Around the World of Antibiotic Resistance and Stewardship Policy

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Disclosure

- ReadyDock, Inc
  - Advisory Board, consultant
  - Not relevant to this presentation

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THE LANCET

LONDON : SATURDAY, MAY 21, 1955

Abuse of Antibiotics

But in three other hospitals the proportions of general medical patients treated with antibiotics were 32%, 38%, and 41%; and in HUSSAR's view these higher figures reflect a too liberal use of antibiotics. He proposed: (1) a press release from the symposium condemning the irrational use of antibiotics; (2) systematic education of students and doctors on how to use antibiotics; (3) education to persuade the lay public that antibiotics are not invariably required; and (4) organisation of a National Registry of Fatal Antibiotic Reactions to reveal the true incidence of such accidents.

Allen Hussar

This is Medical Progress?

Trends and Consequences of Antibiotic Use in the United States

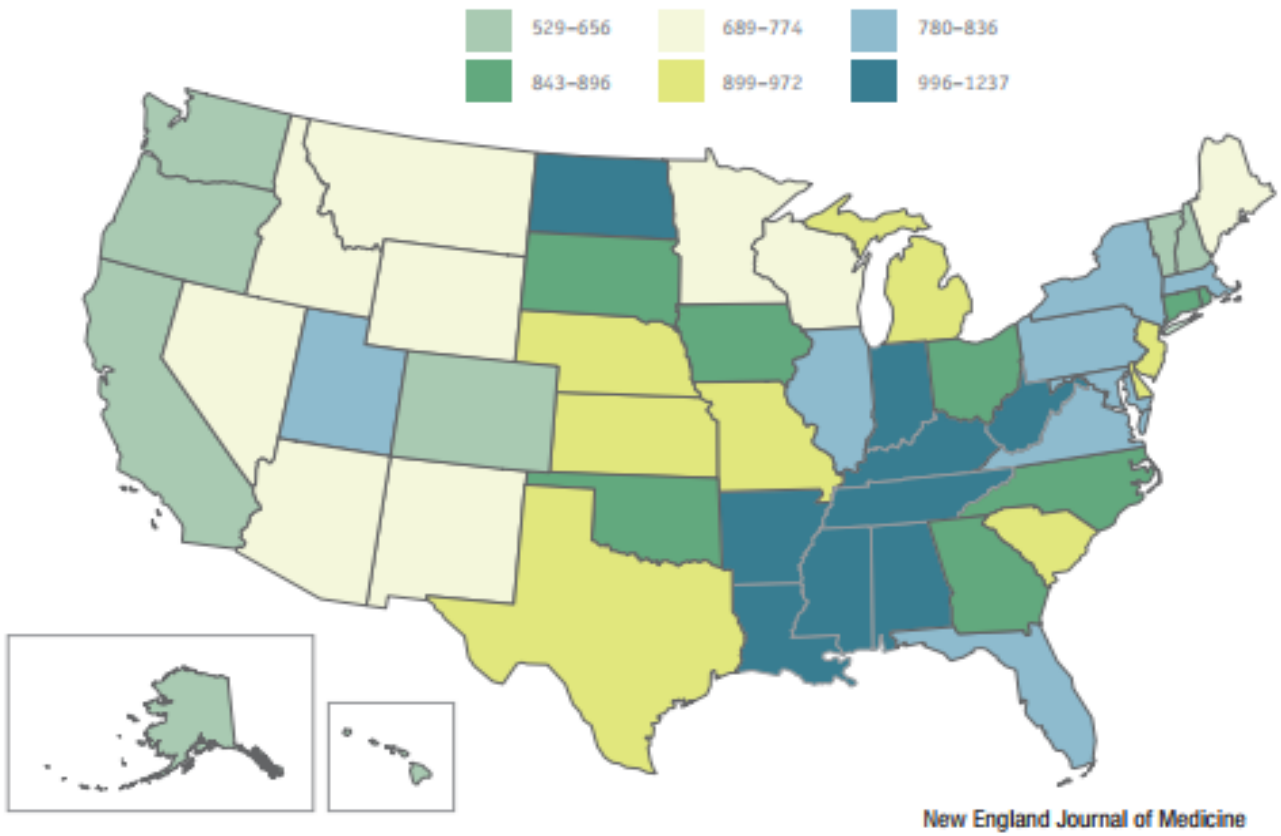
JAMA
THE JOURNAL of the American Medical Association
March 4, 1974 Vol 227, No 9

This group agreed that there appears to be "an inappropriate use of antibiotics and a massive overuse." They recommended the initiation of antibiotic usage review programs in hospitals that would contain the following features:

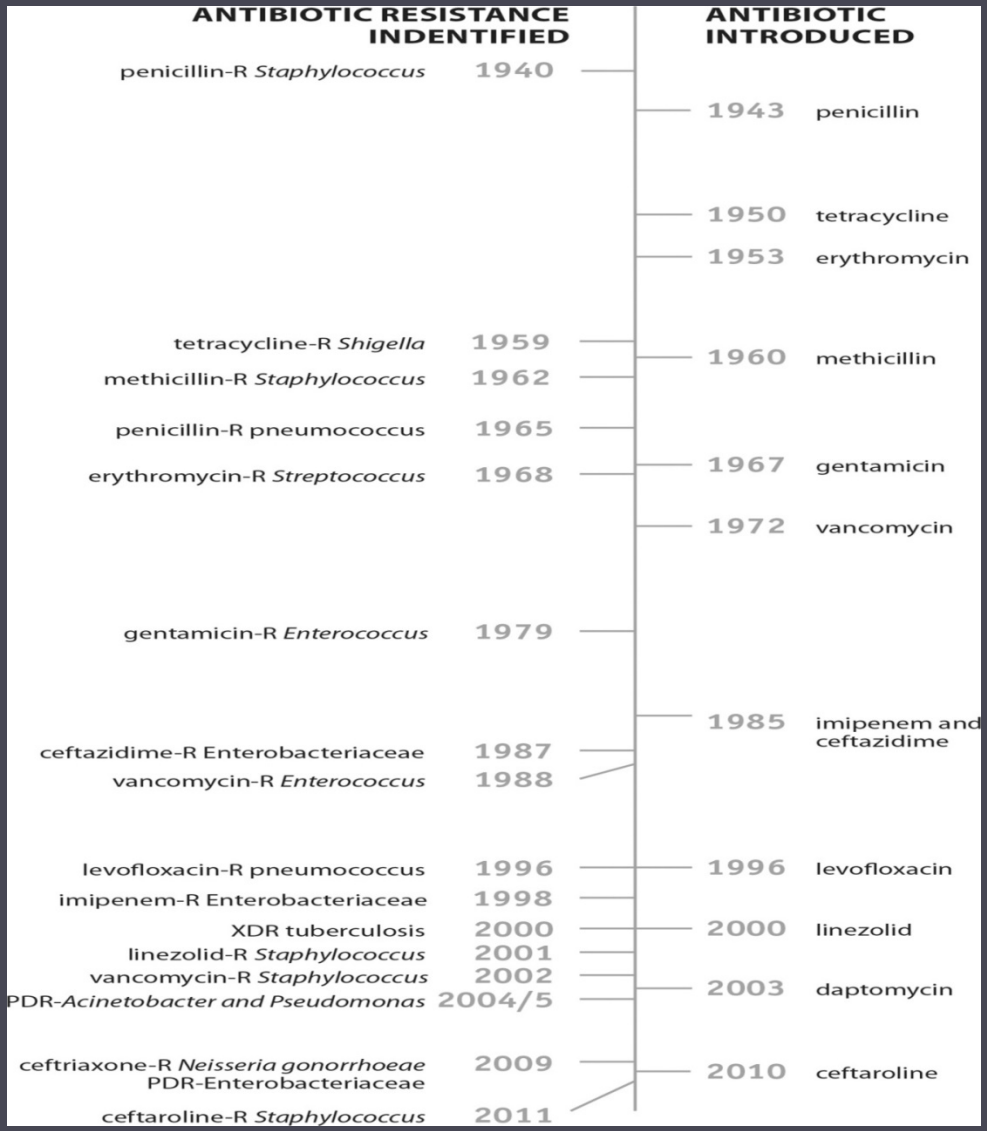
1. Each hospital should form a committee to monitor antibiotic usage.
2. The committee should develop individualized guidelines for appropriate antibiotic usage both for treatment and prophylaxis. These guidelines should be approved by the executive committee of the medical staff.
3. The report of the antibiotic committee would be distributed internally to the medical staff and the executive committee.
4. There would be an annual review of antibiotic usage by an outside consultant who would submit written recommendations to the executive committee.

Henry Simmons and Paul Stolley

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



The frequency with which doctors prescribe antibiotics varies greatly from state to state. The reasons for this variation are being studied and might suggest areas where improvements in antibiotic prescribing (fewer unnecessary prescriptions) would be most helpful.



- Resistance is an inevitable evolutionary outcome
- All organisms develop genetic mutations to avoid lethal selection pressure
- More than 70% pathogenic bacteria resistant to ≥1 antibiotic

Infectious Disease Clinics 2016 30, 313-322DOI: (10.1016/j.idc.2016.02.001)

Environmental reserves of resistance

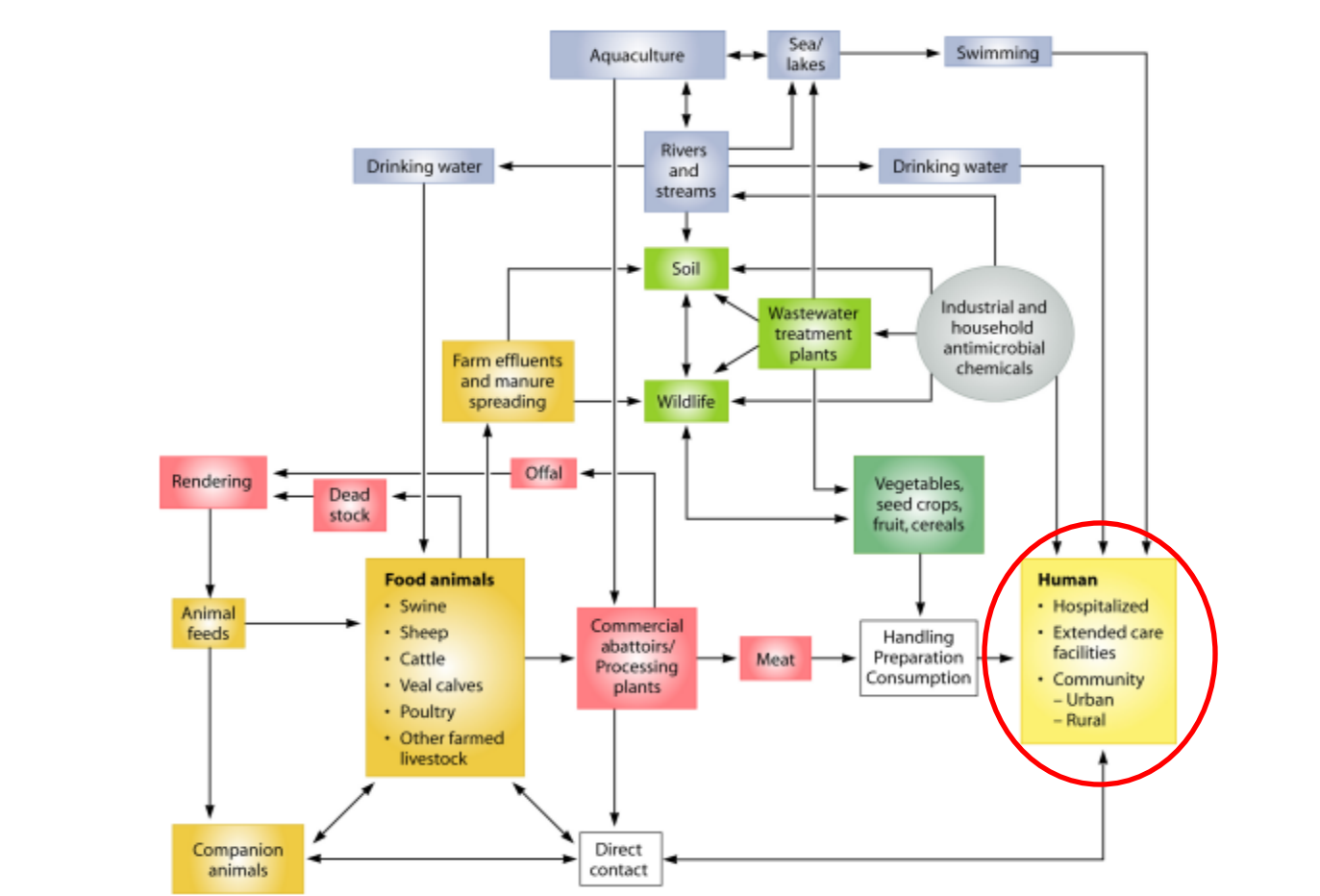
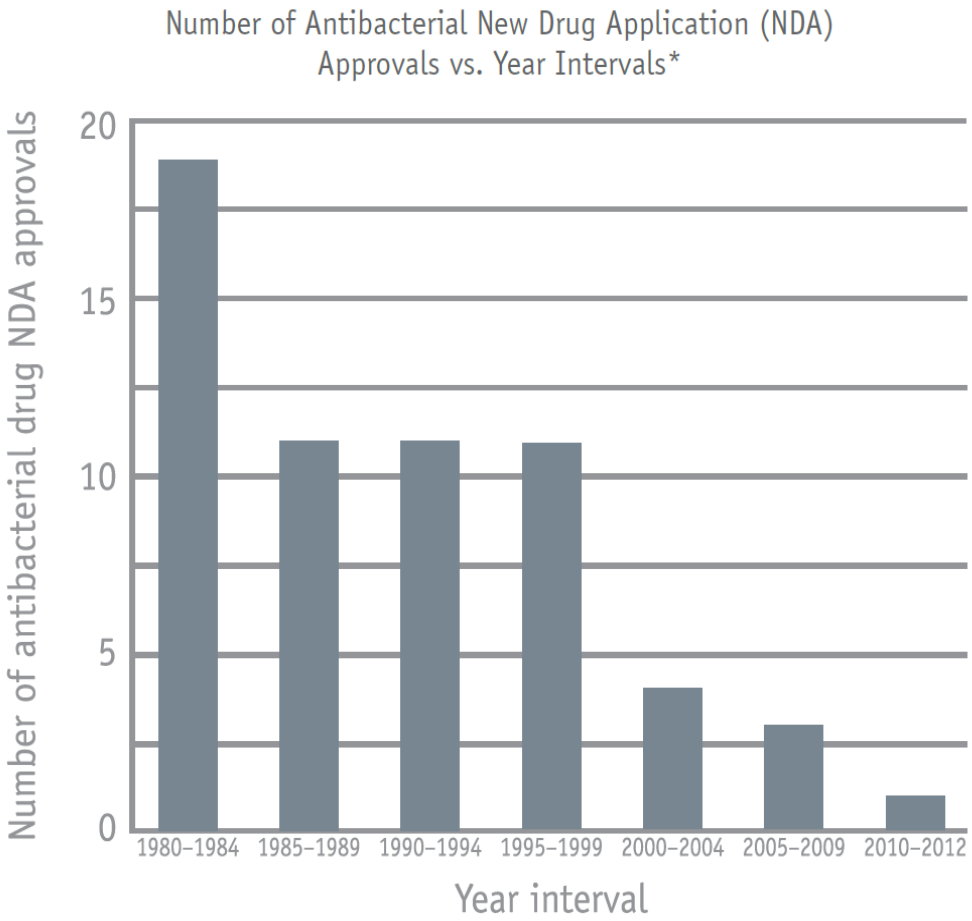


FIG. 4. Dissemination of antibiotics and antibiotic resistance within agriculture, community, hospital, wastewater treatment, and associated environments. (Adapted from reference 49 and reference 83a with permission of the publishers.)

