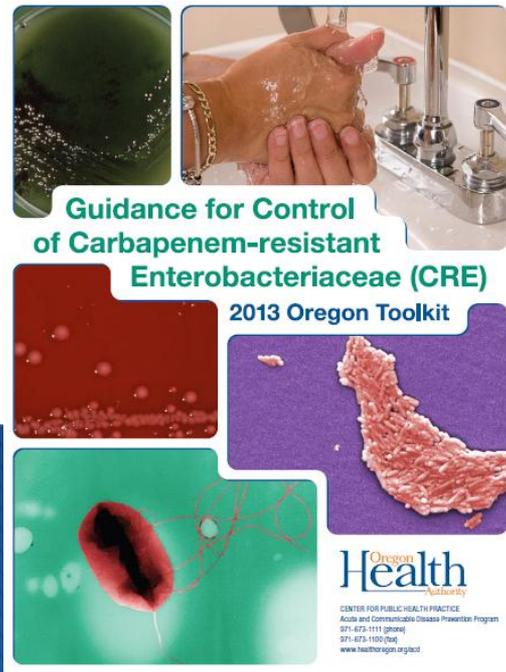


Carbapenem-Resistant Enterobacteriaceae (CRE) Regional Prevention of a Global Threat



OHSU Telehealth Webinar
Christopher D. Pfeiffer, MD, MHS
Jan 16, 2014

Current Practice?

- ▶ 63 y.o. female is transferred to your nursing home from OHSU. She has an active CRE urinary tract infection for which she is on IV antibiotics.
 - What is the mortality?
 - What transmission-based precautions are necessary to implement...
 - while she is being treated (i.e., during active infection)?
 - after treatment is completed (i.e., for colonization)?

This is her prior susceptibility report

| Antibiotic | <i>K. pneumoniae</i> 05-560 |
|---------------|--------------------------------|
| Ampicillin | >256 |
| Piperacillin | >256 |
| Cephalothin | >256 |
| Cefoxitin | >256 |
| Cefotaxime | >256 |
| Cefuroxime | >256 |
| Ceftazidime | >256 |
| Aztreonam | >256 |
| Cefepime | >256 |
| Ertapenem | >32 |
| Imipenem | >32 |
| Meropenem | >32 |
| Ciprofloxacin | >32 |
| Colistin | 0.75 |



CARBAPENEM-RESISTANT ENTEROBACTERIACEAE



9,000

DRUG-RESISTANT INFECTIONS PER YEAR



600

DEATHS

CARBAPENEM-RESISTANT *KLEBSIELLA* SPP.

7,900



1,400

CARBAPENEM-RESISTANT *E. COLI*

THREAT LEVEL
URGENT



This bacteria is an immediate public health threat that requires urgent and aggressive action.



CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS



Hunting the Nightmare Bacteria

October 22, 2013



Hunting the Nightmare Bacteria

FRONTLINE investigates the rise of deadly drug-resistant bacteria. (53:41)

Frontline Report: 3 stories

- ▶ 11 yo F with MRSA bacteremia, complicated by VAP due to pan-resistant *Stenotrophomonas*
 - Survived after undergoing lung transplant
- ▶ 19 yo M with traumatic injury in Calcutta complicated by NDM-1 CRE infection ultimately treated in Seattle (amputation, many surgeries)
- ▶ NIH KPC CRE outbreak:
 - 18 patients infected or colonized
 - 6 deaths (33%) due to the infection

Learning Objectives / Outline

1. Understand: what are CRE? Which CRE are most important?
 2. Become acquainted with CRE epidemiology, clinical importance, and treatment.
 3. Learn about the regional CRE Prevention efforts including the DROP-CRE Network and the Oregon CRE Toolkit.
- 

Important Multidrug-Resistant Gram Negative Bacilli (MDR-GNB)

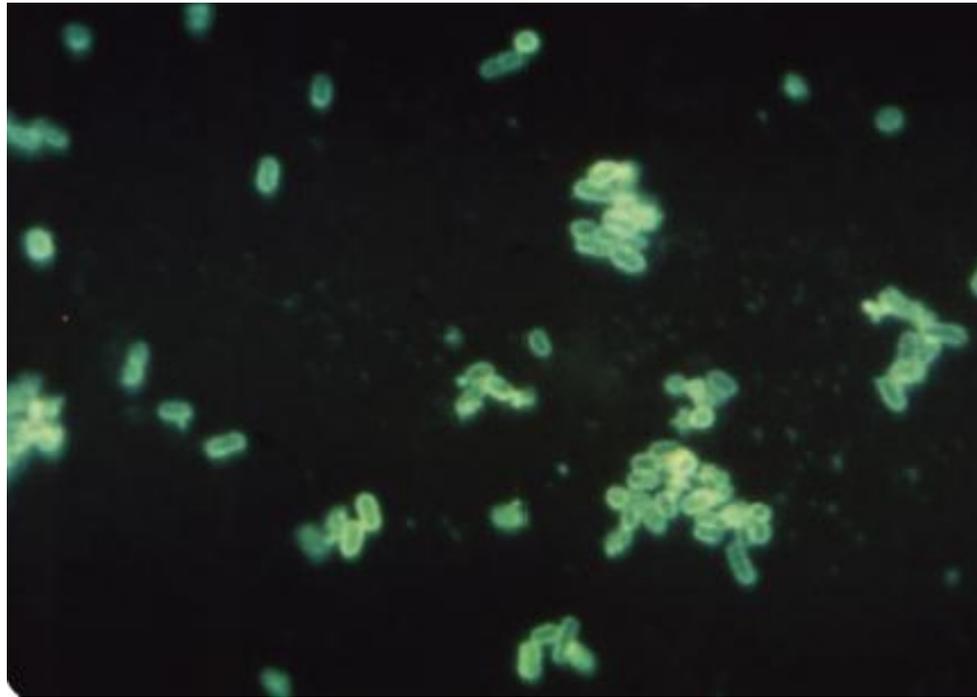
- ▶ *Pseudomonas aeruginosa*
- ▶ *Acinetobacter baumannii*
- ▶ **MDR-Enterobacteriaceae**
 - Examples of Enterobacteriaceae: *E. coli*, *Klebsiella* spp., and *Enterobacter* spp.
 - The mechanism of resistance is important: ESBLs, AMPCs, CREs (next page)

Enterobacteriaceae

Resistance Mechanisms

| Drug Class | Examples | Resistance Mechanism |
|--|--|--|
| β -lactams | PCN, Amoxicillin | β -lactamases |
| β -lactam/ β -lactamase inhibitors | Amoxicillin-clavulanic acid (Augmentin) | Extended-spectrum β - lactamases (ESBLs) |
| Cephalosporins | Cephalexin (Keflex) Ceftriaxone (Rocephin) Cefepime (Maxipime) | Extended spectrum cephalosporinases (e.g., AmpC) |
| Carbapenems | Ertapenem (Invanz) Imipenem (Primaxin) Meropenem (Merrem) Doripenem (Doribax) | Carbapenemases |

What are CRE?



