Know your Antibiotics II

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Disclosures

- None

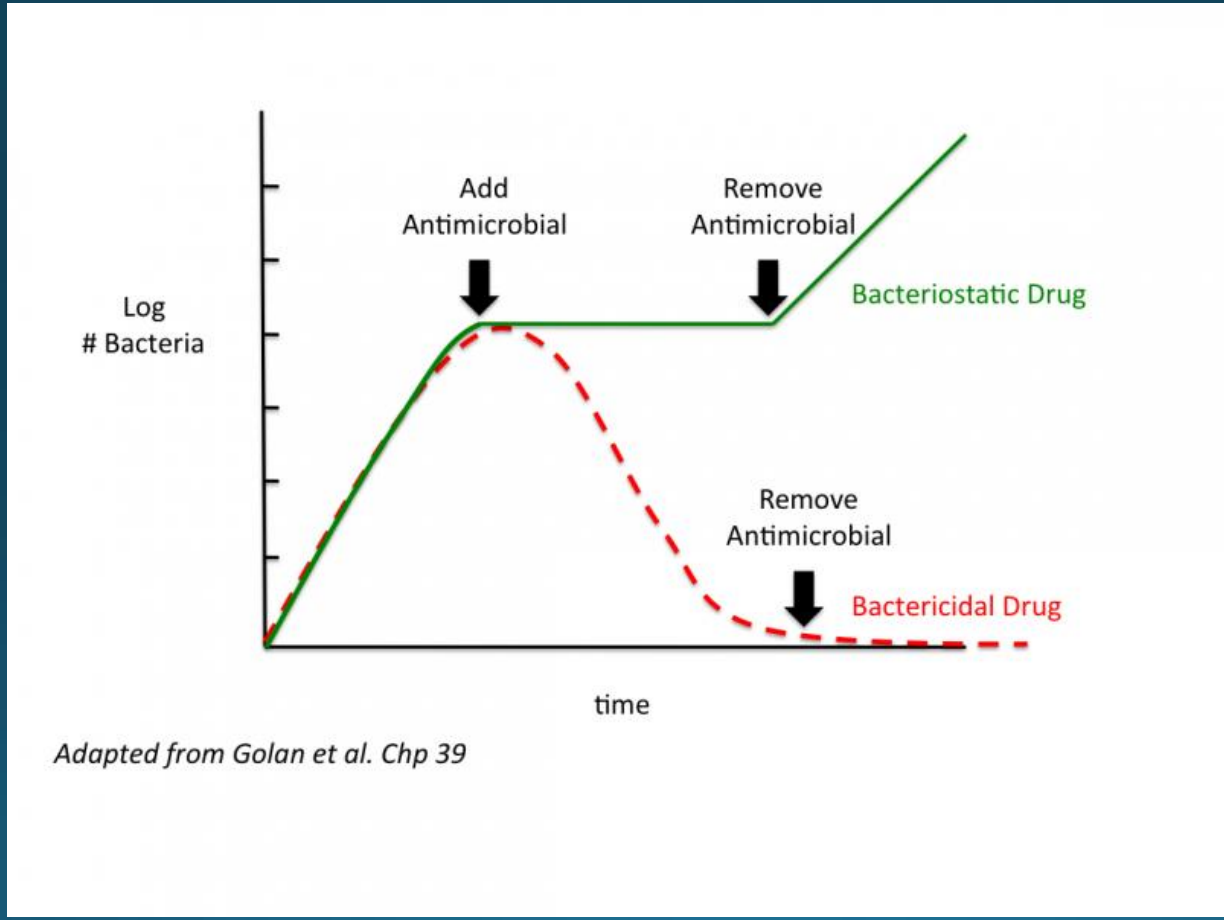
Outline

Antibiotic use principles:

- Static vs cidal
- PK/PD
- Drug penetration
- Rise of antimicrobial resistance
- Double coverage

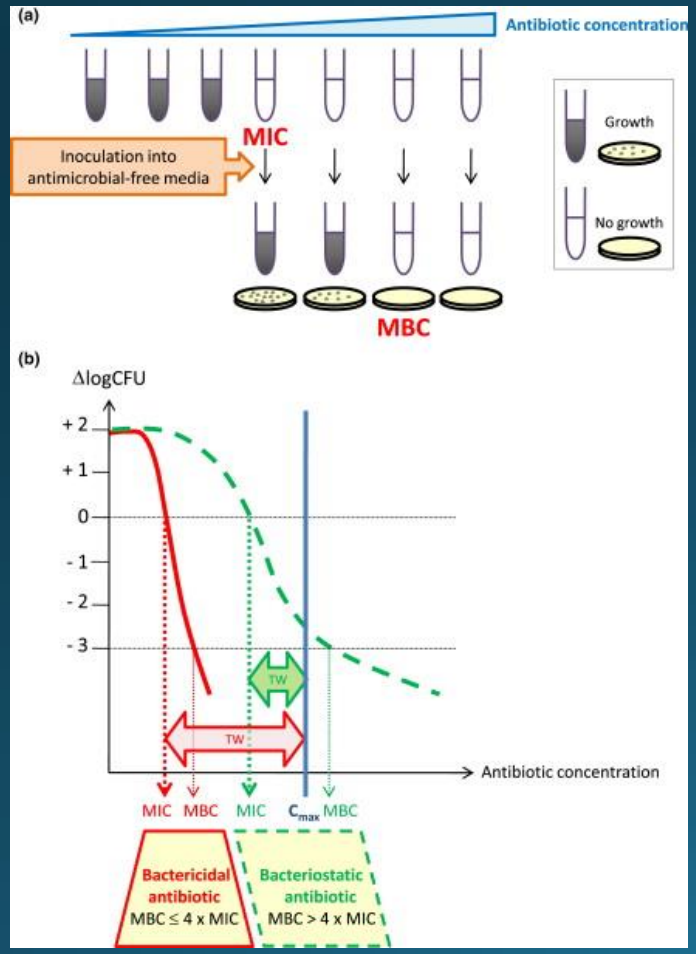
Bactericidal vs Bacteriostatic

Bactericidal vs Bacteriostatic



Adapted from Golan et al. Chp 39

- In vitro microbiological techniques to determine the bactericidal activity of antibacterial agents against different isolates include the minimum bactericidal concentration (MBC) and time-kill curve



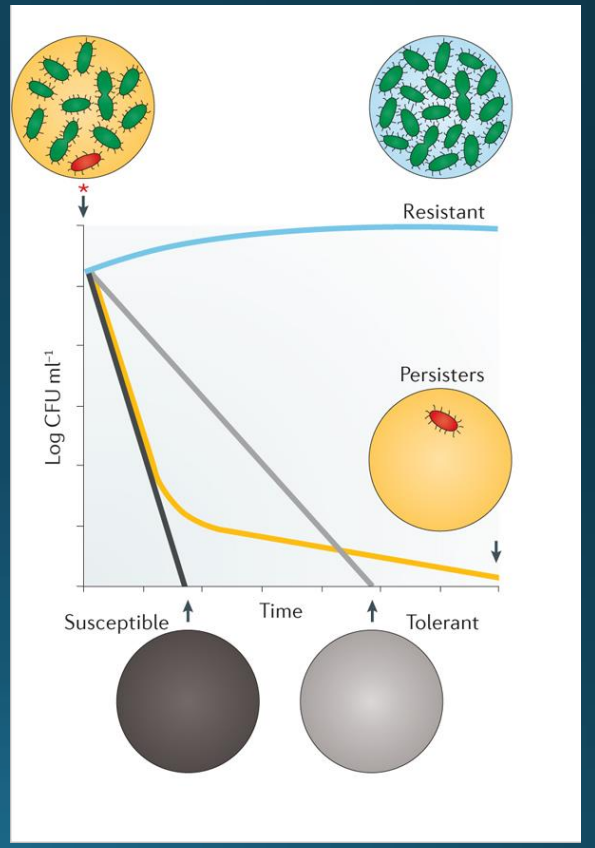
Bactericidal drugs: Beta lactams, Aminoglycosides, Fluoroquinolones, Daptomycin, Vancomycin

Bacteriostatic drugs: Macrolides, clindamycin, sulfonamides, linezolid

Jill E Maddison in Small Animal Clinical Pharmacology (Second Edition), 2008.

Of course, things are not that simple…

- Cidal vs static can depend on:
- Bacterial species: Vancomycin, for example, is normally bactericidal against *S. aureus* and pneumococci, but bacteriostatic against enterococci. Linezolid is bacteriostatic against staphylococci and enterococci, but may be bactericidal against streptococci.
- Tolerance: Reversible phenotypic response depending on the growth conditions, in vitro produced by limiting glucose in growth media. May explain phenomenon of persister cells (~0.1% of culture) which grow slower than the rest.



Nature Reviews Microbiology (2017)

Table 1 | **Examples of bacterial species that cause persistent infections**

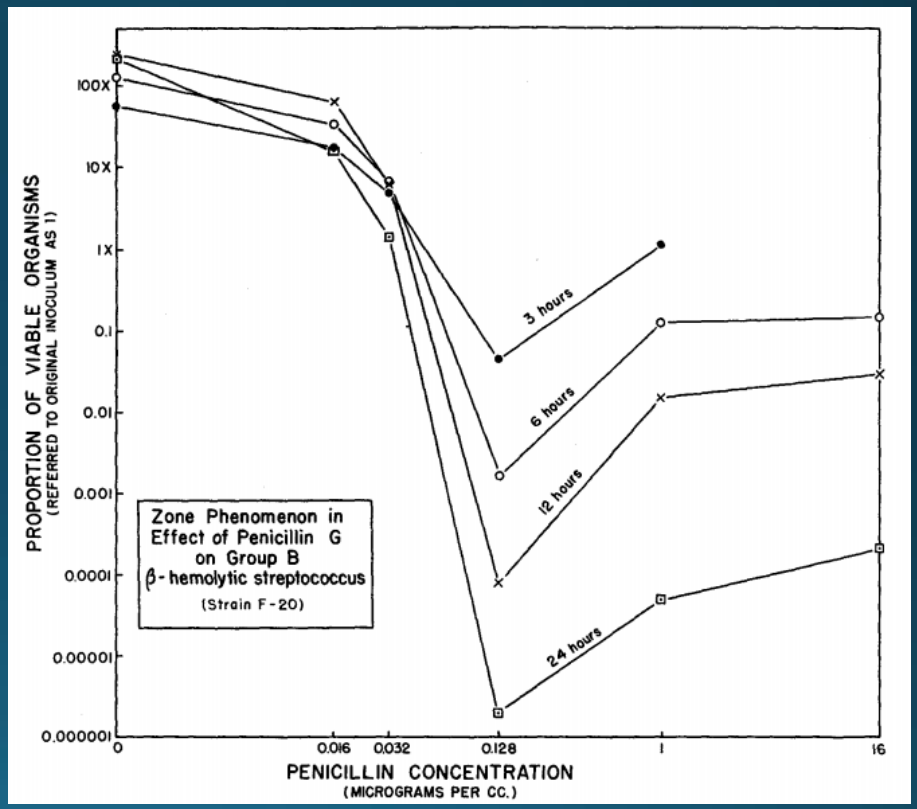
Bacterial species	Site of infection	Form of persistent infection
Mycobacterium tuberculosis[36]	Respiratory	Symptomatic or asymptomatic (latent)
Pseudomonas aeruginosa[53]	Respiratory	Symptomatic
Burkholderia cepacia[147]	Respiratory	Symptomatic
Haemophilus influenzae[148]	Respiratory	Symptomatic
Helicobacter pylori[36]	Gastrointestinal	Asymptomatic (active)
Brucella abortus[149]	Gastrointestinal	Asymptomatic (active or latent)
Escherichia coli[150]	Gastrointestinal	Symptomatic
Clostridium difficile[151]	Gastrointestinal	Symptomatic
Salmonella enterica subsp. *enterica* serovar Typhi or *S.* Paratyphi[36]	Systemic	Asymptomatic (active or latent)
Nontyphoidal invasive *Salmonella* spp.[152]	Systemic	Asymptomatic (active or latent)
Borrelia burgdorferi[30]	Systemic	Symptomatic
Staphylococcus aureus[153]	Systemic	Symptomatic
Streptococcus pyogenes[50]	Systemic	Asymptomatic (latent)
Chlamydia trachomatis[154]	Sexually transmitted infection	Asymptomatic (active)
Treponema pallidum[155]	Sexually transmitted infection	Asymptomatic (latent)
Uropathogenic *E. coli*[63]	Urinary tract infection	Asymptomatic (latent)

