Carbapenem-Resistant Enterobacteriaceae (CRE) in California: Guidance for Regions with Few CRE

Including the following Counties:

Alameda	Lake	San Benito	Shasta	Trinity
Butte	Lassen	San Francisco	Sierra	Yuba
Colusa	Mendocino	San Luis Obispo	Siskiyou	
Contra Costa	Modoc	San Mateo	Solano	
Del Norte	Monterey	Santa Barbara	Sonoma	
Glenn	Nevada	Santa Clara	Sutter	
Humboldt	Plumas	Santa Cruz	Tehama	

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Presented via Webinar

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Guidance for Regions with Few CRE

Learning Objectives

- Review CDC Toolkit core CRE prevention strategies for ALL healthcare facilities
- Describe the background, methods, and results of the statewide CRE 2012 Prevalence Survey
- Describe CRE control in regions where there are few CRE

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Enterobacteriaceae

- Normal human gut flora
  - More than 70 species, including *K. pneumoniae* and E. coli
- Cause a wide range of human infections
  - UTI, wound infections, pneumonia, bacteremia
- Important cause of healthcare and community-associated infections

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Carbapenem-resistant *Enterobacteriaceae* (CRE)

- One of three pathogens on CDC's most urgent threat list

- CRE infections result in 40-50% mortality
- CRE carry genes that can confer resistance to many other antimicrobials, leaving limited treatment options
  - Pan-resistant CRE Klebsiella have occurred

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Definitions of CRE

- Nonsusceptible to **one** of the following carbapenems:

  doripenem, meropenem, or imipenem

- AND -

- Resistant to **all 3** of the following 3rd generation cephalosporins (or all that were tested):

  ceftriaxone, cefotaxime, and ceftazidime

  - Note: All three of these antimicrobials are recommended as part of the primary or secondary susceptibility panels for *Enterobacteriaceae* testing

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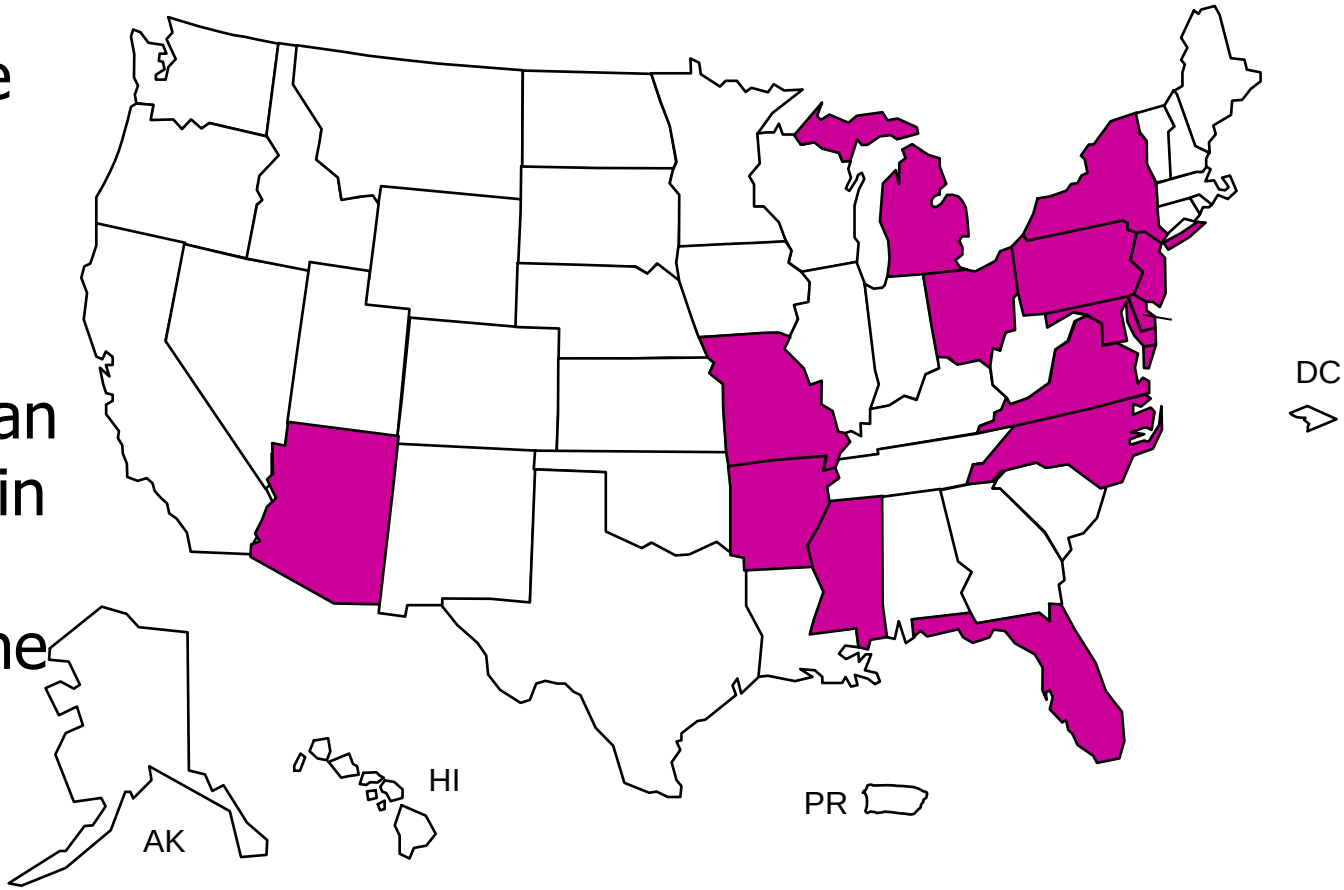
Emergence of CRE in United States

