

Guidance on screening and confirmation of carbapenem resistant *Enterobacteriaceae* (CRE)

December 12, 2011



Objectives:

- To discuss the guidelines for detection of CRE in the laboratory setting.
- To review process for submission of isolates to PHO Laboratory.
- To review the voluntary surveillance program for CRE.

The Issue

- Transmission of CRE has been identified in some Ontario hospitals
- To date we have limited epidemiology on the actual status of CRE in Ontario
- Without this information, we may be unable to prevent CRE from becoming endemic in Ontario hospitals and our communities

What are CRE?

- Carbapenem-resistant *Enterobacteriaceae* are *Enterobacteriaceae* that are resistant to carbapenem antimicrobials through the production of carbapenemase
- To date, carbapenemases have been found most commonly in *E. coli* and *Klebsiella* spp – but have also been found in other Gram-negative species
- Carbapenemases are a class of enzymes that inactivate carbapenem antibiotics
- The genetic information to produce carbapenemases is often located on a mobile genetic element
 - Can carry this resistance to other classes of antimicrobials

Classes of carbapenemase

- Several different classes exist
- Each class has a three-letter acronym
 - KPC = *Klebsiella pneumoniae* carbapenemase
 - NDM = New Delhi metallo- β -lactamase
 - VIM = Verona integron-encoded metallo- β -lactamase
- Enzymes other than NDM have almost exclusively been found in hospitals
- NDM has been found in both hospitals and the community

Acquisition of CRE

- Risk factors for infection and colonization with CRE will be similar to those of other Gram-negative bacteria
- To date, the major risk factor appears to be receipt of health care in setting that have CRE
 - Hospitals along the eastern US seaboard -particularly New York City (KPC)
 - Greece (KPC)
 - Israel (KPC) and
 - The Indian subcontinent (NDM-1) – people coming from the Indian subcontinent with or without exposure to healthcare are also a risk

Transmission of CRE

- Transmission is via direct and indirect contact
- Site of colonization is the lower gastrointestinal tract
- Although the environment has rarely been implicated in outbreaks, sinks and other environmental surfaces have been implicated in transmission of *Klebsiella* and *Pseudomonas* spp.
- Acquisition of resistance may also occur by transmission of the mobile genetic element carrying the carbapenemase between different bacterial strains and species

Work to date

- PIDAC-IPC has updated the best practice document on Routine Practices and Additional Precautions and added information on CRE to Annex A to provide guidance to healthcare providers
 - As part of the process, PIDAC conducted a literature search for scientific information on CRE
- PHO Laboratory convened a working group to provide guidance to laboratories to assist in identification of CRE
 - Many community laboratories stated that they were unable to identify CRE within their own laboratories

The Challenge

- Information on CRE continues to evolve as additional surveillance data becomes available
- So far PHO Laboratory has confirmed and identified following carbapenemases:
 - 28 NDM
 - 27 KPC
 - 5 OXA-48
 - 3 VIM
 - ❖ This is a partial list as not all hospital labs send their specimens to PHO Laboratory. Academic health science centres perform their own testing
- Experience in other settings has demonstrated that an active surveillance program is central to controlling CRE

TESTING AND REPORTING CARBAPENEMASE-PRODUCING CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (CRE)

QMP-LS Recommendations

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Vice Chair, Microbiology Committee, QMP-LS

Sent: December 7, 2011 12:24 PM

Subject: QMP-LS Notice – Bacteriology Consensus Recommendations – Antimicrobial Reporting

QMP-LS NOTICE

The document [Consensus Recommendations - BACT - AST Reporting – 2011](#) is now available in QView™. It has been posted in the folder: [General - EQA / EQA Guidelines and Recommendations / Microbiology / BACT / Antimicrobial Susceptibility Reporting Recommendations – BACT](#)

IMPORTANT

This updated consensus document (previously named a guideline)—*Antimicrobial Susceptibility Testing and Reporting on Bacteriology Specimens*—contains significant changes from the previous version (March 16, 2010). Key changes are found in the appendices:

Appendix A (ESBL) and Appendix B (AmpC) were formerly housed in the broadsheet “Extended-Spectrum β -lactamase and AmpC Resistance in Gram-negative Bacilli.” These have been updated and added to this document. The broadsheet has been archived.

NEW Appendix C (carbapenemase-producing, carbapenem-resistant *Enterobacteriaceae*) has been developed by the QMP-LS Microbiology Committee with stakeholder input from Public Health Ontario and other key experts in microbiology and infection control.

