The Threat of Multidrug Resistant Organisms in Hospitalized Patients

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Overview

1. Antimicrobial resistance (AMR)
2. Drivers of AMR
3. Consequences/costs of AMR
4. Populations at risk for MDRO infections
5. Superbugs & super-resistance
6. The impact of MDRO on outcomes
7. Prevention of MDRO infections
8. Treatment of MDRO infections

1. Antimicrobial resistance

NOTE: Antibacterial resistance refers to when antibiotics become ineffective against bacteria

"Antibiotic resistance is perhaps the single most important infectious disease threat of our time."

—Beth Bell, MD, MPH, Director, National Center for Emerging and Zoonotic Infectious Diseases at the Centers for Disease Control[5]

2016

Which is NOT true about antimicrobial resistance (AMR)?

A. AMR is when microorganisms change so that the drugs typically used to treat people infected by them are no longer effective.

B. The only people are risk for AMR are those in the hospital and those who are immunocompromised, such as chemotherapy and transplant patients.

C. When the microorganisms become resistant to most antimicrobials they are often referred to as “superbugs”.

D. Antimicrobial resistance increases the cost of health care with lengthier stays in hospitals and more intensive care required.

Which is NOT true about antimicrobial resistance (AMR)?

B. **The ~~only~~ people MOST are risk for AMR are those in the hospital and those who are immunocompromised, such as chemotherapy and transplant patients.**

WHERE DO INFECTIONS HAPPEN?

Antibiotic-resistant infections can happen anywhere. Data show that most happen in the general community; however, most deaths related to antibiotic resistance happen in healthcare settings, such as hospitals and nursing homes.

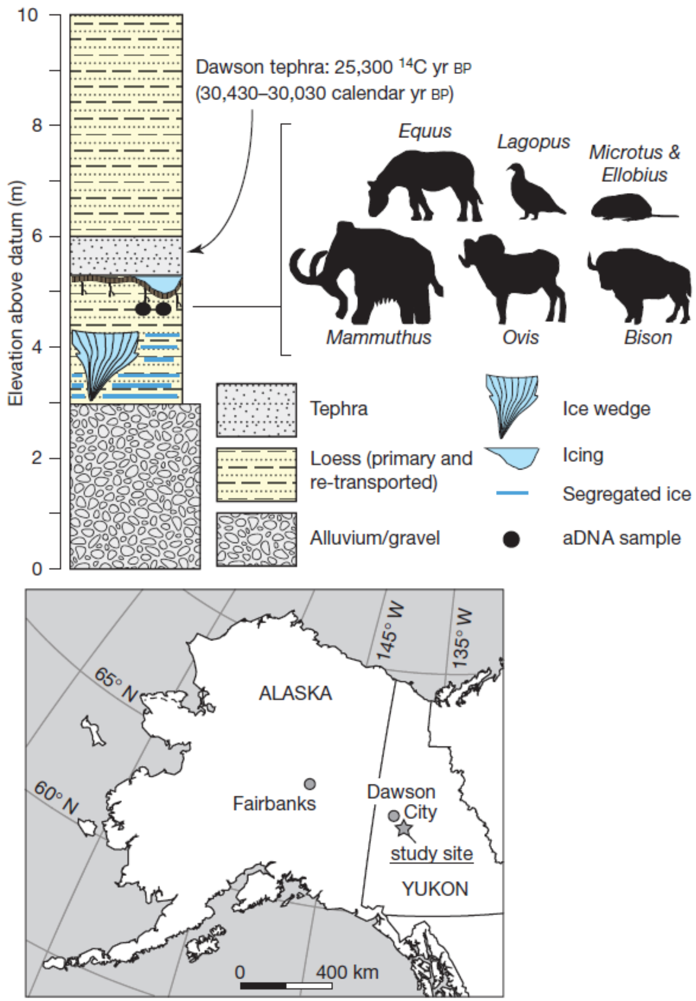
What is the earliest known antibacterial resistance?

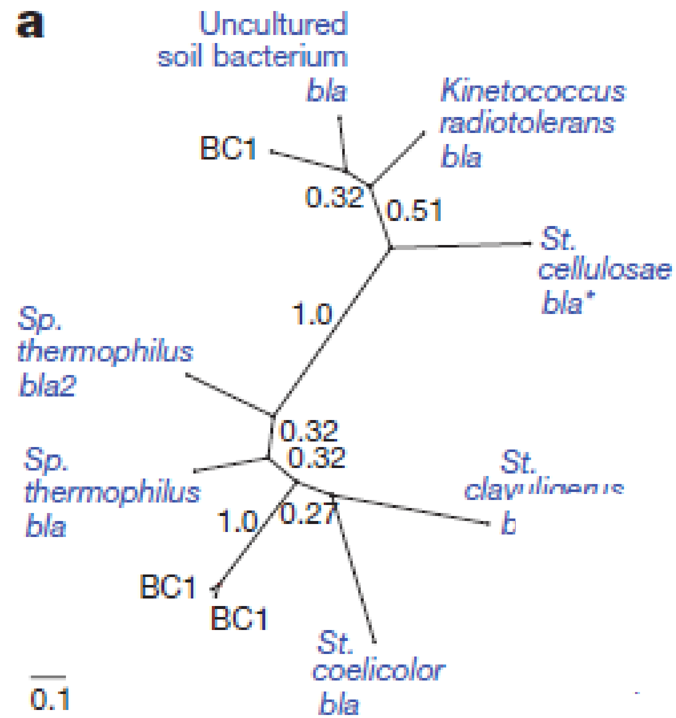
A. In 1940, 12 years after Flemming discovered penicillin, but 6 years before it was commercially available

B. In 1950, after scientists discovered that adding antibiotics to chicken feed accelerated growth

C. Genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics have been found in specimens from 30,000 years ago

Antibacterial resistance is ancient

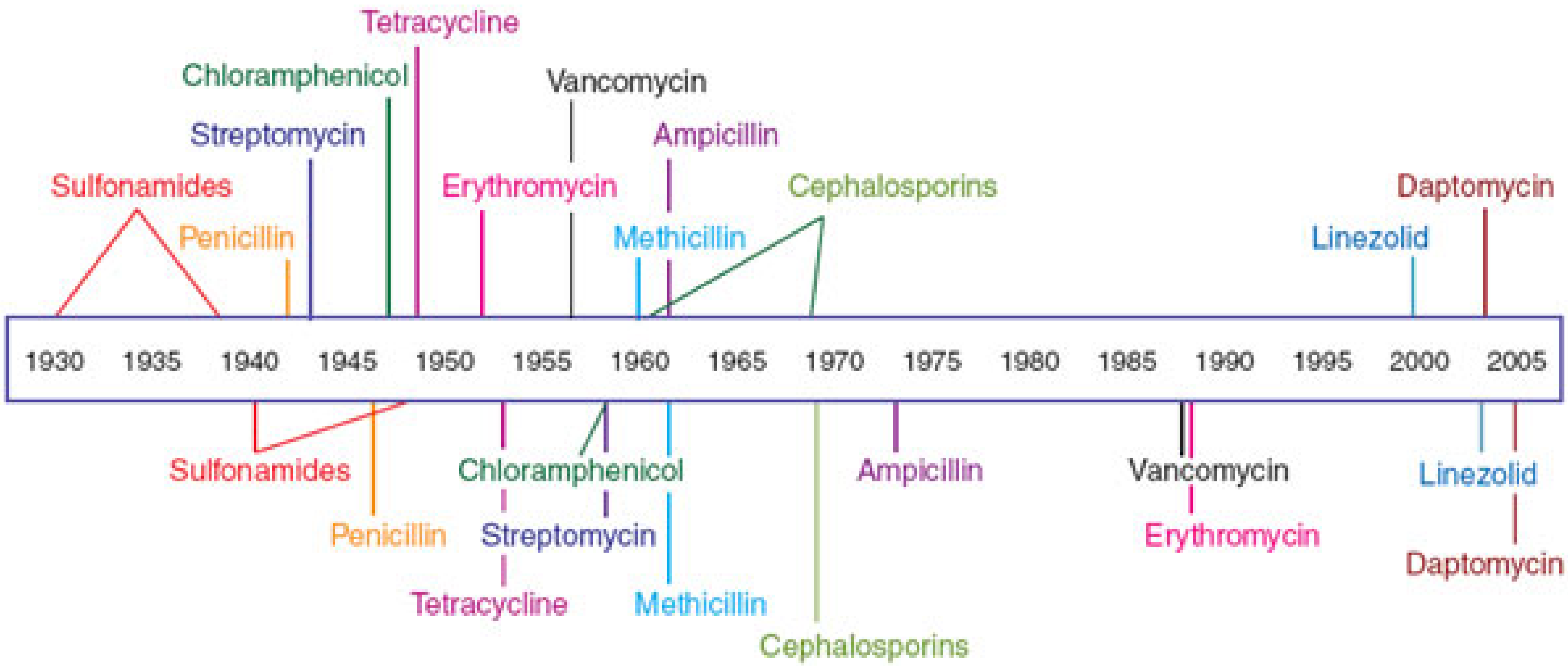




D'Costa et al. Nature 2011;477:457

Antibiotic resistance timeline

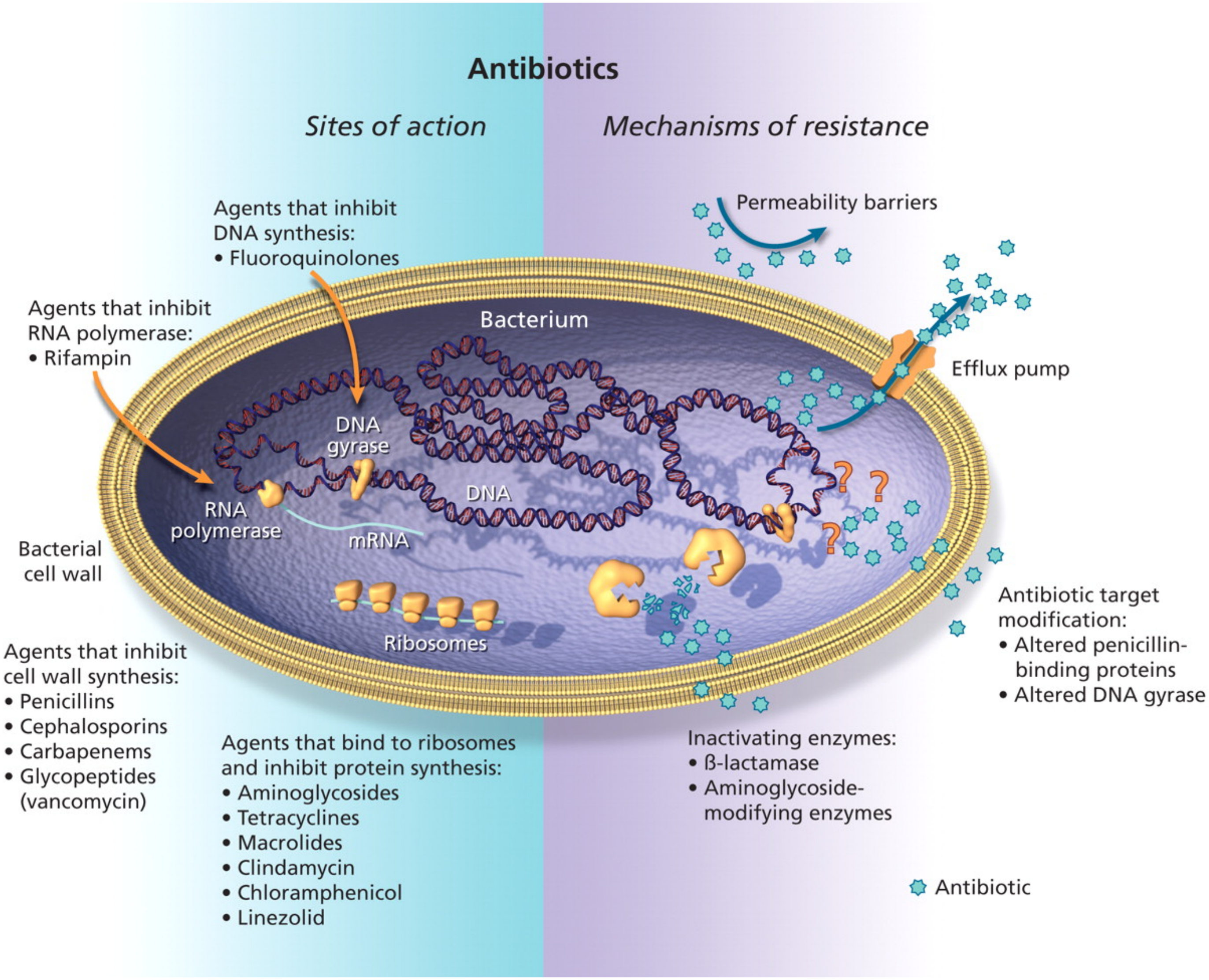
Antibiotic first used



Resistance first observed

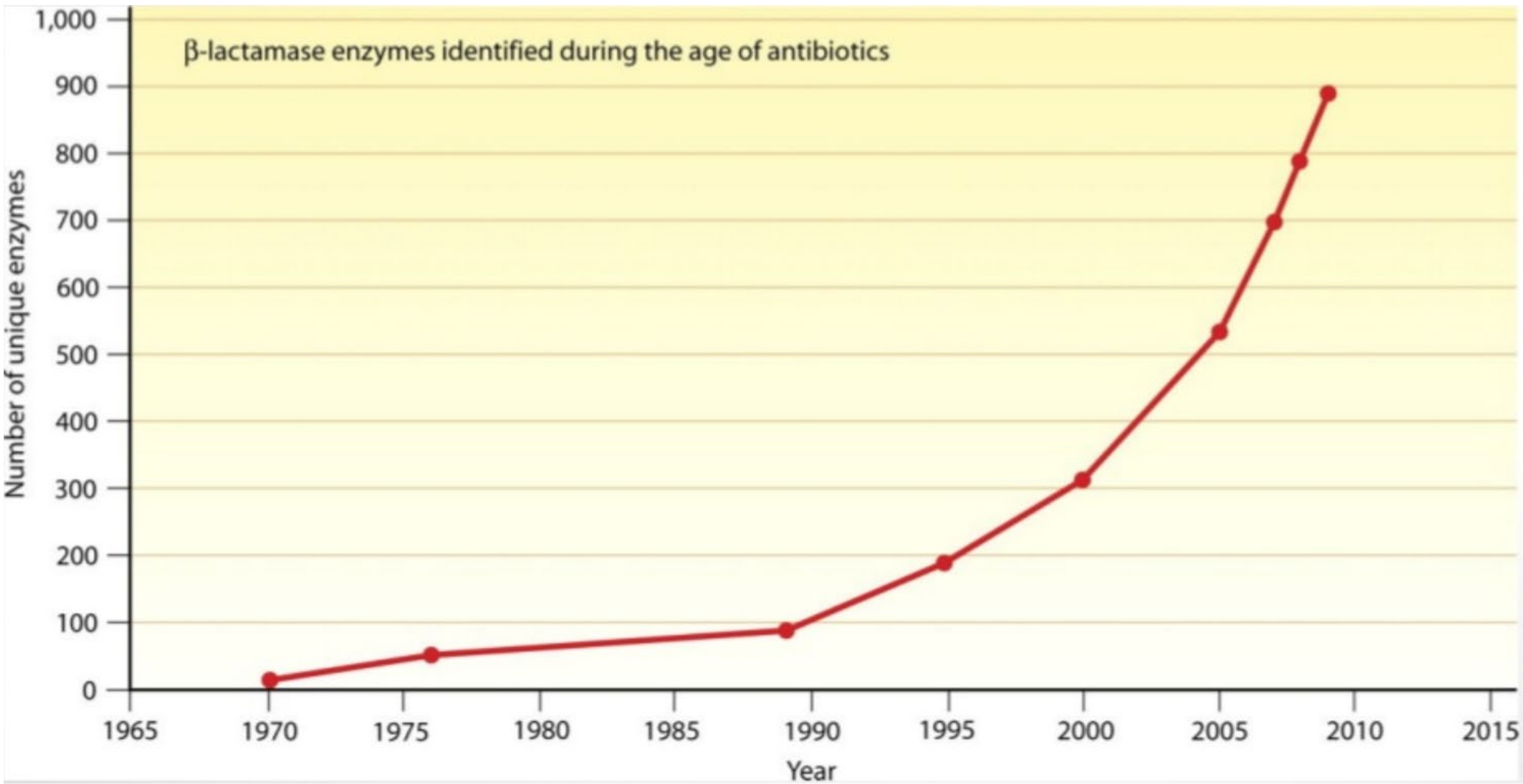
Clatworthy et al. Nature Chem Biol 2007:3;541

Mechanisms of resistance



Mulvey & Simor CMAJ 2009;180:408

Numbers of unique β-lactamase enzymes identified since the introduction of the first β-lactam antibiotics



Davies & Davies. Microbiol Mol Biol Rev. 2010;74: 417

Which of the following is a key factor for emergence of AMR?

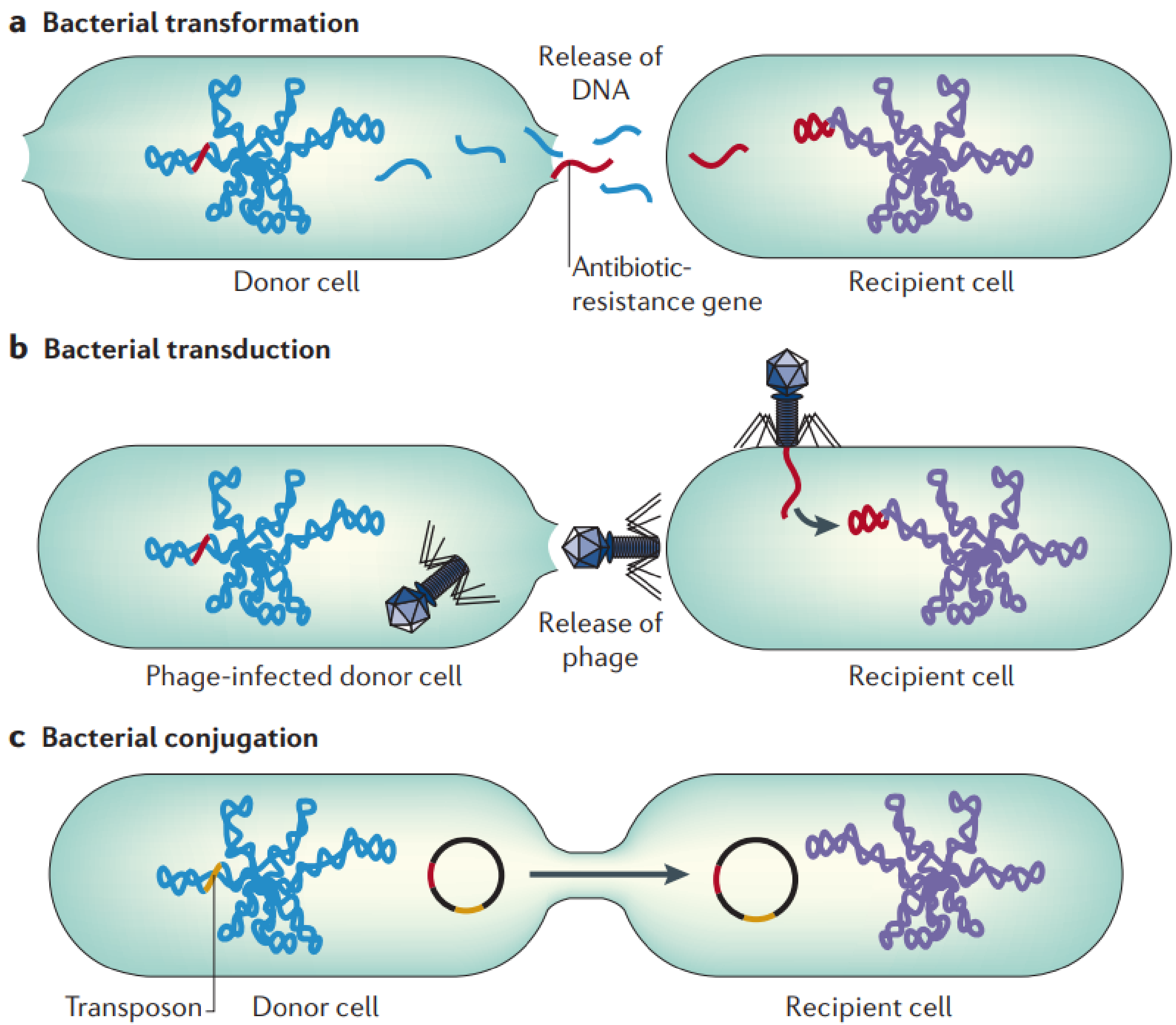
A. Association of resistance gene(s) with mobile genetic elements

B. Close contact between bacteria in a polymicrobial environment

C. Selective pressure imposed by the use of antimicrobials

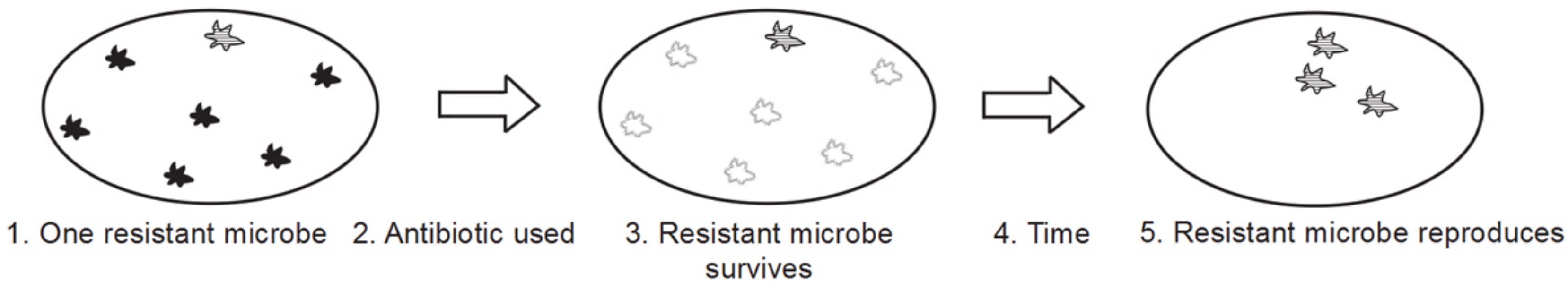
D. All of the above

Horizontal gene transfer between bacteria may share resistance genes



Furuya & Lowy. Nat Rev Microbiol. 2006;4:36

Selective antibiotic pressure



- Antimicrobial resistance occurs naturally
- If an antimicrobial is used when a pathogen is present, the antimicrobial resistant pathogen will have a competitive advantage over its susceptible isolates
- If the antimicrobial continues to be used, the resistant pathogens will survive, reproduce and become more common & susceptible pathogens gradually become scarcer
- Eventually, the antimicrobial becomes less effective or ineffective

Clonal dissemination of strains

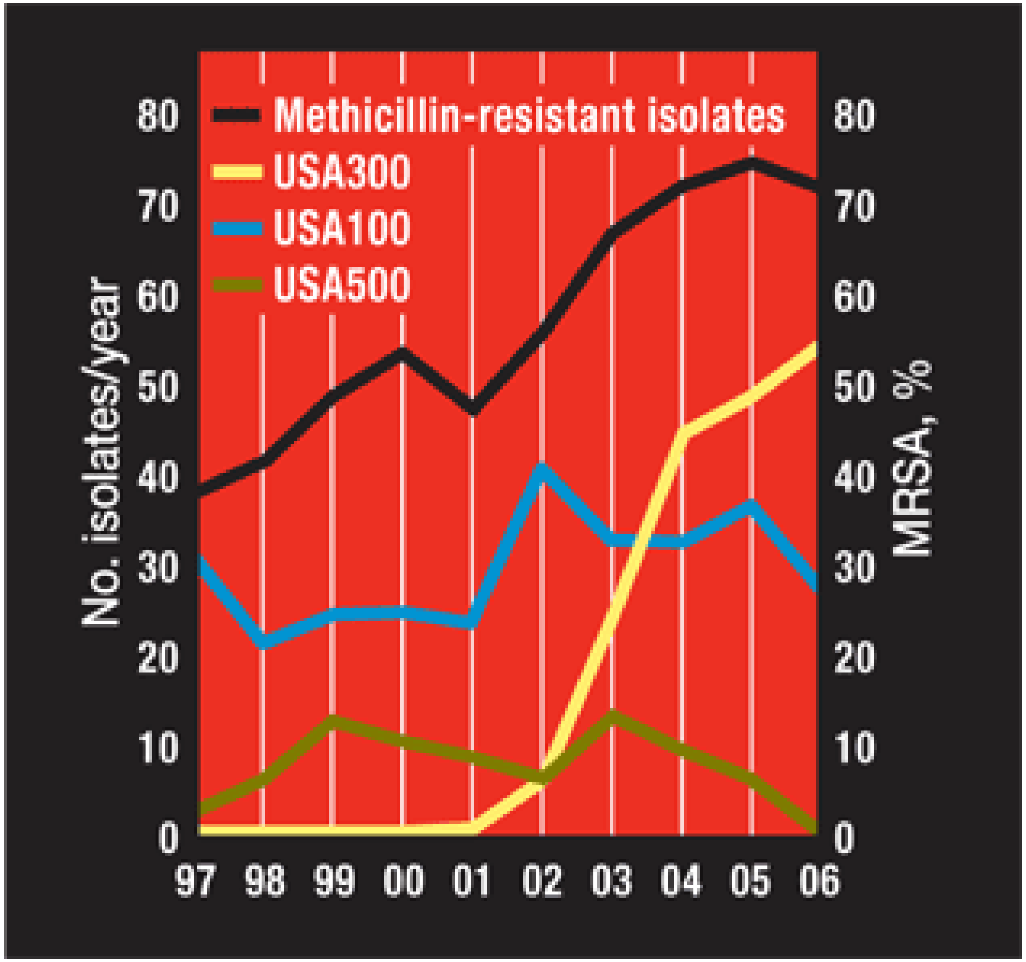
Some strains disseminate that have unique survival advantages in addition to antibiotic resistance

e.g. in early 2000s, USA300 became the predominant CA-MRSA strain and was highly virulent

