Extending contact screening to 50 metre around tuberculosis patients in urban Pakistan

Follow-up of a large Active Case-finding Project

Mahboob Ul Haq

Thesis for the degree of Philosophiae Doctor (PhD)
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List of Abbreviations

AFB	Acid Fast Bacilli
MTB	Mycobacterium Tuberculosis
TB	Tuberculosis
EPTB	Extra Pulmonary Tuberculosis
PTP	Pulmonary Tuberculosis
MDR-TB	Multi-drug Resistant Tuberculosis
ACF	Active Case Finding
ECS	Extended Contact Screening
PCF	Passive Case Finding
DOTS	Directly Observed Treatment Short-course
NTP	National TB Control Program
WHO	World Health Organization
UN	United Nation
UHC	Universal Health Coverage
WHA	World Health Assembly
HIV	Human Immunodeficiency Virus
SDG	Sustainable Development Goal
NNS	Number Needed to Screen

Scientific environment

This thesis is a result of collaboration between the Centre for International Health (CIH) at the University of Bergen (UiB), Norway and National TB Control Program (NTP), Pakistan. The thesis is based on the studies on Tuberculosis conducted at the NTP Pakistan.

The National TB Control Program and the TB REACH project (funded by the Stop TB Partnership) signed a Grant agreement in February 2013 for the study entitled *"Effectiveness of widening circle of contact screening from within the household to 100 m around the house of index TB case on case finding through outreach using GIS"*. The project was implemented in four districts: Lahore, Rawalpindi, Faisalabad and Islamabad.

The grant funded the larger project, has nested sub-studies included in this thesis. The first study was written through the Structured Operational Research and Training Initiative (SORT IT), a global partnership between Medicine Sans Frontiers, the Union, and the Special Programme for Research and Training in Tropical Diseases at the World Health Organization (WHO/TDR). The 2nd and 3rd research studies were done at the NTP Islamabad, Pakistan, with technical support from NTP and CIH.

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Introduction

This thesis is based on a large project in TB REACH WAVE III that was funded by the secretariat of the Stop TB Partnership in 2013; with the title *“Effectiveness of widening circle of contact screening from within the household to 100 m around the house of index case on case finding through outreach using GIS”*. The project introduced active contact investigation of tuberculosis patients in three large cities of Punjab province including Lahore, Faisalabad, Rawalpindi and Islamabad, the capital territory of Pakistan. Household contacts usually resident or sharing the same territory, were initially screened by asking orally for symptoms of TB, which was followed by similar screening of close community contacts. Additional yield was obtained in the project among smear negatives and chest X-ray suggestive by Gene-Xpert testing.

This thesis includes three research papers, which have been published in international peer reviewed journals.

Abstract in English

Missing tuberculosis (TB) cases is a major public health issue in Pakistan. In 2020, around 52% of incident TB cases were not notified to the national tuberculosis programme, Pakistan (NTP). These missing cases are the means of transmitting TB and sustain the global TB epidemic. To detect TB patients, NTP, Pakistan implemented several strategies, and one among them was through extended contact screening (ECS). In the ECS, contact investigation was conducted among household and close community in four selected districts with a high concentration of slums; Lahore, Rawalpindi, Faisalabad and Islamabad from July 2013 to June 2015. All the people were screened for tuberculosis who were residing within a radius of 50 metres (using Geographical Information System) from the household of a smear positive TB patient. All the diagnosed TB patients were linked to TB treatment and care.

In **Paper I,** our objective was to evaluate the impact of household and close community contact screening on tuberculosis case detection in Pakistan.

This was a before and after intervention study, based on retrospective record review. Routine passive case finding (PCF) and household contact investigation was conducted in the pre-intervention period (July 2011 to June 2013), and it was compared with the intervention period (July 2013 to June 2015) using ECS as addition.

A total number of 783,043 contacts were screened for tuberculosis, among them 23,741(3.0%) presumptive TB cases were identified, 4710 (19.8%) were all forms, and 4084 (17.2%) bacteriologically confirmed patients with TB were detected. Xpert MTB/RIF contributed 7.6% to bacteriologically confirmed TB patients. Among investigated, the overall yield of all forms of TB patients was 22.3% in household contacts, 19.1% in close community contacts and 5.1% was among presumptive child TB cases investigated. There was around 8% increase in case detection of all forms and 7% in bacteriologically confirmed patients with TB due to intervention.

We concluded that household and close community contact investigation not only increased TB case notification but also identified additional TB patients. However, more long-term assessments and cost effectiveness studies are needed before the national scale-up.

In **Paper II,** our objective was to compare the characteristics of patients with pulmonary tuberculosis who were detected through extended contact screening with those detected by routine passive case finding in Pakistan during 2013-15.

A cross-sectional study was conducted based on the data that was collected from ECS and from the routine program (PCF) data from Lahore, Faisalabad, Rawalpindi and Islamabad in 2015.

We included 12,114 patients with pulmonary TB in the study where 4,604 (38%) were identified through ECS. The male patients comprised 56.2% (95% confidence interval [CI] 54.8–57.6) were detetected through ECS who were more than 49.7% (95% CI 48.6–50.8) that were identified through PCF. The proportion of bacteriologically confirmed TB patients was 88.0% (95% CI 87.1–88.9) in the ECS group and 50.3% (95% CI 49.2–51.4) in the PCF group. We found through regression analysis, that in comparison with patients who aged 15–44 years, children aged <15 years had higher chances of being detected through ECS (adjusted odds ratio 2.69; 95% CI 2.21–3.28). There was a higher chance of TB cases being detected by ECS in Faisalabad (adjusted odds ratio 2.57; 95% CI 2.01–3.29) in comparison with the cases identified in Islamabad.

We concluded that ECS identified a higher proportion of male and child patients with pulmonary TB than routine case finding; both of these groups are more often missed through routine TB control.

The objective of **Paper III** was to compare the treatment outcomes of pulmonary TB patients detected by extended contact screening with those patients detected by routine passive case finding in Pakistan during 2013-15.

This was a cohort study conducted in Lahore, Faisalabad, Rawalpindi and Islamabad based on secondary program data in 2013–15. A log binomial regression model was used to assess if ECS was associated with unfavourable treatment outcomes (death, loss-to-follow-up, failure, not evaluated) after adjusting for potential confounders.

