California Antimicrobial Resistance Laboratory Assessment: Results and Next Steps

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Webinar

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Healthcare Associated Infections Program
Center for Healthcare Quality
California Department of Public Health

Objectives

1. Describe the CDPH Healthcare-Associated Infections (HAI) Program activities to address antimicrobial resistance (AR)
2. Present the results of the California AR Lab Assessment
3. Discuss opportunities for enhancing the role of the microbiology laboratory as part of AR prevention and response activities
4. Introduce the proposed California AR Lab Network
   - Goals and Objectives
   - Structure
   - Data Sharing

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CDPH HAI Program
Center for Health Care Quality

Created by mandate to oversee the **prevention, surveillance, and reporting** of healthcare-associated infections, and to:

1. Produce annual HAI public reports to support informed choices for healthcare consumers and prompt clinicians to take actions to prevent infections.
2. Provide consultation and assistance to local public health for infection prevention and outbreaks that occur in healthcare facilities.
3. Actively engage in HAI prevention by performing site visits in hospitals, skilled nursing facilities and other healthcare settings, convening regional collaboratives, and providing education.

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Core Actions to Address Antimicrobial Resistance (AR)

- **Improve antimicrobial prescribing** through antimicrobial stewardship
- **Prevent infections and transmission** of antimicrobial resistant pathogens
- **Track antimicrobial use and resistance** trends

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California Antimicrobial Resistance Laboratory Assessment

- Public Health-led initiative to characterize and map capacity of clinical and public health laboratories to identify and respond to AR pathogens
  - Identification of carbapenem resistance and determination of susceptibility to off-panel and new antibiotics
  - Cumulative antibiogram preparation and selective reporting practices
  - Carbapenemase testing and CRE surveillance cultures

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California AR Laboratory Assessment – Methods

- Survey developed by CDPH HAI Program with University of California Los Angeles collaborators
- Separate versions for clinical and public health laboratories
- Administered between November 2015-May 2016 to laboratory directors or managers via:
  - SurveyMonkey (online)
  - Print (pdf)
  - Phone Interview

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AR Laboratory Assessment Respondents

Clinical Lab Respondent Characteristics

136 Clinical Labs representing 263 hospitals

Hospital Characteristics	Respondents (n= 263) (%)	Non-Respondents (n=128) (%)
Median Hospital Beds (IQR)	178 (90-308)	110 (46-208)
Academic	29 (11)	7 (5)
Long Term Acute Care	19 (7)	5 (4)
Region		
Northern	82 (31)	50 (39)
Central	17 (6)	16 (13)
Southern	164 (62)	61 (48)