- CRE was 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



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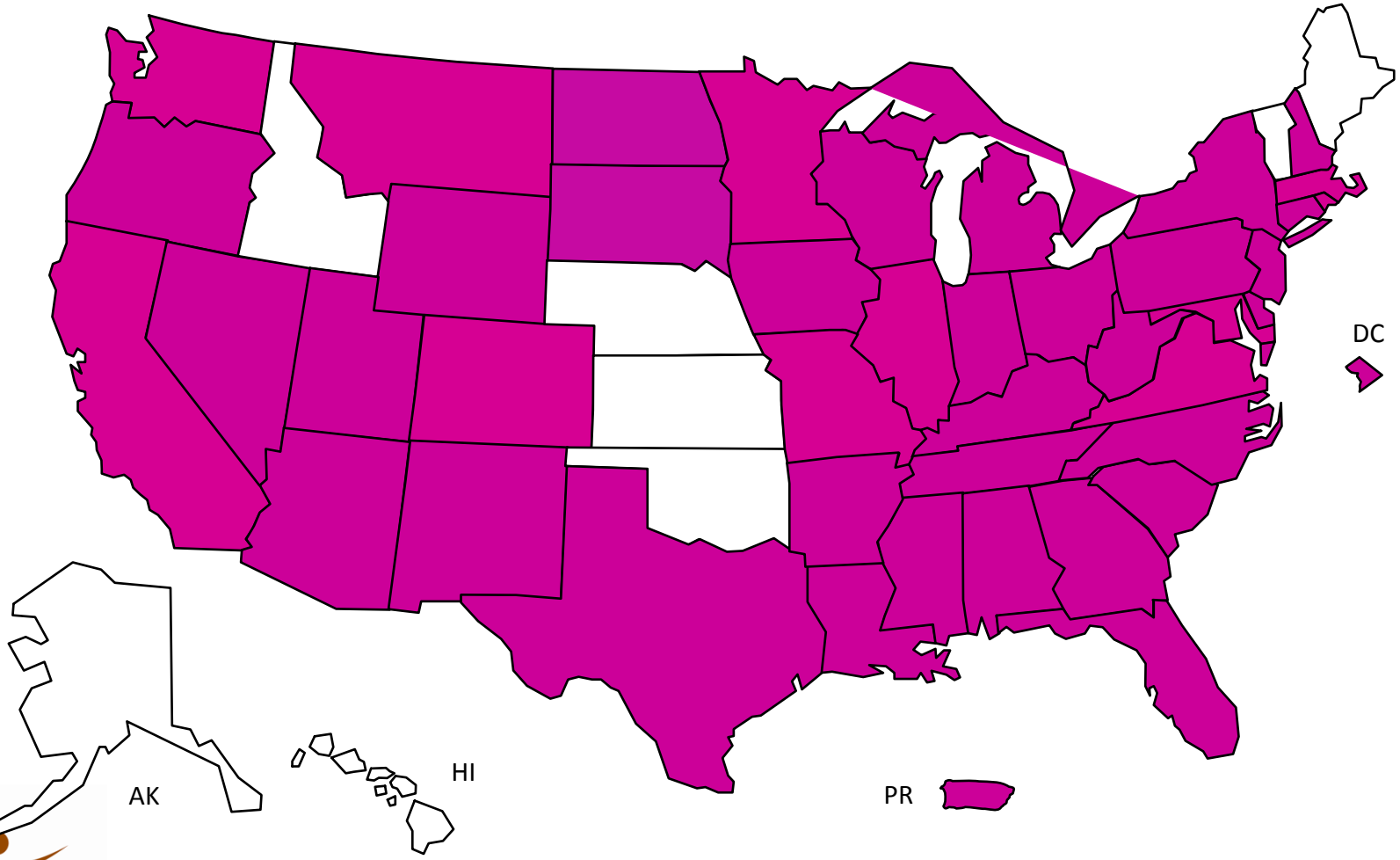
KPC-Producing CRE in US, 2013



Courtesy of Alex Kallen, CDC

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Klebsiella pneumoniae Carbapenemases (KPCs)

- Enzyme that confers resistance to all β-lactams antibiotics
- Most common type of CRE
- Resides on transferable plasmids and hydrolyzes all penicillins, cephalosporins and carbapenems
- Limits options for treatment
  - Colistin/Polymyxins used for therapy, but each have problems with nephrotoxicity

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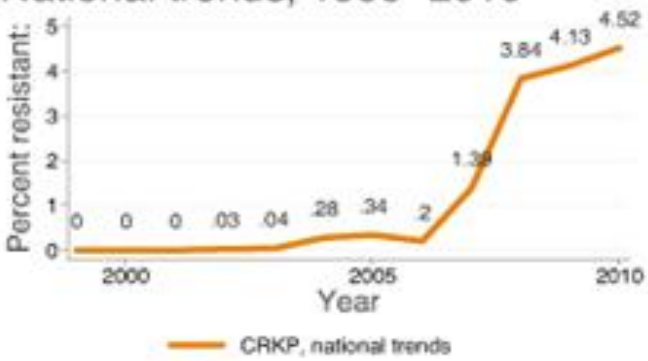
Carbapanem-resistant *Klebsiella pneumoniae*

