
Carbapenem-Resistant *Enterobacteriaceae* (CRE) Update, 2016

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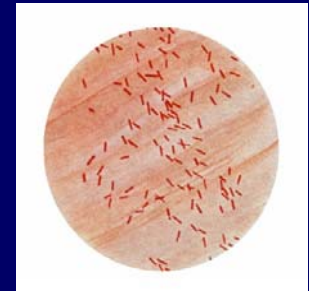
Oregon
Health
Authority

Objectives

- Explain the 2 mechanisms of resistance
- Discuss case definitions
- Review Data
- Review laboratory testing and isolate submission
- Local Health CRE follow up in various settings
- Additional surveillance

CRE Review

- **Enterobacteriaceae** – Gram negative bacilli of the gastrointestinal tract
- **Carbapenems** – class of β -lactam antibiotics with a broad spectrum of antibacterial activity
 - Considered antibiotics of last resort



Categories of Resistance

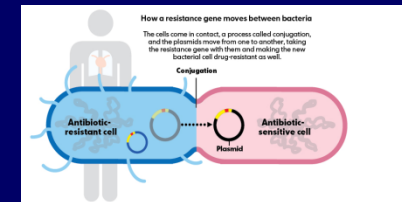
Non-carbapenemase

- Multiple mechanisms - typically ESBL or AmpC
- Decreased cell wall permeability (porins)
- Epidemiology: Stable incidence ~ 20 years

Categories of Resistance

Carbapenemases – Most Concerning

CP-CRE



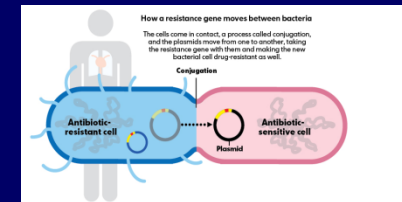
- Spread to other bacteria via plasmids
- Directly inactivate carbapenems
- Responsible for **rapid global spread**
- Increased morbidity and mortality

Categories of Resistance

Carbapenemases – Most Concerning

CP-CRE

- Plasmid-mediated enzymes
 - *Klebsiella pneumoniae* carbapenemase (**KPC**)
 - New Delhi metallo- β -lactamase (**NDM**)
 - Verona integron encoded metallo- β -lactamase (**VIM**)
 - Imipenemase metallo- β -lactamase (**IMP**)
 - Oxacillinase – 48 (**OXA-48**)



Current CRE Surveillance Definition

1. Resistance to doripenem, ertapenem, imipenem, or meropenem using the current CLSI breakpoints
2. OR positive for a carbapenemase (PCR)
3. OR positive by a phenotypic test
(Modified Hodge if *E. coli* or *Klebsiella sp.*, or **Carba NP** on any *Enterobacteriaceae*)

Clinical and Laboratory Standards Institute Information

	Current MIC Breakpoints ($\mu\text{g/mL}$) ¹		
	MIC Interpretation ²		
Carbapenems	Susceptible	Intermediate	Resistant
Doripenem	≤ 1	2	≥ 4
Ertapenem	≤ 0.5	1	≥ 2
Imipenem	≤ 1	2	≥ 4
Meropenem	≤ 1	2	≥ 4

¹MIC = minimum inhibitory concentration
²CLSI. Performance Standards for Antimicrobial Susceptibility Testing Twenty-Fifth Informational Supplement
 CLSI document M100-S25, Wayne, PA: Clinical and Laboratory Standards Institute: January 2015.

	Current Disk Diffusion Zone Diameters (mm) ³		
	Zone Size Interpretation ²		
Carbapenems	Susceptible	Intermediate	Resistant
Doripenem	≥ 23	20–22	≤ 19
Ertapenem	≥ 22	20–21	≤ 18
Imipenem	≥ 23	20–21	≤ 18
Meropenem	≥ 23	20–21	≤ 18

³mm = millimeters
²CLSI. Performance Standards for Antimicrobial Susceptibility Testing Twenty-Fifth Informational Supplement
 CLSI document M100-S25, Wayne, PA: Clinical and Laboratory Standards Institute: January 2015.