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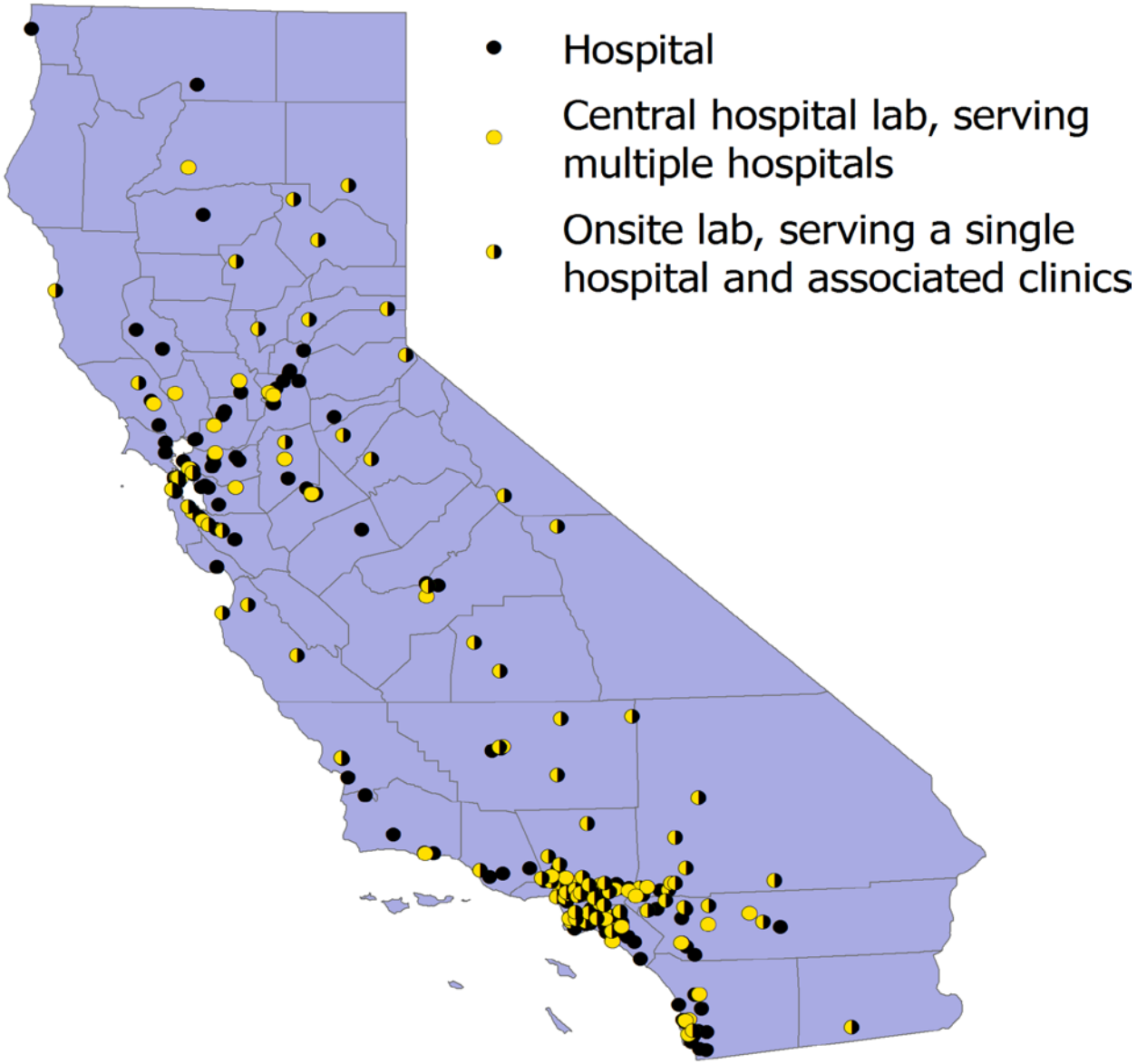
Clinical Lab Respondent Characteristics

Laboratory Characteristic (n=136)	No.(%)
Respondent	
Clinical Lab Scientist	69(51)
Microbiology Director	65(48)
Infection Preventionist	2(1)
Laboratory Type	
Central lab, serving multiple hospitals	38(28)
Onsite lab, serving single hospital	93(68)
Missing	5(4)
Specimens in 12 month period*	28,859 (7,250-75,000)

*Median (Interquartile Range)