	HA-MRSA	**CA-MRSA**
Health care contact	Yes	No
Mean age at infection	Older	Younger
Skin and soft tissue infections	35%	75%
Antibiotic resistance	Many agents	Some agents
Resistance gene	SCC*mec* Types I, II,III, V	SCC*mec* Type IV
Strain type	USA 100 and 200	USA 300 and 400
PVL toxin gene	Rare (5%)	Frequent (almost 100%)

https://www.dhs.wisconsin.gov/publications/p4/p42160.pdf

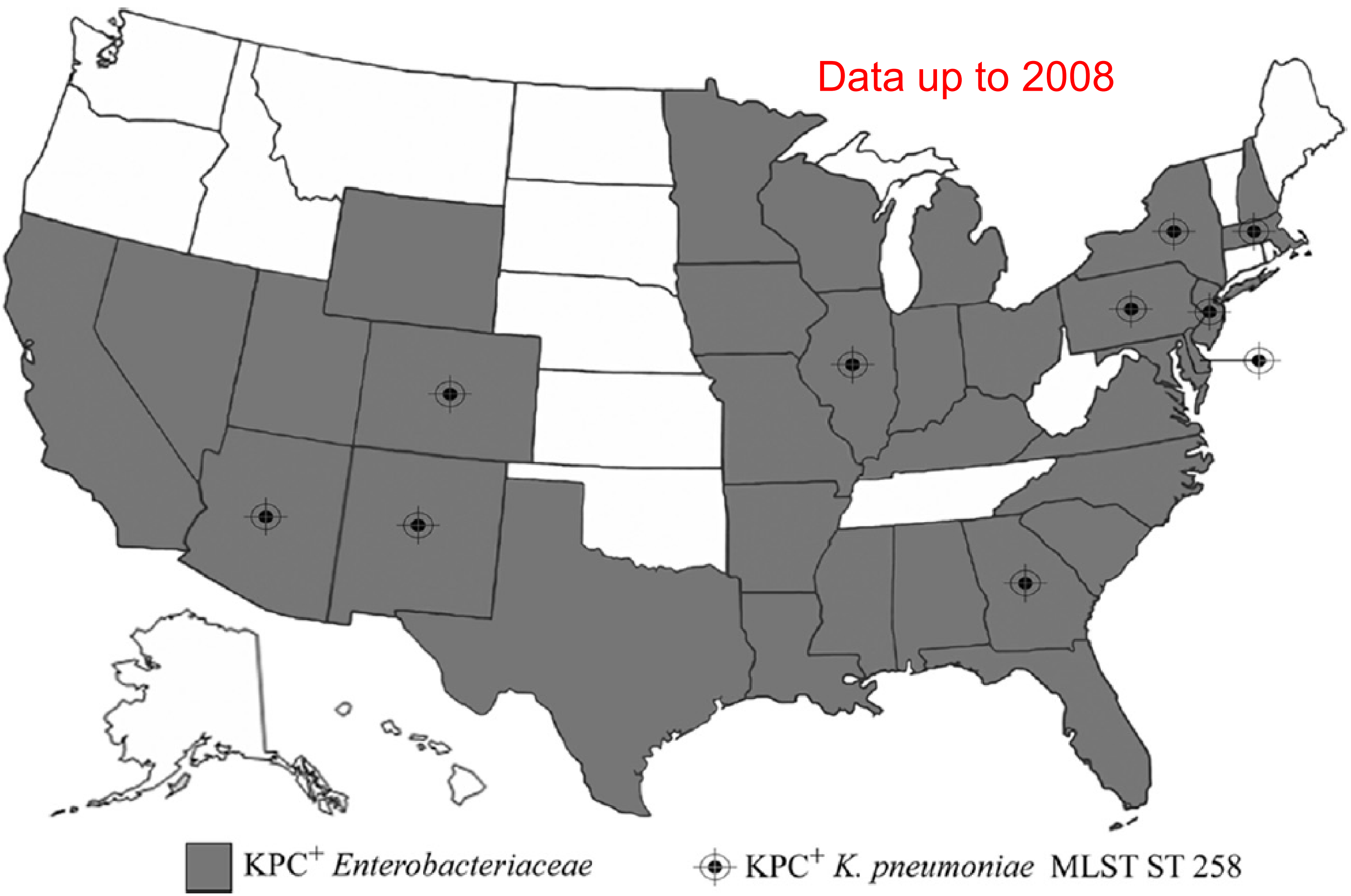
Clonal dissemination of strains



Clonal dissemination of CA-MRSA strain USA300 in early 2000s

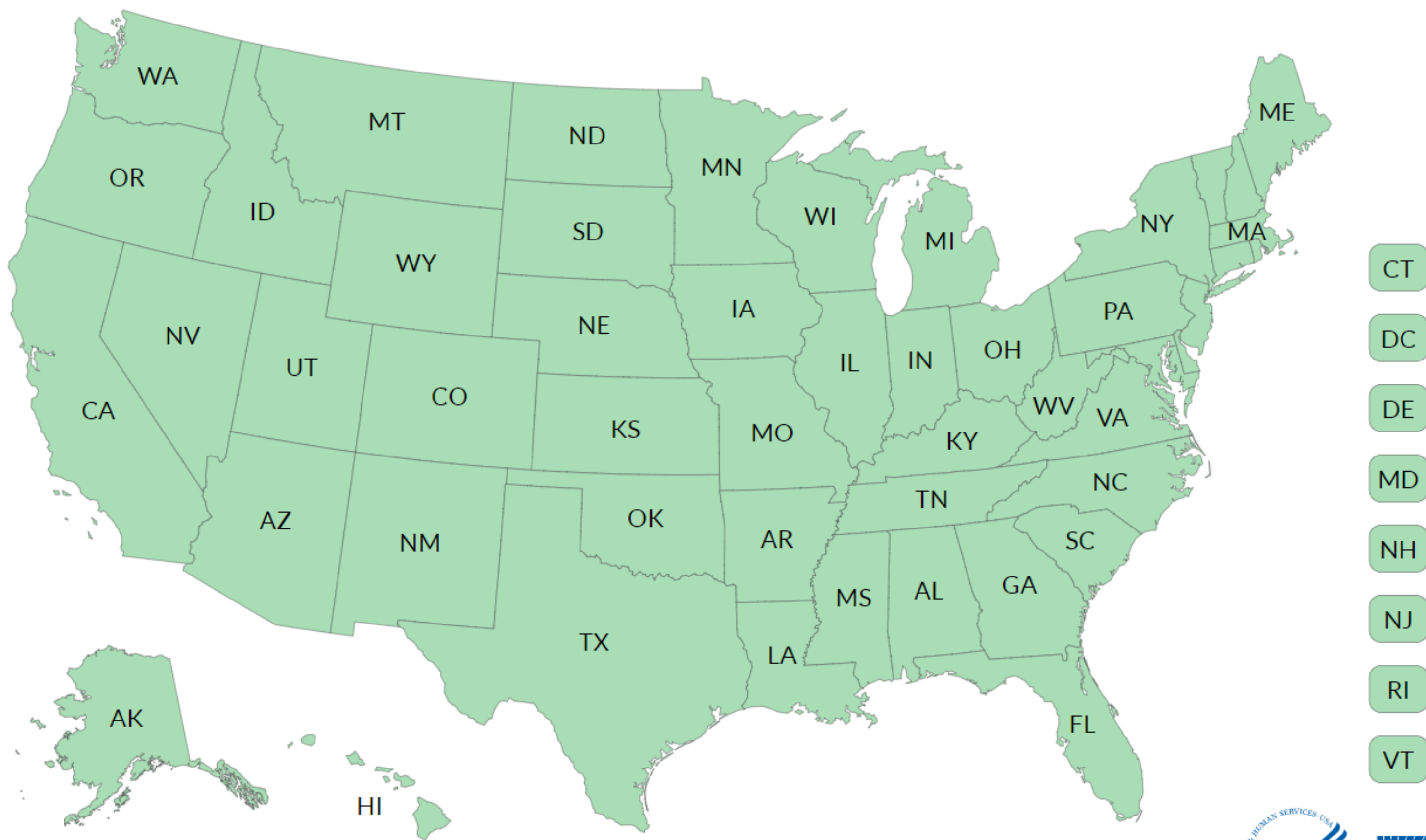
http://mrsa-research-center.bsd.uchicago.edu/our_projects.html

Predominance of ST258 *K. pneumoniae*



Kitchel et al, AAC 2009;53:3365

Patients with KPC-producing *Carbapenem-resistant Enterobacteriaceae* (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of December 2017, by state



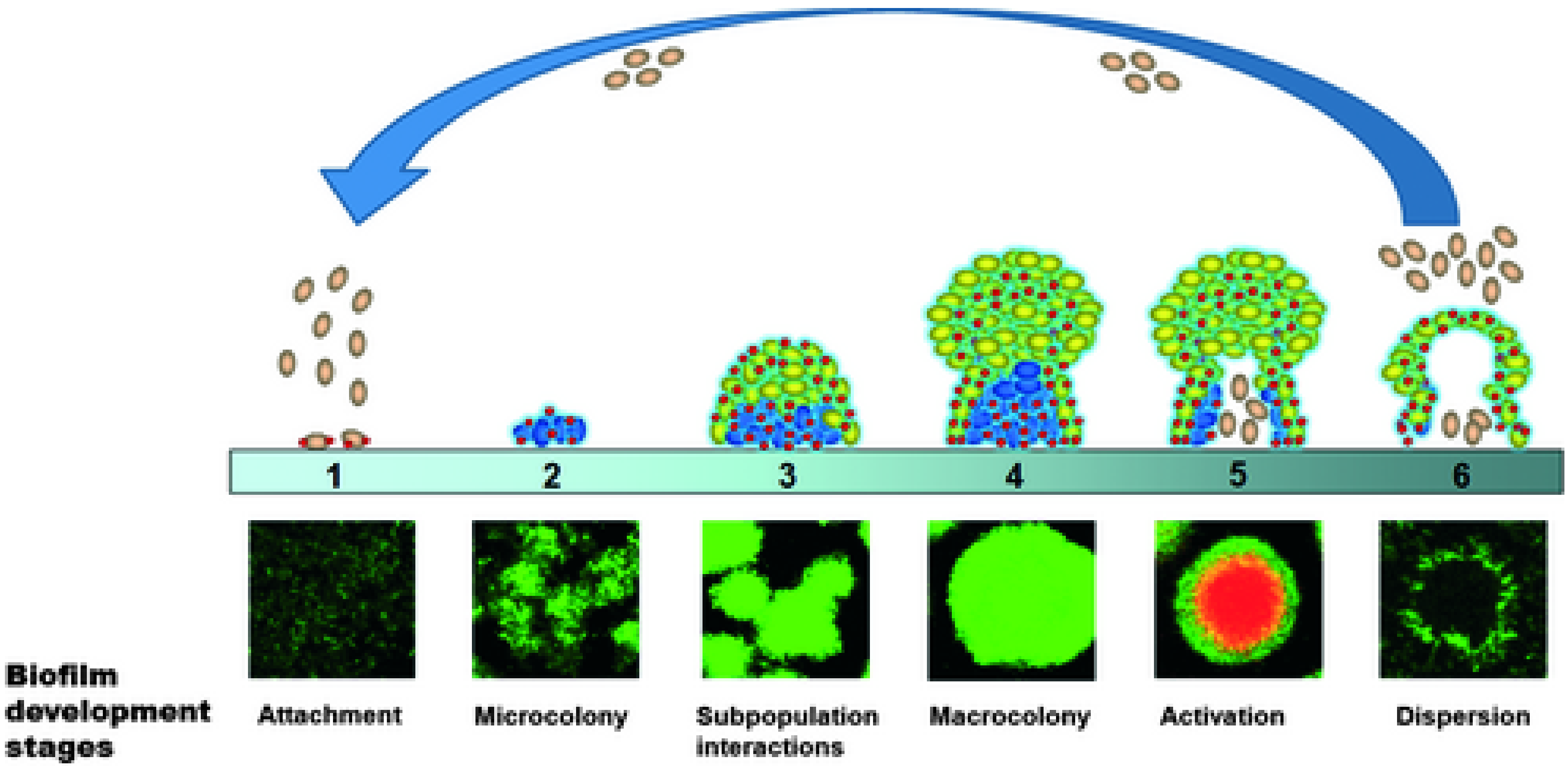
KPC enzyme

- None
- Reported

https://www.cdc.gov/hai/organisms/cre/trackingcre.html

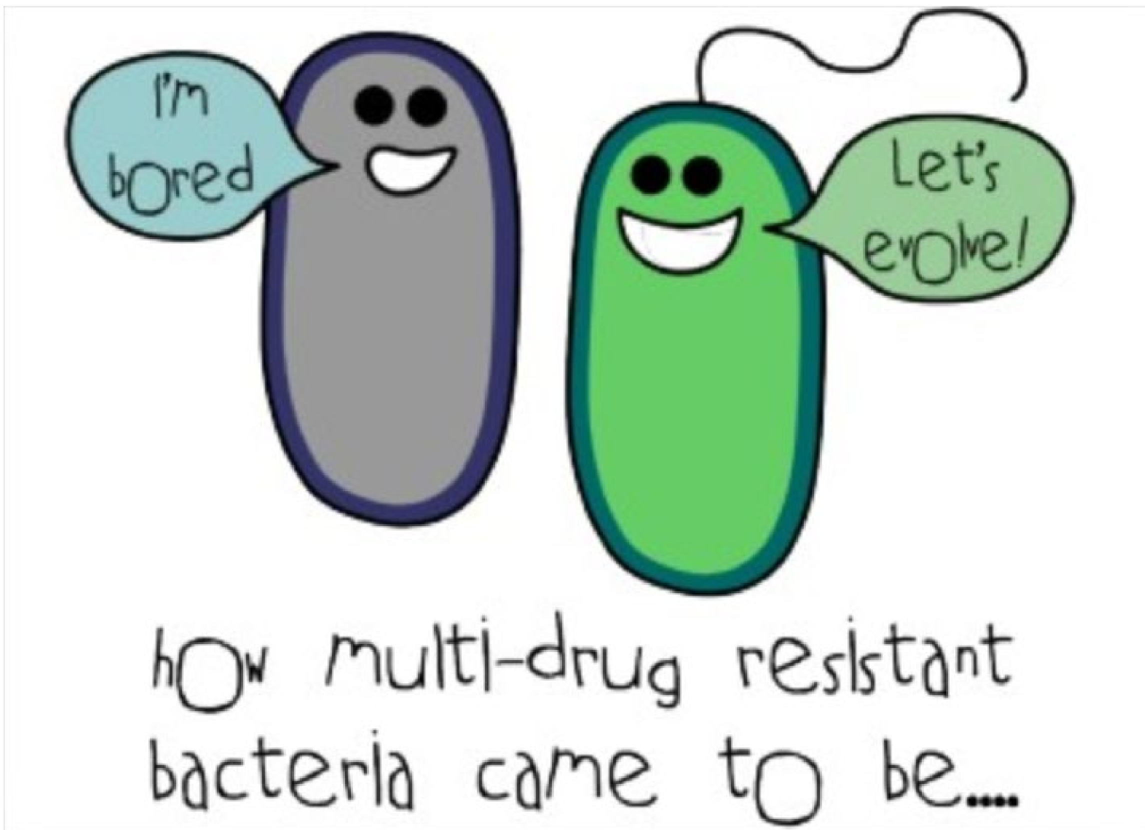
Accessed March 25, 2019

Bacteria that attach to a surface and grow as a biofilm are protected from killing by antibiotics



Yang et al. FEMS Immunol Med Micro 2012;65;146

2. Drivers of antimicrobial resistance



The most important modifiable driver of antimicrobial resistance is?

A. Human overuse or misuse

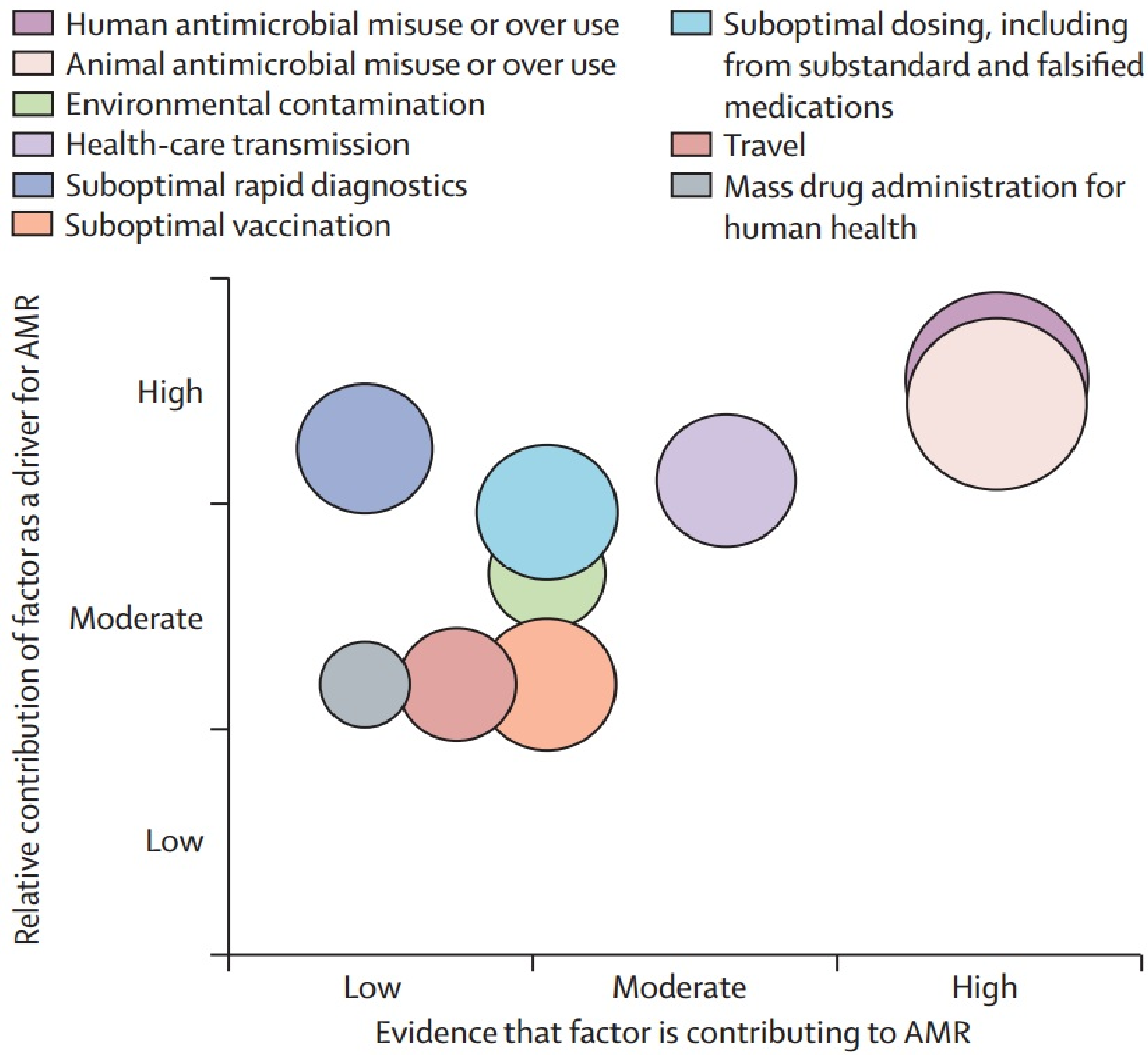
B. Animal overuse of misuse

C. Environmental contamination

D. Healthcare transmission

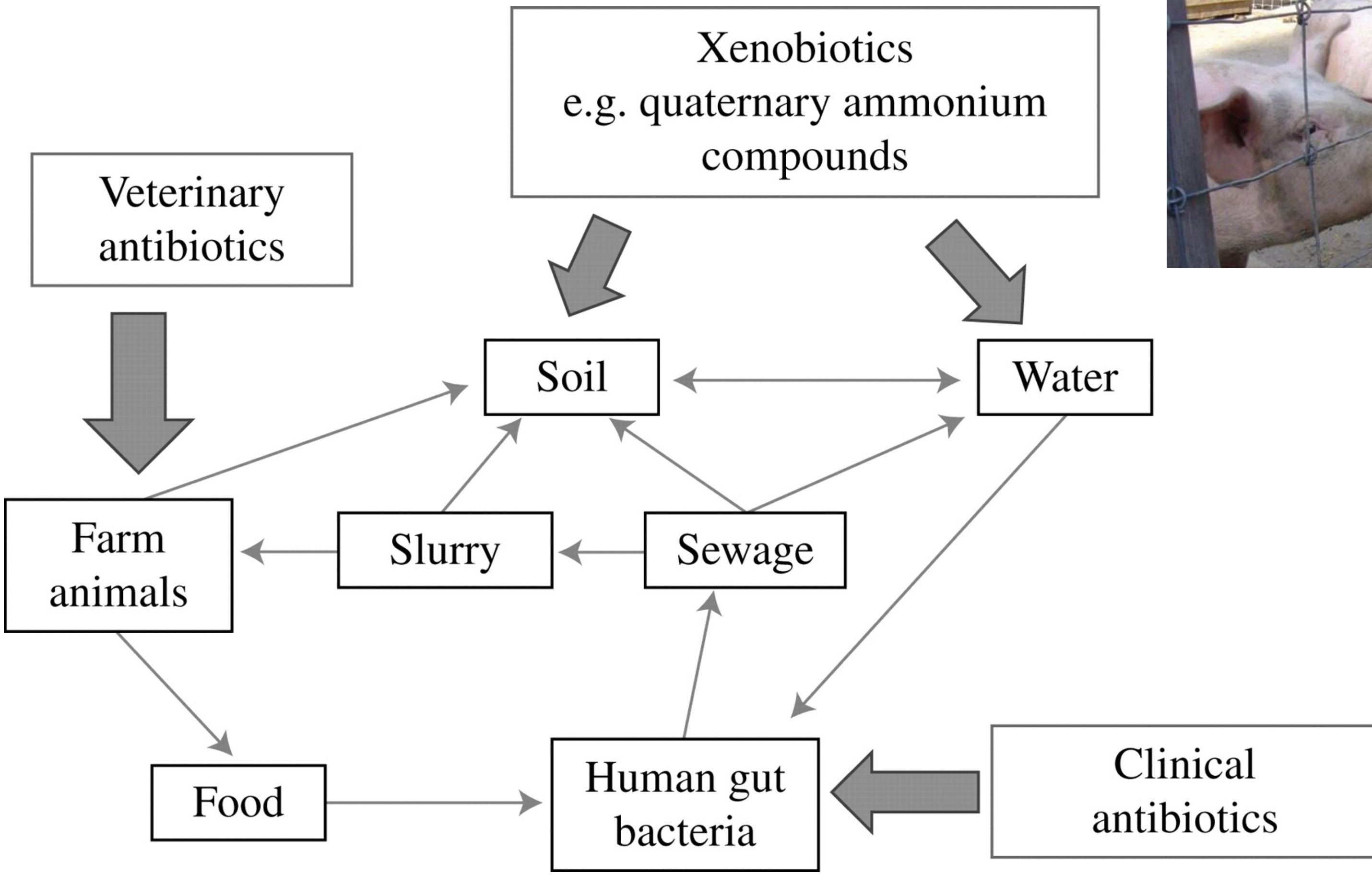
E. No one knows for sure but probably both misuse/overuse in humans or animals

Role of modifiable drivers towards antimicrobial resistance: a conceptual framework



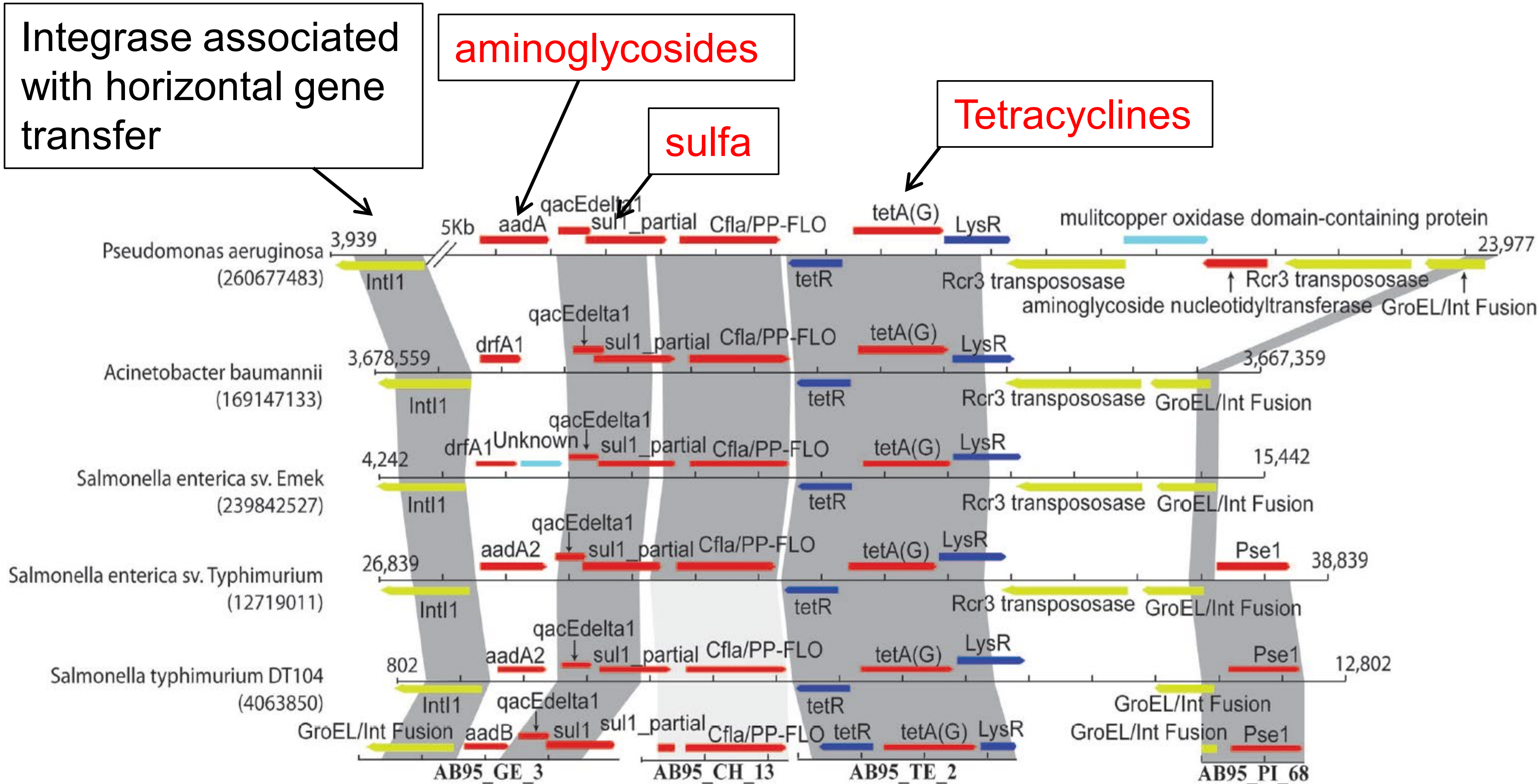
Holmes et al. Lancet 2016;387:176

Drivers of resistance



Hawkey et al. JAC 2009;64:i3

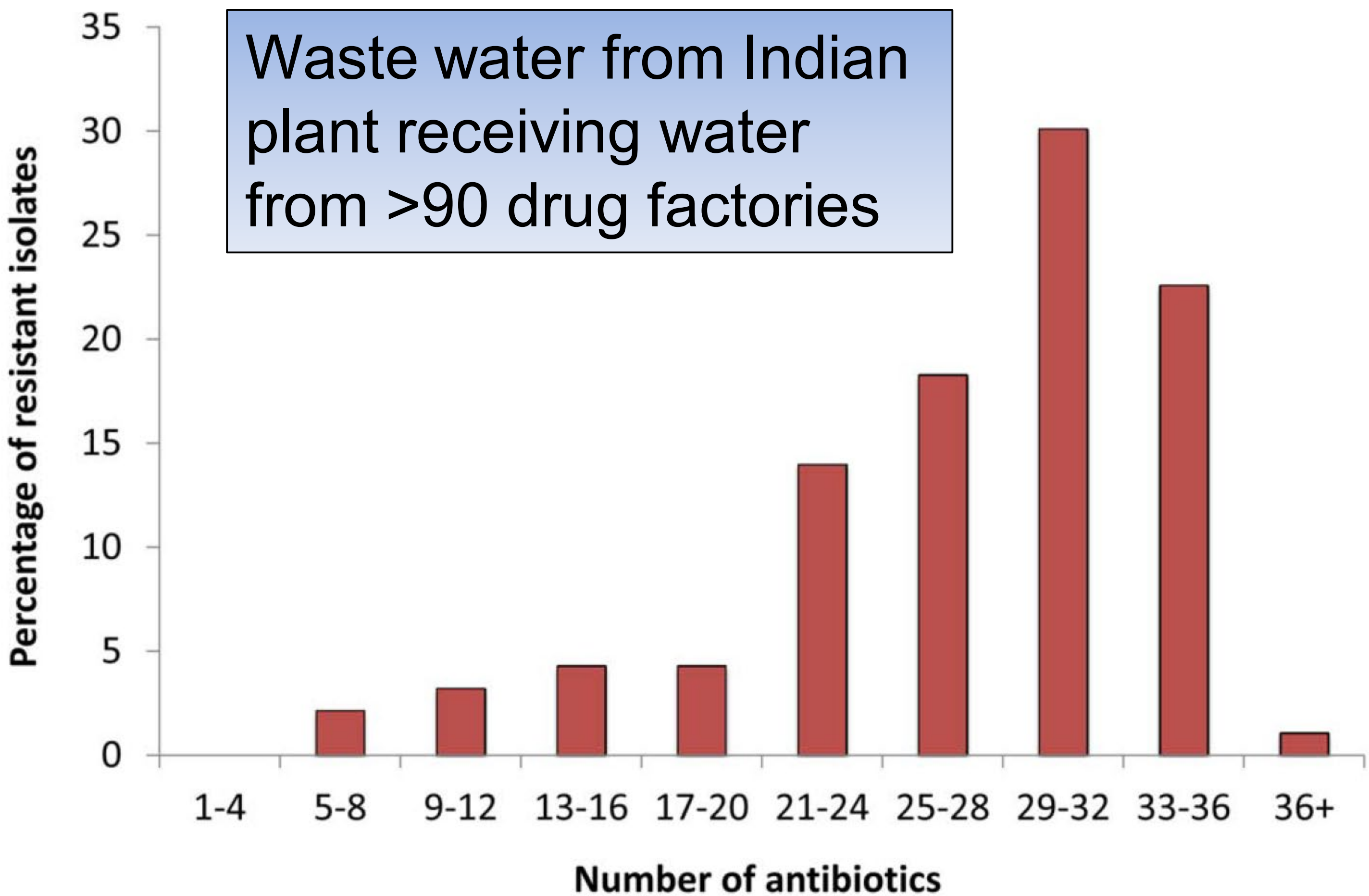
Transfer of resistance genes from soil bacteria to pathogens



