

## The performance and yield of tuberculosis testing algorithms using microscopy, chest x-ray, and Xpert MTB/RIF

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### ABSTRACT

**Setting:** The introduction of Xpert MTB/RIF (Xpert) and renewed interest in chest x-ray (CXR) for tuberculosis testing has provided additional choices to the smear-based diagnostic algorithms used by TB programs previously. More programmatic data is needed to better understand the implications of possible approaches.

**Objective:** We sought to evaluate how different testing algorithms using microscopy, Xpert and CXR impacted the number of people detected with TB in a district hospital in Nepal.

**Design:** Consecutively recruited patients with TB-related symptoms were offered smear microscopy, CXR and Xpert. We tested six hypothetical algorithms and compared yield, bacteriologically positive (Bac+) cases missed, and tests conducted.

**Results:** Among 929 patients, Bac+ prevalence was 17.3% ( $n = 161$ ). Smear microscopy detected 121 (75.2% of Bac+). Depending on the radiologists' interpretation of CXR, Xpert testing could be reduced by (31%–60%). Smear microscopy reduced Xpert cartridge need slightly, but increased the overall diagnostic tests performed.

**Conclusion:** Xpert detected a large proportion of Bac+ TB cases missed by microscopy. CXR was useful in greatly reducing the number of diagnostic tests needed even among presumptive TB patients. Loose CXR readings should be used to identify more people for TB testing. More analysis of costs and standardized CXR reading should be considered.

### 1. Background

The World Health Organization (WHO) estimates that 1.6 million people died from tuberculosis (TB) in 2017 making it the leading killer among infectious diseases [1]. Many deaths occur among people who are missed by the health system and thus are not properly detected or treated, or those who have drug resistant forms of the disease.

Global efforts to increase the number of people detected and treated for TB and ultimately save lives has manifested in a number of different approaches. Active case finding strategies, using outreach efforts to reach people before passive presentation to health facilities, have been used [2–5] but moving outside a facility is generally more expensive [6]. Approaches focused on better case finding inside facilities, through systematic screening [7] and/or expanding the TB testing algorithms are also used. This approach was used to improve the detection of TB among people living with HIV (PLHIV) by using a multi-symptom

screen [8]. Considerable efforts have also been made to improve diagnostic testing, initially with fluorescent microscopy (FM) [9] and more recently with Xpert MTB/RIF (Cepheid, Inc., Sunnyvale, CA, USA, “Xpert”) [10] as well as a renewed interest in chest x-ray (CXR) [11]. Xpert has a higher sensitivity than smear microscopy [12,13], but also a higher cost [14]. The high costs of Xpert have led to interest in using less expensive triage tests that can identify people who need further testing and a discussion about what diagnostic algorithms might be used to identify more people with TB [15].

In Nepal, Xpert was used as a follow on diagnostic test earlier than many other countries [16]. Nepal has a high TB burden, with an estimated 44,000 people developing TB every year, of whom, one in five remain undiagnosed and unnotified to the national TB program (NTP) and one in seven die [1]. Using Xpert as a diagnostic test following smear microscopy and CXR improved bacteriologically positive TB notifications by 15.2% in Eastern Nepal and almost doubled the number

