Epidemiology of CRE

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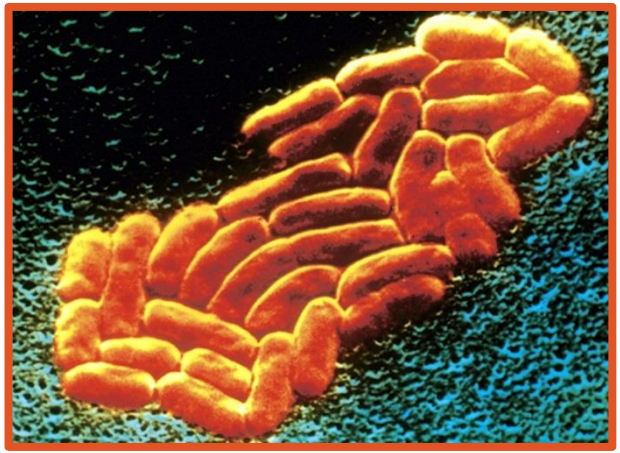
Enterobacteriaceae

- Large family of gram negative rods with >25 recognized genera
- Normal gut flora & opportunistic pathogens
- Most common family encountered in clinical microbiology labs
  - Most common are *Klebsiella* spp., *Escherichia coli*, and *Enterobacter* spp.
  - Also *Proteus*, *Providencia*, and *Morganella*



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

Carbapenem-Resistant Enterobacteriaceae (CRE)

- Carbapenems used to treat highly resistant infections
- Often multidrug resistant
- Cause infections with high mortality rates
- Multiple resistance mechanisms
  - Often a combination of mechanisms contributes to resistance
  - Some mechanisms have potential for epidemic spread

Carbapenem Resistance Mechanisms

- Chromosomal mutations
  - Examples include mutations affecting efflux pumps, porins
  - Can pass resistance vertically but not horizontally
  - Often incur fitness defect
- Plasmid encoded
  - Examples include Extended Spectrum β-lactamases (ESBLs) and carbapenemases
  - Can pass resistance vertically and horizontally
  - No/minimal fitness defect

Why Are Plasmid-Encoded Carbapenemases a Public Health Priority?

- Potential for swift, epidemic spread
- Can dramatically increase proportion of resistant isolates
- Examples
  - 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

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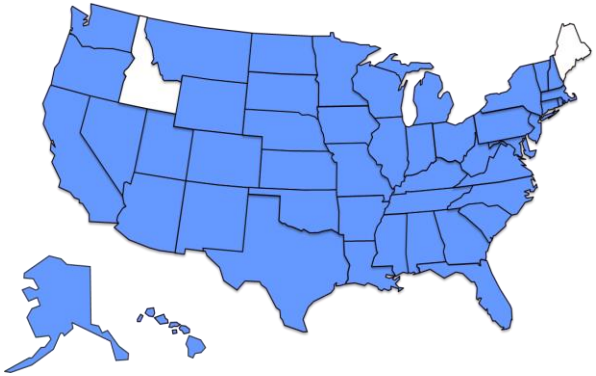
- Can dramatically increase proportion of resistant isolates

States with KPC-CRE Reported to CDC

2001



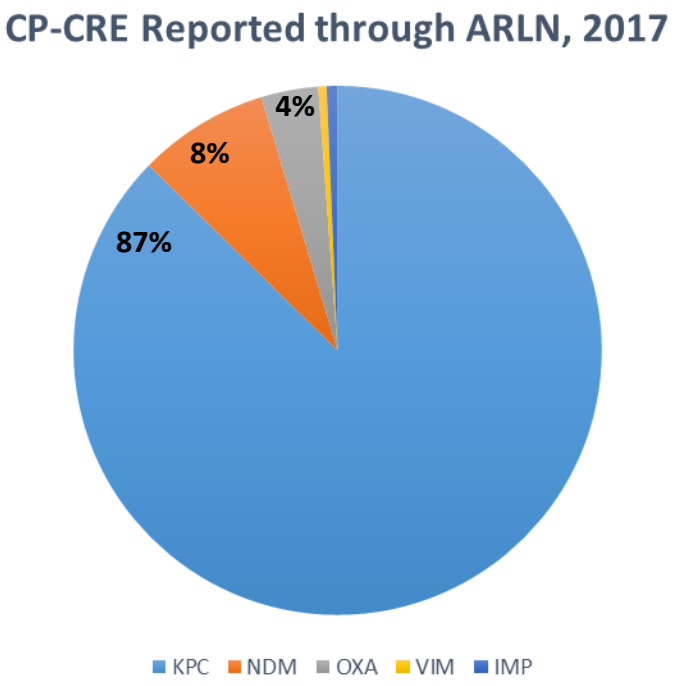
2016

Carbapenemases

- Enzymes that degrade carbapenem antibiotics
- 5 plasmid-encoded enzymes of primary public health concern
  - *K. pneumoniae* carbapenemase (KPC)
  - New Delhi Metallo-β-lactamase (NDM)
  - Verona Integron Mediated Metallo-β-lactamase (VIM)
  - Imipenemase (IMP)
  - OXA-48-type
- Other carbapenemases less frequently encountered
  - Chromosomally encoded (e.g., SME in *Serratia*)
  - No spread beyond country of origin (e.g., SPM, GIM, SIM)

