Super Bugs, Super Strategies: Where are we with CRE?

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Learning Objectives

• Provide an overview of CRE
• Review the epidemiology of CRE in MA
• Discuss laboratory identification of CRE at MA SPHL and the ARLN
• Review infection control recommendations for CRE in acute care, long-term acute care, and long-term care settings
• Highlight CRE resources
What are CRE?

- **CRE**: Carbapenem-resistant Enterobacteriaceae
- **CP-CRE**: Carbapenemase-producing CRE
- Enterobacteriaceae are bacteria (gram-) found in the gut
  - *E. coli*
  - *Klebsiella pneumoniae*
  - *Klebsiella oxytoca*
  - *Enterobacter cloacae*
  - *Enterobacter aerogenes*
Carbapenem= class of antibiotics
   – Ertapenem
   – Meropenem
   – Imipenem
   – Doripenem

Usually reserved to treat serious infections, particularly drug-resistant infections

Sometimes considered “last resort” for some infections
What is a carbapenemase?

• An enzyme carried by some CRE bacteria that can break down (and resist) many classes of antibiotics:
  – Penicillins (i.e., Penicillin, Amoxicillin, Augmentin)
  – Cephalosporins (i.e., Ceftriaxone)
  – Quinolones (i.e., Ciprofloxacin)
  – Aminoglycosides (i.e., Gentamicin)
  – Carbapenems

• CP-CREs are of great concern and are very difficult to treat
  KPC (*Klebsiella pneumoniae* carbapenemase)
  NDM (New Delhi metallo-beta-lactamase)
  VIM (Verona integron-encoded metallo-beta-lactamase)
  IMP (Imipenemase metallo-beta-lactamase)
  OXA (Oxacillin carbapenemases)

  – These enzymes can sometimes be transferred to other bacteria
CRE

CRE in Massachusetts

Cases of CRE reported to MDPH in 2016 and 2017

- **Klebsiella pneumoniae**: 83 cases
- **Klebsiella oxytoca**: 6 cases
- **Escherichia coli**: 40 cases
- **Enterobacter cloacae**: 114 cases
- **Enterobacter aerogenes**: 30 cases

Number of Cases
Cases of CP-CRE reported to MDPH in 2016 and 2017

<table>
<thead>
<tr>
<th>Organism</th>
<th>Carbapenemase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KPC</td>
</tr>
<tr>
<td>Enterobacter aerogenes</td>
<td>2</td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>11</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>0</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
<td>2</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
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</tbody>
</table>
CRE PREVENTION AND RESPONSE
How CRE are spread

- CRE are usually spread person to person through contact with infected or colonized people, particularly contact with wounds or stool.
- CRE can cause infections when they enter the body, often through medical devices like ventilators, intravenous catheters, urinary catheters, or wounds caused by injury or surgery.

Source: CDC CRE FAQ
Broad prevention strategies

• Rapid identification of MDROs and containment
  – Communication between laboratory and the provider/infection preventionist
  – Strict infection control practices
  – Communication when patient is transferred

• Appropriate use of antibiotics
  – Antibiotic stewardship across the continuum of care (acute care, long-term acute care, long-term care, and outpatient settings)
Facilities work together to protect patients.

**Common Approach (Not enough)**
- Patients can be transferred back and forth from facilities for treatment without all the communication and necessary infection control actions in place.

**Independent Efforts (Still not enough)**
- Some facilities work independently to enhance infection control but are not often alerted to antibiotic-resistant or *C. difficile* germs coming from other facilities or outbreaks in the area.
- Lack of shared information from other facilities means that necessary infection control actions are not always taken and germs are spread to other patients.

**Coordinated Approach (Needed)**
- Public health departments track and alert health care facilities to antibiotic-resistant or *C. difficile* germs coming from other facilities and outbreaks in the area.
- Facilities and public health authorities share information and implement shared infection control actions to stop spread of germs from facility to facility.