Oregon CRE Definition (2013)

Carbapenem-resistant Enterobacteriaceae...

Are non-susceptible (i.e., intermediate or resistant) to ANY carbapenem (e.g., doripenem, ertapenem, imipenem, or meropenem)
AND
resistant to ANY of the following 3rd generation cephalosporins tested:
cefotaxime, ceftriaxone, or ceftazidime

—OR—

Possess/contain a gene sequence specific for carbapenemase (PCR)

—OR—

Are positive for carbapenemase production by a phenotypic test
(e.g., Modified Hodge Test)

Oregon CRE Definition (2014)

- ▶ **New in 2014 for labs using the current CLSI breakpoints:**
 - **ertapenem** is no longer one of the carbapenems used in the definition
 - all (not just any) 3rd generation cephalosporin tested should be **resistant**.
- ▶ These changes increase the specificity of the definition to detect carbapenemase-producing organisms

CRE Resistance Mechanisms

1. Carbapenemase

- ❑ Enzymes produced by bacteria which **directly** inactivate carbapenem antibiotics

2. Non-Carbapenemase

- ❑ Multiple resistance mechanisms combine to confer carbapenem resistance

Tier 1 CRE:

Carbapenemase-producing CRE

- ▶ #1 Organism: *Klebsiella* spp.
- ▶ Carbapenemases to know:
 - *Klebsiella pneumoniae* carbapenemase (KPC)
 - New Delhi metallo- β -lactamase (NDM)
 - Oxacillinase-48 (OXA-48)
 - Verona integron encoded metallo- β -lactamase (VIM)
 - Imipenemase metallo- β -lactamase (IMP)
- ▶ Epidemiology: rapid **worldwide** dissemination
 - plasmid-mediated spread

Tier 2 CRE:

Acquired resistance NOT due to a carbapenemase

▶ #1 Organism: *Enterobacter* spp.

▶ Resistance mechanism to know:

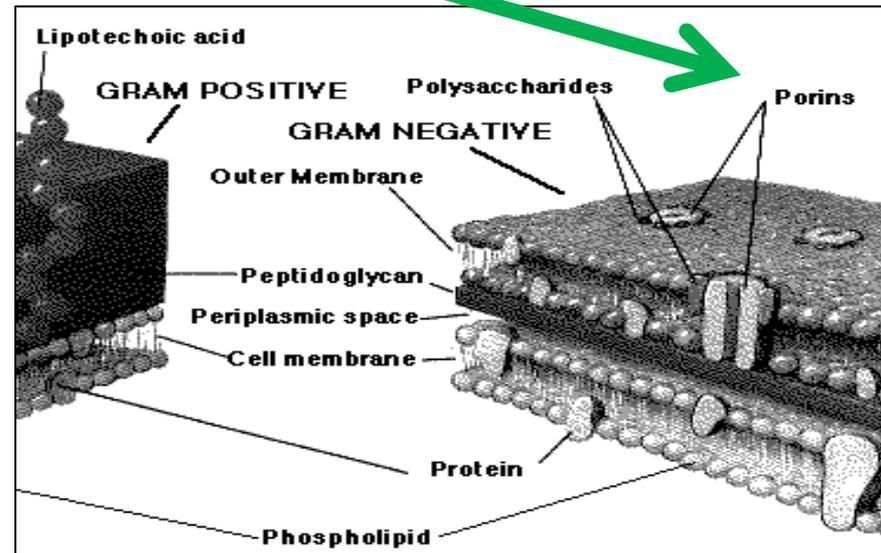
AmpC and/or ESBL

plus

Decreased cell wall permeability (e.g., porin mutation)

▶ Epidemiology

- Incidence stable ~20 years



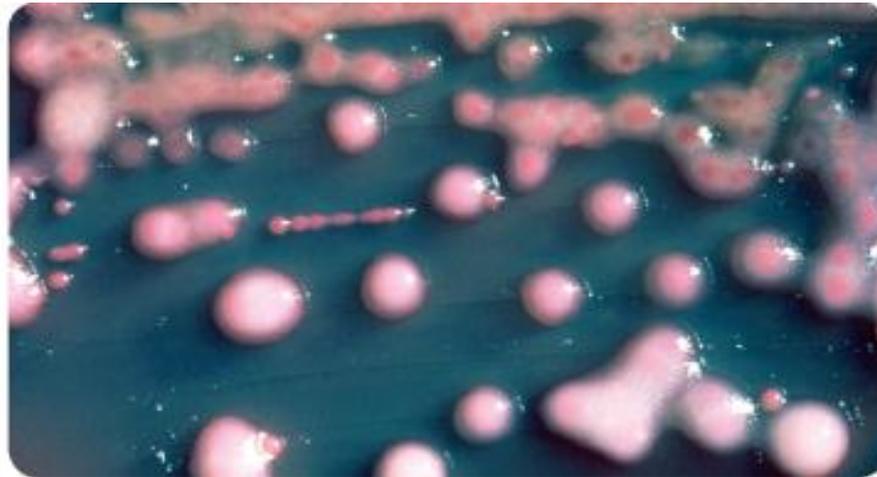
CRE Assessment Tiers*

| Tier | Description | Recommended Action (acute care facilities) |
|------|--|--|
| 1 | Carbapenemase-producing CRE (CP-CRE) | Most aggressive control measures |
| 2 | CRE with acquired resistance NOT due to carbapenemase production | Control measures as for other MDRO infections |