- Concentration of drug → Eagle effect

TABLE III

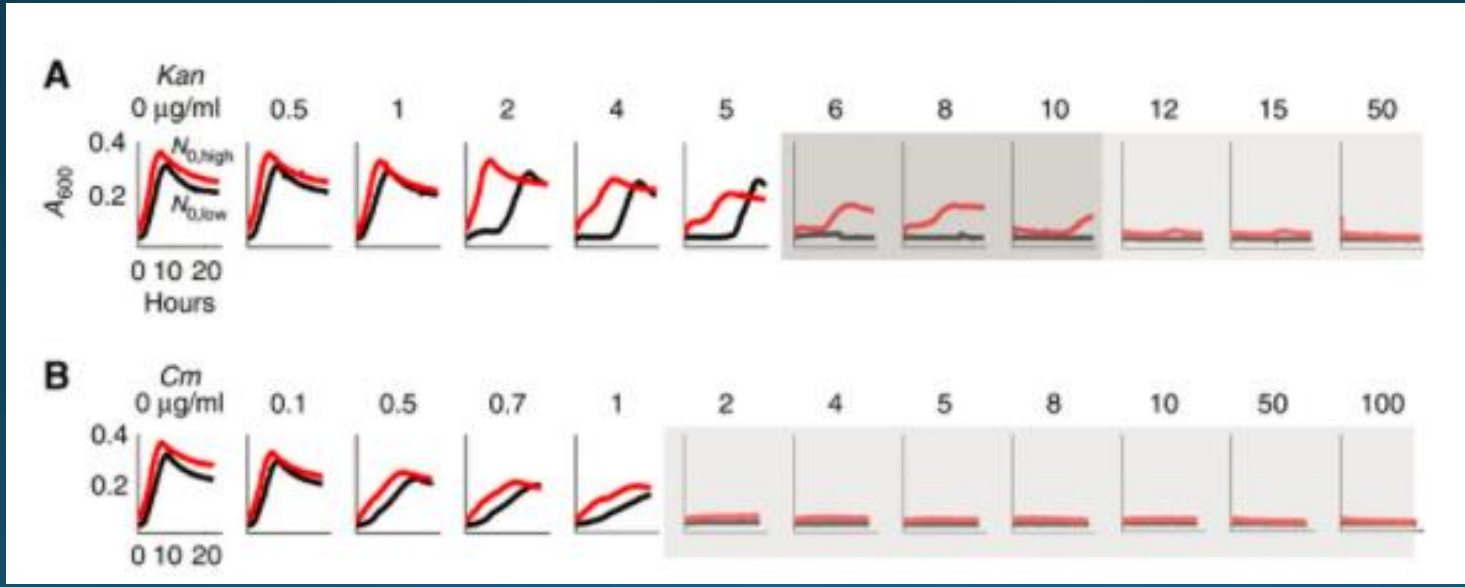
A Paradoxical Zonal Effect in the Susceptibility of a Group B β-Hemolytic Streptococcus (Strain F20) to Penicillin G

Time	Concentration of penicillin, *micrograms per cc.*				
	0	0.032	0.064	0.128	256
	Percentage of organisms still viable (inoculum = 100)				
hrs.					
3	2,600	42	4	1.8	55
6	16,600	32	0.056	0.079	15
12	35,600	52	0.0048	0.016	4
24	47,700	87	0	0.0004	0.08
Time required to kill 99.9 per cent of organisms, *hrs.*		>	5.6	5.8	23



HARRY EAGLE, M.D., AND A. D. MUSSELMAN, 1948

- **Inoculum effect:** In other words over-abundance of drug-target. Originally described in beta-lactams especially in ESBL producers, but seen in others as well.
- May explain benefit of using Clindamycin + beta-lactam.



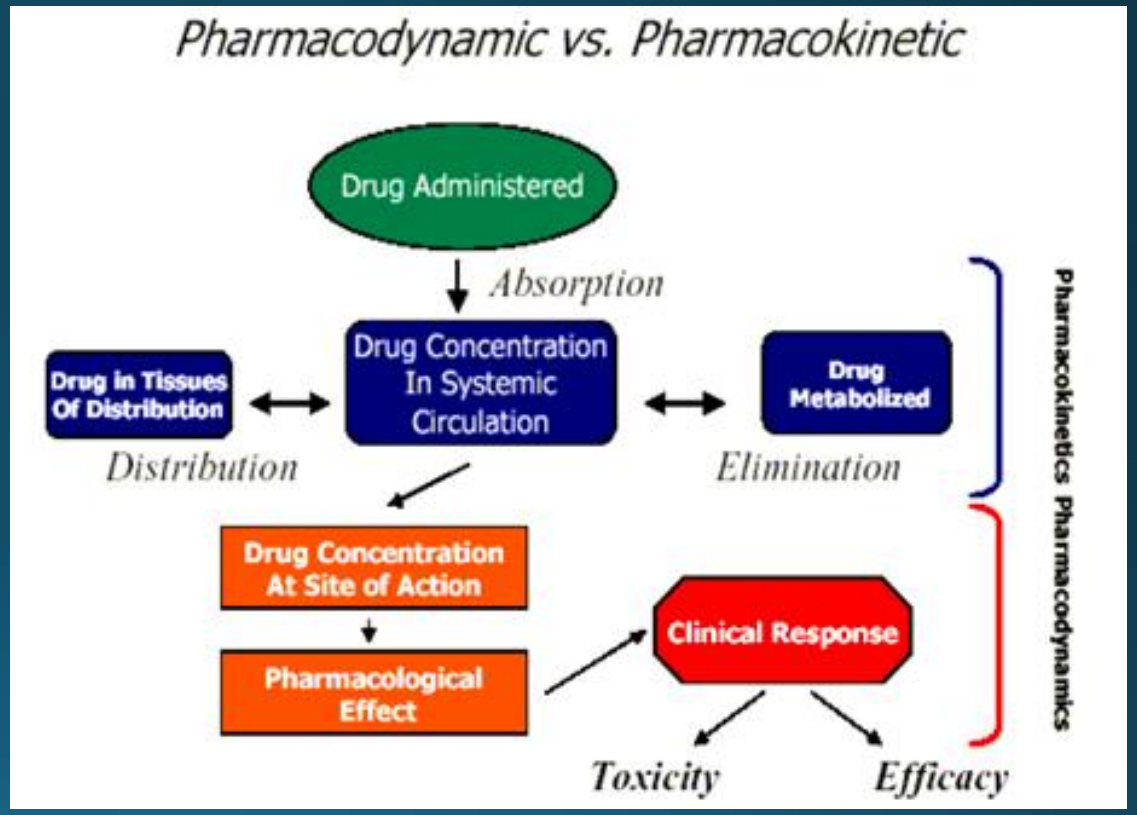
Kanamycin, but not chloramphenicol, led to IE in E. coli strain BL21.

Oct 2012 · Molecular Systems Biology

PK/PD

PK/PD

- Pharmacokinetics: What the body does to the drug, how it is absorbed, distributed, metabolized
- Pharmacodynamics: What the drug does to the body, may be therapeutic or adverse effects



Summary of Drug Absorption

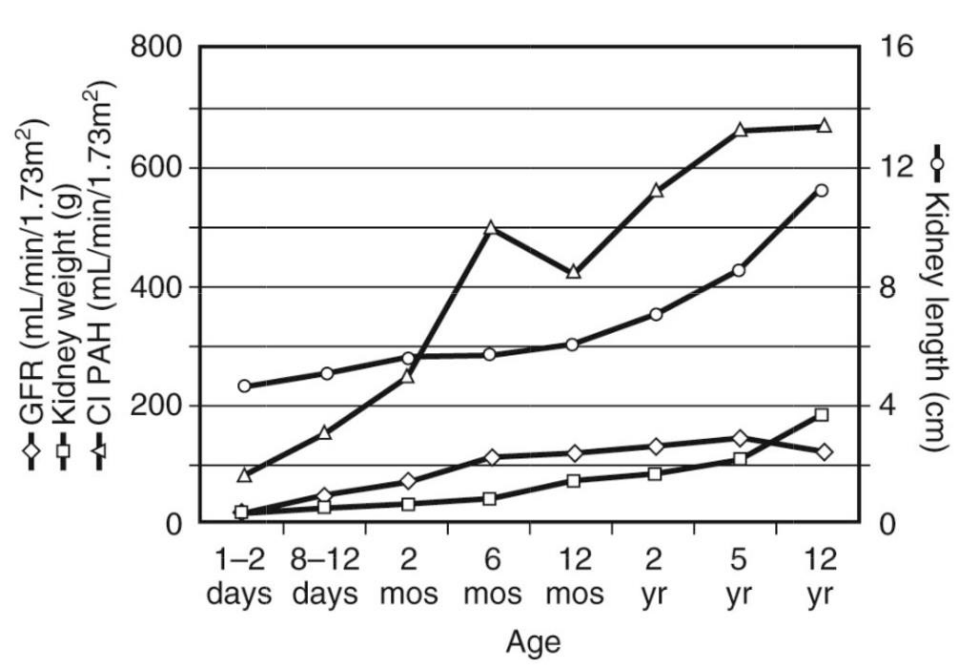
	Neonates	Infants	Children
Physiologic Alteration			
Gastric emptying time	Irregular	Increased	Slightly increased
Gastric pH	>5	4 to 2	Normal (2-3)
Intestinal motility	Reduced	Increased	Slightly increased
Intestinal surface area	Reduced	Near adult	Adult pattern
Microbial colonization	Reduced	Near adult	Adult pattern
Biliary function	Immature	Near adult	Adult pattern
Muscular blood flow	Reduced	Increased	Adult pattern
Skin permeability	Increased	Increased	Near adult pattern
Possible Pharmacokinetic Consequences			
Oral absorption	Erratic: reduced	Increased rate	Near adult pattern
Intramuscular absorption	Variable	Increased	Adult pattern
Percutaneous absorption	Increased	Increased	Near adult pattern
Rectal absorption	Very efficient	Efficient	Near adult pattern
Presystemic clearance	Less than adult	Greater than adult	Greater than adult (increased rate)

Plasma Protein Binding and Drug Distribution

	Neonates	Infants	Children
Physiologic Alteration			
Plasma albumin	Reduced	Near normal	Near adult pattern
Fetal albumin	Present	Absent	Absent
Total protein	Reduced	Decreased	Near adult pattern
Serum bilirubin	Increased	Normal	Normal adult pattern
Serum free fatty acids	Increased	Normal	Normal adult pattern
Blood pH	7.1-7.3	7.4 (normal)	7.4 (normal)
Possible Pharmacokinetic Consequences			
Free fraction	Increased	Increased	Slightly increased
Apparent volume of distribution			
Hydrophilic drugs	Increased	Increased	Slightly increased
Hydrophobic drugs	Reduced	Reduced	Slightly decreased
Tissue-to-plasma ratio	Increased	Increased	Slightly increased

Feigin and Cherry, 2016

Renal function



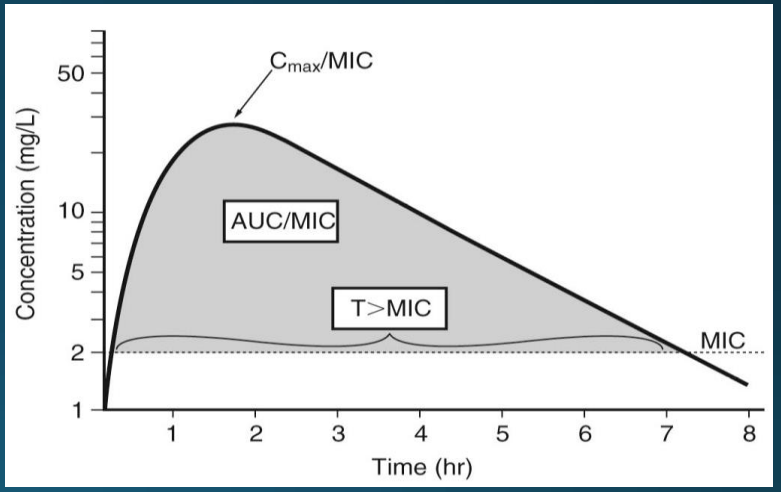
Drug	Cl (mL/hr/kg)	VD (mL/kg)	Elimination $t_{1/2}$ (hr)	
			NEONATE	ADULT
Gentamicin	35-72	350-500	4.4-11.4	2.5
Tobramycin	41-74	590-840	8.2-11.3	2.0
Amikacin	50	570	8.4	2.5
Cefotaxime	50-100	310-790	3.4-6.4	1.2
Ceftriaxone	44-60	530-610	7.7-8.4	6.5
Ceftazidime	31-42	292-363	5.0-8.7	1.8
Vancomycin	36-78	480-680	8.0-17	6.0

Cl, total plasma clearance; $t_{1/2}$, half-life; VD, apparent volume of distribution.