Microbiology and Molecular Biology Reviews 2010; 74:417-433

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

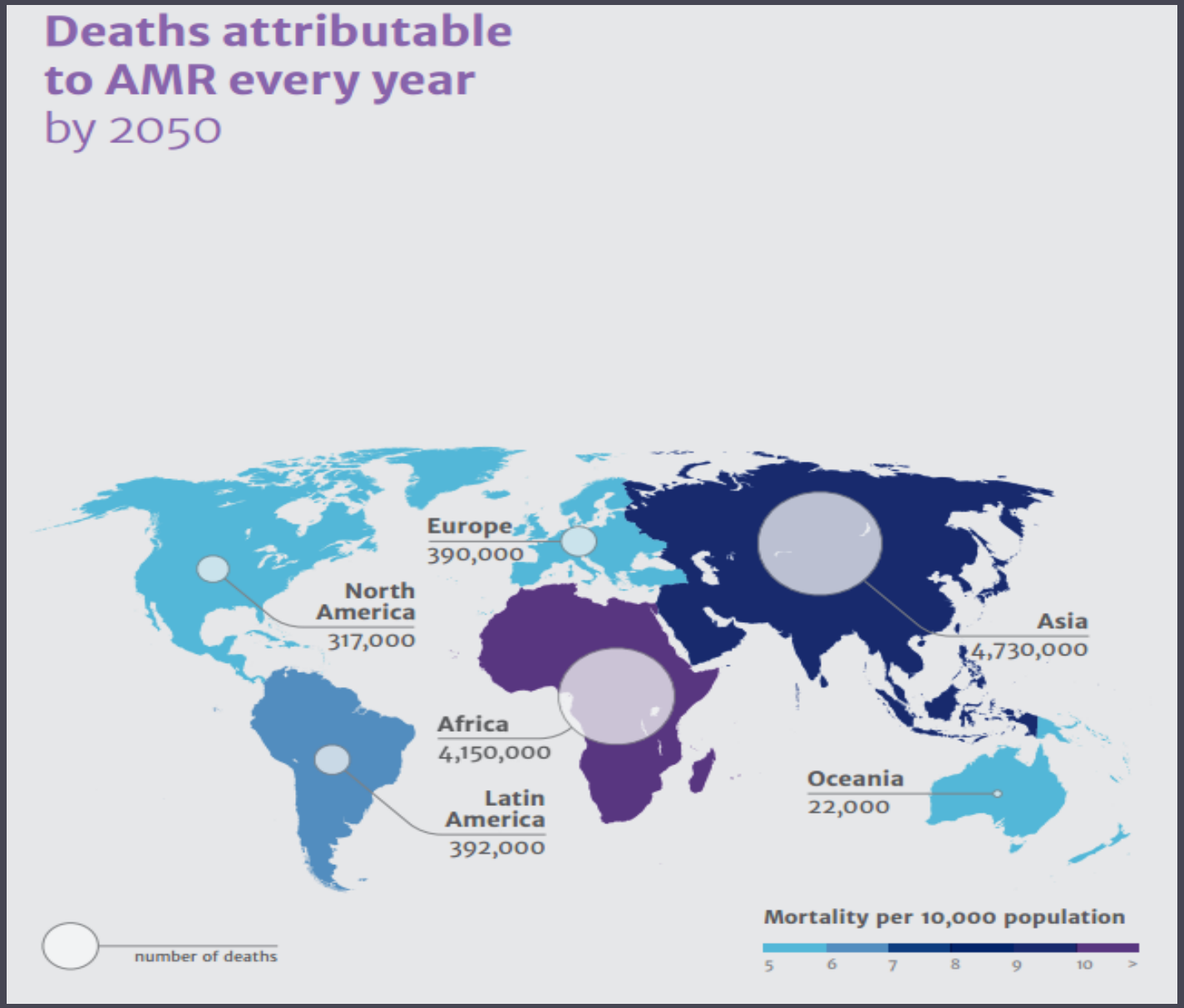


*Intervals from 1980–2009 are 5-year intervals; 2010–2012 is a 3-year interval. Drugs are limited to systemic agents.
Data courtesy of FDA' s Center for Drug Evaluation and Research (CDER).

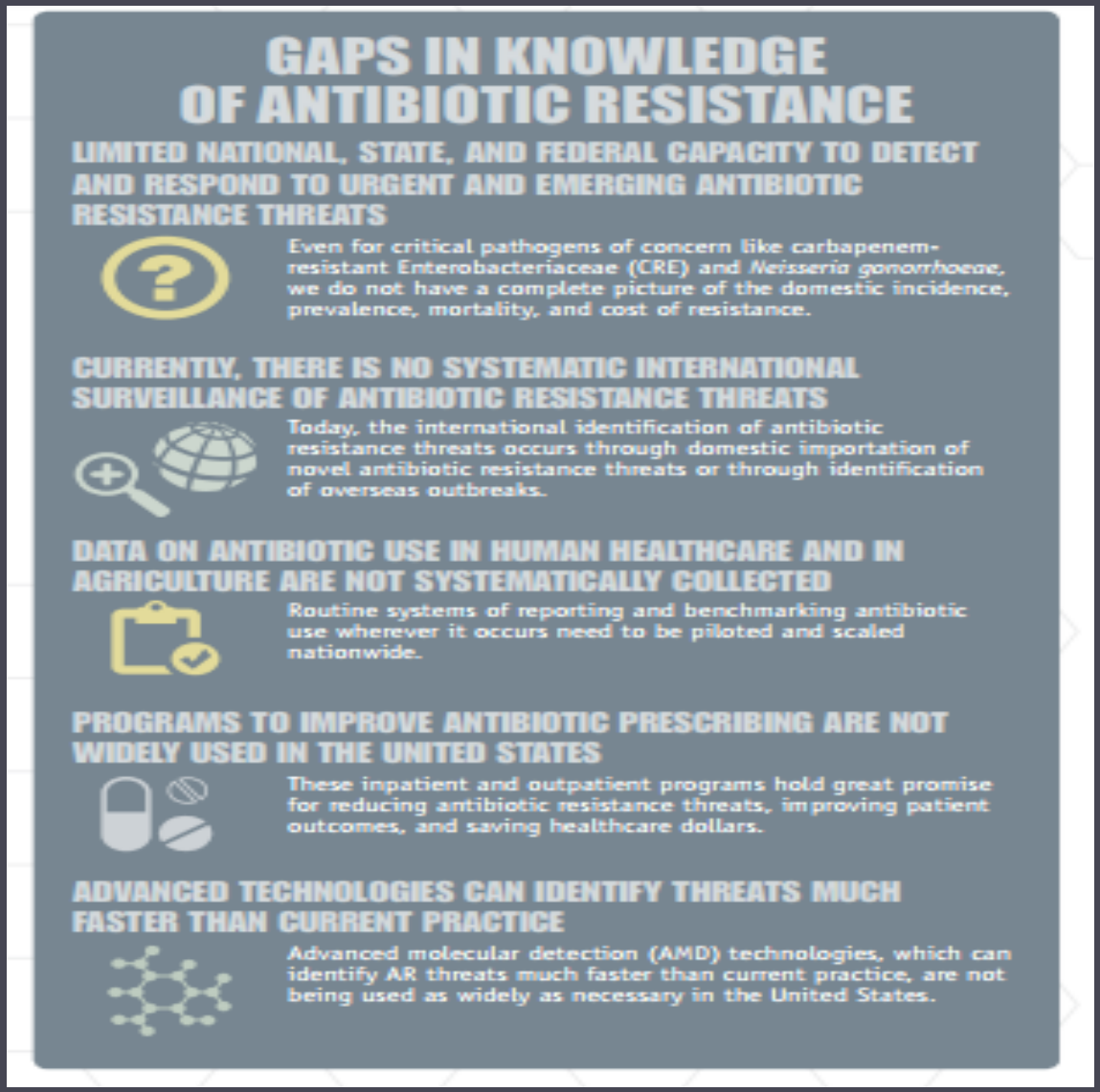
Status of Antimicrobial Resistance: 2017

New resistance mechanisms emerging and spreading globally, threatening ability to treat common infectious diseases, resulting in prolonged illness, disability, and death.

- Pan resistant infections becoming more common
- Global variation in resistance patterns
- Slow pace of discovery of novel antibiotics
- Antibiotic use continues to rise
  - Global consumption increased 40% between 2000 and 2010
- All microbes have the potential to mutate
- Speed and volume of intercontinental travel creates new opportunities to spread resistance

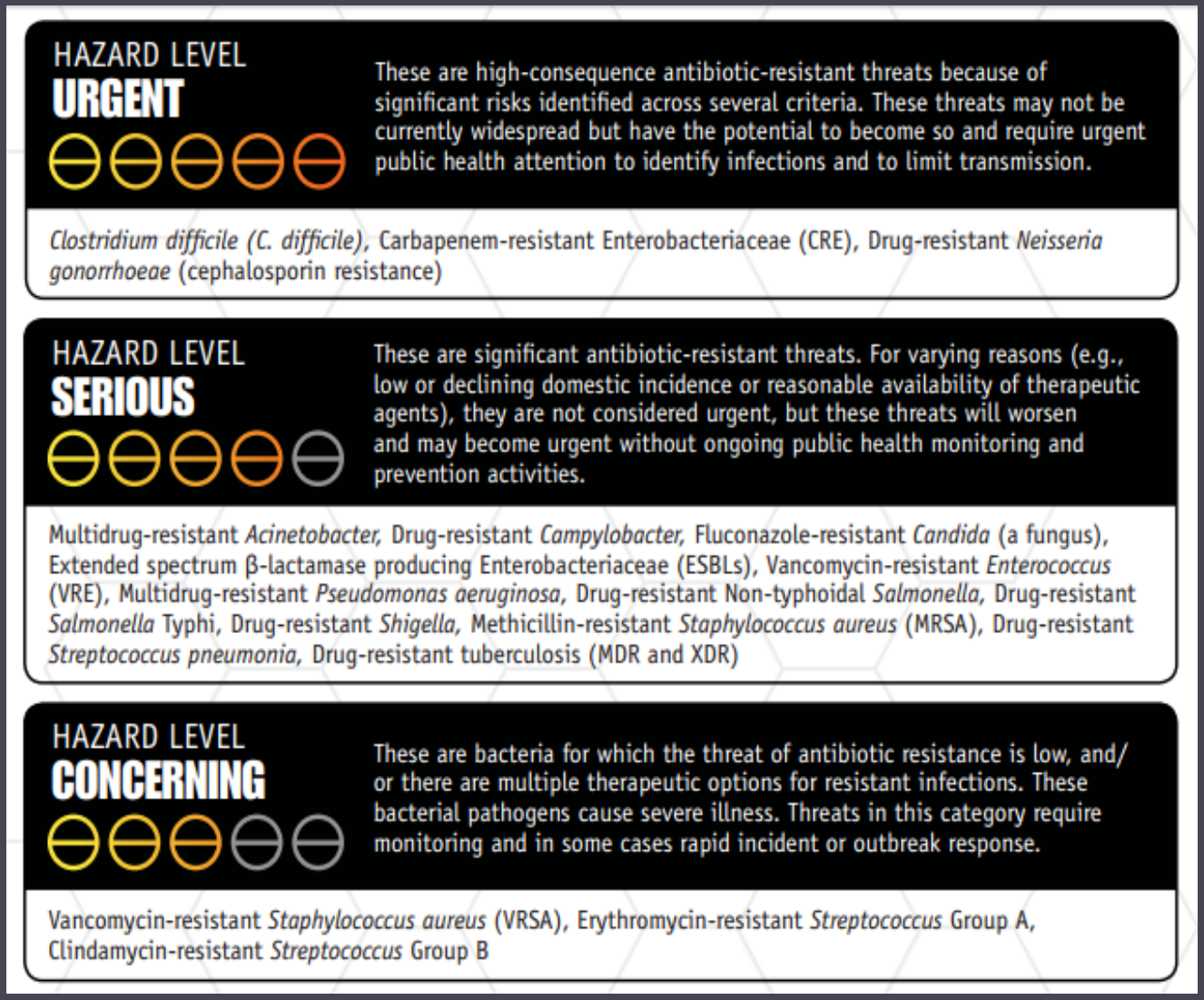


The Review on Antimicrobial Resistance, Chaired by Jim O'Neill


GAPS IN KNOWLEDGE OF ANTIBIOTIC RESISTANCE
LIMITED NATIONAL, STATE, AND FEDERAL CAPACITY TO DETECT AND RESPOND TO URGENT AND EMERGING ANTIBIOTIC RESISTANCE THREATS
Even for critical pathogens of concern like carbapenem-resistant Enterobacteriaceae (CRE) and Neisseria gonorrhoeae, we do not have a complete picture of the domestic incidence, prevalence, mortality, and cost of resistance.
CURRENTLY, THERE IS NO SYSTEMATIC INTERNATIONAL SURVEILLANCE OF ANTIBIOTIC RESISTANCE THREATS
Today, the international identification of antibiotic resistance threats occurs through domestic importation of novel antibiotic resistance threats or through identification of overseas outbreaks.
DATA ON ANTIBIOTIC USE IN HUMAN HEALTHCARE AND IN AGRICULTURE ARE NOT SYSTEMATICALLY COLLECTED
Routine systems of reporting and benchmarking antibiotic use wherever it occurs need to be piloted and scaled nationwide.
PROGRAMS TO IMPROVE ANTIBIOTIC PRESCRIBING ARE NOT WIDELY USED IN THE UNITED STATES
These inpatient and outpatient programs hold great promise for reducing antibiotic resistance threats, improving patient outcomes, and saving healthcare dollars.
ADVANCED TECHNOLOGIES CAN IDENTIFY THREATS MUCH FASTER THAN CURRENT PRACTICE
Advanced molecular detection (AMD) technologies, which can identify AR threats much faster than current practice, are not being used as widely as necessary in the United States.