US Regions, 2009-2010

National trends, 1999–2010



ResistanceMap
cddep.org/map

Courtesy of Arjun Srinivasan, CDC

CRE Risk Factor: Care in LTAC Hospitals

- A Chicago survey found patients in LTAC hospitals had a significantly greater risk of being colonized or infected with CRE than patients in short term stay hospitals
  - RR= 5.94, 95% CI: 3.75-9.39
- In an outbreak of 40 CRE cases in Indiana and Illinois, 24 (60%) were linked to one LTAC hospital

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Lin M et al. Clin Infect Dis. 2013;57:1246-1252
Won S Y et al. Clin Infect Dis. 2011;53:532-540

CRE Risk Factor: Mechanical Ventilation

- CRE acquisition is highly associated with mechanical ventilation
  - OR=11.53, 95% CI: 1.59-83.88
  - NYC data
- Patients admitted from LTAC hospitals or SNFs that perform ventilator care are more likely to be colonized with CRE than patients from facilities that do not have ventilator care
  - OR= 7.0, 95% CI: 1.3-42
  - Illinois data

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Prabaker K et al. ICHE 2012; 33:1193-1199
Swaminathan M et al. ICHE 2013; 34: 809-817

Other CRE Risk Factors

- CRE infection or colonization – New York data
  - Exposure to cephalosporins (OR: 2.65, p=.02)
  - Exposure to carbapenems (OR: 14.97, p<.01)
  - Transplant (OR: 3.71, p=.008)
  - Pre-Infection LOS (OR: 1.05, p=.01)
  - Ventilator (OR: 2.44, p=.04)
- CRE infection – Israel data
  - Poor functional status (OR: 15.4, p<.01)
  - ICU stay (OR: 17.41, p=.02)
  - Receipt of antibiotics (OR: 4.4, p=.05)
    - Fluoroquinolones (OR: 7.2, p=.04)

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Patel et al. Infect Control Hosp Epidemiol 2008;29:1099-1106

Primary Prevention? **CRE Surveillance!**

- Every inpatient healthcare facility needs to have awareness of whether CRE (*E.coli* or *Klebsiella)* have ever been cultured from admitted patients
- Facilities without this information should review archived lab results from previous 6 months or a year
- If CRE have been present, determine
  - If evidence of intra-facility transmission
  - Which units/wards affected
  - Basic epidemiology of CRE patients, including dates of admission, clinical outcomes, medications, common exposures (i.e. wards, surgery, procedures)

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Definitions of CRE Regional Prevalence

- No/Rare CRE Identified
  - Healthcare facilities in region have not identified CRE colonized or infected patients; or some facilities with rare CRE
- Few CRE
  - Most healthcare facilities in region do not regularly admit patients with CRE
  - Several facilities in region identify CRE colonized or infected patients on an infrequent basis (e.g. monthly basis or greater)
  - Some facilities with several CRE colonized or infected patients, but surrounded by facilities with only a few or none
- Common CRE
  - Majority of healthcare facilities in region have identified cases, and regularly have CRE colonized or infected patients admitted (e.g. CRE detected at least weekly)

Note: No regions in CA meet "Common" definition currently

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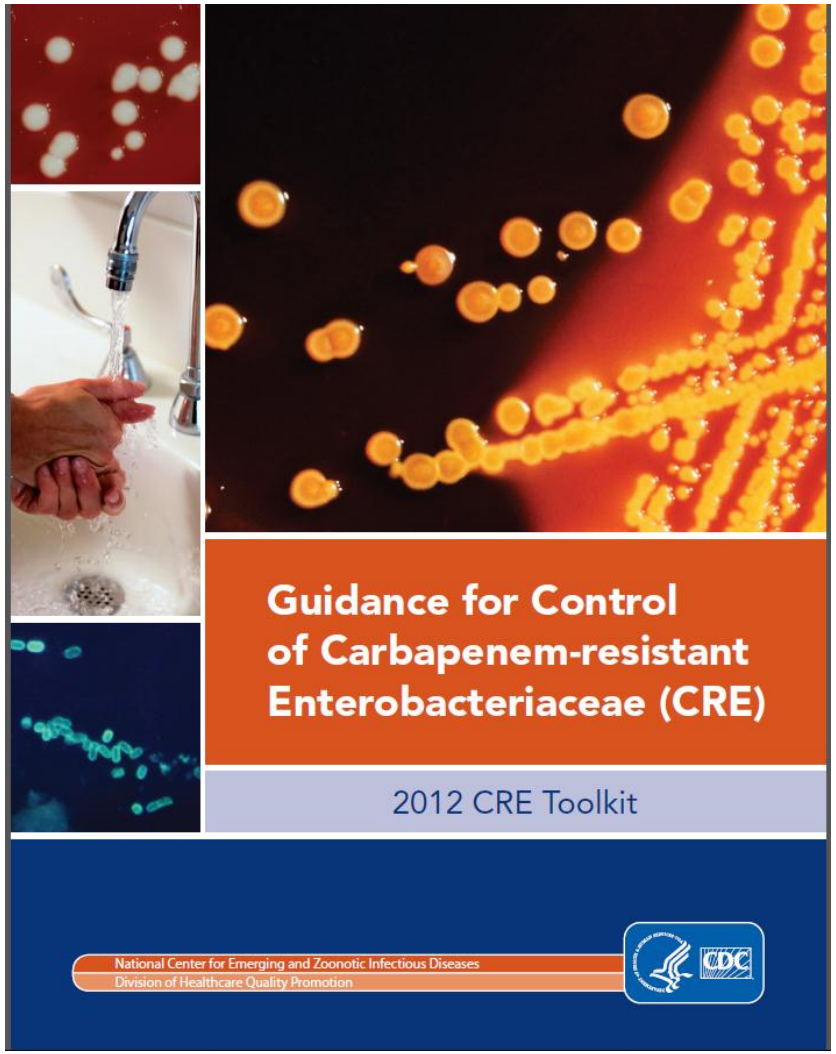
Preventing CRE Transmission

