



Carbapenem-Resistant Enterobacteriaceae (CRE) in California

Tri-Valley APIC
Los Angeles, CA
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Objectives

- Review the history and risk factors of CRE
- Describe the background, methods, results, and conclusions of the statewide CRE prevalence survey
- Discuss next steps - *Where do we go from here?*



Enterobacteriaceae

- Normal human gut flora; commonly found in the environment
 - More than 70 species
- Cause a wide range of human infections
 - UTI, wound infections, pneumonia, bacteremia
- Important cause of healthcare and community-associated infections

CRE Risk Factors

- Antibiotic exposure and time in LTAC hospital
- 2 Case Control studies, NYC
 - Exposure to Cephalosporins
 - Exposure to Carbapenems
 - Transplant Pre-Infection
 - Ventilator
- Case Control study, Israel
 - Poor Functional Status
 - ICU Stay
 - Receipt of Quinolones



Definitions of CRE

- Any *Enterobacteriaceae* species that are intermediate or resistant to at least one carbapenem and resistant to all third-generation cephalosporins tested (ceftriaxone, cefotaxime, and ceftazidime)

- OR -

- Any *Enterobacteriaceae* species that test positive for carbapenemase production by any method (e.g. disk diffusion, PCR)
 - CDPH and other health departments discourage the use of Modified Hodge Test for criteria 2

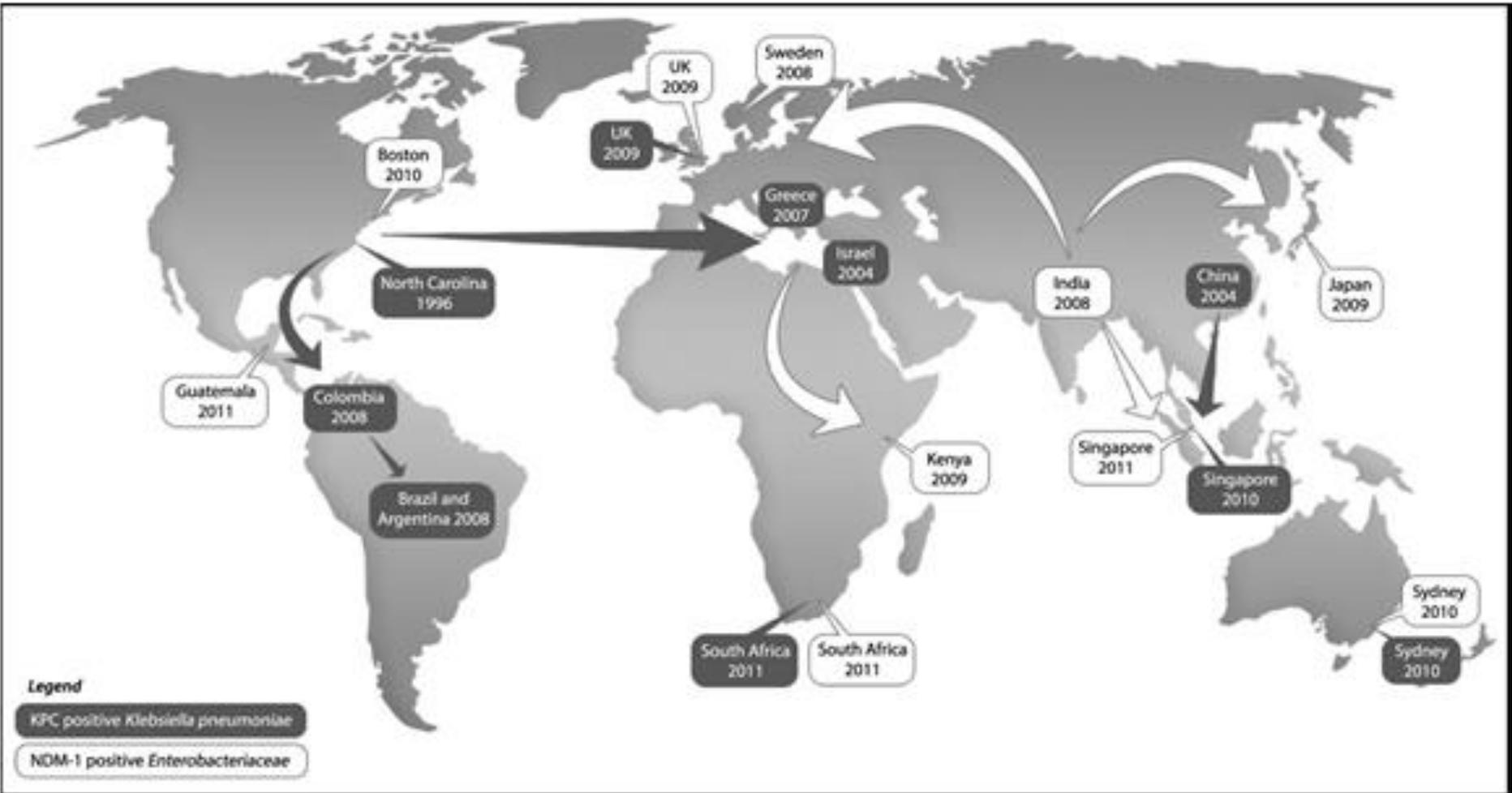
Klebsiella pneumoniae carbapenemases (KPCs)

- A type of CRE
 - Confers resistance to all β -lactams
 - Resides on transferable plasmids and hydrolyzes all penicillins, cephalosporins and carbapenems
 - Limits options for treatment
 - Polymyxins (problems with nephrotoxicity)

