December 2014

Dear Laboratory Director,

The Illinois Department of Public Health (IDPH) amended the Control of Communicable Diseases Code (77 Ill. Adm. Code 690) to require reporting of Carbapenem-Resistant Enterobacteriaceae (CRE) to IDPH as of November 1, 2013. CRE are extensively drug-resistant organisms (XDROs) that can spread quickly and have been increasingly detected among patients in Illinois. All hospitals, long-term care facilities, long-term acute care hospitals, hospital-affiliated clinical laboratories, and independent or free-standing laboratories in Illinois are required to report CRE isolates that meet surveillance criteria to the XDRO registry.

To provide clear communication about CRE and reporting to the XDRO registry, IDPH’s Division of Patient Safety and Quality is providing your laboratory with the attached educational resources developed in collaboration with the Chicago Department of Public Health and input from experts on the CRE Task Force. Materials include:

- “CRE Laboratory Testing” and “CRE Lab Testing Recommendations” — in-depth recommendations on CRE laboratory detection
- “Recommended Laboratory Procedures for Testing CRE” — flowchart to determine whether an isolate is a CRE, with recommended testing and submission procedures for all testing capabilities
- “CRE: Submitting Samples to IDPH” — further guidelines on which CRE isolates should be submitted to the IDPH Laboratory
- “Confirmation of CRE Isolates Reported to the XDRO Registry” — memo to clinical laboratories requesting participation in a CRE laboratory validation project through July 31, 2015
- “Report CRE isolates to the XDRO registry” — flowchart on which isolates meet CRE surveillance criteria and should be reported to the XDRO registry
- “The XDRO Registry” — fact sheet on the XDRO registry and reporting requirements
- “IL CRE Detect and Protect Campaign” — fact sheet on the “Detect and Protect” education campaign

We hope that this will be a useful reference and we thank you for your cooperation in this important initiative to improve CRE control.

Sincerely,

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CRE Laboratory Testing

Background:
Carbapenem-resistant Enterobacteriaceae (CRE) are a growing concern in healthcare settings because these multidrug-resistant bacteria can cause serious and difficult-to-treat infections. CRE have disseminated widely throughout the United States since being first reported to the Centers for Disease Control and Prevention (CDC) in 2001. While Enterobacteriaceae producing Klebsiella pneumoniae carbapenemase (KPC) have been responsible for much of the CRE increase in the United States, other carbapenemases, such as New Delhi-metallo-β-lactamase (NDM), have been identified in the United States since 2009. In response to the CRE public health threat, the Illinois Department of Public Health (IDPH) has amended the Control of Communicable Disease code to require reporting of identified CRE to IDPH through a tool called the XDRO registry.

Laboratory Detection:
Accurately identifying CRE species in the clinical laboratory is an important first step in detecting and preventing transmission of CRE. Susceptibility tests alone may not reliably detect CRE; phenotypic or molecular tests are needed to detect resistant species so that susceptibility reports may be modified. In conjunction with susceptibility testing, phenotypic or molecular tests allow for identification of mechanisms of resistance. These tests are of fundamental importance for the purpose of epidemiological surveillance to ensure recognition of emerging resistant pathogens and to prevent patients from receiving ineffective antibiotics resulting in adverse clinical outcomes.

Testing Recommendations:
In collaboration with local subject matter experts and CDC, the Chicago Department of Public Health has developed laboratory guidance that identifies best practices which can be implemented in any laboratory setting to ensure appropriate testing and identification of CRE in both clinical and surveillance cultures. Recommendations focus on ensuring laboratories implement current CLSI breakpoints for carbapenems and cephalosporins, and perform phenotypic or molecular tests for E. coli and Klebsiella spp. non-susceptible to any of the carbapenems and resistant to all 3rd generation cephalosporins.

