

Antimicrobial Stewardship: Evolution and Updates

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Disclosures

- None

Overview

- Describe current landscape of antimicrobial resistance and antibiotic development and how antimicrobial stewardship programs (ASPs) fit into broader efforts
- Describe how pharmacists play critical roles in antimicrobial stewardship programs
- Learn about the impact of stewardship programs

Power of Antibiotics

Disease	Pre-Antibiotic Death Rate	Death With Antibiotics	Change in Death
Community Pneumonia ¹	~35%	~10%	-25%
Hospital Pneumonia ²	~60%	~30%	-30%
Heart Infection ³	~100%	~25%	-75%
GNB Bacteremia ⁴	~80%	~10%	-70%
Brain Infection ⁵	>80%	<20%	-60%
Skin Infection ⁶	11%	<0.5%	-10%
By comparison...treatment of myocardial infarction with aspirin or fibrinolytic drugs ⁶			-3%

¹IDSA Position Paper '08 Clin Infect Dis 47(S3):S249-65; ²IDSA/ACCP/ATS/SCCM Position Paper '10 Clin Infect Dis 51(S1):S150-70; ³Kerr AJ. Subacute Bacterial Endocarditis. Springfield IL: Charles C. Thomas, 1955 & Lancet 1935 226:383-4; ⁴Lancet '38 231:733-4 & Waring et al. '48 Am J Med 5:402-18; ⁵Spellberg et al. '09 Clin Infect Dis 49:383-91 & Madsen '73 Infection 1:76-81; ⁶88 Lancet 2:349-60; Spittel '54 Staff Proc Mayo Clin; Spittel '56 Ann Int Med 44:302-315; Hall & Gold '55 Arch Int Med 96:403-12

The evolution of bacteria
on a "mega-plate" Petri dish



HARVARD
MEDICAL SCHOOL

<https://www.youtube.com/watch?v=pIVk4NVIUh8>

Antibiotic-Resistant Organisms

Gram-Positives

- **MRSA** (Methicillin-resistant *Staphylococcus aureus*)
- **VISA** (Vancomycin-intermediate *S.aureus*)
- **VRSA** (Vancomycin-resistant *S. aureus*)
- **VRE** (Vancomycin-resistant enterococci)
- **MRSP** (Multidrug-resistant *Streptococcus pneumoniae*)

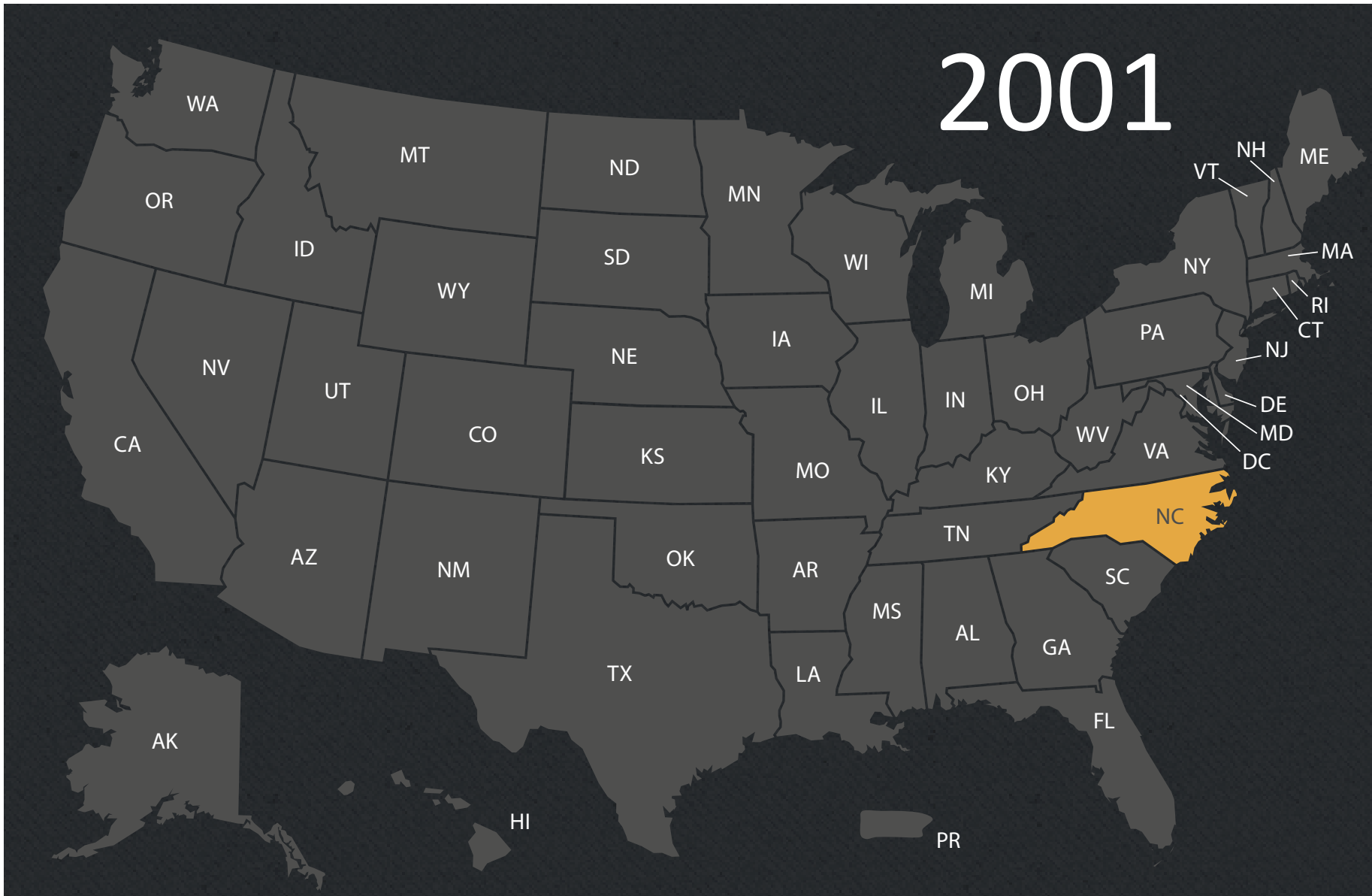
Gram-Negatives

- **MDROs** (Multidrug-resistant organisms)
- **AmpC**-producing SPACE bacteria
- **ESBL** (extended spectrum beta-lactamase)-producing bacteria
- **CRE** (Carbapenem-resistant Enterobacteriaceae)
- MDR/XDR *Pseudomonas aeruginosa* or *Acinetobacter baumannii*

Antibiotic Susceptibility Report for CRE *E. coli*

Antibiotic Name	MIC ($\mu\text{g/mL}$)	Interpretation
Aztreonam	> 16	Resistant
Cefoxitin	> 32	Resistant
Ceftriaxone	> 32	Resistant
Ceftazidime	> 16	Resistant
Tobramycin	> 8	Resistant
Ciprofloxacin	> 2	Resistant
Ertapenem	> 4	Resistant
Imipenem	> 8	Resistant
Meropenem	> 8	Resistant
Pip/tazo	> 64/4	Resistant
SMX/TMP	> 2/38	Resistant