Carbapenemases Found in the US

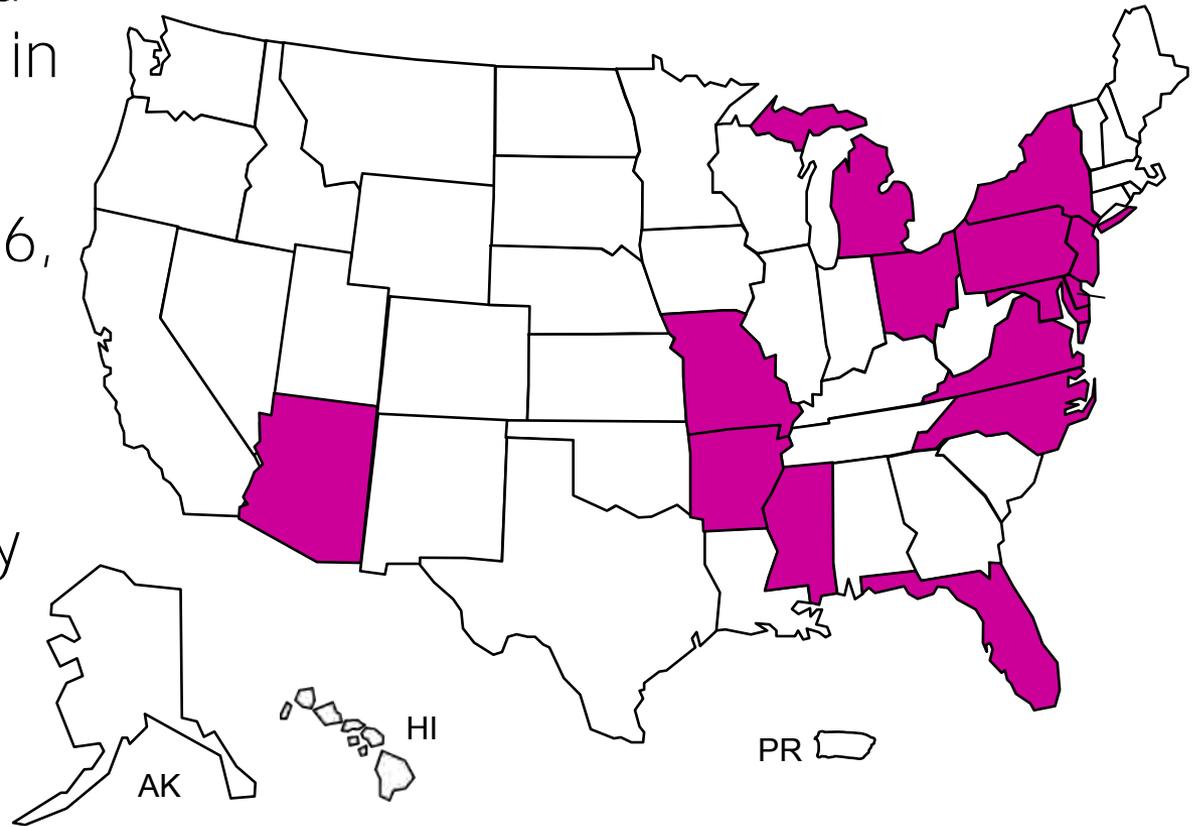
Enzyme	Classification	Activity
KPC	Class A	Hydrolyzes all β -lactam agents
NDM-1 IMP VIM	Class B, Metallo- β -lactamase (MBL)	Hydrolyzes all β -lactam agents except aztreonam
OXA	Class D	Hydrolyzes carbapenems but not active against 3 rd generation cephalosporins