CDC Toolkit, 2012

- Recommends Core prevention strategies for the control of CRE in ALL hospitals and LTC facilities
- Recommends public health action based on regional CRE prevalence



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CDC Prevention Strategies

Core Strategies

- High levels of scientific evidence
- Demonstrated feasibility

- Should become standard practice

Supplemental Strategies

- Some scientific evidence
- Variable levels of feasibility

- Consider implementing in addition to Core when infections persist or rates are high

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CORE CRE Prevention Strategies for ALL Acute and LTC Facilities

1. Hand Hygiene
2. Contact Precautions
3. Healthcare Personnel Education
4. Minimize Device Use
5. Patient and Staff Cohorting
6. Laboratory Notification
7. Antimicrobial Stewardship
8. CRE Screening

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SUPPLEMENTAL Prevention Strategies for Healthcare Facilities with CRE Transmission

1. Active Surveillance Testing
2. Chlorhexidine Bathing

1. Hand Hygiene

CORE

- Ensure healthcare personnel are familiar with proper hand-hygiene and its rationale
  - Make hand hygiene accessible, easy, and convenient
  - Emphasize use of hand hygiene in view of the patient and always prior to patient contact

- Perform adherence monitoring for hand hygiene!
  - Periodically record adherence via direct observation studies
  - Consider routine monitoring via volume of alcohol-based hand rub used
  - When outbreaks occur, assess adequacy of existing policies, procedures, and adherence monitoring practices

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2. Contact Precautions

CORE

- Patients infected or colonized with CRE must be placed Contact Precautions
  - Educate HCP about use and rationale behind Contact Precautions for CRE
  - Perform adherence monitoring for Contact Precautions
- Systems should be in place to identify patients at readmission
- Consider pre-emptive Contact Precautions of patients transferred from CRE high-risk settings or regions
- Notify receiving healthcare facility when transferring patients

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Contact Precautions in Skilled Nursing or Long Term Care Facilities

CORE

- Implement contact precautions for LTC residents who are at higher risk for transmitting CRE
  - Totally dependent upon HCP for their activities of daily living
  - Ventilator-dependent
  - Incontinent of stool
  - Wounds with difficult-to-control drainage
- For other CRE colonized residents, the requirement for Contact Precautions might be relaxed
- As with all care, Standard Precautions should be maintained

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Maintain Contact Precautions CORE

- The duration of CRE carriage is very extended in comparison to other healthcare pathogens
- An Israeli study (2010) found that among 97 patients positive for CRKP, time to 1st negative negative (without subsequent positive)

  Mean 387 days and Median 295 days
- Recommendation to discontinue precautions only if 2 screening cultures are both negative

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Zimmerman FS, et al. AJIC 2013: 190-194

3. Healthcare Provider Education

CORE

- Education is key to help staff identify those at high risk for CRE acquisition and transmission
  - Review CRE risk factors
  - Describe lack of treatment options
  - Explain necessity for extended contact precautions due to duration of carriage

- AHRQ Toolkit - http://www.ahrq.gov/cretoolkit
  - Provides tools for assessment of HCP attitudes and knowledge of CRE control and prevention

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4. Minimize Device Use

CORE

- Presence of medical devices such as catheters, tubes, drains, and ventilators are significant risk factors for CRE
  - Monitor for necessity on a daily basis
  - Require documentation of daily necessity
  - Remove as soon as possible

- Refer to CDC published guidelines for preventing device-associated infections
  www.cdc.gov/hicpac/pdf/CAUTI/CAUTIguideline2009final.pdf
  www.cdc.gov/hicpac/BSI/BSI-guidelines-2011.html
  www.cdc.gov/mmwr/preview/mmwrhtml/rr5303a1.htm

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5. Patient and Staff Cohorting

CORE

- CRE patients, whether colonized or infected, should be placed in single rooms when possible
- Implement staff cohorting, dedicating staff to care only for CRE patients during their shift
- If single rooms are not available for all CRE patients:
  - Preference for private rooms should be given to patients at highest risk for transmission such as patients with incontinence, medical devices, or wounds with uncontrolled drainage
  - If room sharing necessary, try to place patients together only if infected with same pathogen / carbapenemase

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6. Laboratory Notification

CORE

- Hospital personnel should receive timely notification from laboratory when a CRE result is identified
  - Preliminary alerts should be sent even before final results are confirmed
  - All final notifications should be received within 24 hours of the initial result

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7. Antimicrobial Stewardship **CORE**