**Abstract**

**Background:** Approaches to controlling emerging antibiotic resistance in health care settings have evolved over time. When resistance to broad-spectrum antimicrobials mediated by extended-spectrum β-lactamases (ESBLs) arose in the 1980s, targeted interventions to slow spread were not widely promoted. However, when Enterobacteriaceae with carbapenemases that confer resistance to carbapenem antibiotics emerged, directed control efforts were recommended. These distinct approaches could have resulted in differences in spread of these two pathogens. CDC evaluated these possible changes along with initial findings of an enhanced antibiotic resistance detection and control strategy that builds on interventions developed to control carbapenem resistance.

**Methods:** Infection data from the National Healthcare Safety Network from 2006–2015 were analyzed to calculate changes in the annual proportion of selected pathogens that were nonsusceptible to extended-spectrum cephalosporins (ESBL phenotype) or resistant to carbapenem (carbapenem-resistant Enterobacteriaceae [CRE]). Testing results for CRE and carbapenem-resistant \textit{Pseudomonas aeruginosa} (CRPA) are also reported.

**Results:** The percentage of ESBL phenotype Enterobacteriaceae decreased by 2% per year (risk ratio \(RR = 0.98, p<0.001\)); by comparison, the CRE percentage decreased by 15% per year (\(RR = 0.85, p<0.01\)). From January to September 2017, carbapenemase testing was performed for 4,442 CRE and 1,334 CRPA isolates; 32% and 1.9%, respectively, were carbapenemase producers. In response, 1,489 screening tests were performed to identify asymptomatic carriers; 171 (11%) were positive.

**Conclusions:** The proportion of Enterobacteriaceae infections that were CRE remained lower and decreased more over time than the proportion that were ESBL phenotype. This difference might be explained by the more directed control efforts implemented to slow transmission of CRE than those applied for ESBL-producing strains. Increased detection and aggressive early response to emerging antibiotic resistance threats have the potential to slow further spread.

**Introduction**

The emergence and spread of antibiotic resistance threats to outpace the development of new antimicrobials, and slowing the spread of these organisms has become a priority. Among Enterobacteriaceae, the family of pathogens most frequently associated with health care-associated infections (HCAIs), resistance to the broad-spectrum antimicrobials extended-spectrum cephalosporins and carbapenems has been driven largely by the spread of plasmid-mediated resistance genes encoding extended-spectrum β-lactamases (ESBLs) and
● The AR Lab Network provides enhanced lab capacity in all 50 states and six local health departments, including specialty testing from seven regional labs.

● In 9 months, in all states and Puerto Rico, health departments in the AR Lab Network tested 5,776 samples of highly resistant organisms.

● These samples were immediately tested for unusual resistance (highly resistant or rare with special resistance genes) that could be shared.

● Of the 5776, about 1 in 4 of had a gene that facilitates spread of resistance.

● There were 221 instances of an especially rare resistance gene.

● These results prompted an aggressive response, including many infection control assessments and colonization screenings.

● These screenings showed that about 1 in 10 tests were also positive, meaning the unusual resistance may have spread to other patients and could have continued spreading if left undetected.

● When screening tests were positive, vigilant infection control and screenings continued until spread was stopped.
Conclusions: The proportion of *Enterobacteriaceae* infections that were CRE remained lower and decreased more over time than the proportion that were ESBL phenotype. This difference might be explained by the more directed control efforts implemented to slow transmission of CRE than those applied for ESBL-producing strains. Increased detection and aggressive early response to emerging antibiotic resistance threats have the potential to slow further spread.
CRE TESTING THROUGH THE ARLN AND MA SPHL
ARLN Background

- Antibiotic Resistance Laboratory Network
- Started in 2016
- Funded through CDC to collect, confirm, and characterize
  - carbapenem-resistant Enterobacteriaceae (CRE) and Pseudomonas aeruginosa (CRPA),
  - CRE and CRPA which are carbapenemase-producing strains
ARLN: Organisms being collected

- *E. coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterobacter species*

- *Pseudomonas aeruginosa*

- *Acinetobacter baumanii* (targeted surveillance)
  - resistant to imipenem, meropenem, doripenem, ertapenem
ARLN: the Network

7 regional labs, the National Tuberculosis Molecular Surveillance Center, labs in 50 states, Six cities, and Puerto Rico
ARLN in Massachusetts
What is Reportable?