Spread of KPC and NDM-1 Worldwide

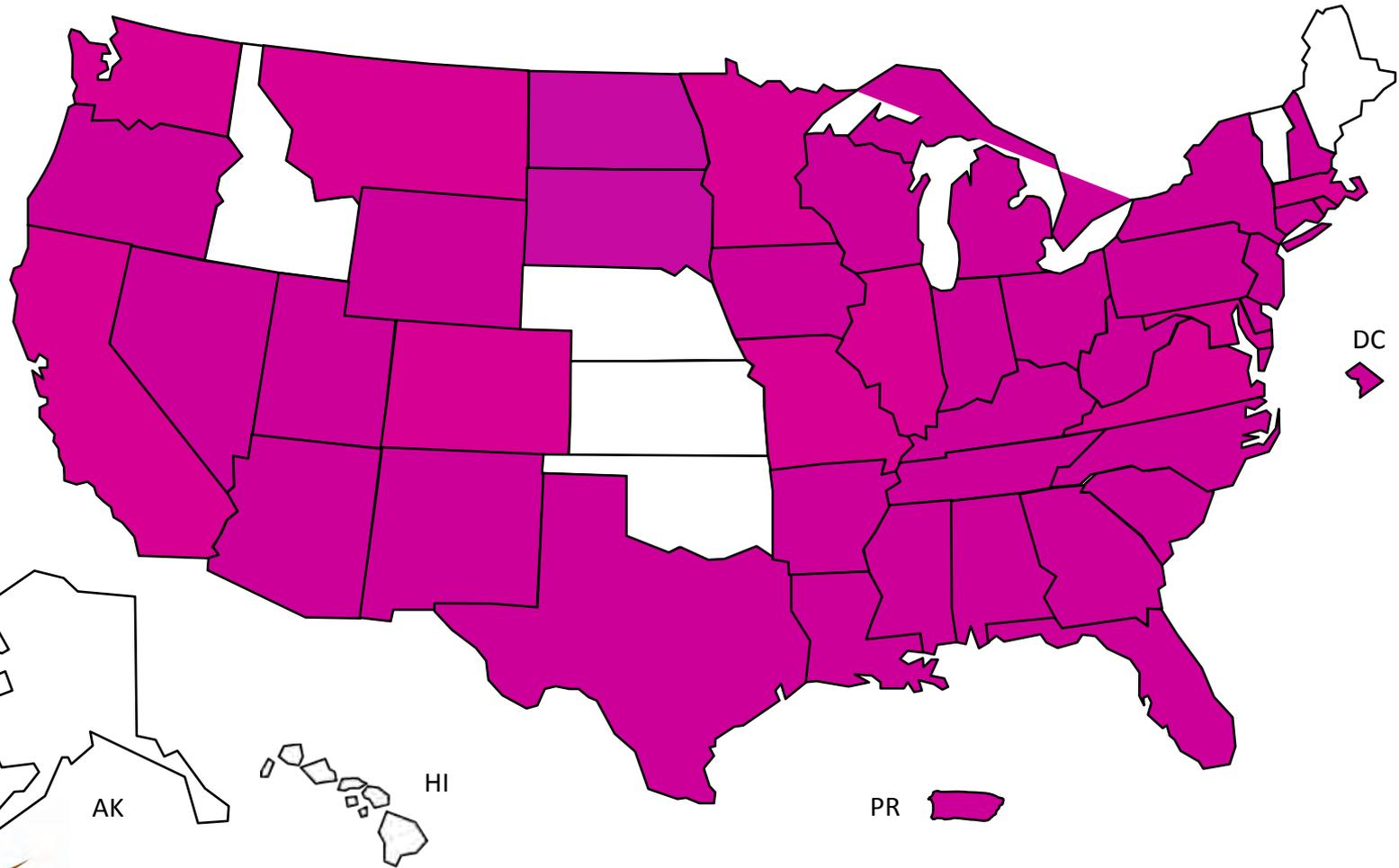


Emergence of CRE in United States

- CRE first identified in the US in 1996 in North Carolina
- By November 2006, CRE began to be reported in a number of states across the country

