Carbapenem-Resistant Enterobacteriaceae (CRE) in California

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Sam Horwich-Scholefield, MPH
CDC/CSTE Applied Epidemiology Fellow
Healthcare-Associated Infections Program
Center for Health Care Quality

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California Department of PublicHealth

Presentation Objectives

- Describe CRE as an urgent public health problem
- Review statewide CRE 2012 Prevalence Survey
  - Great variation in regional prevalence indicates need for different approaches to control
  - Majority of hospitals not performing screening cultures to identify CRE colonized patients
- Review CDC Toolkit CRE transmission prevention strategies and describe CRE control in different regions:
  - Zero-Rare, Few, and Common CRE

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Note: No regions in 2012 met "Common" definition

Discussion Objectives

- Discuss State and Local Public Health roles for a coordinated regional approach to control CRE
  - Surveillance
  - Outbreak/cluster investigation
  - Facilitating inter-hospital communication

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Enterobacteriaceae

- Normal human gut flora
  - >70 species, including *K. pneumoniae* and *E. coli*
  - Also commonly present in respiratory tract and urine in patients and residents in healthcare facilities
- Cause a wide range of community and healthcare-associated infections
  - UTI, wound infections, pneumonia, bacteremia

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Carbapenem-resistant *Enterobacteriaceae* (CRE)

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

- Genetic mechanisms confer resistance to other antimicrobials, leaving limited treatment options
  - Invasive infections result in 40-50% mortality
- Highly transmissible between patients

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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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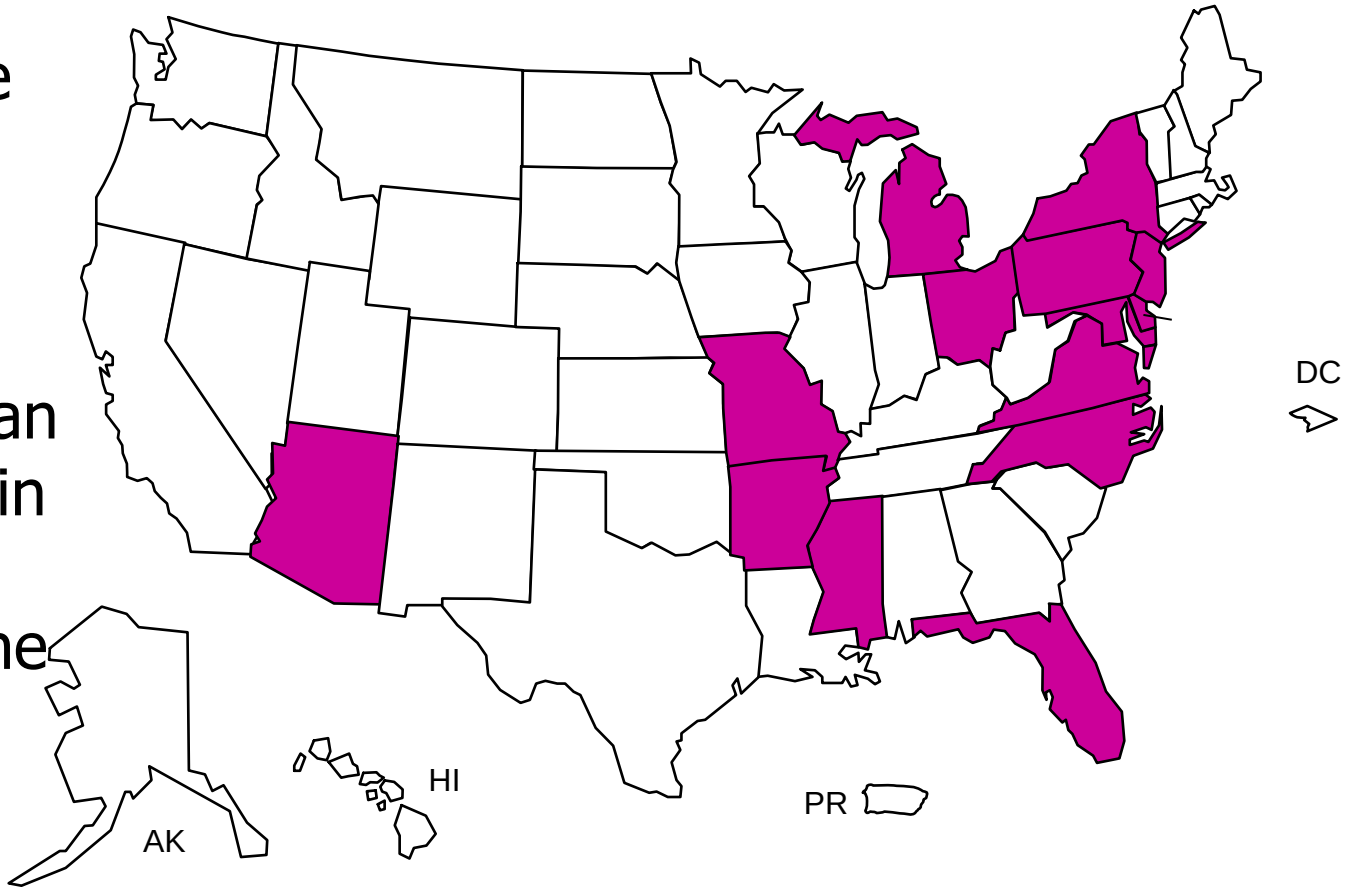
Carbapenemases