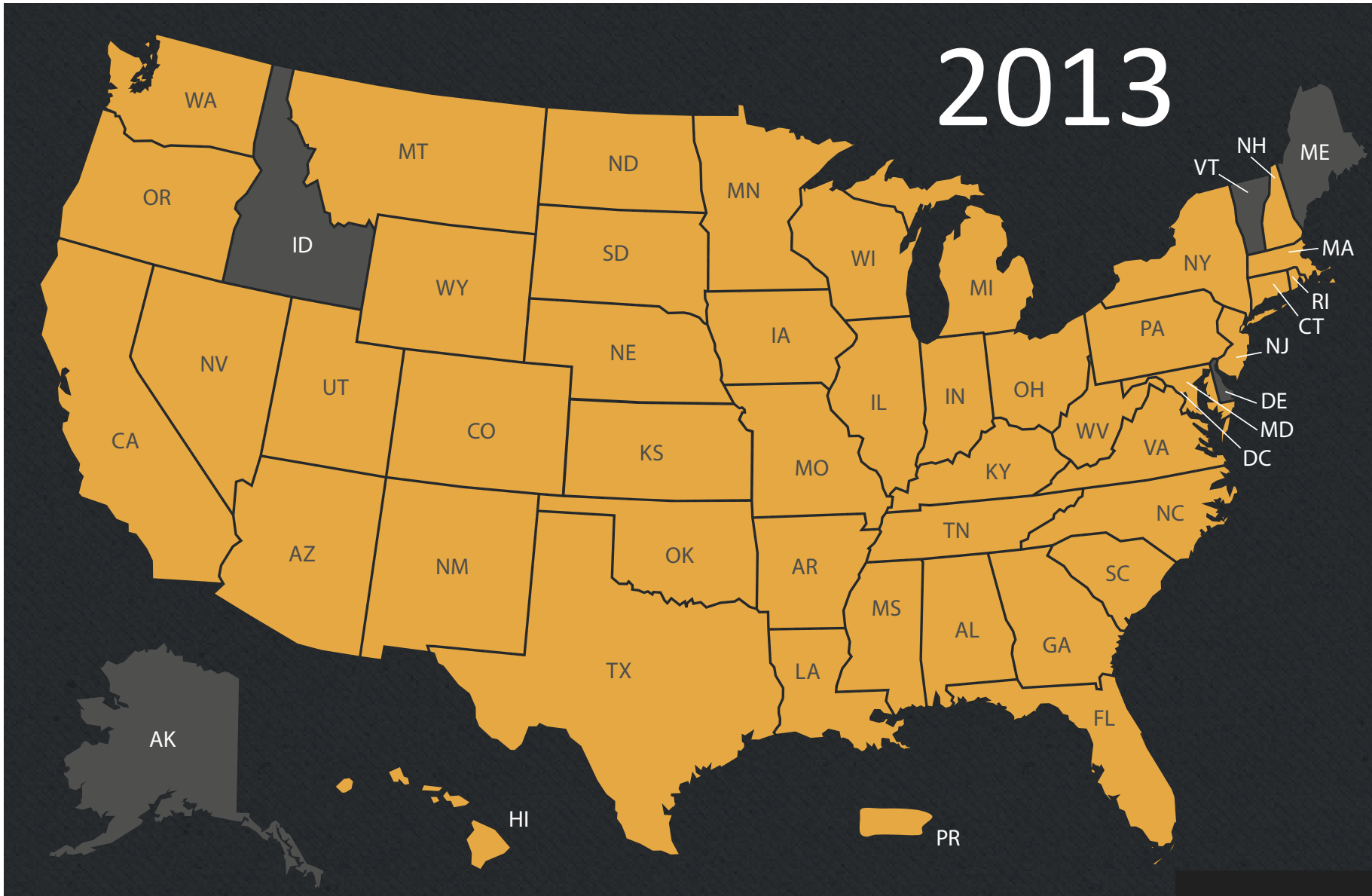
CP CRE (KPC)



Source: CDC

CP CRE (KPC)

