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The Feasibility, Accuracy, and Impact of Xpert MTB/RIF Testing in a Remote Aboriginal Community in Canada

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BACKGROUND: Xpert MTB/RIF testing for *Mycobacterium tuberculosis* and rifampin resistance is being used extensively in countries with a high burden of TB. However, recent evidence suggests that it may not have the same accuracy or impact in high-income, low-burden TB countries.

METHODS: A prospective, pragmatic study was done between March 2012 and March 2014 to determine the feasibility, accuracy, and impact on TB disease management provided by the Xpert test in a remote, medically underserved, predominantly Inuit population in Iqaluit, Nunavut, Canada.

RESULTS: A total of 453 Xpert tests were run on sputum samples from 344 patients with suspected TB. Twenty-seven patients were identified as having active TB disease by culture. There were no cases of drug-resistant TB. Using culture as the gold standard, one Xpert test compared with one, two, or three sputum samples cultured per patient had a sensitivity of 85% (95% CI, 66%-95%) and a specificity of 99% (95% CI, 97%-100%) for detection of *M tuberculosis*. The indeterminate rate was 4.4% of all samples run. Treatment initiation was significantly shortened using Xpert vs the national standard of three smears (1.8 days vs 7.7 days, $P < .007$) and particularly shorter in smear-negative, culture-positive cases (1.8 days vs 37.1 days, $P < .008$).

CONCLUSIONS: In a predominantly Inuit population in a remote region of Canada where the burden of TB is high and no TB testing facilities are available, onsite Xpert testing was feasible and accurate and shortened the time to TB treatment initiation.

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ABBREVIATIONS: MTB = *Mycobacterium tuberculosis*; NPV = negative predictive value; PPV = positive predictive value

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The incidence of active TB disease in the territory of Nunavut located in the Canadian Arctic has been rising over the past 10 years.[1] In 2010, the trend reached 304 per 100,000 (representing 101 active cases) compared with the Canadian rate of 4.6 per 100,000.[1,2] Inuit represent 85% of the population of the Nunavut territory[3] and have a disproportionately high burden of TB disease across Canada compared with other Canadian-born aboriginal people.[4] In this remote region of the country, no infrastructure for TB testing exists because of a scarcity of public health and laboratory human resources. All microscopy and culture testing is outsourced by airplane to the south of the country.

Xpert MTB/RIF (Cepheid) is an automated, cartridge-based, real-time polymerase chain reaction assay for rapid detection of *Mycobacterium tuberculosis* (MTB) and rifampin resistance. Globally, > 7 million Xpert tests have been procured in high-burden countries. The Xpert test was approved for laboratory use by Health Canada in 2012 and by the US Food and Drug Administration in 2013.[5]

Studies from low-income, high-burden countries have shown the test to be accurate when compared against culture.[6,7] A recent meta-analysis confirmed these initial findings.[8] However, few studies have evaluated the feasibility and accuracy of Xpert in high-income, low-burden countries.[9,10] A reference laboratory with full TB diagnostic capacity in Switzerland found that Xpert was accurate for cases with a high pretest probability for TB.[9] However, in Montreal, Quebec, Canada, a study done in a low-incidence, ambulatory setting supported by a full on-site TB diagnostic laboratory suggested a limited impact of Xpert testing, resulting in lower sensitivity and no improvement in time to diagnosis, especially for patients with few symptoms and predominantly smear-negative TB.[10]

A pragmatic, real-world study was undertaken to determine the feasibility, accuracy, and impact of Xpert testing in a remote high-burden region in the Canadian Arctic with no on-site TB testing capacity. The three objectives of the study were to determine (1) whether the test was feasible under local conditions in this region, (2) the accuracy between a single Xpert test vs three sputum smears using MTB culture as a gold standard, and (3) the impact on TB disease management as measured by a reduction in time to treatment initiation compared with standard testing.

Materials and Methods

Setting and Participants

The population of Nunavut is 31,700, of which Inuit represent 85%.[11] Iqaluit, the capital of Nunavut, is located in the Canadian Arctic. Its population is 7,250. Iqaluit can be accessed only by plane during the winter months and ship or plane during its brief summer. The local hospital laboratory does not have TB testing capacity. Samples are flown on weekdays to the nearest major center (Ottawa, Ontario, Canada) for smear and culture. Flying time is 3 h.

