

# Carbapenem-resistant Enterobacteriaceae: Epidemiology and Prevention Update

**Alex Kallen, MD, MPH**

Division of Healthcare Quality Promotion  
Centers for Disease Control and Prevention

*The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention.*

# Objectives

- ❑ **Summarize recent epidemiologic trends for CRE**
- ❑ **Discuss pragmatic high-level approaches to prevention and control strategies**
- ❑ **Discuss regional and collaborative experiences regarding implementation of prevention efforts**

# **EPIDEMIOLOGY**

# Change in CRE Incidence, 2001-2011

	National Nosocomial infection Surveillance system, Number (%) of isolates			National Healthcare Safety Network, Number (%) of isolates		
	2001			2011		
Organism	Isolates	Tested	Non-susceptible	Isolates	Tested	Non-susceptible
<i>Klebsiella pneumoniae</i> and <i>oxytoca</i>	654	253 (38.7)	4 (1.6)	1,902	1,312 (70.0)	136 (10.4)
<i>E. coli</i>	1,424	421 (29.6)	4 (1.0)	3,626	2,348 (64.8)	24 (1.0)
<i>Enterobacter aerogenes</i> and <i>cloacae</i>	553	288 (52.1)	4 (1.4)	1,045	728 (69.7)	26 (3.6)
<b>Total</b>	<b>2,631</b>	<b>962 (36.6)</b>	<b>12 (1.2)</b>	<b>6,573</b>	<b>4,388 (66.8)</b>	<b>186 (4.2)</b>

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## Facilities Reporting at least One CRE (CAUTI or CLABSI) to NHSN, First Half of 2012

Facility characteristic	Number of facilities with CRE from a CAUTI or CLABSI (2012)	Total facilities performing CAUTI or CLABSI surveillance (2012)	(%)
All acute care hospitals	181	3,918	(4.6)
Short-stay acute hospital			
Long-term acute care hospital			

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All acute care hospitals	181	3,918	(4.6)
Short-stay acute hospital	145	3,716	(3.9)
Long-term acute care hospital	36	202	(17.8)

## **Incidences of CRE and Other Well-Characterized Multidrug-resistant Organisms**

- ❑ **CRE: 3.08 per 100,000 population**
- ❑ **Methicillin-resistant *Staphylococcus aureus*: 25.1 per 100,000 population**
- ❑ ***Clostridium difficile*: 147.3 per 100,000 population**

# Annual Crude Incidence Rates (MuGSI)

Emerging Infections Program site	CRE cases				
	Number of cases		Crude annual incidence rates (per 100,000 population)		SIR (95% confidence intervals)
	2012 <sup>a</sup>	2013	2012 <sup>a</sup>	2013	-
<b>Colorado</b>	-	27	-	1.05	0.52 (0.39-0.71)
<b>Georgia</b>	175	181	4.58	4.68	1.65 (1.21-2.24)
<b>Maryland</b>	-	92	-	4.80	1.46 (1.07-1.97)
<b>Minnesota</b>	31	40	1.82	2.32	0.94 (0.69-1.26)
<b>New Mexico</b>	-	6	-	0.89	0.41 (0.30-0.55)
<b>New York</b>	-	27	-	3.60	1.42 (1.05-1.91)
<b>Oregon</b>	6	14	0.35	0.82	0.28 (0.21-0.38)
<b>Total</b>	212	388	2.94	3.08	-

# Number of Carbapenem-Resistant Enterobacteriaceae Organisms by Site, 2012-2013

Site	Number of CRE organisms or isolates (%)					
	Total	<i>E. aerogenes</i>	<i>E. cloacae</i>	<i>E. coli</i>	<i>K. pneumoniae</i>	<i>K. oxytoca</i>
Colorado	27	7 (25.9)	10 (37.0)	3 (11.1)	7 (25.9)	0 (0)
Georgia	356	22 (6.2)	38 (10.7)	56 (15.7)	235 (66.0)	5 (1.4)
Maryland	92	8 (8.7)	6 (6.5)	9 (9.8)	69 (75.0)	0 (0)
Minnesota	71	29 (40.9)	16 (22.5)	10 (14.1)	16 (22.5)	0 (0)
New Mexico <sup>a</sup>	6	2 (33.3)	0 (0)	3 (50.0)	1 (16.7)	0 (0)
New York <sup>a</sup>	27	3 (11.1)	2 (7.4)	5 (18.5)	17 (63.0)	0 (0)
Oregon	20	4 (20.0)	7 (35.0)	3 (15.0)	6 (30.0)	0 (0)
Total	599	75 (12.5)	79 (13.2)	89 (14.7)	351 (58.6)	5 (0.8)

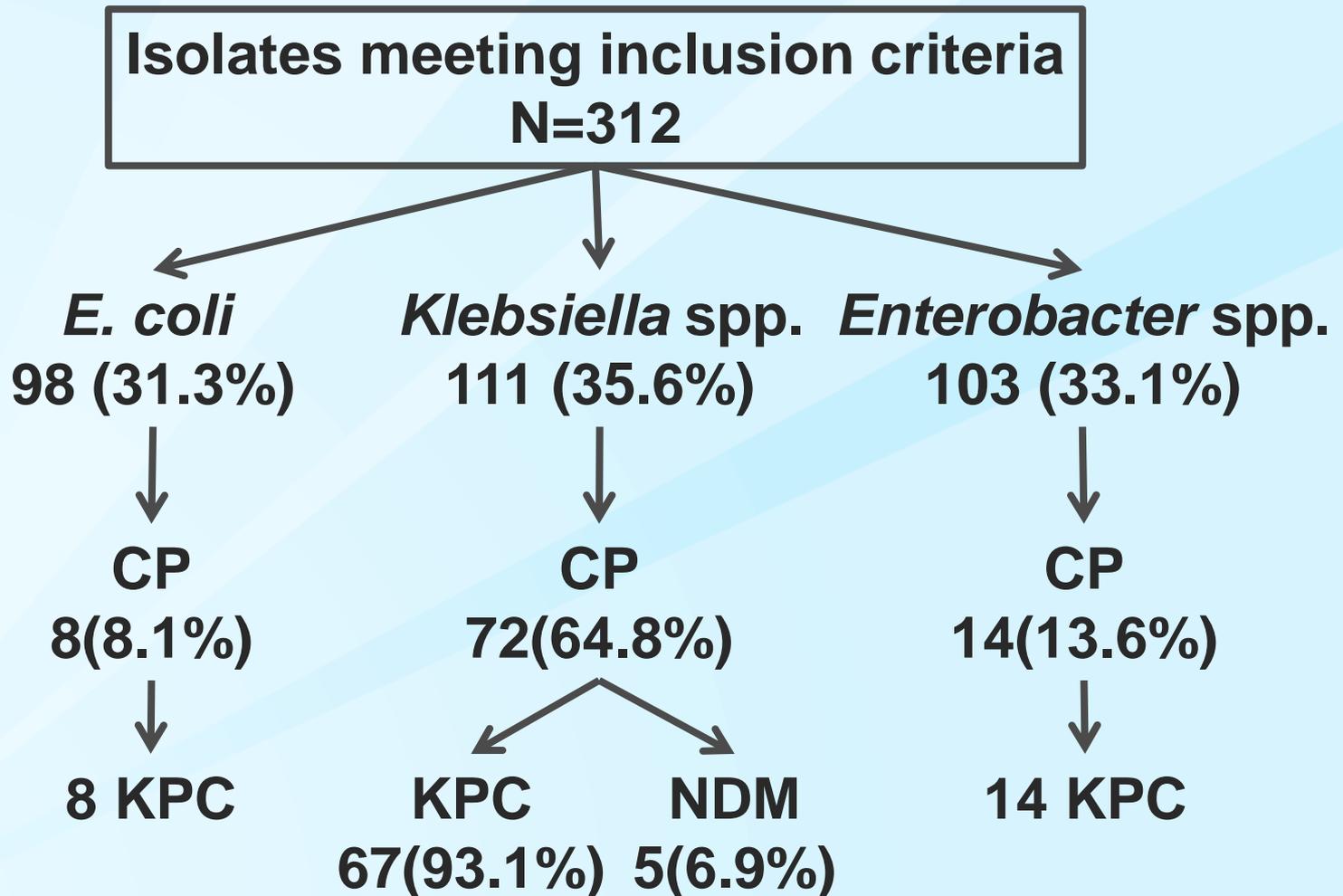
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# Distribution of Carbapenemase-Producing CRE (CREDS)



