



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 Mountain Region Antibiotic Resistance (AR) Laboratory based at the Utah Public Health Laboratory (UPHL) in Utah,**
- **A reminder about reporting and isolate submission requirements, and**
- **Changes to the Utah Communicable Disease Rule (R386-702).**

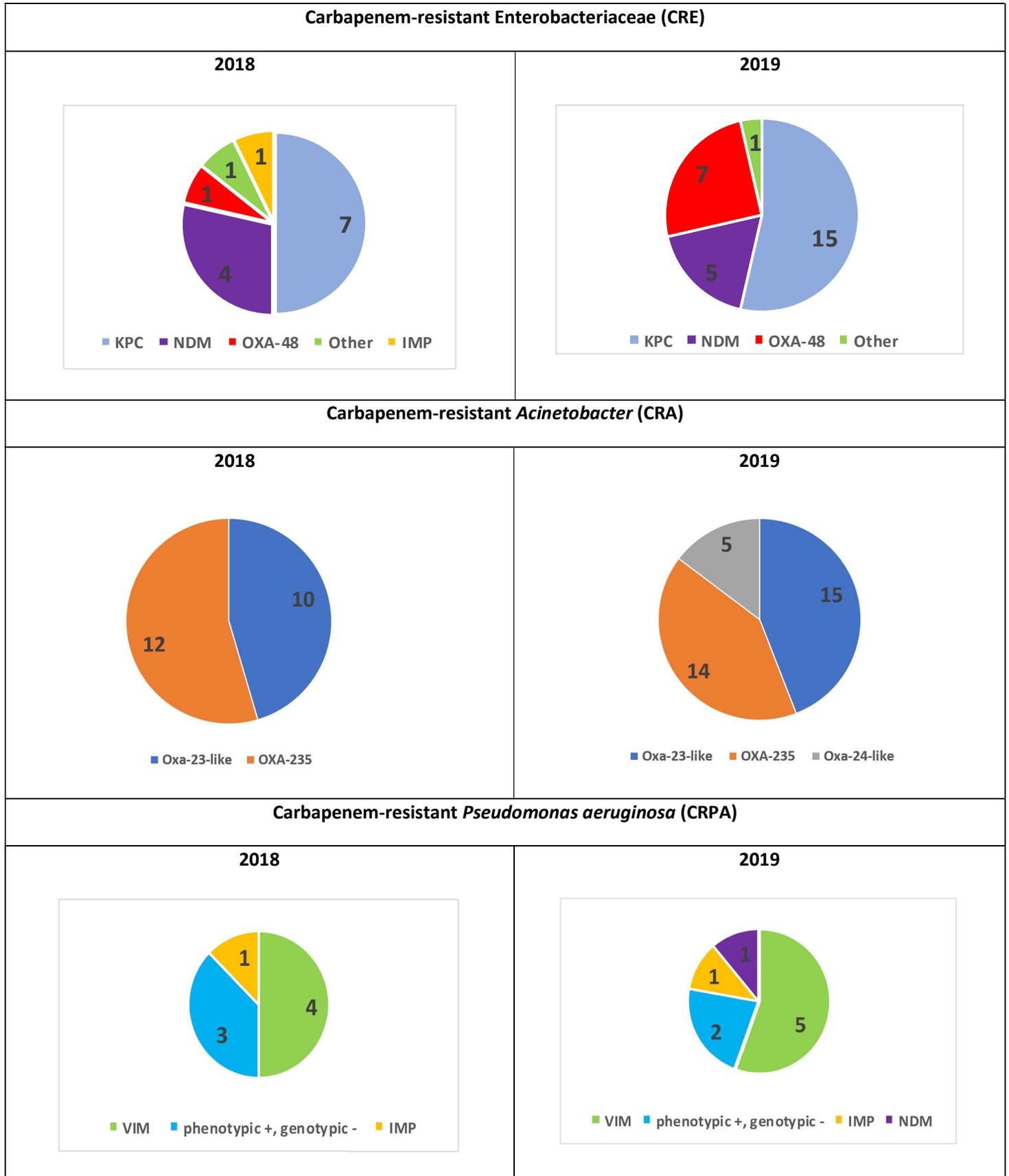
Situational Awareness

In 2019, laboratories reported 173 cases of carbapenem-resistant *Enterobacteriaceae* (CRE), 55 cases of carbapenem-resistant *Acinetobacter* (CRA) and 472 cases of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) to the Utah Department of Health (UDOH). A total of 458 carbapenem-resistant bacterial isolates including CRE, CRA and 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 2018 and 2019 summary of carbapenem-resistant organisms (CRO) reported to public health is shown in Table 1, and isolates positive for carbapenemase genes (by mechanism) broken down by CRE, CRA and CRPA are shown in the pie charts in Figure 1. Additionally, the UDOH assisted with 8 outbreaks in acute care hospitals and 4 outbreaks in long-term care facilities. 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. CRE, CRA and CRPA reported to public health—Utah 2018 and 2019

