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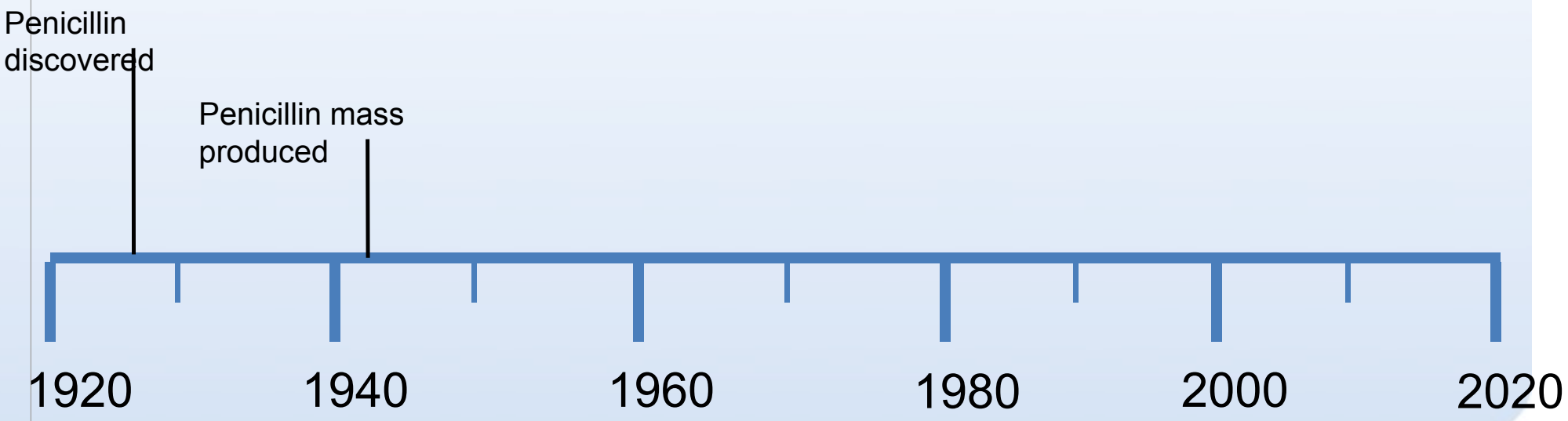
Antimicrobial stewardship:

“Quick, don’t just do something! Stand there!”

Stanley I. Martin, MD, FACP, FIDSA
Director, Division of Infectious Diseases
Director, Antimicrobial Stewardship Program
Geisinger Health System

It starts with a simple observation


Penicillin discovered
Penicillin mass produced
1920
1940
1960
1980
2000
2020

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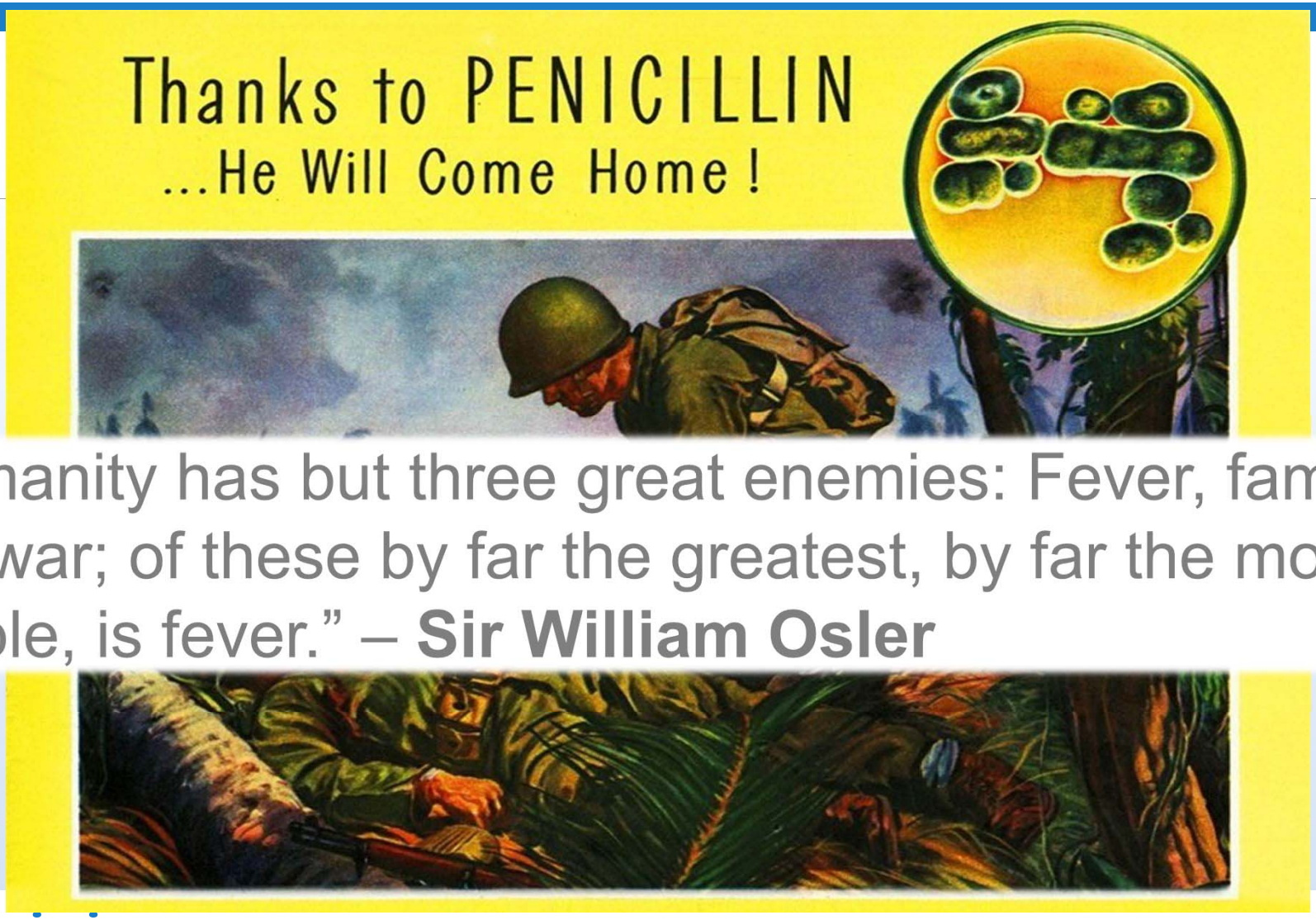

"Humanity has but three great enemies: Fever, famine and war; of these by far the greatest, by far the most terrible, is fever." – **Sir William Osler**


BUY BONDS
PENICILLIN
CURES
GONORRHEA
IN 4 HOURS
SEE YOUR DOCTOR TODAY

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"But I would like to sound one note of warning… It is not difficult to make microbes resistant to penicillin… Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug *make them resistant*."

-- A. Fleming, 1945, Nobel Prize Acceptance Speech

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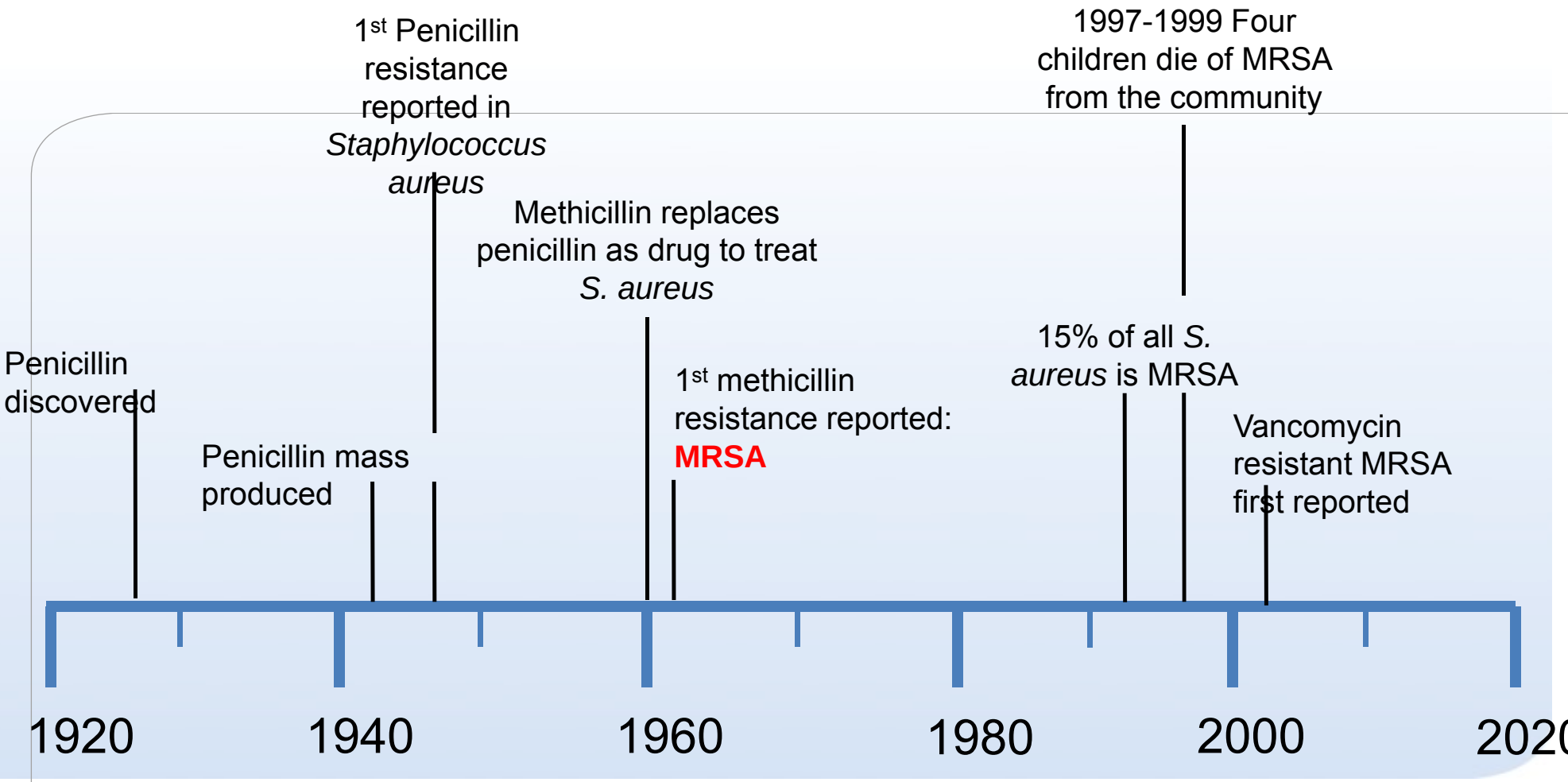
1st Penicillin resistance reported in *Staphylococcus aureus*
1997-1999 Four children die of MRSA from the community
Methicillin replaces penicillin as drug to treat *S. aureus*
Penicillin discovered
15% of all *S. aureus* is MRSA
1st methicillin resistance reported: **MRSA**
Penicillin mass produced
Vancomycin resistant MRSA first reported
1920
1940
1960
1980
2000
2020