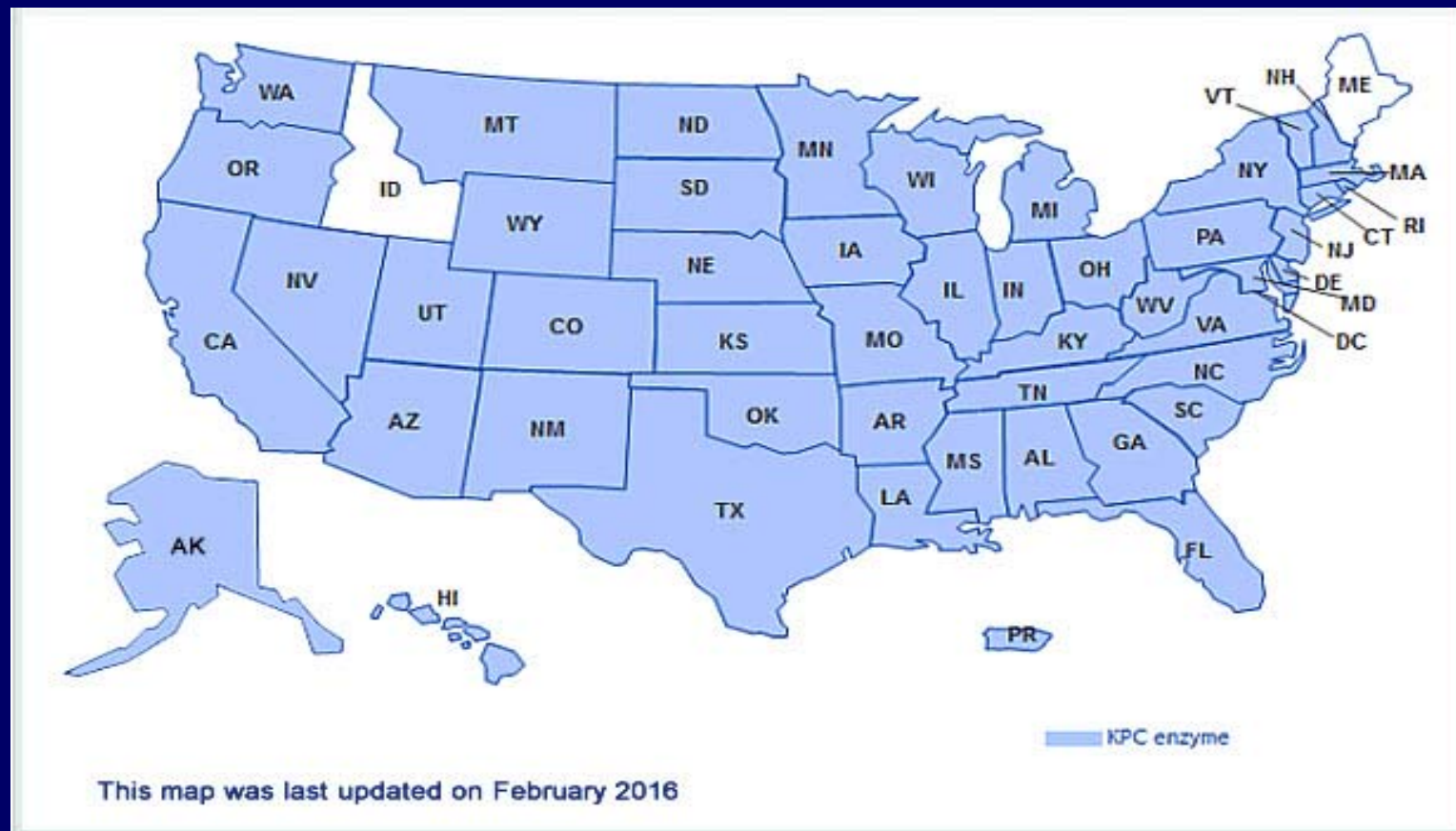
Oregon's CRE Definition Changes

- Evolution/Rationale
 - **2013: NS to all carbapenems + R to ANY 3rd gen ceph**
 - Too nonspecific
 - **2014: NS to mero/imi/dori only + R to ALL 3rd gen ceph**
 - Too insensitive (CDC CREDS study data)
 - **July, 2015: R to any carbapenem**
 - Simpler, align with CDC/CSTE

2016 CRE Epidemiology - US

Carbapenemase	1 st Report Worldwide	1 st Report US	Current US Epidemiology
KPC (<i>Klebsiella pneumoniae</i> carbapenemase)	2001 North Carolina	2001 North Carolina	Most common (~10% of <i>Klebsiella</i> spp. in NHSN, 2013)
NDM (New Delhi metallo- β -lactamase)	2009 Sweden (India)	2010 Traveler (India)	Uncommon n=157 (CDC, April, 2016)
OXA-48 (Oxacillinase-48)	2004 Turkey	2012 SMART surveillance, unknown location	Less common than NDM n=61 (CDC, April, 2016)
IMP (Imipenemase metallo- β -lactamase)	1994 Japan	2011 California (NICU)	Rare n=17 (CDC, April, 2016)
VIM (Verona integron encoded metallo- β -	2002/2003 Greece, Korea	2010 Traveler (Greece)	Rare n=10 (CDC, April, 2016)