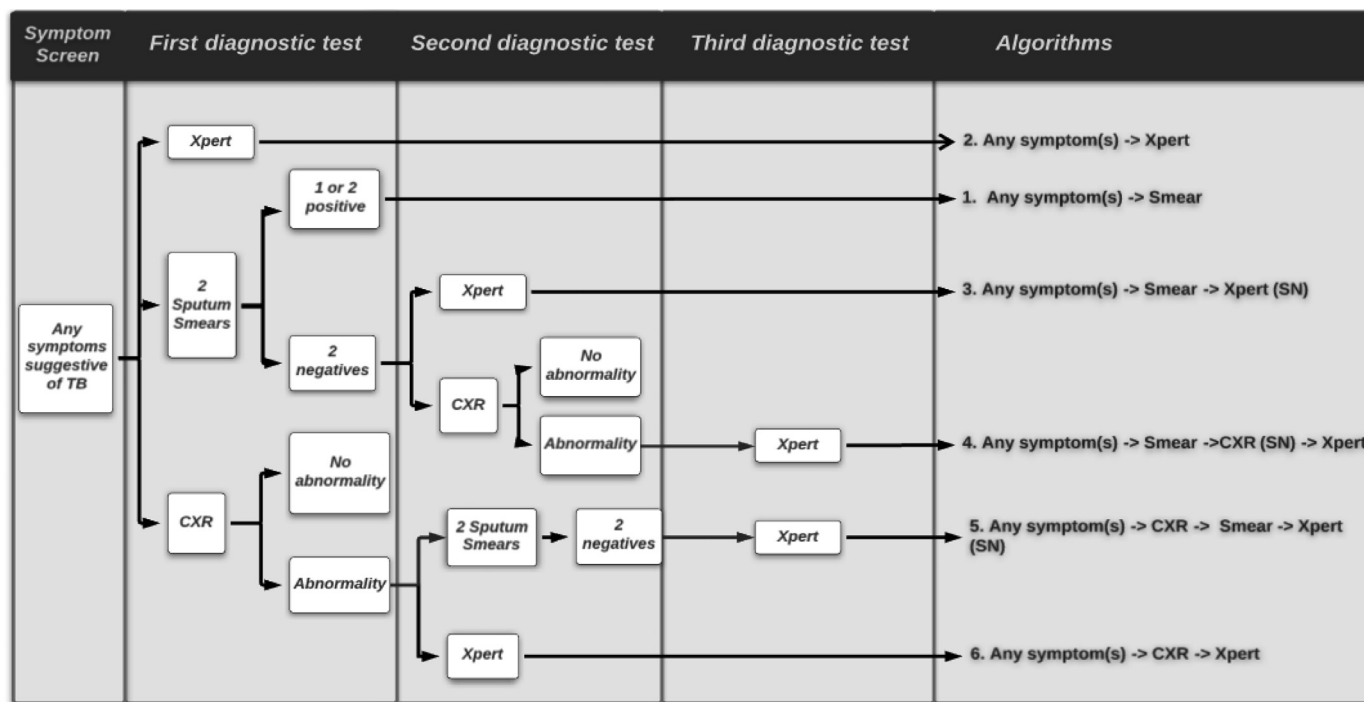
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Abbreviations: TB = tuberculosis, CXR = chest x-ray, SN = Smear negative.

Fig. 1. Tuberculosis testing algorithms evaluated in a district hospital in Nepal  
Abbreviations: TB = tuberculosis, CXR = chest x-ray, SN = Smear negative.

of people started on MDR-TB regimens [17].

Despite the advantages of Xpert, smear microscopy remains the initial diagnostic test used in Nepal, and overwhelmingly, in most high burden countries [18]. The current national diagnostic algorithm for TB is based on microscopy due to its low cost and ability to detect TB among people with highly infectious disease. The standard approach to case finding in Nepal, as in most countries, is symptom screening, followed by smear microscopy and depending on the clinician's decision, a CXR which is paid by the person seeking care. Many countries including Nepal use CXR to aid diagnosis [19] as CXR has high sensitivity for pulmonary TB when any abnormality is considered [20,21]. However, many diseases have similar radiologic appearance as TB, hence, CXR usually has low specificity [22].

While many studies have compared the performance of smear microscopy to Xpert, and the diagnostic accuracy of the tests are well documented [12,13], there have been fewer studies that have evaluated CXR and other tests together in diagnostic algorithms, especially as part of routine care [23]. Modeling suggests that CXR may be a useful tool to improve diagnostic accuracy [15]. We examined the performance of smear microscopy, CXR, and Xpert in a tertiary care setting in Nepal to provide an initial evaluation of how the use of these different tests could affect the number of people detected with TB.

## 2. Methods

### 2.1. Study design and enrollment

We performed a cross-sectional study at B.P. Koirala Institute of Health Sciences (BPKIHS) in Sunsari district in Eastern Nepal. Between March 1 and December 31, 2015 all individuals aged 15 years or older at the pulmonary outpatient department in BPKIHS who presented with any TB-suggestive symptom (coughing >14 days, fever, weight loss, night sweat, hemoptysis) and no prior history of TB were referred by triage physicians to be enrolled in the study. The study protocol was approved by the Ethics Committee, Institutional Reviewing Board,

BPKIHS, Nepal.

