Antibiotic Resistance: Current Status and Long-term Outlook

American Council of Life Insurers (ACLI)

Medical Section Annual Program

24 February 2020

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Disclosures

I have received:

- consultant fees from Ferring Pharmaceuticals
- research support from Cepheid (molecular diagnostics company that markets—in part—tests to detect drug-resistant organisms)
- research support from the National Institutes of Allergy and Infectious Diseases
  - NIAID K23AI114845-01

Objectives

1. Discuss the current state of antibiotic resistance in the inpatient/institutionalized and outpatient populations in the United States, focusing on the related morbidity and mortality
2. Discuss how differences in international antibiotic resistance could impact insurance underwriting of foreign nationals, immigrants, and travelers in the United States.
3. Discuss the long-term sequelae and excess medical costs of those who have had invasive MRSA, macrolide-resistant pneumococcus, resistant Gram-negative, *Candida auris*, and *C. difficile* infections.
4. Discuss current antibiotic development/research along with the concept of antimicrobial stewardship and the related responsibilities that physicians and the lay public have.

Challenges

- Large-scale actuarial data from US re impact of antibiotic resistance is sparse
  - VA datasets (mostly male >17 yo)
  - CMS datasets (mostly age >65)
  - NIS/HCUP data (all-payer inpatient data from AHRQ)
- Attributable morbidity and mortality for MDROs is difficult
- Most economic and epidemiological analyses about MDROs are small, single-center studies

Example: Case 1

38 yo previously healthy male is hospitalized with respiratory failure after influenza A (2009 H1N1). His ICU stay is complicated by MRSA pneumonia requiring IV vancomycin on his 7th day of intubation. He is extubated day #15 and completes 14 days of IV antibiotics at subacute rehab. He is readmitted to ICU with fevers and dies of a pulmonary embolism day #28 after illness onset.

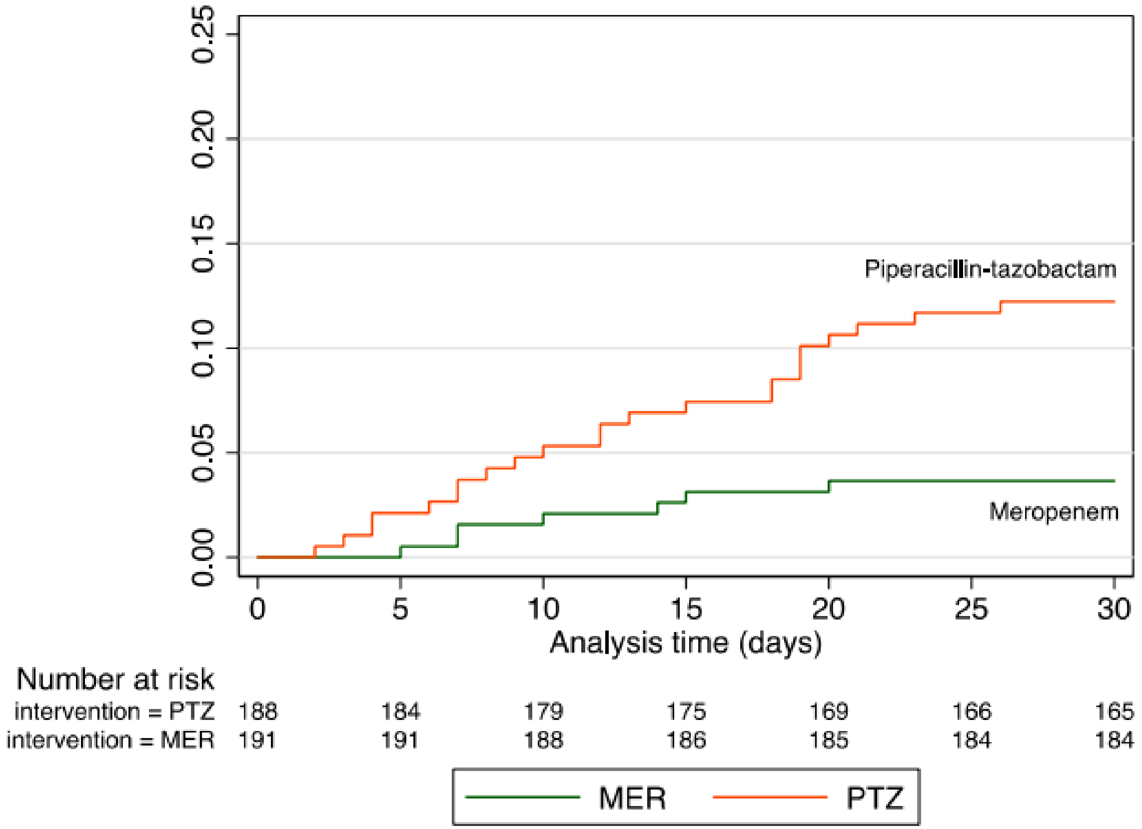
1. What causal role did MRSA play in his death?
2. How many patient-days on the ventilator should be attributed to MRSA vs influenza?
3. How much of either hospitalization should be attributed to failure to vaccinate this patient against influenza?

Example: Case 2

84 yo female with chronic obstructive pulmonary disease on 2L home oxygen, hypertension, chronic renal insufficiency, history of heavy smoking (quit 2 years ago) admitted with large L MCA distribution stroke with dense R paresis. While on neurology floor she develops aspiration pneumonia with ESBL (*Klebsiella* resistant to pip-tazo) requiring initiation of colistin and transfer to the ICU hospital day 9. Antibiotics are changed to meropenem on hospital day 12. She dies in the ICU of sepsis and acute renal failure on hospital day 13.

1. What goes on the death certificate as the proximate cause of death?
2. If the patient died of pneumonia, was the resistance to initial therapy causal, or would this not have mattered much?

ESBL bacteremia: The MERINO Trial



Harris PNA, et al. *JAMA*. 2018 Sep 11;320(10):984-994

10 Leading Causes of Death in US, 2017

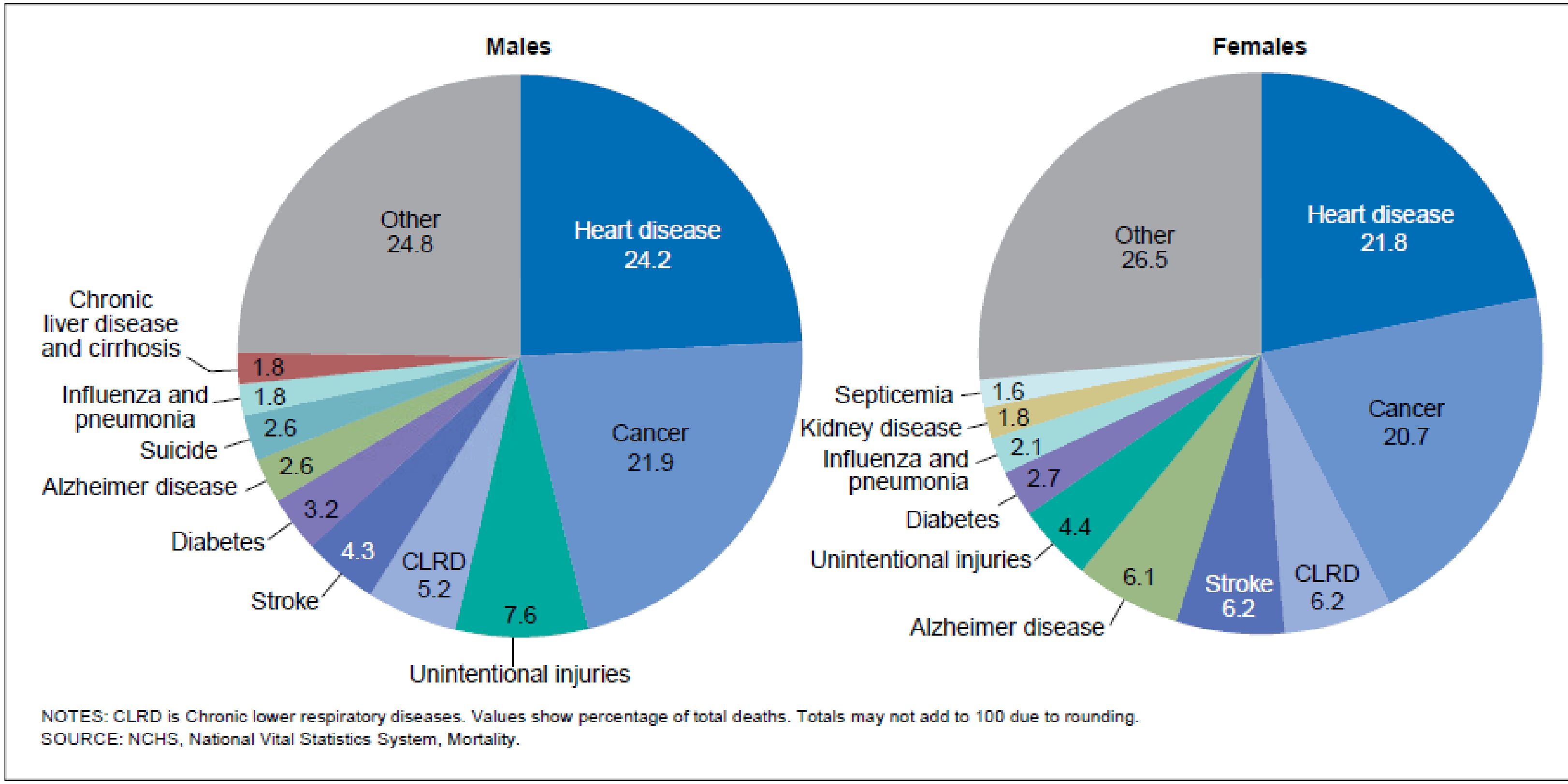


Figure 1. Percent distribution of the 10 leading causes of death, by sex: United States, 2017

Heron M, CDC, National Vital Statistics Reports, Vol. 68, No. 6, June 24, 2019

ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES

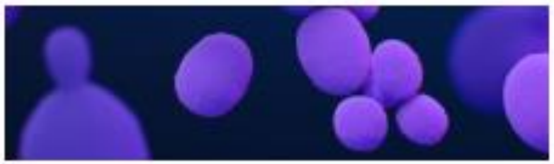
2019

CDC
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Urgent Threats

These germs are public health threats that require urgent and aggressive action:

CARBAPENEM-RESISTANT
ACINETOBACTER



CANDIDA AURIS

CLOSTRIDIOIDES DIFFICILE

CARBAPENEM-RESISTANT
ENTEROBACTERIACEAE

DRUG-RESISTANT
NEISSERIA GONORRHOEAE

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Serious Threats

These germs are public health threats that require prompt and sustained action:

DRUG-RESISTANT
CAMPYLOBACTER

DRUG-RESISTANT
CANDIDA

ESBL-PRODUCING
ENTEROBACTERIACEAE

VANCOMYCIN-RESISTANT
ENTEROCOCCI

MULTIDRUG-RESISTANT
PSEUDOMONAS AERUGINOSA

DRUG-RESISTANT
NONTYPHOIDAL *SALMONELLA*

DRUG-RESISTANT
***SALMONELLA* SEROTYPE TYPHI**

DRUG-RESISTANT
SHIGELLA

METHICILLIN-RESISTANT
STAPHYLOCOCCUS AUREUS

DRUG-RESISTANT
STREPTOCOCCUS PNEUMONIAE

DRUG-RESISTANT
TUBERCULOSIS

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Resistant germ	Threat Estimate, 2019 report	What CDC Counted, 2019 report	What CDC Did Not Count, 2019 report	Threat Estimate, 2013 report	New 2013 Threat Estimate, 2019 report	Can Data be Compared? 2013 vs 2019 reports	Year-to-Year Comparison Provided, 2019 report	Resistant Infection Increase/ Decrease, 2019 report
Drug-resistant *Neisseria gonorrhoeae*	550,000 infections	All infections	N/A	246,000 infections & <5 deaths	N/A	Yes	Resistance over time from 2000-2017	⬆ Increase
Candida auris	323 clinical cases	Clinical cases	Colonization/ screening cases	N/A—was not listed in 2013 report	N/A	N/A	Cases over time from 2015-2018	⬆ Increase
ESBL-producing Enterobacteriaceae	197,400 cases & 9,100 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	26,000 healthcare associated infections & 1,700 deaths	131,900 cases & 6,300 deaths (2012 estimates)	No	Cases over time from 2012-2017	⬆ Increase
Erythromycin-resistant group A *Streptococcus*	5,400 infections & 450 deaths	Invasive infections	Non-invasive infections including common upper-respiratory infections like strep throat	1,300 infections & 160 deaths	N/A	Yes	Invasive infection rates over time from 2010-2017	⬆ Increase
Carbapenem-resistant Enterobacteriaceae	13,100 cases & 1,100 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	9,300 healthcare associated infections & 600 deaths	11,800 cases & 1,000 deaths (2012 estimates)	No	Cases over time from 2012-2017	Stable
Carbapenem-resistant *Acinetobacter* (formerly multidrug-resistant *Acinetobacter*)	8,500 cases & 700 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	N/A—was listed as multidrug-resistant in 2013 report	11,700 cases & 1,000 deaths (2012 estimates)	No	Cases over time from 2012-2017	⬇ Decrease
Drug-resistant *Candida* (formerly fluconazole-resistant *Candida*)	34,800 cases & 1,700 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	N/A—was listed as fluconazole-resistant Candida in 2013 report	44,800 cases & 2,200 deaths (2012 estimates)	No	Cases over time from 2012-2017	⬇ Decrease
Vancomycin-resistant *Enterococcus*	54,500 cases & 5,400 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	20,000 healthcare associated infections & 1,300 deaths	84,800 cases & 8,500 deaths (2012 estimates)	No	Cases over time from 2012-2017	⬇ Decrease

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

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Multidrug-resistant *Pseudomonas aeruginosa*	32,600 cases & 2,700 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	6,700 healthcare associated infections & 440 deaths	46,000 cases & 3,900 deaths (2012 estimates)	No	Cases over time from 2012-2017	⬇ Decrease
Methicillin-resistant *Staphylococcus aureus*	323,700 cases & 10,600 deaths	Incident hospitalized positive clinical cultures, including hospital- & community-onset	Non-hospitalized cases	80,000 healthcare associated infections & 11,000 deaths	401,000 cases & 13,600 deaths (2012 estimates)	No	Cases over time from 2012-2017	⬇ Decrease
Drug-resistant Tuberculosis	847 cases & 62 deaths	Cases	N/A	1,042 cases & 50 deaths	N/A	Yes	Cases over time from 2012-2017	Stable
Clostridioides difficile	223,900 estimated cases in hospitalized patients & 12,800 deaths	Infections requiring hospitalizations or in already hospitalized patients	Non-hospitalized infections	250,000 infections & 14,000 deaths	N/A	No	Cases over time from 2012-2017	⬇ Decrease*
Drug-resistant *Campylobacter*	448,400 infections & 70 deaths	All infections	N/A	310,000 infections & 28 deaths	N/A	No	Percentage of resistance over time from 1997-2017	N/A
Drug-resistant non-typhoidal *Salmonella*	212,500 infections & 70 deaths	All infections	N/A	100,000 infections & 3 8 deaths	N/A	Yes	Percentage of resistance over time from 2009-2017	⬆ Increase
Drug-resistant *Salmonella* Serotype Typhi	4,100 infections & <5 deaths	All infections	N/A	3,800 infections & <5 deaths	N/A	No	Percentage of resistance over time from 1999-2017	N/A
Drug-resistant *Shigella*	77,000 infections & <5 deaths	All infections	N/A	27,000 infections & <5 deaths	N/A	No	Percentage of resistance over time from 2009-2017	N/A
Drug-resistant *Streptococcus pneumoniae*	900,000 infections & 3,600 deaths	All infections	N/A	1,200,000 infections & 7,000 deaths	N/A	No	Invasive infection rates over time from 2005-2017	N/A
Clindamycin-resistant group B *Streptococcus*	13,000 infections & 720 deaths	Invasive infections	Non-invasive infections & asymptomatic intrapartum colonization requiring prophylaxis	7,600 infections & 440 deaths	N/A	No	Invasive infection rates over time from 2012-2016	N/A

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Does antibiotic resistance independently impact life expectancy?

MRSA: the longest-running drug resistance paradigm

- ~50% of all *Staphylococcus aureus* is MRSA
- Common skin commensal (nares, axillae, groin, throat, GI tract)
- Spectrum of disease:
  - Self-limited skin infections
  - 100% fatal endocarditis
- Appeared in US hospitals 1960s
- Appeared in US communities 1980s (IVDU)
- Treatable, but
  - More relapses
  - Drugs have more side effects, fewer oral options
  - Serious infections have lower cure rates

Prevalence of MRSA colonization: a recent snapshot

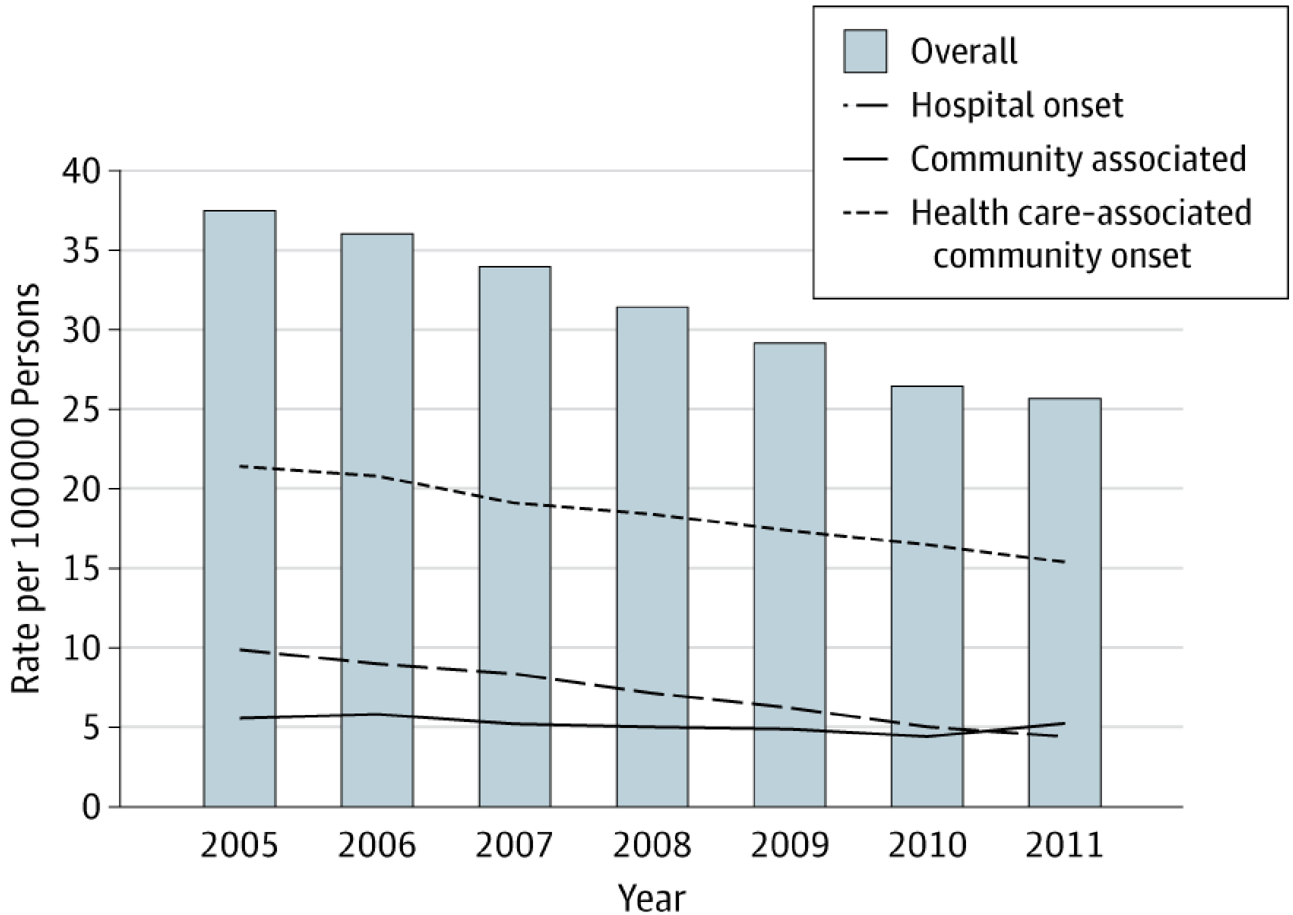
Population	% colonized	reference
US swine veterinarians	9.5%	*BMC Infect Dis*. 2017 Oct 19;17(1):690.
Military trainees with SSTI	25.7%	*Infection.* 2019 Oct;47(5):729-737.
Healthy US adults	4.8%	*Medicine (Baltimore).* 2019 May;98(18):e15499
Refugees in Switzerland	15.7%	*PLoS One.* 2017 Jan 13;12(1):e0170251
ER patients without SSTI	18.4%	*J Clin Microbiol.* 2015 Nov;53(11):3478-84
Healthy US servicemembers	4.0%	*BMC Infect Dis*. 2013 Jul 16;13:325.
ER healthcare professionals	6.6%	*Infect Control Hosp Epidemiol.* 2010 Jun;31(6):574-80.