• Any CRE (isolated from any source), including CP-CRE (reportable since December 2013)
  • *Klebsiella pneumoniae*
  • *Klebsiella oxytoca*
  • *Enterobacter cloacae*
  • *Enterobacter aerogenes*
  • *E. coli*

• Any identified novel resistance (isolated from any source) or organism of concern
  — — This includes mcr-1 and *Candida auris*

105 CMR 300.000 Reportable Diseases, Surveillance, and Isolation and Quarantine Requirements.
(Latest version from January 2017):
http://www.mass.gov/eohhs/docs/dph/cdc/reporting/rptbldiseases-labs.pdf
AR Lab in Massachusetts
What must be submitted?

- Any of the following *Enterobacteriaceae* (isolated from any source):
  - *Klebsiella pneumoniae*
  - *Klebsiella oxytoca*
  - *Enterobacter cloacae*
  - *Enterobacter aerogenes*
  - *E. coli*

- With resistance to **one or more** of the following **THREE** carbapenems:
  - Imipenem (MIC >= 4 μg/ml)
  - Meropenem (MIC >= 4 μg/ml)
  - Doripenem (MIC >= 4 μg/ml)

- OR, demonstrate carbapenemase production (CP-CRE)

- One isolate per patient per admission, regardless of source
AR Lab in Massachusetts
What must be submitted?

– CRPA: Carbapenem Resistant
  *Pseudomonas aeruginosa*: Submit only the first isolate per month

– CRAB: Carbapenem Resistant
  *Acinetobacter baumanii*: Do NOT submit at this time
How to submit your CRE and CRPA

- **CRE**: One isolate per patient per admission, regardless of source
- **CRPA**: Submit only the first isolate per month
- Please use general state lab requisition found:
- Please send to the clinical microbiology lab
- Please include all susceptibility data generated at your facility
  - Your results may help inform our testing
What testing will be done?

- Isolate identification will be confirmed via Maldi-TOF or API 20E
- mCIM to determine carbapenemase production
- AST testing via sensititre**, Kirby Bauer disk diffusion, or both
- PCR to detect resistance genes: $\text{bla}_{kpc}$, $\text{bla}_{ndm}$, $\text{bla}_{imp}$, $\text{bla}_{vim}$, $\text{bla}_{oxa-48like}$, $\text{bla}_{mcr}$ (1 AND 2)

* Will be live in May 2018
** Still undergoing validation
Discordant results

- Testing done at the MA-SPHL & ARLN/CDC is for surveillance purposes
- MA SPHL may generate different results than the submitting lab—these will be submitted to NYS Wadsworth for additional testing
- Treatment decisions should be based on your facility susceptibility results

Notes:
The test results included in this report will be used to support infection prevention measures. This report should not be used as a substitute for diagnostic procedures or used to guide clinical decisions.
## Isolates tested

September 2017-March 2018

<table>
<thead>
<tr>
<th>Tested at MA SPHL</th>
<th>CRE (n=94)</th>
<th>CRPA (n=58)</th>
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<tbody>
<tr>
<td>North</td>
<td>6</td>
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<tr>
<td>Greater Boston</td>
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<tr>
<td>Southeast</td>
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<td>12</td>
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<tr>
<td>Inside 495</td>
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<tr>
<td>Western MA</td>
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<tr>
<td>Cape</td>
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<td>4</td>
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<tr>
<td>Reference Labs</td>
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</table>
## Source of Isolates