2016 KPC CRE Epidemiology in US

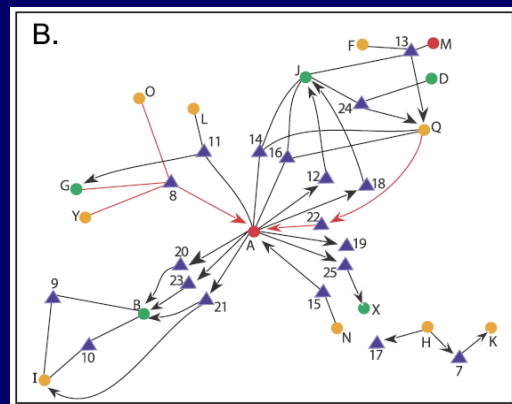


CRE Prevalence

- ✓ CRE prevalence varies
 - Region: Israel \neq Chicago \neq Oregon
 - Facility type: LTACH \neq Acute Care Hospital
- ✓ Unidentified CRE in inter-facility patient transfer promotes outbreaks

KPC outbreak, Chicago-area, 2008

Figure:
Exposure
Network
Analysis



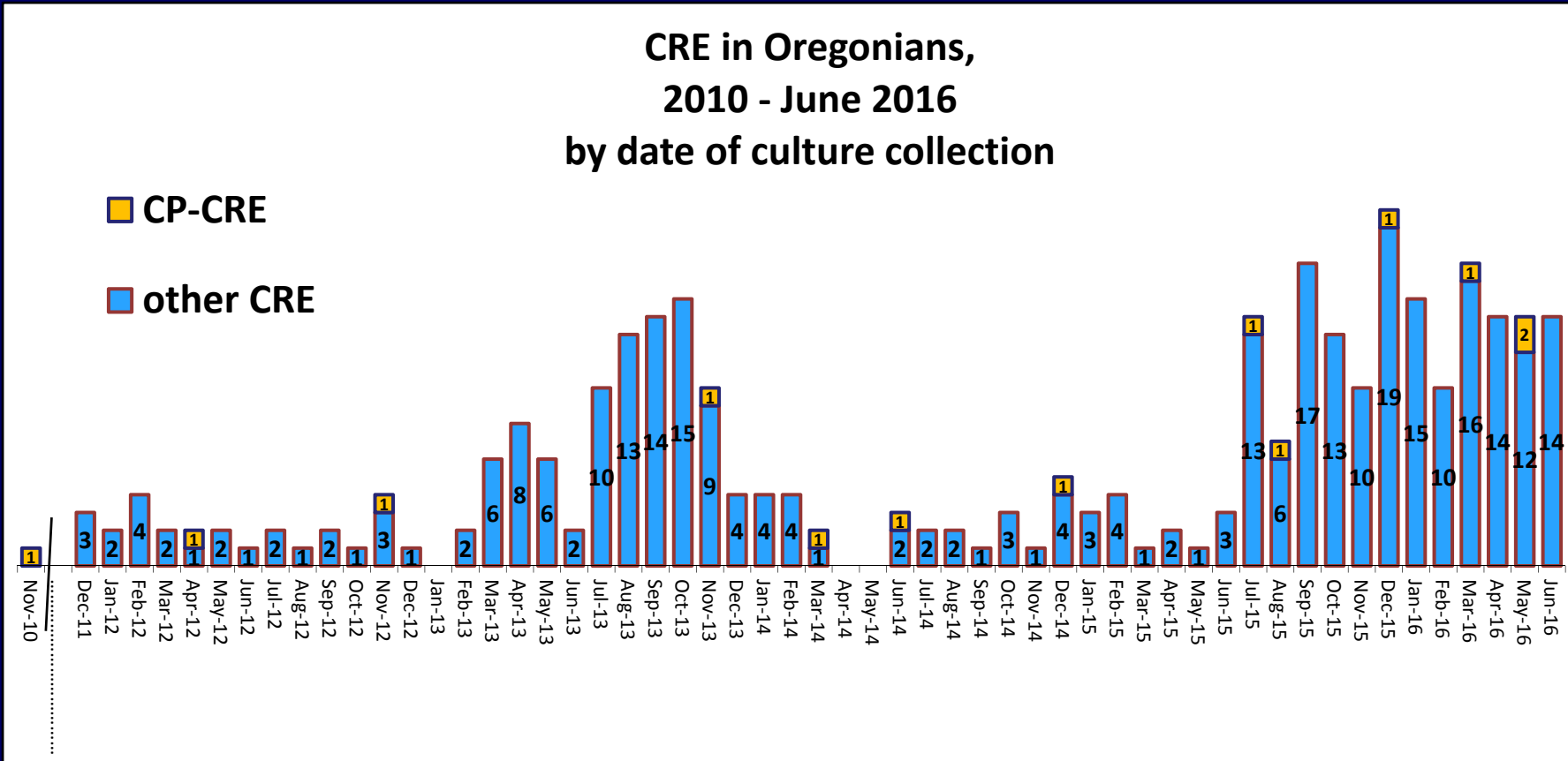
n=10
n=14
n=2
n=40

Won S. *et al.* Clin Infect Dis 2011;53:532-40