Carbapenemases Vary Globally

- KPC is most prevalent mechanism in U.S.
  - NDM, OXA-48, VIM, and IMP also identified
- Other carbapenemases more common in other countries
  - India: NDM
  - Japan: IMP
  - France: OXA-48



Data are preliminary and subject to change

CDC Data Sources for Understanding CRE Epidemiology

- National Healthcare Safety Network (NHSN)
  - Device and Procedures Module (CAUTI, CLABSI, SSI)
  - MDRO Module, LabID Event
- Emerging Infections Program Multisite Gram Negative Surveillance Initiative (MuGSI)
  - Population-based surveillance for CRE at 9 sites
- Passive surveillance for non-KPC CP-CRE
  - 2009 to present
  - Epi on healthcare outside of U.S.
- ARLN work at state and regional labs

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
- In 2014, 7.8% of SSACH doing surveillance for CAUTI or CLABSI had at least one CRE
  - 24% of LTACHs
- Facilities reported 0-13 LabID CRE Events per month in 2015
  - High incidence states: mean 1.5 events/month
  - Low incidence states: mean 0.08 events/month

Vasquez, A. et al., ID Week Poster, 2016

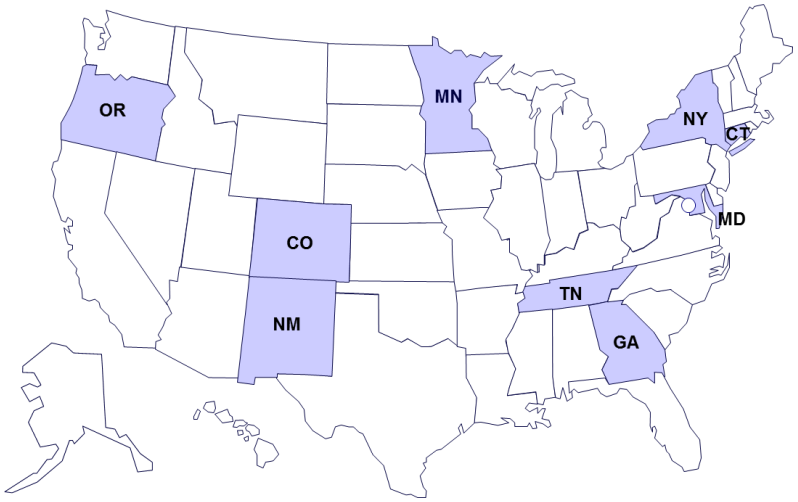
Annual Incidence of CRE Compared to Other MDROs

- Carbapenem-resistant *Acinetobacter baumannii*: 1.4 per 100,000 population
- **CRE: 2.93 per 100,000 population**
- Methicillin-resistant *Staphylococcus aureus*: 25.1 per 100,000 population
- *Clostridium difficile*: 147.3 per 100,000 population

Source: CDC Emerging Infections Program

EIP MuGSI Surveillance

- *E. coli, E. aerogenes, E. cloacae, K. pneumoniae, K. oxytoca*
- Definition beginning January 1, 2016: R to any carbapenem
  - Prior definition: NS to doripenem, imipenem, or meropenem and R to all third-generation cephalosporins tested
  - From urines and normally sterile sites
- Population-based surveillance in nine metropolitan areas
- 15.1 million persons under surveillance in 2017



CRE Incidence

Table 2. Carbapenem-Resistant Enterobacteriaceae (CRE) Cases and Individuals With CRE, Annual Crude Incidence, and Standardized Incidence Ratio by Emerging Infections Program Site, 2012-2013

