Carbapenem-Resistant Enterobacteriaceae (CRE): Regional Prevention of an Urgent Global Threat

OHSU Medicine Grand Rounds

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Oct 22, 2013

Conflict of Interest Disclosure

Disclosure

I do not have any relationship(s) to disclose.

OREGON HEALTH & SCIENCE UNIVERSITY

Current Practice?

- A 63 y.o. Indian female is transferred from a hospital in India for treatment of end-stage lung disease per her son's request. She arrives intubated/sedated. Sparse transfer documents.
- 2 days later, new fever (103°F). BP drops. No immediately obvious etiology.
  - What antibiotics would you start?
- 12 hours later, blood cultures +GNB

This

SET EDITION: U.S. | INTERNATIONAL | MÉXICO | ARABIC

TV: CNN | CNNi | CNN en Español | HLN

CNN Health

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CDC: 'Nightmare bacteria' spreading

By **William Hudson**, CNN

updated 11:02 AM EST, Thu March 7, 2013

Yong et al. Antimicrob Agents Chemo 2009:5046-5054

Learning Objectives / Outline

1. Understand: what are CRE? Which CRE are most important?

2. Become acquainted with CRE epidemiology, detection, clinical importance, and treatment.

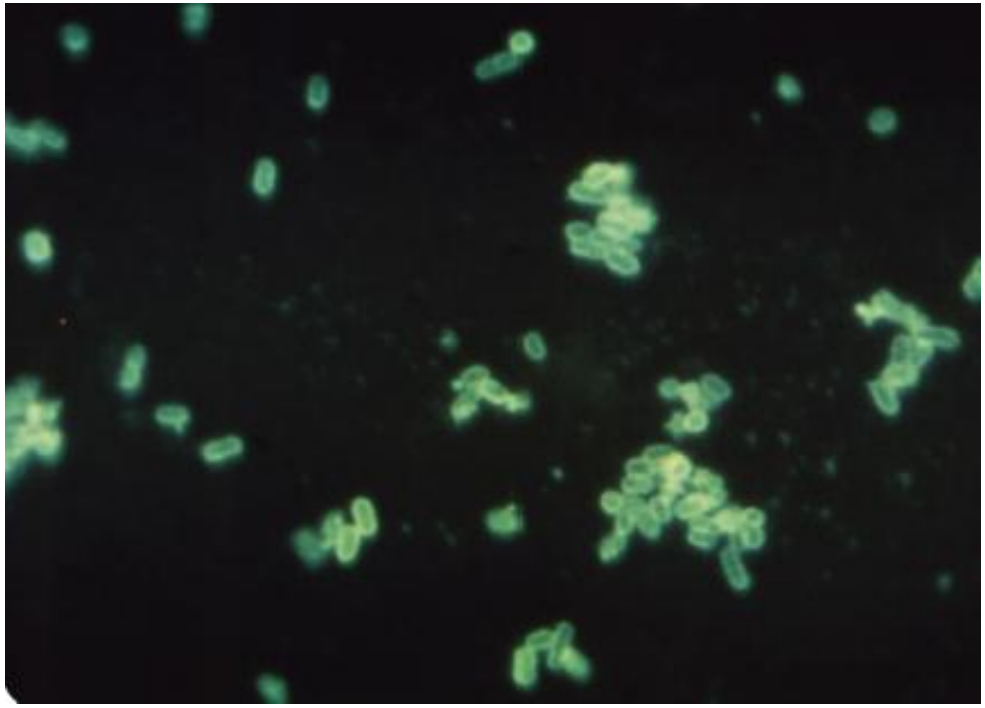
3. Learn about the regional CRE Prevention efforts including the DROP-CRE Network and the Oregon CRE Toolkit.

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

- *Pseudomonas aeruginosa*
- *Acinetobacter baumannii*
- **MDR-Enterobacteriaceae***
  - Extended spectrum cephalosporinase (e.g., **AmpC**)
  - Extended-spectrum β-lactamases **(ESBLs)**
  - **CRE**

*Common Enterobacteriaceae include *E. coli, Klebsiella* **spp., and** *Enterobacter* **spp.**

What are CRE?



Oregon CRE Definition

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)

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

CRE Assessment Tiers*

Tier	Description	Recommended Action
1	Carbapenemase-producing CRE (CP-CRE)	Most aggressive control measures
2	CRE with acquired resistance NOT due to carbapenemase production	Intensified control measures including contact precautions
3	CRE with intrinsic (natural) imipenem resistance	No special control measures needed

*see Oregon CRE Toolkit 2013

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

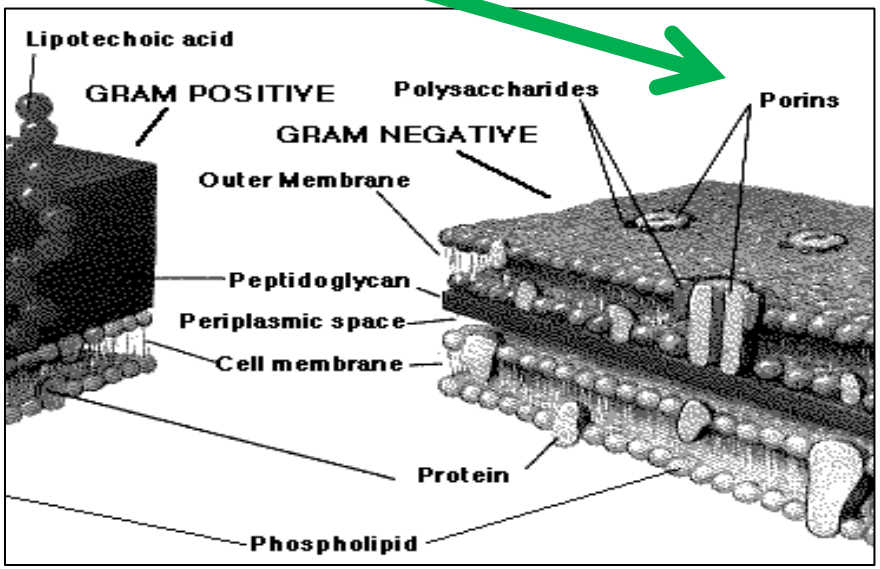
- #1 Organism: *Enterobacter* spp.
- Resistance mechanism to know:

AmpC and/or ESBL

plus

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

- Epidemiology
  - Incidence stable ~20 years



Tier 3 CRE:

Naturally imipenem-resistant Enterobacteriaceae

Proteus spp., *Providencia* spp., and *Morganella* spp. may test imipenem-nonsusceptible (MICs 2-4 µg/mL) using 2012 updated susceptibility testing breakpoints.

- **Example: PVAMC Antibiogram for *Morganella morganii***

  2009 100% imi-S
  2010 100% imi-S
  2011 20% imi-S
  2012 34% imi-S

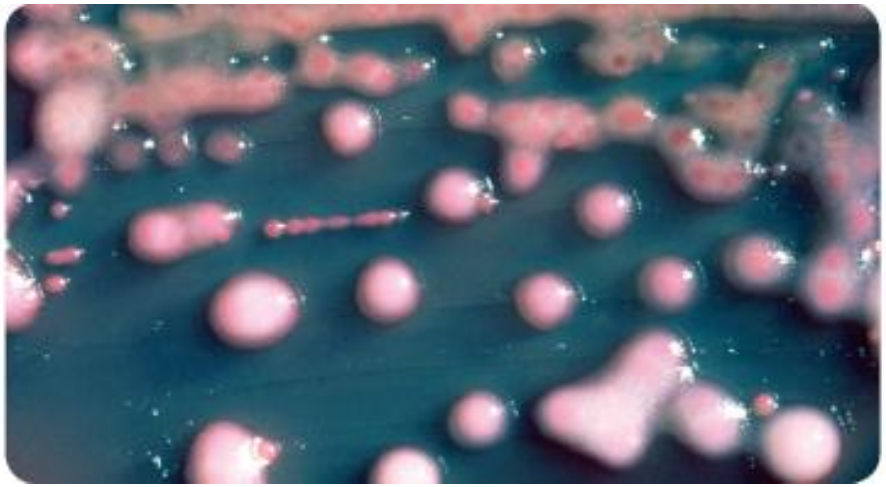
- However, non-susceptibility to *any other* carbapenem is unusual and concerning.

