

The promise of rapid detection of active pulmonary tuberculosis in rural Alaska

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Abstract

Background: The process by which active pulmonary tuberculosis (TB) is detected can be tediously slow in rural and often roadless Alaska, where several hundred air or boat miles can separate a patient from a chest x-ray and/or sputum collection. Additionally, the only TB reference lab in the state is many hundreds of air miles away, albeit centrally located in Anchorage. Under such conditions, it may take up to a week to process serial sputum AFB smears. This can result in either delayed onset of treatment or unnecessary empiric treatment, all while safety for the community is being considered. This dilemma often results in precautionary hospital isolation of a patient who might otherwise have been able to travel home by air. This article proposes a roadmap for remote health care settings that might bridge our current TB diagnostic ability to a better way in the future.

Methods: Current TB diagnostic guidelines in our area (Yukon-Kuskokwim Delta) were reviewed for integration of the Xpert MTB/RIF assay with the purpose of improving TB health care while emphasizing patient benefits and cost savings.

Results: A clinical guideline that integrates the rapid TB assay into the current TB diagnostic algorithms for adults and adolescents is proposed. Crude cost savings at our hospital resulting from this guideline are estimated to be \$316,000 per year.

Conclusion: The proven utility of a new rapid TB diagnostic, the Xpert MTB/RIF assay, offers the promise of more efficient TB medical care, improved patient human rights and improved hospital and community environmental safety, all with likely huge reduced health care costs in remote Alaska.

Introduction

Tuberculosis continues to be a major health concern in Alaska, where it usually ranks highest among states¹, followed in rank order by Hawaii and California², and it has shown no decline in the past 15 years. Nowhere is this more apparent than in rural and remote Western Alaska, a wide swath of land (approximating half the area of the state) bordering the Bering Sea on the west and the Arctic Ocean on the north, where high rates are again climbing (*Figure 1*), despite the best public health practices. This area is where the first major isoniazid (INH) trials were conducted 60 years ago and demonstrated drug effectiveness³ while stopping a devastating TB epidemic and as a result guiding future TB control strategy in the United States.

The process by which active pulmonary tuberculosis is detected can be tediously slow in rural and often roadless Alaska, where several hundred air or boat miles can separate a patient from a chest x-ray and/or sputum collection. Additionally, the only TB reference lab in the

state is many hundreds of air miles away, albeit centrally located in Anchorage. Under such conditions, serial acid fast bacillus (AFB) sputum samples may take up to a week to process. This can result in either delayed onset of treatment or unnecessary empiric treatment calculated to both treat the patient and protect the community. This dilemma often results in precautionary hospital isolation of a patient who might otherwise be able to travel home by air.

With the recent emergence of the Xpert MTB/RIF assay (Cepheid Inc., Sunnyvale, Calif.), which is both rapid (less than two hours) and highly accurate for a single sputum specimen – 90.4 percent sensitivity, 98.4 percent specificity for culture-positive pulmonary TB in an 18-study 10,224-patient meta-analysis⁴, far exceeding AFB (smear) microscopy sensitivity of 67.5 percent⁵ – this article proposes a roadmap for remote health care settings in Alaska that might bridge our current TB diagnostic ability with a better way in the future.