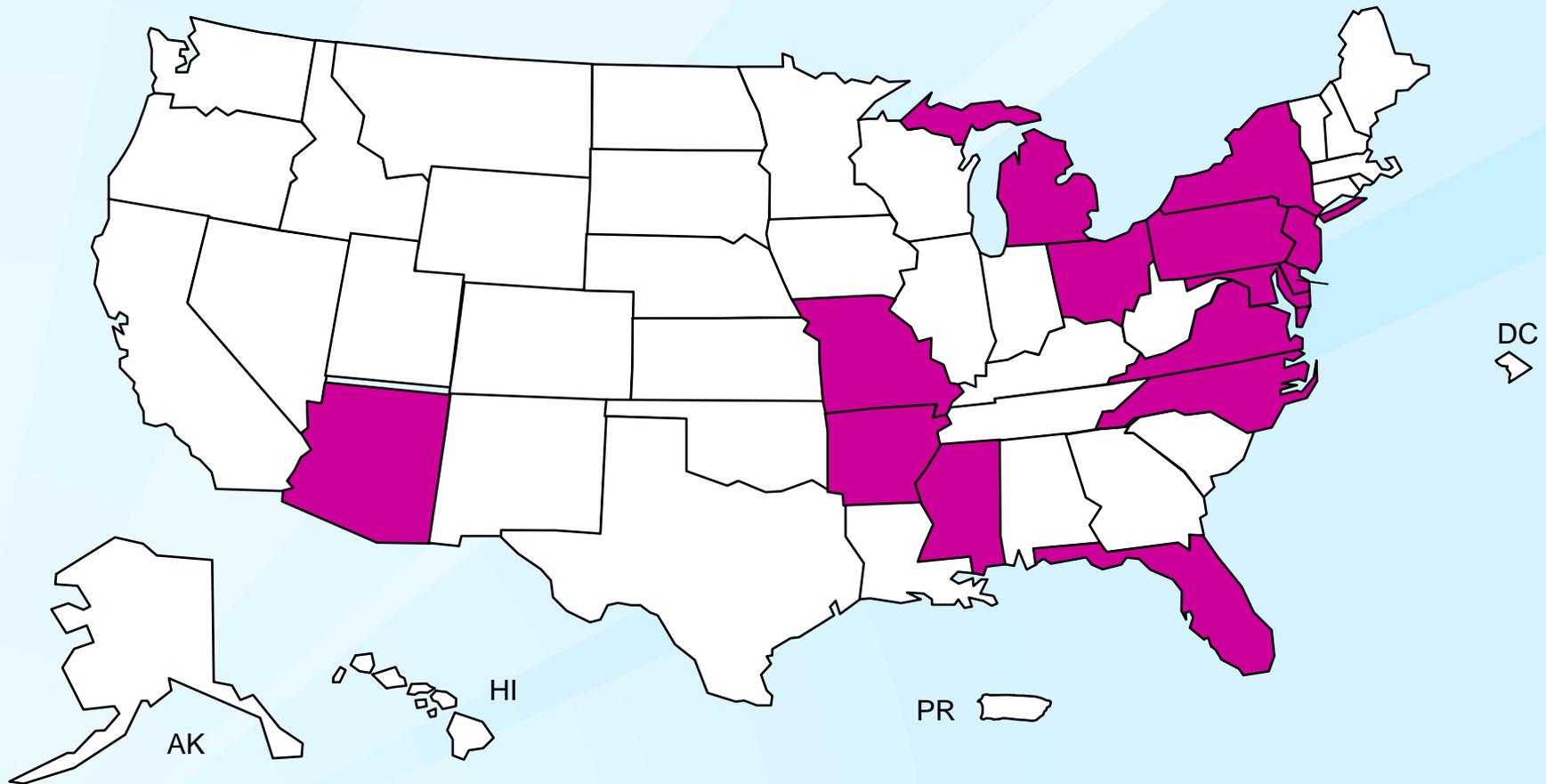
*see Oregon CRE Toolkit 2013

CRE:

**Epidemiology, clinical impact,
and treatment**



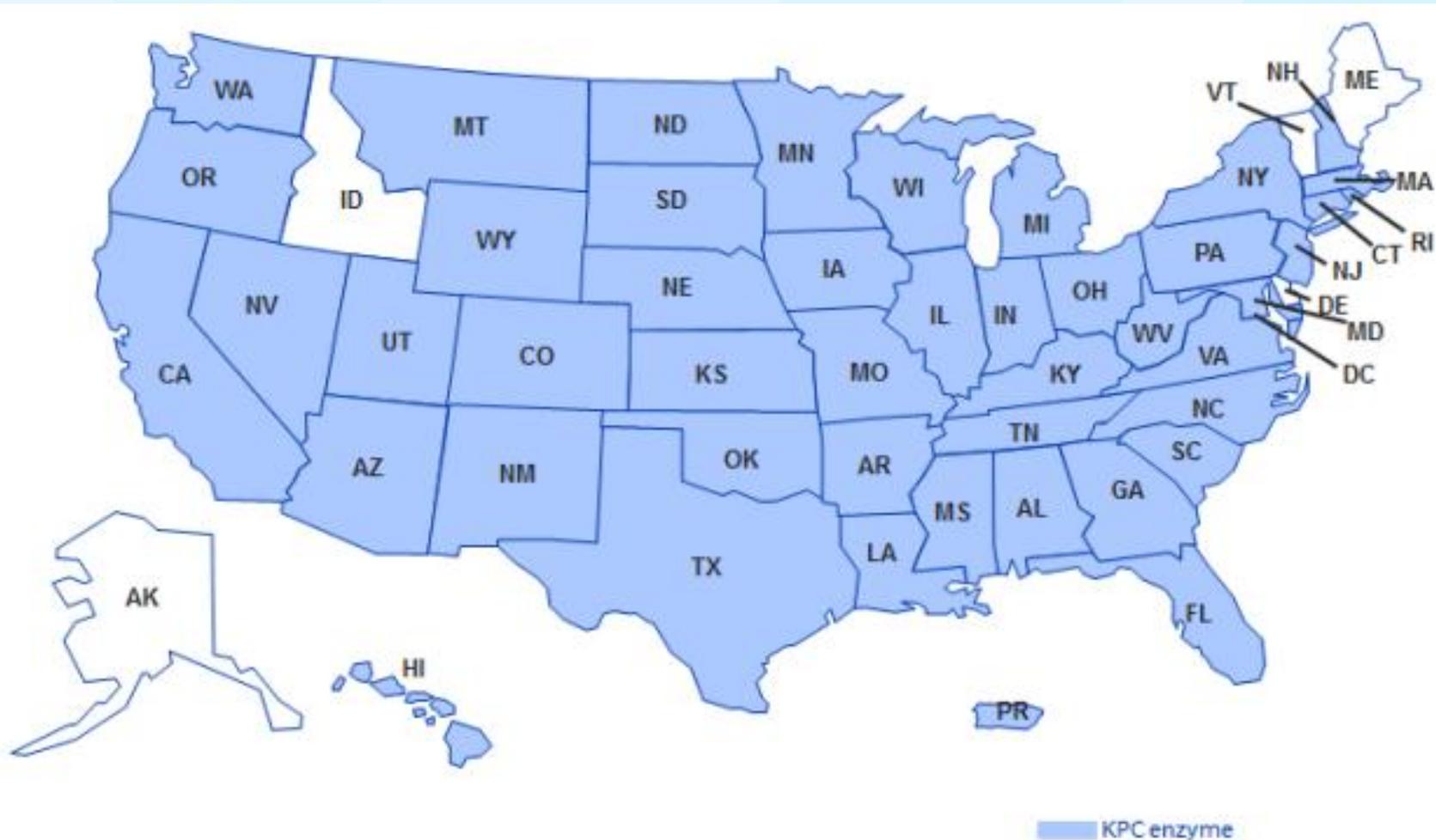
Carbapenemase-producing CRE in the United States circa 2009



