



Responding to Emerging Antimicrobial Resistance Threats

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**Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention**

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No Disclosures

Agenda

- Review what we are learning about emerging antibiotic-resistant pathogens
- Discuss new tools and approach to controlling emerging resistant organisms

Antibiotic Resistance in the United States

- Sickens >2 million people per year
- Kills at least 23,000 people each year
 - Plus 15,000 each year from *C. difficile*
- >\$20B/year in healthcare costs



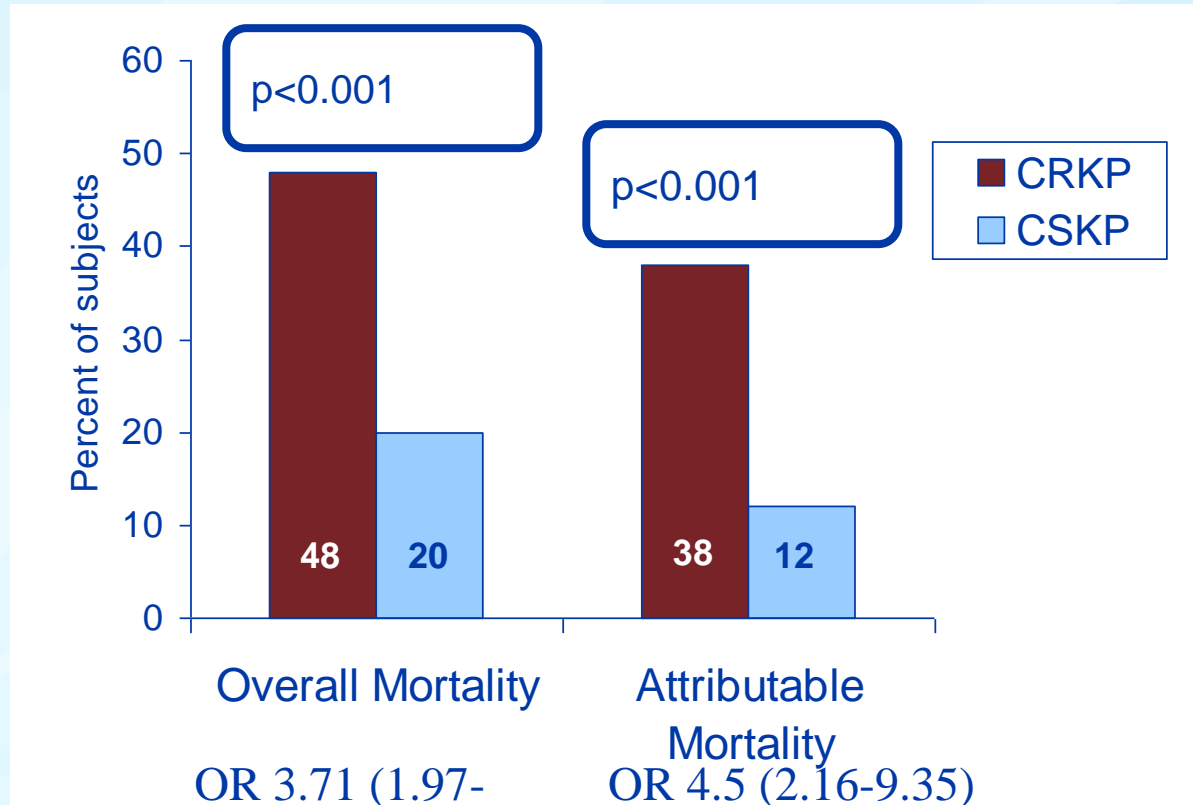
Why Focus on Antibiotic Resistance?

- Antibiotic resistant (AR) germs reduce the effect of the drugs designed to kill them
 - Life-saving treatments depend on antibiotics that work
 - Second line antibiotics can lead to more toxicities
- AR affects all communities and, without action, will continue to get worse
 - Resistance is outpacing new drug development
 - Challenge is greater in places without access to newer drugs
- AR can move outside of healthcare settings and lead to difficult to treat infections in the community
- AR pathogens might lead to increase in mortality...

Resistant germs can be anywhere and can affect every aspect of human life

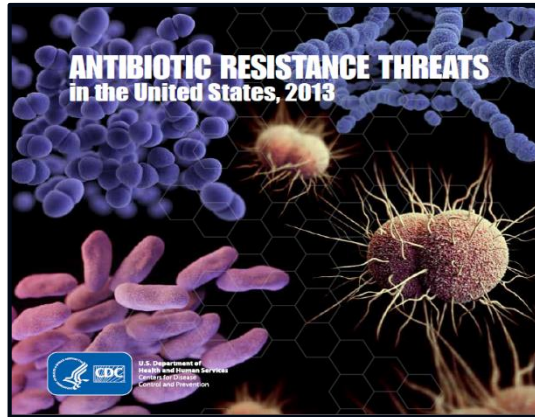


Mortality



Emerging MDROs

Antibiotic Resistance: Old Challenge, New Opportunity



ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES, 2013

Executive Summary

Antibiotic Resistance Threats in the United States, 2013 is a snapshot of the complex problem of antibiotic resistance today and the potentially catastrophic consequences of inaction. The overriding purpose of this report is to increase awareness of the threat that antibiotic resistance poses and to encourage immediate action to address the threat. This document can serve as a reference for anyone looking for information about antibiotic resistance. It is specifically designed to be accessible to many audiences. For more technical information, references and links are provided.

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 pneumoniae*, 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* (VISA), Erythromycin-resistant *Streptococcus* Group A, Clindamycin-resistant *Streptococcus* Group B

Urgent Threats

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

Serious Threats

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

Concerning Threats

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

Urgent Threats

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

Serious Threats

- Multidrug-resistant *Acinetobacter*
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Concerning Threats

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

Emerging MDROs – Carbapenemase Producing Organisms

Gram-Negative Rods

- Encompass large number of pathogenic and non-pathogenic bacteria
- Glucose fermenters
 - Gut commensals and pathogens
 - Enterobacteriaceae: e.g., *Escherichia coli*, *Klebsiella pneumoniae*, *Salmonella enteritidis* spp.
- Glucose non-fermenters
 - Opportunistic pathogens
 - *Pseudomonas aeruginosa*, *Acinetobacter baumannii*
 - Intrinsically non-susceptible to many commonly used antimicrobials

Enterobacteriaceae

- Large family of gram negative rods with >25 recognized genera
- Most common family encountered in clinical microbiology labs
 - Most common are *Klebsiella* spp., *Escherichia coli*, and *Enterobacter* spp.
 - Also *Proteus*, *Providencia*, and *Morganella*
- Many are susceptible to many antibiotics including members of the penicillin family
 - Some have enzymes called β -lactamases that lead to reduced susceptibility to penicillins



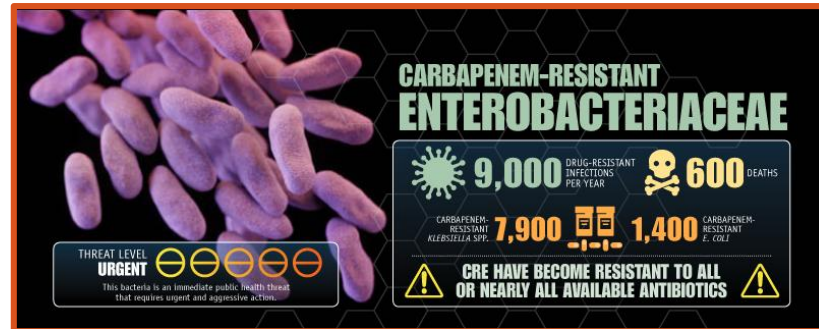
K. pneumoniae, scanning electron micrograph
<http://www.ppdictionary.com/bacteria/>

Carbapenems

- Broad spectrum “antibiotics of last resort” for highly resistant infections
- Increasingly important due to emergence and spread of extended-spectrum β -lactamases (ESBLs) beginning in the 1990s
- Four approved carbapenems in US (imipenem, meropenem, doripenem, ertapenem)
 - Ertapenem less active against some bacteria, does not cover *Pseudomonas*

Carbapenem-Resistant Enterobacteriaceae (CRE)


- Often multidrug resistant
- Cause infections with high mortality rates
- Multiple resistance mechanisms, two main types
 - Carbapenemase-producing CRE (CP-CRE)
 - Non carbapenemase-producing CRE (non CP-CRE)



Non-Carbapenemase Producing CRE (non CP-CRE)

- Often a combination of mechanisms contributes to resistance
- Chromosomal mutations such as porin loss combined with plasmid mediated mechanisms like Extended Spectrum β -lactamase (ESBL) or AmpC
- Can pass resistance vertically but not horizontally
- Often incur fitness defect

Carbapenemase-Producing CRE (CP-CRE)

- Carbapenemases are enzymes that digest carbapenems
 - Found in lactose non-fermenters in addition to Enterobacteriaceae
- Plasmid encoded
 - Can pass resistance vertically and horizontally
 - No/minimal fitness defect
- 5 carbapenemases of primary public health concern
 - *K. pneumoniae* carbapenemase (KPC) 
 - New Delhi Metallo- β -lactamase (NDM)
 - Oxacillinase (OXA-48-type)
 - Verona Integron Mediated Metallo- β -lactamase (VIM)
 - Imipenemase (IMP)

Why Are Plasmid-Encoded Carbapenemases a Public Health Priority?