The XDRO registry aims to improve CRE surveillance and improve inter-facility communication. However, both of these goals are tied to the ability of clinical laboratories to effectively detect CRE. It is therefore important that laboratories implement testing procedures that include methodologies to detect CRE in clinical and surveillance cultures and promptly notify infection preventionists when CRE is identified.
CRE Laboratory Testing Recommendations

Carbapenem-resistant Enterobacteriaceae (CRE) are a growing problem in healthcare settings because these multidrug-resistant bacteria can cause serious and difficult-to-treat infections. Organisms that express Klebsiella pneumoniae carbapenemase (KPC) and New Delhi metallo-beta-lactamase (NDM) are of particular concern in the Chicago area. Laboratory ability to accurately detect bacteria capable of producing these enzymes is essential to controlling and preventing the spread of infections with these organisms.

Pre-2010 CLSI minimum inhibitory concentration (MIC) breakpoints on automated antimicrobial susceptibility testing (AST) instruments may misidentify some isolates that are producing carbapenemases as susceptible (S) on the automated report. Additionally, determination of mechanisms of resistance by phenotypic or molecular techniques is fundamental for precise reporting of results, epidemiological investigations and targeted implementation of infection control precautions.

Susceptibility Testing Interpretive Criteria for Carbapenems

Updates for laboratories using automated AST systems:

1. If using CLSI breakpoints from 2010 or later, report as interpreted by automated AST system.
2. For susceptibility testing of Enterobacteriaceae performed using 2009 CLSI carbapenem MIC breakpoints:

   Review AST report. If a validation study has been completed, edit the report to reflect updated CLSI MIC breakpoints as follows:

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>≤ 4</td>
<td>8</td>
<td>≥ 16</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≤ 4</td>
<td>8</td>
<td>≥ 16</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≤ 2</td>
<td>4</td>
<td>≥ 8</td>
</tr>
<tr>
<td>Doripenem</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

   In the absence of a validation study, consider all isolates with imipenem, meropenem or doripenem MIC ≥ 2 µg/mL, or ertapenem MIC ≥ 1, to be non-susceptible to any carbapenem.

Updates for laboratories using disk diffusion methods:

For susceptibility testing of Enterobacteriaceae phenotypic detection of beta-lactam resistance using disk diffusion methods:

Review susceptibility report. Edit the report to reflect updated CLSI disk zone breakpoints as follows:

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imipenem</td>
<td>≥ 16</td>
<td>14-15</td>
<td>≤ 13</td>
</tr>
<tr>
<td>Meropenem</td>
<td>≥ 16</td>
<td>14-15</td>
<td>≤ 13</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>≥ 19</td>
<td>16-18</td>
<td>≤ 15</td>
</tr>
<tr>
<td>Doripenem</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Revised 12/2014
Phenotypic Detection of Carbapenemase Production in Isolated Bacterial Colonies

For *E. coli* and *Klebsiella* spp. non-susceptible to any carbapenem and resistant to all 3rd generation cephalosporins, test for carbapenemases. Testing should include a method for detection of metallo-beta-lactamase (MBL). Examples of acceptable testing methods are shown below.

- **Modified Hodge Test (MHT)**
- MBL Etest
- MBL Screen test
- Tablet/disc diffusion detection of KPC/MBL resistance mechanisms
- Boronic Acid Inhibition Test for KPC and AmpC
- Broth microdilution-BMD MBL screen
- CarbaNP test to detect carbapenemases
- MALDI-TOF detection of carbapenemases

*These tests have the potential to detect MBL production.*

An example of an acceptable testing and reporting strategy is given below.