CLSI Breakpoint Changes:
Enterobacteriaceae to carbapenems

	Breakpoints Predating 2010 Update (µg/mL) (through Jan. 2010; M100-S19)			2012 Breakpoints (µg/mL) (revised Jun. 2010 and Jan. 2012; M100-S22)		
	S	I	R	S	I	R
Doripenem	n/a	n/a	n/a	≤1	2	≥4
Ertapenem	≤2	4	≥8	≤0.5	1	≥2
Imipenem	≤4	8	≥16	≤1	2	≥4
Meropenem	≤4	8	≥16	≤1	2	≥4

CLSI = Clinical and Laboratory Standards Institute

CRE:
Epidemiology, detection, clinical impact, and treatment

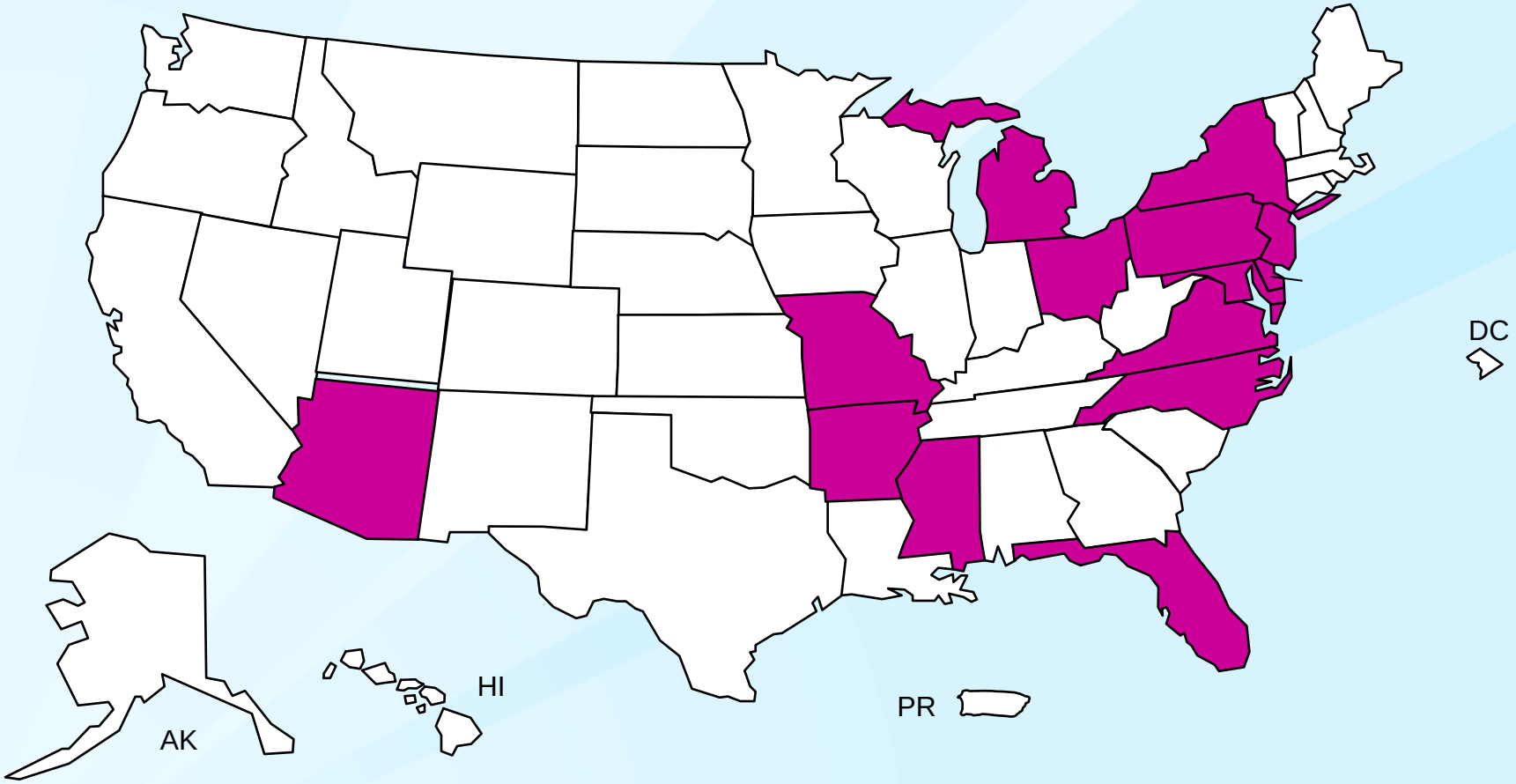


CRE Epidemiology, 2013

Name	1st Report Worldwide	1st Report US	Current US Epidemiology
KPC	2001 North Carolina	2001 CDC surveillance (NC)	**Widespread:** ~11% of *Klebsiella* spp. reported to NHSN were carbapenem-R
NDM	2009 Sweden (from India)	2010 Returned travelers, India	**Uncommon:** 49 cases reported to CDC (July 1)
OXA-48	2004 Turkey	2012 SMART surveillance, unknown location	Rare
IMP	1994 Japan	2011 CA (3 cases/NICU, source unknown)	Rare
VIM	2002/2003 Greece, Korea, Taiwan	2010 Returned traveler, Greece	Rare

Slide from Alex Kallen,MD, MPH)