- Examples of Spread
 - Israel: KPC outbreak
 - 11% carbapenem resistant in 2006
 - 22% carbapenem resistant in 2007
 - Greece: Dissemination of VIM
 - <1% carbapenem resistant in 2001
 - 20%-50% carbapenem resistant in 2006

Schwaber and Carmeli, JAMA. 2008;300(24):2911-2913. doi:10.1001/jama.2008.896
Vatopoulos, EuroSurveillance, Volume 13, Issue 4, 24 January 2008

The US Experience: KPC

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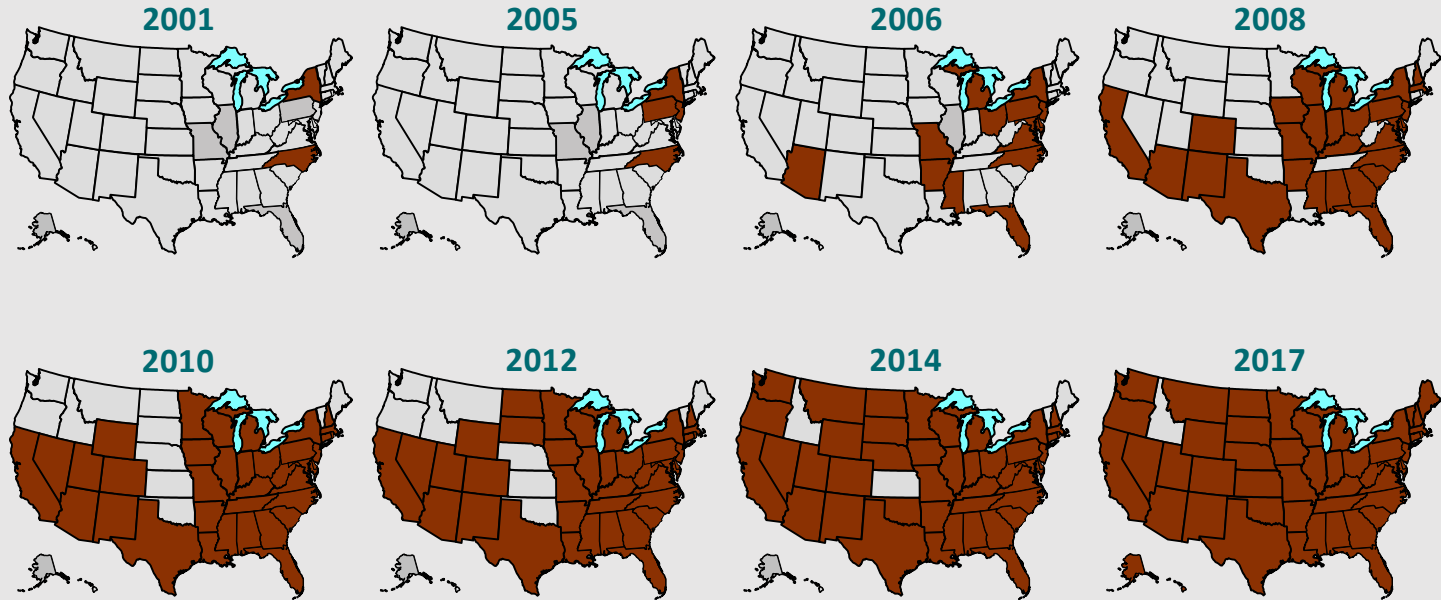
Vol. 45, No. 4

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

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

- Isolate collected in 1996 during an ICU surveillance project from NC

KPC-CRE found in the US spread from 2 states in 2001 to 49 states, DC, and PR in 16 years



States with *Klebsiella pneumoniae* carbapenemase (KPC)-producing Carbapenem-resistant Enterobacteriaceae (CRE) confirmed by CDC

How Common are CRE in the United States?

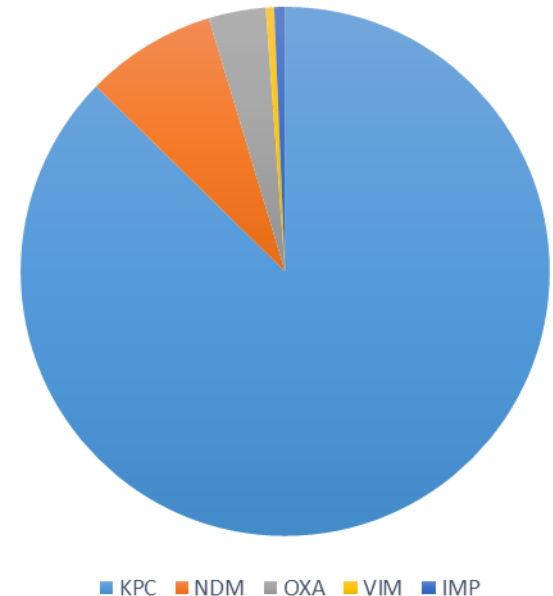
- Among HAIs submitted to National Healthcare Safety Network (NHSN)
 - ~3-4% of Enterobacteriaceae NS to a carbapenem during 2011 to 2014
 - In 2001, only 1.2% NS to a carbapenem
- Incidence 2.93 per 100,000 population across 8 metropolitan areas
 - About 25.1 per 100,000 population for MRSA
 - About 147.2 per 100,000 population for CDI

Weiner, L. et al., Infect Control Hosp Epidemiol 2016;1-14
Guh et al. JAMA, 2015;314(14):1479-1487

What Proportion of CRE are Carbapenemase Producers?

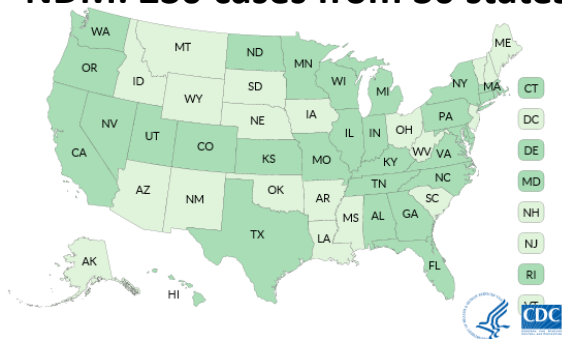
- Between January 1 and August 31, 2017, 2669 CRE were tested at state laboratories across the U.S.
 - 832 (33%) were carbapenemase-producers
 - Primarily *K. pneumoniae*
 - 90 (11%) carbapenemases were non-KPC (e.g., NDM, VIM, IMP, OXA-48)