CRE in Oregon

CRE in Oregonians,
2010 - June 2016
by date of culture collection

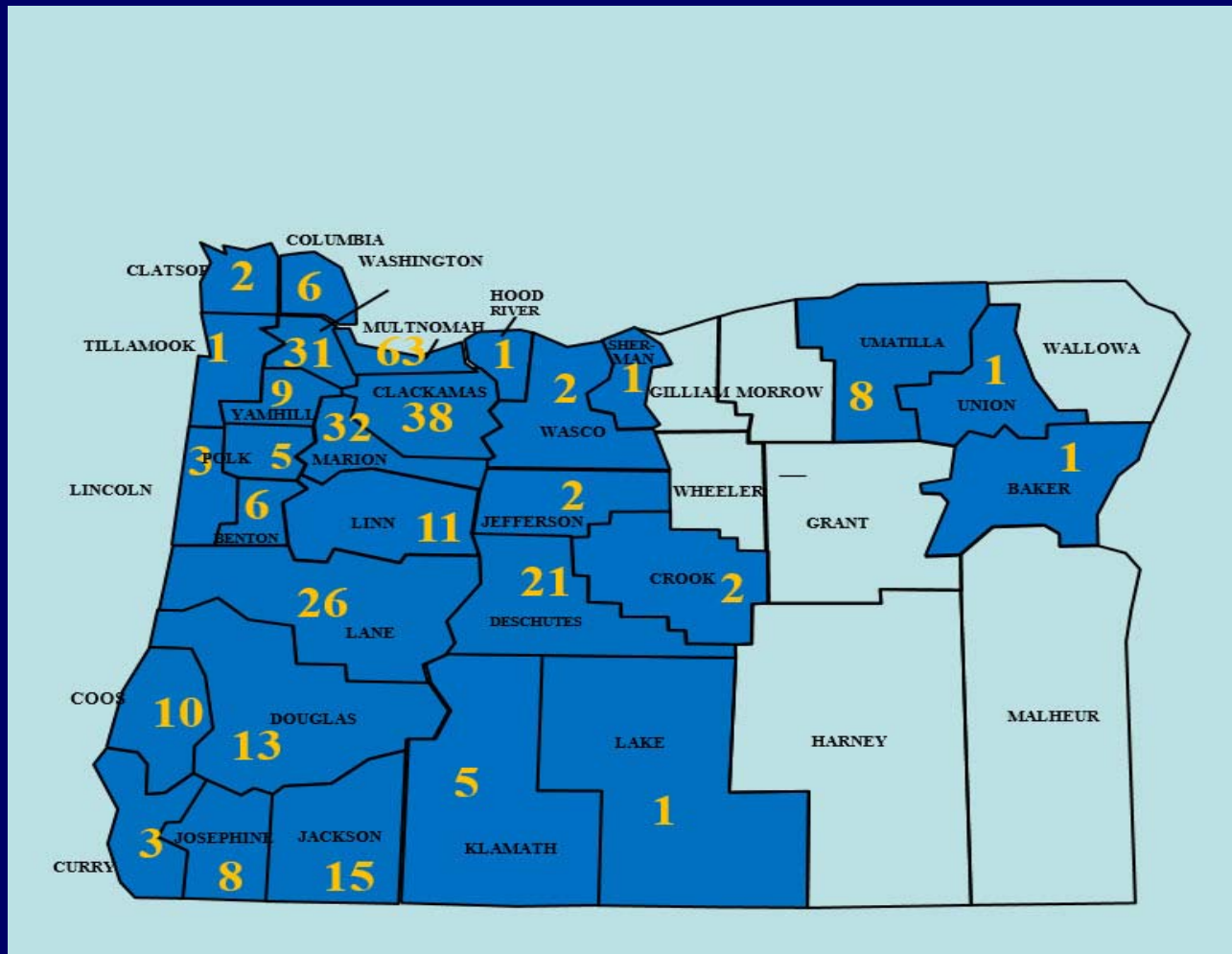
■ CP-CRE
■ other CRE



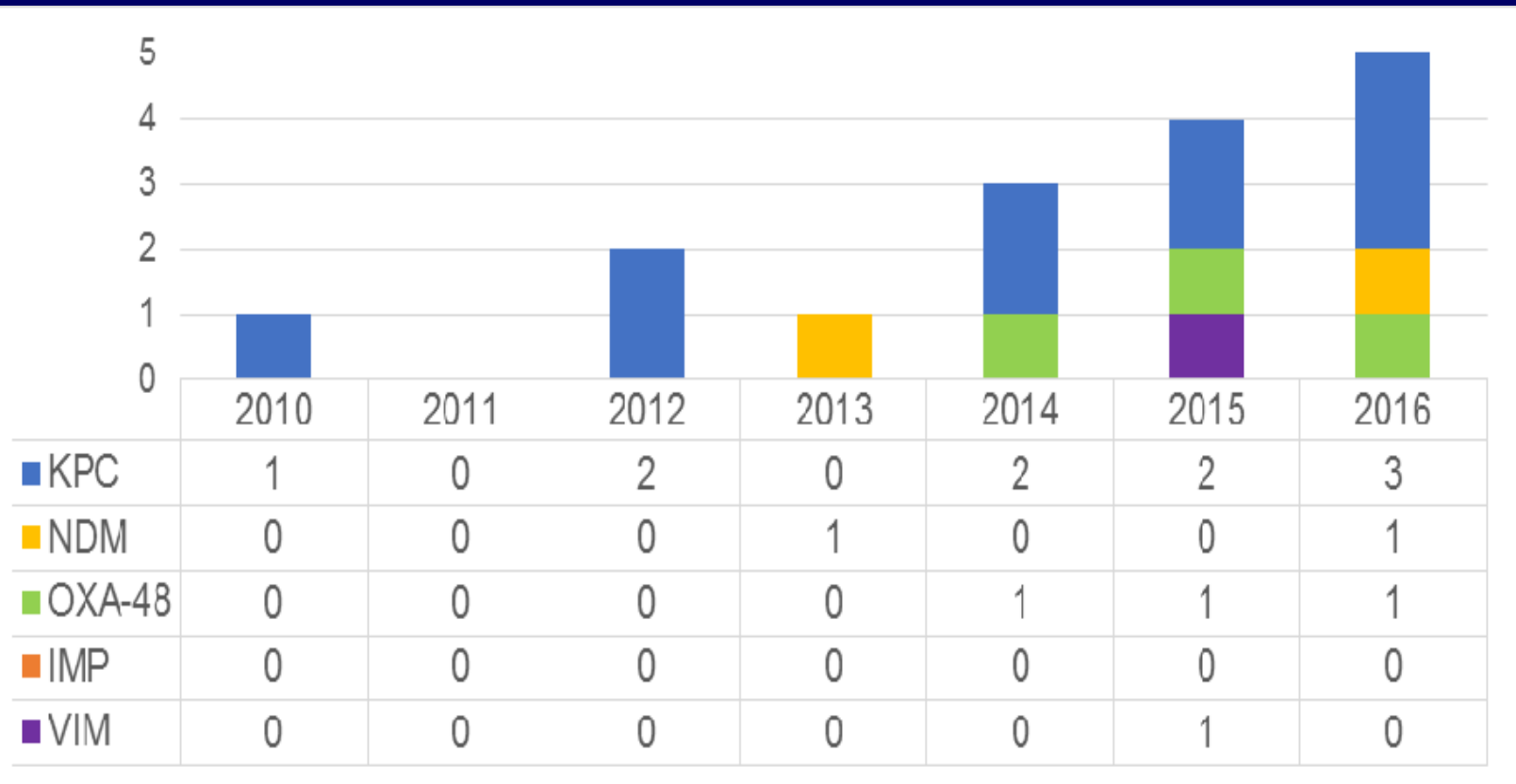
CRE by Subtype and Specimen Source, 2010 – June 2016

Organism	Anatomical Site of culture					Total
	Urine	Blood	Respiratory	Wound	Other	
<i>Enterobacter aerogenes</i>	25	1	2	3	3	34
<i>Enterobacter cloacae</i>	117	8	16	20	11	172
<i>Escherichia coli</i>	40	2	0	6	3	51
<i>Klebsiella pneumoniae</i>	18	2	1	3	2	26
<i>Serratia marcescens</i>	9	1	5	1	0	16
Other	17	1	1	8	1	28
Total	226	15	25	41	20	327

CRE in Oregon by county, 2010 – June 2016



CP-CRE identified by Oregon Labs, by year, n=16



CP-CRE Oregon Residents 2010-2016, n=13

- Sex: 7 (54%) males
- Age: years (median: 76)
- Sources: 5 urines, 3 wounds, 1 blood, 1 respiratory, 1 tissue, 1 ostomy, 1 pleural fluid
- 10 (77%) hospitalized at collection