1. Perform **Modified Hodge Test (MHT)** for carbapenemase detection AND Perform MBL Etest.

2. If MBL Etest positive, regardless of MHT results, report results as follows:
   
   “**Carbapenem resistant Enterobacteriaceae (CRE) detected by EDTA Inhibition Test –probable MBL type. Implement infection control measures according to facility policy.**”
   
   **Isolates that are MBL positive should be forwarded to IDPH lab for confirmation and further characterization. Prior to sending specimens, laboratories should contact local health department for approval. The authorization number provided by the LHD must be printed on the laboratory test requisition form in order for the specimen to be tested.**

3. If MHT positive, but MBL Etest negative report results as follows:
   
   “**Carbapenem resistant Enterobacteriaceae (CRE) detected by Modified Hodge Test –probable KPC type. Implement infection control measures according to facility policy.**”

**Molecular Methods for Carbapenemase Detection in Isolated Bacterial Colonies**

Where available, nucleic acid-based detection methods are rapid and sensitive means to determine the mechanism of carbapenem resistance. Molecular methods allow for detection of resistance genes that encode for specific beta-lactamase enzymes. **PCR testing** of Enterobacteriaceae allows for detection of genes that encode carbapenemases such as KPC and NDM.
Active Surveillance for CRE

Active surveillance allows for detection of patients colonized with CRE in the intestinal tract. Patients who are found to be colonized or infected with CRE should be placed on Contact Precautions in order to prevent transmission of the resistant bacteria.

Screening methods for CRE include:

- Broth enrichment followed by selective culture on MacConkey agar\textsuperscript{10}.
- Direct Kirby Bauer disk test\textsuperscript{11,12,13}.
- Chromogenic agar\textsuperscript{14,15,16,17}.
- Real-Time PCR\textsuperscript{18,19,20}. 
References:


10. Laboratory protocol for detection of carbapenem-resistant or carbapenemase-producing Klebsiella spp. and E. coli from rectal swabs. Centers for Disease Control and Prevention, Atlanta, GA; 2009.


Recommended Laboratory Procedures for Testing Carbapenem-Resistant Enterobacteriaceae (CRE)

Susceptibility Testing

- Is the isolate:
  - a) in the Enterobacteriaceae family
  - b) RESISTANT to all tested third generation cephalosporins (e.g., ceftaxone, cefotaxime, & ceftazidime)

  **NO**

  Likely not CRE. No further testing.

  **YES**

  Isolate I or R to imipenem, meropenem, and/or doripenem (ignore ertapenem)?

  **NO**

  Is lab using CLSI 2010 or later carbapenem breakpoints?

  **YES**

  NO (using old breakpoints)

  Is imipenem and/or meropenem MIC = 2 or 4 ug/ml?

  **YES**

  (or UNKNOWN [lower dilutions not on panel])

  **NO**

  Possible CRE. Continue Testing below

  For all possible CRE, labs should attempt to identify mechanism of resistance: Is the isolate a carbapenemase producer?

**Option A: Genotypic testing**
- **e.g., PCR**
  - Positive PCR
  - Negative PCR

**Option B: Phenotypic testing**
- For example: Modified Hodge Test (MHT) AND meropenem MBL Etest
  - Both tests Negative
  - Either test Positive
  - No other testing done

**Option C: Lab unable to identify mechanism of resistance**
- (No further testing or ONLY Modified Hodge Test done)

Carbapenemase-producing CRE (e.g., KPC, NDM, VIM, IMP, OXA)
- Submit isolate to IDPH if carbapenemase is NOT KPC.

Likely NOT carbapenemase-producing CRE
- Do not routinely submit isolate to IDPH.

Likely carbapenemase-producing CRE

Discuss result and epidemiologic risk factors with referring facility.
- Submit isolate to IDPH if patient has risk factors for non-KPC carbapenemase (e.g., international travel in last 6 months, exposure to non-KPC strains, or newly recognized cluster).

Negative MBL ETest and **Positive** MHT
- Likely KPC-producing CRE
  - Do not submit isolate to IDPH unless KPC has not previously been identified in your laboratory.

Positive MBL ETest (MHT positive OR negative)
- Likely MBL-producing CRE (e.g., NDM, VIM)
  - Submit isolate to IDPH.

*Other phenotypic tests are available and may be used; this two-step process is most common.*
Carbapenem-Resistant Enterobacteriaceae (CRE):
Submitting Samples to the Illinois Department of Public Health

IDPH and CDC want to prioritize sample submission of CRE isolates other than KPC for further (genotypic) testing.