CP-CRE Reported through ARLN, 2017

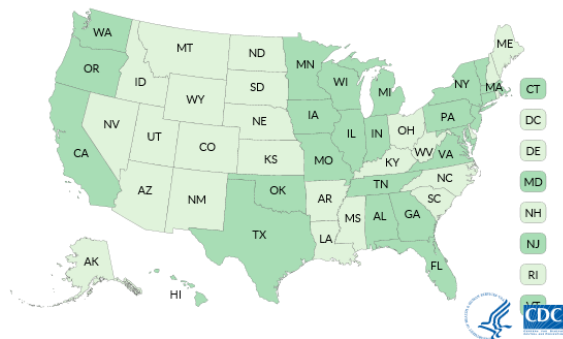


Patients with CP-CRE reported to CDC as of June 2017

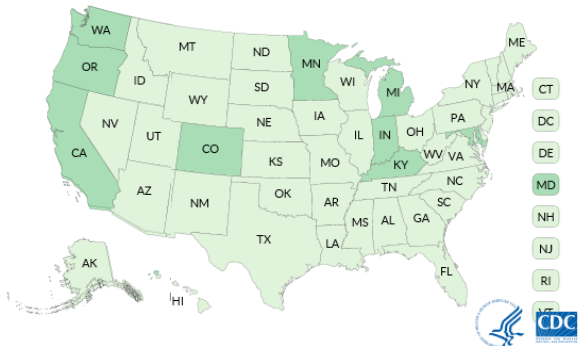
NDM: 230 cases from 30 states



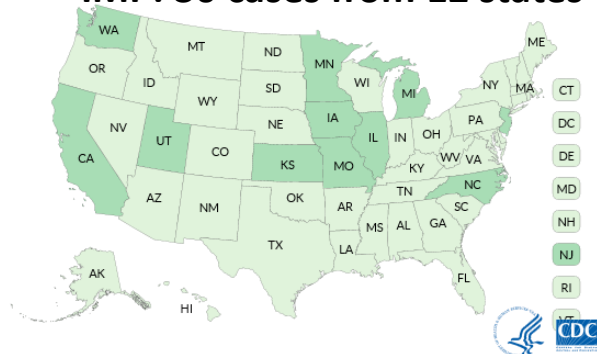
OXA: 101 cases from 25 states



VIM: 41 cases from 9 states



IMP: 30 cases from 12 states



Carbapenem-Resistant Non-Fermenters

- NHSN: 19% of *P. aeruginosa* and 53% of *Acinetobacter* R to carbapenem
- Sentinel surveillance at 5 US sites in 2015
 - 2% of CRPA tested produced carbapenemase
 - IMP, VIM, and novel enzyme
- Other countries have higher prevalence
 - Brazil 1998-2012: 39% of CRPA produced carbapenemase
 - Europe 2009-2011: 20% of CRPA produced carbapenemase
- VIM is most commonly reported worldwide
 - IMP, KPC, and NDM also reported in U.S

Antibiotic Resistance Patient Safety Atlas: <https://gis.cdc.gov/grasp/PSA/>
Rizek, C., *Annals of Clinical Microbiology*, 2014, 13: 43
Castanheira, M., *J. Antimicrob Chemother*, 2014, 69: 1804-1014

Candida auris

First Reports of *C. auris*

- Discovered during the course of a study to analyze antifungal yeast diversity in humans



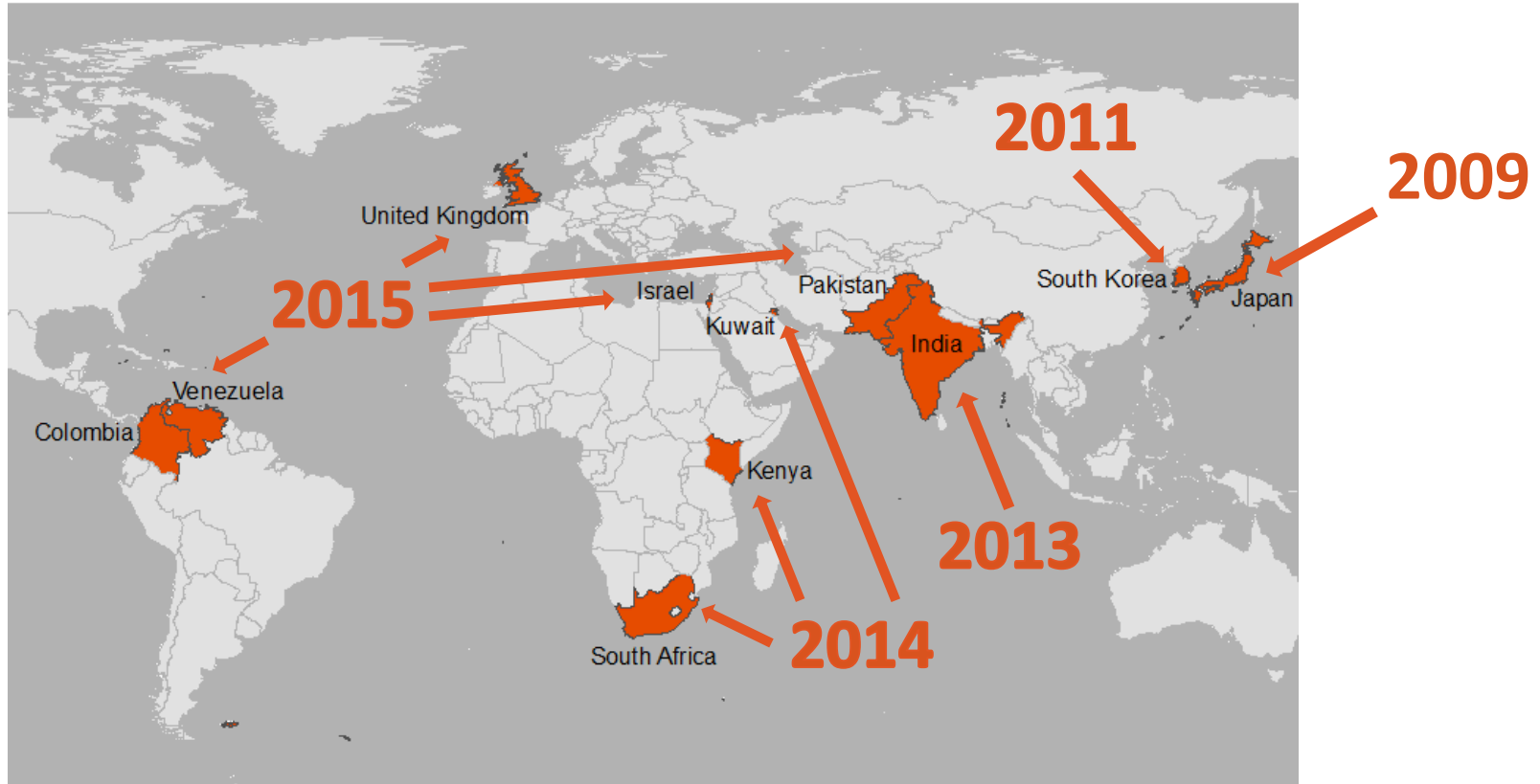
ORIGINAL ARTICLE

***Candida auris* sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital**

Kazuo Satoh^{1,2}, Koichi Makimura^{1,3}, Yayoi Hasumi¹, Yayoi Nishiyama¹, Katsuhisa Uchida¹ and Hideyo Yamaguchi¹

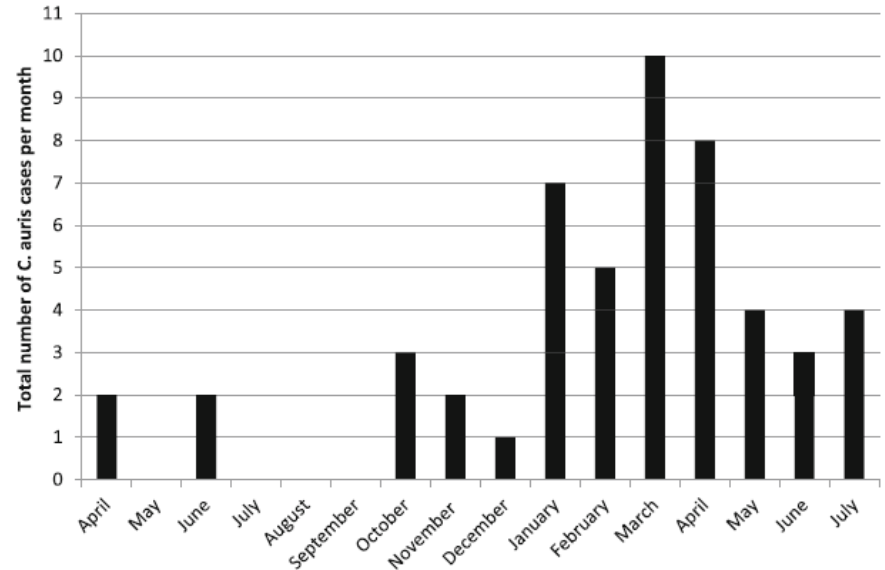
¹Teikyo University Institute of Medical Mycology, 359 Otsuka, Hachioji, Tokyo 192-0395, ²Japan Health Sciences Foundation, 13-4 Nihonbashi-Kodenmachi, Chuo-ku, Tokyo 103-0001 and ³Genome Research Center, Graduate School of Medicine and Faculty of Medicine, Teikyo University, Otsuka 359, Hachioji, Tokyo 192-0395, Japan

