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The additional yield of GeneXpert MTB/RIF test in the diagnosis of pulmonary tuberculosis among household contacts of smear positive TB cases

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A B S T R A C T

Objective: The objective of this study was to compare the diagnostic yield of GeneXpert MTB/RIF with Ziehl-Neelson (ZN) sputum smear microscopy among index TB cases and their household contacts.
Methods: A cross sectional study was conducted among sputum smear positive index TB cases and their household contacts in Northern Ethiopia.
Results: Of 353 contacts screened, 41 (11%) were found to have presumptive TB. GeneXpert test done among 39 presumptive TB cases diagnosed 14 (35.9%) cases of TB (one being rifampicin resistant), whereas the number of TB cases diagnosed by microscopy was only 5 (12.8%): a 64.3% increased positivity rate by GeneXpert versus ZN microscopy. The number needed to screen and number needed to test to diagnose a single case of TB was significantly lower with the use of GeneXpert than ZN microscopy. Of 119 index TB cases, GeneXpert test revealed that 106 (89.1%) and 5 (4.2%) were positive for rifampicin sensitive and rifampicin resistant TB, respectively.
Conclusion: GeneXpert test led to increased TB case detection among household contacts in addition to its advantage in the diagnosis of Rifampicin resistance among contacts and index TB cases. There should be a consideration in using GeneXpert MTB/RIF as a point of care TB testing tool among high risk groups.

1. Background

Globally, there were an estimated 9.6 million incident cases of TB in 2014. The best estimate of the case detection rate for all forms of TB globally in 2014 was 63%, whereas 3.6 million cases remained undetected[1]. The cases that remained undetected continue to suffer from TB disease and also transmit the disease to their contacts[2]. The regions that contributed for most of the undetected all-forms incident TB cases are south-east Asia and Africa[3]. The passive TB case finding has contributed significantly in the identification and management of TB cases presenting to health facilities[3,4]. There is still the need to exert further efforts geared toward improving TB case findings and possibly identify the undetected TB cases that would have been missed while using the conventional passive TB case finding approaches[5–7].

The World Health Organization (WHO) recommends systematic screening for active TB with the aim of early detection of TB cases and prompt treatment that ensures better treatment outcome and reduced TB transmission to contacts[8]. There is a strong recommendation that household contacts and other close contacts should be systematically screened for active TB[8,9]. The globally recommended initial diagnostic tests for presumptive TB cases identified among contacts were either sputum smear microscopy to identify acid fast bacilli (AFB) or a rapid molecular test like GeneXpert MTB/RIF[8,9].

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A total of 137,081 incident TB cases were diagnosed in Ethiopia in the 2014/15 fiscal year with a case detection rate of 67%[10]. In Ethiopia, TB case finding was mainly focused on passive case finding at health facilities and referrals by community health workers which were able to detect up to two-third of the annually estimated TB cases[11]. To improve the TB case finding, one of the new approaches recommended by the national TB program is TB screening among close and household contacts of infectious TB cases. The first line laboratory test for presumptive TB cases identified in the contact screening is sputum smear microscopy while GeneXpert MTB/RIF test is also recommended if the index TB case is a drug resistant TB patient or is at risk of harboring drug resistant TB[11].

The national GeneXpert MTB/RIF implementation guideline recommends its use among presumptive MDR TB cases that include symptomatic contacts of MDR-TB cases, and presumptive TB cases among HIV positive individuals and children below 14 years of age[12]. Studies have been confirming that GeneXpert MTB/RIF test had significantly higher yield than sputum smear microscopy in different settings including Ethiopia[13–15]. However, the wider decentralization and use of GeneXpert MTB/RIF in low income countries needs to be evaluated in terms of its cost, ongoing supplies, maintenance issues and the need for uninterrupted electric supplies. There is also a need to demonstrate the added advantage of GeneXpert MTB/RIF over conventional sputum smear microscopy in different settings including contacts[16,17]. Studies that compared the yield of GeneXpert MTB/RIF with smear microscopy among contacts of index TB cases are scarce.