CDC 2013

CDC's Antibiotic-Resistant Threats (2013)



Colistin resistance: mcr-1 gene

- mcr-1 gene found in Chinese livestock and hospital patients in 2015
  - Plasmid mediated colistin resistance
  - Reported in companion animals associated with a patient
  - One of world's largest producer and user of colistin
    - Agriculture and livestock
- *E. coli* with mcr-1 (colistin resistance) and *bla*NDM-5 (carbapenem resistance) genes
  - August 2014, urine sample in US (first reported 2016)
    - 76 yo man, emigrated from India, lived in US continuously for 1 year
    - Separate plasmids, could spread to other bacteria

"Colistin resistance: a major breach in our last line of defense"

Patterson DJ, Harris PNA; Lancet Inf Dis, November 18, 2015

FIGHTING BACK AGAINST ANTIBIOTIC RESISTANCE

Four Core Actions to Prevent Antibiotic Resistance

1 PREVENTING INFECTIONS, PREVENTING THE SPREAD OF RESISTANCE

Avoiding infections in the first place reduces the amount of antibiotics that have to be used and reduces the likelihood that resistance will develop during therapy. There are many ways that drug-resistant infections can be prevented: immunization, safe food preparation, handwashing, and using antibiotics as directed and only when necessary. In addition, preventing infections also prevents the spread of resistant bacteria.

2 TRACKING

CDC gathers data on antibiotic-resistant infections, causes of infections and whether there are particular reasons (risk factors) that caused some people to get a resistant infection. With that information, experts can develop specific strategies to prevent those infections and prevent the resistant bacteria from spreading.

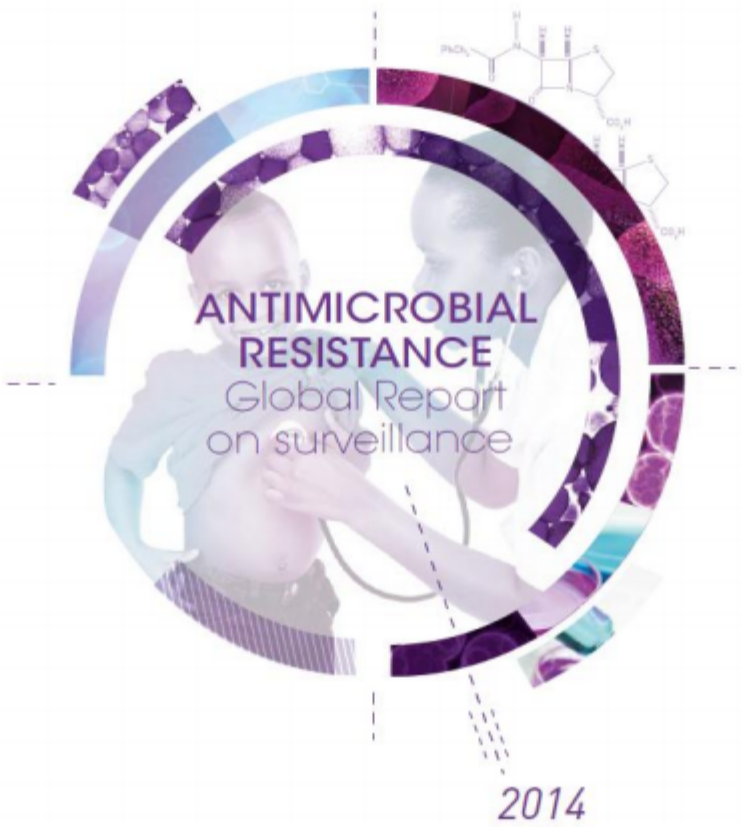
3 IMPROVING ANTIBIOTIC PRESCRIBING/STEWARDSHIP

Perhaps the single most important action needed to greatly slow down the development and spread of antibiotic-resistant infections is to change the way antibiotics are used. Up to half of antibiotic use in humans and much of antibiotic use in animals is unnecessary and inappropriate and makes everyone less safe. Stopping even some of the inappropriate and unnecessary use of antibiotics in people and animals would help greatly in slowing down the spread of resistant bacteria. This commitment to always use antibiotics appropriately and safely—only when they are needed to treat disease, and to choose the right antibiotics and to administer them in the right way in every case—is known as antibiotic stewardship.

4 DEVELOPING NEW DRUGS AND DIAGNOSTIC TESTS

Because antibiotic resistance occurs as part of a natural process in which bacteria evolve, it can be slowed but not stopped. Therefore, we will always need new antibiotics to keep up with resistant bacteria as well as new diagnostic tests to track the development of resistance.

CDC 2013



World Health Organization

Estimates of Burden of Antibacterial Resistance

European Union
population 500m

25,000 deaths per year

2.5m extra hospital days

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

Source: ECDC 2007

Thailand
population 70m

>38,000 deaths

>3.2m hospital days

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

Source: Pumart et al 2012

United States
population 300m

>23,000 deaths

>2.0m illnesses

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

Source: US CDC 2013

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

Selected Bacteria/Resistance Combinations

Bacterium	Resistance/ decreased susceptibility to:
Escherichia coli	3rd generation cephalosporins, fluoroquinolones
Klebsiella pneumoniae	3rd generation cephalosporins, carbapenems
Staphylococcus aureus	Methicillin (beta-lactam antibiotics) i.e. MRSA
Streptococcus pneumoniae	Penicillin
Nontyphoidal *Salmonella* (NTS)	Fluoroquinolones
Shigella species	Fluoroquinolones
Neisseria gonorrhoeae	3rd generation cephalosporins

Bacteria Commonly Causing Infections in Hospitals and Communities

Name of bacterium/ resistance	Examples of typical diseases	No. of 194 MS providing national data	No. of WHO regions with national reports of 50 % resistance or more	Range of reported proportion of resistance
Escherichia coli	Urinary tract infections, blood stream infections			
-vs 3rd gen. cephalosporins		84	5/6	0-82
-vs fluoroquinolones		90	5/6	3-96
Klebsiella pneumoniae	Pneumonia, blood stream infections, urinary tract infections			
-vs 3rd gen. cephalosporins		85	6/6	2-82
-vs carbapenems		69	2/6	0-68
Staphylococcus aureus	Wound infections, blood stream infections			
-vs methicillin "MRSA"		83	5/6	0.3-90

Bacteria Mainly Causing Infections in the Community

Name of bacterium/ resistance	Examples of typical diseases	No. of 194 MS providing national data	No. of WHO regions with national reports of 25 % resistance or more	Range of reported proportion of resistance
Streptococcus pneumoniae	Pneumonia, meningitis, otitis			
-non-susceptible to penicillin		66	6/6	0-73
Nontyphoidal *Salmonella*	Foodborne diarrhoea, blood stream infections			
-vs fluoroquinolones		66	3/6	0-96
***Shigella* species**	Diarrhoea ("bacillary dysenteria")			
- vs fluoroquinolones		34	2/6	0-47
Neisseria gonorrhoeae	Gonorrhoea			
-vs 3rd gen. cephalosporins		42	3/6	0-36

World Health Organization

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL#

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae**, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter*, fluoroquinolone-resistant
- *Salmonella* spp., fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

Mycobacteria (including *Mycobacterium tuberculosis*, the cause of human tuberculosis), was not subjected to review for inclusion in this prioritization exercise as it is already a globally established priority for which innovative new treatments are urgently needed.

* Enterobacteriaceae include: *Klebsiella pneumonia*, *Escherichia coli*, *Enterobacter* spp., *Serratia* spp., *Proteus* spp., and *Providencia* spp, *Morganella* spp.

The goal of the global action plan is to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them. It is expected that countries will develop their own *national action plans* on antimicrobial resistance in line with the global plan.

To achieve this goal, the global action plan sets out five strategic objectives: (1) to improve awareness and understanding of antimicrobial resistance; *(2) to strengthen knowledge through surveillance and research*; (3) to reduce the incidence of infection; (4) to optimize the use of antimicrobial agents; and (5) to ensure sustainable investment in countering antimicrobial resistance.

Global Antimicrobial Resistance Surveillance System (GLASS)

Surveillance of antimicrobial resistance

In May 2015, the Sixty-eighth World Health Assembly adopted the global action plan on antimicrobial resistance. One of the five strategic objectives of the action plan is to strengthen the evidence base through enhanced global surveillance and research.

Table 1. Five-year road map for implementation of GLASS

Year	Targets
2015	Prepare manual, set up IT hub and plan support for implementation of GLASS. Establish a platform for international collaboration with WHO collaborating centres, national and regional networks and other laboratories and institutions to allow WHO to support countries in implementing GLASS. Initiate country enrolment.
2016	Start collection of baseline data on human antibacterial-resistant infections from WHO Member States. Report on progress in implementation. Target the participation of 15% of Member States.
2017	Consolidate baseline data collection on human antibacterial-resistant infections from WHO Member States. Increase the capacity of the platform to build relations with other AMR surveillance systems (e.g. in animal health, agriculture and use and consumption of antibiotics). Extend Member States participation to 20%.
2018	Report on the global and regional AMR data in human health. Explore the feasibility of case-finding by surveillance of clinical syndromes at selected surveillance sites. Extend Member States participation to 30%.
2019	Review lessons learnt from early implementation to inform further development of GLASS. Extend Member States participation to 40%.

Antibiotic Resistance (AR) Solutions Initiative: State HAI/AR Prevention Programs

With State Healthcare-Associated Infections and Antibiotic Resistance (HAI/AR) Prevention Programs, healthcare facilities and public health work together to better prevent infections and protect patients.

Lack of prevention coordination between facilities can put patients at increased risk of infection.

- Patients can be transferred between healthcare facilities for treatment without communication or necessary infection control actions in place.
- Germs can spread within and between healthcare facilities, so precautions must be in place at facilities transferring and receiving patients to stop spread.
- Even as some facilities work independently to improve infection control, they may not be alerted to resistant threats occurring in other facilities or outbreaks in the area.

Work together to better detect outbreaks, prevent infections, and improve prescribing.

With a coordinated approach, healthcare facilities and public health authorities share information and implement targeted infection prevention and control actions.

The Coordinated Approach

Public health departments will
- Use HAI/AR data to target infection prevention and outbreak control
- Enhance communication between facilities for patient transfer
- Improve infection control, prevention, and antibiotic stewardship across healthcare and communities

Healthcare facilities will
- Use CDC's National Healthcare Safety Network and other data systems to track resistance, antibiotic use, and to target prevention
- Share information and work with local public health authorities to prevent and control infections
- Send isolates to the AR Lab Network to identify outbreaks and emerging threats

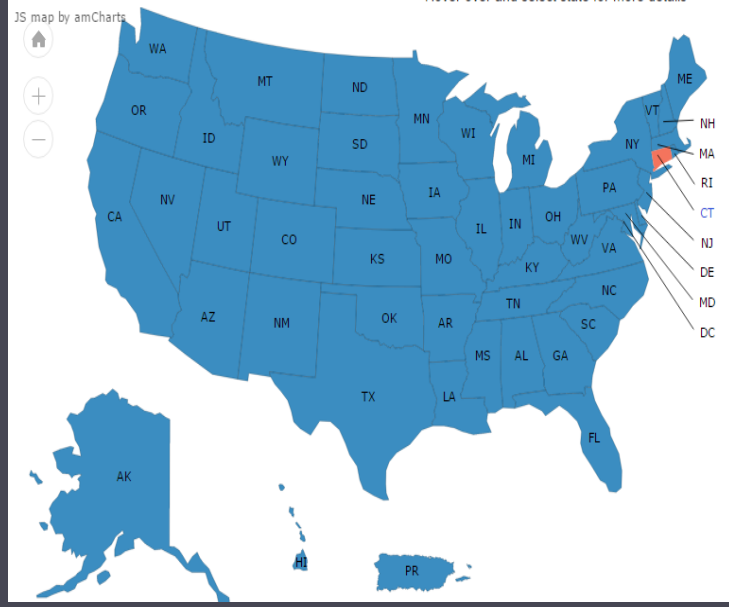
CDC will continue to
- Detect, track, and control outbreaks
- Promote infection prevention and appropriate antibiotic use
- Detect AR by providing gold-standard laboratory methods and isolates that support development of new diagnostics

When healthcare facilities and public health work together, we can protect patients and slow antibiotic resistance.

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

Key Investments to Combat Antibiotic Resistance

*Hover over and select state for more details



Learn more about CDC activities to combat antibiotic resistance.


AR Solutions in Action
CDC's Investments to Combat Antibiotic Resistance Threats Nationwide
FISCAL YEAR 2016

CONNECTICUT

$2,411,720

Funding for AR Activities
Fiscal Year 2016

One of 10 sites for the Emerging Infection Program

FUNDING TO STATE HEALTH DEPARTMENTS

$573,719

HAI/AR DETECT & RESPOND PROGRAMS quickly detect and then contain the spread of resistant infections, protecting patients from new resistance threats.

$560,446

FOOD SAFETY projects protect communities by rapidly identifying drug-resistant foodborne bacteria to stop and solve outbreaks and improve prevention.

$1,027,834

EMERGING INFECTIONS PROGRAM (EIP) sites improve public health by translating population-based surveillance and research activities into informed policy and public health practice.

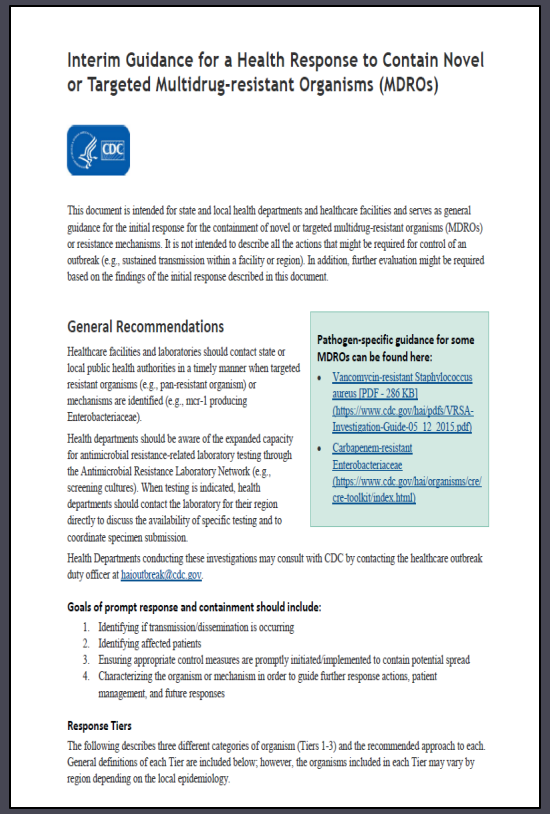
Critical support empowering the nation to tackle antibiotic resistance, the global threat jeopardizing modern medicine.

www.cdc.gov/drugresistance

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

3-Tier System

- *Tier 1* Organisms
  - 'Novel' resistance mechanisms (never previously identified or very rarely identified in US)
  - Pan-resistant isolates
  - Resistance mechanisms with limited experience regarding risks of transmission, groups at risk
- *Tier 2* Organisms
  - Resistance mechanisms rare to region
  - Defined risks of transmission, groups at risk
- *Tier 3* Organisms
  - Established resistance mechanisms
  - Defined risks of transmission, groups at risk



Interim Guidance for a Health Response to Contain Novel or Targeted Multidrug-resistant Organisms (MDROs)

This document is intended for state and local health departments and healthcare facilities and serves as general guidance for the initial response for the containment of novel or targeted multidrug-resistant organisms (MDROs) or resistance mechanisms. It is not intended to describe all the actions that might be required for control of an outbreak (e.g., sustained transmission within a facility or region). In addition, further evaluation might be required based on the findings of the initial response described in this document.