Emerging Infections Program Site	Incident CRE Cases[a]					Individuals With CRE			
	No. of Cases		Crude Annual Incidence Rate/100 000 Population		Standardized Incidence Ratio (95% CI)[c]	No. of Case-Patients[d]		Crude Annual Incidence Rate/100 000 Population	
	2012[b]	2013	2012[b]	2013		2012[b]	2013	2012[b]	2013
Colorado		27		1.05	0.53 (0.39-0.71)		26		1.01
Georgia	175	181	4.58	4.68	1.65 (1.20-2.25)	136	154	3.56	3.99
Maryland		92		4.80	1.44 (1.06-1.96)		74		3.86
Minnesota	31	40	1.82	2.32	0.94 (0.69-1.27)	29	35	1.70	2.03
New Mexico		6		0.89	0.41 (0.30-0.55)		6		0.89
New York		27		3.60	1.42 (1.05-1.92)		18		2.40
Oregon	6	14	0.35	0.82	0.28 (0.21-0.38)	6	14	0.35	0.82
Total	212	387	2.94	2.93		171	327	2.37	2.47

Guh et al. JAMA, 2015;314(14):1479-1487.

CRE Species Vary Regionally

Table 1. Carbapenem-Resistant Enterobacteriaceae (CRE) Organisms and Carbapenemase-Producing Isolates by Emerging Infections Program Site, 2012-2013

Emerging Infections Program Site	Total No.	CRE Organism or Isolate, No. (%)					Isolates Submitted for Carbapenemase Testing	No. of Carbapenemase-Producing Isolates/Total No. of Isolates Submitted for Testing (%)[a]
		Enterobacter aerogenes	*Enterobacter cloacae* Complex	*Escherichia coli*	*Klebsiella pneumoniae*	*Klebsiella oxytoca*		
Colorado[b]	27	7 (25.9)	10 (37.0)	3 (11.1)	7 (25.9)	0	16 (59.3)	5/16 (31.3)
Georgia	356	22 (6.2)	38 (10.7)	56 (15.7)	235 (66.0)	5 (1.4)	75 (21.1)	48/75 (64.0)
Maryland[b]	92	8 (8.7)	6 (6.5)	9 (9.8)	69 (75.0)	0	17 (18.5)	13/17 (76.5)
Minnesota	71	29 (40.8)	16 (22.5)	10 (14.1)	16 (22.5)	0	58 (81.7)	17/58 (29.3)
New Mexico[b]	6	2 (33.3)	0	3 (50.0)	1 (16.7)	0	[c]	[c]
New York[b]	27	3 (11.1)	2 (7.4)	5 (18.5)	17 (63.0)	0	9 (33.3)	5/9 (55.6)
Oregon	20	4 (20.0)	7 (35.0)	3 (15.0)	6 (30.0)	0	13 (65.0)	2/13 (15.4)
Total	599	75 (12.5)	79 (13.2)	89 (14.9)	351 (58.6)	5 (0.8)	188 (31.4)	90/188 (47.9)

[a] Only *K pneumoniae* carbapenemase was detected among the submitted CRE isolates.

[b] Only 2013 data are available.

[c] New Mexico did not submit any CRE isolates during 2012-2013 for molecular characterization.

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CRE Culture Source, 7 U.S. Sites, 2012-2013 (N=599)

CultureSource	
Urine	520/599 (86.8)
Blood[a]	68/599 (11.4)
Peritonealfluid	8/599 (1.3)
Pleuralfluid	3/599 (0.5)
Other normallysterilesites	7/599 (1.2)

Guh et al. JAMA, 2015;314(14):1479-1487.

Location of Culture Collection, 7 U.S. Sites, 2012-2013 (N=584)

Collection Location	
Short-stay acute care hospital	198/584 (33.9)
Outside acute care hospital	386/584 (66.1)
Outpatient setting or emergency department	253/386 (65.5)
Long-term care facility	104/386 (26.9)
Long-term acute care facility	29/386 (7.5)

Guh et al. JAMA, 2015;314(14):1479-1487.

Prior Healthcare Exposures, 7 U.S. Sites, 2012-2013 (N=531)

Health Care Exposures During Prior Year	
Acute care hospitalization	399/531 (75.1)
Resident of a long-term care facility	259/531 (48.8)
Admission to a long-term acute care hosptial[c]	42/318 (13.2)
Inpatient or outpatient surgery	194/531 (36.5)
Current maintenance dialysis	60/531 (11.3)
Indwelling device (2 calendar days prior to culture)	382/525 (72.8)
Urinary catheter	285/382 (74.6)
Central venous catheter	163/382 (42.7)
Gastrostomy or jejunostomy tube	151/382 (39.2)
Trachoestomy	120/382 (31.4)
Other device	81/382 (21.2)

Guh et al. JAMA, 2015;314(14):1479-1487.

