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Comparison in the yield of tuberculosis among contacts of multidrug-resistant and drug-sensitive tuberculosis patients in Ethiopia using GeneXpert as a primary diagnostic test

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Highlights

- Using GeneXpert in testing of presumptive DS TB/MDR TB contacts has shown considerable yield with more RR TB cases diagnosed among MDR TB contacts than DS TB contacts
- The use of GeneXpert in DS TB contact investigation has an added advantage of diagnosing RR cases in contrast to using the nationally recommended AFB microscopy for DS TB contact investigation
- The finding in this study can serve as a reference in TB case finding planning and evaluation in Ethiopia and similar settings

Abstract

Objectives: This study compared the yield of TB among contacts of multidrug-resistant tuberculosis (MDR-TB) index cases with that of drug-sensitive TB (DS-TB) index cases in a program setting.

Methods: A comparative cross-sectional study was conducted among contacts of sputum-smear-positive new index DS-TB cases and MDR-TB index cases. After contacts were screened, we used GeneXpert for the diagnosis of TB.

Results: The study included 111 MDR-TB and 119 DS-TB index cases. A total of 340 and 393 contacts of MDR-TB and DS-TB index cases, respectively, were traced, of whom 331 among MDR-TB contacts and 353 for DS-TB contacts were screened. The presumptive TB cases were 20 (6%) and 41 (11%) for MDR-TB and DS-TB contacts, respectively. The prevalence of TB among MDR-TB and DS-TB contacts was 2.7% and 4.0%, respectively. The majority of the MDR-TB contacts diagnosed with TB had MDR-TB; the reverse was true for drug-sensitive TB.

Conclusions: The yield of TB among contacts of MDR-TB and DS-TB using GeneXpert was high as compared to population-level prevalence. The likelihood of diagnosing RR (Rifampicin Resistant)-TB among contacts of MDR-TB index cases is higher in comparison with contacts of DS-TB index cases. The use of GeneXpert in DS TB contact investigation has an added
advantage of diagnosing RR cases in contrast to using the nationally recommended AFB microscopy for DS TB contact investigation

**Keywords:** contact investigation; multi drug-resistant tuberculosis; drug-sensitive tuberculosis

**INTRODUCTION**

In 2016 the population of Ethiopia was estimated to be 92.2 million, with more than half of the population living in the Amhara and Oromia regions—34.6 and 20.8 million people respectively.\(^1\) According to the World Health Organization Global Tuberculosis Report, Ethiopia was among the 30 high-burden countries for tuberculosis (TB). The incidence rate of all forms of TB was 192 per 100,000 population. Mortality was 26 per 100,000 (excluding HIV-positive people). About 2.7% of new TB cases and 14% of previously treated TB cases are estimated to have drug resistant TB. In 2015, treatment success rate for MDR TB cases in Ethiopia was reported to be 68%.\(^2\)

Studies have shown that screening contacts of TB index cases yields more cases than community-level screening for TB.\(^3,4\) The aim of our study was to compare the yield of household contact screening of MDR-TB and drug-sensitive TB index cases in a routine program setting using GeneXpert as a primary diagnostic method.

**METHODS**

**Study Design**

This study was conducted in TB DOT (directly observed treatment) centers and treatment initiating centers (TICs) for multidrug-resistant TB (MDR-TB) of Amhara and Oromia regions of Ethiopia. The MDR-TB patients enrolled in treatment in 22 TIC hospitals in two quarters of 2015 were included.

We trained TB focal persons in 11 health centers on contact screening of drug sensitive TB (DS-TB) index cases, data collection, symptomatic screening, sputum sample collection, and referral.
New AFB (acid-fast bacilli) sputum-smear-positive patients diagnosed in these health centers during the study period who had at least one household family member were included in the study. A total of 119 consecutive smear-positive index DS TB cases were registered in the study. All these smear-positive index cases were either asked to bring their family members to the health center or visited at home by the study team within 2 weeks of diagnosis. The team was composed of supervisors and community health workers, called health extension workers (HEWs).