DNA fragments derived from soil dwelling bacteria

Forsberg et al. Science 2012;337:1107

MDR bacteria in waste water



Marathe et al. Plos One 2013;8:e77310

Antibiotic consumption in livestock

FIGURE ES-3: Antibiotic consumption in livestock, top ten countries 2010–2030 (projected for 2030) Source: Van Boeckel et al. 2015

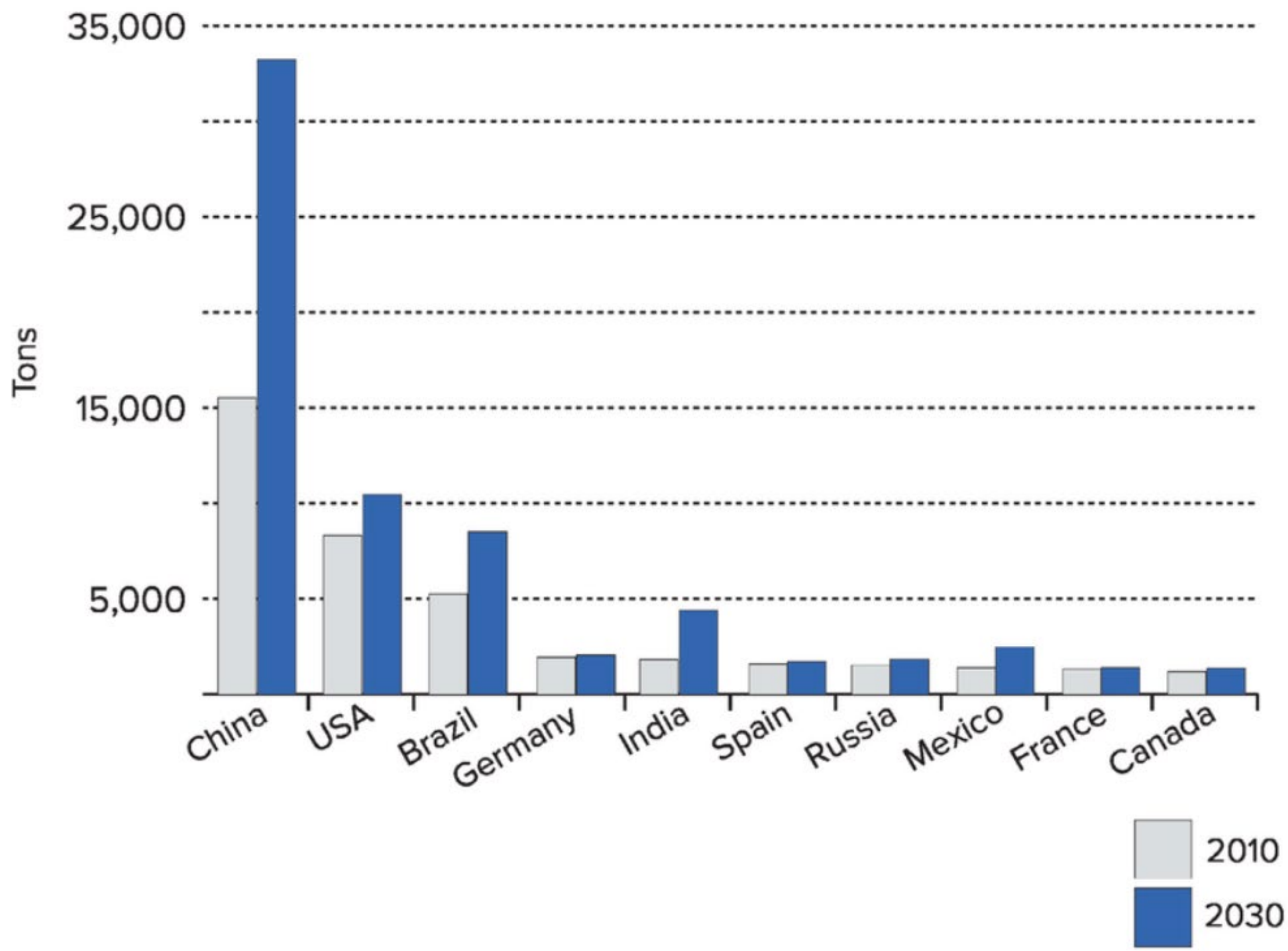
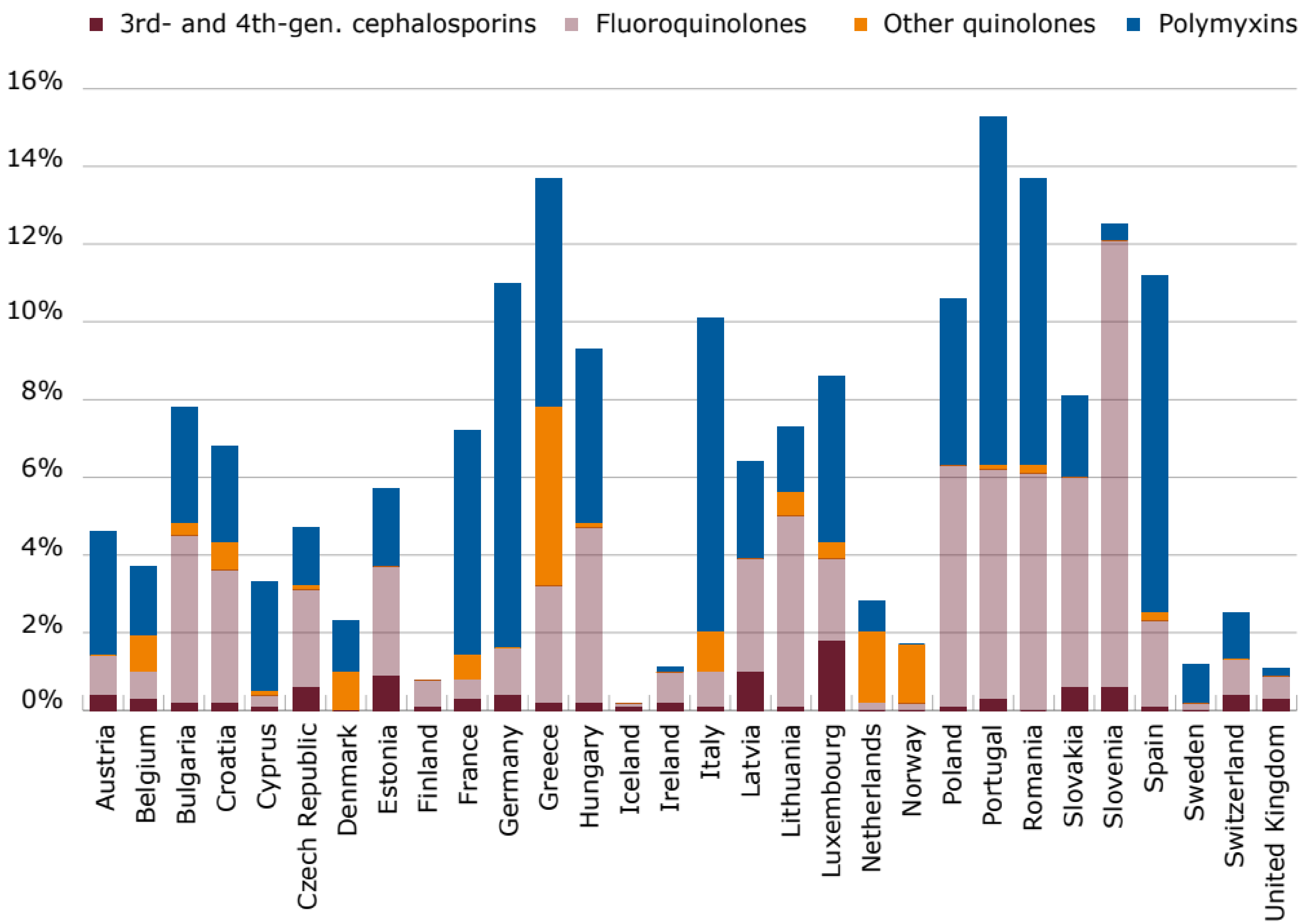


Figure 12. Spatial distribution of overall sales of all antimicrobials for food-producing animals, in mg/PCU, for 30 countries, for 2015

PCU = population correction unit

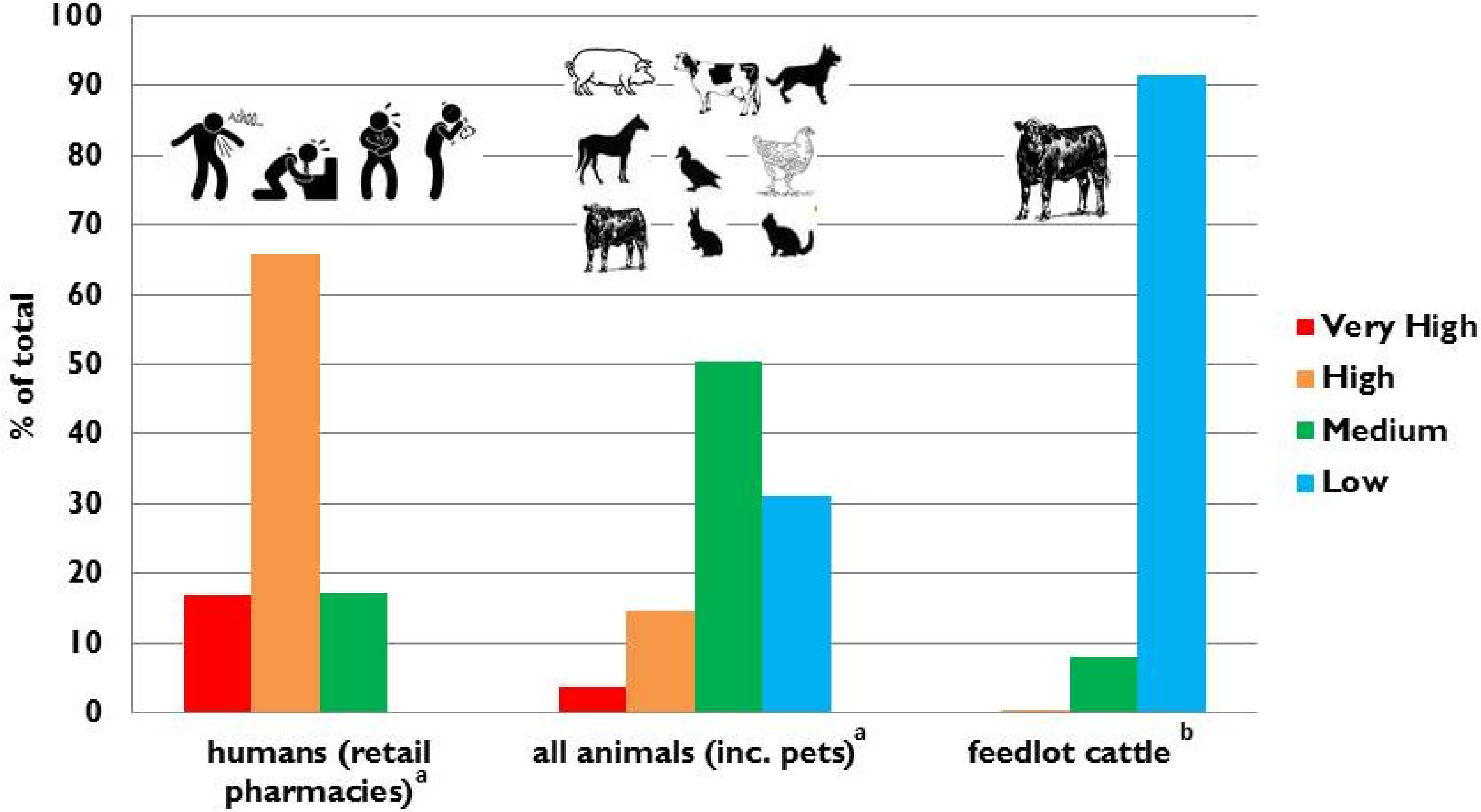
European Surveillance of Veterinary Antimicrobial Consumption, 2017

Figure 8. Proportion of the total sales of 3rd- and 4th-generation cephalosporins, fluoroquinolones, other quinolones and polymyxins for food-producing species, in mg/PCU, for 30 European countries, in 2015[1,2,3]



European Surveillance of Veterinary Antimicrobial Consumption, 2017

Antimicrobial use by category



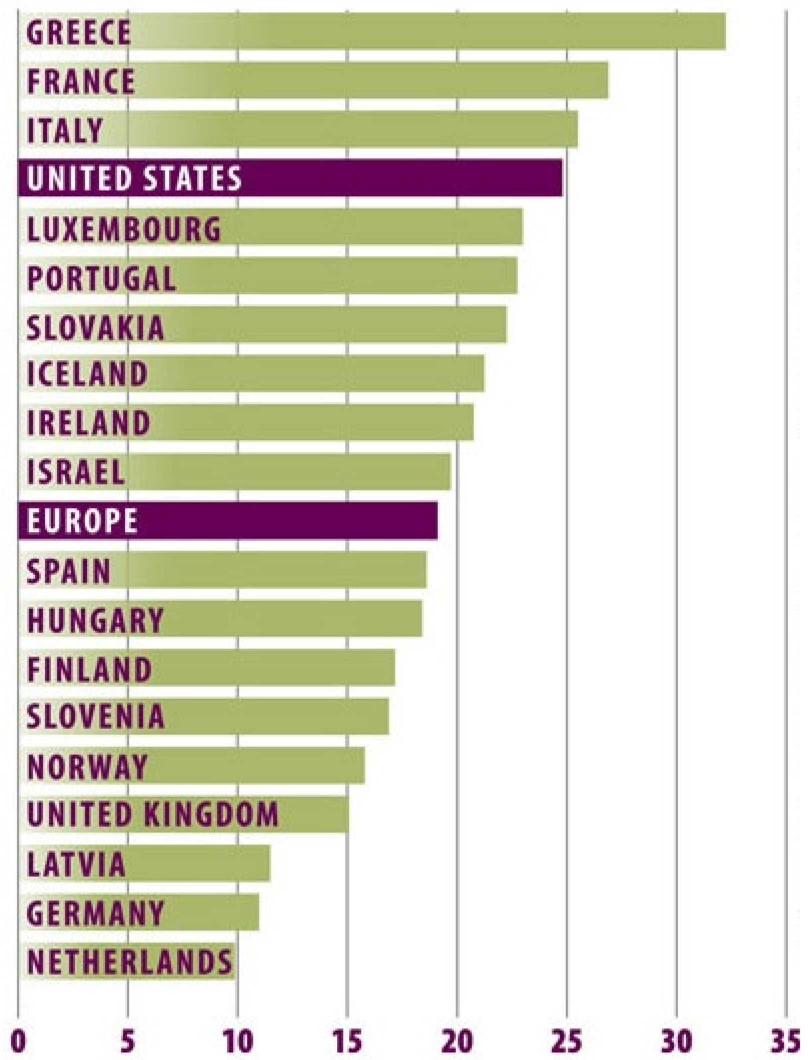
aCanadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) Annual Report, 2009
bDevelopment of a Longitudinal Antimicrobial Resistance and Antimicrobial Use Surveillance Program for the Feedlot Sector in Western Canada (BCRC 6.41)

Source: BeefResearch.ca

Human antibiotic usage

- Outpatient antibiotics
- Defined daily dose per 1,000 inhabitants per day
- 2004 data

Source: CDC.gov

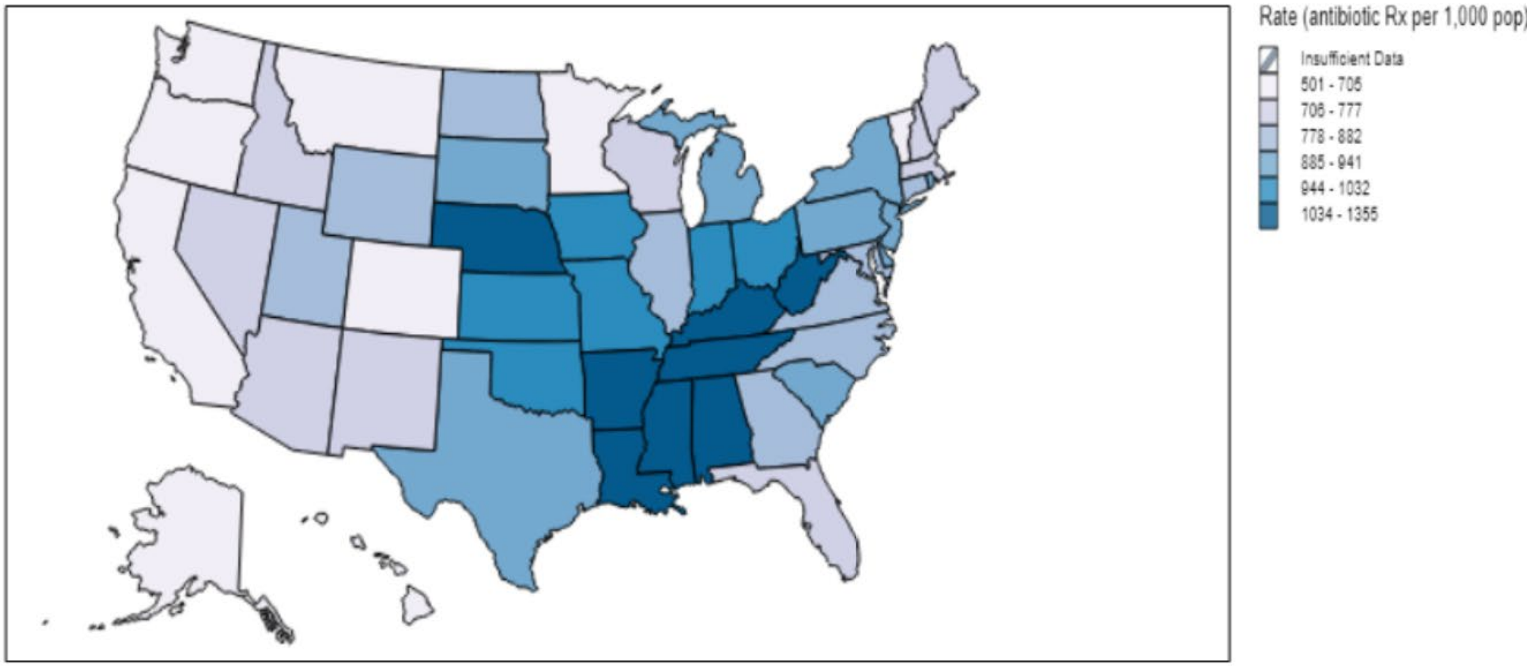


Goossens et al. CID 2007;44:1091

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People™

AR PATIENT SAFETY ATLAS

Antibiotic Prescriptions Dispensed in U.S. Community Pharmacies Per 1000 Population | All classes | 2015



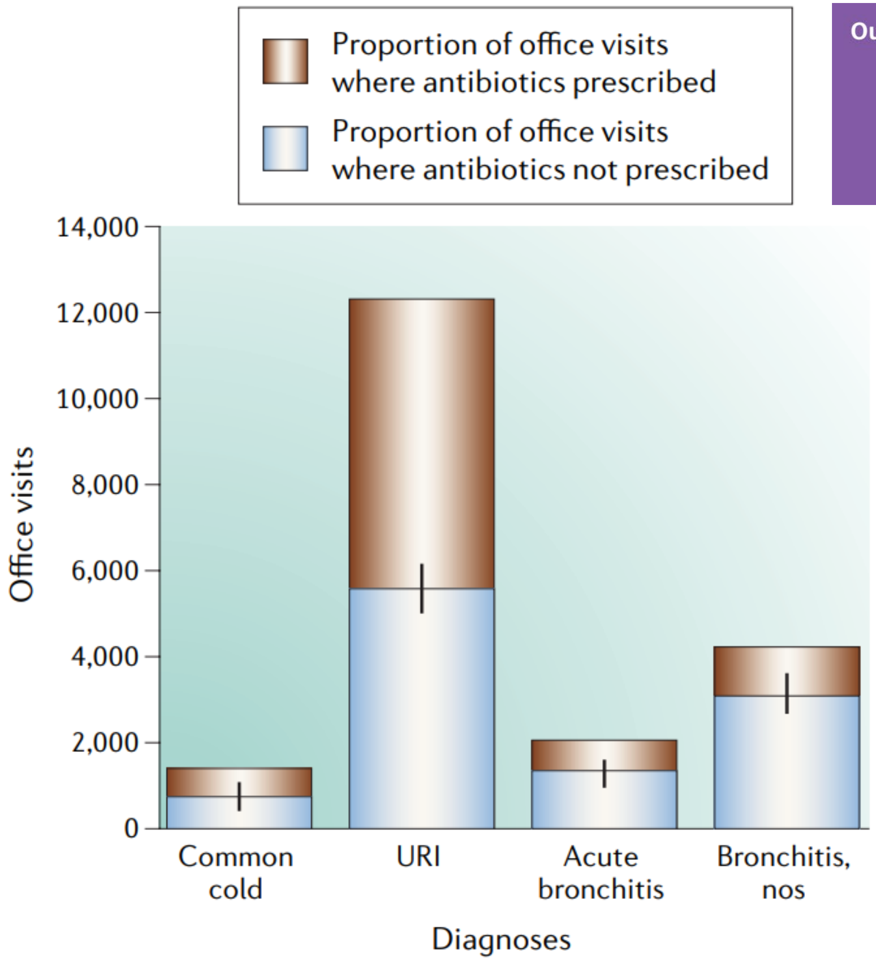
NATIONAL

838

Antibiotic prescriptions dispensed

PER 1000 POPULATION

Inappropriate use of antibiotics



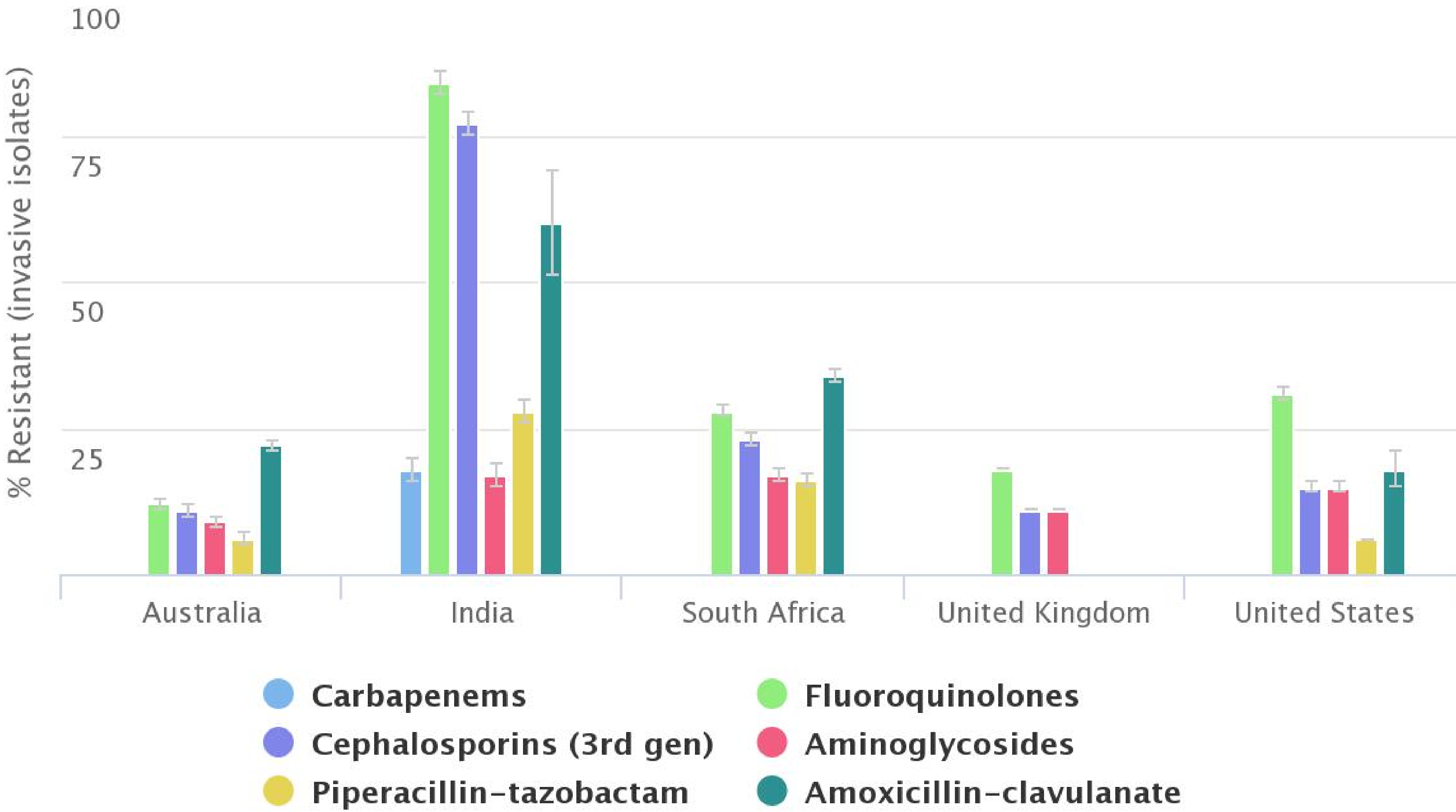
Furuya & Lowy. Nat Rev Microbiol. 2006;4:36