Carbapenemase-producing CRE in the United States circa 2009

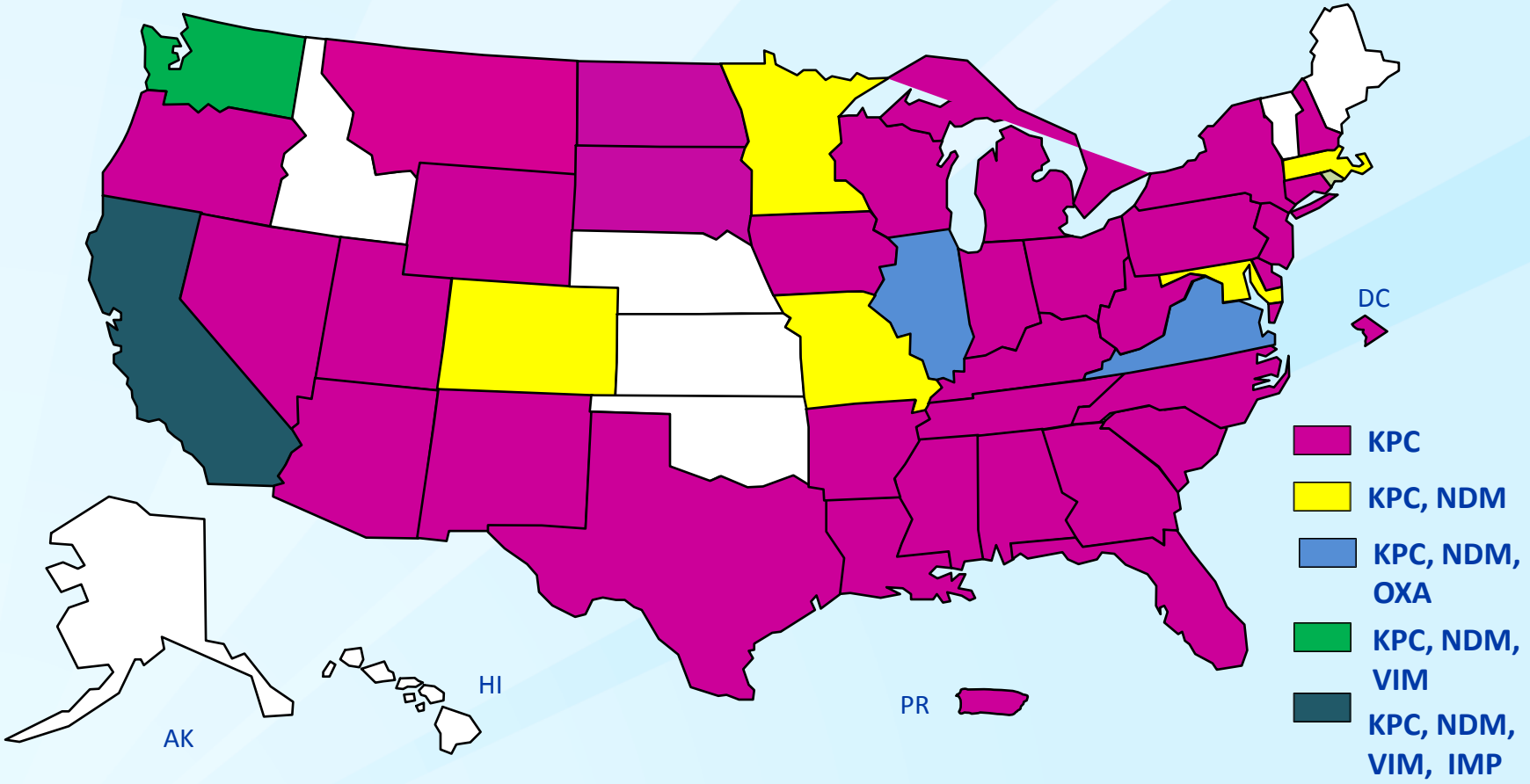


Patel, Rasheed, Kitchel. 2009. Clin Micro News

CDC, unpublished data

Slide from Alex Kallen,MD, MPH)

Carbapenemase-producing CRE in the United States, 2013



Patel, Rasheed, Kitchel. 2009. Clin Micro News
MMWR MMWR Morb Mortal Wkly Rep. 2010 Jun 25;59(24):750.
MMWR Morb Mortal Wkly Rep. 2010 Sep 24;59(37):1212.
CDC, unpublished data

CRE burden by facility type

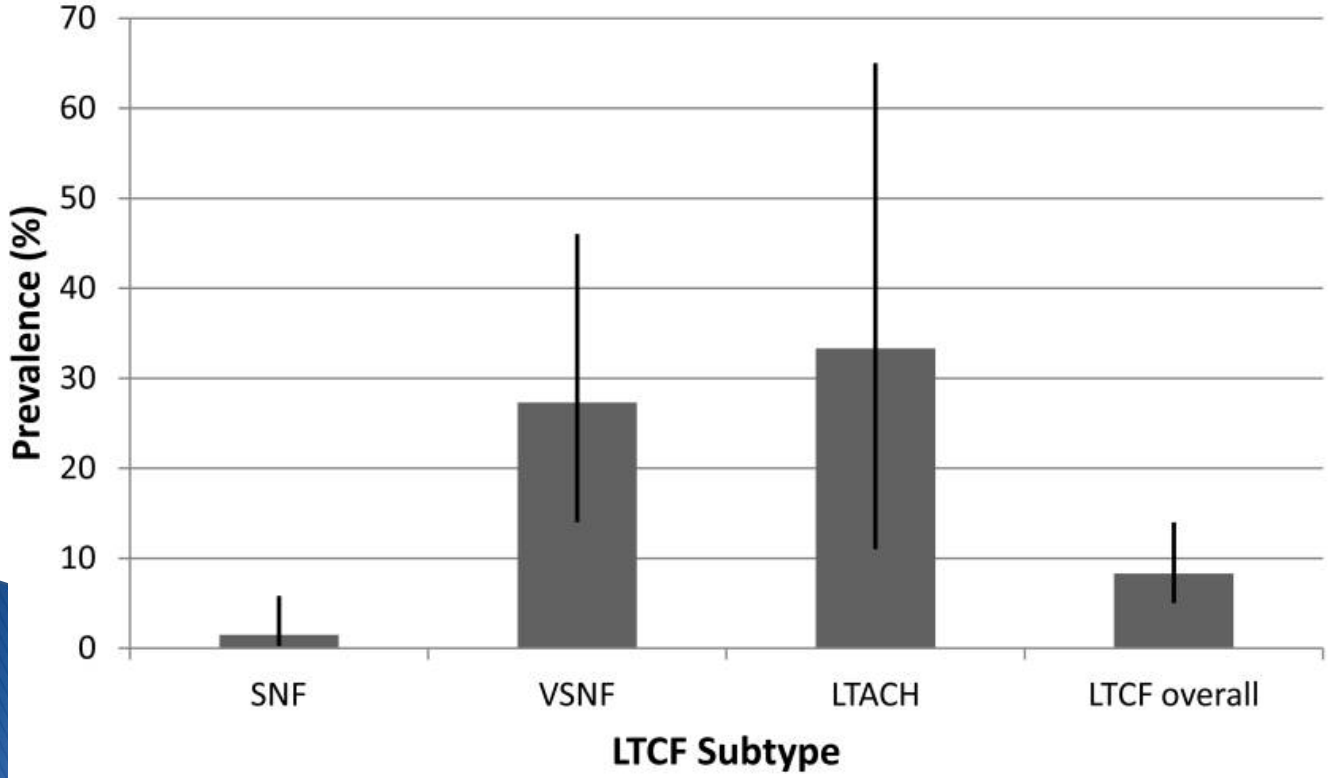
Characteristic	No. of facilities with carbapenem-resistant Enterobacteriaceae from CAUTI or CLABSI	Total no. of facilities performing CAUTI or CLABSI surveillance (N = 3,918)	(%)[§¶]
Facility type			
All acute-care hospitals	181	3,918	(4.6)
Short-stay acute-care hospital	145	3,716	(3.9)
Long-term acute-care 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

MMWR 2013 Mar 8;62(9):165-170

CRE prevalence on admission

- 180 matched pairs of LTCF and community patients admitted to Chicago 4 hospitals had KPC surveillance via rectal swabs
- Patients matched by age, admission date, and admitting service
- LTCF patients had higher rates of dementia, incontinence, trachs, decubitus ulcers, etc.