Of the total 79,431 PTB patients, 4,604 (5.8%) were detected through ECS with 4,052 (88%) bacteriologically confirmation. There was no significant difference between the proportions with unfavourable outcomes in ECS group (9.6%) and the PCF (9.9%) in all PTB patients. However, unfavourable outcomes were significantly lower in ECS (9.9%) than PCF group (11.6%, P = 0.001) among the bacteriologically confirmed patients. ECS was associated with a lower risk of unfavourable outcomes (adjusted relative risk (aRR) 0.90; 95% CI 0.82–0.99) compared to PCF both among all patients with PTB and among bacteriologically confirmed PTB patients (aRR 0.91; 95% CI 0.82–1.00).

In conclusion, PTB patients detected by ECS had treatment outcomes that were not inferior to those detected by PCF.

Abstract in Norwegian

Tuberkulose pasienter som ikke er diagnostisert er et stort helseproblem i samfunnet i Pakistan. I 2020 var det 52% av det antatte totale nye tilfeller som ikke var registrert i det nasjonale TB programmet (NTP) i Pakistan, selv om det er meldeplikt for sykdommen. Disse pasientene som ikke er diagnostisert er smitteførende og vedlikeholder epidemien. For å finne flere pasienter som har tuberkulose har NTP i Pakistan hatt flere strategier, og en av dem var å systematisk undersøke flere kontakter i nærheten av disse pasientene. Dette ble gjort både i husene der disse pasientene bodde og i nabolaget; prosjektet ble gjort fra 2013 til 2015 i fire distrikter med mye slum: Lahore, Rawalpindi, Faisalabad og Islamabad. De som var naboer og bodde innenfor en radius av 50 meter rundt pasienter som hadde oppspytt-prøver med *m.tuberculosis* ble identifisert og sporet opp ved hjelp av GIS Geographical Information System. Alle nye identifiserte pasienter ble henvist til behandling.

I **Paper-I** var målet å evaluere effekten av denne strategien i Pakistan. Studien var en før-og-etter intervensjon, basert på pasient register og dokumenter. Før intervensjonen (Juli 2011-juni 2013) var det vanlig diagnostikk med rutinemessig nærkontakt undersøkelser i pasientens hus. Dette ble sammenlignet med intervensjonsperioden (Juli 2013-juni 2015) der personer i nærmiljøet innenfor 50 meter fra pasientene ble undersøkt. Det ble kontaktet 783043 nærkontakter og av dem hadde 23741 symptomer som passet med tuberkulose; av disse ble i alt 4710 (19.8%) diagnostisert med tuberkulose og 4084 (17.2%) hadde prøver som viste *m.tuberculosis.* Av disse pasientene med påvist bakterier ble 7.6% påvist med Xpert MTB/RIF prøve. Av alle som ble undersøkt var 22.3% i huset til pasienten, 19.1% var i nærmiljøet; 5.1% var blant barn. I løpet av intervensjonen økte antall diagnostiserte med 8% blant alle som ble nærmere undersøkt, og økte med 7% blant de som var bakteriologisk positive. Vi konkluderte med at nærkontakt undersøkelse omkring hus med kjente TB pasienter økte både antallet diagnostiserte pasienter og antallet som ble registrert av

tuberkuloseprogrammet. For oppskalering på nasjonalt nivå og evaluering over lengre tid trengs kost-nytte studier.

I **Paper-II** var målet vårt å sammenligne karakteristika på pasienter med lungetuberkulose som ble diagnostisert ved «utvidet» (50m) nærkontakt undersøkelser i 2013-15 med pasientene som ble diagnostisert i rutineprogrammet i 2011-13 i Pakistan. En tverrsnittsstudie ble utført basert på data fra denne intervensjonen og det nasjonale TB programmet med data fra Lahore, Faisalabad, Rawalpindi and Islamabad. I studien registrerte vi 12114 pasienter med lungetuberkulose, av dem ble 4604 (38%) diagnostisert i prosjektet med undersøkelse av nærkontakter og naboer. Blant de som ble diagnostisert i prosjektet var 56.2% (95% konfidens intervall [CI] 54.8–57.6) menn, mens blant de som ble funnet av rutine var 49.7% (95% CI 48.6–50.8) menn. Blant de som ble diagnostisert i prosjektet var 88.0% (95% CI 87.1–88.9) diagnostisert bakteriologisk, mens i rutine programmet var 50.3% (95% CI 49.2–51.4) bakteriologisk. I justerte regresjonsanalyser fant vi høyere sjanse for å bli diagnostisert med tuberkulose blant barn (0-14 år) enn hos unge voskne (15-44 år), og høyere sjanse i Faisalabad enn i Islamabad. Vi konkluderte med at prosjektet identifiserte en høyere andel menn og barn enn rutine programmet, og disse gruppene blir oftere miskjent i det nasjonale programmet.

I **Paper-III** var målet å sammenligne behandlingsutfall mellom de som ble diagnostisert av prosjektet med de i rutineprogrammet i Pakistan i 2013-15. Dette var en oppfølginsstudie i Lahore, Faisalabad, Rawalpindi og Islamabad basert på data fra det nasjonale TB programmet. Vi brukte en log binomial regresjonsmodell for å undersøke om pasientene i prosjektet hadde dårligere behandlingsresultat enn rutine (dårlig behandlingsresultat var et av de følgende: død, tapt for oppfølging, mislykket, ikke evaluert).

Av de 79431 lungetuberkulose pasientene som ble diagnostisert var 4604 (5.8%) oppdaget i prosjektet med kontakt og nabo undersøkelser, og 4052 (88%) hadde *m.tuberculosis* i prøven. Det var ingen forskjell i andelen med dårlig resultat i prosjektet (9.6%) og i rutine (9.9%) bland alle pasientene. Imidlertid, blant de som hadde påvist *m.tuberculosis* i prøvene var det lavere andel dårlig resultat blant de i prosjektet (9.9%) sammenlignet med rutine (11.6%, p=0.001). I justerte regresjonsanalyser fant vi noe lavere risiko for dårlig behandlingsresultat i prosjektet enn i rutineprogrammet både når vi analyserte alle (aRR 0.90; 95% CI 0.82–0.99), og med subanalyser av pasienter med påvist *m.tuberculosis (aRR 0.91; 95%CI 0.82-1.00)*.

Vi konkluderte med at pasienter med lungetuberkulose som ble diagnostisert i prosjektet med undersøkelse av kontakter og naboer ikke hadde dårligere behandlingsresultat.

