Novel Multi-Drug Resistant Organisms (N-MDROs): How to Detect, Report, and Contain

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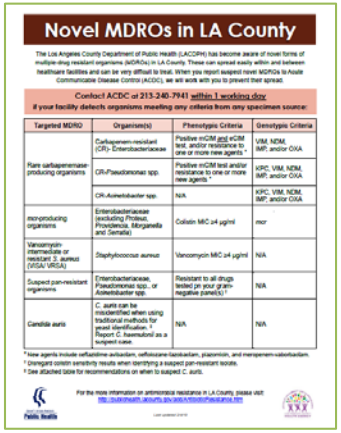
Objectives

- Review novel multi-drug resistant organisms (N-MDROs)
- Describe the epidemiology of and response efforts to N-MDROs
- Discuss the role of infection preventionists in detecting, reporting, and containing novel MDROs

What "Novel" MDRO Means

- "Rare" or non-endemic types of MDROs
- For LA County, organisms in this group include:
  - Rare carbapenemase producing organisms (CPO)
  - *mcr*-producing organisms
  - Pan-resistant organisms
  - Vancomycin-resistant *Staphyloccocus aureus* (VRSA)
  - *Candida auris*



Novel MDROs in LA County

The Los Angeles County Department of Public Health (LACDPH) has become aware of novel forms of multiple-drug resistant organisms (MDROs) in LA County. These can spread easily within and between healthcare facilities and can be very difficult to treat. When you report suspect novel MDROs to Acute Communicable Disease Control (ACDC), we will work with you to prevent their spread.

Contact ACDC at 213-240-7941 within 1 working day
if your facility detects organisms meeting any criteria from any specimen source:

Targeted MDRO	Organism(s)	Phenotypic Criteria	Genotypic Criteria
Rare carbapenemase-producing organisms	Carbapenem-resistant (CR)- Enterobacteriaceae	Positive mCIM and eCIM test, and/or resistance to one or more new agents †	VIM, NDM, IMP, and/or OXA
	CR-Pseudomonas spp.	Positive mCIM test and/or resistance to one or more new agents †	KPC, VIM, NDM, IMP, and/or OXA
	CR-Acinetobacter spp.	N/A	KPC, VIM, NDM, IMP, and/or OXA
mcr-producing organisms	Enterobacteriaceae (excluding Proteus, Providencia, Morganella and Serratia)	Colistin MIC ≥4 µg/ml	mcr
Vancomycin-intermediate or resistant S. aureus (VISA/ VRSA)	Staphylococcus aureus	Vancomycin MIC ≥4 µg/ml	N/A
Suspect pan-resistant organisms	Enterobacteriaceae, Pseudomonas spp., or Acinetobacter spp.	Resistant to all drugs tested on your gram-negative panel(s) ‡	N/A
Candida auris	C. auris can be misidentified when using traditional methods for yeast identification. § Report C. haemulonii as a suspect case.	N/A	N/A

† New agents include ceftazidime-avibactam, ceftolozane-tazobactam, plazomicin, and meropenem-vaborbactam.
‡ Disregard colistin sensitivity results when identifying a suspect pan-resistant isolate.
§ See attached table for recommendations on when to suspect C. auris.

For the more information on antimicrobial resistance in LA County, please visit:
http://publichealth.lacounty.gov/acd/InfectiousDisease.htm

RARE CARBAPENEMASES in LAC

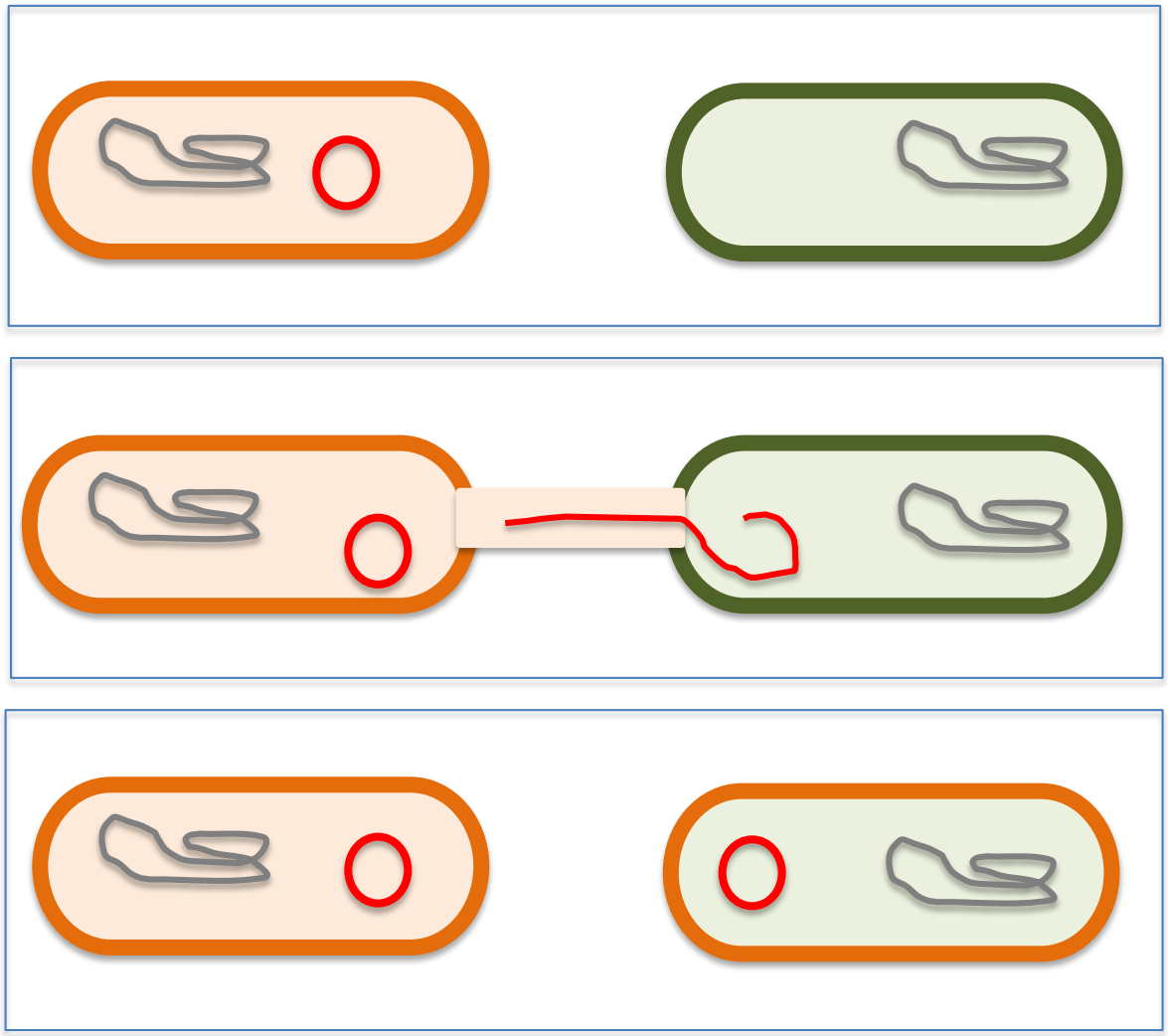
CRE isolates that have a non-KPC carbapenemases identified; or CR-*Pseudomonas* spp. or CR-*Acinetobacter* spp. isolates that have any carbapenemase detected