Feigin and Cherry, 2016

General terms

- Area under the curve: Measure of both the extent of drug absorbed and its persistence in the body, and is an integral of blood drug levels over time.
- Clearance: volume of blood from which a certain amount of un-metabolized drug is removed (i.e., cleared) per unit of time. Is a function of drug dose and AUC.
- Half life: The time taken for the plasma concentration to fall to half its original value
- Volume of distribution: The volume that the drug is distributed into

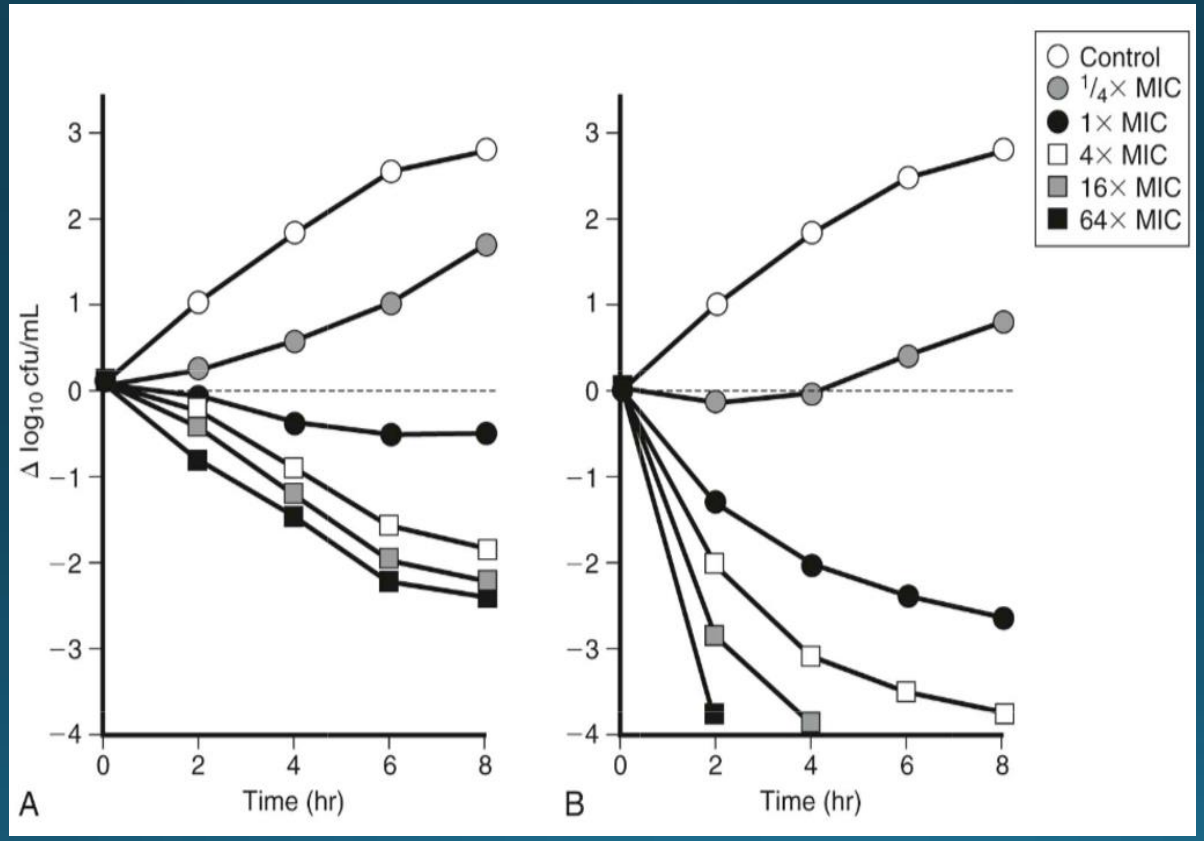


Feigin and Cherry, 2016

Concentration Dependent vs. Time Dependent

Time dependent killing:
The maximal rate of killing is quickly saturated at reasonably low multiples of the MIC, i.e. greater T>MIC equals more bactericidal activity.

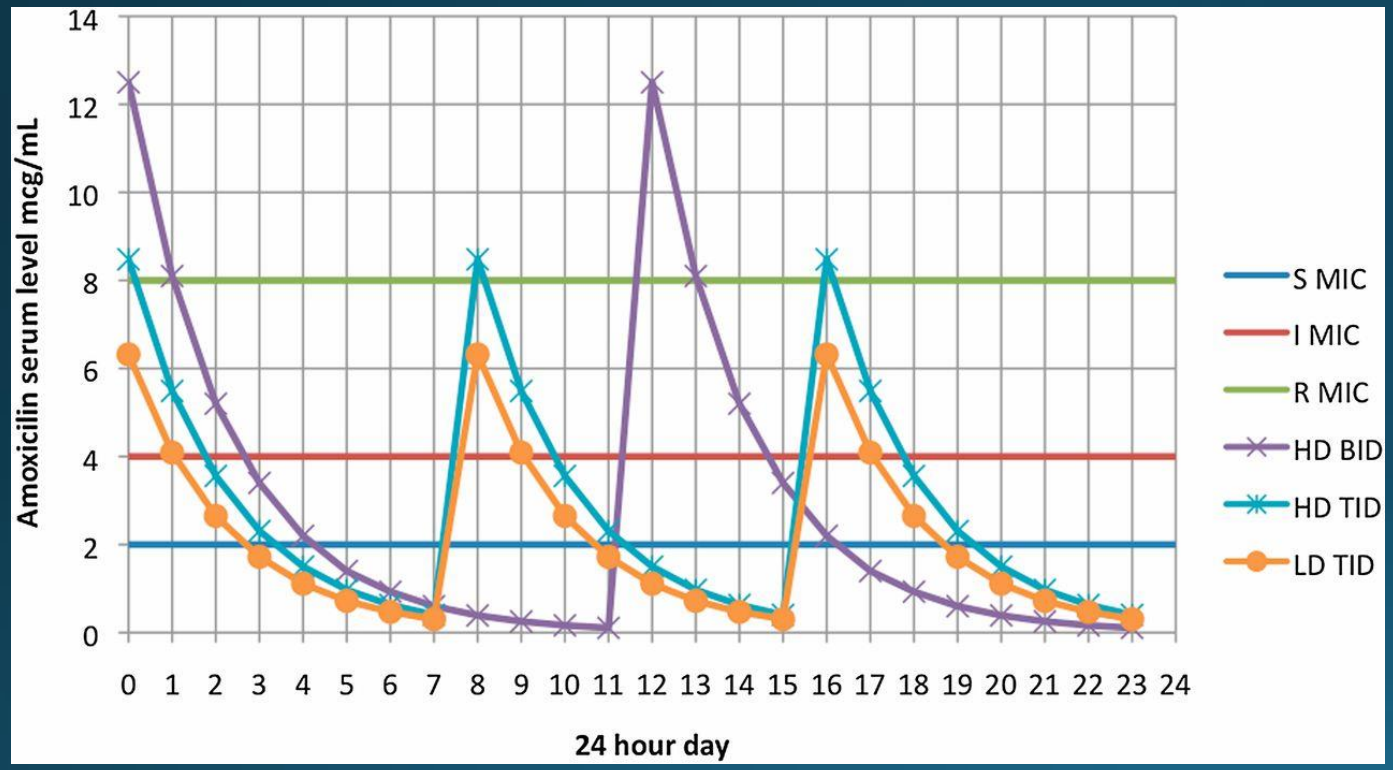
Antibiotics:
Beta-lactams
Macrolides
Vancomycin
Linezolid
Tetracyclines
Clindamycin



Conc. dependent killing:
The magnitude of antimicrobial effect increases in direct proportion to increasing drug concentrations, i.e. greater AUC>MIC equals more bactericidal activity.

Antibiotics:
Fluoroquinolones
Aminoglycosides
Metronidazole
Daptomycin

Use of amoxicillin when treating Otitis Media



Low dose amoxicillin: 40-45 mg/kg daily
High dose amoxicillin: 90-150 mg/kg daily

Pediatrics in Review. November 2013, 34(11)

Aminoglycosides

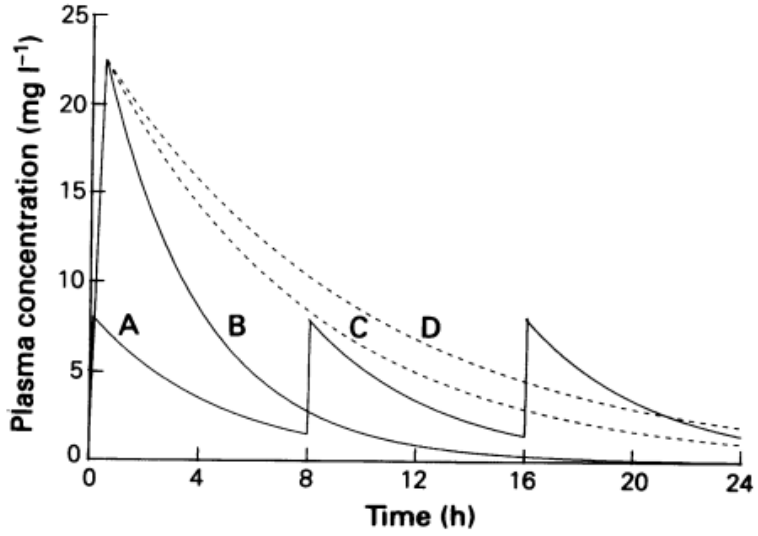


Figure 1 Aminoglycoside concentration *vs* time curves for different dosage regimens. A) dosing every 8 h to achieve a peak concentration of 8 mg l^{-1} and trough concentration of 1.5 mg l^{-1}, and B) once-daily dosing (same total daily dose) to give the same AUC. The two dashed lines (C and D) show once-daily dosing concentration-time curves when trough concentrations of 1 mg l^{-1} and 2 mg l^{-1} are obtained. For curves C and D, the AUC is 1.8- and 2.3-fold higher, respectively, than that of curves A and B.

Br J Clin Pharmacol. 1995 Jun;39(6):605-9.

TABLE 2. Efficacy Outcome Data

Outcome (Studies)	Events/Total* (%)		Risk Ratio (95% CI)
	ODD	MDD	
Combined clinical or microbiologic failure (n = 13)	23/501 (5)	34/494 (7)	0.71 (0.45–1.11)
Per clinical setting			
NICU (n = 2)[24,44]	0/37 (0)	0/39 (0)	NE
CF (n = 1)[46]	0/12 (0)	0/10 (0)	NE
Cancer (n = 1)[43]	1/13 (8)	1/10 (10)	NE
UTI (n = 4)[23,30,37,47]	1/261 (0)	0/256 (0)	1.43 (0.24–8.43)
Others (n = 5)[26,31,39,40,45]	21/178 (12)	33/179 (18)	0.65 (0.40–1.06)
Per aminoglycoside type			
Gentamicin (n = 7)[23,24,26,30,31,37,39]	12/301 (4)	9/302 (3)	1.32 (0.64–2.70)
Amikacin (n = 4)[40,43–45]	10/114 (9)	25/112 (22)	0.41 (0.22–0.77)
Tobramycin or netilmicin (n = 2)[46,47]	1/86 (1)	0/80 (0)	1.82 (0.17–19.21)
Clinical failure (n = 10)[24,26,31,37,39,40,43–46]	22/330 (7)	34/327 (10)	0.67 (0.42–1.07)
Microbiologic failure (n = 7)[23,30,31,37,39,45,47]	5/283 (2)	11/275 (4)	0.51 (0.22–1.18)

NICU: neonatal intensive care unit; CF: cystic fibrosis; UTI: urinary tract infections; Others: infectious diseases occurring in diverse settings; NE: not estimable (zero counts or very small numbers).
* Total refers to patients or episodes.

Pediatrics. 2004 Jul;114(1):e111-8.

Drug Penetration

Factors effecting drug penetration

The ability of a chemical entity to cross from one compartment to another is dictated by several physicochemical properties:

- Molecular weight: Use of Nafcillin (MW 441 g/mol) vs Vancomycin (MW 1449 g/mol) in MSSA infections

- Lipophilic vs. hydrophilic: soluble drugs, such as chloramphenicol, metronidazole, and rifampin, penetrate tissue better than agents that are more water soluble, such as b-lactams, aminoglycosides, and glycopeptides

- Plasma protein-binding affinity: Bound drug becomes part of a large molecular complex that does not diffuse easily out of capillaries.

