



State of Utah

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Dear Laboratory Managers, Microbiology Supervisors and Infection Preventionists,

Thank you for your assistance during the past few years to raise awareness of antibiotic resistance in Utah. The purpose of this letter is to provide:

- **A situational awareness update on antibiotic resistance trends in Utah,**
- **Information about new testing capacity at the Utah Public Health Laboratory (UPHL) and the Regional Antibiotic Resistance Laboratory Network (ARLN) in Texas,**
- **A reminder about reporting and isolate submission requirements, and**
- **A preview of some upcoming changes to the Utah Communicable Disease Rule (R386-702).**

Situational Awareness

In 2018, laboratories reported **109** cases of carbapenem-resistant *Enterobacteriaceae* (CRE) and **76** cases of carbapenem-resistant *Acinetobacter* (CRA) to the Utah Department of Health (UDOH). Additionally, the UDOH provided assistance with outbreaks in four acute care and seven long-term care facilities and two nationwide outbreaks. A total of **387** carbapenem-resistant bacterial isolates including CRE, CRA and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) were submitted to the Utah Public Health Laboratory (UPHL) to rule out carbapenemase production (CP) by both phenotypic and/or genotypic mechanism testing. A summary of 2017 and 2018 positive carbapenemase results performed at UPHL for carbapenem-resistant organisms (CRO) is shown in Tables 1-3. While these data likely under represent Utah's actual multi-drug resistant organism (MDRO) disease burden, your continued efforts regarding reporting and submission of isolates to public health will increase knowledge regarding Utah's current burden of these concerning organisms and help facilitate future prevention and containment activities within the state.

Table 1: Carbapenemase producing carbapenem-resistant Enterobacteriaceae (CP-CRE) by mechanism in Utah, 2017-2018

CP-CRE	NDM	KPC	VIM	IMP	OXA-48-like	OXA-23	OXA-235	Potential Novel	TOTAL
<i>E. coli</i>	3	3	0	0	1	0	0	0	7
<i>Enterobacter</i> spp.	0	0	0	0	0	0	0	2	2
<i>Klebsiella</i> spp.	3	7	0	0	0	0	0	0	10
Other Enterobacteriaceae spp.	0	2	0	0	0	0	0	0	2
									21

Table 2: Carbapenemase producing carbapenem-resistant *Acinetobacter* (CP-CRA) by mechanism in Utah, 2017-2018

CP-CRA	NDM	KPC	VIM	IMP	OXA-48-like	OXA-23	OXA-235	Potential Novel	TOTAL
<i>Acinetobacter</i> spp.	0	0	0	0	0	20	3	0	23

Table 3: Carbapenemase producing carbapenem-resistant *Pseudomonas aeruginosa* (CP-CRPA) by mechanism in Utah, 2017-2018

CP-CRPA	NDM	KPC	VIM	IMP	OXA-48-like	OXA-23	OXA-235	Potential Novel	TOTAL
<i>Pseudomonas aeruginosa</i>	0	0	4	1	0	0	0	2	7

New Testing Capacity at the Utah Public Health Laboratory (UPHL) and Antibiotic Resistance Laboratory Network (ARLN) Regional Laboratory

UPHL testing processes for CRE, CRA and CRPA

UPHL utilizes a combination of phenotypic [the modified carbapenem inactivation method (mCIM)] and genotypic tests [Cepheid, OXA-carbapenemase-PCR and whole genome sequencing (WGS)] for carbapenemase identification. The testing algorithms are detailed in Figures 1 and 2.