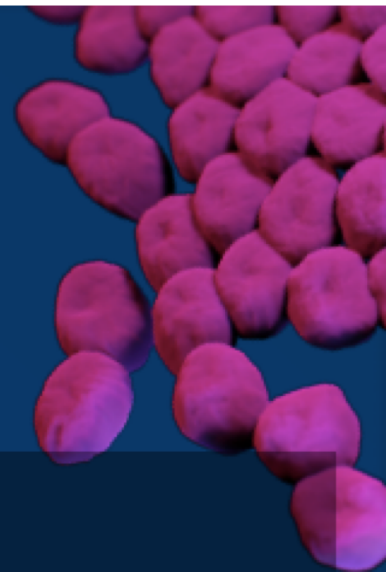
2013



Source: CDC

The Threat of Antibiotic Resistance in the United States

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



New National Estimate*

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



2,868,700
infections



35,900 deaths



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

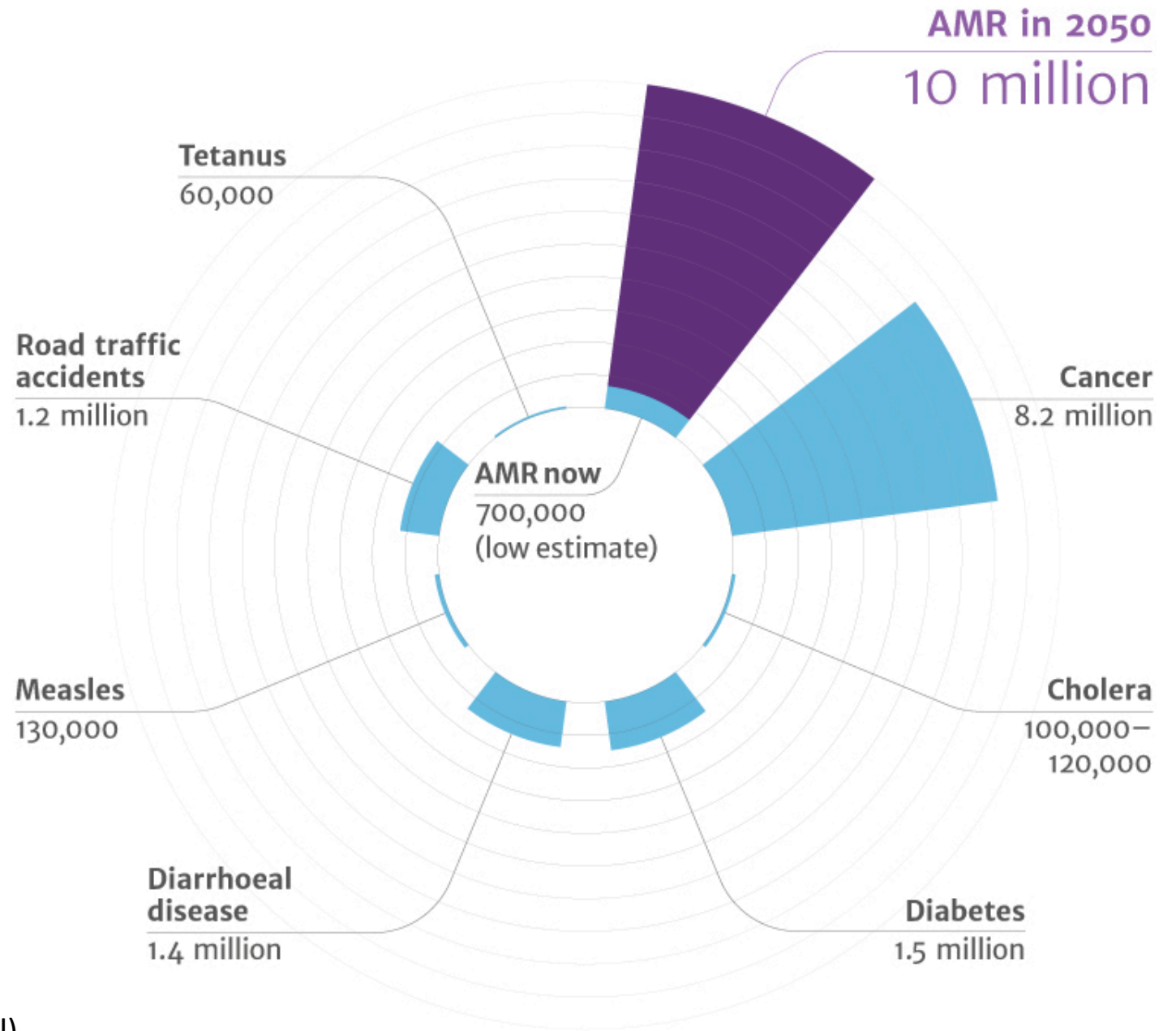


223,900
cases

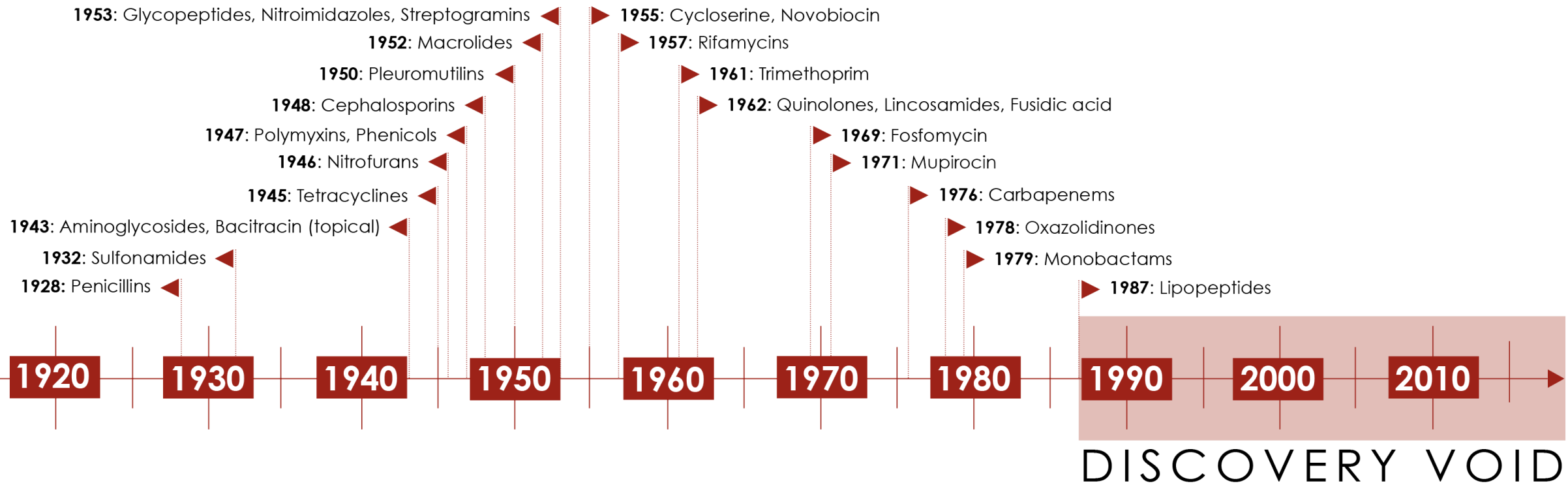


12,800 deaths

Future Magnitude of AMR?

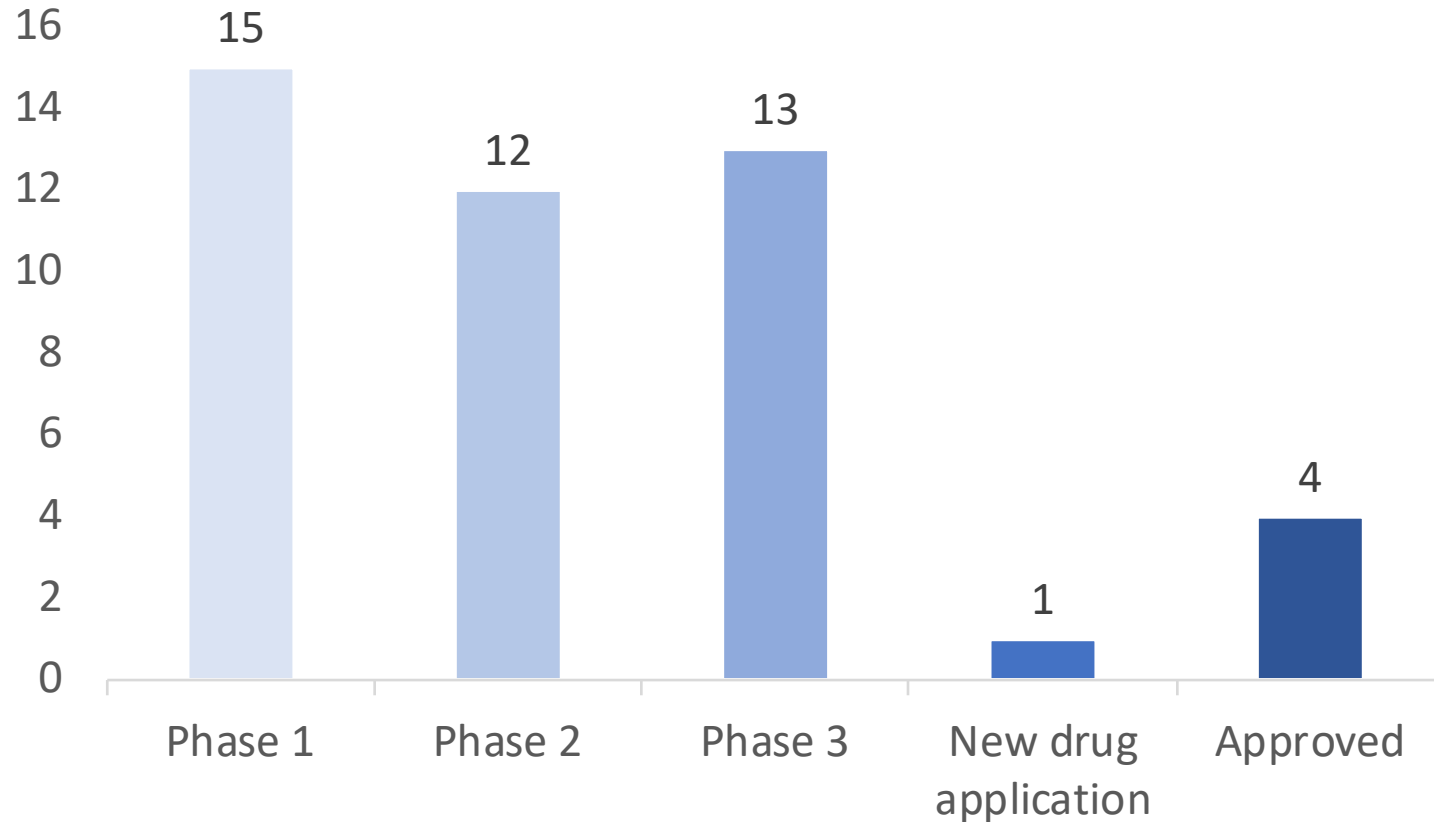


Antibiotic Development Timeline



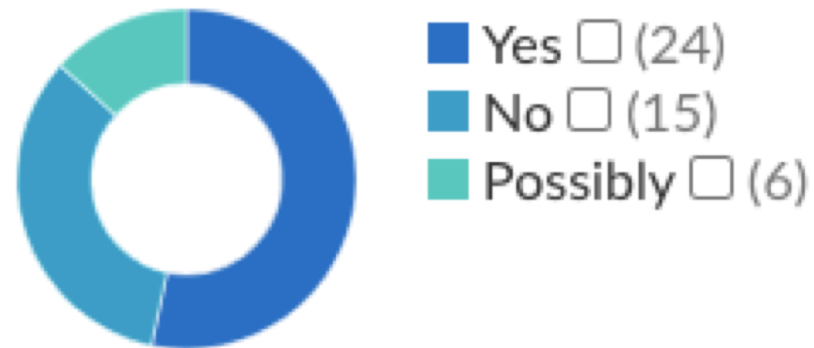
© ReAct Group 2015

How about Now (Dec 2019)?



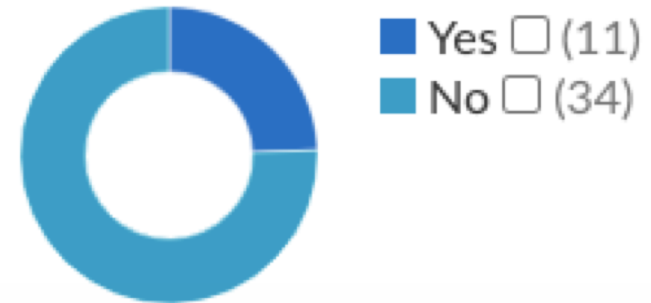
How about Now (Dec 2019)?