- Enzyme that confers resistance to all β-lactam antibiotics
- Resides on transferable plasmids and hydrolyzes all penicillins, cephalosporins and carbapenems, limiting options for treatment
  - Colistin/Polymyxin used for therapy, problems with nephrotoxicity
  - Pan-resistant CRE *K. pneumoniae* have occurred
- KPC is the most common type of CRE, though NDM-1, VIM, and IMP have also been identified in California

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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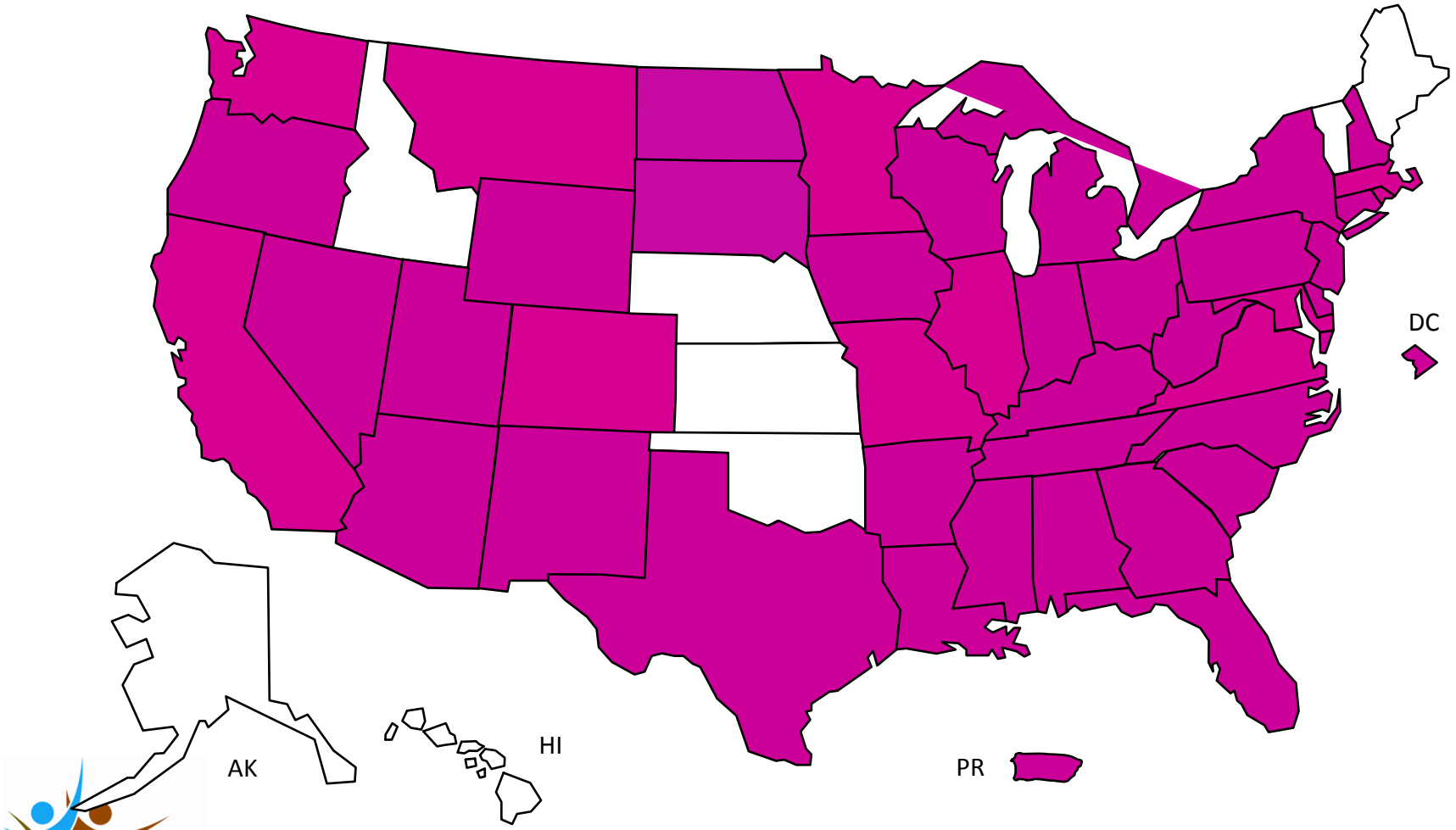
KPC-Producing CRE in US, 2013



Courtesy of Alex Kallen, CDC

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CRE Risk Factor: Care in Long Term Acute Care (LTAC) Hospitals