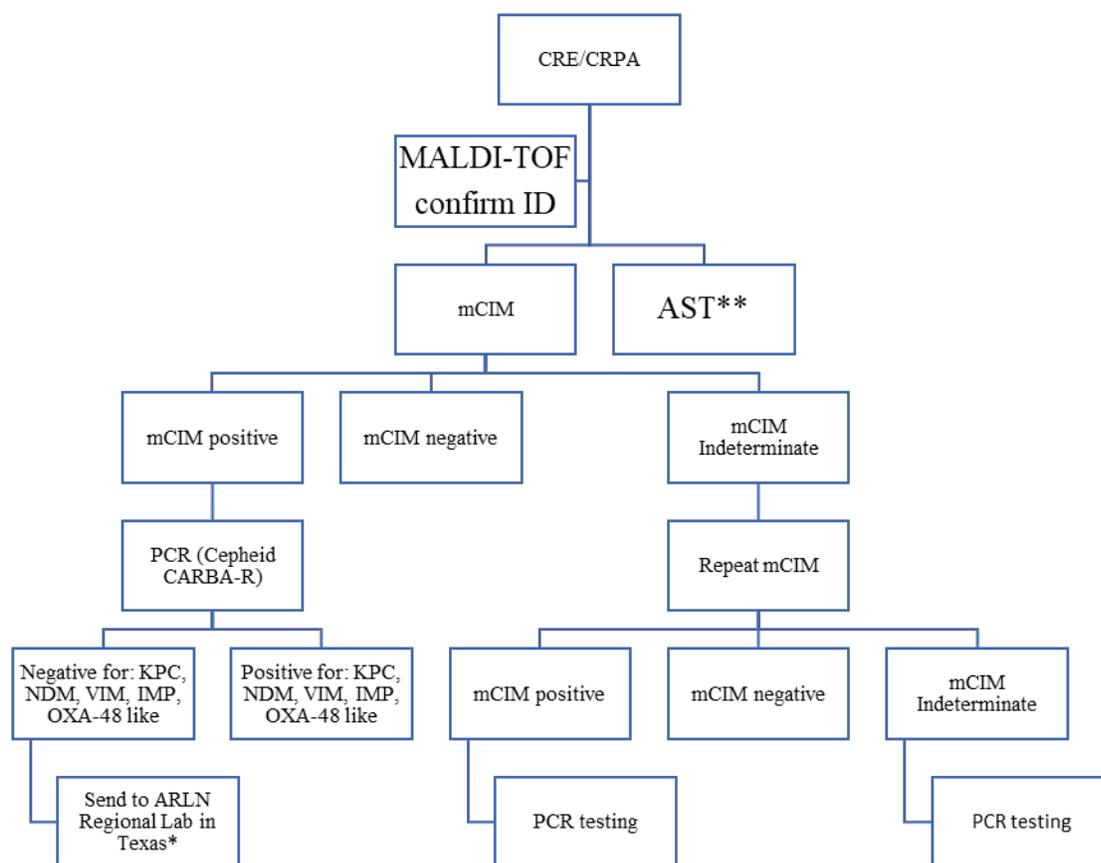


Figure 1: Carbapenemase testing flow-chart used at the Utah Public Health Lab for Carbapenem-resistant Enterobacteriaceae (CRE) and Carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) isolates.

*Potential novel carbapenemase producer

**For CRPA isolates antibiotic susceptibility testing (AST) is case by case. If colistin-resistant, the isolate is sent to the ARLN Regional Lab for *mcr1/2* PCR testing.

(modified carbapenem inactivation method (mCIM) is a phenotypic (yes/no) test for carbapenemase production)

