International Journal of Infectious Diseases 104 (2021) 634–640

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Extending contact screening within a 50-m radius of an index tuberculosis patient using Xpert MTB/RIF in urban Pakistan: Did it impact treatment outcomes?

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ARTICLE INFO

Article history:
Received 9 November 2020
Received in revised form 20 January 2021
Accepted 21 January 2021

Keywords:
Pulmonary tuberculosis
Treatment outcomes
Extended contact screening
Passive case findings
Favorable and unfavorable outcomes

ABSTRACT

Background: Pakistan implemented initiatives to detect tuberculosis (TB) patients through extended contact screening (ECS); it improved case detection but treatment outcomes need assessment.
Objectives: To compare treatment outcomes of pulmonary TB (PTB) patients detected by ECS with those detected by routine passive case finding (PCF).
Methods: A cohort study using secondary program data conducted in Lahore, Faisalabad and Rawalpindi districts and Islamabad in 2013–15. We used log binomial regression models to assess if ECS was associated with unfavorable treatment outcomes (death, loss-to-follow-up, failure, not evaluated) after adjusting for potential confounders.
Results: We included 79,431 people with PTB; 4604 (5.8%) were detected by ECS with 4052 (88%) bacteriologically confirmed. In all PTB patients the proportion with unfavorable outcomes was not significantly different in ECS group (9.6%) compared to PCF (9.9%), however, among bacteriologically confirmed patients unfavorable outcomes were significantly lower in ECS (9.9%) than PCF group (11.6%, $P = 0.001$). ECS was associated with a lower risk of unfavorable outcomes (adjusted relative risk (aRR) 0.90; 95% CI 0.82–0.99) among 'all PTB' patients and bacteriologically confirmed PTB patients (aRR 0.91; 95% CI 0.82–1.00).
Conclusion: In PTB patients detected by ECS the treatment outcomes were not inferior to those detected by PCF.

Introduction

Pakistan has a high burden of tuberculosis (TB) with an estimated 5,70,000 incident TB patients and 42,000 deaths in 2019; only 58% of the estimated patients were diagnosed, notified and started on treatment (World Health Organization, 2020a). Therefore, complementing standard "passive" case finding with active case finding has been strongly encouraged (Ho et al., 2016; World Health Organization, 2013). A cluster-randomized controlled trial conducted in Vietnam in 2010–15 showed that household-contact investigation with standard passive case finding was more effective than standard passive case finding alone for the detection of TB in a high-prevalence setting (Fox et al., 2018).

Contact tracing and screening initiatives among contacts of TB patient, including in urban slums, have shown an increase in case detection and notification and therefore an opportunity to reduce diagnostic delay (Dowdy et al., 2013; Fatima et al., 2014; Lorent et al., 2014; Miller et al., 2010; World Health Organization, 2012, 2011).

The National TB control program (NTP) of Pakistan achieved nationwide coverage of TB services in the public health sector by 2005 with the DOTS strategy (Directly Observed Treatment, Short course) now updated to the "End TB strategy" (National

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https://doi.org/10.1016/j.ijid.2021.01.054

Tuberculosis Programme, 2019a). The majority of the case finding is through the public sector (National Tuberculosis Programme, 2019b) where people with presumptive TB come to a public health facility and are investigated for TB; this is called "passive case finding" (PCF) and the initiative comes from the patients. Often such patients are referred by the private health sector where diagnostic services are not available. Other patients who do not visit the health facility despite having symptoms may be identified by "active case finding (ACF)", where the health system tries to reach out into the community to identify and diagnose patients with TB (World Health Organization, 2012). ACF is also done in populations with high prevalence of undetected TB or in marginalized and vulnerable populations with poor access to health services (World Health Organization, 2013).

Pakistan NTP implemented an innovative type of ACF, an 'extended contact screening' (ECS) strategy. This involved community contact investigation beyond the routine household contacts: all individuals in households within a 50-m radius from the home of an index smear-positive TB patient were asked about TB symptoms; if they had symptoms they were investigated. The ECS strategy increased case finding by around 8%, which is more than expected from normal annual increases in routine TB control (Fatima et al., 2016).