In this study, the diagnostic yield of GeneXpert MTB/RIF was compared with that of Ziehl-Neelson (ZN) sputum smear microscopy among index TB cases and their household contacts.

2. Methods

2.1. Study design and setting

A cross sectional study was conducted among sputum smear positive index TB cases and their household contacts. The study was done at eleven TB diagnostic and treatment health centers in North Gondar zone of Amhara region, Ethiopia between May 2013 and April 2015. North Gondar Zone has a total population of 3.6 million with TB case notification rate of 119 per 100,000 population (Unpublished data, Management Sciences for Health, 2015). There are three hospitals and 133 public health centers providing TB prevention and control services in the zone. Health centers are operated by Nurses, Health Officers, Laboratory Technicians, Pharmacy Technicians and administrative staff. The eleven health centers included in the study were selected as they are closer to Gondar University Hospital so that sputum specimens for GeneXpert test could be transported easily. These health centers have been participating in the external quality assurance (EQA) program of the country for ZN microscopy. The false positivity and false negativity rate of AFB slide readings at health facilities against the EQA center readings in the study area were found to be 0.19% and 0.17% respectively (Unpublished data, Management Sciences for Health, 2015).

2.2. Identification of index TB cases and their household contacts

We trained TB focal persons in the eleven health centers on the data collection, symptomatic screening, sputum sample collection and referral. New AFB sputum smear positive patients diagnosed in the 11 health centers during the study period who had at least one household family member were included in the study. Once the patient was diagnosed, the address of the patient was recorded. The contact details of 119 consecutive smear positive index TB cases were noted. All index cases were either asked to bring their household contacts to the health center or visited at home by the study team composed of supervisors and community health workers called health extension workers (HEW) within 2 weeks of diagnosis. Household contact was defined as a person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode[9]. TB focal persons and both urban and rural HEWs were involved in registering the household contacts and screening of contacts for symptoms suggestive of TB.

2.3. Data collection and TB symptom screening

A baseline data was filled in a standardized questionnaire for each index smear positive TB case by the TB focal person in the health centers. The major information collected was socio-demographic data, signs and symptoms, duration of illness, contact history and the laboratory results. A family matrix form was used to register all household contacts. A standard questionnaire was administered by the TB focal person or HEWs to each household contact independently that included socio-demographic characteristics and relationship status to the index case. The TB focal person or HEWs registered the household contacts and screened them for the major signs and symptoms of TB. Household contacts with history of cough for two or more weeks or with two or more symptoms suggestive of TB were considered to have presumptive TB[8]. Presumptive TB cases were referred to the health center for further evaluation and laboratory investigation (ZN microscopy and GeneXpert).

2.4. TB diagnosis

Three sputum samples (Spot-Morning-Spot) were collected at the health centers from each household contact with presumptive TB. Morning sputum specimens were also collected from the 119 index TB cases for GeneXpert test. All the 119 index TB cases were already put on first line anti-TB drug treatment based on the ZN microscopy result and continued the treatment even if the GeneXpert test result turned out negative. The TB focal persons in the respective health centers transported the sputum samples to Gondar University hospital following the standard infection control and specimen transportation procedures (using cold box) for GeneXpert test. Trained senior laboratory personnel in the health centers and Gondar University hospital were engaged in conducting the ZN microscopy and GeneXpert tests, respectively. The laboratory personnel doing ZN microscopy and GeneXpert MTB/RIF test were blinded. The three samples from contacts were tested for AFB by ZN sputum smear microscopy and GeneXpert test was also done on the morning sputum sample. In addition, GeneXpert test was done on the morning sputum specimens collected from the index TB cases.

2.5. Data analysis

Data entry and analysis was performed using SPSS, Version 13 (SPSS Inc., Chicago, Illinois). Data was entered by an experienced data clerk under the supervision of the principal investigator. Frequency, percentage and 95% confidence interval of proportions were computed. The number needed to screen (NNS) and number needed to test (NNT) was also computed. NNS is the number of contacts required to be screened to detect a single case of active TB; NNT is the number of contacts with presumptive TB required to be investigated in the laboratory to detect a single case of active TB. The 95% confidence intervals of proportion among different categories were compared: absence of overlap in 95% confidence intervals is considered as a statistically significant difference.