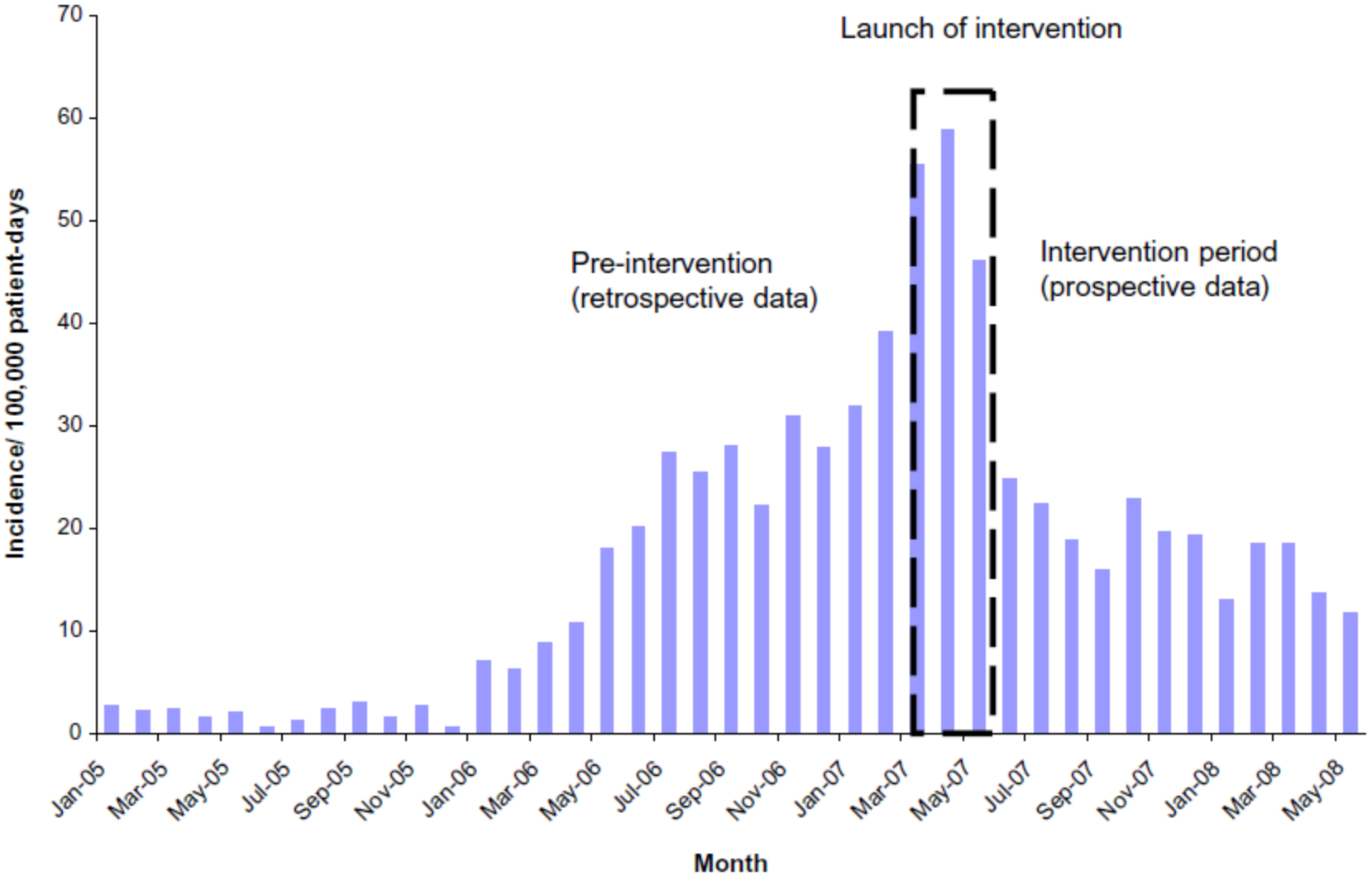
Prabakar et al. ICHE 2012;33:1193-99

Israel's CRE Outbreak

- 2005: CRE thought to be imported to Israel
- 2006: Multiple CRE outbreaks occurred in hospitals
- March 2007: the Ministry of Health issued guidelines for country-wide CRE control
- Initial intervention period: Apr 2007-May 2008
- Intervention included:
  - mandatory CRE reporting to public health;
  - mandatory isolation of hospitalized CRE carriers; and
  - creation of a multi-disciplinary task force which paid site visits and supervised adherence to the guidelines

Schwaber MJ, et al. Clin Infect Dis 2011;52:848-55

Incidence of clinical CRE cases



Next potential frontier

- ESBLs (on *E. coli*) are in the community.
- Is CRE next?

Doi et al. Clin Infect Dis 2013;56:641-648

Colpan A et al. Clin Infect Dis 2013;57:1256-65

CRE/Carbapenemase Detection

1. Antimicrobial susceptibility testing
   - Neither specific nor sensitive for carbapenemases
2. Nucleic acid amplification test (NAAT; e.g., PCR)
   - Current gold standard for *known* carbapenemases
3. Phenotypic detection of carbapenemases
   - Variable performance (next slide)

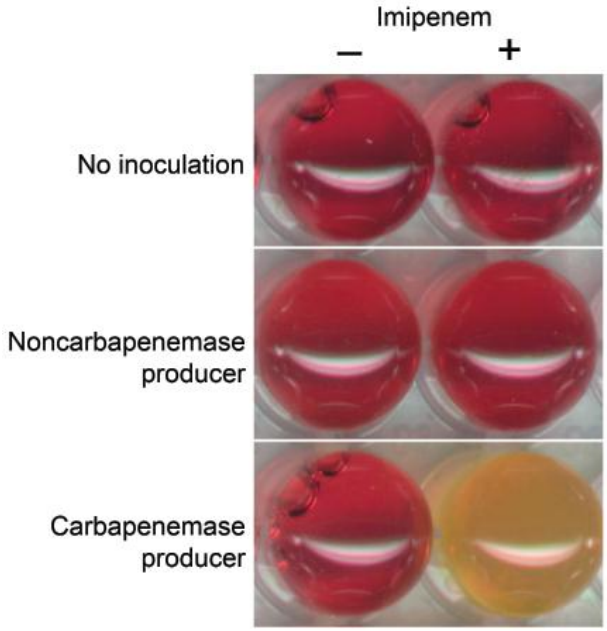
Phenotypic Carbapenemase Detection

Modified Hodge Test (MHT)

- Carbapenemase diffused into media if present (18 hours, hard to interpret).
- Good for detection of KPC on *Klebsiella* spp. and *E. coli.*
- Performance is otherwise unreliable
  - >50% of *Enterobacter* spp. CRE in Oregon are MHT+ (all PCR negative).

CarbaNP (*NEW)

- Test measures in vitro hydrolysis of imipenem (2 hours, cheap, easy).
- Highly sensitive and specific for ALL carbapenemases in several reports.



Nordmann P et al. Emerg Infect Dis 2012;18:1503-1505

CRE: Clinical Impact

- 30-50% mortality of invasive infection across multiple studies (with exceptions)

- Limited treatment options
  - Colistin
  - Tigecycline (black box warning)
  - Aminoglycoside
  - Fosfomycin (UTIs)

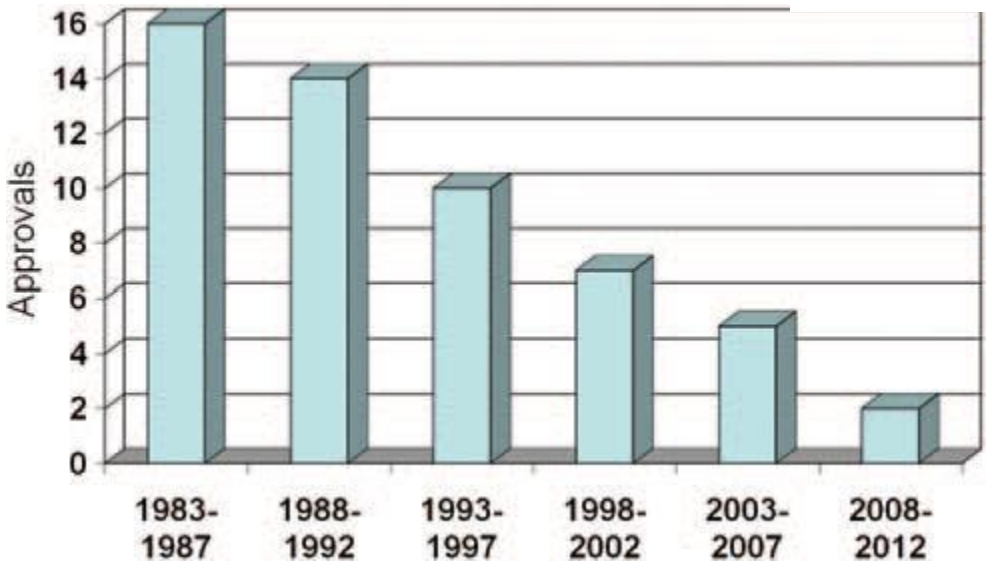
- Some CRE are “pan-resistant”

Patel et al. ICHE 2008;29:1099-1106

Antibiotic Pipeline?

