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Comparison of 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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ABSTRACT

Objectives: This study compared the yield of tuberculosis (TB) among contacts of multidrug-resistant tuberculosis (MDR-TB) index cases with that in 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 DS-TB index cases and MDR-TB index cases. After contacts were screened, GeneXpert was used 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 among DS-TB contacts were screened. There were 20 (6%) presumptive TB cases for MDR-TB contacts and 41 (11%) for DS-TB contacts. The prevalence of TB among MDR-TB contacts was 2.7% and among DS-TB contacts was 4.0%. The majority of the MDR-TB contacts diagnosed with TB had MDR-TB; the reverse was true for DS-TB.
Conclusions: The yield of TB among contacts of MDR-TB and DS-TB patients using GeneXpert was high as compared to the population-level prevalence. The likelihood of diagnosing rifampicin-resistant TB among contacts of MDR-TB index cases was higher in comparison with contacts of DS-TB index cases. The use of GeneXpert in DS-TB contact investigation has the added advantage of diagnosing rifampicin-resistant TB cases when compared to the use of the nationally recommended acid-fast bacillus (AFB) microscopy for DS-TB contact investigation.

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 million and 20.8 million people, respectively (Federal Democratic Republic of Ethiopia and CSA, 2013). According to the World Health Organization (WHO) 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 and 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, the treatment success rate for multidrug-resistant (MDR)-TB cases in Ethiopia was reported to be 68% (WHO, 2016).

Studies have shown that screening contacts of TB index cases yields more cases than community-level screening for TB (Jerene et al., 2015; Otero et al., 2016). The aim of this study was to compare the yield of household contact screening of MDR-TB and drug-sensitive (DS)-TB index cases in a routine program setting, using GeneXpert as a primary diagnostic method.

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Methods

Study design

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

TB focal persons at 11 health centers were trained on contact screening of DS-TB index cases, data collection, symptomatic screening, sputum sample collection, and referral. New acid-fast bacillus (AFB) sputum smear-positive patients diagnosed at 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 DS-TB index cases were registered in the study. All of these smear-positive index cases were either asked to bring their family members to the health center or were 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 either by culture and drug-susceptibility testing for isoniazid and rifampicin, or via diagnosis with GeneXpert MTB/rifampicin resistance, which is treated as MDR-TB as per the national guidelines (Federal Democratic Republic of Ethiopia and MOH, 2016). The management of MDR-TB in Ethiopia uses a mixed model of care, both 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 1 or 2 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. Registration of contacts of MDR-TB index patients was introduced 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 DS-TB contacts. For this study, GeneXpert was also used for contacts of DS-TB cases so that the yield of TB could be compared in the two groups of contacts. The resistance pattern here is presented only for GeneXpert, because the MDR-TB treatment decision is made on the basis of rifampicin resistance alone. In the baseline follow-up test, culture and drug-susceptibility testing for isoniazid and rifampicin was performed for the purposes of follow-up, but the data were not available for this publication.

Definitions

A TB index case was defined as a DS-TB or MDR-TB patient enrolled in treatment. A household contact was defined as a person who had shared the same enclosed living space for one or more nights a week, or for frequent or extended periods of time during the day, with the index patient during the 3 months before the current treatment episode began (Jerene et al., 2015; WHO, 2012; Fair et al., 2015).

TB diagnosis

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

Data analysis

Data entry and analysis were performed using SPSS version 13 (SPSS Inc., Chicago, IL, USA). Frequencies, percentages, and the 95% confidence intervals of proportions were computed. The numbers needed to screen and 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 (Jerene et al., 2015).

Ethical considerations

Contact investigation of patients with MDR-TB and DS-TB is a routine health procedure for all patients (Federal Democratic Republic of Ethiopia and MOH, 2016); however ethical clearance was obtained from the Amhara and Oromia regional health bureaus to utilize the information for publication. Each study participant provided oral informed consent and permission for TB screening and diagnosis. Diagnosis of and treatment for all presumptive TB patients are provided free of charge (Fair et al., 2015). MDR-TB patients were also provided with an ambulance service to the TIC for the 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 DS-TB cases were diagnosed in the study health facilities. Three hundred and forty contacts were registered for MDR-TB index cases and 393 contacts were registered for DS-TB index cases. The contact-to-index case ratio was 3.1 for MDR-TB contacts and 3.3 for DS-TB contacts.

Of the 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, nine (45%; 95% CI 24.6–66.7%) were diagnosed with TB, and of those, eight (88.9%; 95% CI 56.1–99.4%) had rifampicin-resistant TB and one had rifampicin-sensitive TB (Figure 1).

Among the 393 DS-TB contacts, 353 (89.9%) were screened and 41 (11%; 95% CI 9.7–17.4%) were found to be presumptive TB cases. With the exception of two children under 5 years of age diagnosed with TB empirically, 39 presumptive TB cases had a sputum test done using GeneXpert. Fourteen (35.9%; 95% CI 20.9–49.5%) were diagnosed with TB, one of whom (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 with TB, while the yield among contacts of the new DS-TB patients was 4.0% ($p > 0.05$). In the MDR-TB contacts, the yield of rifampicin-resistant TB was 2.4% (Table 1).