## Number and Proportion of Carbapenemase-producing CRE by Site

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State	CP-CRE (%)
MD	43 (73.8)
MN	33 (29.6)
TN	13 (18.8)
NY	3 (5.6)
NM	1 (6.6)
CO	0 (0)

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# Collection Site CRE, 7 U.S. Sites, 2012-2013 (N=584)

Collection site	Number (%)
SS Acute Care Hospital	198 (33.9%)
Community	386 (66.1%)
Outpatient or ED	253 (65.5%)
LTCF	104 (26.9%)
LTACH	29 (7.5%)

# Prior Healthcare Exposures, 7 U.S. Sites, 2012-2013 (N=575)

Exposure	Number (%)
Healthcare exposure	531 (92.3%)
Hospitalization	399 (75.1%)
LTCF	259 (48.8%)
Surgery	194 (36.5%)
LTACH	59/392 (15.1%)
Current chronic dialysis	60 (11.3%)
Presence of indwelling device (in 2 days prior)	413 (71.9%)
Urinary catheter	285/531 (53.7%)
CVC	163/531 (30.7%)
No healthcare exposure	44 (7.7%)

Note: MuGSI collects isolates from sterile sites and urine only

## CRE Source, 7 U.S. Sites, 2012-2013 (N=599)

Source	Number (%)
Urine	520 (86.8%)
Blood	68 (11.4%)
Peritoneal fluid	8 (1.3%)
Other	3 (0.5%)
Other	7 (1.2%)

Note: MuGSI collects isolates from sterile sites and urine only

# Antimicrobial Susceptibility of CRE Based on Testing at Local laboratory

Antimicrobial agent	Number of susceptible isolates / total number tested (%)
Any aminoglycoside	470 / 575 (81.7)
Amikacin	294 / 499 (58.9)
Gentamicin	367 / 575 (63.8)
Tobramycin	181 / 536 (33.8)
Any fluoroquinolone	136 / 537 (25.3)
Ciprofloxacin	124 / 537 (23.1)
Levofloxacin	111 / 499 (22.2)
Moxifloxacin	10 / 35 (28.6)
Aztreonam	19 / 423 (4.5)
Colistin	9 / 12 (75.0)
Piperacillin / tazobactam	68 / 517 (13.2)
Tigecycline	262 / 295 (88.8)

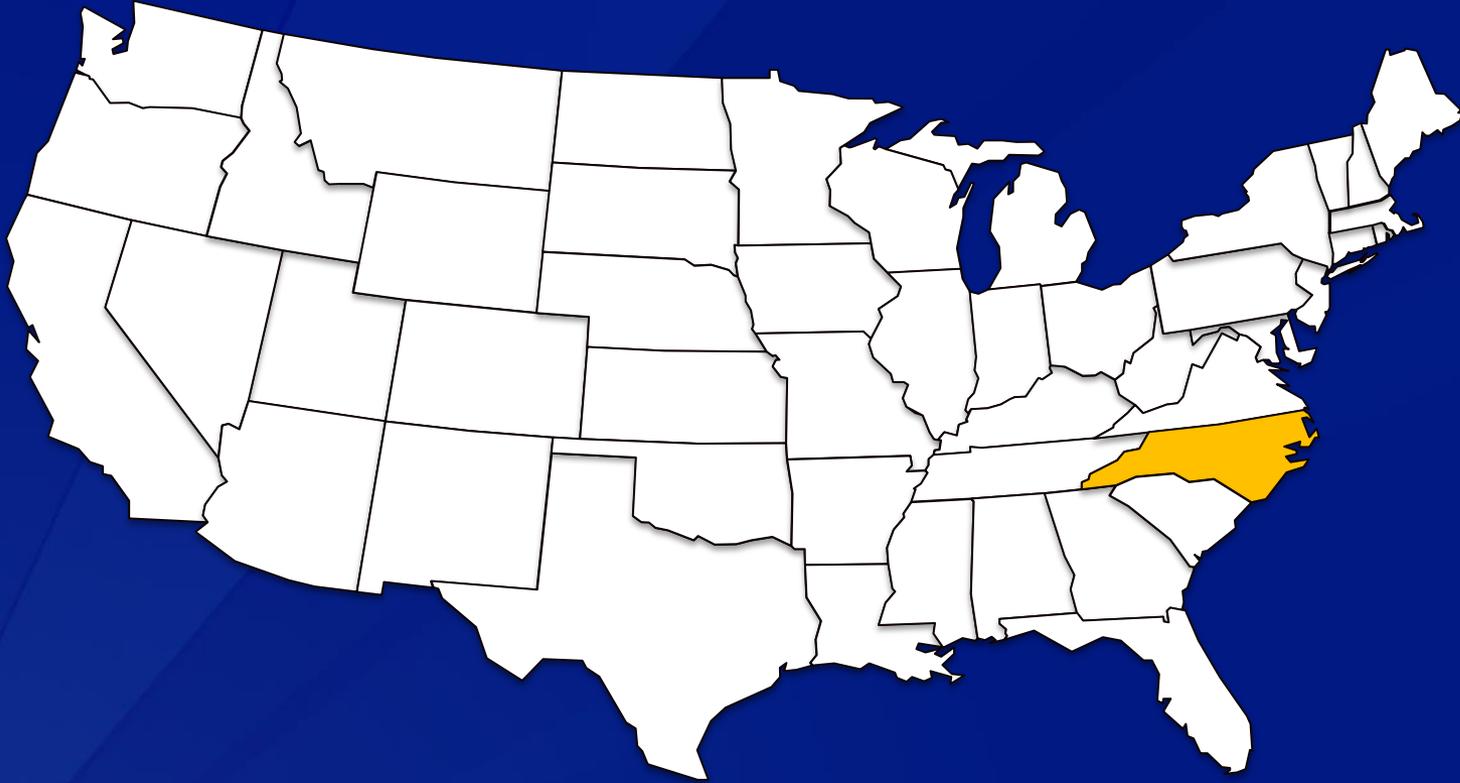
Antimicrobial agent	Number of susceptible isolates / number tested (%)	
	Carbapenemase-producing isolates	Non-carbapenemase producing isolates
<b>Any aminoglycoside</b>	68 / 90 (75.6)	85 / 96 (88.5)
<b>Amikacin</b>	37 / 83 (44.6)	68 / 82 (82.9)
<b>Gentamicin</b>	44 / 90 (48.9)	72 / 96 (75.0)
<b>Tobramycin</b>	12 / 86 (14.0)	58 / 92 (63.0)
<b>Any fluoroquinolone</b>	6 / 89 (6.7)	48 / 95 (50.5)
<b>Ciprofloxacin</b>	6 / 89 (6.7)	47 / 95 (49.5)
<b>Levofloxacin</b>	4 / 71 (5.6)	41 / 88 (46.6)
<b>Moxifloxacin</b>	2 / 10 (20.0)	1 / 5 (20.0)
<b>Aztreonam</b>	1 / 62 (1.6)	4 / 60 (6.7)
<b>Colistin</b>	1 / 2 (50.0)	1 / 2 (50.0)
<b>Piperacillin / tazobactam</b>	1 / 80 (1.3)	21 / 86 (24.4)
<b>Tigecycline</b>	48 / 53 (90.6)	35 / 36 (97.2)

