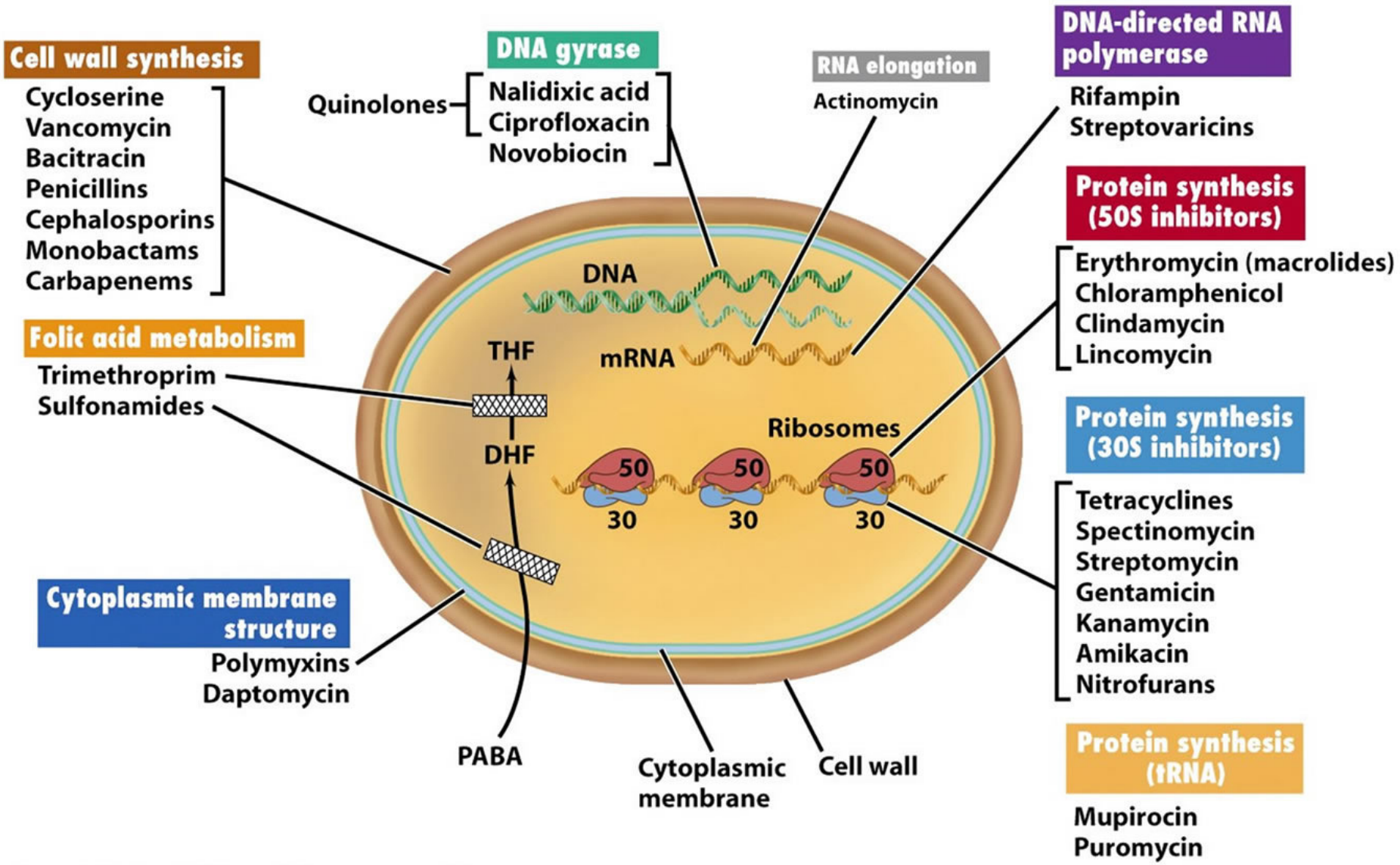
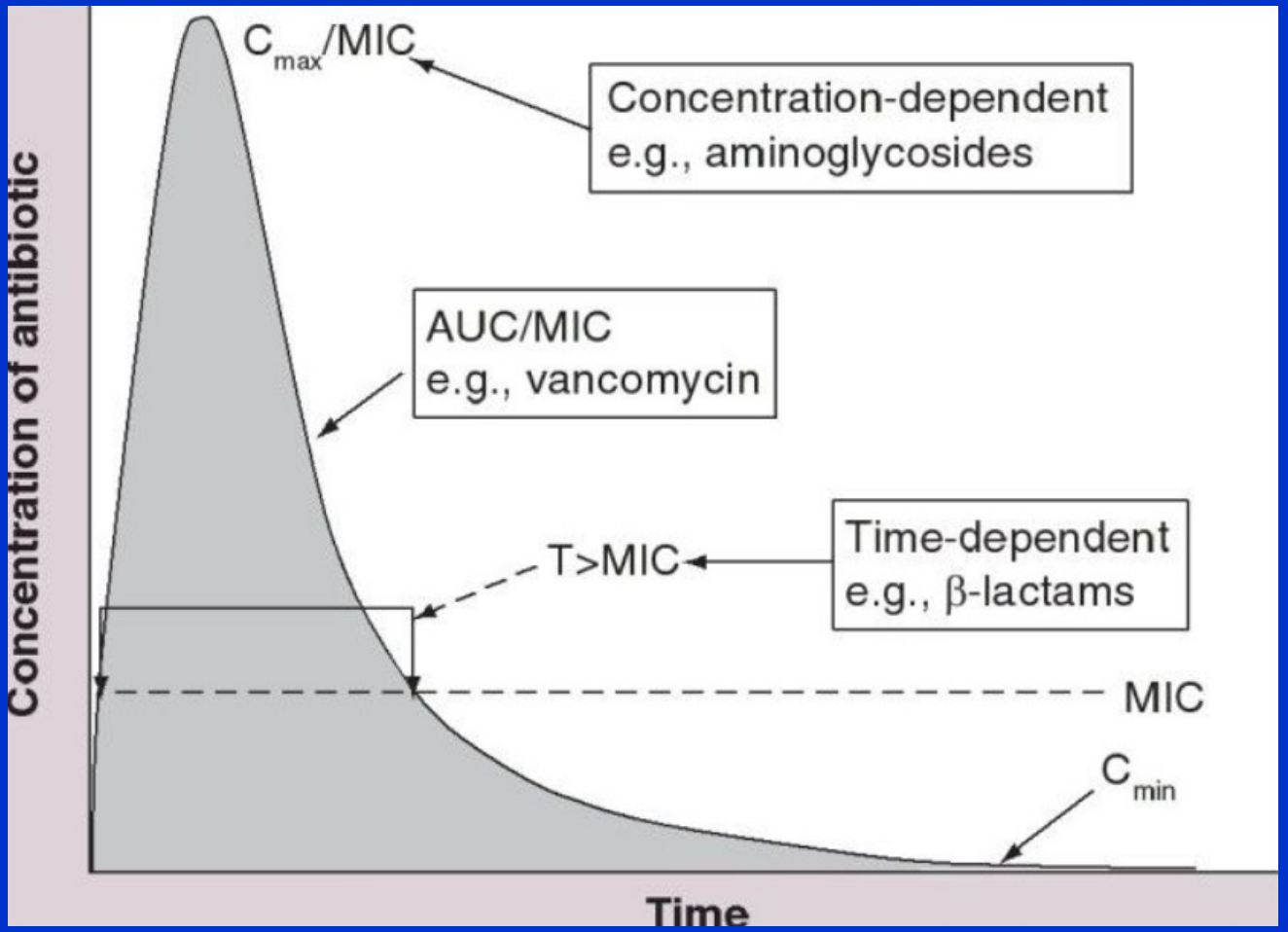


Figure 20-14 Brock Biology of Microorganisms 11/e

PK / PD Considerations in Antibiotic Dosing



Cunha CB, Cunha BA. Antibiotic Essentials (18 ed). Jaypee Publishing, New Delhi, 2024.