Invasive MRSA infections in the US

- 2005 estimate from 9 US communities (ABCs/EIP)
- Only includes diseases for which cultures were performed
  - 58.4% health-care associated, community-onset
  - 26.6% health-care associated, hospital-onset
  - 13.7% community-associated

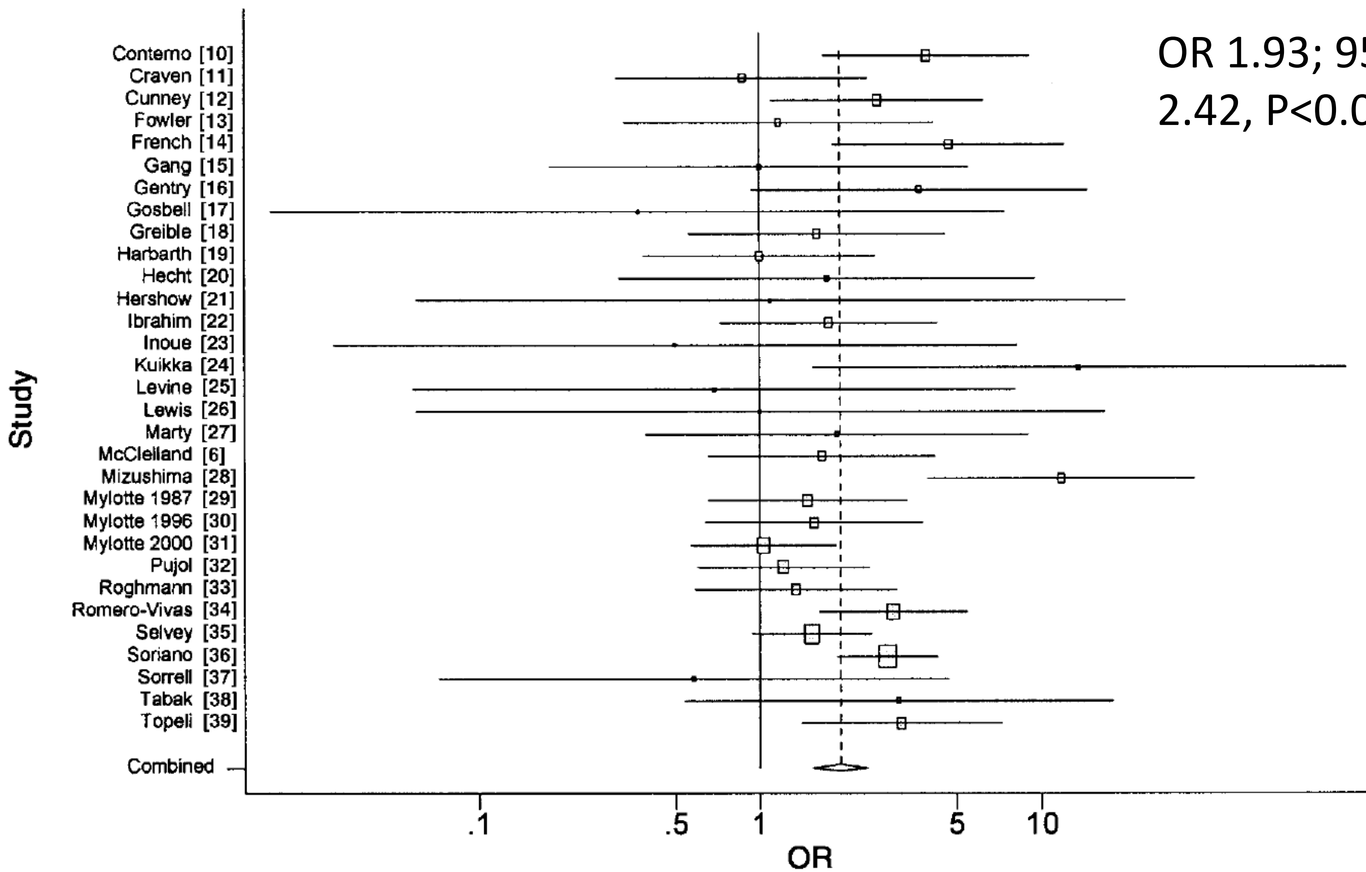
Klevens RM et al. *JAMA*. 2007 Oct 17;298(15):1763-71

Updated burden of invasive MRSA infections, US in 2011



Dantes R et al. *JAMA Intern Med*. 2013 Nov 25;173(21):1970-8

Meta analysis: MRSA bacteremia associated with higher in-hospital mortality compared with MSSA

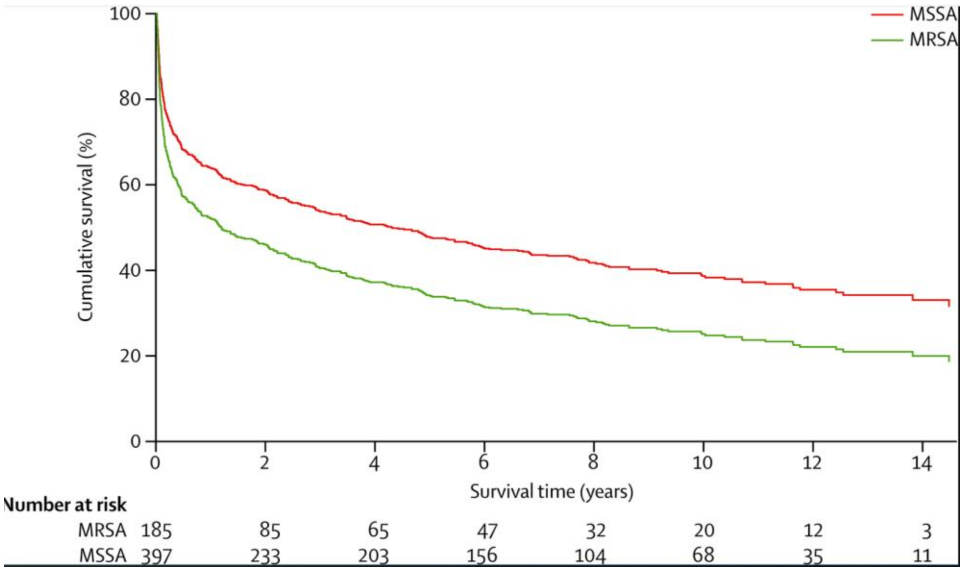


OR 1.93; 95% CI 1.54-2.42, P<0.001)

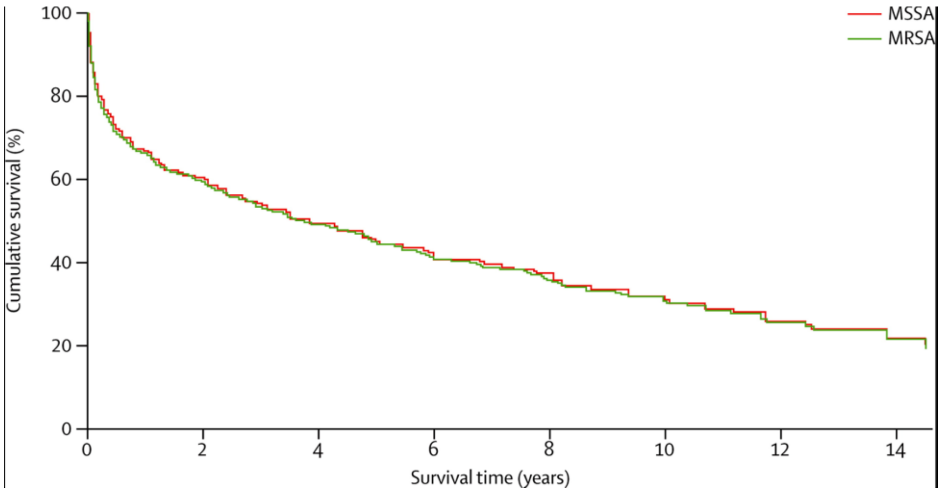
Cosgrove SE et al. *Clin Infect Dis*. 2003 Jan 1;36(1):53-9.