Methods

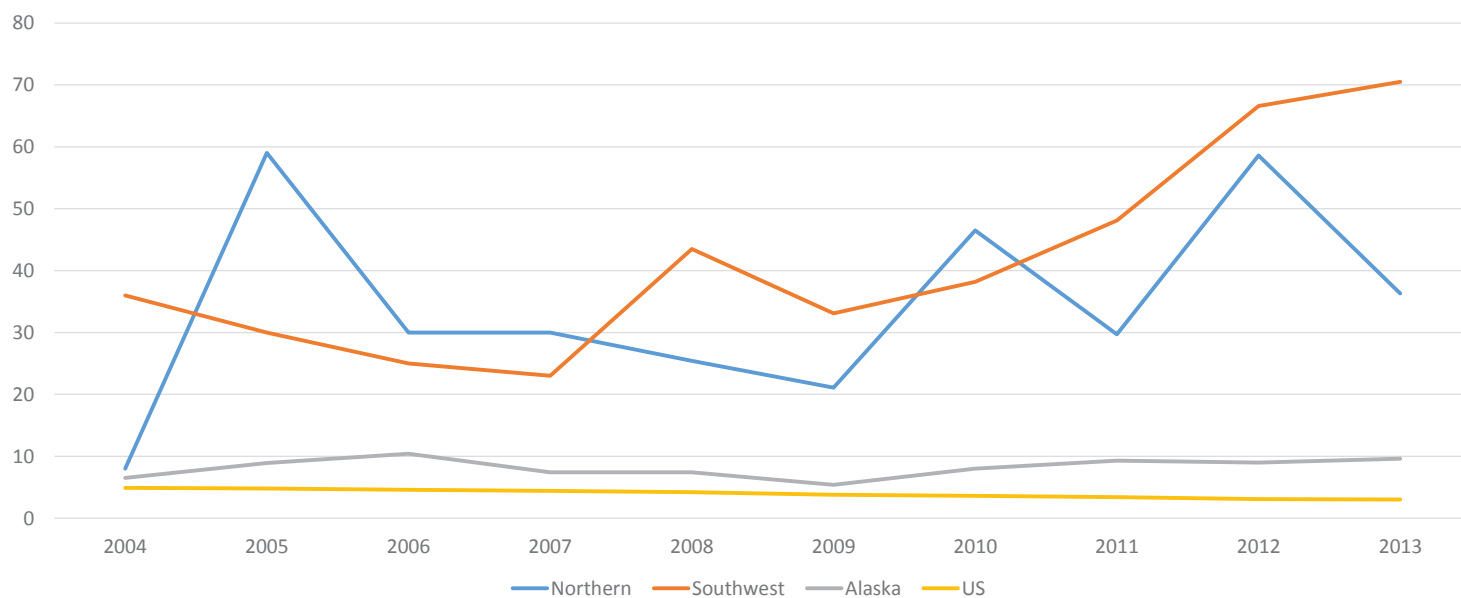
The 2013⁶ and expanded 2015⁷ intended use clearance indications by the Food and Drug Administration (FDA) for the Xpert MTB/RIF (rapid TB) assay were used to develop a new guideline for diagnosing and managing active pulmonary TB in rural Alaska by integrating this new landmark assay into the already excellent TB control program. As this study is merely anticipatory to the preparation and planned use of this assay, no data is available for testing of performance characteristics at this time.

Crude cost savings, based on what impact this assay might have on the health care system by making admissions solely for isolation unnecessary, are estimated based on the number of recent inpatients who had AFB sputum collection recorded in the send-out area of lab (n=24 from May 2014 to May 2015) without a subsequent active pulmonary TB diagnosis (confirmed sputum culture-negative) together with the current Medicaid daily hospital rate of \$2,850 (per our Utilization Management Department) for an average five-day stay. Any cost savings from not needing to airborne-isolate an otherwise acutely ill patient or any increased hospital costs from increased TB admissions directly relating to the increased diagnostic ability of this rapid TB assay are not included in the analysis.

Similarly, the Cepheid GeneXpert test platform and cartridge costs together with any extra lab staffing required are not calculated. This is because other (non-TB) assays will run on the same platform and therefore share operating costs, making TB-related costs unknowable until testing begins. Also, large presumed public health cost savings from the direct result of using the rapid TB assay⁸ have not been included in this study.