Outcomes Among CRE Cases, 7 U.S. Sites, 2012-2013

Table 5. Outcome of Carbapenem-Resistant Enterobacteriaceae Cases

Required hospitalization at the time of or within 30 d after initial positive culture	371/569 (65.2)
Required intensive care unit stay in the 7 d after positive culture	128/368 (34.8)
Discharge disposition	
Home (private residence)	141/322 (43.8)
Other setting	
Long-term acute care facility or long-term acute care hospital	180/322 (55.9)
Inpatient hospice	1/322 (0.3)
Died during hospitalization or at the end of the 30-d evaluation	51/566 (9.0)
Among any sterile-site positive culture	25/91 (27.5)
Among non–sterile-site positive culture only (ie, urine specimen)	26/475 (5.5)

Guh et al. JAMA, 2015;314(14):1479-1487.

CRE Definitions and CRE Definition Study (CREDS)

- Old definition: NS to doripenem, imipenem, or meropenem and R to all third-generation cephalosporins tested
  - Designed to be more specific for CP-CRE
  - Difficult to implement
  - Unclear how well it performed relative to other definitions
- Evaluation of multiple definitions
  - Determined based on testing *Klebsiella*, *Enterobacter*, and *E. coli* isolates from 6 EIP sites*
    - NS to carbapenems using local laboratory results

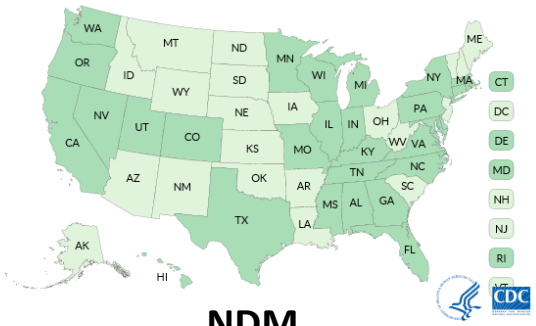
*Chea et al., *Emerging Infectious Diseases*. 2015;21(9):1611-1616. doi:10.3201/eid2109.150198.

CREDS Findings

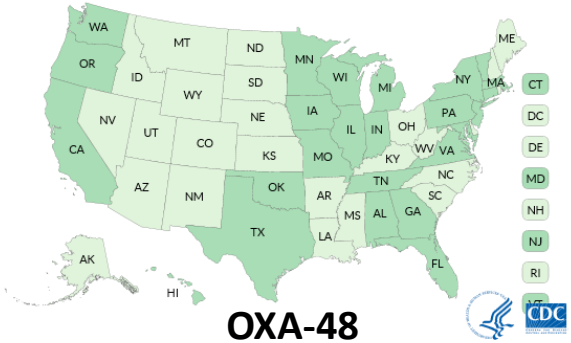
- Old definition
  - Missed 21% of KPC-*Klebsiella*
    - Most R only to Ertapenem
  - 26.7% of isolates were false positives
- 2015 definition: R to any carbapenem
  - Missed 1% of KPC-*Klebsiella*
  - 55% of isolates were false positives
    - Decreased to 12% when MHT added

Chea et al., *Emerging Infectious Diseases*. 2015;21(9):1611-1616. doi:10.3201/eid2109.150198.

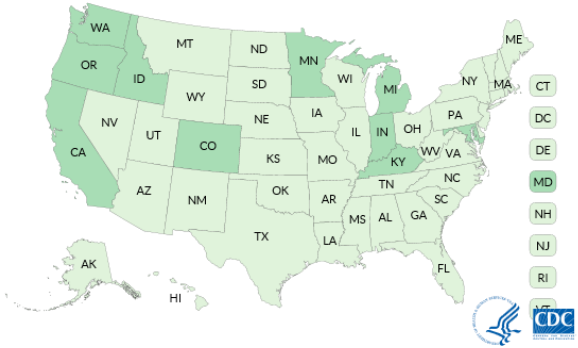
Patients with CP-CRE reported to the Centers for Disease Control and Prevention (CDC) as of January 2017