- Since 2008, California law requires every acute care hospital to implement a program to monitor "the judicious use of antibiotics"
- Critically important to prevent the spread of CRE
  - Ensure antibiotic prescribed is appropriate for indication
  - Select narrowest spectrum possible
- For assistance, the CDPH HAI Program recently launched "Spotlight on ASPs"
  - Provides criteria for development of basic, intermediate, and advanced tiers of ASPs
  - Lists hospital experts willing to mentor others

www.cdph.ca.gov/programs/hai/Pages/AntimicrobialStewardshipProgramInitiative.aspx

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8. CRE Screening

CORE

- Conduct surveillance cultures of patients with epidemiologic links to known CRE patients
- Rationale: Only a minority of patients colonized with CRE will have positive clinical cultures
  - Israeli hospitals found only 5 of 16 patients had positive CRE clinical cultures
  - NY hospital found 2/3 more CRE patients by screening than were identified by clinical culture, resulting in 1400 days of unprotected exposure
- For guidance on performing CRE rectal or peri-rectal swabs, refer to the CDC laboratory protocol at www.cdc.gov/ncidod/dhqp/pdf/ar/Klebsiella_or_E.coli.pdf

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Weiner-Well et al. J Hosp Infect 2010;74:344-9
Calfee et al. ICHE 2008;29:966-8

1. Active Surveillance Testing

SUPPLEMENTAL

- Consider Active Surveillance Testing for:
  - All patients admitted to facility
  - Patients admitted to high-risk settings (e.g. ICU)
  - Patients at highest risk of being colonized with CRE
    - Extended ICU, LTAC hospital or LTC facility stay
    - Extensive antimicrobial exposure
    - Presence of indwelling medical device

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2. Chlorhexidine Bathing

SUPPLEMENTAL

- Has been used successfully to prevent some types of HAIs (i.e. CLABSI, CDI) and to decrease colonization with specific MDRO (i.e. MRSA, VRE)
- Consider daily bathing of high risk patients
  - Use either diluted 2% liquid chlorhexidine or chlorhexidine-impregnated wipes
- Usually applied to all patients regardless of CRE colonization status if targeting a specific patient population, e.g. ICU patients

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California Statewide CRE Prevalence Survey

California CRE Prevalence Survey

Objectives

1. To educate California hospital infection prevention personnel about CRE
   - Facilitate communication and collaboration between infection prevention and microbiology
2. Determine regional prevalence of CRE in California among general acute care hospitals in 2012
   - Assist local public health and healthcare facilities to better utilize the CDC CRE toolkit

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Methods

- Developed in conjunction with CDC
- All 387 eligible California acute care hospitals including long-term acute care (LTAC) contacted
- 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
- 5 CDPH staff members and 1 volunteer conducted surveys from May 2013 – March 2014

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Methods - continued

Survey included:

- Assessment of CRE infection prevention measures, screening practices, laboratory protocols, and staff awareness
- 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. and *Escherichia coli* isolates
- Collection of 2012 antibiograms
  - Aggregated antimicrobial susceptibility data

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High Variability of CRE *Klebsiella* Prevalence Across California

Hospital Type	Hospitals	Non Susceptible Isolates	Total Isolates	Pooled Mean Prevalence	Percentile Distribution				
					10th	25th	50th	75th	90th
General Acute Care	297	2,264	72,387	3.1%	0%	0%	0%	3%	8%
Long Term Acute Care	22	1,152	2,220	51.9%	2%	25%	41%	66%	76%

Important to note: Even though more than half of all hospitals reported zero resistant isolates in 2012, CRE prevalence varied widely ***within regions*** and across CA

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Results from California's Few CRE Prevalence Regions

	Number of Hospitals	Non-susceptible Isolates	Total Isolates	Adjusted Prevalence Rate* (95% CI)
Regions				
Northern California	29	13	4,244	4.18 (1.8-7.6)
Bay Area	49	41	11,596	5.20 (3.4-7.3)
Central Coast	16	13	2,015	9.72 (4.8-16.4)
Total	94	67	17,855	

* All rates are per 1000 isolates tested and adjusted for patient days; LTAC hospitals are excluded; confidence intervals for directly standardized rates calculated using the gamma distribution (Fay and Feuer, 1997)