Penicillin

- **Route:** IV = G; PO = V or VK
- **Mode of elimination:** Renal

- **Hits**: Streptococci
  Gram negative diplococci (MC & GC)
  Oral anaerobes
  Syphilis

- **Misses**: MSSA/MRSA, ? *E. faecalis* (VSE), / *E. faecium* (VRE), GNBs, *B. fragilis*

- **Monotherapy:** Group A Streptococci (GAS), *S. pneumoniae*, syphilis
- **Oral PCN V/VK:** prophylaxis / therapy dental infections

- **SE**: Drug fever, drug rash, serum sickness

Penicillin Allergy Facts

- ~10 % of all patients **reports** an allergy to PCN
- <1% of the population has a true IgE-mediated reaction
- ~80% of patient with IgE-mediated reactions lose sensitivity within 10 years
- Broad-spectrum antibiotics are often used as an alternative to penicillins. The use of broad-spectrum antibiotics in patients labeled “penicillin-allergic” is associated with higher healthcare costs, increased risk for antibiotic resistance
- Correctly identifying those who are not truly penicillin-allergic can decrease unnecessary use of broad-spectrum antibiotics

Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma and Immunology; American College of Allergy, Asthma and Immunology; JointCouncil of Allergy, Asthma and Immunology. Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol. 2010 Oct;105(4):259-273.

Supplement Figure 1. Beta-lactam Cross-Reactivity Chart

Antibiotic Ordered	Antibiotic Allergy: "Penicillin"	"Cephalosporin"	Amoxicillin/Amox/clav	Ampicillin/Amp/sulb	Aztreonam	Cefaclor	Cefazolin	Cefepime	Cefotaxime	Cefoxitin	Cefdinir	Ceftaroline	Ceftriaxone	Cefuroxime	Cephalexin	Ceftazidime/avibactam	Ceftolozane/tazobactam	Nafcillin	Penicillin G	Piperacillin/tazobactam
Amoxicillin/Amox/clav [16-21]	N	CPa,b		Nb	Yb	Na,b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Nb	Yb	Yb	CPb	Nb	CPb
Ampicillin/Amp/sulb [16-21]	N	Cpa,b	Nb		Yb	Na,b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Nb	Yb	Yb	CPb	Nb	CPb
Aztreonam [17, 19, 21]	Yb	Yb	Yb	Yb		Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Nb	CPb	Yb	Yb	Yb
Cefaclor [16-21]	N	N	Na,b	Na,b	Yb		Yb	Ya,b	Yb	Yb	Yb	Yb	UAa	UAa	Na,b	Yb	Yb	Yb	UAb	CPb
Cefazolin [16-21]	Ya,b	N	Yb	Yb	Yb	Yb		Yb	Yb	Ya,b	Yb	Yb	Ya,b	Ya,b	Yb	Yb	Yb	Yb	Yb	Yb
Cefepime [16-19, 21]	Ya,b	N	Yb	Yb	Yb	Ya,b	Yb		Nb	Yb	UAb	UAb	Na,b	Na,b	Yb	CPb	CPb	Yb	Yb	Yb
Cefotaxime [16-21]	Ya,b	N	Yb	Yb	Yb	Yb	Yb	Nb		UAb	UAb	UAb	Na,b	Na,b	Ya,b	Na,b	CPb	Yb	Yb	Yb
Cefoxitin [16-21]	UAb	N	Yb	Yb	Yb	Yb	Ya,b	Yb	UAb		Yb	Yb	UAb	Nb	Ya,b	Yb	Yb	Yb	Nb	Yb
Cefdinir [16-19, 21]	Yb	N	Yb	Yb	Yb	Yb	Yb	UAb	UAb	Yb		UAb	UAb	Yb	Yb	UAb	UAb	Yb	Yb	Yb
Ceftaroline [17-19, 21]	Yb	N	Yb	Yb	Yb	Yb	Yb	UAb	UAb	Yb	UAb		UAb	UAb	Yb	UAb	UAb	Yb	Yb	Yb
Ceftriaxone [16-21]	Ya,b	N	Yb	Yb	Yb	UAa	Ya,b	Na,b	Na,b	UAb	UAb	UAb		Na,b	UAa,b	Na,b	UAb	Yb	Yb	Yb
Cefuroxime [16-21]	Ya,b	N	Yb	Yb	Yb	UAa	Ya,b	Na,b	Na,b	Nb	Yb	UAb	Na,b		Ya,b	UAa,b	UAb	Yb	Yb	Yb
Cephalexin [16-21]	Na,b	N	Nb	Nb	Yb	Na,b	Yb	Yb	Ya,b	Ya,b	Yb	Yb	UAa,b	Ya,b		UAa	Yb	CPa	Nb	CPb
Ceftazidime/avibactam [16-21]	Ya,b	N	Yb	Yb	Nb	Yb	Yb	CPb	Na,b	Yb	UAb	UAb	Na,b	UAa,b	UAa		Nb	Yb	Yb	Yb
Ceftolozane/tazobactam [17, 19, 21]	Yb	N	Yb	Yb	CPb	Yb	Yb	CPb	CPb	Yb	UAb	UAb	UAb	UAb	Yb	Nb		Yb	Yb	Nc
Ertapenem [18]	Ya,b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb
Meropenem [18]	Ya,b	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb
Nafcillin [17, 19]	CPb	Yb	CPb	CPb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	CPa	Yb	Yb		CPb	CPb
Penicillin G [16-21]	N	CPb	Nb	Nb	Yb	UAb	Yb	Yb	Yb	Nb	Yb	Yb	Yb	Yb	Nb	Yb	Yb	CPb		CPb
Piperacillin/tazobactam [17-19]	N	UA	CPb	CPb	Yb	CPb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	Yb	CPb	Yb	Nc	CPb	CPb	

aComparison data in beta-lactam allergic patients; bSide chain extrapolation of beta-lactam antibiotic; cExtrapolation of beta-lactamase inhibitor

Y The order may be ordered/verified as long as any reaction other than type I-IV hypersensitivity reactions (HSRs). This includes general or non-specific allergy listings. For type I HSRs, a beta-lactam with a different side chain CAN be safely administered; however, prescribers should be notified to communicate this information and confirm the order. Avoid use in type II-IV HSRs.

UA "OK Unless Anaphylaxis" Agent may have limited or conflicting data or share a similar (not identical) side chain. Order/verify as long as the reaction is NOT listed as a type I-IV HSR.

N Should not be ordered/verified due to a higher likelihood of cross-reactivity. If ordered, the prescriber should be notified, and a different agent considered.

CP "Call Prescriber" The agent may have limited or conflicting data or share a similar (not identical) side chain. Risk/benefit should be evaluated.

Ampicillin

- **Route: IV / PO**
- **Mode of elimination: Renal**
- **Hits**: Same as penicillin plus Enterococci (VSE), Listeria
- **Misses**: MSSA / MRSA, VRE, most GNBs, *B. fragilis*
- **Monotherapy:** Enterococcal endocarditis (usually ~~+ gent~~ / ceftriaxone), Listeria
- **SE**: Drug fever, drug rash
- **Pearls & Pitfalls (P&P):** No role for PO ampicillin, use PO amoxicillin instead
  - Ampicillin/sulbactam – may be active against MDR-Acinetobacter

Macrolides

- **Azithromycin**
- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** GPCs (resistance in *S. pneumoniae*, MSSA), atypicals, some zoonotic pathogens, *H. flu*, *Bordetella pertussis*

- **Misses:** Most GPCs due to increasing resistance

- **Therapy:** CAP with beta-lactam, AECB, Babesiosis (with atovaquone)

- **SE**: QT prolongation (far less than IV erythro), GI upset

Cephalosporins

- **1st generation (IV cefazolin; PO cephalexin, cefadroxil)**
- **Route:** IV *HD / PO
- **Mode of elimination: Renal**

- **Hits:** Streptococci, MSSA, *E. coli*

- **Misses:** Listeria, VSE/VRE, MRSA, atypicals, Enterobacter, Serratia, *P. aeruginosa, B. fragilis*

- **Monotherapy:** MSSA infections (not primary CNS), SSSIs, surgical ppx

- **SE**: Generally favorable / well tolerated
  cefazolin – unique side chain
  cephalexin 1G PO q6h = 1G cefazolin IV q8h
  cefadroxil effective with BID dosing

Cephalosporins

- **2nd generation (IV cefoxitin, cefotetan; PO cefuroxime)**
- **Route: IV / PO**
- **Mode of elimination: Renal**

- **Hits:** All from 1st gen plus *B. fragilis* (cefoxitin / cefotetan)

- **Misses:** Listeria, VSE/VRE, MRSA, atypicals, Enterobacter, Serratia, *P. aeruginosa*

- **Monotherapy:** mild to moderate IAI, DM foot infections (MSSA, GBS, GNBs, *B. fragilis*)

- **SE**: Cefotetan - disulfiram reaction from MTT side chain

Cephalosporins

- **3rd generation** (IV ceftriaxone, ceftazidime; PO cefpodoxime)
- **Route: IV *HD (ceftazidime) / PO**
- **Mode of elimination: Renal** (ceftriaxone is renal / hepatic, cefoperazone is hepatic)