If you have questions please contact Christine Fleming

Tel: 416.323.9540/1.877.323.9540 ext. 238

fleming@qmpls.org

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QView



Documents

[-] EQA Guidelines and Recommendations

Anatomical Pathology

[+] Chemistry

[+] Cytology

Genetics

[+] Hematology

[-] Microbiology

[-] BACT

[+] Anaerobes Guideline - BACT

[-] Antimicrobial Susceptibility Reporting Recommendations - BACT

Announcement - PHO Webinar Guidance on Screening and Confirmation of CRE

Committee Comments - BACT 0606 PP

Consensus Recommendations - BACT - AST Reporting - 2011

Participant Feedback - BACT - Antimicrobial Susceptibility Reporting

QView



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 - Announcement - PHO Webinar Guidance on Screening and Confirmation of CRE
 - Committee Comments - BACT 0606 PP
 - Consensus Recommendations - BACT - AST Reporting - 2011
 - Participant Feedback - BACT - Antimicrobial Susceptibility Reporting

Background

- June 2010 – CLSI changed the carbapenems breakpoints so that CRE screening and confirmatory testing would no longer be necessary for directing therapy
- QMP-LS Recommendation:
Regardless of the screening breakpoints used, continue CRE screening and confirmatory testing

Background

- CLSI previously recommended the Modified Hodge Test which detects class A carbapenemase such as KPCs but it may miss metallo- β -lactamases such as NDM-1.
- Phenotypic inhibitor disks/tablets, on the other hand reliably detect NDM-1 and KPCs but will not detect Class D carbapenemases, such as OXA-48.

Algorithm

APPENDIX C: ALGORITHM FOR TESTING AND REPORTING CARBAPENEMASE-PRODUCING CARBAPENEM-RESISTANT *ENTEROBACTERIACEAE* (CRE) (CONT'D)

NOTE: *This algorithm is based on the best data currently available but may change as new information is published.*

Test the Following Organisms *Enterobacteriaceae*

Screening (use one or more of the following tests)*

Standard meropenem (10 µg) disk diffusion zone diameter \leq 25 mm

Rosco MRP10 meropenem tablet zone diameter \leq 26 mm

Broth microdilution/agar dilution meropenem MIC \geq 0.25 mg/L

Commercial Test Card/Panel†

*Screening criteria are based on EUCAST epidemiologic cut-offs.††

†Until automated instruments make panels/cards available that are able to report meropenem MICs as low as 0.25 mg/L, laboratories should either include a meropenem disk in parallel with their panel/card or use an ertapenem MIC screening cut-off of \geq 1 mg/L from their commercial system. Due to lack of specificity of this ertapenem cut-off, ertapenem screen-positive isolates should be followed by one of the meropenem disk/tablet screen tests as described above. Laboratories must validate commercial test cards/panels to ensure that there is agreement with a reference CLSI method.

Preliminary Reporting if Screen-Positive

A preliminary report such as the following should be released for all positive screen results and susceptible β -lactam, β -lactam/ β -lactamase inhibitor combinations and carbapenem results should not be reported:

“Screening tests suggest this organism may produce a carbapenemase. Further report to follow.”

Also consider adding susceptibility testing for tigecycline and colistin if there are no other susceptible reportable agents.

Confirmatory Test if Screen-Positive

All meropenem screen-positive isolates should be sent to a reference laboratory for confirmatory testing by PCR.

NOTE: Laboratories are also encouraged to simultaneously perform phenotypic testing using β -lactamase inhibitors (e.g. KPC + MBL Confirm Kit, Rosco Diagnostica, Denmark; Pro-Lab, Canada) in order to expedite preliminary reports of the type of carbapenemase present. Updated reports should be released as indicated in Table 1 on page 11.

Final Reporting

Carbapenemase PCR Positive

Enterobacteriaceae possessing a carbapenemase should be reported as resistant to all β -lactams, β -lactam/ β -lactamase inhibitor combinations and carbapenems. In addition, a note such as the following should be appended to the report alerting the clinician and Infection Control of the presence of a carbapenemase:

“This organism is POSITIVE for _____ carbapenemase (add specific carbapenemase that is confirmed) based on PCR. It is resistant to all penicillins, cephalosporins, β -lactam- β -lactamase inhibitor combinations and carbapenems (ertapenem, imipenem, meropenem and doripenem). Infection control precautions should be followed.”

