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TUBERCULOSIS AND RIFAMPICIN RESISTANCE AMONG MIGRANTS IN KYRGYZSTAN: DETECTION BY A NEW DIAGNOSTIC TEST

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ABSTRACT

This cross-sectional study aimed to describe suspected tuberculosis (TB) cases among migrants in Kyrgyzstan and to estimate the accuracy of Xpert MTB/RIF, which has been operated in Kyrgyzstan since 2012. Characteristics of 3,714 suspected cases among migrants were analysed. In addition, by using data of 300 cases with culture results, sensitivity and specificity of Xpert MTB/RIF, both for detection of TB and rifampicin susceptibility, were assessed. Among 3,714 suspected cases, 56.1% were male, and the median age was 35 years old. Of the suspected cases, 17.2% were previously-treated. In total, 809 (21.8%) were smear-positive; 36.8% among previously-treated cases and 18.7% among new cases. Among 300 selected participants, 235 (78.3%) were culture-positive. Of those who were confirmed as TB positive, recurrent cases showed a higher proportion of rifampicin resistance than new cases (59.3% vs 42.6%). For detection of TB, the sensitivity and specificity of XpertMTB/RIF (81.3% and 98.2%) were higher than those of microscopy (70.2% and 71.4%). Sensitivity and specificity for detection of rifampicin resistance were 96.8% and 91.8%, respectively. The rifampicin resistance rate in the study population was higher than the national average. Xpert MTB/RIF showed higher accuracy in detecting TB cases than microscopic diagnosis. Higher accuracy and earlier detection of drug susceptibility is especially important for those who have difficulty in accessing healthcare and those who are easily lost from tracking, including migrants.

Key Words: Tuberculosis, MDR-TB, Migrants, Xpert MTB/RIF, Kyrgyzstan

INTRODUCTION

The global burden of tuberculosis (TB) cases and its drug resistance has been increasing both in developing and developed countries. According to the World Health Organization (WHO), multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis which is resistant to isoniazid and rifampicin, with or without resistance to other first-line drugs.[1] Globally, 3.7% of new cases and 20% of previously-treated cases were estimated to have MDR-TB.[2] Development of resistance to these main anti-TB drugs, even without resistance to additional drugs, is a major

obstacle to successful treatment and increases the number of MDR-TB patients.

Microscopic examination of sputum smear is widely used to detect TB patients because it is simple, inexpensive, and quickly detects pulmonary tuberculosis. Meanwhile mycobacterial culture and species identification provide a definitive diagnosis as well as the necessary material for conventional drug-susceptibility testing.[3] Recently, rapid progress has been made in tuberculosis diagnostics; the Xpert MTB/RIF assay on the GeneXpert multi-disease platform, which is a fully automated diagnostic molecular test that simultaneously detects TB and rifampicin resistance, was recommended by WHO in 2010 as the initial diagnostic test for suspected MDR-TB or HIV-associated TB.[4-7]

In Kyrgyzstan, TB has been becoming more problematic with the appearance of MDR forms since the early 1990s. Currently, the country is one of the 27 countries with the largest MDR-TB burdens in the world.[8, 9] WHO data in 2011 showed that the proportions of MDR-TB in Kyrgyzstan were 52% and 26% among all the retreatment and new cases, respectively.[9] Since 2004, the country has promoted directly observed treatment short course with a component for MDR-TB (DOTS Plus). TB is considered to be one of the prioritized diseases in the new national health strategy for 2012–2016, and as a major public challenge in Kyrgyzstan.[10] In Kyrgyzstan, both internal migrants and cross-border migrants are recognized as one of the most vulnerable groups responsible for spreading TB and MDR-TB. Migrants are prone to TB infection because of their poor living and working conditions.[11, 12] Due to lack of proper treatment abroad, the patients' disease can be transformed from drug-susceptible TB into drug-resistant TB. Existing health systems in populous cities do not fully cover the growing population of internal migrants.