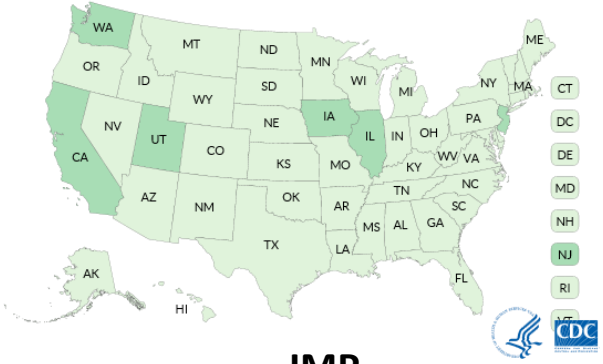
NDM



OXA-48



VIM



IMP

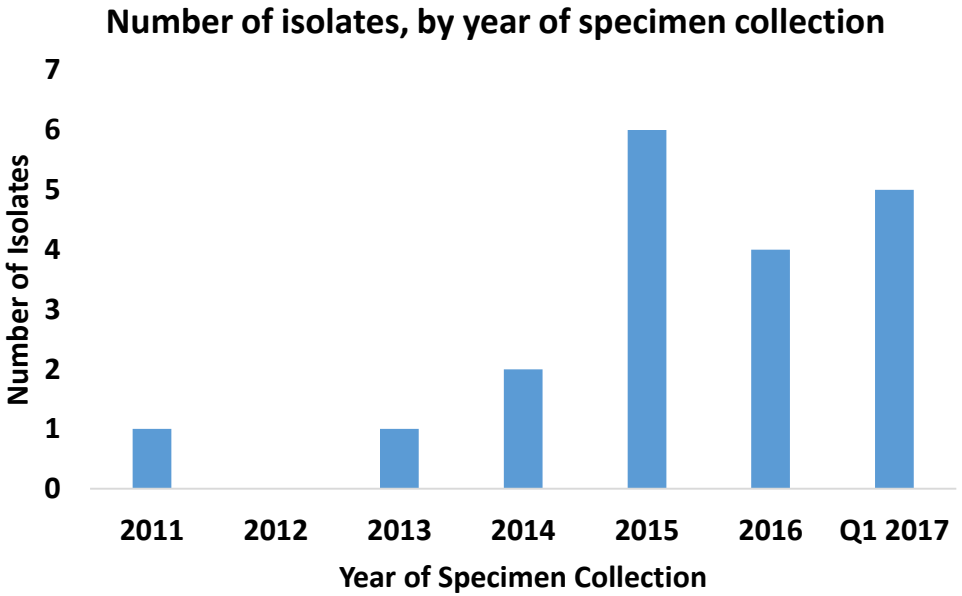
https://www.cdc.gov/hai/organisms/cre/trackingcre.html

Emerging Issues in Epidemiology of CP-Organisms

#1: Increase of non-KPC carbapenemases reported in Enterobacteriaceae other than *Klebsiella*, *Enterobacter*, and *E. coli*