Clinical Lab Respondents and Associated Hospitals



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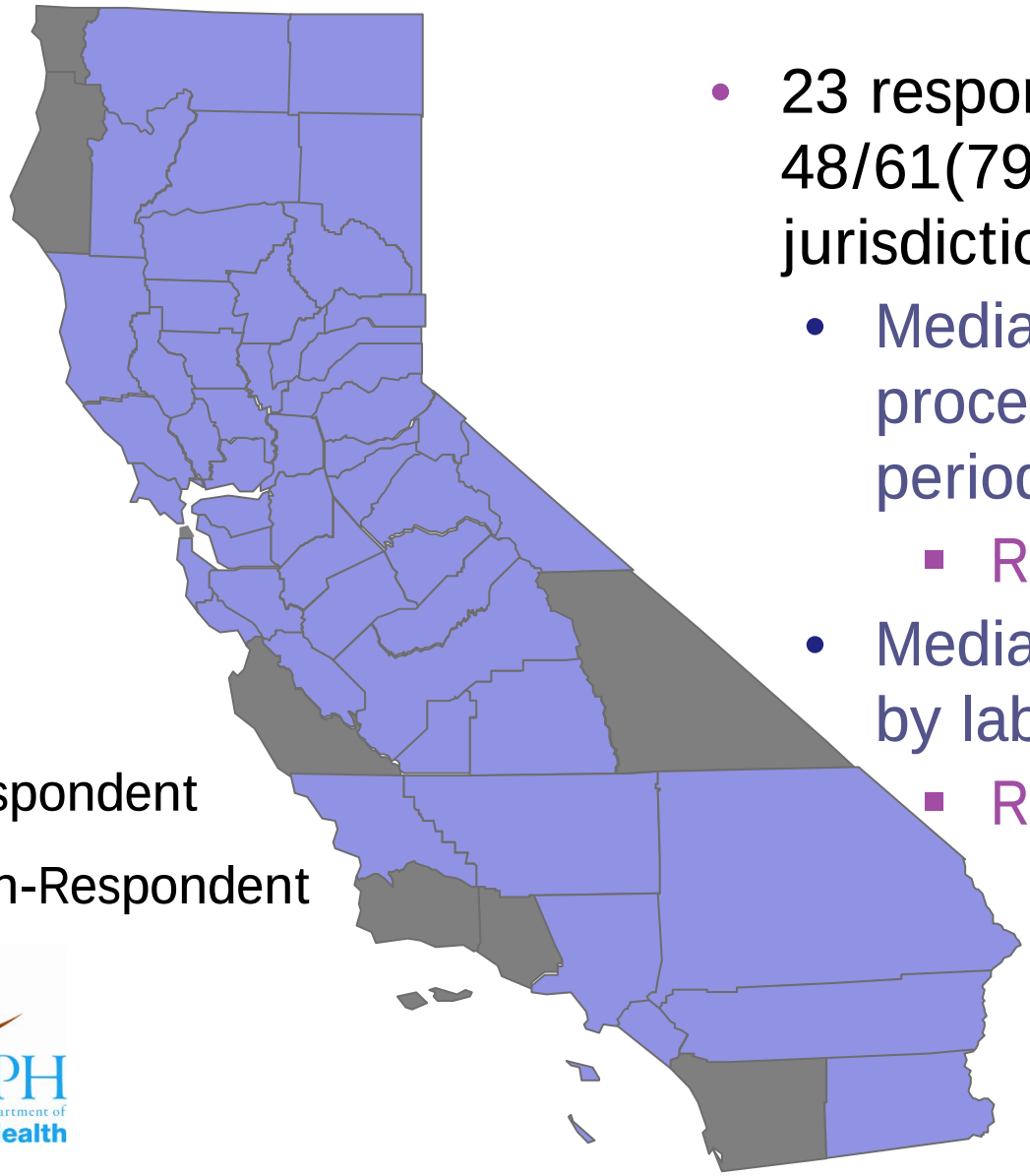
Public Health Lab Respondents



Respondent

Non-Respondent

- 23 respondents representing 48/61(79%) local public health jurisdictions
  - Median 2,400 specimens processed in 12-month period
    - Range 2-35,000
  - Median 5 hospitals served by lab in 12-month period
    - Range 1-21

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Identification of carbapenem resistance and assessment of susceptibility to off-panel and new antibiotics

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Clinicians depend on accurate antimicrobial susceptibility test results to guide clinical decision making

- Infections with carbapenem resistant Enterobacteriaceae (CRE) are associated with poor outcomes
  - CRE patients had 4x odds of death than patients with carbapenem susceptible Enterobacteriacae[1]
  - 27% excess hospital mortality in patients with CRE bloodstream infection or pneumonia compared with CRE-colonized patients[2]
- Treatment options are limited; antimicrobial susceptibility testing (AST) is critical to identify appropriate therapy

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[1]Schwaber et al. Antimicrob Agents Chemotherapy 2008
[2]Hauck et al. Clin Microb Infect 2016

Updated Carbapenem Breakpoints for Enterobacteriaceae

- In 2010, Clinical and Laboratory Standards Institute (CLSI) updated carbapenem breakpoints for Enterobacteriaceae

	Updated Carbapenem Breakpoints			Previous Carbapenem Breakpoints		
	S	**I**	**R**	**S**	**I**	**R**
Doripenem	≤1	2	≥4	--	--	--
Ertapenem	≤0.5	1	≥2	≤2	4	≥8
Imipenem	≤1	2	≥4	≤4	8	≥16
Meropenem	≤1	2	≥4	≤4	8	≥16

- Labs that use revised breakpoints detect significantly more CRE

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Hombach et al. J Antimicrob Chemotherapy 2011

Results: CLSI Carbapenem Breakpoints Reported by Clinical Labs

Clinical Labs (n=136)	No. (%)
Enterobacteriaceae	
Current breakpoints	92 (68)
Pre 2010 breakpoints + test for carbapenemase	23 (17)
Pre 2010 breakpoints	14 (10)
Missing	7 (5)
***Pseudomonas* spp.**	
Current breakpoints	93 (68)
Pre 2011 breakpoints	33 (24)
Missing	10 (7)
***Acinetobacter* spp.**	
Current breakpoints	93 (68)
Pre 2011 breakpoints	31 (23)
Missing	12 (9)
Overall	**No. (%)**
Current breakpoints	84 (62)
Breakpoints not updated	43 (32)
Missing	9 (7)

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Results: Off-panel Antimicrobial Agents