However, there has been no assessment on whether ECS affected the treatment outcomes. A systematic review published in 2013 identified similar treatment outcomes among ACF and PCF-detected patients (Lönnroth et al., 2013); while more recent papers show ACF to have similar (Khaing et al., 2018; Shewade et al., 2019) or worse outcomes (Sengai et al., 2020; Singh et al., 2020). We have not found any study from Pakistan comparing treatment outcomes by case detection strategy.

Therefore, our objective was to compare the treatment outcomes of TB patients detected by the ECS strategy with those detected in routine PCF in selected districts of Pakistan.

Methods

Study design

This was a cohort study involving analysis of routine program data.

Setting

General setting

Pakistan has a population of over 200 million (WorldBank, 2018). The health system includes government (public) institutions, parastatal health institutions (armed forces, Sui Gas, WAPDA (Pakistan Water and Power Development Authority), Railways, Fauji Foundation), the private sector, civil society and philanthropic institutions. The private sector is large and unregulated, with qualified and unqualified health service providers that deliver general curative services to about 75% of Pakistan's population; nearly 90% of patients with TB initially seek care in the private sector (Fatima et al., 2017).

Public health care is delivered through a network of primary, secondary and tertiary level health facilities. The primary health care facilities include civil dispensaries, basic health units, rural health centers, mother-child healthcare centers, urban health units, and urban health centers. The secondary level health care facilities comprise sub-district hospitals and district hospitals. Tertiary level health care is provided through teaching and specialized hospitals.

TB basic management units (BMUs) are located at the district and sub-district hospitals, the rural health centers, and some basic health units. A BMU has a staffed laboratory doing smear microscopy (a few facilities also do Xpert MTB/RIF assays) and a doctor/qualified medical staff trained to diagnose and initiate TB treatment. TB treatment involves 6–8 months of treatment provided under daily direct observation by a health care provider, a community volunteer or a family member. The BMU is also a facility where TB patients return for re-examinations and confirmation of cure. The BMU maintains records in standard formats and provides periodic reports to the district coordinator, including reports on treatment outcome (World Health Organization, 2020b). Sputum microscopy services, Xpert MTB/RIF testing and TB treatment are provided free of charge. During 2013–15, all the BMUs followed the algorithm in Figure 1 to diagnose TB.

All the patients in this study were treated in line with national TB guidelines (2013–15) and under direct observation as is routine for PCF. New patients (never been treated before or treated <30 days) were treated with 6 months' treatment regimen, which consisted of 2 months of HRZE (H-Isoniazid, R-Rifampicin Z-Pyrazinamide, E-Ethambutol) in intensive phase and 4 months of HR in continuation phase. Previously treated patients (treated for >30 days in the past) were treated with 8 months' regimen that consisted of 2 months HRZES (S-Streptomycin), 1 month HRZE and 5 months of HRE. Patients who were diagnosed as having rifampicin resistance were referred to drug-resistant TB sites for second line treatment. HIV testing was not routinely offered to patients (PCF or ECS).

Extended contact screening

During 2013–15, ECS was implemented in 4 mainly urban districts: Lahore, Rawalpindi, Faisalabad and Islamabad. (Figure 2). There were 98 BMUs for the population of 18 million. More than 80% of the population in these districts live in urban areas. The average socio-economic status of people living in the project districts is better than the average of Pakistan because of better jobs and business opportunities. However, half of the population live in slums with poor socio-economic conditions.

The Pakistan NTP had a project funded by TB-REACH wave III, intended to facilitate detection of more TB cases (Fatima et al., 2016).

All people staying within a 50-m radius (ascertained using geographic information system, GIS) from the households of known TB patients were contacted and screened for TB by trained project staff. A 50-m radius was chosen based on the data from the electronic TB surveillance system which revealed the presence of many cases coming from the same family, same address, or neighboring areas; suggesting high rates of geographical clustering. The approximate number of households in this radius was deemed feasible to be covered under close community screening by the NTP. Mobile phones enabled with ARC GIS (version 10) software were used by field workers to identify households within a 50-m radius of the index case and collect data. All available people permanently residing within a 50-m radius were contacted. The participants were informed about a TB patient in the neighborhood (50-m radius) but care was taken not to disclose the name. Measures were taken to safeguard the confidentiality of the index patient. Any person with a productive cough for more than 2 weeks was defined as a 'presumptive TB' patient. One spot sputum sample was collected and transported to the closest BMU for diagnostic testing. The same diagnostic algorithm as mentioned in Figure 1 was followed except for the use of Xpert MTB/RIF (if available) assay among sputum smear microscopy negative presumptive TB. Patients bacteriologically positive for TB were contacted by the project staff and referred to the nearest BMU for registration and treatment initiation. All presumptive TB patients aged <15 years were referred to specialist pediatric care for