Carbapenemase PCR Negative

Interpret and report the carbapenems using CLSI interpretive criteria and add the following note to the report:

“This organism is NEGATIVE by PCR for carbapenemase genes.”

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Carbapenemase PCR Negative

Interpret and report the carbapenems using CLSI interpretive criteria and add the following note to the report:
"This organism is NEGATIVE by PCR for carbapenemase genes."

Screening

Preliminary Reporting

Confirmatory Test

Final Reporting

Algorithm

APPENDIX C: ALGORITHM FOR TESTING AND REPORTING CARBAPENEMASE-PRODUCING CARBAPENEM-RESISTANT *ENTEROBACTERIACEAE* (CRE) (CONT'D)

NOTE: *This algorithm is based on the best data currently available but may change as new information is published.*

Test the Following Organisms
Enterobacteriaceae

Screening (use one or more of the following tests)†

Standard meropenem (10 µg) disk diffusion zone diameter ≤ 25 mm
Kovacs MEMO meropenem tablet zone diameter ≤ 25 mm
Broth microdilution agar dilution meropenem MIC ≤ 0.25 mg/L
Commercial Test Card Panel*

*Screening criteria are based on EUCAST epidemiologic cut-off.

† Until automated instruments make panel cards available that are able to report meropenem MICs as low as 0.25 mg/L, laboratories should either include a meropenem disk in parallel with their panel card or use an meropenem MIC screening cut-off of 0.25 mg/L from their commercial system. Due to lack of specificity of this meropenem cut-off, meropenem screening positive isolates should be followed by one of the meropenem disk tablet screen tests as described above. Laboratories must validate commercial test card panels to ensure that there is agreement with a reference CLSI method.

Preliminary Reporting if Screen Positive

NOTE: *This algorithm is based on the best data currently available but may change as new information is published.*

Final Reporting

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Enterobacteriaceae possessing a carbapenemase should be reported as resistant to all β -lactams, β -lactam- β -lactamase inhibitor combinations, and carbapenems. In addition, a note such as the following should be appended to the report alerting the clinician and infection control of the presence of a carbapenemase.

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Carbapenemase PCR Negative

Interpret and report the carbapenemase screen CLSI susceptibility criteria and add the following note to the report:

"This organism is NEGATIVE by PCR for carbapenemase genes."