Global Emergence of *C. auris*



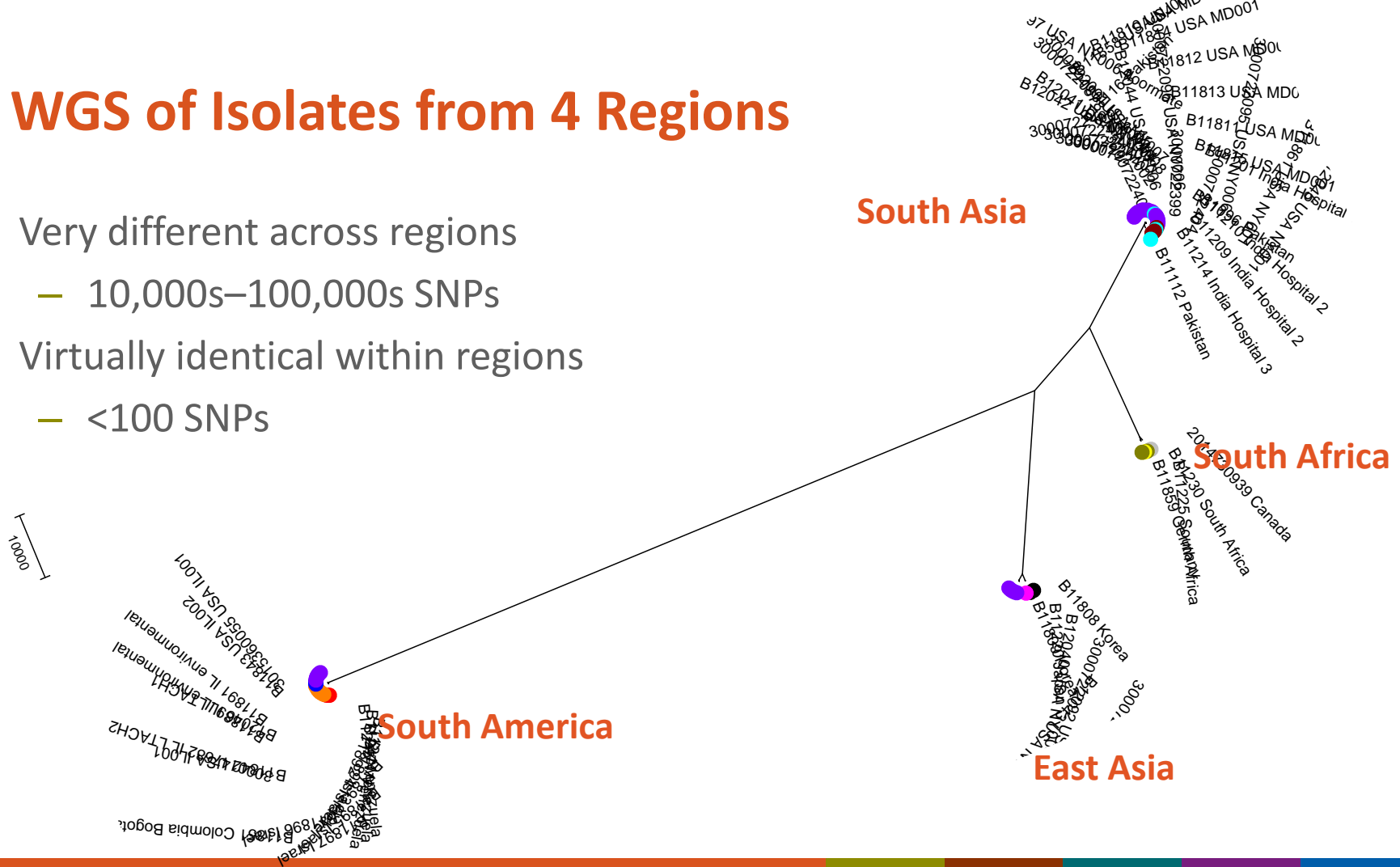
Outbreak in the United Kingdom?

- ICU in large referral center with >50 *C. auris* infections
 - 20% with candidemia
- Difficult to contain despite intensive infection control efforts
- Patients found to be colonized on the skin
- Environmental sampling showed extensive contamination around bed space areas



WGS of Isolates from 4 Regions

- Very different across regions
 - 10,000s–100,000s SNPs
- Virtually identical within regions
 - <100 SNPs



Recent Emerging Threat: *Candida auris* (C. auris)

- Causes invasive infections, high mortality, can be resistant to multiple antifungal drugs

C. auris is Highly Resistant

Polyenes



Azoles



Echinocandins



C. glabrata

<1% resistant to amphotericin B

11% resistant to fluconazole

Up to 12% resistant to echinocandins

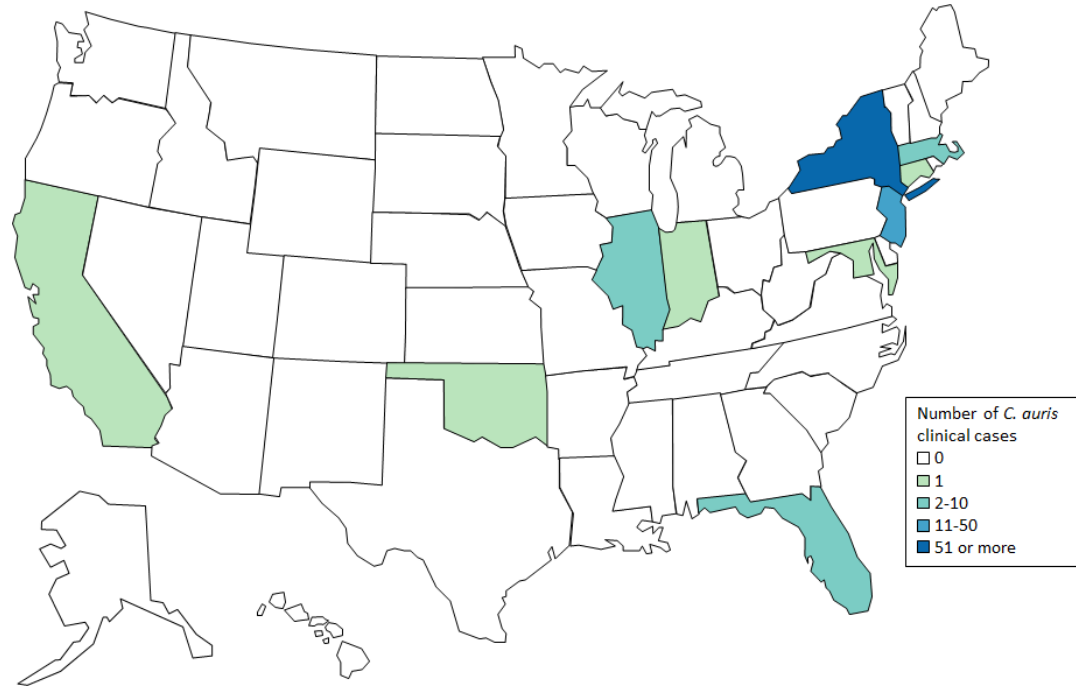
C. auris

35% resistant to amphotericin B

93% resistant to fluconazole
54% resistant to voriconazole

7% resistant to echinocandins

C. auris Clinical Cases Reported by State, United States, September 30, 2017, n=137



An additional 184 asymptomatically colonized patients have been identified in four states with clinical cases.