MICs and CP- CRE cases

Antibiotic	KPC KP	KPC KP	KPC KP	NDM <i>E.coli</i>	KPC KP	OXA-48 KP	KPC KP/ <i>Raoultella</i>
Cefotaxime	NA	>64/R	32/R	NA	NA	NA	NA
Ceftriaxone	R	>32/R	>32/R	>32/R	>32/R	>64/R	2/I
Ceftazidime	R	>128/R	>128/R	>16/R	>16/R	>64/R	16/R
Doripenem	NA	>8/R	4/R	NA	NA	NA	NA
Ertapenem	NA	>8/R	>8/R	NA	NA	≥8/R	≤0.5/S
Imipenem	R	16/R	8/R	NA	NA	NA	NA
Meropenem	R	>8/R	8/R	>8/R	>64/R	4/R	≥16/R

MICs and CP- CRE cases

Antibiotic	KPC KP	OXA-48 E.coli	VIM E. cloacae	KPC E. cloacae	OXA-48 KP	KPC KP
Cefotaxime	>32/R	NA	NA	NA	≥64/R	NA
Ceftriaxone	>32/R	>32/R	≥64/R	>32/R	≥64/R	32/R
Ceftazidime	>16/R	NA	≥64/R	>16/R	NA	32/R
Doripenem	NA	NA	NA	NA	NA	NA
Ertapenem	>4/R	4/R	4/R	>1	NA	≥8/R
Imipenem	>8/R	NA	NA	NA	1.5/I E-test	NA
Meropenem	>8/R	21mm/I	8/R	>8/R	1 Vitek 4.0/R E- test	≥16/R

MICs and CP- CRE cases

Antibiotic	KPC KP	NDM KP	KPC EH
Cefotaxime	NA	NA	NA
Ceftriaxone	16/R	≥64/R	32/R
Ceftazidime	32/R	≥64/R	NA
Doripenem	NA	NA	NA
Ertapenem	≥8	≥8/R	>1/R
Imipenem	≥16	NA	≤1
Meropenem	NA	≥16/R	≥16/R

Location of healthcare previous to CP-CRE

Carbapenemase	Health Care Location
KPC (8)	Pennsylvania 2 weeks previous, Ohio 5 months previous, Southern California (CA) 16 months previous, Southern CA before admit, North Dakota 10 months previous, Alaska cruise ship 8 weeks previous, Washington 2 months previous, Tennessee 1 month previous
OXA-48 (3)	Romania 8 days previous; Ghana in weeks previous; Vancouver, WA, previous to admit with exposure to case from Russia via Southern CA
VIM (1)	Germany and Bulgaria 1 month previous
NDM (1)	Vietnam previous to Oregon admit

Laboratory Testing

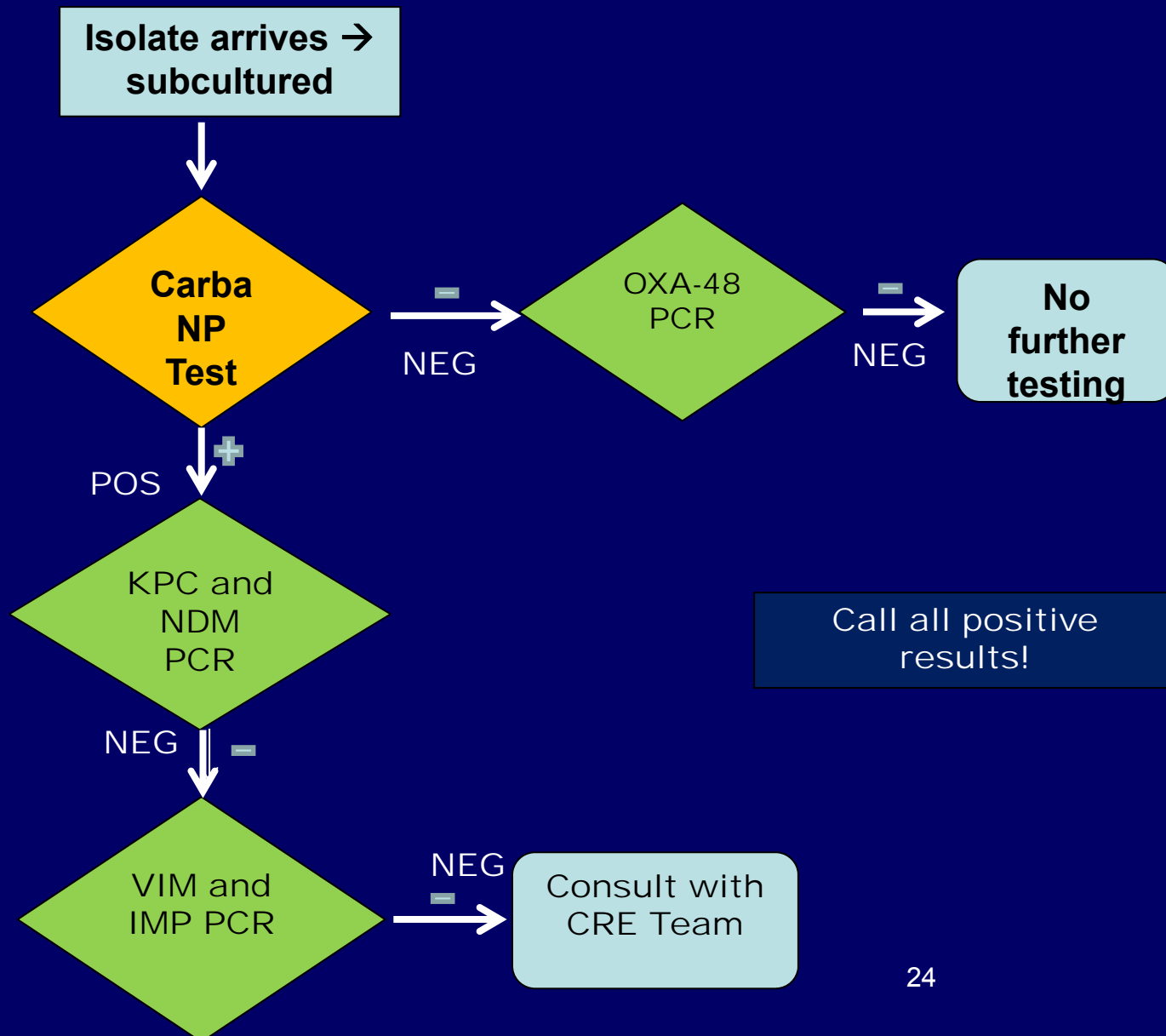
- Labs submit isolates to OSPHL with the print out directly from the test instrument
- Print outs are faxed to me
- OSPHL subcultures the isolates
- Carbapenemase testing is done weekly
 - Carba NP
 - Multiplex PCR