Expected Activity Against ESKAPE Bugs

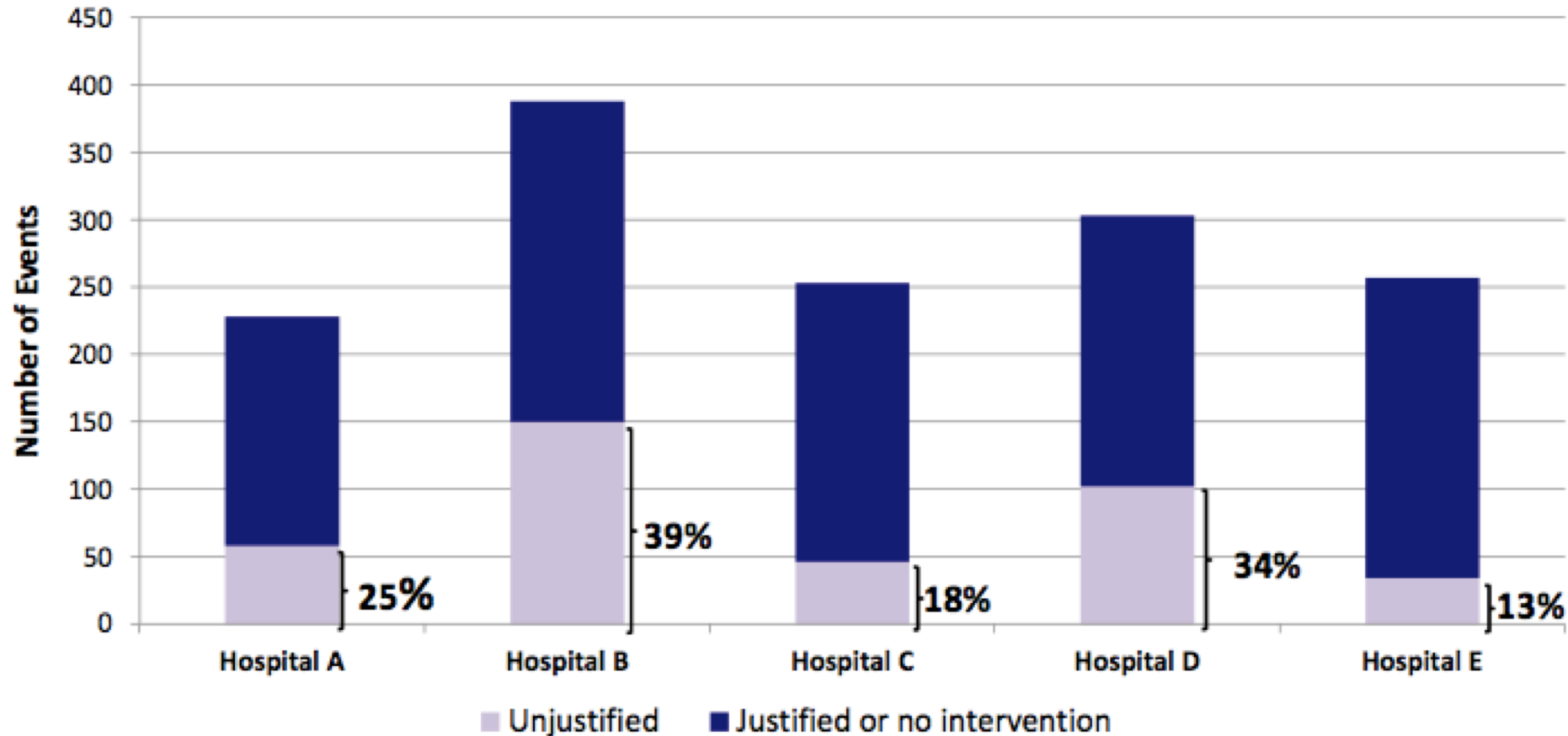


How about Now (Dec 2019)?

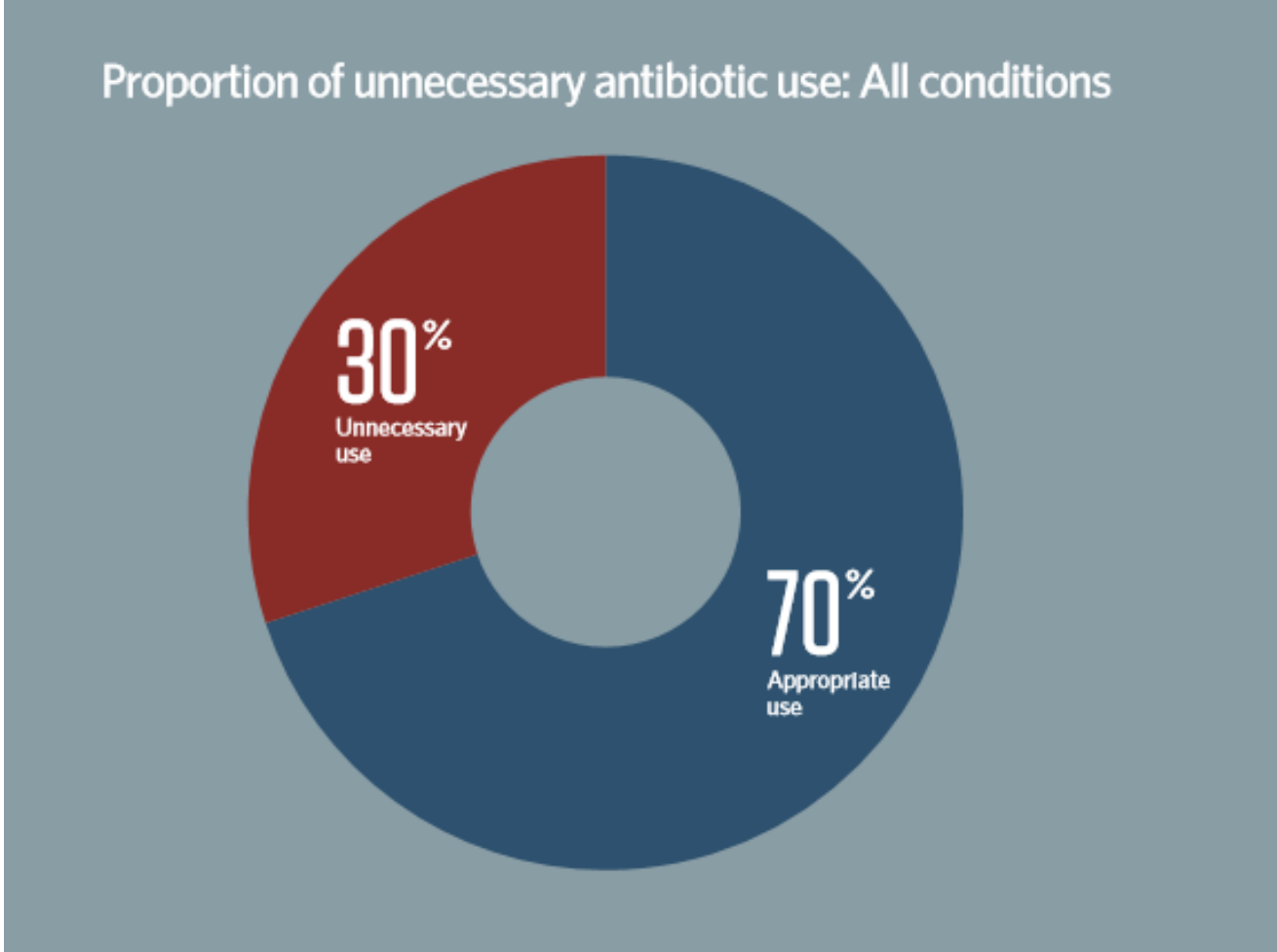
By novel class or target



Acute Care Hospitals: Still Room for Improvement with ABX Prescribing



Ambulatory Settings: Antibiotic Prescribing Can Improve Here, Too!



How To Keep Ourselves in Check?

- Self-stewardship would be ideal
- Yet when you ask...
 - Inpatient providers
 - APPs
 - Ambulatory providers



Abbo L et al. ICHE 2011.