O'Neil. Review on Antimicrobial Resistance 2016

3. Consequences and costs of antimicrobial resistance

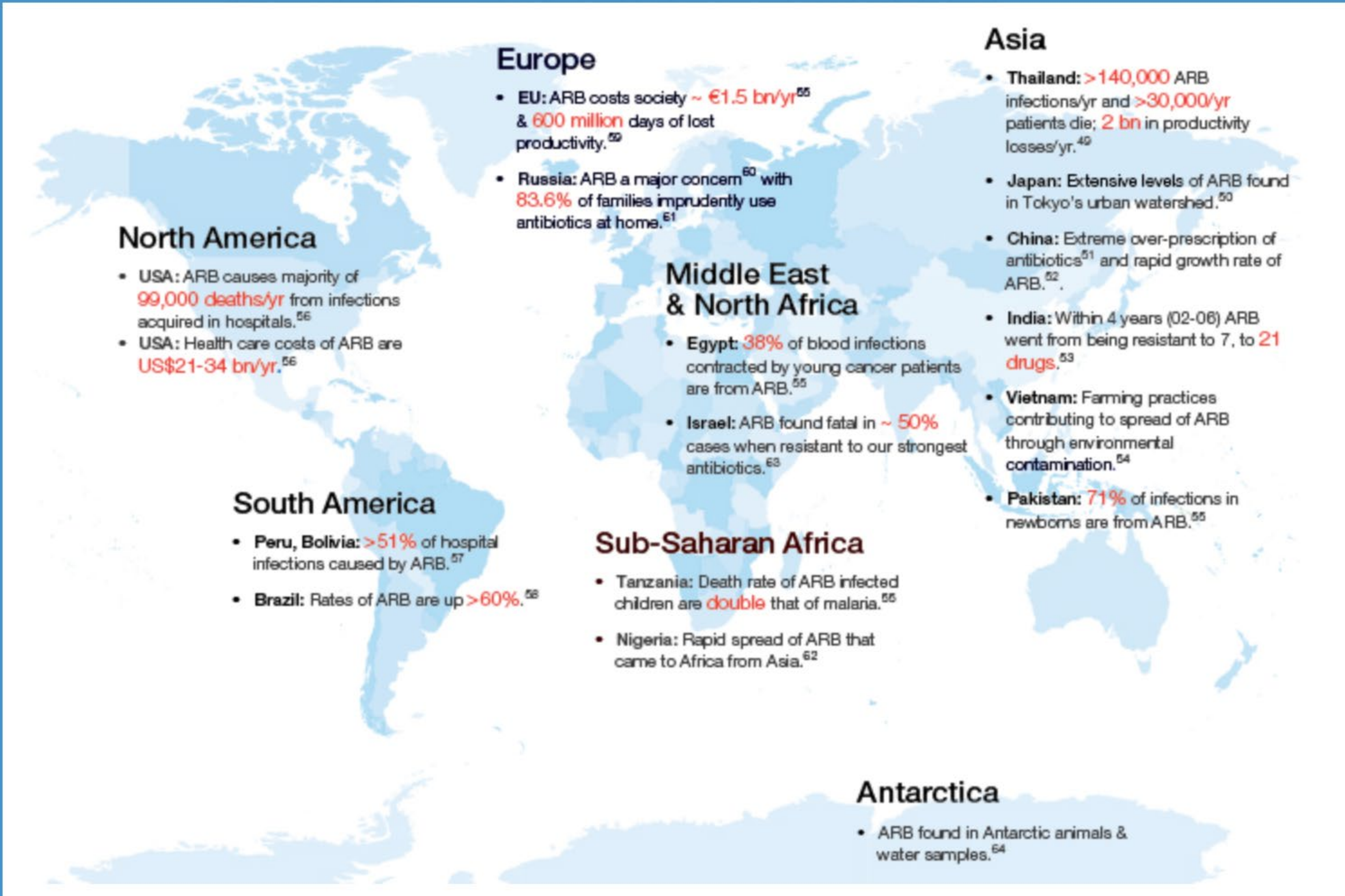
> “Antibiotic resistance - one of the three greatest threats to human health.”
>
> World Health Organisation, 2009

Resistance is global: Antibiotic resistance of *Escherichia coli*



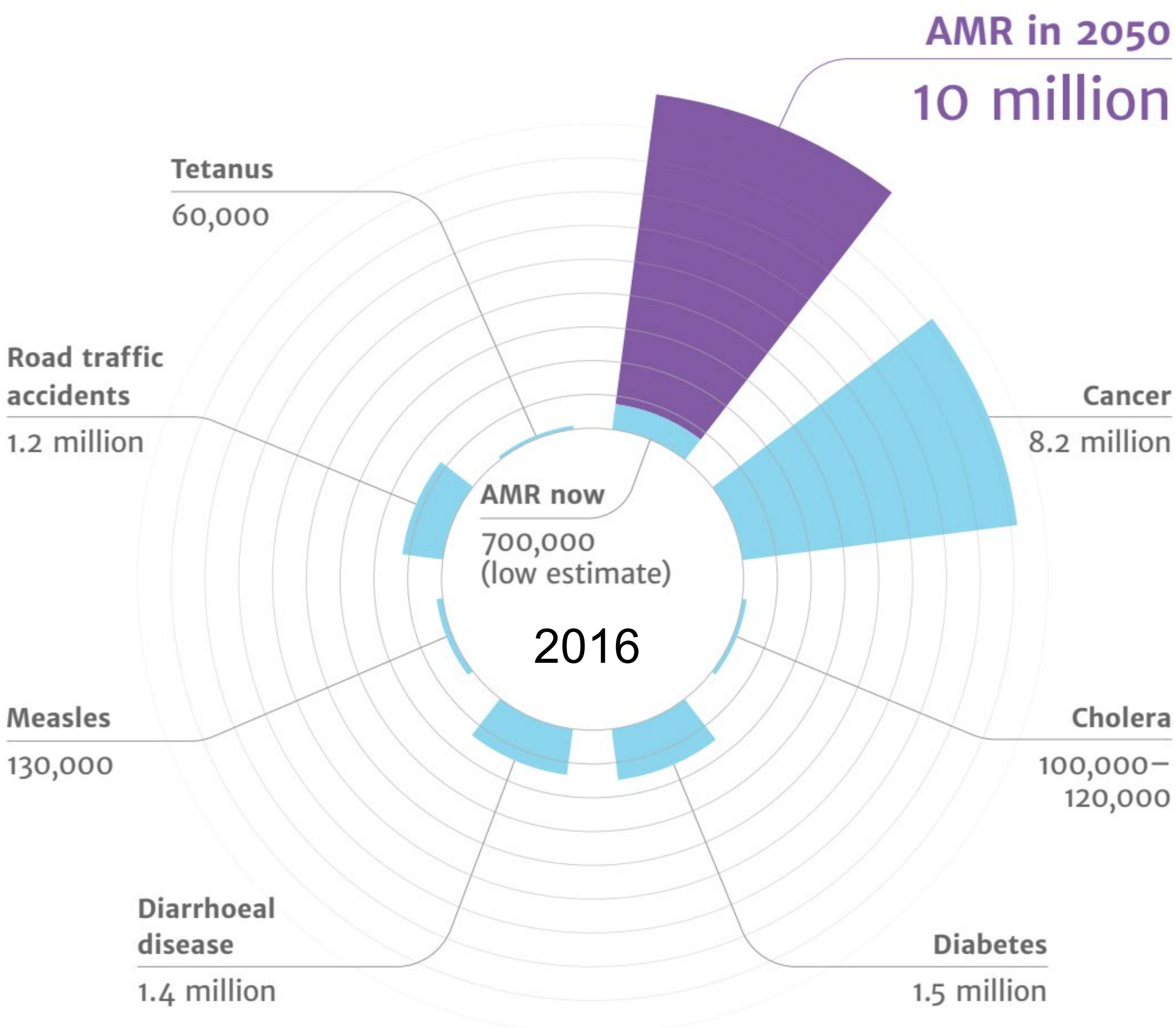
The Center for Disease Dynamics Economics & Policy. ResistanceMap. 2018.
https://resistancemap.cddep.org/AntibioticResistance.php

Figure 17: Spread of Antibiotic-Resistance Bacteria (ARB)



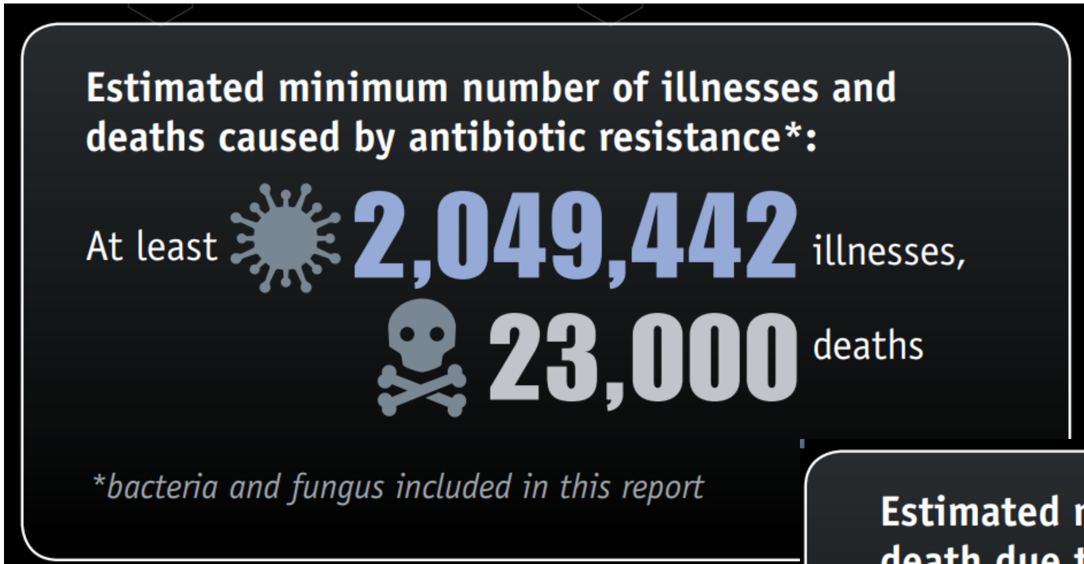
Source: World Economic Forum

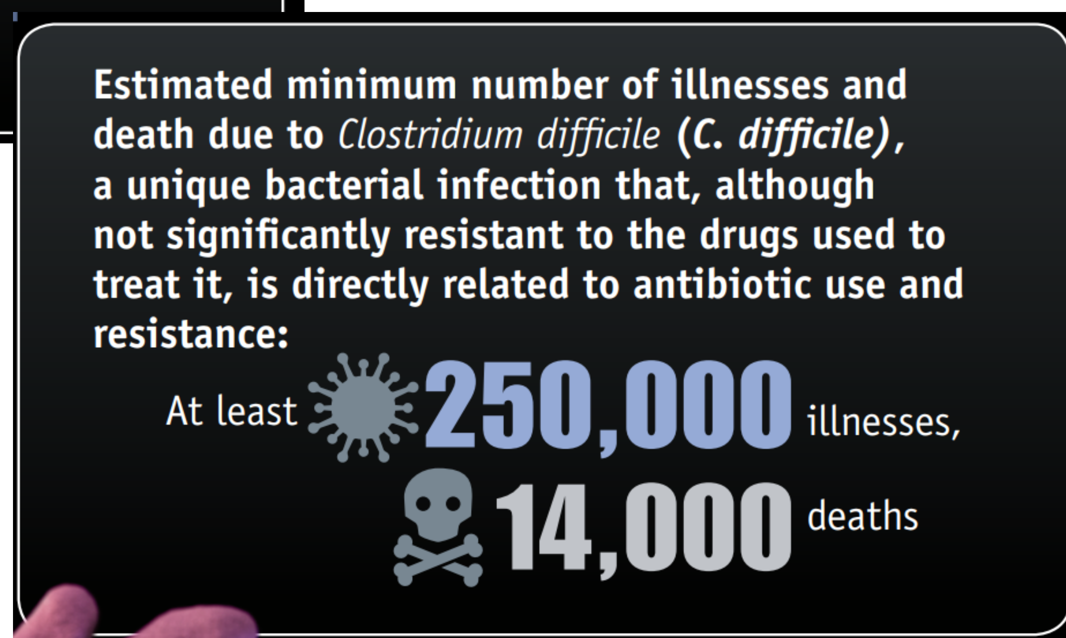
DEATHS ATTRIBUTABLE TO AMR EVERY YEAR



O'Neil. Review on Antimicrobial Resistance 2016

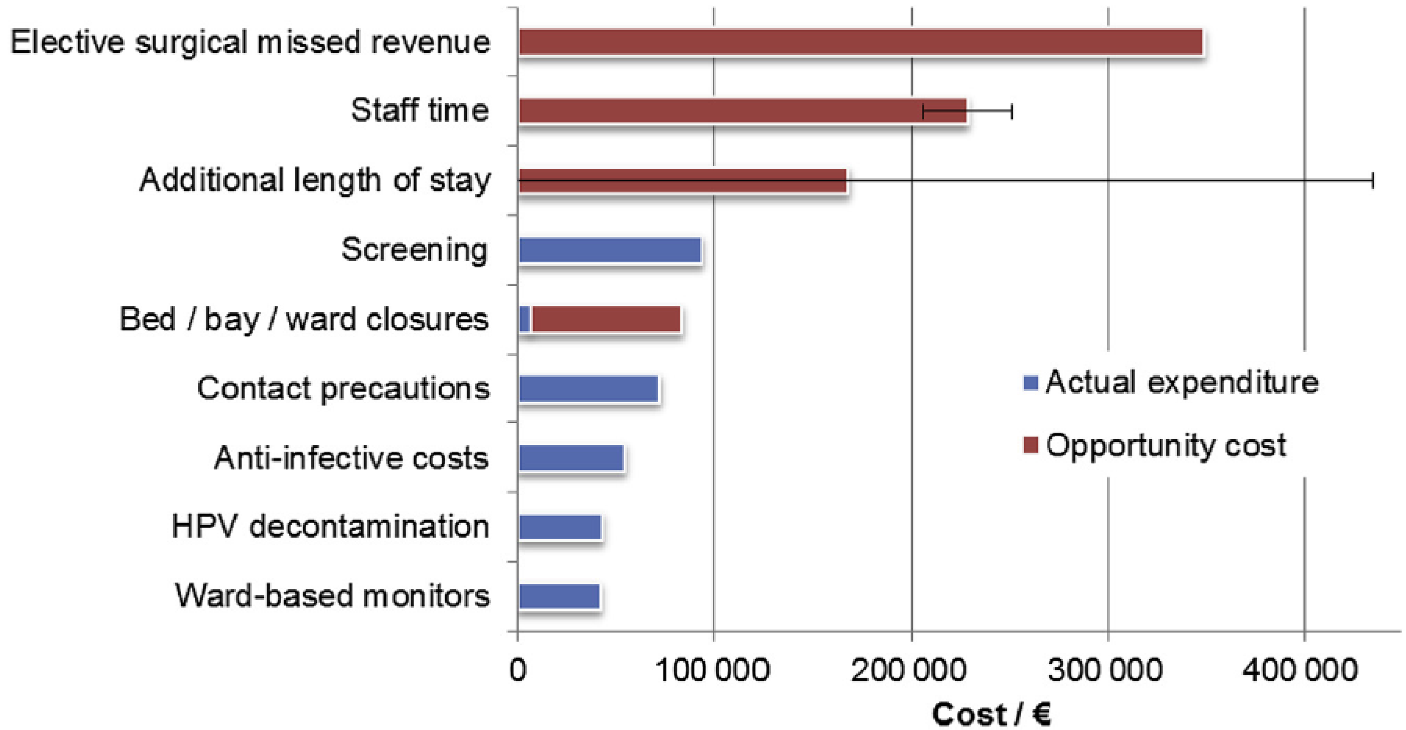
CDC antibiotic resistance threats in the United States, 2013





Financial cost of CRE

- NDM-producing CRE outbreak in UK
  - 40 patients in 5 hospitals
- Total costs €1,100,000 ($1,163,415)



Otter et al. CMI 2017;23:188

4. Populations at risk for MDRO infections

Which hospitalized patients are at least risk for MDRO infection?

A. Patients with kidney disease on dialysis
B. Burn ICU or complex surgery patients
C. Organ and bone marrow transplant recipients
D. Oncology patients on chemotherapy
E. Pediatric patients

Commonality of risk factors

Risk Factors	Odds Ratio or Relative Risk (References)			
	Methicillin-Resistant *Staphylococcus aureus* (11, 12, 16–26)	Vancomycin-Resistant Enterococcus (27–48)	Extended-Spectrum β-Lactamase–Producing Gram-Negative Bacilli (49–57)	*Clostridium difficile* (58–77)
Advanced age	1.2 to 1.3 (17, 23)	2.6 (45)	NS (49, 51, 54, 56)	1.0 to 14.1 (60, 69, 74, 77)
Underlying disease			† (51), NS (49, 56, 57)	
Renal failure	† (12, 17, 18, 22, 23, 26)	4.4 to 6.98 (35, 42)		1.71 to 6.7 (66, 76)
Hematologic cancer	† (12, 17, 23, 26), NS (22)	8.4 (33)		
Hepatic failure	† (12, 17, 23, 26)			
Severity of illness‡	1.9 (24)	2.3 to 6.1 (29, 30, 32, 47)	11.6 (53)	2.0 (63)
Interhospital transfer of a patient; patient from a nursing home	6.9 (24)	4.1 to 2.9 (32, 45)	3.6 (52)	3.1 (66)
Extended length of stay	1.7 to 17.5 (16–19, 21–23, 25, 26)	1.1 to 2.9 (28, 31–34, 38, 44)	1.1 to 9.0 (49, 50, 57)	1.3 to 3.6 (62, 67, 75)

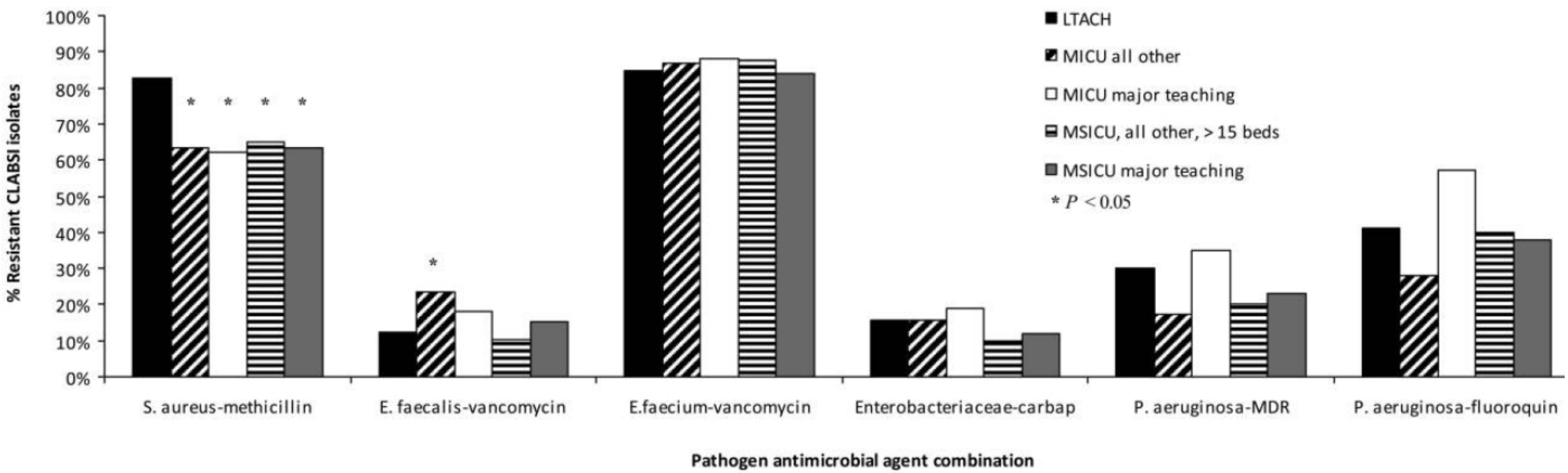
Safdar & Maki. Ann Intern Med 2002;136:834

Multidrug resistant bacterial outbreaks in burn units

Girerd-Genessay et al. J Burn Care Res. 2016;37:172

Study	Microorganism	Outbreak Duration	Patients Hospitalized, N	Cases, N (%)		
				Colonization	Infection	Total (Attack Rate)
Babík et al[13]	*Acinetobacter baumannii*	—	73	—	—	8 (10.96)
Bayat et al[11]	*A. baumannii*	12 mo	—	7 (54)	6 (46)	13
Herruzo et al[29]	*A. baumannii*	1 yr	72	—	—	21 (29)
Lyytikäinen et al[15]	*A. baumannii*	12 mo	—	—	—	21
Roberts et al[30]	*A. baumannii*	3 mo	—	1 (7)	14 (93)	15
Simor et al[19]	*A. baumannii*	16 mo	247	13 (42)	18 (58)	31 (12.55)
Fujioka et al[26]	*Alcaligenes xylosoxidans*	1 mo	—	—	2	2
Falk et al[37]	*Enterococcus faecium*	1 yr	—	17 (81)	4 (19)	21
Sanchez et al[24]	*Klebsiella pneumoniae*	10 mo	—	18 (69)	8 (31)	26
Douglas et al[31]	*Pseudomonas aeruginosa*	3 mo	30	—	4	4 (13.33)
Hsueh et al[32]	*P. aeruginosa*	2 mo	16	1 (25)	3 (75)	4 (25)
Tredget et al[16]	*P. aeruginosa*	2 yr	—	—	17	—
Saida et al[28]	*Providencia stuartii*	3 mo	—	—	17	17
Tsai et al[12]	*Stenotrophomona maltophilia*	9 yr	666	—	—	13 (1.95)
Edgar et al[20]	*Serratia marcescens*	1 mo	—	—	—	3
Boers et al[17]	MRSA	2½ yr	—	12 (71)	5 (29)	17
Dansby et al[27]	MRSA	7 yr	—	—	—	21.9/1000 PD
Embil et al[14]	MRSA	2 mo	126	11 (92)	1 (8)	12 (9.52)
Espersen et al[36]	MRSA	1 mo	23	—	10	10 (43.48)
Fuchs et al[10]	MRSA	8 mo	43	6 (75)	2 (25)	8 (18.60)
Hunt et al[21]	MRSA	8 yr	—	—	—	56
Lilly et al[22]	MRSA	2 yr	—	—	—	74
Meier et al[34]	MRSA	4 mo	—	6 (60)	4 (40)	10
Patel et al[23]	MRSA	1 mo	—	—	4	4
Rashid et al[9]	MRSA	5½ mo	176	15 (83)	3 (17)	18 (10.23)
Roberts et al[33]	MRSA	18 mo	1896	—	—	109 (5.75)
Rutala et al[35]	MRSA	—	—	—	—	66 (70)
Safdar et al[18]	MRSA	5 mo	—	7	5	12 (723/1000 PD)
Teare et al[25]	MRSA	16 mo	—	—	—	19

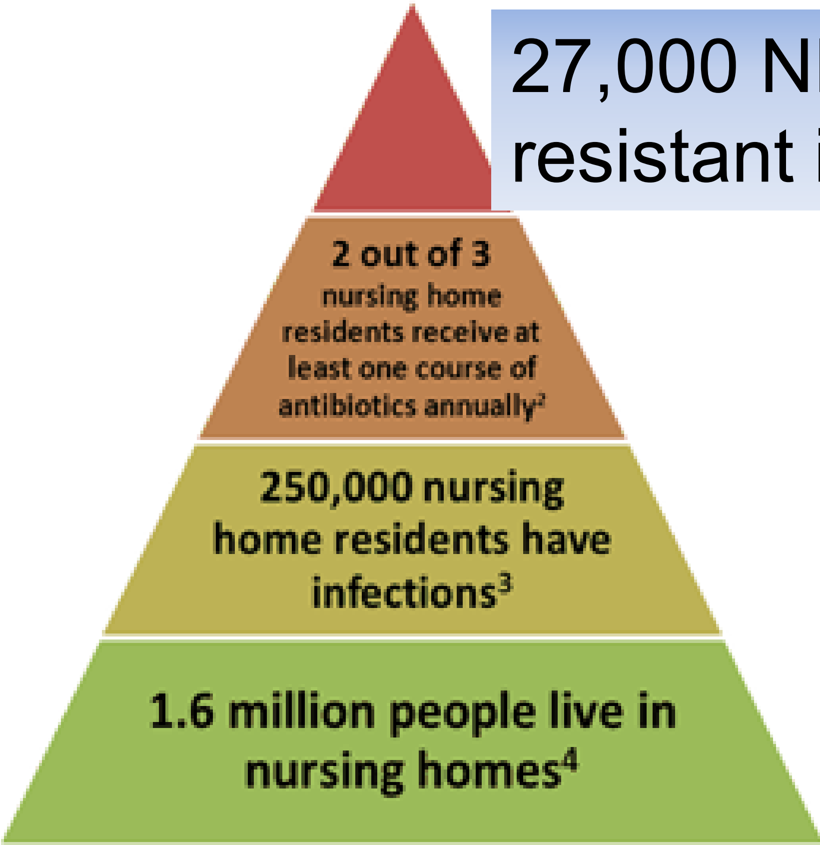
Long term acute care facilities and ICUs