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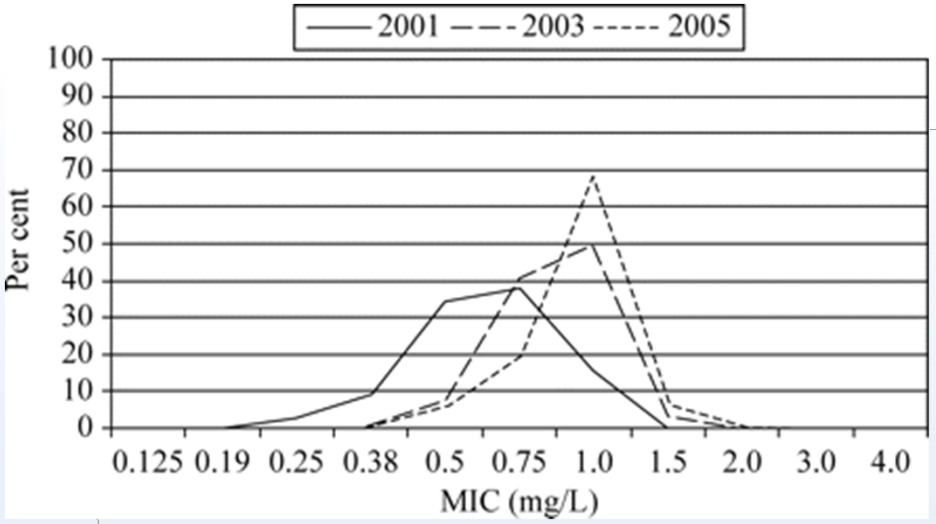
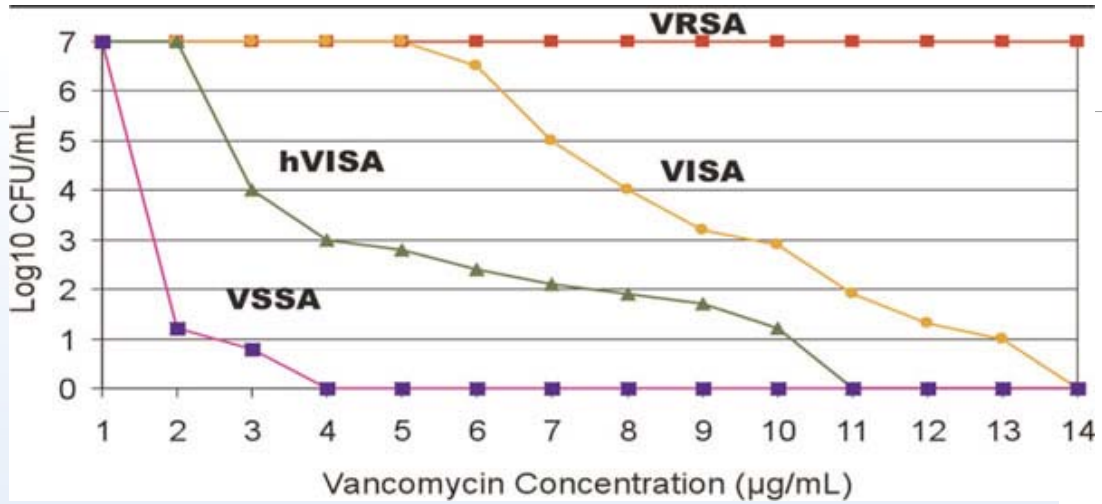
Vancomycin resistant *S. aureus* (VRSA)

- First reported in 2002
- Found on a dialysis catheter in a 40yo male from Michigan with ESRD, DM, and PVD
- Case from Pennsylvania reported later the same year
- Fifteen cases in the literature from the US so far
- Most recently reported in Delaware this past year (February 2015)





- Existing limitations in optimizing vancomycin dosing
- Slow bacterial killing of vancomycin compared to beta-lactams
- Poor tissue penetration by vancomycin

Steinkraus G, et al. J Antimicrob Chemother 2007;60:788
Antimicrob Agents Chemother 2003;47:3040

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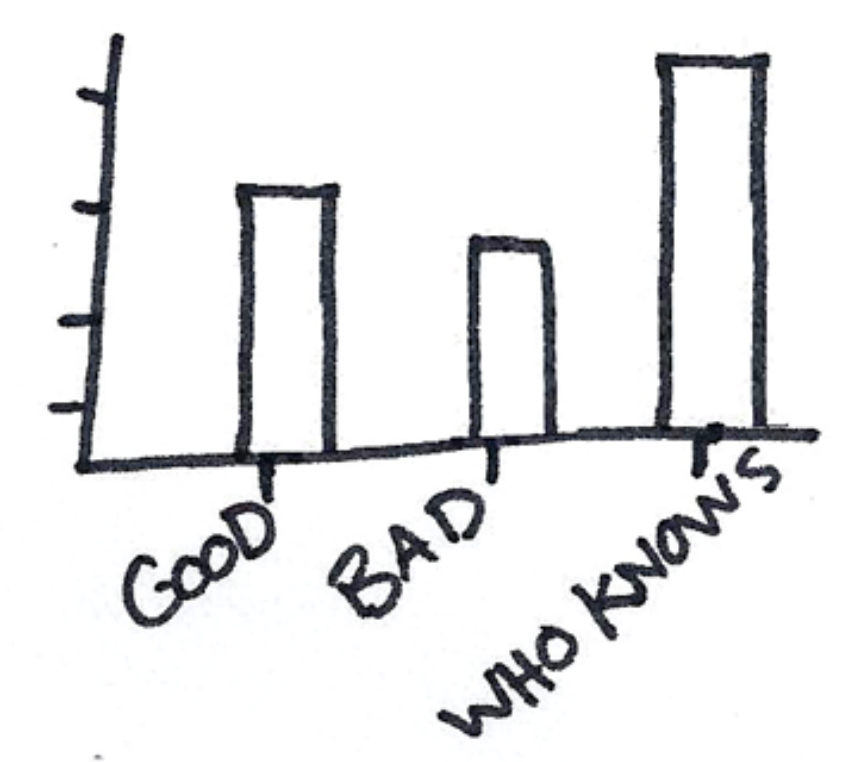
What to use for serious MRSA infections?