	Onsite testing (%)	Offsite Reference Lab (%)	Do not obtain additional testing (%)	Missing (%)
Tobramycin	97 (71)	8 (6)	17 (13)	14 (10)
Amikacin	101 (74)	5 (4)	17 (13)	13 (10)
Tigecycline	88 (65)	22 (16)	17 (13)	9 (7)
Polymixins/ Colistin	65 (48)	44 (32)	22 (16)	5 (4)

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New Antimicrobial Agents for Treatment of Antibiotic Resistant Infections

- Ceftolozane-tazobactam
  - Ceftolozane is more active than ceftazidime against *P. aeruginosa*
  - Not active against KPC or Metallo-β-lactamases
- Ceftazidime-avibactam
  - Active against Enterobacteriacaeae and *P. aeruginosa*
  - Active against ESBLs, KPC and OXA-48
  - Not active against Metallo-β-lactamases or strains with both a KPC and AmpC
- No surrogate agent can predict activity, so specific AST is necessary prior to use of these agents

Humphries et al. Clin Infect Dis 2016

Results: AST for New Antimicrobial Agents

Clinical Labs	Ceftazidime -avibactam (%)	Ceftolozane -tazobactam (%)
Yes, plan to provide onsite testing	54 (40)	48 (35)
Yes, plan to send to reference lab	26 (19)	23 (17)
No plan to add testing for this agent	55 (40)	58 (43)
Missing	1 (1)	7 (5)

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Challenges with Implementation of Current AST Recommendations

- Laboratory adoption of updated CLSI breakpoints is challenged by several factors
  - Not all commercial AST systems have obtained clearance for updated carbapenem breakpoints
- Currently, few commercial AST devices are cleared to test new antibiotics with activity against CRE and other multidrug resistant organisms

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Humphries et al. Clin Infect Dis 2016

Clinical Microbiology Practices Related to Antimicrobial Stewardship

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The microbiology laboratory can play an important role in antimicrobial stewardship

IDSA FEATURES

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Implementing an Antibiotic Stewardship Program: Guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America

Tamar F. Barlam,[1] Sara E. Cosgrove,[2] Lilian M. Abbo,[3] Conan MacDougall,[4] Audrey N. Schuetz,[5] Edward J. Septimus,[6] Arjun Srinivasan,[7] Timothy H. Dellit,[8] Yngve T. Falck-Ytter,[9] Neil O. Fishman,[10] Cindy W. Hamilton,[11] Timothy C. Jenkins,[12] Pamela A. Lipsett,[13] Preeti N. Malani,[14] Larissa S. May,[15] Gregory J. Moran,[16] Melinda M. Neuhauser,[17] Jason G. Newland,[18] Christopher A. Ohl,[19] Matthew H. Samore,[20] Susan K. Seo,[21] and Kavita K. Trivedi[22]

"*We suggest development of* ***stratified antibiograms*** *over solely relying on nonstratified antibiograms to* ***assist ASPs in developing guidelines for empiric therapy***"

Institution-specific empiric therapy guidelines can be tailored to antimicrobial susceptibility patterns associated with particular patient populations or clinical syndromes

Results: Preparation of Stratified Antibiograms

Do you ever develop_____ antibiograms? (n=99)

	Yes (%)	No (%)	Unknown (%)
Population-specific	37 (37)	54 (54)	8 (8)
Source-specific	36 (36)	60 (61)	3 (3)

Population Specific Antibiograms (n=37)

	No. (%)
ICU vs Ward	15 (41)
Inpt vs Outpt	28 (76)

Source Specific Antibiograms (n=36)

	No. (%)
Urine	31 (86)
Non-Urine	22 (61)
Blood	13 (36)
Respiratory	6 (17)

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Selective/Cascade Reporting

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"*We suggest* ***selective and cascade reporting of antibiotics*** *over reporting of all tested antibiotics*"

Selective reporting can encourage prescribing of narrower or more appropriate antibiotic therapies

Results: Selective Reporting Practices

Response	No. (%)
Selective reporting for certain bug-drug combinations	91 (67)
Have the capability, but have not been asked to do so by clinicians or hospital	22 (16)
Laboratory information system challenges	7 (5)
Missing	16 (12)

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Results: Selective Reporting of Specific Bug-Drug Combinations