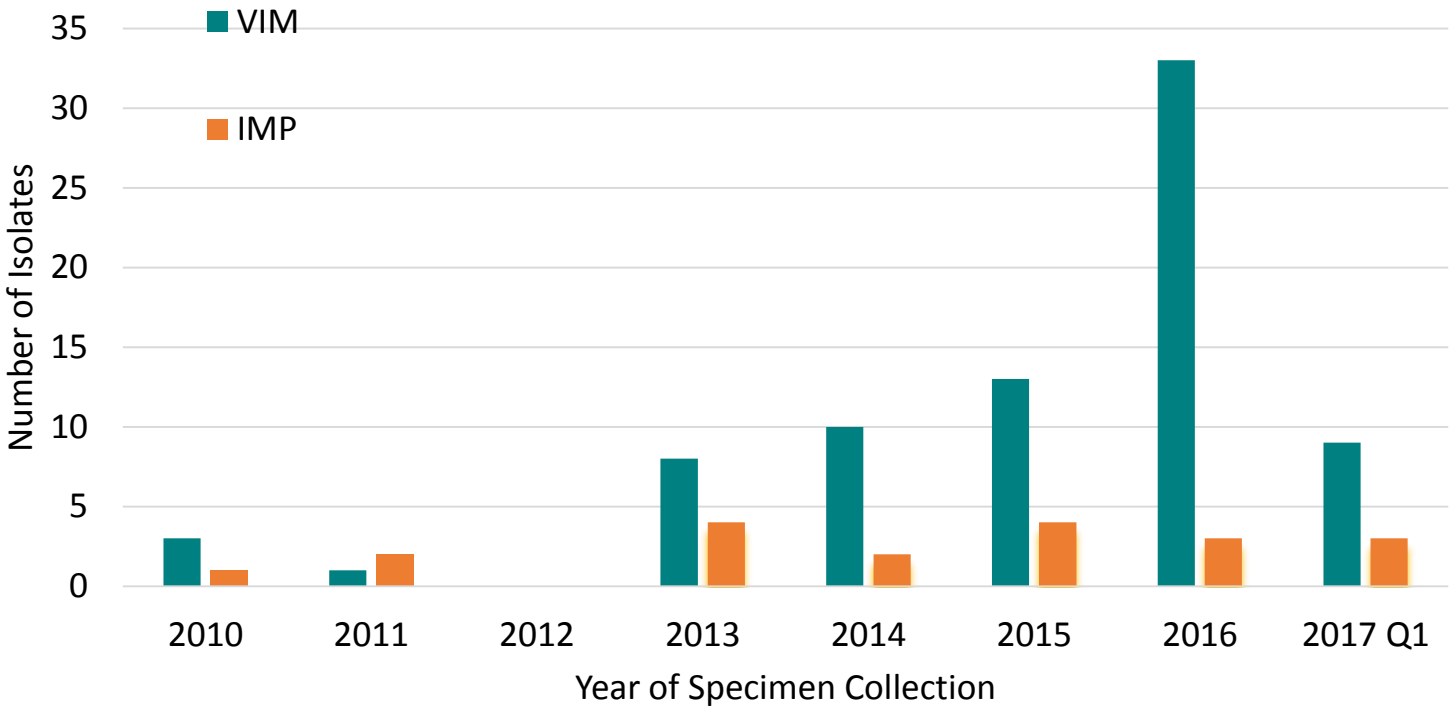
Number of isolates, by organism

Organism	Number of Isolates
Proteus mirabilis	5
Providencia rettgeri	5
Morganella morganii	4
Citrobacter freundii	3
Serratia marcescens	3
Salmonella seftenberg	1
Providencia stuartii	1
Grand Total	**22**



Emerging Issues in Epidemiology of CP-Organisms

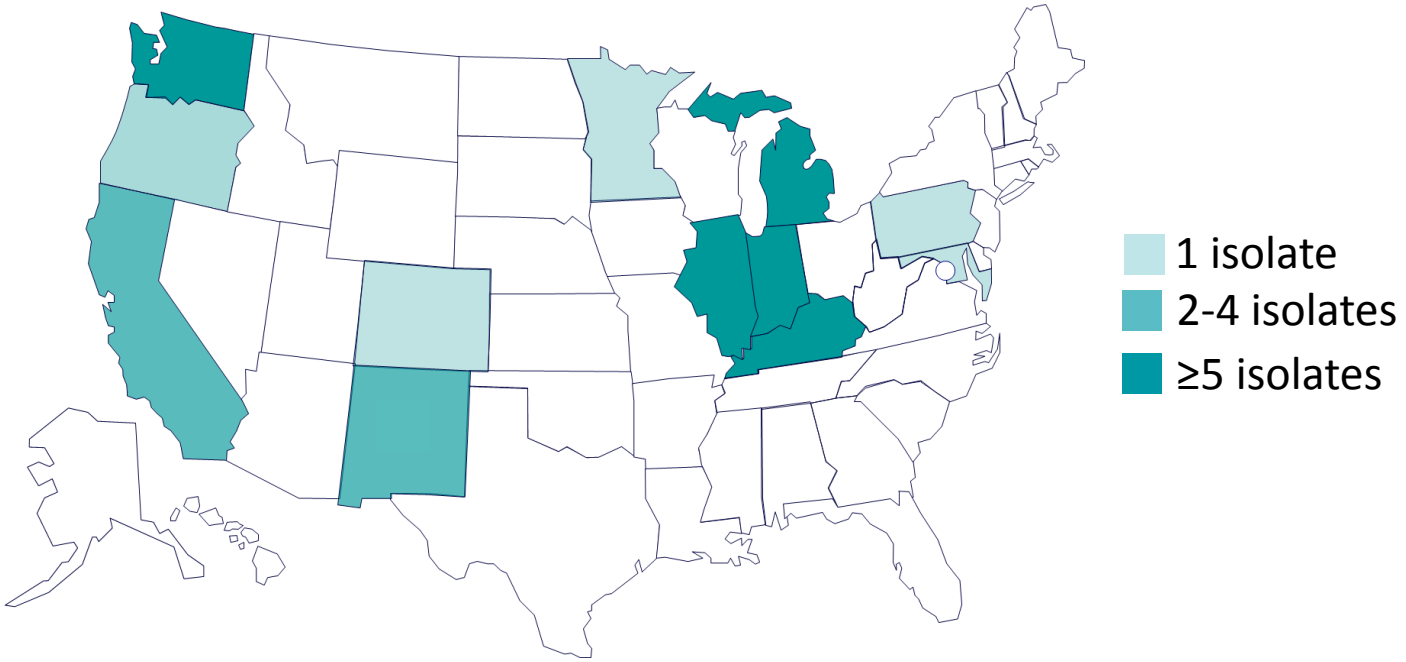
#2. Reports of Rare Carbapenemases Increasing



Emerging Issues in Epidemiology of CP-Organisms

#3: Increased detection of VIM metallo-β-lactamase identified “VIM-belt”