Vancomycin, or…

Daptomycin
Linezolid
Tedizolid
Ceftaroline
Televancin
Dalbavancin
Oritavancin
Tigecycline



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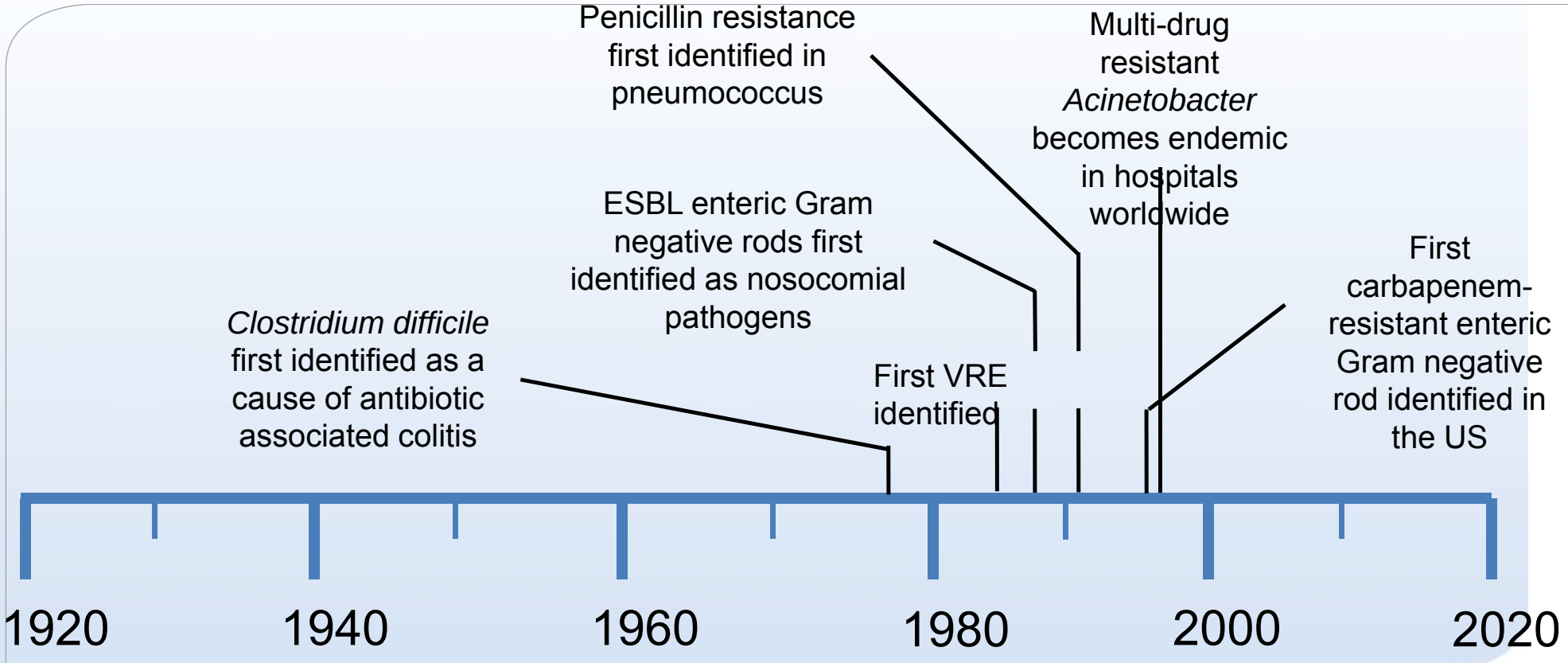
The story is about more than just one bug


Penicillin resistance first identified in pneumococcus
Multi-drug resistant *Acinetobacter* becomes endemic in hospitals worldwide
ESBL enteric Gram negative rods first identified as nosocomial pathogens
First carbapenem-resistant enteric Gram negative rod identified in the US
Clostridium difficile first identified as a cause of antibiotic associated colitis
First VRE identified
1920
1940
1960
1980
2000
2020

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To Your Health

The superbug that doctors have been dreading just reached the U.S.

By Lena H. Sun and Brady Dennis May 27, 2016

The Post's Lena Sun visited Walter Reed Army Institute of Research in Silver Spring, Md., where scientists there identified a strain of bacteria resistant to the last-resort antibiotic, colistin. The bacteria was found in a Pennsylvania woman. Microbiologist Patrick McGann explains how his team identified the gene that gives the bacteria this resistance (Monica Akhtar, Lena Sun/The Washington Post)

For the first time, researchers have found a person in the United States carrying bacteria resistant to antibiotics of last resort, an alarming development that the top U.S. public health official says could mean "the end of the road" for antibiotics.

The antibiotic-resistant strain was found last month in the urine of a 49-year-old Pennsylvania woman. Defense Department researchers determined that she

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HOME / HEALTH NEWS

'Superbug' resistant to all antibiotics killed Nevada woman

By HealthDay News | Jan. 13, 2017 at 3:30 PM

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FRIDAY, Jan. 13, 2017 -- A Nevada woman in her 70s who'd recently returned from India died in September from a "superbug" infection that resisted all antibiotics, according to a report released Friday.

The case raises concern about the spread of such infections, which have become more common over past decades as germs have developed resistance to widely used antibiotics.

TRENDING STORIES

Common NSAID pain relievers not effective for back pain: Study

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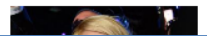
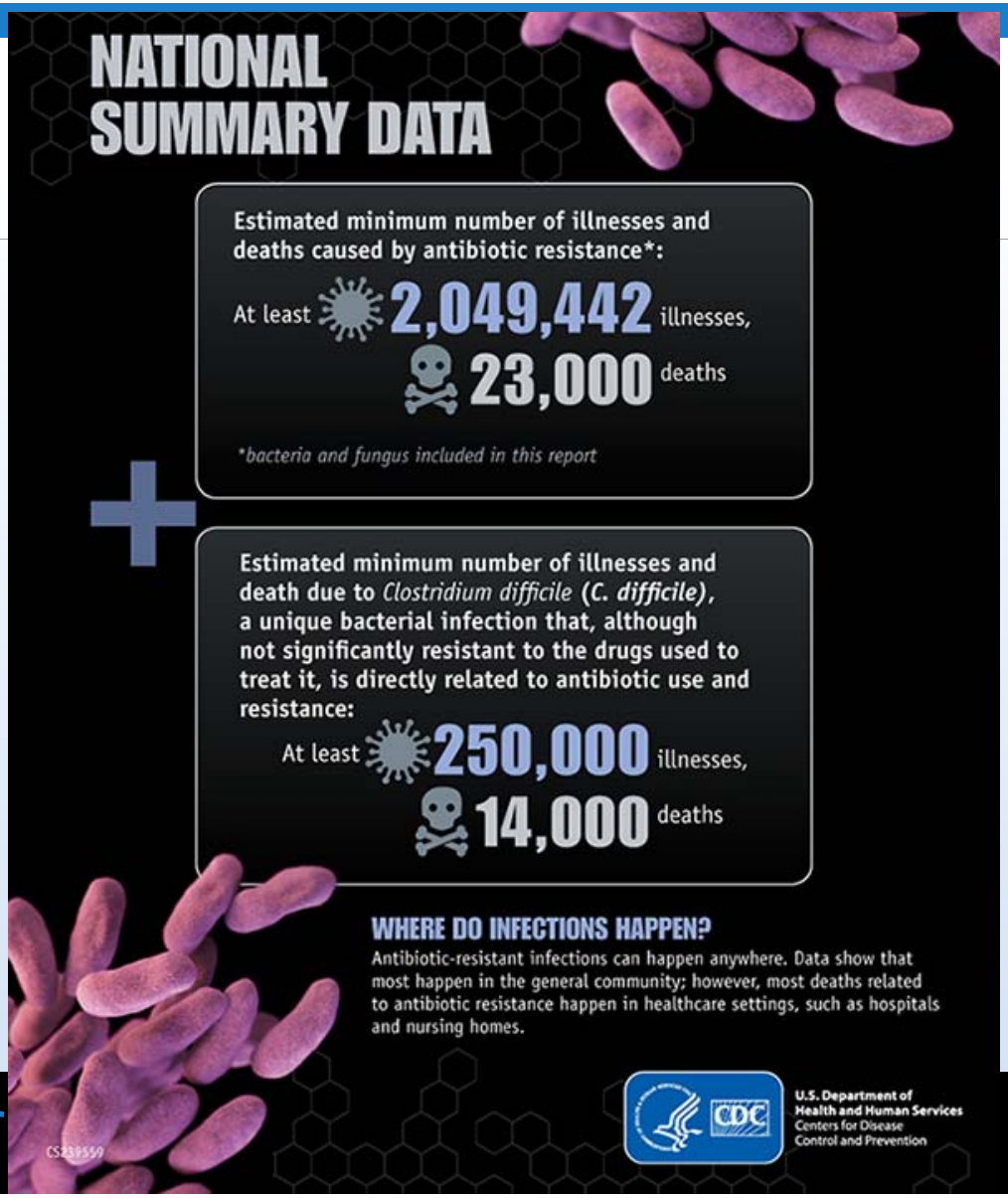
Thousands of seniors die within a week of ER discharge every year, study says