- LTAC hospitals are certified as acute care hospitals that treat patients:
  - Expected to stay ≥ 25 days
  - Have one or more serious conditions
  - Expected to improve with care and time
- Many LTAC patients transferred directly from ICUs
- LTAC hospital services typically include
  - Comprehensive rehabilitation
  - Respiratory therapy
  - Head trauma treatment
  - Pain management

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CRE Risk Factor: Care in LTAC Hospitals continued

- A Chicago survey found patients in LTAC hospitals had a significantly greater risk of being colonized or infected with CRE than patients in short-stay acute care 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
- Los Angeles County found that the pooled mean incidence rate of CRE from LTAC hospitals was 6-fold higher than in non-LTAC hospitals

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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
Marquez P et al. Infect Control Hosp Epidemiol. 2013;34:144-50

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)
    - Flouroquinolones (OR: 7.2, p=.04)

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

CRE Prevalence in US Hospitals

- CDC reports that 4% of acute care hospitals nationwide have identified CRE in catheter-associated UTIs or central line associated BSIs

- Fivefold increase in CRE incidence in Southeastern U.S. community hospitals during past 5 years

"Rates of CRE, while still infrequent, are increasing dramatically in community hospitals…these organisms are increasingly important and relevant in all areas of healthcare, including small community hospitals."

Thaden et al. Infect Control Hosp Epidemiol 2014; 35:978-83

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CRE Beyond Hospital Settings

- Genes for carbapenemases can be transferred between bacterial species, including *E. coli*, a common cause of community-acquired infections

- KPC has been documented in the non-hospital settings in Israel and NDM-1 has been found in both the community and the environment in parts of Indian subcontinent

Nordmann P, et al., Lancet Infect Dis. 2009 Apr; 9(4):228-36
Poirel L, et al., Lancet Infect Dis. 2010 Dec; 10(12):832
Walsh TR, et al., Lancet Infect Dis. 2011 May; 11(5):355-62.

California Statewide CRE Prevalence Survey

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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 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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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 not included; confidence intervals for directly standardized rates calculated using the gamma distribution (Fay and Feuer, 1997)

Sierras

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

0 (0-0.1)

Includes Alpine, Amador, Calaveras, Inyo, Mariposa, Mono, and Tuolumne counties

Key to California Regional CRE *Klebsiella* Rates*

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

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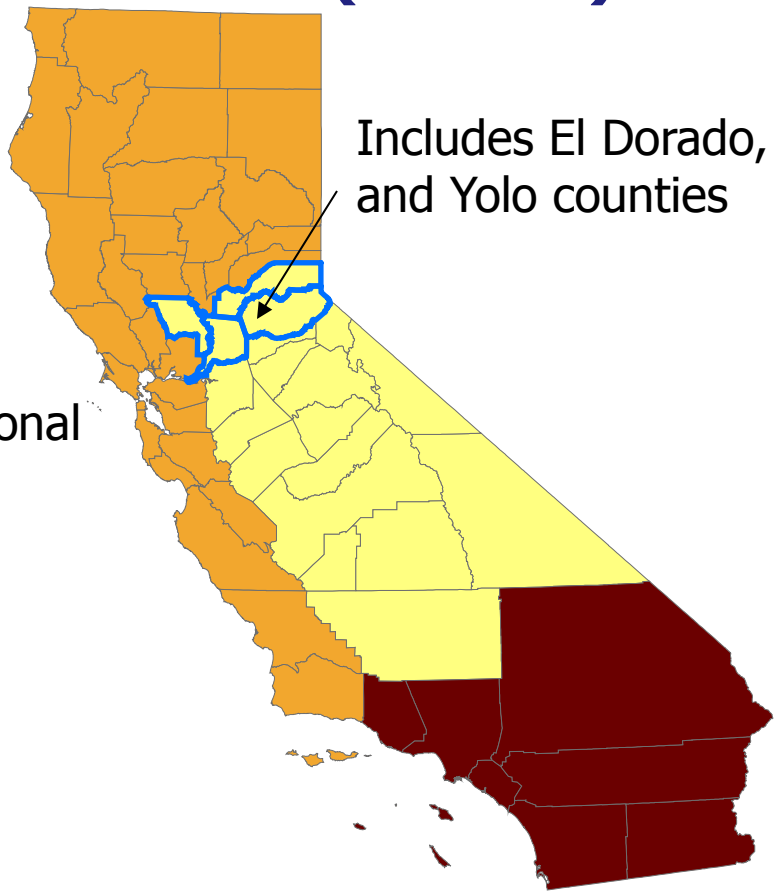
*Rates are per 1000 isolates and adjusted for patient days

Sacramento Metro

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

0.90 (0.1-2.6)