2.6. Ethical considerations

Ethical approval was obtained from the University of Gondar ethical review board [reference number RCS/P/05/485/2013 dated June 4th 2013]. Each study participant provided a written informed consent and permission was obtained from all health facilities. Written parental consent was also obtained for participants below the age of 18 years. Household contacts with positive TB result were treated in accordance with the national tuberculosis program recommendations[11]. Rifampicin resistant results by GeneXpert test were immediately communicated to each health centers for proper management of patients as per the national tuberculosis program recommendations[11].

3. Result

3.1. Characteristics of index cases

A total of 119 newly diagnosed index TB cases were registered during the study period. They were sputum smear positive by the ZN staining done in the laboratory of the respective health center. The index cases lived in 119 different households. Two-thirds of the index cases were urban residents and the male to female ratio was 1.38. Four-fifths of the index cases were in the age range 15 to 44 years with mean (SD) age of 31.2 (14.1) years (Table 1). Only 6 (5%) had past history of TB. GeneXpert MTB/RIF test was done for all index TB cases. The GeneXpert test among index TB cases revealed that 8/119 (6.7%) were negative for TB while 106/119 (89.1%) and 5/119 (4.2%) were rifampicin sensitive and rifampicin resistant TB, respectively.

3.2. The yield of active TB case finding among household contacts

A total of 393 contacts were identified in 119 households with contact to index TB cases ratio of 3.3. The contacts were between 1 and 94 years of age with Mean (SD) age of 24.6 (18.2). Out of 393 contacts, 353 (89.8%) were screened for symptoms suggestive of tuberculosis. A total of 41 (11%) of the screened contacts were found to have presumptive TB of which all with the exception of two under-five children were checked with ZN microscopy (spot-morning-spot) and GeneXpert MTB/RIF test. Of 39 presumptive TB cases with sputum samples, GeneXpert test diagnosed 14 (35.9%) cases of TB whereas the number of TB cases diagnosed by ZN microscopy was 5 (12.8%): a 64.3% increased positivity rate by GeneXpert versus ZN microscopy. The entire five cases positive by ZN microscopy were also positive for TB in the GeneXpert test. Two under-five children were diagnosed clinically and using X-ray as smear negative pulmonary TB cases (Figure 1). Of the 14 bacteriologically confirmed TB cases, one was found to be rifampicin resistant TB. A total of 108 (90.8%) households did not have any active TB case among the contacts, 8 households (6.7%) had one TB case each, 2 (1.7%) households had 2 TB cases each and 1 (0.8%) household had four TB cases diagnosed among the contacts.

Table 1
Socio-demographic characteristics of smear positive index tuberculosis cases

Characteristics	Frequency (%)
Residence	
Rural	44 (37.0)
Urban	75 (63.0)
Gender	
Male	69 (58.0)
Female	50 (42.0)
Age in years	
12-14	5 (4.2)
15-24	39 (32.8)
25-34	35 (29.4)
35-44	22 (18.5)
45+	18 (15.1)
Educational background	
No formal education	48 (40.3)
Primary education	24 (20.2)
Secondary education	40 (33.6)
Diploma and above	7 (5.9)
Occupation	
Farmer	25 (21.2)
Government employee	7 (5.9)
Domestic work	9 (7.6)
Petty trade	3 (2.5)
Daily laborer	32 (27.1)
Driver	5 (4.2)
Student	29 (24.6)
Other	9 (7.6)