List of Publications

I. Fatima R, Qadeer E, Yaqoob A, **Ul Haq M**, Majumdar SS, Shewade HD, et al. Extending "contact tracing" into the community within a 50-metre radius of an index tuberculosis patient using Xpert MTB/RIF in urban, Pakistan: Did it increase case detection? PLoS One 2016;11. https://doi.org/10.1371/journal.pone.0165813.

II. **Haq MU**, Hinderaker SG, Fatima R, Qadeer E, Habib H, Hussain K, et al. Are patients with pulmonary tuberculosis identified by active and by passive case detection different? A cross-sectional study in Pakistan. Int J Infect Dis 2022;121:39–46. https://doi.org/https://doi.org/10.1016/j.ijid.2022.04.055.

III. **Haq MU**, Hinderaker SG, Fatima R, Shewade HD, Heldal E, Latif A, et al. 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? Int J Infect Dis 2021;104:634–40. https://doi.org/https://doi.org/10.1016/j.ijid.2021.01.054.

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1. Background

1.1 Tuberculosis (TB)

Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis (MTB). MTB is estimated to have originated 150 million years ago. The infectious nature of TB was demonstrated by Jean-Antoine Villemin in 1865 when he inoculated a rabbit with some purulent material extracted from the lungs of a patient who died of TB (1). Robert Koch, in 1882 applied a new staining method to the sputum of a patient and named this causative agent as Mycobacterium tuberculosis complex (2).

Bacteriology

MTB is a non-motile rod shaped bacterium. Many non-pathogenic mycobacteria are present in the environment of humans. The rods are 2-4 micrometres in length and 0.2-0.5 um in width. MTB is an obligate aerobe that is often found in the well-aerated upper lobes of the lungs. MTB has a relatively slow generation time, 15-20 hours, and has a physiological characteristic that influences the host response. The bacteria contain peptidoglycan (murein) in their cell walls which is rich in lipids such as mycolic acid. It can withstand weak disinfectants and can survive in a dry state for weeks. The cell wall is likely to be responsible for resistance to desiccation and a key virulence factor. Mycobacterium species are classified as acid-fast bacteria because after staining they cannot be decolorized by acids (3).

Mode of transmission

TB spreads among people through the air when a person with pulmonary TB cough, sneeze or spit, they expel tiny droplets with MTB into the air. A person inhaling this air is exposed and can become infected if the bacteria settle in the alveoli. The disease mostly affects the lungs (pulmonary TB) but it can also affect almost any other site (Extra-Pulmonary).

The stages of TB are:

1. **Exposure.** The exposure happens when a person gets in contact with, or exposes to, another person who suffers from TB. In practical terms, this means staying in the same room with an active TB patient. According to "*Epidemiologic Basis of Tuberculosis Control by Hans L. Rieder, 1999*" significant exposure depends on the presence of incident cases, but important modifiers determine the magnitude of exposure. These include, in particular, the duration of infectiousness and the number of contacts with a case per unit of time. These modifiers may vary greatly across populations, population density, time, climatic conditions and other factors.
2. **Infection.** This happens when a person inhales MTB that settles in the alveoli. The infection may lead directly to disease. Usually the immune system takes care of the TB organisms entered in the body and kills the bacteria. Therefore, some may go into latency and survive in this state inside immune cells. In such cases, the person would have a positive tuberculin skin test or IGRA test. TB is not easily transmitted like any other airborne communicable diseases. The probability to get infected with MTB depends on the number of infectious droplets nuclei per volume of air (infectious particle density) and the duration of exposure of a susceptible individual to that density. Patients, with sputum smear positive for acid-fast bacilli through direct sputum smear microscopy, are the major source of infection in the community.
3. **TB disease.** When the infection is followed by active multiplication of the bacteria and leads to pathology, the person gets signs and symptoms of tuberculosis disease.

1.2 Classification of TB

Classification of TB based on anatomical site of disease

TB is classified according to its level of contagiosity: (a) pulmonary tuberculosis which accounts 80% of all cases of tuberculosis. It is the infectious form of the disease; and (b) extra-pulmonary tuberculosis which is less common, non-infectious, that may affect any part of the body besides the lungs, such as lymph nodes, skin, meninges, spine, pericardium, pleura, joints, genitourinary tract, and abdomen. A patient, with both the pulmonary and extra-pulmonary, should be classified as a case of PTB because of its infectious nature (4).

(a) **Pulmonary tuberculosis (PTB)** "refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs".

(b) **Extra-pulmonary tuberculosis (EPTB)** "refers to any TB case involving organs other than the lungs.
Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra-pulmonary TB".

PTB is further classified as either bacteriologically confirmed or clinically diagnosed TB case.

A **bacteriologically confirmed TB case** may have a biological sample positive by smear microscopy by culture or by a WHO-recommended rapid diagnostic test like Xpert MTB/RIF. All such cases should be notified, regardless of whether or not TB treatment has been initiated.
A **clinically diagnosed TB case** is one who does not meet the criteria for bacteriological confirmation. but has been diagnosed with active TB by a physician or another medical practitioner who has decided to give the patient a full course of TB treatment. The definition for clinical diagnosis includes TB cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extra-pulmonary cases without being confirmed by laboratory.

Classification based on history of previous TB treatment

TB is also further classified on the basis of history of previous TB treatment. Classification based on previous TB treatment history is slightly different from that previously published (2009). They focus only on previous treatment history and are independent of bacteriological confirmation or site of disease. These definitions were revised in 2013, further updated in 2014 and in 2020 by the WHO. During our project, we followed the guidelines applicable for that time period.

New patients have never got any treatment for TB or taken anti-TB drugs for less than one month. **Previously treated patients** have received treatment for one month or more of anti-TB drugs in the past. Previously treated patients are further classified by the outcome of their most recent course of treatment;

Relapse patients: These patients, who were previously treated for TB, were declared cured or treatment completed at the end of their most recent course, and they are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).

Treatment after failure patients are those who have previously been treated for TB but the treatment failed at the end of their most recent course of treatment.

Treatment after loss to follow-up patients; such patients have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment. (These were previously known as treatment after default patients.)

Other previously treated patients are those who have previously been treated for TB but the outcome after their most recent course of treatment is unknown or not documented.

Patients with unknown previous TB treatment history do not fit into any of the categories listed above. The recent WHO TB management guidelines (2019) do not recommend a standard regimen for all retreatment patients but suggests testing for drug resistance, and if negative, they use the regimen for new cases.