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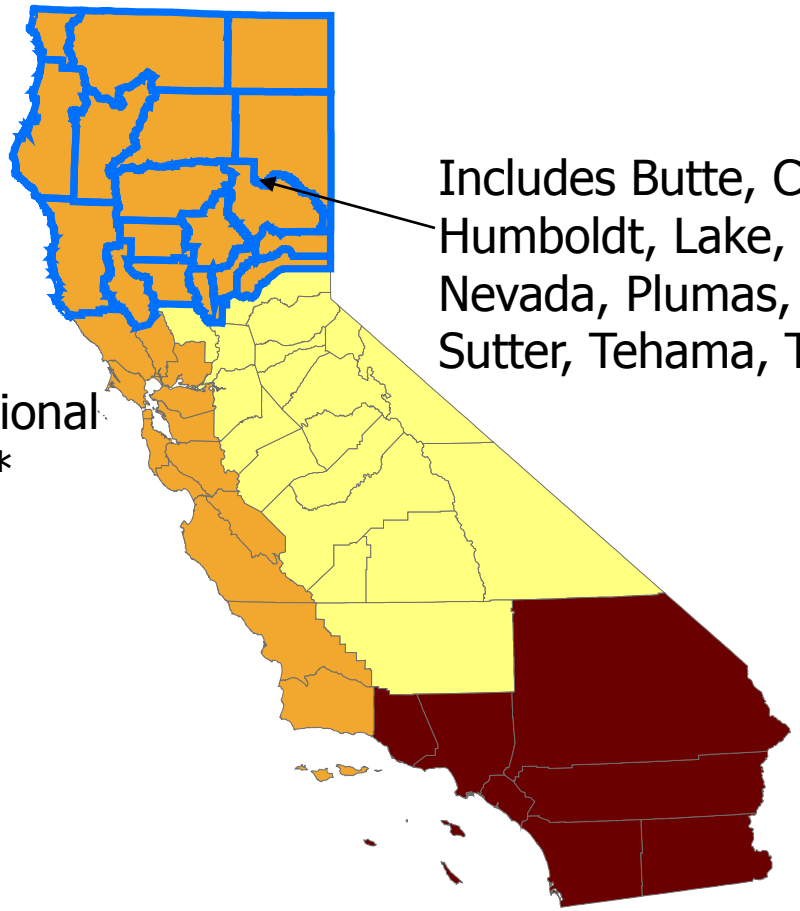
Northern California

Regional Prevalence of CRE *Klebsiella* Species per 1000 Isolates (95% Confidence Interval)

4.2 (1.7-7.6)



Includes Butte, Colusa, Del Norte, Glenn, Humboldt, Lake, Lassen, Mendocino, Modoc, Nevada, Plumas, Shasta, Sierra, Siskiyou, Sutter, Tehama, Trinity, and Yuba

Key to California Regional CRE *Klebsiella* Rates*

- 0.00-2.99
- 3.00-24.99
- 26.00-65.00

*Rates are per 1000 isolates and adjusted for patient days

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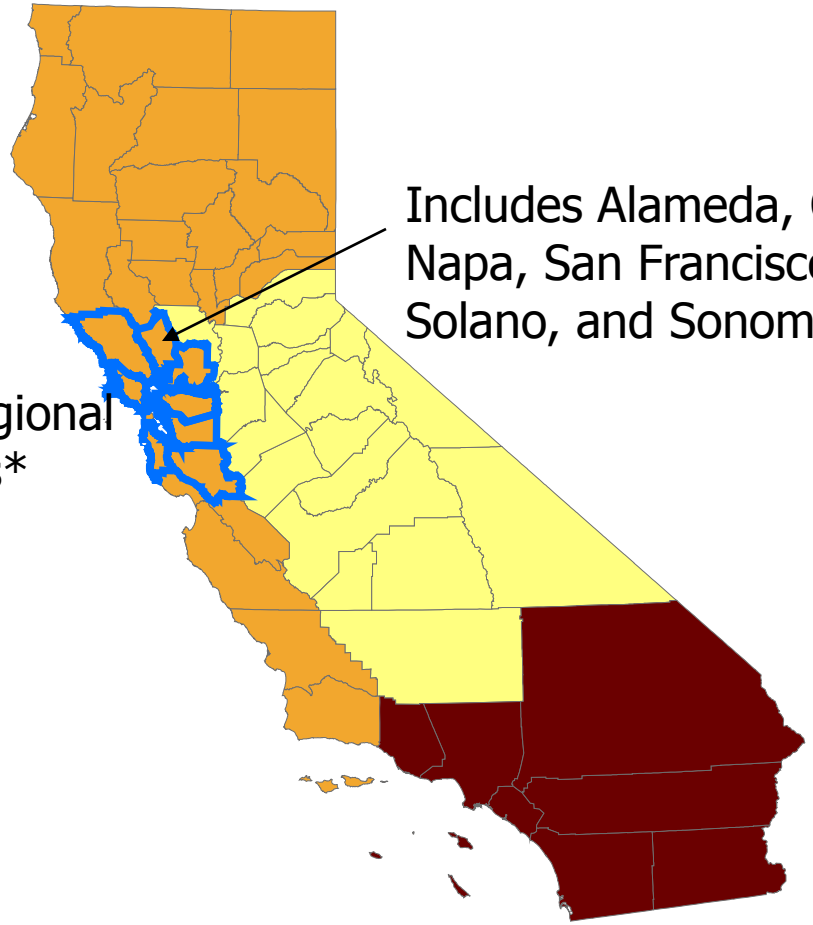
Bay Area

Regional Prevalence of CRE *Klebsiella* Species per 1000 Isolates (95% Confidence Interval)

5.2 (3.4-7.3)



Includes Alameda, Contra Costa, Marin, Napa, San Francisco, San Mateo, Santa Clara, Solano, and Sonoma