3.3. The prevalence of TB among household contacts

Sixteen cases of tuberculosis were identified (two clinical and X-ray diagnosis; and one rifampicin resistant) through the household TB contact screening with overall prevalence of 4,532.6 per 100,000 contacts: bacteriologically confirmed TB was 3,966 per 100,000, rifampicin sensitive TB was 3,682.7 per 100,000 and rifampicin resistant TB was 283.3 per 100,000. The prevalence of TB in rural and urban residence was 4,458.6 and 4,591.8 per 100,000, respectively ($p>0.05$). The prevalence of TB among male and female contacts was 4,545.5 and 4,522.6 per 100,000, respectively ($p>0.05$). TB prevalence per 100,000 ranged from 2343.8 in the age group 15 to 34 years to 11,111.1 in the age group 60 years and above ($p>0.05$). With regard to relationship status with the index case, the prevalence of TB per 100,000 ranged from 2702.7 among sibling contacts to 6666.7 among other relatives ($p>0.05$) (Table 2).

3.4. Comparison of the performance of GeneXpert MTB/RIF versus ZN microscopy in TB household contact investigation

The prevalence of TB by using the GeneXpert diagnostic test was 3966.0 per 100,000 contacts while it was 1416.4 per 100,000 contacts by ZN microscopy. The number of contacts needed to screen (NNS) to find a single case of TB while using GeneXpert as a diagnostic test was 25 as compared to the 70 while using ZN microscopy. The number of presumptive TB cases needed to test (NNT) to diagnose a single case of TB while using GeneXpert was three and the corresponding number in using ZN microscopy was eight.

4. Discussion

The performance of GeneXpert MTB/RIF in identifying TB among household contacts of index cases was significantly higher as compared with ZN microscopy. Out of 14 bacteriologically confirmed TB cases among household contacts, nine cases (64.3%) would have been missed if we had relied on ZN microscopy alone. The number needed to screen and number needed to test to diagnose a single case of TB was significantly lower with the use of GeneXpert than ZN microscopy indicating the better efficiency of the former laboratory test. ZN microscopy needed three consecutive sputum samples while GeneXpert test was done using a single, morning sputum sample but with additional diagnostic yield.

Studies have shown that smear microscopy is able to detect TB in patients with advanced disease who discharge sufficient number of bacilli[18,19]. In our study, two-thirds of the TB cases among household contacts would have remained undiagnosed if