1.3 Burden of TB

The global burden

Globally, an estimated 9.9 million people (95% UI (uncertainty interval): 8.9–11 million) fell ill with TB in 2020, which is equivalent to 127 cases (UI: 114–140) per 100 000 populations. Geographically, in the year 2020, more cases of TB were identified in the WHO regions of South-East Asia (43%), Africa (25%) and the Western Pacific (18%), with lesser shares in the Eastern Mediterranean (8.3%), the

Americas (3.0%) and Europe (2.3%). Globally, the thirty countries with the highest burden of TB account for 86% of all estimated incident cases of TB. Among these, eight countries that accounted for two thirds of the total global burden includes India (26%), China (8.5%), Indonesia (8.4%), Philippines (6.0%), Pakistan (5.8%), Nigeria (4.6%), Bangladesh (3.6%) and South Africa (3.3%) (5). Approximately, 4.3 million (41%) were not identified and registered during 2020 out of the estimated 9.9 million new TB cases. These 'missing' cases in 2020 were fewer than those went unreported in 2019. Globally, the corona pandemic, reversed years of the TB control progress. The global targets of TB are mostly reported off-track, though there are some success stories at the country or regional level. The noticeable impact of the pandemic was a huge drop in the number of people who were newly diagnosed with TB and were also reported. This drop was from 7.1 million in 2019 to 5.8 million in 2020, that is a decline of about 18%, taking the world back to the level that was observed during 2012. It is also far short of about 10 million people who developed TB in 2020 (5).

TB is equally infectious for everyone, regardless of the age or sex. About 90% people were adults who developed the disease in 2020 and notified. Among them, more men 56% contracted the disease; followed by 33%women; and 11% were children. The higher share of the TB cases is consistent among men with evidence from national TB prevalence surveys, which also shows that TB disease affects the women less than men. Hence, the gaps in case detection and reporting are also higher among men than women. Among all incident cases of TB, the people who were living with HIV were 8%. The proportion of cases of TB co-infected with HIV was highest in the countries of WHO African Region, exceeding 50% in parts of southern Africa (5).

MTB has infected approximately a quarter of the world's population., this is an estimated built on population-based testing of infection, like tuberculin skin test. TB can be cured and prevented. At least 85% of the people, who develop TB and who get treatment, could be successfully treated with a 6-month drug multi-drug regimen. However, the treatment regimens of 1–6 months could be used to treat the infection caused by TB. All those people, who suffer from disease, are ensured to get access to these treatments by the universal health coverage (UHC). The well-known risk factors for developing TB disease causing a number of deaths are poverty, under nutrition, HIV infection, smoking and diabetes. The burden of TB has been reduced to fewer than 10 cases and less than 1 death per 100 000 population per year by some of the countries. For a speedy decrease in the number of new cases of TB, research breakthroughs (e.g. a new vaccine) are required to eliminate them worldwide every year (5).

In the year 2020, there were approximately 1.3 million (95% UI: 1.2–1.4 million) deaths among HIV-negative people across the world. There was an increase in deaths from 1.2 million (UI: 1.1–1.3 million) in 2019, of these additional 214 000 (UI: 187 000–242 000) deaths in HIV infected people, moreover, a small increase was observed from 209 000 (UI: 178 000–243 000) in 2019. For the first time in a period of ten years, the number of deaths due has increased for having of poor access to TB diagnosis and to treatment services because of lockdown during COVID-19 pandemic (5).

The burden of TB in Pakistan

Pakistan ranks fifth amongst the 30 countries highly burdened with TB having an estimated incidence TB rate of 259 per 100,000 populations. In the year 2020, the cases of TB estimated 0.6 million of whom 272,990 (48%) were notified and about 300,000 (52%) 'Missing' cases which were either not notified or were not detected. The estimated TB incidence among children (<15 years) in 2020 was around 13% and men around 58%. During 2020 an estimated 46,000 people died of TB. Pakistan contributes around 65% out of the total burden of tuberculosis in the Eastern Mediterranean Region (5).

1.4 TB control globally

TB was declared as global health emergency by WHO in 1993 (6). In 1991, the efforts of controlling TB were revived when it was recognised as a major global public health problem by the World Health Assembly (WHA) resolution (7). Two targets were established for controlling TB such as detection of 70% of new smear-positive TB cases, and cure of 85% of such cases, by the year 2000.

In 1994, DOTS was launched as a control strategy which was recommended internationally (8). The strategy contained main components: government commitment, case detection with priority on bacteriological diagnosis, standardized short-course of chemotherapy to all sputum smear-positive cases directly observed to protect rifampicin, a mechanism of uninterrupted drug supply, and a monitoring system for programme supervision and evaluation. The TB-DOTS framework has been expanded subsequently (9) that was clarified further and implemented in 182 countries. The implementation of this framework has helped the NTPs in controlling TB.

Globally, more than 20 million TB patients had been treated in DOTS programmes by 2004 where more than 16 million had been declared cured. Deaths due to TB are declining and incidence is decreasing or stabilizing across the world except to some extent in sub-Saharan Africa and Eastern Europe. By 2005, globally, the treatment success rate among new smear-positive cases of TB had reached 83% against the target of 85%, and the case detection rate to 53% against the set target of 70%. The first Global Plan to Stop TB started the actions required to control TB over the period 2001 to 2005 (10) and help to steer global TB control efforts during the period.

The increased political commitment has boosted global TB control from the countries with high-burden and partners in the Amsterdam Declaration (in 2000), the Washington Commitment to Stop TB (2001), and the Stop TB Partners' Forum in Delhi (2004). The WHA passed a resolution in 2005, advocating the "sustainable financing for TB control and prevention", making a commitment to strengthen efforts to achieve the targets related to TB, was included in the MDGs with Member States (11). This resolution was based on the report of the Commission on Macroeconomics and Health (2001), the High-Level Forum on the Health Millennium Development Goals (MDGs) in 2004, and the Second Ad Hoc Committee on the Epidemic of TB (2005) (12).