Study: High school students in U.S. abandon sweetened sodas

Pain meds used for colds, flu may raise heart attack risk

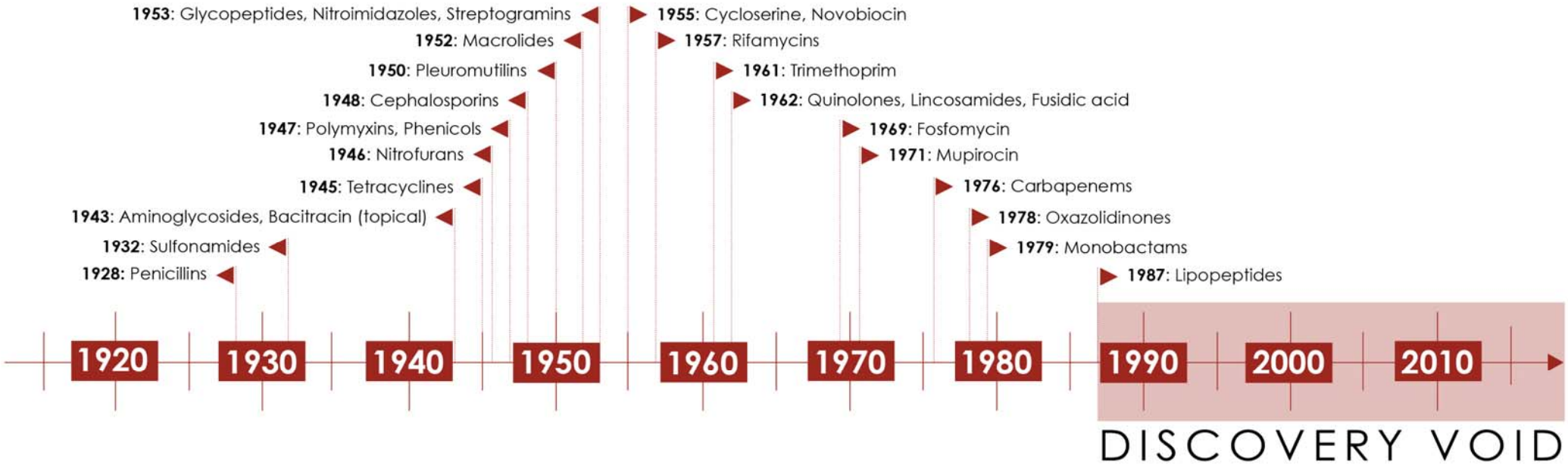
PHOTOS




NATIONAL SUMMARY DATA
Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:
At least 2,049,442 illnesses,
23,000 deaths
*bacteria and fungus included in this report
Estimated minimum number of illnesses and death due to Clostridium difficile (C. difficile), a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:
At least 250,000 illnesses,
14,000 deaths
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.
CDC
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention
CS239559

	Estimated annual cases	
	Infections (No.)	Deaths (No.)
Carbapenem-resistant enteric Gram negative rods	9,300	610
Drug-resistant Gonococci	2,467,000	<5
Multidrug resistant *Acinetobacter*	7,300	500
Extended-spectrum beta-lactamase (ESBL) enteric Gram negative rods	26,000	1,700
Vancomycin resistant Enterococci (VRE)	20,000	1,300
Multi-drug resistant *Pseudomonas*	6,700	440
Methicillin-resistant *S. aureus* (MRSA)	80,000	11,000

Boucher HW. IDSA 2015, San Diego, CA



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Source: Spellberg, CID 2004, modified

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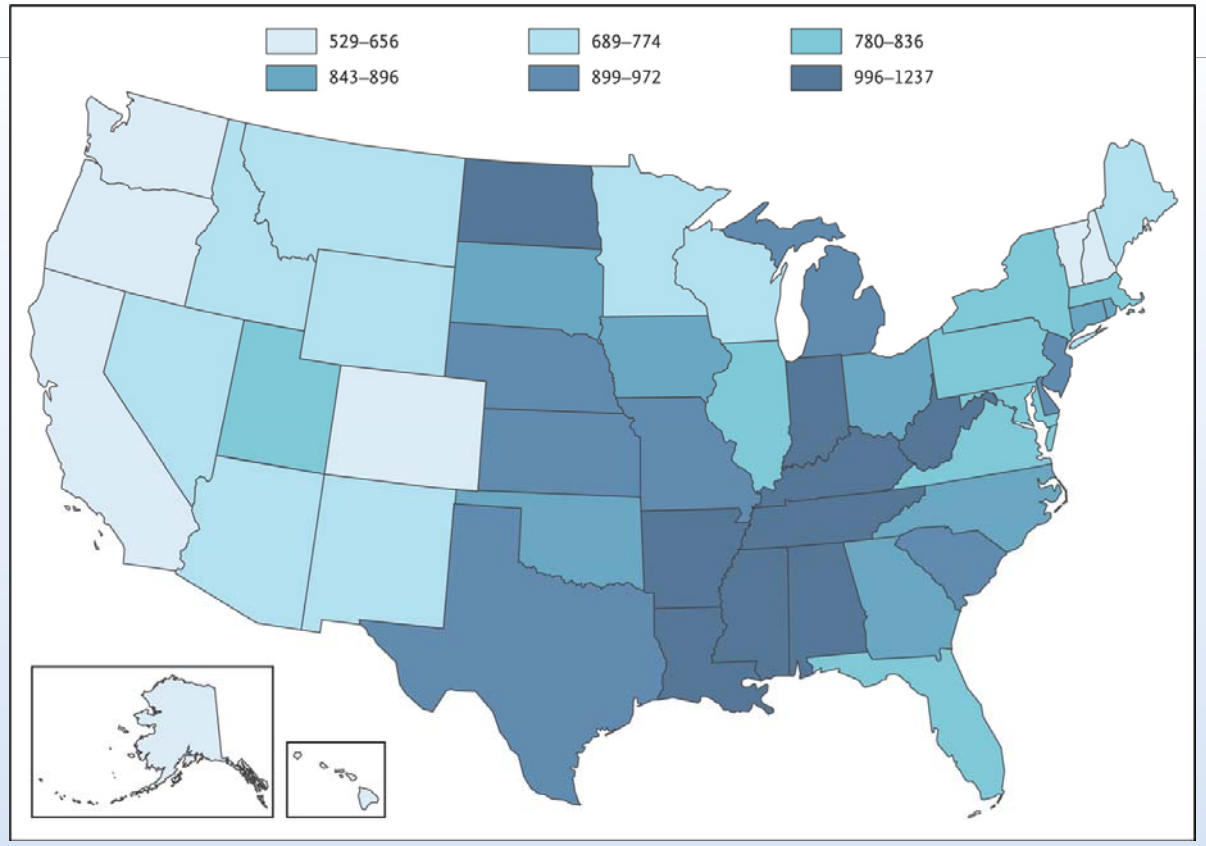
"… the aging of the US population has shifted drug discovery efforts towards agents that treat chronic medical conditions that are more prevalent among elderly persons, such as hypercholesterolemia, hypertension, mood disorders, dementia, and arthritis. Conversely, antimicrobials are usually used for short-course therapies that cure disease and thus eliminate their own need in a given patient." – B. Spellberg

Americans love their antibiotics

Antibiotic Prescriptions per 1000 Persons of All Ages According to State, 2010.