Types of Carbapenemases

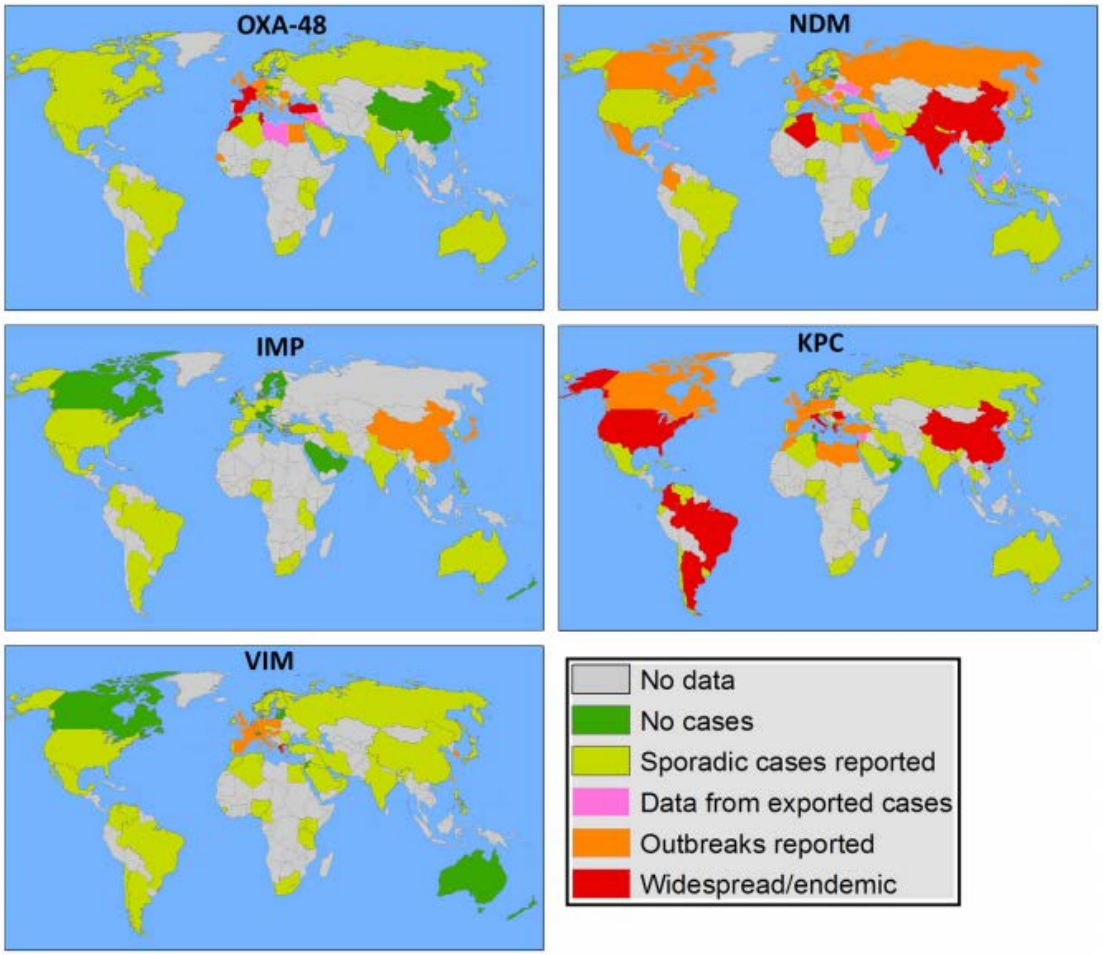
- *Klebsiella pneumoniae* carbapenemase (KPC)
- New Delhi Metallo-β−lactamase (NDM)
- Oxacillinase/ Class D β−lactamase (OXA)
- Verona Integron-encoded Metallo-β-lactamase (VIM)
- Imipenem Metallo-β-lactamase (IMP)

- *All are plasmid-mediated*

Wait… What is a plasmid?



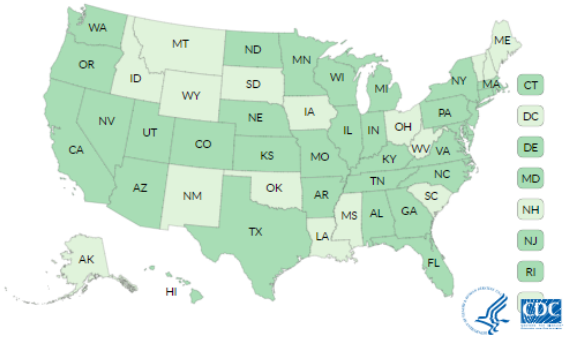
Worldwide Distribution of Carbapenemases



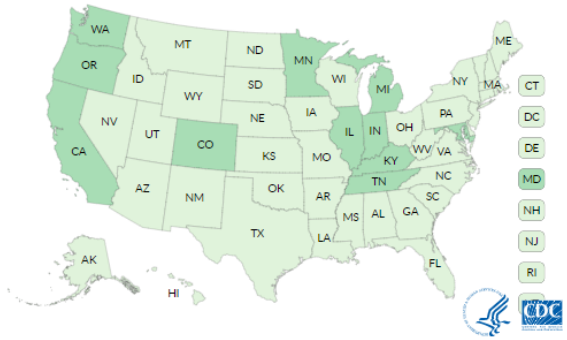
Friedman, N., Carmeli, Y., Walton, A., & Schwaber, M. (2017). Carbapenem-Resistant Enterobacteriaceae: A Strategic Roadmap for Infection Control. Infection Control & Hospital Epidemiology, 38(5), 580-594. doi:10.1017/ice.2017.42