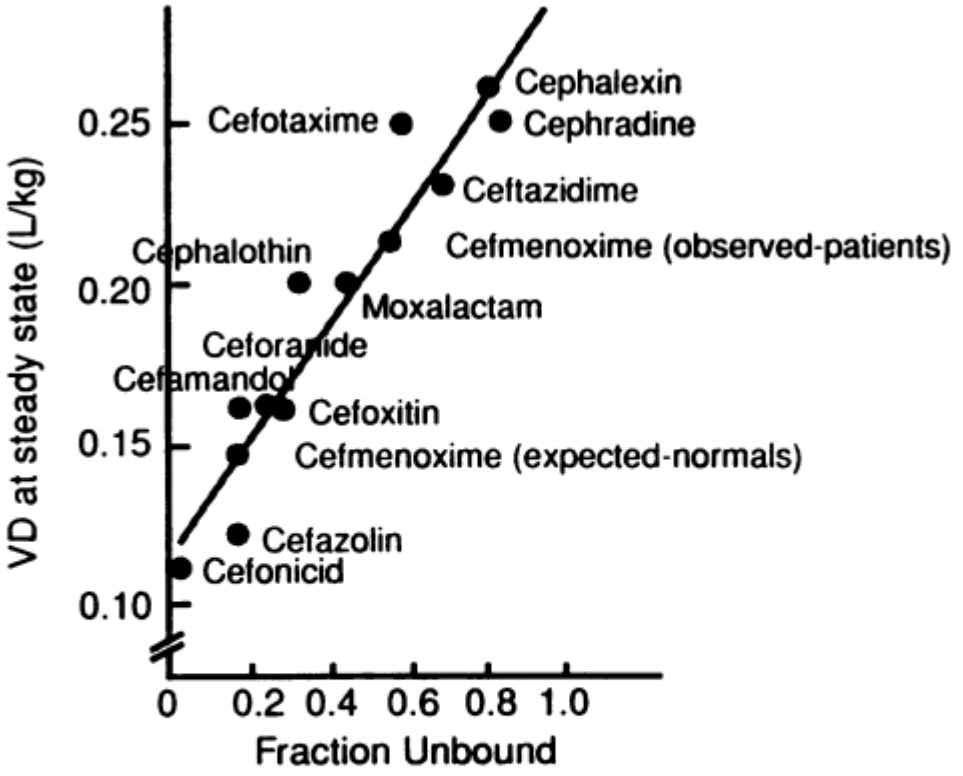


FIG. 1. Relationship between fraction of unbound drug (F_c) in serum and total volume of distribution at steady state (V_{ss}) for 11 cephalosporins (1-g intravenous dose). The cefmenoxime coordinate observed in 20 pneumonia patients is illustrated, as is the expected coordinate for normal sera on the basis of the observed protein binding in normal individuals. The regression equation is as follows: total $V_{ss} = 0.0167F_c + 0.115$ ($r = 0.948$). This figure is adapted from Fig. 1 of reference 75.

- Pt's age and on-going inflammation

- Ceftriaxone:

- CSF concentrations following intravenous administration peak within 2–5 h of dosing
- 1.5 to 4-fold greater in children with confirmed bacterial meningitis than in children with no evidence of meningeal inflammation
- Neonates <30 days of age demonstrate higher CSF peak and trough concentrations than do infants 1.5–9 months of age
- Both in the presence (peak: 19.5 ± 10.1 vs. 16.8 ± 8.4 ug/mL) and absence (peak: 7.2 ± 1.8 vs. 2.6 ± 0.5 ug/mL) of inflammation

J Pediatr. 1984;105:475–81

Table 3
Antibiotic levels in cerebrospinal fluid collected on repeat lumbar puncture

Ceftriaxone					Cefotaxime				
Patient ID number	Causal isolate	Level (μg/mL)	Post-dose interval (h)	WCC	Patient ID number	Causal isolate	Level (μg/mL)	Post-dose interval (h)	WCC
10	Hib	0.58	24	nr	27	Hib	0.45	6	317
[a]	Hib	1.0	24	nr	21	Hib	0.7	6	nr
1	Hib	1.1	1	30	75	Hib	0.74	5.75	100
34[b]	Nmen	1.5	64	1700	4	Hib	0.8	1.16	150
31	SPn	1.75	22	22800	[a]	Hib	0.9	24	nr
35[b]	Hib	2.1	26.6	142	76	Hib	1	3.6	57
15	Hib	3.0	48	150	140	Nmen	1	70	30
9	Hib	3.4	12	nr	79[c]	Hib	1.35	7.75	nr
108	Hib	3.8	15	9655	55[b]	Hib	2.8	nr	1450
125	Hib	3.8	11	1800	12	Hib	7.2	5.5	79
35[b]	Hib	5.4	3	142	55[b]	Hib	8.4	1	1450
34[b]	Nmen	6.1	20	1700	26	Hib	11	0.5	9440
101	SPn	24	1	nr	66	Hib	12	2.75	nr
[a]	Hib	28	14	nr	11	SPn	12	4	57
[a]	Hib	35	0.75	nr	86	Hib	14	3	nr
					23	Hib	15	2	365
					[a]	Hib	15	2	nr
					[a]	Hib	15.2	8	nr

WCC, white cell count; Hib, *Haemophilus influenzae* type b; Nmen, *Neisseria meningitidis*; SPn, *Streptococcus pneumoniae*; nr, not recorded.

[a] Patients excluded from trial.

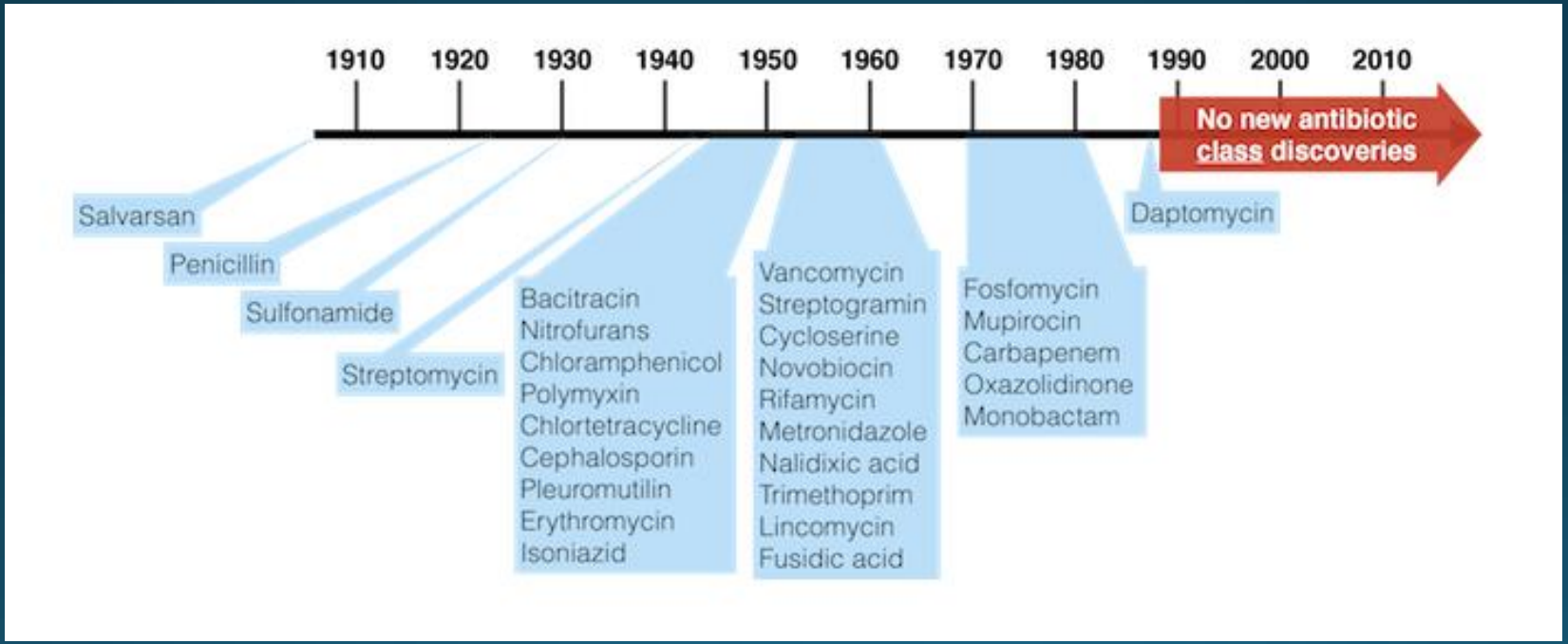
[b] Two separate CSF samples collected from these patients.

[c] Received steroids.

Int J Antimicrob Agents. 2005 Nov;26(5):408-11

Anti-microbial resistance: a global emergency

Drug development



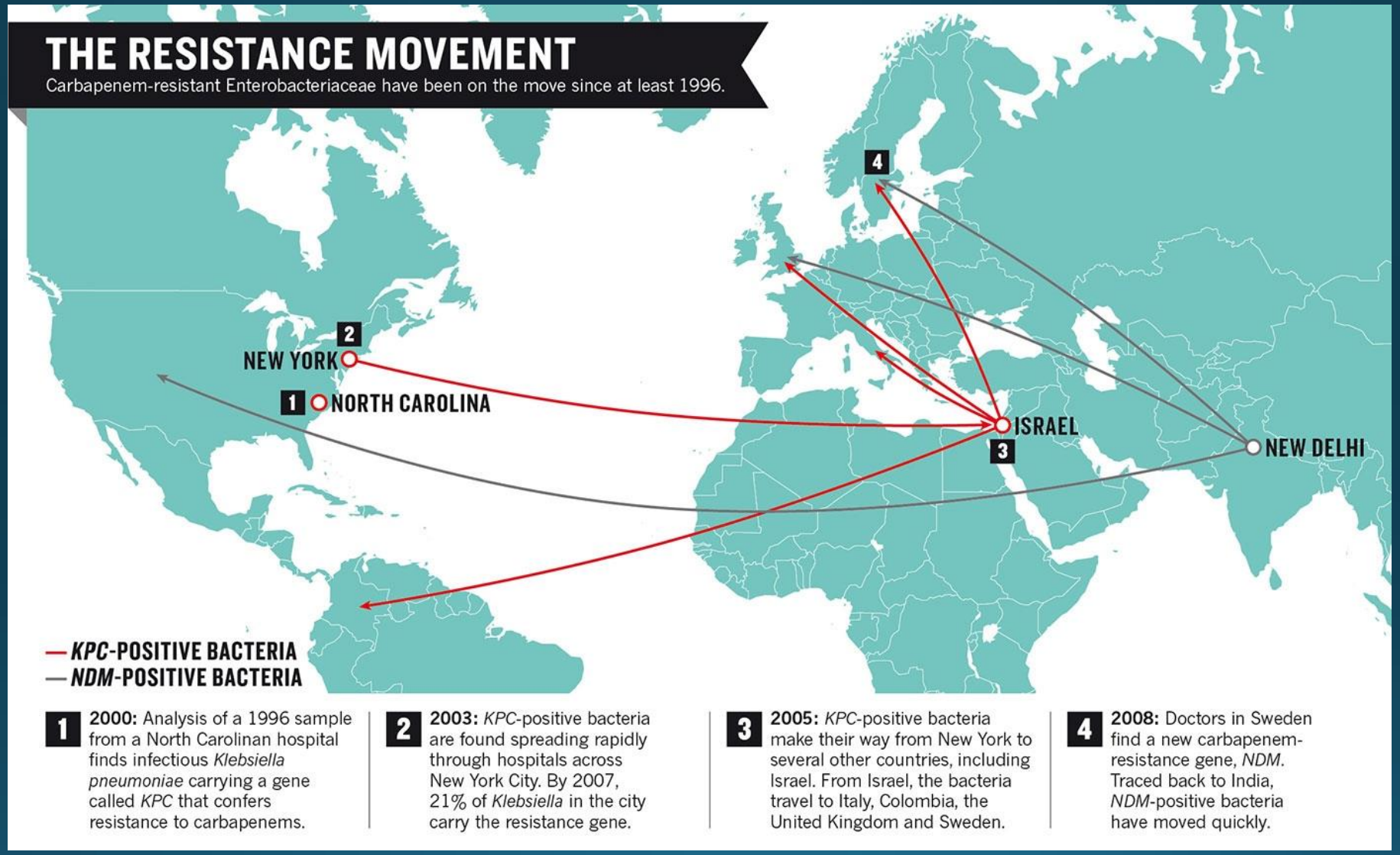
... The global burden of infections resistant to existing antimicrobial medicines is growing at an alarming pace...