Figure 1: Western Alaska* TB Incidence, 2004-2013

Cases per 100,000



*Northern+Southwest regions

-Northern: North Slope, Maniilaq, and Norton Sound health districts

-Southwest: Y-K Delta, Bristol Bay, Eastern Aleutian, and Aleutian-Pribilof Islands health districts

Graph data from: 1. Alaska Epidemiology Bulletin No. 31; December 1, 2009. Available at: http://www.epi.alaska.gov/bulletins/docs/b2009_31.pdf

2. State of Alaska. Tuberculosis in Alaska 2013 Annual Report. Available at: http://www.epi.hss.state.ak.us/pubs/webtb/TB_Report_2013.pdf

Results

A clinical guideline that integrates the rapid TB assay into the current TB diagnostic algorithms for adults and adolescents (age 12 and older) has been proposed (*Figure 2*). The point-of-care (POC) Xpert MTB/RIF assay “in-house” result (presumably with its less than two-hour turnaround time) is a key element to efficiently manage such patients in the hospital setting.

In addition, the common medically stable patient in remote Alaska who instead presents to any number of village clinics (no x-ray available) with TB risk factors and symptoms of pneumonia also has been included in the above guideline.

This “village” presentation in the guideline is based on the same rapid assay but requires at least one additional day for diagnostic clarity due to necessary sputum transport to a regional hospital with the assay test platform. A specific guideline for children (younger than 12) or an adult or adolescent patient at a subregional clinic (village clinic with added capacity including x-ray) are not considered in this paper. Additionally, extrapulmonary TB is not considered in the guideline.

Based on several assumptions (*see Methods*), the crude estimated cost savings is enormous at \$316,000 for our 28-bed adult-pediatrics medical-surgery inpatient unit. That annual amount could vary between \$171,000 and \$513,000 as a range for an average monthly number of such admissions between one and three.