The WHO and their partners have worked on the complementary policies and strategies to address the remaining main challenges to achieve the targets of global TB control since the development of the DOTS strategy. These include increasing access to TB diagnosis and treatment through community care, and public–private mix (PPM) approaches that are aimed at engaging all the care providers both in the public and the private in implementing DOTS. Innovative approaches have been developed to improve access to quality-assured affordable medicines in setting with limited resource. These innovative mechanisms are Global Drug Facility and the Green Light Committee. The collaborative activities and strategies for the management of multidrug-resistant TB (MDR-TB) have been developed and tested. These activities are required for implementation by the TB and HIV/AIDS control programmes. Impacts are being considered as a means of assessing progress towards MDGs. The results of new partnerships and educational research initiatives are beginning to emerge for the development of new tools. Furthermore, developing of many new diagnostics, drugs, and vaccines are in progress.

The formerly decreasing TB incidence gradually increased after 1986 account of emergence of HIV because of which WHO declared TB as a global health emergency in 1993. The recommended DOTS Strategy was adopted by the Member States for controlling TB in 1995. In 2003, the Expanded Framework for DOTS Strategy was launched; it incorporated response to TB/HIV co-infection and multi-drug resistant TB. This preceded launching of the Stop TB Strategy in 2006. In May 2014, the 67th WHA adopted a strategy for the prevention, care and control of TB beyond 2015 called the End TB Strategy. The purpose of this strategy is to eradicate the global epidemic (TB) till 2035. In the year 2015, the United Nations (UN) Sustainable Development Goals (SDGs) were adopted, which are completely in alignment with the WHO End TB Strategy. The SDGs have set the target of eradicating the TB epidemic till 2030.

To achieve the indicated goal and targets, the implementation of End TB Strategy will be helpful in supporting countries. The AU adopted a road map in November 2015, and it is followed by the Catalytic Framework to End TB, AIDS and Eliminate Malaria from Africa by 2030. The End TB Strategy provides a comprehensive, multi-sectoral response to address the issues and challenges, and end the epidemic in the context of the UN SDGs for 2030. This framework provides Member States with the necessary policy and technical guidance for the adaptation and implementation of the End TB Strategy from 2016 to 2020.

1.5 TB control in Pakistan

In 1995, WHO launched the Directly Observed Treatment Short-course (DOTS) strategy for cure and control of TB, but major progress in TB control was achieved only after the revival of the NTP in 2001 under the leadership of Dr Karam Shah (as NTP manager). When TB was declared as a national public health emergency through the "Islamabad Declaration". This gave NTP a mandate to design and regulate the activities of TB control in the country by exploiting the resources both the domestic and donors. Four million patients have been treated by the TB control Programme with quality assured drugs since its revival maintaining more than 90% of success rate of treatment. TB remains a major public health problem in Pakistan although there has been steady progress since 2001 to improve the detection of TB cases.

The TB programme has been decentralized to provincial and district levels. Moreover, it is integrated with services of Primary Health Care. It is also on its way to be integrated with the secondary and tertiary care services. In the light of the 18th Constitutional Amendment in 2011, addressing the health issues is one of the prime responsibilities of the provincial government which is in their jurisdiction. The TB control Programs at the Provincial levels are now responsible for organising and managing TB services in their respective provinces.

The headquarters of the NTP functions as a department of the Ministry of National Health Services Regulations and Coordination (MoNHSR&C). From the federal level, the NTP collaborates with several technical and implementing partners such as; the WHO, the International Organisation for Migration, the US Agency for International Development, the Pakistan Chest Society, the National Rural Support Programme, the Pakistan Paediatric Association, Indus Hospital Network, Mercy Corps, Green Star Social Marketing, the Aga Khan University, the Pakistan Anti TB Association (PATA), and other national NGOs.

NTP endeavours for TB free Pakistan by reducing 50% prevalence of TB in general population till 2025 in comparison to 2012 through universal access to quality TB care and achieving Zero deaths due to this disease.

The NTP in Pakistan has taken some key steps for TB control as listed below:

- **TB management information system**

Integrated District Health Information System (DHIS-2) for TB, HIV and Malaria has been developed and expanded to the district level; the majority of Gene Xpert machines are connected by the automated GxAlert system; the first prevalence survey of TB using current international standards (2010-11), and the first drug resistance survey (DRS) carried out by NTP in Pakistan.

- **TB care provision**

Various components of TB care programme includes: provision of anti-TB medicines free of cost at 5,000+ public sector health facilities, provision of free diagnostics through more than 1,400 public sector facilities, Twenty two biosafety laboratories for culture and DST (BSL2 & BSL3), established rapid testing (Xpert testing) at 450 centres which is recommended by WHO, thirty four special centres for DR TB patient management, offered social support to all DR TB patients, provided guidelines and training material for patient management, provided operational guidelines and training material to engage 5,000 private health care providers to manage TB, and awareness campaign through both the print and electronic media.

- **TB Legislation**

The PTPs have been assisted by NTP with developing and implementing Bills "Mandatory TB Case Notification". These Bills have been passed by the three Provincial Assemblies; the bylaws have been developed; the pilot intervention for legislation for the mandatory TB case notification has also been conducted. However, the Bill in Balochistan is still in process. The mandatory TB notification act states, "Within a week of examining the patient, a registered medical practitioner shall submit a complete Notification Form to the District Health Officer."

- **TB case finding**

Currently in Pakistan, the case finding strategy is based on routine passive case finding where individuals with TB symptoms visit health facility by themselves and are investigated for TB. Furthermore, due to a big challenge of undetected and unreported TB cases, NTP Pakistan implemented several ACF projects, including includes health care providers' specific activities to detect the missing cases of TB in the community and screening the household contact. Examples of intensified case finding are, using chest camps to find cases in slums, household, close community contact screening, and the current ACF in Afghan refugee villages.

- **Engagement of private healthcare providers and laboratories**

The private health care system in Pakistan is very large but uncontrolled. It lacks regulation in prescribing the practices as well as the required qualifications for prescribing these medications. Some large private hospitals are engaged in TB control; NTP/PTPs directly supervises the implementation of TB DOTS that provides drugs and training, and generates the quarterly reports.

- **Public-Private Mix (PPM)**

The main purpose of PPM is to establish linkages between the private and public sectors to improve access to TB care services and standardize the TB care. In 2017, PPM contributed 30% to overall TB case notification in Pakistan

In Pakistan, the private healthcare sector is large but not duly regulated with the services of qualified and non-qualified health care providers who provides general curative health services to around 75% of the population in Pakistan. Approximately 90% of patients with TB initially seek care in the private sector (13). It is presumed that a large number of TB patients seeks TB care from the private sector which is not engaged with National TB Control program. There are almost 10 000 private hospitals and diagnostic laboratories in Pakistan, which represent about 83% of all the facilities in the country (14). Despite a large contribution, the private health sector reports only about 5% TB cases to the NTP (15,16).