Hicks LA et al. N Engl J Med 2013;368:1461

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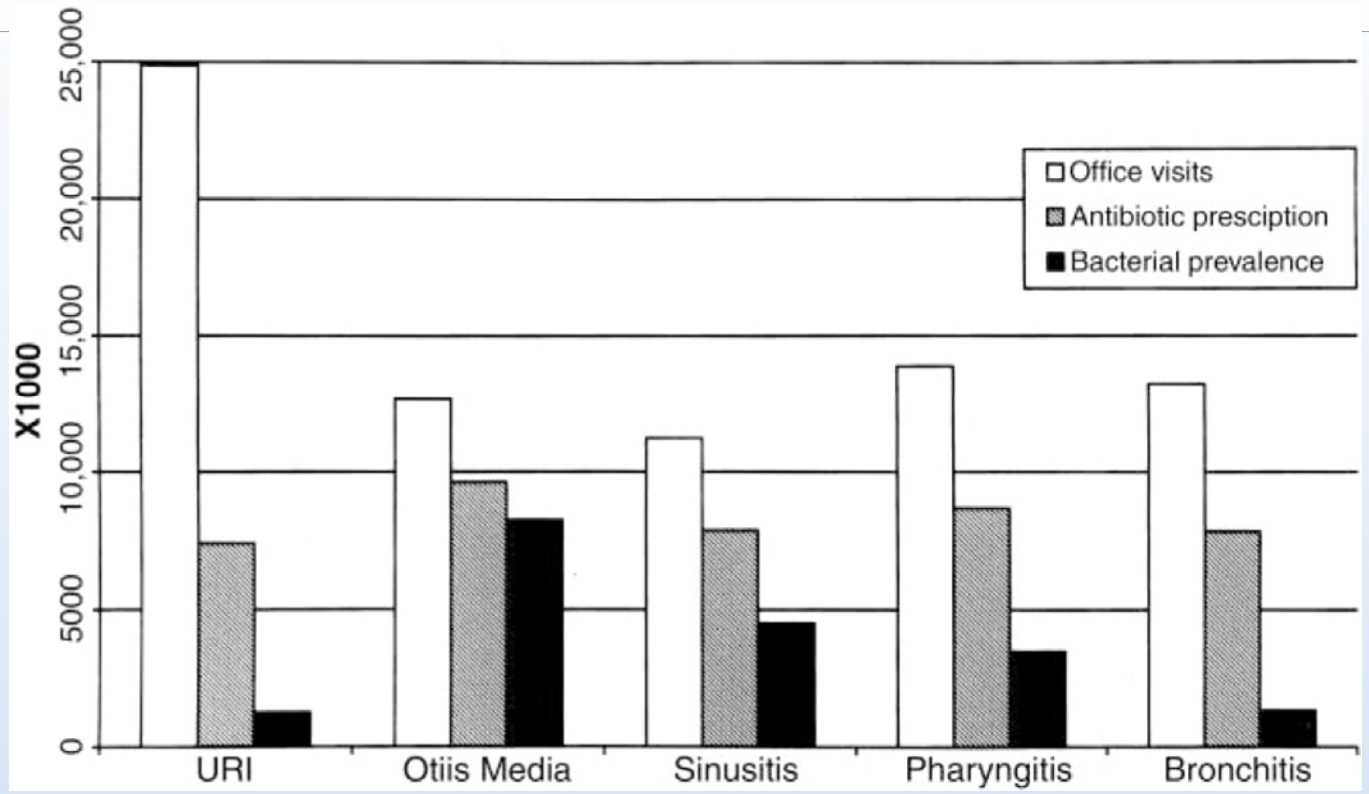
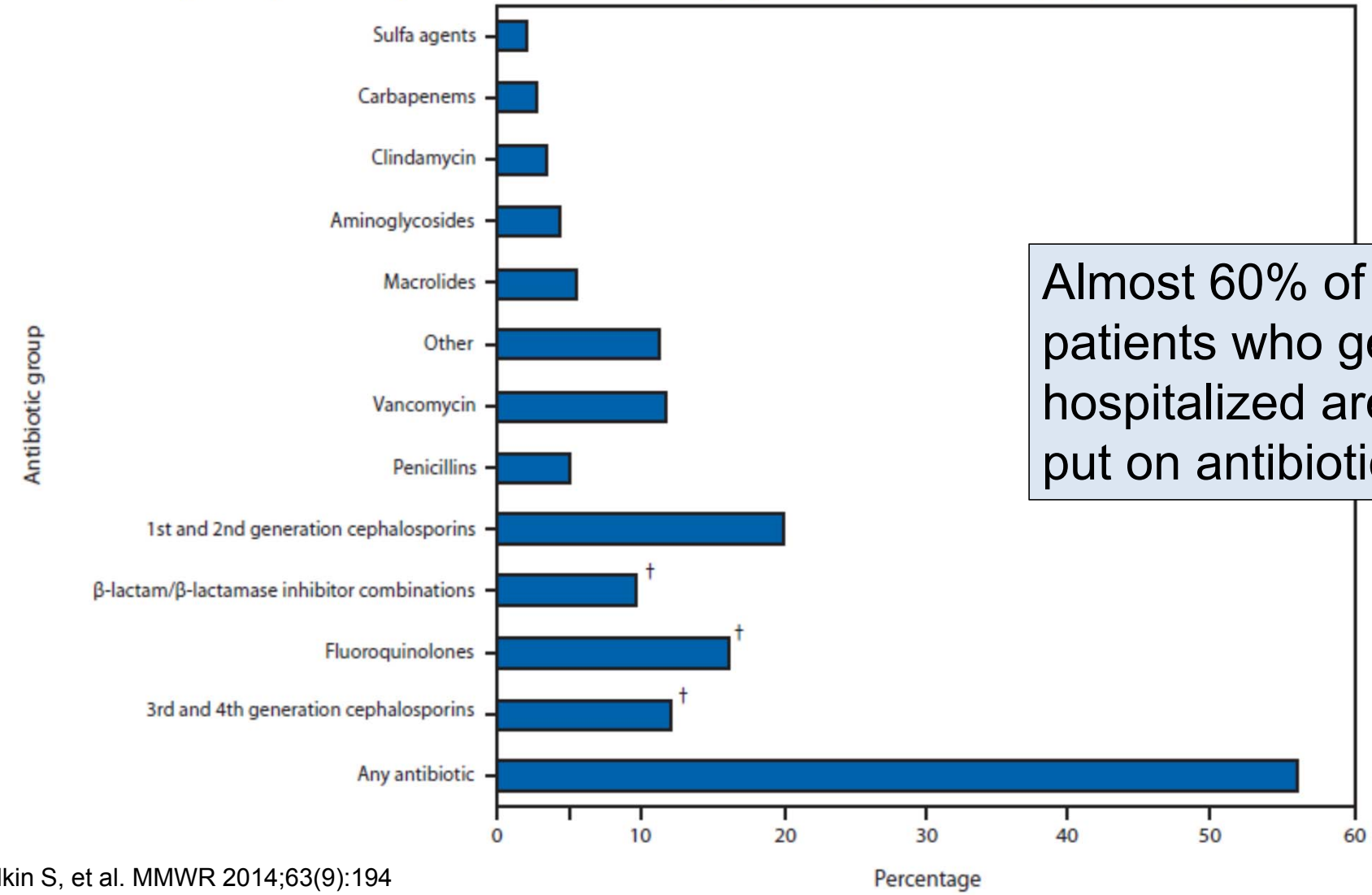
Primary care office visits and antibiotic prescriptions for acute respiratory illnesses in the United States



Ralph Gonzales et al. Clin Infect Dis. 2001;33:757-762

FIGURE 1. Percentage of hospital discharges with at least one antibiotic day, by antibiotic group — 323 hospitals, United States, 2010*



Almost 60% of patients who get hospitalized are put on antibiotics

Fridkin S, et al. MMWR 2014;63(9):194

Hospitals treat patients the same, right?

Characteristic	DOT/1000 PDs							
	2006	2007	2008	2009	2010	2011	2012	All Years
Antibiotic class								
All	732.5	736.9	755.6	766.8	755.4	770.0	767.5	754.8
Teaching	713.8	725.3	734.0	741.3	724.3	735.3	740.7	730.5
Nonteaching	752.9	749.1	778.8	792.9	787.2	805.7	796.9	780.4
No. of beds, <300	739.0	739.1	768.1	790.2	776.0	804.1	818.3	775.5
No. of beds, ≥300	726.7	734.9	744.9	747.4	738.6	742.2	725.4	737.2
Large, urban teaching hospital	713.6	724.7	729.1	733.1	717.3	722.7	711.8	721.8
Hospitals other than large, urban, teaching	744.2	744.2	771.9	786.9	777.9	797.0	801.6	774.6

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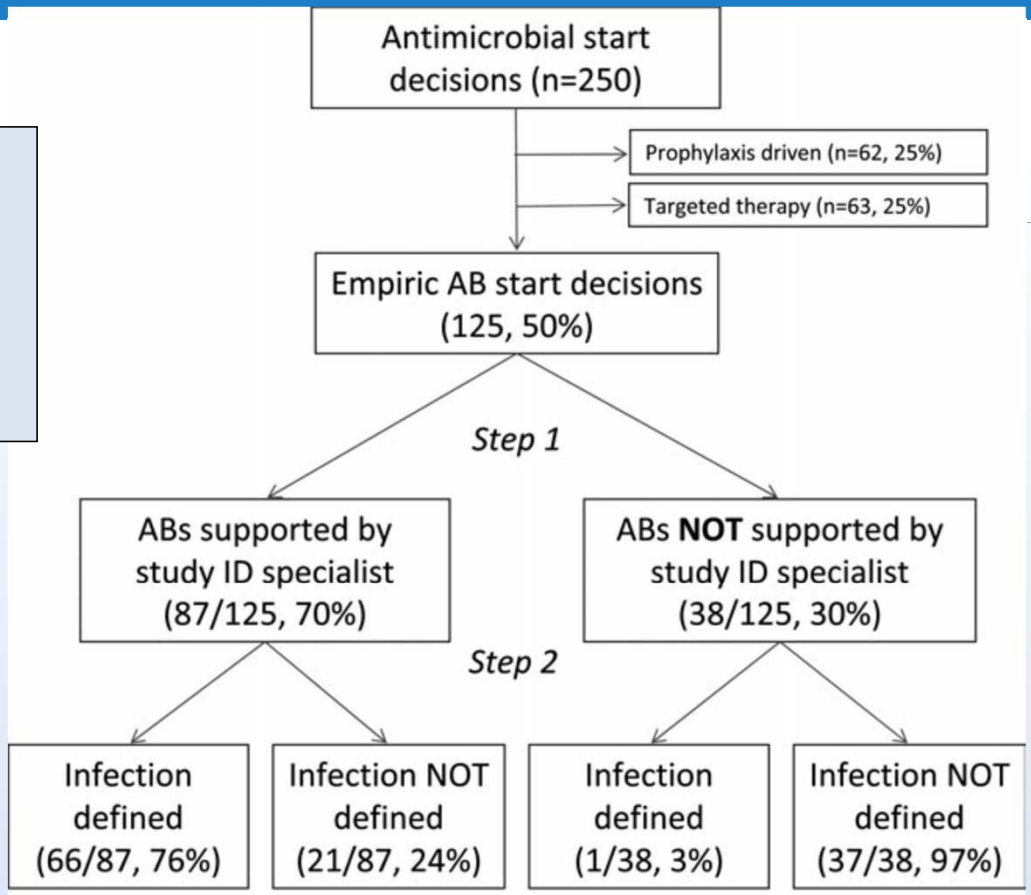
Baggs J, et al. JAMA Intern Med. 2016

As a general rule, we are not always very good at picking the right antibiotics



$$\text{Clinician accuracy} = \frac{\text{Defined infections (n=67)}}{\text{Empiric AB decisions (n=125)}} = 54\%$$

$$\text{Study ID accuracy} = \frac{\text{Defined Infections (n=66)}}{\text{Antimicrobials supported (n=87)}} = 76\%$$

Levin PD, et al. J Hosp Med 2012;7:672

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TABLE 2. Assessment of antibiotic prescribing among inpatients in 36 hospitals treated for urinary tract infection (UTI) without indwelling catheter or treated with intravenous vancomycin — Emerging Infections Program health-care–associated infections and antimicrobial use prevalence survey, United States, 2011

Treatment	No.	(%)
Patients treated for UTI present on admission, without indwelling catheter	**111**	—
Urine culture was not ordered, although standard practice before treatment	18	(16.2)
Urine culture was positive, but no documented symptoms were present	23	(20.7)
Urine culture was negative, and no documented symptoms were present	3	(2.7)
No. of patients with potential for improvement in prescribing	44	(39.6)
Patients treated with intravenous vancomycin	**185**	—
No diagnostic culture obtained around antibiotic initiation, although standard practice with most infections	17	(9.2)
Diagnostic culture showed no Gram-positive bacterial growth, but patient still treated for long duration (>3 days) (excludes presumed SSTI, which often can be culture negative)	40	(21.6)
Diagnostic culture grew only oxacillin-susceptible *Staphylococcus aureus*, but patient still treated for long duration (>3 days) (likely missed opportunity to switch antibiotic based on culture result)	9	(4.9)
No. of patients with potential for improvement in prescribing	66	(35.7)
Combined UTI or vancomycin prescribing	**296**	—
Total no. of patients with potential for improvement in prescribing	110	(37.2)

Abbreviation: SSTI = skin and soft tissue infection.