Between March 2012 and March 2014 sputum samples obtained in Iqaluit were sent for Xpert testing at the local laboratory at the Qikiqtani General Hospital (e-Appendix 1). Local laboratory technologists trained by the study investigators ran Xpert tests between 8:00 AM and 5:00 PM Monday through Friday. Sample processing and cartridge preparation was performed in a class II biological safety cabinet in a dedicated room separated from the main laboratory by a door. The specimens were shipped promptly each weekday morning on the daily flight to the laboratory in Ottawa. No specimens were held back, and specimens were not batched together for transport.

The Xpert test was used for all eligible sputum samples produced by patients presenting to Iqaluit Public Health for TB testing or admitted to the local Qikiqtani General Hospital for investigation of active TB disease. Samples were obtained either spontaneously or by sputum induction. The majority of patients who presented to Iqaluit Public Health for TB testing were identified as having had contact with an individual with active TB disease. Other reasons for testing included employment screening, school screening, referrals from other health-care professionals, and walk-ins. Per the current Nunavut TB standards for testing by microscopy or culture, sputum was collected from patients who had received a new diagnosis of latent TB infection; who had contact with individuals with active TB disease with a previous diagnosis of latent infection; or who had symptoms, chest radiograph, or both suggestive of active TB disease.

For a sputum sample to be considered for Xpert testing, the following criteria were applied: (1) no TB treatment longer than 3 days prior to producing the sputum sample, (2) adequate sample quality (free from saliva and food particles), (3) adequate sample quantity (minimum of 3 mL or enough volume for Xpert, microscopy, and culture), and (4) all sputum samples provided within a 2-week period. Samples were excluded if they did not have a corresponding smear and culture or if they did not have an Xpert test done on one of the three samples provided. Patients provided one sputum sample during the assessment visit and returned for two additional early morning samples taken on consecutive days per Nunavut standards; however, given the pragmatic nature of this study, some patients produced one, two, or three sputum samples for analysis. Some patients were assessed for TB more than once over the course of the 2-year study.

Main Measurements and Data Analysis

Feasibility was defined by the capacity of the assay to retain its accuracy and have an acceptable rate of indeterminate test results in this remote setting. Test accuracy was measured by the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), using culture as the gold standard. A case of active TB disease was defined from sputum that was culture positive for MTB on either liquid or solid media. The main analysis was performed by comparing one Xpert test to all sputum samples provided by a patient whether it was one, two, or three. Using this group of all-comers allowed us to measure test performance in real-world conditions.

The time to obtain a result was measured from the time stamped on the specimens arriving at the laboratory to the time the result was posted on the electronic health record for access by the health-care team. The sputum sample used for all three tests (Xpert, smear, and

culture) was also used to compare turnaround times among Xpert, smear microscopy, and culture per patient. The treatment initiation time was recorded from the time the specimen arrived at the laboratory to the time the patient took the first dose of TB medication. Treating clinicians were given the results of the Xpert test in real time. Informed consent from each patient was not obtained because all sputum specimens were sent for routine TB testing and only if enough sputum was available to perform the Xpert test. Ethics approval was obtained from the Ottawa Hospital Research Ethics Board (#2011691-01H). A Nunavut Research License was obtained. The Standards for Reporting of Diagnostic Accuracy were used in the reporting of the study results.[12]

Results

Feasibility

Three hundred sixty-eight patients were considered for the study between March 2012 and March 2014, 344 of whom were included in the final analysis (Table 1). Of the 24 patients excluded, 15 had indeterminate results, two did not have corresponding smears or cultures, and seven were on treatment for > 3 days (e-Fig 1). Some patients had more than one assessment for TB, including Xpert testing, during the study period, including 29 with two Xpert tests and 16 with three or more Xpert tests, resulting in 453 samples considered for the study (Fig 1). Of these samples, 422 (93%) were obtained through spontaneous sputum production, 30 (7%) through sputum induction, and one through an unknown method. Although the Nunavut TB guidelines ask that patients provide three sputum samples (immediate, morning, morning), in this pragmatic study, 59% provided three samples, 18% provided two samples, and 23% provided one sample.

Indeterminate and Rifampin Resistance Results: The indeterminate rate was 4.4% (20 of 453 samples), with 10 samples showing an error and 10 being invalid. Of the 20 samples with indeterminate results, none was smear or culture positive. No rifampin resistance was detected in any of the samples tested. One test result was indeterminate for rifampin resistance. Repeat testing of this sample did not detect rifampin resistance, and cultures of the samples were pansusceptible to all first-line drugs. Six sputum samples were culture positive for a nontuberculous mycobacteria. None of these samples yielded a false-positive Xpert result. These samples were included in the final analysis because they were considered TB culture negative.