Patel, Rasheed, Kitchel. 2009. Clin Micro News
CDC, unpublished data



Carbapenemase-producing CRE in the US, 2013



This map was last updated on December 31, 2013

<http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html> accessed Jan 2014



Vital Signs: Carbapenem-Resistant Enterobacteriaceae

| Characteristic | Number of CREs ^a | (N = 5,210) | (%) |
|------------------------------------|-----------------------------|-------------|--------|
| Facility type | | | |
| All acute-care hospitals | 181 | 3,918 | (4.6) |
| Short-stay acute-care hospital | 145 | 3,716 | (3.9) |
| Long-term acute-care hospital | 36 | 202 | (17.8) |
| Hospital size (no. of beds) | | | |
| <100 | 48 | 1,609 | (3.0) |
| 100–299 | 46 | 1,480 | (3.1) |
| 300–499 | 41 | 541 | (7.6) |
| ≥500 | 45 | 258 | (17.4) |
| Medical school affiliation | | | |
| Yes | 102 | 1,079 | (9.5) |
| No | 53 | 2,839 | (1.9) |

From facilities reporting CRE to NHSN, Jan–June 2012

CAUTI=catheter-associated UTI; CLABSI=central-line-associated bloodstream infection

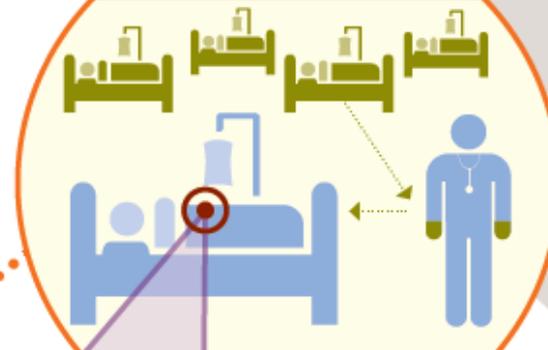
Risk of CRE Infections

1. Local Short-Stay Hospital



Jan has a stroke and is in the hospital. She is stable but needs long-term critical care at another facility.

2. Long-Term Acute Care Hospital



Other patients in this facility have CRE. A nurse doesn't wash his hands, and CRE are spread to Jan. She develops a fever and is put on antibiotics without proper testing.

3. Local Short-Stay Hospital



Jan becomes unstable and goes back to the hospital, but her new doctors don't know she has CRE. A doctor doesn't wash her hands after treating Jan. CRE are spread to other patients.

How CRE Take Over

1. Lots of germs, 1 or 2 are CRE



2. Antibiotics kill off good germs



3. CRE grow

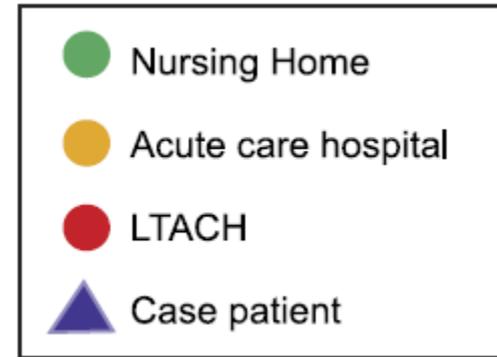
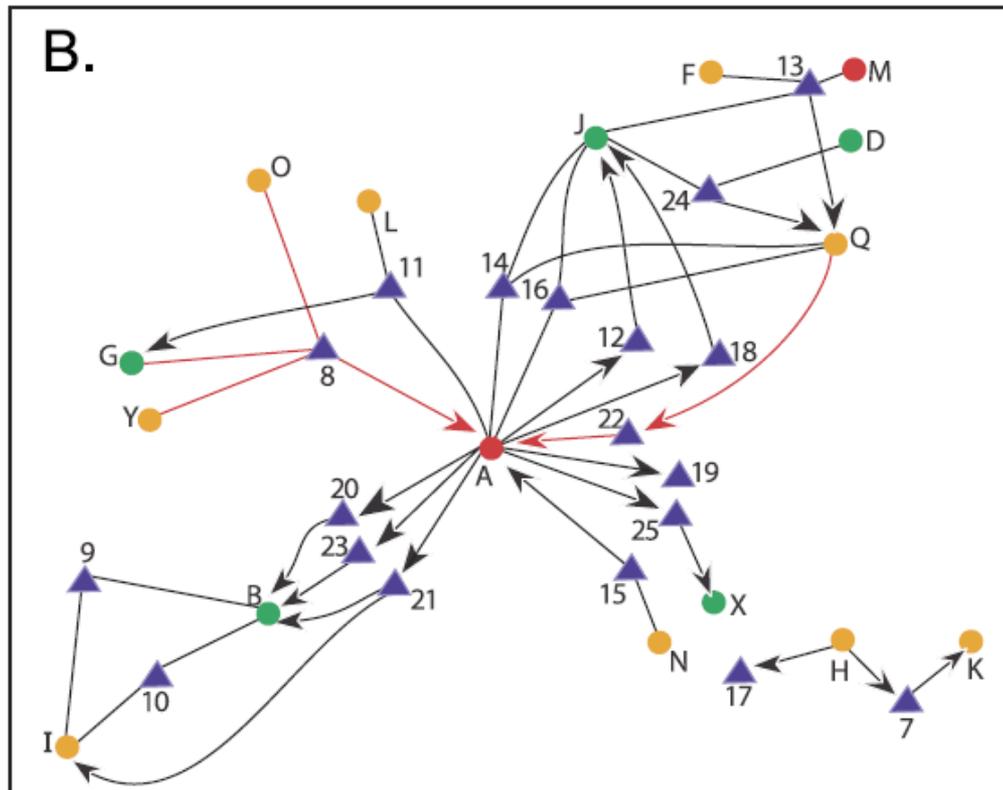