	If *E.coli/Klebsiella* ceftriaxone susceptible, then carbapenem results suppressed?	If *P. aeruginosa* cefepime+pip/tazo susceptible, then carbapenem results susceptible?	If *Acinetobacter* ceftazidime susceptible, then carbapenem results susceptible?
	No. (%)	No. (%)	No. (%)
Yes	46 (34)	35 (26)	33 (24)
No	66 (49)	76 (56)	76 (56)
No AST on antimicrobial	4 (3)	3 (2)	4 (3)
Missing	19 (14)	21 (15)	20 (15)

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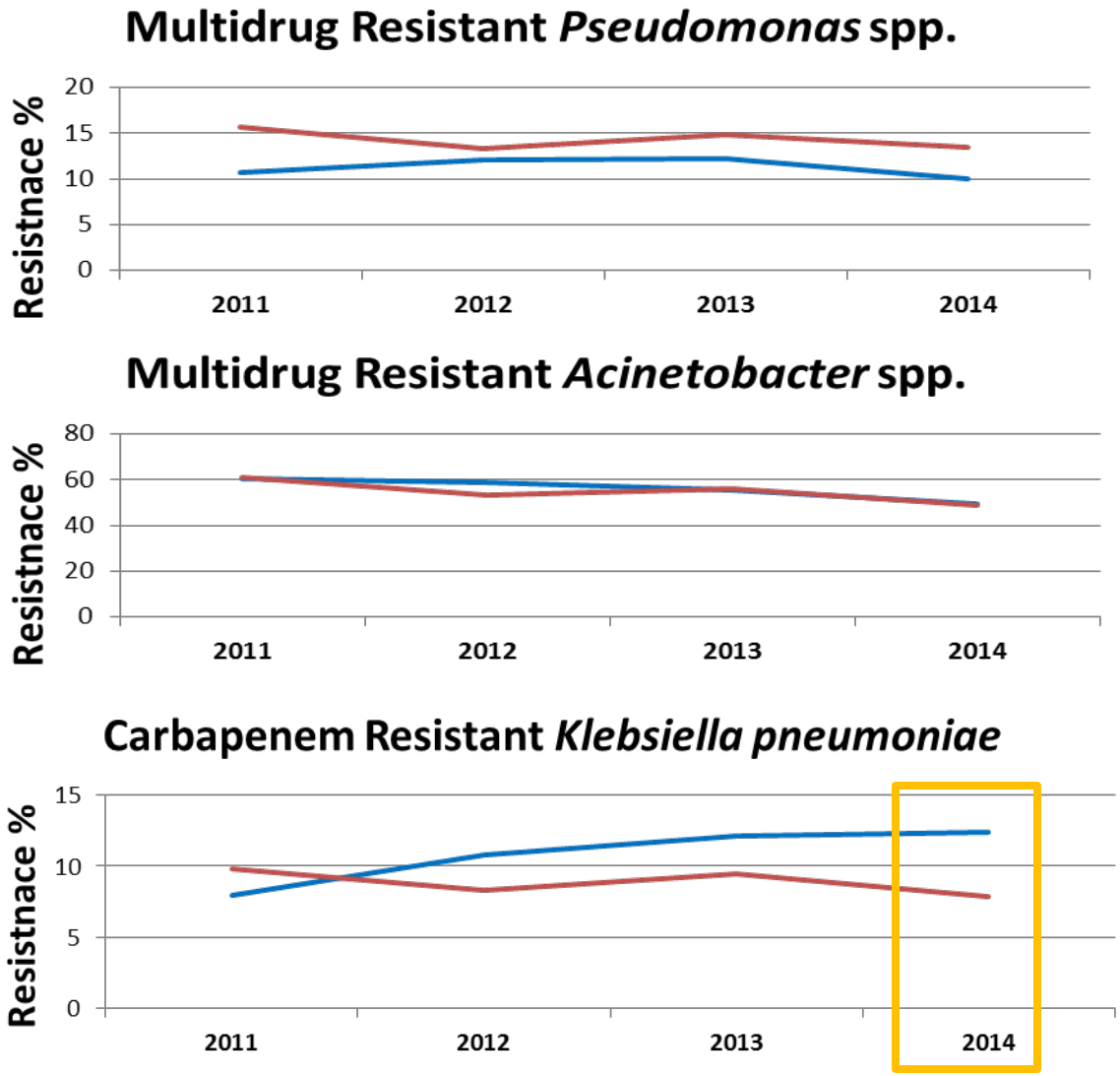
Support of Infection Control and Public Health Response to AR Pathogens

Healthcare Associated AR Pathogens in California, 2011-2014



National
California

Antibiotic Resistance Patient Safety Atlas: Data available at http://gis.cdc.gov/grasp/PSA

