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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.

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 chromosomomal 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, Kowalczuk 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/arln-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 *Enterobactericeae* (CRE)
 	
E. coli
 	
Klebsiella spp.
 	
Enterobacter spp.
	• Statewide reporting (within 3 working days)
	• Submission of screening/surveillance and clinical isolates
	• Documented production of carbapenemase is reportable in all *Enterobactericeae*
	• Please note: although there is no current requirement for reporting/submission of other members of the *Enterobacteriaceae* family, these isolates can be submitted to UPHL for rule out of carbapenemase production using the listed criteria:
	  ○ *Providencia* spp., *Proteus* spp. and *Morganella* spp. with resistance to a carbapenem antibiotic (excluding imipenem)
	  ○ *Citrobacter* spp. *and Serratia* spp. *w*ith resistance to any carbapenem antibiotic

Carbapenem-resistant *Acinetobacter* spp. (CRA)	• Statewide reporting (within 3 working days) and isolate submission • Documented carbapenemase production reportable
Carbapenem-resistant Pseudomonas aeruginosa (*CRPA)	• Statewide reporting by ELR for surveillance only and submission • Documented carbapenemase production reportable *see section on submission of CRPA isolates
Candida auris	• Statewide reporting and submission of both screening/surveillance clinical isolates • *Candida haemulonii* and other rare *Candida* spp. or *Candida* spp. from sterile sites implicated in invasive disease that cannot be accurately speciated should also be submitted
Vancomycin-resistant *Staph aureus* (VRSA)	• 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,

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