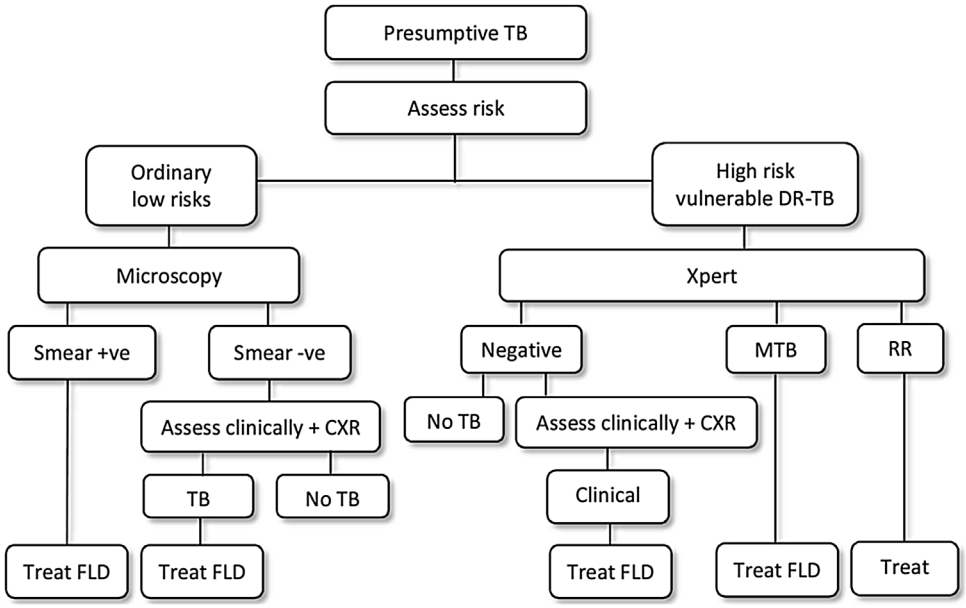

Figure 1. Algorithm used by Pakistan NTP for assessing a patient with presumptive tuberculosis in routine (PCF) program (2013–15).
TB = tuberculosis, sm+ve = Smear positive, sm-ve = Smear negative, FLD = First Line Drug, CXR = Chest X-ray, MTB = Mycobacterium tuberculosis, RR = Rifampicin resistant, SLD = Second line drug.