Abbo L et al. J Nurse Practitioners 2012.

Intersection of All These Forces?

- Impacts ABX treatment of common infections
- Limits other advances in healthcare
 - Chemotherapy for cancer treatment
 - Increasing immunosuppression for autoimmune diseases
 - Solid organ and stem cell transplantation
 - Complex surgeries
 - Patients on dialysis/end stage renal disease
- Greater costs and potential harms to patients

What Can Be Done?

NATIONAL
ACTION PLAN
FOR COMBATING
ANTIBIOTIC-RESISTANT BACTERIA

The goals of the *National Action Plan* include:

- 1.** Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections.
- 2.** Strengthen National One-Health Surveillance Efforts to Combat Resistance.
- 3.** Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria.
- 4.** Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines.
- 5.** Improve International Collaboration and Capacities for Antibiotic-resistance Prevention, Surveillance, Control, and Antibiotic Research and Development.

Empowering Antimicrobial Stewardship Programs

2014 – CDC issued Core Elements for Inpatient Hospitals

2015 – CDC issued Core Elements for Nursing Homes

2016 – CDC issued Core Elements for Outpatient Settings

– [IDSA Guidelines](#) for ASPs last updated

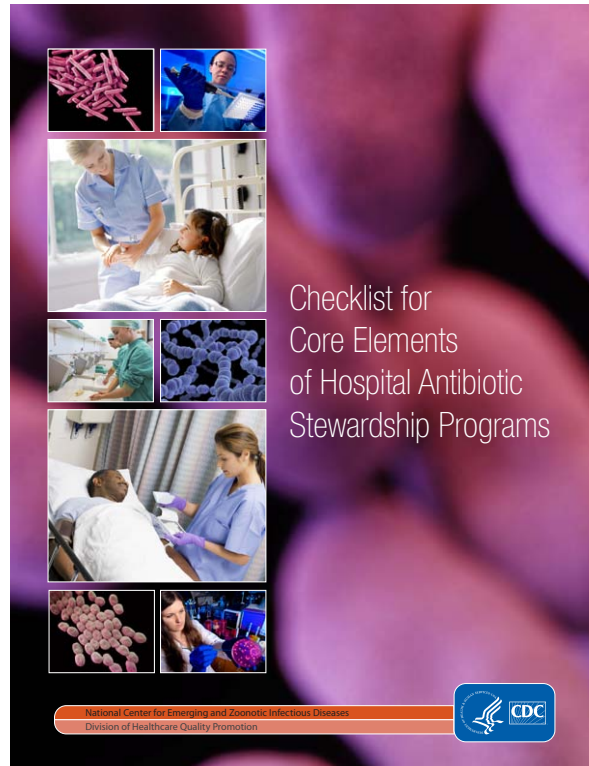
2017 – [TJC added Inpatient ASPs](#) under Medication Management Standard

2019 – [CDC updated Core Elements](#) for Inpatient Hospitals

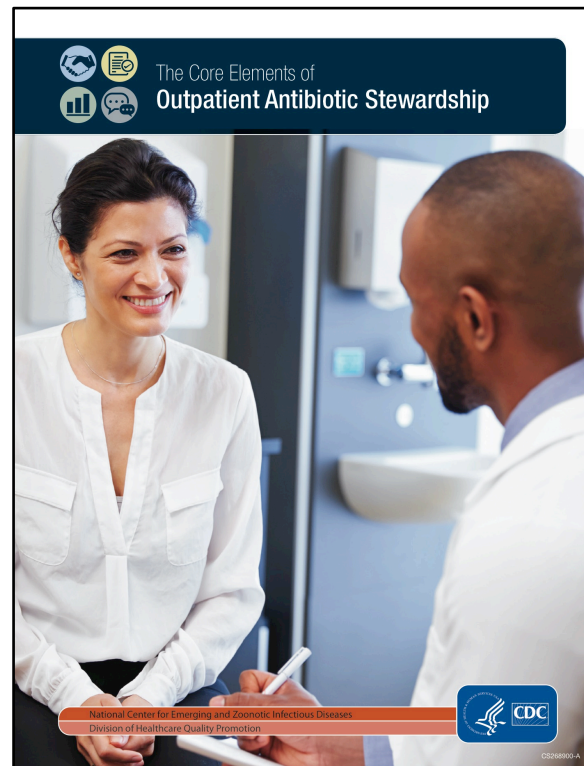
– [Centers for Medicare and Medicaid Services \(CMS\)](#) created a federal reg for hospital ASPs

2020 – [TJC added Ambulatory ASPs](#) under Medication Management Standard

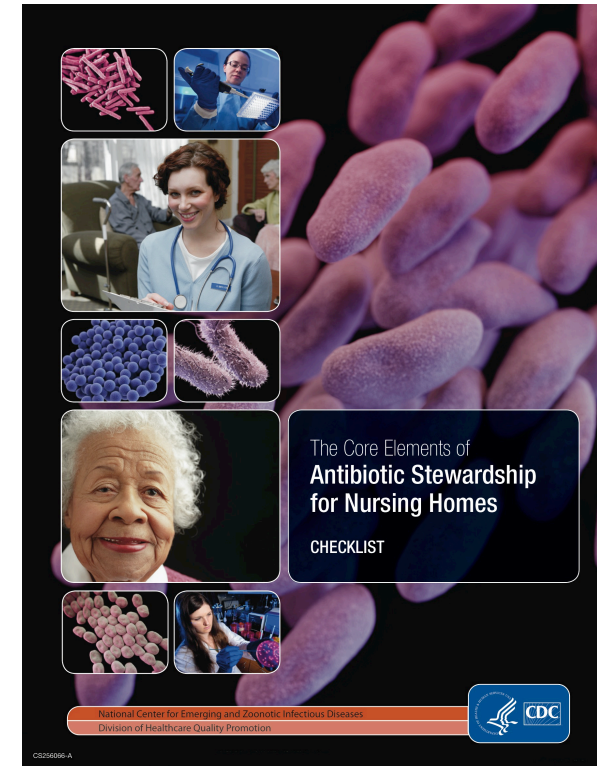
Where Can Antimicrobial Stewardship Programs (ASPs) be Established?



Hospitals

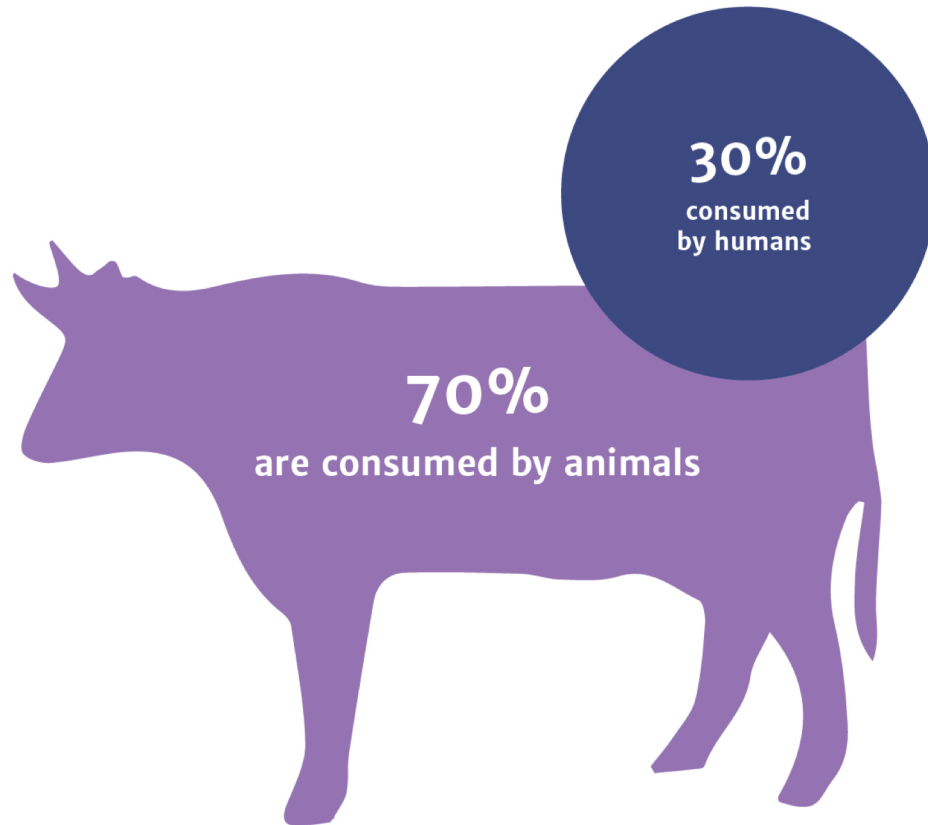


Outpatient Setting



Nursing Homes

The Other 70%: Time for a One Health Approach?