4. CRE share genetic defenses to make other bacteria resistant



KPC: a Regional Problem

Figure: Exposure Network Analysis



Letter = Facility

Number = Patient

Black = clinical Cx

Red = surveillance Cx

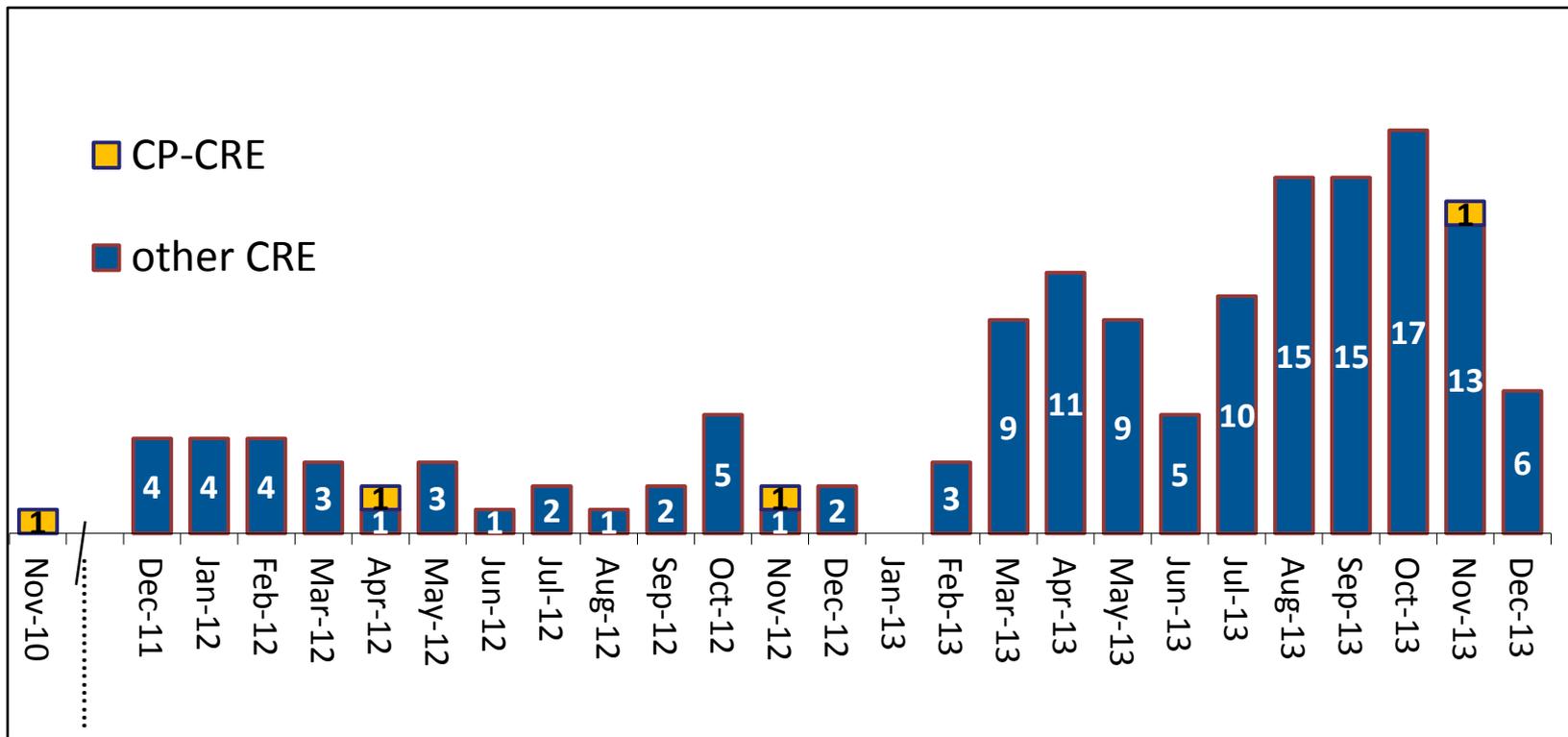
Arrow = origin of CRE
could be determined