### 2.2. Testing procedure and TB diagnosis

After providing a verbal explanation of the study and obtaining informed consent, each participant received a posteroanterior CXR taken by a Phillips DigitalDiagnost machine. Each radiograph was read by a senior Professor of Radiology at BPKIHS and was graded according to one of the following five categories: 'Highly suggestive of TB', 'Possibly TB', 'Other finding', 'Normal', and 'Image not clear'.

Each participant was asked to provide two sputum samples. A spot sputum sample was collected during the outpatient visit, and a morning sample was collected the next day. Both sputum samples were examined using fluorescent microscopy (FM). Smears were read and graded according to the GLI Microscopy Handbook [24]. A smear was recorded positive if it was graded as scanty, 1+, 2+, or 3+. One of the samples was also used for an Xpert test. For the participants recruited between March 1 and July 31, 2015, an Xpert was performed on the spot sample. For participants recruited between August 1 and December 31, 2015, an Xpert was performed on the morning sample. If the initial Xpert test failed (no result, invalid, error) it was repeated using the same sample. If rifampin resistance was detected, a repeat test was conducted from a new sample following national guidelines, and the result was recorded as final.

### 2.3. Definition of TB cases and treatment

Participants with a positive Xpert or one positive smear were defined as bacteriologically positive TB (Bac+) as per national guidelines. Culture testing is not routinely used in Nepal and was not performed in this study due to funding and logistical constraints. For individuals who had rifampicin resistance detected on the repeated Xpert assay, an additional sample was collected for follow-up culture and drug susceptibility testing at the National Reference Laboratory in Katmandu and the individual was referred to the second line treatment center

nearest their residence in accordance with national policy. Individuals with negative bacteriological test results but with a continued suspicion of TB were managed as per national guidelines for possible clinical diagnosis or other morbidities at the hospital.

#### 2.4. Testing algorithms

We constructed six hypothetical testing algorithms. The algorithms are presented in Fig. 1. In brief, they are (1) smear alone, (2) Xpert alone, (3) smear followed by Xpert on all smear negatives, (4) smear followed by CXR on all smear negatives, and Xpert for those with abnormal CXR images, (5) CXR followed by smear for those with abnormal CXR images, followed by Xpert for smear negatives, and (6) CXR followed by Xpert for those with abnormal CXR images.

The CXR results for the hypothetical algorithms were analyzed using a 'loose' reading (assuming all people with symptoms were tested unless they had a 'Normal' reading) an 'intermediate' reading (only people with 'Highly suggestive of TB' and 'Possibly TB' readings were further tested), and a strict reading where only people with 'Highly suggestive of TB' readings were sent for further testing.

#### 2.5. Data analysis

All statistical analyses were conducted in R (R Foundation for Statistical Computing, Vienna, Austria) [25]. The diagnostic accuracy of smear using spot and morning sputum samples and CXR was compared to Xpert. For the six testing algorithms, we calculated the number of people diagnosed with bacteriologically positive (Bac+) TB, percentage of Bac+ TB missed, and the total number of each diagnostic test required.

### 3. Results

#### 3.1. Patient characteristics

From March 2015 to December 2015, 1010 individuals with TB symptoms, but no prior TB history, who visited the chest outpatient department in BPKIHS were consecutively recruited for the study and all agreed to participate. Of these, 81 people had incomplete results, so the final analysis includes results from 929 participants (Fig. 2). Among all participants, the median age was 44 (interquartile range [IQR] 26–60); 56.3% ( $n = 523$ ) were males; and HIV status was unknown in most participants (88.5%) (Table 1). The vast majority of participants (90%) had cough for more than 14 days, around half of the participants reported having fever (55.5%), and weight loss (49.2%). Most of the participants (75.2%) had multiple symptoms.

#### 3.2. Test results

A total of 161 Bac+ TB cases were detected by smear or Xpert and all were enrolled in care, representing 17.3% overall prevalence of PTB. Four people (2.5% of Bac+) had rifampicin resistant TB.

