Carbapenemase Producting – Carbapenem Resistant *Enterobacteriaceae*

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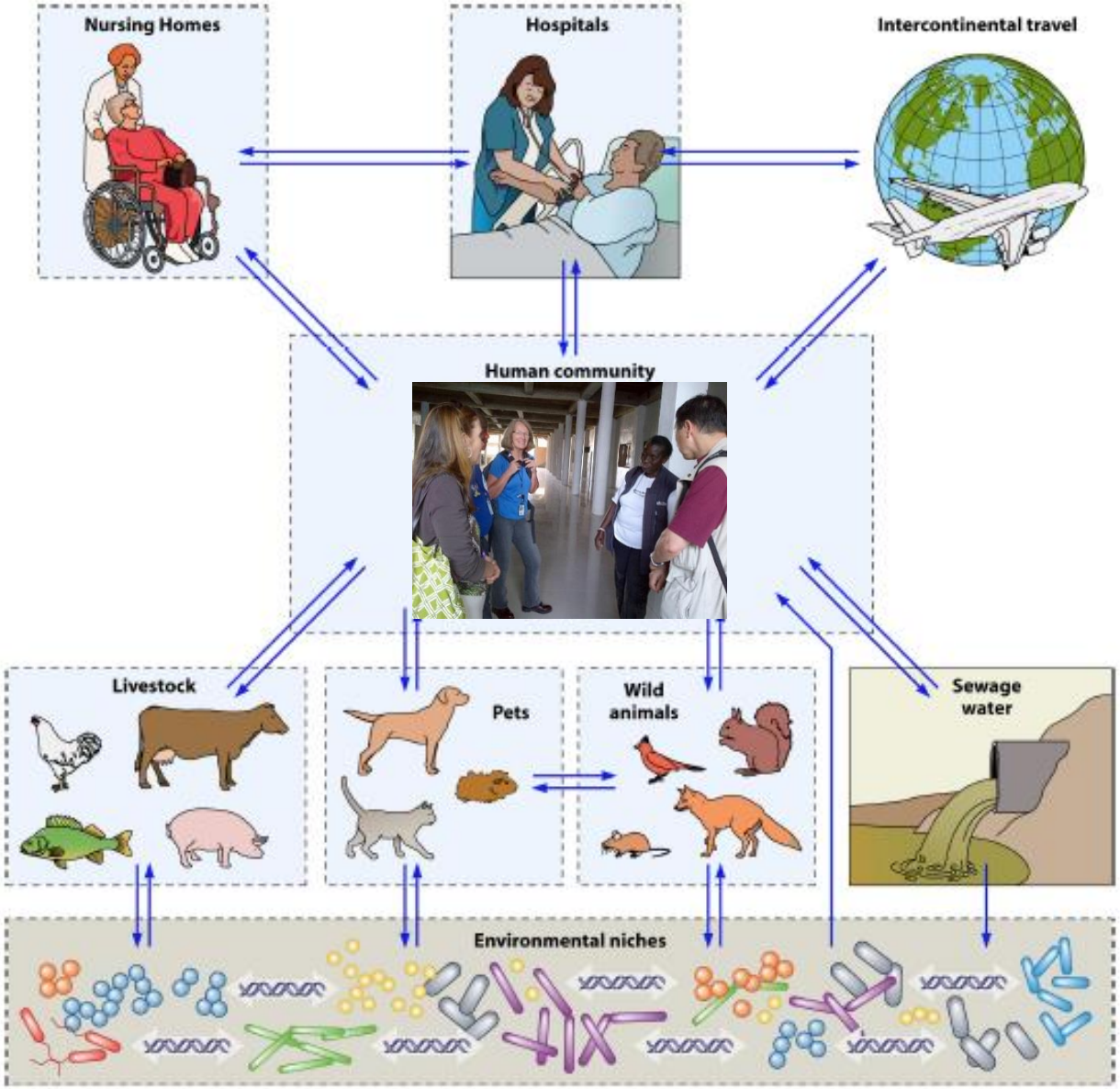
Our Goals for Today:

1. Understand the differences between CRE and CP-CRE and how this impacts transmission
2. Understand how to screen for CP-CRE and submit isolates to ISDH for confirmation
3. Learn some new (or old) lab methods
4. Ask Lots of Questions!
5. Make some new contacts!