# Outcome of Carbapenem-Resistant Enterobacteriaceae Cases

Outcome	Number (%)
Required hospitalization within 30 days of initial positive culture (n=569)	371 (65.2)
Required intensive care unit stay in the seven days after positive culture (n=368)	128 (34.8)
Discharge disposition (n=322):	
Home (private residence)	141 (43.8)
Other settings	
Long-term acute care facility (including LTACH)	180 (55.9)
Inpatient hospice	1 (0.3)
Died (during hospitalization or at the end of 30-day evaluation) (n=566)	51 (9.0)
Among any sterile-site positive culture	25 / 91 (27.5)
Among nonsterile-site positive culture only (i.e., urine )	26 / 475 (5.5)

# **NON-KPC CARBAPENAMSES**

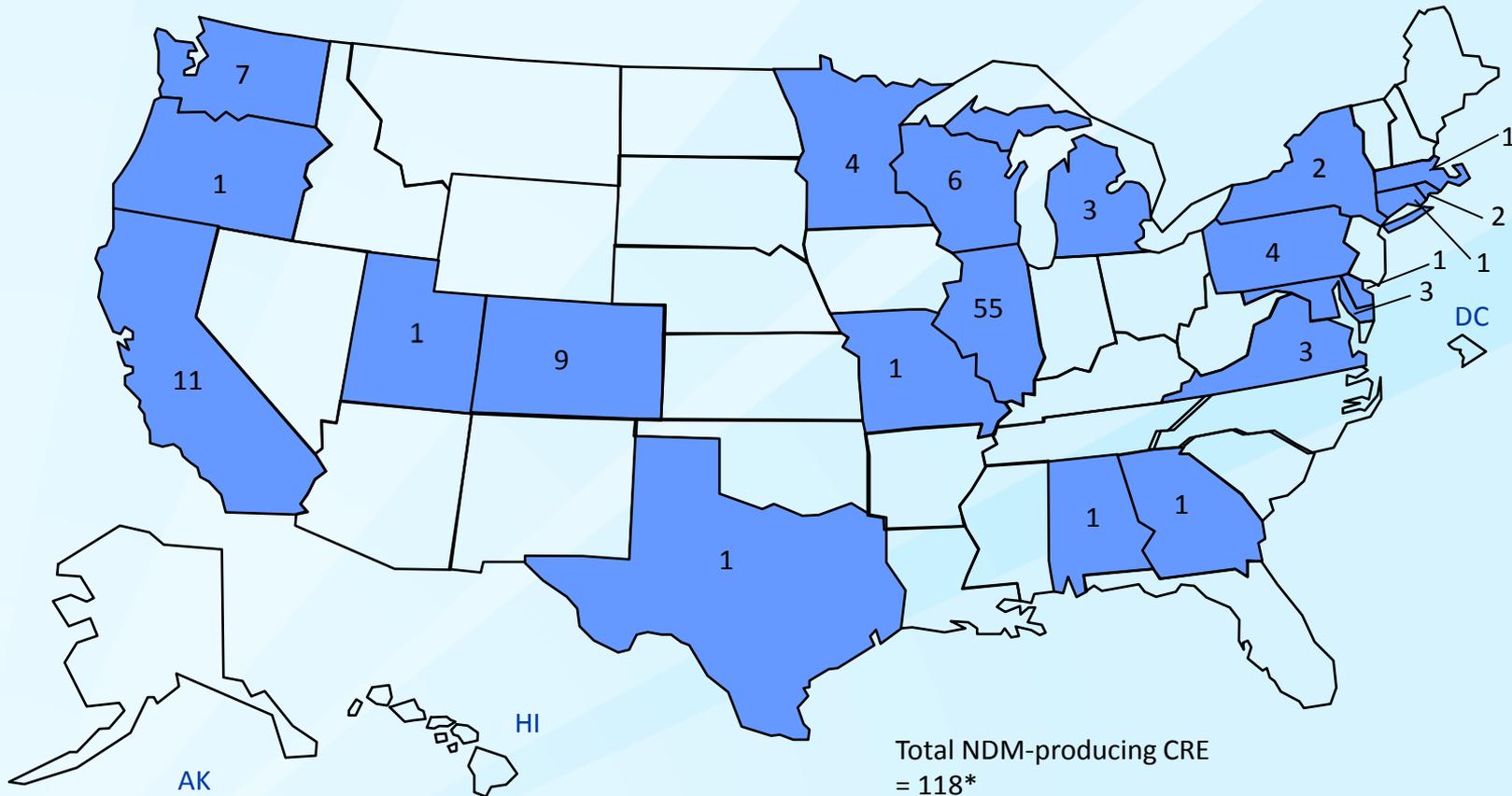
## First Report of CP-CRE



North Carolina, 2001: *Klebsiella pneumoniae*



# New Delhi Metallo- $\beta$ -lactamase-producing Carbapenem-resistant Enterobacteriaceae (CRE) isolates reported to the Centers for Disease Control and Prevention (CDC) as of January 2015, by state



# Number of Patients with NDM-producing CRE Reported to CDC, by Year



# Proportion of Patients Without Overnight Healthcare Stay Outside the US, by Year



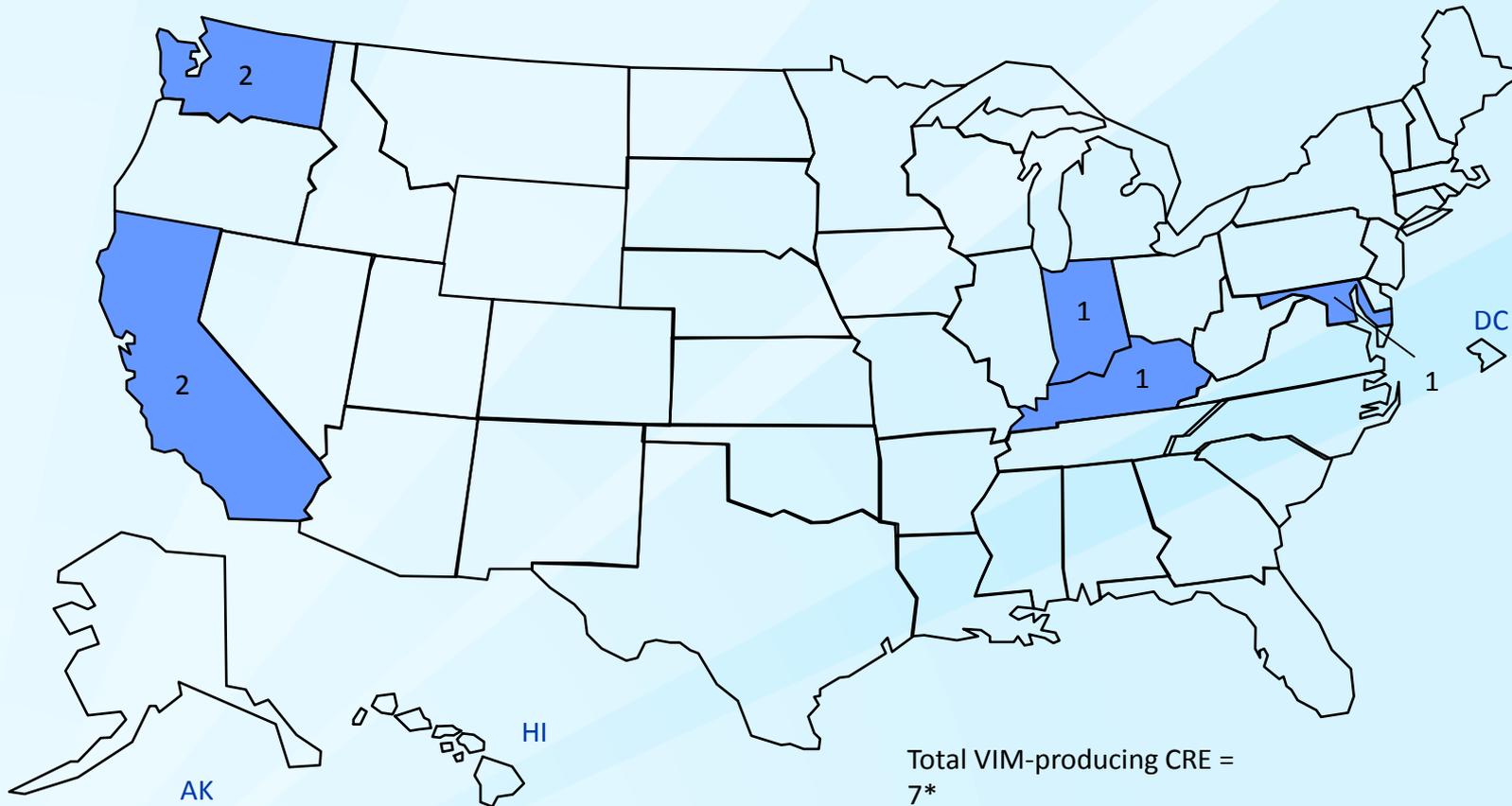
In 2012, 1 clusters accounted for 8/10 cases without healthcare exposure outside the US