Algorithm - Screening

Test the Following Organisms

Enterobacteriaceae

Screening (use one or more of the following tests)*

Standard meropenem (10 µg) disk diffusion zone diameter ≤ 25 mm

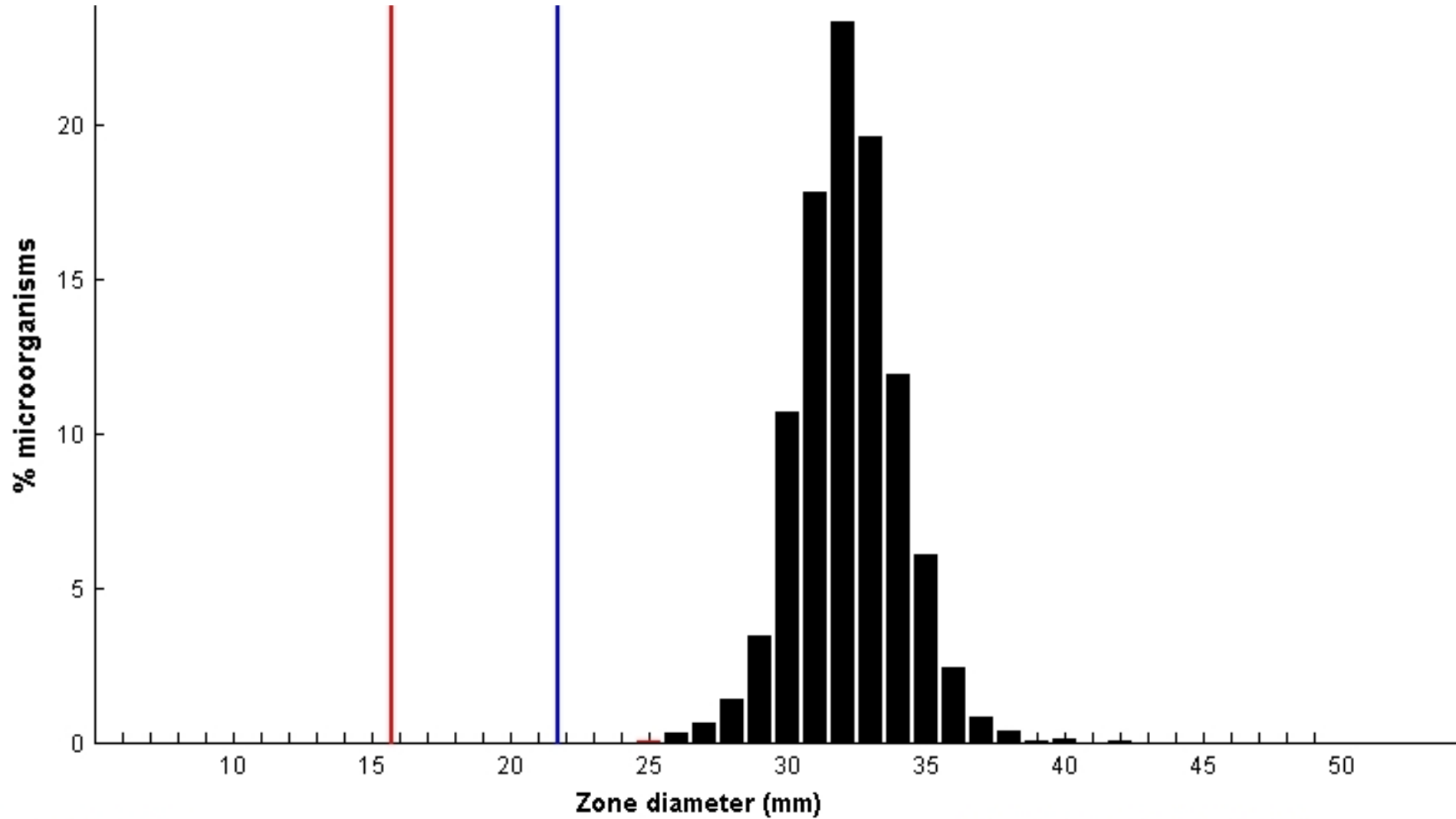
Rosco MRP10 meropenem tablet zone diameter ≤ 26 mm

Broth microdilution/agar dilution meropenem MIC ≥ 0.25 mg/L

Commercial Test Card/Panel†

**Screening criteria are based on EUCAST epidemiologic cut-offs.††*

E. coli Meropenem Disk Zone Diameter Distribution



Epidemiological cut-off: wild-type ≥ 26 mm (MIC ≤ 0.125 mg/L)

Algorithm - Screening

Test the Following Organisms

Enterobacteriaceae

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Standard meropenem (10 µg) disk diffusion zone diameter ≤ 25 mm

Rosco MRP10 meropenem tablet zone diameter ≤ 26 mm

Broth microdilution/agar dilution meropenem MIC ≥ 0.25 mg/L

Commercial Test Card/Panel†

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Algorithm - Screening

- † *Until automated instruments make panels/cards available that are able to report meropenem MICs as low as 0.25 mg/L, laboratories should either:*
 - 1) *include a meropenem disk in parallel with their panel/card or*
 - 2) *use an ertapenem MIC screening cut-off of ≥ 1 mg/L from their commercial system*
 - *Ertapenem screen-positive isolates should be followed by one of the meropenem disk/tablet screen tests.*
 - *Laboratories must validate commercial test cards/panels to ensure that there is agreement with a reference CLSI method.*

Algorithm – Preliminary Reporting

“Screening tests suggest this organism may produce a carbapenemase. Further report to follow.”


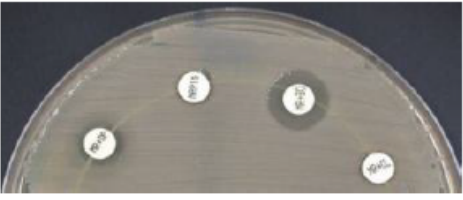

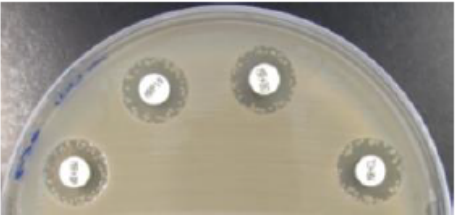
- *Susceptible β -lactam, β -lactam/ β -lactamase inhibitor combinations and carbapenem results should not be reported.*
- *Consider adding susceptibility testing for tigecycline and colistin if there are no other susceptible reportable agents.*

Algorithm – Confirmatory Test

All meropenem screen-positive isolates should be sent to a reference laboratory for confirmatory testing by PCR.