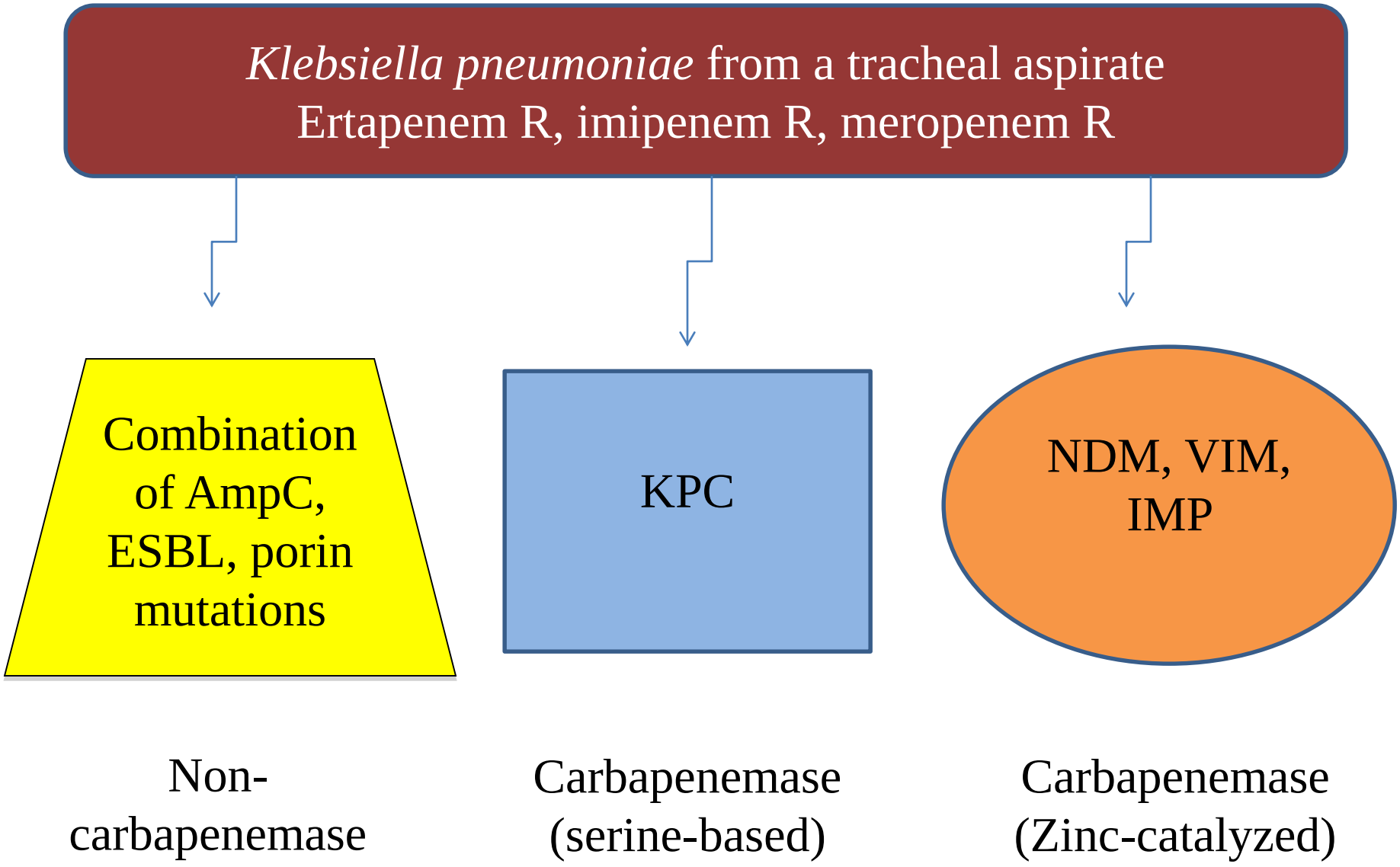
NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

Epidemiology and Laboratory Capacity Cooperative Agreement

Antibiotic Resistance Threats in the United States, 2013



Woerther *et al*., 2013. Clin Microbiol Rev 26(4):744-58; phil.cdc.gov


Klebsiella pneumoniae from a tracheal aspirate
Ertapenem R, imipenem R, meropenem R
Combination of AmpC, ESBL, porin mutations
KPC
NDM, VIM, IMP
Non-carbapenemase
Carbapenemase (serine-based)
Carbapenemase (Zinc-catalyzed)

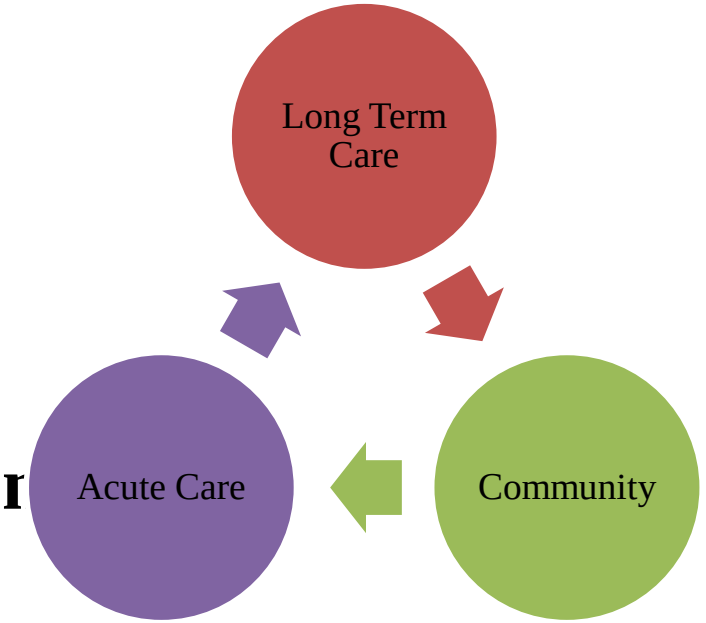
What about all of these acronyms?

Organism Group	**Glucose Non-Fermenters**		**Enterobacteriaceae**	
Resistance Mechanism	Inherent	Carbapenemase	ESBL or AmpC plus porin loss	Carbapenemase
CRE	-	-	Y	Y
CP-CRE	-	-	-	Y

CRE – Carbapenem Resistant *Enterobacteriaceae*
CP-CRE – Carbapenemase Producing-Carbapenem Resistant *Enterobacteriaceae*

In Indiana, CP-CRE is reportable for both isolates and condition.