In 2013, 3 clusters accounted for 47/56 cases without healthcare exposure outside the US



2 unknown in 2013

# VIM-producing Carbapenem-resistant Enterobacteriaceae (CRE) isolates reported to the Centers for Disease Control and Prevention (CDC) as of January 2015, by state



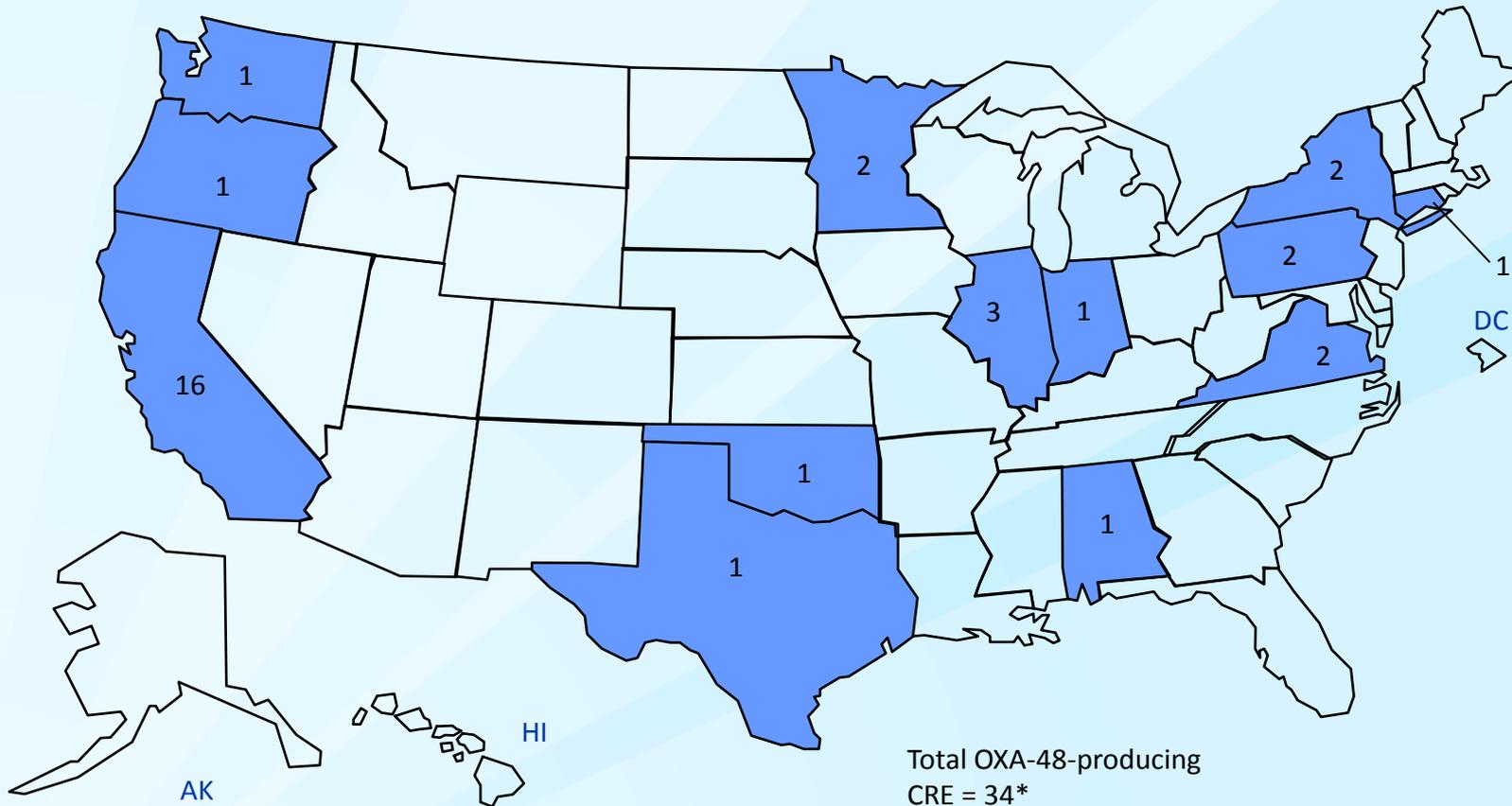
Total VIM-producing CRE = 7\*

\*Isolates were identified by CDC from isolates either sent for reference carbapenemase testing or as part of a CDC surveillance program for CRE.

These isolates are likely an underestimation of the true number of VIM-producing CRE because CRE mechanism testing is not routinely performed in US clinical laboratories and, if performed, isolates might not be sent to CDC for this testing.



# OXA-48-Type-producing Carbapenem-resistant Enterobacteriaceae (CRE) isolates reported to the Centers for Disease Control and Prevention (CDC) as of January 2015, by state