General Recommendations

Healthcare facilities and laboratories should contact state or local public health authorities in a timely manner when targeted resistant organisms (e.g., pan-resistant organism) or mechanisms are identified (e.g., mcr-1 producing Enterobacteriaceae).

Health departments should be aware of the expanded capacity for antimicrobial resistance-related laboratory testing through the Antimicrobial Resistance Laboratory Network (e.g., screening cultures). When testing is indicated, health departments should contact the laboratory for their region directly to discuss the availability of specific testing and to coordinate specimen submission.

Pathogen-specific guidance for some MDROs can be found here:

- Vancomycin-resistant Staphylococcus aureus [PDF - 786 KB] (https://www.cdc.gov/hai/pdfs/VRSA-Investigation-Guide-05_12_2015.pdf)
- Carbapenem-resistant Enterobacteriaceae (https://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html)

Health Departments conducting these investigations may consult with CDC by contacting the healthcare outbreak duty officer at haioutbreak@cdc.gov.

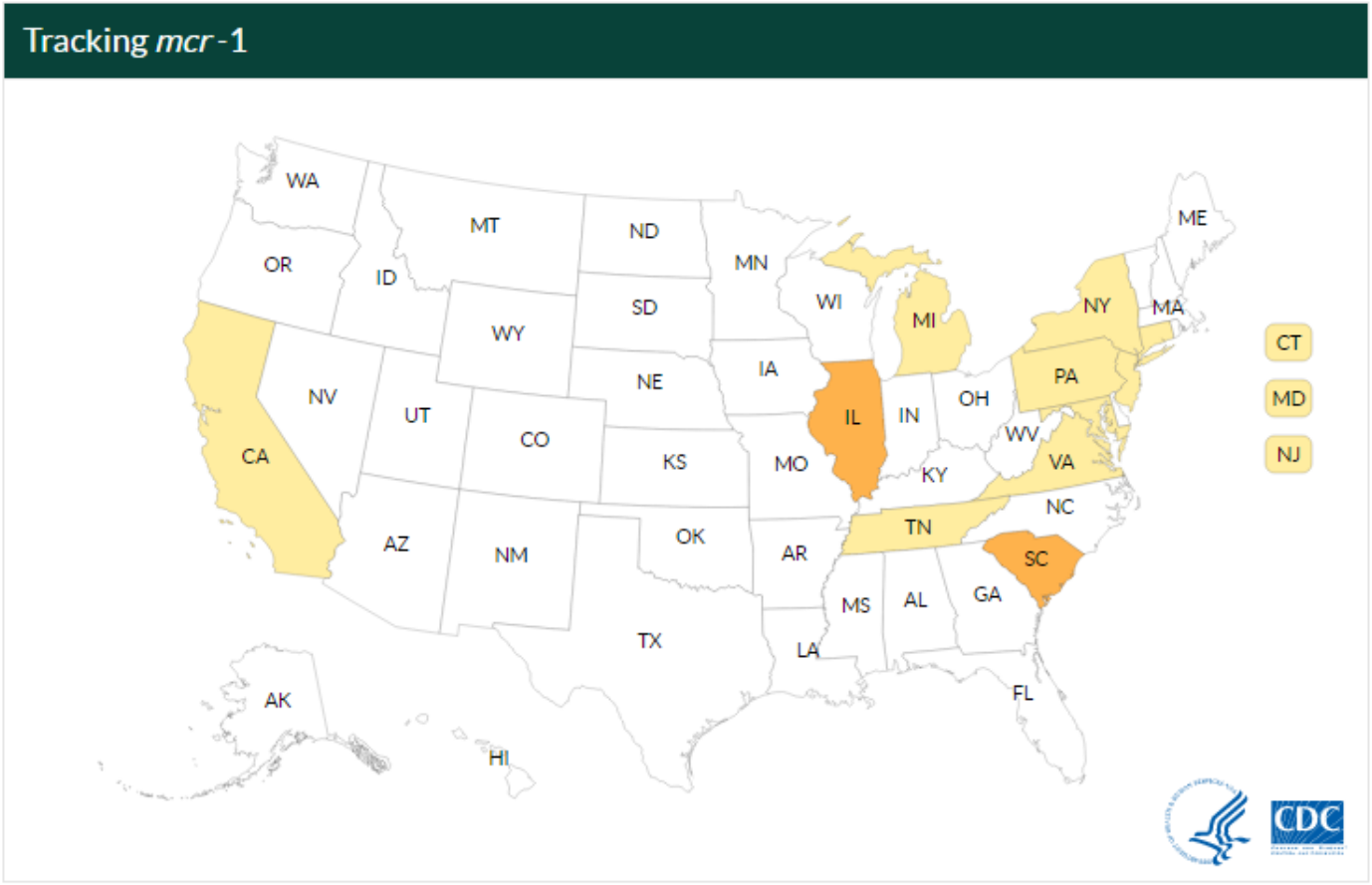
Goals of prompt response and containment should include:

1. Identifying if transmission/dissemination is occurring
2. Identifying affected patients
3. Ensuring appropriate control measures are promptly initiated/implemented to contain potential spread
4. Characterizing the organism or mechanism in order to guide further response actions, patient management, and future responses

Response Tiers

The following describes three different categories of organism (Tiers 1-3) and the recommended approach to each. General definitions of each Tier are included below; however, the organisms included in each Tier may vary by region depending on the local epidemiology.

Keeping Connecticut Healthy
DPH
Connecticut Department of Public Health

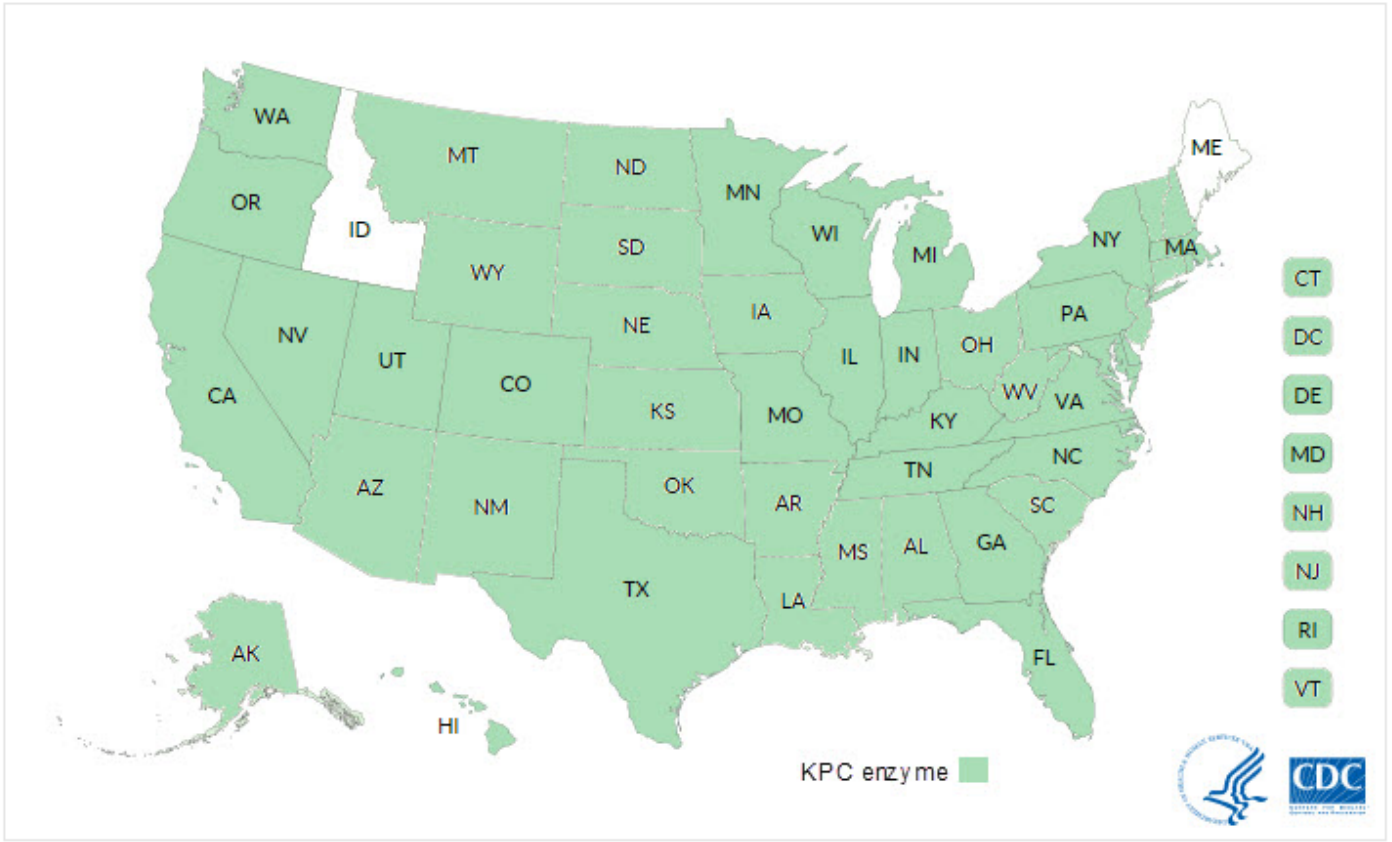


Total *mcr-1* producing human isolates reported to CDC to date: 13
CT isolates: 2

https://www.cdc.gov/drugresistance/tracking-mcr1.html

Keeping Connecticut Healthy
DPH
Connecticut Department of Public Health

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



Top of Page

KPC-producing CRE is considered widespread- exact case counts are not provided

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

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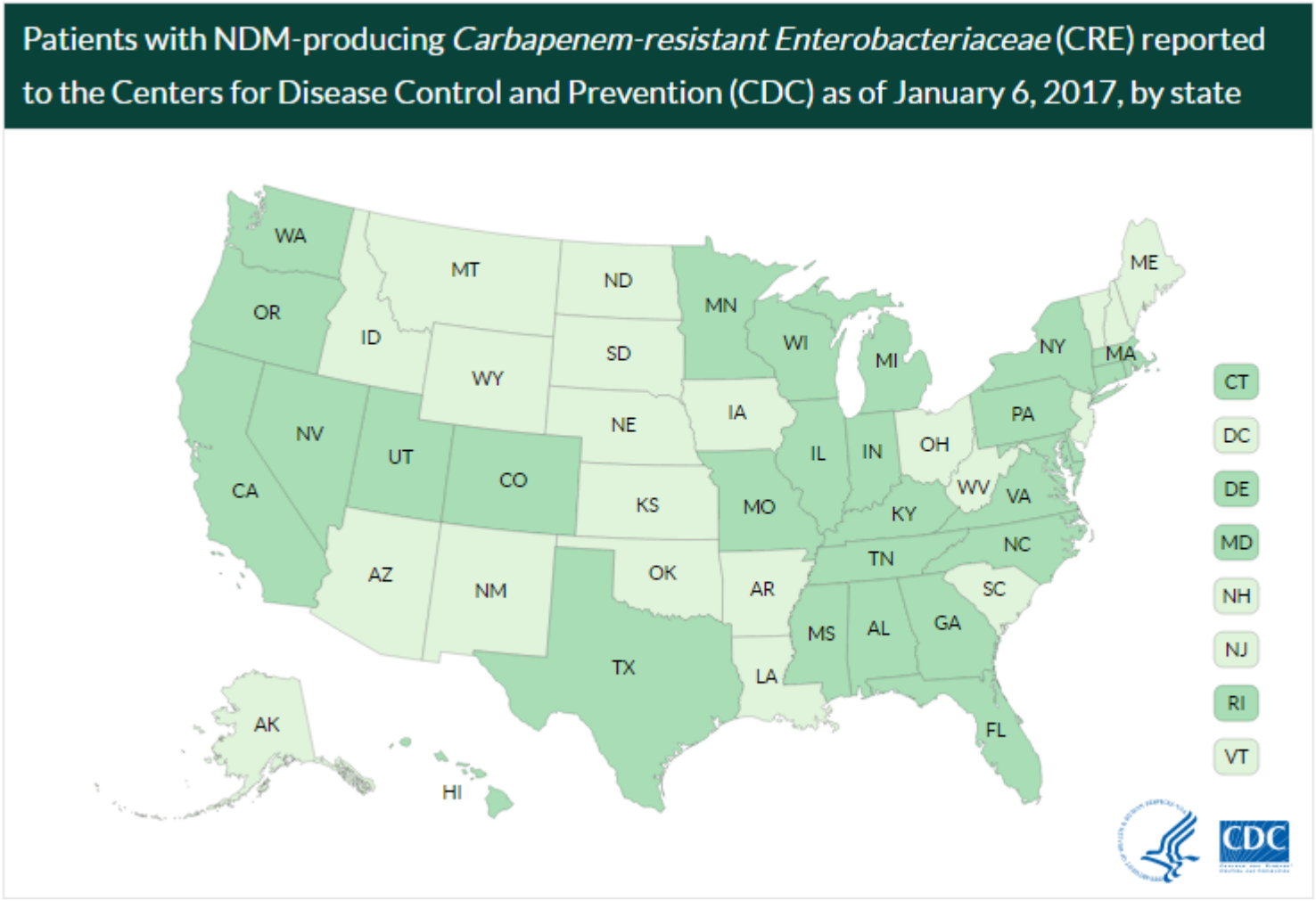