[New Report: Antimicrobial-resistant pathogens affecting animal health in the U.S.](#)

AMVA, August 2020

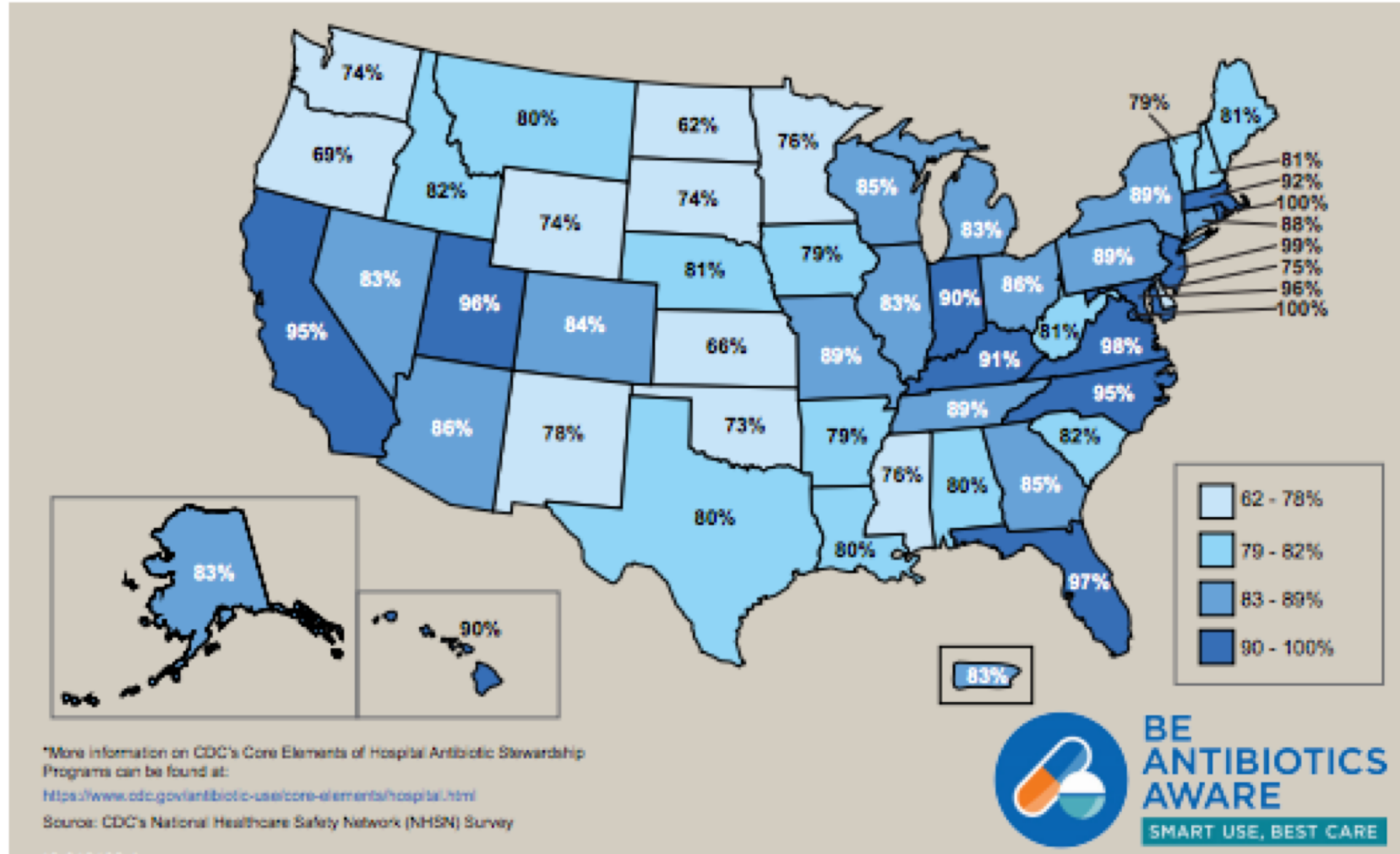
Role of ASP in Healthcare

- Primary goal: Getting patients on
 - Right antibiotic (infection type, patient allergies) with
 - Right dose
 - Right route
 - Right duration
 - Right times

(while minimizing adverse effects).

- Secondary goals:
 - Improve patient outcomes
 - Reduce collateral damage/adverse effects
 - Reduce AMR

Percentage of Hospitals Meeting All 7 Core Elements by State, 2018



In 2018, 85% of acute care hospitals reported having all seven of the Core Elements in place, compared to only 41% in 2014 ⁽¹⁵⁾.

<https://www.cdc.gov/antibiotic-use/healthcare/pdfs/hospital-core-elements-H.pdf>

Core Elements of Hospital Antibiotic Stewardship Programs



Hospital Leadership Commitment

Dedicate necessary human, financial, and information technology resources.



Accountability

Appoint a leader or co-leaders, such as a physician and pharmacist, responsible for program management and outcomes.



Pharmacy Expertise (previously “Drug Expertise”):

Appoint a pharmacist, ideally as the co-leader of the stewardship program, to help lead implementation efforts to improve antibiotic use.



Action

Implement interventions, such as prospective audit and feedback or preauthorization, to improve antibiotic use.



Tracking

Monitor antibiotic prescribing, impact of interventions, and other important outcomes, like *C. difficile* infections and resistance patterns.



Reporting

Regularly report information on antibiotic use and resistance to prescribers, pharmacists, nurses, and hospital leadership.



Education

Educate prescribers, pharmacists, nurses, and patients about adverse reactions from antibiotics, antibiotic resistance, and optimal prescribing.

Reframing Our Relationship with Antibiotics

What's the big deal about prescribing ABX? Might be congestive heart failure but it could be pneumonia.



ABX are not benign (short-term and long-term consequences)

The patient's crashing!



Antibiotics remain "Drugs of Fear"

I'll just keep the patient on Zosyn



De-escalation is standard of care

I'm going to treat for 10 days instead of 7 days...



Shorter courses are often appropriate and safe

Rethinking Our Relationship with Antibiotics

- Antibiotics are not benign
 - Short-term consequences
 - Long-term consequences
- Antibiotics remain “Drugs of Fear”
- De-escalation is standard of care
- Shorter courses could be more common

How Frequent Are Adverse Effects from Antibiotics?