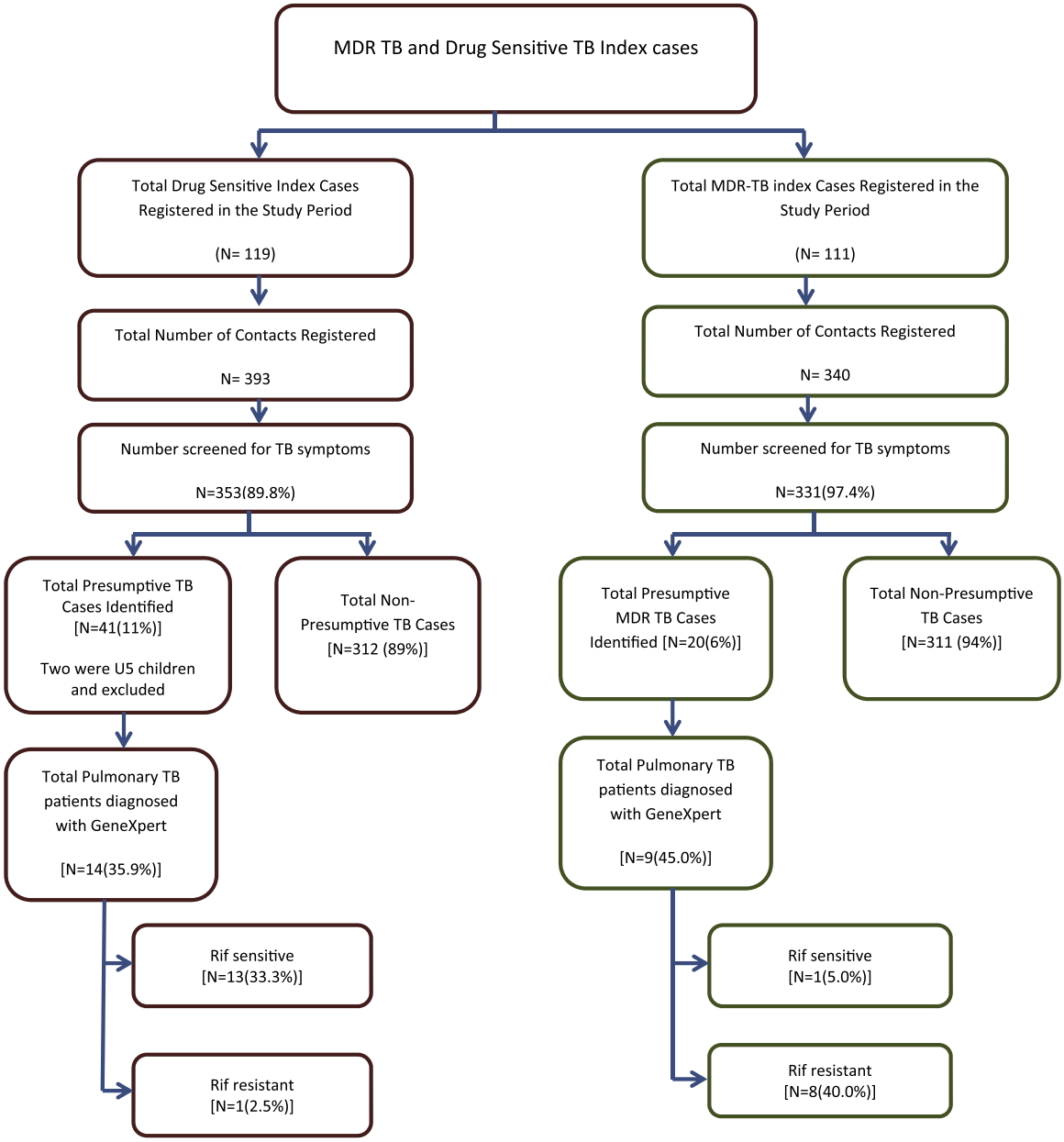

Figure 1. The procedures followed in screening and diagnosis among contacts of drug sensitive and MDR-TB index cases.

Table 1
Comparison of the prevalence of TB among contacts of DS-TB and MDR-TB index cases diagnosed with GeneXpert

Variables	DS-TB	MDR-TB/Rif	*p*-Value
Number of index cases registered	119	111	–
Number of contacts registered	393	340	–
Number of household/close contacts screened for TB	353	331	–
Number (percentage) of all TB cases diagnosed by GeneXpert	14 (4)	9 (2.7)	>0.05
Number (percentage) of rifampicin-resistant TB cases diagnosed	1 (0.3)	8 (2.4)	<0.05
Number (percentage) of rifampicin-sensitive TB cases diagnosed	13 (3.7)	1 (0.3)	<0.01

TB, tuberculosis; DS, drug-sensitive; MDR, multidrug-resistant; Rif, rifampicin.