TABLE 1] Patient Characteristics

Characteristic	Value (n = 344)
Age, y	36 (25-38)
Male sex	220 (64)
Inuit	315 (92)

Data are presented as median (interquartile range) or No. (%).

Test Accuracy

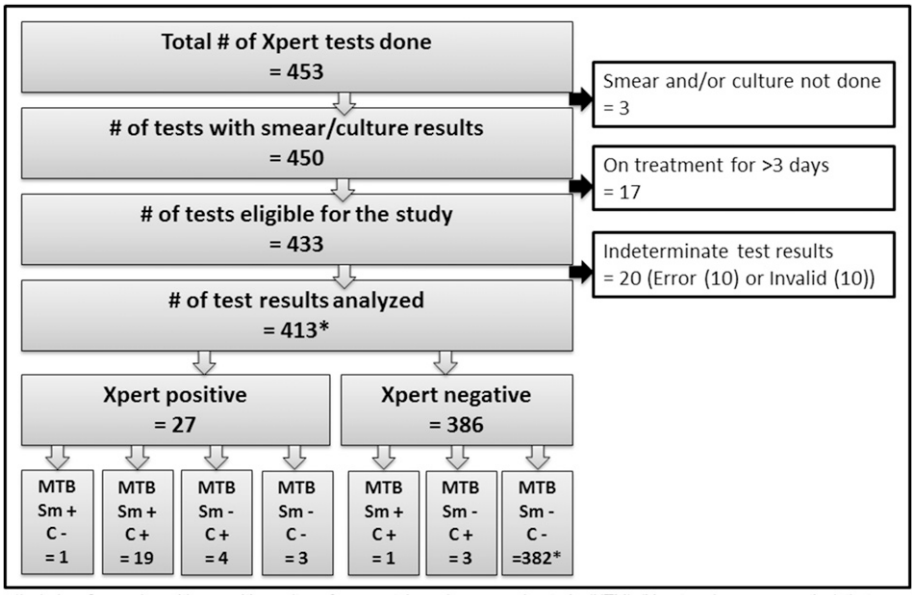
The accuracy of smear against culture for all-comers (either one, two, or three samples provided by each patient) demonstrated a sensitivity of 74% (95% CI, 54%-89%), a specificity of 99% (95% CI, 99%-100%), a PPV of 95% (95% CI, 76%-100%) and an NPV of 98% (95% CI, 96%-99%) (Table 2). The accuracy of Xpert against culture demonstrated a sensitivity of 85% (95% CI, 66%-95%), a specificity of 99% (95% CI, 97%-100%), a PPV of 85% (95% CI, 66%-95%), and an NPV of 99% (95% CI, 97%-100%) (Table 3).

Compared with smear, Xpert increased TB detection among culture-confirmed cases among all-comers, although the increase was not statistically significant (23 of 27 culture-confirmed cases [85%] were detected by Xpert vs 20 of 27 cases [74%] detected by smear; difference, 11%; 95% CI, −14% to 36%; $P = .499$). (See e-Table 1 for the incremental percent increase in sensitivity of Xpert over smear when compared with one, two, or three samples.)

Test Accuracy Stratified by Smear Result: In patients with smear-negative results, the Xpert test increased detection of TB, although the increase was not statistically significant (Table 4). There were seven smear-negative cases, of which four (57%) were detected by Xpert and none (0%) detected by smear ($P = .076$). Compared with culture, the smear-positive group demonstrated a sensitivity of 95% (95% CI, 76%-100%) and a PPV of 95% (95% CI, 76%-100%). Specificity and NPV estimates could not be calculated because no Xpert-negative culture-negative results were found in the smear-positive group. The smear-negative group demonstrated a sensitivity of 57% (95% CI, 18%-90%), a specificity of 99% (95% CI, 98%-100%), a PPV of 67% (95% CI, 22%-95%), and an NPV of 99% (95% CI, 98%-100%) (Table 4). Among smear-negative, culture-positive cases, Xpert increased case detection by 57% in all-comers (ie, either one, two, or three sputum samples were provided by the patient).