Carbapenemase-producing CRE (CP-CRE) are a Public Health Priority

- **Carbapenemase-producing** (CP) CRE
  - Make enzymes that inactivate carbapenems
    - KPC, NDM, VIM, IMP, OXA, and others
    - **Carbapenemase genes be transmitted between bacteria → potential for widespread transmission of carbapenem resistance**

- **Non-carbapenemase producing** (non-CP) CRE
  - AmpC-type enzyme or an ESBL combined with porin loss

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AST identifies carbapenem resistance, but does not distinguish between CP-CRE and non-CP CRE

1. **Phenotypic Tests**
   - Can tell if a carbapenemase is present, but not which kind
     - Modified Hodge Test, Carba-NP, Carbapenem Inactivation Method (CIM)
2. **Molecular Tests**
   - Can identify which kind of carbapenemase is present
     - PCR
     - Whole genome sequencing

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Updated CRE Surveillance Definition to Improve Identification of Carbapenemase Producers

Improved Phenotype-Based Definition for Identifying Carbapenemase Producers among Carbapenem-Resistant *Enterobacteriaceae*

Nora Chea, Sandra N. Bulens, Thiphasone Kongphet-Tran, Ruth Lynfield, Kristin M. Shaw, Paula Snippes Vagnone, Marion A. Kainer, Daniel B. Muleta, Lucy Wilson, Elisabeth Vaeth, Ghinwa Dumyati, Cathleen Concannon, Erin C. Phipps, Karissa Culbreath, Sarah J. Janelle, Wendy M. Bamberg, Alice Y. Guh, Brandi Limbago, Alexander J. Kallen

*"To further **reduce the number of non–carbapenemase-producing CRE strains falsely identified as carbapenemase-producing CRE**, health care facilities could **consider adding resistance-mechanism testing for isolates that meet [the updated] definition**...Such testing may be particularly helpful in areas with a low prevalence of CRE"*

Results: Carbapenemase Testing Performed by Clinical and Public Health Laboratories

	Perform CP Testing						No CP testing
	MHT		PCR		Carba-NP		No. (%)
	Onsite	Offsite	Onsite	Offsite	Onsite	Offsite	
Clinical Labs	52	14	14	2	2	0	32 (24)
Public Health Labs	2	0	1	8	0	0	12 (52)

- Overall, 96 (70%) clinical labs and 11 (48%) public health labs obtain some form CP testing for CRE isolates, either onsite or offsite

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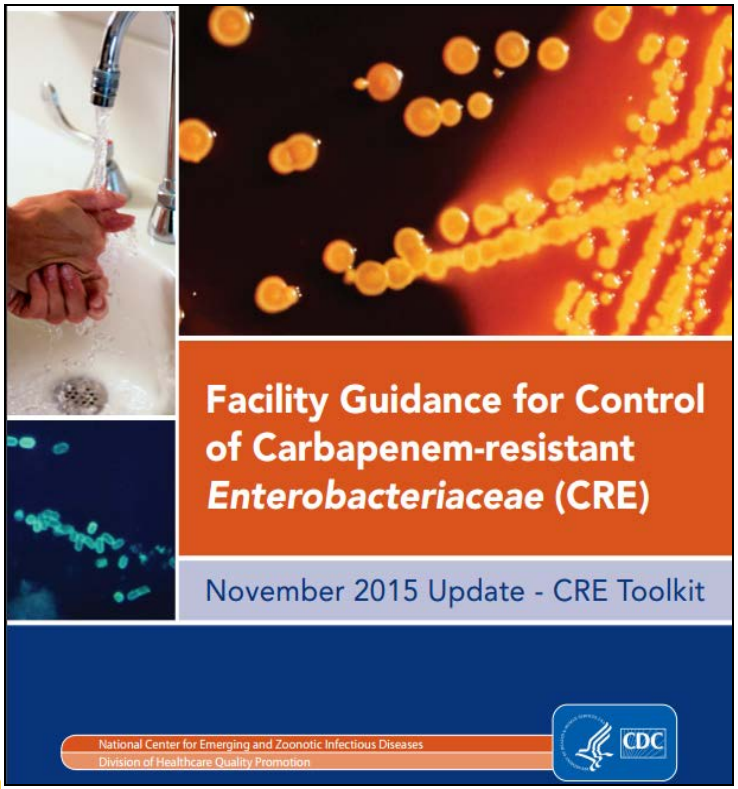
The laboratory has a prominent role to play in preventing spread of CRE