- **Hits:** All from 1st gen plus GNBs (Klebsiella, Enterobacter, Serratia)

- **Misses:** Listeria, VRE (cefoperazone hits VSE), MRSA, atypicals, *B. fragilis*, *P. aeruginosa* except for cefoperazone & ceftazidime

- **Monotherapy:** Acute bacterial meningitis (excluding Listeria), CAP (typical), viridans Strep SBE, Lyme disease

- **Combination therapy:** IAI if used with *B. fragilis* drug (metronidazole)

- **SE**: Biliary sludging with ceftriaxone (reversible)

- P&P: Use meningeal dose for ABM (2 G IV q12h), ceftazidime has little MSSA activity
  - 1 G ceftriaxone OK for most infections other than CNS

Cephalosporins

- **4rd generation (IV cefepime)**
- **Route: IV *HD**
- **Mode of elimination: Renal**

- **Hits:** All from 3rd gen plus *P. aeruginosa*

- **Misses:** MRSA, VSE/VRE, atypicals, Listeria, *B. fragilis*

- **Monotherapy:** Febrile neutropenia, nosocomial PNA, *P. aeruginosa* infection

- **Combination therapy:** IAI if used with *B. fragilis* drug (metronidazole)

- **SE**: Seizures - usually in patients with renal insufficiency, high dose

Cephalosporins

- **5th generation (Anti-MRSA) cephalosporin - ceftaroline**
- **Route: IV**
- **Mode of elimination: Renal**

- **Hits:** MSSA, MRSA, VISA, CoNS, Streptococci, aerobic GNBs other than as noted below

- **Misses:** *P. aeruginosa*, Enterobacter, Serratia, Acinetobacter, *B. cepacia, S. maltophilia, B. fragilis*, VSE/VRE

- **Monotherapy:** cSSSIs, MRSA / MSSA infection

- **SE**: Drug fever, drug rash, serum sickness

Carbapenems

- **Imipenem - cilastatin**
- **Route: IV**
- **Mode of elimination: Renal**

- **Hits:** GNBs including *P. aeruginosa*, MSSA, Streptococci, VSE, *B. fragilis*, some Nocardia

- **Misses:** MRSA, VRE, *S. maltophilia, B. cepacia*, Legionella / atypicals

- **Monotherapy:** ESBL infections, IAIs, DM foot infections

- **SE**: Seizures, particularly in those with renal failure
  Nausea if rapidly infused

Carbapenems

- **Meropenem**
- **Route: IV *HD**
- **Mode of elimination: Renal**

- **Hits:** GNBs including *P. aeruginosa*, MSSA, Streptococci, VSE, *B. fragilis*, Listeria

- **Misses:** MRSA, VRE, Legionella / atypicals

- **Monotherapy:** ESBL infections, IAIs, DM foot infections, nosocomial PNA, meningitis in PCN allergic patients

- **P&P:** No cross-reaction with PCN, safe to use if PCN allergic patients
  DDI with valproic acid

Carbapenems

- **Ertapenem**
- **Route: IV *HD / IM**
- **Mode of elimination: Renal**
- **Hits:** GNBs, MSSA, Strep, *B. fragilis*
- **Misses:** *P. aeruginosa*, VSE/VRE, MRSA, Legionella / atypicals
- **Monotherapy:** IAIs, DM foot infections, ESBL infections
- **P&P:** Once a day dosing. (50% serum levels with IM dose)
  No cross-reaction with PCN, safe to use if PCN allergic pat

Lincosomides (Clindamycin)

- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** MSSA, some MRSA, Streptococci, *S. pneumoniae*, *B. fragilis* (less reliable), Babesia

- **Misses:** VSE / VRE, aerobic GNBs

- **Monotherapy:** SSSI (MSSA, Strep), dental infections

- **Combination therapy**: Babesiosis (combo), adjunct in toxin mediated Staph / Strep infection

- **SE:** *C. difficile!!!!!!*

- **P&P:** May be useful in PCN allergy. Increased resistance and C. diff risk make it less helpful in adults.

  Interferes with toxin of GAS / Staph *IF* susceptible

Trimethoprim-Sulfamethoxazole

- **Route: IV/PO**
- **Mode of elimination: Renal**

- **Hits:** Most GNBs, MSSA, MRSA, Pneumocystis, Nocardia, Toxoplasmosis, Listeria

- **Misses:** *P. aeruginosa, B. fragilis*, ? Streptococci

- **Monotherapy:** MSSA / MRSA, PCP, Nocardia, Toxoplasmosis, Listeria

- **SE:** TMP: Folate deficiency, hyperkalemia; SMX: SJS, hepatotoxicity, falsely elevates creatinine

- **P&P:** Active against Klebsiella in vitro but not in vivo.
  Trimethoprim alone is available PO

Glycopeptides

- **Vancomycin**
- **Route: IV *HD / PO**
- **Mode of elimination: Renal**

- **Hits:**
  - **PO:** *C. difficile*
  - **IV:** Gram positive organisms (no role in *C. diff* diarrhea / colitis)

- **Misses:** VRE, VRSA, GNBs, *B. fragilis*

- **Monotherapy: PO:** *C. difficile*; **IV:** GPC systemic infections

- **SE:** ? Nephrotoxicity. Vancomycin flushing syndrome ("Red man")

- **P&P:** Use may increase VRE prevalence
  Monitoring, challenges with infusions makes alternatives preferable

Lipopeptides

- **Daptomycin**
- **Route: IV *HD**
- **Mode of elimination: Renal**

- **Hits:** Gram positive organisms (MRSA, VRE, Streptococci)

- **Misses:** GNBs, *B. fragilis*

- **Monotherapy:** Systemic GPC infection

- **SE:** myositis, eosinophilic pneumonia (rare)

- **P&P**: Prior exposure of Staph to vancomycin may thicken cell wall leading to daptomycin resistance

  Inactivated by surfactant

  Need higher doses for Enterococci (10-12 mg/kg)

Oxazolidones

- **Linezolid / tedizolid**
- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** MSSA, MRSA, CoNS, VSE, VRE, Streptococci