- *Laboratories are also encouraged to simultaneously perform phenotypic testing using β -lactamase inhibitors (e.g. KPC + MBL Confirm Kit, Rosco Diagnostica, Denmark; Pro-Lab, Canada) in order to expedite preliminary reports of the type of carbapenemase present.*

Phenotypic Testing using Inhibitors

Inhibitor Testing Results		Interpretation	Recommended Updated Report
Examples Disks are in the following order: MR-DP MRP10 MR-BO MR-CL	Inhibition detected		
	<input checked="" type="checkbox"/> DP only	Class B carbapenemase (MBL) (e.g. NDM-1)	“Additional testing suggests this organism produces a metallo-beta-lactamase carbapenemase (e.g. NDM-1). Confirmation to follow.”
	<input checked="" type="checkbox"/> BO only	Class A carbapenemase (e.g. KPC)	“Additional testing suggests this organism produces a class A carbapenemase (e.g. KPC). Confirmation to follow.”
	<input checked="" type="checkbox"/> Any other combination of inhibition	Possible carbapenemase	Keep the preliminary report unchanged.
	x	Suspicious for Class D carbapenemase (e.g. OXA-48)	Keep the preliminary report unchanged.

Algorithm – Final Reporting

Carbapenemase PCR POSITIVE

“This organism is POSITIVE for ____ carbapenemase (add specific carbapenemase that is confirmed) based on PCR. It is resistant to all penicillins, cephalosporins, β -lactam- β -lactamase inhibitor combinations and carbapenems (ertapenem, imipenem, meropenem and doripenem). Infection control precautions should be followed.”

Algorithm – Final Reporting

Carbapenemase PCR NEGATIVE

“This organism is NEGATIVE by PCR for carbapenemase genes.”

- *Interpret and report the carbapenems using CLSI interpretive criteria.*

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Screening

Preliminary Reporting

Confirmatory Test

Final Reporting



Questions?

Screening for colonization with carbapenem-resistant *Enterobacteriaceae* (CRE)

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Objectives

- To present overview of guidance document on laboratory methods for screening of CRE
- Risk factors
- To address laboratory procedures on identification of CRE with focus on:
 - Specimen collection
 - Initial screening
 - Confirmation of CRE
- Role of PHL in confirmation of CRE

The issue

- Prevalence of CRE is increasing
- In Ontario, transmission of CRE among hospitalized patients has been reported
- Screening for CRE colonization is challenging
- No reliable screening medium commercially available

Why guidance document was developed?

- PIDAC has recommended hospitals implement surveillance program for screening of CRE
- Patients with risk factors at admission should be screened for carriage
- Hospitalized patients exposed to known CRE should be screened for possible transmission
- There has not been any clear recommendations published on how labs should screen for CRE from screening specimens

Who should be screened for CRE?

- To date, the major risk factor appears to be receipt of health care in setting that have CRE
- United States (KPC)
- Greece (KPC)
- Israel (KPC)
- Turkey (OXA-48)
- Greece and Italy (VIM)
- Indian subcontinent (NDM-1)

What did PHOL do?

- A thorough literature was conducted to determine best method for detection of CRE organisms
- A group of experts discussed the need for a guidance document to inform laboratories how they can screen for CRE
- A consensus document was developed

Recommended specimens for screening

- Rectal swabs are recommended for screening patients for CRE carriage.
- Stool specimens are also acceptable but may be more difficult to obtain.
- Urine specimens may be considered in addition to rectal swabs for screening in patients with indwelling catheters and/or those who have had CRE isolated from urine specimens in the past.
- During outbreaks, the outbreak management team may consider requesting other specimens (e.g., sputum in intensive care unit patients, in whom CRE have caused pneumonia) for screening.