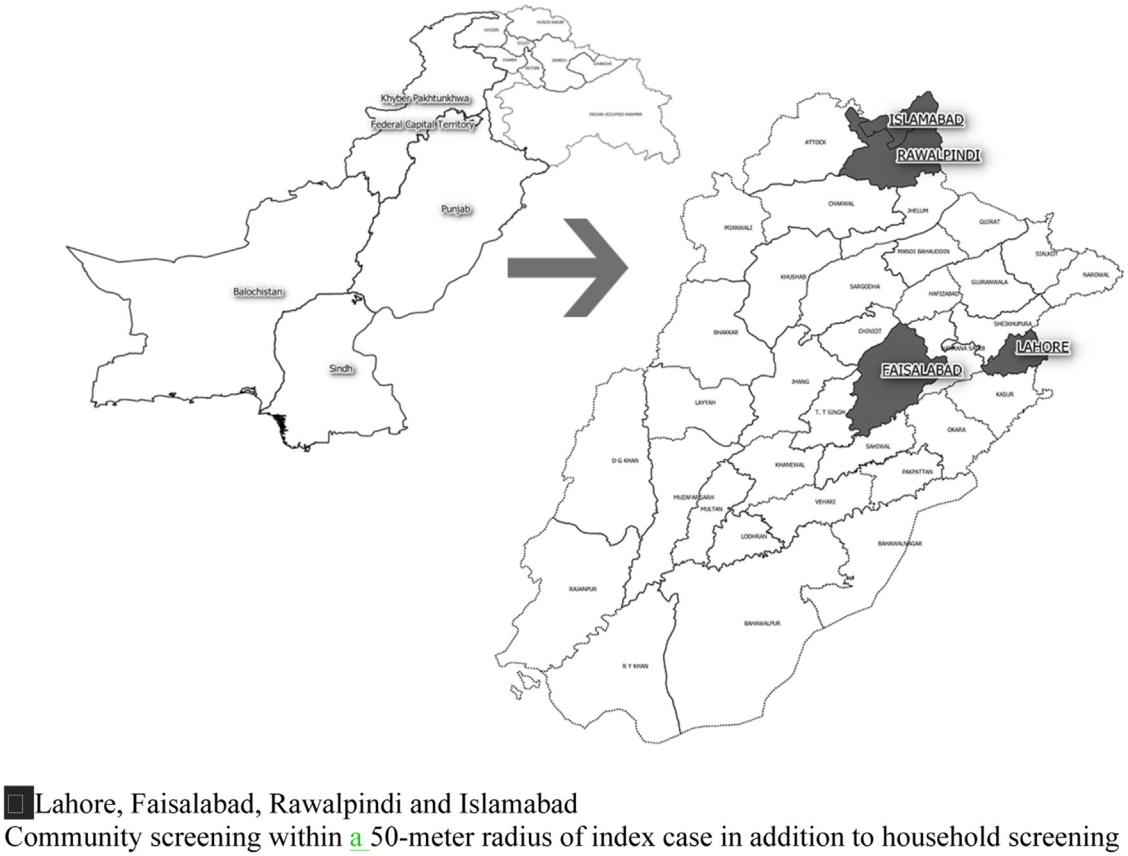

Figure 2. Map of Pakistan showing the 4 selected districts for extended contact screening for tuberculosis (2013–15).

diagnosis and management. People whose sputum tested negative on both microscopy and X-pert MTB/RIF were referred to the nearest BMU for follow-up according to national guidelines. Patients identified by ECS were marked "TB REACH" in the TB register.

Study population

We included all people with pulmonary TB (PTB) registered and treated at public or private facility engaged with the NTP in Lahore, Rawalpindi, Faisalabad, and Islamabad between July 2013 and June

2015. They were classified based on case detection strategy, i.e., detected by PCF or by ECS. The cases identified through ECS were marked as "TB REACH" in the TB registers at facility level and their registration for treatment was assured by the field health officers. All patients were considered as PCF unless referred by TB REACH Wave III project field health workers (through household and community-based contact screening). This was confirmed by reviewing the project records. Patients with known rifampicin resistance and treated with second-line drugs were not included.

Data variables and sources

Case-based data was entered from facility-based TB registers into MS Excel. For quality assurance, our database was compared with aggregated data in the routine quarterly reports, and disparities were manually re-checked with the original TB registers.

Patient characteristics included case detection strategy, age, gender, district, TB category, bacteriological confirmation and diabetes mellitus status. Treatment outcomes were classified as favorable (treatment completed and cured) and unfavorable outcomes (treatment failure, lost to follow up, died or not evaluated) (Table 1).

Analysis and statistics

Data were entered into Microsoft Excel (Microsoft, Redmond, WA, USA) and analyzed using STATA (version 12.1, copyright 1985–2011 Stata Corp LP USA).

Comparison of demographic and clinical characteristics of patients detected using ECS and PCF was done using χ^2 test. The case finding strategy (ECS or PCF) was our exposure of interest and the treatment outcome (unfavorable or favorable) was our outcome of interest. We used log binomial regression models to assess the association between ECS and unfavorable outcome after adjusting for potential confounders, giving crude and adjusted relative risk (95% CIs).

Results

We included 79 431 persons with PTB of whom 4604 (5.8%) were detected by ECS; of these a total of 4052 (88%) were bacteriologically confirmed, with a similar proportion in both household (3058/3477 = 87.9%) and community contacts (994/1127 = 88.2%). Out of 4052 bacteriologically confirmed patients, 3573 (88.2%) were positive on smear microscopy only, 172 (4.2%) on Xpert only (of these 160 were microscopy negative and 12 had no microscopy result) and 307 (7.6%) were positive on both. We do not have similar information for the PCF group.