Antimicrobial Resistance Growing Global Treat
June 15, 2015 | United Nations Headquarters

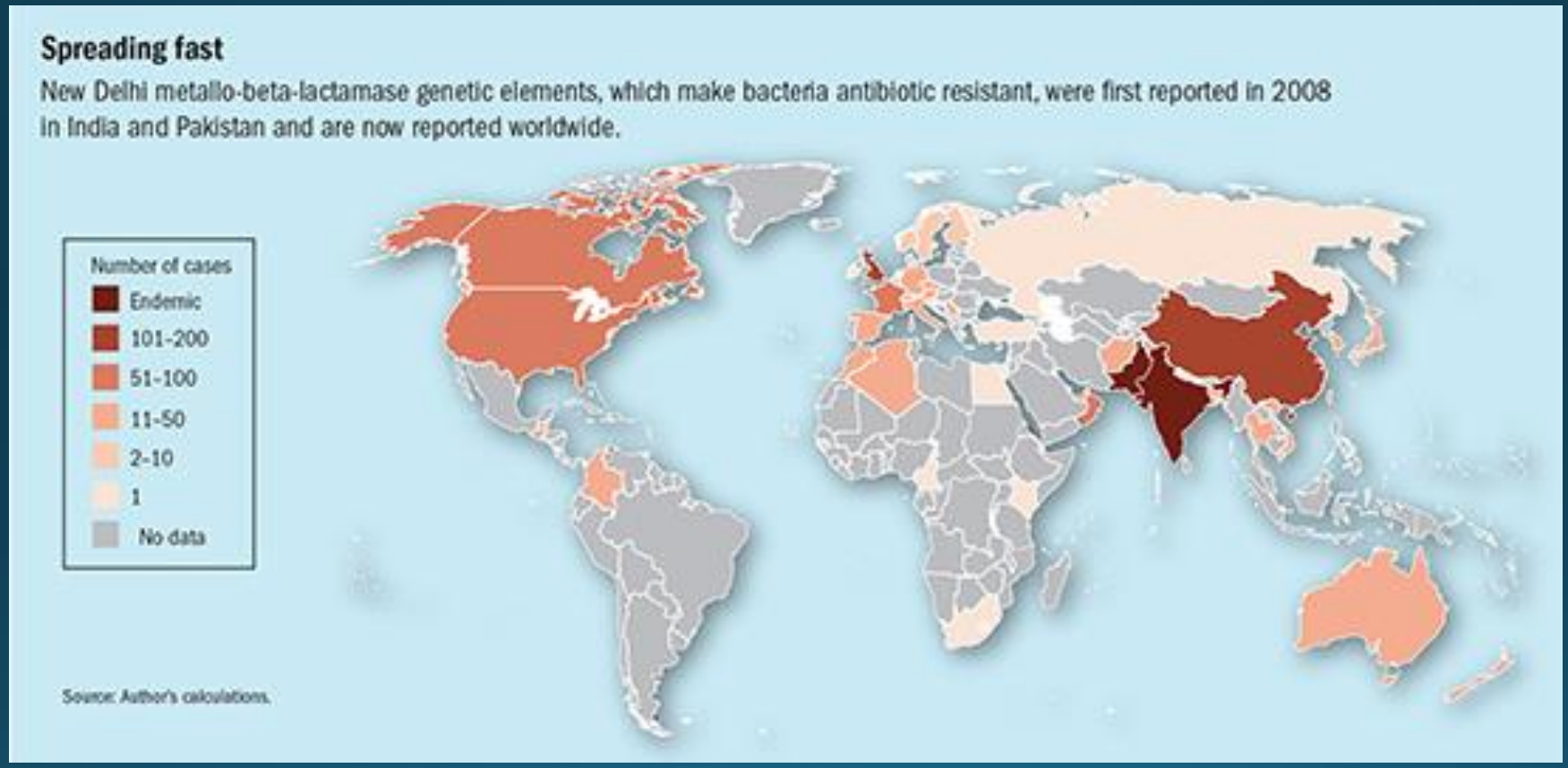
UN agrees to fight 'the biggest threat to modern medicine': antibiotic resistance

All 193 UN member states are set to sign a declaration to fight drug-resistant superbugs that are estimated to kill more than 700,000 people each year

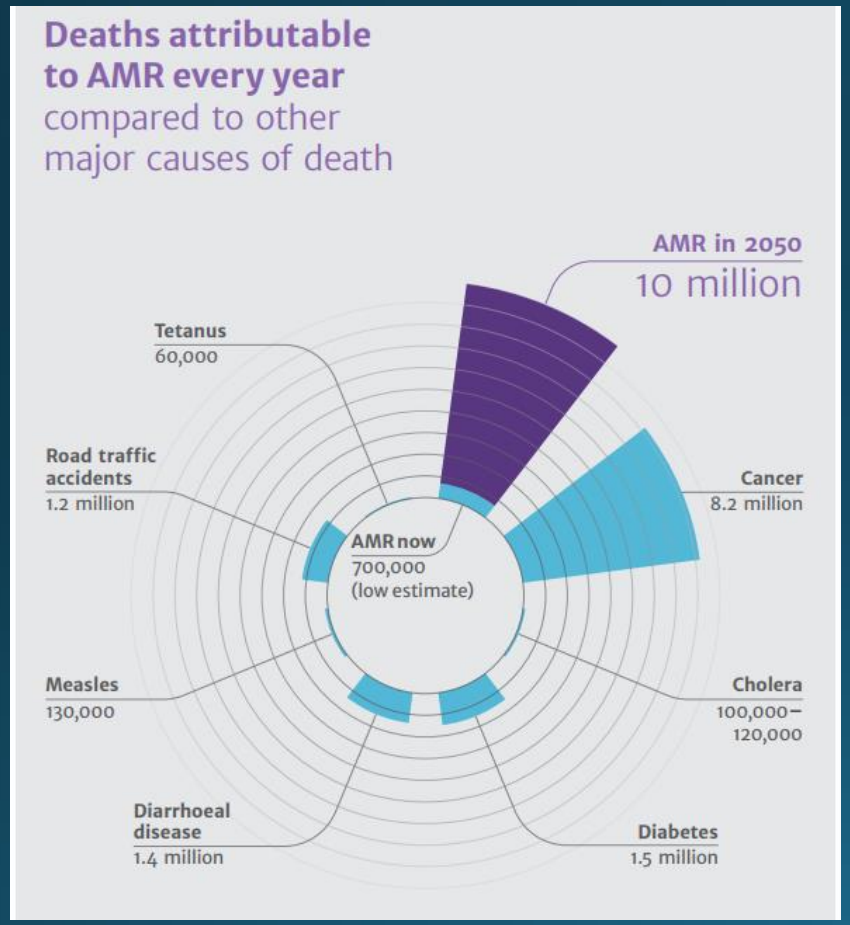
© David Goldman/AP in the guardian

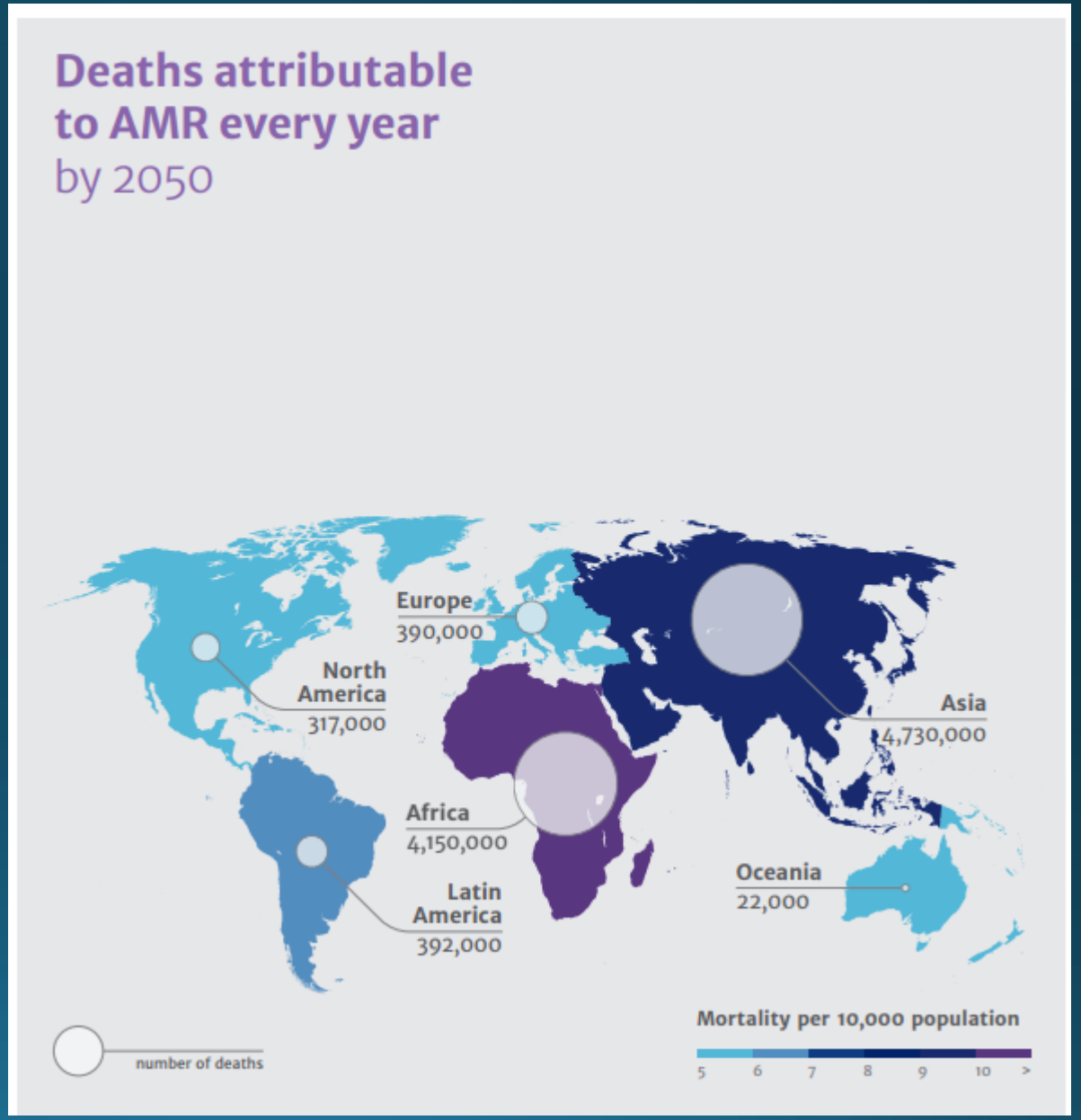


Nature 499, 394–396 (25 July 2013)