Connecticut	Reported	1

Total NDM-producing CRE reported to CDC to date: 175

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

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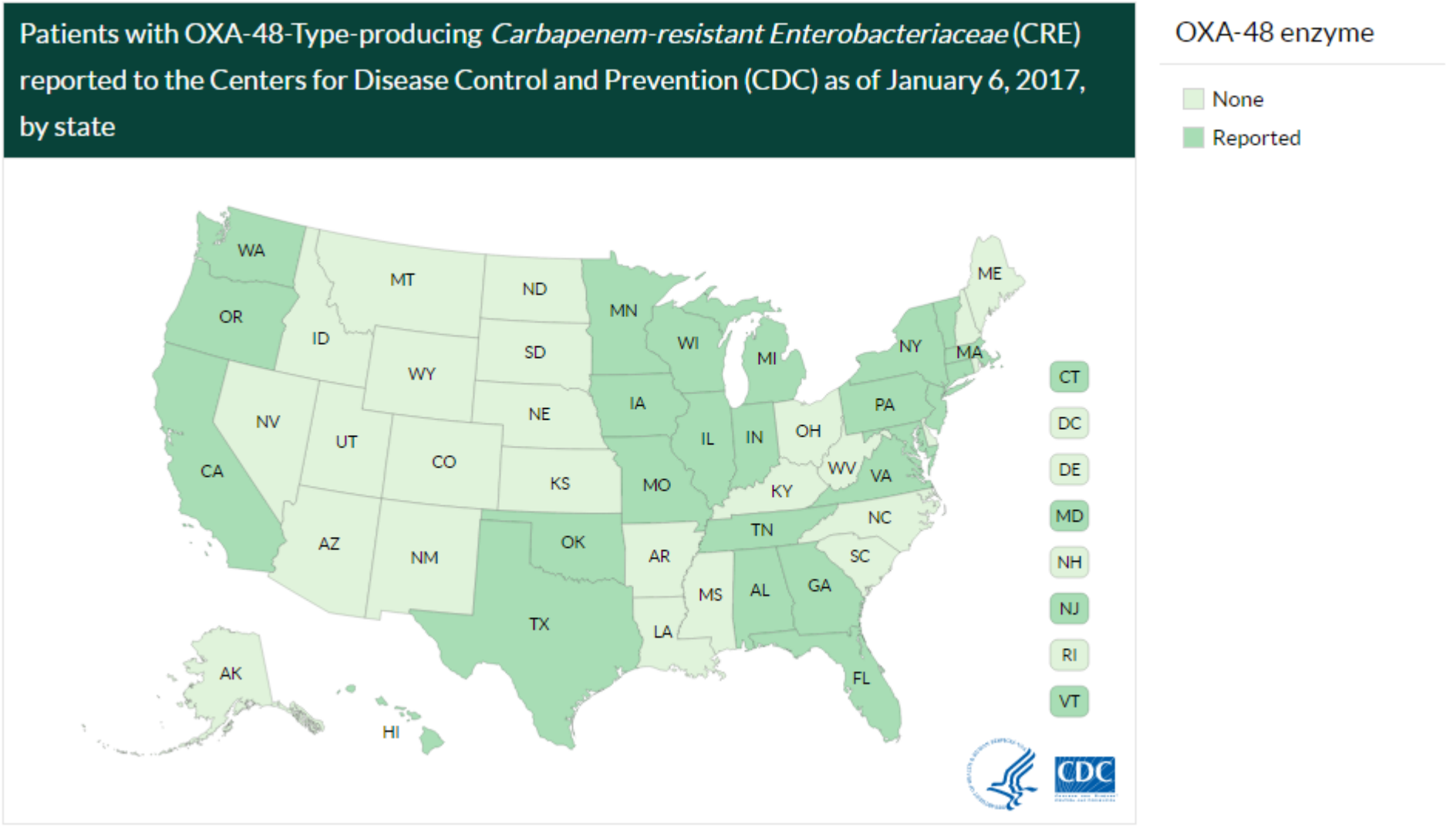

Connecticut	Reported	1

Total OXA-48-producing CRE reported to CDC to date: 73

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

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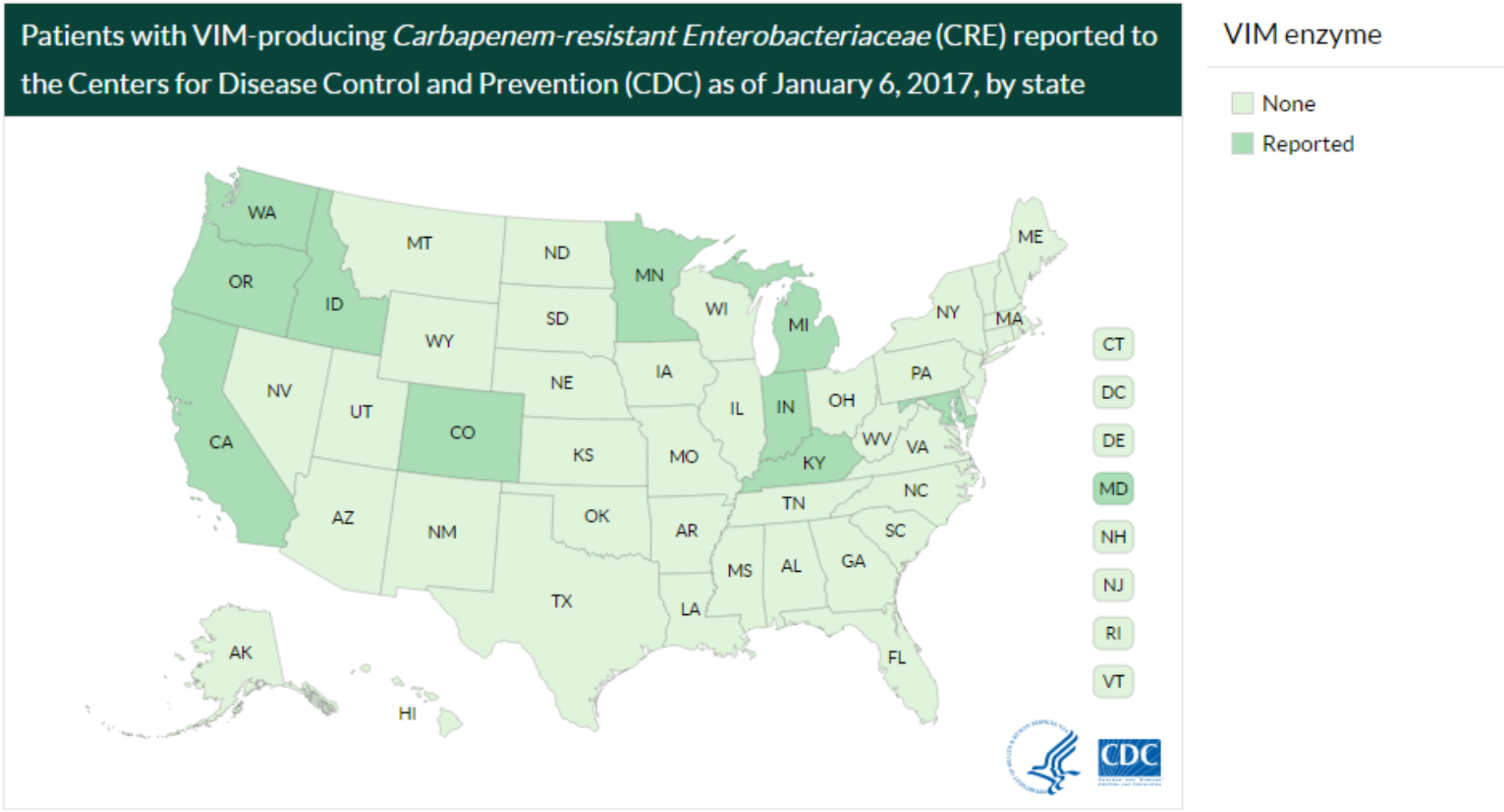

Total VIM-producing CRE reported to CDC to date: 27

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

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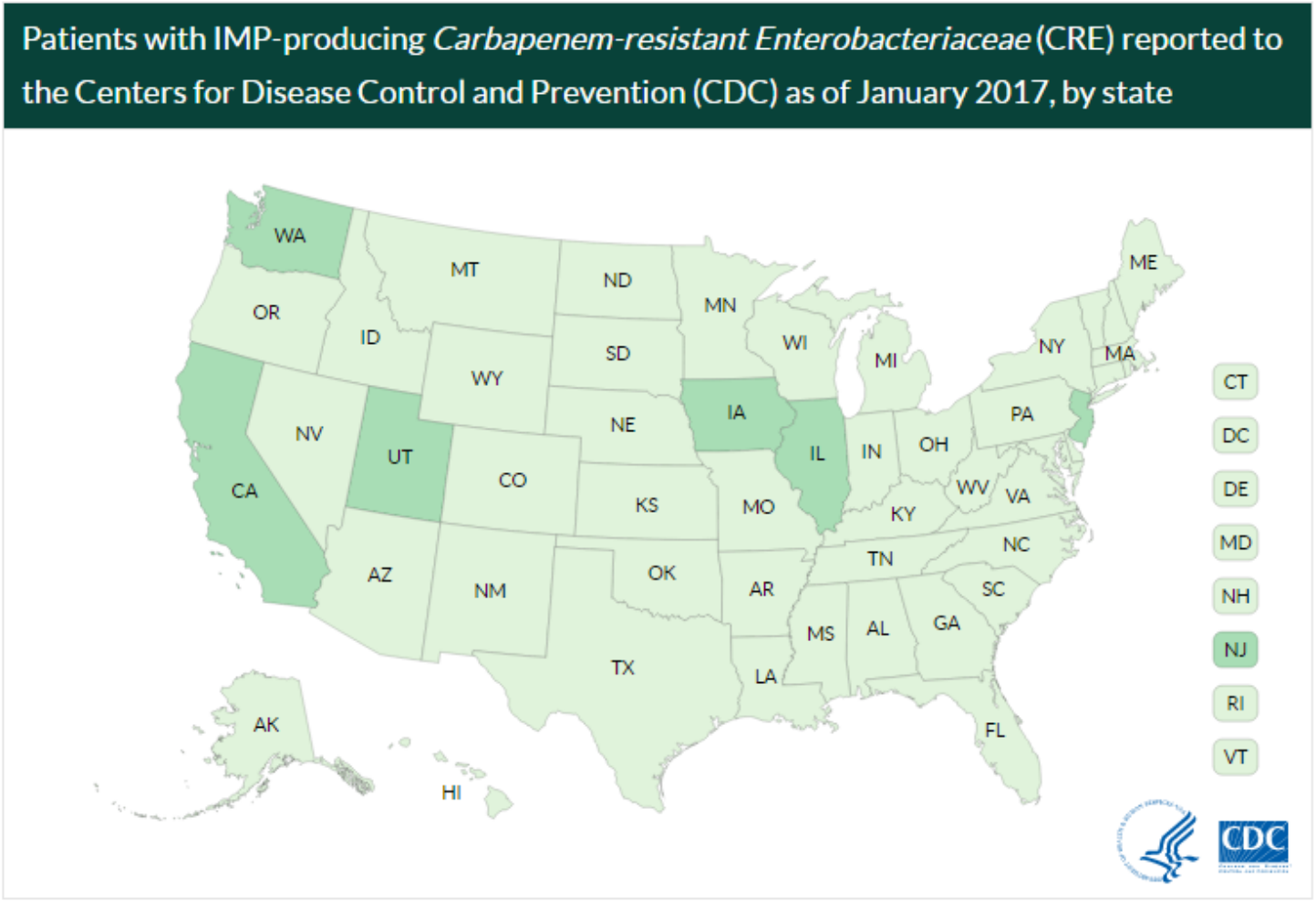

Total IMP-producing CRE reported to CDC to date: 11

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

Keeping Connecticut Healthy
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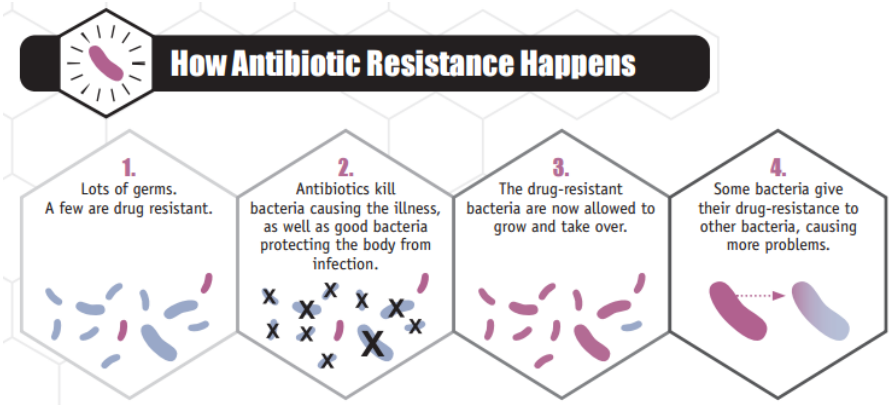
Strategies Common to all Tiers

- Prompt notification of healthcare personnel, DPH
- Timely implementation of appropriate control measures
- Notification of patient and family
- Prospective laboratory surveillance
- Retrospective review of laboratory results
- Implementation of a system to ensure adherence to infection prevention measures



Keeping Connecticut Healthy
DPH
Connecticut Department of Public Health

Expansion of the Tiered Response Plan

- Additional Multi-Drug Resistant Organisms (MDROs) can be added to the response plan as our ability to detect and respond to these threats increases
- Short-term future prospective targets include: Carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA), Extended-spectrum β-lactamase producing Enterobacteriaceae (ESBL), *Candida auris*

HAZARD LEVEL URGENT

These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridium difficile (C. difficile), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

HAZARD LEVEL SERIOUS

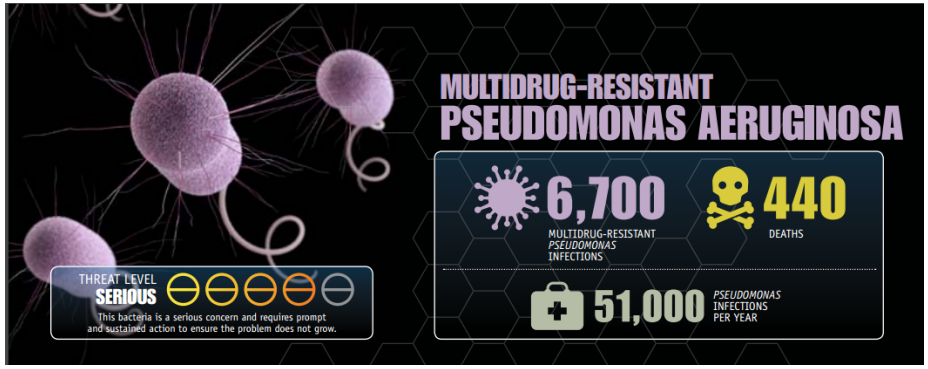
These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.

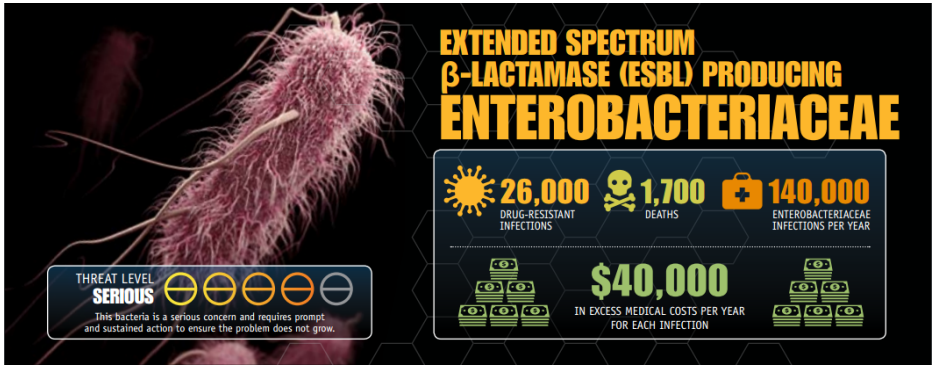
Multidrug-resistant *Acinetobacter*, Drug-resistant *Campylobacter*, Fluconazole-resistant *Candida* (a fungus), Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs), Vancomycin-resistant *Enterococcus* (VRE), Multidrug-resistant *Pseudomonas aeruginosa*, Drug-resistant Non-typhoidal *Salmonella*,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

HAZARD LEVEL CONCERNING

These are bacteria for which the threat of antibiotic resistance is low, and/or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response.