Fridkin S, et al. MMWR 2014;63(9):194

Review of meropenem use at Geisinger

Review of 255 meropenem orders

6 month period

Only 36% of meropenem orders were for generally appropriate indications:

- Patients with a history of ESBL, or having documented ESBL enteric Gram negative rod infection
- History of, or documented *Pseudomonas* infections
- *Acinetobacter* infections
- Empiric use for meningitis in patients with penicillin/cephalosporin allergies

ID service consulted in less than half of cases

Review of Fluoroquinolone use at Geisinger

	Yes (%)	No (%)	Unknown (%)
Documented infection present	53 (55.2%)	43 (44.8%)	--
Alternative oral option available	39 (40.6%)	57 (58.3%)	1 (1.1%)
Duration of therapy appropriate	59 (61.5%)	37 (38.5%)	--

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C diff. C diff run. Run, diff, run!

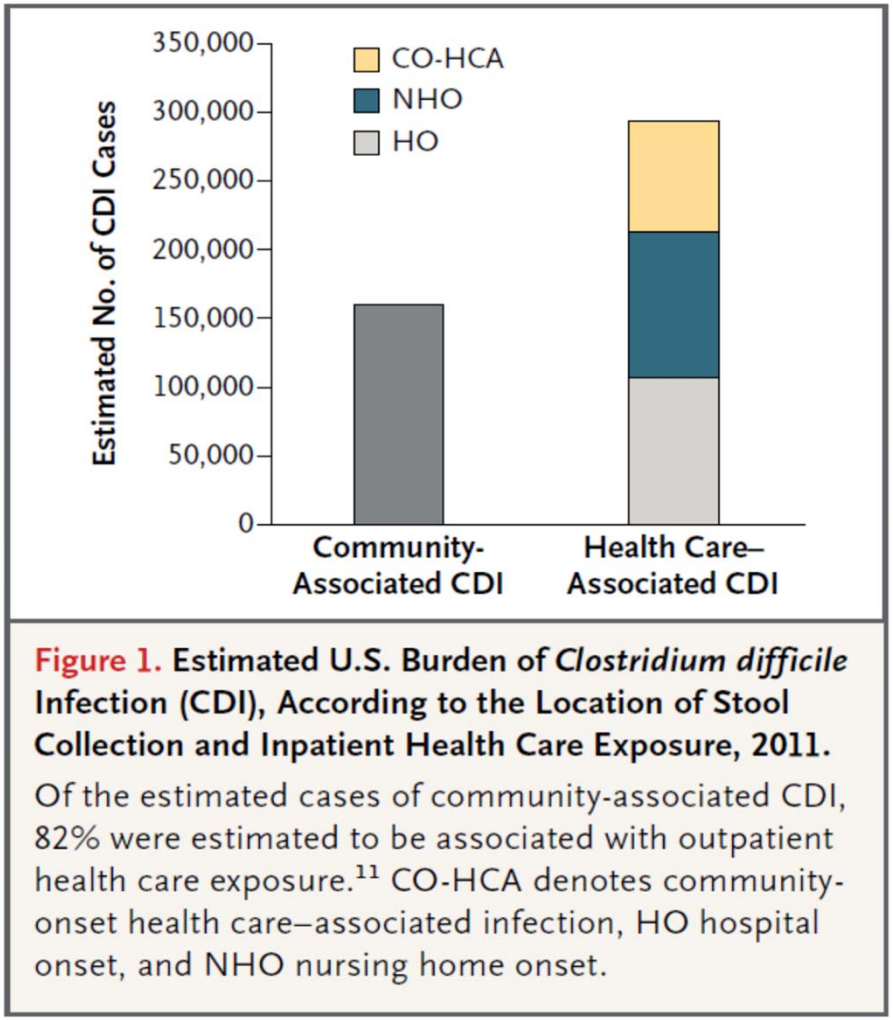

Figure 1. Estimated U.S. Burden of *Clostridium difficile* Infection (CDI), According to the Location of Stool Collection and Inpatient Health Care Exposure, 2011.

Of the estimated cases of community-associated CDI, 82% were estimated to be associated with outpatient health care exposure.[11] CO-HCA denotes community-onset health care–associated infection, HO hospital onset, and NHO nursing home onset.

- Estimated number of cases of C diff infection in the United States: **453,000 annually**
- Associated with **29,000 deaths**
- Female slightly more affected than male: **256,000 cases vs. 197,000 cases**
- Age group >65 years disproportionately affected: **259,800 cases**

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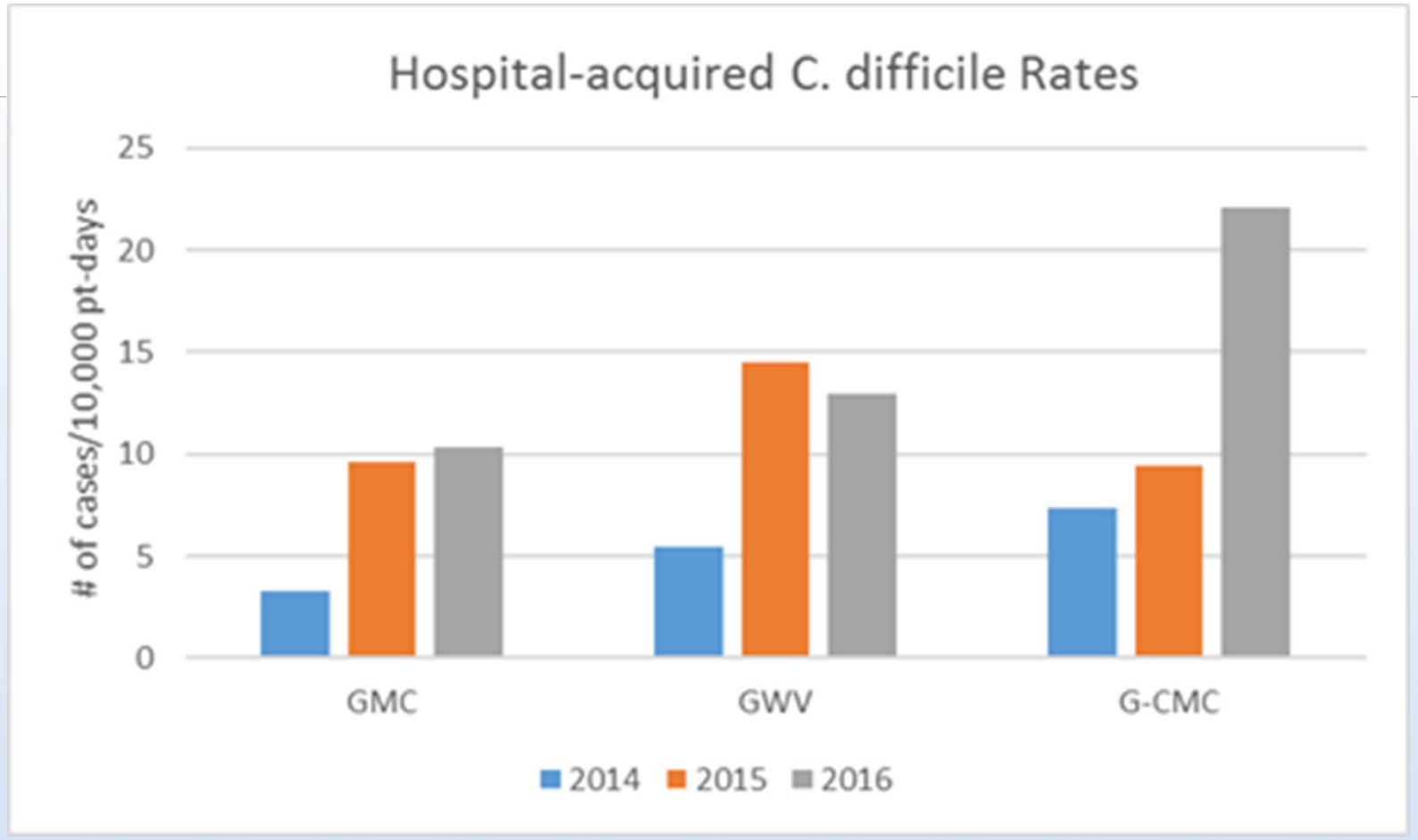
Lessa FC, et al. New Engl J Med 2015;372:825


Hospital-acquired C. difficile Rates
# of cases/10,000 pt-days
25
20
15
10
5
0
GMC
GWV
G-CMC
2014
2015
2016

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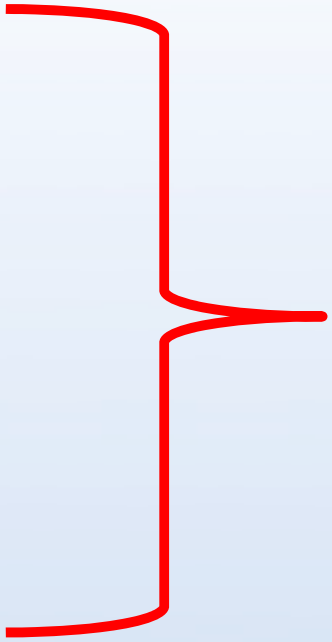
Consequences of *C diff*

- Longer length of stay (13.2 vs 8.5 days)
- Higher rates of inpatient mortality (OR 1.13 95%CI 1.09-1.17)
- Higher cost of care (39.3% higher on avg)
- Higher 30-day, 60-day, and 90-day readmission rates (OR 1.77-1.83 with 95%CI 1.73-1.87)



P value <0.01

Magee G, et al. Am J Infect Con. 2015;43:1148

What can antimicrobial stewardship hope to accomplish?