The baseline characteristics of the PTB patients detected by ECS by routine PCF are shown in Table 2. The mean age was 36 years and standard deviation 18 years for both groups. There were more males (56.2%) in the ECS group than in the PCF group (49.6%, $P < 0.001$). In the ECS group, bacteriological confirmation was higher (88.0%) than in PCF group (36.5%, $P < 0.001$) and the history of previous TB treatment was lower (0.5%) compared to the PCF group (6.4%, $P < 0.001$).

We have depicted the treatment outcomes for all patients, bacteriological confirmed PTB patients, and clinically diagnosed PTB patients, and stratified by case finding strategy in Table 3. On crude analysis, the proportion with unfavorable outcomes was lower in the ECS group when compared to PCF in all three groups, but was significantly lower among bacteriologically confirmed PTB in the ECS group (9.9%) compared to PCF (11.6%; ($P < 0.05$). Among all PTB patients, there was a higher contribution of cure to treatment success in the ECS group (48.1%) when compared to PCF (18%). The ECS patients identified by Xpert (160) had outcomes similar to those in Table 3: cured 86 (54%), completed 59 (37%), died 1 (1%), lost to follow-up 7 (4%), not evaluated 7 (4%).

Among the bacteriologically confirmed patients in the ECS group those detected in the index household had similar unfavorable outcomes (85 of 994; 9%) to those detected in the community (316 of 3058; 10%) ($P = 0.06$, data not in the tables). In clinically diagnosed cases, the difference in proportions was also not significant (7.2% household vs 8.9% community).

Less than 5% of patients were enrolled at private hospitals in both groups, the same protocol was followed for these patients, and no difference was observed.

Table 4 shows the association between the case finding strategy and unfavorable outcomes after adjusting for potential confounders. ECS was associated with lower unfavorable outcomes for all PTB patients and this was statistically significant. A similar association was observed in the bacteriologically confirmed PTB patient group with a lower risk of unfavorable outcomes (adjusted relative risk 0.91; 95% CI 0.82–1.00) compared to routine case finding; this association was not statistically significant in the clinically diagnosed PTB cohort.

Discussion

In this large study from 4 districts of Pakistan, we found that the treatment outcomes among PTB patients detected by ECS were similar to those detected by PCF. While the ECS group was associated with a marginally lower risk of unfavorable outcomes among bacteriologically confirmed PTB patients, this was not the case among clinically diagnosed patients.

This study had several strengths. It was the first study in Pakistan to evaluate the treatment outcomes of PTB patients

Table 1
Operational definitions of TB treatment outcomes used in Pakistan's national TB program (2013-15).

Outcome	Definition
End of treatment	
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more.
Died	A TB patient who dies for any reason before starting or during the course of treatment.
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes patients "transferred out" to another treatment unit as well as patients for whom the treatment outcome is unknown to the reporting unit.
Favorable outcome	The sum of cured and treatment completed
Unfavorable outcome	All outcomes other than cured and treatment completed

TB – tuberculosis.

Table 2
Characteristics of patients with pulmonary tuberculosis in 4 districts of Pakistan detected by passive case finding and by extended contact screening[a], 2013-15.

	Extended contact screening		Passive case finding		p value*
	n	(%)	n	(%)	
Total	4604	(100)	74,827	(100)	
Demographic characteristics					
Age in years					0.971
<15	391	(8.4)	6508	(8.7)	
15–44	2613	(56.8)	42,384	(56.6)	
45–64	1192	(25.9)	19,293	(25.8)	
≥65	408	(8.9)	6642	(8.9)	
Sex					
Male	2587	(56.2)	37,144	(49.6)	<0.001
Female	2017	(43.8)	37,683	(50.4)	
District					
Lahore	1994	(43.3)	33,375	(44.6)	<0.001
Faisalabad	1619	(35.2)	19,611	(26.2)	
Rawalpindi	899	(19.5)	19,551	(26.1)	
Islamabad	92	(2.0)	2290	(3.1)	
Clinical characteristics					
Classification by laboratory					
Bacteriologically confirmed	4052	(88.0)	27,299	(36.5)	<0.001
Clinically diagnosed	552	(12.0)	47,528	(63.5)	
Type of patient					
New patient	4579	(99.5)	70,090	(93.6)	<0.001
Previously treated	25	(0.5)	4737	(6.4)	
Diabetes Mellitus status					
Yes	192	(4.2)	3176	(4.2)	0.419
No	4412	(95.8)	71,651	(95.8)	

* Chi square test.
[a] Community screening within a 50-m radius of index case in addition to household screening.

