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Telephone 971-673-1111
Fax 971-673-1100

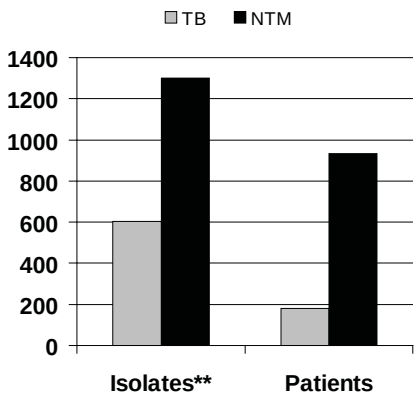
cd.summary@state.or.us
http://oregon.gov/dhs/ph/cdsummary

OREGON PUBLIC HEALTH DIVISION • DEPARTMENT OF HUMAN SERVICES

TB ALERT: PESKY NAAT SEASON

Definitive diagnosis of tuberculosis (TB) requires isolating *Mycobacterium tuberculosis* (MTB) in culture from patient sputum or other source. MTB grows slowly; isolation can require up to eight weeks. Culture delays often lead to unnecessary treatment and costly contact investigations in suspected cases that don't rule in, or delayed contact investigation and additional spread in cases where TB is not initially suspected but grows belatedly. These are more than hypothetical or occasional dilemmas. We recently conducted a survey of all laboratories that isolated pathogenic mycobacteria from Oregon residents during 2005–2006. We found that patients with laboratory confirmed non-tuberculous mycobacterial (NTM) disease outnumber patients with tuberculosis by nearly 5:1. (Figure)

NTM vs. TB disease in Oregon patients: 2005–2006.



**Isolates' might include multiple isolates from individual patients while patients are only counted once in the 'Patients' column.

A new test known as the Mycobacterium Direct Test (MTD-2) is likely to help. MTD-2 is a Nucleic Acid Amplification Test (NAAT)* for TB available already at several clinical laboratories in Oregon and beginning in late April from the Oregon State Public Health Laboratory (OSPHL). MTD-2 identifies MTB genetic material directly from the clinical respiratory specimen, such as sputum. Though laboratory isolation of MTB remains the linchpin of the TB case definition for both clinical and public health circumstances, the MTD-2 will help us make more accurate immediate determinations about whether or not a patient has TB.

A LITTLE HISTORY

NAAT's for TB have been commercially available for more than a decade but little utilized. The first two were approved by the Food and Drug Administration (FDA) in the mid- 1990's: Gen-Probe AMPLIFIED *Mycobacterium tuberculosis* Direct (MTD) Test, and Roche AMPLICOR MTB Test. However, FDA only approved these for 'smear-positive' respiratory specimens, (i.e. specimens in which acid-fast bacteria [AFB] were microscopically visible). NAAT's do have high sensitivity (95%) and specificity (98%) when used to test respiratory specimens from smear-positive, previously untreated patients for whom there is a high clinical suspicion of TB. However, while this was helpful to distinguish between MTB and NTM (e.g., *Mycobacterium avium*) and avoid unnecessary treatment and contact investigations, it did nothing to address the problem of unsuspected TB in people whose sputum was 'smear-negative.' In 1998, FDA approved the MTD-2 for use with both smear-positive and smear-negative respiratory specimens.[1]

USING THE MTD-2

In the June 2009 "Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis," the Centers for Disease Control and Prevention (CDC) recommends testing at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but hasn't yet been established and for whom the result would alter case management or TB control activities.[2]

The test is likely to provide useful information in patients with smear negative-specimens or smear-positive specimens where TB is not the most likely mycobacterial offender (see *M. avium*, etc.) but remains a possibility. Although sensitivity decreases to as low as 66% for smear-negative specimens, specificity remains close to 100%. This means that if a NAAT is positive, MTB is highly likely, even if TB wasn't suspected, reducing the occurrence of missed cases.[3]

Be wary of using MTD-2 for patients who have taken TB medications in the last twelve months or for more than 7 days. In fact, MTD-2 is not FDA approved for such patients. NAAT's can detect nucleic acids from dead as well as live organisms. Thus the test can remain positive after all bacilli have been killed by treatment. Also, information is limited regarding NAAT performance on extra-pulmonary specimens.[3]