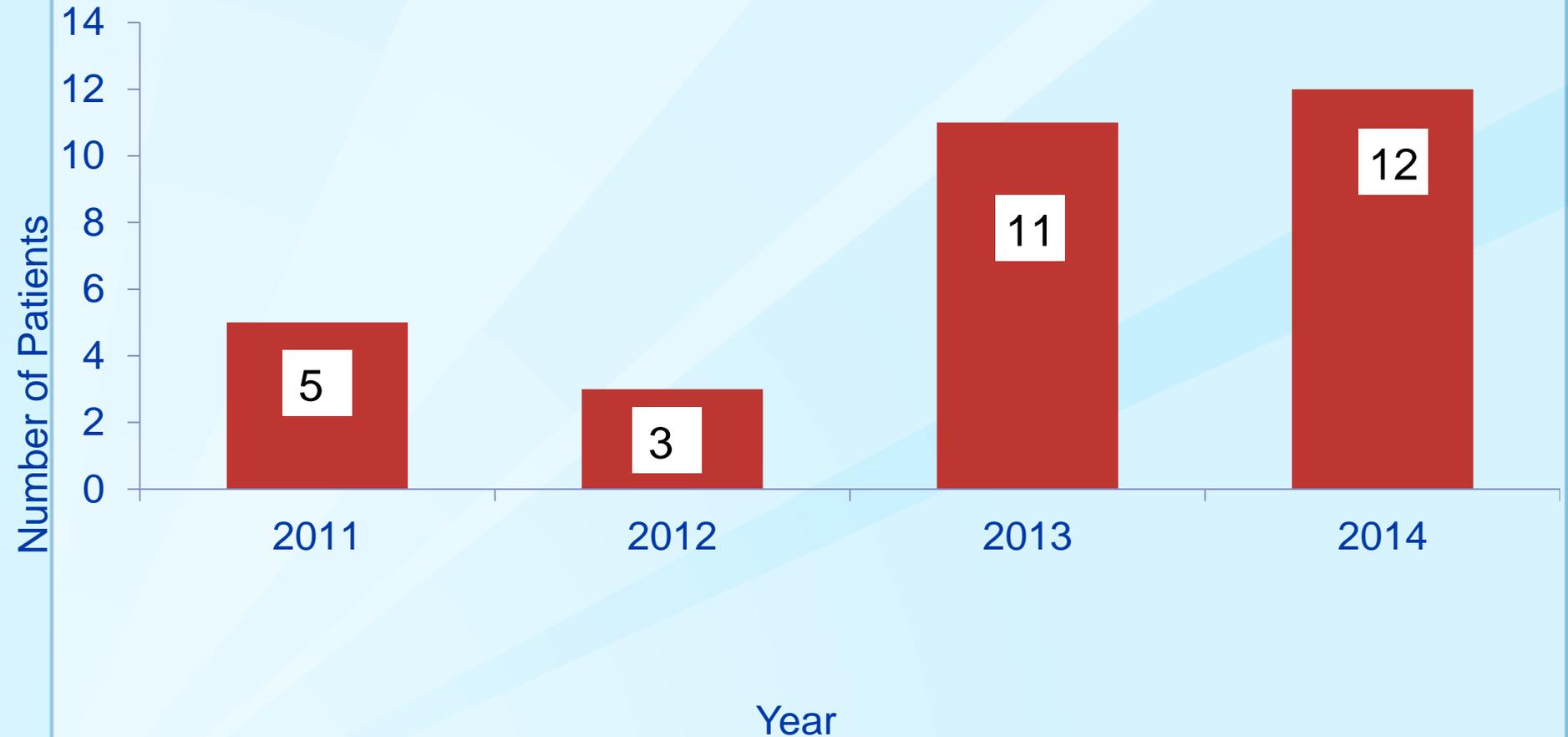


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These isolates are likely an underestimation of the true number of OXA-48--producing CRE because CRE mechanism testing is not routinely performed in US clinical laboratories and, if performed, isolates might not be sent to CDC for this testing.



# Number of Patients with OXA-48-like-producing CRE Reported to CDC, by Year



## **CDC HAN February 14, 2013**

- When a CRE is identified in a patient with a history of an overnight stay in a healthcare facility (within the last 6 months) outside the United States, send the isolate for confirmatory susceptibility testing and test to determine the resistance mechanism; at a minimum this should include evaluation for KPC and NDM**
- For patients admitted to healthcare facilities in the US after recently being hospitalized (within the last 6 months) in countries outside the US, consider the following:**
  - Rectal screening for CRE**
  - CP pending results of the screening cultures**

# CRE Among Healthy Travelers

- ❑ **430 Finns cultured before and after travel outside Scandinavia**
  - 90 (21%) became colonized with ESBL, 0 colonized with CRE
    - All negative at 1 year follow up
  - 46% from South Asia colonized
  - TD and antimicrobials were risk factors
- ❑ **Report of three healthy French travelers that acquired OXA (2) or NDM (1) following travel to India (no contact with healthcare system)**
  - Durations of colonization (<1 month)
- ❑ **94 International patients presenting for hospitalization at Mayo Clinic (primarily Middle East)**
  - 23 (%) positive for ESBLs, No CRE

Kantele A, et al. CID 2015; 60:837-848

Rupe E et al. Eurosurveillance 2014;19

Vasoo S et al. ICHE 2014; 35:182-186

# **CRE DEFINITION**

# CRE Definitions

- ❑ **Critical for surveillance and prevention to have definition that captures what is important**
  - CR in Enterobacteriaceae is complicated
- ❑ **Much of the CRE prevention effort has targeted CP strains**
  - Mechanism testing not often performed
  - Having a phenotypic definition that is relatively specific for CP-CRE would help target prevention
- ❑ **Current CDC CRE surveillance definition designed to be more specific for CP-CRE**
  - ❑ NS to imipenem, meropenem, or doripenem AND R to third-generation cephalosporins tested

## Issues with CDC CRE definition

- ❑ Complicated, difficult to apply
- ❑ Different definitions differ between NHSN and CRE Toolkit
- ❑ Definition might miss OXA-48
- ❑ Previously some cards only included ertapenem
- ❑ Might miss some CRE that posses *blaKPC*

## Percent of Selective False Negative among KPC-producing *Klebsiella* spp. Isolates

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	sFN
Current CDC Definition	21%
R to any carbapenem	<1%
R to any carbapenem excluding ertapanem	21%

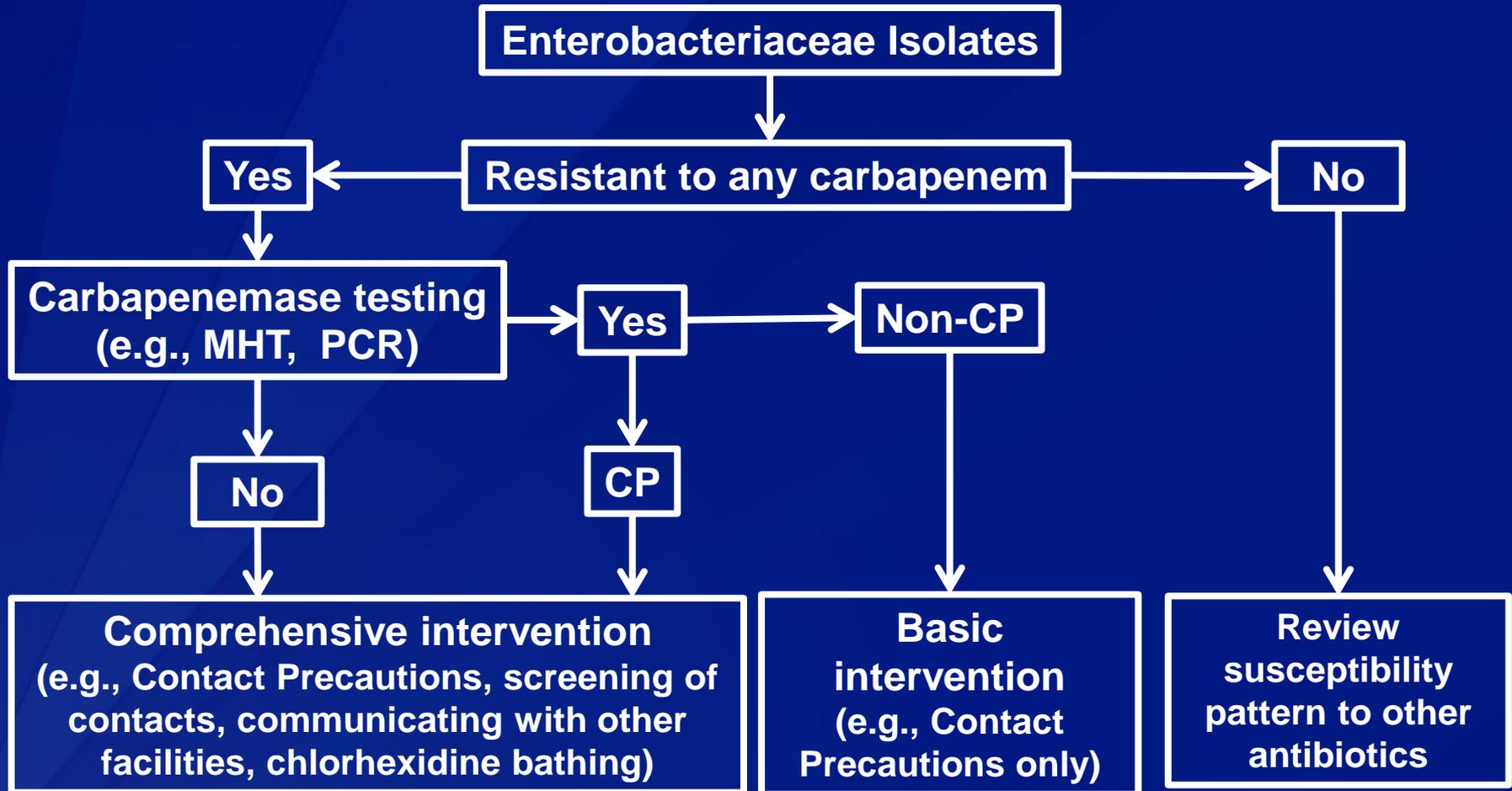
## 2015 CRE definition

- ❑ R to imipenem, meropenem, doripenem, or ertapenem
- ❑ More sensitive for capturing CP-CRE
- ❑ Increase in false positives
  - Low prevalence areas
  - *E. coli* and *Enterobacter spp.*
  - R to only one carbapenem