	2018	2019
Carbapenem-resistant <i>Enterobacteriaceae</i> (CRE)		
<i>E. coli</i>	39	27
<i>Enterobacter</i> spp.	62	91
<i>Klebsiella</i> spp.	27	40
Other <i>Enterobacteriaceae</i> e.g., <i>Citrobacter</i> spp., <i>Providencia</i> spp., etc.	6	15
Carbapenem-resistant <i>Acinetobacter</i> spp. (CRA)	81	55
Carbapenem-resistant <i>Pseudomonas</i> <i>aeruginosa</i> (CRPA)	473	472

Figure 1. Carbapenemase gene targets detected in CRE, CRA and CRPA—Utah 2018 and 2019



Antibiotic Resistance Laboratory Network (ARLN) Activities at the Utah Public Health Laboratory (UPHL)

Overview of activities

With CDC oversight, the Antibiotic Resistance Laboratory Network (ARLN) supports nationwide lab capacity to rapidly detect antibiotic resistance and inform local responses to prevent spread. In August 2019, the Utah Public Health Laboratory (UPHL) became the reference lab for 8 Mountain Region states (AZ, CO, WY, NM, TX, MT, ID), including Utah (Figure 2).

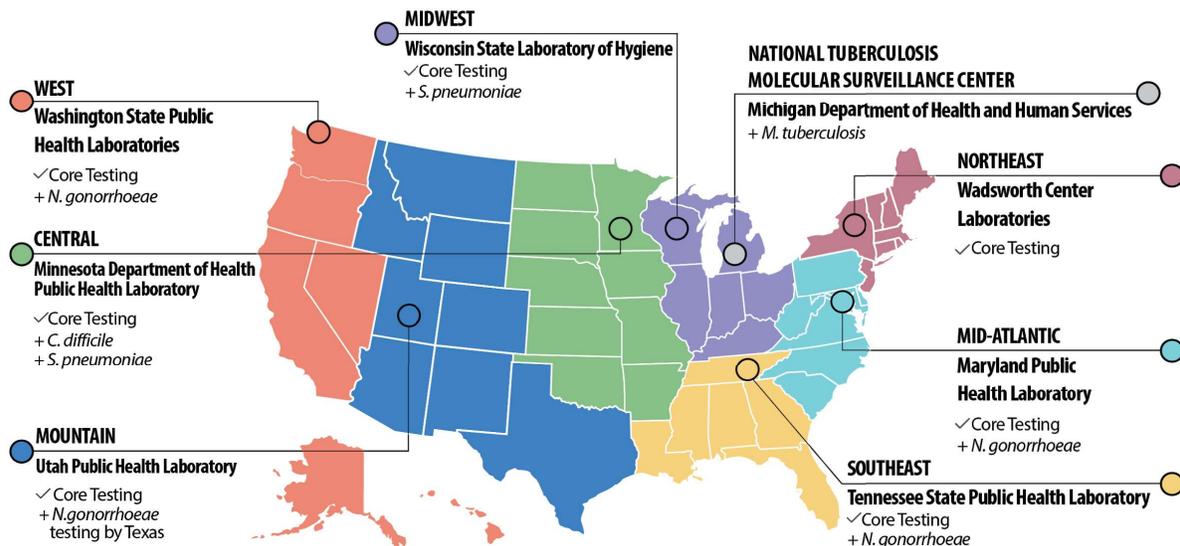


Figure 2. AR Lab Network Regional Labs and TB Center

UPHL works closely with the Healthcare-associated Infections Program within the Utah Department of Health to offer testing and support in the following areas:

Surveillance

- Characterization of presumptive CRE, CRPA, CRA (species ID, antibiotic susceptibility testing (AST), phenotypic and molecular carbapenemase production assays)
- Presumptive VRSA (species ID and vancomycin resistance confirmation*)
- Yeast speciation (including *C. auris*) and antifungal susceptibility
- Colistin resistance (AST and molecular detection)

IP support

- *Colonization screening for CRE, CRPA, CRA and *C. auris* (culture-based and molecular detection)
- Outbreak investigation support (Whole genome sequencing and molecular epidemiology analyses)

Patient care

- **Extended AST (including aztreonam/avibactam combination) for difficult-to-treat infections (only for *Enterobacteriaceae* producing IMP, VIM and NDM carbapenemases)

Training and education

- Assistance for small clinical labs in implementing AR testing

+ Currently referred to CDC.