Table 3
Comparison of treatment outcomes of people with pulmonary tuberculosis in 4 districts of Pakistan detected by passive case finding vs extended contact screening[a], 2013–15.

Treatment outcomes	Extended contact screening		Passive case finding		P value* for unfavorable outcome
	n	(%)	n	(%)	
All TB [N = 79,431]	4604		74,827		
Favorable (F)	4163	(90.4)	67,421	(90.1)	
Unfavorable (U)	441	(9.6)	7406	(9.9)	0.480
Cured (F)	2217	(48.1)	13,496	(18.0)	
Treatment completed (F)	1946	(42.3)	53,925	(72.1)	
Treatment failed (U)	39	(0.9)	485	(0.6)	
Died (U)	93	(2.0)	1183	(1.6)	
Lost to follow up (U)	203	(4.4)	4185	(5.6)	
Not evaluated (U)	106	(2.3)	1553	(2.1)	
Bacteriologically confirmed [N = 31,351]	4052	(100)	27,299	(100)	
Favorable (F)	3651	(90.1)	24,126	(88.4)	
Unfavorable (U)	401	(9.9)	3173	(11.6)	0.001
Cured (F)	2217	(54.7)	13,496	(49.5)	
Treatment completed (F)	1434	(35.4)	10,630	(38.9)	
Treatment failed (U)	39	(0.9)	298	(1.1)	
Died (U)	91	(2.3)	679	(2.5)	
Lost to follow up (U)	171	(4.2)	1344	(4.9)	
Not evaluated (U)	100	(2.5)	852	(3.1)	
Clinically diagnosed [N = 48,080]	552	(100)	47,528	(100)	
Favorable (F)	512	(92.8)	43,295	(91.1)	
Unfavorable (U)	40	(7.2)	4,233	(8.9)	0.173
Treatment completed (F)	512	(92.7)	43,295	(91.0)	
Treatment failed (U)	0	(0)	187	(0.4)	
Died (U)	2	(0.4)	504	(1.0)	
Lost to follow up (U)	32	(5.8)	2841	(5.9)	
Not evaluated (U)	6	(1.1)	701	(1.4)	

* Chi square test.
[a] Community screening within 50-m radius of index case in addition to household screening.

Table 4
Effect of extended contact screening[c] on unfavorable treatment outcomes when compared to passive case finding among people with pulmonary TB in 4 select districts, Pakistan 2013-15.

Pulmonary TB	Case finding strategy	Total	Unfavorable outcome		RR	(95% CI)	aRR[a]	(95% CI)
		N	n	(%)				
All TB								
	Extended contact screening	4604	441	(9.6)	0.97	(0.88, 1.06)	0.90	(0.82, 0.99)[b]
	Passive case finding	74,827	7406	(9.9)	Ref			
Bacteriologically confirmed								
	Extended contact screening	4052	401	(9.9)	0.85	(0.77, 0.94)	0.91	(0.82, 1.00)[b]
	Passive case finding	27,299	3173	(11.6)	Ref			
Clinically confirmed								
	Extended contact screening	552	40	(7.3)	0.81	(0.60, 1.10)	0.79	(0.59, 1.07)
	Passive case finding	47,528	4233	(8.9)	Ref			

TB – Tuberculosis.
[a] Log binomial regression, adjusted for potential confounders (age, sex, district, previous treatment and classification by laboratory), age and gender were adjusted as they are universal confounders. Diabetes status was not associated with outcome of interest but associated with the exposure of interest (case finding and therefore not a potential confounder.
[b] $P < 0.05$.
[c] Community screening within a 50-m radius of index case in addition to household screening.

detected by the ECS strategy and compare with routine PCF. We had a large sample size of PTB patients enrolled for treatment in 4 highly populated urban districts with slums. This was the first time that Xpert MTB/RIF assay was used to improve bacteriological confirmation among smear negative contacts in Pakistan. Also, data related to case notification of both ECS and PCF were obtained from routine data recorded at NTP sites; findings therefore reflected conditions on the ground.