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





The goal of the global action plan is to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them. It is expected that countries will develop their own *national action plans* on antimicrobial resistance in line with the global plan.

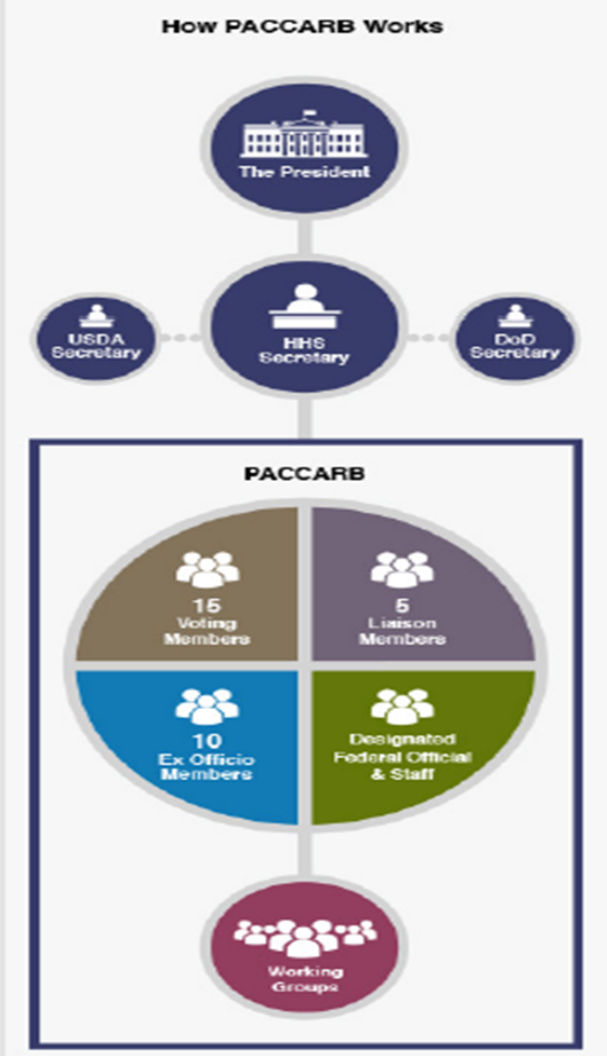
To achieve this goal, the global action plan sets out five strategic objectives: (1) to improve awareness and understanding of antimicrobial resistance; (2) to strengthen knowledge through surveillance and research; (3) to reduce the incidence of infection; *(4) to optimize the use of antimicrobial agents*; and (5) to ensure sustainable investment in countering antimicrobial resistance.

NATIONAL STRATEGY FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Vision: *The United States will work domestically and internationally to prevent, detect, and control illness and death related to infections caused by antibiotic- resistant bacteria by implementing measures to mitigate the emergence and spread of antibiotic resistance and ensuring the continued availability of therapeutics for the treatment of bacterial infections.*

September 2014

THE WHITE HOUSE
WASHINGTON



CARB Goals

- Slow the development of resistant bacteria and prevent the spread of resistant infections
- Strengthen national one-health surveillance efforts to combat resistance
- Advance development and use of rapid and innovative diagnostic tests for identification and characterization of resistant bacteria
- Accelerate basic and applied research and development for new antibiotics, other therapeutics, and vaccines
- Improve international collaboration and capacities for antibiotic research and development

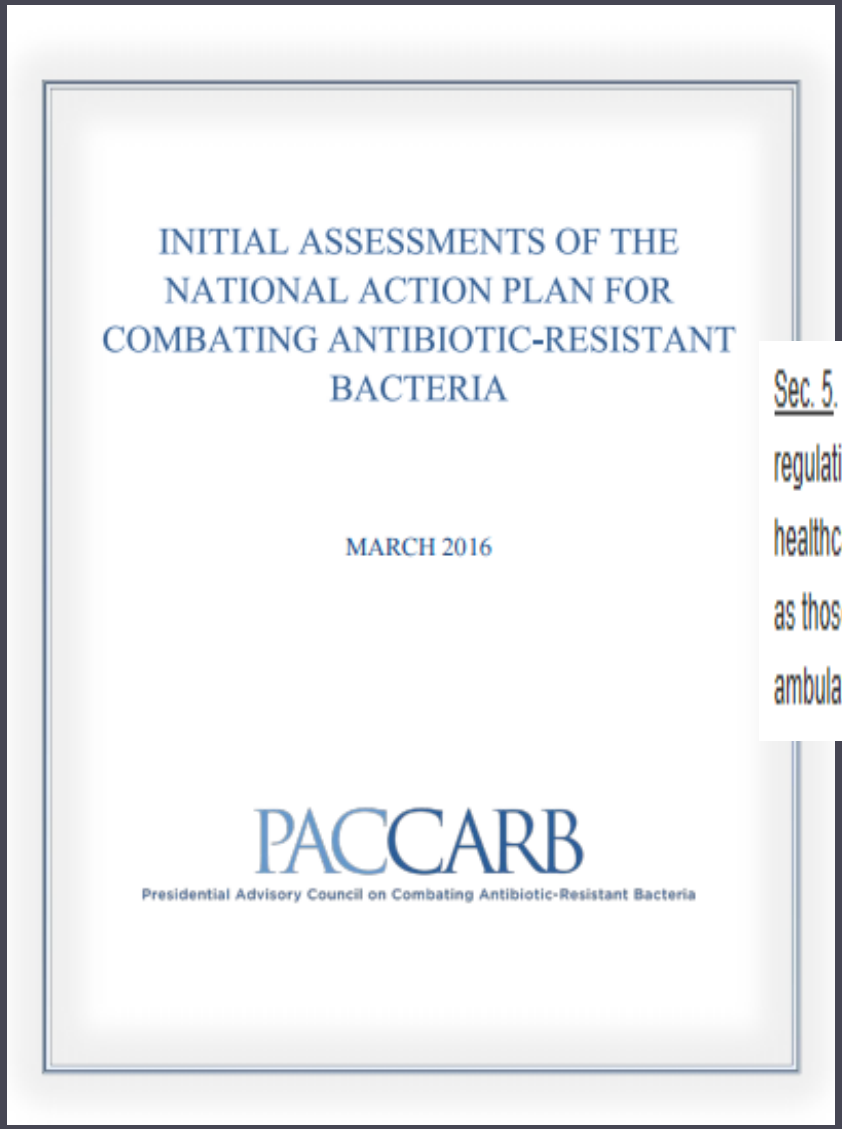
TABLE 1: National Targets to Combat Antibiotic-Resistant Bacteria
By 2020, the United States will:
For CDC Recognized Urgent Threats:
Reduce by 50% the incidence of overall *Clostridium difficile* infection compared to estimates from 2011.
Reduce by 60% carbapenem-resistant Enterobacteriaceae infections 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.

Anticipated Outcomes (2020)

All States, the District of Columbia, and Puerto Rico will have:

- Implemented antibiotic stewardship activities in human healthcare delivery settings
- Established or enhanced regional efforts to reduce transmission of antibiotic resistant pathogens and improve appropriate antibiotic use in healthcare facilities across the continuum of care (e.g., acute care, long term care, and outpatient care)
- HHS, DOD, and VA will review existing regulations and propose new regulations and other actions, as appropriate, which require hospitals and other inpatient healthcare delivery facilities to implement robust antibiotic stewardship programs that adhere to best practices, such as those defined by the CDC's Core Elements of Hospital Antibiotic Stewardship Programs
- At least 95% of eligible hospitals will report antibiotic use data to the National Healthcare Safety Network (NHSN)
- Inappropriate inpatient antibiotic use for monitored conditions/agents will be reduced by 20% from 2014 levels
- Inappropriate outpatient antibiotic use for monitored conditions/agents will be reduced by 50% from 2010 levels
- Eliminate the use of medically important antibiotics for growth promotion in animals
- Use of medically important antibiotics in food-producing animals will require veterinary oversight
- Research efforts will generate validated alternatives to traditional uses of antibiotics, such as changes to health and other management practices, to reduce the need for antibiotics for prevention and treatment of animal diseases
- The Department of Health and Human Service's Agency for Healthcare Research & Quality and CDC will expand its focus on research and evaluation to develop improved methods and approaches for combating antibiotic resistance and conducting antibiotic stewardship



Sec. 5. Improved Antibiotic Stewardship. (a) By the end of calendar year 2016, HHS shall review existing regulations and propose new regulations or other actions, as appropriate, that require hospitals and other inpatient healthcare delivery facilities to implement robust antibiotic stewardship programs that adhere to best practices, such as those identified by the CDC. HHS shall also take steps to encourage other healthcare facilities, such as ambulatory surgery centers and dialysis facilities, to adopt antibiotic stewardship programs.

CDC: 7 Core Elements of Hospital Antibiotic Stewardship Programs

- Leadership commitment: resources
- Accountability: leader responsible for outcomes
- Drug expertise: pharmacist leader
- Action: implement ≥ 1 recommended action
- Tracking: prescribing and resistance patterns
- Reporting: regular, relevant staff
- Education: resistance, optimal prescribing

Optimize the treatment of infections and reduce adverse events associated with antibiotic use

- http://www.cdc.gov/getsmart/healthcare/pdfs/core-elements.pdf (2014)

- Implement policies that support optimal antibiotic use
  - Document dose, duration, and indication
  - Facility specific treatment recommendations
- Utilize specific interventions
  - Broad
    - Time outs
      - Does this patient have an infection that will respond to antibiotics?
      - If so, is the patient on the right antibiotic(s), dose, route of administration?
      - Can a more targeted antibiotic be used (de-escalate)?
      - How long should the patient receive the antibiotic(s)
    - Prior authorization
    - Prospective audit and feedback
      - Critically ill patients
      - Broad spectrum or multiple agents

- Utilize specific interventions (cont.)
  - Pharmacy driven
    - Automatic iv to oral change
    - Dose adjustments and optimization
    - Automatic alerts for duplicative therapy
    - Time sensitive automatic stop orders
    - Detect and prevent drug-drug interactions
  - Infection and syndrome specific
    - CAP, UTI, SSTI, CDI
    - Empiric coverage of MRSA infections
    - Treatment of culture proven invasive infections

Avoid implementing too many policies and interventions simultaneously

Emerging Developments in Antibiotic Stewardship

- Integration of IT into clinical data presentation and decision making
- Diagnostic laboratory testing, rapid diagnostic tests
- Better characterization of impact of stewardship interventions on resistance
- Evaluate which interventions or antibiotic targets yield the greatest benefit in combating resistance
  - CDC/NHSN Antimicrobial Resistance (AR) option, use standardized approach

Clinical Infectious Diseases Advance Access published April 13, 2016

Clinical Infectious Diseases

IDSA FEATURES

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,[1] Sara E. Cosgrove,[2] Lilian M. Abbo,[3] Conan MacDougall,[4] Audrey N. Schuetz,[5] Edward J. Septimus,[6] Arjun Srinivasan,[7] Timothy H. Dellit,[8] Yngve T. Falck-Ytter,[9] Neil O. Fishman,[10] Cindy W. Hamilton,[11] Timothy C. Jenkins,[12] Pamela A. Lipsett,[13] Preeti N. Malani,[14] Larissa S. May,[15] Gregory J. Moran,[16] Melinda M. Neuhauser,[17] Jason G. Newland,[18] Christopher A. Ohl,[19] Matthew H. Samore,[20] Susan K. Seo,[21] and Kavita K. Trivedi[22]

28 recommendations 'graded'

- Interventions
- Optimization
- Microbiology and Laboratory Diagnostics
- Measurement
- Special Populations

- Endorsed 5 antibiotic stewardship interventions
  - Pre-authorization and/or prospective feedback
  - Implementation of interventions designed to reduce the use of antibiotics with a high risk for *C. difficile* infection
  - Interventions to reduce antibiotic therapy to the shortest effective duration
  - Implementation of pharmacokinetic monitoring with dose adjustment for aminoglycosides
  - Promotion of switching from intravenous to oral administration when clinically feasible

Measurement

Table 3. Possible Metrics for Evaluation of Interventions to Improve Antibiotic Use and Clinical Outcomes in Patients With Specific Infectious Diseases Syndromes

Process Measures	Outcome Measures
Excess days of therapy (ie, unnecessary days of therapy avoided based on accepted targets and benchmarks)[a]	Hospital length of stay
Duration of therapy	30-day mortality
Proportion of patients compliant with facility-based guideline or treatment algorithm[a]	Unplanned hospital readmission within 30 d
Proportion of patients with revision of antibiotics based on microbiology data	Proportion of patients diagnosed with hospital-acquired *Clostridium difficile* infection or other adverse event(s) related to antibiotic treatment[a]
Proportion of patients converted to oral therapy	Proportion of patients with clinical failure (eg, need to broaden therapy, recurrence of infection)

Sources: [39, 50–57, 189–191].

[a] These metrics are applicable for antibiotic stewardship program interventions to reduce antibiotic treatment of asymptomatic bacteriuria, which, in most cases, should not be treated; therefore, the other metrics do not apply.

