DOH 343-262

Interim Guidance for Treatment of Tuberculosis in the Absence of Phenotypic Pyrazinamide Susceptibility Testing
Tuberculosis Program, Washington State Department of Health
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To: Tuberculosis Control Officers
Washington State Local Health Jurisdictions

Requested Actions:

- Be aware of the potential for false positive phenotypic results for pyrazinamide (PZA) resistance on testing of *M. tuberculosis* isolates conducted since May 2023.
- Be aware that due to a nationwide unavailability of phenotypic PZA susceptibility test kits, PZA drug susceptibility testing (DST) results will not be routinely available until further notice.
- Consider the guidance below when addressing the treatment of affected patients.
- Please forward this advisory to clinicians in your jurisdiction who treat active TB cases.
- Consider seeking expert consultation in ambiguous or difficult cases.

Background

- Due to intermittent quality control issues and increased rates of false PZA-resistance observed across the United States, Becton, Dickinson and Company (BD) has instructed specific lots of BD BACTEC™ MGIT™ 960 pyrazinamide (PZA) test kits to be discarded immediately. Accordingly, the Washington State Public Health Laboratory (PHL) is suspending all phenotypic PZA susceptibility testing effective immediately. BD has identified the cause of the false resistance and is taking actions to prevent recurrence. Currently, the timeline for release of the new product is unknown.
- To-date, 30 such cases have been identified in Washington State since May 2023. For these cases, the PHL Tuberculosis Laboratory have issued amended drug susceptibility result reports as necessary to appropriate LHJs. Notwithstanding all this, you can trust other PZA results that have not been amended. Specifically, prior results indicating "sensitive to PZA" can be taken as true or correct.
- The understanding of PZA-resistance associated mutations has advanced and the positive predictive value is high for many *pncA* mutations. Detection of *pncA* mutations is predictive of phenotypic and clinical resistance, while the absence of a *pncA* mutation is predictive of phenotypic and clinical susceptibility. Demand for Molecular Detection of Drug Resistance (MDDR) at the Centers for Disease Control and Prevention (CDC) and *pncA* sequencing at reference laboratories may exceed capacity, and molecular testing will be prioritized for patients with complex or weighty drug susceptibility issues (e.g., rifampin-resistant, MDR or poly-drug resistance, suspected treatment failure).
- PZA monoresistance is closely associated with *M. bovis* disease primarily but not exclusively transmitted via ingestion of unpasteurized dairy products. Nevertheless, airborne transmission of *M. bovis* from person-to-person does occur.
- Data regarding PZA monoresistance in Washington State over the past decade reveals the following trends that may inform clinical management under these circumstances:
    - Patients born in Mexico and South-plus-SE Asian countries (i.e., Vietnam, Cambodia, Laos, Burma [Myanmar], and India) account for approximately two-thirds of PZA monoresistance.
    - PZA monoresistance is more common among patients with extrapulmonary involvement, especially of the lymphatics and abdomen. However, pulmonary cases of PZA-monoresistance can and do occur.

  - Age and gender do not appear to be useful in predicting the risk of PZA monoresistance.
- CDC has no plans to change national guidance for treating TB in response to this situation and encourages that treatment strategies be individualized by jurisdiction and patient.

Guidelines for Clinical Management

Resistance Profile	Timing	Suggested approach
PZA + other drugs	Adequate course of therapy for drug resistance profile completed	No action necessary.
	Treatment continues	Consider MDDR or *pncA* sequencing.
PZA monoresistance[1]	Adequate course of therapy for PZA monoresistance completed	No action necessary.
	Treatment continues at >2 months	Continue current regimen designed for PZA-monoresistance (e.g., INH+RIF x 9 months).[2]
	Treatment continues at <2 months	Consider whether PZA should be resumed for 8 weeks and then stopped.[3]
	Not yet started	Consider standard regimen with or without extension of continuation phase from 4 to 7 months to complete a total of 9 months of therapy to cover for PZA-monoresistance.[3] The 4-month regimen would also be reasonable for appropriately selected patients.[4]
No PZA results	New and future cases	Consider standard regimen with or without extension of continuation phase from 4 to 7 months to complete a total of 9 months of therapy to cover for PZA-monoresistance.[5] The 4-month regimen would also be reasonable for appropriately selected patients.[4]

[1] Assumes (a) validity of the initially reported PZA resistance result is in question and (b) other DST results are pending or the organism is sensitive to isoniazid (INH), rifampin (RIF), and ethambutol (EMB).

[2] PZA's primary contributions to TB treatment are (a) sterilization during the initial phase of therapy and (b) as a complement to other drugs in cases of INH resistance with or without resistance to other drugs. Addition or resumption of PZA during the continuation phase for treatment of an organism that is sensitive to INH-and-RIF probably makes little-to-no contribution to outcomes while significantly adding risk of intolerance and toxicity.

[3] Factors to consider would include duration of therapy to-date (less is better in this case), country of birth, site of disease, and anticipated ability to tolerate PZA (e.g., age, liver disease, gout). Even with addition or resumption of PZA for an 8-week period, clinicians may consider covering for PZA-monoresistance by extending the continuation phase to complete a total of 9 months of therapy with INH and RIF (rather than 6 months total).

[4] The 4-month regimen consists of 8 weeks of daily INH, high-dose RIF, moxifloxacin (MFX) and PZA followed by 9 weeks of daily INH, high-dose rifapentine (RPT), and MFX (2HPMZ+2HPM).

[5] **Among patients who are sensitive to INH, RIF and EMB, the likelihood of PZA monoresistance is low (e.g., <5%), and it is not necessary to routinely extend the continuation phase to cover PZA monoresistance empirically.** Doing so would add 50% to treatment duration and program burden while benefiting only a small proportion of cases with PZA monoresistance, most of whom probably would not relapse after a standard course of therapy. Factors to consider, however, when contemplating extending duration to 9 months to cover for PZA monoresistance include but may not be limited to: pre-treatment bacillary load, country of birth (e.g., Mexico, South-and-SE Asia), site of disease (e.g., extrapulmonary, LN, abdominal), history of ingestion of unpasteurized dairy products, and clinician judgment.