At a minimum, prior to submission, laboratories should confirm the identification of the organism, ensure pure cultures, and repeat resistance testing on isolates, with a different method if possible, to confirm resistance patterns.

Submit likely MBL-producing CRE isolates:

1) Must exhibit carbapenem resistance (I or R to imipenem, doripenem, or meropenem using updated breakpoints) and resistance (R) to all third-generation cephalosporins tested (e.g., ceftriaxone, cefotaxime, and ceftazidime)

AND

2) Must have phenotypic testing suggesting MBL (e.g., + MBL Etest or +multi-disk test) OR, if phenotypic testing not done, be isolated from a patient with international travel in last 6 months or epidemiologic link to a patient with non-KPC CRE.

Additional Recommended Trainings

Sentinel Labs TRAIN courses: www.train.org

- Sentinel220 Transportation Security Awareness (20 minutes)
- Sentinel221 Packaging and Shipping Infectious Substances (1.5 hours)

IDPH
Illinois Department of Public Health

Revised 11/2014
TO: Hospital Laboratories, Laboratory Directors, Sentinel Laboratories

FROM: Bernard T. Johnson  
Chief, Division of Laboratories

Mary Driscoll  
Chief, Division of Patient Safety and Quality

DATE: December 2, 2014

SUBJECT: Confirmation of Carbapenem-Resistant Enterobacteriaceae (CRE) Isolates Reported to the Illinois Extensively Drug-Resistant Organism (XDRO) Registry

The Illinois Department of Public Health (IDPH) Divisions of Laboratories (DOL) and Patient Safety and Quality (DPSQ) request your assistance in confirming CRE isolates that you are reporting in the Illinois XDRO registry.

According to current Illinois surveillance criteria, CRE are Enterobacteriaceae with one of the following laboratory test results:

1. Molecular test (e.g., polymerase chain reaction [PCR]) specific for carbapenemase; or
2. Phenotypic test (e.g., Modified Hodge) specific for carbapenemase production; or
3. Susceptibility test (for *E. coli* and *Klebsiella spp* only): non-susceptible (intermediate or resistant) to ONE of the following carbapenems (doripenem, meropenem, or imipenem) AND resistant to ALL of the following third-generation cephalosporins tested (ceftriaxone, cefotaxime, and ceftazidime). *Note: ignore ertapenem for this definition.*

To ensure that CRE isolates identified in Illinois and entered in the XDRO registry meet this definition, and to better characterize isolates being reported based on susceptibility testing and/or phenotypic testing, the IDPH has engaged in a program with Rush University to confirm and further characterize reported CRE isolates.

IDPH asks that your facility please submit up to five (5) CRE isolates to the IDPH Laboratory in Chicago between now and July 31, 2015.

- Submit isolates on slants (see shipping and contact information below). If your facility’s testing methods are different for clinical versus screening isolates, submit a mix of these isolates up to a total of 5. Please indicate whether the submitted isolate is a clinical or screening isolate.
- Submit the standard IDPH test requisition form.
- Indicate the CRE genus and species.
- Indicate the test/methods used to determine that the isolate is a CRE and any further characterization done at your facility. Please be specific about the methods employed in your facility, e.g.,
  - “Susceptibility testing only”
  - “Susceptibility testing and Modified Hodge”
  - “Modified Hodge and MBL (E test)”
  - “Molecular testing”
  - “Other—provide details”
- Please provide results of all CRE testing that was done.
Isolates will be sent to Rush University laboratory, where conventional methods will be used to confirm the isolate as CRE as defined above. Once confirmed, the laboratory will use molecular methods to detect the *Klebsiella pneumoniae* carbapenemase (bla*<sub>KPC</sub>*) and/or New Delhi metallo-β-lactamase (bla*<sub>NDM</sub>*) genes. Organisms that produce a carbapenemase other than these may be shipped to the CDC for further molecular characterization.