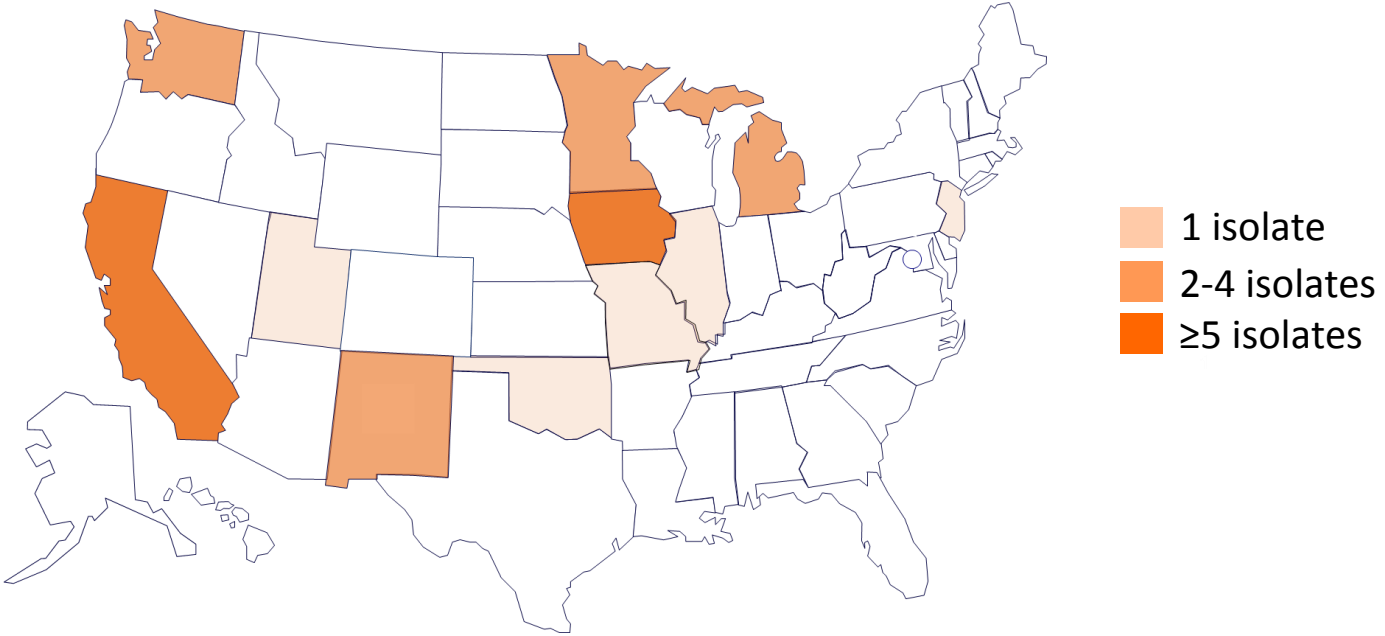
VIM-producing organisms, by state and number of isolates



Emerging Issues in Epidemiology of CP-Organisms

#4: Increased detection of IMP metallo-β-lactamase is regional

IMP-producing organisms, by state and number of isolates



- 12/15 isolates identified in 2016-2017 from 5-state region in upper midwest

Emerging Issues in Epidemiology of CP-Organisms

#5: CP-CRE in U.S. patients without healthcare or international travel

- EIP CRE surveillance: 13% of all cases are community-associated*
- Colorado: 6/10 recent NDM community-associated**
  - 2 had recent international travel
- Source currently unknown
  - CP-CRE found in community sources in U.S.
    - OXA-48 in municipal water that failed fecal coliform testing[$]
    - IMP-27 in environmental samples on pig farm[#]
  - Asymptomatic travelers in community
  - Hospital sewage effluent, surface water

*CDC EIP Unpublished data

**Janelle, S., et al., MMWR Morb Mortal Wkly Rep 2016;65:1414–14
DOI: http://dx.doi.org/10.15585/mmwr.mm6549a6.

[$] Tanner, W.D., poster presentation

[#]Mollenkopf, D.F., Antimicrob Agents Chemother 61:e01298-16. DOI: https://doi.org/10.1128/AAC.01298-16.