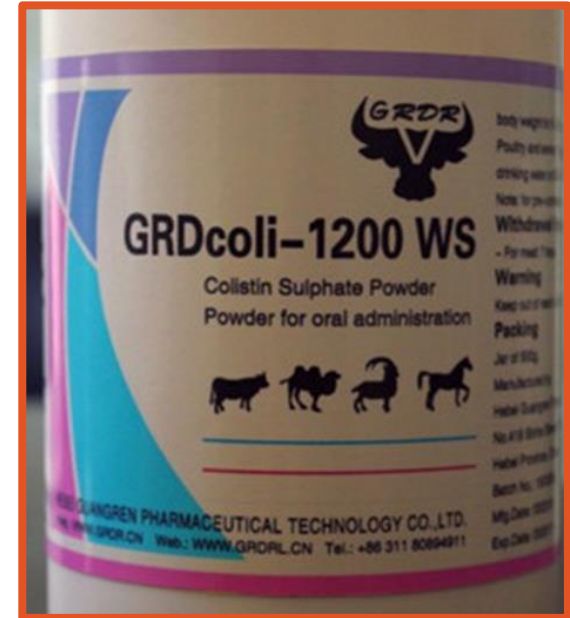
Candida auris Infection Control Recommendations

- *Candida auris* Interim Recommendations for Healthcare Facilities and Laboratories (www.cdc.gov/fungal/diseases/candidiasis/c-auris-infection-control.html)
 - Single room and CP
 - Screening high risk contacts – healthcare exposures
 - Roommates (even if discharged)
 - Other depending on clinical characteristics and los
 - Daily and terminal cleaning with agent active against CD spores
- Recommendations for identification – *C. haemulonii*
 - www.cdc.gov/fungal/diseases/candidiasis/recommendations.html
- Reporting: candidaauris@cdc.gov

Colistin resistance and *mcr-1*

Colistin (Polymyxin E)

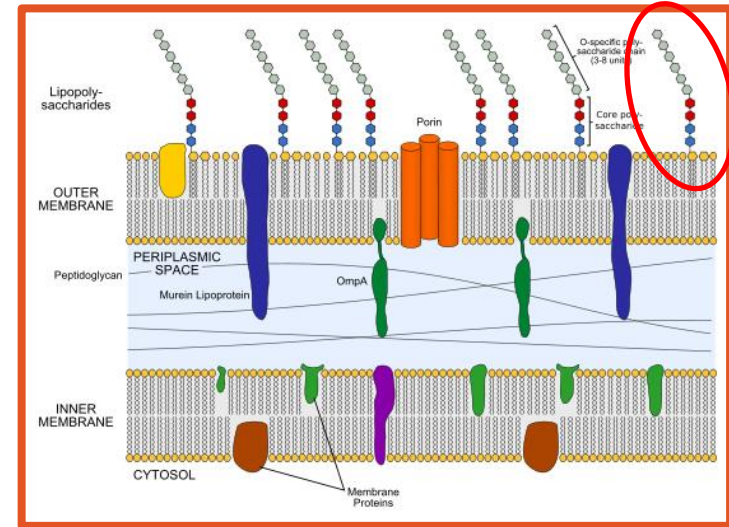
- Polymyxin class of antibiotics
- Antibiotic used to treat serious, highly resistant infections
 - Broad activity against gram negative bacteria
 - Available in U.S. in topical and IV formulations
 - IV use associated with toxicities
 - Used elsewhere orally for selective digestive decontamination
- Used widely in veterinary medicine outside the U.S.
- Resistance to colistin has the potential to cause pan-resistant CRE



www.alibaba.com

Colistin Resistance

- Chromosomal resistance well-documented
- Plasmid-mediated resistance first reported in November 2015 in China*
 - *mcr-1*: mobile colistin resistance
 - *E. coli* (primarily) and *K. pneumoniae*
 - Meat, animal isolates, clinical isolates



www.bio101.info

*Liu, *Lancet Infect Dis* 2016; 16: 16-68

Global Emergence of *mcr-1*

- Since initial report November 2015 in China, found globally
 - >20 countries and 6 continents
 - Food animals, meat, vegetables, surface water
 - Ill patients, asymptotically colonized patients
- Multiple species: *E. coli*, *K. pneumoniae*, *Salmonella enterica*, *Shigella sonnei*
- Earliest isolates identified from 1980s (chickens, *E. coli*, China)
- Earliest human isolate from 2008 (*Shigella sonnei*, Vietnam)
- Highly transmissible among different bacterial strains
- Increases colistin MICs 8 to 16-fold
 - Typical MICs 4 to 8 µg/ml

Liu, *Lancet Infect Dis* 2016; 16: 16-68

Skov, *Euro Surveill* 2016; 21(9):pii=30155

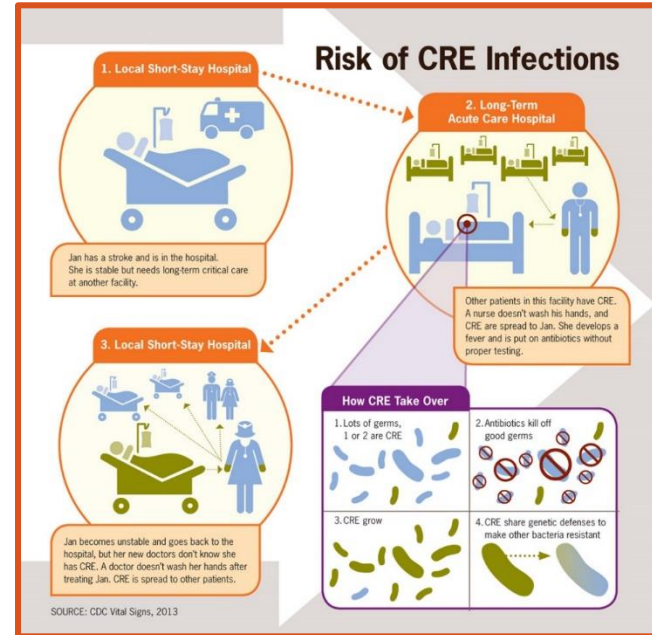
mcr in the U.S.

- 30 cases identified as of January 23, 2018 – *mcr-1*, *mcr-3*
- Of first 26, 14 *E. coli* (including 1 STEC), 10 *Salmonella*, 2 *Klebsiella pneumoniae*
- 22/26 had international travel in year prior
 - Bahrain, Cambodia (n=2), China (n=2), Columbia, Dominican Republic (n=6), Jamaica/St. Vincent/Bahamas, Lebanon, Mexico (n=2), Portugal, Thailand, Vietnam (n=3)
- 1 potential transmission in healthcare

Regional Prevention

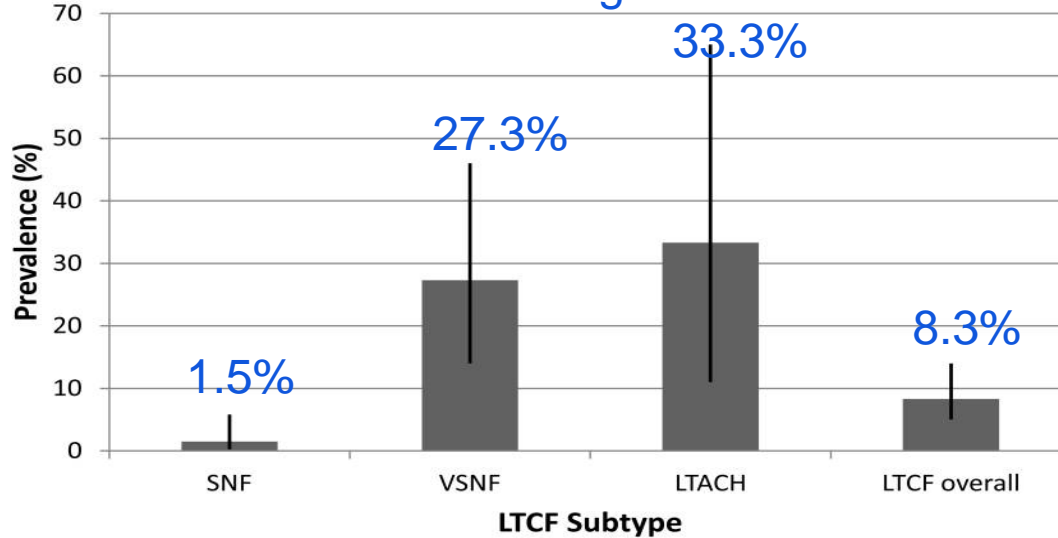
How Does AR Spread in a Healthcare Facility?

- On the hands and clothes of healthcare workers
 - Long length of stay
 - High acuity of care



CRE Prevalence in LTCF: By Type

Prevalence of CRE Carriage at admission to 4 acute care hospitals



0% from those
admitted to the
community

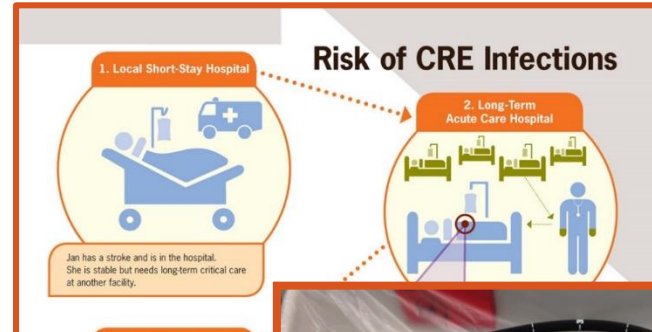
How Does CP-CRE Spread in a Healthcare Facility?