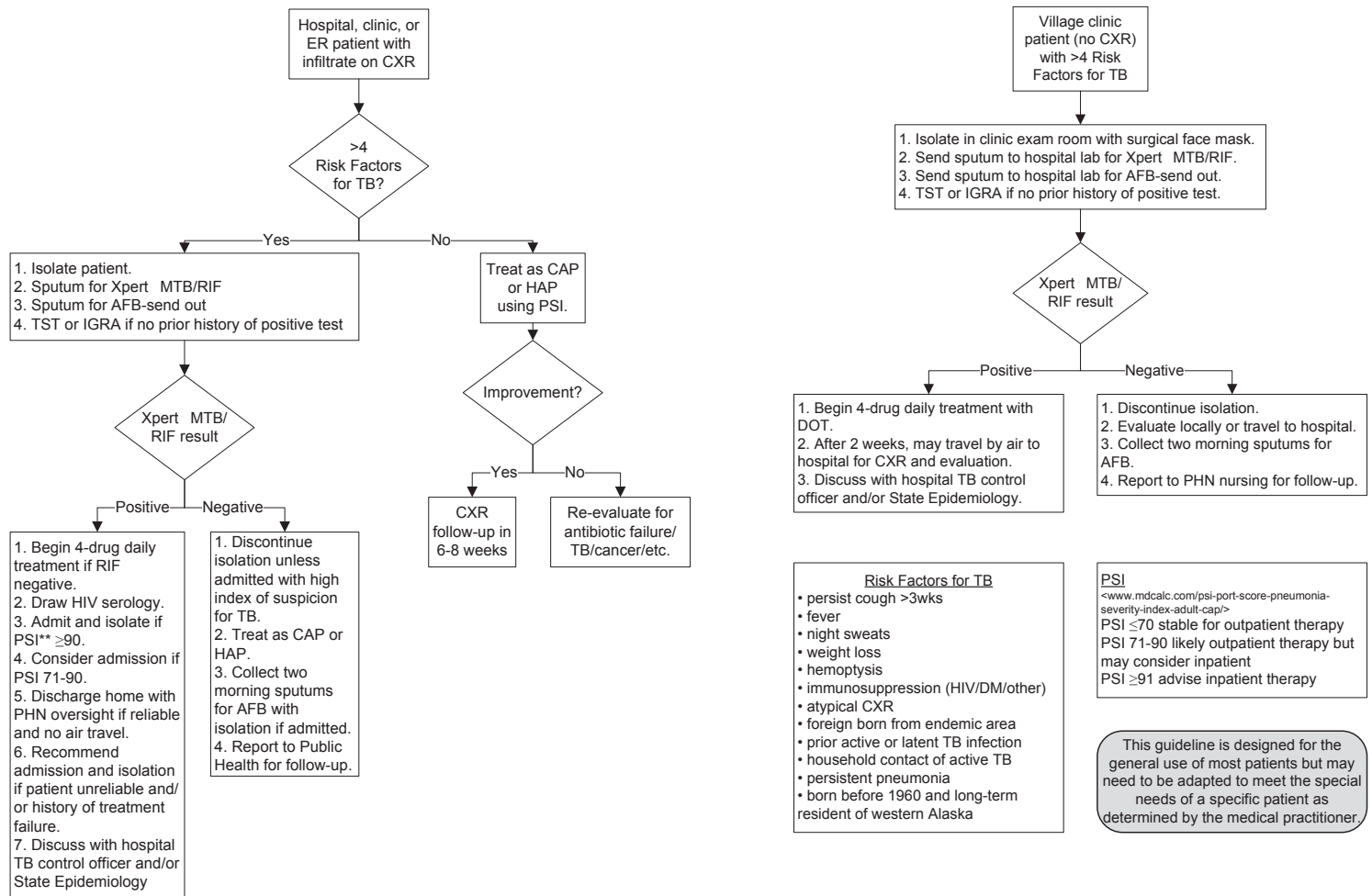
Discussion

The future is here! There is a growing body of evidence for a new approach to diagnosing pulmonary TB.⁹ We now have a commercially available cartridge-based automatic diagnostic test that can detect DNA sequences specific to TB including any associated rifampin

(or additional drugs by proxy) resistance mutations. Highly sensitive and specific test results¹⁰ can be obtained from unprocessed sputum requiring little technical training [Clinical Laboratory Improvement Amendments (CLIA) moderate complexity] using PCR amplification and identification by molecular beacon. Also, there is virtually no contamination risk due to the sealed cartridge test chamber. This can all be accomplished within a two hour period and on a portable Cepheid GeneXpert platform that can be used simultaneously for other types of assays. That being said, collection of additional sputum samples is advised for proper TB culture identification and drug sensitivity testing for a rapid TB-positive result. Also, since one Xpert MTB/RIF assay is only 90.4 percent sensitive⁴ (and still far exceeds AFB smear microscopy of 67.5 percent⁵) for culture-positive pulmonary TB and therefore misses approximately 10 percent of mostly smear-negative pulmonary TB cases, additional sputum samples are recommended also for rapid TB-negative results for early culture identification of this group. Lastly, although there is growing data for this assay’s use for other body fluids and tissues¹¹, FDA clearance currently is lacking for anything other than sputum.

The World Health Organization (WHO) endorsed the Xpert MTB/RIF assay in December 2010, when there was a huge need to accurately diagnose and treat pulmonary TB while assessing for drug resistance in a timely fashion often in high-burden TB remote areas of the world.¹² In 2013 this assay gained entrance into the United States⁶ with FDA followed by CLIA clearance. Although this test is still applicable in the setting of low TB prevalence¹³, it is ideal for testing in a moderate TB prevalence area such as Western Alaska which in many ways mimics the non-U.S. TB situation. In South Africa the Xpert MTB/RIF assay

Figure 2: Active Pulmonary TB Adult & Adolescent Guideline (using rapid TB assay)



Abbreviations: AFB-acid fast bacilli; CA-cancer; CAP-community acquired pneumonia; CXR-chest x-ray; DOT-direct observational therapy; ER-emergency room; HAP-healthcare associated pneumonia; HIV-human immunodeficiency virus; IGRA-interferon gamma release assay; PHN-public health nurse; PSI-pneumonia severity index; RIF-rifampin resistance; TB-tuberculosis; TST-tuberculin skin test

is being used in place of AFB microscopy as the initial diagnostic test for TB nationally for a three-year trial as a cost-cutting and practical measure¹⁴.