Rare Carbapenemases: Epidemiology in US

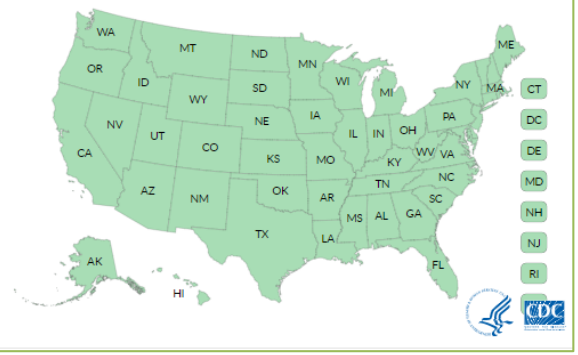
Patients with NDM-producing *Carbapenem-resistant Enterobacteriaceae* (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of December 2017, by state



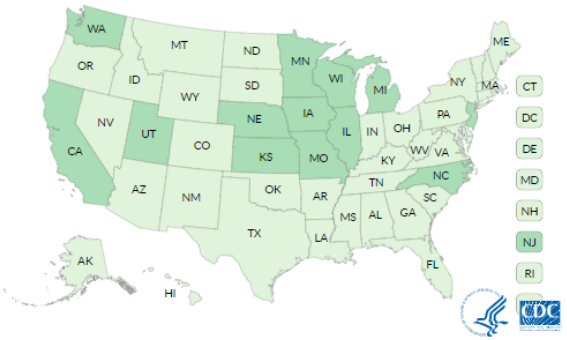
Patients with VIM-producing *Carbapenem-resistant Enterobacteriaceae* (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of December 2017, by state



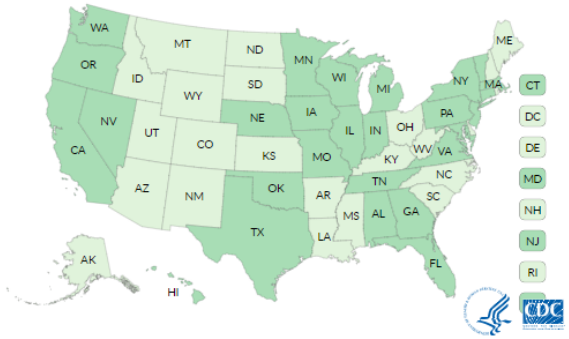
Patients with KPC-producing *Carbapenem-resistant Enterobacteriaceae* (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of December 2017, by state



Patients with IMP-producing *Carbapenem-resistant Enterobacteriaceae* (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of December 2017, by state



Patients with OXA-48-Type-producing *Carbapenem-resistant Enterobacteriaceae* (CRE) reported to the Centers for Disease Control and Prevention (CDC) as of December 2017, by state



https://www.cdc.gov/hai/organisms/cre/trackingcre.html

Rare Carbapenemases: Epidemiology in LA County

- Overall, 71% of CR isolates submitted to LAC DPH Public Health Laboratory between 2015-2019 were carbapenemase-positive
  - 6% were non-KPC-producing organisms, which include:
    - 26 OXA (first detected 2015)
    - 25 NDM (first detected 2015)
    - 13 VIM (first detected 2016)
    - 5 IMP (first detected 2017)

Rare Carbapenemases: Clinical Impact

- Different types of carbapenemases have different antimicrobial activity
  - Metal-containing carbapenemases (NDM, IMP, VIM) may be more difficult to treat
- Carbapenemase-producing organisms (CPOs) can be more difficult to treat because the plasmid may carry additional resistance genes

Rare Carbapenemases: Laboratory Detection

Genotypic

- PCR-based molecular tests can detect and identify specific carbapenemase genes

Phenotypic

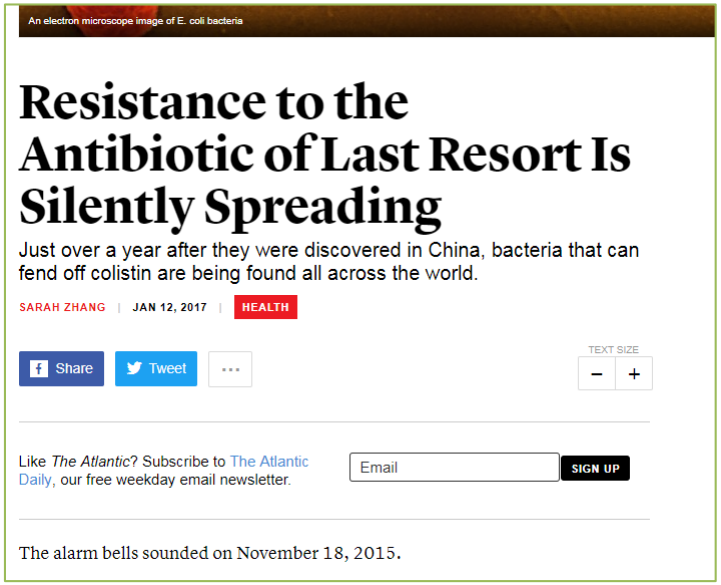
- eCIM (EDTA-modified carbapenem inactivation method) can detect metal-containing carbapenemases (i.e., NDM, VIM, IMP)
  - Must be done in addition to mCIM test
- Resistant to new antibiotic agents (only for CRE and *Pseudomonas* spp.):
  - Ceftazidime-avibactam, ceftolozane-tazobactam, plazomicin, and meropenem-vaborbactam

MCR-TYPE RESISTANCE

Production of the *mcr* gene as demonstrated by PCR.

mcr-Type Resistance: Clinical Impact

- Plasmid-mediated
- Colistin is considered to be a "last line" antibiotic for difficult-to-treat infections
  - However, newer, less toxic agents are being approved


An electron microscope image of E. coli bacteria

Resistance to the Antibiotic of Last Resort Is Silently Spreading

Just over a year after they were discovered in China, bacteria that can fend off colistin are being found all across the world.

SARAH ZHANG | JAN 12, 2017 | HEALTH

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The alarm bells sounded on November 18, 2015.


Newly Reported Gene, *mcr* -1, Threatens Last-Resort Antibiotics

Story Highlights

- Through CDC's Antibiotic Resistance Solutions Initiative, the agency is transforming the nation's capacity to further detect, respond, and prevent antibiotic resistant threats across healthcare settings and in communities to protect Americans and save lives.
- A new gene known as *mcr* -1—which can make bacteria resistant to colistin, a last-resort drug for some multidrug-resistant infections—was first reported in China in November 2015 and in the United States in May 2016.
- CDC, FDA, and USDA began searching for *mcr* -1 in bacterial samples from human, retail meat, and food animal sources. USDA discovered *mcr* -1 in bacteria from the intestines of two pigs in spring 2016.
- After DoD found that a Pennsylvania patient carried a bacteria with the gene, CDC and state and local health departments in Pennsylvania immediately launched a coordinated public health investigation to potentially prevent *mcr* -1 from becoming widespread in the United States.

mcr-Type Resistance: Epidemiology

- First identified in China in 2015
- First US case in May 2016
- First LA County case in December 2016 – total of 3
- Total 29 human cases reported across US
  - 85% had history of international travel