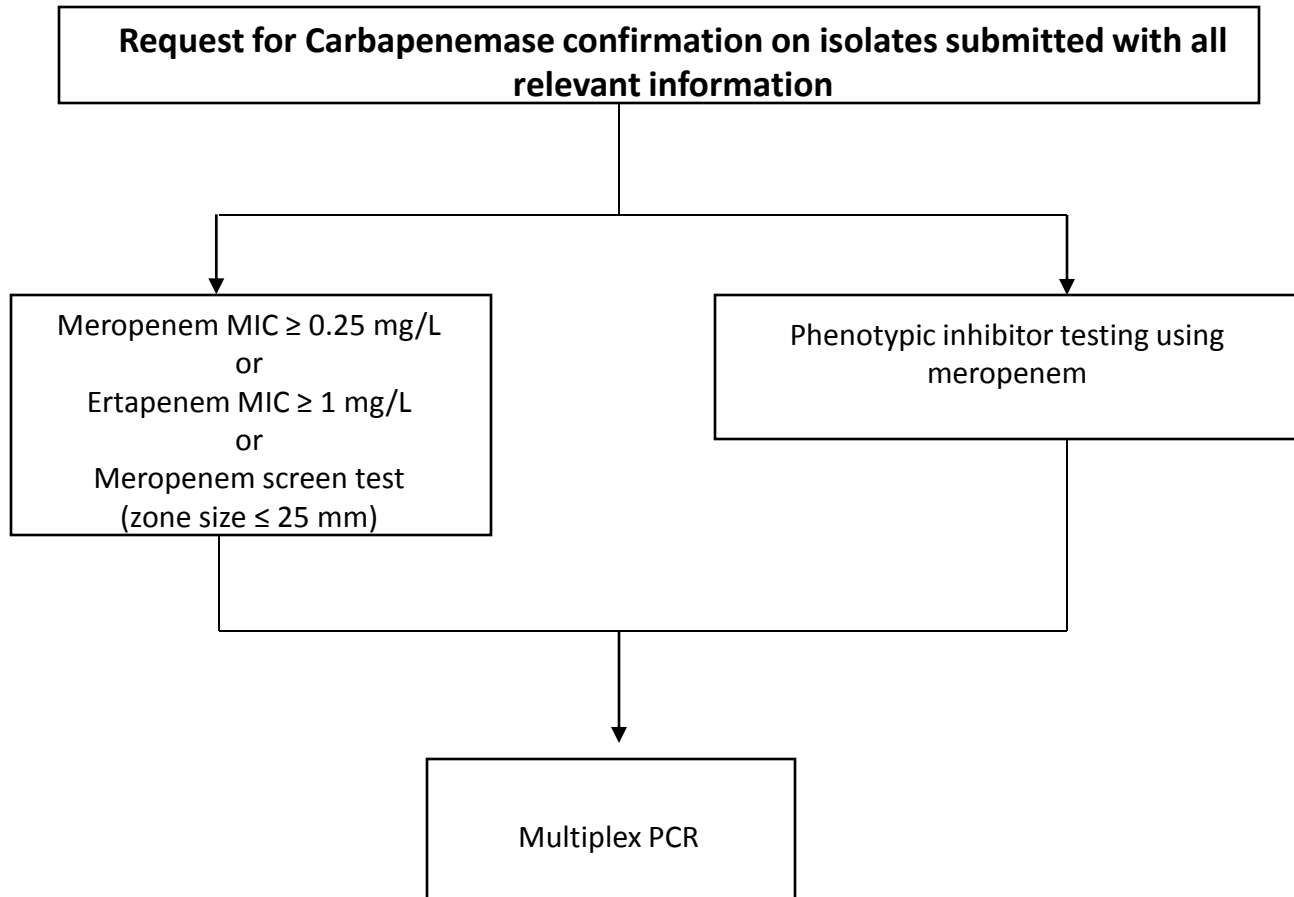
Processing Specimens in Laboratory

- Selective media currently available for isolation of ESBL-producing *Enterobacteriaceae* are recommended
- Chromogenic ESBL selective media should be avoided since most contain inhibitor of ampC
- *Enterobacteriaceae* grown on ESBL-selective medium should warrant further work-up
- Perform disk diffusion test using meropenem disc on Mueller-Hinton agar plate
- Isolates exhibit zone size ≤ 25 mm should be screened using phenotypic inhibitor test and/or molecular testing methods
- Isolates should be forwarded to PHL confirmation

Isolates forwarded to PHL

- In order to receive confirmation result from PHL in a timely manner, following information MUST be provided on requisitions:
 - Identification of isolate
 - Carbapenem susceptibility testing results
 - Meropenem screening results
 - Phenotypic inhibitor testing results (if available)
- Isolates with incomplete information will result in longer delays