##### 3.2.1. Smear results

Smear microscopy detected 121 (75.2%) of the Bac+ cases including two of the four cases who had rifampicin resistance while the other two were smear-negative. The sensitivity of smear was 69.1% (95% CI: 57.9–78.9%) for spot sample and 77.5% (95% CI: 66.8–86.1%) for the morning samples compared to Xpert results. The performance of microscopy did not vary between morning and spot specimens, although smear grading was higher in morning specimens (Table 2).

##### 3.2.2. Radiological results

The radiologist graded 187 (20.1%) CXR images as 'Highly suggestive of TB', 205 (22.1%) as 'Possibly TB', 129 (13.9%) as 'Other

finding', 406 (43.7%) as 'Normal' and 2 as 'Image not clear' (Table 1). More than half of the participants whose CXRs were graded as Highly Suggestive of TB were Xpert positive  $n = 111$  (59.4%). The proportion decreased to 19.0% ( $n = 39$ ) among participants whose CXRs were graded as 'Possibly TB'. The results were similar for smear with 48.7% of smears among those with 'Highly suggestive of TB' images were positive on smear while 12.2% of those with 'possibly TB' CXR readings had smear positive results. Almost all Xpert positive results ( $n = 150$ , 93.2% of total Bac+ cases) came from people with CXR graded as either 'Highly suggestive' or 'Possibly TB' (Fig. 2).

#### 3.3. Comparing diagnostic testing algorithms

The results of the different testing algorithms are presented in Table 3. Algorithm 1, smear testing alone, detected 121 Bac+ cases on 929 samples. Algorithm 2, direct Xpert testing detected 161 Bac+ TB cases using 929 Xpert tests, an increase of 40 (33.1%) more people identified with TB than smear testing alone. Algorithm 3, where the first test is smear microscopy and then Xpert for those with negative smear results 161 Bac+ cases were identified but the number of Xpert tests needed decreased to 808 although the total number of tests was 1737.

Algorithm 4, which adds a CXR after a negative smear followed by Xpert, reduced Xpert testing to 555–178 depending on the grading criteria used for the CXR. Using the strict reading of the CXR image (only 'including highly suggestive of TB') 12.4% of all Bac+ patients were missed but this reduced to 3.7% using the loose reading of CXR (all except 'Normal' readings).

Using CXR before smear and Xpert (Algorithm 5), the yield of Bac+ was slightly lower than Algorithm 4 but the number of Xperts needed also reduced. Removing smear microscopy completely so that all people with symptoms first received a CXR followed by Xpert (Algorithm 6), the Bac+ yield depended on the CXR grading criteria. Overall yield and Xpert tests used was similar to Algorithm 4 using strict or intermediate CXR cutoff points. However, a 15% increase (808–929) in CXR in Algorithm 6 compared to 4 allowed for removing all smear testing using a loose reading of CXR images. Of note, using a strict CXR reading in Algorithm 5 or 6 missed 31% of Bac+ patients which is higher than smear microscopy alone.

### 4. Discussion

Our results add to a growing body of work analyzing the potential yield of different diagnostic tests for TB showing the importance of Xpert to detect more Bac+ and drug-resistant TB, and utility of CXR in reducing the number of Xpert tests needed. We evaluated possible benefits of using Xpert MTB/RIF and CXR against the standard diagnostic algorithm used by most high TB burden countries. Using Xpert in the diagnostic algorithm increased the bacteriologically confirmed cases by up to 33% and identified four people with rifampicin resistance early that would have been put on a first line regimen if only microscopy was used. The wider use of tests that provide drug sensitivity results will be critical to meet the global TB targets outlined in the Global Plan and End TB Strategy [26,27]. Using CXR can also provide a vital tool to reduce the number of more expensive Xpert tests used in places where it is available. In our study, the use of CXR reduced the number of Xpert tests needed by 31–60% depending on the algorithm and reading criteria used.