Includes El Dorado, Placer, Sacramento, and Yolo counties

Key to California Regional CRE *Klebsiella* Rates*

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

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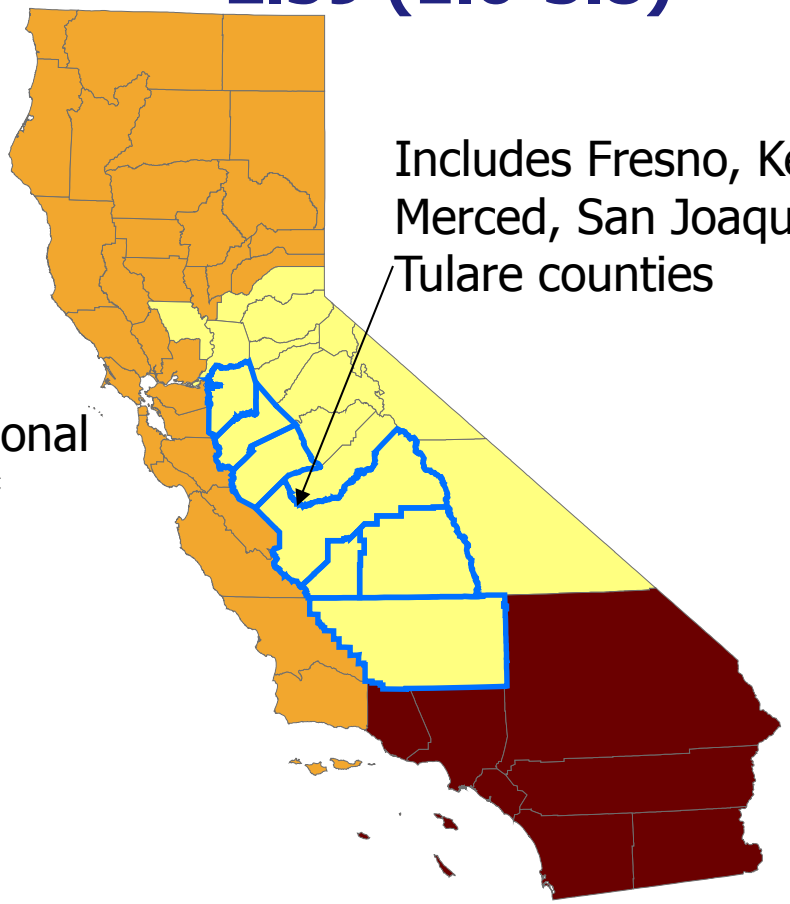
*Rates are per 1000 isolates and adjusted for patient days

San Joaquin Valley

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

2.59 (1.6-3.8)



Includes Fresno, Kern, Kings, Madera, Merced, San Joaquin, Stanislaus, and Tulare counties

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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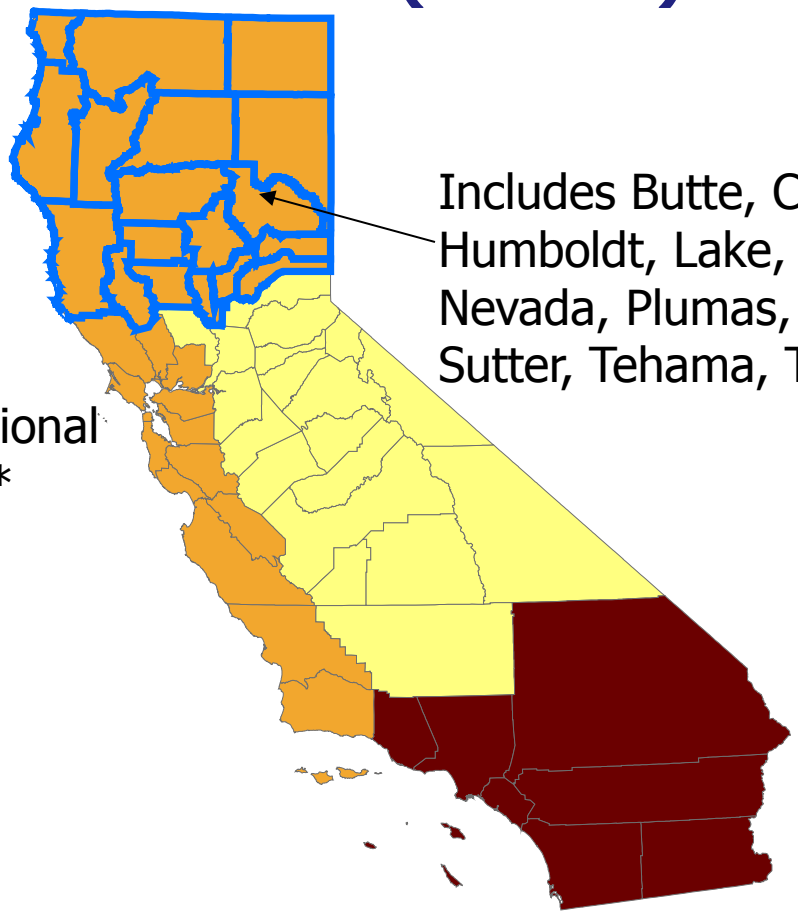
Northern California