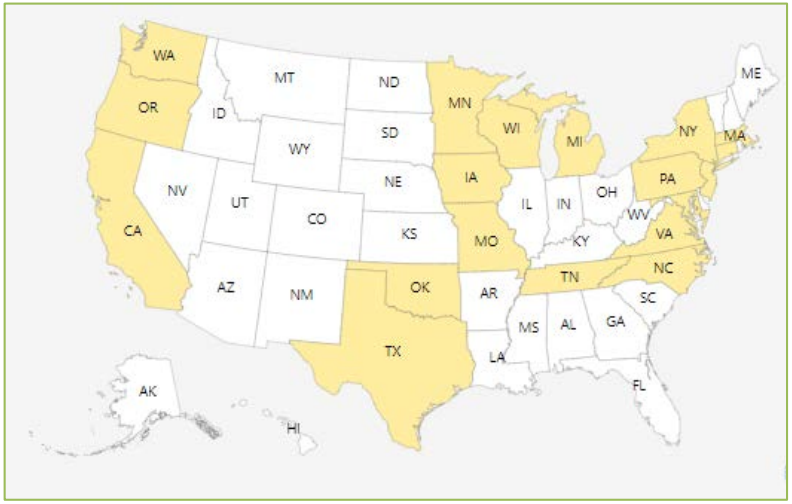


Photo credit: CDC. https://www.cdc.gov/drugresistance/biggest-threats/tracking/mcr.html

mcr-Type Resistance: Laboratory Detection

Genotypic	Phenotypic
• PCR-based molecular tests can detect and identify *mcr* genes	• None…

SUSPECT PAN-RESISTANT ORGANISMS

Enterobacteriaceae, *Pseudomonas* spp., or *Acinetobacter* spp. resistant (R) to all drugs tested

Suspect Pan-Resistant Organisms: Epidemiology

- Organisms that are resistant to ALL antimicrobials are very uncommon in US
- None identified in LA County
  - However, 20% of CRE sent to the LAC Public Health Laboratory are resistant to all drugs tested

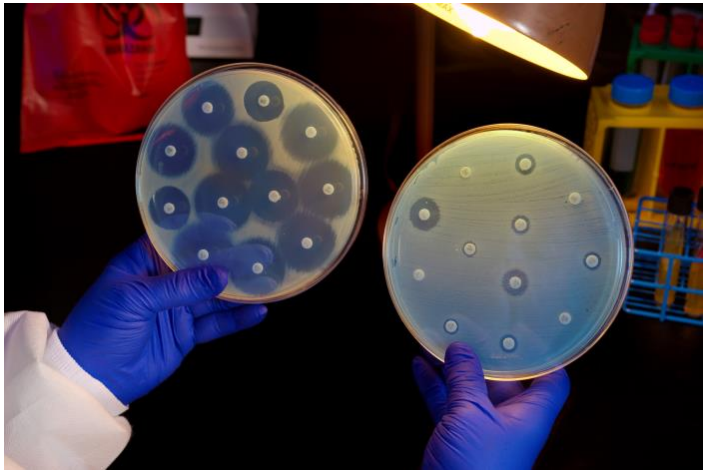


Photo credit: CDC.

Suspect Pan-Resistant Organisms: Clinical Impact

- If truly pan-resistant, will be EXTREMELY difficult to treat
- New drugs being approved by FDA = hope!

Suspect Pan-Resistant Organisms: Lab Detection

- Look for organisms that are resistant (R) to all drugs tested on your gram negative panel
  - Ensure isolate was not susceptible (S/I) to secondary drugs tested

Klebsiella pneumoniae	
NBC44	**Interpretation MIC Value**
Amikacin	Resistant >32
Amoxicillin/K Clavulanate	Resistant >16/8
Ampicillin	Resistant >16
Ampicillin/Sulbactam	Resistant >16/8
Aztreonam	Resistant >16
Cefazolin	Resistant >16
Cefepime	Resistant >16
Cefotaxime	Resistant >32
Cefoxitin	Resistant >16
Ceftazidime	Resistant >16
Ceftriaxone	Resistant >32
Cefuroxime	Resistant >16
Cephalothin	Resistant >16
Ciprofloxacin	Resistant >2
Ertapenem	Resistant >4
Gentamicin	Resistant >8
Imipenem	Resistant >8
Levofloxacin	Resistant >4
Meropenem	Resistant >8
Nitrofurantoin	Resistant >64
Piperacillin/Tazobactam	Resistant >64
Tetracycline	Resistant >8
Tobramycin	Resistant >8
Trimeth/Sulfa	Resistant >2/38

Organism #1: Klebsiella pneumoniae ssp pneumoniae (klepne)

Antibiotics	klepne	
Amikacin	>=64	R
Ampicillin	>=32	R
Ampicillin/Sulbactam	>=32	R
Cefazolin	>=64	R
Cefepime		R
Ceftazidime	>=64	R
Ceftriaxone	>=64	R
Ciprofloxacin	>=4	R
ESBL	Neg	-
Ertapenem	>=8	R
Gentamicin	8	I
Imipenem	>=16	R
Levofloxacin	>=8	R
Nitrofurantoin	256	R
Piperacillin/Tazobac	>=128	R
Tobramycin	>=16	R
Trimethoprim/Sulfame	>=320	R

VANCOMYCIN-INTERMEDIATE or -RESISTANT STAPHYLOCOCCUS AUREUS (VISA/VRSA)

Staphylococcus aureus isolates with MIC $\geq$ 4 µg/ml

VRSA: Epidemiology

- 14 VRSA infections in US
  - All carried *vanA* vancomycin resistance gene (plasmid-mediated)
- None identified in LA County nor California

VRSA: Clinical Impact

- Vancomycin is drug of choice for MRSA infections, and is used empirically in populations where MRSA rate is high
- Infections are treatable; all isolates reported to CDC have been susceptible to other drugs

VRSA: Laboratory Detection

- Look for *S. aureus* isolates with a vancomycin MIC
  - 4-8 µg/ml for VISA
  - ≥ 16 µg/ml for VRSA
- All automated susceptibility testing (AST) systems can reliably detect VISA/VRSA

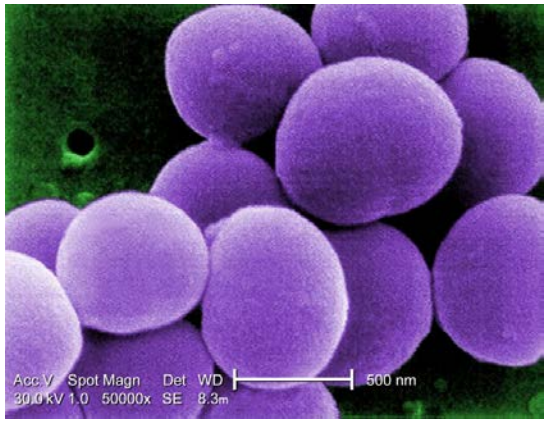


Photo credit: CDC

CANDIDA AURIS

Confirmed *C. auris*, possible *C. auris,* or isolates of *C. haemulonii* and *Candida spp*. that cannot be identified after routine testing.