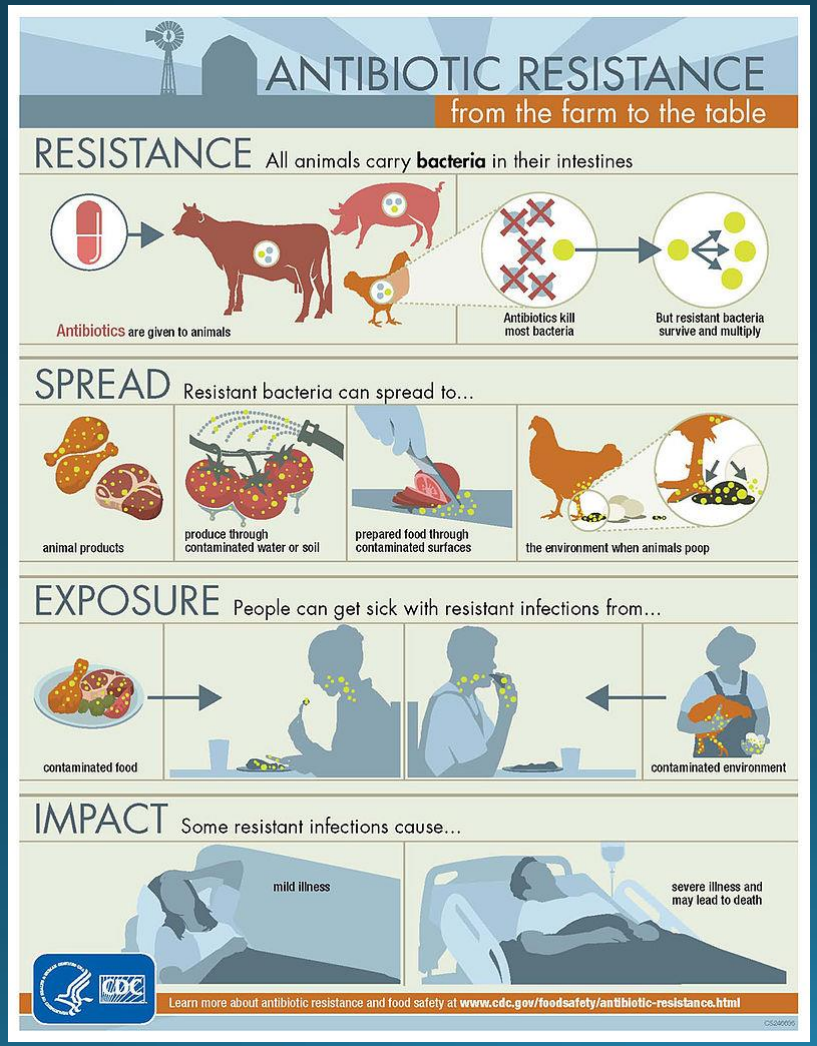
IMF report Dec 2014



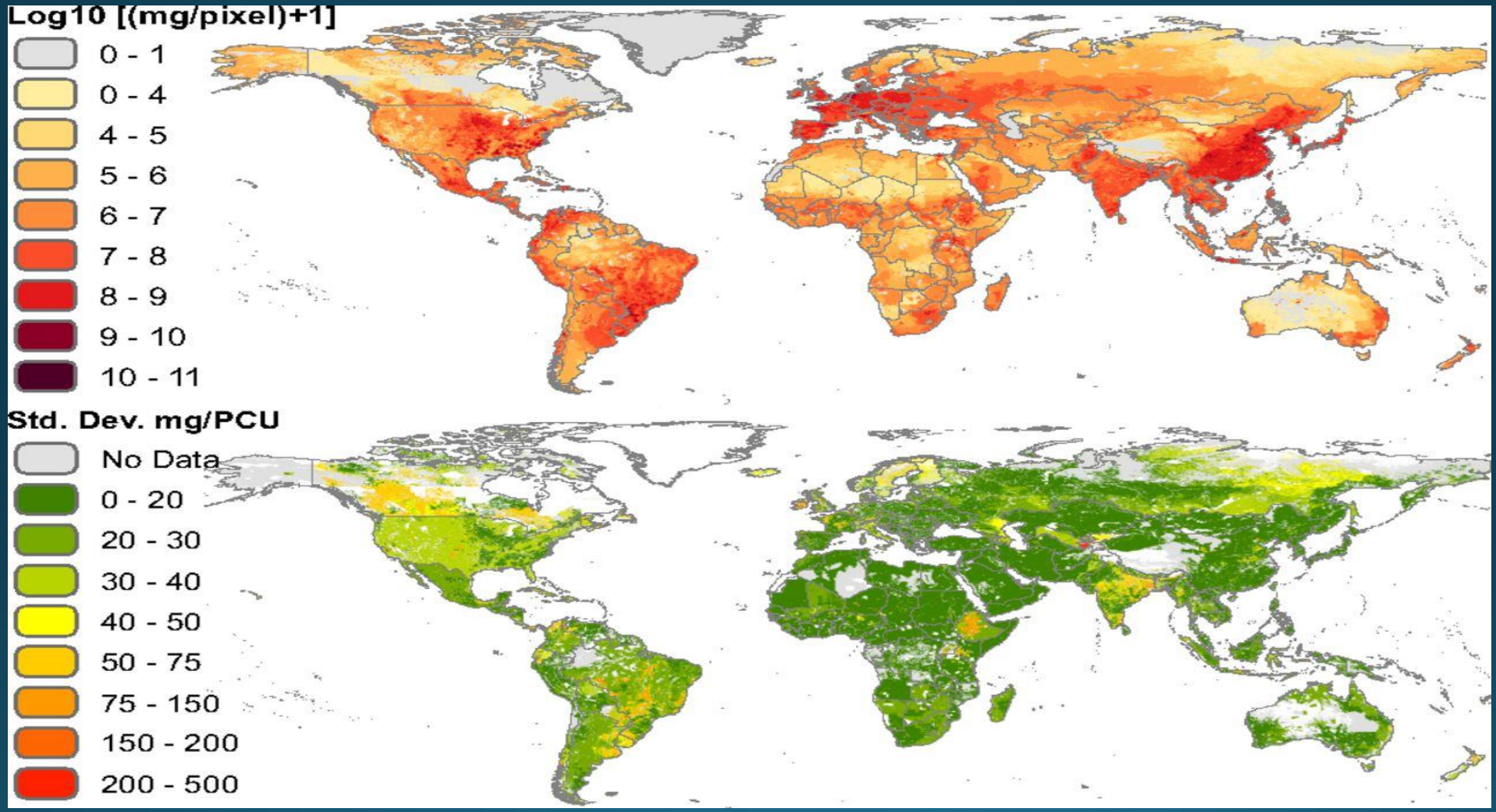


Review of AMR: report sponsored by UK govt in 2014

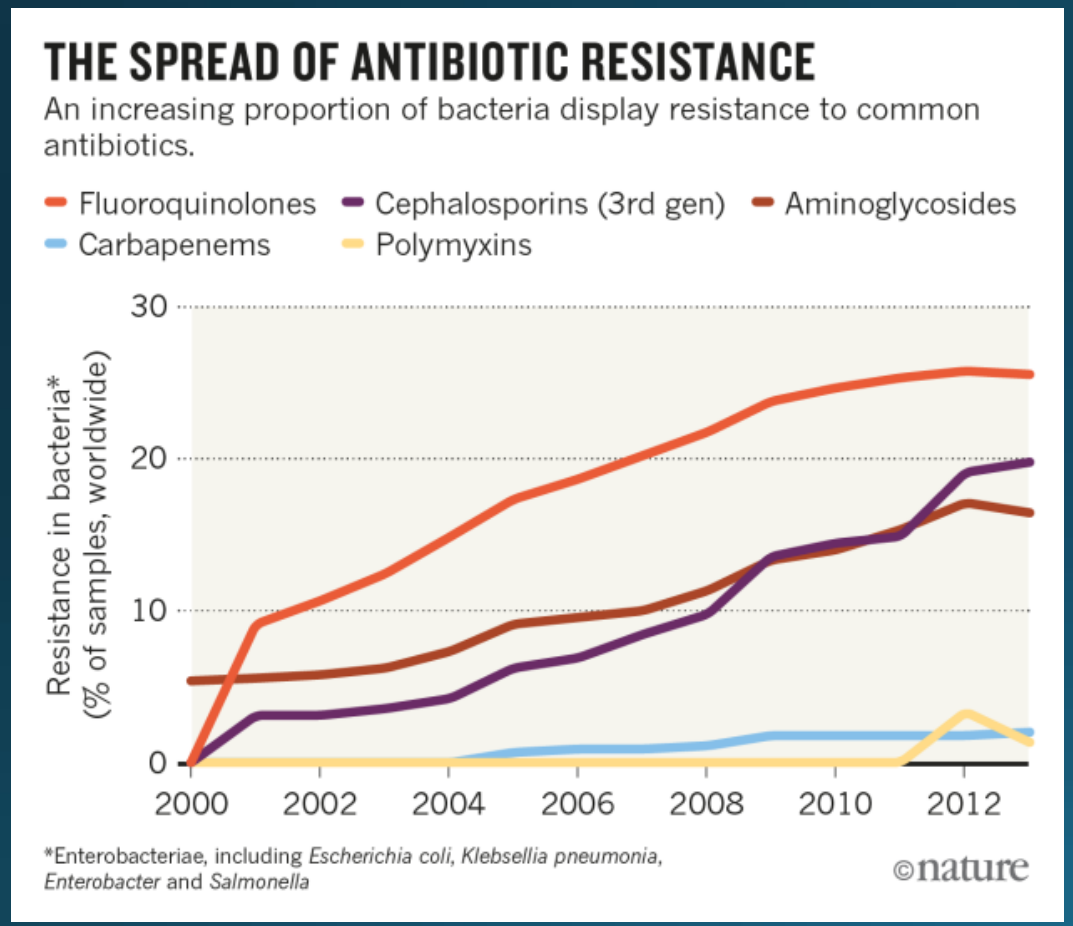
Antibiotic use in animals

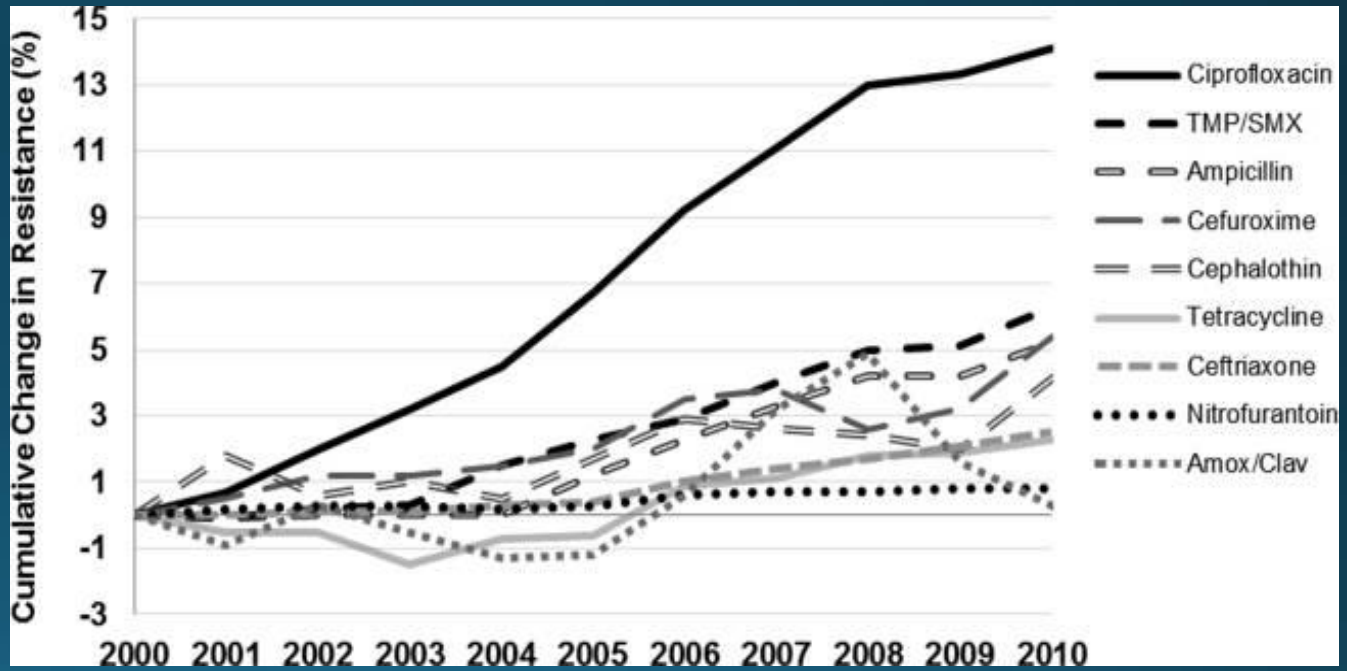


Global antimicrobial consumption in livestock in milligrams per 10 km2 pixels (Top) and average SD of estimates of milligrams per PCU (Bottom).



Thomas P. Van Boeckel et al. PNAS 2015;112:5649-5654





Antimicrob Agents Chemother. Apr 2012; 56(4): 2181–2183.

Estimates of Burden of Antibacterial Resistance

European Union
population 500m

25,000 deaths per year

2.5m extra hospital days

Overall societal costs
(€ 900 million, hosp. days)
Approx. €1.5 billion per year

Source: ECDC 2007

Thailand
population 70m

>38,000 deaths

>3.2m hospital days

Overall societal costs
US$ 84.6–202.8 mill. direct
>US$1.3 billion indirect

Source: Pumart et al 2012

United States
population 300m

>23,000 deaths

>2.0m illnesses

Overall societal costs
Up to $20 billion direct
Up to $35 billion indirect

Source: US CDC 2013

Global information is insufficient to show complete disease burden impact and costs