In the same way as for DS TB, contacts of 111 MDR-TB patients registered in the 22 TICs were screened for TB. The diagnosis of MDR-TB index cases was made with either culture and DST for INH and rifampicin or diagnosed with GeneXpert MTB/ Rifampicin resistance, which is treated as MDRTB as per the national guideline. MDR-TB management in Ethiopia uses a mixed model of care, ambulatory and inpatient. Patients who are critically ill or cannot start treatment on an ambulatory basis because of distance are admitted to TICs. Patients who live within walking distance of the TIC can start as ambulatory patients. After one or two months, if there are no side effects and if a patient can walk, s/he is discharged to follow up with daily MDR-TB DOT at the health center nearest to the patient’s residence, called a treatment follow-up center (TFC). Every month, patients visit the TICs for clinical and laboratory follow-up tests. By the end of June 2015, there were 22 TICs and 193 TFCs in the two regions.

MDR-TB focal persons in both the TICs and TFCs were trained on clinical management of MDR-TB and contact screening. We introduced registration of contacts of MDR-TB index patients at the beginning of the project, which involved counseling every patient and registering his/her close contacts in the contact registration book. Patients then brought their contacts to a TIC or TFC, whichever was more convenient, for screening for TB symptoms.

Both DS-TB and MDR-TB contacts with a cough that had lasted 2 weeks or more and other constitutional symptoms were asked to provide sputum for an AFB or GeneXpert test. The national guidelines recommend GeneXpert as the primary test for presumptive cases among MDR-TB contacts and AFB for drug-sensitive TB contacts. For this study we also used GeneXpert for contacts of drug-sensitive cases, so that we could compare the yield of TB in the two groups of contacts. The resistance pattern here is presented is only for GenXpert because MDR-TB treatment decision is made by Rifampicin resistance alone. In the baseline follow up
test culture and DST for INH and Rifampicin is done for the follow up purpose but we did not have the data for this publication.

Definitions

A TB index case is defined as DS-TB and MDR-TB patient enrolled in treatment. A household contact is a person who shares the same enclosed living space for one or more nights a week or for frequent or extended periods during the day with the index patient during the 3 months before the current treatment episode began.\textsuperscript{3,6,7}

TB Diagnosis

Morning sputum was collected from all presumptive MDR-TB and drug-sensitive TB patients. Sputum samples were transported to the nearest GeneXpert testing facility using the standard infection control and cold chain system and testing performed using GeneXpert.

Data Analysis

Data entry and analysis were performed using SPSS, Version 13 (SPSS Inc., Chicago, Illinois). We computed frequencies, percentages, and the 95\% confidence intervals of proportions. The number needed to screen and number needed to test were also computed. The number needed to screen is the number of contacts who have to be screened to detect a single case of active TB; the number needed to test is the number of contacts with presumptive TB who have to be investigated in the laboratory to detect a single case of active TB.\textsuperscript{3}

Ethical Considerations

Contact investigation of patients with MDR-TB and drug-sensitive TB is a routine health procedure for all patients\textsuperscript{5}, but we also obtained ethical clearance to utilize the information for publication from the Amhara and Oromia Regional Health Bureaus. Each study participant provided an oral informed consent and permission for TB screening and diagnosis. Diagnosis of and treatment for all presumptive TB patients are free of charge.\textsuperscript{7} MDR-TB patients were also provided with ambulance service to the TIC for initiation of treatment, and they received reimbursement for the cost of transport for the monthly follow-up trip to a TIC.
RESULTS

In total, 111 MDR-TB and 119 new drug-sensitive TB cases were diagnosed in the study health facilities. For MDR-TB and drug-sensitive TB index cases, respectively, 340 and 393 contacts were registered. The contact-to-index case ratio was 3.1 for MDR-TB contacts and 3.3 for drug-sensitive TB contacts.

Of 340 MDR-TB contacts registered, 331 (97.4%) were screened for TB, of whom 20 (6%; 95% confidence interval (CI), 3.8%-9.1%) were found to be presumptive MDR TB cases. Of the 20 presumptive MDR TB cases, 9 (45%; 95% CI, 24.6%-66.7%) were diagnosed with TB; of those, 8 (88.9%; 95% CI, 56.1%-99.4%) were rifampicin resistant, and 1 case was rifampicin-sensitive TB (Figure 1).