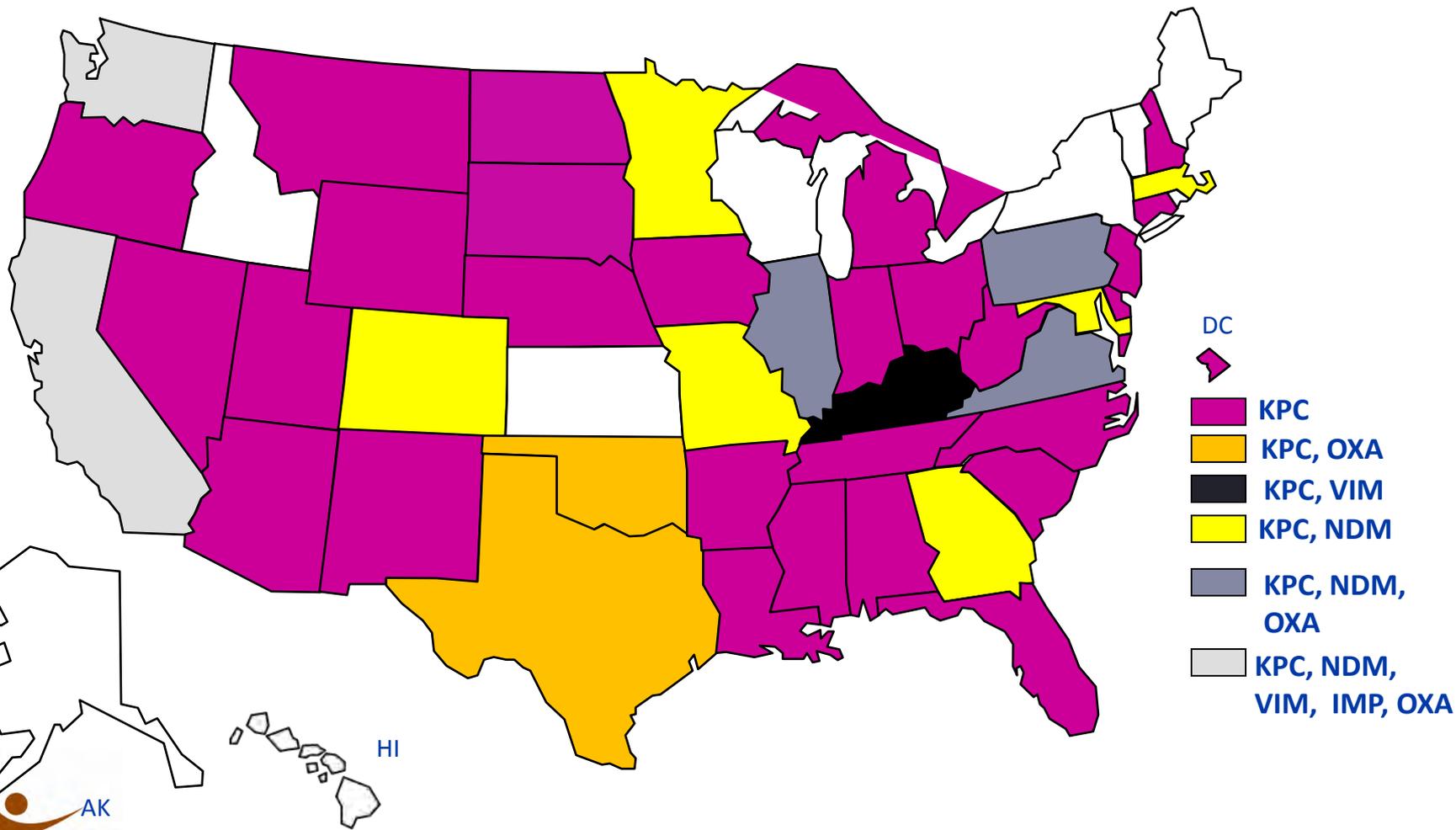


KPC-Producing CRE in US, 2013



Courtesy of Alex Kallen, CDC

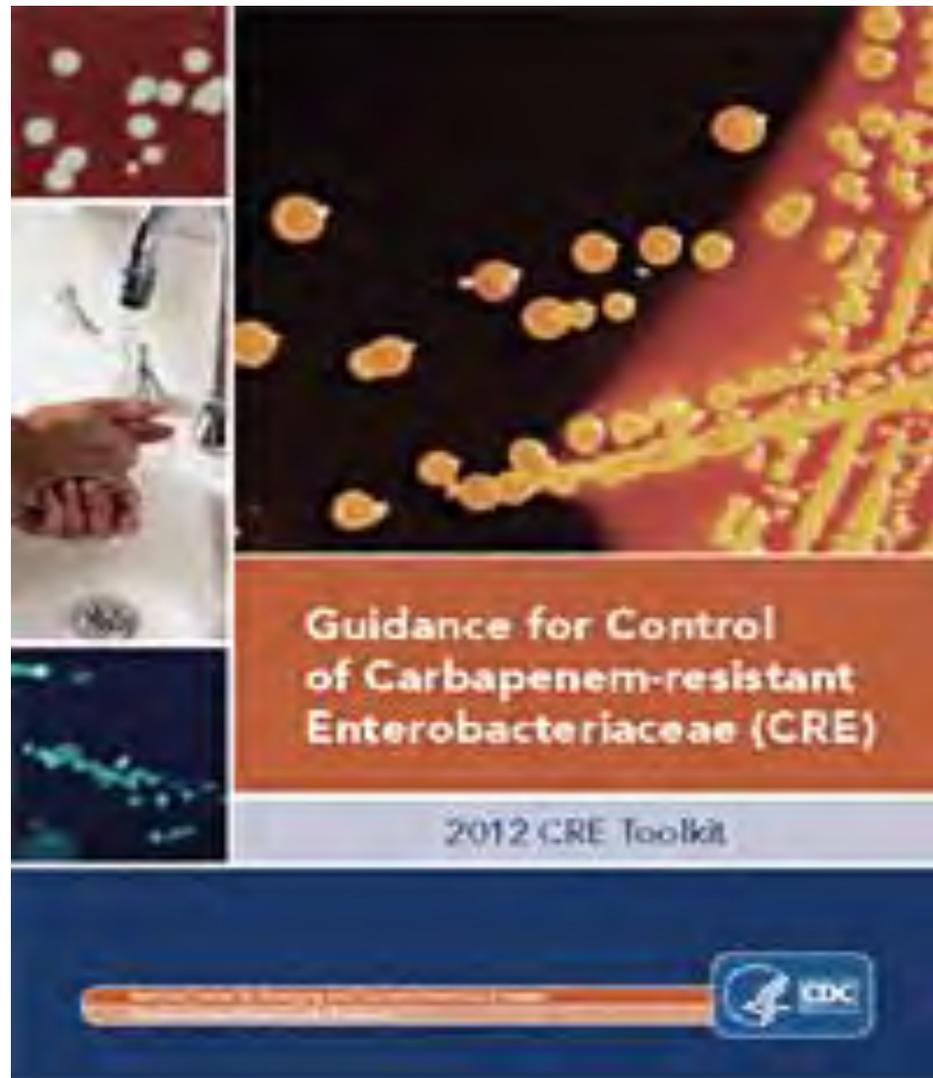
Carbapenemases in the US, 2013



CDC CRE Toolkit, 2012

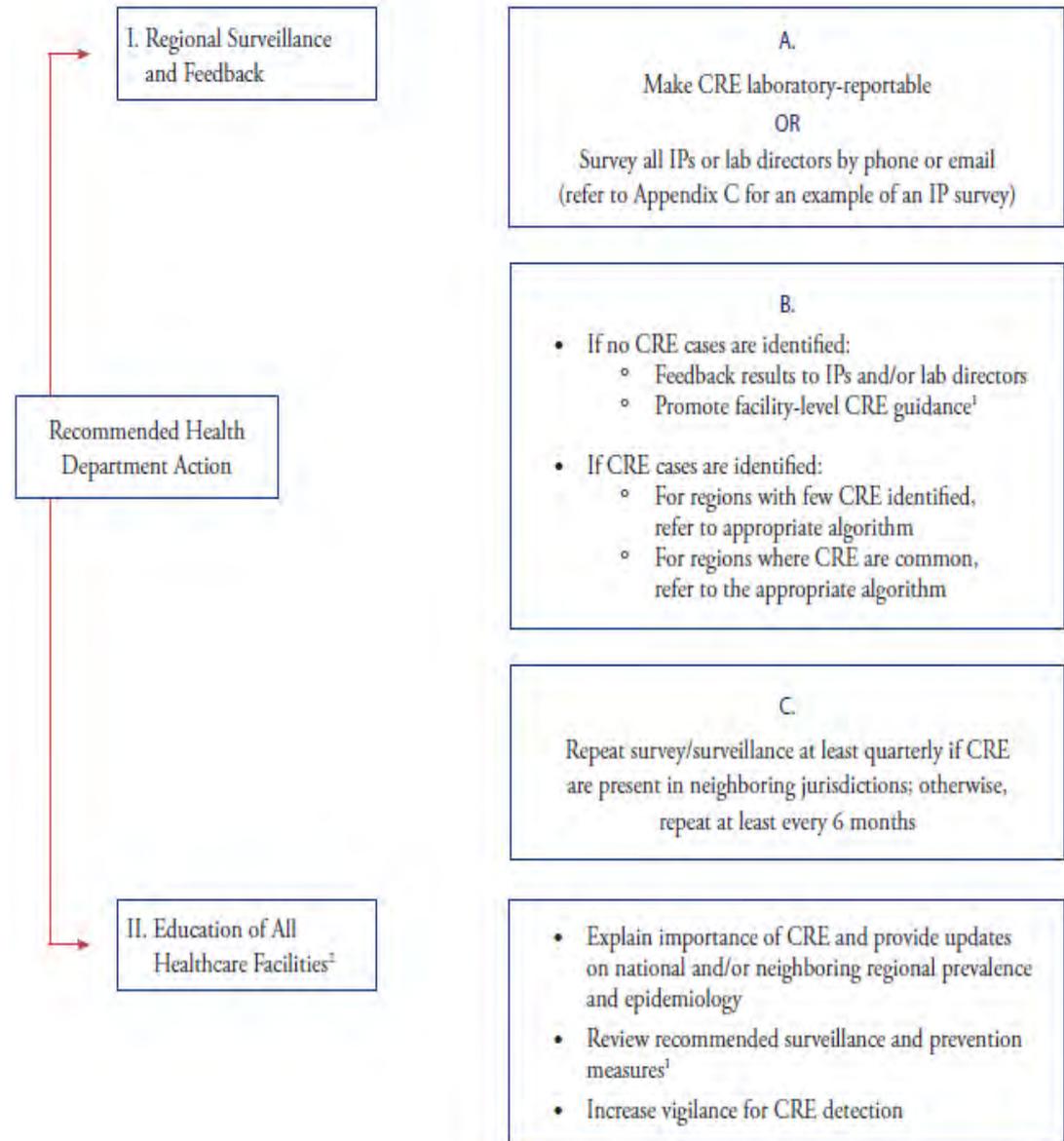
Guidelines for Hospitals

- Recommends prevention, screening, and infection control practices.
- To use toolkit effectively, facilities are encouraged to adjust surveillance and control measures according to CRE regional prevalence.
 - Most hospitals do not know their regional prevalence



In regions without known CRE, the emphasis should be on regional surveillance for CRE and education of healthcare personnel (e.g., infection prevention staff) to increase awareness.