10x'20

Ten new **ANTIBIOTICS** by 2020



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

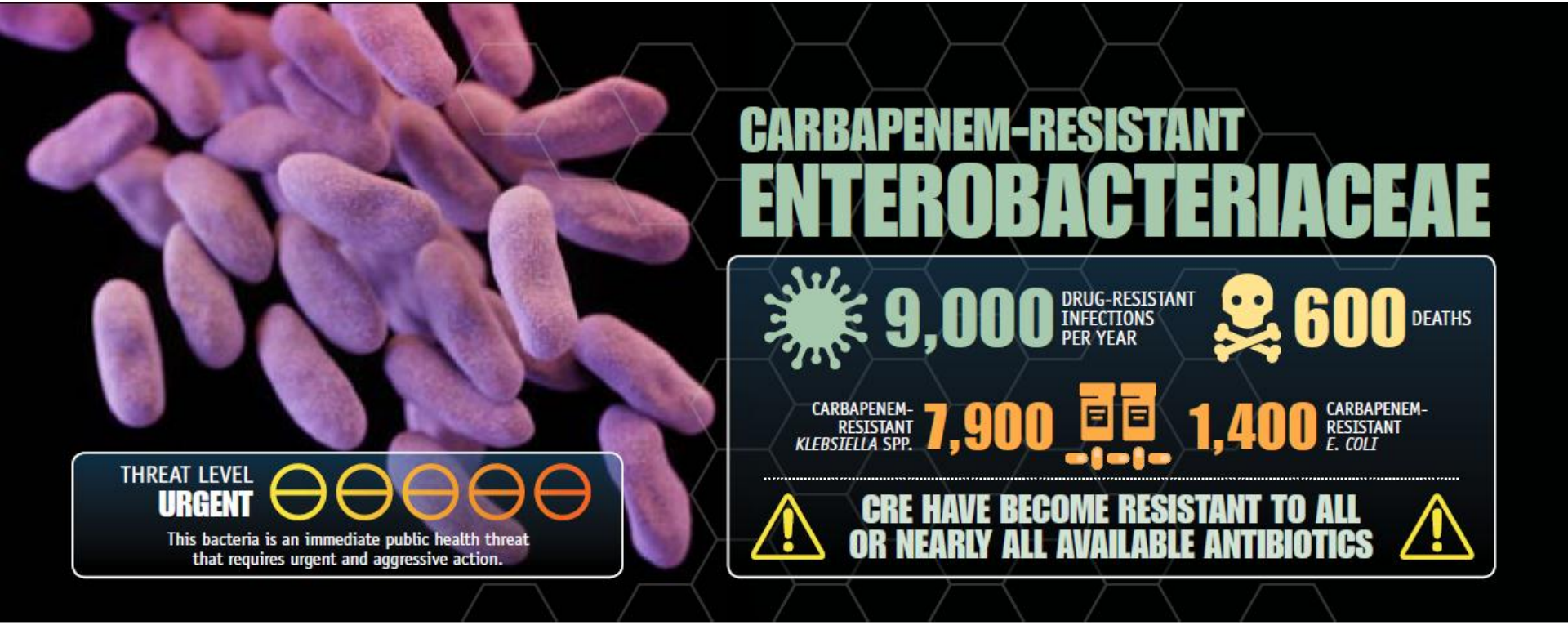
Boucher H, et al. Clin Infect Dis 2013;56:1685-94
http://www.idsociety.org/Index.aspx, accessed 10/20/13

Agents in Clinical Trials

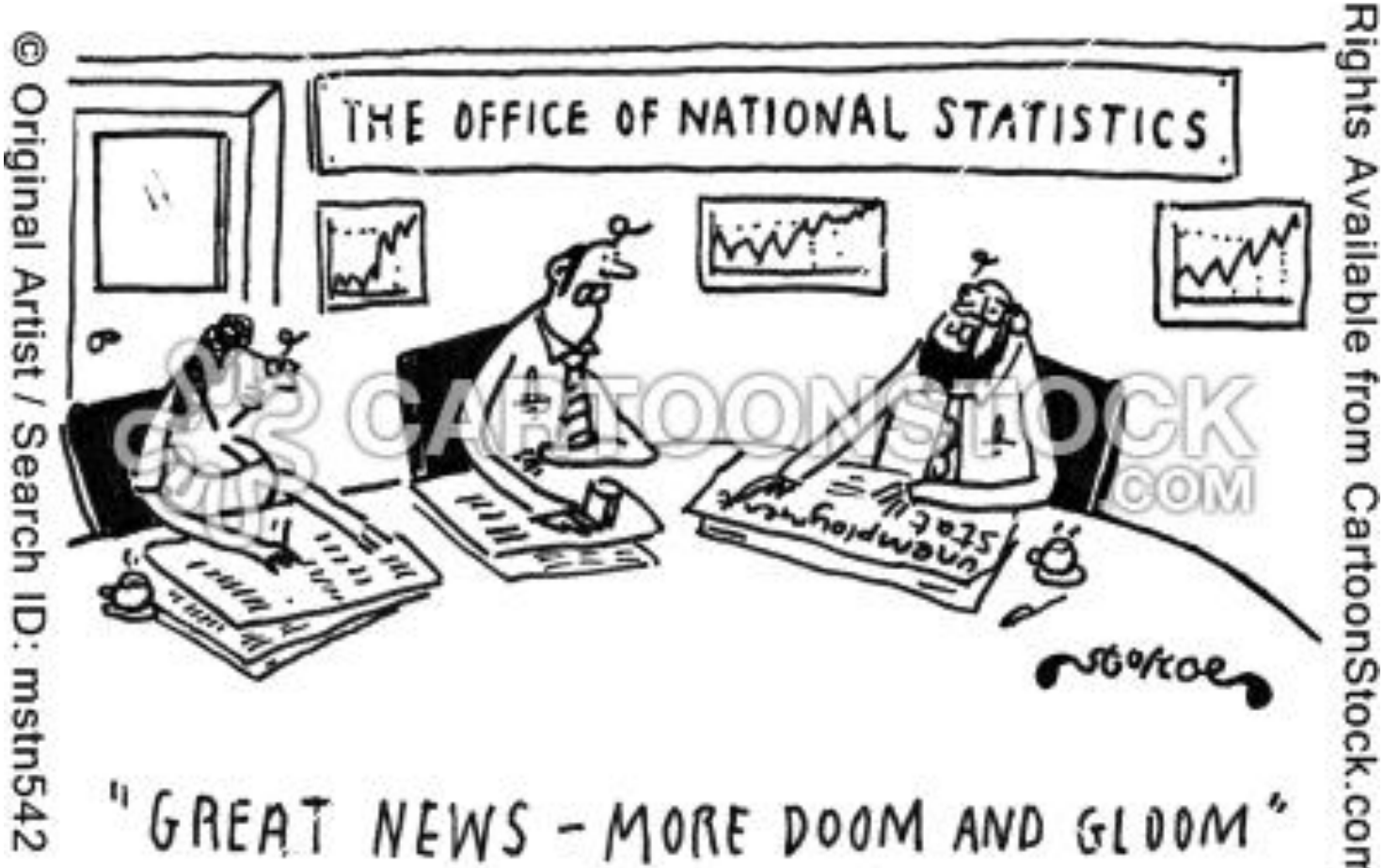
Product	Class (Mechanism of Action)	Novel Mechanism of Action?	Status	Enterobacteriaceae		
				ESBL	sCBP	mCBP
Ceftolozane/taxobactam (CXA-201; CXA-101/tazobactam)	Antipseudomonal cephalosporin/ BLI combination (cell wall synthesis inhibitor)	No	Phase 3 (cUTI, cIAI)	Yes	No	No
Ceftazidime-avibactam (ceftazidime/NXL104)	Antipseudomonal cephalosporin/ BLI combination (cell wall synthesis inhibitor)	No	Phase 3 (cIAI)	Yes	Yes	No
Ceftaroline-avibactam (CPT-avibactam; ceftaroline/NXL104)	Anti-MRSA cephalosporin/ BLI combination (cell wall synthesis inhibitor)	No	Phase 2 (cUTI, cIAI)	Yes	Yes	No
Imipenem/MK-7655	Carbapenem/BLI combination (cell wall synthesis inhibitor)	No	Phase 2 (cUTI, cIAI)	Yes	Yes	No
Plazomicin (ACHN-490)	Aminoglycoside (protein synthesis inhibitor)	No	Phase 2 (cUTI)	Yes[b]	Yes[b]	IE
Eravacycline (TP-434)	Fluorocycline (protein synthesis inhibitor targeting the ribosome)	No	Phase 2 (cIAI)	Yes[b]	Yes	IE
Brilacidin (PMX-30063)	Peptide defense protein mimetic (cell membrane disruption)	Yes?	Phase 2 (ABSSSI)	Yes	IE	IE

sCBP: serine carbapenemase (e.g., KPC, OXA-48)
mCBP: metallo-β-lactamase (e.g., NDM, IMP, VIM)