Line = origin of CRE
uncertain

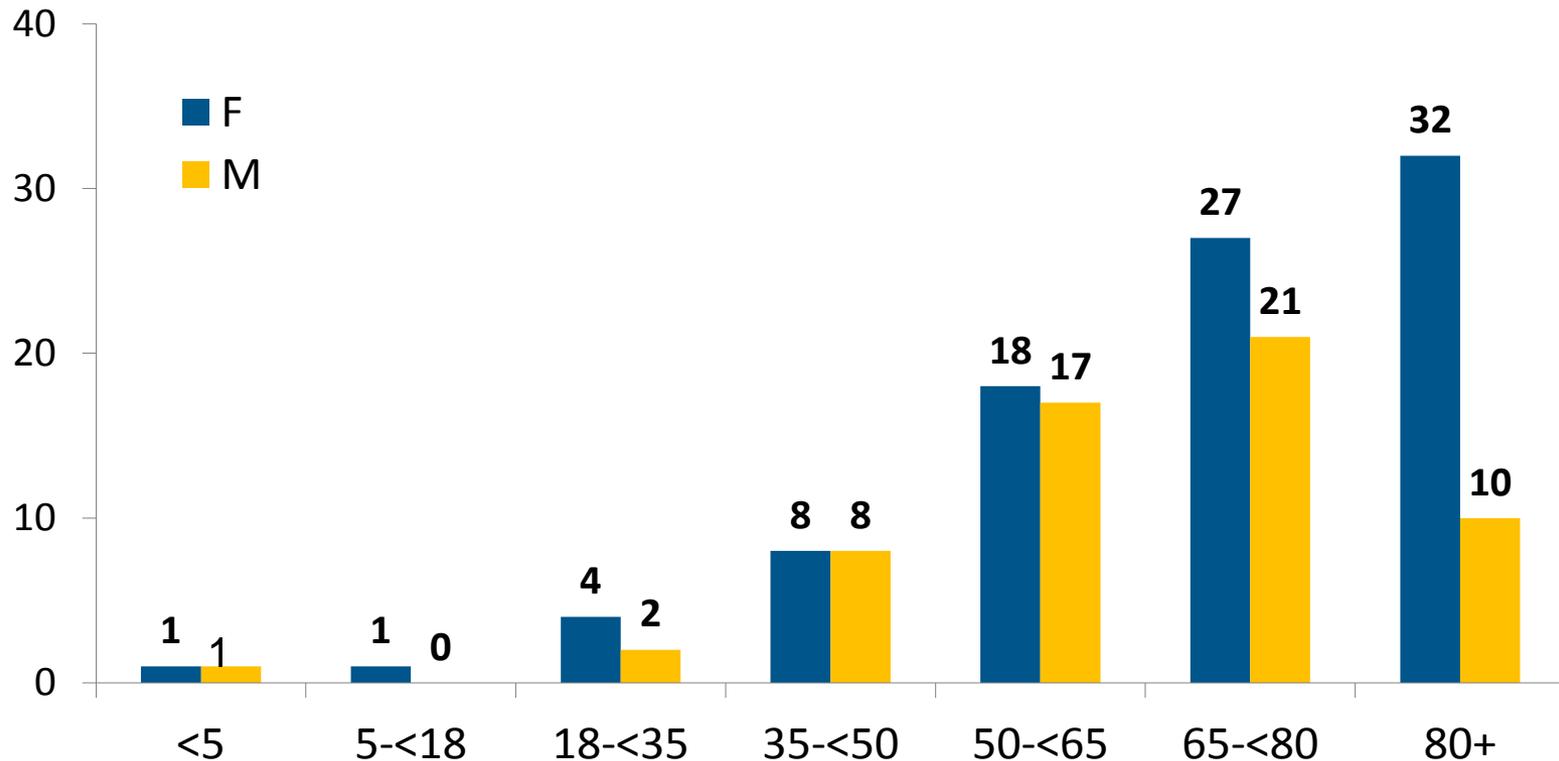
KPC in Chicago

- ▶ “We observed extensive transfer of KPC–positive patients throughout the exposure network of 14 acute care hospitals, 2 LTACHs, and 10 nursing homes. Although few cases were identified at most institutions, many facilities were affected. **Successful control of KPC–producing Enterobacteriaceae will require a coordinated, regional effort among acute and long–term health care facilities and public health departments.**”