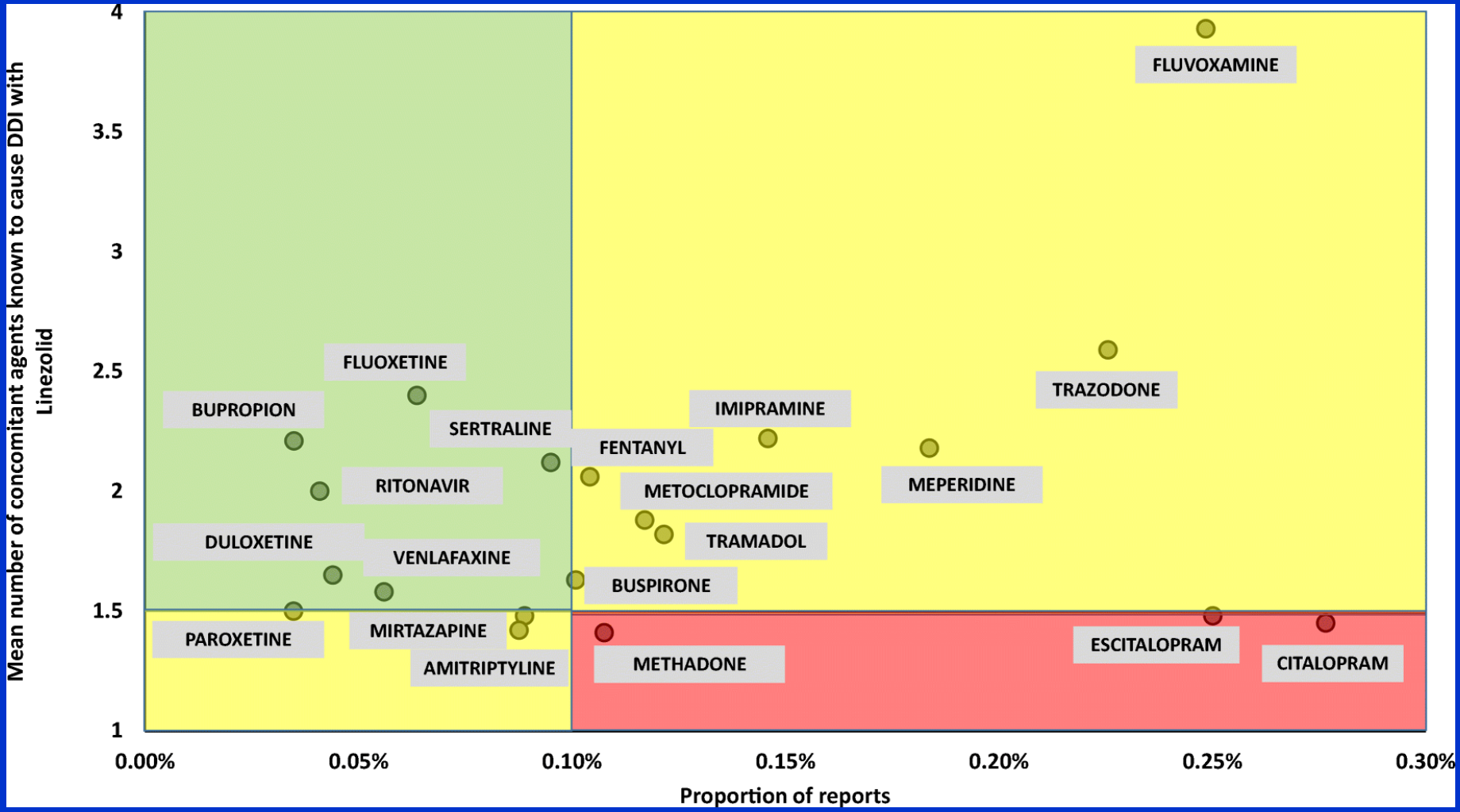
- **Misses:** All GNBs, *B. fragilis*

- **Monotherapy:** ORAL option for severe GPC infection

- **SE**: Dose related / reversible cytopenias (>2 weeks), peripheral neuropathy, serotonin syndrome, optic neuritis

- P&P: Toxin inhibition (like clindamycin)

Oxazolidones



Gatti, M., Raschi, E. & De Ponti, F. Serotonin syndrome by drug interactions with linezolid: clues from pharmacovigilance-pharmacokinetic/pharmacodynamic analysis. *Eur J Clin Pharmacol* **77**, 233–239 (2021). https://doi.org/10.1007/s00228-020-02990-1

Optimize Antibiotic Route
Myth: IV is always better than PO!

- When using highly bioavailable agents, use PO if GI absorption intact
- Do not forget IV to PO switch to a different class
- Consider using PO therapy from the start

Why does it matter?

- IV antimicrobial therapy is not without complications
  - Phlebitis
  - Central line infection
  - DVT
- IV antimicrobial therapy may be more difficult for patients / family (may require staying at facility)
- IV antimicrobial therapy almost always more expensive / has greater environmental impact

Why does it matter?

- Good understanding of PK / PD should make you feel confident using PO therapy
- Well chosen PO therapy is just as effective as IV
- PO therapy should be routinely be considered as an alternative to IV therapy

Requirements of Oral Antibiotic Therapy

- Antibiotic factors:
  - ✓High degree of activity against the presumed / known pathogen
  - ✓High bioavailability that approximates serum / tissue concentrations
  - ✓Well tolerated, good safety profile
  - ✓Low resistance potential (bonus)

Cunha BA Oral Antibiotic Therapy of Serious Systemic Infections, Med Clin of N. America: vol 90, 2006.

Requirements of Oral Antibiotic Therapy

- Host factors:
  - ✓ Therapeutic effect desired in >1 hour
  - ✓ Able to sufficiently absorb an oral antibiotic

Overview of Oral Antibiotic Therapy

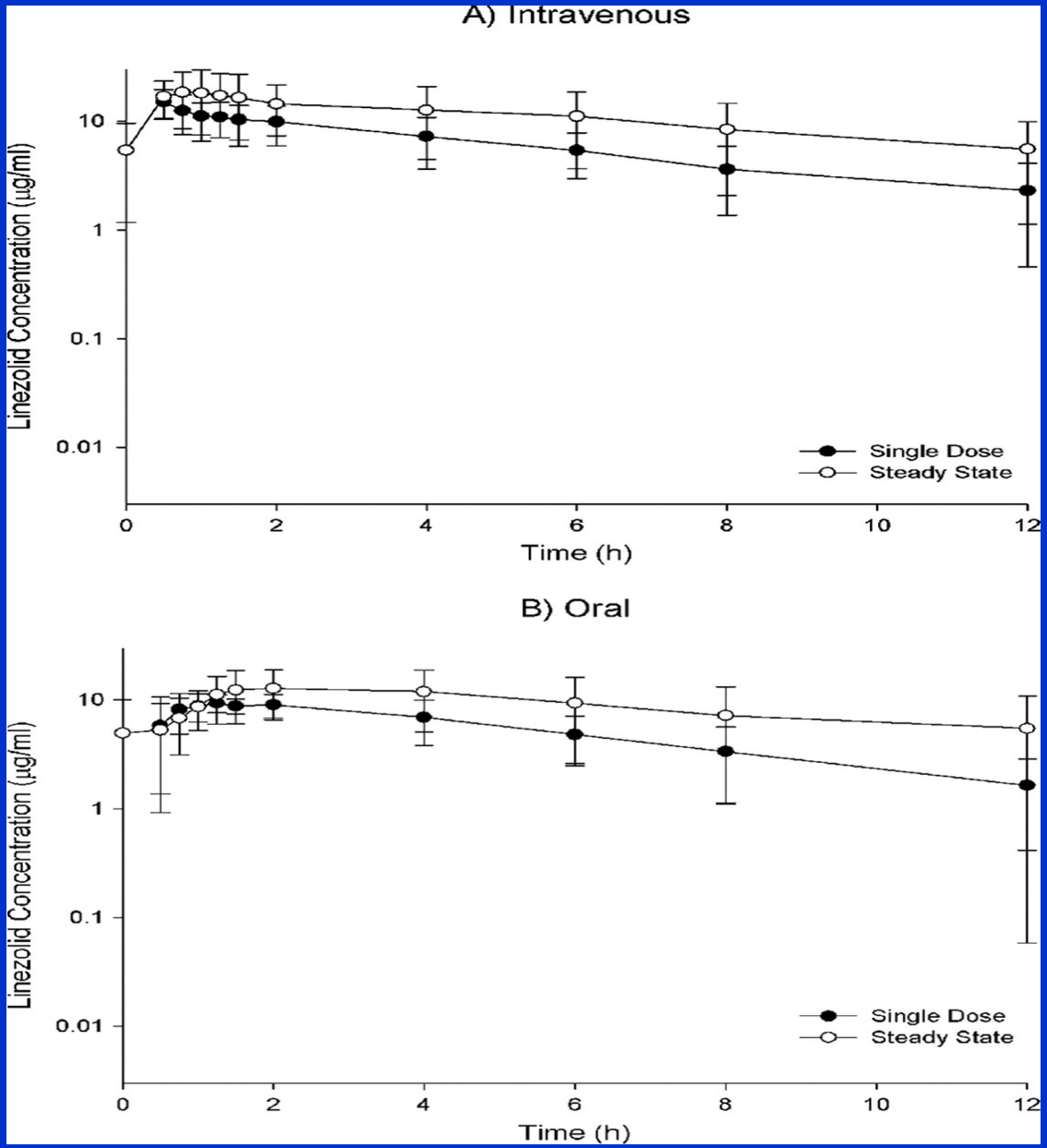
- Bioavailability is a key determinant
  - Low – not well absorbed → unsuitable for serious systemic infections (nitrofurantoin)
  - Good – blood / tissue levels not equal to IV but therapeutic concentration in excess of that needed for clinical effectiveness (cephalexin)
  - High - >90% absorption blood and tissue levels comparable or equal to IV (quinolones)

Table 2. Bioavailability of Oral Antimicrobials

Bioavailability	Antimicrobials		
Excellent (> 90%)	Amoxicillin Cephalexin Cefprozil Cefadroxil Clindamycin Quinolones Chloramphenicol	TMP TMP-SMX Doxycycline Minocycline Fluconazole Metronidazole Cycloserine	Linezolid Tedizolid Isavuconazole Voriconazole Rifampin Isoniazid Pyrazinamide
Good (60 – 90%)	Cefixime Cefpodoxime Ceftibuten Cefuroxime	Valacyclovir Famciclovir Valganciclovir Macrolides Cefaclor Nitrofurantoin	Ethambutol 5-Flucytosine Posaconazole Itraconazole *(solution)* Nitazoxanide *(with food)*
Poor (< 60%)	Vancomycin Acyclovir	Cefdinir Cefditoren	Nitazoxanide *(without food)* Fosfomycin