Candida auris: Epidemiology

- First identified in 2009 in Japan
- Has caused several outbreaks in healthcare settings, including multiple healthcare facilities in Orange County in 2019
  - Over 150 colonized cases identified
- 1 identified in LA County

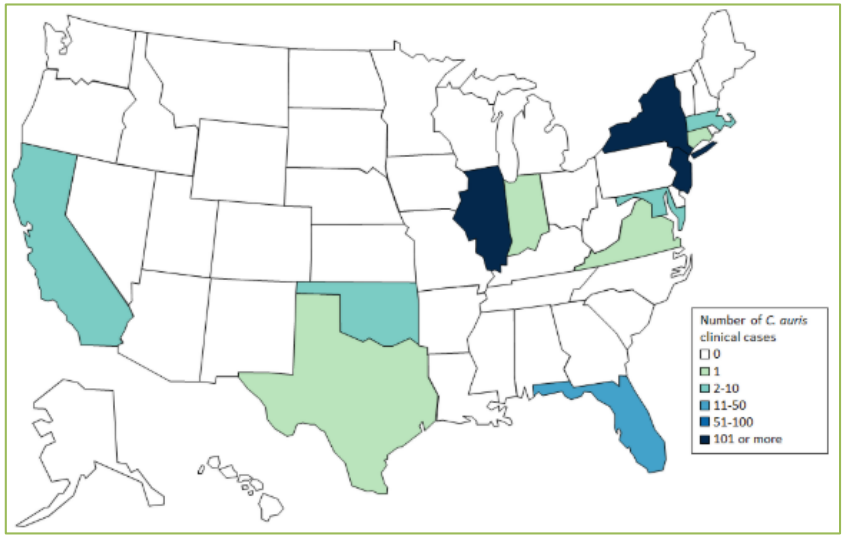


Photo credit: CDC. https://www.cdc.gov/fungal/candida-auris/tracking-c-auris.html

Candida auris: Clinical Impact

- Causes severe infections
  - More than 1 in 3 patients with invasive *C. auris* infection die
  - 50% of central-line bloodstream infections (CLABSI) due to C. auris in New York healthcare facilities
- Difficult to treat
  - Some *C. auris* infections have been resistant to all three available antifungal medications

Candida auris: Laboratory Detection

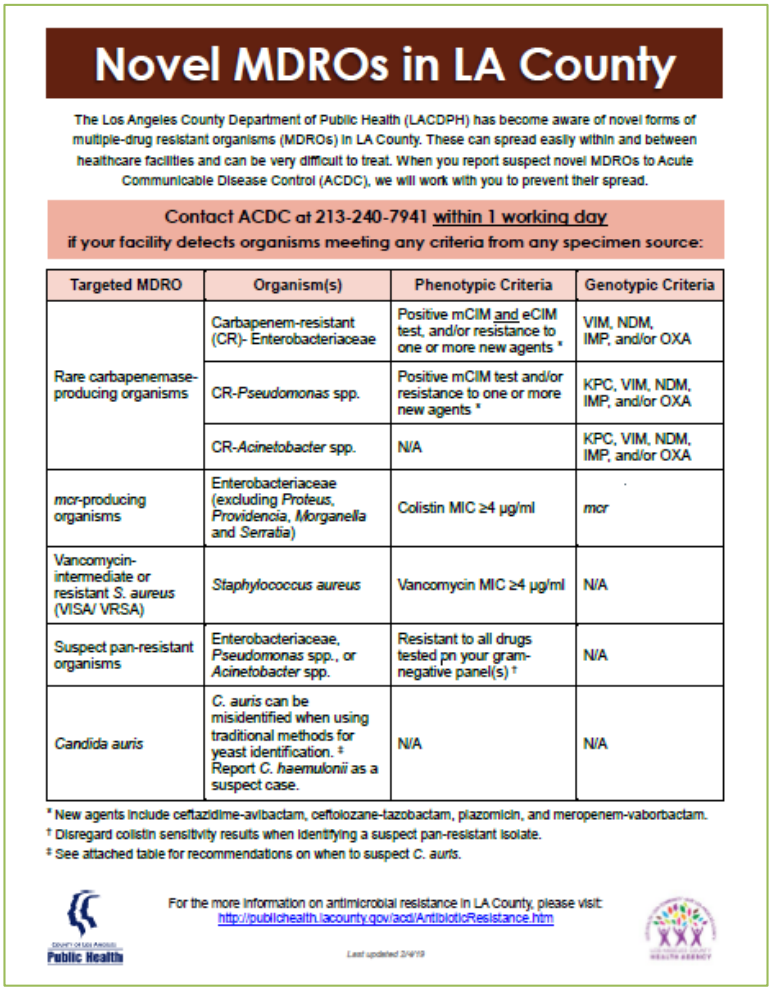
- Can be difficult to identify with standard methods
  - Approximately 40% of LAC labs can accurately detect
- Review CDC site for more details: https://www.cdc.gov/fungal/diseases/candidiasis/recommendations.html
- Determine whether your lab can detect *C. auris* or not

Photo credit: CDC

LAC NOVEL MDRO RESPONSE

Detect, Report, and Contain

Reporting Novel MDROs in LA County



Novel MDROs in LA County

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if your facility detects organisms meeting any criteria from any specimen source:

Targeted MDRO	Organism(s)	Phenotypic Criteria	Genotypic Criteria
Rare carbapenemase-producing organisms	Carbapenem-resistant (CR)- Enterobacteriaceae	Positive mCIM and eCIM test, and/or resistance to one or more new agents *	VIM, NDM, IMP, and/or OXA
	CR-*Pseudomonas* spp.	Positive mCIM test and/or resistance to one or more new agents *	KPC, VIM, NDM, IMP, and/or OXA
	CR-*Acinetobacter* spp.	N/A	KPC, VIM, NDM, IMP, and/or OXA
mcr-producing organisms	Enterobacteriaceae (excluding *Proteus*, *Providencia*, *Morganella* and *Serratia*)	Colistin MIC ≥4 µg/ml	*mcr*
Vancomycin-intermediate or resistant *S. aureus* (VISA/ VRSA)	*Staphylococcus aureus*	Vancomycin MIC ≥4 µg/ml	N/A
Suspect pan-resistant organisms	Enterobacteriaceae, *Pseudomonas* spp., or *Acinetobacter* spp.	Resistant to all drugs tested pn your gram-negative panel(s) †	N/A
Candida auris	*C. auris* can be misidentified when using traditional methods for yeast identification. ‡ Report *C. haemulonii* as a suspect case.	N/A	N/A

* New agents include ceftazidime-avibactam, ceftolozane-tazobactam, plazomicin, and meropenem-vaborbactam.
† Disregard colistin sensitivity results when identifying a suspect pan-resistant isolate.
‡ See attached table for recommendations on when to suspect *C. auris*.