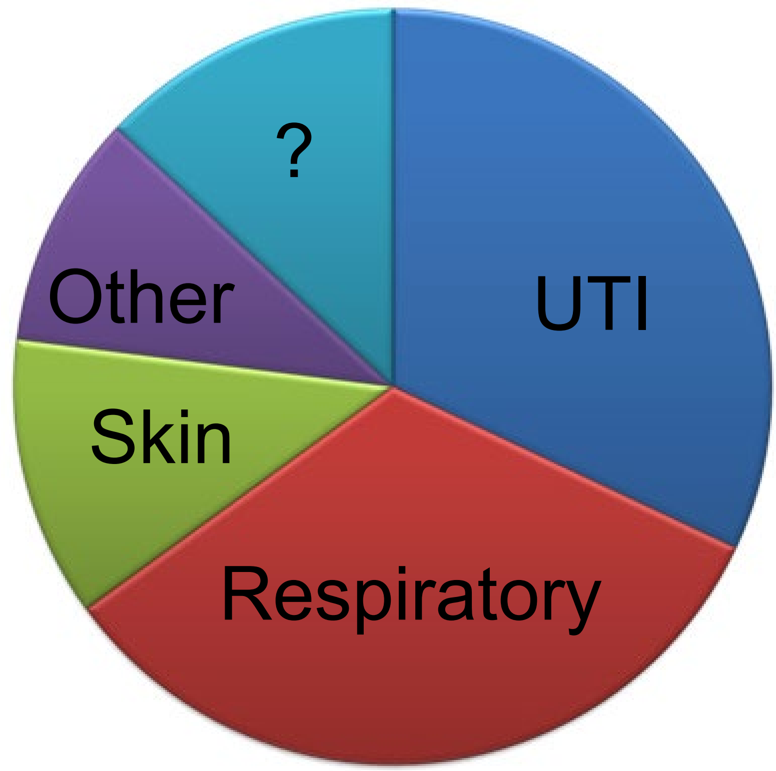


Chitnis et al. ICHE 2012;33:993

The nursing home pyramid

27,000 NH residents have antibiotic-resistant infections



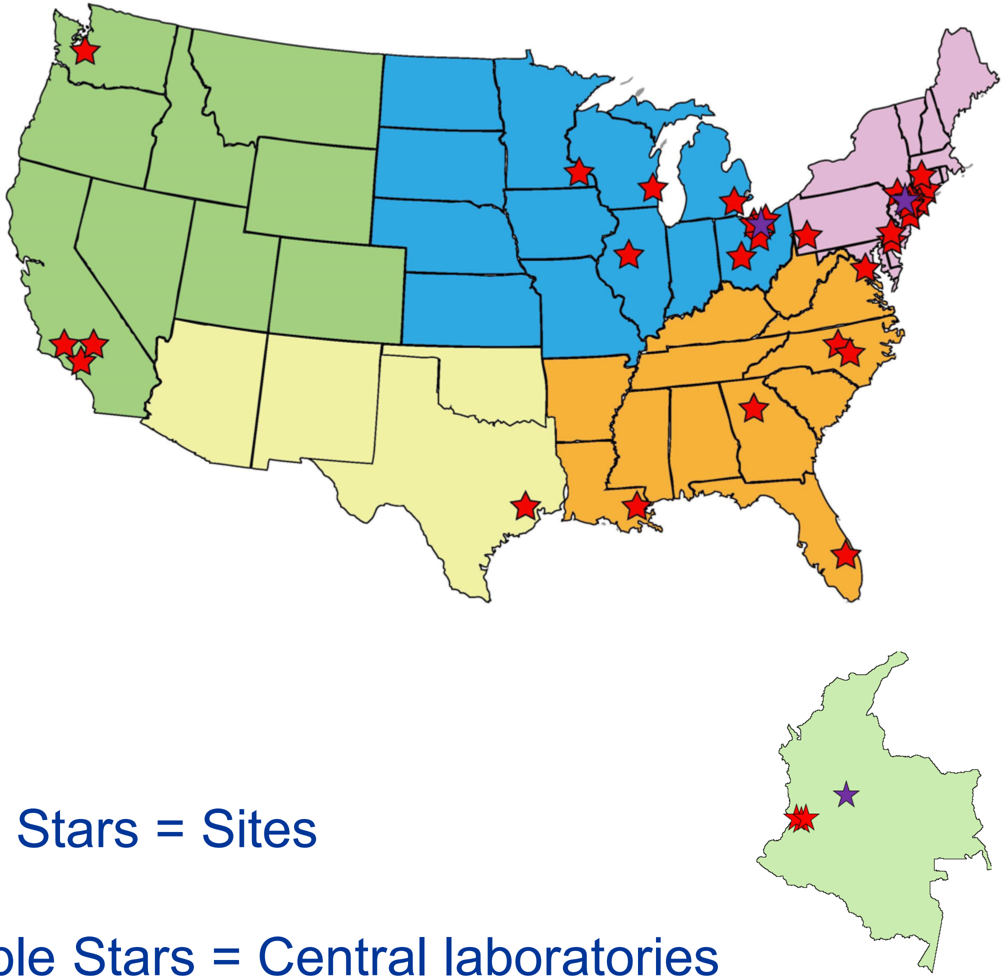


Most commonly treated infections in NH

Source: cdc.gov

CRACKLE-II : Consortium on Resistance Against Carbapenems in *Klebsiella pneumoniae*

- 32 US sites / 79 US hospitals
- 17 States, DC, and Colombia
- 3597 projected patient admissions
- 1000 estimated isolates per year
- Additional sites planned
  - China (n=5)
  - Pacific (n=10)



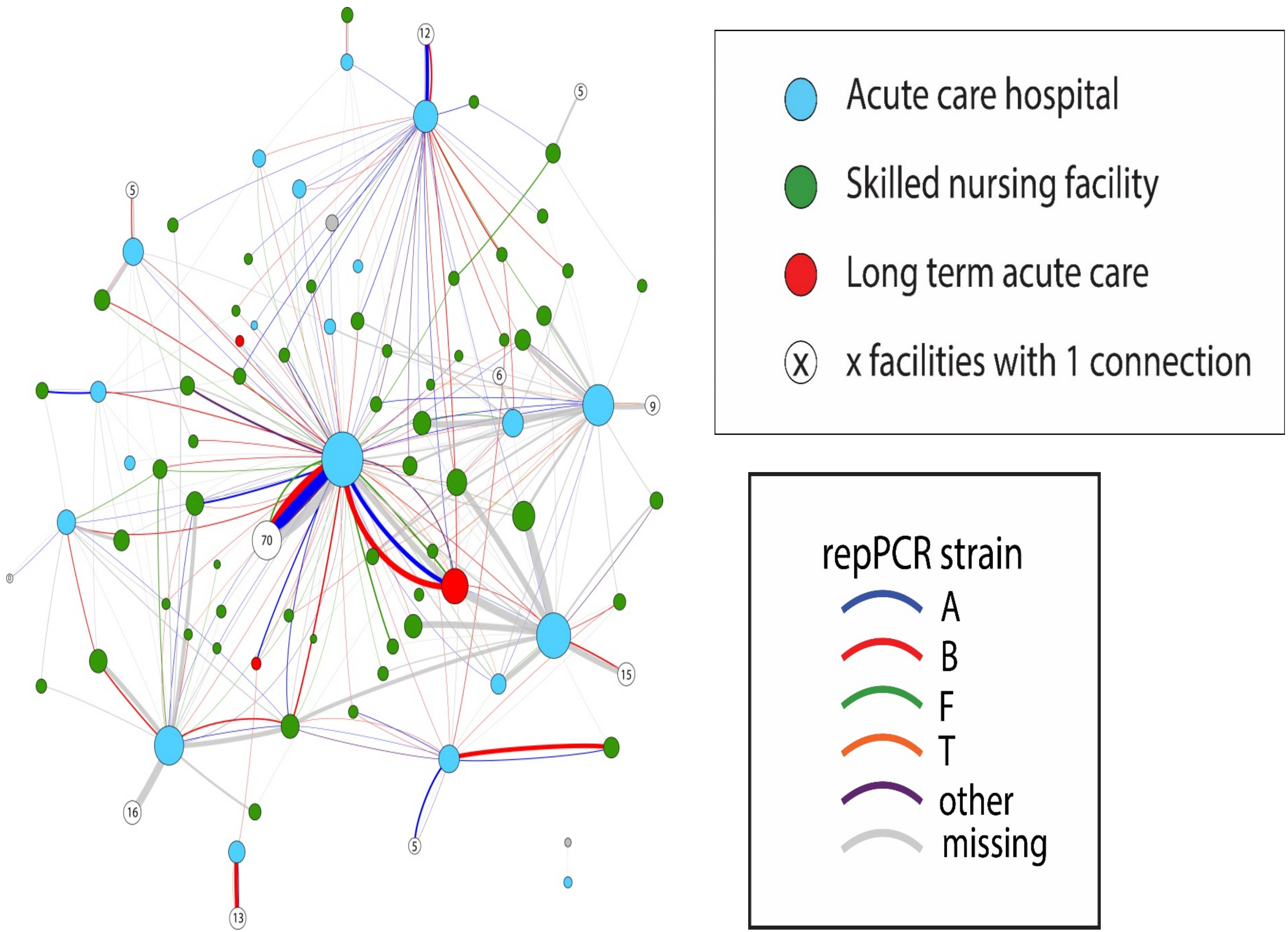
Red Stars = Sites

Purple Stars = Central laboratories

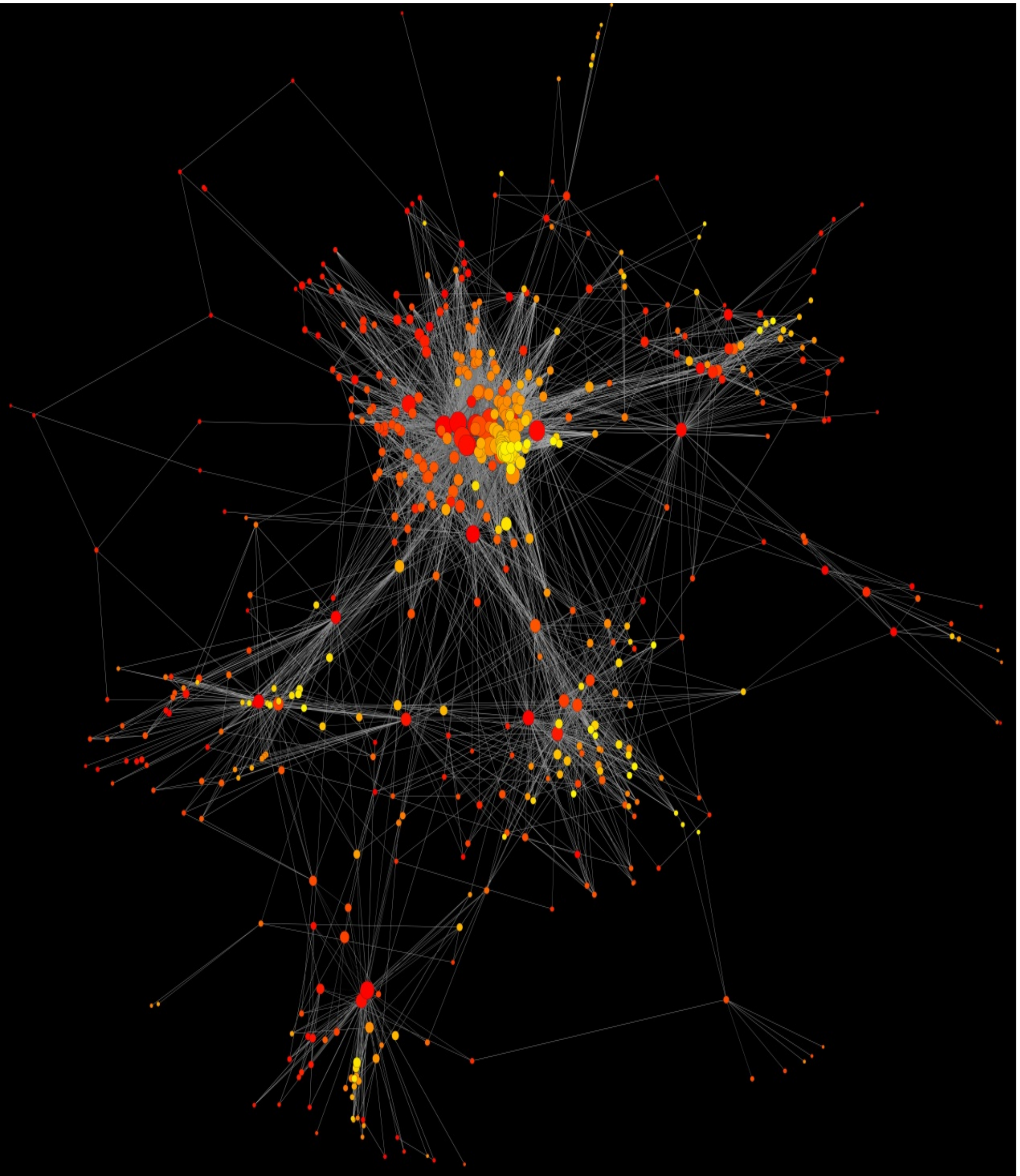
Network: methods

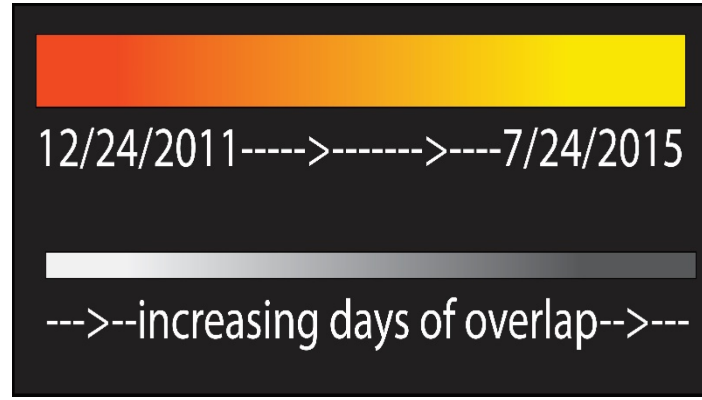
- Study period 12/24/2011 until 6/30/2016
- All hospitalized patients with clinical culture positive for carbapenem-resistant *K. pneumoniae* (CRKP) were included
- RepPCR for strain typing on all available isolates
- Network analyses at the facility and individual level were performed

Network: facilities



Network: individuals





- 572/724 (79%) people “connected”
- i.e. at least 5 days at the same facility

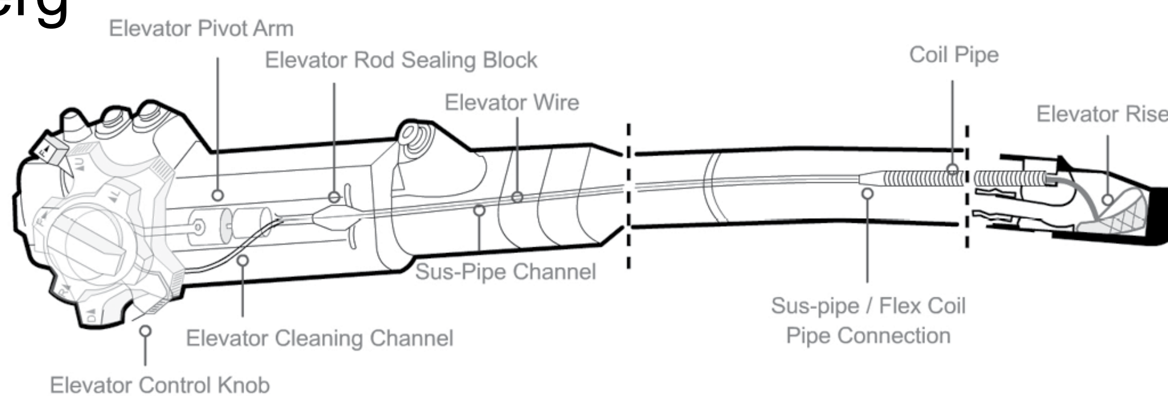
Endoscope-related outbreaks

Several outbreaks featuring carbapenemase-producing Enterobacteriaceae

-NDM and KPC

-possibly related to elevator channel in scopes

-likely "tip of the iceberg"



5. Superbugs & super-resistance

It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

Which superbugs is NOT considered an urgent threat in the US?

A. *Clostridium difficile*

B. Carbapenem-resistant Enterobacteriaceae

C. Vancomycin-resistant *Enterococcus*

D. Drug-resistant *Neisseria gonorrhoeae*

Antimicrobial resistance threats in the US, 2013

Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

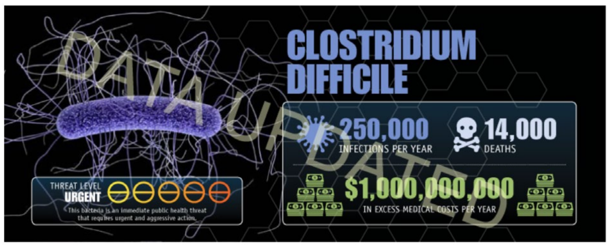
- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal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

Concerning Threats

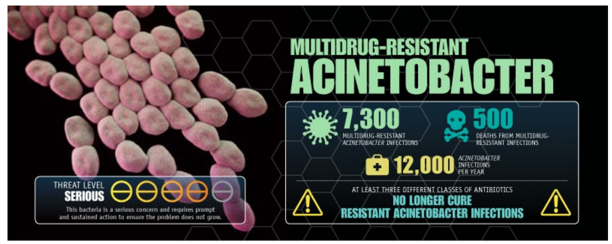
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

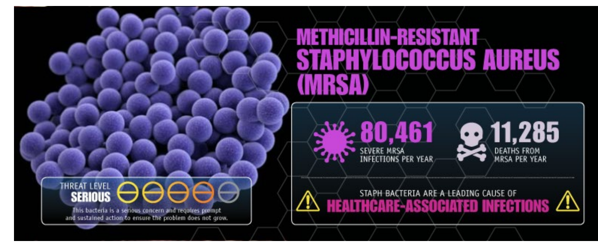
US antimicrobial resistance threats

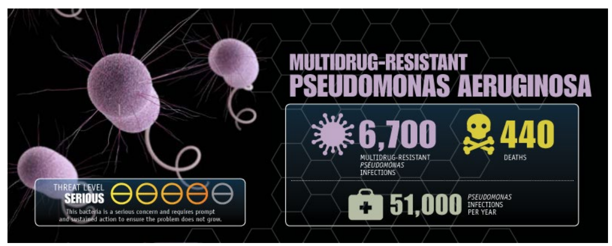
Urgent

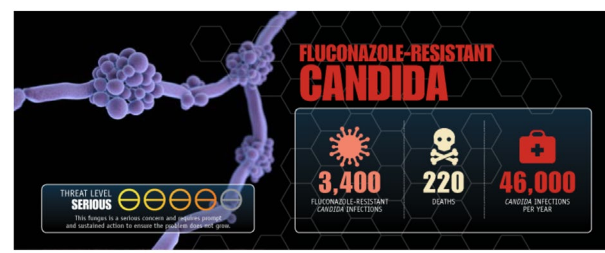


Serious









Global priority list of antibiotic-resistant bacteria

The WHO priority list

PRIORITY: CRITICAL	PRIORITY 2: HIGH	PRIORITY 3: MEDIUM
Acinetobacter baumannii carbapenem-resistant	**Enterococcus faecium** vancomycin-resistant	**Streptococcus pneumoniae** penicillin-non-susceptible
Pseudomonas aeruginosa carbapenem-resistant	**Staphylococcus aureus** methicillin-resistant vancomycin-intermediate and resistant	**Haemophilus influenzae** ampicillin-resistant
Enterobacteriaceae carbapenem-resistant, ESBL-producing	**Helicobacter pylori** clarithromycin-resistant	**Shigella spp.** fluoroquinolone-resistant
	Campylobacter spp. fluoroquinolone-resistant	
	Salmonellae fluoroquinolone-resistant	
	Neisseria gonorrhoeae cephalosporin-resistant fluoroquinolone-resistant	

Source: WHO

World Health Organization

GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

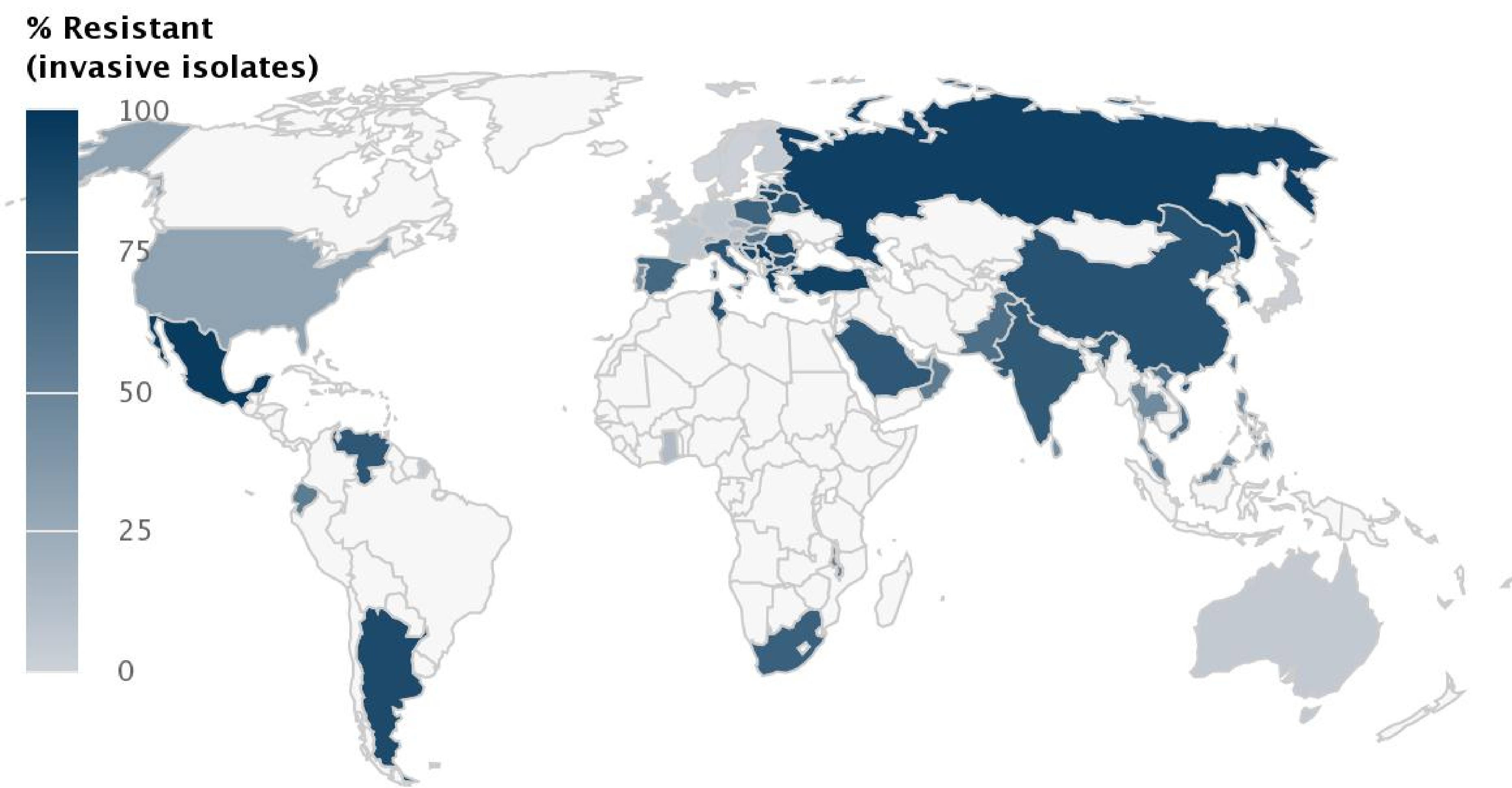
Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

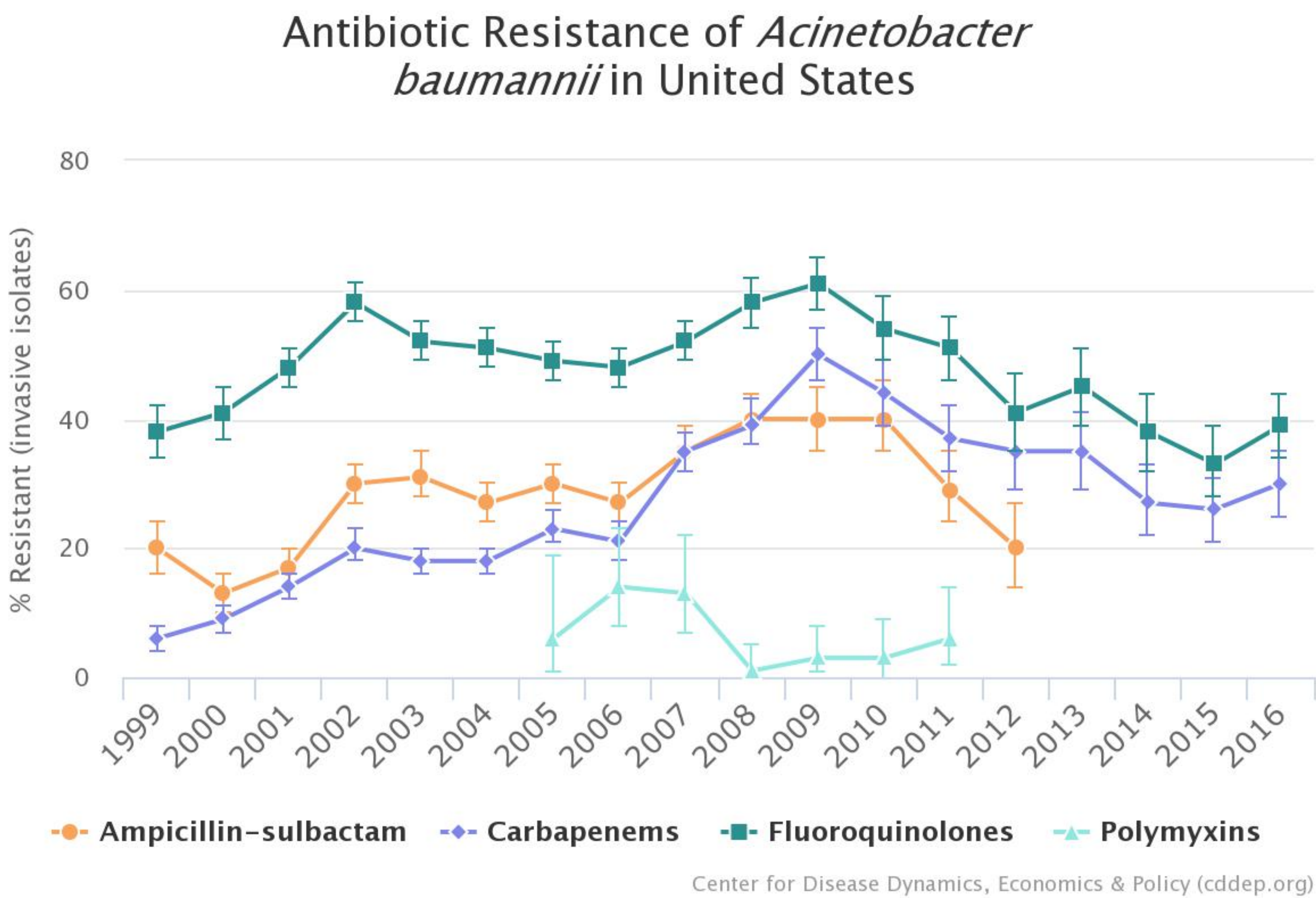
Pseudomonas aeruginosa, carbapenem-resistant