Using the sputum culture-positive as the traditional “gold standard” for an active pulmonary TB diagnosis, the first widely reported sensitivity and specificity for a single sputum sample using the Xpert MTB/RIF assay¹⁵ were:

► Sensitivity for detection of smear-positive pulmonary TB: 98.2 percent (551/561)

► Sensitivity for detection of smear-negative pulmonary TB: 72.5 percent (124/171)

► Specificity for those without pulmonary TB: 99.2 percent (604/609)

From the values in the above study population:

► Positive Predictive Value (PPV) for smear-positive pulmonary TB = 99.1 percent

► PPV for smear-negative pulmonary TB = 96.1 percent

► PPV for combined smear-positive and negative pulmonary TB = 99.3 percent

► Negative Predictive Value (NPV) for smear-positive pulmonary TB = 98.4 percent

In summary, 98.2 percent of AFB smear-positive pulmonary TB

cases were detected by Xpert MTB/RIF. Additionally, 72.5 percent of smear-negative but culture-positive pulmonary TB cases were rapid test positive (this value increased to 90.2 percent by using three sputum samples). Also, 99.2 percent of those without pulmonary TB were correctly diagnosed with a rapid test negative. A positive Xpert MTB/RIF assay essentially rules in active smear-positive or smear negative-pulmonary TB 99.3 percent (675/680) of the time, which is the PPV for combined smear-positive and negative pulmonary TB.

A key finding from the above is the fact that a single rapid test-negative essentially rules out smear-positive pulmonary TB [NPV = 98.4 percent (604/614)]. This test result is equivalent to the NPV of 98.2 percent for three smear-negative results⁵, which is the current U.S. hospital standard for discontinuing TB isolation.

In conclusion, not only will the Xpert MTB/RIF assay (on one sputum sample) diagnose 23 percent (95 percent Credible Interval 15 percent to 32 percent) more pulmonary TB patients with its better test sensitivity over AFB smear microscopy¹⁰, but it also will adequately rule out smear-positive pulmonary TB. Also, since Predictive Values, unlike test sensitivity and specificity, are affected by disease incidence, with most communities – including Western Alaska – having lower TB incidence rates than the study area¹⁵, a lower PPV but higher NPV (i.e. greater than 98.4 percent) would be expected in practice, adding

certainly to the rapid TB assay's ability to rule out smear-positive TB.

The Xpert MTB/RIF assay has the potential to hugely affect medical care, patient human rights, environmental safety and health care cost as follows.

More Efficient TB Medical Care

Like our CT scanner, the greater immediate diagnostic clarity of this rapid and extremely accurate TB assay will promote better care. This is how it might be used in the ER in our remote setting using one sputum sample:

Positive rapid sputum test result = Active Pulmonary TB

Next, classify patient by medical stability and home residence.

1. Stable local patient: Send home on 4-drugs with mask and followup.

2. Stable village patient: Admit to hospital with TB isolation on 4-drugs, send home when AFB smear-negative x3 (as usual) or rapid TB test-negative once.⁷

3. Unstable local patient: Admit to hospital with TB isolation on 4-drugs, send home when stable with mask.

4. Unstable village patient: Admit to hospital with TB isolation on 4-drugs, send home when AFB smear-negative x3 (as usual) or rapid TB test-negative once⁷ and patient stable.

Furthermore, as the Xpert MTB/RIF assay has the ability to detect some smear-negative, culture-positive pulmonary TB patients before they become highly contagious (or AFB smear-positive), diagnosis and treatment can occur sooner, meaning fewer in the community and health care setting will be exposed. An additional advantage of this assay is the RIF component, which tests for rifampin (and as a surrogate marker, other drug) resistance, which alerts for possible multidrug

resistance (MDR), enabling immediate treatment and further specific testing for MDR-TB.

Negative rapid sputum test result = no smear-positive pulmonary TB

This means pneumonia can be treated inpatient or outpatient without concern for TB-isolation unless there is a high index of suspicion for active pulmonary TB and further TB-isolation would be beneficial. Sputum collection for smear microscopy and culture is still recommended for those with TB risk factors, as the rapid TB assay will miss about 10 percent of usually smear-negative cases (90.4 percent sensitivity for culture-positive pulmonary TB⁴).