- Days of therapy (patient level antibiotic use data) vs defined daily doses
- Antibiotic costs: prescriptions or administrations, not purchasing data
- Consider the goals and size of the syndrome specific intervention

Outpatient Antimicrobial Stewardship

- Coordinated efforts to promote appropriate prescribing antibiotics
  - Can be implemented by a variety of stakeholders
  - Overarching goal is to promote adherence to clinical practice guidelines
    - Provide best standard of care
    - Minimize spread of antibiotic resistant bacteria

Outpatient Antibiotic Stewardship

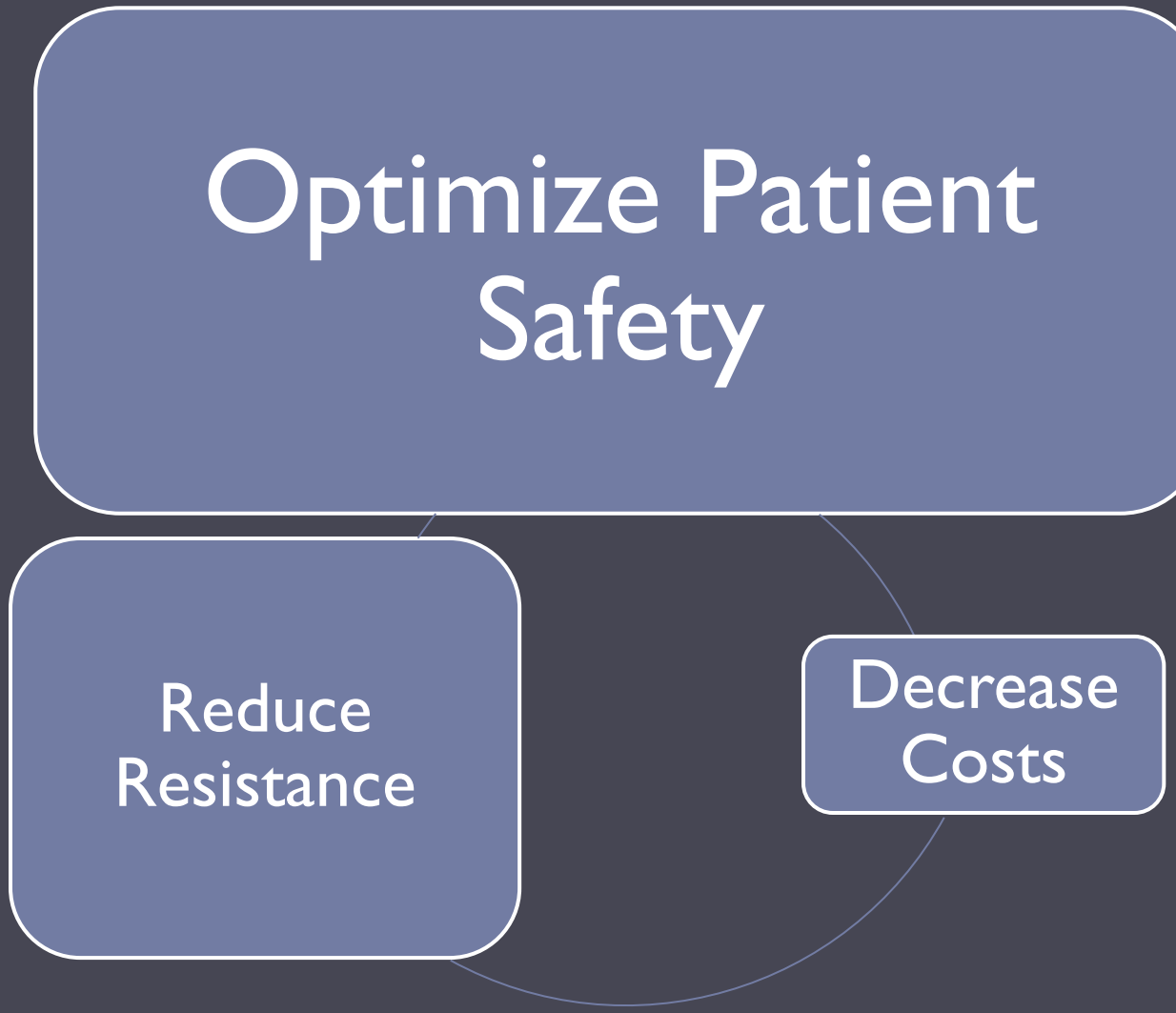
- Audit and feedback
  - Promotes individualized adherence to evidence based practices
- Academic detailing
  - Education to reinforce or change prescribing
- Clinical decision support
  - Provide information at specific times during patient encounter to facilitate accurate diagnoses and treatment
- Poster based interventions
  - Educating clinicians and patients, reducing patient expectations for an antibiotic, advertising clinician commitment to judicious antibiotic prescribing

- Evidence-Based Guidance
  - Sinusitis: no antibiotics until at least 7 days of symptoms
  - Pharyngitis: antibiotics only with a positive group A strep test
  - Acute bronchitis: no sputum culture and no antibiotics unless chest xray shows pneumonia
  - Asymptomatic urinary tract infection: no antibiotics
  - Upper respiratory infection: no antibiotics, ever

  - Improving outpatient antibiotic use:
    - Reframe issue to emphasize *potential patient harm* resulting from adverse reactions rather than public health concerns
    - EHR order entry requirements to justify antibiotic use
    - 'Report cards'
    - Discourage patient outpatient visits for URIs, sinusitis, bronchitis

Antibiotic Stewardship: The New Landscape

Goals of Antibiotic Stewardship Programs Circa 2017

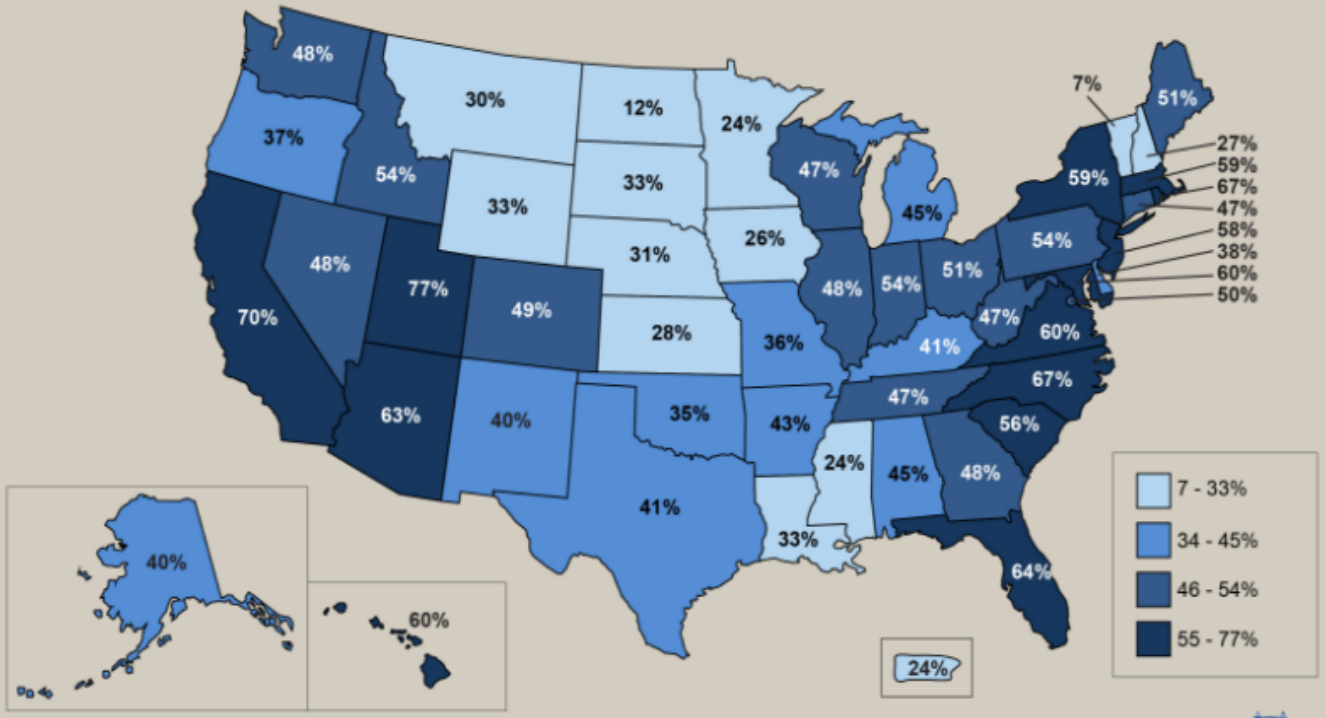


Where Are We Now?

- National requirements for antibiotic stewardship emerging in all healthcare settings
- 48% of hospitals have robust antibiotic stewardship programs as defined by the CDC
- Few LTC or ambulatory practices have organized AS activities
- National surveillance system for inpatient antibiotic use in place but slow uptake

Percent of Hospitals with Antibiotic Stewardship Programs by State, 2015*

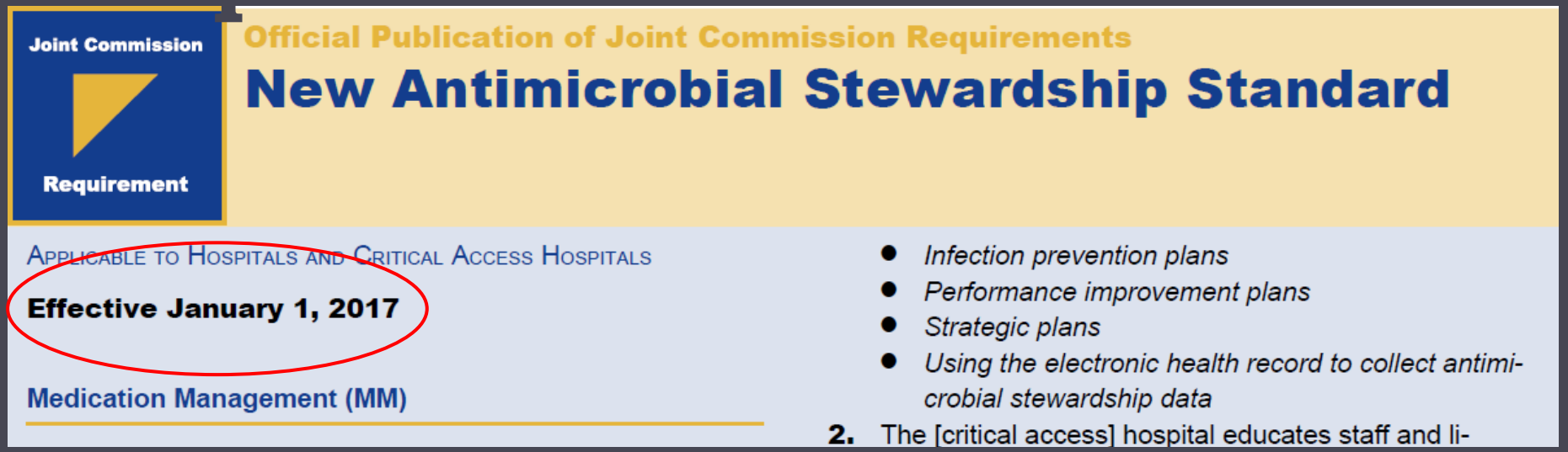
Nationally, 48.1% of all hospitals have stewardship programs (2,199 of 4,549); the national goal is 100% of hospitals by 2020.



*A hospital stewardship program is defined as a program following all 7 of CDC's Core Elements of Hospital Antibiotic Stewardship Programs.

Source: CDC's National Healthcare Safety Network (NHSN) Survey

GET SMART
Know When Antibiotics Work



- Centers for Medicare and Medicaid Services (CMS) Condition of Participation (CoP) for AS in acute care hospitals on hold

- https://www.jointcommission.org/assets/1/6/New_Antimicrobial_Stewardship_Standard.pdf

TJC Eight Elements of Performance

1. AS is an organizational priority
2. Educate staff about AR and AS
3. *Educate patients/families about appropriate antibiotic use*
4. AS multidisciplinary team (ID physician, pharmacist, IP, practitioner)
5. ASP includes the CDC Core Elements
6. Organization-approved multidisciplinary protocols
7. Collect/analyze/reports data on ASP
8. Take action on improvement opportunities identified by ASP

https://www.cdc.gov/getsmart/healthcare/pdfs/core-elements.pdf

Positive Aspects of TJC Standard

- Synergy and alignment with CDC, professional societies and groups writing and enforcing the requirements (TJC and CMS)
  - Contrast with HAI requirements from a decade ago
- Many components of requirements are reasonable and actionable
  - Require leadership support including financial support
  - Under Medication Management
  - Emphasis on interventions

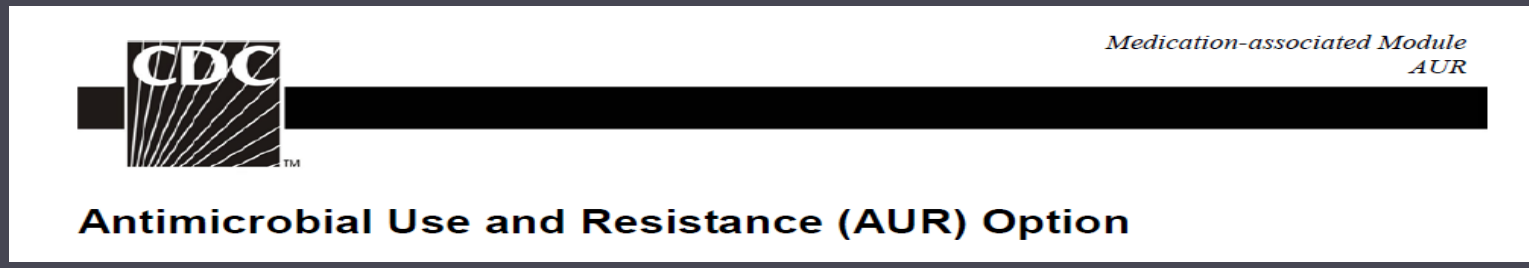
Elements of Performance

- Confusion regarding how TJC is assessing ASPs during surveys
- Focus on patients being discharged on antibiotics which is not the primary focus of an inpatient ASP
  - 'Specific populations that Joint Commission surveyors will focus on during an accreditation survey as follows:
    - Emergency department patients who are prescribed antimicrobials
    - Ambulatory and clinic patients surveyed under the hospital program who are prescribed antimicrobials
    - *Hospitalized patients who will be discharged on antimicrobials'*

https://www.jointcommission.org/standards_information/jcfaq.aspx?ProgramId=5&ChapterId=76&IsFeatured=False&IsNew=False&Keyword

Elements of Performance

- Emphasis on education of HCP and patients is of uncertain value
  - Providing written material such as the antibiogram meets education requirement
  - 'Surveyors will not interview patients or family members regarding education provided on the appropriate use of prescribed antimicrobials'
- ASPs have small budgets; optimize how time is spent
  - Ensure that activities to satisfy TJC do not supersede ability of ASPs to perform effective interventions
- Avoid 'checkbox' ASP compliance particularly in young, emerging programs



- Comparison of antibiotic use among institutions is likely to drive efforts to improve antibiotic use
- All electronic data to NHSN from EHR (dependent on vendors)
- Risk adjustment based on hospital bed size, ICU beds, teaching status
  - Standardized Antibiotic Administration Ratio (SAAR): observed antibiotic use compared to expected antibiotic use
- Status of SAAR as a metric
  - Endorsed by NQF
  - On the CMS Measures Under Consideration (MUC) list as a Pay for Reporting/Performance metric
- Critiques
  - Better risk adjustment needed if sites are to be compared with a Pay for Performance measure
  - *No assessment of appropriateness of use*

Long Term Care and CMS

- ~15,000 facilities with 1.5 million residents reimbursed by CMS
- Revised CMS infection prevention requirements for LTC require ASPs starting 11/28/17
  - Facility must have an IPCP that includes an ASP
  - ASP includes antibiotic use protocols and systems for monitoring antibiotic use and recording incidents and corrective actions taken by the facility
  - An infection control and prevention officer should lead the IPCP
  - Pharmacist must review the resident's medical record when performing the monthly drug regimen review when the patient is receiving an antibiotic
- Interpretive guidance

https://www.gpo.gov/fdsys/pkg/FR-2016-10-04/pdf/2016-23503.pdf

Positive Aspects of the CMS Requirements

- Emphasize the most important components of AS - guidance for use and monitoring use
- Roughly based on CDC Core Elements

https://www.cdc.gov/longtermcare/pdfs/core-elements-antibiotic-stewardship.pdf

Concerns with CMS Requirements

- Federal Register language seems to place leadership responsibility for ASPs in the hands of the infection prevention and control officer
- Physician and pharmacist leadership likely needed for sustained change
  - Systematic review on effective interventions in LTC
    - Success of interventions led by physicians, particularly ID physicians
- Challenge of balancing reality of resources in LTC with what is needed to change prescribing practice
  - Need to employ new strategies such as telemedicine to provide access to expertise