Key to California Regional CRE *Klebsiella* Rates*

- 0.00-2.99
- 3.00-24.99
- 26.00-65.00

*Rates are per 1000 isolates and adjusted for patient days

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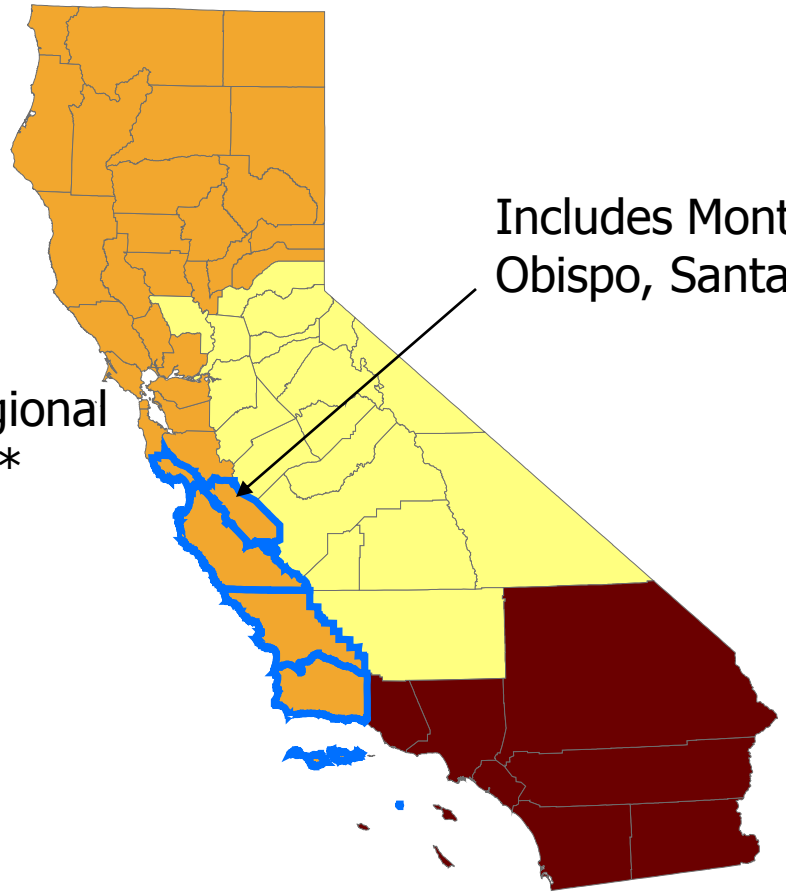
Central Coast Region

Regional Prevalence of CRE *Klebsiella* Species per 1000 Isolates (95% Confidence Interval)

9.7 (4.8-16.4)



Includes Monterey, San Benito, San Luis Obispo, Santa Barbara, and Santa Cruz

Key to California Regional CRE *Klebsiella* Rates*

- 0.00-2.99
- 3.00-24.99
- 26.00-65.00

*Rates are per 1000 isolates and adjusted for patient days

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Preventing CRE Transmission

CDC CRE Guidance for **Healthcare Facilities** When *First* CRE Patient Identified

Step-by-step process to follow when new CRE-colonized or CRE-infected patient is identified

1. Notification

- Notify appropriate personnel, including both clinical and infection prevention staff
- Notify public health if indicated

2. On the Unit/Ward

- Place patient in Contact Precautions in single room
- Reinforce hand hygiene and use of Contact Precautions on affected ward /unit
- Educate healthcare personnel staff about preventing CRE transmission

3. Screening

- Test epidemiologically linked patients (i.e. roommates) using stool or peri-rectal cultures
- Consider point prevalence survey of affected unit
- Consider pre-emptive precautions for epi-linked patients while awaiting test results

4. Evidence of Transmission

- If screening cultures identify additional CRE colonized or infected patients, consider additional surveillance cultures of contacts or point prevalence surveys
- Implement cohorting CRE patients and dedicated staffing

5. Patient Transfer

- Confirm that Contact Precautions are continued on new unit
- Ensure CRE status shared if patient transferred to another facility

CDC CRE Guidance for **State/Local Public Health Departments**

Regions With No CRE Identified **Emphasis on regional surveillance and education.**	
I. **Perform Regional Surveillance and Provide Feedback**	A. Consider making CRE reportable - OR - Survey healthcare facilities by phone or email
	B. If **NO** CRE cases are identified in region: - Feedback results to healthcare facility IPs and lab directors - Promote facility implementation of CRE prevention strategies If CRE cases **ARE** identified in region: - Implement appropriate regional strategy depending if CRE "few" or "common"
	C. Repeat survey at least quarterly if CRE in neighboring jurisdictions. Otherwise, repeat at least every 6 months.
II. **Educate ALL Healthcare Facilities**	- Explain importance of CRE and provide updates on national and/or neighboring regional prevalence and epidemiology - Review recommended surveillance and prevention measures - Increase vigilance for CRE detection

Regions With FEW CRE Identified

Regions where cases remain uncommon. Emphasis on preventing further transmission and widespread emergence. Target select facilities.

I. **Perform Regional Surveillance and Provide Feedback**	A. CRE confirmed by survey or reports
	B. Feedback results to healthcare facility IPs, lab directors, and facility administrators by email or letter - Consider publication of results by facility name, area, type - Engage state hospital association, QIO, and other prevention partners to facilitate communication with facility leaders - Promote facility implementation of CRE prevention strategies
	C. Repeat CRE surveillance and feedback quarterly
II. **Educate ALL Healthcare Facilities**	- Explain importance of CRE and provide updates on national and/or neighboring regional prevalence and epidemiology - Review recommended surveillance and prevention measures - Increase vigilance for CRE detection
III. **Inter-facility Com-munication**	Ensure facilities complete an Inter-facility Transfer Form when transferring CRE patients

Regions With FEW CRE Identified – *continued*

IV. **Infection Prevention**	For facilities **WITH** CRE: 1. Engage facility administrators to prioritize CRE prevention 2. Review practices to ensure core CRE prevention measures are in place 3. Provide in-service training 4. Ensure CRE screening is being performed 5. If CRE rates do not decrease, consult CDC for more guidance
	For facilities **WITHOUT** known CRE but located in region where CRE are present: 1. Engage facility administrators, ensure control plan, and reinforce CRE Core prevention strategies 2. Guide implementation of CRE screening and preemptive Contact Precautions for patients admitted from - Facilities with ongoing CRE transmission - LTAC hospitals or with CRE risk factor

Effective CRE Prevention Will Require Local Partnerships

- Regional prevention collaboratives should include general acute care and LTAC hospitals, SNF/LTC facilities, and public health

"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."