In the current National Tuberculosis Program, all suspected cases are examined both by microscopy (smear of sputum) and by X-ray and clinical symptoms (preliminary diagnosis). All positive patients at the stage of preliminary diagnosis are treated as TB patients, and culture is further tested, including susceptibility tests of TB drugs (definitive diagnosis). A choice of treatment regimen is modified based on the drug susceptibility testing. In the beginning of 2012, the Kyrgyz National TB Program introduced a new diagnostic test, Xpert MTB/RIF, to identify TB as well as rifampicin-resistant forms of TB among migrants. In the new system, all suspected cases are examined both by microscopy and by Xpert MTB/RIF. Diagnosis and drug susceptibility are determined by Xpert MTB/RIF. The government is now extending the new diagnostic testing to all of the population, with all the necessary conditions for training, maintenance, and quality assurance measures.[13] Although research on the sensitivity and specificity of Xpert MTB/RIF has been published,[14, 15] to our knowledge, no such study has been conducted in Kyrgyzstan. Therefore, we aimed: 1) to describe characteristics of the suspected TB patients among the migrant population in Kyrgyzstan, and 2) to evaluate the accuracy of Xpert MTB/RIF by comparing it with other traditional methods, using the samples from the targeted population.

METHODS

This was a cross-sectional study, conducted by an international TB project named TB REACH[16] under the National TB Center of the Ministry of Health (MOH) between April and September, 2012. A total of 3,821 sputum specimens from suspected TB cases were collected by laboratory technicians of primary health care facilities (PHCF) in Bishkek City, and in Chui and Osh regions, and delivered to the four laboratories where GeneXpert MTB/RIF was installed: two laboratories in the capital Bishkek (National Reference Laboratory and Laboratory of the Bishkek City TB Center), one in the Osh region (Laboratory of Osh Interregional Child TB Hospital) and one in the Chui region (Laboratory of Chui Regional TB Center).

Internal and cross-border migrants were targeted in this study. Migrants in the TB REACH project are defined as labour migrants who registered in one region but are working and living permanently in another region without registration and any access to PHCF. In this study, those with at least 2 weeks of cough, accompanied with loss of weight, night sweats and fever, were initially enrolled. Previously-treated cases were also included in our study. However, those who had been given TB medication within the past 60 days were excluded from the study. We also collected and enlisted baseline information of the subjects in official registration books in each of the four target laboratories. From each suspected patient, sputum was collected in accordance with WHO standards.[17] After excluding 64 cases with insufficient medical records and 43 cases without microscopy results, the remaining 3,514 subjects were included in the first-stage analysis. Lowenstein-Jensen medium and the Bactec MGIT 960 system were used for mycobacterial detection and drug susceptibility. Due to a lack of culture facility, specimens from Chui Regional TB Center were sent to National Reference Laboratory in Bishkek. Because not all participants had culture results, we finally included 300 cases with culture results in the second-stage analysis. The inclusion algorithm is shown in Fig. 1. Informed consent was taken from all participants who met inclusion criteria. The National TB Center and Kyrgyz State Medical Academy Ethics Committee approved the study protocol.

Characteristics of the initial 3,714 participants and selected 300 participants (with culture results) were described and compared by chi squared tests. In addition, new cases and previously-treated cases were compared by chi squared tests, using the 3,714 samples and 300 samples. Associations between participants' characteristics and TB-positivity were then analysed by chi squared tests. Based on data from 300 patients whose culture results were available, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of microscopy
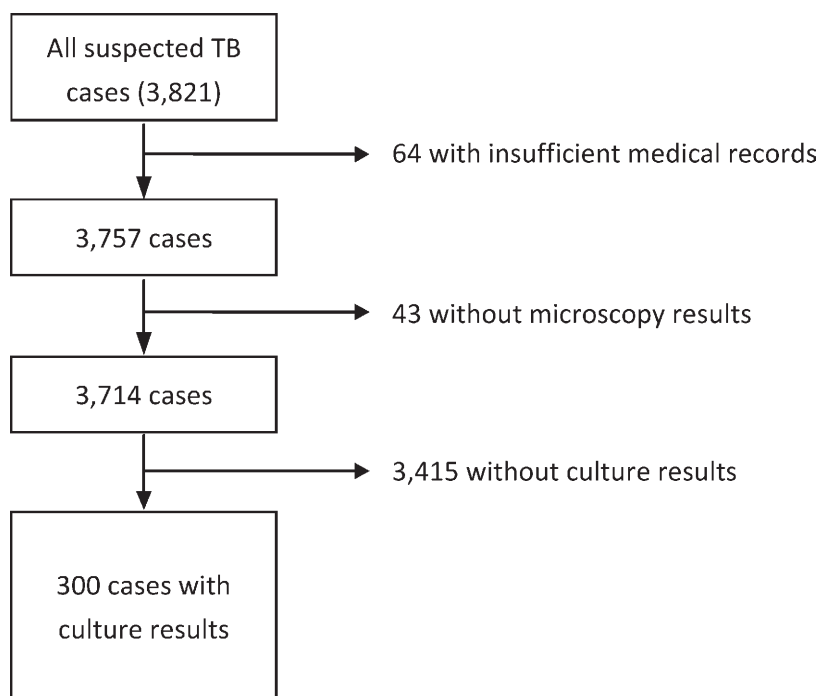