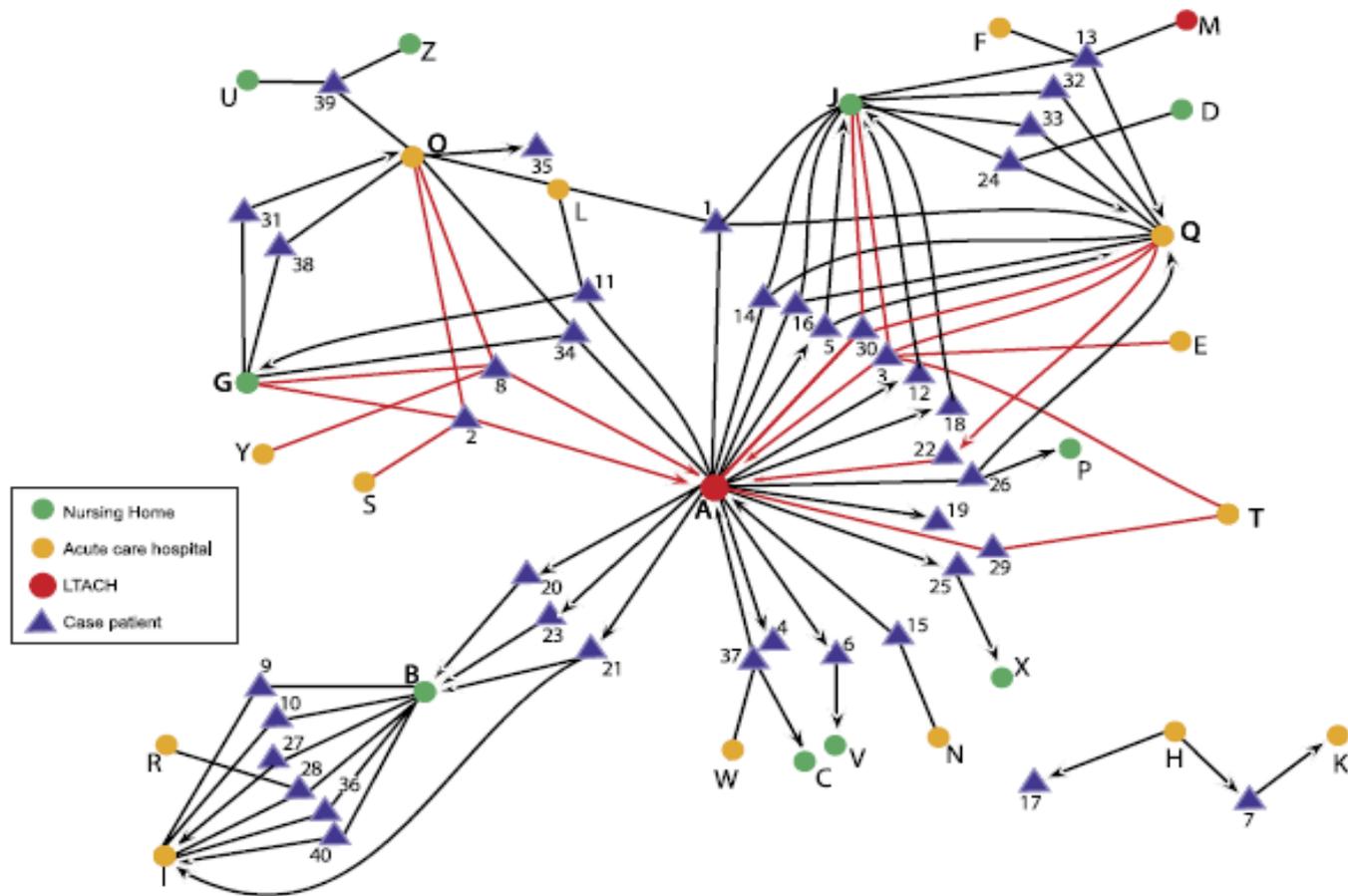
# Ability of Modified Hodge Test to Decrease % False Positive

	Resistant to any carbapenem	Resistant to any carbapenem and MHT positive
FP (%)	55	12
sFN (%)	0.7	0.7

# How do Facilities Apply 2015 CRE Definition for Prevention?



# **REGIONAL PREVENTION**



## KPC outbreak in Chicago, 2008

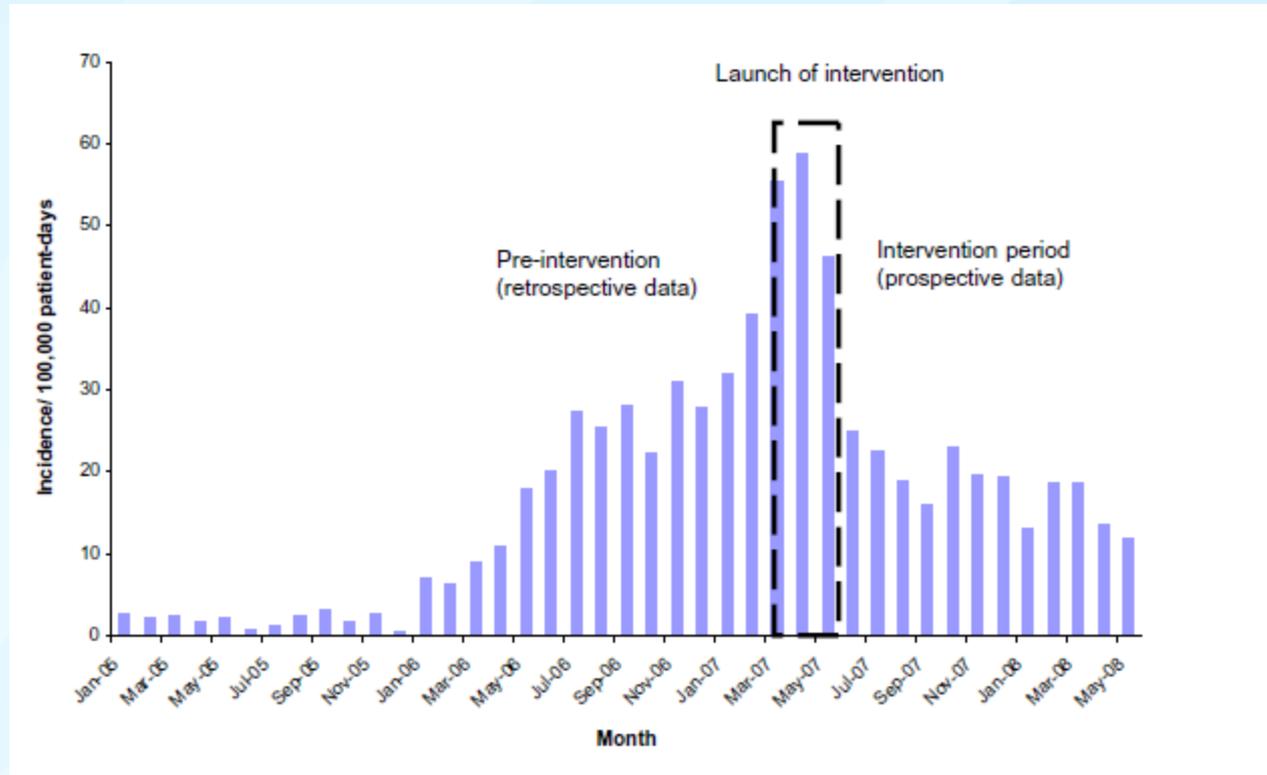
Won et al. Clin Infect Dis 2011; 53:532-540