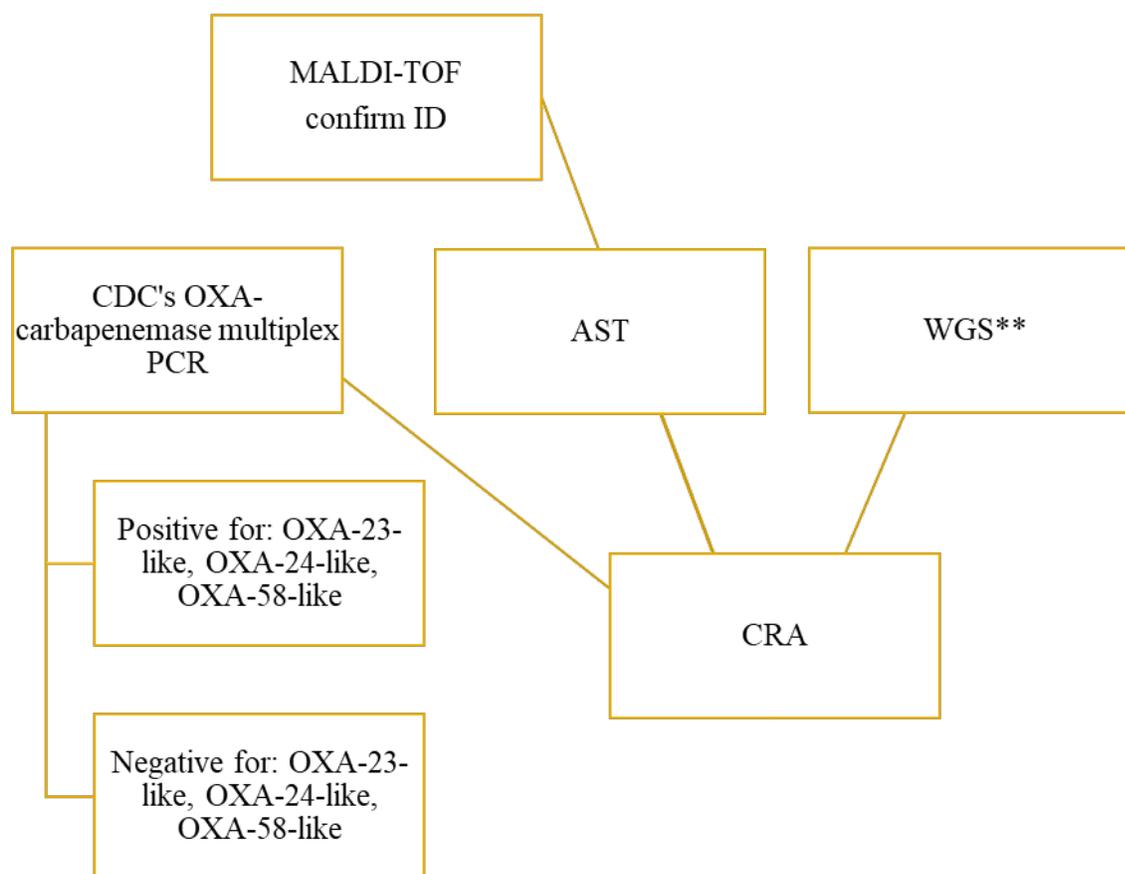


Figure 2: Carbapenemase testing algorithm used at the Utah Public Health Lab for Carbapenem-resistant *Acinetobacter* species (CRA) isolates.

**WGS for CRA is case by case

Identification of *Candida auris* and other yeast by MALDI-TOF

Candida auris became a nationally notifiable condition and was added to the Utah Communicable Disease Rule in 2018. However, to date, no clinical or surveillance cases of this organism have been reported in the state of Utah. The Bruker Biotyper (MALDI instrument) can correctly identify *C. auris* isolates and separate them from other closely-related yeast species like *Candida haemulonii*. Common *C. auris* misidentifications by other identification methods are listed by platform type in Table 5 below:

Table 5: Common *C. auris* misidentifications by platform type.

Identification Method	Common <i>C. auris</i> Misidentification
Vitek 2 YST	<i>Candida haemulonii</i> <i>Candida duobushaemulonii</i>
BD Phoenix yeast identification system	<i>Candida haemulonii</i> <i>Candida catenulate</i>
Microscan	<i>Candida famata</i> <i>Candida guilliermondii</i> <i>Candida lusitaniae</i> <i>Candida parapsilosis</i>
API 20C	<i>Rhodotorula glutinis</i> (no red color) <i>Candida sake</i>
Rapid Yeast Plus	<i>Candida parapsilosis</i>

If any of the species in Table 5 are isolated from invasive sites, report to public health and submit the isolate to UPHL for verification testing. Any patients currently admitted to a healthcare facility with suspect *C. auris* should be placed in contact isolation.