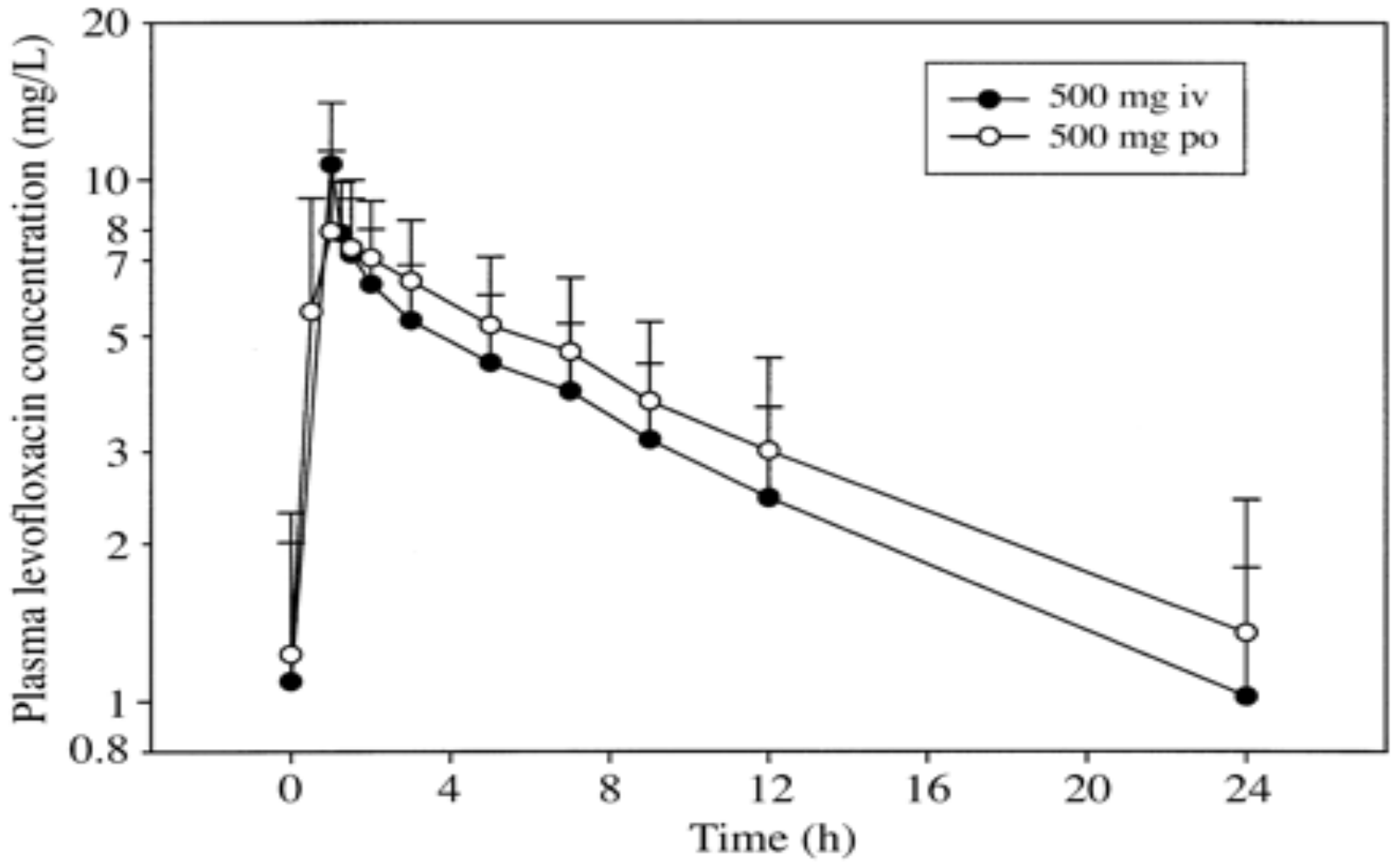
Cunha BA, Cunha CB: Overview of Antimicrobial Therapy in Cunha CB, Cunha BA (eds) (2024) Antibiotic essentials, 18th edn. JayPee Medical Publishers, New Delhi
Cunha CB: Antimicrobial Stewardship Program Perspective: IV-to-PO Switch Therapy. *Rhode Island Medical Journal* 101:31-34, 2018

Mean and standard deviation intravenous (A) and oral (B) linezolid plasma concentrations over 12 h after the first dose and at steady state.



Rebecca A. Keel et al. Antimicrob. Agents Chemother. 2011; doi:10.1128/AAC.01797-10

Figure 1. Mean (±s.d.) steady-state levofloxacin plasma concentration–time profiles following iv and oral administration



Journal of Antimicrobial Chemotherapy, Volume 51, Issue 1, January 2003, Pages 101–106, https://doi.org/10.1093/jac/dkg035

Oral vs. IV Antibiotics RCT Master Table

Diagnosis	# RCTs	# Patients	Result
Osteomyelitis	11*	1,687	Equal
Bacteremia	12*	1,055	Equal
Endocarditis	4*	536	Equal
Intra-Abdominal Infection	7	1,763	Equal
Urinary Tract Infection	7	792	Equal
Pneumonia	12	2,158	Equal
Skin Infections	2	253	Equal
Possible Serious Bact. Infxn <2 mo old	2	12,254	Equal
Pseudomonas in Cystic Fibrosis	1	155	Equal
Neuroborreliosis	3	366	Equal
Bubonic Plague (yeah, seriously!)	1	222	Equal
Cryptococcal Meningitis	1	814	Equal
Malaria	1	50	Equal
Total: 13 Conditions	61*	22,097	All Equal

*1 RCT included both osteo & bacteremia, 1 RCT included each of osteo, bacteremia, and IE; Refs at https://www.bradspellberg.com/oral-antibiotics

Oral vs. IV Abx for Bacteremia

Author	Yr	N	Regimen (Oral vs. IV)	Success
Amodio-Groton	'96	50	Ciprofloxacin oral vs. IV—GNB	83% (20/24) v 77% (20/26)
Deville	'03	36	Linezolid vs. vanco—GPC (peds)	80% (20/25) v 64% (7/11)
Jantausch	'03	103	Linezolid vs. vanco—GPC (peds)	72% (54/75) v 64% (18/28)
Kaplan	'03	80	Linezolid vs. vanco—GPC (peds)	82% (47/57) v 74% (17/23)
Schrenzel	'04	67	FQ + rif vs. βL/vanco—*Staph*	87% (34/39) v 89% (25/28)
Wilcox	'04	56	Linezolid vs. teicoplanin—GPC	89% (23/26) v 57% (17/30)
Wilcox	'09	166	Linezolid vs. vancomycin—GPC	75% (70/93) v 81% (59/73)
Monmaturopaj*	'12	17	Cefditoren vs. ceftriaxone—GNB	100% (6/6) v 91% (10/11)
Park	'14	59	Ciprofloxacin vs. std IV—GNB	93% (27/29) v 93% (28/30)
Omrani	'23	165	FQ/TMPSMX/BL vs. std IV—GNB	78% (65/83) v 74% (61/82)
Kaasch	'24	213	Various Abx IV/Oral—*S. aureus*	87% (94/108) v 88% (92/105)
Juskowich	'25	35	Various Abx IV/Oral, GPC & GNB	100% (25/25) v 100% (10/10)
Total (N=12 RCTs)		1047		82% (485/590) v 80% (364/457)

*N = 82 pts with pyelonephritis of whom 17 were bacteremic with *E. coli*, patients were randomized to continue ceftriaxone or switch to oral ceftditoren at day 3.