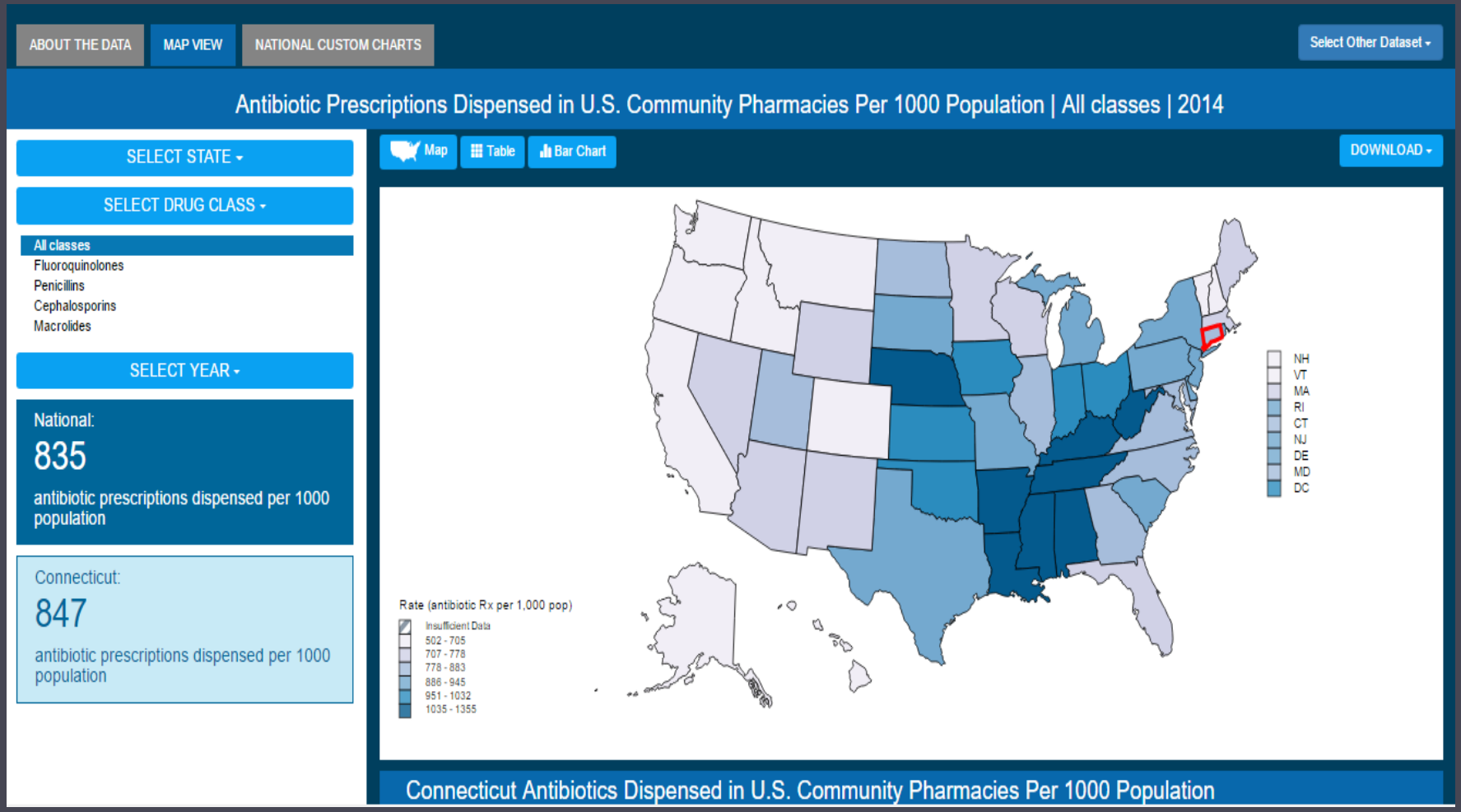
Katz M, submitted data; Siddiqui J et al. *Clin Infect Dis*. 2017. 64:237.

Long-term Care

- ~1,000 facilities accredited by TJC
- TJC Stewardship Standard applies to Nursing Care Centers
  - Not realistic to apply acute care requirements to the LTC setting
  - Surveyor guide notes focus on:
    - List of patients to be discharged who are prescribed antibiotics
    - Documents demonstrating leadership support
    - Document describing how the organization is using the CDC's Core Elements for Nursing Homes
    - Organization approved AS protocols
    - AS data
    - AS reports documenting improvement

Ambulatory Care

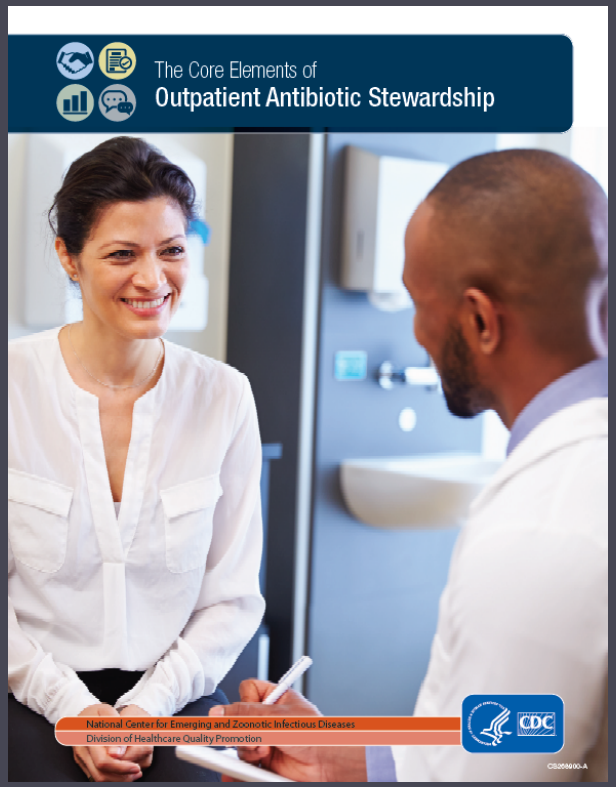
- Increased community use of antibiotics is highly correlated with emerging antibiotic resistant organisms
  - Rates of multidrug resistant pneumococcus highest in areas with greater use of broad spectrum antibiotics (extended spectrum cephalosporins, macrolides)
- >50% antibiotics in outpatient settings may be inappropriate
  - $3 billion unnecessary spending
  - Most inappropriate use is for acute respiratory infections
  - Account for largest number of medication related adverse events
    - 5-25% of patients have an adverse event; 1/1000 serious adverse event
    - 1 in 5 ED visits for ADE are related to antibiotics
    - Mild to life threatening



- https://gis.cdc.gov/grasp/PSA/AUMapView.html

Requirements in Ambulatory Care

- Merit-based Incentive Payment System (MIPS)
  - Under the Medicare Access and CHIP Reauthorization Act (MACRA)
  - Assigns penalties or rewards based on quality and cost of care, participation in practice-based improvement activities and use of EHRs
    - Up to 4% by 2019 and 9% by 2022



Nuckols TK. Ann Intern Med. 2017:166:368.
https://www.cdc.gov/getsmart/community/pdfs/16_268900-a_coreelementsoutpatient_508.pdf

How Does MIPS Work?

You earn a payment adjustment based on evidence-based and practice-specific quality data. You show you provided high quality, efficient care supported by technology by sending in information in the following categories.

 Quality	 Improvement Activities	 Advancing Care Information	 Cost
Replaces PQRS.	New Category.	Replaces the Medicare EHR Incentive Program also known as Meaningful Use.	Replaces the Value-Based Modifier.

Antibiotic-specific quality measures include sinusitis treatment and antibiotic selection, non-antibiotic treatment of acute bronchitis, non-systemic therapy for otitis externa
Select 6 measures
Year 1 weight 50%

"Implementation of an ASP" (ID# IA_PSPA_15) to measure appropriate use of antibiotics
Select a minimum of 1
Year 1 weight 15%

https://qpp.cms.gov/learn/qpp

Requirements

- Choosing a quality measure or improvement activity related to improved antibiotic use is optional
  - Changing antibiotic practice by physicians or patients likely viewed as more challenging than some of the other options in these categories
- Approaches to practice-based quality improvement under-developed in the outpatient arena

What's Next?

- In the US, we are about to dramatically increase the number of hospitals and LTCs with ASPs
  - Future of ambulatory ASP is less clear
- Current requirements don't solve the entire problem
- Continued vigilance on our part to influence how requirements are crafted and applied
- Many unanswered questions about the practice of stewardship and how to change long-standing prescribing practices

What's Needed?

- Understand best practices in stewardship interventions in different settings
- Expand the evidence base for optimal antibiotic use
- Improve measurement of overall and *appropriate* antibiotic use
- Improve integration of efforts across *all* healthcare settings
- Understand how to change prescriber and patient/family behavior
  - Design interventions to engage front line providers in self-stewardship
  - Change the paradigm from stewardship being done to a prescriber to the prescriber doing the stewardship
  - Patient/family engagement

‘The most common cause of failure in leadership is produced by treating adaptive challenges as if they were technical problems.’

Ron Heifetz
The Practice of Adaptive Leadership

Technical vs Adaptive Challenges

Technical

- Clear technical solution
- Fix by providing resources for the solution
- Emphasis on provision of information or supplies

Adaptive

- Requires changes in priorities, beliefs, habits, loyalties, role, way of thinking
- Fix by mobilizing people to tackle challenges together
- Emphasis on teamwork and communication

Examples from Stewardship

Technical	Adaptive
Acute Care: Rapid Diagnostic Tests	
Clinicians not aware the test exists or doesn't know how to respond to results	Clinicians don't want to know the information faster or don't trust the results
Long Term Care: Asymptomatic Bacteriuria	
Clinician not aware of guidelines regarding frequency and lack of benefit of treating ASB	Clinician pressured by family member to test and treat for ASB because resident has responded to such therapy in the past
Ambulatory Care: Acute Bronchitis	
Clinician not aware of guidelines about non-antibiotic treatment of acute bronchitis	Clinician prescribes antibiotic for acute bronchitis at the request of a patient because high Press-Ganey scores linked to pay

- Comprehensive Unit Based Safety Program (CUSP) has been employed to reduce device associated hospital acquired infections
  - An approach to make healthcare safer by improving the foundation of how physicians, pharmacists, nurses, and other team members work together by combining clinical best practices and the science of safety
    - Emphasis on valuing the wisdom of the front line providers
    - Emphasis on teamwork and communication
- Modifications required as primary audience for stewardship is physicians, NPs, PAs, and pharmacists
- Work being done in acute care, long term care and ambulatory care

Leverage and improve new requirements to develop or expand ASP across the healthcare spectrum

Sustained improvement in antibiotic use

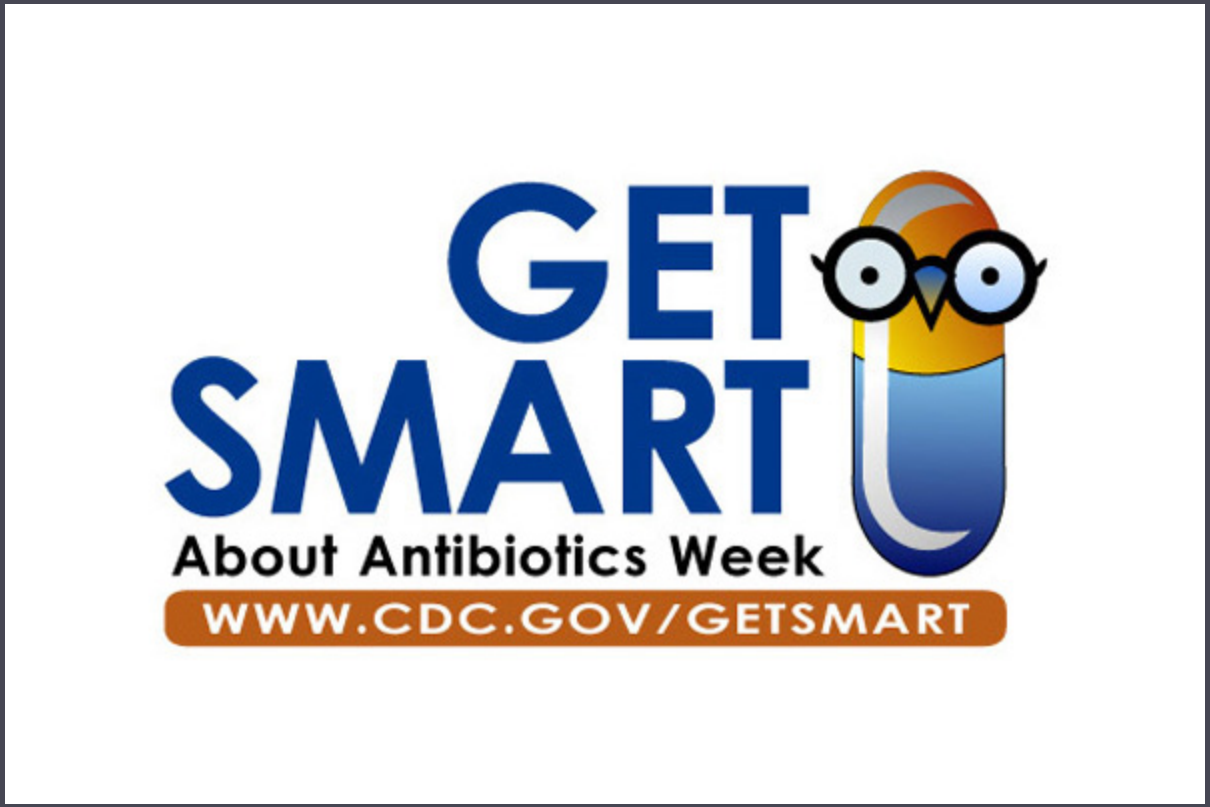
Antibiotics are great again!

Work to modify behavior around antibiotic prescribing by addressing adaptive concerns

ID Workforce: Who is going to do this?

- PACCARB Public Meeting
  - Washington, DC; HHS
  - January 25, 2017
- Panel: APIC, IDSA, PIDS, SHEA, ACGME
- Address workforce, training and education needs

November 12-18, 2017



One-week observance to raise awareness of the threat of antibiotic resistance and the importance of appropriate antibiotic prescribing and use.
CARB goal: reduce outpatient antibiotic use by 50% by 2020