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>CRE</th>
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<tbody>
<tr>
<td>Urine</td>
<td>56</td>
<td>27</td>
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<tr>
<td>Body Fluid</td>
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<tr>
<td>Bronchial</td>
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<tr>
<td>Sputum</td>
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<tr>
<td>Blood</td>
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<td>2</td>
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<tr>
<td>Wound</td>
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<tr>
<td>Tissue</td>
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<td>Rectal Swab</td>
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<td>1</td>
</tr>
<tr>
<td>Other</td>
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<td>6</td>
</tr>
</tbody>
</table>
ARLN Alerts

• Pan Resistance
  – Resistant to all drugs tested by both SPHL and submitting lab

• mcr-resistance by PCR or WGS

• Novel carbapenemase in CRE or CRPA

• Non-KPC carbapenemase in an Enterobacteriaceae

• Any Carbapenemase producing *Pseudomonas aeruginosa*

• Any Carbapenemase producing *Acinetobacter baumanii*

• Any Carbapenemase detected during colonization screening
What happens following an alert?

- MA Lab notifies MA Epi
- Epi sends secure email to CDC ARLN alert mailbox
- ARLN notifies MA Epi and Lab that an alert has been received on the isolate
  - list of instructions
INFECTION CONTROL AND CONTAINMENT FOR CRE
1. Place CRE-infected and CRE-colonized patients on contact precautions. Continue contact precautions for duration of hospitalization.

2. Place CRE-infected and CRE-colonized patients in private rooms. Cohort CRE-positive patients if private rooms are unavailable.

3. Educate staff, affected patients and their visitors about CRE.

4. Consider monitoring adherence to all core MDRO prevention measures (hand hygiene, contact precautions, and environmental cleaning).

5. Notify pertinent clinician groups (infectious diseases, critical care, pharmacy, antibiotic stewardship program [ASP], etc.) of CRE in the facility. Directly interface with clinicians caring for the CRE-infected or CRE-colonized patient.

In summary, act “**NICE**” to prevent the spread of CRE:

- **Notify** MDPH and pertinent clinician groups when any CRE are identified. Additionally, for carbapenemase-producing CRE (CP-CRE), notify hospital administration.

- **Intervene** on all cases with core infection prevention and control strategies, including hand hygiene, contact precautions, private rooms and optimized environmental cleaning. Reduce unnecessary antibiotics and invasive devices.

  Additionally, for CP-CRE:
  - Cohort patients – monitor adherence to hand hygiene, contact precautions;
  - Conduct thorough environmental cleaning and;
  - Screen high-risk patient contacts.

- **Communicate** CRE infection or colonization status to the receiving facility upon patient transfer.

- **Educate** patients, staff, and visitors about CRE.
Recommendations after results of carbapenemase testing

- For non-CP-CRE: continue contact precautions. Per recent CDC guidance; no additional measures are required.
- For CP-CRE: implement the following additional measures:
  - Review microbiology records to identify any other CP-CRE cases at the facility within the past 12 months. Review of microbiology records can detect outbreaks of CRE.
  - Educate staff, patients and visitors about CP-CRE.
  - Alert housekeeping and monitor environmental cleaning. Encourage frequent, thorough cleaning of high-touch surfaces, particularly those near the patient, and common areas outside the room.
  - Verify and audit decontamination, disinfection, reprocessing, and sterilization (when needed) of reusable medical equipment used by CP-CRE patients.
  - In the event of identifications of a novel carbapenemase (NDM, OXA, VIM, or IMP) and in consultation with MDPH, obtain CP-CRE screening cultures for high-risk health care facility contacts.
CP-CRE Contact Screening

- Each situation should be handled on a case by case basis with guidance from MDPH, available 24/7 at 617-983-6800
- Some general guidelines might include:
  - For a single case of novel CP-CRE (NDM, OXA, VIM, or IMP) not on contact precautions, consider screening**:
    - Roommates
    - Patients who overlapped with the index patient on the same unit for at least 3 days while the index patient was not on contact precautions
    - High-risk household contacts
  - For more than one case of any CP-CRE, consider screening the above, where indicated, and:
    - Bi-weekly screening of patients on the affected unit until transmission is no longer detected