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

4.18 (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

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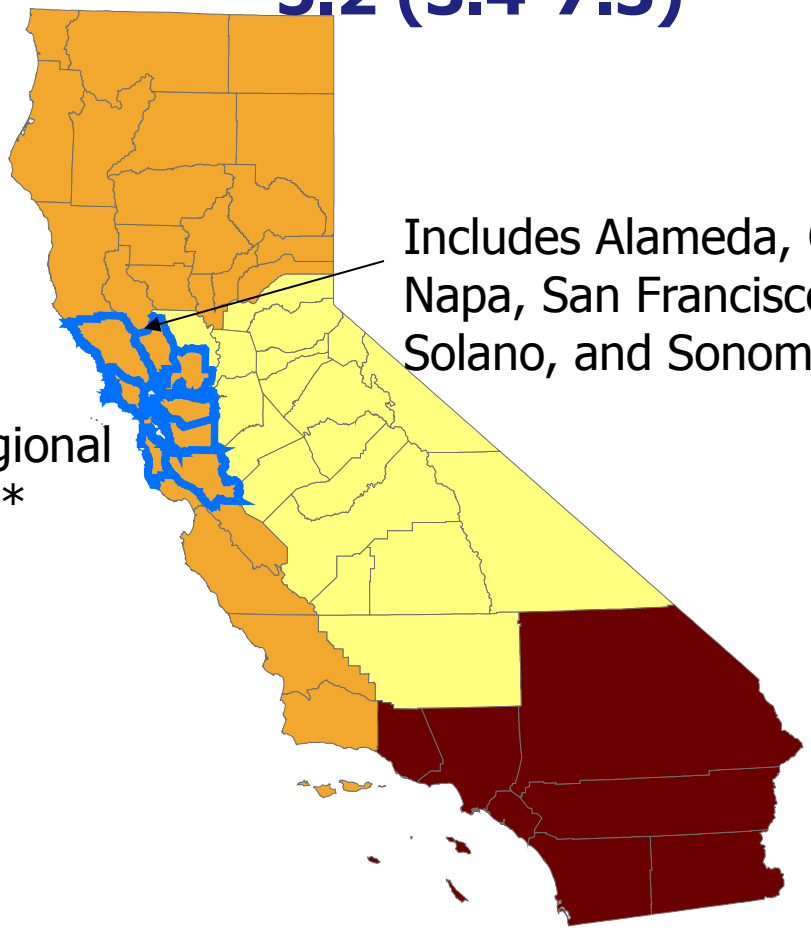
*Rates are per 1000 isolates and adjusted for patient days

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

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*Rates are per 1000 isolates and adjusted for patient days

Central Coast Region

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

9.72 (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

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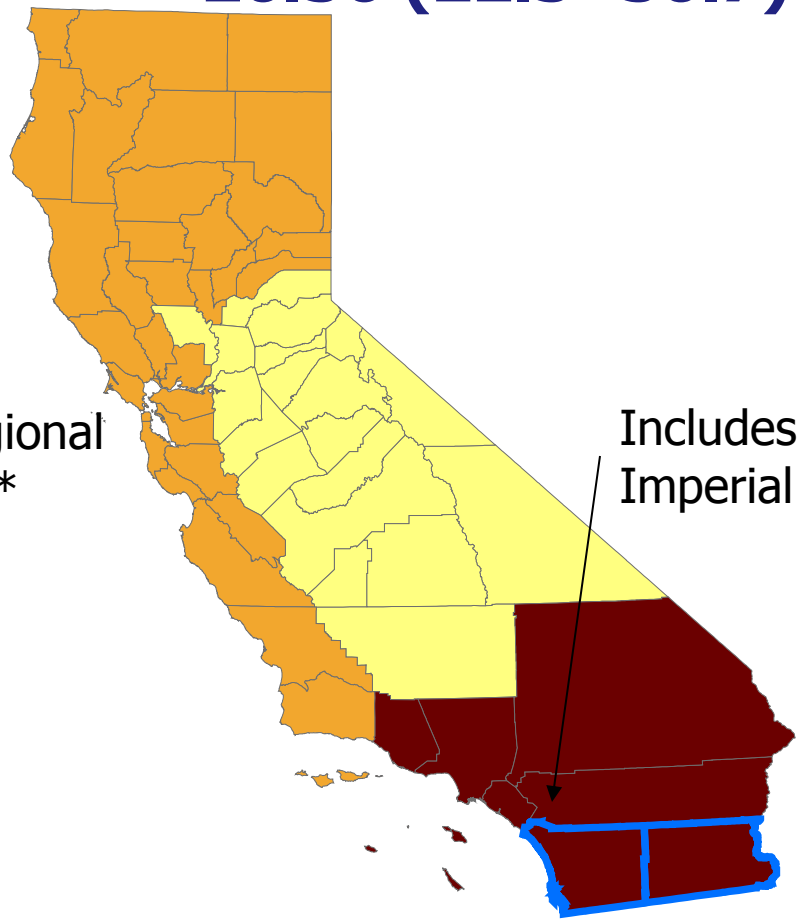
*Rates are per 1000 isolates and adjusted for patient days