Guidance for Regions with **No** CRE Identified

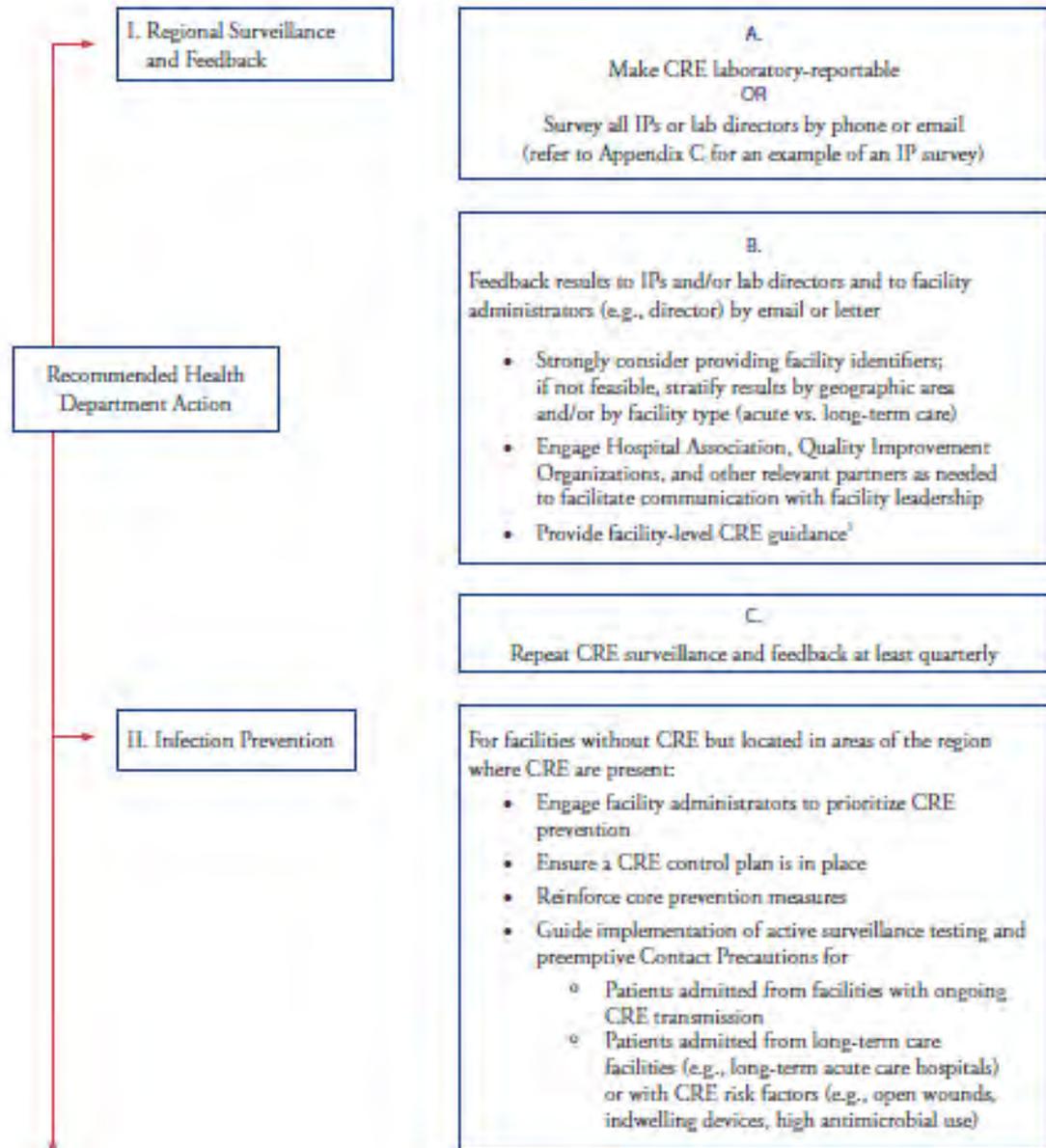


CDC CRE Toolkit, 2012



In regions where CRE have been identified but cases remain uncommon, an aggressive approach to prevention is needed to prevent further transmission and widespread emergence of CRE. This will require increased prevention efforts targeting select facilities in the region where CRE are found.

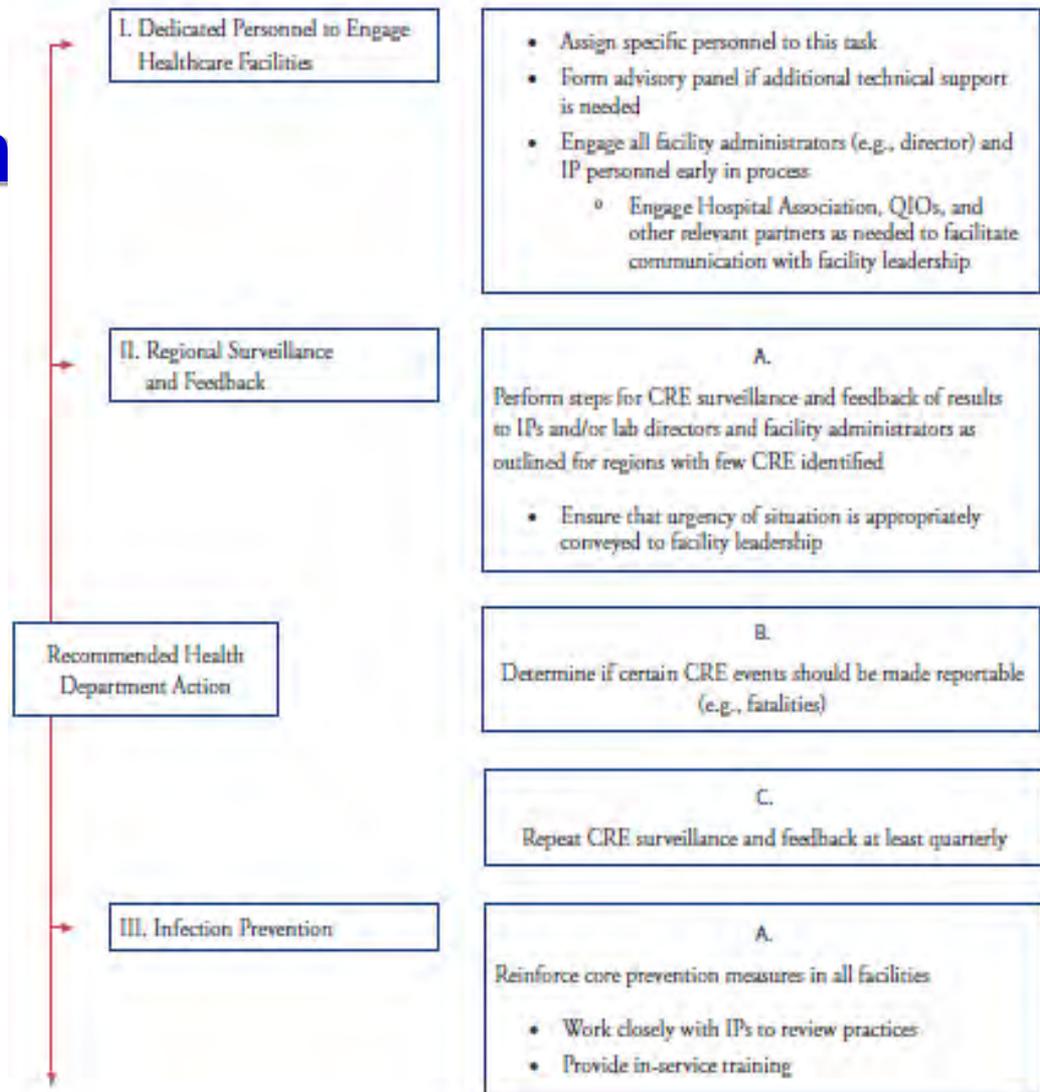
Guidance for Regions with Few CRE Identified



CDC CRE Toolkit, 2012

Guidance for Regions where CRE are **Common**

CRE containment in high-prevalent regions will require the implementation of core and supplemental prevention measures across all acute care and long-term care facilities that provide medical or nursing care (e.g., long-term acute care hospitals and skilled nursing facilities).