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



http://www.cdc.gov/drugresistance/threat-report-2013/
Accessed October 5, 2013



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

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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

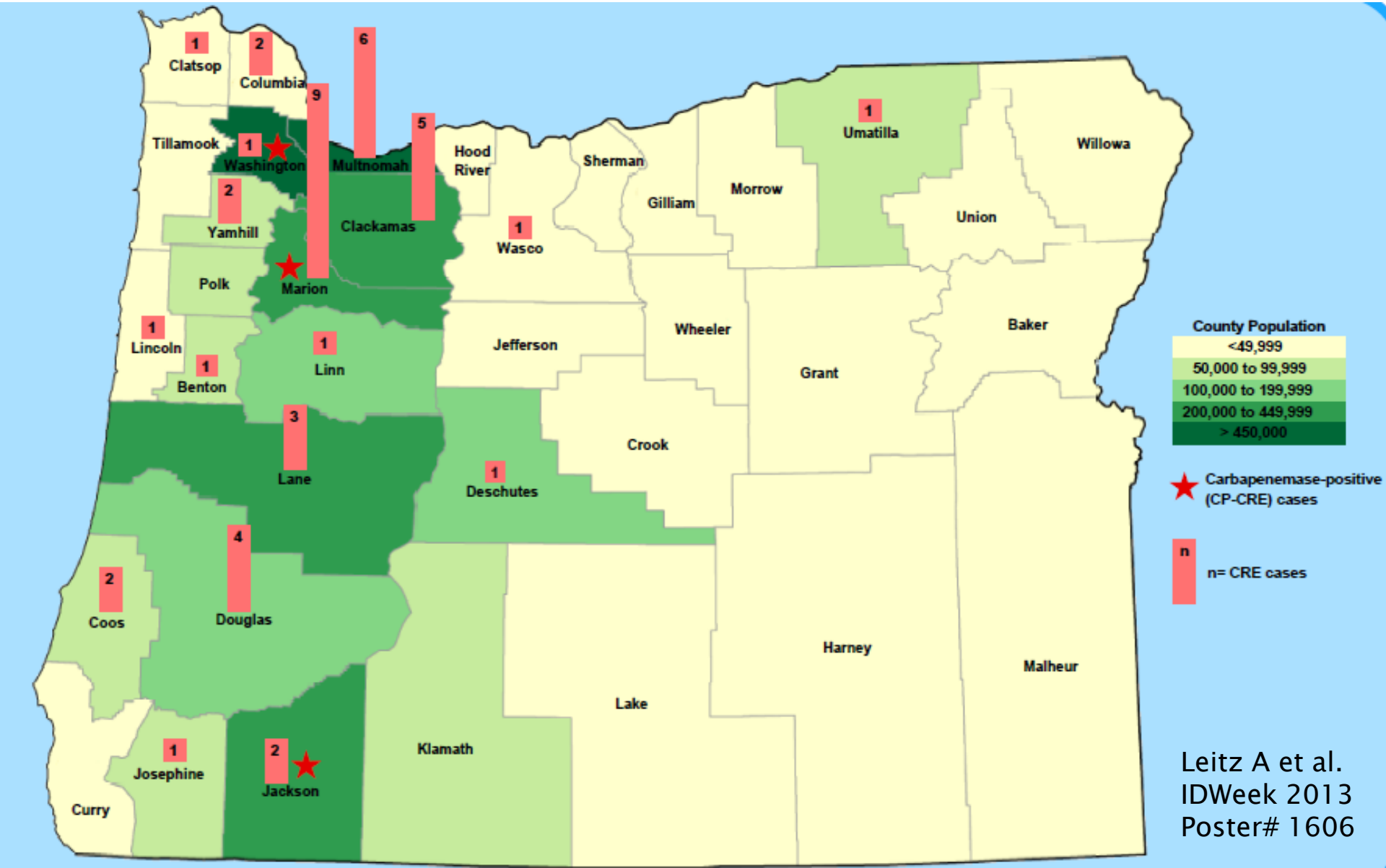
Methods

1. CRE surveillance case definition established
2. CRE database created
3. Real-time outbreak assistance initiated
4. Self-administered surveys performed statewide:
   - Microbiology lab directors
   - Infection preventionists (IPs) in acute care hospitals
   - IPs in long term care facilities (LTCFs)
5. Working group members lectured statewide
6. Oregon CRE Toolkit published

Oregon CRE Surveillance

- Mandated December, 2011.
  - Laboratories and clinicians required to report.
- Laboratories submit certain isolates to OSPHL.
  - *E. coli, Klebsiella* spp., and *Enterobacter* spp. which meet the Oregon CRE case definition.
  - OSPHL performs MHT and KPC/NDM PCR and informs submitting lab of results in 2-3 business days.

Oregon CRE Epidemiology



Leitz A et al.
IDWeek 2013
Poster# 1606

CRE Reported (Dec 2011–Oct 2013)

Organism	Number reported	Modified Hodge Test Positive No. (%)	PCR positive for KPC No. (%)
Enterobacter aerogenes	12	6 (50)	0
Enterobacter cloacae	69	50 (73)	0
Enterobacter spp.	4	1 (25)	0
Escherichia coli	10	3 (30)	0
Klebsiella pneumoniae	11	5 (46)	3 (27)
Proteus mirabilis	1	n/a	0
Citrobacter spp	4	3 (75)	0
Serratia marcescens	2	0	0
Total	113	68 (60)	3 (3)

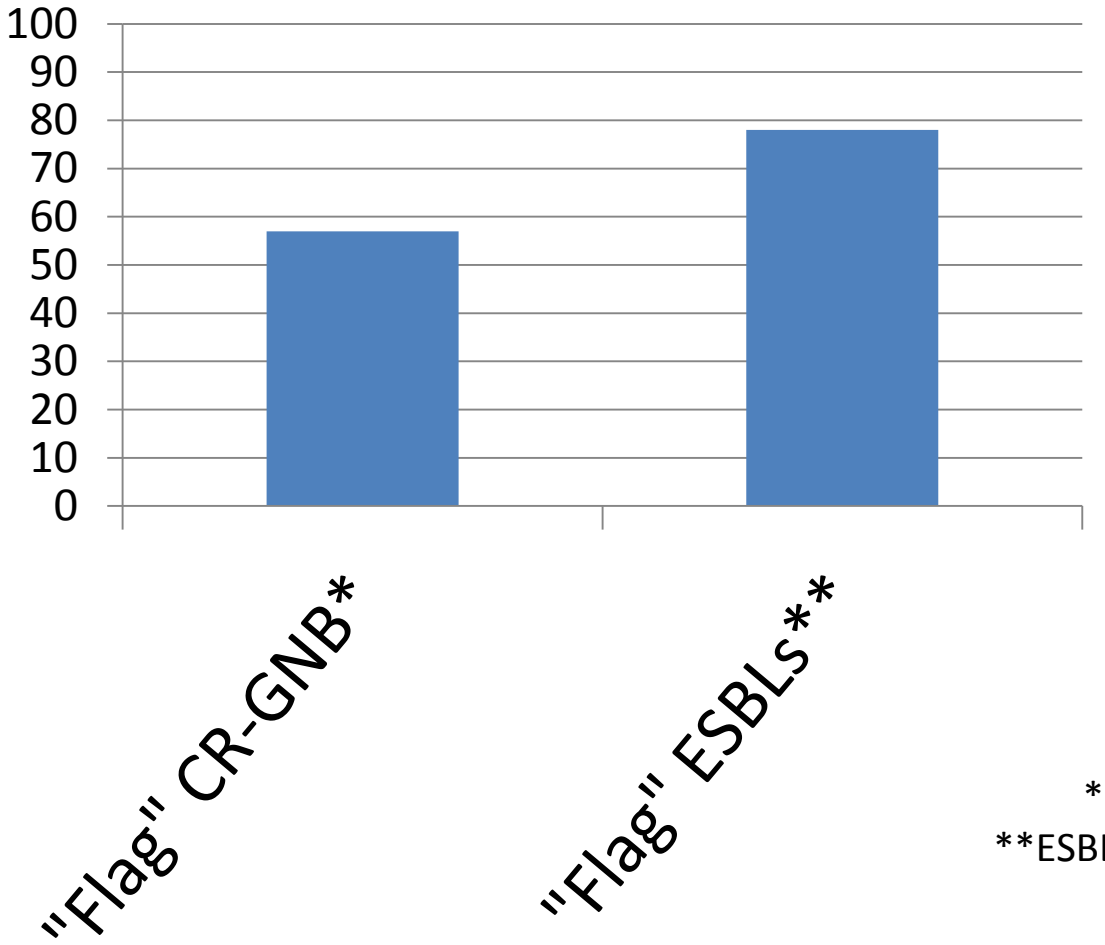
Microbiology Laboratory Survey

37/48 (77%) laboratories responded

- 25 (68%) used the CLSI breakpoints predating the 2010 update
  - Of those, only 2 (8%) *also* performed the Modified Hodge Test
- None performed carbapenemase PCR testing.