CRE in Oregon Laboratories, 2010-13



Oregon CRE cases November 2010 – December 2013, by Age-group and Sex



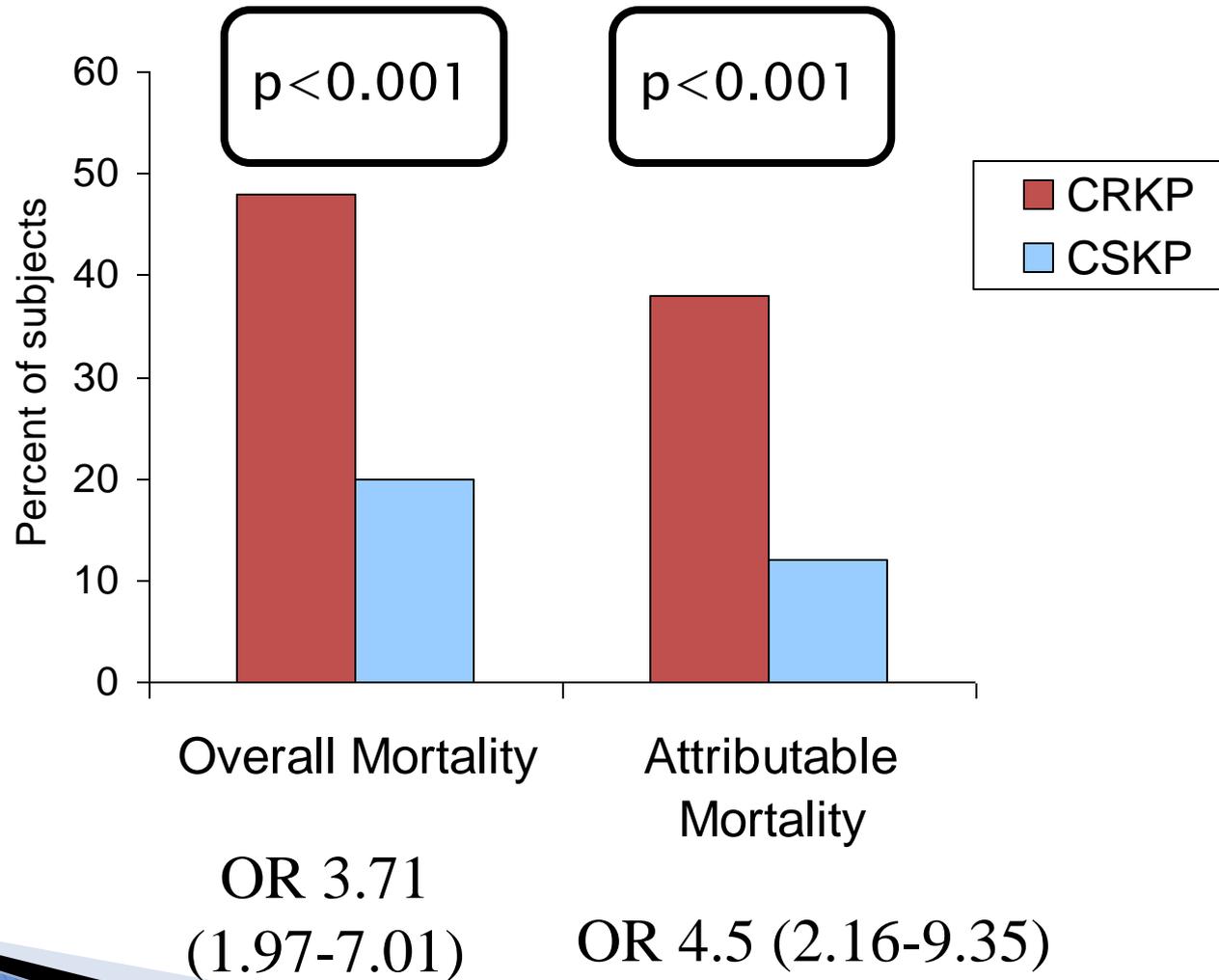
CRE by Subtype and Specimen Source

| Organism | Anatomical Site of culture | | | | | Total |
|-------------------------------|----------------------------|-----------|-------------|-----------|----------|------------|
| | Urine | Blood | Respiratory | Wound | Other | |
| <i>Enterobacter aerogenes</i> | 10 | 1 | 2 | 2 | 0 | 15 |
| <i>Enterobacter cloacae</i> | 51 | 6 | 12 | 14 | 5 | 88 |
| <i>Escherichia coli</i> | 13 | 1 | 0 | 1 | 0 | 15 |
| <i>Klebsiella pneumoniae</i> | 9 | 1 | 0 | 2 | 1 | 13 |
| Other | 13 | 1 | 2 | 3 | 0 | 19 |
| Total | 96 | 10 | 16 | 22 | 6 | 150 |

CRE: Clinical Impact

- ▶ **30–50%** mortality of invasive infection across multiple studies (with exceptions)
 - Infection types include bacteremia, pneumonia, UTI/urosepsis, abdominal abscess
- ▶ Limited treatment options
 - Colistin
 - Tigecycline (black box warning)
 - Aminoglycoside
 - Fosfomycin (UTIs)
- ▶ Some CRE are “pan-resistant”

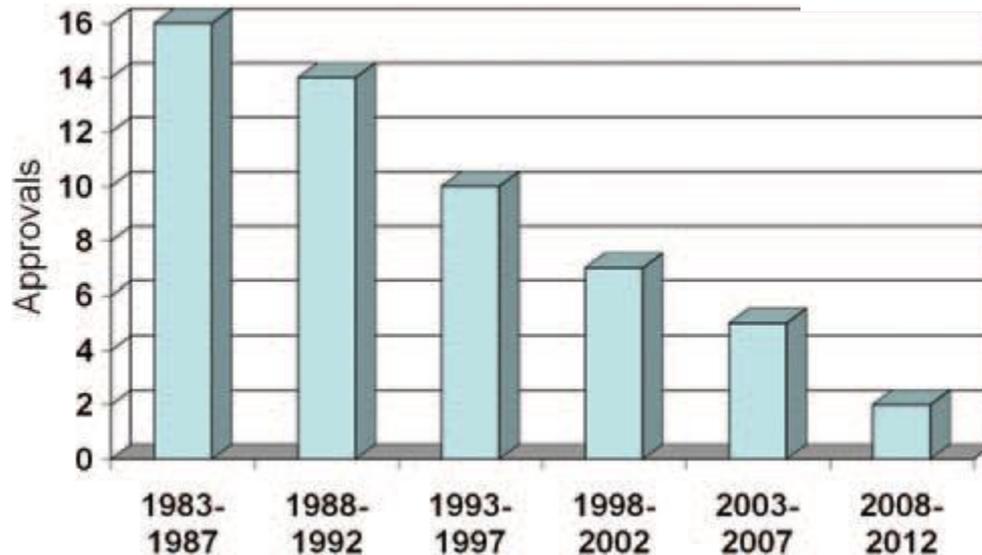
CRE Mortality (example)



Antibiotic Pipeline?



Ten new **ANTIBIOTICS** by 2020



- ▶ New systemic antibacterial agents approved by the US Food and Drug Administration per 5-year period, through 2012.

Boucher H, et al. Clin Infect Dis 2013;56:1685-94

<http://www.idsociety.org/Index.aspx>, accessed 10/20/13

**Given the lack of antibiotics,
stewardship of them is critical!**



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"GREAT NEWS - MORE DOOM AND GLOOM"

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The Oregon Drug-Resistant Organism Prevention and Coordinated Regional Epidemiology (DROP-CRE) Network