Fig. 1 Inclusion algorithm of this study

and Xpert MTB/RIF for TB detection were calculated, using culture results as a gold standard. For those with culture-positive and with susceptibility results based on both culture and Xpert MTB/RIF, the sensitivity, specificity, PPV and NPV of Xpert MTB/RIF were calculated. Binomial distribution was used to calculate 95% confidence interval (CI) for percentage. Data were entered and analysed by Statistical Package of Social Science (SPSS) version 20.0.

RESULTS

Of all the 3,714 suspected cases among migrants who met inclusion criteria, 56.1% were males. The median age of the initial participants was 35 years old with the interquartile range of 25–50 years old. Among the age groups, the group of 20–29 year olds was the largest (27.2%). Of all participants, previously-treated and new cases were 17.2% and 82.8%, respectively. Smear-positive cases were 809 (21.8%). Among the selected 300 participants, whose culture results were available, 57.3% were males, their median age was 34 years old with the interquartile range of 25–45 years old; more than two thirds were in their 20s, 30s or 40s, and 24.7% were previously-treated cases, as shown in Table 1. Gender and age distribution were not significantly different between the initial participants (3,714 cases) and the selected participants with culture results (300 cases). The 300 selected participants with culture results showed a significantly higher proportion of previously-treated cases than all the participants. The distribution of data collection sites was significantly different between the initial participants and the selected participants; more than 80% of the participants with culture results were from two laboratories in the capital city (Table 1). Previously-treated cases were found more in males and in the middle-age group, both among the initial participants and among the selected participants. Among the selected participants, rifampicin resistance was found in 46.8% and it was significantly higher in previously-treated cases than in new cases (59.3% vs 42.6%, *P*=0.03) (Table 2). Table 3 shows participants' characteristics and culture results of TB detection. There was a significant association between TB-positivity and data collection site. The majority of negative specimens were collected at the National Referral Laboratory.

Table 1 Characteristics of initial and selected participants with culture results

	Initial participants (N=3,714)		Selected participants (N=300)		*P*-value[a)]
	n	(%)	n	(%)	
Gender					
Male	2,083	(56.1)	172	(57.3)	0.68
Female	1,631	(43.9)	128	(42.7)	
Age group (years)					
–19	412	(11.1)	36	(12.0)	0.18
20–29	1,010	(27.2)	87	(29.0)	
30–39	722	(19.4)	67	(22.3)	
40–49	576	(15.5)	49	(16.3)	
50–	994	(26.8)	61	(20.3)	
Data collection site					
NRL	1,188	(32.0)	134	(44.7)	<0.01

BCTBC	1,117	(30.1)	111	(37.0)	
OICTBH	1,008	(27.1)	30	(10.0)	
CRTBC	401	(10.8)	25	(8.3)	
Previous TB history					
Previously treated	640	(17.2)	74	(24.7)	<0.01
New	3,074	(82.8)	226	(75.3)	
TB detection (microscopy)					
Positive	809	(21.8)	182	(60.7)	<0.01
Negative	2,903	(78.2)	118	(39.3)	

NRL=National Reference Laboratory; BCTBC=Bishkek City TB Center; OICTBH=Osh Interregional Child TB Hospital; CRTBC=Chui Regional TB Center

[a] chi-squared test

Table 2 Characteristics of participants by previous TB history among initial and selected participants with culture results