Pfeiffer CD et al. ICAAC 2013. Slide presentation K-1534

Reporting Practices



*CR-GNB = carbapenem-resistant GNB
**ESBLs = extended spectrum *β*-lactamases

Pfeiffer CD et al. ICAAC 2013. Slide presentation K-1534

Notification Practices

when MDR-Enterobacteriaceae are encountered*

Action	% of Laboratories
Notify infection control	44%
Notify nursing station	44%
Generate an automated report on medical record	42%
Notify ordering physician	33%
No further action	14%

Note: Similar responses reported for *Pseudomonas aeruginosa and Acinetobacter baumannii*

Pfeiffer CD et al. ICAAC 2013. Slide presentation K-1534

Acute Care Survey

- 45/62 (73%) programs responded

Facility Definitions of MDR-Enterobacteriaceae

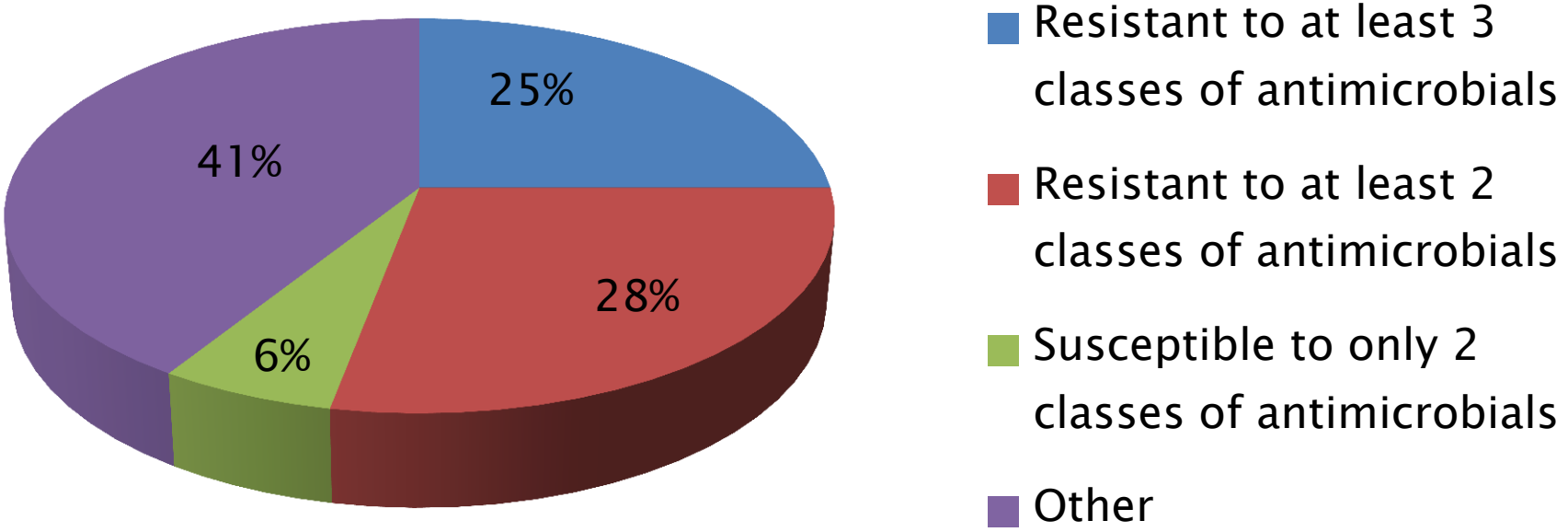
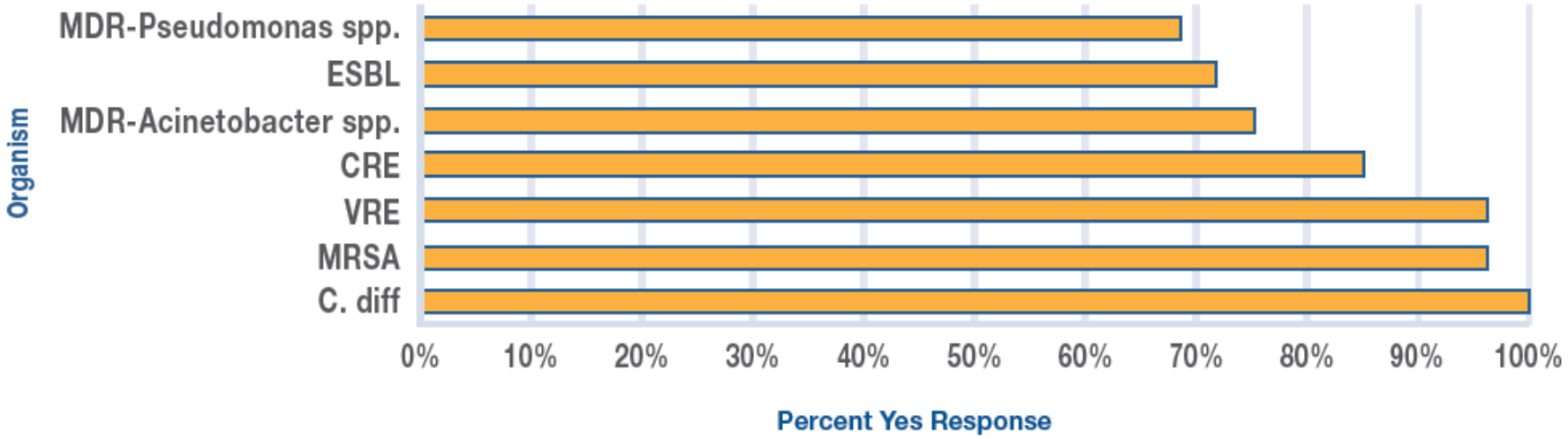