- **Research in TB:**

The capacity building workshops are organized by the NTP through which researchers are equipped with skills across the country. Moreover, about 50 TB papers have been published in national and international journals.

The key strategic area, core component that is identified in Pakistan's National strategic and operational (PC-1) plans, and the WHO END-TB strategy (pillar III) is the research. In 2009, a research unit was established at the National TB Program (NTP) that became fully functional to design and conduct locally relevant operational research.

The research unit has conducted the international Structured Operational Research and Training Initiative course (SORT IT) in Pakistan with the joint collaboration of WHO-TDR and Global Fund at national level since 2016. This initiative led to publish more than 50 research papers in international peer reviewed journals. Research unit has also completed several research projects and national level surveys on priority programme needs including disease burden studies for measuring the transmission of TB i.e. National TB Prevalence Survey, 2010-11 (17), and more similar researches. Many projects that are based on intensified case finding use innovative strategies; engaging private health care providers and conducting chest camps, examined effectiveness of widening the circle of contact screening in increasing TB case detection using GIS, and conducted a trial on MDR to assess effectiveness and feasibility of two months' hospitalization versus one-week hospitalization for MDR-TB in Pakistan.

The NTP research Unit encouraged successful collaboration between various international institutions, namely the University of Bergen, Norway from where the head of research unit completed her PhD in Public health and epidemiology while two more team members are in the process of completion that will further strengthen the department. The collaboration of NTP research unit with other institutes for research projects are London School of Hygiene and Tropical Medicine, University of YORK, University of LEEDs, University of Edinburgh, University of California, University of John Hopkins, and national institutions / health programs including National Institute of Health, Pakistan Health Research Council, Health Services Academy, Quaid-i-Azam University, Institute of Psychology, Islamia University Bahawalpur, University of Sargodha, and Arid Agriculture University.

1.6 Study Rationale

The traditional TB-control strategies of Passive Case Finding (PCF) relies on people with symptoms to seek care, which is insufficient to identify all TB patients. A modelling study reported that a country with a 70% case detection rate may reduce the incidence by only 1-2% per year, so TB programs must achieve more than 70% case-detection (18). Hence, countries are now moving to adopt Active Case Finding (ACF) strategies in addition to PCF to increase case detection and achieve the End TB targets. ACF activities can be conducted for specific groups called targeted screening, or it can be at a population level called mass screening; these activities can be conducted in a stepwise manner. Activities that raise awareness about TB symptoms through health information or education among a population and encourage them to present to health facilities when they developed symptoms of TB are called Enhanced Case Finding (ECF), while active onsite screening and evaluation at health facilities or in the community through an outreach program are called ACF.

Unreported and undetected TB represents a challenge for TB control. According to WHO, globally around 4.3 million (41%) and 300 000 TB cases in Pakistan were not identified and registered during 2020. Eighteen national prevalence surveys in the countries with high burden of TB have found that more than half of the patients with TB remain undetected (19). Patients with TB who are 'missed' may not seek health care, have no symptoms or cannot be recognized or they face some barriers to health care (20). These missing cases may transmit TB, remaining as the sources of transmission to sustain the global TB epidemic (21), and thus represent an obstacle for meeting the ambitious global targets of 90% reduction in the incidences of TB and its mortality by 2035 (20).

Findings from a systematic review (of 62 studies) showed that screening increased the number of TB patients with less severe disease in the short term at their earlier stages.(22). Many other ACF interventions among high risk groups such as close contacts, family members and people who are living in urban slums have shown promising results (23–27). However, there is insufficient evidence regarding the impact on TB transmission and its epidemiology (incidence, prevalence and mortality) is available since there are few studies found with long term follow-up in the presence of a control group (22).

The NTP Pakistan managed to achieve the coverage of TB services in public sector till 2005 with the DOTS strategy nationally. The majority of the cases are reported to be found in the public sector (16) where individuals with TB symptoms come to a public health facility and are further investigated for TB (PCF), which means the first initiative comes from the patients. Such patients are often referred by the private sector where diagnostic services may not exist. The people, who do not visit a health facility despite the TB symptoms, can be identified through ACF, where the health system tries to reach out to the community to identify and diagnose TB patients (28). ACF is useful particularly in high prevalence populations of undetected TB or in marginalized and vulnerable populations with limited access to health services (20).

Progress to achieve the national and global TB targets is required to detect the 'missed' cases. For this purpose, the current strategy of PCF will not suffice. There has been renewed interest and investment for systematic screening or intensified case finding strategies for TB (20). Therefore, complementing standard PCF has been strongly encouraged with ACF (19,29). A cluster-randomized controlled trial conducted in Vietnam during 2010-15, showed that household-contact investigation with standard PCF was more effective than standard PCF alone for the detection of TB in a high burden setting (30). The screening initiatives and contact tracing, among TB contacts in urban slums, have shown an increase in case detection, notification, and may be considered as an approach to reduce diagnostic delay for TB (24,27,28,31–33).

NTP Pakistan implemented an innovative type of ACF, ‘extended contact screening’ (ECS) strategy including household and close community contact investigation. All individuals, in households within a 50-meter radius from the home of an index smear-positive TB case, were asked about TB symptoms. They were investigated in case of having the symptoms. In this project, we investigated how much impact, this intervention had on TB notification.

The characteristics of TB patients identified through ACF may differ from those identified by PCF. The prevalence of TB among men is higher than women in most of the countries (17,34,35), and among the poor segment. In India, ACF helped to find out more female patients suffering from TB (36). Similar studies conducted in Eastern Nepal and Cambodia showed that ACF identified more cases of TB among the women and older (37,38). A combination of both; ACF and PCF was more common in detecting TB cases among males and people age group >15 years in Vietnam (39).

The comparison of treatment outcomes of cases detected by routine PCF and those detected through ACF is very important because no assessment has been made in case ACF affected the TB treatment outcomes. Similar treatment outcomes were identified by a systematic review (published in 2013) among ACF and PCF-detected patients (22). As shown in more recent papers, ACF has similar (40,41) or worse outcomes (42,43). However, we did not find any study from Pakistan comparing treatment outcomes of TB patients by case finding strategies.

1.7 Research questions

With this background, we proposed the following research questions: How many additional cases can be detected with this specific case finding strategy? Are patients detected in ACF different from those detected in routine PCF? Are the treatment outcomes in ACF and PCF different?