Improved Patient/Human Rights

The Xpert MTB/RIF assay gives a test result within hours. Therefore an otherwise stable pneumonia patient who does not have active pulmonary TB does not have to be "isolated" – sometimes against his or her will – three to seven days for the safety of the community while their two or three AFB sputa go through the testing process far away at the state lab in Anchorage to prove this. Similarly, a single sputum sample tested with the rapid TB assay has been shown to reduce isolation time in the hospital setting by an average of 45 hours.¹⁶

Improved Hospital and Community Environmental Safety

There is no data on this but by common sense if more actively infected pulmonary TB patients are discovered with the rapid TB assay (and immediately treated) before becoming highly contagious (unlike the AFB test), predictably fewer highly contagious TB patients will be circulating undiagnosed in the community and health care setting.



Dr. McDonagh



Dr. Ebenhoeh

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THE ALASKA HEART & VASCULAR INSTITUTE IS PLEASED TO ANNOUNCE

that Drs. Scott Ebenhoeh and Jonathan R. McDonagh will be joining our team of highly skilled cardiologists. Dr. Ebenhoeh, a graduate of Michigan State University and general cardiologist, hails from Garden City, Michigan. Dr. McDonagh, who is also from Michigan, specializes in interventional cardiology and graduated from the University of Vermont College of Medicine.



Thus, a safer environment for all. Even those patients who are contagious as determined by AFB microscopy might be diagnosed sooner with the rapid TB assay additionally lowering exposure to active TB for a safer environment. In a moderate- to high-burden TB setting, the focus for controlling TB is to identify and treat those infected to lower transmission. The rapid TB assay does this more efficiently than our current method.

Reduced Health Care Costs

A Johns Hopkins University study evaluating the cost-effectiveness of integrating the Xpert MTB/RIF assay into current TB diagnostic algorithms in the U.S. using a decision-analysis model found it “highly cost-effective.”¹³ The San Francisco General Hospital experience reported that this rapid TB test “could eliminate most unnecessary isolation for inpatients with presumed tuberculosis” with great benefit for patients and the hospital with a single sputum pre-admission sample adequately identifying smear-negative pulmonary TB patients.¹⁶

Conservatively, the rapid TB test might save our small regional hospital \$316,000 (range: \$171,000 to \$513,000 by various assumptions; see Methods) annually through reduced unnecessary admissions for TB isolation of stable patients proved later not to have active pulmonary TB.

Additional savings are possible through:

1. Reduced number of admitted patients not requiring TB-isolation precaution services of health care and ancillary staff.
2. Reduced respiratory therapy services required.
3. Reduced hospital lab and state lab costs for sputum sample processing.
4. Reduced (divert-related) Anchorage medevac costs as more acute beds available by preventing unnecessary rule out TB admissions.
5. Other unforeseen cost savings.

A more accurate accounting of presumed hospital costs from integrating the Xpert MTB/RIF assay into our current TB diagnostic algorithm would best be accomplished through an operational research records review or best, prospectively following each suspected TB patient tested with the new rapid assay.

Although not considered in this study, out-of-hospital health care costs, including public health costs in a TB-endemic region, can be enormous. It has been shown that costs such as unnecessary empiric treatment, contact investigation and housing can be curtailed with the rapid TB assay use.¹⁷ In addition, one public health department calculated it would save 53 percent of all costs associated with TB suspects by using such a rapid TB assay – even with a (slower) three-day turnaround time instead of the recommended POC use.⁸

Conclusion

The proven utility of a new rapid TB diagnostic – the WHO-endorsed, FDA-approved and CLIA-approved Xpert MTB/RIF assay – offers the promise of more efficient TB medical care, improved patient human rights and improved hospital and community environmental safety, all with likely huge reduced health care costs in remote Alaska.

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