Emerging Issues in Epidemiology of CP-Organisms

#6: New modes of transmission: sink drains and hoppers

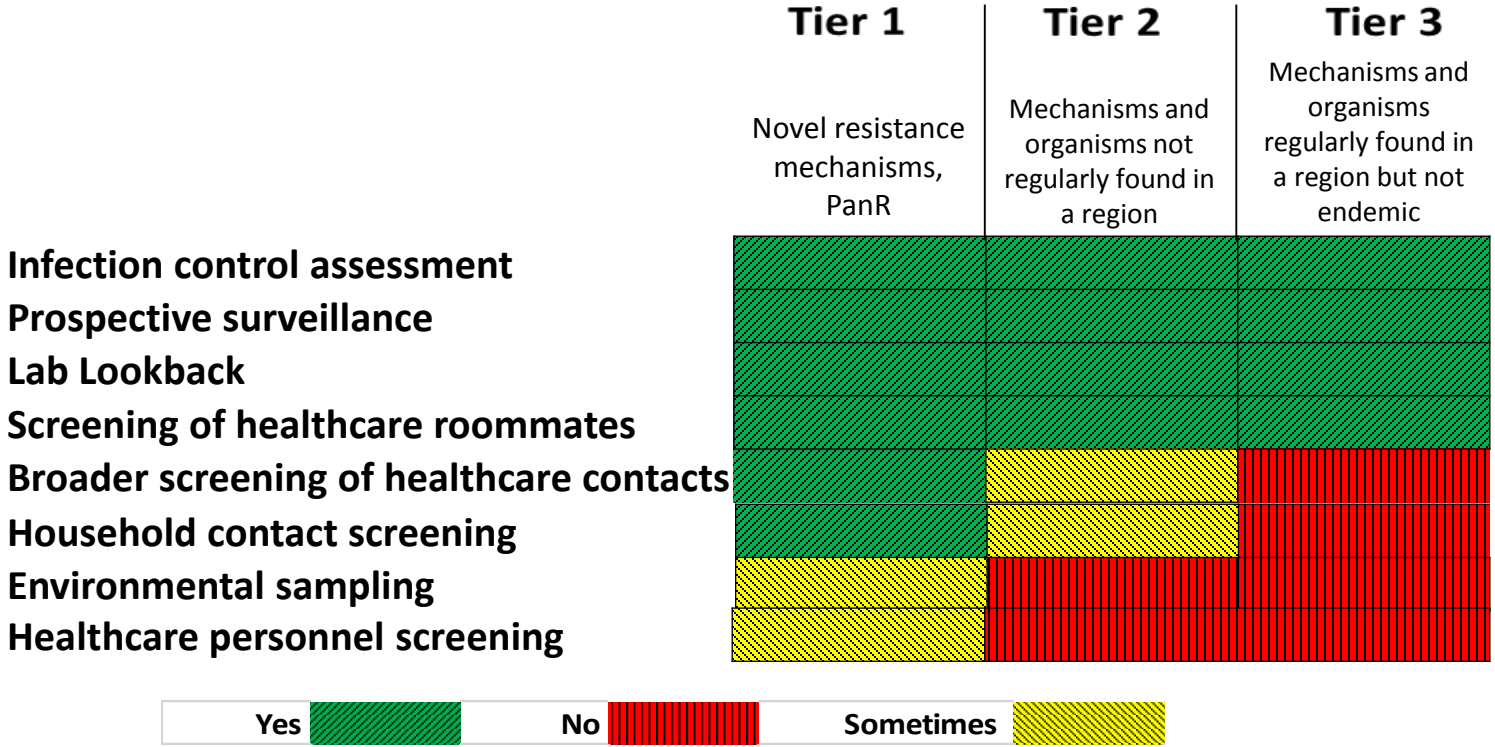
- Hospital sink drains and hoppers can become colonized with CP-CRE and contaminate the patient environment
- Characteristic outbreak “signature”
  - Single mechanism in multiple genus and species
  - Cases persist despite infection control interventions for person to person transmission and environmental cleaning
- Lab work ongoing to describe extent of spread and to evaluate ways to prevent (e.g., lids on hoppers)
- Keep patient supplies away from sink splash zone

Containment Strategy

- Goal: slow spread of novel or rare multidrug-resistant organisms or mechanisms
- Systematic, aggressive response to single cases of high concern antimicrobial resistance
  - Focus on stopping transmission
- Response activities have tiered approach based on organism/mechanism attributes
- Complements existing guidance
  - CRE Toolkit
  - VRSA Investigation Guide

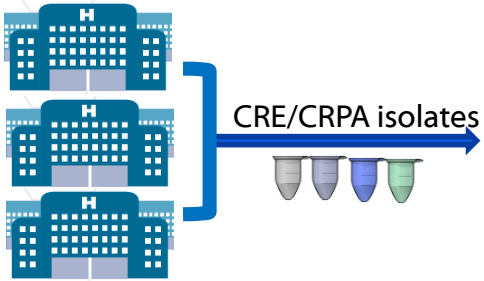
https://www.cdc.gov/hai/outbreaks/mdro/index.html

Containment Response Elements



Antimicrobial Resistance Laboratory Network: Laboratory Support for Containment

Hospitals/Clinical Laboratories



CRE/CRPA isolates

Rectal Swabs

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)

CRE and CRPA Colonization Screening
mcr-1 testing