San Diego Area

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

26.36 (22.3- 30.7)



Key to California Regional CRE *Klebsiella* Rates*

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

Includes San Diego and Imperial

*Rates are per 1000 isolates and adjusted for patient days

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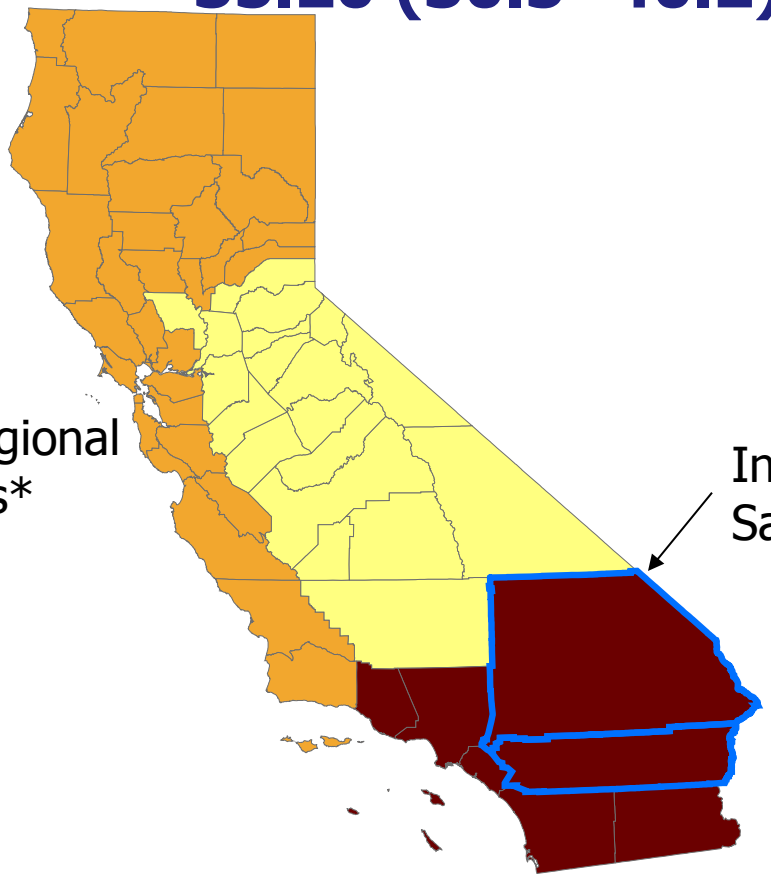
Inland Empire

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

35.20 (30.5- 40.2)



Key to California Regional CRE *Klebsiella* Rates*

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

Includes Riverside and San Bernardino

*Rates are per 1000 isolates and adjusted for patient days

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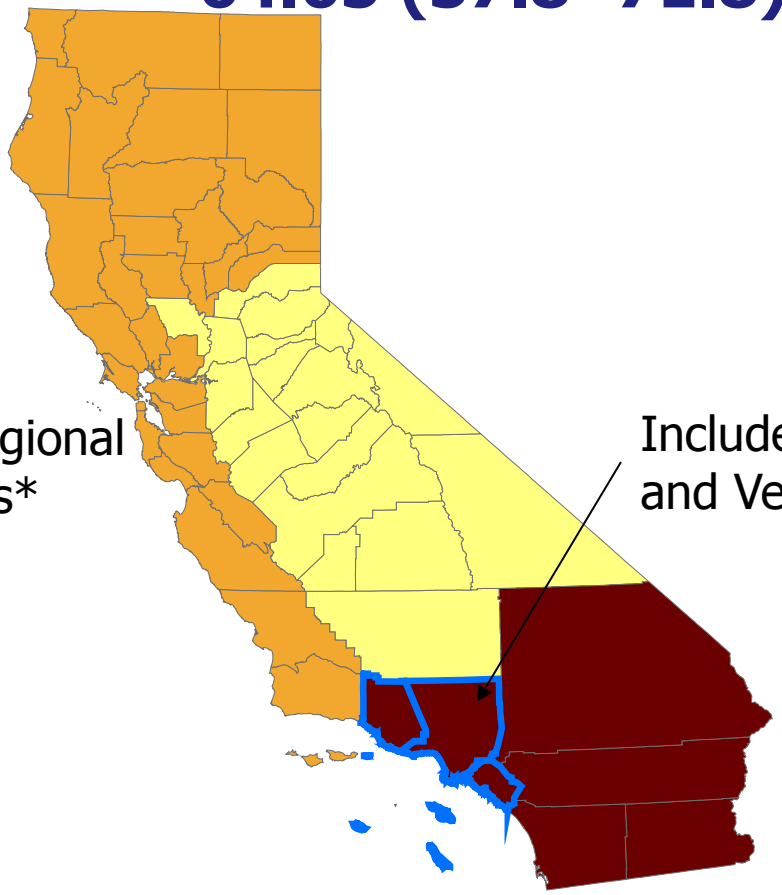
Los Angeles Area

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

64.65 (57.8- 71.8)



Key to California Regional CRE *Klebsiella* Rates*

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

Includes Los Angeles, Orange, and Ventura

*Rates are per 1000 isolates and adjusted for patient days

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How are California Hospitals Doing with CRE Prevention Currently?