OXA Carbapenemase multiplex PCR assay

With this new PCR assay, UPHL can now identify the following carbapenemase genes not currently tested for on routine platforms like *Cepheid* and *Verigene*. These carbapenemases are found in Gram negative bacilli, especially *Acinetobacter*. Table 6 below provides a comprehensive list of genes covered by the new multiplex platform:

Table 6: OXA resistance genes covered by the CDC multiplex PCR assay

Enzyme Group	Enzymes
OXA-23-like	OXA-23 , OXA-27, OXA-49, OXA-73, OXA-102, OXA-103, OXA-105, OXA-133, OXA-134, OXA-146, OXA-165, OXA-171, OXA-225, OXA-239
OXA-24-like	OXA-24/40 , OXA-25, OXA-26, OXA-72 , OXA-139, OXA-160, OXA-207
OXA-58-like	OXA-58 , OXA-96, OXA-97, OXA-164

**Genes in bold represent the main pathogenic strain in each subgroup.

Whole genome sequencing (WGS)

UPHL has the capability to perform whole genome sequencing (WGS) of bacteria using next-generation sequencing (NGS) methods. WGS data along with the advanced bioinformatic analysis workflows developed at UPHL allows for the rapid characterization of bacteria isolates including antimicrobial resistance genes, virulence factors and relatedness between isolates. WGS has become an important tool for supporting outbreak investigations; please contact public health for additional information regarding outbreak support.

Targeted surveillance activities at Antibiotic Resistance Laboratory Network (ARLN) Laboratory

To enhance surveillance of antimicrobial resistant organisms, the AR Lab Network is seeking laboratories to voluntarily submit the following isolates:

- (1) ***Candida* species other than *Candida albicans***, or any difficult to identify yeast isolates, from any specimen source, especially invasive sites. UPHL will identify the yeast and send it on to the Texas Regional Lab for susceptibility testing. Additionally, any known highly-resistant *Candida* species can be submitted for further testing.
- (2) **Any colistin-resistant isolates**. New resistance genes, *mcr-1/mcr-2*, have emerged conferring colistin resistance to some *Enterobacteriaceae* bacteria, particularly species such as *Escherichia coli* and *Klebsiella pneumoniae*. Screening and detection of *mcr*-mediated resistance will lead to timely detection of cases and outbreaks resulting in containment and implementation of appropriate prevention measures. All colistin-resistant isolates will be sent on for *mcr* testing. Please do not submit organisms intrinsically resistant to colistin such as *Serratia*, *Proteus*, *Providencia* and *Morganella*.

Texas Antibiotic Resistance Portal (TARP) portal for colonization screening

The TARP portal is a valuable screening tool for carbapenemase production and is provided free of charge for use by public health, IPs, physicians and healthcare providers. Rectal swabs can be submitted to the ARLN lab in Texas on high-risk incoming patients with travel history and surveillance cultures collected during suspected CRO outbreaks. For more information about this resource and to set up an account, please contact the UDOH Healthcare-associated Infections (HAI) program.

Please note: all identified CRE, CRA and CRPA results are reportable in Utah, including results from identified colonized patients, regardless of infectious status. The Utah Communicable Disease Rule requires reporting of each case and isolate submission to UPHL, even if the patient is known to have had a previously reported CRE or CRA isolate or is not currently exhibiting symptoms.

Reporting and Isolate Submission Requirements

Electronic Laboratory Reporting (ELR)

In 2017, Electronic Laboratory Reporting (ELR) became required for all laboratories reporting to public health per Utah Administrative Rule R386-702. ELR is when laboratory reports are sent electronically from facilities to public health. This is done with the help of automated triggers programmed into the lab information management system. Nevertheless, infection preventionists still have a responsibility to manually report rare or unusual cases or clinically diagnosed reportable conditions to public health regardless of whether the facility reports via ELR. Some of the benefits for labs, clinical facilities and public health of a high-quality, validated feed include:

- Replacement of routine, standard disease notification
- More timely notifications
- More complete data
- Reduce data entry error
- Elimination of manual sending/receiving

Additionally, ELR has been successful in improving data quality, including completeness, timeliness, and accuracy. To date, approximately 90% of the laboratory reports received by the Utah Department of Health are electronic.

For **questions on ELR**, please contact the DCP Informatics Program at (801) 538-6191 or email elr@utah.gov.