Long-term outcomes after MRSA (and MSSA) bacteremia

1997-2007 cohort in Perth, Australia



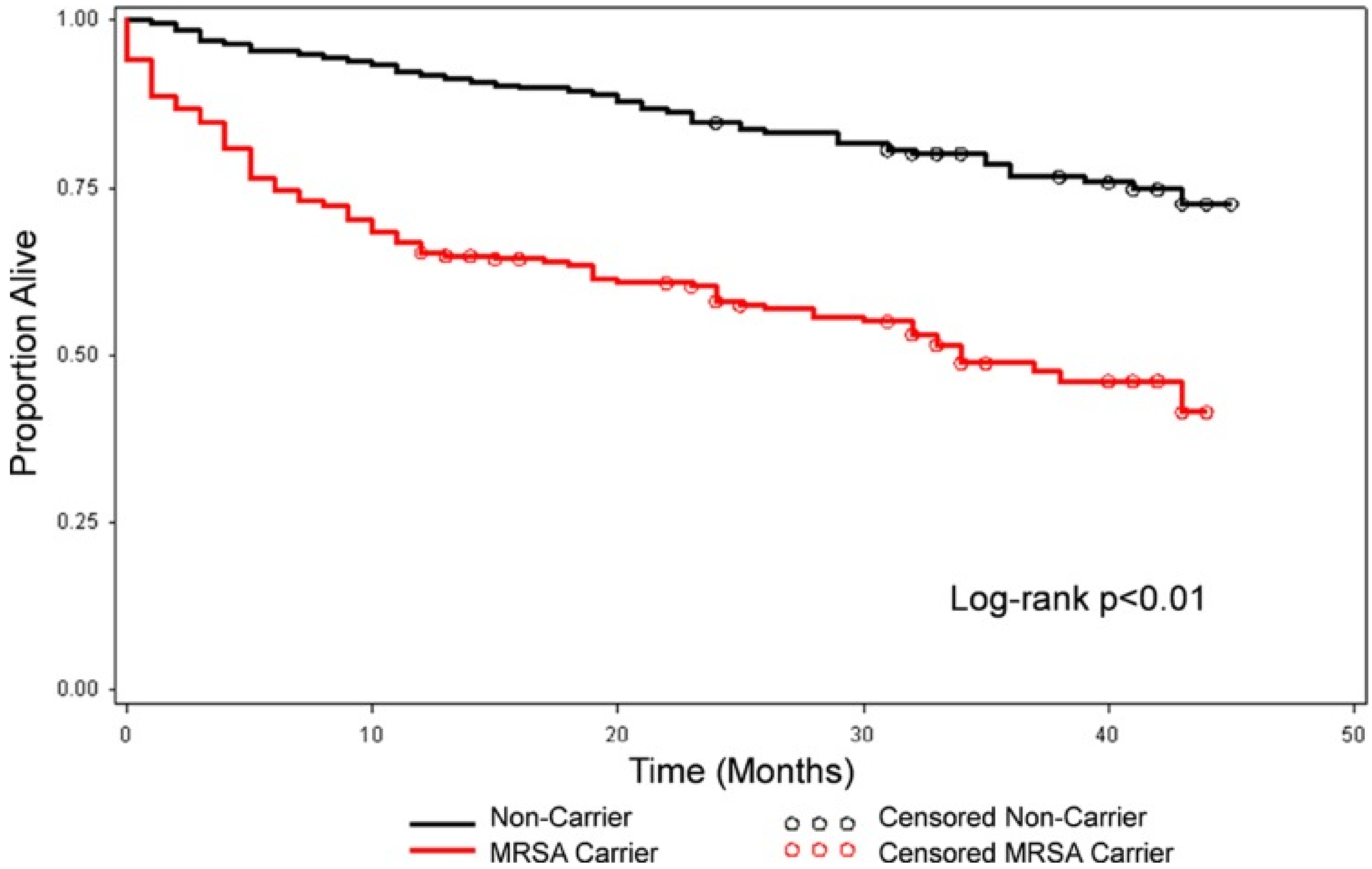
Crude / unadjusted survival rate



Adjusted for confounders

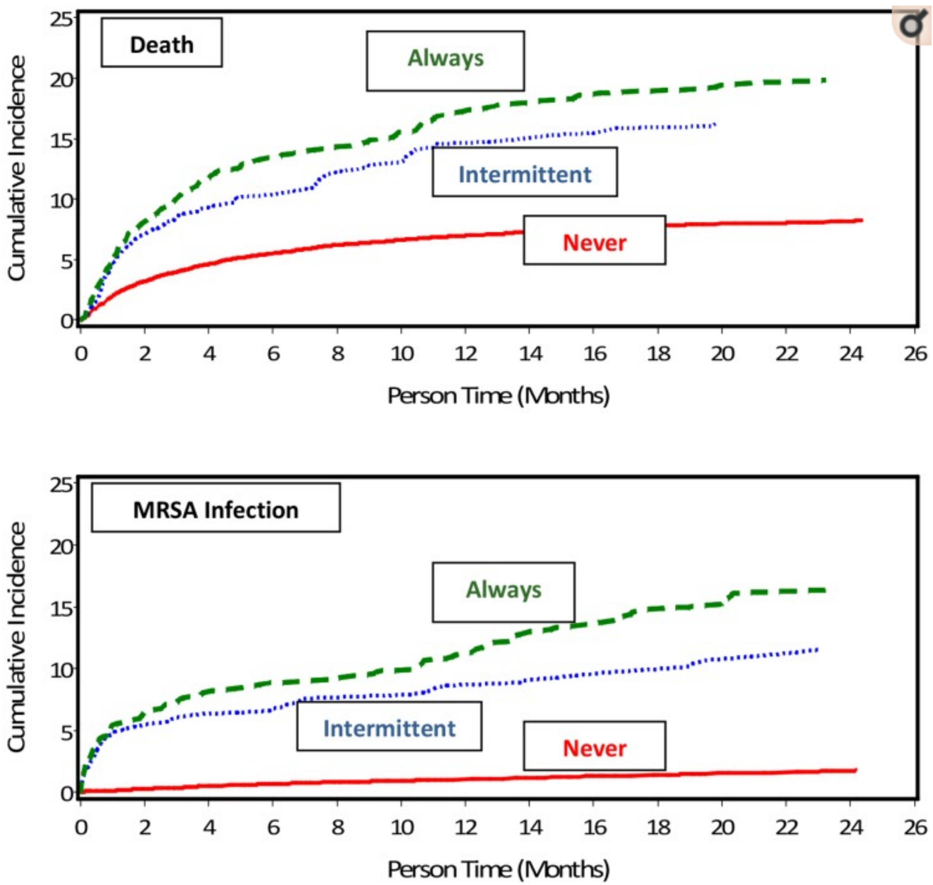
Yaw LK et al. *Lancet Infect Dis*. 2014 Oct;14(10):967-75.

Long-term risk for readmission, MRSA infection and death among veterans discharged from hospital settings



Quezada JNM et al. *Antimicrob Agents Chemother*. 2013 Mar;57(3):1169-72

Long-term risk for MRSA infection and death among 18,038 MRSA-colonized veterans 2008-2010



91.1% never colonized
4.4% intermittently colonized
4.6% always colonized

Always-colonized:

Death HR 2.58 (95% CI 2.18, 3.05)

MRSA infection HR 10.89 (95% CI 8.6, 13.7)

Gupta K, Martinello RA et al. *PLoS One*. 2013;8(1):e53674

MRSA: Morbidity Risk 2017

- 323,700 hospitalizations
- 10,600 deaths
- $1.7 billion in healthcare costs
- IVDU is a consistent risk factor for community-acquired MRSA infection

https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

EXTENDED-SPECTRUM BETA-LACTAMASE (ESBL) PRODUCING **ENTEROBACTERIACEAE**

THREAT LEVEL **SERIOUS**

197,400 Estimated cases in hospitalized patients in 2017

9,100 Estimated deaths in 2017

$1.2B Estimated attributable healthcare costs in 2017

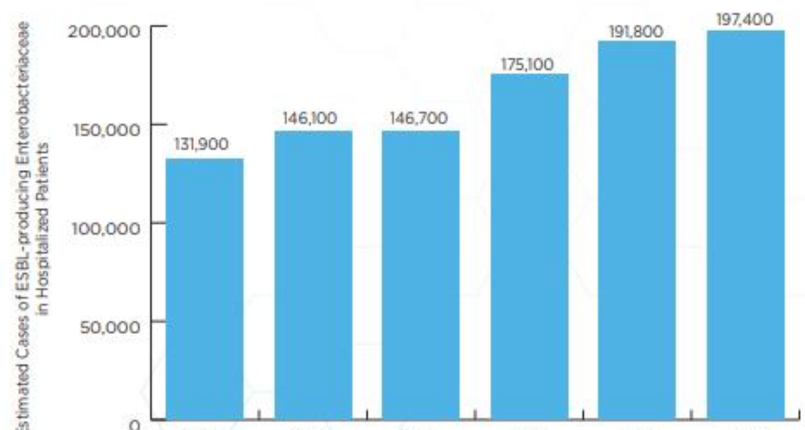
ESBL-producing Enterobacteriaceae (a family of different types of bacteria) are a concern in healthcare settings and the community. They can spread rapidly and cause or complicate infections in healthy people.

WHAT YOU NEED TO KNOW

- ESBLs are enzymes that break down commonly used antibiotics, such as penicillins and cephalosporins, making them ineffective.
- ESBL-producing Enterobacteriaceae often cause infections in otherwise healthy people. About one-quarter of patients with these infections had no known underlying health conditions.
- Antibiotic options to treat ESBL-producing Enterobacteriaceae infections are limited. Healthcare providers often have to use intravenous (IV) carbapenem antibiotics to treat infections that used to be treated with oral antibiotics.

CASES OVER TIME

CDC and partners are working to assess and address why cases of ESBL-producing Enterobacteriaceae have increased since 2012.



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https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Why is ESBL Enterobacteriaceae worse than all the others?

- Unlike MDR-resistant *Pseudomonas*, MDR-*Acinetobacter*, and carbapenem-resistant Enterobacteriaceae:
  - These have moved beyond hospital confines in US
  - Common causes of UTIs (10-30%) in non-hospitalized patients
  - Co-resistance with other antibiotic classes is common
- Require treating relatively minor infections with parenteral antibiotics

Case: ESBL UTI

54 yo post-menopausal female with history of recurrent UTIs referred to ID clinic with this culture report:

>100,000 cfu/ml ESBL *Klebsiella pneumoniae*

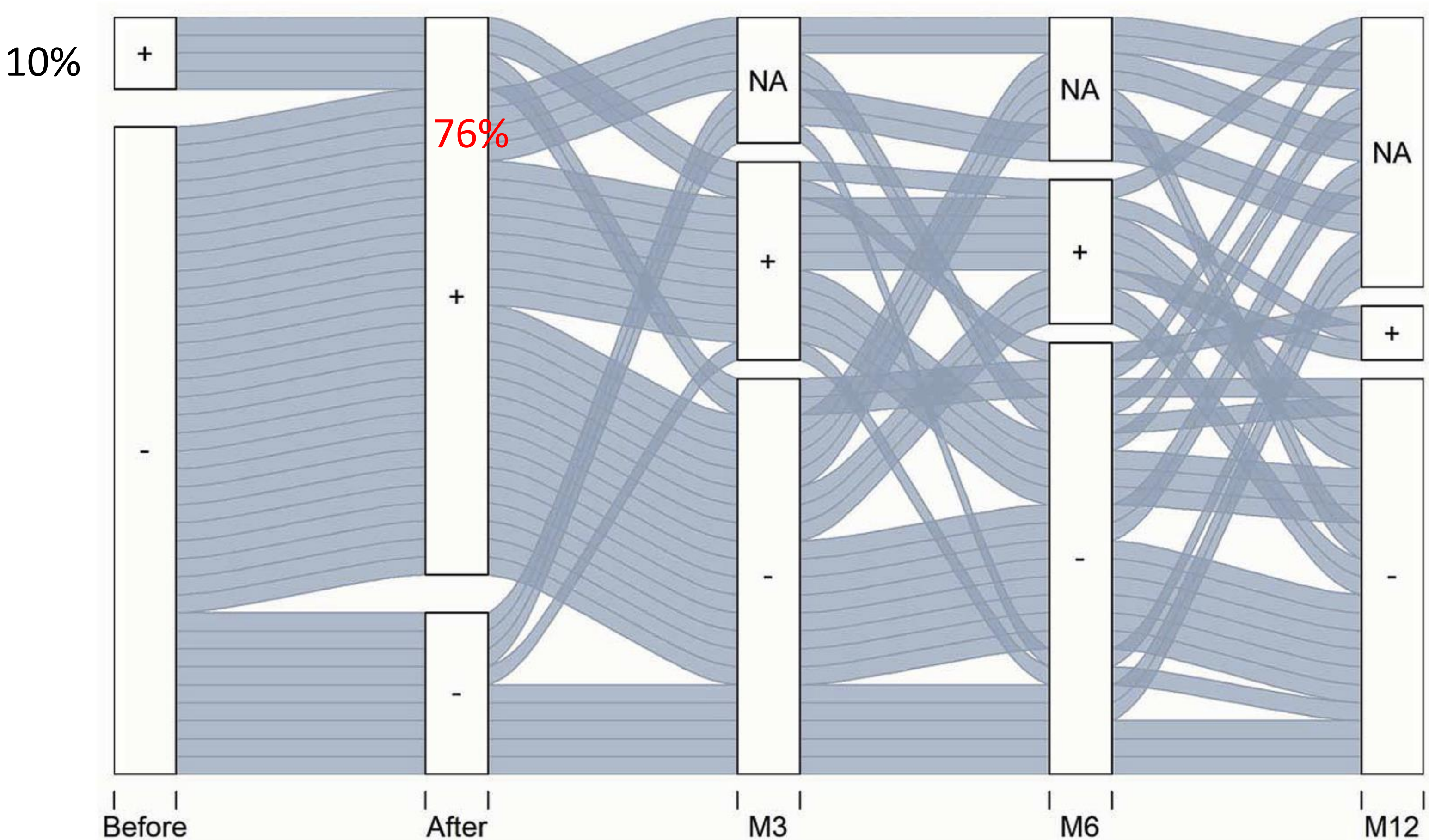
Amoxicillin-clavulanic acid	R
Cefepime	R
Ciprofloxacin	R
Nitrofurantoin	R
TMP-SMX	R
Pip-tazo	R
Meropenem	S
Gentamicin	S
Doxycycline	R

Patient recovers uneventfully after 2 weeks IV ertapenem via PICC.

Case: ESBL UTI

- Where did she get this from?
  - Prior antibiotic exposures?
  - The food supply?
  - Travel overseas?
  - Secondary contact with healthcare?
- How can this be prevented?

ESBL Enterobacteriaceae before and after travel to India in 40 Swiss volunteers



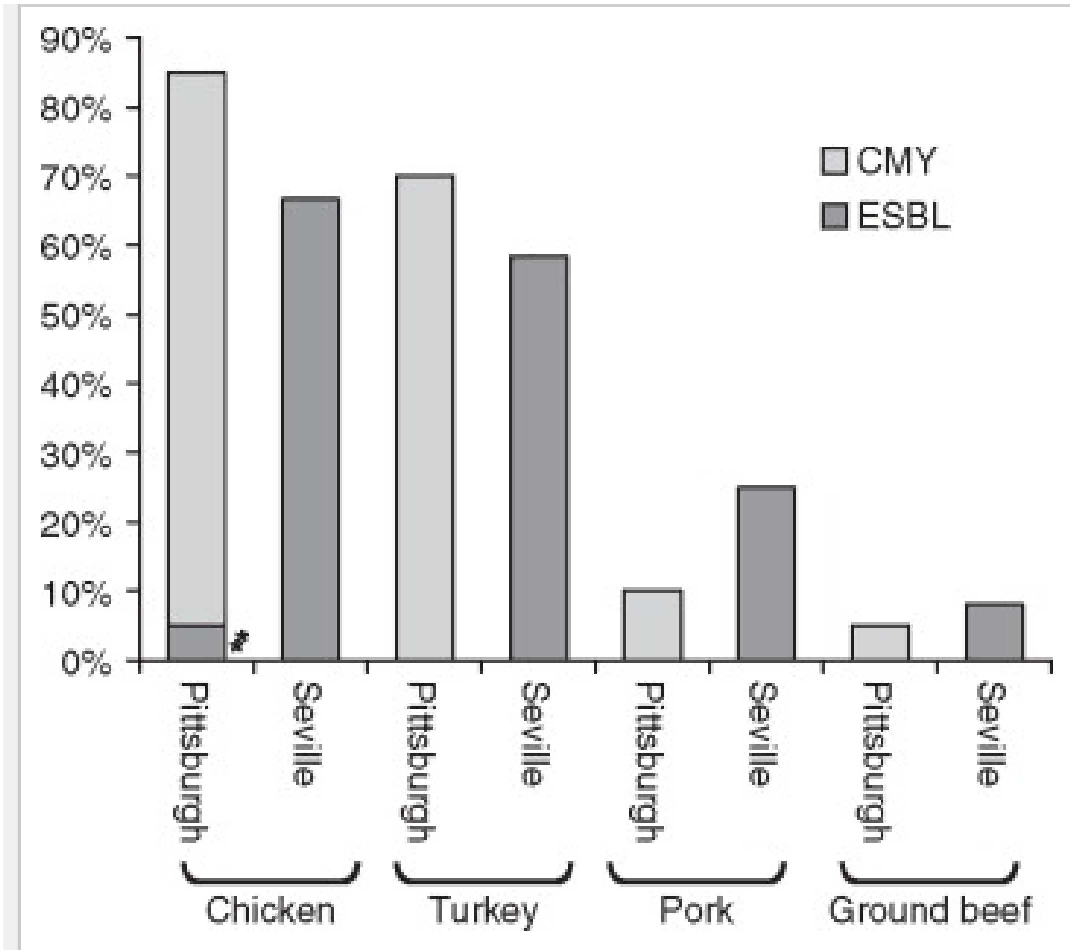
Pires J, Kraemer JG et al. *Travel Med Infect Dis*. 2019 Jan - Feb;27:72-80.

Foreign travel as risk factor for ESBL carriage

- 273 Norwegian patients with gastroenteritis[1]
  - 10.3% without
  - 56.3% ($p<0.001$) vs with history of travel to Asia255 healthy German volunteers before/after travel
- 255 healthy German volunteers before/after travel[2]
  - 14/205 (6.8%) ESBL-colonized pre-travel
  - 58/191 (30.4%) colonized upon return
  - Travel to India = highest acquisition rate (11/15, 73%)
  - 3/35 (8.6%) persistence at 6 months

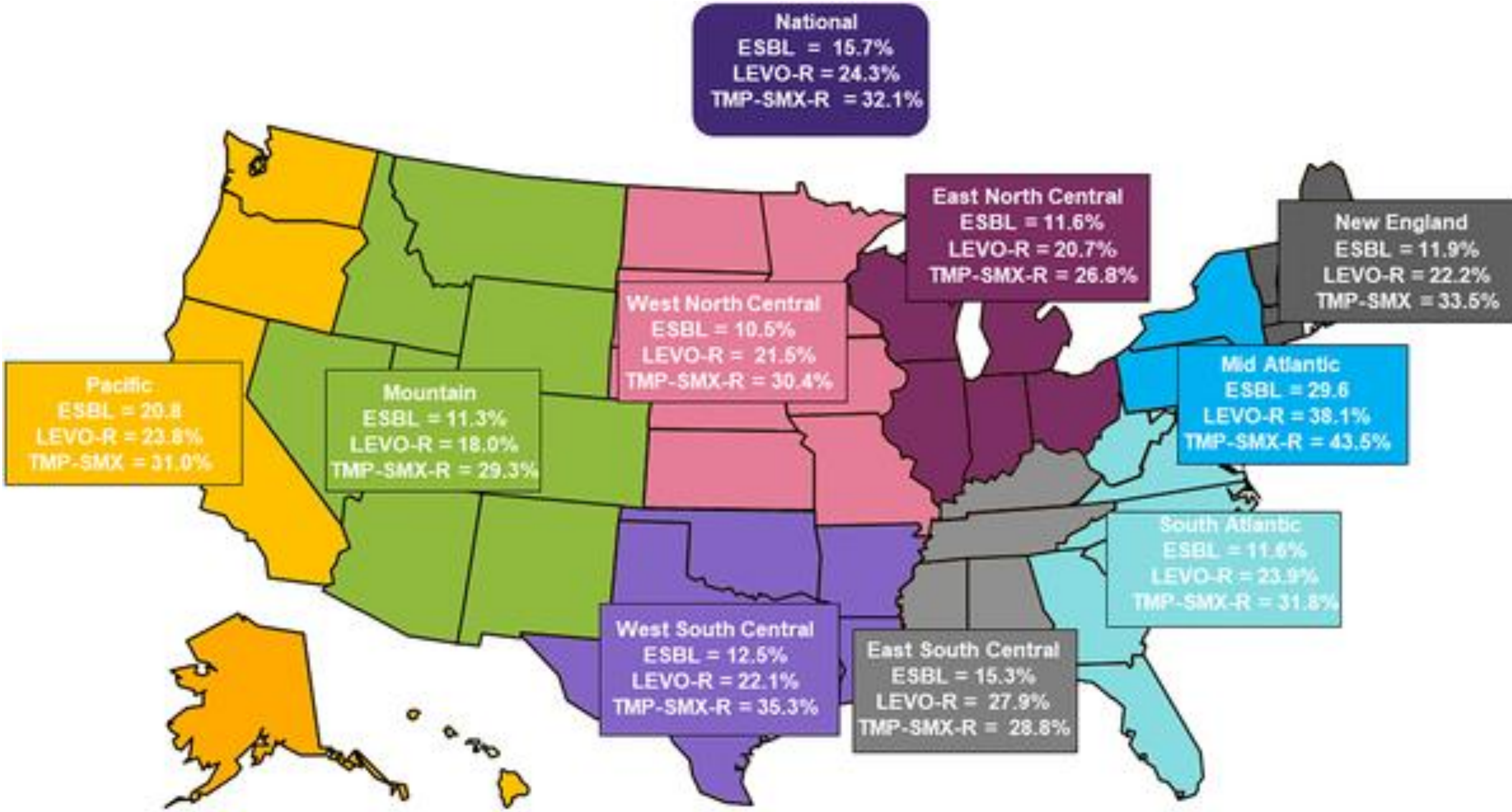
1. Jørgensen SB et al. *Scand J Infect Dis*. 2014 Jun;46(6):462-5.
2. Lübbert C, Straube L et al. *Int J Med Microbiol*. 2015 Jan;305(1):148-56