# Israel Experience

- ❑ **KPCs likely originally from US identified in Israel beginning in late 2005**
- ❑ **By early 2006, increase in cases**
- ❑ **Initiated National effort to control CRE (initial response) in acute care hospitals**
  - **Mandatory reporting of patients with CRE**
  - **Mandatory isolation (CP) of CRE patients**
    - **Staff and patient cohorting**
  - **Task Force developed with authority to collect data and intervene**



79% decrease from highest and last month

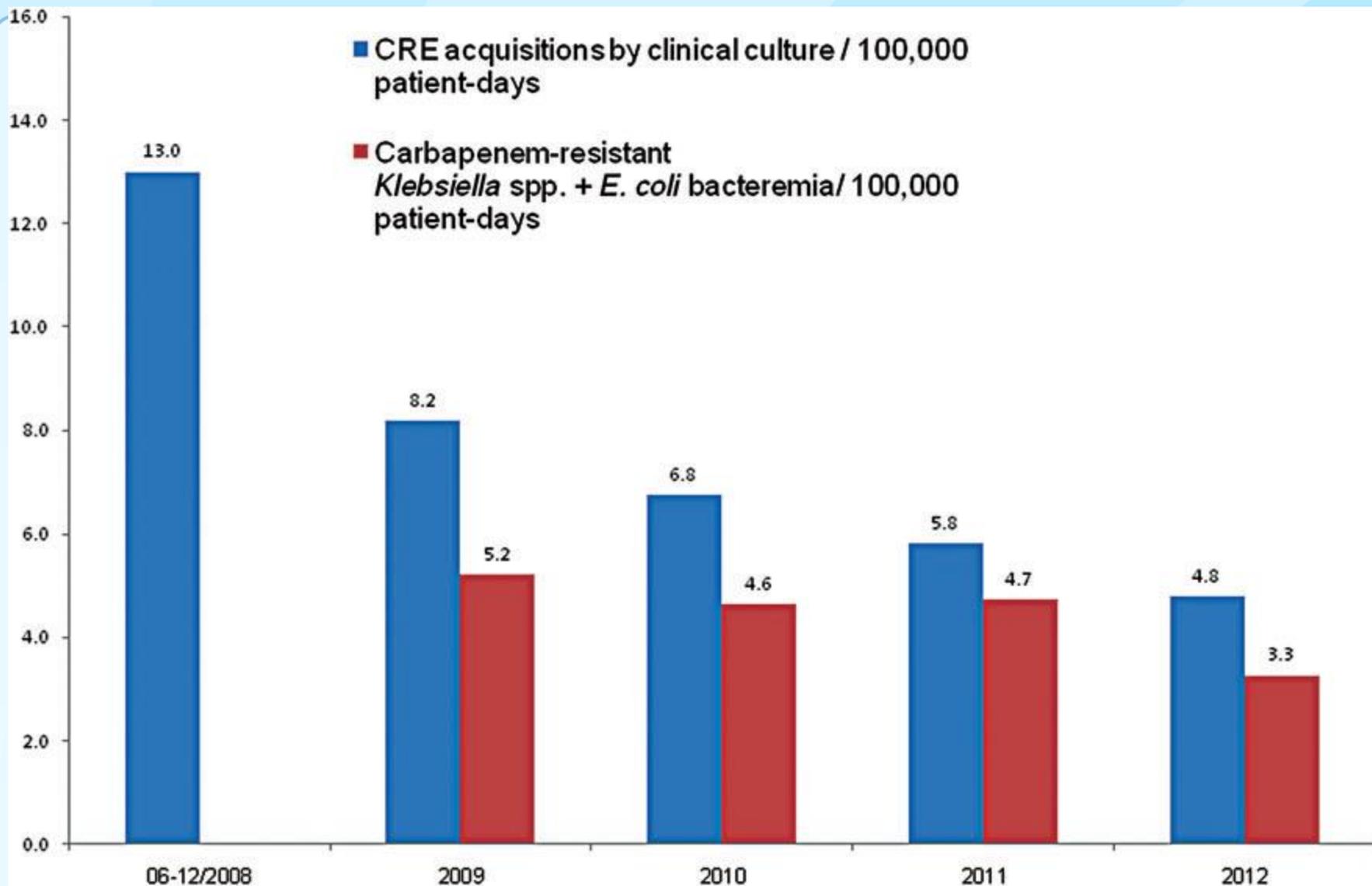


Schwaber et al. CID 2011; 848-855

# Israel Experience

## □ Beyond the first year

- Active surveillance for high-risk patients
- Added long-term care facilities
  - Targeted interventions in facilities from which CRE-patients had been transferred
  - Intervened at 13 high-risk facilities (1/10<sup>th</sup> of LTCF beds in country)
    - Determine CRE prevalence among sample
    - Map infection control infrastructure and policies
    - Developed CRE control measures by ward type
      - Similar to acute care without cohorting or strict CP
    - Visited facilities to ensure implementation



Schwaber MJ et al. Clin Infect Dis 2014



# **DUODENOSCOPES AND CRE**

# Duodenoscopes

- Used for diagnostic and the therapeutic interventions involving pancreas/biliary tree
- About 600,000 procedures a year