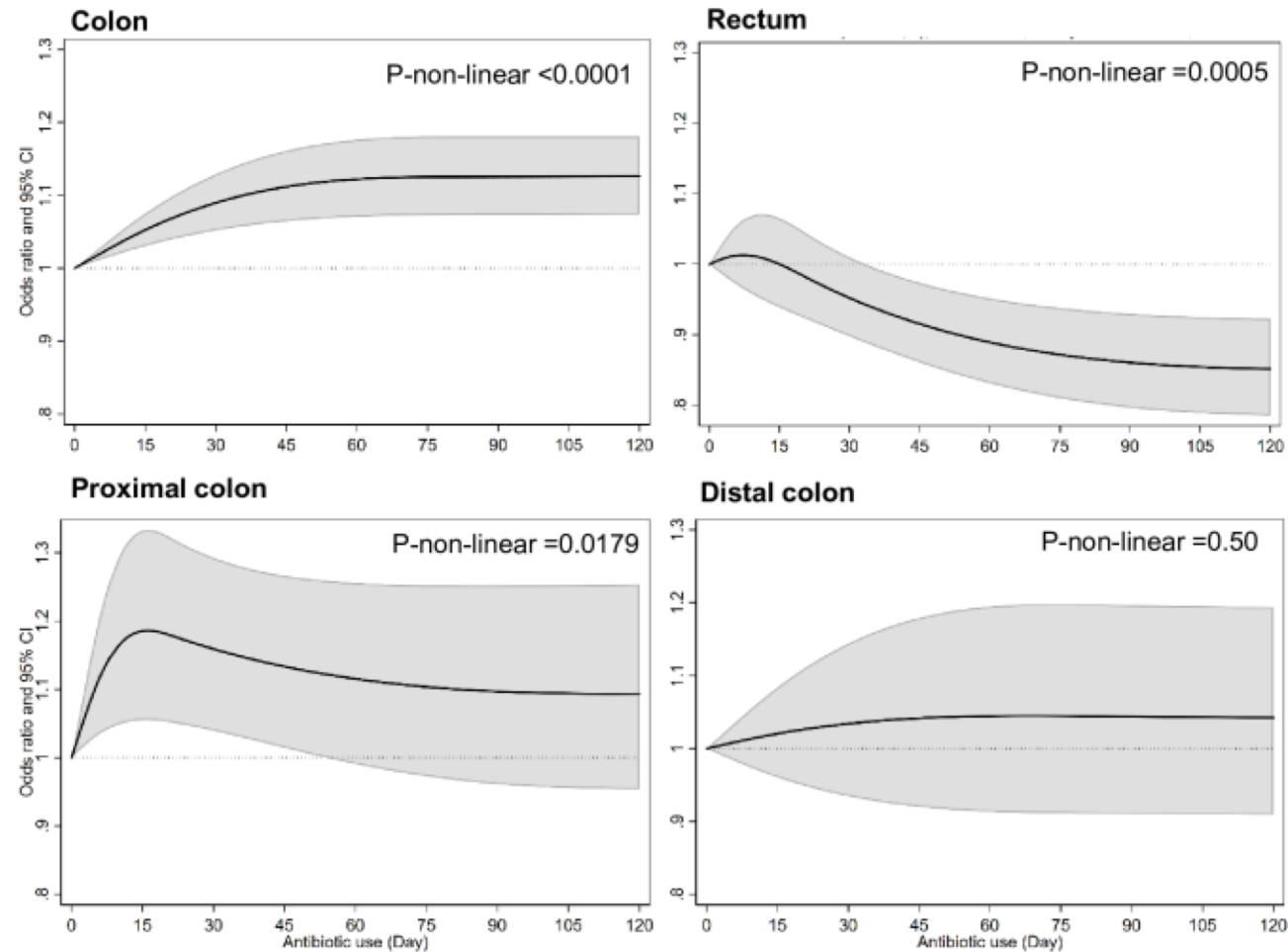
- Retrospective cohort of ~1,500 adult inpatients
- Admitted to general medicine wards
- Single academic medical center
- Reviews for adverse drug event (ADE) 30d after at least 24 hours of any parenteral or oral ABX
 - GI, dermatologic, musculoskeletal, hematologic, hepatobiliary, renal, cardiac and neurologic
 - 90d follow-up: *C difficile* or new multidrug-resistant infection
- Findings
 - 20% experienced at least 1 ADE
 - Of these ~300 patients, 56 (20%) were not clinically indicated
 - Every additional 10d of ABX had a 3% increased risk for ADE
 - GI (42%), renal (24%), and hematologic (15%) were most common
 - Notable differences for ADEs associated with specific ABX

Antibiotic Pressure and Generation of Antibiotic Resistance

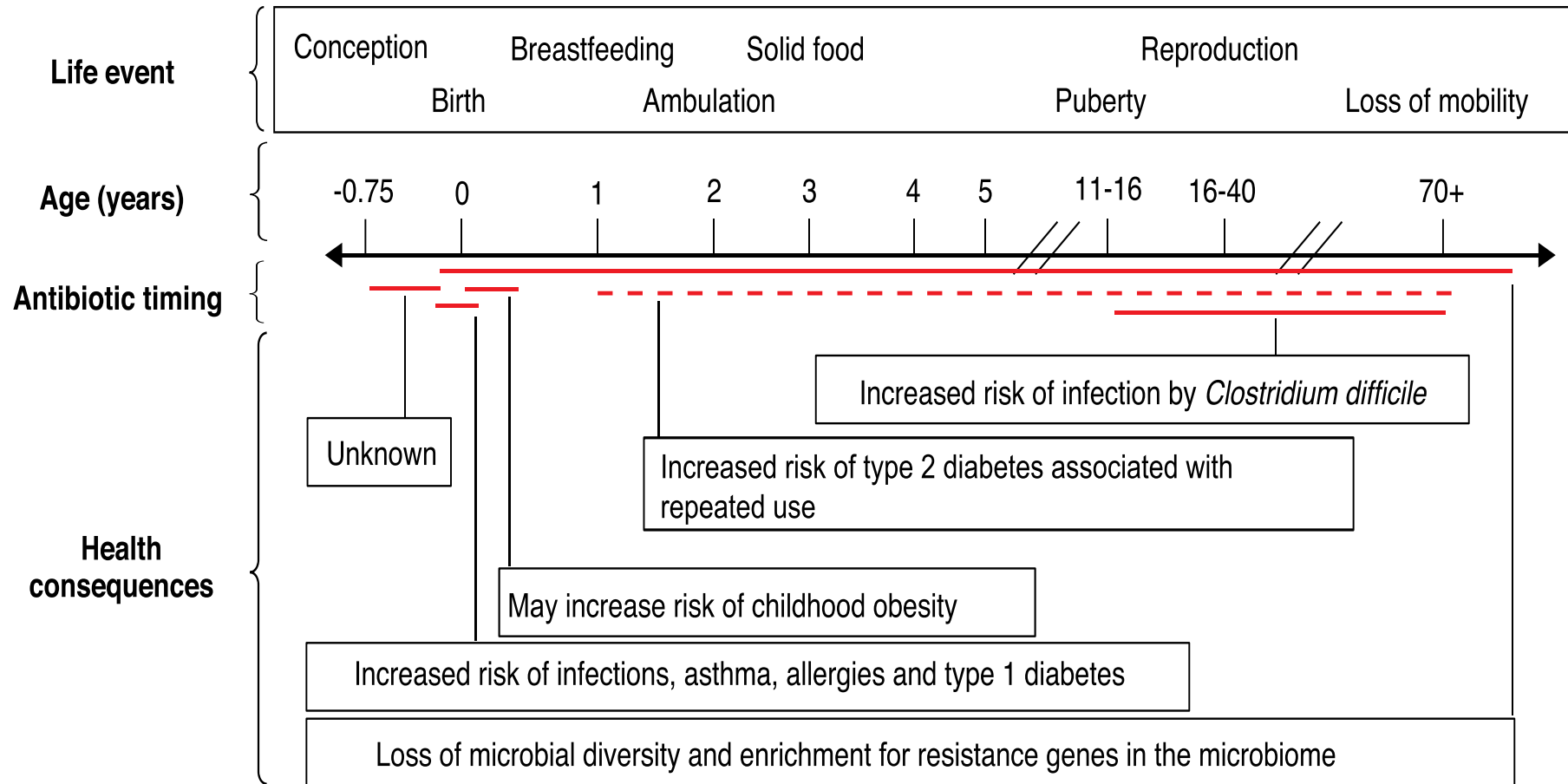
↓↓, Strong suppression; ↓, moderate suppression; ↑, increase in number; ↑↓, positive and negative effects seen in different studies. NC, No change detected; +, resistant strains detected. The table is adapted from the paper by Sullivan *et al.* (2001).

Antibiotic	Impact on:			Emergence of resistant strains in:	
	Anaerobes	Aerobic Gram positive cocci	Enterobacteria	Enterococci	Enterobacteria
Amoxicillin/clavulanic acid	NC	↑	↑	NC	NC
Ciprofloxacin (high conc. in faeces)	NC	NC	↓↓	NC	+
Clarithromycin/metronidazole	↓	↑	↓	+	+
Cephalosporins (high conc. in faeces)	NC	↑	↓↓	NC	+
Clindamycin	↓↓	↑	↑	+	+
Vancomycin	↓	↑↓	NC	+	+

Colorectal Cancer and Microbiome Disruption?