* All AR Lab colonization screening activities and extended AST should be coordinated through Maureen Vowles (801-965-2505) with prior approval from the UDOH HAI Program.

** Pre-authorization form for this test can be downloaded from the website at:

<https://uphl.utah.gov/arIn-utah/>

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 management system. Nevertheless, infection preventionists still have a responsibility to manually report rare or unusual cases or clinically diagnosed reportable conditions to public health even if 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 reportable MDRO isolates (regardless of source) and submit them to the Utah Public Health Laboratory (UPHL) as quickly as possible for confirmation and further characterization. If deemed necessary, UPHL will forward isolates to the Centers for Disease Control and Prevention (CDC) laboratory as appropriate. Please note, 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 of these isolates were shipped to UPHL, several bacterial isolates (especially from urine) were discarded in 2019 with the loss of valuable clinical and epidemiological data. The public health isolate submission form can be found at: https://uphl.utah.gov/wp-content/uploads/UPHL_TEST_REQUEST_FILLABLE.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. 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 (new version released in Feb 2020)*

Current CLSI breakpoints for carbapenem antibiotics used to define cases of CRE, CRA and CRPA are tabulated in Table 2.

Table 2. 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

* Ertapenem is used with Enterobacteriaceae only; *Acinetobacter* spp. and *Pseudomonas aeruginosa* are intrinsically resistant to ertapenem, and therefore, do not create a case.

Submission of carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) isolates

Carbapenem resistance in *Pseudomonas aeruginosa* is mediated by many mechanisms including porin loss, expression of intrinsic beta-lactamases, upregulation of efflux pumps and carbapenemase production (CP). In a CDC 2019 study of 6444 CRPA isolates submitted through the ARLN, 282 (4.4 %) tested positive by the modified carbapenem inactivation (mCIM) method and 203 (3.2 %) tested positive for VIM, KPC, IMP or NDM carbapenemase genes. A closer look at the AST profiles of these CRPA isolates showed that **90% of carbapenemase production in CRPA can be identified by testing isolates resistant to ceftazidime or cefepime in addition to a carbapenem**. Therefore, due to the low rate of CP-production in CRPA, these criteria can be utilized to better target CRPA isolate submission for CP-testing.

Gilbert, S. et al. Identifying CP-CRPA among CRPA isolates. Centers for Disease Control and Prevention: Division of Healthcare Quality Promotion. December 2019.

Submission of *Enterobacter cloacae* 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.

Enterobacter sp. are often submitted to UPHL as CRE. All of these isolates are expected to carry a chromosomal AmpC-family β -lactamase. 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 for candidate carbapenemase genes, may trigger a “*Novel carbapenemase suspected*” alert. Therefore, AR Lab Network mandated avoiding alerts for CRE *Enterobacter* sp. isolates that are susceptible to cefepime (a predictor of AmpC hyper-production).

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 31 *E. cloacae* complex (ECC) isolates, and molecularly characterized them by WGS. We found that:

1. The current mCIM cut-off values established by CLSI are sensitive (100%) but not specific (27-52%) for the detection of ECC carbapenemase producers. We found that employing a stricter cut-off (6-15 mm, positive and ≥ 16 mm, negative regardless of colonies within the zone) improves mCIM specificity for the detection of ECC carbapenemase producers to 86%. **We can conservatively recommend that clinical labs performing mCIM submit only ECC isolates with zone sizes ≤ 15 mm, as larger zones are a reliable predictor of AmpC hyper-production.**
2. About 60% of all the *E. cloacae* complex that meet the CRE definition but were molecularly characterized as AmpC hyperproducers, were resistant to ertapenem only and susceptible to all other carbapenems. This phenomenon has been observed also in other studies.* Furthermore, all encountered ECC carbapenemase producers 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 of ECC isolates to UPHL.**

*Majewski P, Wieczorek P, Ojdana D, Sienko A, Kowalczyk O et al. Altered outer membrane transcriptome balance with AmpC overexpression in carbapenem-resistant *Enterobacter cloacae*. *Front Microbiol* 2016;7:2054.