For the more information on antimicrobial resistance in LA County, please visit:
http://publichealth.lacounty.gov/acd/AntibioticResistance.htm

Last updated 2/4/19

http://publichealth.lacounty.gov/Acd/Diseases/NMDRO.htm

LAC Novel MDRO Response

- Upon receipt of a suspect/confirmed case, LACDPH will:

Conduct initial assessment of affected facility to ensure patient is on appropriate level of precautions (Contact vs. Enhanced Standard)

Determine patient status and risk for transmission

Identify whether transmission may have occurred

Educate facility staff on how to prevent transmission

Ensure communication of patient infection/colonization status

What LACDPH is Looking For

- Implement Contact Precautions for any confirmed or suspected cases
  - If resident is colonized and is a 'low' transmission risk, consider placing on Enhanced Standard Precautions
  - Cohort infected/colonized residents with residents that have no infections/colonizations and are a 'low' transmission risk
    - Use LACDPH Infection Control Risk Assessment Guidelines for LTC

- Provide resident infection/colonization status upon discharge

LA County Novel MDRO Surveillance Findings

http://publichealth.lacounty.gov/Acd/docs/NMDRONewsletter_Issue1.pdf

Figure 1D: High risk cases.

High-risk cases were defined as any of the following: assistance for activities of daily living, ventilator-dependent, incontinent, wounds with unmanageable drainage, or unable to maintain hygiene.

67%

of N-MDRO cases

were considered "High Risk" patients

Figure 1E: High-risk setting.

High risk settings for N-MDRO transmission are SNFs or long-term acute care hospitals (LTACs). (6 months prior to culture collection date).

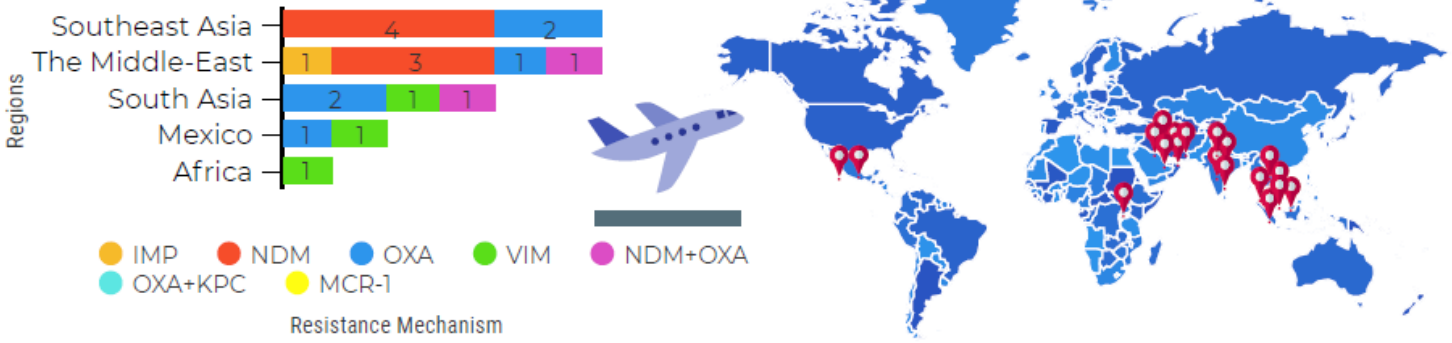
53%

of N-MDRO cases

have stayed in a high risk setting 6 months prior to culture collection date

Figure 1F: Exposure to healthcare internationally.

Among 51 cases with information available, 19 (37.3%) had international healthcare exposure 6 months prior to culture collection. Healthcare exposure is defined as at least 1 overnight inpatient stay.