Refs at https://www.bradspellberg.com/oral-antibiotics

Oral vs. IV Abx for Endocarditis

Author	Yr	N	Regimen (Oral vs. IV)	Success
Stamboulian	'91	30	Amox 1 gm qid vs. CTX—*Strep*	100% (15/15) v 100% (15/15)
Heldman	'96	93	Cipro + Rif vs. std IV—*Staph*	95% (18/19) v 88% (22/25)
Iversen/ Bungaard†	'19	400	Std oral vs. std IV—GPC	74% (146/199) v 62% (125/201)
Juskowich	'25	14	Std oral vs. std IV**	100% (9/9) vs. 100% (4/4)
*Tissot-Dupont**	*'19*	*341*	*TMP-SMX+clinda vs. std IV--Staph*	*81% (138/171) v 70% (119/170)*
Totals (N=3 RCTs)		523		78% (188/242) v 68% (167/246)
(+ 1 quasi expt)*		*(864)*		*79% (326/413) v 69% (286/416)*

*Quasi-experimental, pre-post study. Italicized totals include the quasi-experimental data.
†Iversen reported early follow up, Bungaard 3 year follow up from the same study.
**Not including 7 other endovascular cases caused by MSSA that were not endocarditis (4 oral vs. 3 IV), all of which were successfully treated
Refs at https://www.bradspellberg.com/oral-antibiotics

Oral Antibiotics Bone PK

Drug	Serum	Bone	Ratio	MICs
Linezolid	10-20	5-10	50%	<1
TMP/SMX (2DS)	5-10 (TMP) 100-150 (SMX)	1.5-3 (TMP) 15-20 (SMX)	30%	<10
Levofloxacin	5-8	5-8	100%	<1
Minocycline	4	3.6	90%	<1
Clindamycin	5-10	2-5	40-75%	<2
Rifampin (adjunctive)	2-5	1-10	50-200%	<1

Cunha BA, Cunha CB: Antimicrobial Drug Summaries in Cunha CB, Cunha BA (eds) (2024) Antibiotic essentials, 18th edn. JayPee Medical Publishers, New Delhi
Cunha CB: Antimicrobial Stewardship Program Perspective: IV-to-PO Switch Therapy. *Rhode Island Medical Journal* 101:31-34, 2018

Oral vs. IV Abx for Osteomyelitis

Author	Yr	N	Regimen (Oral vs. IV)	Success
Greenberg	'87	30	Ciprofloxacin vs. std IV	50% (7/14) v 65% (11/16)
Gentry	'90	59	Ciprofloxacin vs. βL+aminoglyc	77% (24/31) v 79% (22/28)
Mader	'90	26	Ciproflox vs. βL/clinda+aminoglyc	79% (11/14) v 83% (10/12)
Gentry	'91	33	Ofloxacin vs. cephalosporin	74% (14/19) v 86% (12/14)
Gomis	'99	32	Ofloxacin vs. imipenem	69% (11/16) v 50% (8/16)
Schrenzel	'04	39	Fleroxacin+rifampin v βL/vanco	82% (18/22) v 65% (11/17)
Euba	'09	48	TMP-SMX+rifampin vs. cloxacillin	81% (17/21) v 77% (21/27)
Li	'19	1054	Std oral vs. std IV	87% (457/527) v 85% (450/527)
Manning	'22	60	PJI/DAIR: Std oral vs. std IV	71% (22/31) v 76% (22/29)
METRC*	'25	233	Std oral vs. std IV	63% (73/115) v 64% (76/118)
Juskowich	'25	73	Std oral vs. std IV	98% (45/46) v 100% (20/20)
Total (N=11 RCT)		1,687		82% (699/856) v 80% (663/824)

*Fracture-related infections; treatment success was a secondary endpoint; Success = absence of osteo at long term follow up (most studies >1 year); std = standard of care, protocol specified; all RCTs comparing oral to IV-only are in adults; 9 other adult & 10 pediatric RCTs or quasi-exptl studies comparing mostly oral vs. mostly oral; refs at https://www.bradspellberg.com/oral-antibiotics

Diagnosis	# RCTs Demonstrating IV Superior to PO	# RCTs Demonstrating PO Equivalent / Superior to IV
Osteomyelitis	0	11
Bacteremia	0	12 (2 showed superior cure for PO)
Endocarditis	0	4 (1 with superior mortality for PO)

Kusha Davar, Devin Clark, Robert M Centor, Fernando Dominguez, Bassam Ghanem, Rachael Lee, Todd C Lee, Emily G McDonald, Matthew C Phillips, Parham Sendi, Brad Spellberg, Can the Future of ID Escape the Inertial Dogma of Its Past? The Exemplars of Shorter Is Better and Oral Is the New IV, Open Forum Infectious Diseases, Volume 10, Issue 1, January 2023, ofac706, https://doi.org/10.1093/ofid/ofac706

Tetracyclines

- **Doxycycline**
- **Route: IV / PO**
- **Mode of elimination:** Hepatic

- **Hits:** MSSA, MRSA, many zoonotic / vector-borne pathogens, Actinomyces, atypicals, some *B. fragilis*, Chlamydia, syphilis

- **Misses:** Streptococci (except *S. pneumoniae*), Babesia, Pseudomonas (unless cystitis)

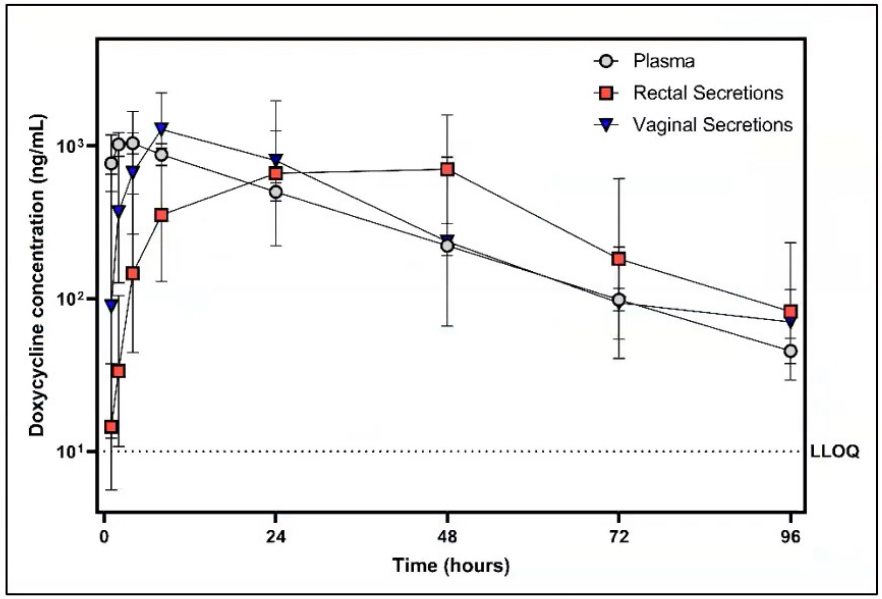
- **Monotherapy:** CAP, syphilis (PCN allergic), Chlamydia, Lyme, Legionella, Whipple's, Q fever (+ HQ), plague, Brucella, cystitis, prostatitis, DoxyPEP

- **SE:** GI upset, photosensitivity reaction

- **P&P:** Not active against Babesiosis
  Avoid concurrent Ca, Fe, Al, Mg administration

	IPERGAY	DoxyPEP	DOXYVAC	DPEP
Location	France 2015-2016	USA 2020-2022	France 2021-2022	Kenya 2020-2022
Eligibility / Population	MSM, TGW on PrEP	Male sex at birth On PrEP or living with HIV ≥1 STI in past 12 months Unprotected sex with ≥1 male partner in past 12 months	MSM, on PreP >6 months Bacterial STI in past 12 months No STI symptoms	Cis women on PrEP between 18-30 years of age
Design	Randomized 1:1 Open label	Randomized 2:1 Open label	Randomized 2:1 to doxy-PEP Open label	Randomized 1:1 Open label
STI Testing	3 site GC/CT + syphilis testing q 2 months	Quarterly 3 site GC/CT + syphilis testing	Quarterly 3 site GC/CT + syphilis testing	Quarterly genital GC/CT + syphilis testing
Primary Endpoint	First STI infection (gonorrhea, chlamydia or syphilis) during a 10-month follow-up period	Relative risk of an STI infection per quarter Time to first STI was secondary endpoint	Impact of doxycycline as PEP on time to first episode of syphilis or chlamydia and impact of 4CMenB vaccine on first episode of gonorrhea	Any incident C. trachomatis, N. gonorrhoeae or T. pallidum
Total N	232	501	502	449

Doxycycline Mucosal Concentrations



	C trachomatis		*T pallidum*		*N gonorrhoeae*	
	C_{max}*	Time >4x MIC	C_{max}*	Time >4x MIC	C_{max}*	Time >4x MIC
Plasma	16x	44h	10x	32h	4x	3h
Rectal Secretions	11x	62h	7x	51h	3x	NA
Vaginal Secretions	20x	45h	12x	38h	5x	11h

*Fold above MIC

Minimum Inhibitory Concentrations (MIC):

N gonorrhoeae (NG) MIC = 250 ng/mL CDC Antimicrob Resist Susc Test

T pallidum (TP) MIC_{90} = 100 ng/mL Edmondson *Antimicrob Agents Chemother* 2020

C trachomatis (CT) MIC_{90} = 64 ng/mL Zheng *Sex Transm Dis* 2015

Haaland CROI 2023, abstract 118

Urinary Spectrum of Oral Tetracyclines [a]