Carbapenemase Testing

- **Carba NP**
 - Colorimetric tests for carbapenemase production
 - Buffer with phenol red indicator, zinc and imipenem solution – add bacteria
 - Yellow indicates a positive
 - Is not a good test for OXA-48 carbapenemase



CRE Isolate Testing Algorithm at OSPHL



CRE Laboratory Testing continued

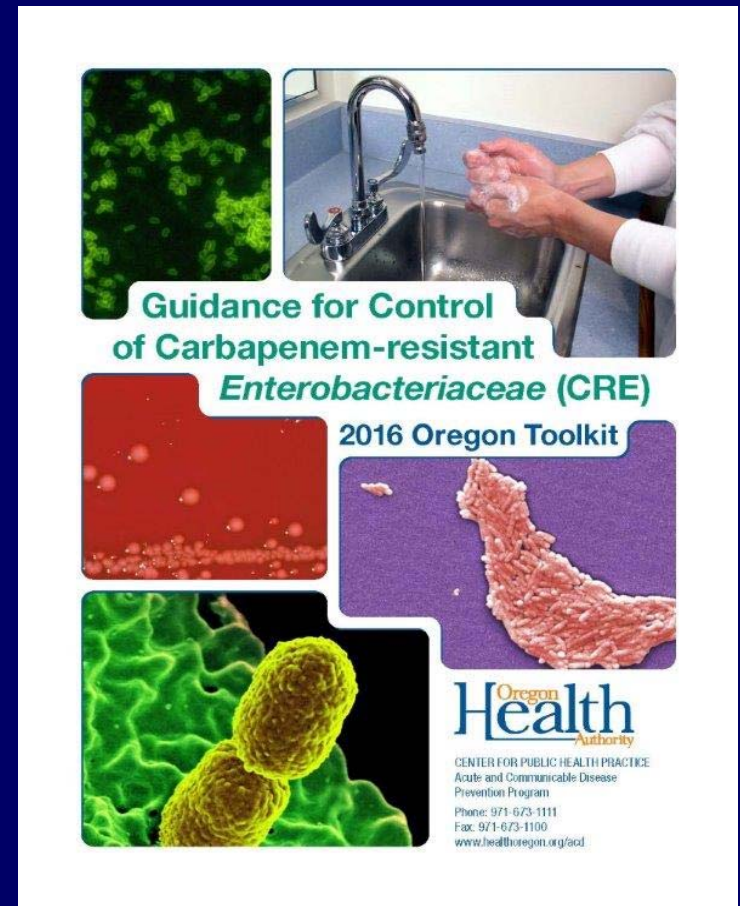
- Required isolates: *Escherichia*, *Klebsiella* and *Enterobacter*
- Optional and on request: other *Enterobacteriaceae* such as *Citrobacter* sp.
- OSPHL does not repeat susceptibility testing
- Be sure to send pure isolates

CRE Laboratory Testing continued

- Rectal swab surveillance cultures at OSPHL
 - OSPHL will start validating a new procedure
 - Adapting methods from British Columbia Public Health Lab
 - PCR technique but not a commercial test
 - Will test for 5 most common carbapenemases