Need for Coordinated Approach to Stop Spread

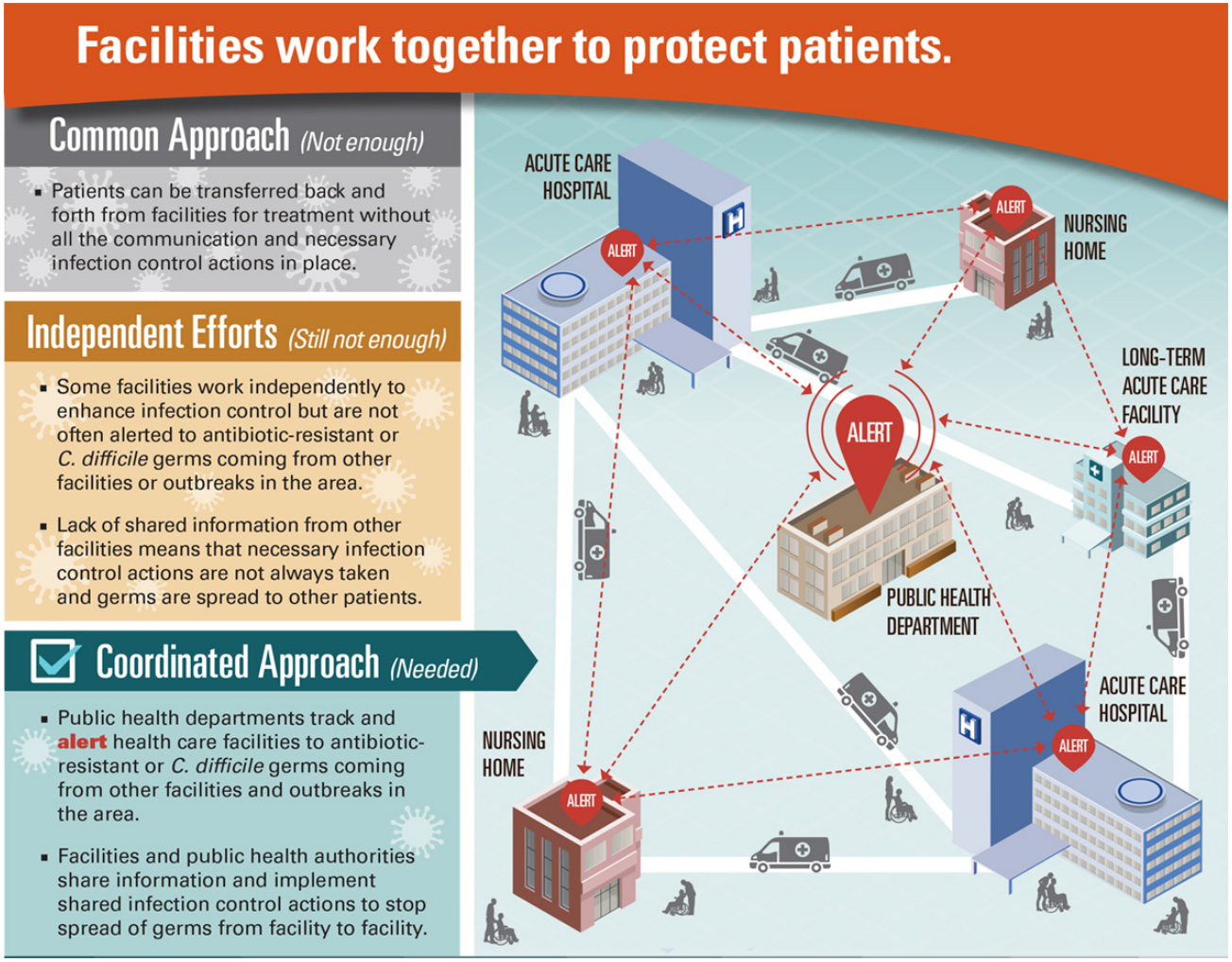
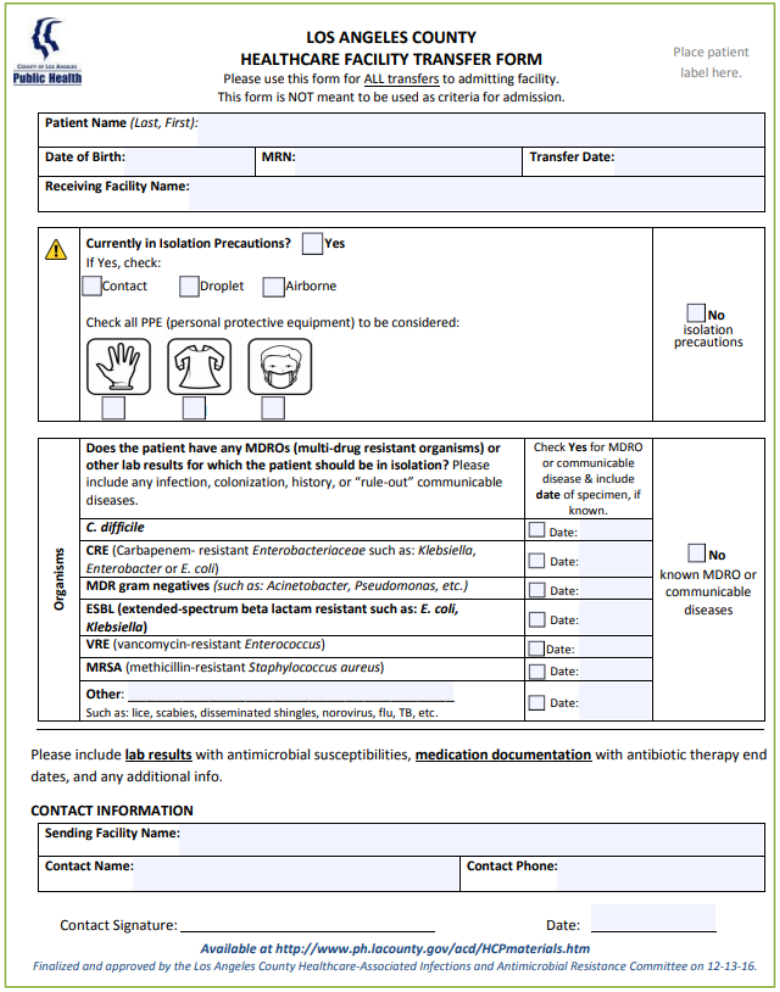


Photo credit: CDC https://www.cdc.gov/vitalsigns/stop-spread/infographic.html#infographic1

Inter-facility Communication is VITAL



LOS ANGELES COUNTY
HEALTHCARE FACILITY TRANSFER FORM
Please use this form for ALL transfers to admitting facility.
This form is NOT meant to be used as criteria for admission.

Place patient label here.

Patient Name *(Last, First)*:

Date of Birth: | **MRN:** | **Transfer Date:**

Receiving Facility Name:

Currently in Isolation Precautions? ☐ **Yes**
If Yes, check:
☐ Contact ☐ Droplet ☐ Airborne

Check all PPE (personal protective equipment) to be considered:

☐ ☐ ☐

☐ **No** isolation precautions

Organisms

Does the patient have any MDROs (multi-drug resistant organisms) or other lab results for which the patient should be in isolation? Please include any infection, colonization, history, or "rule-out" communicable diseases.	Check **Yes** for MDRO or communicable disease & include **date** of specimen, if known.
C. difficile	☐ Date:
CRE (Carbapenem- resistant *Enterobacteriaceae* such as: *Klebsiella, Enterobacter* or *E. coli*)	☐ Date:
MDR gram negatives *(such as: Acinetobacter, Pseudomonas, etc.)*	☐ Date:
ESBL (extended-spectrum beta lactam resistant such as: *E. coli, Klebsiella*)	☐ Date:
VRE (vancomycin-resistant *Enterococcus*)	☐ Date:
MRSA (methicillin-resistant *Staphylococcus aureus*)	☐ Date:
Other: _____ Such as: lice, scabies, disseminated shingles, norovirus, flu, TB, etc.	☐ Date:

☐ **No** known MDRO or communicable diseases

Please include **lab results** with antimicrobial susceptibilities, **medication documentation** with antibiotic therapy end dates, and any additional info.

CONTACT INFORMATION

Sending Facility Name:

Contact Name: | **Contact Phone:**

Contact Signature: _____ Date: _____

Available at http://www.ph.lacounty.gov/acd/HCPmaterials.htm
Finalized and approved by the Los Angeles County Healthcare-Associated Infections and Antimicrobial Resistance Committee on 12-13-16.

http://publichealth.lacounty.gov/acd/docs/FacilityTransferForm.pdf

Remember…

- When in doubt, always contact us!
  - ACDC Phone: 213-240-7941
  - HOU Email: hai@ph.lacounty.gov
- Do not send isolates to LAC Public Health Lab without calling ACDC first
- More information available online:
  - http://publichealth.lacounty.gov/Acd/AntibioticResistance.htm
  - http://publichealth.lacounty.gov/Acd/Diseases/NMDRO.htm
  - http://publichealth.lacounty.gov/acd/Diseases/CandidaAuris.htm
  - http://publichealth.lacounty.gov/Acd/Diseases/CRE.htm

Questions?