Tip, Elevator  
Mechanism

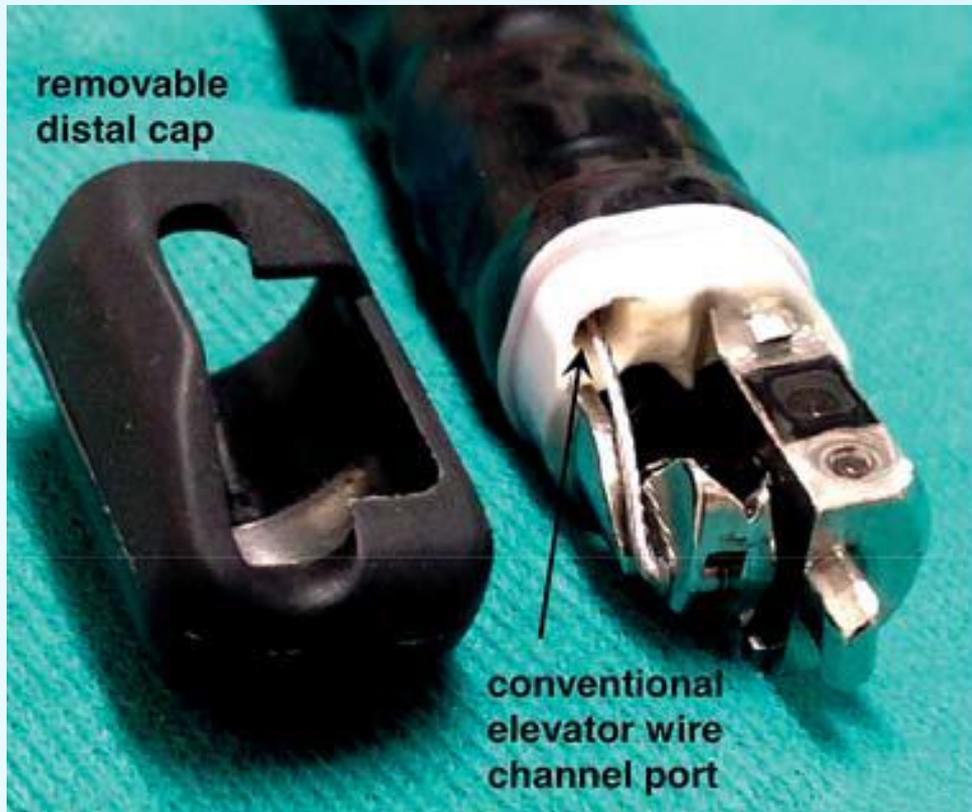


Elevator Mechanism



Method developed and implemented by CDC laboratory

# Open vs. Closed Elevator Wire Channel

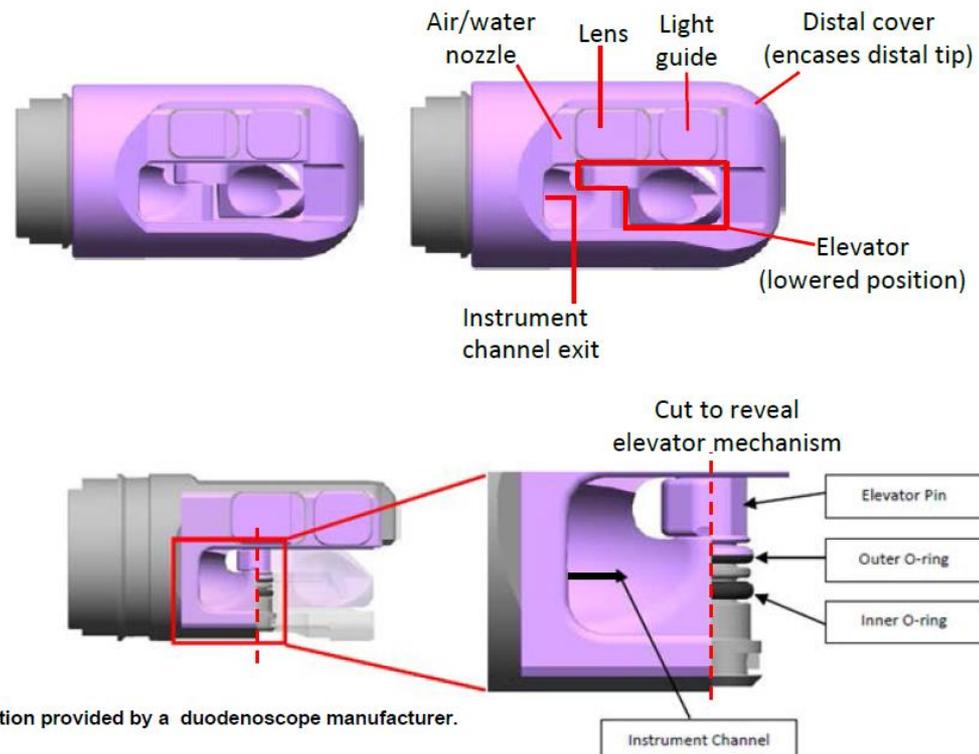


Olympus TJF-160VR



Olympus TJF-Q180V

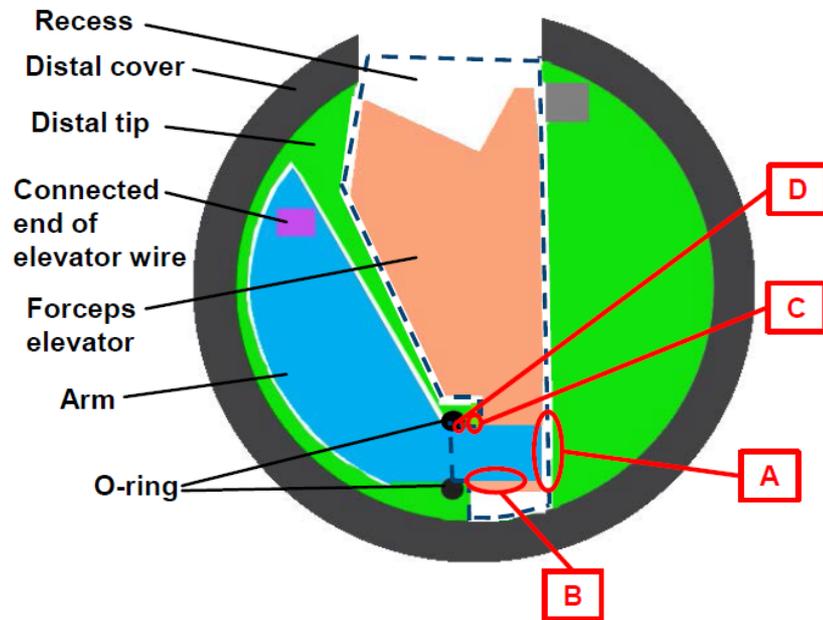
## Cutaway view of duodenoscope distal tip



Adapted from an illustration provided by a duodenoscope manufacturer.

## Device Design

### Closed Elevator Wire Channel Duodenoscope Cross-section



#### Crevices at the distal tip:

- A. Between the elevator pin (arm) and the wall of the elevator recess
- B. Between the elevator pin (arm) and the elevator
- C. Between the elevator pin (arm) and the distal tip hole
- D. The groove next to the o-ring

Areas A, B, and C are present on duodenoscopes with open elevator wire channels.

# Where is persistent contamination? Outbreak of VIM-producing *P. aeruginosa*

- ❑ 2012- 30 patients with related VIM-producing *P. aeruginosa* identified (22 had ERCP)
  - Olympus TJF-180V
- ❑ Duodenoscope and sink cultures in endoscopy suite positive
  - Elevator recess
  - Distal cap



# Dismantling of 13 month-old Duodenoscope



# Identified Breaches - Duodenoscopes

TABLE 4 Infections associated with endoscopic retrograde cholangiopancreatography<sup>a</sup>

Reference	Microorganism(s)	No. of contaminated patients after endoscopy	No. of infected patients	Infection(s)	Detection of endoscope contamination	Cause(s) of contamination
95	<i>P. aeruginosa</i>	1	1	Cholangitis, sepsis	Yes	Inappropriate cleaning and disinfection (ethanol)
96	<i>P. aeruginosa</i>	14	0	No	Yes	Inappropriate cleaning and disinfection (povidone-iodine/ethanol)
97	<i>P. aeruginosa</i>	7	7	Cholangitis	Yes	Inappropriate cleaning and disinfection (ethanol)
100	<i>P. aeruginosa</i>	1	1	Sepsis	Yes	Contaminated water bottles
53	<i>P. aeruginosa</i>	4	3	Sepsis	Yes	Inappropriate disinfection; rinsing with nonsterile tap water
91	<i>P. aeruginosa</i>	5	5	Cholangitis, sepsis, urinary	Yes	Inadequate cleaning and disinfection between uses
141	<i>Serratia marcescens</i>	1	0	No	Yes	(povidone-iodine/ethanol) Inappropriate cleaning and disinfection (povidone-iodine)
52	<i>M. chelonae</i>	14	0	No	No data	Contaminated AER; inappropriate disinfection; rinsing with tap water; lack of drying procedure
147	<i>Methylobacterium mesophilicum</i>	1	1	Bacteremia	Yes	Contaminated endoscope channels
144	ESBL-producing <i>K. pneumoniae</i>	16	12	Bacteremia/sepsis, cholangitis	Yes	Contaminated endoscope channels; insufficient drying procedure
145	KPC-producing <i>K. pneumoniae</i>	7	2	Bacteremia	Yes	Contaminated endoscope channels; insufficient drying procedure
184	HCV	1	1	HCV infection	Not tested	Inadequate disinfection (low concn, insufficient exposure); failure to perfuse elevator channel

<sup>a</sup> AER, automated endoscope reprocessor; ESBL, extended-spectrum  $\beta$ -lactamase; KPC, *Klebsiella pneumoniae* carbapenemase

Inadequate manual cleaning and/or insufficient drying  
 Contaminated or improperly used AER  
 Damage  
 Inadequate disinfection

## Possible Short-Term Solutions

- ❑ **Evaluate practices**
- ❑ **Increased attention to inspection, manual cleaning, and drying**
  - Double HLD?
- ❑ **Use new validated cleaning instructions**
- ❑ **Consider reviewing indications for ERCP**
- ❑ **Sterilization**
  - Ethylene oxide
  - Liquid chemical sterilization
- ❑ **Assessments of cleaning and disinfection**
  - Post-reprocessing cultures



**Thanks for your attention.**

**[Akallen@cdc.gov](mailto:Akallen@cdc.gov)**