ESBL *E. coli* in retail meats



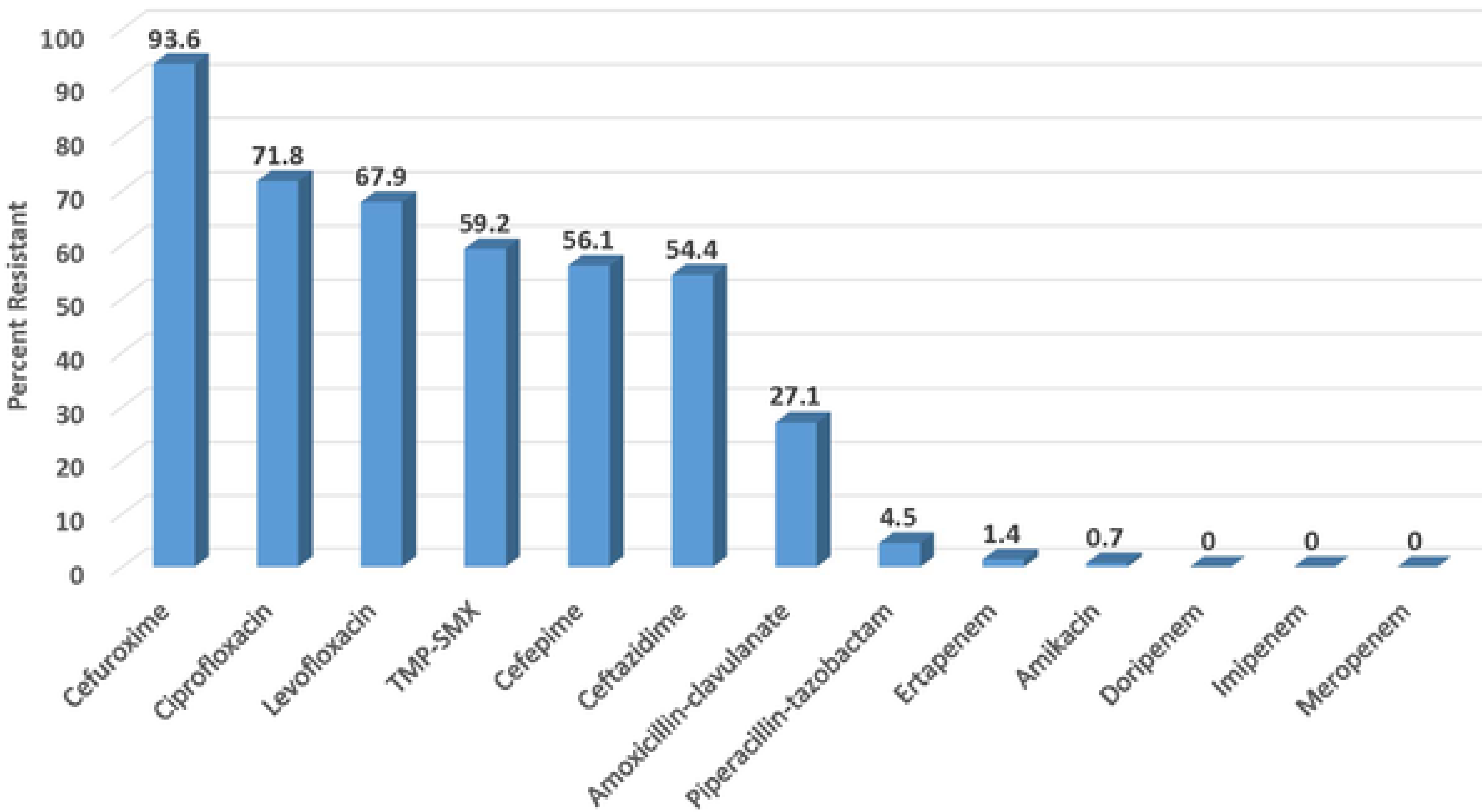
Doi Y, et al. *Clin Microbiol Infect*. 2010 Jan;16(1):33-8.

National and regional prevalence of ESBL phenotypes, levofloxacin- and trimethoprim-sulfamethoxazole-resistant phenotypes among 1831 isolates of *E. coli* from UTIs in the USA in 2017.



Critchley IA, Cotroneo N, Pucci MJ, Mendes R (2019) The burden of antimicrobial resistance among urinary tract isolates of Escherichia coli in the United States in 2017. PLOS ONE 14(12): e0220265. https://doi.org/10.1371/journal.pone.0220265
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0220265

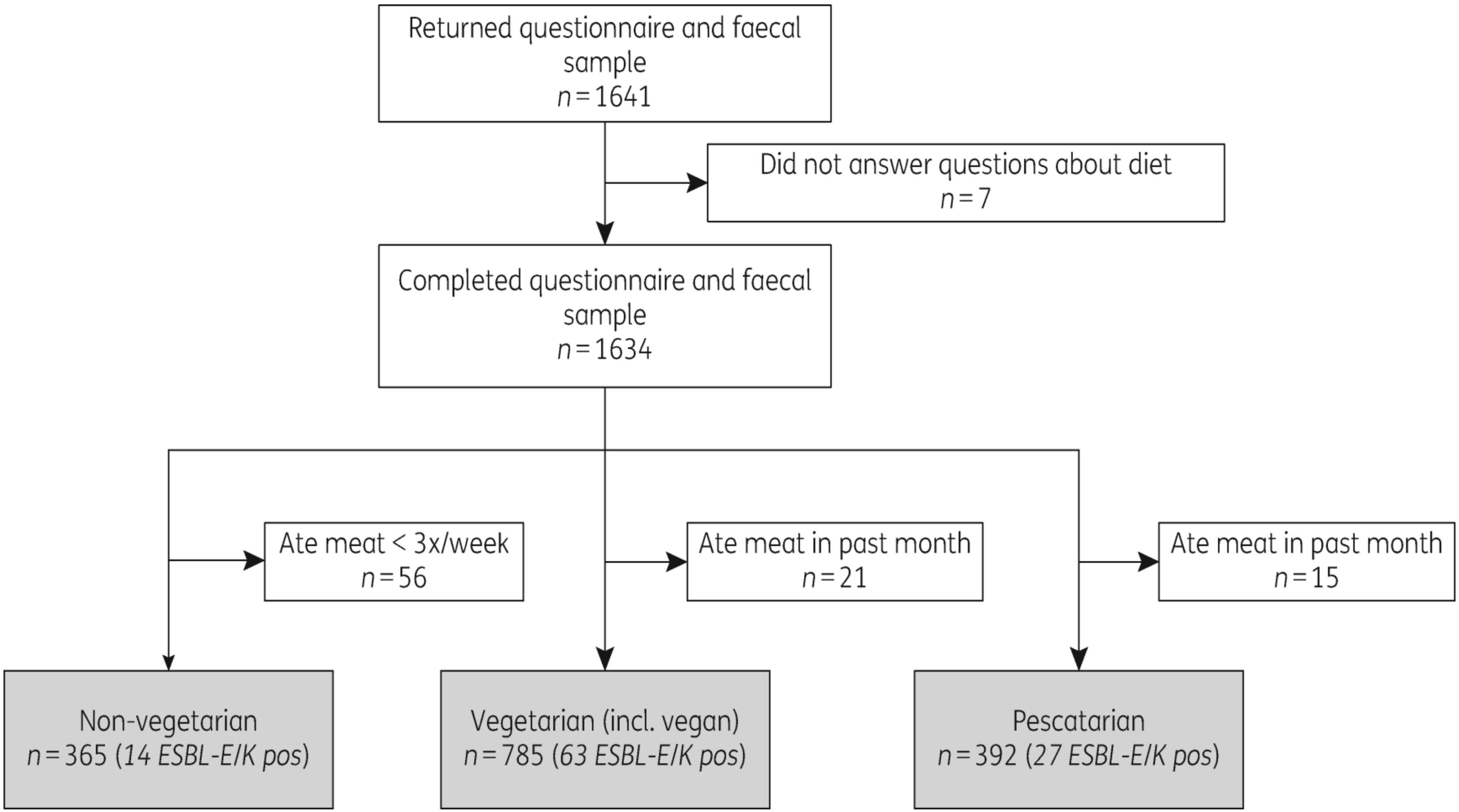
Antibiotic resistance among 287 ESBL phenotypes of UTI isolates of *E. coli* collected in the USA in 2017.



Critchley IA, Cotroneo N, Pucci MJ, Mendes R (2019) The burden of antimicrobial resistance among urinary tract isolates of *Escherichia coli* in the United States in 2017. PLOS ONE 14(12): e0220265. https://doi.org/10.1371/journal.pone.0220265
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0220265

PLOS | ONE

Vegetarianism associated with ESBL colonization



3.8% | 8% | 6.9%

Meijs AP, Gijsbers EF, et al. *J Antimicrob Chemother.* 2020 Mar 1;75(3):550-558.

Have you washed those hands?

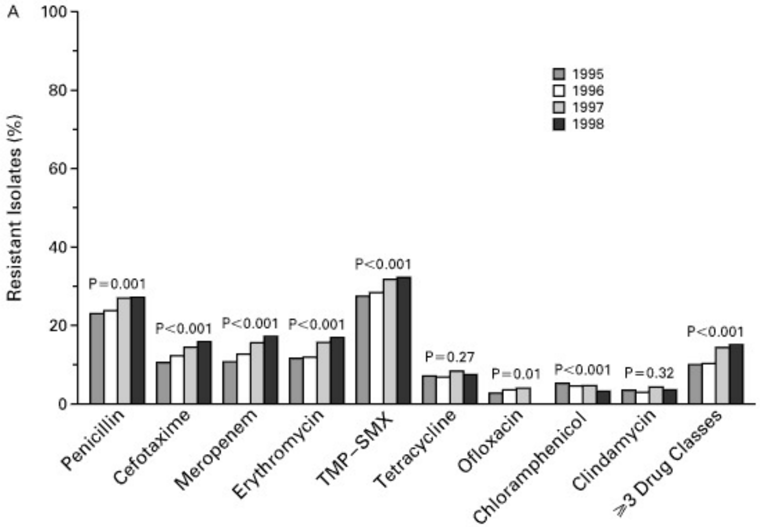
Determinant		Non-vegetarians (n=365)		Vegetarians (n=785)		Pescaterians (n=392)		Multivariable OR (95% CI)
		ESBL-	ESBL+	ESBL negative	ESBL+	ESBL negative	ESBL+	
Hand washing before food preparation	Always	253	9	497	43	290	20	ref
	Some-times	83	3	179	13	57	5	0.98 (0.58-1.64)
	Never	13 (3.7)	2 (14.3)	46 (6.4)	7 (11.1)	18 (4.9)	2 (7.4)	2.47 (1.22-5.01)
Travel in 6 mos	None	231	7	481	29	217	8	ref
	Africa/ Asia/ Latin Am.	42 (12)	4 (29)	65 (9)	16 (25)	49 (13)	11 (40)	4.63 (2.78-7.70)
Visited hospital in last year		262 (75)	11 (79)	495 (69)	39 (63)	264 (72)	16 (59)	