The IDPH DOL will send you test results from Rush University and the CDC (if referred).

Based on the results, the DPSQ may follow up with your facility to change the results entered in the XDRO registry. Results will also be used for future educational workshops.

**NOTE:** After your facility has submitted the 5 isolates for this confirmation program, return to the routine practice of only submitting CRE isolates that have undergone phenotypic or molecular testing suggesting they are producing a carbapenemase other than KPC (e.g., metallo-β-lactamase-producing isolates). Return to your regular algorithm and submit only these isolates to IDPH for further testing by CDC.

Ship specimens meeting the criteria above to:

Illinois Department of Public Health  
Clinical Microbiology Laboratory  
2121 West Taylor Street  
Chicago, IL  60612

If you have any questions for the Division of Laboratories about specimen submission procedures, please call the Clinical Microbiology Laboratory at (312) 793-4760. If you have general questions about this project, please call the Division of Patient Safety and Quality at (312) 814-3143.
Report Carbapenem-Resistant Enterobacteriaceae (CRE) isolates to the XDRO registry

Do NOT report to registry: ESBL, VRE, MRSA, other non-CRE isolates

(1) Is isolate in the Enterobacteriaceae family? (e.g., Klebsiella, Escherichia coli, Enterobacter, Serratia, Proteus, others)
   - NO: Do NOT Report: Pseudomonas, Acinetobacter, other non-Enterobacteriaceae
   - YES

(2) Is isolate non-susceptible (INTERMEDIATE or RESISTANT) to imipenem, meropenem, and/or doripenem?
   - NO: Do NOT Report: Isolates that are non-susceptible ONLY to ertapenem
   - YES

(3) Is isolate RESISTANT to all tested third-generation cephalosporins? (e.g., ceftriaxone, cefotaxime, ceftazidime, others)
   - NO: Do NOT Report: Isolates that are sensitive or intermediate to any third-generation cephalosporin
   - YES

(4) Is isolate E. coli or Klebsiella spp.?
   - NO: Was further laboratory testing (see #6) done that suggests carbapenemase enzyme (e.g., KPC, NDM, VIM, IMP, OXA)?
     - YES: Do NOT Report: Isolates other than E. coli or Klebsiella spp., unless further laboratory testing is positive
     - NO

(5) Report to XDRO registry, even if no further laboratory testing done. Reporting further laboratory results is encouraged.
   - YES

(6) Report CRE laboratory results suggesting carbapenemase production (e.g., likely KPC, NDM, VIM, IMP, OXA)
   - (a) Positive genotypic (PCR) results AND/OR
   - (b) Positive phenotypic (e.g., Modified Hodge with MBL Etest) results

IDPH

XDRO registry website: www.xdro.org ● XDRO registry e-mail: DPH.XDROregistry@illinois.gov
The Extensively Drug Resistant Organism (XDRO) Registry

The Illinois Department of Public Health (IDPH) has guided development of an infection control tool called the XDRO registry. The purpose of the XDRO registry is two-fold:

1. **Improve inter-facility communication:** The registry provides efficient information exchange across the spectrum of healthcare about patients who have tested positive for carbapenem-resistant Enterobacteriaceae (CRE).

2. **Improve CRE surveillance:** The registry stores CRE surveillance data and has features that can help facilities track their CRE submission history.

**Reporting Requirements**

- IDPH amended the Control of Communicable Diseases Code (77 Ill. Adm. Code 690) to require reporting of CRE to IDPH.
- As of November 1, 2013, the **first CRE-positive culture per patient stay** must be reported to the XDRO registry **within 7 calendar days** after the test result is finalized.
- All hospitals, hospital-affiliated clinical laboratories, independent or free-standing laboratories, longer-term care facilities, and long-term acute care hospitals in Illinois are required to report CRE isolates that meet surveillance criteria.