World Health Organization

Antibiotic prescription practices

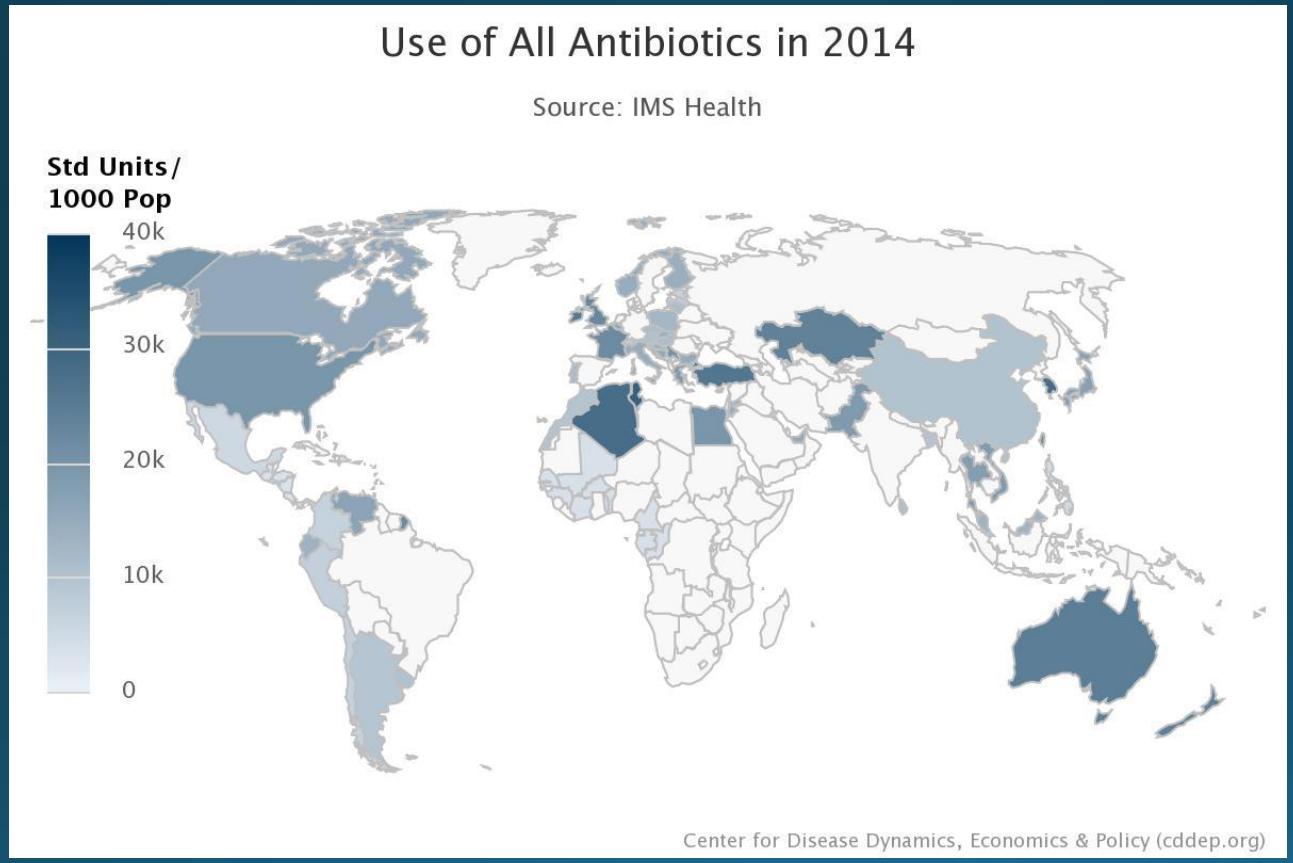


Table 3. Mean Annual Total Visit Rate and Rate of Visits With Antibiotics Prescribed per 1000 Population by US Census Region and Age Group From the US NAMCS/NHAMCS, 2010-2011[a]

Age Group, y	Ambulatory Visits, Weighted Mean Annual Rate per 1000 Population (95% CI)										*P* Value for Weighted Rate	
	Northeast[b]		Midwest[c]		South[d]		West[e]		Total			
	Total	Antibiotics Prescribed	Total	Antibiotics Prescribed	Total	Antibiotics Prescribed	Total	Antibiotics Prescribed	Total	Antibiotics Prescribed	Total Among Regions[f]	Antibiotic Prescriptions Among Regions[g]
0-2	8203 (6078-10 329)	1196 (703-1689)	6021 (4862-7181)	1240 (877-1602)	6837 (5292-8381)	1492 (1098-1885)	6717 (5514-7919)	1071 (752-1390)	6851 (6070-7633)	1287 (1085-1489)	.35	.45
3-9	4178 (3325-5031)	864 (562-1167)	2326 (1925-2726)	535 (398-673)	2862 (2156-3568)	738 (576-899)	2836 (2338-3335)	597 (459-735)	2953 (2617-3289)	680 (590-771)	.002	.11
10-19	3149 (2547-3750)	510 (342-769)	2441 (2015-2866)	406 (331-480)	2654 (2149-3159)	491 (395-587)	2110 (1669-2550)	345 (255-436)	2563 (2307-2819)	441 (388-494)	.05	.11
20-39	3410 (3021-3799)	393 (311-475)	2968 (2329-3606)	418 (314-523)	3024 (2509-3538)	469 (362-576)	2542 (2030-3055)	272 (196-347)	2962 (2689-3235)	397 (346-448)	.07	.01
40-64	4556 (4015-5098)	440 (336-545)	3913 (3161-4664)	463 (351-574)	4031 (3313-4748)	463 (376-551)	3942 (3374-4510)	359 (281-437)	4083 (3732-4434)	435 (387-483)	.37	.27
≥65	7536 (6330-8743)	623 (434-813)	6854 (5610-8097)	592 (453-732)	7056 (5791-8322)	594 (477-711)	8046 (6901-9190)	675 (521-830)	7317 (6676-7959)	617 (544-689)	.51	.85
All ages	4580 (4047-5114)	525 (431-618)	3786 (3155-4418)	497 (398-596)	3970 (3311-4629)	553 (459-648)	3796 (3262-4330)	423 (343-504)	3999 (3678-4320)	506 (458-554)	.15	.18

Abbreviation: NAMCS/NHAMCS, National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey.

[a] Population denominators are based on the July 1, 2010, and July 1, 2011, set of estimates of the civilian, noninstitutional population of the United States, as developed by the Population Division of the US Census Bureau.[21,22] Values are based on 2-year averages.

[b] Northeast region includes Maine, New Hampshire, Vermont, Massachusetts, Rhode Island, Connecticut, New York, New Jersey, and Pennsylvania.

[c] Midwest region includes Ohio, Michigan, Indiana, Illinois, Wisconsin, Missouri, Iowa, Minnesota, Kansas, Nebraska, South Dakota, and North Dakota.

[d] South region includes Delaware, Maryland, District of Columbia, Virginia, West Virginia, North Carolina, South Carolina, Florida, Georgia, Tennessee, Kentucky, Alabama, Mississippi, Louisiana, Arkansas, Oklahoma, and Texas.

[e] West region includes Montana, Wyoming, Colorado, New Mexico, Arizona, Utah, Idaho, Washington, Oregon, Nevada, California, Alaska, and Hawaii.

[f] *P* values are for χ^2 test for heterogeneity for differences among regions for rate of total visits per 1000 population.

[g] *P* values are for χ^2 test for heterogeneity for differences among regions for rate of antibiotics prescriptions per 1000 population.

JAMA. 2016;315(17):1864-1873

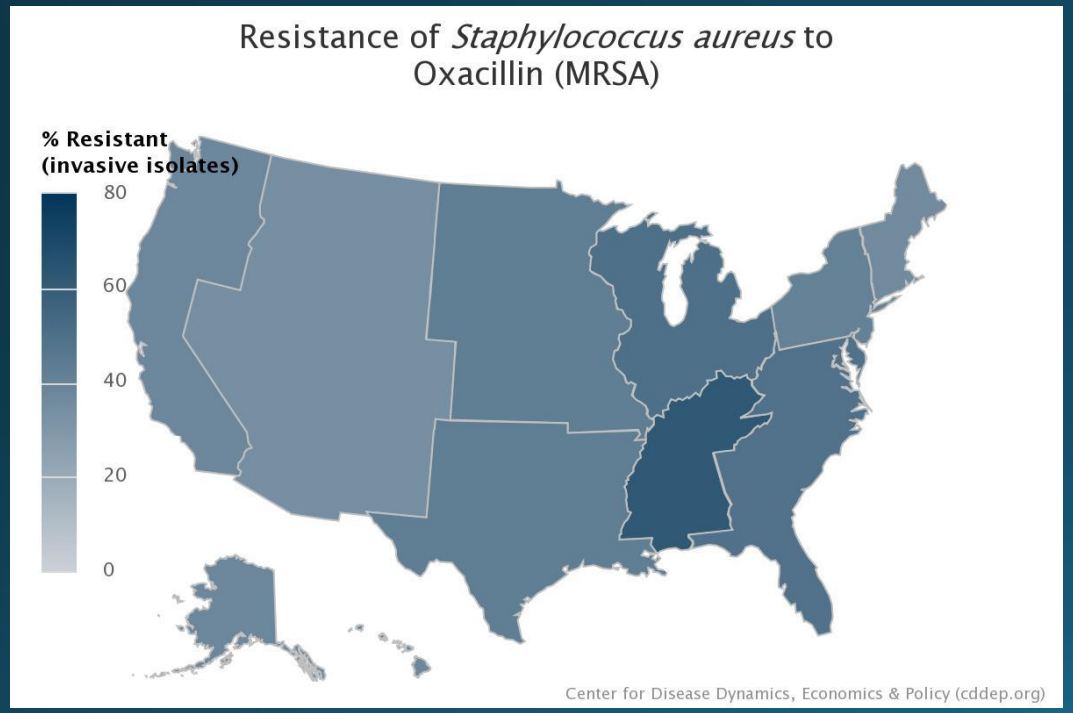
Resistance patterns: *E. coli*

South Atlantic: 58%

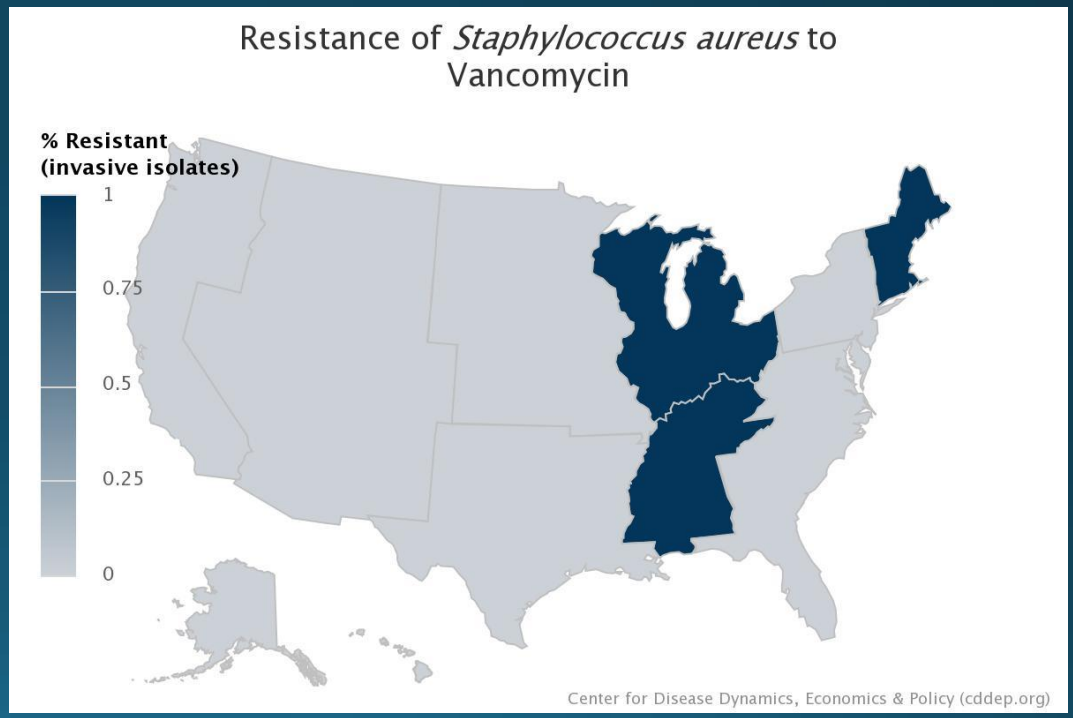
South Atlantic: 12%

South Atlantic: 35%

Resistance pattern: *S. aureus*



49%



<0.25%

WHO Critically Important Antimicrobials for Human Medicine 5th revision

Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR)

October 2016

Summary of classification and prioritization of antimicrobials categorized as Critically Important, Highly Important and Important

Critically Important

Antimicrobial class	Criterion (Yes = ●)				
CRITICALLY IMPORTANT ANTIMICROBIALS	C1	C2	P1	P2	P3
HIGHEST PRIORITY					
Highest Priority — *Cephalosporins (3rd, 4th and 5th generation)*	●	●	●	●	●
Glycopeptides	●	●	●	●	●
Macrolides and ketolides	●	●	●	●	●
Polymyxins	●	●	●	●	●
Quinolones	●	●	●	●	●
HIGH PRIORITY					
Aminoglycosides	●	●		●	●
Ansamycins	●	●	●	●	
Carbapenems and other penems	●	●	●	●	
Glycylcyclines	●	●	●		
Lipopeptides	●	●	●		
Monobactams	●	●	●		
Oxazolidinones	●	●	●		
Penicillins (natural, aminopenicillins, and antipseudomonal)	●	●		●	●
Phosphonic acid derivatives	●	●	●	●	
Drugs used solely to treat tuberculosis or other mycobacterial diseases	●	●	●	●	

Highly Important

HIGHLY IMPORTANT ANTIMICROBIALS	C1	C2	P1	P2	P3
Amidinopenicillins		●			
Amphenicols		●			
Cephalosporins (1st and 2nd generation) and cephamycins		●			
Lincosamides		●			
Penicillins (anti-staphylococcal		●			
Pseudomonic acids		●			
Riminofenazines	●				
Steroid antibacterials		●			
Streptogramins		●			
Sulfonamides, dihydrofolate reductase inhibitors and combinations		●			
Sulfones	●				
Tetracyclines	●				