1. Hand Hygiene
2. Contact Precautions
3. Healthcare Personnel Education
4. Minimize Device Use
5. Rapid Laboratory Notification
6. Interfacility Communication
7. Antimicrobial Stewardship
8. Environmental Cleaning
9. Patient and Staff Cohorting
10. Screening Contacts of CRE Patients
11. Active Surveillance Testing
12. Chlorhexidine Bathing



CRE infected and colonized patients can be a source of transmission

- **Clinical cultures** (collected to evaluate for infection) fail to identify one third to one half of patients with CRE
- **Surveillance cultures identify patients who are colonized with CRE**
  - Identify between 70-80% of colonized patients
  - Enable infection prevention measures to be implemented for colonized patients and prevent transmission

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Tests to Identify CRE Colonization

- Surveillance cultures of rectal swabs
  - Identify patients colonized with CRE in the intestinal tract
  - Further testing is needed to distinguish CP-CRE from non-CP CRE
- CDC published a laboratory protocol to specifically screen for carbapenem resistant bacteria

CDC

Laboratory Protocol for Detection of Carbapenem-Resistant or Carbapenemase-Producing, *Klebsiella* spp. and *E. coli* from Rectal Swabs

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http://www.cdc.gov/HAI/pdfs/labSettings/Klebsiella_or_Ecoli.pdf

Results: Clinical Lab Readiness to Perform CRE Surveillance Cultures

Is your laboratory currently prepared to screen rectal swabs for the presence or absence of CRE?

Response	No. (%)
Yes	
Reference Lab	17 (13)
Within 24 hours	26 (19)
With additional time	42 (31)
No	33 (24)
Unknown	2 (1)
Missing	16 (12)

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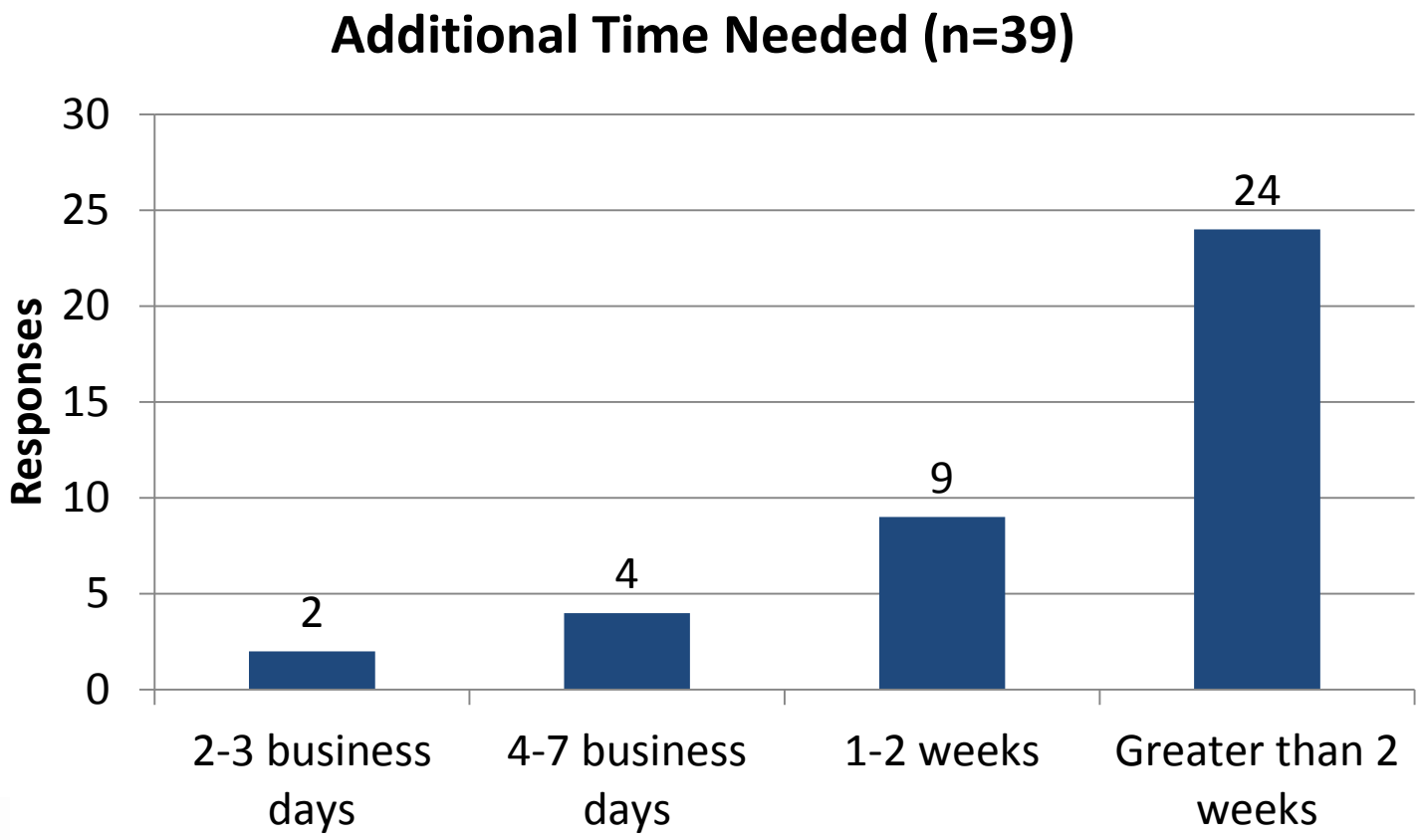
Results: Clinical labs requiring additional time to prepare to screen rectal swabs for CRE