**CRE surveillance criteria**

Enterobacteriaceae (e.g., *E. coli*, *Klebsiella* spp, *Enterobacter* spp, *Proteus* spp, *Citrobacter* spp, *Serratia* spp, *Morganella* spp, or *Providentia* spp) with one of the following laboratory test results:

1. Molecular test (e.g., polymerase chain reaction [PCR]) specific for carbapenemase;
2. Phenotypic test (e.g., Modified Hodge) specific for carbapenemase production;
3. Susceptibility test (**for *E. coli* and *Klebsiella* spp only**): non-susceptible (intermediate or resistant) to ONE of the following carbapenems (doripenem, meropenem, or imipenem) AND resistant to ALL of the following third generation cephalosporins tested (ceftriaxone, cefotaxime, and ceftzidime). **Note: ignore ertapenem for this definition.**

**Highlighted Features**

- The XDRO Dashboard (shown at right) graphically shows data from a user’s facility and the state aggregate.
- The Search Registry function allows facilities to check whether a patient has been previously reported as CRE-positive.

For **more information about and access to the XDRO registry**, visit: [www.xdro.org](http://www.xdro.org)

For XDRO registry questions, contact: DPH.XDROregistry@illinois.gov

Revised 11/2014
Illinois CRE Detect and Protect Campaign

The Illinois Department of Public Health (IDPH) is leading a statewide education campaign to promote practices that prevent carbapenem-resistant Enterobacteriaceae (CRE).

- CRE are extensively drug-resistant organisms (XDROs) that can spread quickly and have been increasingly detected among patients in Illinois.
- IDPH is working with healthcare facilities, laboratories, and local health departments to adopt the Centers for Disease Control and Prevention strategy of detecting CRE and protecting patients through appropriate infection control and prevention measures.
- A statewide CRE Task Force is helping to guide efforts. This multidisciplinary group of over 30 infectious disease, infection prevention, and laboratory experts is developing recommendations to track and control the spread of these deadly superbugs.

During the campaign, IDPH Division of Patient Safety and Quality has provided educational materials and a webinar series on CRE prevention and mandatory reporting of CRE to the XDRO registry. Six archived webinars and presentation slides are available at http://www.idph.state.il.us/patientsafety/cre/webinars.htm:

<table>
<thead>
<tr>
<th>Webinar Title</th>
<th>Topic(s)</th>
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<tbody>
<tr>
<td>Long-Term Care Infection Prevention Starts at the Top</td>
<td>• Building patient safety and quality improvement initiatives in long-term care</td>
</tr>
<tr>
<td>CRE &amp; XDRO for Long-Term Care Facilities</td>
<td>• CRE prevention practices for long-term care</td>
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<tr>
<td></td>
<td>• Interpreting lab reports</td>
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<tr>
<td></td>
<td>• Using the XDRO registry</td>
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<tr>
<td>Patient Safety and Quality Starts at the Top</td>
<td>• Prioritization of infection prevention and patient outcomes through structure, focus, and measurement for hospitals</td>
</tr>
<tr>
<td>CRE &amp; XDRO: What Hospital IC/Ps Need to Know</td>
<td>• CRE prevention practices for hospitals</td>
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<td>• Interpreting lab reports</td>
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<td>• Using the XDRO registry</td>
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<tr>
<td>CRE Detect and Protect: the Role of Local Health Departments</td>
<td>• Outbreak response</td>
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<tr>
<td></td>
<td>• Surveillance and reporting</td>
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<tr>
<td>Laboratory Detection and Reporting of CRE</td>
<td>• Laboratory detection methods</td>
</tr>
<tr>
<td></td>
<td>• Reporting to the XDRO registry</td>
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</tbody>
</table>

For more information, visit: http://www.idph.state.il.us/patientsafety/cre/index.htm or https://www.xdro.org/cre-campaign/index.html

For questions, contact the CRE Project Directors:

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The Illinois CRE Detect and Protect Campaign is funded by an Affordable Care Act award from the U.S. Centers for Disease Control and Prevention.