Turnaround Times and Time to Treatment Initiation

Compared with smear, Xpert increased TB detection among culture-confirmed cases and provided a faster



*Includes 6 samples with a positive culture for a nontuberculous mycobacteria (NTM) (Xpert and smear negative) that for the purposes of the analysis were considered *Mycobacteria tuberculosis* (MTB) culture negative

Figure 1 – *Results of eligible tests from March 1, 2012, to March 30, 2014. C- = culture negative; C+ = culture positive; MTB =* Mycobacterium tuberculosis*; Sm- = smear negative; Sm+ = smear positive.*

turnaround time (Table 5). Treatment start times were correspondingly improved using Xpert vs the standard of three smears (1.8 days vs 7.7 days, $P < .007$) (Table 6). This was also amplified in the Xpert-positive, smear-negative, culture-positive cases (1.8 days vs 37.1 days, $P < .008$), allowing patients to receive treatment earlier.

Discussion

In Iqaluit, Nunavut, Xpert testing was feasible and accurate and had an impact on clinical care in a remote arctic region of Canada that does not have laboratory capacity for TB testing and has limited human resources. The indeterminate rate was low, accounting for 4.4% of all tests run compared with 2% in the largest multicentered pragmatic study[7] and 8.8% in a previous Canadian study.[10] The accuracy of Xpert performed within normal program constraints was maintained compared with other studies performed in low-income, high-burden countries[8] and was higher than in high-resource, low-burden settings.[10] The accuracy of Xpert depends on the number of corresponding smear and culture results to which it is compared. The accuracy of the test done in Iqaluit was comparable to international studies[8] (e-Table 2), even with a real-world approach where all participants had one, two, or three samples analyzed. Compared with smear, Xpert increased TB detection among culture-confirmed cases and provided a faster turnaround time (Table 5). Treatment start times were correspondingly improved using Xpert vs the standard of three smears (1.8 days vs 7.7 days, $P < .007$) (Table 6). This was also amplified in the Xpert-positive, smear-negative, culture-positive cases (1.8 days vs 37.1 days, $P < .008$), allowing patients to receive treatment earlier.

The accuracy of a test should be consistent across populations, but it may change when applied to other patient subgroups due to spectrum of disease bias.[13] More-advanced stages of TB disease are associated with an increased bacillary load, thus potentially increasing the sensitivity of Xpert compared with an earlier stage of the disease with a corresponding lower bacillary load. The present findings demonstrate an overall sensitivity of

TABLE 2] Accuracy of Smear Against Culture for All-Comers (Either One, Two, or Three Samples Provided by Each Patient)

	MTB Culture		
Smear	Positive	Negative	Total
Positive	20	1	21
Negative	7	385	392
Total	27	386	413

MTB = *Mycobacterium tuberculosis*.

TABLE 3] Accuracy of Xpert Against Culture

	MTB Culture		
Xpert	Positive	Negative	Total
Positive	23	4	27
Negative	4	382	386
Total	27	386	413

See Table 2 legend for expansion of abbreviation.

TABLE 4] Accuracy of Xpert Against Culture Stratified by Smear Result

Test	MTB Culture		Total
	Positive	Negative	
Smear positive			
Xpert positive	19	1	20
Xpert negative	1	0	1
Smear negative			
Xpert positive	4	3	7
Xpert negative	3	382	385
Total	27	386	413

See Table 2 legend for expansion of abbreviation.

85% (95% CI, 66%-95%) compared with 46% (95% CI, 26%-67%) for Xpert testing performed in a previous comparison study.[10] When stratified by smear result, the difference in sensitivity was greatest in the smear-negative group (76% [95% CI, 29%-96%] vs 28% [95% CI, 10%-56%]).[10] No differences were noted in the specificity of Xpert between the two sites. In the current pragmatic study, only patients clinically suspected of having TB were tested within regular program conditions. Furthermore, the majority of these patients were able to produce sputum, which may suggest that most were symptomatic compared with the previous study,[10] where sputum induction was done on all patients to obtain a sample.

The ability to report a point-of-care test and act on it is important.[14] Clinicians in this study used the results from Xpert to start patients on treatment in a rapid sequence. Patients with smear-negative, culture-positive TB started treatment 37 days earlier based on Xpert testing. These patient cases represent a small proportion of the TB cases in this study, but given that 66% (298 of 452) of culture-confirmed cases in Nunavut over the past 11 years have been smear negative (M. Baikie, MD, personal communication, September 2014), the impact for patients getting earlier treatment and reducing the risk of transmission could be even greater in this setting, particularly in many of the smear-negative cases detected by culture after 37 days that could potentially develop into smear-positive disease in that time period.