CDC CRE Toolkit, 2012

CDPH CRE Prevalence Survey Objectives

- Determine regional prevalence estimates of CRE in California general acute care hospitals in 2012
 - Assist hospitals in better utilizing the CDC CRE toolkit by classifying them according to no, low or high CRE regional prevalence
- Educate California hospital infection prevention personnel about CRE
 - Facilitate communication and collaboration between infection prevention and microbiology

CRE Prevalence Survey Methods

- Survey developed in conjunction with CDC
- All California general acute care hospitals including long-term acute care (LTAC) were contacted
 - 387 in total
- Conducted over the phone
 - Because survey data gathered from multiple sources, it took several weeks from initial contact to completion
 - Approximately 15 minutes to complete once data gathered
- 5 CDPH staff members and 1 volunteer conducted surveys from May 2013 - present

Methods - continued

Survey included

- Hospital prevalence of specific CRE organisms in 2012
 - Definition of CRE: any *Enterobacteriaceae* that tested non-susceptible to a carbapenem
 - Total numbers of *Klebsiella* spp. *Escherichia coli*
- 2012 antibiograms collected
 - Aggregated antimicrobial susceptibility data
- Infection control measures, screening practices, laboratory protocols, and staff awareness

Comparison of Participating Acute Care and LTAC Hospitals to Non-Participant Hospitals

	Participants N=329 (85%)	Non-Participants N=58 (15%)	
Hospital Type	n(%)	n(%)	P-Value
Community	253(77)	47(81)	0.48
Rehabilitation	6(2)	1(2)	1.00
LTAC	22(7)	1(2)	0.22
Critical Access	23(7)	3(5)	0.78
Teaching	16(5)	4(7)	0.51
Pediatric	9(3)	2(3)	0.67

CRE Prevalence of California Hospitals

	Non-Susceptible Isolates	Total Isolates	Pooled Mean Prevalence (%)
LTAC Hospitals - 22			
<i>Klebsiella</i> spp.	1,152	2,220	51.9
<i>E. coli</i>	20	2,184	0.9
General Acute Care - 303			
<i>Klebsiella</i> spp.	2,264	72,387	3.1
<i>E. coli</i>	444	349,804	0.1
All Hospitals - 325			
<i>Klebsiella</i> spp.	3,416	74,607	4.6
<i>E. coli</i>	464	351,988	0.1

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CA CRE prevalence less than 11.2-12.8% reported by NHSN for CAUTI, VAP, and CLABSI in 2009-2010

Regional Comparison - Acute Care Hospitals

Klebsiella species

	Hospitals Reporting	CRE <i>Klebsiella</i> / Total <i>Klebsiella</i>	Crude CRE Rate	Adjusted* CRE Rate	95% CI
LA / Orange County	101	1,652 / 2,4213	68.22	67.87	60.68-75.47
Rest of CA	197	596 / 46,661	12.8	13.0	11.8-14.3

E. coli

	Hospitals Reporting	CRE <i>E.coli</i> / Total <i>E.coli</i>	Crude CRE Rate	Adjusted* CRE Rate	95% CI
LA / Orange County	101	275 / 103,125	2.67	2.88	1.96-3.97
Rest of CA	197	169 / 239,973	0.7	1.0	0.8-1.3

Regional Comparison – LTAC Hospitals

	LA and Orange Counties N=12		Rest of California N=10		P-value
	Non-Susceptible Isolates/Total	Pooled Mean Prevalence (%)	Non-Susceptible Isolates/ Total	Pooled Mean Prevalence (%)	
<i>Klebsiella</i> spp.	1029/1560	66.0	123/660	18.6	<.01
<i>E. coli</i>	12/634	0.2	8/1550	0.5	<.01

CRE Prevalence Survey Conclusions

- CRE prevalence is significantly higher in the Los Angeles and Orange County region than in the rest of California
- Los Angeles and Orange County LTAC hospitals have significantly higher pooled prevalence than other LTAC or general acute care hospitals
- CRE awareness is high among California IPs, but knowledge of regional prevalence is not
- Adherence to CDC guidelines varies widely
 - Half of respondents routinely assess CRE risk factors upon admission

CRE Transmission Prevention Strategies

- Core
 - Hand hygiene
 - Contact Precautions
 - HCP education
 - Minimize device use
 - Cohort patients and staff
 - Laboratory notification
 - Antimicrobial stewardship
 - CRE Screening
- Supplemental
 - Active surveillance cultures
 - Chlorhexidine bathing

Antimicrobial Stewardship Programs (Core)

- Critically important to prevent the spread of CRE
- More evidence is accumulating that ASPs can prevent the emergence of MDROs like CRE
- CDC released a Vital Signs in March 2014 on antimicrobial resistance and the need for ASP
- **For local assistance, CDPH recently launched “Spotlight on ASPs”**
 - Lists hospital experts willing to mentor others

Rapid Communication between Labs and IP Staff (Core)

- 91% of facilities indicated that they receive timely notification from laboratory facilities when a CRE result is identified
 - 68% received preliminary alerts before the results were confirmed
 - 77% received notifications less than 24 hours after the initial result
- Automated, redundant alerts should be in place whenever possible

Lab Issues- Updated Breakpoints

- Many labs are still using breakpoints for susceptibility testing that have not been updated to the most recent guidelines

Agent	Previous Breakpoints (M100-S19) MIC (µg/mL)			Current Breakpoints (M100-S22) MIC (µg/mL)		
	Susceptible	Intermediate	Resistant	Susceptible	Intermediate	Resistant
Doripenem	-	-	-	≤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

Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing; Twenty Second Informational Supplement (January 2012). CLSI document M100-S22. Wayne, Pennsylvania, 2012.