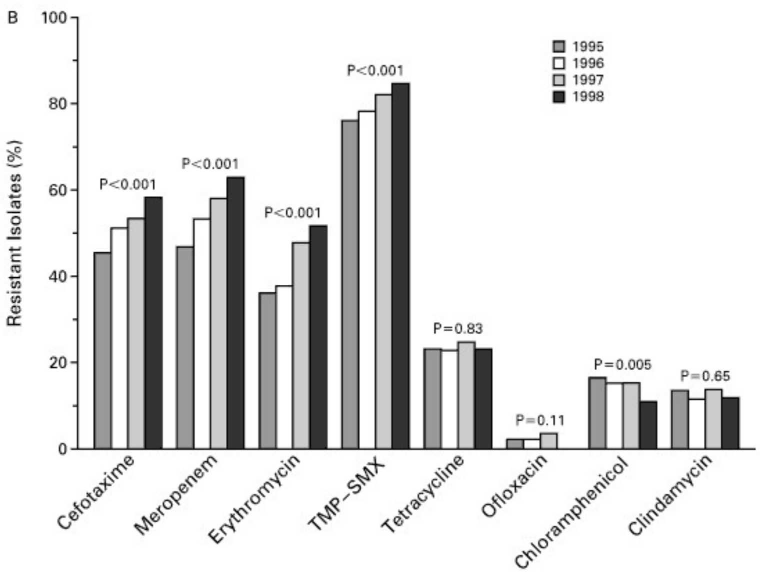
Meijs AP, Gijsbers EF, et al. *J Antimicrob Chemother.* 2020 Mar 1;75(3):550-558.

ESBL Enterobacteriaceae

- Significant threat to community-dwellers in the US
- Gut colonization results from several plausible sources
- No vaccines on the horizon
- May render common infections (UTIs) and common surgical conditions in community dwellers (appendicitis, cholangitis, elective colon surgery) difficult to treat
- Increasing use of carbapenems to treat these increases pressure for the evolution of CRE in hospitals and in the community

Multidrug resistant *Streptococcus pneumoniae*





Panel A: All invasive isolates 1995-1998

Panel B: All penicillin-resistant isolates 1995-1998

Data: ABCs

Whitney CG et al. *N Engl J Med*. 2000 Dec 28;343(26):1917-24.

Direct costs in patients hospitalized with pneumonia after non-response to macrolide antibiotics

Infection characteristics	All patients[a]	*S. pneumoniae* susceptible	*S. pneumoniae* non-susceptible	p-Value, susceptible vs non-susceptible
CAP ± bacteraemia				
Number of patients	122	35	87	
Hospital costs per patient[b]	12 678 (13 346)	9 014 (7 086)	14 153 (14 937)	0.011
CAP with bacteraemia				
Number of patients	63	25	38	
Hospital costs per patient[b]	13 378 (12 288)	8 537 (5 060)	16 563 (15 345)	0.004
CAP without bacteraemia				
Number of patients	59	10	49	
Hospital costs per patient[b]	11 931 (13 891)[c]	10 206 (10 918)	12 283 (14 493)	0.613

a Patients had received outpatient treatment with azithromycin (n = 88), clarithromycin (n = 28) or erythromycin (n = 6).

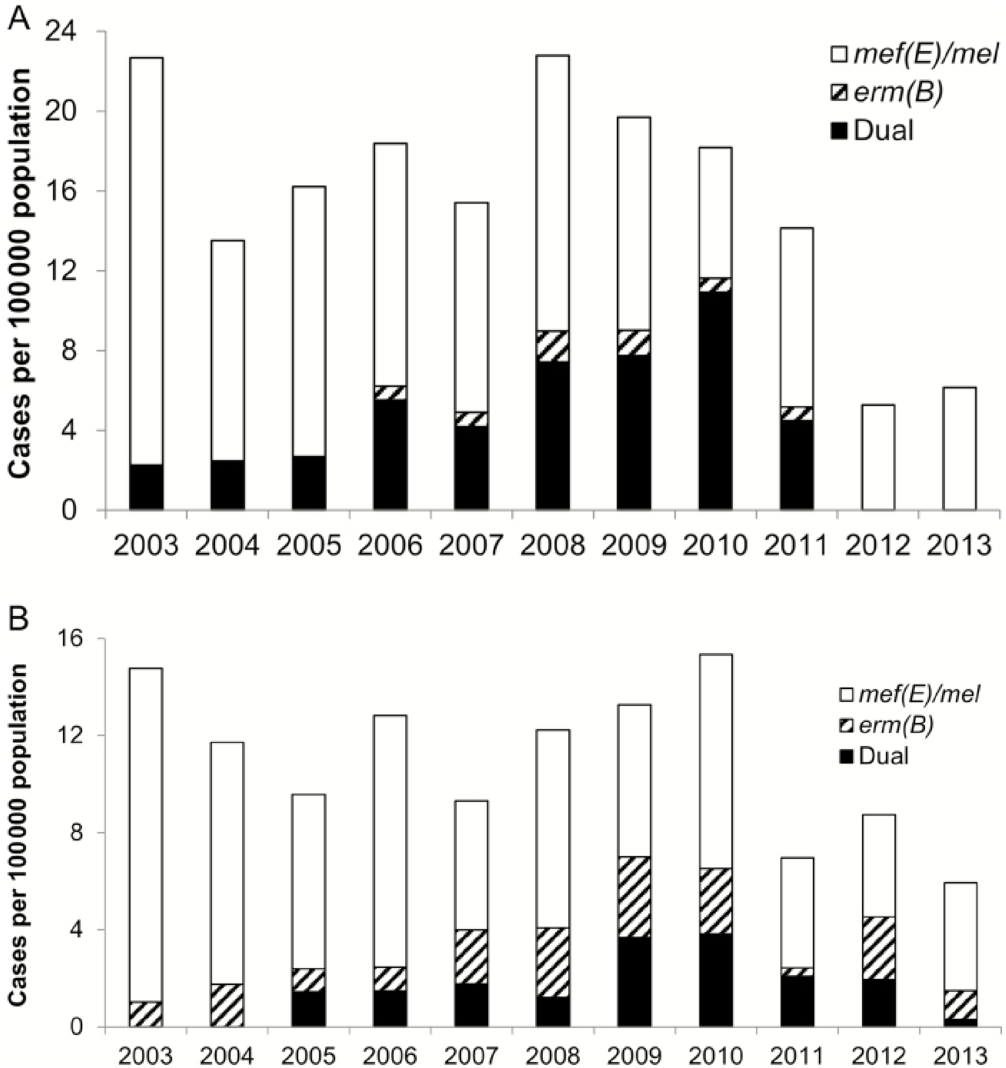
b Data are mean (SD).

c p = 0.553 vs patients with bacteraemia.

Hospital costs ($US, year 2004 values) for community-acquired pneumonia (CAP) with and without bacteraemia, associated with macrolide-susceptible or non-susceptible *Streptococcus pneumoniae* in patients who had received outpatient treatment with macrolides

Paladino JA et al. *Pharmacoeconomics*. 2007;25(8):677-83.

The incidence (2003–2013) in metropolitan Atlanta, Georgia, of macrolide-resistant invasive pneumococcal disease in individuals (A) aged <2 years and (B) aged ≥65 years



Schroeder MR, Chancey ST et al. *Clin Infect Dis.* 2017 Sep 15;65(6):990-998.

DRUG-RESISTANT *STREPTOCOCCUS PNEUMONIAE*

THREAT LEVEL **SERIOUS**

900,000 Estimated infections in 2014

3,600 Estimated deaths in 2014

Streptococcus pneumoniae **(pneumococcus) is a leading cause of bacterial pneumonia and meningitis in the United States. It also is a common cause of bloodstream infections, and ear and sinus infections.**

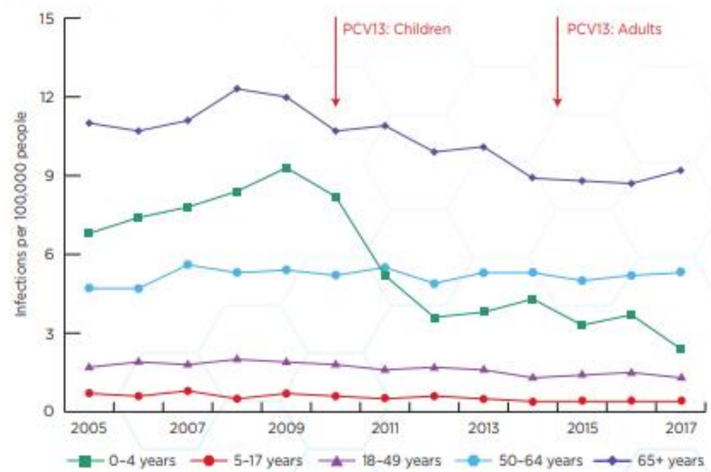
WHAT YOU NEED TO KNOW

- Overall, there are more than 2 million pneumococcal infections each year in the United States, resulting in more than 6,000 deaths and $4 billion in total costs. In more than 30% of infections, the bacteria are resistant to one or more clinically relevant antibiotics.
- Pneumococcal pneumonia leads to an estimated 150,000 hospitalizations for adults each year and accounts for $1.3 billion in direct medical costs (65% of direct costs for all adult pneumococcal disease treatment).
- Drug-resistant *S. pneumoniae* is one of the only germs listed in this report with an effective vaccine to prevent infections, called pneumococcal conjugate vaccine (PCV).

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

INFECTIONS OVER TIME BY AGE

Rates of antibiotic-resistant invasive pneumococcal infections have decreased across age groups in the United States from 2005 to 2017.



https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Burden of *C. difficile* infection in the US

CDC estimates for US based on lab and population-based estimates in 2011:[1]

- 453,000 new cases/year (95% CI 397,000-508,000)
- 83,000 first recurrences per year (95% CI 57,000-108,900)
- 29,300 deaths per year (95% CI 16,500-42,100)

Approximately same number as MRSA-related hospitalizations per year in US[2]

C. difficile infections have overtaken MRSA as most common healthcare-associated infection[3]

[1]Lessa FC et al. *N Engl J Med*. 2015 Feb 26; 372(9):825-34.