Laboratory saving, storing, and submission of suspected MDRO isolates

Laboratories are required to save all suspected MDRO isolates (regardless of source) and submit them to UPHL as quickly as possible for confirmation and further testing. UPHL has significant storage space available for this purpose. If deemed necessary, UPHL will forward isolates to the Antibiotic Resistance Laboratory Network (ARLN) laboratory in Texas or the Centers for Disease Control and Prevention (CDC) laboratory as appropriate. Submission of clinical material does not replace the requirement for laboratories to report the event to public health (see R386-702-6, R386-702-7). Although most reportable isolates were shipped to UPHL, several bacterial isolates (especially from urine) were discarded in 2018 with the loss of valuable clinical and epidemiological data.

The public health isolate submission form can be found at: <http://health.utah.gov/lab/infectious-diseases/documents/UPHL%20ID%20requisition%20form.pdf>

Submitted isolates and clinical material should be clearly labeled with patient name, date of birth, collection date and source; and shipped with the completed requisition form **and a copy of the AST report**.

Reporting of antibiotic susceptibility testing (AST) results and breakpoints

Full panel susceptibility test results including minimum inhibitory concentration (MIC) values or Kirby Bauer (K-B) zone sizes, and results suppressed by the ordering clinician, are reportable (R386-702-6, R386-702-7). Reports should include interpretations, complete antibiotic susceptibilities after repeat testing and standard purity checks, and suppressed results to ensure accurate, complete, and standardized reporting. Current CLSI breakpoints for carbapenem antibiotics used to define cases of CRE, CRA and CRPA are summarized in Table 4. For more information regarding this reporting requirement, please refer to the Council of State and Territorial Epidemiologists (CSTE) 2017 Position Statement 17-ID-04, and the *Recommendation: Use the most current Clinical & Laboratory Standards Institute (CLSI) guidelines (M100-S27) for minimum inhibitory concentration (MIC) breakpoints*, available at: http://em100.edaptivedocs.info/Login.aspx?_ga=2.127404686.2066098109.1514932533-945308666.1514932533 (free web version).

Table 4: MIC values that define carbapenem resistance for CRE, CRA and CRPA

	Doripenem	Ertapenem	Imipenem	Meropenem
<i>E. coli</i>	≥4 µg/ml	≥ 2 µg/ml	≥4 µg/ml	≥4 µg/ml
<i>Klebsiella</i> spp.	≥4 µg/ml	≥ 2 µg/ml	≥4 µg/ml	≥4 µg/ml
<i>Enterobacter</i> spp.	≥4 µg/ml	≥ 2 µg/ml	≥4 µg/ml	≥4 µg/ml
<i>Acinetobacter</i> spp.	≥8 µg/mL	*N/A	≥8 µg/mL	≥8 µg/mL
<i>Pseudomonas aeruginosa</i>	≥8 µg/mL	*N/A	≥8 µg/mL	≥8 µg/mL

Enterobacter aerogenes genus change

Although attempts had been made since the 1960s to change the name of the organism *Enterobacter aerogenes* to *Klebsiella aerogenes* (Tindall et al, 2017), this genus change was only recently announced by the American Society for Microbiology (ASM) (Munson & Carroll, 2019). However, since many commercial systems in routine use such as the Microscan have not updated their databases, this organism will still go into the EpiTrax surveillance system as *Enterobacter aerogenes* and investigated by public health as such until further notice.

Submitting *Enterobacter cloacae* complex isolates

Enterobacteriaceae can display a carbapenem-resistant phenotype without producing carbapenemase enzymes. Hyper-production of ESBL or AmpC β -lactamases, together with porin loss of function or up-regulation of efflux systems, typically generate carbapenem-resistance. When these determinants of resistance are not present on mobile elements, non-carbapenemase-producing CRE do not constitute a priority for surveillance and infection control.

Enterobacter sp. are often submitted to UPHL as CRE. All of these isolates are expected to carry a chromosomal AmpC-family β -lactamase. Unfortunately, it has been noted that AmpC hyper-producers yield false positives in the mCIM phenotypic test. In these cases, a positive mCIM result and a subsequent negative PCR test, may trigger a “*Novel carbapenemase suspected*” alert. Therefore, ARLN mandated avoiding alerts for CRE *Enterobacter* sp. isolates that are susceptible to cefepime.