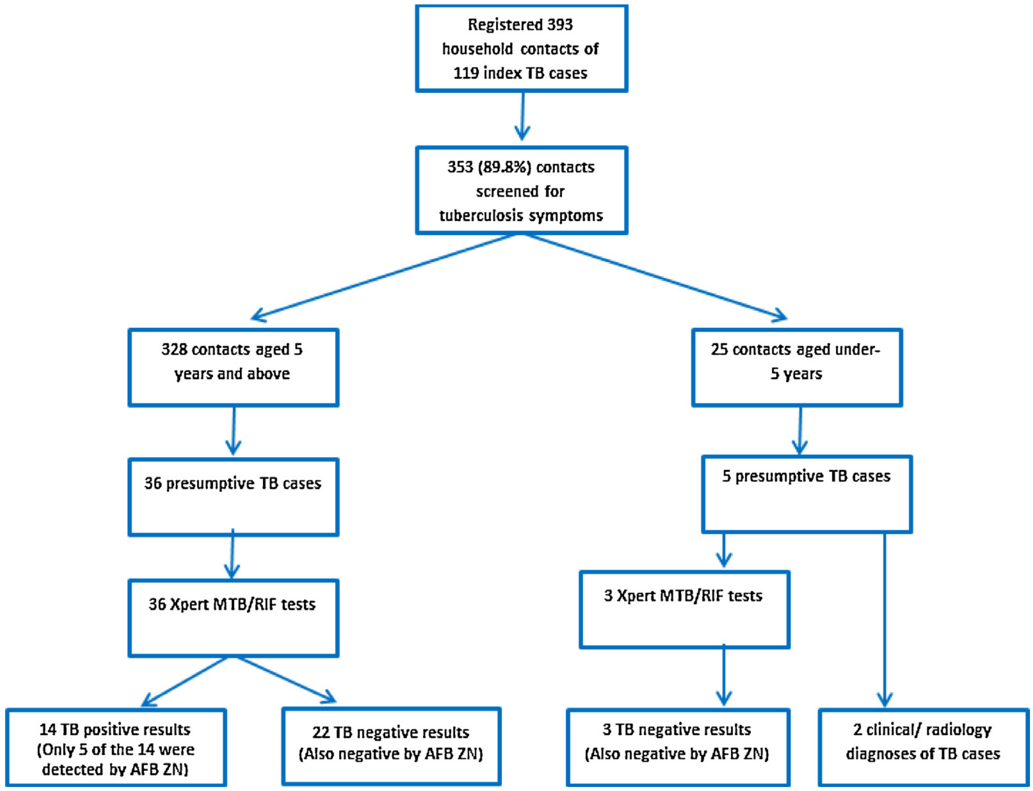

Fig. 1. Active case finding among household contacts of smear positive index TB cases.

GeneXpert test was not done. Hence, the contacts who harbor and discharge TB bacilli but couldn't be detected by the conventional smear microscopy would continue suffering with the disease and transmit the disease to their contacts unless we use a more sensitive test like GeneXpert to enable early identification of cases. Although the use of GeneXpert enabled better case detection among contacts, the wider use of GeneXpert in low income settings needs to be evaluated in terms of its cost-effectiveness, feasibility and the priority group to be targeted by the service[16,17]. Further clinical characterization of subsets of presumptive TB cases among TB contacts who would benefit most from GeneXpert MTB/ RIF testing could help to optimize its use in settings with limited resources.

Significant proportions of smear positive index TB cases by ZN microscopy were also confirmed positive by GeneXpert which signifies the quality of ZN microscopy service in the health centers. Eight (6.7%) of the already smear positive index TB cases (ZN microscopy) were negative for TB in the GeneXpert test. The incongruity can be attributed to either a false positive result by the ZN microscopy even though the EQA false positivity rate in the study area was 0.19% or the bacilli might have been mycobacteria other than tuberculosis as the GeneXpert only detects *Mycobacterium tuberculosis* complex strains. Rifampicin resistant TB, a surrogate marker for MDR-TB, was also diagnosed among 5 (4.2%) index cases who were put on first line anti-TB drugs based on ZN microscopy result alone at the health centers. It would have taken time for the health centers to suspect drug resistance TB in the course of first line treatment and consider drug susceptibility testing (DST). The rifampicin resistant TB burden among index cases in our study is greater than the 2.3% rate of MDR-TB (resistant to at least rifampicin and isoniazid) among new cases of TB and less than the 17.8% rate reported in previously treated TB cases in the national TB drug resistance survey[20]. One of the components of the End TB strategy emphasized on early diagnosis of tuberculosis including universal drug-susceptibility testing which is also supported by the findings of this study[21].

Although GeneXpert test has a cost implication, a single sputum test using GeneXpert would have improved the diagnostic capacity, reduced the number of sputum samples to be collected and enabled the immediate identification of drug resistant TB. A survey done in 24 countries in 2015 revealed that 8 countries, including Swaziland and South Africa from Africa, adopted GeneXpert test as a first line diagnostic test in the diagnosis of TB replacing smear microscopy[22]. It is advisable that countries like Ethiopia learn from the experience of countries that are using GeneXpert as a first line test for possible scale up of the GeneXpert test. There is a critical need for operational research to understand the pros and cons of decentralizing GeneXpert MTB/RIF test at the district level[16].

There were two households with four and two TB cases diagnosed among the contacts. It appears that there were households who had higher risk of transmission with resultant clustering of TB cases in the households. The clustering of TB cases in a household is more likely to be due to shared risk factor rather than individual level risk factor such as nutritional status, ventilation, air pollution or any other factor shared by household members[23–26]. Further analysis on the factors that fueled the TB transmission in those households was not done. There is a need to strengthen community TB care to ensure early diagnosis and treatment of index TB cases and reduce the risk of transmission to household and close contacts. TB infection control at household level is also an area that can be improved by educating community members regarding TB transmission, prevention and earlier health care seeking.