- On the hands and clothes of healthcare workers
- Through inadequately reprocessed devices and equipment



How Does CP-CRE Spread in a Healthcare Facility?

- On the hands and clothes of healthcare workers
- Through inadequately reprocessed devices and equipment
- From the “Environment”
 - Devices rooms contaminated from other patients
 - Through hospital sink drains and hoppers that become colonized with AR pathogens and contaminate patient supplies or environment



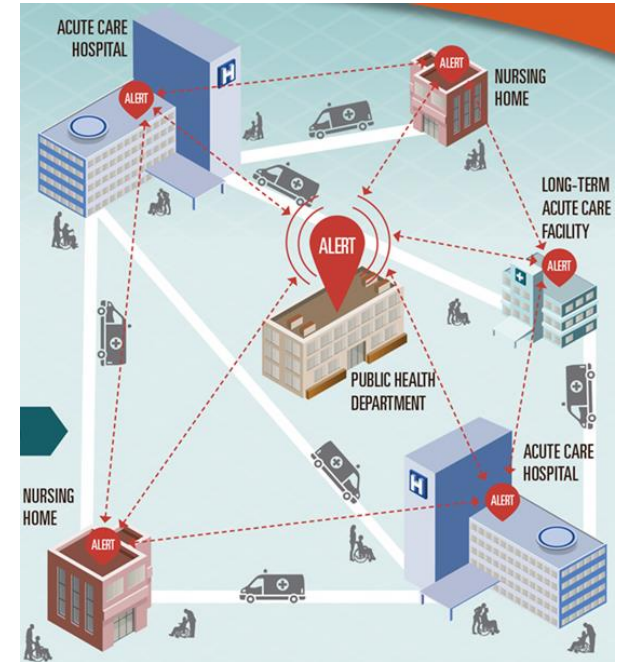
Horizontal vs. Vertical Interventions

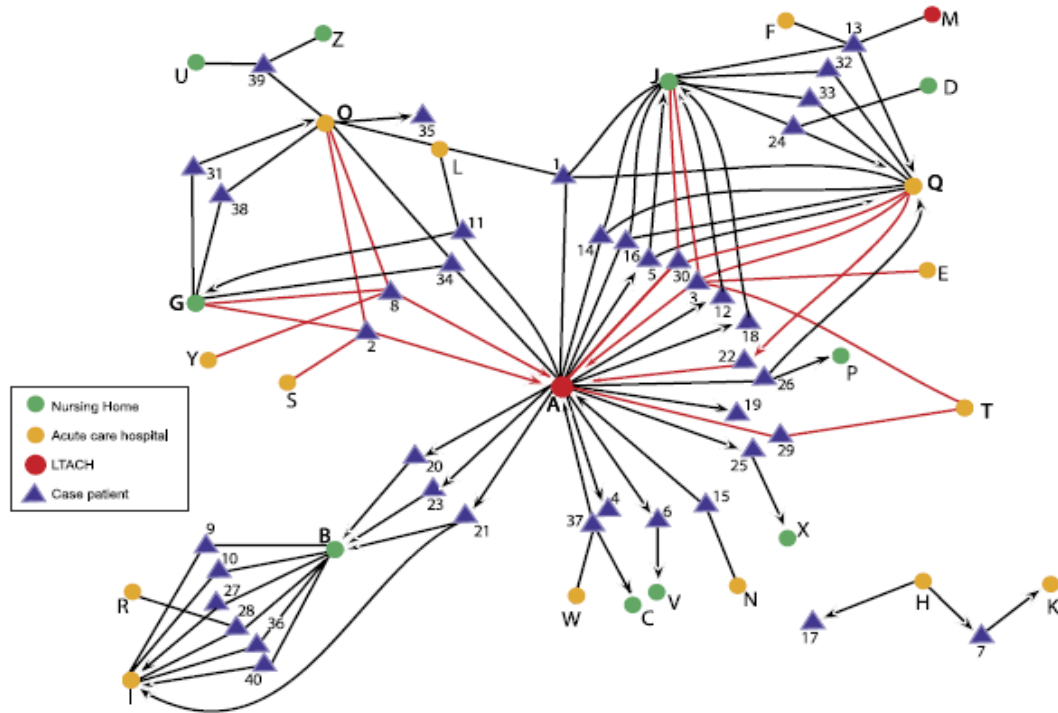
- Horizontal – non-organism specific interventions
 - Hand hygiene
 - Preventing healthcare-associated infections
 - Removing devices promptly
 - Chlorhexidine bathing
 - Antibiotic stewardship
 - Environmental cleaning/device and equipment reprocessing
- Vertical – organism specific interventions
 - Single rooms and Contact Precautions
 - Screening
 - Decolonization

Preventing AR Transmission

■ Traditional Approach

- Promotion of prevention efforts independently implemented by individual health care facilities
- Does not account for inter-facility spread through movement of colonized/infected patients

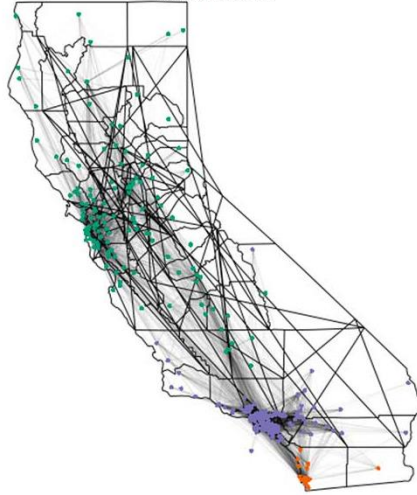




KPC outbreak in Chicago, 2008

Hospital Transfers are a Significant Predictor of *Clostridium difficile* Burden

FIGURE 2 Map of hospitals (dots) and transfers (dark lines) on a map of California. The same connections from Figure 1 are projected onto a map of California. Major clusters are colored separately (San Diego in orange, Los Angeles in purple, and San Francisco and Northern California in green), and the map shows how transfers create closely connected hospitals, despite geographic distance.



“*Clostridium difficile* burden at a hospital level can be better understood by knowing how a hospital is connected to other hospitals in terms of patient transfers”

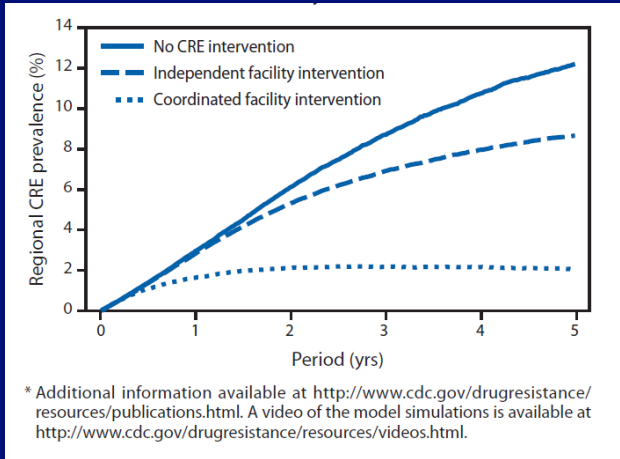
Concept 1: Working Together

Vital Signs: Estimated Effects of a Coordinated Approach for Action to Reduce Antibiotic-Resistant Infections in Health Care Facilities — United States