[2]Klein EY et al. *Am J Epidemiol*. 2013 Apr 1; 177(7):666-74.

[3]Miller BA et al. *Infect Control Hosp Epidemiol.* 2011 Apr;32(4):387-90.

Populations at exceptional CDI Risk

Population	setting	Incidence (%)	Ref
ulcerative colitis	US (NIS)	3.73	1
Crohn's disease	US (NIS)	1.09	1
solid organ transplant	US (NIS)	2.7	2
solid organ transplant	Quebec, CA	12.4	3
lung transplant	Pittsburgh, PA	17.1	4
liver transplant	Pittsburgh, PA	11.9	4
allogeneic BMT	US (NIS)	8.4	5

1. Nguyen *Am J Gastroenterol.* 2008 Jun;103(6):1443-50
2. Pant et al. *Transpl Infect Dis*. 2012 Oct;14(5):540-7
3. Boutros et al. *Transplantation*. 2012 May 27;93(10):1051-7
4. Hong Nguyen, UPMC, personal communication
5. Guddati AK et al. Int J Hematol 2014 Jun; 99(6):758-65.

C. difficile as drug resistance threat?

- Not technically (never resistant to 2 FDA-approved antibiotics)
- Incidence in hospitals is decreasing
- Incidence in the community (~50% cases) is flat
- In part an over-diagnosis problem
- New therapies have emerged for recurrent CDI
  - Extended vancomycin
  - Fecal microbiota transplantation
  - Monoclonal antibodies

DRUG-RESISTANT *CANDIDA AURIS*

THREAT LEVEL **URGENT**

323 Clinical cases in 2018

90% Isolates resistant to at least **one** antifungal

30% Isolates resistant to at least **two** antifungals

Candida auris (C. auris) **is an emerging multidrug-resistant yeast (a type of fungus). It can cause severe infections and spreads easily between hospitalized patients and nursing home residents.**

WHAT YOU NEED TO KNOW

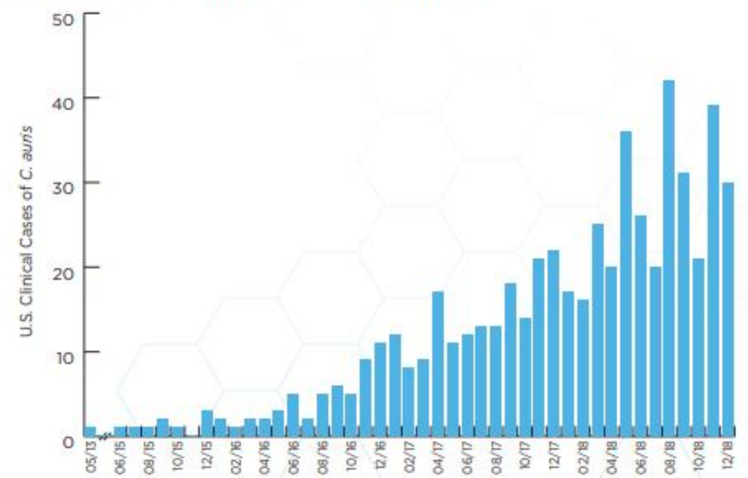
- *C. auris*, first identified in 2009 in Asia, has quickly become a cause of severe infections around the world.
- *C. auris* is a concerning drug-resistant fungus:
  - Often multidrug-resistant, with some strains (types) resistant to all three available classes of antifungals
  - Can cause outbreaks in healthcare facilities
  - Some common healthcare disinfectants are less effective at eliminating it
  - Can be carried on patients' skin without causing infection, allowing spread to others

Data represents U.S. cases only. Isolates are pure samples of a germ.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

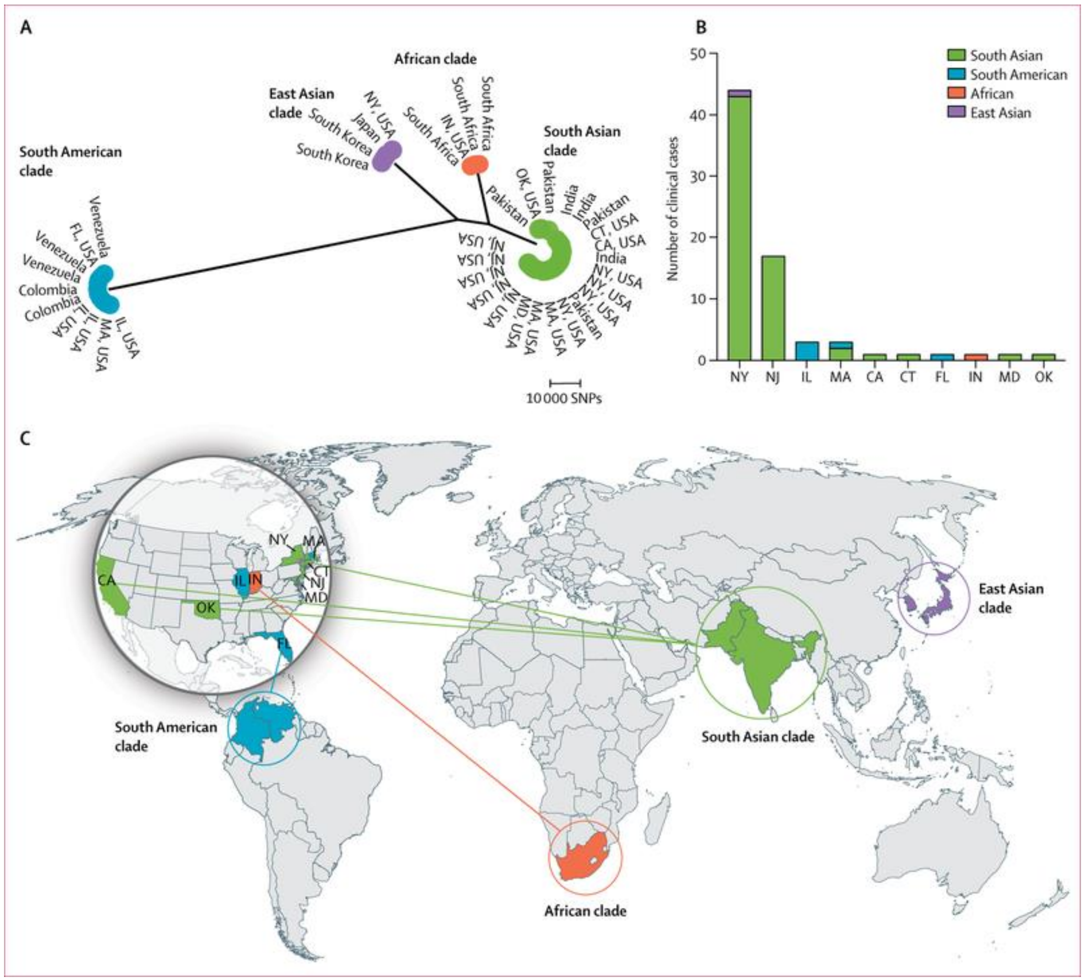
CASES OVER TIME

C. auris began spreading in the United States in 2015. Reported cases increased 318% in 2018 when compared to the average number of cases reported in 2015 to 2017.



https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Distribution of *Candida auris* clades within the USA



Chow NA, Gade L et al. *Lancet Infect Dis*. 2018 Dec;18(12):1377-1384

Why I don't lose (much) sleep over *Candida auris*

- 100% opportunistic pathogen (like almost all Candida)
- Threat in community-dwelling, healthy adults is near 0
- Significant threat (like all else on CDC resistance list) to:
  - Neutropenic patients / BMT / Chemotherapy
  - Patients with central venous lines
  - Dialysis patients
  - Burn ICU patients
  - Premature neonates

Antibiotic resistance: the way forward

Pathogen	Next steps / Research agenda
Candida auris	Infection control (horizontal controls) Infection control (vertical controls) Antifungal stewardship Novel antifungals
C. difficile	Community antibiotic stewardship Outpatient infection control Improved diagnostic testing (multiplex PCRs)
MDR. *S. pneumoniae*	Expand use of PCV-13 vaccine Improved vaccines of wider valencies
MRSA	Rapid diagnostics (PCR in blood cultures) Rapid identification of carriers / vertical infection control measures Patient hand hygiene Decolonization of at-risk patients

Wait, you forgot ESBL Enterobacteriaceae

Next steps / research agenda	Status
New antibiotics	17 drugs in pipeline as of June 2019 4 INDs before FDA Only 1 (tebipenem) is oral
Source control: food supply / antibiotic use in food animals	Almost no research permitted by agriculture / USDA-FDA
Source control: community infection control	Limited studies, doubtful benefit if widespread prevalence
Source control: hospital infection control / clinical screening	Potential benefit of vertical controls for selected patients (pre-prostate biopsies, for example)
Vaccines	Nearly impossible for this class of organisms
Non-antibiotic treatments	Fecal microbiota transplantation (trials underway)

Top Ten List of Things Physicians Could Do To Improve Matters

1. Stop prescribing antibiotics for bronchitis/URIs
2. Stop treating asymptomatic bacteriuria
3. Regard most acute sinusitis as viral, regardless of snot color, pain, and fevers.
4. Significantly curtail use of clindamycin and fluoroquinolones
5. Use traditional and rapid molecular diagnostics to make microbiologic diagnoses
6. Don’t treat proved viruses with antibiotics
7. Practice hand hygiene (WHO 5 Moments)
8. Stop eye-rolling at contact precautions for vertical control of drug-resistant pathogens.
9. Think as carefully before you start wide-spectrum antibiotics as you would before starting cyclophosphamide.
10. Upgrade from clean to aseptic access technique for central lines.

Conclusions / summary

- Most drug-resistant pathogens on CDC's threat list are opportunists
  - Threat is more related to underlying condition than the specific infection
- Only 4 pathogens are widespread in community-dwellers with large US morbidity/mortality impact:
  - MRSA
  - *C. difficile* infection
  - ESBL Enterobacteriaceae
  - Drug-resistant *Streptococcus pneumoniae*
- Insufficient epidemiology to guide medical / life insurance underwriting decisions for even those 3 independent of other health conditions
  - Childhood and adult immunization is making significant impact on *S. pneumoniae*
  - Colonization is very widespread for all of the other 3
  - Community penetration of infection is widespread and unpredictable
  - Travel and foreign residence raise risk for colonization but have not been described as risks for infection in US/European settings