Table 1 Clinical outcomes in a randomized controlled trial comparing the Hospital of the University of Pennsylvania (HUP)* program to usual practice

Outcome	HUP Program (n = 96)	Usual Practice (n = 95)	Relative Risk (95% CI)
Antimicrobial appropriate	86 (90%)	30 (32%)	2.8 (2.1–3.8)
Cure	52/57 (91%)	34/62 (55%)	1.7 (1.3–2.1)
Failure†	5 (5%)	29 (31%)	0.2 (0.1–0.4)
Clinical	4 (4%)	10 (11%)	—
Microbiologic	0	8 (8%)	—
Superinfection	0	8 (8%)	—
Service changed antibiotic	0	5 (5%)	—
Adverse drug effect	0	2 (2%)	—
Recurrent infection	1 (1%)	1 (1%)	—
Resistance	1 (1%)	9 (9%)	0.13 (0.02–1.0)

CI = confidence interval.
*Philadelphia, PA.
†Sum may be >100% because individuals can fail for multiple reasons.

Fishman N. Am J Med 2006;119:S53

TABLE 2. Appropriateness of Antibiotic Use in Randomized Controlled Trial of Impact of Antimicrobial Utilization Teams

Variable	Proportion (%) of prescriptions		Risk ratio (95% CI)	*P*
	Intervention group	Control group		
Antibiotic use deemed appropriate				
Initial (<72 hours)	305/390 (78)	229/394 (58)	1.35 (1.22–1.49)	<.001
Empirical	242/294 (82)	211/291 (73)	1.14 (1.04–1.24)	.005
Definitive	92/112 (82)	60/138 (43)	1.89 (1.53–2.33)	<.001
Appropriate cultures obtained	188/270 (70)	193/286 (67)	1.03 (0.92–1.15)	.59
Changed to recommended antibiotics[a]	168/186 (90)	85/199 (43)	2.11 (1.79–2.50)	<.001
Appropriate end antimicrobial usage	367/390 (94)	277/394 (70)	1.34 (1.25–1.43)	<.001

NOTE. CI, confidence interval.

[a] In the control group, a blinded assessment of the appropriateness of the antimicrobial therapy was still made by the medical director of the antimicrobial utilization program. However, any recommendations for optimization of therapy were only recorded and never conveyed to the control group physicians.

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Camins BC, et al. Infect Control Hosp Epidemiol 2009;30:931

Where do we go from here?

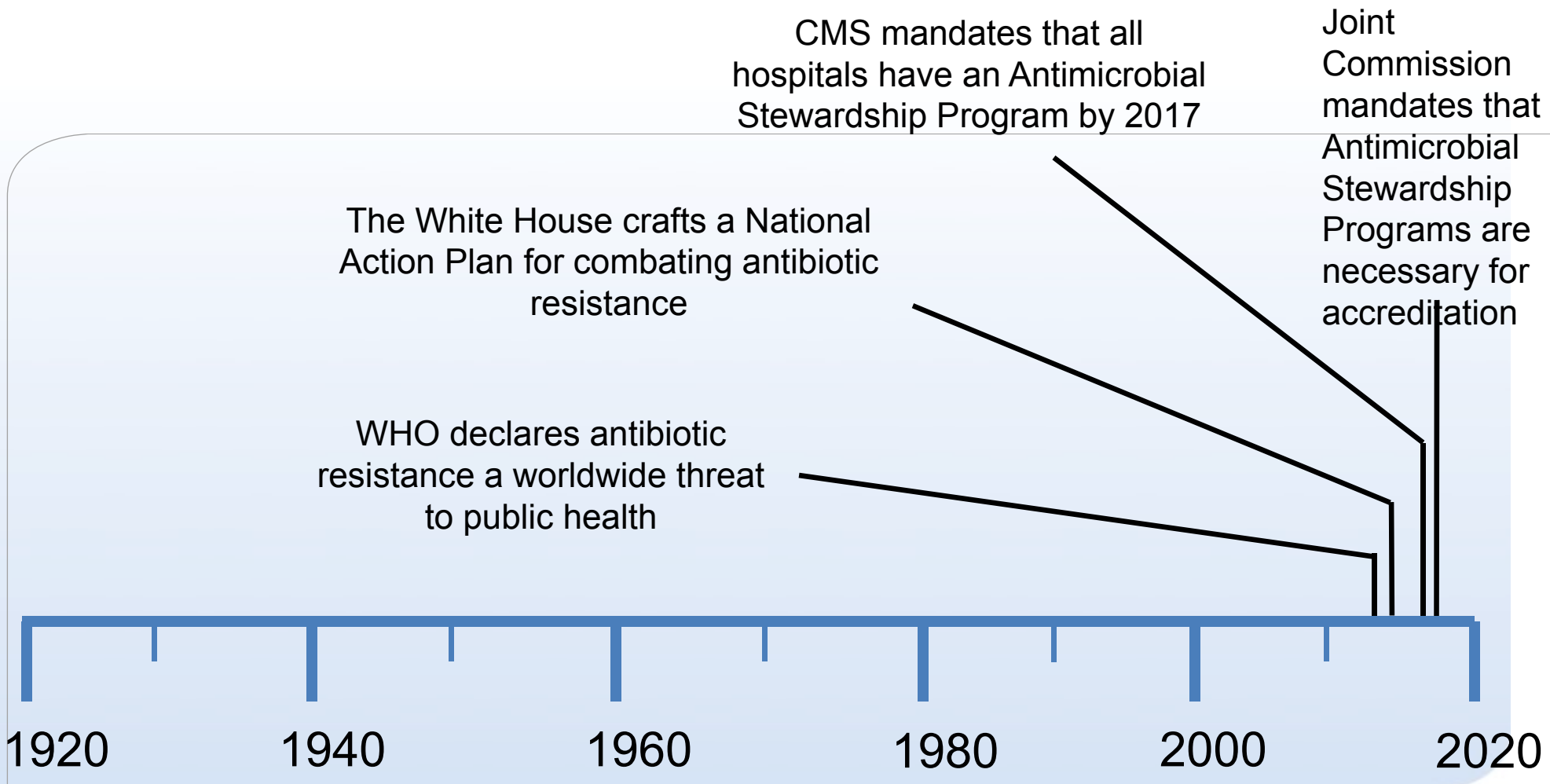
CMS mandates that all hospitals have an Antimicrobial Stewardship Program by 2017
Joint Commission mandates that Antimicrobial Stewardship Programs are necessary for accreditation
The White House crafts a National Action Plan for combating antibiotic resistance
WHO declares antibiotic resistance a worldwide threat to public health
1920
1940
1960
1980
2000
2020