**For patients who meet the criteria for screening, but have been discharged from your facility, MDPH will coordinate their testing. MDPH currently only recommends colonization screening testing for patients admitted to a healthcare facility (including rehabs and nursing homes).
The recommended test for the detection of CP-CRE colonization is direct PCR testing using a Cepheid (no culture) from a rectal swab:

- Rectal swab kits are available by request only from the MDPH Epidemiology Program, available 24/7 at 617-983-6800
- Testing will take place at the Wadsworth Laboratory (the Northeast ARLN) and results are available within 1 business day of receipt of the specimen
- Only one specimen is needed for testing
  - Cepheid Rectal Swab Collection Device (Liquid Stuart Swabs 900-0370)
- Consent for screening should be obtained from the patient
1. Promote hand hygiene and monitor staff adherence to hand hygiene: this is the single most important aspect of preventing CRE transmission!

2. Consult with MDPH at 617-983-6800 about developing the appropriate infection prevention plan for the resident, including the need for contact precautions, based on the resident’s clinical status and other medical and social needs.

For CP-CRE: implement the following measures:
- Review your facility’s microbiology records within the past 12 months to identify any other suspect CP-CRE cases.
- Educate staff, affected residents and their visitors about CP-CRE.
- Monitor facility-wide hand hygiene adherence, particularly for the room(s) of CP-CRE-positive residents.
- We strongly encourage private single bed rooms for all residents infected or colonized with CP-CRE. Note: this recommendation is separate from and does not mean “isolation,” which would typically be reserved for residents with active CRE infection with high transmission risk due to their inability to contain their body fluids or wound drainage.
In summary, act “NICE” to prevent the spread of CRE:

**Notify** MDPH and pertinent clinician groups when any type of CRE are identified. Additionally, for carbapenemase-producing CRE (CP-CRE), notify facility administration.

**Intervene** on all cases with improved facility-wide hand hygiene and environmental cleaning, while reducing unnecessary antibiotics and use of invasive devices. Place residents with CP-CRE in private rooms, if available, and use contact precautions for in-room care.

**Communicate** CRE infection or colonization status to the receiving facility upon patient transfer.

**Educate** patients, staff, and visitors about CRE.
Contact precautions are a part of transmission-based precautions, where the type of personal protective equipment (PPE) is chosen to fit the clinical situation.

For example, contact precautions involve using gown and gloves when administering care to a resident or contacting their room environment. “Precautions” DO NOT mean “isolation.”

For whom:

- CP-CRE-infected or colonized residents;
- Residents *infected* with non-CP-CRE or other target MDROs; and
- Residents colonized with non-CP-CRE or other target MDROs *who are at higher-risk for transmission.*
When can contact precautions for residents with CP-CRE be discontinued?

- Discontinue contact precautions when the resident has at least three negative screening cultures per the following algorithm:
  - Three negative screening cultures that are:
  - At least three months after the last positive culture; AND At least three months after last course of antibiotics; AND Each culture obtained ≥1 week apart.
  - The recommended screening sites are either rectal or perirectal swabs. If the original site of infection is still present such as a wound that hasn’t healed or urine from a chronically catheterized patient, at least one culture from such sites should be added to the screening from the GI tract.
New AR Website

https://www.mass.gov/antibiotic-resistance-information-for-health-professionals

Antibiotic resistance information for health professionals

Information about multi-drug resistant organisms (MDROs)

Infection control guidelines and recommendations for MDROs are available in the additional resources below.
CARBAPENEM-RESISTANT ENTEROBACTERIACEAE (CRE) INFORMATION FOR PROVIDERS

Learn about CRE and steps to take when treating CRE infections.