***Enterobacteriaceae**,** carbapenem-resistant, 3rd generation cephalosporin-resistant

Resistance of *Acinetobacter baumannii* to Carbapenems

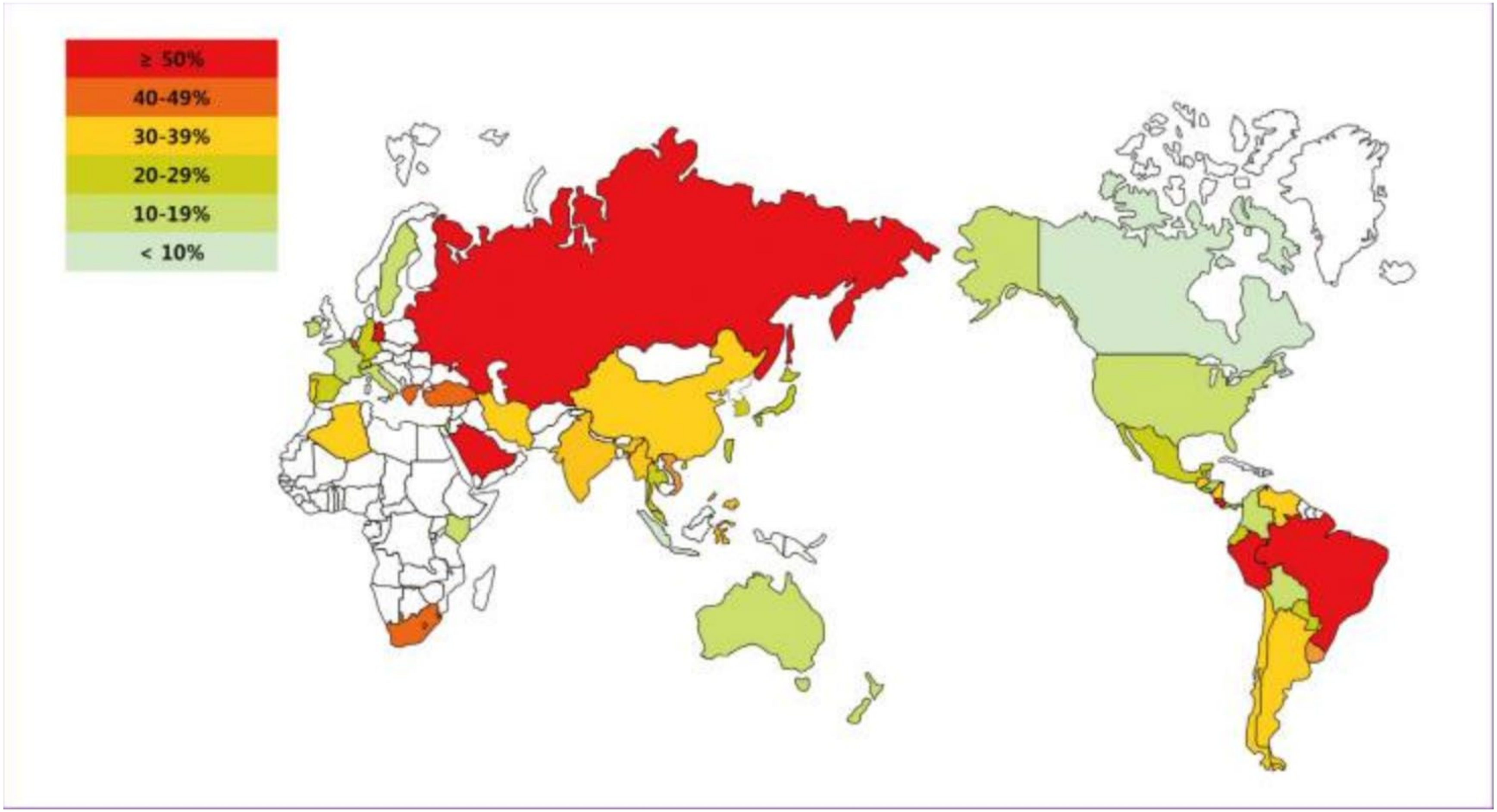


The Center for Disease Dynamics Economics & Policy. ResistanceMap. 2018. https://resistancemap.cddep.org/AntibioticResistance.php



The Center for Disease Dynamics Economics & Policy. ResistanceMap. 2018. https://resistancemap.cddep.org/AntibioticResistance.php

Distribution of carbapenemase-resistant *Pseudomonas aeruginosa*

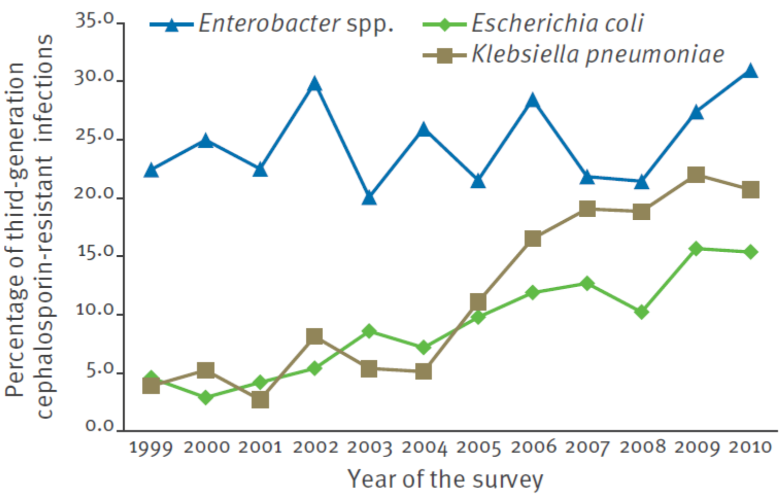


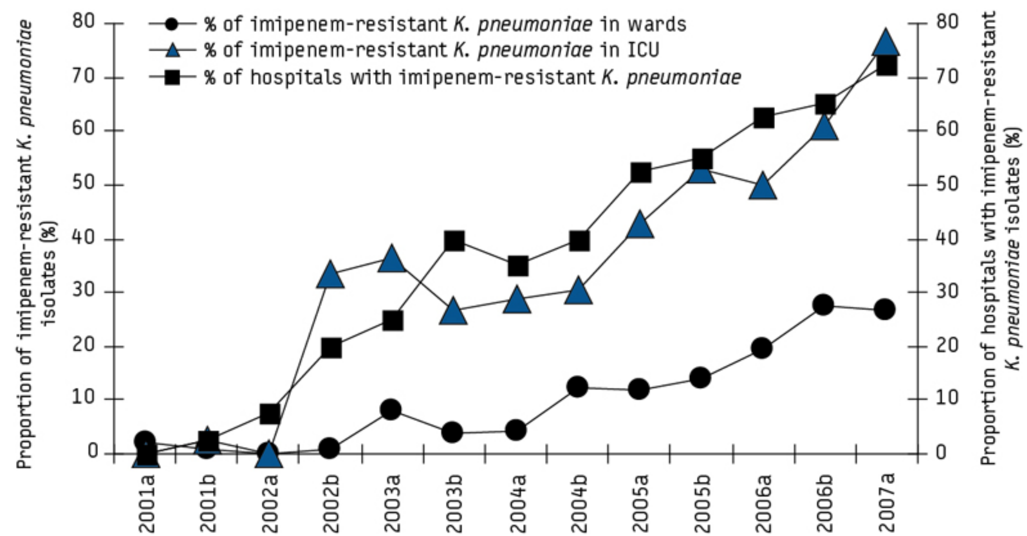
Hong et al. Infect Chemother. 2015;47:81.

Trends in resistance in Enterobacteriaceae, late 2000s

Figure 2

Annual rates of *Enterobacteriaceae* resistant to third-generation cephalosporins, Spain, 1999–2010





Data from the Greek System for the Surveillance of Antimicrobial Resistance (http://www.mednet.gr/whonet)

Spain

Greece

Asensio et al. Eurosurveillance 2011;16:1

Vatopoulos. Eurosurveillance 2008;1-3:1

Carbapenem-resistant Enterobacteriaceae

TABLE 1

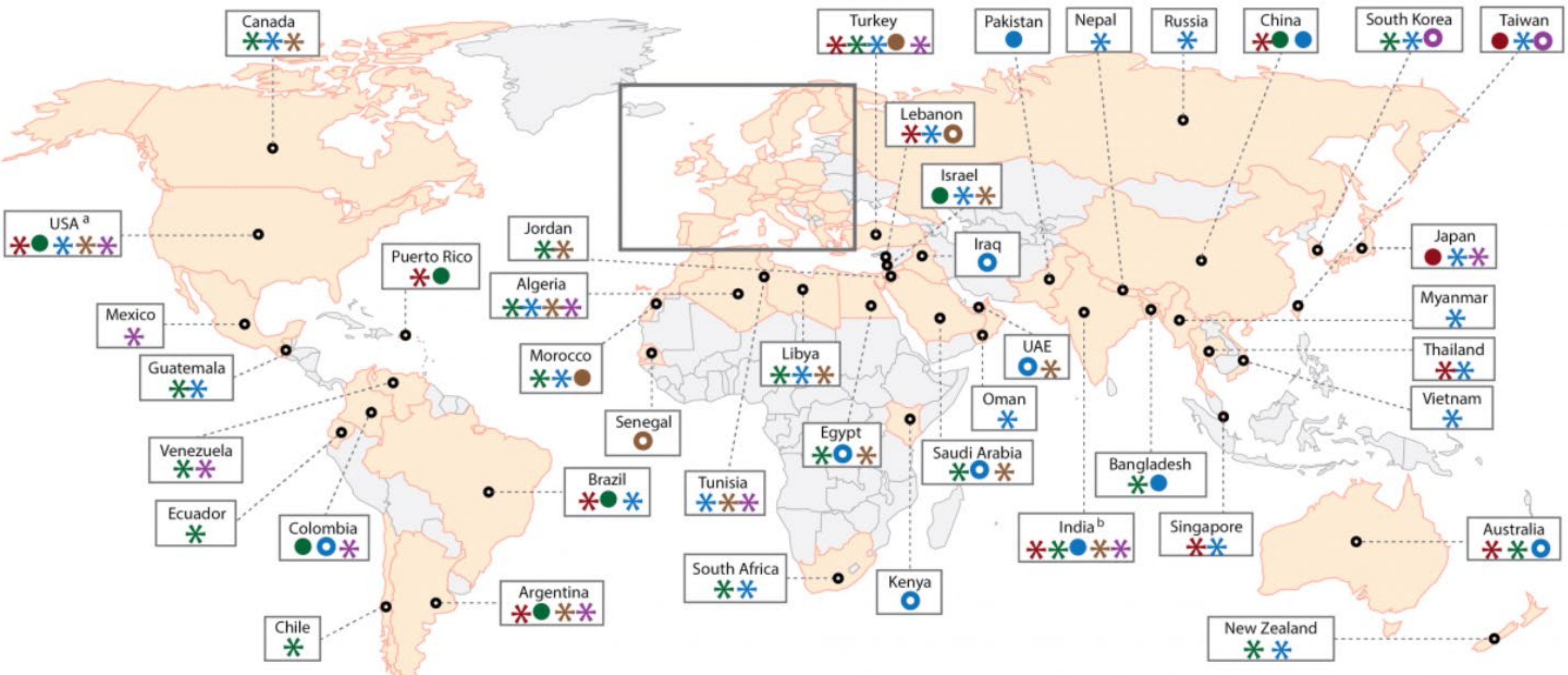
Enzymes conferring carbapenem resistance in Enterobacteriaceae

Enzyme	Common genetic platform	Species distribution in Enterobacteriaceae	Geographic distribution
KPC (Klebsiella pneumoniae carbapenemase)	*K pneumoniae* sequence type 258, various plasmids types, transposon Tn*4401*x	*K pneumoniae, Escherichia coli, Enterobacter* species, diverse Enterobacteriaceae	Endemic in the United States, Greece, Israel, Italy, Puerto Rico, China, and South America
NDM (New Delhi metallo-beta-lactamase)	Various plasmid types	*K pneumoniae* and *E coli* predominantly, diverse Enterobacteriaceae	Indian subcontinent and the Balkan region, and around the world
OXA-48 (oxacillinase)	IncI/M-type plasmid	*K pneumoniae* predominantly, diverse Enterobacteriaceae	Southern and Western Europe, Turkey and North Africa; rare in the United States
VIM (Verona integron-encoded metallo-beta-lactamase)	Gene cassettes in class 1 integrons	*K pneumoniae* predominantly	Common in Italy, Greece, and the Far East, sporadic globally
IMP	Gene cassettes in class 1 integrons	*K pneumoniae* predominantly	Common in the Far East and South America, sporadic globally
SME	Chromosome	*Serratia marcescens*	Sporadic in North America and South America

BASED ON INFORMATION IN TZOUVELEKIS LS, MARKOGIANNAKIS A, PSICHOGIOU M, TASSIOS PT, DAIKOS GL. CARBAPENEMASES IN *KLEBSIELLA PNEUMONIAE* AND OTHER ENTEROBACTERIACEAE: AN EVOLVING CRISIS OF GLOBAL DIMENSIONS. CLIN MICROBIOL REV 2012; 25):682–707.

Perez & van Duin, CCJM 2013;80:225

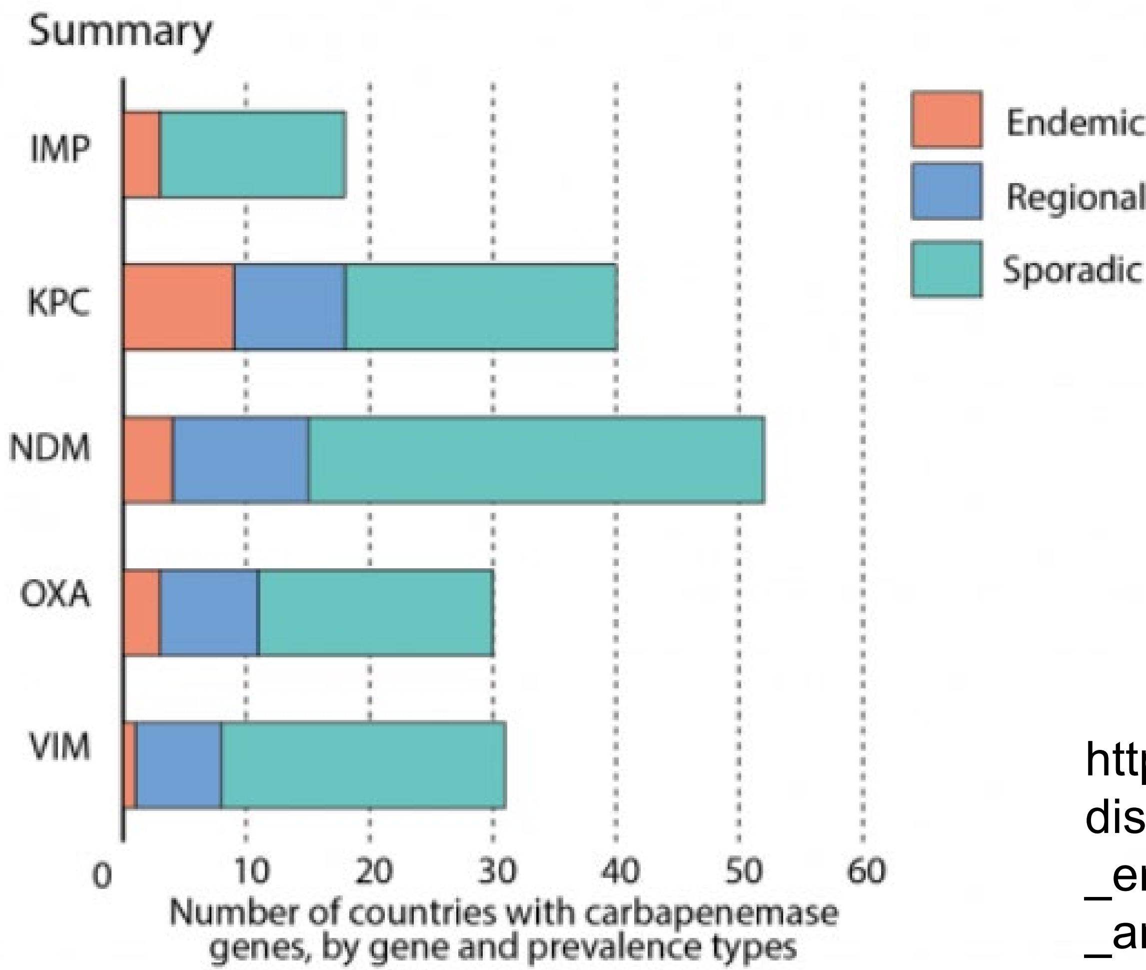
Global Distribution of Carbapenemases in Enterobacteriaceae, by Country and Region



	IMP	KPC	NDM	OXA	VIM
Endemic/nationwide distribution	●	●	●	●	●
Significant outbreaks/ regional spread	○	○	○	○	○
Sporadic outbreak/ occurences	*	*	*	*	*

https://cddep.org/tool/global_distribution_carbapenemases_enterobacteriaceae_country_and_region/

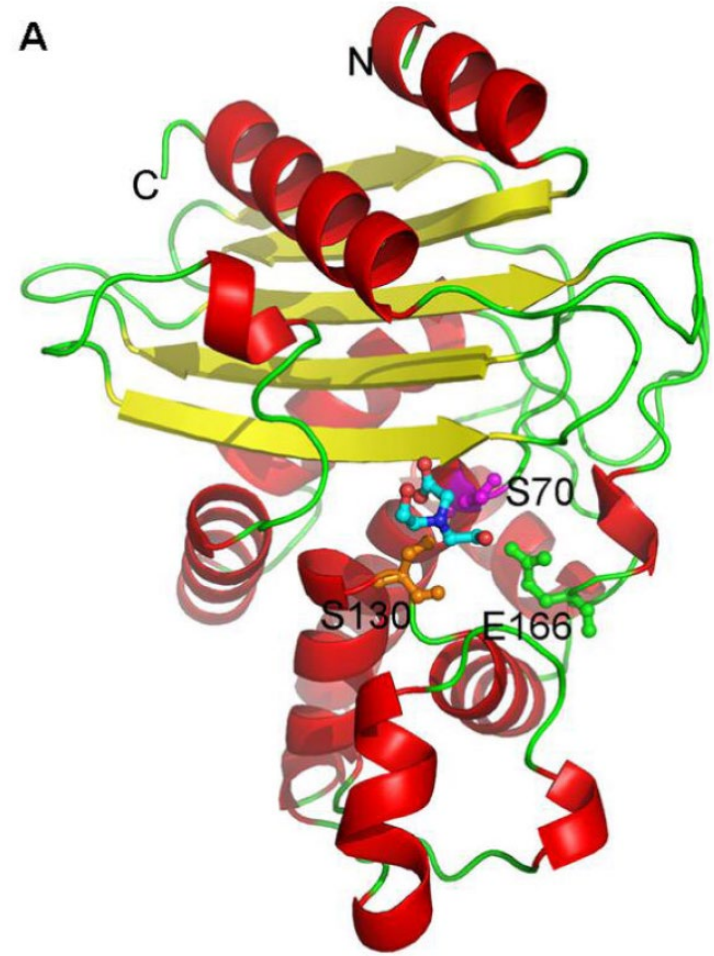
Global Distribution of Carbapenemases in Enterobacteriaceae, by Country and Region



https://cddep.org/tool/global_distribution_carbapenemases_enterobacteriaceae_country_and_region/

K. pneumoniae carbapenemase

- Most common carbapenemase encountered in Enterobacteriaceae
- 13 variants;
  KPC-2 and KPC-3 most common
- Class A serine-carbapenemase
- Hydrolyzes carbapenems, cephalosporins, penicillins, aztreonam



Ke et al. Biochem 2007;46:5732

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1151–1161 Vol. 45, No. 4
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1151–1161.2001

Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

HESNA YIGIT,[1] ANNE MARIE QUEENAN,[2] GREGORY J. ANDERSON,[1] ANTONIO DOMENECH-SANCHEZ,[3] JAMES W. BIDDLE,[1] CHRISTINE D. STEWARD,[1] SEBASTIAN ALBERTI,[4] KAREN BUSH,[2] AND FRED C. TENOVER[1]*

Hospital Infections Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia 30333[1]; The R. W. Johnson Pharmaceutical Research Institute, Raritan, New Jersey 08869[2]; and Unidad de Investigacion, Hospital Son Dureta, Andrea Doria, Palma de Mallorca, 07014,[4] and Área de Microbiologia, Universidad de las Islas Baleares, Crtra. Valldemosa, Palma de Mallorca, 07071,[3] Spain

- First report of *Klebsiella pneumoniae* carbapenemase (KPC) in US
- 1996 patient in North Carolina
- Participant in project Intensive Care Antimicrobial Resistance Epidemiology (iCARE)

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2009, p. 5046–5054 Vol. 53, No. 12
0066-4804/09/$12.00 doi:10.1128/AAC.00774-09

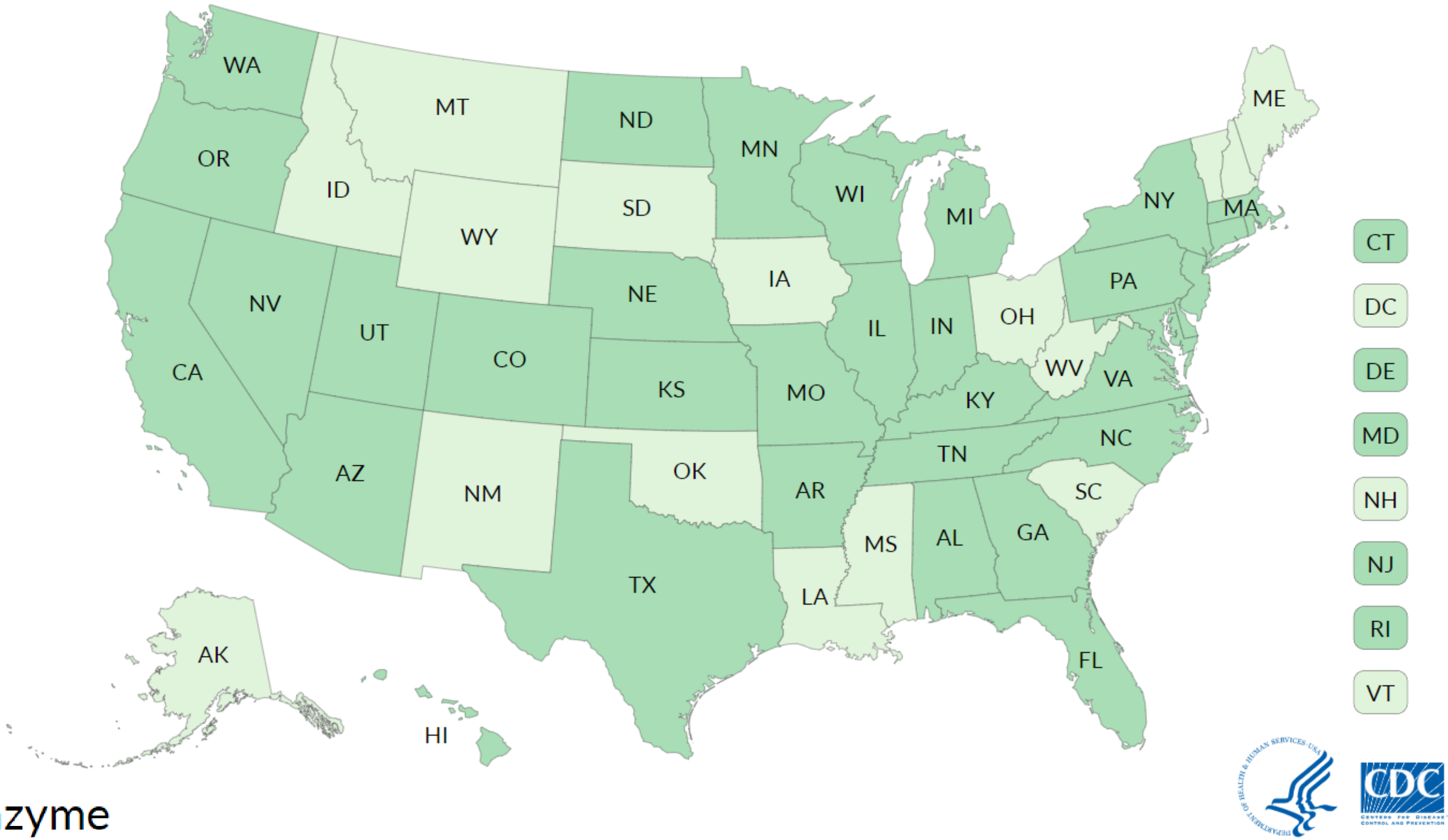
Characterization of a New Metallo-β-Lactamase Gene, *bla*$_{\text{NDM-1}}$, and a Novel Erythromycin Esterase Gene Carried on a Unique Genetic Structure in *Klebsiella pneumoniae* Sequence Type 14 from India[▽]

Dongeun Yong,[1,2] Mark A. Toleman,[2] Christian G. Giske,[3] Hyun S. Cho,[4] Kristina Sundman,[5] Kyungwon Lee,[1] and Timothy R. Walsh[2]*

Yonsei University College of Medicine, Research Institute of Antimicrobial Resistance, Seoul, Republic of Korea[1]; Department of Medical Microbiology, Cardiff University, Cardiff, United Kingdom[2]; Clinical Microbiology, MTC—Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden[3]; Yonsei University College of Life Science and Biotechnology, Seoul, Republic of Korea[4]; and Department of Clinical Microbiology, Örebro University Hospital, Örebro, Sweden[5]

- NDM: New Delhi metallo-β-lactamase
- Zinc-containing Class B carbapenemase
- Hydrolyzes carbapenems, cephalosporins, penicillins, but not aztreonam
- First isolated from a Swede who was hospitalized in New Delhi, India

Patients with NDM-producing *Carbapenem-resistant Enterobacteriaceae* (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of December 2017, by state