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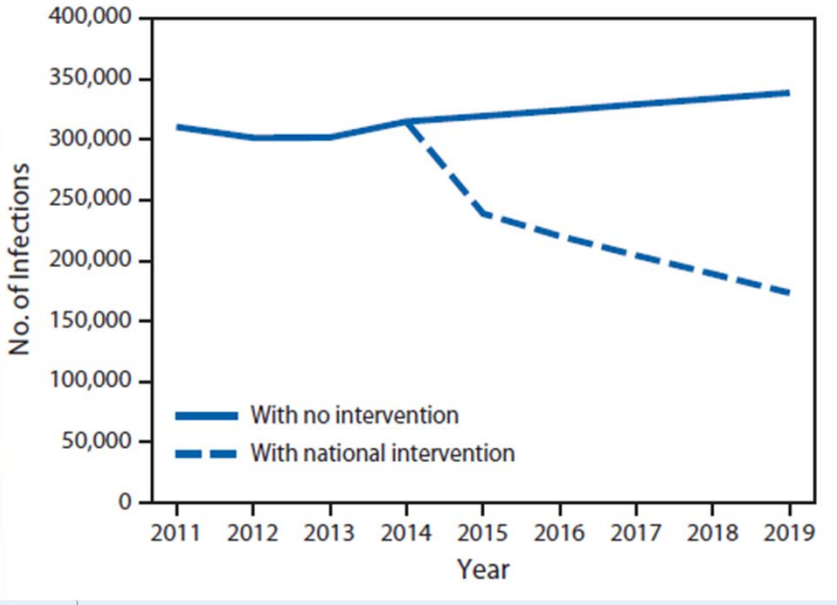
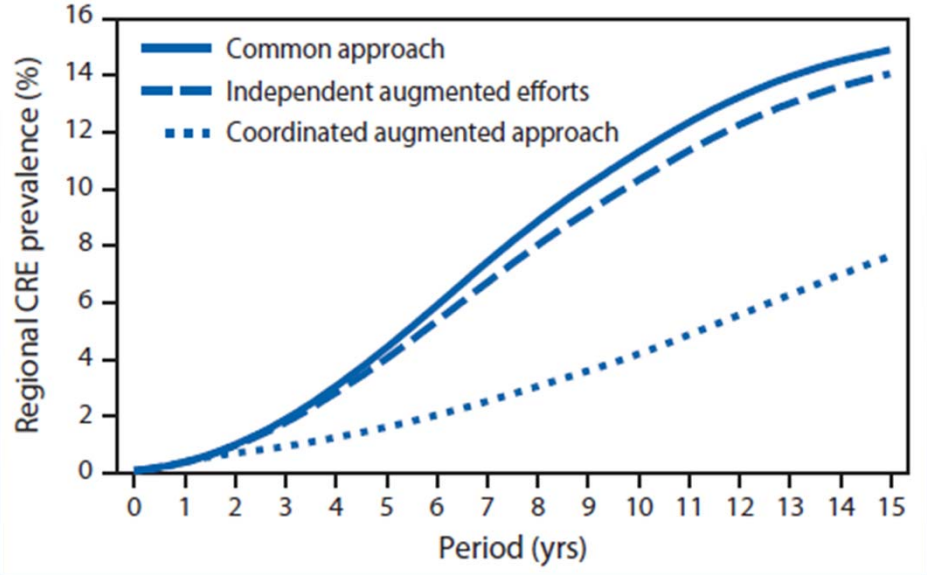
TABLE 1: National Targets to Combat Antibiotic-Resistant Bacteria
By 2020, the United States will:
For CDC Recognized Urgent Threats:
Reduce by 50% the incidence of overall *Clostridium difficile* infection compared to estimates from 2011.
Reduce by 60% carbapenem-resistant Enterobacteriaceae infections acquired during hospitalization compared to estimates.
Maintain the prevalence of ceftriaxone-resistant *Neisseria gonorrhoeae* below 2% compared to estimates from 2013.
For CDC Recognized Serious Threats:
Reduce by 35% multidrug-resistant *Pseudomonas spp.* infections acquired during hospitalization compared to estimates from 2011.
Reduce by at least 50% overall methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections by 2020 as compared to 2011.*
Reduce by 25% multidrug-resistant non-typhoidal *Salmonella* infections compared to estimates from 2010-2012.
Reduce by 15% the number of multidrug-resistant TB infections.[1]
Reduce by at least 25% the rate of antibiotic-resistant invasive pneumococcal disease among <5 year-olds compared to estimates from 2008.
Reduce by at least 25%the rate of antibiotic-resistant invasive pneumococcal disease among >65 year-olds compared to estimates from 2008.

* This target is consistent with the reduction goal for MRSA bloodstream infections (BSI) in the *National Action Plan to Prevent Healthcare-Associated Infections (HAI): Road Map to Elimination*, which calls for a 75% decline in MRSA BSI from the 2007-2008 baseline by 2020. Additional information is available at http://www.health.gov/hai/prevent_hai.asp#hai_plan.





- Immediate nationwide infection control and antibiotic stewardship interventions, over 5 years, could avert an estimated 619,000 HAIs resulting from CRE, multidrug-resistant *Pseudomonas aeruginosa*, invasive methicillin-resistant *Staphylococcus aureus* (MRSA), or *C. difficile*
- A coordinated response to prevent CRE spread across a group of inter-connected health care facilities resulted in a cumulative 55-74% reduction in acquisitions

Slayton RB, et al. MMWR 2015;64:1

What should an antimicrobial stewardship program consist of?

Prospective monitoring of antibiotic use with intervention and feedback
Formulary restriction and preauthorization
Education
Guidelines and clinical pathways
Streamlining or de-escalation of therapy
Dose optimization
IV to PO switch

Clin Infect Dis 2007;44:159-177

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Antimicrobial Stewardship at Geisinger

- Use of restricted antimicrobials and reviewing them for appropriateness within 2-3 days
- Help ensure clearly documented approved indications for antibiotics
- Review antimicrobial sensitivity patterns and develop evidence-based treatment guidelines with input from local susceptibility patterns
- Formal Infectious Diseases consultation in the following situations:
  - Continued use of restricted Antimicrobials
  - Severe Complicated *Clostridium difficile* Disease
  - All patients receiving simultaneously ≥ 3 antimicrobials
  - Any documented *Staphylococcus aureus* bacteremia
  - Any patients expected to be discharged on intravenous antimicrobial therapy
- IV to PO conversion when appropriate
- Automatic stop dates of 5 days
- Daily review for “drug/bug” mismatches

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The need for a cultural change

The concept of an “Antibiotic time out”:

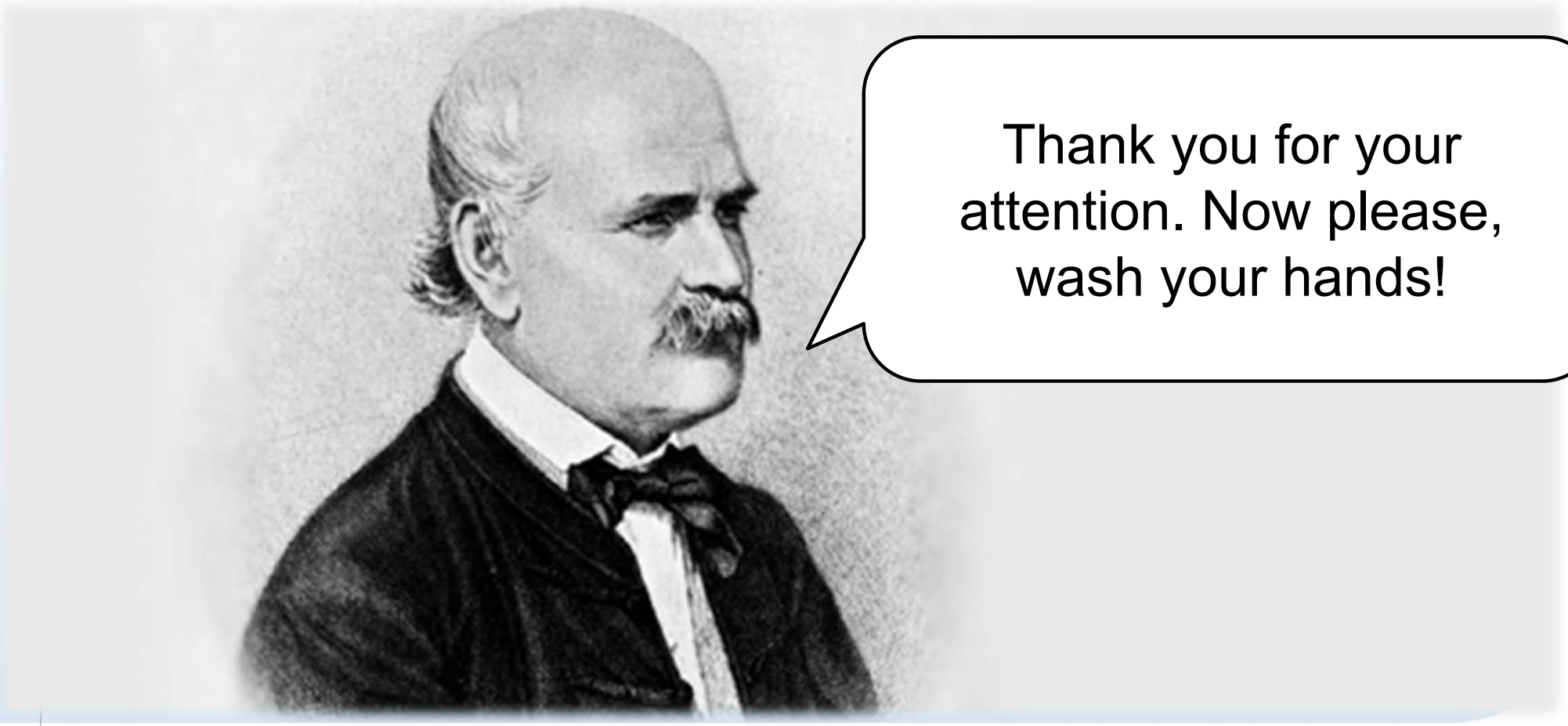
- What bacterial infectious syndrome are we actually treating?
- What diagnostic studies need to be done/have been done? What are the results?
- Is this drug really the one needed?
- Is this drug being dosed and administered properly?
- Are there any side effects from this antibiotic we should be monitoring for?

Emphasis should be on the patient

Historically the emphasis of antimicrobial stewardship was on cost savings

Primary purpose of any Antimicrobial Stewardship Program should be to optimize clinical outcomes and minimize unintended consequences of antimicrobial use:

- Improve patient outcomes
- Toxicity
- Selection of antimicrobial resistance
- *Clostridium difficile*
- Appropriate monitoring and follow-up


Thank you for your attention. Now please, wash your hands!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