Among the 393 drug-sensitive TB contacts, 353 (89.9%) were screened, and 41 (11%; 95% CI, 9.7%-17.4%) were found to be presumptive TB cases. Except for 2 children under 5 years of age diagnosed with TB empirically, 39 presumptive TB cases had a sputum test done using GeneXpert, and 14 (35.9%; 95% CI, 20.9%-49.5%) were diagnosed with TB, of which 1 patient (7.1%) was found to have rifampicin-resistant TB (Figure 1).

Among the household contacts of MDR-TB patients screened, 2.7% of the contacts were diagnosed to have TB while the yield among contacts of the new drug-sensitive TB patients was 4.0% (p > 0.05). Of the MDR-TB contacts, the yield of rifampicin resistant TB was 2.4%. (Table 1).

A significant proportion of the TB cases diagnosed among contacts of drug-sensitive index patients were drug-sensitive TB cases (3.7% versus 0.3 for MDR-TB index contacts (P < 0.01). On the contrary, the majority of the TB cases diagnosed in contacts of MDR-TB index case were rifampicin resistant (2.4% versus 0.3% among drug-sensitive TB index cases [P < 0.05]) (Table 1).

The number needed to screen for drug-sensitive TB index contacts was 25, and it was 37 for the MDR-TB contacts. The number needed to test for the contacts of drug-sensitive TB index cases was 2.8, while it was 2.2 for contacts of MDR-TB index cases.

DISCUSSION
The yield of TB among contacts of DS TB index patients was about 20 times the estimated national prevalence of TB.\textsuperscript{2,8} The TB yield among the contacts of DR-TB index patients of 2.7% was higher than the national estimated MDR-TB prevalence of 2.3% among new TB cases.\textsuperscript{9}

Our results further confirm the need to scale up contact investigation among index patients as a high yield strategy for identifying more missing TB cases in Ethiopia. The overall yield for DS TB was higher than previous reports from Ethiopia and elsewhere. Studies in Ethiopia and Peru have showed that the yield of all forms of TB from contact investigation was 10 times higher than the national prevalence.\textsuperscript{3, 4} In another retrospective screening of contacts who had completed treatment of 6 months to 3 years, the yield was 6 times higher than the national prevalence.\textsuperscript{10} In a meta-analysis of 19 studies, yields ranged from 1% to 14.1%, with a pooled estimate of 1.8%.\textsuperscript{11} Since most of the previous studies used AFB microscopy as primary test for screening contacts, it is likely that the expanded use of GeneXpert for contact investigation would yield better results.

Another finding of this study is that 92.8% of the TB cases diagnosed among drug-sensitive TB contacts were rifampicin sensitive, whereas 88.8% of the newly diagnosed TB cases among MDR-TB contacts were rifampicin resistant. These finding are similar to those of two studies, which reported that 80% and 88.4% of the cases diagnosed among MDR-TB contacts were MDR-TB.\textsuperscript{4, 12} Two other studies reported that more than 50% of secondary cases with drug-sensitive TB were concordant with the index case.\textsuperscript{13, 14} This finding indicates that MDR-TB contacts, if they are diagnosed as having TB, are highly likely to be rifampicin resistant. A recent study of DS contact investigation in Ethiopia using the nationally recommended AFB microscopy showed that 12.4% of the presumptive TB cases had smear positive TB who were all considered as DS TB cases and treated by first line drugs.\textsuperscript{3} In our study, we used GeneXpert test as a diagnostic modality among DS TB contacts from which RR TB as well as RR sensitive TB cases were diagnosed that signifies the added advantage of the new diagnostics in any kind of TB contact screening.

The same high yield of TB is also reported in many studies among contacts of MDR-TB index cases. In a study in Ethiopia, of the 155 family contacts of MDR-TB patients, 16 (10.3%) were found to have TB where all of them had MDR-TB.\textsuperscript{12} In an Indian study, of 302 MDR-TB contacts, 16 (5.2%) developed TB and 2 (0.66%) had MDR-TB.\textsuperscript{15} A study in Peru indicated that
5% of the household contacts of MDR-TB index cases developed TB of which 80% also had MDR-TB. In Brazil, among contacts of MDR-TB and drug-sensitive TB patients, about 4% developed TB, and 5 of the 6 diagnosed with TB among MDR-TB contacts had MDR-TB.