In order to identify criteria to minimize submission and workup of *Enterobacter* AmpC hyper-producers, UPHL has evaluated the mCIM results and AST profiles of 26 *E. cloacae* complex isolates, and molecularly characterized 16 of them by WGS. We found that:

- 1) The current zone sizes established for the mCIM detection of CRE are not specific ($\leq 50\%$) for the detection of *E. cloacae* complex carbapenemase producers. However, mCIM correctly detected two organisms carrying the chromosomal carbapenemases IMI-12 and NMC-A (100% sensitivity). As such, while gathering more data, **we can conservatively recommend that clinical labs performing mCIM submit only *E. cloacae* complex isolates with zone sizes ≤ 15 mm (positives with zone sizes of 16-18 mm and colonies within are most likely AmpC hyper-producers).**
- 2) Cefepime susceptibility could predict AmpC hyperproduction only in 60 % of the cases. Therefore, cefepime susceptibility should not be the only criterion used to guide the release of a “*Novel carbapenemase suspected*” alert or for labs to decide whether submitting an isolate to UPHL.
- 3) About 60% of all the *E. cloacae* complex that could be confirmed as CRE by AST were resistant to ertapenem only and susceptible to all other carbapenems. Furthermore, both the IMI-12 and NMC-A isolates displayed resistance to all four carbapenems. Based on this limited data, **resistance to more than one carbapenem can be used as a criterion to prioritize submission and testing of *Enterobacter cloacae* complex isolates at UPHL.**

UDOH and UPHL contact information

For any questions regarding multidrug-resistant organism (MDRO) reporting requirements as specified by the Utah Communicable Disease Rule, or for assistance with investigation questions or needs, please contact the UDOH MDRO Epidemiologists in the HAI Program, Maureen Vowles (mvowles@utah.gov, (801) 538-6172) or Amanda Smith (amandarsmith@utah.gov, (801) 538-6247). For questions regarding submission, testing, courier support, shipping requirements, or further information regarding available testing, please contact Lori Smith, Bacteriology Supervisor, (lhsmith@utah.gov, (801) 965-2503) or Alessandro Rossi, Infectious Disease Chief Scientist, (arossi@utah.gov, (801) 965-2554) at UPHL. For more information about WGS please contact Kelly Oakeson, Next Generation Sequencing and Bioinformatics Chief Scientist, (koakeson@utah.gov, (801) 965-2423). For more information about UPHL testing, please visit their new website at: <https://uphl.utah.gov/>

Upcoming Changes to the Utah Communicable Disease Rule (R386-702)

Additions to Utah reportable conditions and isolate submission

Updates to Utah's Communicable Disease Rule (R386-702) will aid increased understanding of Utah's MDRO burden. We respectfully request that laboratory staff and infection preventionists be aware of these updates. All carbapenemase-producing organisms will be added to the Utah Communicable Disease Rule. Any lab testing for carbapenemase production, regardless of species, is reportable and isolates should be submitted to public health for further testing. Additionally, while not currently reportable, all carbapenem-resistant *Enterobacteriaceae* can be submitted to the Utah Public Health Laboratory (UPHL) for carbapenemase testing. If submitting *Enterobacteriaceae* other than *Enterobacter*, *E. coli* or *Klebsiella* to rule out carbapenemase production, note that in bacteria that have intrinsic imipenem nonsusceptibility (i.e., *Morganella morganii*, *Proteus* spp., *Providencia* spp.), resistance to carbapenems other than imipenem is required.

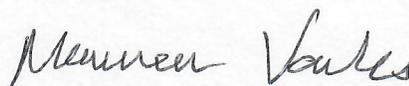
A list of current reporting requirements with specific disease and reporting timelines will soon be updated and available at R386-702, The Utah Communicable Disease Rule can be found at the Division of Administrative Rules website: <https://rules.utah.gov/publicat/code/r386/r386-702.htm>. Additional information is also available at <http://health.utah.gov/epi/reporting>.

The UDOH is grateful for your continued commitment to quality laboratory practices and patient care, and for your cooperation in ensuring reporting and isolate submission are consistent with requirements of Utah's Communicable Disease Rule. Together, we can prevent transmission and enhance containment of these concerning MDROs in Utah.

Sincerely,



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nomenclatural type (ATCC 13048) on the Approved Lists and are homotypic synonyms, with
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