COLLECTION AND SUBMISSION

Happily, you need do nothing special to order MTD-2. Simply collect 3 sputum specimens at least eight hours apart with one specimen collected in the morning as you would ordinarily do for suspected pulmonary TB. Order AFB smears and cultures on these 3 specimens. If you entertain substantial clinical suspicion of TB, order a NAAT, too, on the first specimen you send. When local health departments (LHD) send sputum to the OSPHL for AFB smear and culture, the first sputum sent for each patient will *automatically* be tested unless otherwise specified on the lab slip. If your laboratory has already grown a mycobacterium and you would like a NAAT test, contact OSPHL for instructions on specimen delivery.

*Note that we use "MTD-2"and "NAAT" interchangeably herein.

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INTERPRETING RESULTS

Although MTD-2 serves a useful diagnostic role, always interpret results within the context of a patient's signs and symptoms. Also, always use it in conjunction with AFB smear and culture results. See box for recommendations about interpreting and reacting to MTD-2 results under varying clinical scenarios. You will find this matrix and additional information about ordering and interpreting MTD-2 at the TB Program website *(www.oregon.gov/DHS/ph/tb/tools/NAATguide.pdf.)*

OSPHL will report results as "POSITIVE: *Mycobacterium tuberculosis* complex rRNA detected" or "NEGATIVE: *Mycobacterium tuberculosis* complex rRNA not detected."

SUMMARY

NAAT's, in conjunction with AFB smears and cultures, provide additional diagnostic information to assist you with diagnosis of patients who might have TB, improving the alacrity and accuracy of infection control and patient management. Interpreting results from this test can be tricky. Consultation is available from the Oregon TB Control program at 971-673-0174 or OSPHL at 503-693-4100.

REFERENCES

1. Centers for Disease Control and Prevention. Nucleic acid amplification tests for tuberculosis. MMWR 1996;45(43):950–2.
2. Centers for Disease Control and Prevention. Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. MMWR 2009;58(1):7–10.
3. Dinnes J, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. Health Technol Assess 2007;11:1–196.

MTD-2	Acid Fast Smear	Recommendations for clinicians	LHD Roles
Positive	Positive	Presume MTB; start TB treatment and airborne isolation; notify local health department; confirm findings with culture.	Follow case for confirmation; coordinate directly observed therapy (DOT); conduct contact investigation
Positive	Negative	MTB likely; contact LHD; consider repeat NAAT if TB disease unlikely; TB treatment probably indicated; confirm findings with culture.	Follow case for confirmation; consult on need for treatment and isolation; coordinate DOT; determine need for contact investigation; conduct contact investigation if indicated.
Negative	Positive	Suspect NTM (result does not rule out MTB); consider delaying treatment and relaxing isolation precautions unless TB strongly suspected and/or high-risk setting; consider repeat NAAT (Patient can be presumed to have an infection with a NTM if a second specimen is smear positive and NAAT negative.); confirm findings with culture.	Follow case for confirmation; consult on need for treatment and isolation; coordinate DOT if indicated; determine need for contact investigation; conduct contact investigation if indicated
Negative	Negative	Cannot exclude MTB (NAAT sensitivity low [66%] for smear-negative specimens); consider additional diagnostic work up and treatment if TB strongly suspected and/or high-risk setting; relax airborne isolation if two smears and one NAAT are negative unless TB strongly suspected and/or high risk setting; consider repeat NAAT; confirm findings with culture.	Follow case for confirmation; consult on need for treatment and isolation; coordinate DOT if indicated; determine need for contact investigation; conduct contact investigation if indicated.
Inhibited	N/A	Lab detected amplification inhibitors (most commonly blood) present can cause false negative results); lab will contact to submit another specimen for testing; contact LHD if TB suspected or consultation needed regarding additional evaluation/treatment.	Follow case for definitive diagnosis if contacted; consult on need for additional evaluation, treatment or isolation.