	Initial participants (N=3,714)					Selected participants (N=300)				
	Previously treated (N=640)		New (N=3,074)		P-value[a]	Previously treated (N=74)		New (N=226)		P-value[a]
	n	(%)	n	%		n	(%)	n	%	
Gender										
Male	418	(65.3)	1,665	(54.2)	<0.01	52	(70.3)	120	(53.1)	0.01
Female	222	(34.7)	1,409	(45.8)		22	(29.7)	106	(46.9)	
Age group (years)										
–19	42	(6.6)	370	(12.0)	<0.01	3	(4.1)	33	(14.6)	0.05
20–29	160	(25.0)	850	(27.7)		21	(28.4)	66	(29.2)	
30–39	144	(22.5)	578	(18.8)		18	(24.3)	49	(21.7)	
40–49	140	(21.9)	436	(14.2)		18	(24.3)	31	(13.7)	
50–	154	(24.1)	840	(27.3)		14	(18.9)	47	(20.8)	
Data collection site										
NRL	260	(40.6)	928	(30.2)	<0.01	27	(36.5)	107	(47.3)	0.07
BCTBC	172	(26.9)	945	(30.7)		28	(37.8)	83	(36.7)	
OICTBH	103	(16.1)	905	(29.4)		13	(17.6)	17	(7.5)	
CRTBC	105	(16.4)	296	(9.6)		6	(8.1)	19	(8.4)	
TB detection (microscopy)										
Positive	235	(36.8)	574	(18.7)	<0.01	49	(66.2)	133	(58.9)	0.26
Negative	404	(63.2)	2,499	(81.3)		25	(33.8)	93	(41.1)	
TB detection (culture)										
Positive	NA		NA			59	(79.7)	176	(77.9)	0.94
Negative	NA		NA			13	(17.6)	43	(19.0)	

Contamination	NA	NA	2	(2.7)	7	(3.0)	
Rifampicin susceptibility[b]						
Resistant	NA	NA	35	(59.3)	75	(42.6)	0.03
Sensitive	NA	NA	24	(40.7)	101	(57.4)	

NRL=National Reference Laboratory; BCTBC=Bishkek City TB Center; OICTBH=Osh Interregional Child TB Hospital; CRTBC=Chui Regional TB Center [a] chi-squared test; [b] based on culture susceptibility testing, N=235

Table 3 Characteristics of participants by culture results of TB detection

	Positive (N=235)		Non-positive[a] (N=65)		*P*-value[b]
	n	(%)	n	%	
Gender					
Male	137	(58.3)	35	(53.9)	0.52
Female	98	(41.7)	30	(46.2)	
Age group (years)					
–19	25	(10.6)	11	(16.9)	0.21
20–29	66	(28.1)	21	(32.3)	
30–39	53	(22.6)	14	(21.5)	
40–49	44	(18.7)	5	(7.7)	
50–	47	(20.0)	14	(21.5)	
Data collection site					
NRL	87	(37.0)	47	(72.3)	<0.01
BCTBC	104	(44.3)	7	(10.8)	
OICTBH	23	(9.8)	7	(10.8)	
CRTBC	21	(8.9)	4	(6.2)	
Previous TB history					
Previously treated	59	(25.1)	15	(23.1)	0.74
New	176	(74.9)	50	(76.9)	

NRL=National Reference Laboratory; BCTBC=Bishkek City TB Center; OICTBH=Osh Interregional Child TB Hospital; CRTBC=Chui Regional TB Center
[a] including 9 contaminated cases; [b] chi-squared test

Among the selected 300 cases, 182 (60.7%) were smear-positive and 118 (39.3%) smear-negative, while 195 (65.0%) were Xpert MTB/RIF-positive, 96 (32.0%) Xpert MTB/RIF-negative, and 9 (3.0%) invalid. Culture results showed that 235 (78.3%) were positive, 56 (18.7%) negative, and 9 (3%) contaminated. Defining the culture result as the gold standard, the sensitivity of the Xpert MTB/RIF test for detection of TB was 81.3% (95% CI, 75.7–86.1), the specificity was 98.2% (95% CI, 90.4–99.9), the PPV was 97.9% (95% CI, 94.8–99.4), and the NPV was 57.3% (95% CI, 46.8–67.3). Those of microscopy results were 70.2% (95% CI, 63.9–76.0), 71.4%

Table 4 Sensitivity, specificity, PPV and NPV to detect tuberculosis (TB) infection and rifampicin resistance based on a culture method as a gold standard

Method	Sensitivity		Specificity		PPV		NPV	
	% (n)	95% CI	% (n)	95% CI	% (n)	95% CI	% (n)	95% CI
Detection of TB infection								
Microscopy	70.2 (165/235)	63.9–76.0	71.4 (40/56)	57.8–82.7	90.6 (165/182)	85.5–94.5	33.9 (40/118)	25.4–43.2
Xpert MTB/RIF	81.3 (191/235)	75.7–86.1	98.2 (55/56)	90.4–99.9	97.9 (191/195)	94.8–99.4	57.3 (55/96)	46.8–67.3
Detection of rifampicin resistance								
Xpert MTB/RIF	96.8 (91/94)	90.9–99.3	91.8 (89/97)	84.4–96.4	94.8 (91/96)	88.3–98.3	97.8 (89/91)	92.3–99.7

PPV = positive predictive value, NPV = negative predictive value, CI = confidence interval

(95% CI, 57.8–82.7), 90.6% (95% CI, 85.5–94.5), and 33.9% (95% CI, 25.4–43.2), respectively (Table 4).