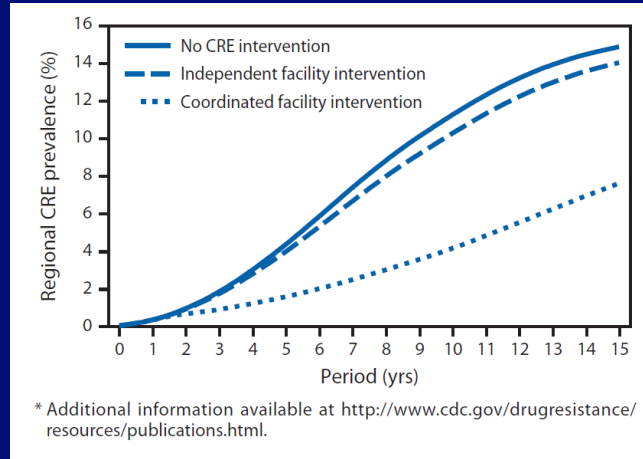
Rachel B. Slayton, PhD¹; Damon Toth, PhD²; Bruce Y. Lee, MD³; Windy Tanner, PhD²; Sarah M. Bartsch, MPH³; Karim Khader, PhD²; Kim Wong, PhD⁴; Kevin Brown, PhD²; James A. McKinnell, MD⁵; William Ray²; Loren G. Miller, MD⁶; Michael Rubins, MD, PhD²; Diane S. Kim⁷; Fred Adler, PhD⁸; Chenghua Cao, MPH⁷; Lacey Avery, MA¹; Nathan T.B. Stone, PhD⁹; Alexander Kallen, MD¹; Matthew Samore, MD⁹; Susan S. Huang, MD⁷; Scott Fridkin, MD¹; John A. Jernigan, MD¹

- ❑ **Developed two complementary agent-based models**
 - Model 1: 10-facility model based upon VA data
 - Model 2: 102-facility model of Orange County, California
- ❑ **Simulated the spread of CRE among patients in**
 - Acute care hospitals, Long-term acute care hospitals (LTACs), Free-standing nursing homes
- ❑ **Three intervention scenarios:**
 - Common Approach: infection control activity currently in common use
 - Independent Efforts: augmented efforts implemented independently at individual subsets of facilities
 - Coordinated approach: coordinated augmented approach across a health care network

Projected Prevalence of CRE Based on Modeling



Projected regional prevalence of CRE over a 5-year period under three different intervention scenarios 10 facility model, United States



Projected countywide prevalence of CRE over a 15-year period under three different intervention scenarios — 102 facility model, Orange County, California

Conclusion: Coordinated prevention approaches assisted by public health agencies have the potential to more completely address emergence and dissemination of MDROS and in comparison to independent facility based efforts

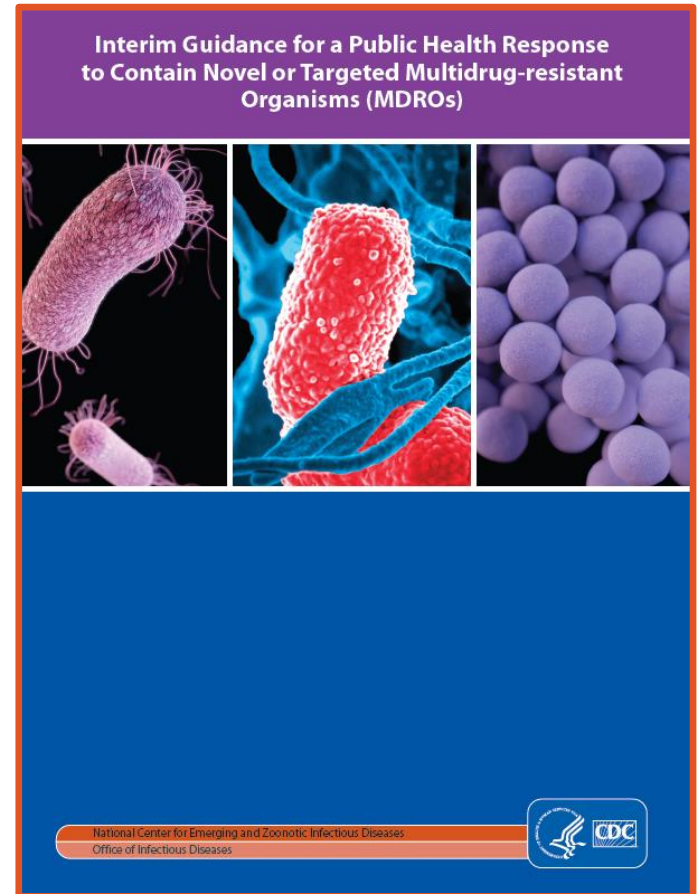
Concept 2: Intervening Early

Containment Strategy – Responding to Emerging Resistance

- Systematic approach to slow spread of novel or rare multidrug-resistant organisms or mechanisms through aggressive response to ≥ 1 case of targeted organisms
 - Carbapenemase-producing organisms, *mcr-1*
 - Pan-resistant organisms
 - *Candida auris*
- Emphasis on settings that historically are linked to amplification
 - Long term care facilities (e.g., skilled nursing)
 - Long term acute care facilities and high acuity skilled nursing (e.g., vSNF)

Containment Approach

- Main components
 - Detection
 - Infection control assessments
 - Screening for asymptomatic colonization
- Response tiers based on pathogen/resistance mechanism
- Guidance document available on CDC website



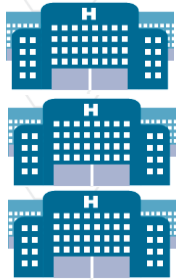
Containment Response Elements

	Tier 1	Tier 2	Tier 3
	Novel resistance mechanisms, PanR	Mechanisms and organisms not regularly found in a region	Mechanisms and organisms regularly found in a region but not endemic
Infection control assessment	Yes	Yes	Yes
Prospective surveillance	Yes	Yes	Yes
Lab Lookback	Yes	Yes	Yes
Screening of healthcare roommates	Yes	Yes	Yes
Broader screening of healthcare contacts	Yes	Sometimes	No
Household contact screening	Yes	Sometimes	No
Environmental sampling	Sometimes	No	No
Healthcare personnel screening	Sometimes	No	No



Antimicrobial Resistance Laboratory Network (ARLN): Laboratory Support for Containment

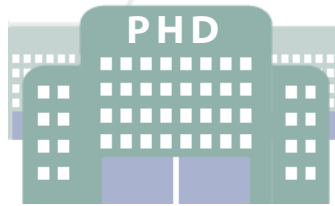
Hospitals/Clinical Laboratories



CRE/CRPA isolates



Public Health Laboratories 50 States 5 Local Health Departments



Species identification
Confirmatory AST
Phenotypic screening for
carbapenemase production
Carbapenemase mechanism testing
mcr-1 testing (some labs)