A significant proportion of the TB cases diagnosed among contacts of DS-TB index patients were DS-TB cases (3.7% versus 0.3% for MDR-TB index contacts; $p < 0.01$). In contrast, the majority of the TB cases diagnosed among contacts of MDR-TB index cases had rifampicin-resistant TB (2.4% versus 0.3% among DS-TB index cases; $p < 0.05$) (Table 1).

The number needed to screen for DS-TB index contacts was 25, and for the MDR-TB contacts was 37. The number needed to test for

the contacts of DS-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 (WHO, 2016; Federal Democratic Republic of Ethiopia et al., 2011). The TB yield among the contacts of MDR-TB index patients of 2.7% was higher than the national estimated MDR-TB prevalence of 2.3% among new TB cases (Federal Democratic Republic of Ethiopia and EPHI, 2012).

These 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 reported in previous studies from Ethiopia and elsewhere. Studies in Ethiopia and Peru showed that the yield of all forms of TB from contact investigation was 10 times higher than the national prevalence (Jerene et al., 2015; Otero et al., 2016). In another retrospective screening of contacts who had completed treatment of 6 months to 3 years, the yield was six times higher than the national prevalence (Gashu et al., 2016). In a meta-analysis of 19 studies, yields ranged from 1% to 14.1%, with a pooled estimate of 1.8% (Blok et al., 2015). Since most of the previous studies used AFB microscopy as the primary test for screening contacts, it is likely that the expanded use of GeneXpert for contact investigation will yield better results.

Another finding of this study is that 92.8% of the TB cases diagnosed among DS-TB contacts had rifampicin-sensitive TB, whereas 88.8% of the newly diagnosed TB cases among MDR-TB contacts had rifampicin-resistant TB. These findings are similar to those of two studies, which reported that 80% and 88.4% of the cases diagnosed among MDR-TB contacts had MDR-TB (Otero et al., 2016; Titiyos et al., 2015). Two other studies reported that more than 50% of secondary cases with DS-TB were concordant with the index case (Parr et al., 2014; Shah et al., 2014). This finding indicates that MDR-TB contacts, if they are diagnosed as having TB, are highly likely to have rifampicin-resistant TB. A recent DS-TB contact investigation study 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 with first-line drugs (Jerene et al., 2015). In the present study, the GeneXpert test was used as a diagnostic modality for DS-TB contacts, and rifampicin-resistant TB as well as rifampicin-sensitive TB cases were diagnosed. This shows the added advantage of the new diagnostics in any kind of TB contact screening.

The same high yield of TB among contacts of MDR-TB index cases has also been reported in many studies. In a study in Ethiopia, of the 155 family contacts of MDR-TB patients, 16 (10.3%) were found to have TB, all of whom had MDR-TB (Titiyos et al., 2015). In an Indian study of 302 MDR-TB contacts, 16 (5.2%) developed TB and two (0.66%) had MDR-TB (Singla et al., 2011). A study in Peru indicated that 5% of the household contacts of MDR-TB index cases developed TB, of whom 80% also had MDR-TB (Grandjean et al., 2011). In Brazil, among contacts of MDR-TB and DS-TB patients, about 4% developed TB, and five of the six diagnosed with TB among MDR-TB contacts had MDR-TB (Teixeira et al., 2001).

Some studies have shown that the yield of TB among contacts of MDR-TB and DS-TB patients is comparable (Teixeira et al., 2001; Cohn et al., 1954; Snider et al., 1985), while others have reported that TB disease among MDR-TB household contacts is half that among DS-TB contacts (Grandjean et al., 2015). Other studies have shown that the yield among MDR-TB household contacts is lower than the yield in contacts of DS-TB index cases (Teixeira et al., 2001; Cohn et al., 1954; Snider et al., 1985; Barnett et al., 1953). 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 (Van Soolingen et al., 1999; Nitta et al., 2002). However the yields of TB among close contacts of MDR-TB and DS-TB patients in this 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 (Otero et al., 2016; Barnett et al., 1953; Mitchison, 1954; Windlock et al., 1955). In another study, *Mycobacterium 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 (Burgos et al., 2003). A molecular epidemiological study in Mexico reported that drug-resistant strains of *M. tuberculosis* may have a diminished capacity to spread and cause disease (García-García et al., 2000).

As the data for this study came from routine program implementation, information about variables such as socio-demographic characteristics and duration of illness were lacking. The drug sensitivity pattern of the newly diagnosed DS-TB index cases was also not known, 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 the DS-TB index cases, although this 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 this study is the use of the GeneXpert test in both DS-TB and MDR-TB contacts, which enabled plausible comparison between the two groups. The authors also recommend conducting culture and drug-susceptibility testing for all Xpert/MTB Rif resistance cases to determine the pattern of drug resistance.

Conclusions

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

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Conflicts of interest

None.

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