NDM enzyme

None

Reported

https://www.cdc.gov/hai/organisms/cre/trackingcre.html
Accessed March 25, 2019

Dissemination of mcr-1 gene

plasmid-mediated colistin resistance

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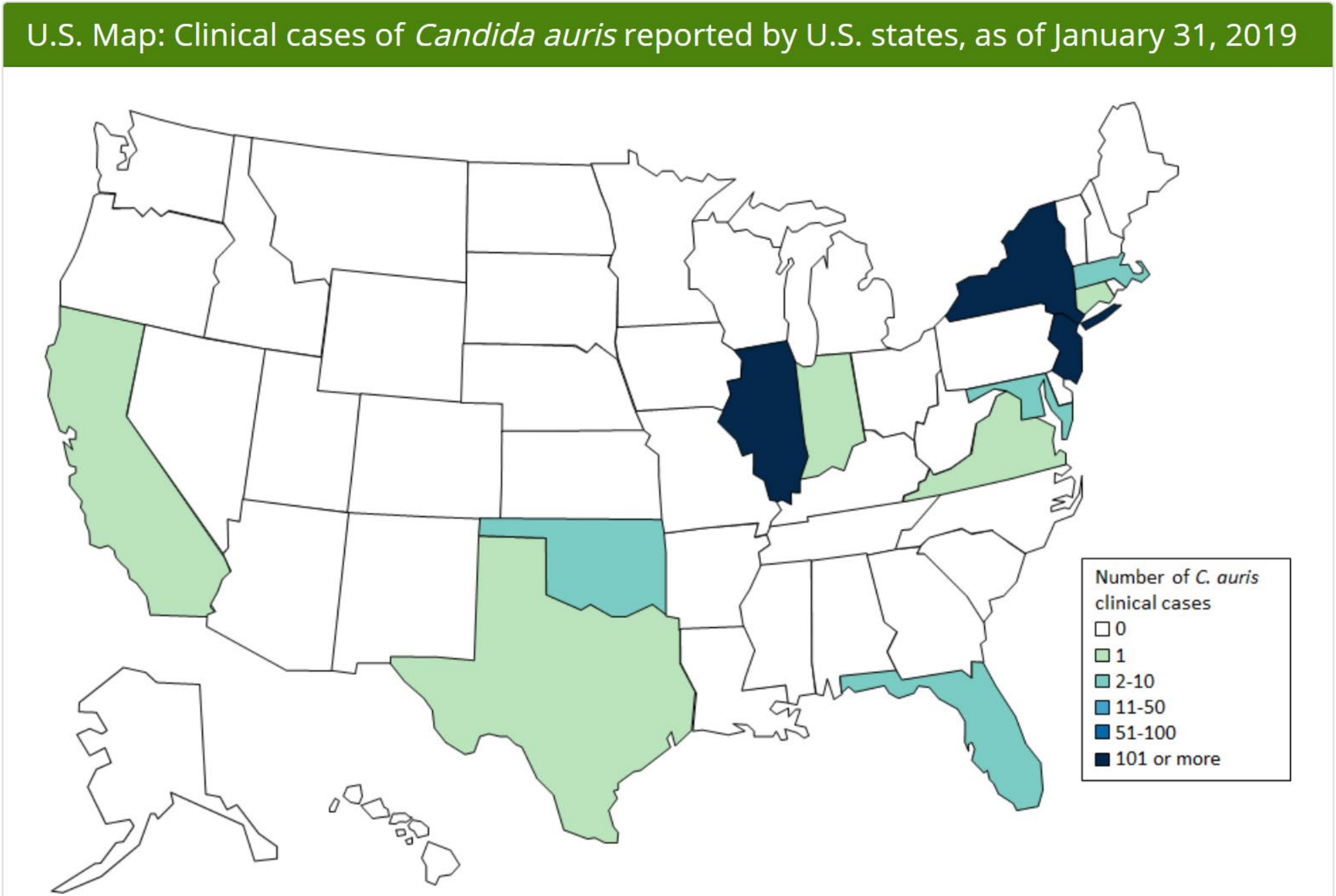
Colistin- and Carbapenem-Resistant *Escherichia coli* Harboring *mcr-1* and bla_{NDM-5}, Causing a Complicated Urinary Tract Infection in a Patient from the United States

José R. Mediavilla,[a] Amee Patrawalla,[b] Liang Chen,[a] Kalyan D. Chavda,[a] Barun Mathema,[c] Christopher Vinnard,[a] Lisa L. Dever,[d] Barry N. Kreiswirth[a]

Public Health Research Institute Tuberculosis Center, New Jersey Medical School, Rutgers University, Newark, New Jersey, USA[a]; Division of Pulmonary and Critical Care Medicine, New Jersey Medical School, Rutgers University, Newark, New Jersey, USA[b]; Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York, USA[c]; Division of Infectious Diseases, New Jersey Medical School, Rutgers University, Newark, New Jersey, USA[d]

Candida auris:
A drug-resistant germ that spreads in healthcare facilities

- *Candida auris* is an emerging MDR yeast that can cause invasive infections & is associated with high mortality
- 1st described in 2009 in Japan, but CDC released an alert to US healthcare facilities in June 2016
- *C. auris* may acquire antibiotic resistance during treatment
- Disinfection with an EPA-registered disinfection effective against C dif spores is recommended (quaternary ammonium-based disinfectants may be insufficient)



https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html.
Accessed March 25, 2019

6. The impact of multi-drug resistant organisms on patient outcomes

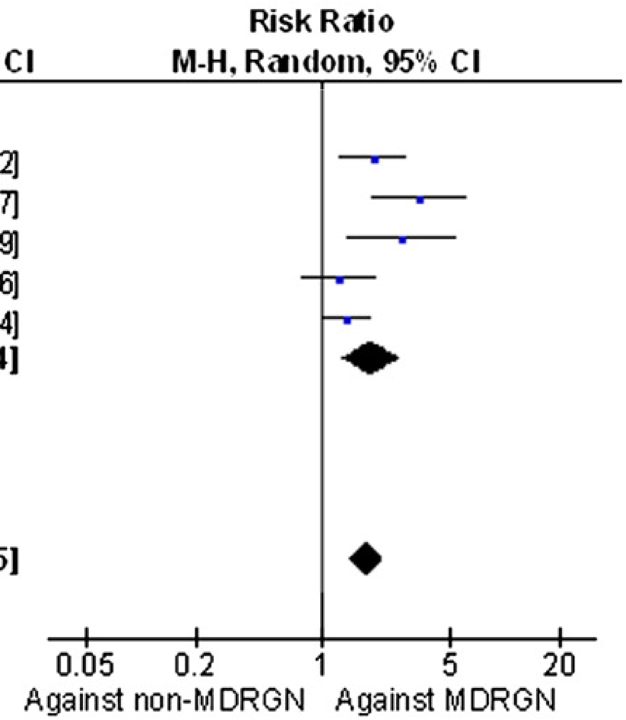
The impact of MDRO on outcomes

- Difficult to study
- Reports vary in their definitions of MDR
- Many confounders
- Patients with MDR-O tend to be:
  - More chronically ill
  - More acutely ill
  - Treated differently

Impact of MDR on mortality

A

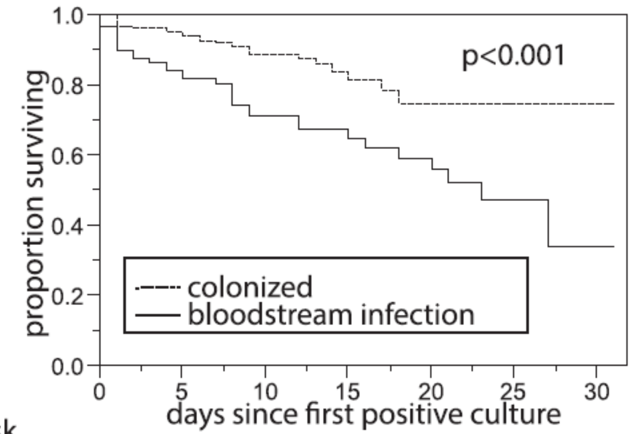
Study or Subgroup	MDR Events	MDR Total	non-MDR Events	non-MDR Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.2 Definition >3 classes						
Annunatsiri et al 2011	22	24	12	25	5.9%	1.91 [1.25, 2.92]
Cao et al 2004	24	44	11	68	4.7%	3.37 [1.84, 6.17]
Kwa et al 2007	14	41	11	88	4.2%	2.73 [1.36, 5.49]
Lee et al 2007	22	46	18	46	5.6%	1.22 [0.76, 1.96]
Metan et al 2009	35	48	28	52	6.7%	1.35 [1.00, 1.84]
Subtotal (95% CI)		**203**		**279**	**27.2%**	**1.84 [1.29, 2.64]**
Total events	117		80			
Heterogeneity: Tau² = 0.10; Chi² = 11.43, df = 4 (P = 0.02); I² = 65%						
Test for overall effect: Z = 3.35 (P = 0.0008)						
Total (95% CI)		**1320**		**2372**	**100.0%**	**1.75 [1.42, 2.15]**
Total events	510		441			
Heterogeneity: Tau² = 0.14; Chi² = 64.72, df = 18 (P < 0.00001); I² = 72%						
Test for overall effect: Z = 5.25 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%						



Vardakas et al. J Infect 2013;66;401

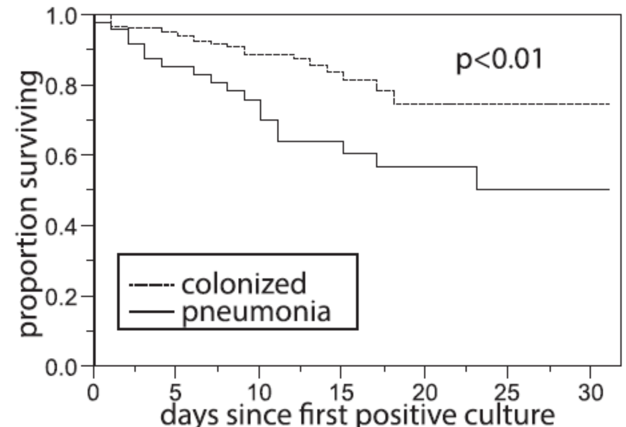
Outcomes in CRE infections

(a)



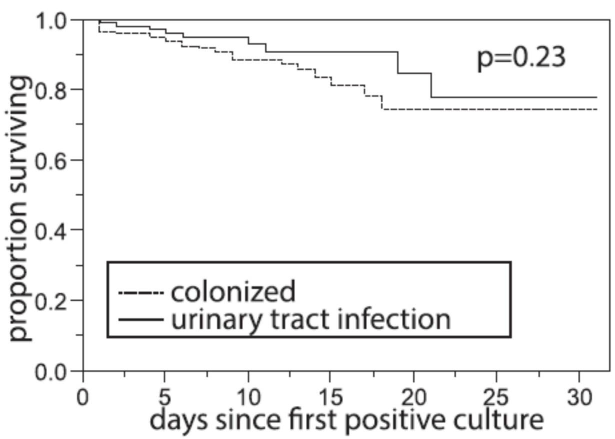
No. at risk							
colonized	223	170	85	43	19	13	11
BSI	90	73	48	29	20	11	7

(b)



No. at risk							
colonized	223	170	85	43	19	13	11
pneumonia	49	40	29	21	15	8	4

(c)



No. at risk							
colonized	223	170	85	43	19	13	11
UTI	121	98	56	24	15	9	7

- BSI/pneumonia: All-cause hospital mortality 39% (“excess mortality” 27%)
- Adjusted HR 30-d mortality
  - BSI 2.59 (1.52-4.50)
  - Pneumonia 3.44 (1.80-6.48)

Hauck et al. CMI 2016;22:513

Carbapenemase production in CRE: does it matter?

Table 4. Fourteen-Day Mortality for Patients With Carbapenemase-Producing Carbapenem-Resistant *Enterobacteriaceae* (CP-CRE) Compared With non-CP-CRE Bacteremia

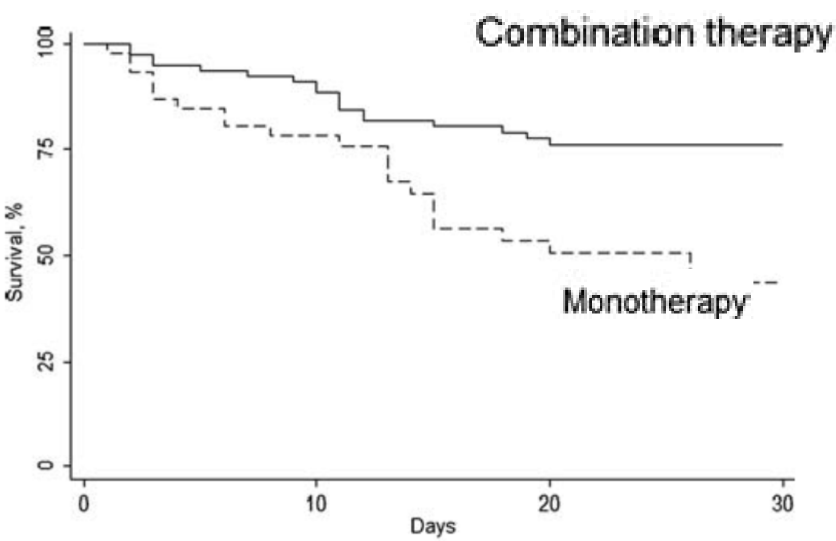
Covariate	Odds Ratio (95% CI)	*P* Value	Adjusted Odds Ratioa (95% CI)	*P* Value
Carbapenemase-producing carbapenem-resistant *Enterobacteriaceae* bacteremia	3.20 (1.06–9.61)	.04	4.92 (1.01–24.81)	.05
Pitt bacteremia score ≥4	9.13 (2.39–34.86)	.001	11.89 (2.38–59.30)	.005
Active empiric antibiotic therapy	.79 (0.27–2.29)	.67	2.46 (0.53–11.48)	.25
Active directed antibiotic therapy	.17 (0.04–0.72)	.01	0.10 (0.004–2.22)	.14
Days of combination antibiotic therapy	.89 (0.79–1.00)	.07	0.73 (0.59–0.93)	.01
Polymixin therapy administered	4.61 (1.16–18.3)	.03	5.57 (1.07–28.96)	.04
Diabetes	3.12 (0.99–9.84)	.05	3.42 (0.62–19.07)	.16
Immunocompromised	.45 (0.14–1.40)	.17	–	–
Carbapenem therapy administered	.82 (0.27–2.52)	.74	–	–
Meropenem minimum inhibitory concentration ≥16 µg/mL	1.40 (0.38–5.01)	.61	–	–

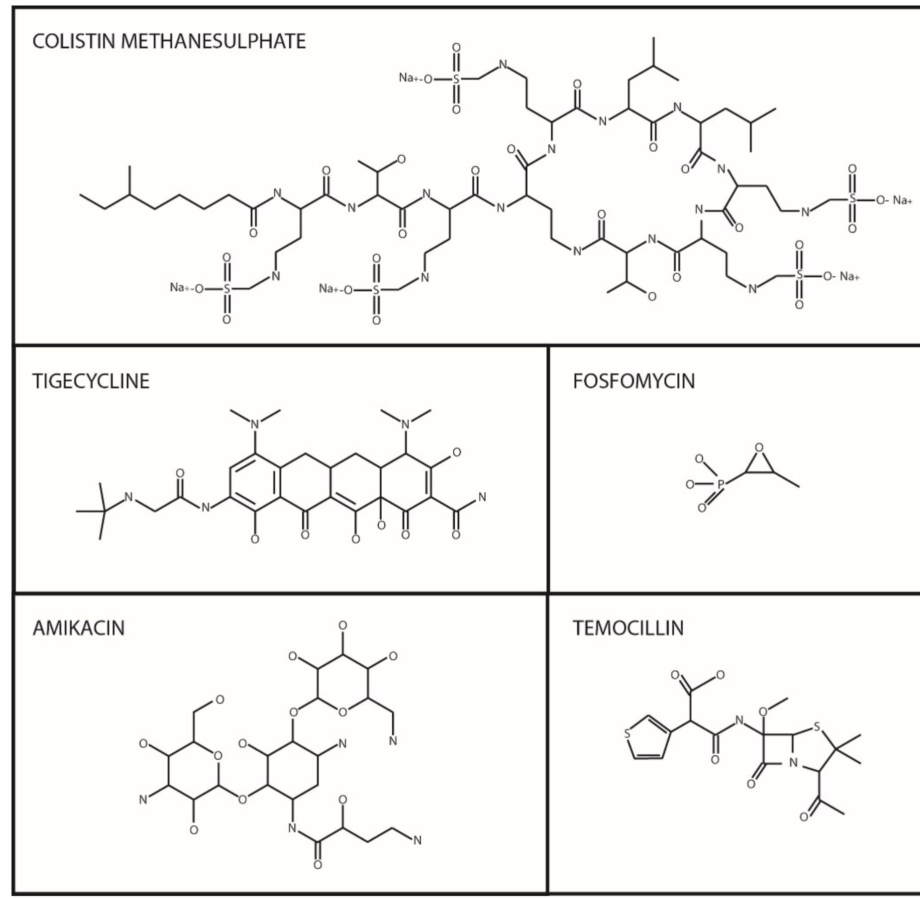
- Single center, retrospective cohort
- carbapenemase vs.
  non-carbapenemase producing CRE
- n=83

Tamma et al. CID 2017:64;257

Treatment of CRE

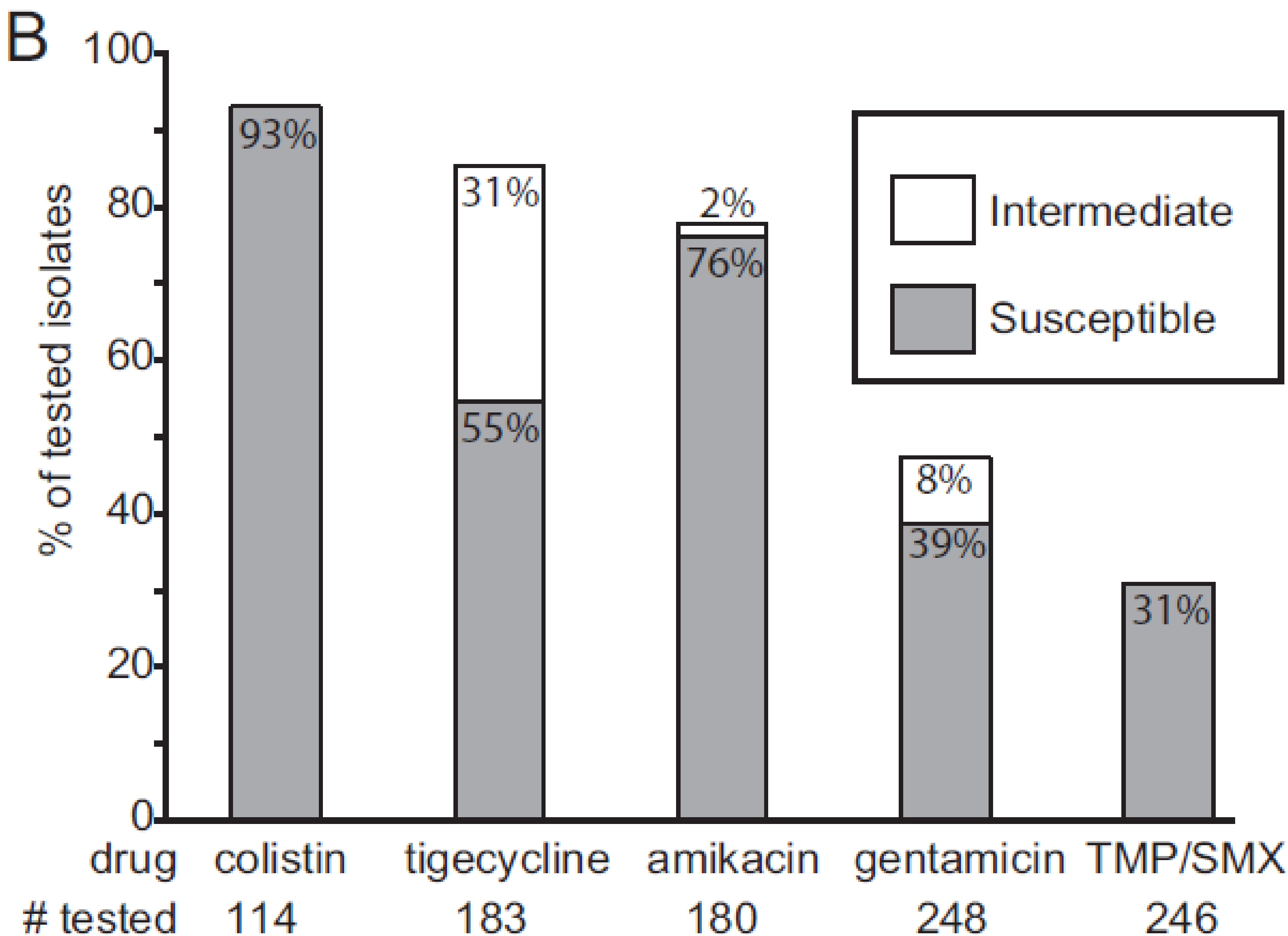
- Limited options…
- Toxicity
- Efficacy concerns
- ?combination therapy





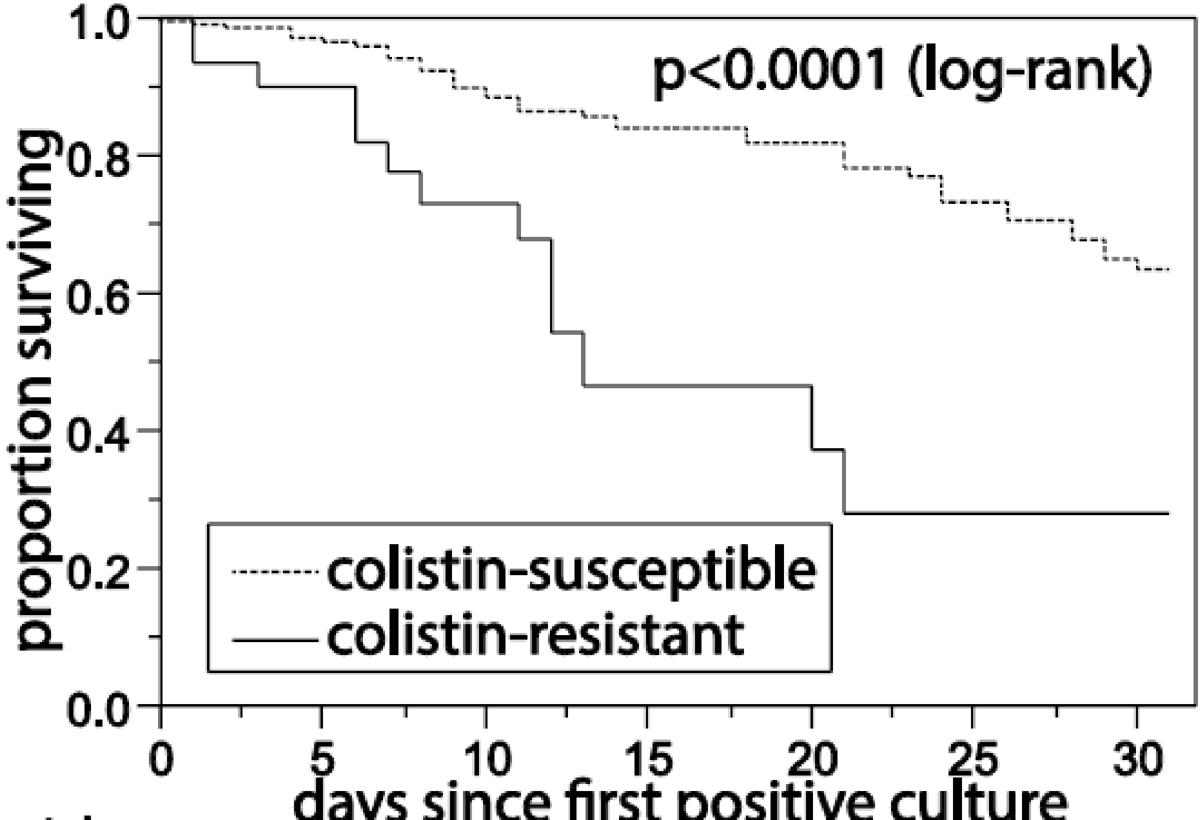
van Duin et al. DMID 2013;75:115
Tumbarello et al. CID. 2012;55:943

Antibiotic susceptibility of KPC-KP isolates



van Duin et al. AAC 2014;58:4035

Colistin resistance in KPC-KP isolates

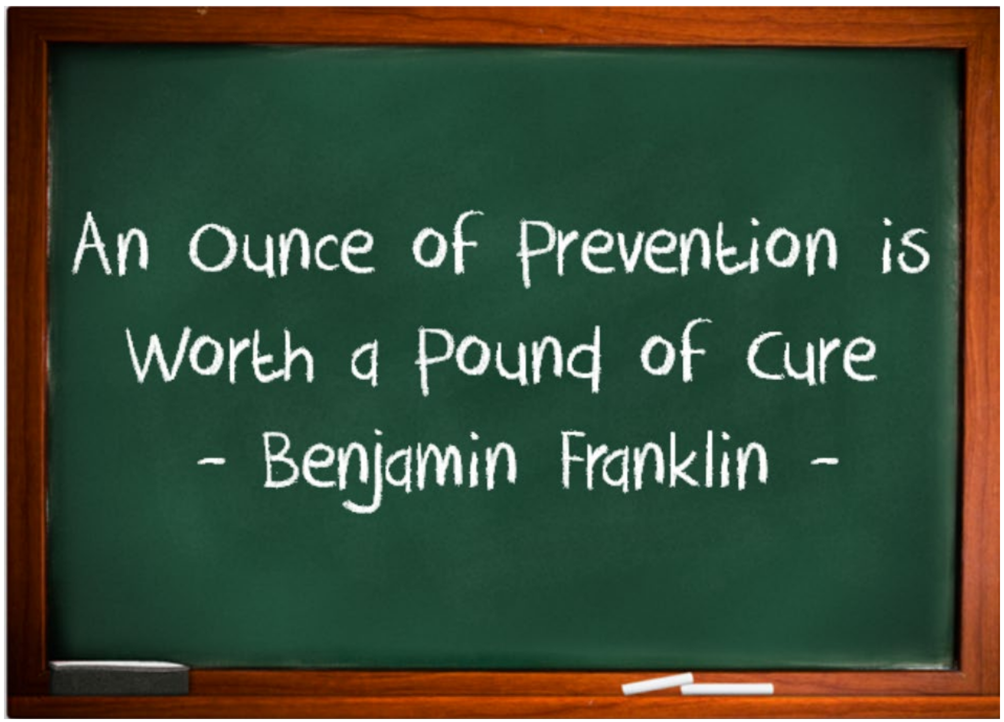


No. at risk

colistin-S	215	195	145	103	73	61	48
colistin-R	31	27	15	7	7	4	4

Rojas et al. Clin Infect Dis. 2017;64:711

7. Prevention of MDR infections



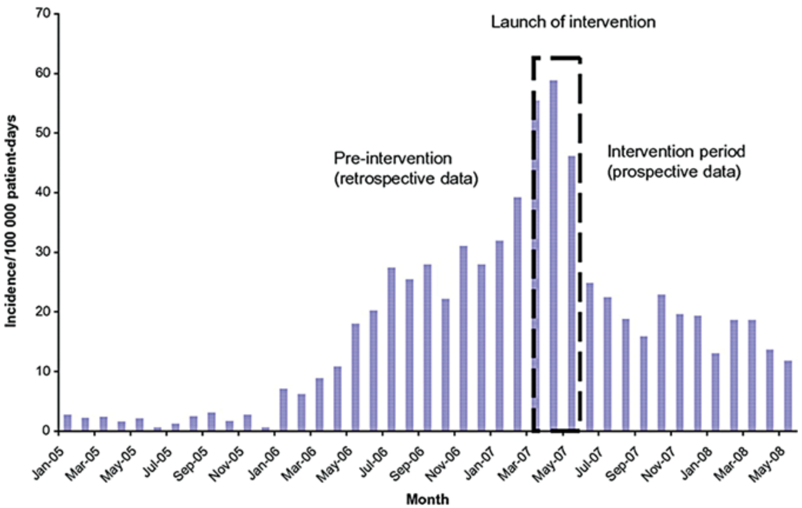
What’s the best way to prevent transmission of MDR organisms?