Some studies have shown that the yield of TB among contacts of MDR-TB and drug-sensitive TB patients is comparable, while others report that TB disease among MDR-TB household contacts was half that of drug-sensitive contacts. Other studies have shown that the yield among MDR-TB household contacts is lower than the yield in contacts of drug-sensitive index cases. The possible reason for the low transmission rate of MDR-TB is mainly related to the evolutionary change of the mycobacterium to become resistant to drugs. However, the yields of TB among close contacts of MDR-TB and drug-sensitive TB in our study were not statistically different, even though there was a significant difference in the type of TB diagnosed.

Earlier studies from animal models have shown that the higher the degree of resistance, the lower the virulence. In another study, M. tuberculosis strains resistant to isoniazid resulted in fewer secondary cases, but rifampicin-resistant strains were more likely to result in a secondary case of TB. A molecular epidemiologic study in Mexico reported that drug-resistant strains of M. tuberculosis may have a diminished capacity to spread and cause disease.

Because the data for this study came from routine program implementation, we lacked information about variables such as socio-demographic characteristics and duration of illness. We also did not know the drug sensitivity pattern of the newly diagnosed DS-TB index cases as AFB microscopy alone was used to reach the diagnosis. The results among DS-TB contacts indicate that the new cases were most likely drug sensitive, assuming that the contacts acquired the infection from DS-TB index cases—although that might not always be true. More molecular studies and strain typing are needed to show the link between the index cases and TB-positive contacts. The strength of the study was the use of Genexpert test among both DS-TB and MDR TB contacts which enabled plausible comparison between the two groups. We also recommend conducting culture and DST for all Xpert/MTB Rif resistance cases to know the pattern of drug resistance.
CONCLUSIONS

In this study, we further confirm the usefulness of contact investigation as a high yield strategy for finding missing people with TB. Moreover, the use of GeneXpert improved the yield of TB among contacts and had the added value of identifying DR TB patients. The diagnosis of MDR-TB among contacts of MDR-TB index cases is higher than DS-TB contacts. We recommend further larger scale studies on the additional yield of TB if GeneXpert is used as a primary diagnostic tool for drug-sensitive TB versus the costs that would be incurred to avert the disease and achieve the End TB Strategy. Molecular epidemiological studies to understand the Mycobacterium tuberculosis genetic diversity and link the index cases with the secondary infection among close contacts would be valuable.

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Conflicts of interest:

None
REFERENCES


Figure 1: The procedures followed in screening and diagnosis among contacts of drug sensitive and MDR-TB index cases
Table 1: Comparison of the prevalence of TB among contacts of drug-sensitive and MDR-TB index cases diagnosed with GeneXpert

<table>
<thead>
<tr>
<th>Variables</th>
<th>Drug-Sensitive TB</th>
<th>MDR-TB/Rif TB</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of index cases registered</td>
<td>119</td>
<td>111</td>
<td>-</td>
</tr>
<tr>
<td>Number of contacts registered</td>
<td>393</td>
<td>340</td>
<td>-</td>
</tr>
<tr>
<td>Number of household/close contacts screened for TB</td>
<td>353</td>
<td>331</td>
<td>-</td>
</tr>
<tr>
<td>Number (percentage) of all TB cases diagnosed by GeneXpert</td>
<td>14 (4)</td>
<td>9 (2.7)</td>
<td>P &gt;0.05</td>
</tr>
<tr>
<td>Number (percentage) of rifampicin-resistant TB cases diagnosed</td>
<td>1 (0.3)</td>
<td>8 (2.4)</td>
<td>P &lt;0.05</td>
</tr>
<tr>
<td>Number (percentage) of rifampicin-sensitive TB cases diagnosed</td>
<td>13 (3.7)</td>
<td>1 (0.3)</td>
<td>P &lt;0.01</td>
</tr>
</tbody>
</table>