Rectal Swabs

Regional Lab

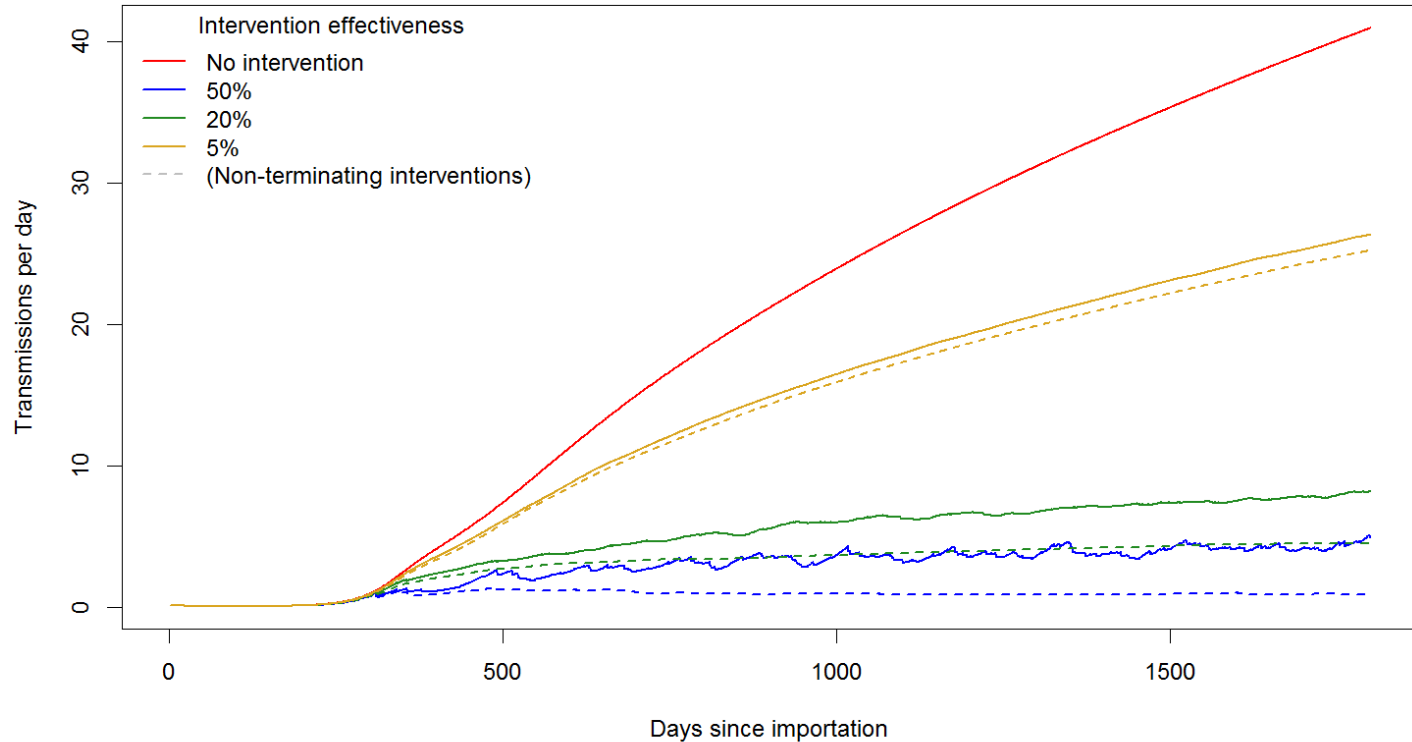


CRE and CRPA Colonization Screening

Infection Control Considerations

- Notify patients of their results
- Educate and inform healthcare personnel and visitors
- Ensure adequate supplies are available and appropriate infection control practices in place:
 - hand hygiene
 - transmission-based precautions
 - environmental cleaning
- Flag patient record
- Ensure patient's status and infection control precautions are communicated at transfer
- If MDRO present at admission, notify transferring facility

Simulating an Outbreak: The Containment Strategy Can Slow Transmission

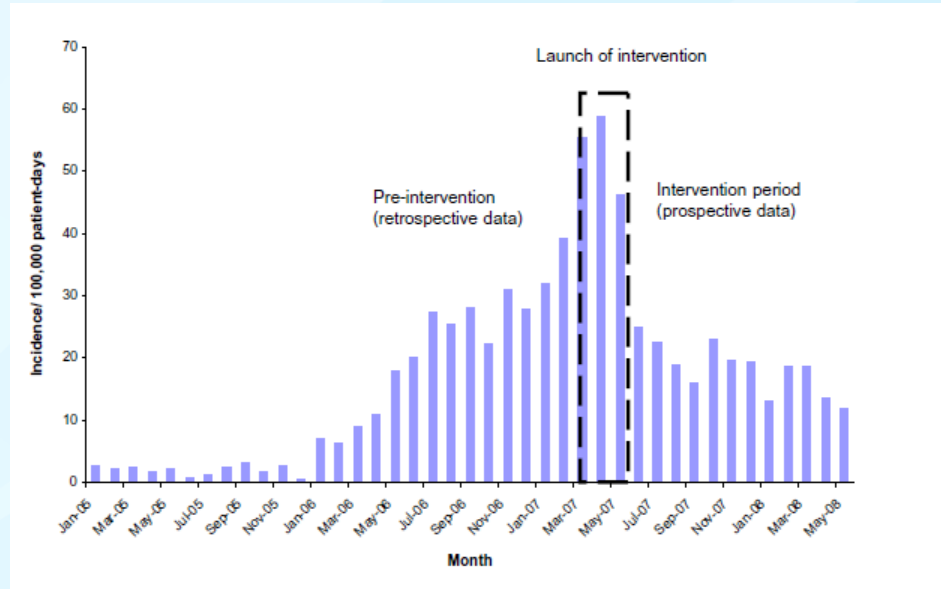


Concept 3: Addressing Endemic Resistance Israel Experience

- ❑ **KPCs likely originally from US identified in Israel beginning in late 2005**
- ❑ **By early 2006, increase in cases**
- ❑ **Initiated National effort to control CRE (initial response) in acute care hospitals**
 - Mandatory reporting of patients with CRE
 - Mandatory isolation (CP) of CRE patients
 - Staff and patient cohorting
 - Task Force developed with authority to collect data and intervene



79% decrease from highest and last month

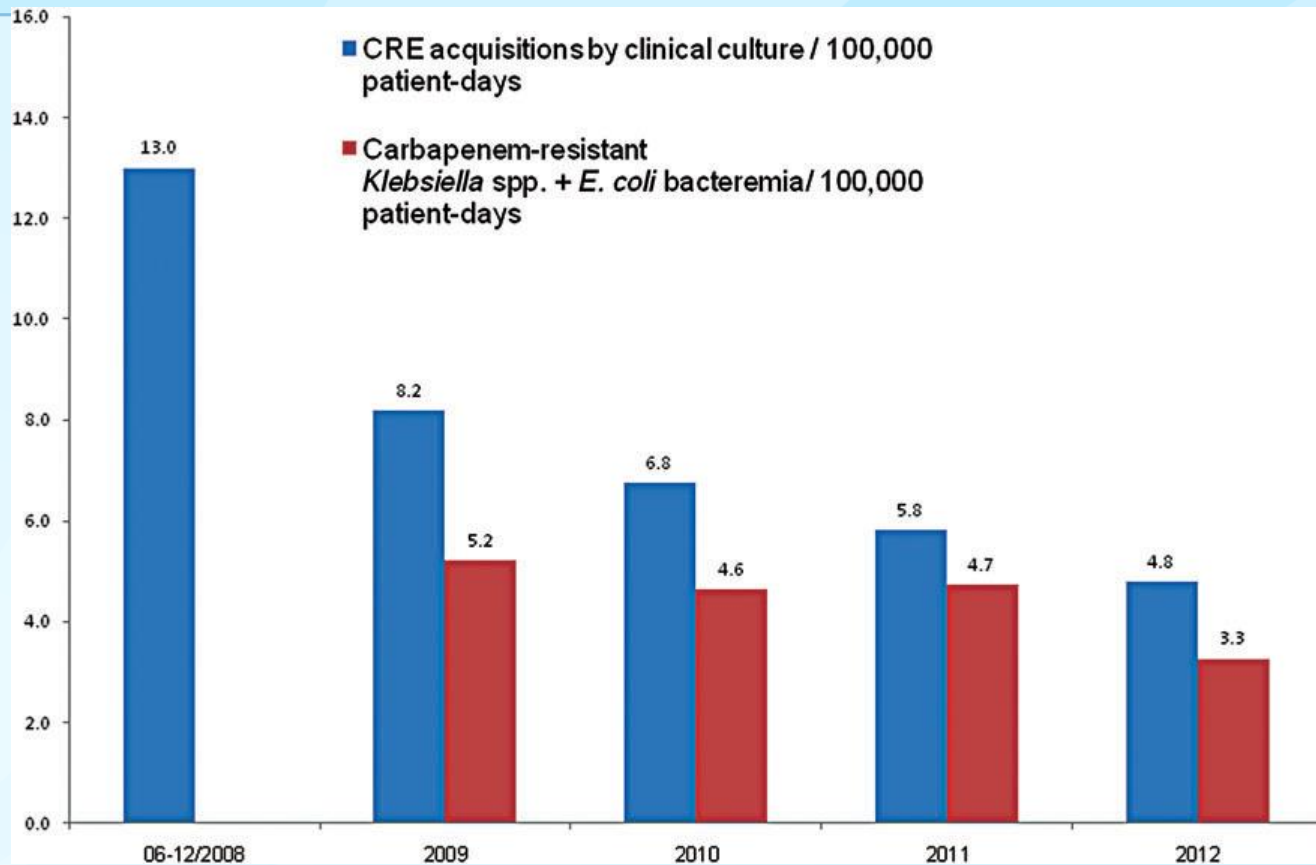


Schwaber et al. CID 2011; 848-855

Israel Experience

□ Beyond the first year

- Active surveillance for high-risk patients
- Added long-term care facilities
 - Targeted interventions in facilities from which CRE-patients had been transferred
 - Intervened at 13 high-risk facilities (1/10th of LTCF beds in country)
 - Determine CRE prevalence among sample
 - Map infection control infrastructure and policies
 - Developed CRE control measures by ward type
 - Similar to acute care without cohorting or strict CP
 - Visited facilities to ensure implementation



Schwaber MJ et al. Clin Infect Dis 2014: epub

Summary

- Novel MDROs continue to emerge
- Coordinated aggressive response has potential to slow spread of these organisms
- Keys to reducing transmission
 - HH
 - CP
 - Environmental cleaning
 - Interfacility communication
- New resources available for facilities to assist in response

Thanks for Your Attention

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