- **CDR Modification Highlights Actionable Interventions**
- **Sets a timeline (72 hours) for investigation**
- **Puts a focus on acute care and long term care**
- **Prevent spread by encouraging:**
  - **Contact precautions**
  - **CDC CRE Toolkit Use**
  - **Screening for colonizatior**
  - **Chlorhexidine bathing**



Based on the potential for transmissibility, the Communicable Disease rule focuses on CP-CRE.

In order to narrow the amount of isolates required to submit to the state, the following isolate submission criteria were adopted:

The new CDR requires laboratories to submit organisms that are

nonsusceptible to at least one (1) carbapenem antibiotic

AND

are phenotypic positive for carbapenemase production
(ex. Modified Hodge, CarbaNP, etc.)

or

are nonsusceptible to at least three (3) carbapenem antibiotics

or

are positive for a carbapenemase gene marker

Isolates include organisms that are non-susceptible to at least one carbapenem antibiotic with MIC >=2 μg/ml or zone diameter <=22 mm (<=21 mm for ertapenem)

AND one of the following criteria:

1. Are positive for carbapenemase production by a phenotypic test (e.g. Modified Hodge, or Carba NP).

2. Are non-susceptible to at least three carbapenem antibiotics with MIC >=2 μg/ml or zone diameter <=22 mm (<=21 mm for ertapenem).

3. Are positive for a carbapenemase gene marker.

Only one isolate that meets these criteria should be submitted if the same organism is repeatedly recovered from the same patient.

Why these criteria?

How were they selected?

How does that impact my lab?

Some history…..

In 2013 Indiana began receiving and testing CRE isolates based on the CDC's recommendation that were resistant to