Doumith M, Ellington MJ, Livermore DM, Woodford N. Molecular mechanisms disrupting porin expression in ertapenem-resistant *Klebsiella* and *Enterobacter* spp. *Clinical isolates from the UK. J Antimicrob Chemother* 2009;63(4):659-667. 7.

Yang FC, Yan JJ, Hung KH, Wu JJ. Characterization of ertapenem-resistant *Enterobacter cloacae* in a Taiwanese university hospital. *J Clin Microbiol* 2012;50(2):223-6.

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 or to schedule a colonization screening, contact Maureen Vowles, Mountain Region AR Lab Coordinator, (mvowles@utah.gov, (801) 965-2505) and the Utah HAI/AR program (hai@utah.gov). For further information regarding 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 information about WGS, please contact Kelly Oakeson, Next Generation Sequencing and

Bioinformatics Chief Scientist, (koakeson@utah.gov, (801) 965-2423). For more information about AR Lab testing activities at UPHL, please visit their new website at: <https://uphl.utah.gov/arIn-utah/>.

Changes to the Utah Communicable Disease Rule (R386-782)

A summary of surveillance for multidrug-resistant organisms (MDROs) is outlined in Table 3, with 2019 changes to the Utah Communicable Disease Rule highlighted in yellow. For a comprehensive list of organisms reportable under R386-782, please access the following link: http://health.utah.gov/epi/reporting/Rpt_Disease_List.pdf.

Table 3. Surveillance for multidrug-resistant organisms in Utah, 2020

Genus & species	Reporting and submission notes
Carbapenem-resistant <i>Enterobacteriaceae</i> (CRE) <i>E. coli</i> <i>Klebsiella</i> spp. <i>Enterobacter</i> spp.	<ul style="list-style-type: none"> • Statewide reporting (within 3 working days) • Submission of screening/surveillance and clinical isolates • Documented production of carbapenemase is reportable in all <i>Enterobacteriaceae</i> • Please note: although there is no current requirement for reporting/submission of other members of the <i>Enterobacteriaceae</i> family, these isolates can be submitted to UPHL for rule out of carbapenemase production using the listed criteria: <ul style="list-style-type: none"> ○ <i>Providencia</i> spp., <i>Proteus</i> spp. and <i>Morganella</i> spp. with resistance to a carbapenem antibiotic (excluding imipenem) ○ <i>Citrobacter</i> spp. and <i>Serratia</i> spp. with resistance to any carbapenem antibiotic
Carbapenem-resistant <i>Acinetobacter</i> spp. (CRA)	<ul style="list-style-type: none"> • Statewide reporting (within 3 working days) and isolate submission • Documented carbapenemase production reportable
Carbapenem-resistant <i>Pseudomonas aeruginosa</i> (*CRPA)	<ul style="list-style-type: none"> • Statewide reporting by ELR for surveillance only and submission • Documented carbapenemase production reportable <p>*see section on submission of CRPA isolates</p>
<i>Candida auris</i>	<ul style="list-style-type: none"> • Statewide reporting and submission of both screening/surveillance clinical isolates • <i>Candida haemulonii</i> and other rare <i>Candida</i> spp. or <i>Candida</i> spp. from sterile sites implicated in invasive disease that cannot be accurately speciated should also be submitted
Vancomycin-resistant <i>Staph aureus</i> (VRSA)	<ul style="list-style-type: none"> • Statewide within 24 hours (immediately notifiable) • Suspected VRSA isolates should be verified through repeat testing to confirm vancomycin-resistance (MIC >or =16 ug/mL) • Suspected VRSA isolates will be referred to the CDC for confirmation

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 Utah's Communicable Disease Rule. Together, we can prevent transmission and enhance containment of these concerning MDROs in Utah.

Sincerely,



Alessandro Rossi, PhD D(ABMM)
Chief Scientist, Infectious Disease Laboratory



Maureen Vowles, MPH, M(ASCP), CIC
AR Laboratory Coordinator—Mountain Region



Erik D. Christensen, MD
Interim Laboratory Director



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