Parameters	Tetracycline	Doxycycline	Minocycline
Oral dose	500 mg	100 / 200 mg	100 mg
Serum levels	2 mcg/ml	4 / 8 mcg/ml	4 mcg/ml
Urine levels	~300 mcg/ml	~60 - 300 mcg/ml	~300 mcg/ml
Urinary spectrum	*E. coli* Klebsiella sp. Enterobacter sp. Indole + Proteus sp., *Pseudomonas aeruginosa*[b]		

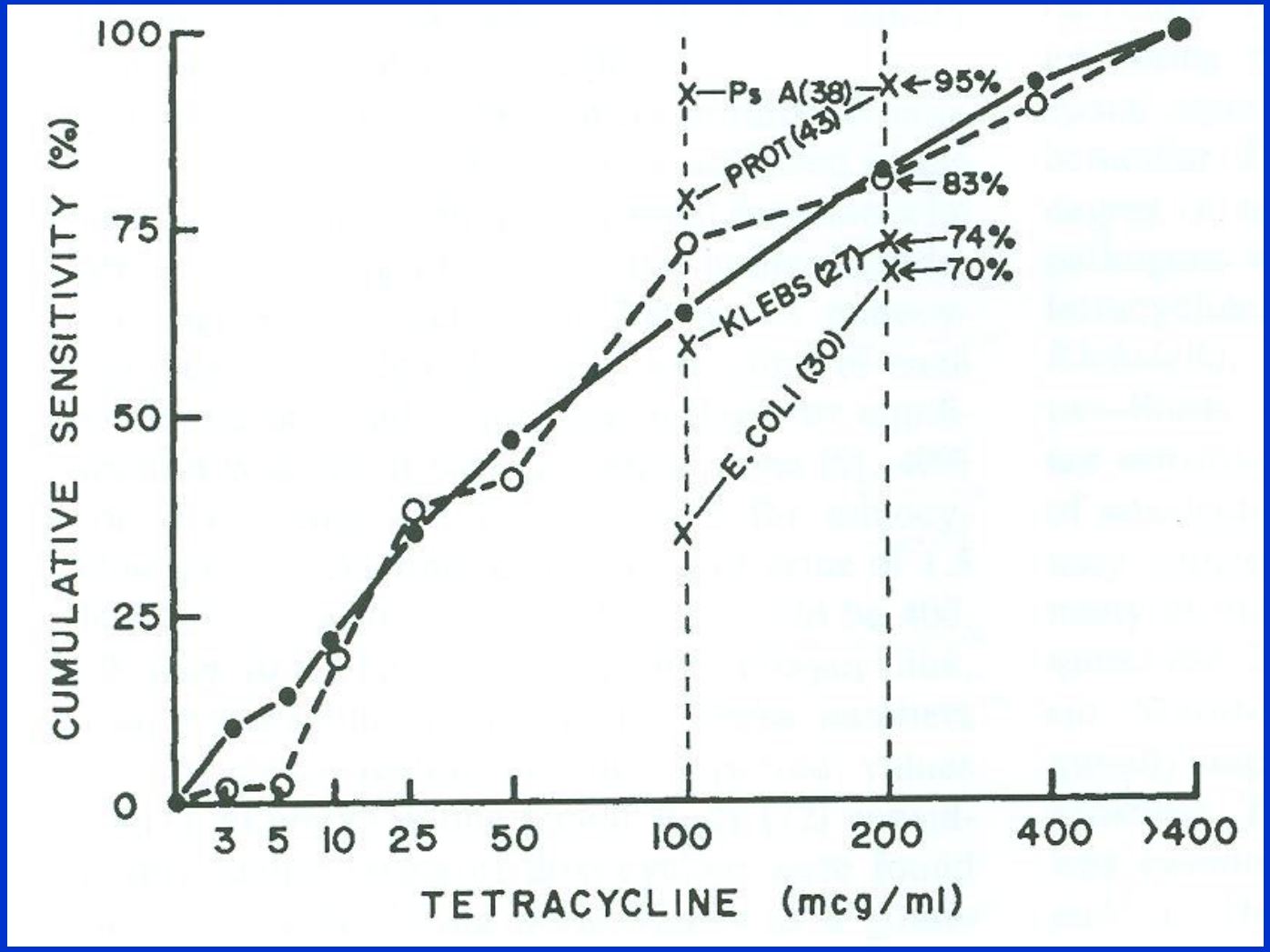
[a] With normal renal function

[b] MICs < 150 mcg/ml

White CR, Jodlowski TZ, Atkins DT, Holland NG. Successful Doxycycline Therapy in a Patient With Escherichia coli and Multidrug-Resistant Klebsiella pneumoniae Urinary Tract Infection. J Pharm Pract. 2017 Aug;30(4):464-467. doi: 10.1177/0897190016642362. Epub 2016 Apr 12. PMID: 27071978.

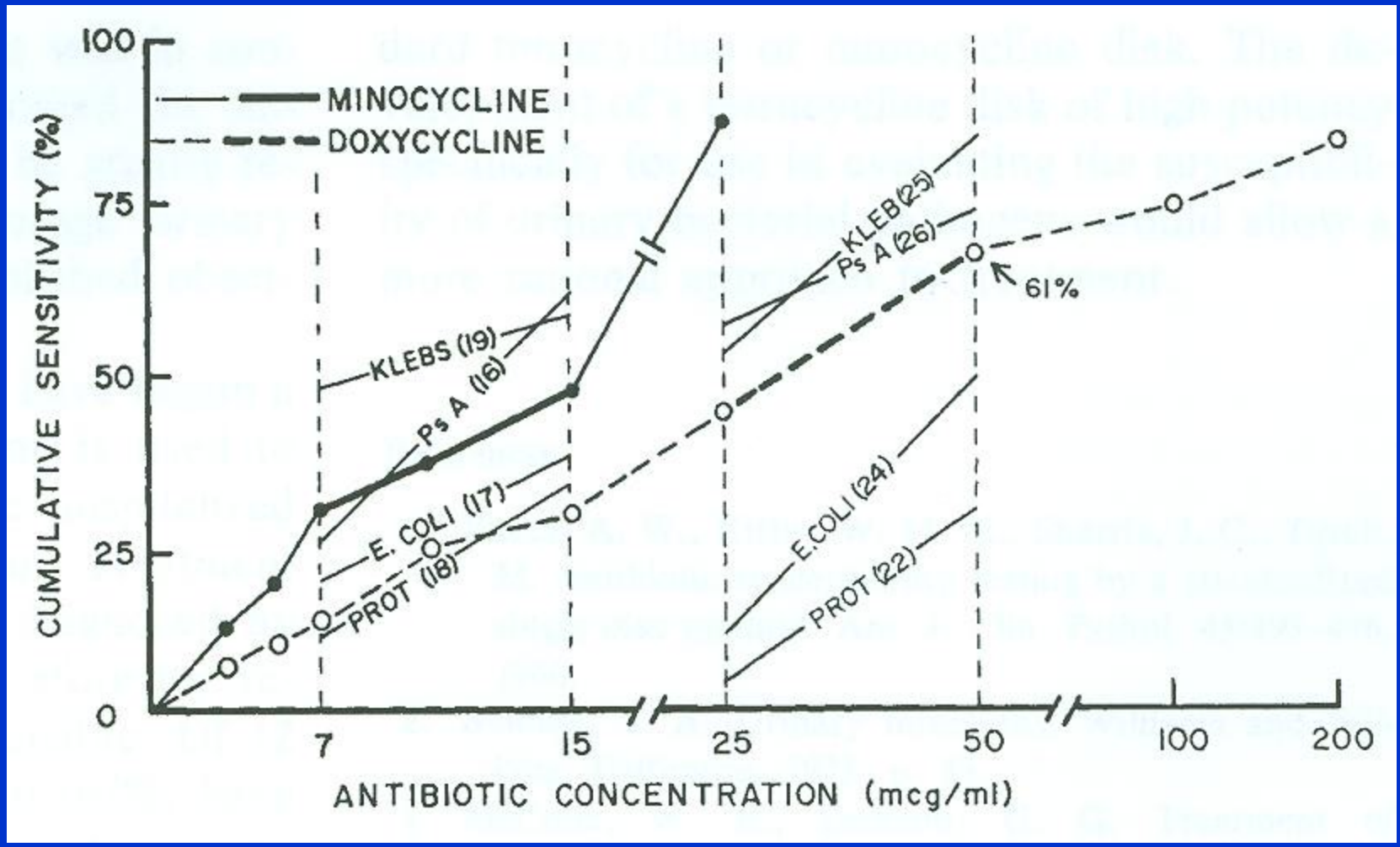
Cunha BA. Oral doxycycline for Non-systemic Urinary Tract Infections (UTIs) due to P. aeruginosa and other Gram Negative Uropathogens. Eur J Clin Microbiol Infect Dis 31:2865-2868, 2012.