<u>all 3rd-generation cephalosporins</u>

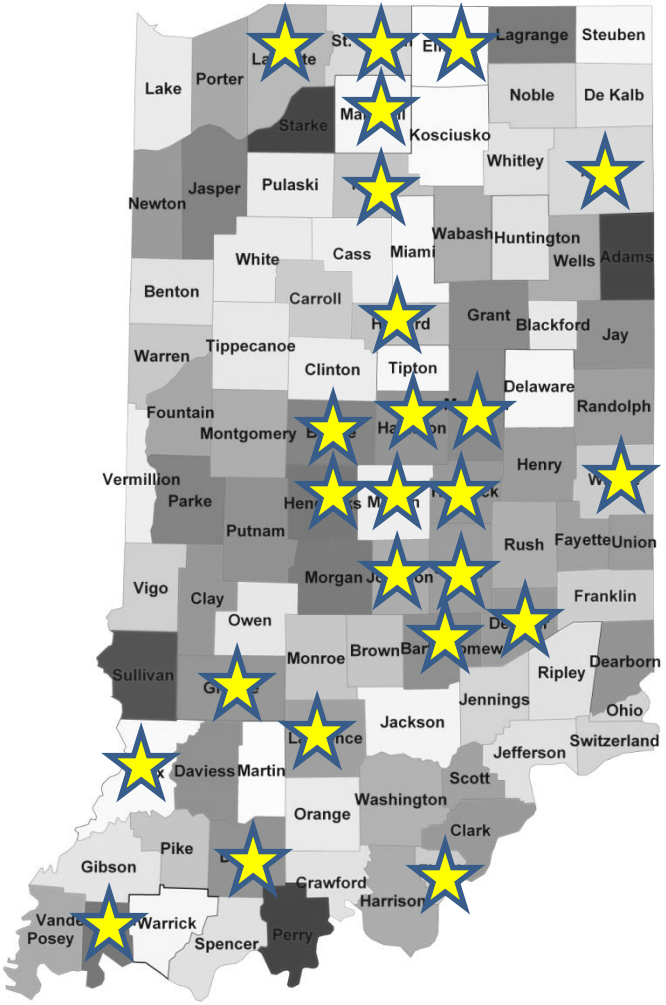
& at least

<u>one carbapenem antibiotic</u>

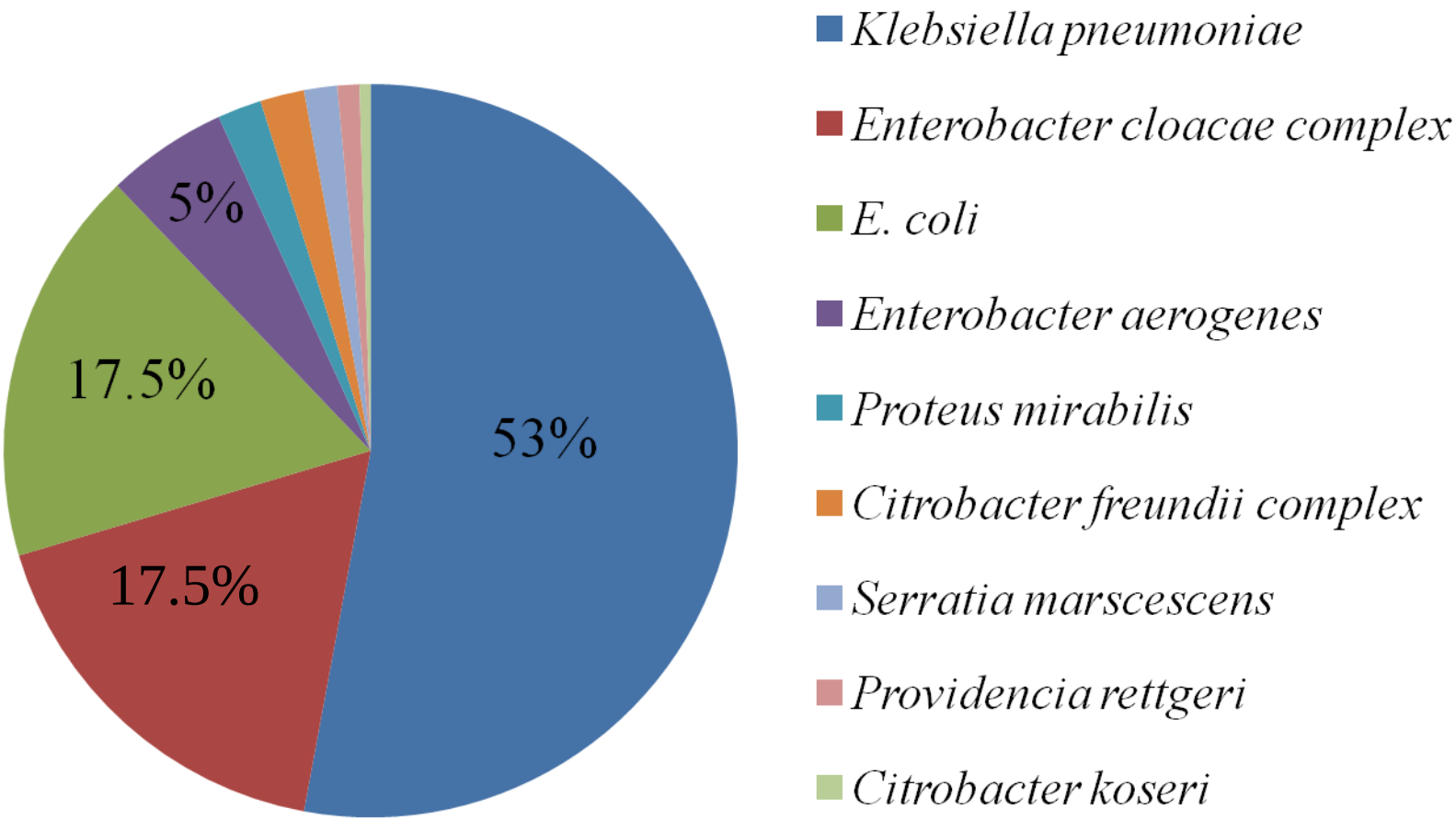
Indiana CRE Pilot: 2013-2015

Year	Submitters (n)	Isolates Submitted (n)
2013	24	167
2014	19	201
2015*	18	191
Total	32	559