Our results provide a broad overview of the different yields from triage and diagnostic tests that can be used when contemplating different algorithms for TB diagnosis. As other demonstration studies and programmatic evaluations have shown, Xpert will identify a large proportion of people with TB that smear microscopy misses [10,12,28]. CXR can also be a useful tool for screening out people who likely do not have TB, even among symptomatic individuals [29,30]. This could potentially save costs of more expensive Xpert testing, but the costs

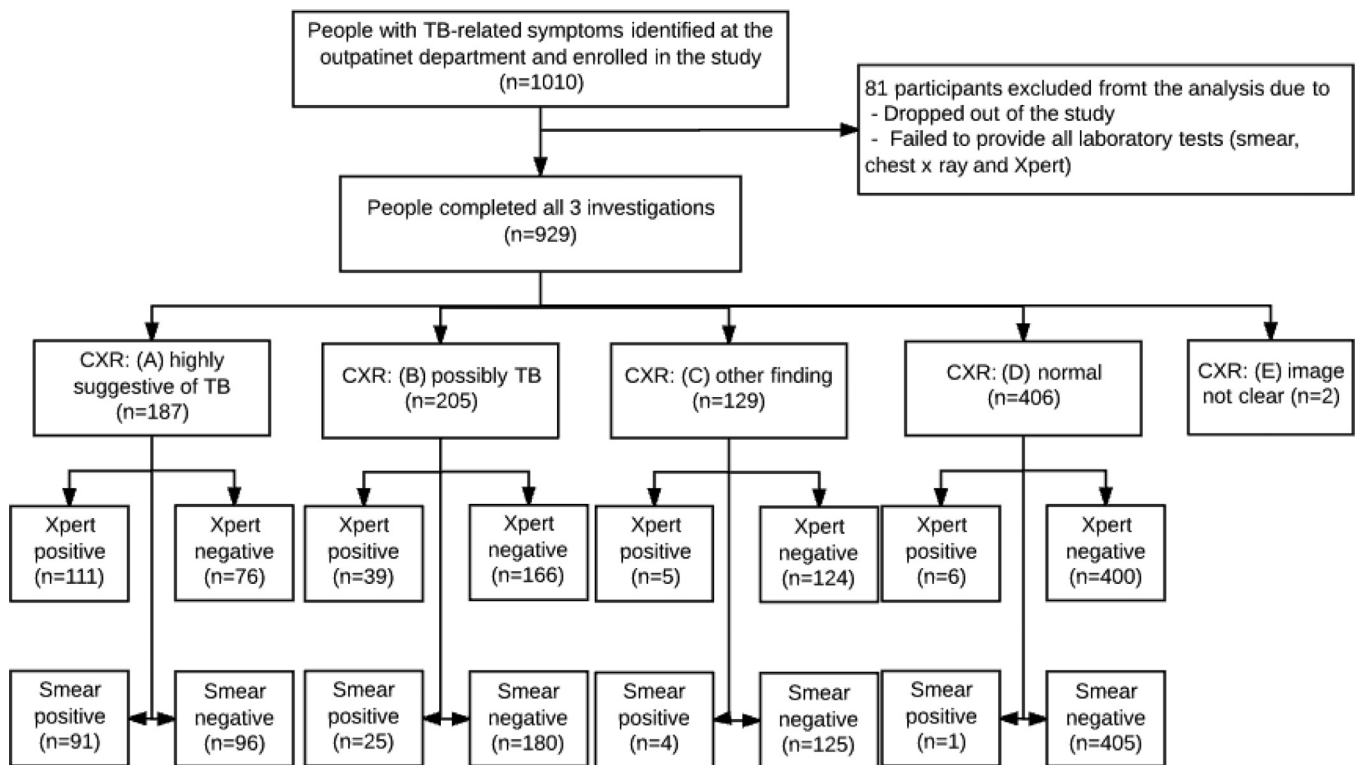


Fig. 2. Patient and testing flowchart in a district hospital in Nepal.

Table 1

Characteristics of people with presumptive TB at a district hospital in Nepal

N	Overall (%)
<b>Median Age</b>	
[IQR Age]	44 [26–60]
<b>Sex</b>	
Male	523 (56.3)
<b>Symptoms</b>	
Cough > 14 days (%)	836 (90.0)
Fever = Yes (%)	516 (55.5)
Weight Loss = Yes (%)	457 (49.2)
Night Sweat = Yes (%)	253 (27.2)
Hemoptysis = Yes (%)	258 (27.8)
<b>Number of symptoms</b>	
1 symptom only	230 (24.8)
2–3 symptoms	506 (54.5)
> 3 symptoms	193 (20.7)
<b>HIV Status (%)</b>	
Negative	104 (11.2)
Positive	3 (0.3)
Unknown	822 (88.5)
<b>Smear Result = Positive</b>	
<b>CXR Result</b>	<b>121 (13.0)</b>
(A) Highly suggestive of TB	187 (20.1)
(B) Possibly TB	205 (22.1)
(C) Other finding	129 (13.9)
(D) Normal	406 (43.7)
(E) Image not clear	2 (0.2)
<b>XPERT MTB = Positive (%)</b>	
<b>RIF Resistant</b>	<b>161 (17.3)</b>
RIF Resistant	4 (0.4)
RIF Sensitive	155 (16.7)
RIF Indeterminate	2 (0.2)