The overall prevalence of tuberculosis among household contacts using GeneXpert was 3,966 per 100,000 which is 20 fold of the estimated national prevalence of TB[1]. There was no significant difference in the diagnosis of TB among household

Table 2
Prevalence of TB among contacts by socio-demographic characteristics

Characteristics	Number of contacts	Number of presumptive TB (Row %)	Prevalence of TB diagnosis per 100,000; N (prevalence: 95% CI)[a]
Overall	353	41 (11.6%)	16 (4.5:2.8, 7.2)[b,c]
Residence			
Rural	157	13 (8.3%)	7 (4.4: 2.2, 8.9)
Urban	196	28 (14.3%)	9 (4.6: 2.4, 8.5)
Gender			
Male	154	15 (9.7%)	7 (4.5: 2.2, 9.1)
Female	199	26 (13.1%)	9 (4.5: 2.4, 8.4)
Age in years			
0-4	25	5 (20.0%)	2 (8.0: 2.2, 2.5)
5-14	106	10 (9.4%)	6 (5.7: 2.6, 1.2)
15-34	128	17 (13.3%)	3 (2.3: 0.8, 6.7)
35-59	67	6 (9.0%)	2 (2.9: 0.8, 10.2)
60 & above	27	3 (11.1%)	3 (11.1: 3.9, 28.1)
Educational background			
No formal education	147	18 (12.2)	12 (8.2: 4.7,13.7)
Primary education	97	13 (13.4)	4 (4.1: 1.6, 10.1)
Secondary education	56	9 (16.1)	-
Diploma and above	11	1 (9.1)	-
Marital status			
Single	217	26 (12.0)	9 (4.1: 2.2, 7.7)
Married	112	11 (9.8)	4 (3.6: 1.4, 8.8)
Divorced	10	1 (10.0)	1 (10.0: 1.8, 40.4)
Separated	2	0	-
Widowed	12	3 (25.0)	2 (16.7: 4.7,44.8)
Relation to index			
Head/ Spouse	93	8 (8.6%)	4 (4.3: 1.7, 10.5)
Son/Daughter	117	14 (12.0%)	7 (5.9: 2.9, 11.8)
Parent	33	4 (12.1%)	1 (3.0: 0.5, 15.3)
Sibling	74	8 (10.8%)	2 (2.7: 0.7, 9.3)
Other relative	30	5 (16.7%)	2 (6.7: 1.8, 21.3)
Non-relative	6	2 (33.3%)	-

[a] prevalence & 95% CI in thousands
[b] One case is RR TB
[c] Two cases are clinical diagnosis of TB

contacts by residence type, age, gender and type of relationship to the index case. However it is worth noting that the diagnosis of TB in the contacts was made largely based on laboratory confirmation except the two Pediatric cases diagnosed clinically and using X-ray. It is likely that more cases of clinical and extra-pulmonary TB might have been diagnosed subsequently from the presumptive TB cases which were not captured here due to the cross sectional nature of this study. It could have led to possible underestimation of the prevalence of all forms of TB among the household contacts.

The study needs to be interpreted with the following limitations in mind. The study did not consider some risk factors like HIV status of study participants and the condition of households, and the associated risk in the development of TB. The study also did not include the gold standard culture test to evaluate the sensitivity and specificity of ZN and GeneXpert test results. The use of standard operating procedures, availability of quality assurance mechanisms in the laboratories and involvement of highly qualified laboratory personnel are amongst the strengths of this study.

Our findings suggest that GeneXpert MTB/RIF test could lead to increased TB case detection among household contacts in addition to its advantage in the diagnosis of rifampicin resistant TB among contacts. The use of GeneXpert also helped in the identification of rifampicin resistant TB among newly diagnosed index TB cases in the health centers. There should be a consideration in using GeneXpert MTB/RIF as a point of care TB testing tool among high risk groups such as contacts especially in settings like Ethiopia where the burden of TB is high. Further study is recommended to analyze the cost-effectiveness and feasibility of scaling up GeneXpert as a first line test.

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Conflicts of interest: None

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