*Through August 2015



Broad Distribution of Pilot Organisms

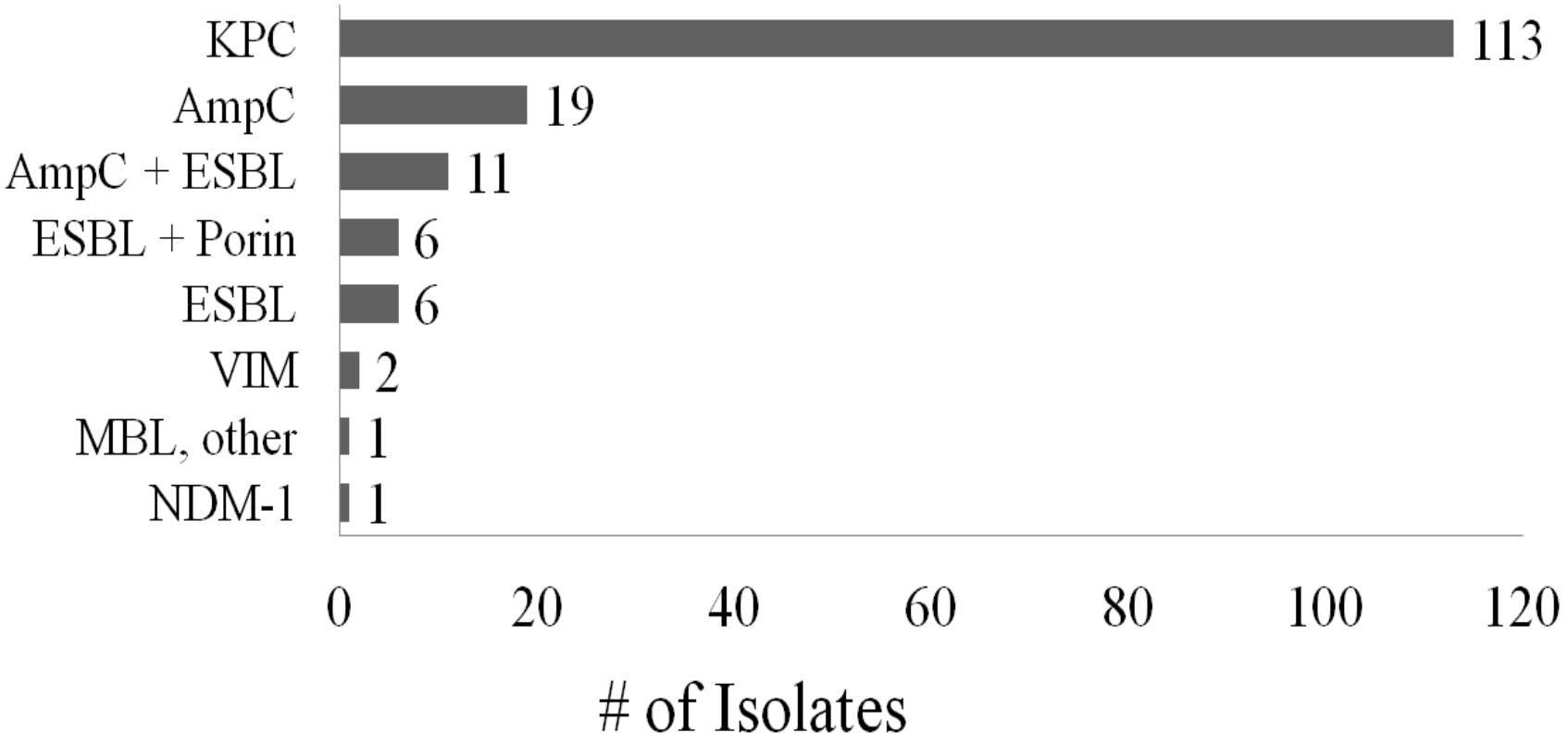


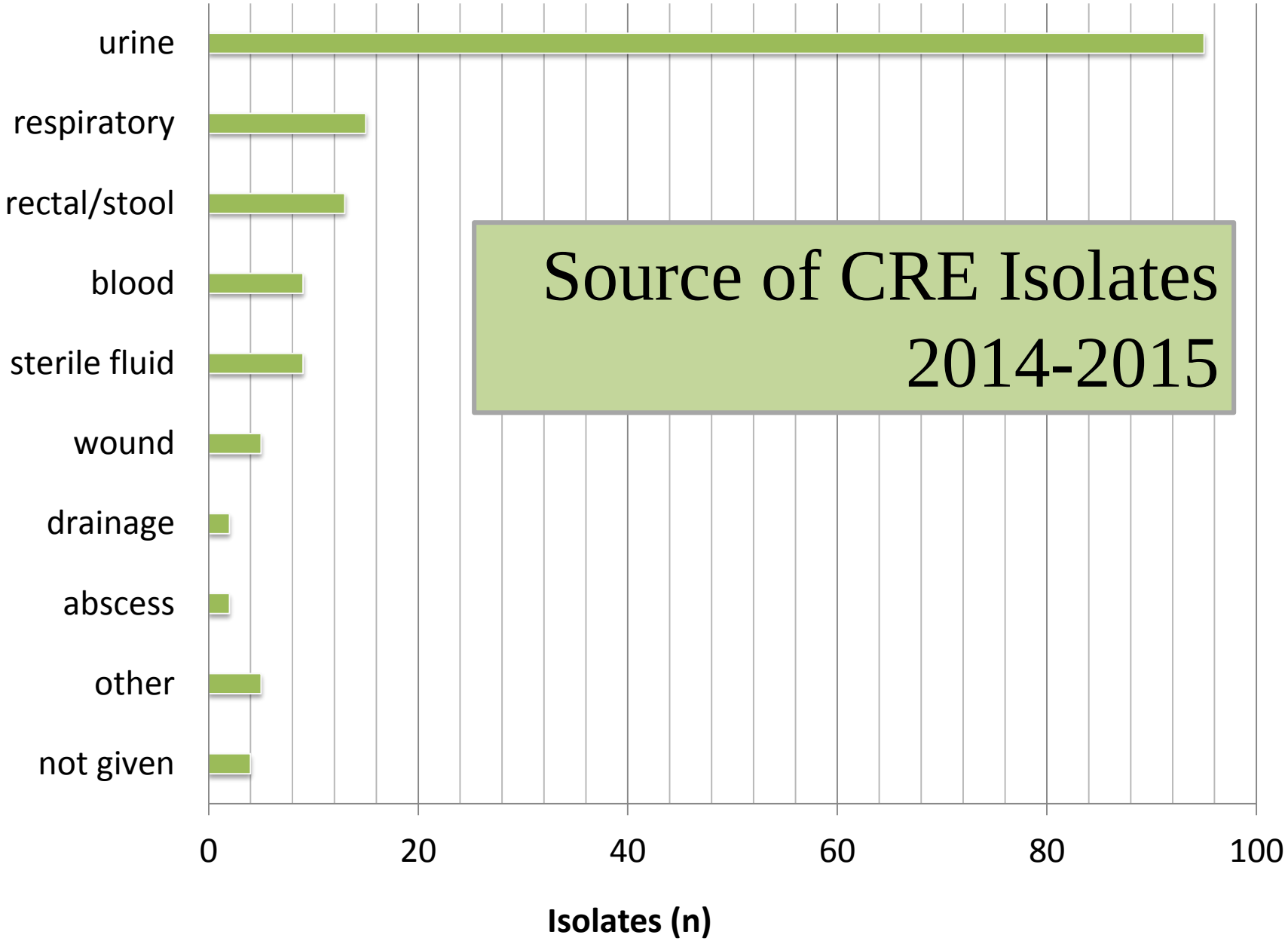
August 2014 – July 2015

ISDH performed CRE testing on 206 isolates submitted from 21 laboratories across the state.