CRE, which stands for carbapenem-resistant Enterobacteriaceae, are a family of germs that are difficult to treat because they are highly resistant to antibiotics. Klebsiella species and Escherichia coli (E. coli) are examples of Enterobacteriaceae, a normal part of the human gut bacteria that can become carbapenem-resistant. The reason why CREs are resistant to carbapenems is because they produce carbapenemases such as KPC (Klebsiella pneumoniae carbapenemase), NDM (New Delhi Metallo-beta-lactamase), OXA-48 like (Oxacillinase) and IMP (Imipenemase Metallo-beta-lactamase). These are all enzymes that break down carbapenems and make them ineffective. KPC and NDM, as well as the enzyme VIM (Verona Integron-Mediated Metallo-β-lactamase) have also been reported in Pseudomonas.
Additional Resources

CDC: Carbapenem-resistant Enterobacteriaceae (CRE) Infection: Clinician FAQs

CDC: Carbapenem-resistant Enterobacteriaceae in Health Care Settings

CDC: Tracking CRE

MDPH CRE Toolkit Ver 1.0 (DOCX 1.09 MB)

Guidance for Control of Carbapenem Resistant Enterobacteriaceae (CRE)

Toolkit for Acute and Long-Term Care Settings

Division of Epidemiology and Immunization
Massachusetts Department of Public Health
Phone: 617-983-6800
Fax: 617-983-5813
www.mass.gov/dph
December 8, 2017, ver 1.0
Additional MDPH Infection Control Guidance for LTCFs


Infection Control

Long Term Care Facilities Infection Control Guidelines

- *Clostridium difficile* (2016)
- *Control of Influenza and Pneumococcal Disease in Long-Term Care Facilities*
- *Gastrointestinal Disease (PDF)*
- *Herpes Zoster (Shingles) (PDF)*
- *Multidrug Resistant Organisms (MDRO) (2016)*
- *Scabies (PDF)*
- *Tuberculosis*
  - *Two-Step Skin Testing: Nursing Home and Rest Home Residents (PDF)*
  - *Policy: Tuberculosis Testing and Treatment for Nursing Homes and Rest Homes (PDF)*

Controlling the Spread of Infectious Diseases

- *Transmission of Respiratory Pathogens (PDF)*
- *General Infection Control Measures (PDF)*
- *Cleaning and Disinfection (PDF)*
- *Isolation and Quarantine (PDF)*
INFECTION PREVENTION IN LONG TERM CARE
Multidrug Resistant Organisms
Massachusetts Department of Public Health

DISEASE OVERVIEW
Multidrug resistant organisms (MDROs) are not limited to hospitals. MDROs, such as methicillin resistant *Staph aureus* (MRSA), vancomycin-resistant enterococci (VRE), drug resistant *Streptococcus pneumoniae*, and multidrug resistant gram-negative bacteria are important causes of colonization and infection in long term care facilities (LTCFs).

In LTCFs, residents may be colonized with MDROs on transfer from acute-care hospitals or other healthcare facilities. Colonized residents are a concern for LTCFs because they can introduce new organisms that can go on to cause infections; infections that are costly to treat. Once MDROs, such as MRSA and VRE, have become established in a facility, they are rarely eliminated. Effective infection control policies and procedures are essential to prevent the transmission of MDROs, but application of hospital infection control guidelines to LTCFs is often difficult, if not unrealistic. The facility is the resident’s home and every effort must be made to allow residents to ambulate, socialize and participate in group activities. Since many residents interact freely with each other, controlling transmission is challenging and the psychosocial needs of the residents must be balanced with good infection control practices.

Colonization and Infection
In order to implement infection control measures to prevent the spread of MDROs in LTCFs, it is important for healthcare workers to understand the difference between colonization and infection.

- **Colonization:** MDRO is present in or on a body site; no clinical signs or symptoms of illness or infection are present. A colonized person is sometimes referred to as a “carrier”.
- **Infection:** Presence of an MDRO in a body site accompanied by clinical signs and symptoms of infection (e.g., fever, lesions, wound drainage) or laboratory evidence of infection. Infection usually warrants treatment.
Additional Resources

• CDC: CRE Webpage

• CDC: CRE Clinician FAQs

• CDC: CRE Tracking map

• MDPH CRE Toolkit (2017)
  – https://www.mass.gov/service-details/carbapenem-resistant-enterobacteriaceae-cre-information-for-providers (Scroll to bottom of page)
Questions?