Among the TB-positive 235 cases confirmed by culture, results of Xpert MTB/RIF testing for rifampicin susceptibility were: 96 (40.9%) resistant, 91 (38.7%) sensitive, 4 (1.7%) intermediate, and 44 (18.7%) missing. Using the culture results as the gold standard, among 191 cases whose Xpert MTB/RIF results for rifampicin susceptibility were available, the sensitivity, specificity, PPV and NPV of Xpert MTB/RIF for rifampicin resistance were 96.8% (95% CI, 90.9–99.3), 91.8% (95% CI, 84.4–96.4), 94.8% (95% CI, 88.3–98.3), and 97.8% (95% CI, 92.3–99.7), respectively (Table 4).

DISCUSSION

Among suspected cases in the migrant population we studied, more than half were male, and nearly half were in the 20–39 age group, who were considered to be actively working. Approximately two thirds of specimens were collected from two laboratories in the capital city. Among suspected cases, 78.2% were diagnosed as TB by microscopic examination of sputum smear. The tendency to be male, middle-aged, and a capital city dweller was observed more dominantly in previously-treated cases than in new cases. Among the TB-positive cases confirmed by culture, rifampicin-resistant cases were 59.3% among the previously-treated cases and 42.6% among the new cases, both of which were higher than the national data.[9] This study confirmed that Xpert MTB/RIF had significantly higher sensitivity and specificity for detection of TB than microscopic examination of sputum smear in a Kyrgyz population, and described the sensitivity and specificity of the Xpert MTB/RIF test to detect TB cases and rifampicin resistance for the first time in Kyrgyzstan. For rifampicin susceptibility testing, the Xpert MTB/RIF test produced a sensitivity of 96.8% and a specificity of 91.8%.

The Xpert MTB/RIF is one of the new generation diagnostic tests. It is easy to use by routine staff of the health system even in rural areas.[18, 19] The test is particularly useful for migrant people who are easily lost from tracking, because they can start correct and prompt treatment before leaving the health facility where they are diagnosed.

Among the participants who had results from the three tests, the overall sensitivity of the Xpert MTB/RIF test was 81.3% and the specificity was 98.2%. Compared with the pooled sensitivity

and specificity of a meta-analysis of 15 studies (90.4% and 98.4%, respectively),[14] our sensitivity was lower and our specificity was similar.

Although the Xpert MTB/RIF test has a high sensitivity and specificity for the detection of TB cases, there are some difficulties in scaling up the test nationwide in Kyrgyzstan. The GeneXpert device requires a stable electricity supply, a temperature below 30°C, and yearly calibration, which are recommended by the manufacturer. Cartridges also need to be kept at 2–28°C.[20] Under some conditions, generator instalment is necessary for the GeneXpert device to maintain a continuous electricity supply. These cannot always be maintained in rural areas of Kyrgyzstan.

Our study has several limitations. First, we included only 300 cases with culture results among the initially enrolled 3,714 participants. Generally, rifampicin-resistance results by the Xpert MTB/RIF testing should be verified by culture results. However, not all results were confirmed by culture. Regarding the discrepancy between the number of TB detection tests by Xpert MTB/RIF and the number of rifampicin resistance tests by Xpert MTB/RIF, this might be due to recording failure because Xpert MTB/RIF can detect TB and rifampicin resistance simultaneously. Second, the distribution of the sputum-negative cases was much skewed toward the National Referral Laboratory. This implies that there might have been some differences in the selection of cases, or possibly technical issues, such as false negative cases.

Higher accuracy and earlier detection of drug susceptibility is especially important for those who have difficulty in obtaining continuous access to healthcare, including migrants. Further studies of Xpert MTB/RIF in a general population with better adherence to laboratory protocol and solid recording systems may yield more accurate information.

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CONFLICTS OF INTERSEST

The authors declare no conflict of interest.

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