Table 2

Chest x-ray, smear and Xpert results from patients in a district hospital in Nepal

	(A) Highly suggestive of TB	(B) Possibly TB	(C) Other finding	(D) Normal	(E) Image not clear
N	187 (%)	205 (%)	129 (%)	406 (%)	2 (%)
<b>Smear Positive (Individuals)</b>					
Morning Smear					
Positive (3 +)	37 (19.8)	7 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Positive (2 +)	29 (15.5)	10 (4.9)	1 (0.8)	0 (0.0)	0 (0.0)
Positive (1 +)	22 (11.8)	6 (2.9)	1 (0.8)	1 (0.2)	0 (0.0)
Positive (Scanty)	2 (1.1)	2 (1.0)	1 (0.8)	0 (0.0)	0 (0.0)
Negative	97 (51.9)	180 (87.8)	126 (97.7)	405 (99.8)	2 (100.0)
<b>Spot Smear</b>					
Positive (3 +)	28 (15.0)	3 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Positive (2 +)	28 (15.0)	10 (4.9)	1 (0.8)	0 (0.0)	0 (0.0)
Positive (1 +)	29 (15.5)	9 (4.4)	1 (0.8)	1 (0.2)	0 (0.0)
Positive (Scanty)	4 (2.1)	1 (0.5)	2 (1.6)	0 (0.0)	0 (0.0)
Negative	98 (52.4)	182 (88.8)	125 (96.9)	405 (99.8)	2 (100.0)
<b>Xpert</b>					
<b>MTB = Positive</b>	<b>111 (59.4)</b>	<b>39 (19.0)</b>	<b>5 (3.9)</b>	<b>6 (1.5)</b>	<b>0 (0.0)</b>
RIF Resistant	1 (0.5)	2 (1.0)	0 (0.0)	1 (0.2)	0 (0.0)
RIF Sensitive	108 (57.8)	37 (18.0)	5 (3.9)	5 (1.2)	0 (0.0)
RIF Indeterminate	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

should ideally be supported by the health system or insurance instead of the patient as is often the case [30]. Our results of the performance of CXR are similar to those documented in an Indian sub-district hospital [23] and in Vietnam at an HIV clinic [31]. Although we do not have the

number of people screened verbally for symptoms at the outpatient department to properly document the number needed to screen, it is noteworthy that placing microscopy before CXR and Xpert was slightly more sensitive than the direct CXR to Xpert algorithm which has been generally assumed to provide the best approach in terms of true positive yield [15,32]. Using smear microscopy after CXR and before Xpert

**Table 3**  
Evaluating the performance of different testing algorithms for tuberculosis in a district hospital in Nepal

Algorithms: All Participants (n = 929)		CXR cut-off*	#Bac+ detected	Bac + missed	# smear	# CXR	# Xpert
1	Any symptom(s) → Smear	–	121	24.8%	929	–	–
2	Any symptom(s) → Xpert	–	161	0.0%	–	–	929
3	Any symptom(s) → Smear → Xpert(SN)	–	161	0.0%	929	–	808
4_loose	Any symptom(s) → Smear-> CXR (SN) → Xpert	A + B + C	156	3.1%	929	808	555
4_median	Any symptom(s) → Smear-> CXR (SN) → Xpert	A + B	155	3.7%	929	808	409
4_strict	Any symptom(s) → Smear-> CXR (SN) → Xpert	A	141	12.4%	929	808	178
5_loose	Any symptom → CXR → Smear → Xpert(SN)	A + B + C	155	3.7%	521	929	401
5_medium	Any symptom → CXR → Smear → Xpert(SN)	A + B	150	6.8%	392	929	276
5_strict	Any symptom → CXR → Smear → Xpert(SN)	A	111	31.1%	187	929	96
6_loose	Any symptom(s) → CXR → Xpert	A + B + C	155	3.7%	–	929	559
6_medium	Any symptom(s) → CXR → Xpert	A + B	150	6.8%	–	929	437
6_strict	Any symptom(s) → CXR → Xpert	A	111	31.1%	–	929	288

CXR: chest x-ray, TB: tuberculosis.