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Survey Results: Awareness of CRE in Facility

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 any group of patients for CRE upon Admission	23 / 325	7%

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%

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Survey Results: Laboratory Notification Protocol

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%

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Preventing CRE Transmission

Primary Prevention Requires 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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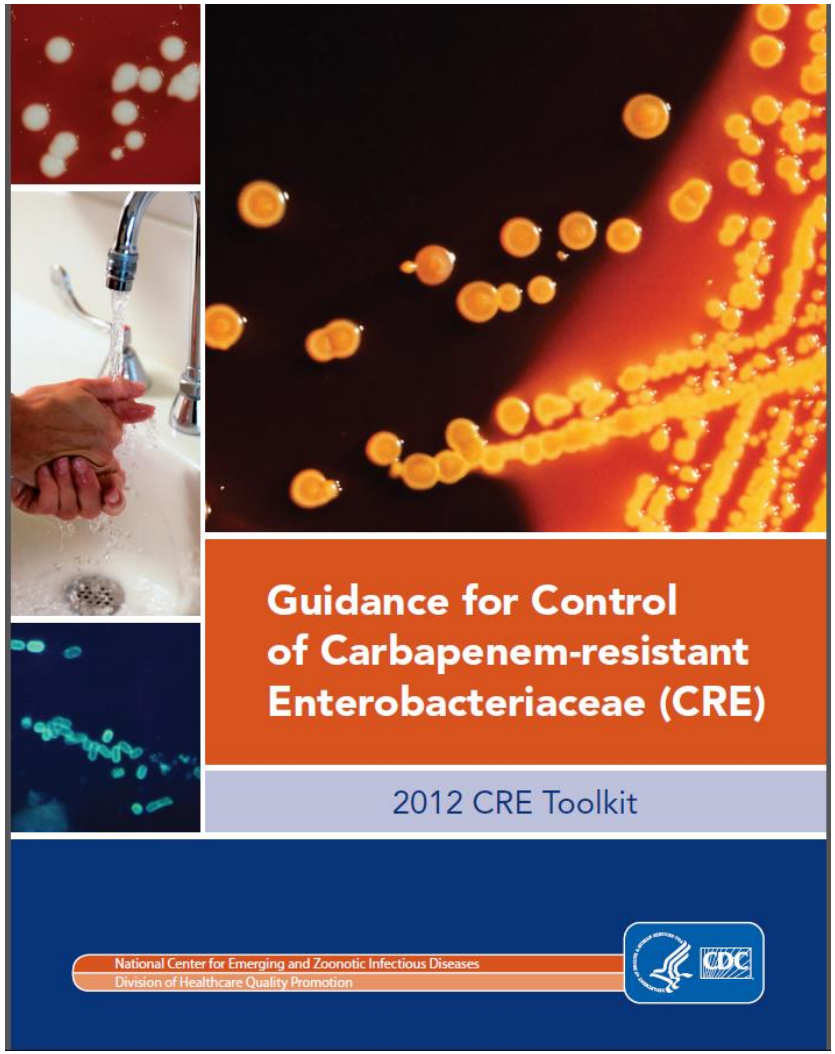
Preventing CRE Transmission

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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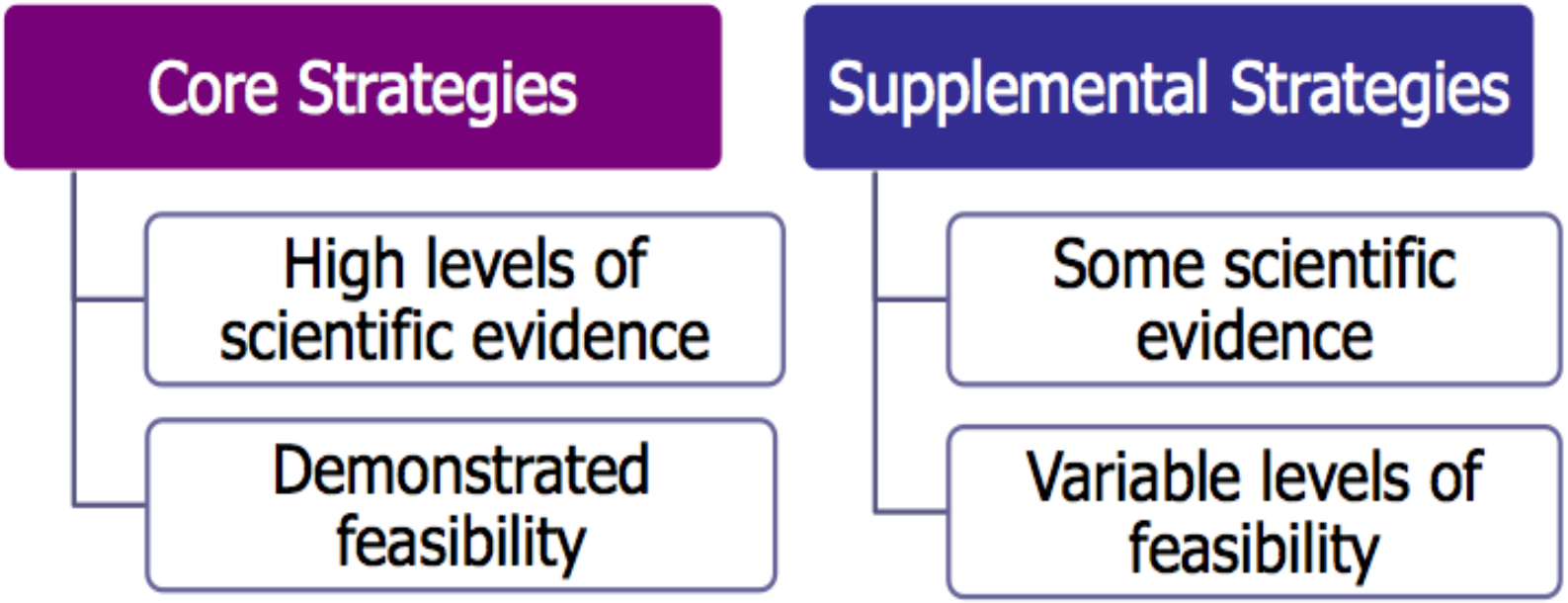
CDC Prevention Strategies