The turnaround time difference of 8 h vs 4 days for Xpert vs smear, respectively, in this population is also important to ruling out active disease in decisions related to isolation in the hospital, medical evacuation by air, employment screening for remote work camps, and management of patients from high-risk congregate settings. Xpert has been shown to shorten airborne isolation time in hospitalized patients in one American study.[15] If we applied the high NPV and rapid turnaround times for locally performed Xpert testing, it is likely that time spent in airborne isolation in the hospital would be reduced, resulting in improvements in patient comfort and potential cost savings. A cost-effectiveness study is currently under way to explore the cost savings potential of Xpert testing for TB diagnosis and care in the region.

Limitations

Detailed information on each patient's clinical presentation was not collected in this study; therefore, comments

TABLE 5] Turnaround Times for Xpert, AFB Smear, and Culture for the Same Single Sputum Sample for Each Participant

Time Interval[a] (Specimen Received to)	No. Samples	Turnaround Time, h	Turnaround Time, d
All samples (No. = 413)			
Xpert result	393	9 (3-25)	0.4 (0.1-1.0)
AFB smear result	408	97 (64-129)	4.0 (2.7-5.4)
Culture result	412	1,279 (1,246-1,320)	53.3 (51.9-55.0)
Smear positive, culture positive (No. = 16)			
Xpert result	15	5 (3-26)	0.2 (0.1-1.1)
AFB smear result	16	112 (71-140)	4.7 (3.0-5.8)
Culture result	16	382 (317-449)	15.9 (13.2-18.7)
Smear negative, culture positive (No. = 7)			
Xpert result	7	20 (2-21)	0.8 (0.1- 0.9)
AFB smear result	7	69 (52-264)	2.9 (2.2-11.0)
Culture result	7	715 (527-1,358)	29.8 (22.0- 56.6)

Data are presented as median (interquartile range) unless otherwise indicated. AFB = acid-fast bacilli.
[a]Excluding any time intervals with a negative or missing value.

TABLE 6] Time to Treatment Initiation From the Time Sputa Were Received in the Laboratory for Xpert-Positive Culture-Confirmed Cases

Case	Xpert, d	Smear, d	*P* Value[a]
Xpert positive, smear positive	1.8	7.7	.007
Xpert positive, smear negative	1.8	37.1[b]	.008

Data are presented as mean. Xpert-positive culture-confirmed cases (n = 18, excluding patients with Xpert-positive culture results who were started empirically on treatment before any testing was completed [n = 5]).

[a]Paired *t* test comparison.

[b]Diagnosis based on culture result.

cannot be made based on disease severity of the study population. However, only people who were being investigated for active TB were tested. Between-test comparisons were limited by the relatively small number of patients in the study with positive culture results for MTB, but in all instances, the trend was for the Xpert test to be more sensitive than smear for detection of culture-positive MTB (e-Table 1). The time the result was entered into the electronic health record system, used as an end point to measure turnaround time, may not reflect the actual time that the health-care provider accessed the result. Although time to start of treatment was used to improve this measurement, this information was only available for patients within the study who were found to have active TB disease. A single sputum specimen was divided for Xpert, smear, and culture testing, which could have diluted the ability of each test to detect TB and, thus, underestimate the accuracy of the test compared with a single, undivided sample. In an effort to maintain the standard of care in this pragmatic study, only specimens with enough volume of sputum (inclusion criterion) to run all three tests (Xpert, smear, and culture) were used. It is possible that the ability of individuals to spontaneously produce a greater volume of sputum may indicate a more advanced disease state, which may be correlated with a higher number of smear-positive cases.

Conclusions

In a predominantly Inuit population in a remote region of Canada where the burden of TB is high and no TB laboratory facilities are available, Xpert was feasible and accurate and reduced treatment delays. This technology could play an important role in improving health equity in TB diagnosis in remote, high-burden regions of Canada.

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Author contributions: G. G. A. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. G. G. A., M. D., S. D. A., D. W. C., and M. P. contributed to the study design; G. G. A., D. D. V. D., A. S. Y., S. D. A., D. W. C., and M. P. contributed to the data analysis; and G. G. A., D. D. V. D., M. D., A. S. Y., S. D. A., D. W. C., N. O., M. B., S. P., C. M. D., H. S., and M. P. contributed to the data interpretation and preparation of the manuscript.

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Additional information: The e-Appendix, e-Figure, and e-Tables can be found in the Supplemental Materials section of the online article.

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