Lab Issues- Identifying Carbapenemases

Ability of Modified Hodge Test to Identify KPC Among Sample of Carbapenem Non-susceptible Isolates

Organism	Total Number	Modified Hodge Test + n (%)	KPC+ n (%)
<i>E. coli</i>	8	3 (38)	2 (25)
<i>E. cloacae</i>	12	10 (83)	7 (58)
<i>E. aerogenes</i>	14	7 (50)	0 (0)
<i>K. pneumoniae</i>	14	11 (79)	11 (79)
Total	48	31 (65)	20 (42)

- MHT has good sensitivity for KPC and OXA, but low sensitivity for NDM; in addition, it has low specificity across the board

Contact Precautions (Core)

- 98% of facilities indicated that they would place CRE in contact precautions
- Patients colonized or infected with CRE
 - Systems in place to identify patients at readmission
 - Education of HCP about use and rationale behind CP
 - Adherence monitoring
 - Consideration of pre-emptive CP in patients transferred from high-risk settings

Duration of CRE Carriage

- An Israeli study (2010) found that among 97 patients positive for CRKP, time to 1 culture negative (without subsequent positive)
 - Mean 387 days | Median 295 days
 - Proportion positive by time from first positive
 - 3 mos = 78%
 - 6 mos = 65%
 - 9 mos = 51%
 - 1 year = 39%

Patient and Staff Cohorting (Core)

- 96% of facilities indicated that they would place CRE patients in single rooms when available
- Cohorting practices include:
 - CRE patients in single rooms (when available)
 - Cohorting (even when in single rooms)
 - Staff cohorting
 - Preference for single rooms should be given to patients at highest risk for transmission such as patients with incontinence, medical devices, or wounds with uncontrolled drainage

Targeted Surveillance Cultures (Core)

- Only 39% of facilities in our survey reported conducting surveillance cultures of patients with epidemiologic links to CRE patients.
- Used to identify unrecognized CRE colonization among contacts of CRE patients
- Stool, rectal, peri-rectal
- Applicable to both acute and long-term care settings

Link to CDC laboratory protocol

www.cdc.gov/ncidod/dhqp/pdf/ar/Klebsiella_or_E.coli.pdf

Targeted Surveillance Cultures (Core)

- Only minority of patients colonized with CRE have positive clinical cultures
 - In Israel only 5/16 (31%) CRE+ patients had a positive clinical culture for CRKP
 - Surveillance cultures at a US hospital identified 1/3 of all positive CRKP patients
 - Not having these patients in Contact Precautions resulted in 1400 days of unprotected exposure

Weiner-Well et al. J Hosp Infect 2010;74:344-9

Calfee et al. ICHE 2008;29:966-8

Chlorhexidine Bathing (Supplemental)

- Limited evidence for CRE
 - Used effectively in outbreak in LTAC as part of a package of interventions
 - Applied to all patients regardless of CRE colonization status
 - Has shown decrease transmission of MRSA and VRE
- Some studies suggest CHG bathing may not be done **“well”**

Surveillance Cultures upon Admission (Supplemental)

- 4% of facilities in our survey reported conducting surveillance cultures of patients upon admission
- Facilities in regions with higher than average incidence of CRE should consider surveillance cultures upon admission with select CRE risk factors:
 - Extended ICU, LTAC Hospital or LTC Facility stay
 - Ventilator exposure
 - Poor functional Status
 - Previous carbapenem exposure
 - Recipient of Transplant

CRE Prevention Regional Partnerships: Public Health, Hospitals, LTC Facilities

"An effective intervention at containing the spread of CRE should ideally be implemented before CRE have entered a region, or at the very least, immediately after its recognition. Policy makers and public health authorities must ensure the early recognition and coordinated control of CRE."

Carbapenem-Resistant Enterobacteriaceae A Potential Threat

Mitchell J. Schwaber, MD, MSc

Yehuda Carmeli, MD, MPH

AFTER MORE THAN 7 DECADES OF ANTIBIOTIC USE, A RECURRENT pattern of antimicrobial resistance spread is evident among certain bacterial pathogens. In this pattern, resistance occurs first among the most severely ill hospitalized patients, then spreads to involve other

tant among these are carbapenemases, primarily the serine β -lactamase KPC and the metallo- β -lactamase VIM.³ The genes coding for these enzymes are carried by plasmids that often carry other resistance factors as well, resulting in extensively drug-resistant (XDR) bacteria. Moreover, plasmids carrying resistance genes also may carry virulence factors, thus leading to severe infections. Since plasmids are readily transferred, these resistance genes can easily spread within species and even from species to species of Enterobacteriaceae.

Schwaber MJ, Carmeli Y. JAMA. 2008 ; 300(24):2911-2913

Questions?

For more information, please contact any
HAI Liaison Team member or
Sam Horwich-Scholefield at shorwich@cdph.ca.gov

Thank you