- Each laboratory submitted on average 9-10 isolates [range 1-57]
- 77.2% met the CDC CRE-definition
- Testing Performed: 12-disc AST, MBL Etest, Modified Hodge, CarbaNP, KPC/NDM-1 PCR

Resistance Mechanisms of Submitted Isolates 2014-2015




Source of CRE Isolates 2014-2015
urine
respiratory
rectal/stool
blood
sterile fluid
wound
drainage
abscess
other
not given
0
20
40
60
80
100
Isolates (n)

Approximately 23% of CRE isolates submitted during this time period did not meet the CDC Definition.

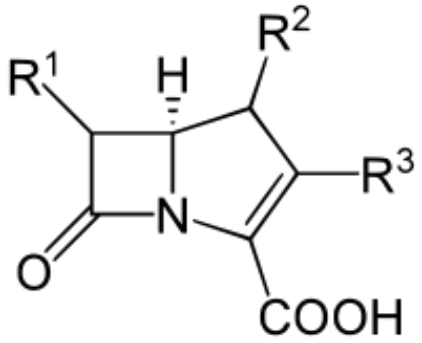
Sources of this potential discrepancy included:

1) Differences in AST interpretation
2) Number of 3rd generation cephalosporins routinely tested by the submitting laboratory
3) Center-specific differences in interpretation

AST-based Review and Reporting: A Data-Driven Decision

Review of unnecessary submissions from 2013-2015:

- 98.8% of these submissions could have been prevented with the CDR algorithm:
  - 55.6% by specifying the MIC or Zone Diameter
  - 43.2% by assessing phenotypic carbapenemase production
- Only 58% of these submissions would have been prevented with an alternative submission criteria of resistance to only 2 carbapenems



Structure of carbapenem backbone, wikipedia.org

Challenges for Laboratories: AST-based Review and Reporting

- CLSI-independent criteria: MIC or zone diameter
- Resistance to 3 carbapenems removes requirement for phenotypic carbapenemase assessment
- Projected use of molecular markers as a means for screening in the future (ex. PCR, CarbaR)

Three day submission criteria …

(1) CP-CRE

(2) Haemophilus influenzae, invasive disease.

(3) Neisseria meningitidis, invasive disease.

(4) STEC

(5) VRSA

(6) Mycobacterium tuberculosis.

(7) S. pneumoniae invasive disease (<5yo)

(8) Listeria monocytogenes (sterile sites)

(9) Salmonella sp. (clinical specimen)

(10) Shigella sp. (clinical specimen)

(11) Vibrio cholerae (stool or vomit)

(12) Vibrio sp. (clinical specimen)

Day 1 – Receive isolate and subculture

Day 2* – Confirm ID and Perform PCR

- MALDI-TOF MS
- Multiplex PCR [KPC, NDM-1, OXA-48, IMP, VIM]

If Positive, report Finalized result.

- Ex. *Klebsiella pneumoniae*, KPC positive

If Negative – report Preliminary Negative.

Day 3 – CarbaNP on PCR negative specimens

If Positive, send to CDC for further testing.

If Negative, report out as Negative.