Figure 2 MDROs indicating placement in contact precautions



Poissant T et al. IDWeek 2013. Poster# 1605

Patient Transfer

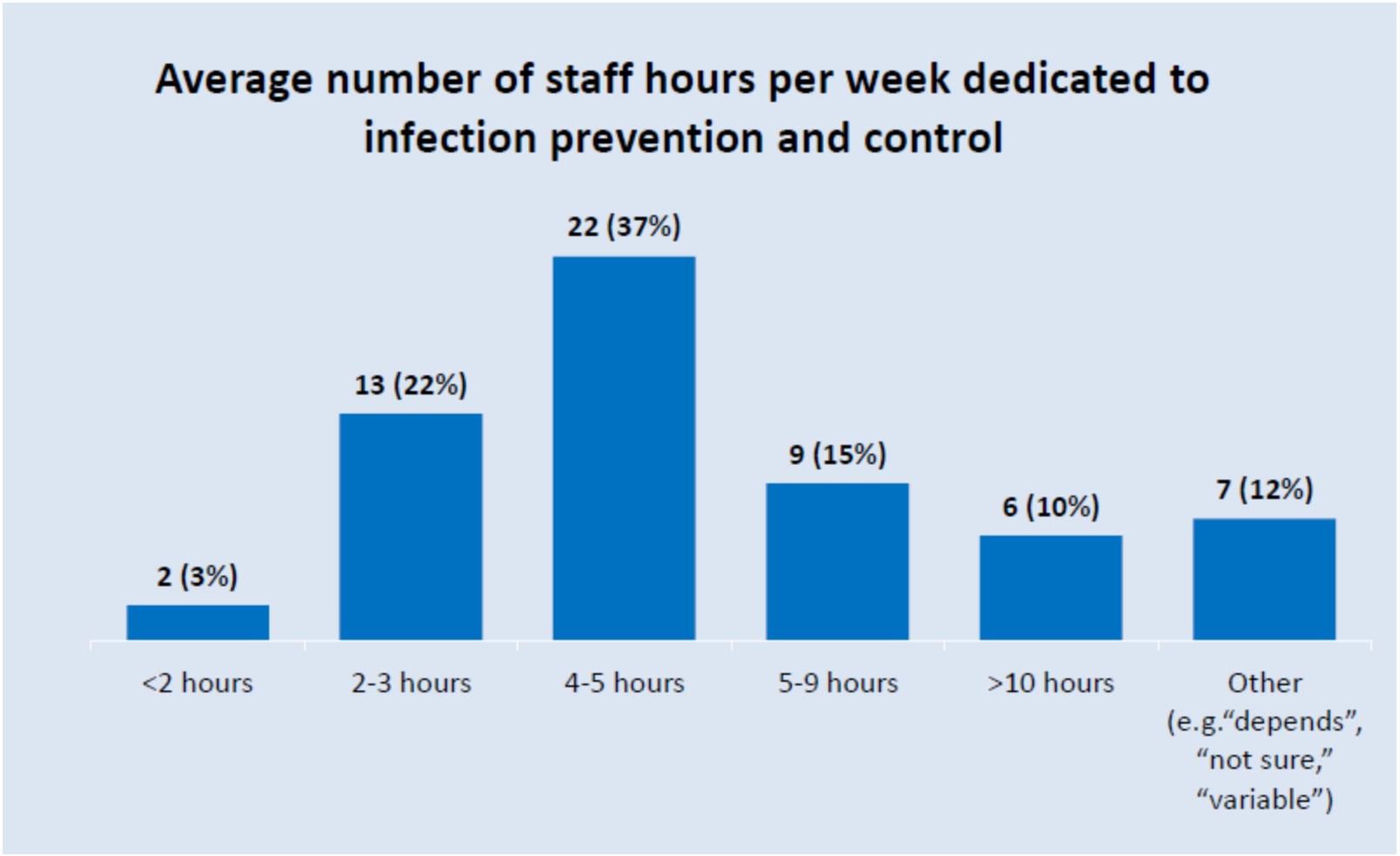
- Only 58% of respondents agreed that their facility is made aware of patients' MDRO status upon admission.
- 82% believed that the receiving facility was made aware of patients' MDRO status on discharge.

Poissant T et al. IDWeek 2013. Poster# 1605

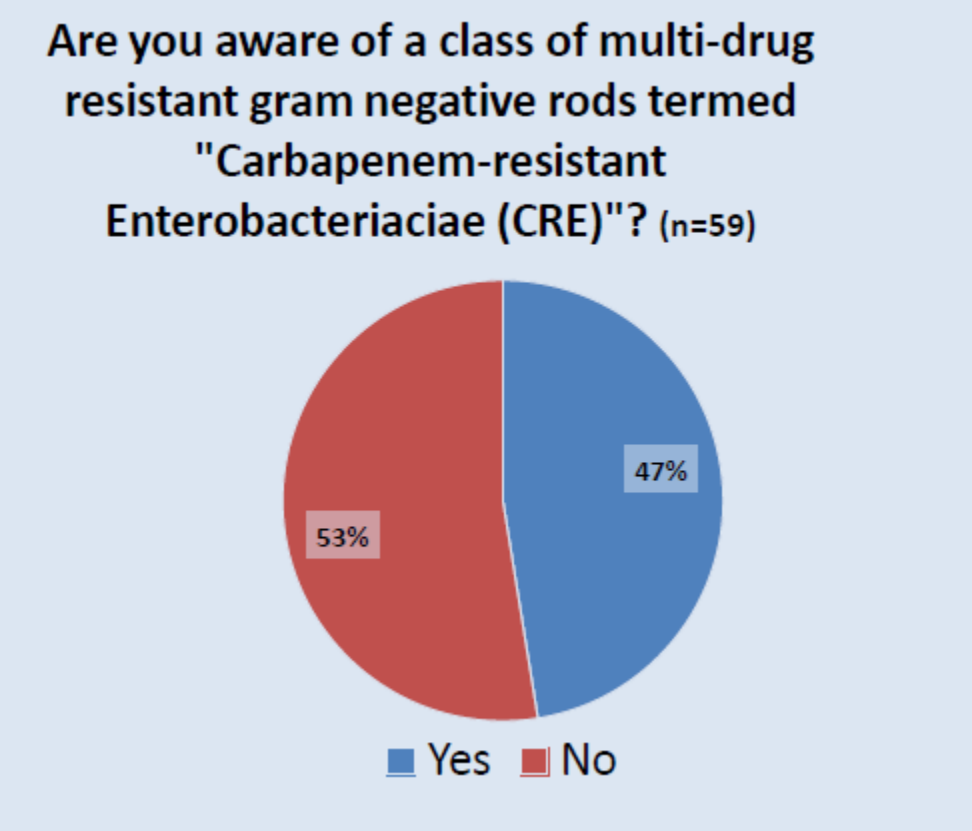
Long Term Care Survey

- 59/140 (42%) responded
- Average daily census: 48
- Types of care provided
  - Long-term custodial care (97%)
  - Skilled nursing/short-term rehabilitation (87%)
  - Manage ventilated residents (none)

Cunningham MC et al. IDWeek 2013. Poster# 1539



Cunningham MC et al. IDWeek 2013. Poster# 1539



Cunningham MC et al. IDWeek 2013. Poster# 1539

The Oregon CRE Toolkit

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

Oregon CRE Toolkit

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

General Measures for CRE Prevention in Acute Care

- Educate clinical staff
- Ensure reporting of CRE (per correct definition)
- Ensure Infection Prevention & Control is rapidly notified when CRE is detected
- Review lab records for previously unrecognized CRE
- Consider active surveillance cultures for CRE colonization in select patients on admission

Think "NICE" when CRE are encountered:

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

Intervene on all cases with core infection prevention and control strategies: hand hygiene, contact precautions, private rooms, and optimized environmental cleaning. Reduce unnecessary antibiotics and use of invasive devices. Additionally, for CP-CRE, screen patient contacts and cohort staff and patients.

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

Educate patients, staff, and visitors about CRE.

CRE Education/Resources

- Oregon CRE website (and Toolkit)
  - http://public.health.oregon.gov/diseasesconditions/diseasesaz/pages/disease.aspx?did=108
- Oregon CD Summary (April 23, 2013)
  - "Drop everything, the CRE are coming!"
  - http://public.health.oregon.gov/DiseasesConditions/CommunicableDisease/CDSummaryNewsletter/Documents/2013/ohd6209.pdf
- CDC CRE website (and Toolkit)
  - http://www.cdc.gov/HAI/organisms/cre/

Future Directions

- Continue CRE surveillance and education
  - Tweak definition?
  - Point prevalence survey?
  - Active CRE surveillance for high risk admissions?
- Improve Communication
  - Create regional MDRO collaboratives
- Apply lessons learned to focus on other MDROs

Summary

- CRE are an urgent global threat.
- CRE cases are currently uncommon in Oregon.
- Weaknesses in CRE prevention practices and knowledge of front-line personnel have been identified and are targeted for improvement.
- Oregon has implemented a regional, collaborative approach towards CRE prevention.

Acknowledgements

Current Working Group
Zintars Beldavs, MS
Gen Buser, MD, MSHP
Maureen Cassidy, MT, MPH
Ann Thomas, MD, MPH
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PVAMC and the OHSU ID Division
Brian Wong, MD
Tom Ward, MD
Graeme Forrest, MBBS
And others

And of course, Janice Jou, MD, MHS

THANK YOU!