Health Consequences of Microbiome Disruption Across a Lifetime



Rethinking Our Relationship with Antibiotics

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 - Long-term consequences
- **Antibiotics remain “Drugs of Fear”**
- De-escalation is standard of care
- Shorter courses could be more common

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Shorter is More Common

- “The Antibiotic Course has had its Day” from BMJ July 2017
- Stopping early does NOT increase resistance
- What increases/causes resistance?
 - Inadequate dosing
 - Monotherapy where multiple drugs are required
 - Collateral selection
- Where did the idea of completing the full prescription for ABX come from?



https://en.wikipedia.org/wiki/Alexander_Fleming#/media/File:Synthetic_Production_of_Penicillin_TR1468.jpg

Few Controlled Trials – What’s Too Short of a Course?

Table 1| Indications for which duration of antibiotic treatment has been evaluated by randomised controlled trial

Indication	No of days treatment		Main evidence	Evidence on resistance
	Standard	Evaluated		
Otitis media ¹⁹	10	5	Clinical failure higher with 5 days than 10 days treatment (1 trial)	Similar short term selection of resistance in nasopharyngeal organisms
Streptococcal pharyngitis ²⁰	10	3-6	Comparable effect of 3-6 days oral antibiotics to 10 days penicillin in children with streptococcal throat infection (Cochrane review of 20 studies)	Not assessed
Community acquired pneumonia ²¹	7-10	5	Non-inferiority of 5 day course once afebrile and clinical stability improving compared with physician guided therapy (median 10 days) for clinical success (1 trial)	Not assessed. β -lactam treatment >5 days associated with greater carriage of resistant <i>S pneumoniae</i>
Cellulitis ²²	7-14	5	Non-inferiority of 5 day course compared with 10 days for clinical resolution (1 trial)	Not assessed
Pyelonephritis ^{23 24}	14	5-7	Non-inferiority of 7 v 14 days ciprofloxacin for cure ¹² and 5 days levofloxacin v 10 days ciprofloxacin for eradication of infection and clinical cure ¹³	Not assessed
Nosocomial pneumonia ^{25 26}	10-15	7-8	Non-inferiority of short course treatment of suspected pneumonia among critical care patients on ICU mortality and infection recurrence (multiple trials)	Lower risk of further or resistant infection in patients receiving shorter duration therapy
Intra-abdominal sepsis ²⁷	7-14	4	Non-inferiority of fixed 4 day course compared with physician guided therapy (median 8 days) for surgical site infection, recurrent intraabdominal infection, or death (1 trial)	Non-significantly lower rates of extra-abdominal resistant infection in short course group

Fear of undertreatment persists...

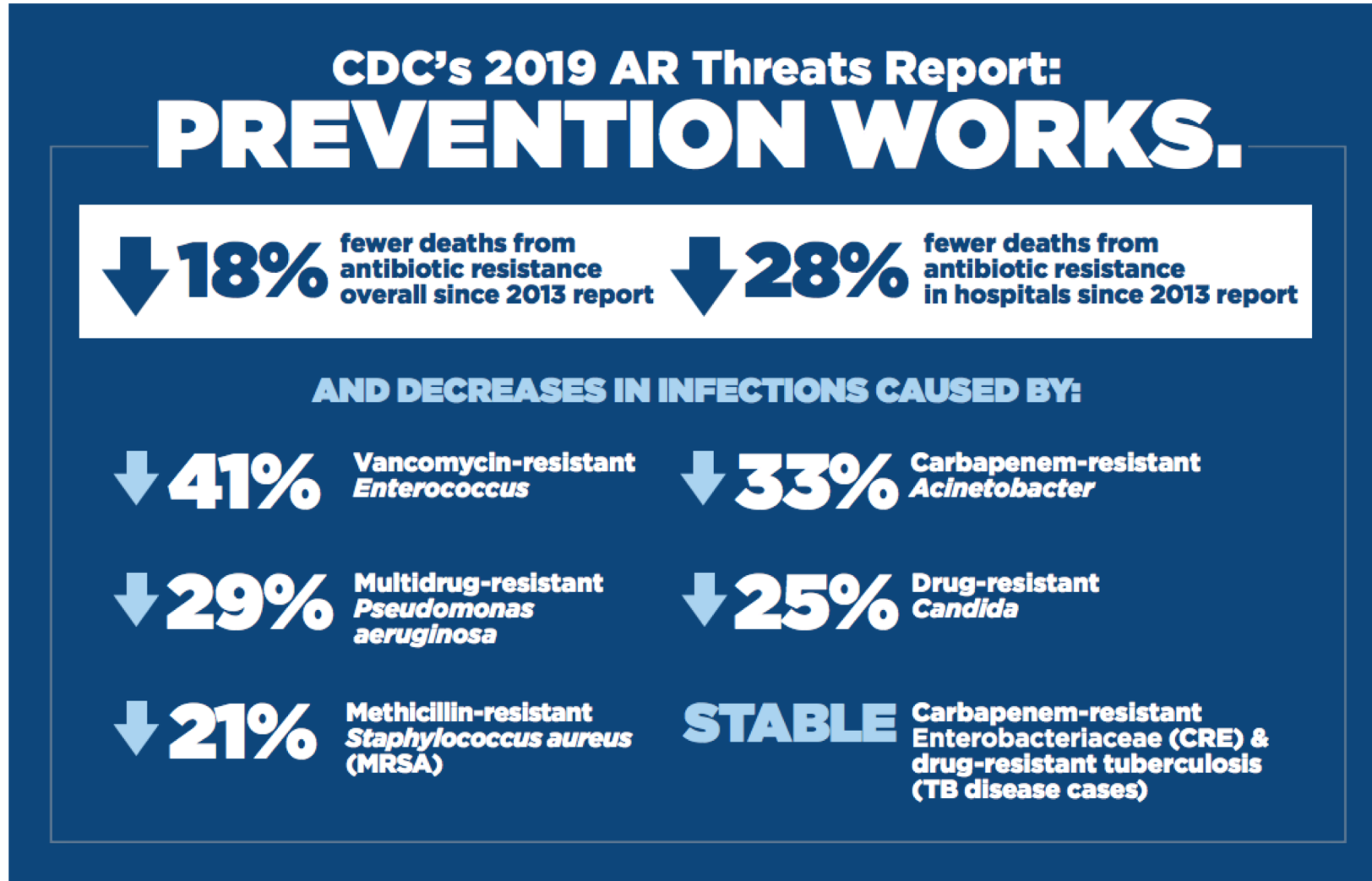
Info and Data to Improve Transparency: Pharmacy Can Help!

- Inpatient setting
 - Education → Just-in-time feedback
 - Antibiotic use measurements (AUR CDC NHSN)
 - Focused by type of antibiotic (broad vs. narrow) and by unit types
 - Prescriber report cards for antibiotics or specific infections
 - Clinical Pathways
- Outpatient settings
 - Education → public awareness
 - Communications training
 - Audit/feedback strategies
 - Clinical decision support
 - Delayed prescriptions

Impact of Antimicrobial Stewardship Programs

- 32 studies in a meta-analysis
- ASPs
 - Reduced incidence of infections and colonization with MDR gram negatives (IR 0.49), ESBLs (0.52), and MRSA (0.63)
 - Reduce incidence of *C difficile* infections (0.68)
- More effective with infection control measures (0.34) than alone

Impacts of Prevention/Intervention?



ASPs and COVID-19

Chinese Characters for Crisis



危機

Summary

- Antimicrobial resistance is a growing issue but pipeline for ABX development remains weak
- Antimicrobial stewardship programs in all healthcare settings are important to improve patient safety, tend to our antibiotics, and reduce AMR and collateral damage
- Pharmacists are critical for their expertise, their ability to intervene and coach prescribers, and are able to impact outcomes