Schwaber MJ Carmeli Y ICHE 2008; 300: 2911-2913

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So How are California Hospitals Doing with CRE Prevention Currently?

Survey Results: CRE Awareness and Surveys

Awareness and Surveys	Adherent / Total Responses	
Read CDC CRE Health Alert Network (HAN)	281 / 315	89%
Uses inter-facility transfer form	236 / 321	74%
Conducted point prevalence survey	12 / 326	4%
Found any CRE	2 / 11	18%
Used CDC protocol	7 / 11	64%

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Survey Results: CRE Screening Practices

Screening Practices	Adherent/ Total Responses	
Ask about recent travel history	128 / 324	39%
Ask about healthcare exposures in past 6 months	100 / 323	31%
Epidemiologically linked to a positive CRE patient	117 / 303	39%
Screen for CRE upon Admission	23 / 325	7%
All patients	1 / 325	<1%
Patients hospitalized overnight outside US <6 mo	4 / 325	1%
Patients admitted from LTAC hospital	5 / 325	2%
Patients admitted from SNF/LTC facility	5 / 325	2%
Patient with history of MDRO	1 / 325	<1%
Patient admitted from ICU	3 / 325	1%

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Survey Results: Laboratory

Laboratory Notification and Record Review	Adherent / Total Responses	
Timely Notification	298 / 326	91%
Preliminary Alerts	203 / 298	68%
Estimated Time till Notification		
<24 hours	224 / 292	77%
24-48 hours	53 / 292	18%
>48 hours	8 / 292	3%
Retain Isolates	156 / 322	48%
Perform Micro Record Review	122 / 326	37%
Found any CRE	31 / 122	25%

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Lab Issue - Breakpoints for Identifying Resistance

- Ensure your laboratory is using updated breakpoints for susceptibility testing

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 Issue – Identifying Carbapenemases

- The Modified Hodge Test (MHT) has good sensitivity for some carbapenemases, such as KPC-producing *Klebsiella*, but low sensitivity for others (false negatives), and low specificity for all (false positives)
- PCR is the preferred method for identifying carbapenemases, but may not be widely available without the use of reference lab

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Courtesy of Alex Kallen, CDC

Lab Capacity

Save all CRE lab isolates!

- Either local public health or CDPH may provide additional reference testing
- CDPH is developing a roadmap and increasing personnel to enhance lab capacity at the state level

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CRE Outbreaks

- Suspected CRE outbreaks or clusters (i.e. an unusual occurrence of CRE) must be reported to local public health
- CRE outbreaks have been serious and difficult to control
  - Outbreak of CRE *Klebsiella* at National Institutes of Health hospital in 2011 resulted in person-to-person transmission causing 18 infections and 11 deaths
  - Outbreak of CRE *E. coli* in Chicago area in 2013 associated with a single endoscope, resulted in 8 infections and 44 colonizations

CA Regional Prevalence of CRE *Klebsiella*

	Number of Hospitals	No. Hosp with ≥1 CRE Isolate	Nonsuscep-tible Isolates	Total Isolates	Adjusted Prevalence Rate* (95% CI)
Regions					
Sierras	5	**0**	0	467	0.00 (0.0-0.1)
Sacramento Metro	13	**2**	2	3,643	0.92 (0.1-2.6)
San Joaquin Valley	36	**11**	27	9,102	2.59 (1.6-3.8)
Northern California	29	**6**	13	4,244	4.18 (1.8-7.6)
Bay Area	49	**18**	41	11,596	5.20 (3.4-7.3)
Central Coast	16	**4**	13	2,015	9.72 (4.8-16.4)
San Diego Area	18	**16**	230	8,122	26.36 (22.3-30.7)
Inland Empire	31	**24**	270	7,472	35.20 (30.5-40.2)
Los Angeles-Orange-Ventura	100	**75**	1,668	25,828	64.65 (57.8-71.8)
Total	297	**156**	2,264	72,387	34.60 (31.8-37.6)

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*All rates are per 1000 isolates tested and adjusted for patient days; LTAC hospitals are excluded; confidence intervals for directly standardized rates calculated using the gamma distribution (Fay and Feuer, 1997)

In Summary: California CRE Prevalence and Prevention

1. CRE prevalence is significantly higher in the southern regions of California
2. LTAC hospitals have significantly higher pooled prevalence than other general acute care hospitals
3. CRE awareness is high among California IPs, however adherence to CDC prevention guidelines varies widely
4. Less than half of respondents are screening other patients when a CRE case is identified
5. Regional efforts to contain CRE will require collaboration between public health and healthcare facilities

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A heartfelt thanks to all of California hospital personnel who participated in the survey and continue the fight against CRE

For more information, please contact
Sam Horwich-Scholefield at sam.horwich-scholefield@cdph.ca.gov

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