WHAT HEALTHCARE FACILITIES CAN DO

It Takes a TEAM to Detect, Report, Contain, and Prevent Novel MDROs

- Infection Preventionists
- Laboratorians
- Clinicians
- Pharmacists
- Nurses

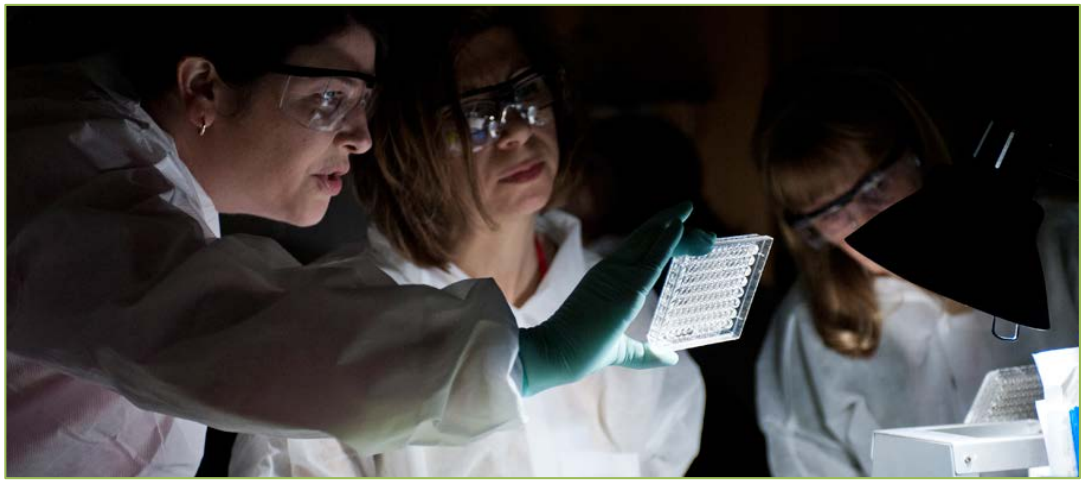
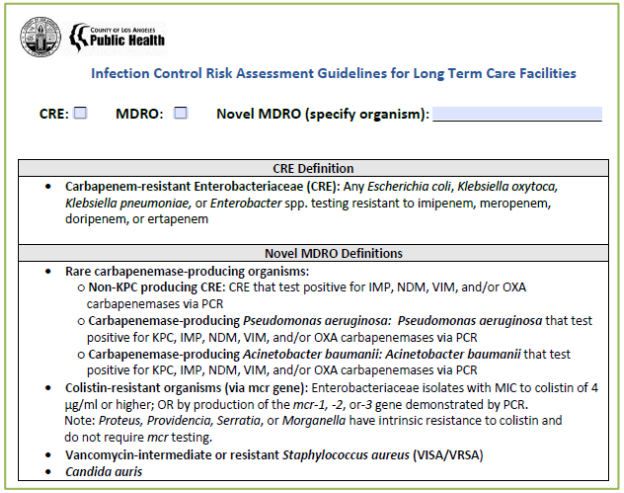


Photo credit: CDC

Actions for Infection Preventionists

- Identify colonized and infected residents in the facility
  - Suspect novel MDROs amongst residents with recent healthcare exposure outside the US
    - LAC DPH has criteria available for patients at high-risk for *C. auris*
  - Find out when a patient with an MDRO transfers into your facility.
- Ensure appropriate precautions are strictly adhered to
  - Use LACDPH Infection Control Risk Assessment Guidelines
- Work with EVS to ensure thorough cleaning & disinfection practices



Public Health

Infection Control Risk Assessment Guidelines for Long Term Care Facilities

CRE: ☐ MDRO: ☐ Novel MDRO (specify organism): _____

CRE Definition

- **Carbapenem-resistant Enterobacteriaceae (CRE):** Any *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, or *Enterobacter* spp. testing resistant to imipenem, meropenem, doripenem, or ertapenem

Novel MDRO Definitions

- **Rare carbapenemase-producing organisms:**
  - **Non-KPC producing CRE:** CRE that test positive for IMP, NDM, VIM, and/or OXA carbapenemases via PCR
  - **Carbapenemase-producing *Pseudomonas aeruginosa*:** ***Pseudomonas aeruginosa*** that test positive for KPC, IMP, NDM, VIM, and/or OXA carbapenemases via PCR
  - **Carbapenemase-producing *Acinetobacter baumanii*:** ***Acinetobacter baumanii*** that test positive for KPC, IMP, NDM, VIM, and/or OXA carbapenemases via PCR
- **Colistin-resistant organisms (via mcr gene):** Enterobacteriaceae isolates with MIC to colistin of 4 µg/ml or higher; OR by production of the *mcr-1, -2,* or-*3* gene demonstrated by PCR.
  Note: *Proteus, Providencia, Serratia,* or *Morganella* have intrinsic resistance to colistin and do not require *mcr* testing.
- **Vancomycin-intermediate or resistant *Staphylococcus aureus*** (VISA/VRSA)
- ***Candida auris***

Actions for Clinicians

- Ensure timely, appropriate antibiotic therapy
- Perform hand hygiene ALWAYS: use alcohol-based hand rub or wash hands with soap and water before and after contact with the resident or their environment
- Stay aware of facility and community antibiotic resistance rates
  - LA County Regional Antibiogram available: http://publichealth.lacounty.gov/acd/antibiogram.htm

Actions for Pharmacists

- Promote antimicrobial stewardship
- Look for novel agents but ensure they are ONLY used when needed
- Track facility and community antibiotic resistance rates
  - LA County Regional Antibiogram available: http://publichealth.lacounty.gov/acd/antibiogram.htm

Actions for Microbiologists

- Make sure the lab can accurately identify novel MDROs
  - Our Public Health Lab can provide guidance and/or free testing services, if needed
  - This includes *C. auris* detection- see CDC algorithm for details: https://www.cdc.gov/fungal/diseases/candidiasis/pdf/Testing-algorithm-by-Method-temp.pdf
- Immediately alert clinical and infection prevention staff when novel MDROs are suspected/identified
- Ensure lab reports easy to read, and suppress unnecessary information

Actions for Nurses

- Ask if a resident has received medical care outside the US in the past 12 months
- Wear a gown and gloves when caring for residents with novel MDROs
- Perform hand hygiene ALWAYS: use alcohol-based hand rub or wash hands with soap and water before and after contact with the resident or their environment
- Discontinue devices (i.e., catheters) as soon as no longer necessary
- Alert the receiving facility when you transfer an MDRO-positive resident