DROP-CRE Network Personnel

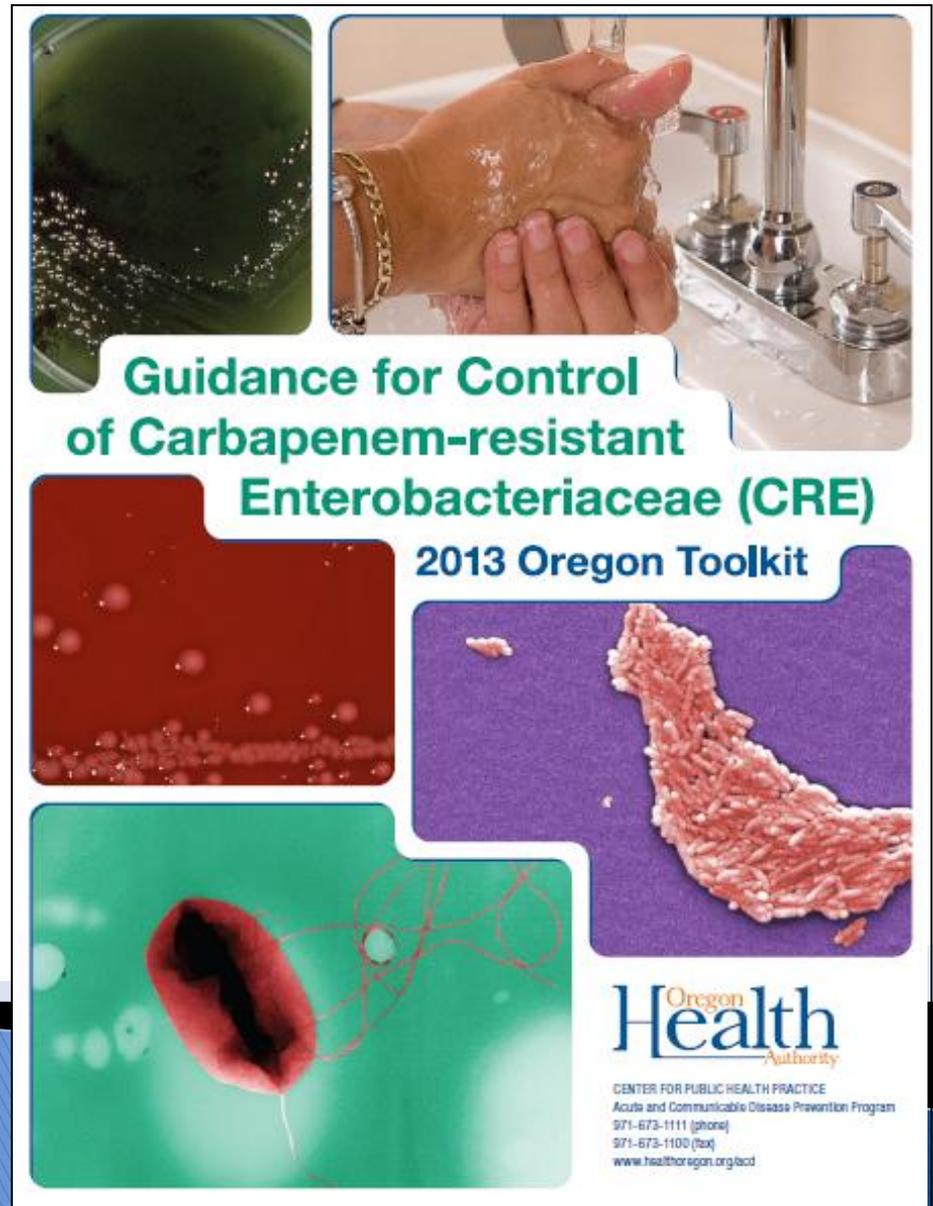
- ▶ Zintars Beldavs, MS (OHA)
 - ▶ Genevieve Buser, MD (OHA)
 - ▶ Maureen Cassidy, MT, MPH (OHA)
 - ▶ Ann Thomas, MD, MPH (OHA)
-
- ▶ Jon Furuno, PhD (OSU College of Pharmacy)
 - ▶ Chris Pfeiffer, MD, MHS (PVAMC, OHSU)
 - ▶ John Townes, MD (OHSU)
 - ▶ Andy Leitz, MD (OHSU, Infectious Diseases fellow)

Initial Goals

- ▶ Develop a CRE surveillance and response plan
 - ▶ Assess statewide needs and capabilities for MDRO/CRE response
 - ▶ Coordinate statewide MDRO/CRE education
 - ▶ Develop and disseminate an Oregon-specific CRE Toolkit
- 

The Oregon CRE Toolkit

- Published June, 2013
- Contains specific recommendations for Oregon facilities.



Oregon CRE Toolkit

1. Overview
 2. OHA CRE Definition and CRE Reference Guide
 3. Prevention and Control in Acute Care
 4. Prevention and Control in Long Term Care
 5. Prevention and Control in Ambulatory Care
 6. Recommendations for Microbiology Laboratories
 7. References
 - 8. Appendices** (response diagrams, laboratory protocols, educational material including patient/staff FAQs, environmental cleaning monitoring tool, inter-facility transfer form)
- 

General Measures for CRE Prevention in LTCFs

- ▶ Educate clinical staff
 - ▶ Ensure reporting of CRE (per correct definition)
 - ▶ Ensure that lab results are quickly alerted to person(s) responsible for infection control.
- 

Recommendations for CRE Infection Prevention and Control in Long-Term Care Facilities³

Think “NICE” when CRE are encountered:

Notify the county health department and pertinent clinician groups to presence of CRE in the facility. Additionally, for carbapenemase-producing CRE (CP-CRE), notify facility administration.

Intervene on all cases with core infection prevention and control strategies: hand hygiene, standard or contact precautions (when indicated), private rooms (if feasible), and optimized environmental cleaning. Reduce unnecessary antibiotics and use of invasive devices.

Communicate CRE infection or colonization status to the receiving facility upon patient transfer.

Educate patients, staff, and visitors about CRE

When are Contact Precautions Indicated?

4. **Place residents who are at higher risk for CRE-transmission in contact precautions.** Contact precautions are recommended for higher risk residents when they are in their room receiving care (and not when residents leave their room for group activity). Residents with CRE should not be discouraged from participating in daily community meals and activities.

Examples of higher risk residents for whom contact precautions are strongly recommended:

- Post-acute care residents still debilitated by recent hospitalization;
- Totally dependent on assistance for activities of daily living (ADLs);
- Ventilator-dependent;
- Uncontained incontinence of stool;
- Uncontained incontinence of urine (if site of CRE is urinary);
- Wounds with difficult to control drainage.

When are Standard Precautions Indicated?

Examples of lower risk residents for whom contact precautions are not specifically recommended:

- Residents who are able to perform hand hygiene, continent of stool, less dependent on staff for their activities of daily living, and without draining wounds.
- Residents whose incontinence or draining wounds can be contained.

Important!!!

Standard Precautions includes...

- ▶ Hand Hygiene
 - Before *and* after resident contact
- ▶ Gowns / Gloves / Face Shields
 - Use when contact with blood/body fluid/ drains/tubes/non-intact skin/etc. of hands/body/face is anticipated

New Oregon Regulations require communication of MDROs between health care facilities*

- ▶ Effective January 1, 2014
- ▶ When a referring health care facility transfers or discharges a patient who is infected or colonized with an MDRO, it must include written notification of the infection or colonization to the receiving facility in transfer documents.

Real-Time Outbreak Assistance

- ▶ DROP-CRE working group is available to support the local facility as needed via phone or on-site consultation

Future Directions in Oregon

- ▶ Continue CRE surveillance and education
 - Update the CRE Toolkit with new definition
 - Focus efforts on LTC community
 - ▶ Improve Communication
 - Learn from regional MDRO collaboratives
 - ▶ Apply lessons learned to focus on other MDROs
- 

Summary

- ❖ CRE are an urgent global threat; however, cases are currently uncommon in Oregon.
 - ❖ A regional approach to CRE control is important, and the DROP-CRE Network is uniquely positioned to coordinate a such an approach.
 - ❖ In the LTC setting, place CRE-colonized residents at high risk for CRE-transmission in Contact Precautions
 - ❖ Use the OR CRE Toolkit and our DROP-CRE team as a resource for CRE prevention at your facilities.
- 

Acknowledgements

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