Investigating CRE to prevent spread - role of county public health

- Confirm that it meets definition
- Find the CRE ToolKit



Case Investigations Hospitalized Cases



- Notify the Infection Preventionist
- Recommend/verify transmission-based precautions (contact)
- Emphasize hand hygiene
- Interfacility transfer notification is required
- Refer to CRE Toolkit – private room

Case Investigations

Hospitalized Cases, CP-CRE

- LHD should be notified when case transfers
- LHD and OHA will work together on screening cultures for high risk contacts
 - Sent to OSPHL
 - Recommended site: rectal swabs
- Cohorting of staff is recommended

Promote hand hygiene (HH) and monitor adherence

CRE-infected and CRE-colonized patients should be:

- Placed in Contact Precautions *
- Placed in Private Rooms *

CRE identified as carbapenemase producer?

Yes

- Notify Facility Administration
- Notify Facilities Management Services
- Notify Antibiotic Stewardship Program
- Notify pertinent clinician groups in facility
- Consider cohorting nursing staff that care for CRE-positive patients/residents*

Consult OHA regarding screening cultures for high-risk contacts

No

Oregon Regulations on Interfacility Transfer (IFT) Notification, 2014*

- When a health care facility transfers a patient who is infected or colonized with an MDRO, it must include written notification of the MDRO to the receiving facility in transfer documents.

*OAR 333-019-005

Case Investigations Skilled Nursing Facility (SNF) Cases

- Notify the Director of Nursing
- Emphasize the importance of hand hygiene
- Standard precautions at all times and recommend/verify transmission-based precautions (contact) with infection
- Interfacility transfer notification is required
- Refer to CRE Toolkit

Case Investigations

SNF, CP-CRE

- LHD should be notified when case transfers
- LHD and OHA will work together on screening cultures for high risk contacts
- Cohorting of staff is recommended

Summary of Recommendations for Management of SNF Residents with CRE

Measure	CP-CRE infection	CP-CRE colonization	Non-CP-CRE infection	Non-CP-CRE colonization
Notify receiving facility*	Yes	Yes	Yes	Yes
Notify county health upon transfer or death	Yes	Yes	No	No
Standard Precautions	Yes	Yes	Yes	Yes
Contact Precautions†				
Gown/gloves for in-room resident care	Yes	Yes	Yes	For residents at higher risk of CRE transmission
Door signage	Yes	Yes	Yes	For residents at higher risk of CRE transmission
Private room	Yes (strongly encouraged)	Yes (strongly encouraged)	Yes	No
Restricted to room	Yes	No**	No**	No**
Enhanced environmental cleaning	Yes	Yes	Yes	No
Designated or disposable equipment	Yes	Yes	Yes	No
If >1 case, cohort staff if feasible	Yes	Yes	Optional	Optional
If >1 case, cohort residents if feasible	Yes	Yes	Optional	Optional
Consult with OHA regarding screening cultures	Yes	Yes	No	No
Visitor recommendations:				
Perform Hand Hygiene often, particularly after leaving the resident's room.	Yes	Yes	Yes	Yes
Gown/gloves if contact with body fluids is anticipated.	Yes	Yes	Yes	Yes
Gown/gloves if no contact with body fluids is anticipated.	No	No	No	No

Case Investigations

Assisted Living, Adult Foster Care Facilities

- Reinforce good hand hygiene
 - Soap and water with soiled hands
 - Alcohol-based hand rub if not
- CRE Education
- Standard precautions – proper use of personal protective equipment (PPE) when handling body fluids



Case Investigations

Living at home

- Reinforce good hand hygiene
 - Soap and water with soiled hands
 - Alcohol-based hand rub if not
- CRE Education
 - Include facility transfer
- Standard precautions – Home care agencies should use personal protective equipment (PPE) properly when handling body fluids



New surveillance: Carbapenem-resistant *Pseudomonas aeruginosa* (CR-PA)

- Tri-county area around Portland
- Case definition: CR-PA isolated from sterile site, urine, lower respiratory or wound (30 day time period)
- MIC criteria: doripenem, imipenem or meropenem ≥ 8

CR-PA Surveillance continued

Objectives:

- Evaluate incidence of CR-PA
- Understand epidemiologic characteristics and risk factors
- Describe resistance mechanisms

CR-PA Surveillance continued

- Isolate collection starts November, 2016
 - No isolates from cystic fibrosis patients
 - 60 isolates/year from each site
- CDC Testing
 - MALDI-TOF
 - Susceptibilities by broth microdilution
 - Screen for carbapenemases: Rosco Disk and Carba NP
 - PCR for KPC, NDM, VIM, IMP
 - Whole genome sequencing

Thank You Any Questions?

<http://public.health.oregon.gov>

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