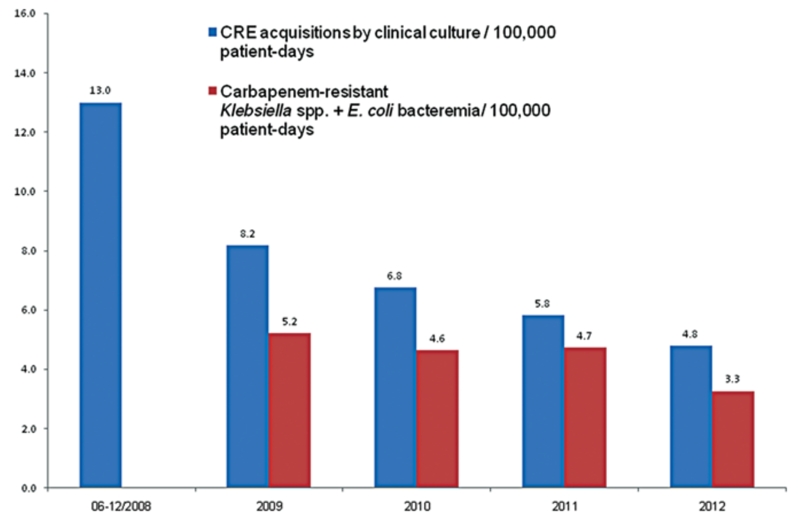
A. Use contact precautions when caring for patients with MDROs
B. Cohort patients with MDROs during an outbreak
C. Perform routine assessments of environmental surfaces and healthcare providers to track presence of MDROs
D. Clean hands with soap and water or an alcohol-based hand rub before and after caring for every patient

Prevention: prevention of spread

Prevention: the Israel experience

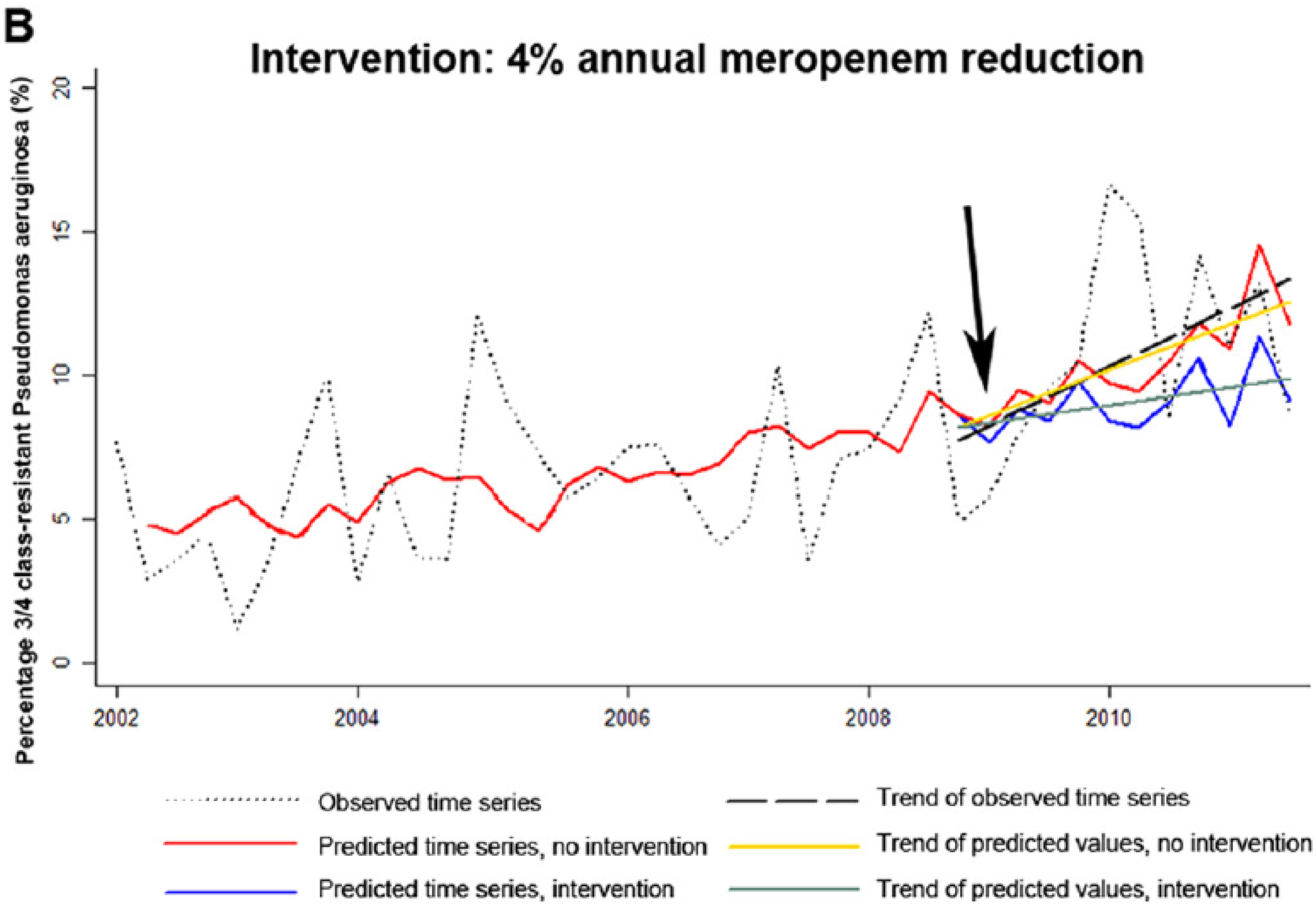
- 2007: 22% *K. pneumoniae* R to carbapenem
- National intervention:
  - Cohorting/isolation
  - Dedicated nursing staff
  - CRE task force
  - Screening of carriers
  - Long-term care facilities
  - Hand hygiene
  - Standardized methods
    - Laboratory detection
    - Environmental cleaning



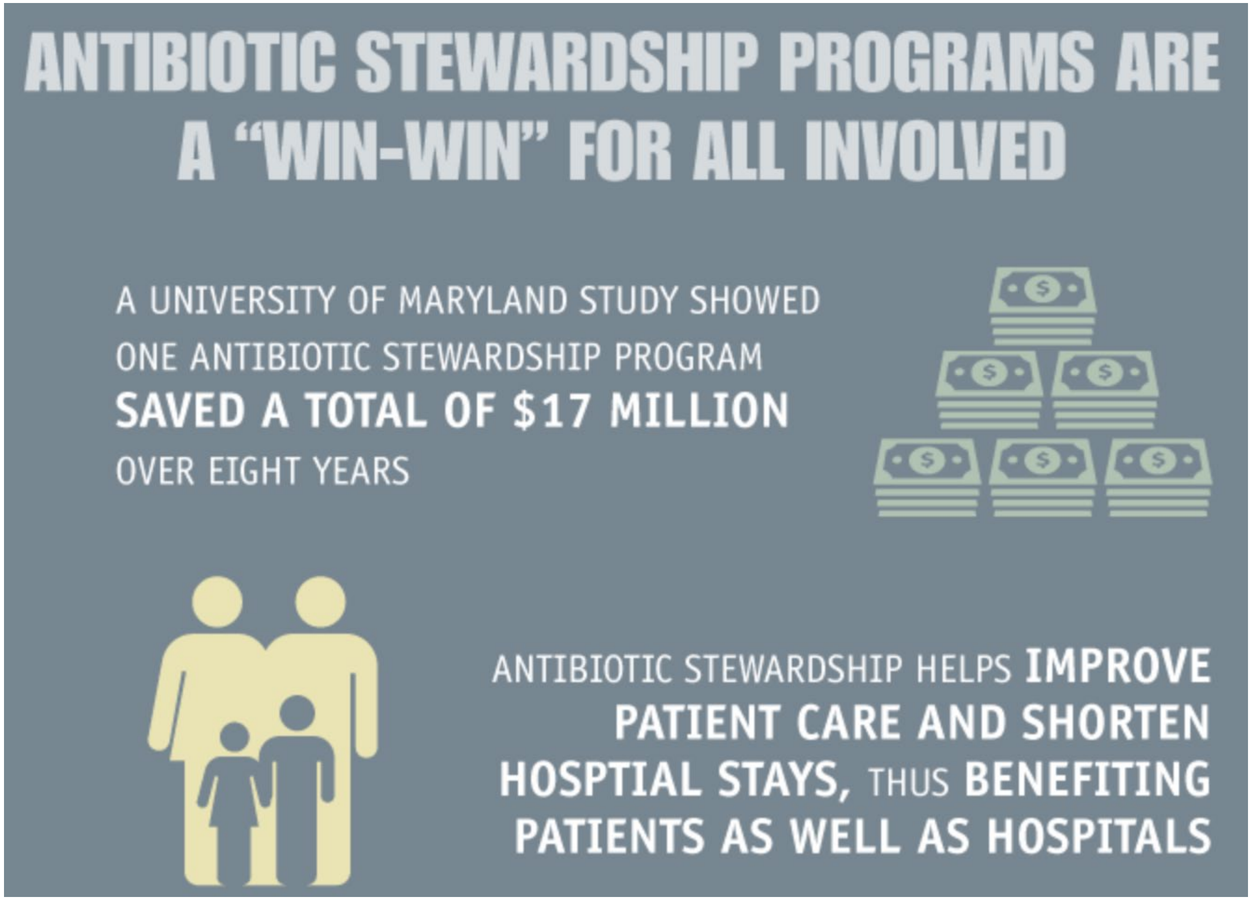


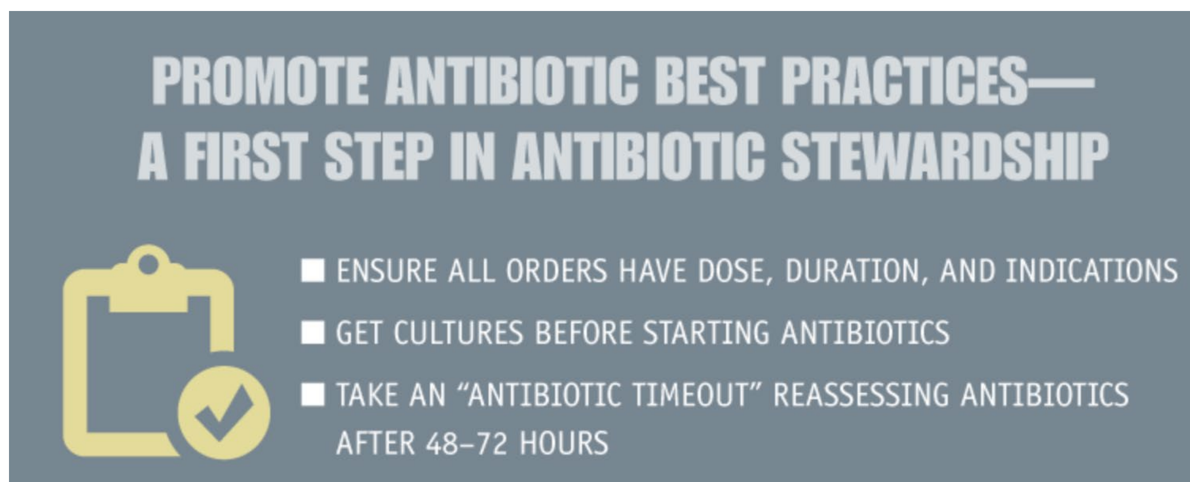
Swaber & Carmeli, Clin Infect Dis. 2013;58(5):697

Prevention: antimicrobial stewardship



Willmann. AAC 2013,57:1797





https://www.cdc.gov/drugresistance/cdc_role.html

Prevention: isolation of MDRO carriers

Harris et al.

- RTC with 26,180 patients in 20 US ICUs
- Gown/glove vs. standard of care
- MRSA acquisition decreased
- No difference in VRE acquisition
- Gown/glove led to less room entry by health care workers

Harris et al. JAMA 2013,310:1571

Prevention: isolation of MDRO carriers

Derde et al.

- 3 phases in 13 European ICUs
  - 6 mo baseline period
  - 6 mo universal chlorhexidine body-washing plus hand hygiene improvement
  - 12–15 mo cluster RCT of screening & isolation of MRSA, VRE, HRE carriers
- Improved hand hygiene + unit-wide chlorhexidine body-washing reduced acquisition of antimicrobial-resistant bacteria, particularly MRSA
- Screening & isolation of carriers had no addition benefit

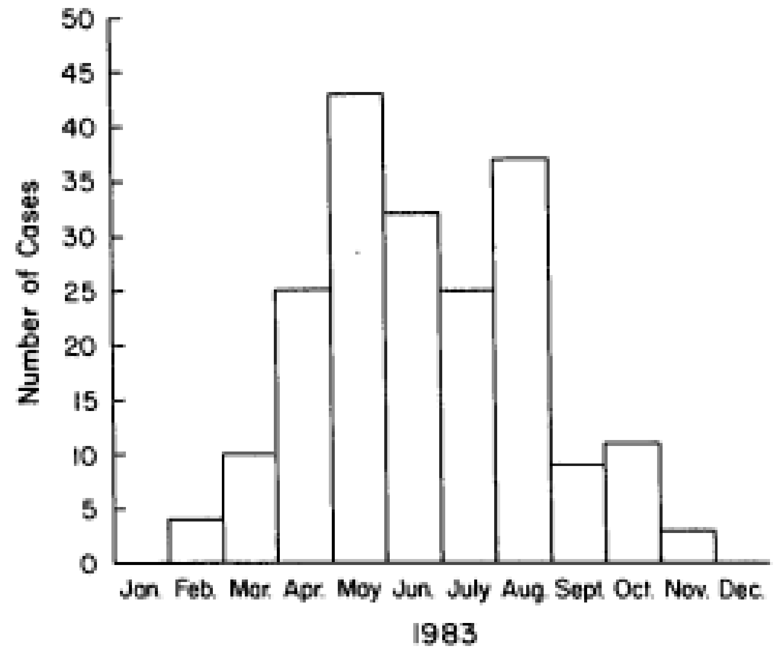
Derde et al. Lancet Inf Dis 2014,14:31

Prevention: treat and destroy

A COMMUNITY-BASED OUTBREAK OF INFECTION WITH PENICILLIN-RESISTANT *NEISSERIA GONORRHOEAE* NOT PRODUCING PENICILLINASE (CHROMOSOMALLY MEDIATED RESISTANCE)

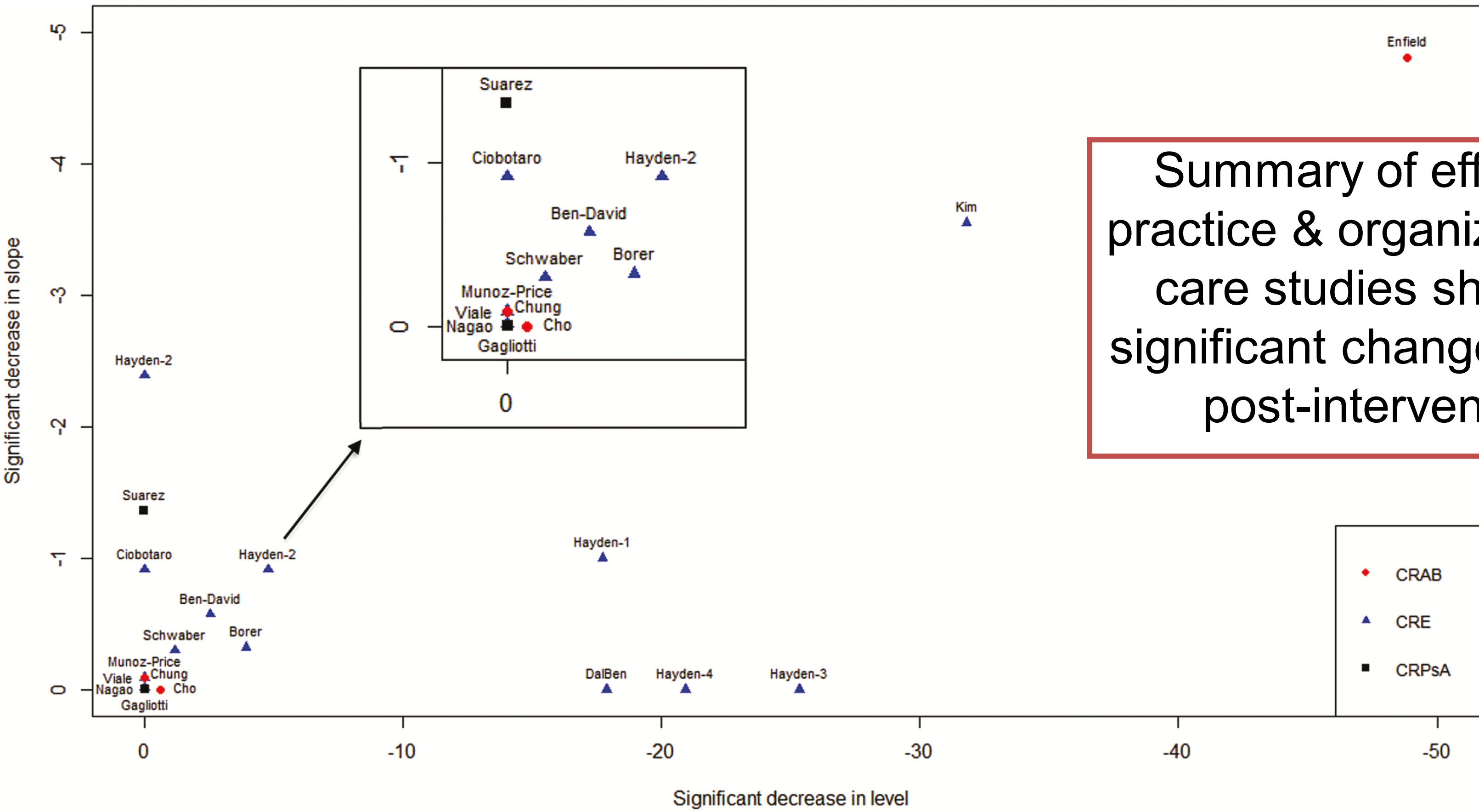
HAWAZIN FARUKI, DR.P.H., ROBERT N. KOHMESCHER, M.S., W. PAUL MCKINNEY, M.D., AND P. FREDERICK SPARLING, M.D.

- Outbreak with PCN-R *N. gonorrhoeae*
- 372 contacts identified
- 165 contacts had PCN-R *N. gonorrhoeae* and were treated



Faruki et al. NEJM 1985,313:607

Control of Carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* in Healthcare Facilities: A Systematic Review and Reanalysis of Quasi-experimental Studies



Summary of effective practice & organization of care studies showing significant change pre- to post-intervention

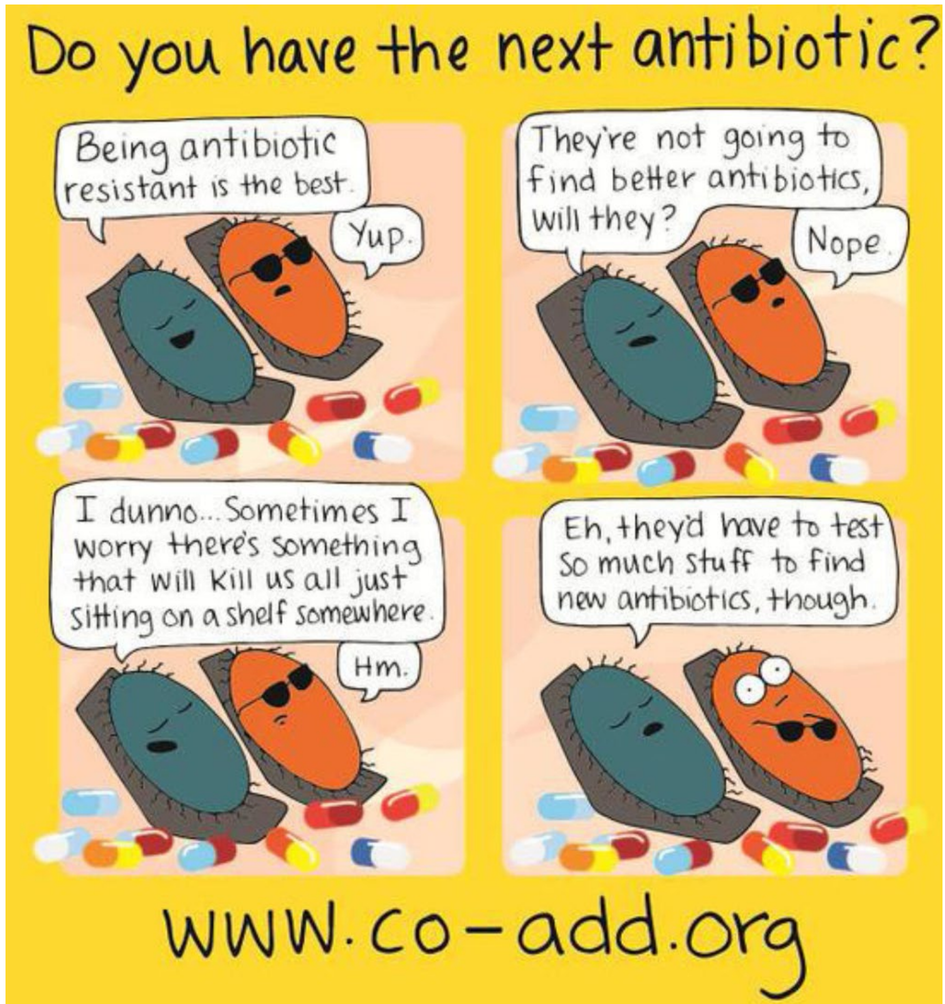
Tomczyk et al. Clin Infect Dis 2019; 68: 873–884

Control of Carbapenem-resistant Enterobacteriaceae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* in Healthcare Facilities: A Systematic Review and Reanalysis of Quasi-experimental Studies

- Overall, multimodal IPC strategies (ie, ≥3 components implemented in an integrated way) appear to be highly effective for CRE-CRAB-CRPsA prevention and control
- Strong evidence on the role of active surveillance for infection and asymptomatic colonization was found for CRE
- Implementation of hand hygiene best practices was reported in fewer studies (only 50% ?Standard of care)
- The importance of environmental cleaning and environmental surveillance cultures was most often reported in CRAB and CRPsA studies

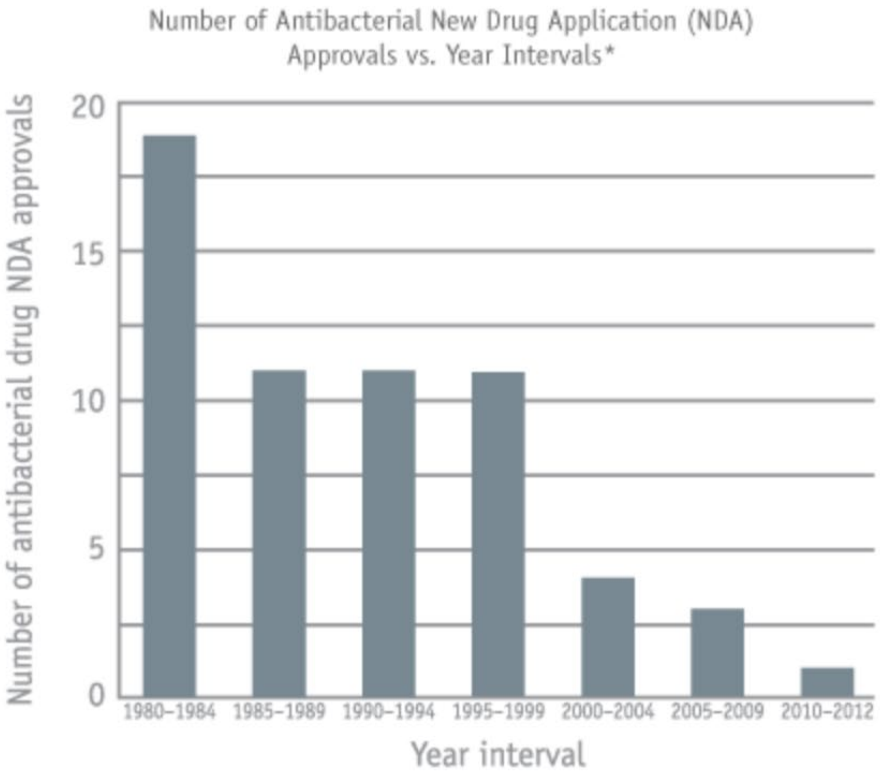
Tomczyk et al. Clin Infect Dis 2019; 68: 873–884

8. Treatment of MDR organisms



Fewer new antibiotics are available

The number of new antibiotics developed and approved has steadily decreased in the past three decades, leaving fewer options to treat resistant bacteria.



*Intervals from 1980–2009 are 5-year intervals; 2010–2012 is a 3-year interval. Drugs are limited to systemic agents. Data courtesy of FDA' s Center for Drug Evaluation and Research (CDER).

https://www.cdc.gov/drugresistance/cdc_role.html

In vitro activity of new antibiotics for MDR gram-negative organisms

	ESBL-E	KPC-CRE	OXA-CRE	MBL-CRE	MDR Psa	*CR-Ab*	*Stenotrophomonas*
Ceftolozane/tazobactam	+	-	-	-	+	-	-
Ceftazidime/avibactam	+	+	+	w/ aztreonam?	+	-	w/ aztreonam?
Meropenem/vaborbactam	+	+	-	-	-	-	-
Imipenem/relebactam	+	+	-	-	+	-	-
Plazomicin	+	+	+	+/-*	+/-	-	-
Cefiderocol	+	+	+	+	+	+	+

*most NDM-producers also carry 16s rRNA methyltransferases

Summary

- MDRO are an ongoing and growing threat to hospitalized patients
- Outcomes of patients with MDRO infections likely worse vs. susceptible organisms
- Carbapenem-resistant Enterobacteriaceae especially worrisome
  - Limited treatment options
  - Poor outcomes

Questions?

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