NA

Important

IMPORTANT ANTIMICROBIALS	C1	C2	P1	P2	P3
Aminocyclitols					
Cyclic polypeptides					
Nitrofurantoins					
Nitroimidazoles					
Pleuromutilins					

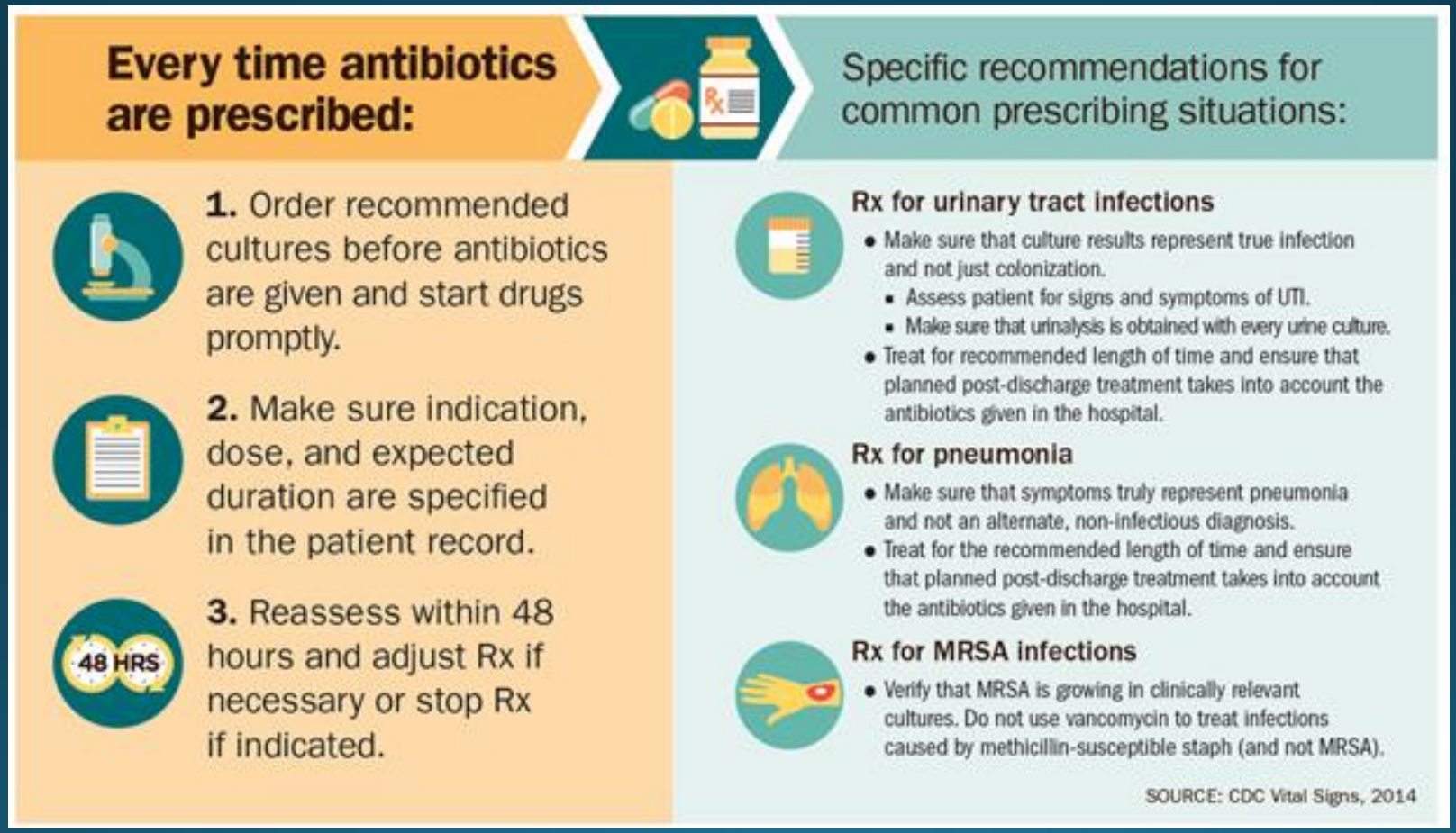
NA

Table 4. Mean Annual Antibiotic Prescribing Rates in 2010-2011 US NAMCS/NHAMCS vs Estimated Appropriate Antibiotic Prescribing Annual Rates per 1000 Population by Age Group and Diagnosis

	Rates per 1000 Population		Potential Reduction in Annual Antibiotic Prescription Rates, %
	2010-2011 Weighted Mean Annual Rate of Antibiotic Prescriptions (95% CI)	Estimated Appropriate Annual Rate of Antibiotic Prescriptions[a]	
0-19 y			
All acute respiratory conditions[b]	421 (369 to 473)	278[c]	−34
Sinusitis	65 (51 to 79)	59	−9
Suppurative otitis media	154 (131 to 177)	138	−10
Pharyngitis	91 (76 to 105)	60	−34
Asthma or allergy; bronchitis or bronchiolitis; influenza; nonsuppurative otitis media; viral URI; and viral pneumonia[e]	90 (71 to 108)	0	−100
Pneumonia	22 (16 to 27)	22	0
Other conditions[d]	225 (197 to 252)	180[f]	−20
Urinary tract infection	23 (17 to 28)	23	0
Miscellaneous bacterial infections	20 (13 to 26)	20	0
Remaining other conditions[g]	182 (160 to 205)	137	−25
Total[h]	646 (571 to 721)	458	−29

JAMA. 2016;315(17):1864-1873

Antimicrobial stewardship



Double coverage

Intuitive appeal

- **The use of combination therapy for infections with GNR bacteria is often justified by one of the following three reasons:**

- To broaden the empiric coverage provided by two antimicrobial agents with different spectra of activity (an effort to ensure that the pathogen is adequately covered by at least one of the two components of the regimen)
- To exploit the synergy observed in vitro between two antibiotic agents compared to one (and hence improve clinical outcomes)
- To prevent or delay the emergence of resistance during antimicrobial therapy e.g. in AmpC producing SPACE organisms

Downside of double coverage

- Increased antimicrobial resistance
- Increase in adverse effects
- Increase costs
- Antagonism between antibiotics, downregulation of drug-targets or blocking access to drug targets

Empiric combination therapy

- A retrospective, cohort study involving 28 ICUs was done to to evaluate the therapeutic benefit of empiric combination therapy (β-lactams in combination with aminoglycosides, fluoroquinolones, or macrolides/clindamycin) compared with β-lactam monotherapy in 4,662 eligible cases of culture-positive bacterial septic shock.
- Empiric combination therapy was associated with
- decreased 28-day mortality (36% versus 29%; P = 0.0002)
- increases in mechanical ventilation-free days (median [interquartile range], 10 [0 to 25] versus 17 [0 to 26]; P = 0.008)
- pressor-free days (23 [0 to 28] versus 25[0 to 28]; P = 0.007)

However, when patients received antipseudomonal penicillins, antipseudomonal cephalosporins, and carbapenems there was nobenefit with the addition of a second agent.

Crit. Care Med (2010) 38:1773–1785.

Use of local epidemiology and pt data

- Increasing prevalence of MDR GNRs makes it harder to not do double coverage
- A meta-analysis of 16 studies found that ESBL production is associated with a delay in effective antimicrobial therapy for patients with Gram-negative bacteremia and a subsequent increased mortality.
- Though if using broad-spectrum carbapenems no data to suggest worse outcomes.

J. Antimicrob. Chemother. (2007) **60**:913–920

- Patient characteristics should be an important determinant when choosing empiric therapy
- Thirty-seven percent of patients receiving piperacillin-tazobactam in the month prior to their current infection were infected with piperacillin-tazobactam-resistant *P. aeruginosa* in the subsequent month.
- Add an aminoglycoside or broaden to carbapenems

Int. J. Antimicrob. Agents (2007) **30**:458–462

Synergy: *in vitro* data

- Most well studied is Beta-lactam + AG
- β-Lactams create a disturbance of the cell walls of Gram-negative bacilli which facilitates passage of aminoglycosides into the periplasmic space
- Synergy shown in animal models of endocarditis:

- Enterococcus: Ampicillin + AG
- *S. viridans*: Penicillin + streptomycin
- *S. aureus*: Nafcillin + low-dose Gentamicin
- *P. aeruginosa* : Carbenicillin + gentamicin

Synergy: conflicting clinical evidence

- A prospective cohort study of 200 patients with *P. aeruginosa* bacteremia (both neutropenic and nonneutropenic patients) was undertaken to compare *in vitro* susceptibility results with mortality. No significant correlation between *in vitro* synergy testing (either time-kill or checkerboard) and clinical outcome was demonstrated. (Am. J. Med. **87**:540–546)
- A retrospective study of 444 cases of Gram-negative bacteremia, there was an 80% clinical response rate in patients who received antibiotic therapy that was synergistic against the organism (using the checkerboard technique), compared to a 64% response rate in patients who received single drug ($P < 0.05$). Synergism correlated with better clinical responses in patients with neutropenia, shock, and *P. aeruginosa* infections. Rev. Infect. Dis.**13**:550–558.

MRSA bacteremia

Table 3. Microbiologic outcomes of patients with pMRSA bacteremia

Outcome	Combination ($n = 16$)	Monotherapy ($n = 60$)	Total ($n = 76$)	*P* value
Microbiologic clearance at end of treatment, *n* (%)	14 (87.5)	47 (78.3)	61 (80.3)	0.505
Microbiologic clearance at day 21, *n* (%)	10 (62.5)	37 (61.7)	47 (61.8)	0.951
Duration of bacteremia, median (range)	19 (10–76)	14 (8–49)	15 (8–76)	*0.023*

Table 4. Clinical outcomes of patients with pMRSA bacteremia

Outcome	Combination ($n = 21$)	Monotherapy ($n = 55$)	Total ($n = 76$)	*P* value
30-d mortality, *n* (%)	2 (9.5)	14 (25.5)	16 (21.1)	0.208
In-hospital mortality, *n* (%)	5 (23.8)	19 (34.5)	24 (31.6)	0.368
Infection-related mortality, *n* (%)	6 (28.6)	20 (36.4)	26 (34.2)	0.522
Clinical improvement at D14, *n* (%)	15 (71.4)	32 (58.2)	47 (61.8)	0.288
Recurrent MRSA culture[a], *n* (%)	4 (22.2)	7 (18.9)	11 (20.0)	1.000
Hospitalization days after index culture, median (range)	38 (18–98)	26 (9–147)	30.5 (9–147)	0.058
Total duration of hospitalization, median (range)	41 (20–128)	33 (11–223)	37.5 (11–223)	0.646

Virulence. 2013 Nov 15; 4(8): 734–739.

FQ synergy

- A retrospective cohort study incorporating propensity scores evaluated 28-day mortality in 702 patients with Gram-negative bacteremia receiving a combination of β-lactam and fluoroquinolone or β-lactam monotherapy.
- Combination therapy was associated with:
- lower 28-day mortality than monotherapy (4.2% versus 8.8%; P = 0.04)
- however, the additional benefit of fluoroquinolones was not evident for critically ill patients

Caveat: FQ dosing in children is not well studied and has an FDA black box warning

Agents Chemother. (2009) **53**:1386–1394

Emergence of resistance

- *In vitro* data: CF *P. aeruginosa* strains show delayed resistance in presence of carbapenem + FQ (Clin. Infect. Dis (2015). 40: S105–S114)

- Clinical data:

- A prospective cohort study of 271 adults examined the emergence of resistance to ceftazidime, imipenem, ciprofloxacin, and piperacillin during therapy with the respective agents. Resistance was not delayed with addition of AG (Antimicrob. Agents Chemother. (199) **43**:1379–1382)
- A meta-analysis of 8 randomized, controlled trials comparing β-lactam monotherapy with β-lactam and aminoglycoside combination therapy. The summary OR for the emergence of resistance suggested that combination therapy and monotherapy were equivalent in the development of subsequent resistant organisms (OR, 0.90; 95% CI, 0.56 to 1.47). (Clin. Infect. Dis. (2005) **41**:149–158)

Take home points!

- Drugs that are –cidal may be –static depending on the bacterial species or if infected with a large inoculum
- Drug pharmacokinetics are not constant in the Pediatric population
- Optimal dosing of antibiotics depend on their concentration or time dependent activity
- Early on in infections, increased capillary leakage helps facilitate better distribution of drug
- There is a rapid increase in antimicrobial resistance across the world. Antimicrobial stewardship through out the healthcare system is critical!
- Empiric double coverage may be warranted depending on prevalence of MDR organisms or patient characteristics, however there is no clear evidence that continued double coverage after speciation is of any added benefit

Thank you!