- Should become standard practice

- 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

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
- No recommendation made by CDC for discontinuation of Contact Precautions

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

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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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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CRE Screening

CORE

- Culture 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 http://www.cdc.gov/hai/pdfs/labsettings/klebsiella_or_ecoli.pdf

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

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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Definitions of CRE Prevalence

- No CRE
  - No identified CRE colonized or infected patients
- Few CRE
  - Majority of healthcare facilities do not regularly have patients with CRE admitted
  - Several facilities may have identified CRE colonized or infected patients on an infrequent basis (e.g. monthly basis or greater)
  - Some facilities may have several CRE colonized or infected patients but are surrounded by facilities with only a few or none
- Common CRE
  - Majority of healthcare facilities have identified cases, and these facilities regularly have CRE colonized or infected patients admitted (e.g. CRE detected at least weekly)

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2012 CRE Prevalence Type by County

- No to Rare CRE

Alpine	Inyo	Merced	Stanislaus
Amador	Kern	Mono	Tuolumne
Calaveras	Kings	Placer	Tulare
El Dorado	Madera	Sacramento	Yolo
Fresno	Mariposa	San Joaquin	

- Few CRE

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

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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

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

Regions Where CRE are COMMON **Emphasis on implementation of core and supplemental prevention measures across all acute care and LTC facilities**	
I. Dedicated Personnel to Engage HC Facilities	• Assign specific personnel to this task • Form advisory panel if additional technical support is needed • Engage all facility administrators and IP personnel early in process • Hospital Association, QIOs, and other relevant partners
II. **Perform Regional Surveillance and Provide Feedback**	A. Perform steps for CRE surveillance and feedback of results to IP and/or lab directors and facility administrators
	B. Determine if certain CRE events should be made reportable
	C. Repeat survey at least quarterly

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Regions With COMMON CRE Identified - *continued*

IV. **Infection Prevention**	A. Reinforce core prevention measures in all facilities • Work closely with IPs to review practices • Provide in-service training

	B. Consider supplemental measures in all facilities
	• Active surveillance testing and preemptive CP
	  ○ Patients admitted from facilities with ongoing CRE transmission or high CRE prevalence
	  ○ Patients admitted from LTC or with risk factors (open wounds, indwelling devices, high antimicrobial use)
	  ○ Patients being admitted to high-risk units (ICUs)
	• Chlorhexidine bathing on high-risk patients

	C. Assess Compliance to Prevention Measures (monthly) • Share performance measures with facility • Provide in-service training, as needed

CRE Outbreaks

- Suspected CRE outbreaks or clusters (i.e. an unusual occurrence of CRE) must be reported to local public health, and CDPH-HAI Program can support CRE investigations

- CRE outbreaks have been serious and difficult to control
  - Outbreak of CRE *K. pneumoniae* 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

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The Role of Public Health in Outbreaks and Clusters

- CDPH is developing a roadmap and increasing laboratory capacity to support outbreak investigations and carbapenemase detection

- Coordinate Response and Facilitate Communication
  - Outbreak of 8 cases of NDM-1 producing *K. pneumoniae* in Colorado was contained using aggressive surveillance cultures, targeted infection control measures, and enhanced communication between facilities coordinated by public health

CDPH California Department of PublicHealth

Epson, E et al. Infect Control Hosp Epidemiol. 2014;35(4):390-7

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

CDPH California Department of PublicHealth

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**

CDPH California Department of PublicHealth

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

CDPH California Department of PublicHealth