The study had a number of limitations. Some patients detected by ECS may have been wrongly categorized as PCF in TB registers at the health facility, but not vice versa. We see no reason why these few wrongly categorized patients should have different outcomes, and hence bias our results. By slightly reducing the sample size of the smallest group it might marginally reduce the statistical power. We believe that there were other predictors of TB treatment outcomes in our setting which could not be assessed, as these were not routinely captured by the NTP in the study period; examples could be severity of disease, socioeconomic status, nutritional status, and smoking. Therefore, residual confounding cannot be ruled out. The TB recording and reporting system had no data related to patient HIV status. According to 2016 Integrated Biological Behavioral Surveillance Survey (IBBS) HIV prevalence in Pakistan is low (0.12%) and limited to special risk groups, such as intravenous drug users and sex workers. Our study included only those TB patients who were started on treatment–thus the impact of pre-treatment loss to follow-up on overall outcomes could not be assessed. It is possible that the ECS and PCF groups might have experienced different rates of pre-treatment losses and this might have influenced the treatment outcomes. This is a limitation and we are unable to quantify its impact on overall results. Another limitation might be related to the differences in the way Xpert was used in the 2 groups. While about 12% of patients in the ECS group received an Xpert test (and thus the rifampicin resistance was excluded), we do not know what proportion of the patients in PCF group had received Xpert and had rifampicin resistance excluded prior to first-line treatment. This might have introduced a bias making the 2 groups different and might have impacted outcomes.

Our study suggests that the treatment outcomes among PTB patients in the ECS group are not inferior to that of the PCF group. The marginally better outcomes in bacteriologically confirmed patients may be due to better follow-up in the ECS group (reflected by the lower rates of patients not evaluated for outcomes) and possibly better exclusion of rifampicin resistance before starting treatment. Overall, we feel that the differences are marginal and though statistically significant (driven by large sample size), they are not programmatically significant.

There may be some sort of Hawthorne effect, where participants in our ECS group got (perhaps marginally) more attention from the health system facilitating better follow up compared with routine TB control. Our study results are similar to recent studies in India and Myanmar, which showed no difference in treatment outcomes; in India the proportion of unfavorable outcomes was 10.2% in the ACF and 12.5% in the PCF group ($P = 0.468$), in Myanmar the proportions were respectively 12.4% and 14.6% with no significant differences found between ACF and PCF (Khaing et al., 2018; Shewade et al., 2019). A systematic review in 2013 also found no difference in the treatment outcomes for both groups (Lönnroth et al., 2013). In contrast, another study from India found worse treatment outcomes in ACF than PCF (33% vs 14%) (Singh et al., 2020). These studies had smaller sample size and did not use Xpert MTB/RIF among smear negative contacts, as we did in our study.

Conclusion and recommendations

In conclusion, we found that treatment outcomes among PTB patients detected by ECS were not inferior to those for patients detected by PCF. Statistically, the ECS group had marginally better outcomes among bacteriologically confirmed patients; but this was driven by large sample size and we do not think these differences are programmatically significant. These findings should encourage stakeholders in Pakistan to support case finding projects among household contacts and community contacts to find and treat missed TB cases, to complement the indispensable routine PCF.

Funding

TB REACH secretariat of Stop TB Partnership funded the main project. No specific funding was obtained from any organization for this study. Publication fee in an international journal is covered by the University of Bergen.

Conflict of interest

None declared.

Ethics

Ethics approval was obtained from the Ethics Advisory Group of International Union Against Tuberculosis and Lung Disease, Paris, France (EAG number-58/16) and the Regional Ethics Committee in

Norway (REK-Vest 2018/57). Administrative approvals were obtained from the National and Provincial TB Program, Pakistan. As this research involved analysis of secondary data, the need for written informed consent was waived by the ethics committees.

Acknowledgements

We are thankful to the field health workers for their efforts and to the University of Bergen, Norway for providing a good academic background, the TB REACH secretariat of Stop TB Partnership for funding the main project and the Provincial TB Control Programs Pakistan. We highly acknowledge the corporation and facilitation of National TB Control Program, Provincial TB Program Managers, District TB Coordinators, Provincial Program Officers and DOTs facilitators of Punjab and Islamabad.

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