Subject: Impacts to availability of PZA susceptibility testing due to manufacturer instruction to discard specific lots

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Dear Colleagues,

Intermittent quality control failures and increased rates of false PZA-resistance have been reported for several months from laboratories across the United States. Becton, Dickinson and Company (BD), the manufacturer of the BD BACTEC™ MGIT™ 960 pyrazinamide (PZA) kit, wrote to customers on July 18, 2024, reporting specific lots of the PZA test kit should not be used and should be discarded immediately. BD indicated the root cause of the false resistance has been found and action is being taken to prevent recurrence. At this time, it is unknown when new product may be released.

Given this communication and instruction to discard testing kits, some laboratories may be unable to perform phenotypic PZA susceptibility testing. **CDC's TB Reference Laboratory is impacted, and effective immediately, we will be suspending phenotypic PZA susceptibility testing.**

Until new phenotypic PZA susceptibility testing kits are available, the following information is provided for consideration.

1. PZA monoresistance for non-multidrug-resistant (MDR) *Mycobacterium tuberculosis* complex (MTBC) is rare except for *M. bovis,* which is intrinsically resistant to PZA because of a specific nonsynonymous mutation (Asp57His) in the *pncA* gene. When feasible, *M. bovis* should be identified to differentiate from other members of the MTBC. This may require referral to another laboratory for identification.

2. Sequencing of *pncA* is an acceptable approach for determining PZA susceptibility as most PZA resistance is associated with mutations in *pncA*.
    a. Wild-type *pncA* (i.e., no mutations detected) correlates well with susceptibility to PZA.
    b. The understanding of PZA-resistance associated mutations has advanced and the positive predictive value is high for many *pncA* promoter and nonsynonymous mutations. The WHO Catalogue of mutations in Mycobacterium tuberculosis complex and their association with drug resistance, 2nd ed. is an available resource for interpretation.
    c. The correlation of some *pncA* mutations with PZA resistance is unknown. In these cases, healthcare providers should be advised to seek expert consultation through the jurisdictional TB program or CDC's TB Centers of Excellence for Training, Education, and Medical Consultation (COE).
3. Capacity for *pncA* sequencing is limited to a few U.S. laboratories. Resources for additional test volume may be constrained, especially considering that many laboratories might need to suspend phenotypic PZA susceptibility testing. Therefore, TB programs may need to prioritize which isolates will be referred for *pncA* sequencing. These might include isolates that are rifampin-resistant or multidrug-resistant (MDR) or isolates from patients whose treatment response is of concern. PZA resistance is more common in MDR isolates.
4. For situations when PZA might be essential for building a multidrug treatment regimen, but PZA susceptibility cannot be ascertained, COE consultation in conjunction with the TB program is strongly recommended.

Submitters may reach out to CDC's TB Reference Laboratory (TBLab@CDC.gov) to determine if capacity is available to assist with *pncA* sequencing. CDC's Division of TB Elimination (DTBE) Laboratory Branch is working with the Association of Public Health Laboratories (APHL) to determine which laboratories may be able to assist with testing. Partners may reach out to the assigned CDC TB Laboratory Consultant, or to Sarah Buss (sarah.buss@aphl.org) at APHL for additional assistance.

We will provide updates as they become available.

Best,

Angela

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