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Results: Public Health Lab Readiness to Perform CRE Surveillance Cultures

Response (n=23)	No.	(%)
Yes		
Reference Lab*	7	(30)
Within 24 hours	2	(8)
With additional time		
2-3 Days	1	(4)
> 2 weeks	2	(8)
No	9	(39)
Unknown	1	(4)
Missing	1	(4)

*3 identified CDPH Microbial Diseases Laboratory as their reference laboratory

AR Lab Assessment Results – Summary of Key Findings

- Some California hospital laboratories are not yet implementing updated CLSI breakpoints
- The majority of California hospitals have access to laboratories with selective/cascade reporting capabilities
- Carbapenemase testing capacity and readiness to perform CRE screening cultures are limited

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California Antimicrobial Resistance Laboratory Network

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AR Lab Network Goals

1. **Enhance situational awareness** of healthcare associated AR pathogens by facilitating information and data sharing

2. **Connect healthcare facilities and laboratories to additional laboratory testing resources** to enhance patient care and infection control activities

3. **Strengthen collaboration** among clinical and public health lab laboratorians, infection control practitioners, and public health epidemiologists

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AR Lab Network – Proposed Data Sharing

- Quarterly (or other frequency) aggregated reports
  - Enterobacteriaceae
  - *Pseudomonas aeruginosa* or *Acinetobacter baumanii* resistant to any carbapenem tested
  - Annual antibiogram

- For labs that perform carbapenemase testing: numbers of carbapenemase-producing isolates, by specific carbapenemase (where possible)

- Any other unusual or novel resistance phenotype or mechanism

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AR Lab Network – Discussion & Education Opportunities

- Quarterly conference calls
- Summary reports of shared AR data
- Guest speakers and discussants
- Practical case studies or other topics as determined by the network

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AR Lab Network Next Steps

- CDPH HAI Program will send out sign up sheet for all interested stakeholders
- Will set time and date of AR Lab Network kick-off Session (~September/October 2016)

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We acknowledge collaboration and invaluable assistance from:

- **Romney M Humphries, PhD D(ABMM) M(ASCP)CM**
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  Assistant Professor, David Geffen School of Medicine, UCLA
- **Varvara Kozyreva, PhD**
  Acting Chief, Bacterial Diseases Section
  Microbial Diseases Laboratory Program (MDL), CDPH
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  Assistant Professor of Medicine, David Geffen School of Medicine, UCLA
- **Mark Pandori, PhD**
  Director, Alameda County Public Health Laboratory
- **Jeff Schapiro, MD D(ABMM)**
  Associate Medical Director, Kaiser Permanente Regional Laboratory
- **Lauri Thrupp, MD**
  Senior Hospital Epidemiologist & Consultant Clinical Microbiology Laboratory, UCI

Questions?

For more information, please contact
The HAI Program at
HAIProgram@cdph.ca.gov

Thank you

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CDC's CRE surveillance definition was updated in 2015

- Enterobacteriaceae that meet *either* of the following criteria:

  Resistant* to any of the carbapenems

  -OR-

  Documented to **possess a carbapenemase** by a recognized test

  *Using updated laboratory breakpoints

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Old (2012) CRE Surveillance Definition

- Enterobacteriaceae that meet both of the following criteria:

Nonsuceptible – Intermediate or Resistant – to specific carbapenems (ertapenem excluded)

-AND-

Resistant to specific cephalosporins

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