2. Aim and Objectives

The main aim of this thesis is to assess, the impact of extended contact screening strategy in Pakistan, which includes household and close community contact screening of smear positive pulmonary tuberculosis patients.

Specific objectives

Specific objectives of this research project in the selected districts of Pakistan were:

1. To determine the proportion of presumptive TB cases identified, TB patients detected and initiated on treatment. (Paper –I)

2. To determine the increase in percentage of TB case detection (2016-2017) relative to baseline (2011 –2013). (Paper –I)

3. To compare the characteristics of patients with pulmonary tuberculosis identified through ECS with those of patients identified through routine passive case finding. (Paper –II)

4. To compare treatment outcomes of pulmonary TB patients detected by ECS with those detected by routine PCF. (Paper –III)

3. Methods

In this section, some topics are common for all the papers such as; study setting, Pakistan National TB Program, extended contact screening intervention, study area, data collection, data validation, and ethical approval, which is same for all three papers. After this general part, we have specific section methods for each paper.

3.1 Study setting

The Islamic Republic of Pakistan is located in South Asia and is bordered by India to the east, Afghanistan to the west, Iran to the southwest and China to the northwest. With Afghanistan, a 2,430 km long border is mainly important for TB care and prevention in Pakistan. The movement of people across the border from Afghanistan into Pakistan, is to seek medical care, particularly in facilities offering specialized services. Pakistan is administratively divided into 5 provinces, Punjab, Khyber–Pakhtunkhwa (KP), Balochistan, Sindh and Gilgit Baltistan (GB) in addition to the Islamabad Capital Territory (ICT).; Moreover, Azad Jammu and Kashmir (AJK) is a region that is nominally autonomous entity administered by the government of Pakistan. It forms the western part of the larger region of Kashmir, which has been disputed between India and Pakistan since 1947. The FATA (Federally Administered Tribal Areas) is officially now merged in KP.

Pakistani population has been growing steadily in recent years, which was officially estimated at 212 million in 2018 based on the 2017 census, with an estimated 2% annual increase. (44).

Great social changes have taken place in Pakistan, ushering in a new era of urbanization and the creation of a couple major cities within the country - Karachi and Lahore. The country's most urbanized cities and city dwellers make up about 36% of the total population. About 50% of Pakistani citizens live in an area where at least 5,000 other citizens also live (44).

The population growth rate is projected to reduce to half or reaches to less than 1% by the year 2050 in Pakistan. By 2030, the population is predicted to reach nearly 245 million, but is not expected to stabilize by the end of this century.

Our study was conducted in Punjab province; some details are mentioned as follow. Punjab is the second largest and most populous province of Pakistan. It covers 205, 345 km (23.3% of the national area). Punjab constitutes about 56% of the population of the country, and in terms of International standing, it is slightly less than the 11th most populous country of the world with an estimated population of 110,012,442 as of 2017. The province shares its borders with the Indian states of Punjab, Rajasthan and Jammu and Kashmir. It occupies 25.8% of the total landmass of Pakistan. It has 9 divisions and 36 districts while 62.6% of its population lives in rural areas. On an average 60% of all TB cases are notified from Punjab.

Health system in Pakistan

In Pakistan, the health system consists government (public) institutions, para-statal health institutions (armed forces, Railways, Sui Gas, Fauji Foundation, Pakistan Water & Power Development Authority (WAPDA) etc.), the private health sector, institutions of civil society, and the philanthropic institutions. Private sector is comparatively large but not properly regulated, with qualified and unqualified healthcare service providers who provides overall curative services to about 75% population. Approximately 90% of TB patients initiate health care seeking from the private sector in Pakistan (13).

Pakistan National TB Control Program (NTP)

Pakistan's mixed public-private healthcare system has both vertical and horizontal components within the public sector and the largely un-regulated private sector (45).

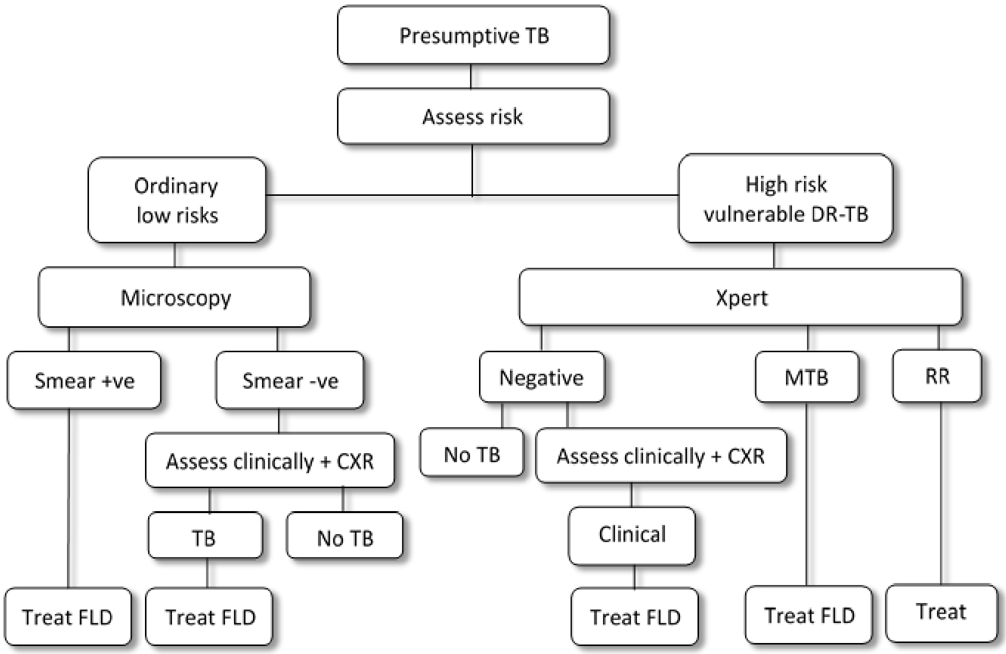
In Pakistan, "health devolution" is a process initiated in 2009 intending to transfer the power to provinces from federal level. Prior to the health devolution, there was a fundamental change in the 2009 federal-provincial resource allocation formula, with the majority of (56% –58%) going to the provinces. It is also an equity-based formula for resource allocation in sparsely populated provinces taking into account the development needs and the security challenges. Transfer of power from the federal to the provincial government began abruptly. The 2010 transition abolished the Concurrent Legislative List and replaced it with a shorter list of federal powers and a longer list of special provincial powers. The functions of health planning, legislation, service regulation, financing service delivery, human resource production, and service delivery programming were devolved by the provinces. During the 14 months, between devolution being promulgated into law (April 2010) to abolishment of the Ministry of Health (MoH) (June 2011), there was scant discussion and planning undertaken by the federal ministry with provinces. Hence, there was an overnight confrontation of provinces with additional responsibilities, resourcing, and planning that were yet to be worked out.