\* (A) = “Highly suggestive of TB”, (B) = “Possibly TB”, (C) = “Other finding”, (D) = “Normal”, and (E) = “Image not clear.”

testing resulted in similar numbers of Bac+ patients as direct CXR to Xpert, however, it considerably reduced the number of Xpert tests needed but used many more microscopy tests. Since human readers of CXR vary in their grading [33,34], and clinical reading is different than the approaches taken in prevalence surveys, having more CXR image readers including automated reading software which is being increasingly used could improve the results [30,35]. It will also be helpful to look beyond the yield of the different algorithms and evaluate the cost-benefit of the approaches as well as use culture to provide a proper reference standard which we were not able to do in the current study. As Xpert is increasingly procured and used and CXR is also being promoted again by WHO as a useful tool [11], considerations of which testing algorithm to use in different situations will be needed from different cost and yield standpoints (workload, health systems, and patient). Even among individuals with presumptive TB, using CXR can reduce the numbers of smear and Xpert tests needed with minimal loss of Bac+ TB cases. Different studies have estimated cost of a CXR at 20–30% of the costs of Xpert testing, meaning that using it as an initial test to save Xpert cartridges could potentially save significant costs overall compared to Xpert testing for all [36,37]. In Nepal, patients bear the costs of CXR in most cases, but smear and Xpert are provided for free. Expanding the use of CXR in the diagnostic algorithm should then be accompanied by policy reforms and measures to ensure that patients are not burdened with any added out of pocket costs.

Among the limitations of our study is the fact that our results only include bacteriologically-positive TB and in any setting clinical diagnosis will be used to treat people with negative laboratory results. We were not able to capture these clinical decisions for the people enrolled. An earlier study from the same region showed that introducing Xpert actually decreased the number of people placed on anti-TB treatment overall likely due to the reluctance of clinicians to treat people with negative Xpert results [17]. We also did not use culture as a reference standard which would have allowed a more robust comparison between the different diagnostic tests. However, the sensitivity of microscopy and Xpert compared to culture has been well documented [12] and culture is almost never used to diagnose pulmonary TB in high burden countries. The newest version the Xpert assay, MTB/RIF Ultra, would also likely change the results of the analysis due to the higher sensitivity [38]. Our sample also only includes people with TB symptoms and prevalence surveys have shown that a large proportion of people with prevalent TB in a community setting do not report symptoms [29]. We were not able to test all attendees regardless of symptoms with CXR due to logistical and budgetary constraints, but doing so may provide a clearer picture of the overall prevalence of TB in different settings. A study from Vietnam in an HIV clinic recently showed a number of TB cases were missed using a symptom-screen [31]. We were only able to obtain HIV results of a small proportion. This both limits the overall results and also the interpretation of CXR results due to

unknown HIV status, but TB/HIV coinfection rates are 1% in Nepal and unlikely to have a huge impact [1]. The high prevalence of TB among the study population may also not be similar to other facility-based settings where TB rates may be lower, but the yield from routine case finding in other settings has been 10–20% in many countries.

## 5. Conclusion

Improved and expanded diagnostic algorithms are likely needed to improve the numbers of people detected with TB and placed on appropriate treatment. Using Xpert in the diagnostic algorithm in a district hospital in Nepal allowed the detection of a sizable number of bacteriologically positive cases as well as drug-resistant cases that would not have been identified with smear microscopy. CXR can be used to reduce the number of people who need further testing even among individuals with presumptive TB, likely saving costs. The cost-benefit of different algorithms should be the subject of future analysis.

## Ethics statement

The study protocol was approved by the Ethics Committee, Institutional Reviewing Board, BPKIHS, Nepal.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jctube.2018.11.002.

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