Tetracyclines: Urinary Spectrum



Musher DM, et al. Effectiveness of Achievable Urinary Concentrations of Tetracycline Against Tetracycline Resistant Pathogenic Bacteria. JID 131: 540-44, 1975.

Tetracyclines: Urinary Spectrum



Musher DM, et al. Effectiveness of Achievable Urinary Concentrations of Tetracycline Against Tetracycline Resistant Pathogenic Bacteria. JID 131: 540-44, 1975.

Tetracyclines

- **Minocycline**
- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** MSSA, MRSA (more active than doxy), VRE, Nocardia, MDR-Acinetobacter, Actinomyces, some *B. fragilis*

- **Misses:** Streptococci (except *S. pneumoniae*)

- **Monotherapy:** MRSA, Acinetobacter, etc.

- **SE:** drug induced lupus, vertigo, skin discoloration with prolonged use (months)

- **P&P:** Better CSF penetration than doxy (50%)
  Tetra / doxy susceptibility does not predict mino activity
  More reliable than doxy for severe *S. aureus* infections

Tigecycline

- **Route: IV**
- **Mode of elimination: Hepatic**

- **Hits:** GPCs including MSSA / MRSA, VSE / VRE, most GNBs, MDR *K. pneumoniae*, Metallo-beta-lactamase, Acinetobacter, *B. fragilis, C. difficile*

- **Misses:** *P. aeruginosa*, Proteus, Providencia

- **Monotherapy:** IAIs, SSSI, *C. difficile*

- **SE:** GI upset, ?pancreatitis

- P&P: Once daily dosing better
  Can use higher doses in serious infection / UTI / bacteremia

Tigecycline

- PK / PD suggests package insert dosing (100mg IV x1, then 50mg BID) is suboptimal
- Half life is 27 hours after one dose, 42 hours after multiple doses
- Once daily dosing / higher dosing necessary for more severe infections. GI effect mitigated by infusing in larger volume / more slowly.

Loading dose x1, then maintenance daily dose	Peak serum concentration (Ug/mL)
100 mg / 50 mg	1.5
200 mg / 100 mg	3
400 mg / 200 mg	6

Metronidazole

- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** *C. difficile*, *B. fragilis*, trichomonas, BV, amoeba
- **Misses:** Everything else

- **Monotherapy:** BV, Trichomonas

- **Combination therapy:** IAIs, DM foot infections / osteo in combination with a GNB drug (ceftriaxone, aztreonam, aminoglycoside), *C. difficile* colitis

- **SE**: Encephalopathy, seizures

- **P&P:** Suboptimal for *C. difficile* diarrhea

  1 G q24h (or 500 mg q12h) OK for most non-*C. difficile* infections

Nitrofurantoin

- **Route: PO**
- **Mode of elimination: Renal**

- **Hits:** GNB uropathogens (other than noted below) including ESBLs, CREs, VSE / VRE

- **Misses:** *P. aeruginosa*, Serratia, Proteus, GBS

- **Monotherapy:** Cystitis, CAUTI

- **SE**: Pneumonitis, pulmonary fibrosis, hepatitis

- **P&P:** For lower UTIs only
  Optimal effectiveness in CrCl >60 mL/min
  Usually still effective in CrCl 30-60 mL/min
  May not be effective in patients with CrCl <30 mL/min

Fosfomycin

- **Route: PO / IV (not in US)**
- **Mode of elimination: Renal**

- **Hits:** MDR GNB uropathogens including *P. aeruginosa*, Serratia, Proteus, VSE / VRE

- **Misses:** GBS, *S. maltophilia*

- **Monotherapy:** Cystitis, CAUTI, pyelonephritis (no bacteremia)

- **Combination therapy:** chronic bacterial prostatitis (with doxy / quinolone)

- **SE**: minimal, GI upset

- **P&P:** Excellent prostate concentrations (inflamed / noninflamed)
  May fail with chronic prostatitis in setting of prostatic calcifications

Quinolones

- **Ciprofloxacin (non-respiratory quinolone)**
- **Route: IV / PO**
- **Mode of elimination: Renal**

- **Hits:** GNBs (including P. aeruginosa), Strep spp., some VSE.

- **Misses:** Most MSSA, MRSA, S. pneumoniae, VRE, B. fragilis

- **Monotherapy:** UTIs, P. aeruginosa infections

- **Combination therapy:** IAI

- **SE:** Seizures, QT prolongation, tendon rupture, neuropathy, ?AAA

- **P&P**: Avoid concurrent Ca, Fe, Al, Mg administration (binds quinolones)

Quinolones

- **Levofloxacin**
- **Route: IV / PO**
- **Mode of elimination: Renal**

- **Hits:** MSSA, Streptococci (including S. pneumoniae), GNBs (including P. aeruginosa), some VSE, some zoonotic pathogens, atypicals

- **Misses:** MRSA, VSE / VRE, B. fragilis

- **Monotherapy:** CAP, nosocomial pneumonia, susceptible zoonoses

- **Combination therapy:** IAI

- **SE**: QT prolongation, tendon rupture (rare), neuropathy, ? AAA

- **P&P**: Use 750mg dose for Pseudomonas / nosocomial PNA

Quinolones

- **Moxifloxacin**
- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** MSSA, Streptococci (including *S. pneumoniae*), GNBs, most VSE, atypicals, *B. fragilis*

- **Misses:** MRSA, P. aeruginosa

- **Monotherapy:** CAP, IAI (liver abscess), DM foot infections

- **SE**: QT prolongation, tendon rupture (rare), neuropathy, ? AAA

- **P&P**: Moxifloxacin has the best anti-VSE activity of FQs
  No need for dose adjustment in patients with renal insufficiency

Quinolones

- **Delafloxacin**
- **Route: IV / PO**
- **Mode of elimination: Hepatic**

- **Hits:** MSSA, MRSA, Streptococci (including *S. pneumoniae*), GNBs, atypicals, *B. fragilis, P. aeruginosa*

- **Misses:** Enterococci (VRE)

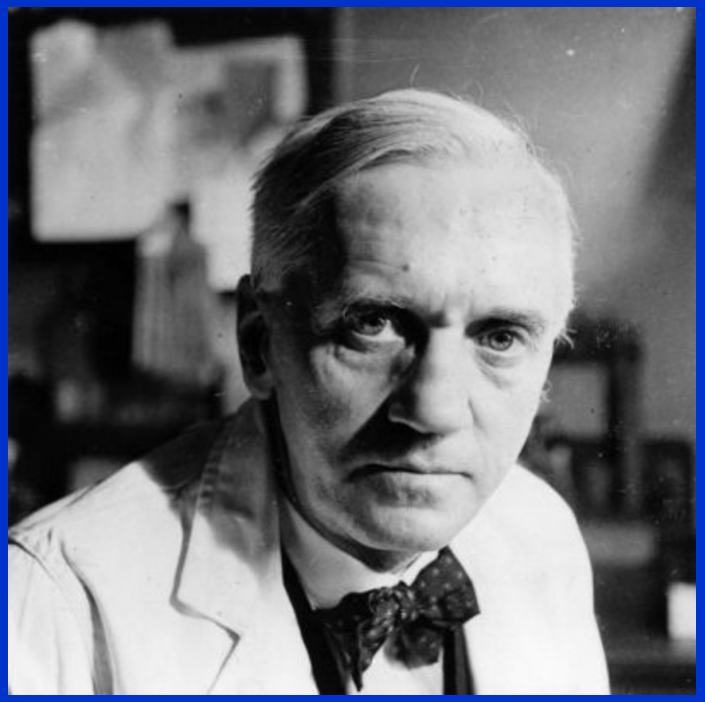
- **Monotherapy:** ABSSI, but may have similar utility to moxifloxacin

- **SE**: tendon rupture (rare), neuropathy, ? AAA

- **P&P**: No Qtc prolongation (compared to moxifloxacin)
  May retain Pseudomonas activity even if ciprofloxacin R
  Avoid with sever renal impairment

Alexander Fleming - 1945

"The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out… In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted."



Penicillin Finder Assays its Future. New York Times, June 26, 1945 :21

Thank you!