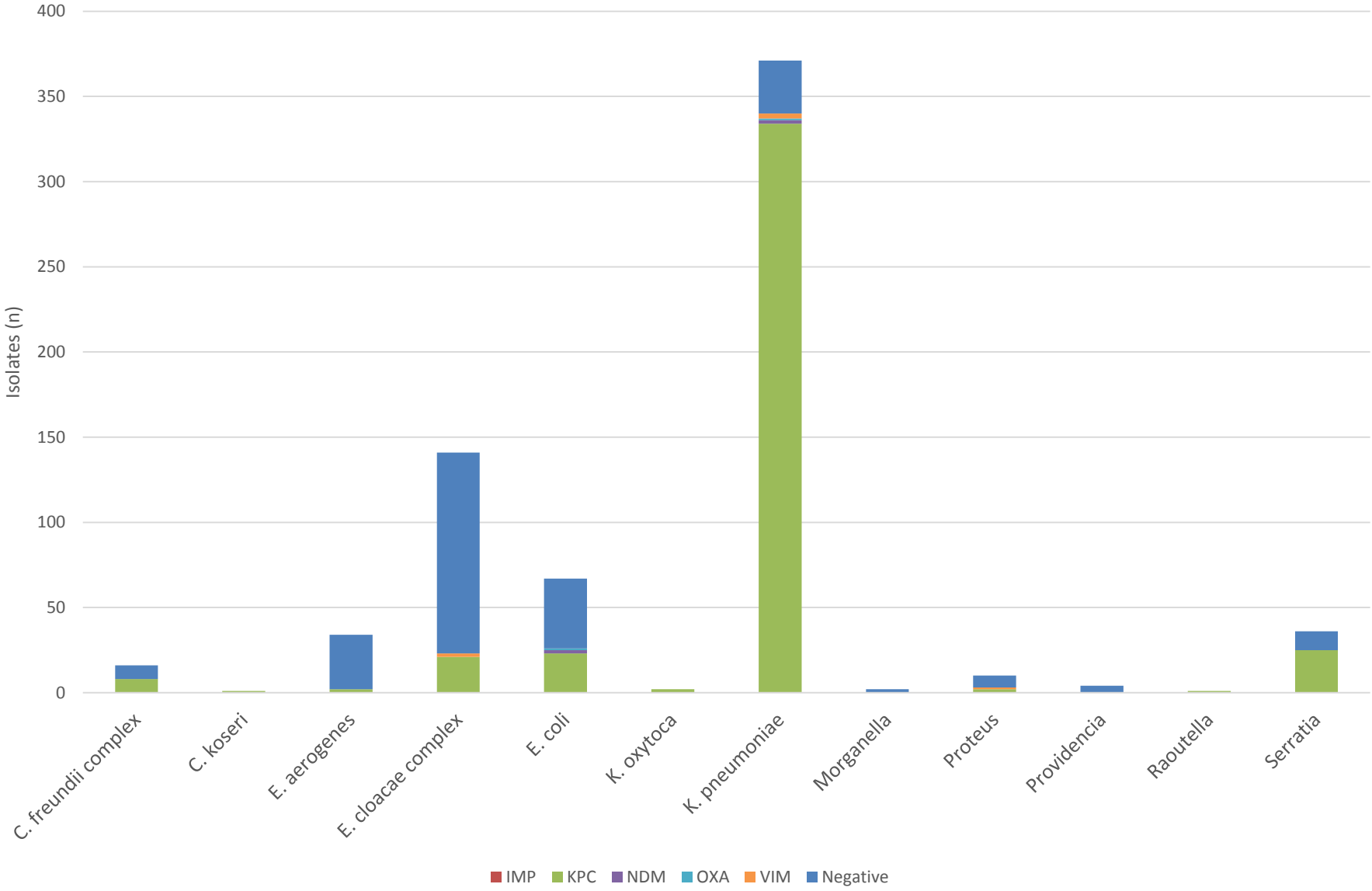
ISDH Algorithm

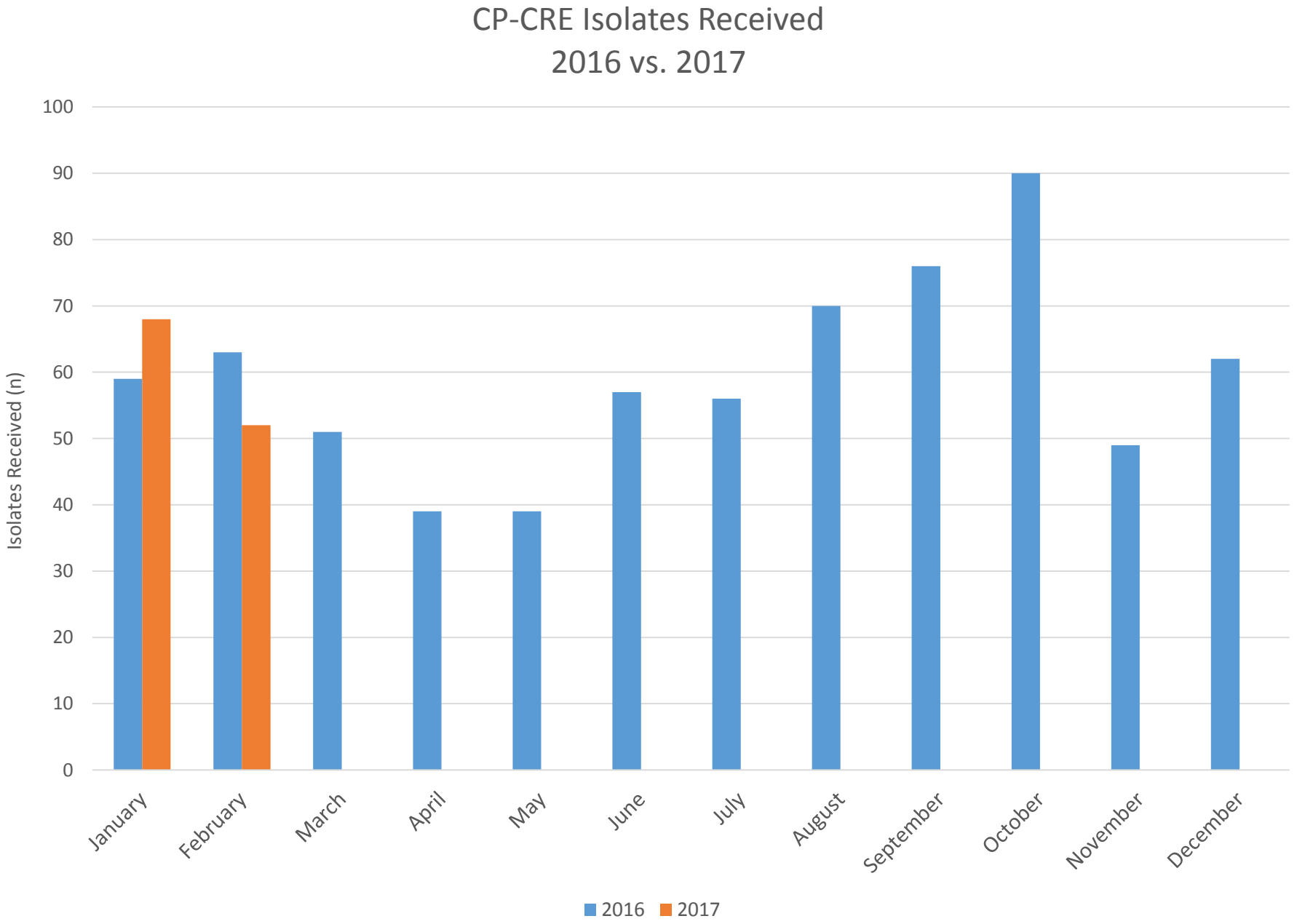
CDR went into effect December 25, 2015

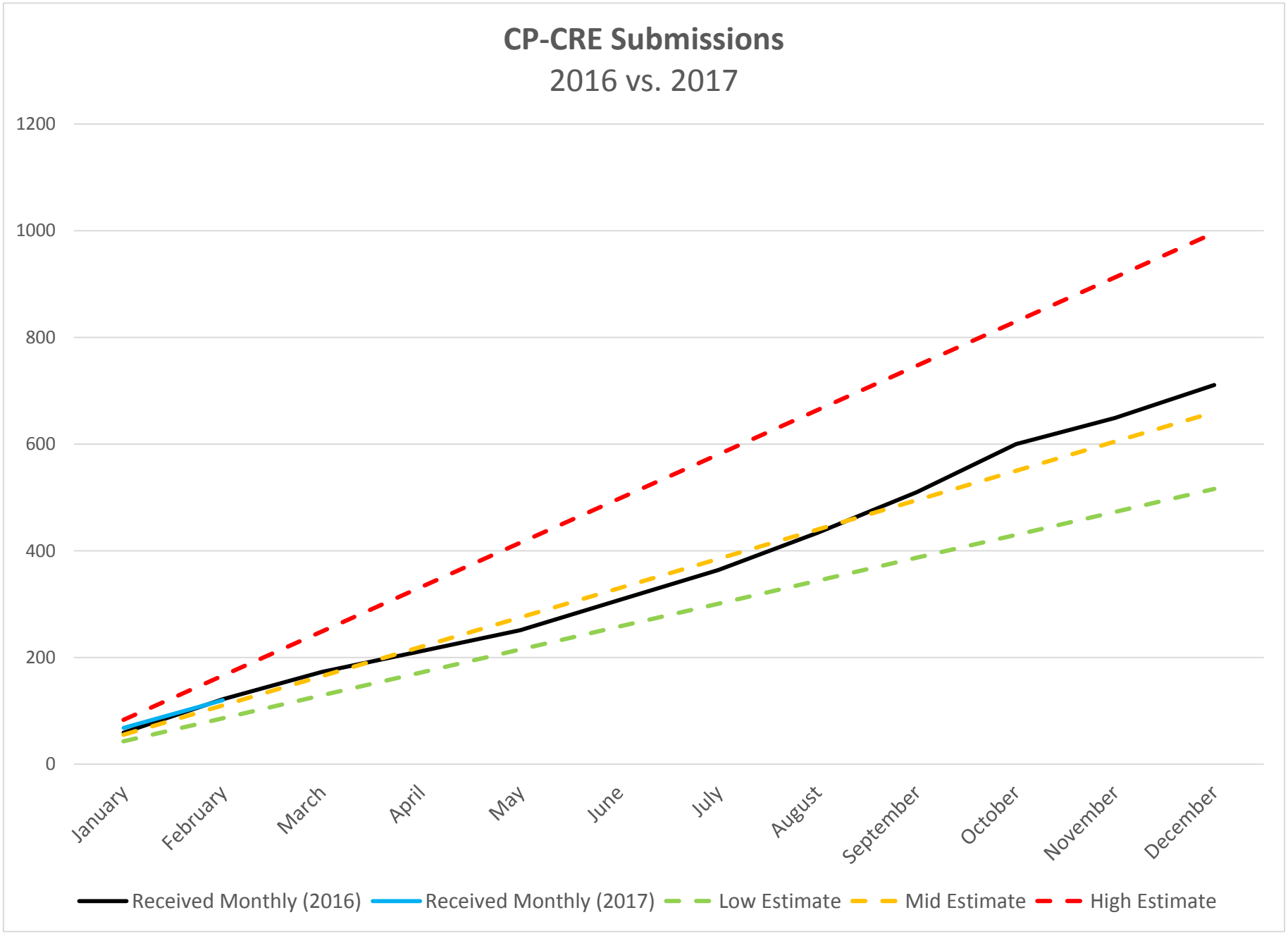
What does CP-CRE look like now?

ISDH Isolate Results

December 25, 2015 - February 28, 2017




CP-CRE Isolates Received
2016 vs. 2017
Isolates Received (n)
100
90
80
70
60
50
40
30
20
10
0
January
February
March
April
May
June
July
August
September
October
November
December
2016
2017


CP-CRE Submissions
2016 vs. 2017
1200
1000
800
600
400
200
0
January
February
March
April
May
June
July
August
September
October
November
December
Received Monthly (2016)
Received Monthly (2017)
Low Estimate
Mid Estimate
High Estimate

CP-CRE Submissions by County

December 25, 2015
through
October 15, 2016

Thanks to …

Jon Radosevic, Kelly Tippmann
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Mark Glazier
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Jyl Madlem

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NEXT UP: Break

THEN: Overview of CarbaNP Test