Algorithm at PHL



The Challenge

- The information on epidemiology, transmission, and detection of CRE is evolving rapidly
- Early detection is essential in preventing transmission among hospitalized patients and spreading into community settings
- As more data become available, algorithm may change to improve sensitivity/specificity and efficiency

Thank you

- For more information:

www.oahpp.ca

--Management of carbapenem resistant *Enterobacteriaceae*
(CRE)

Dr. Samir Patel

Clinical microbiologist

Reference antimicrobial susceptibility testing

samir.patel@oahpp.ca

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Carbapenamase-resistant Enterobacteriaceae (CRE) Surveillance

Camille Achonu

Epidemiologist, Hospital Infections



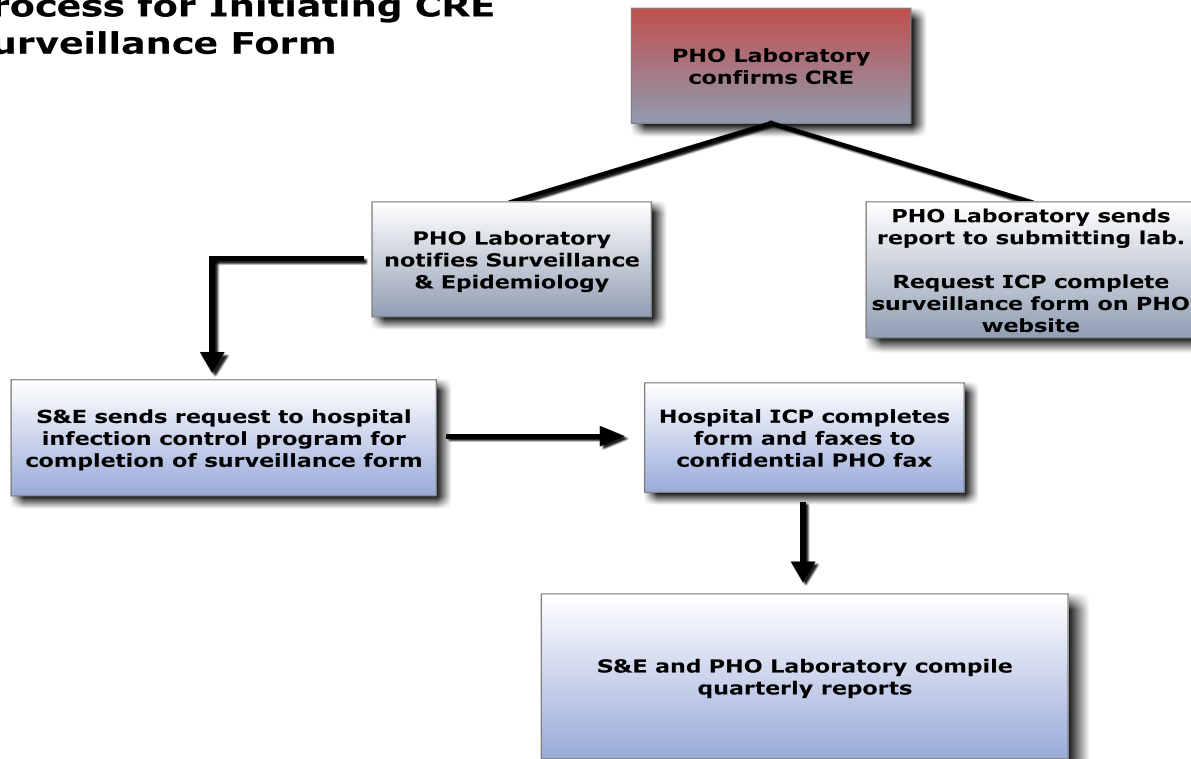
Why is CRE surveillance important?

- Little is known about the epidemiology of CRE in Ontario
- Information on CRE incidence and epidemiology is critical for informing infection prevention and control policies and procedures
- Early action may help limit the likelihood of CRE becoming endemic in Ontario

Surveillance process

- Case Definition: patients positive with laboratory confirmed carbapenemase resistant enterobacteriaceae

Process for Initiating CRE Surveillance Form



Information Being Collected

- Submitter contact details
- Patient demographics
- Specimen information
- Risk factors

Quarterly Reports

- Descriptive summary of cases
- All data will be aggregated and no hospitals shall be identified
- Distributed internally to PHO scientific directors in S&E, PHOL, IDPC and externally to hospitals, health unit MOHs

Contact Information

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