Regardless of the devolution of the MoH, vertical programs such as NTP comes under the MoNHSR&C, which is at the federal level; while the Provincial TB Control Program (PTP) is run by the management of TB and the relevant centres at the provincial level. This has significant implications for planning, resource allocation, coordination and standardized implementation between the federal and provincial levels at a national scale in a sustainable manner. However, the public sector remained the main source of TB care with TB-DOTS in the country since 2010 historically. Efforts are being made to implement public-private partnership models of care under district leadership. Preliminary results were reported on how to engage the private pharmacies in early case identification during 2016 (46).

Public health care is mainly provided through a network of primary, secondary and tertiary level health facilities. Primary health care facilities include basic health units, civil dispensaries, mother-child-healthcare centres, rural health centres, urban health centres and urban health units. Secondary level health care facilities consist of sub-district hospitals and district hospitals. Tertiary level health care is provided by teaching and specialized hospitals.

The basic administrative unit (BMU), which contains staff and resources for diagnosing; performs smear microscopy, some facilities are also perform Xpert

MTB/RIF assays, and a physician or qualified medical staff is trained to diagnose and initiate TB treatment, record and report the progress of the patient's treatment, and manage supplies. BMUs are situated at the district and sub-district hospitals, the rural health centres, and at some basic health units. The treatment of TB consists of six to eight months provided under daily direct observation by a trained healthcare provider, a family member or a community volunteer. The TB patients also return to BMU for follow-up; re-examinations and confirmation of cure. The BMU keep and maintains records using standard formats and delivers reports to the district coordinator, including reports on treatment outcome periodically (4). There is well-organized system for vertical reporting, supervision and monitoring system in place, which is the backbone of maintaining the quality of TB services in the country. Regular surveillance meetings are conducted at national, provincial, and district levels. The data is generated at BMU level, at the end of each quarter. The data transfer mechanism at district level is through intra-district meetings that subsequently transfers to provinces during inter district meetings and finally to NTP in interprovincial meetings. Sputum smear microscopy facilities, Xpert MTB/RIF testing and TB treatment are provided free of cost in the country. During 2013-15, all the BMUs followed the algorithm provided in Figure 1 for TB diagnosis.



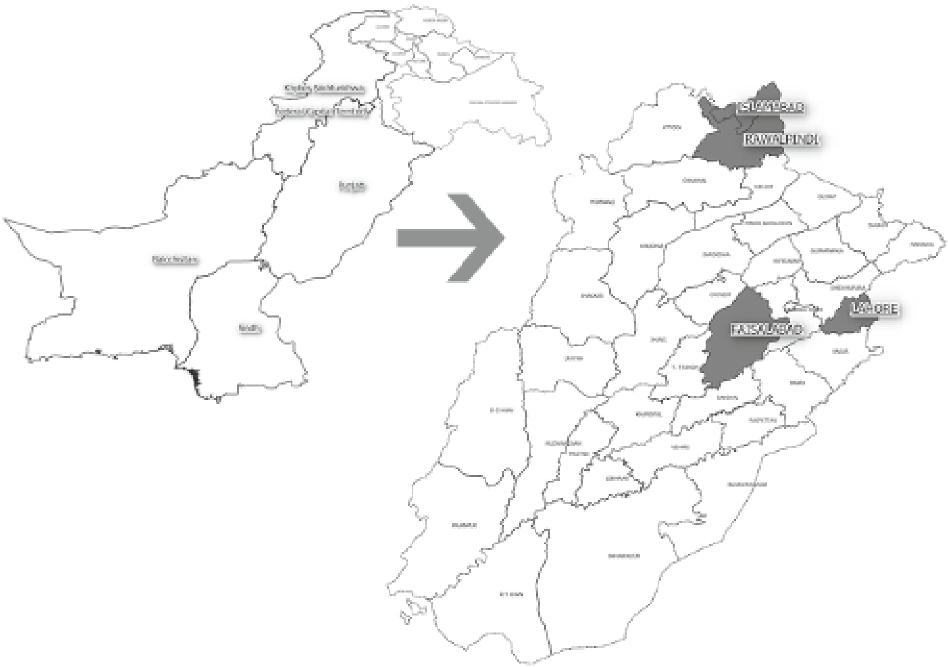
TB = tuberculosis, sm+ve = Smear positive, sm-ve = Smear negative, FLD = First Line Drug, CXR = Chest X-ray, MTB = Mycobacterium tuberculosis, RR = Rifampicin resistant, SLD = Second line drug

Figure 1: Algorithm used by Pakistan NTP for assessing a patient with presumptive tuberculosis in routine (PCF) program (2013-15). (47)

All TB patients were treated according to national TB guidelines (2013-15) and were kept under a direct observation routinely (PCF). New patients (those who never been treated before or treated less than 30 days) were treated with six months' treatment regimen, containing two months of HRZE (H-Isoniazid, R-Rifampicin Z-Pyrazinamide, E-Ethambutol) in the intensive phase and four months of HR in continuation phase. Previously treated TB patients (in past, treated for more than 30 days) were treated with eight months' regimen that comprised of two months HRZES (S-Streptomycin), a one month HRZE and five months of HRE. Patients diagnosed with resistance to rifampicin were referred to drug-resistant TB sites for second line treatment. In both groups (PCF as well as ECS), HIV testing was not routinely offered to patients.

3.2 Extended contact screening intervention:

ECS was implemented during 2013-15 mainly in four urban districts: Lahore, Rawalpindi, Faisalabad, and Islamabad. (**Figure 2**). There were total 98 BMUs for the population of 18 million. More than 80% of the population live in urban areas in these project districts. The average socio-economic status of people living in these districts is better than the average of Pakistan because of better jobs and business opportunities. However, around 50% of the population lives in slums with poor socio-economic conditions. This was focus on ECS.



Lahore, Faisalabad, Rawalpindi and Islamabad
Community screening within 50-meter radius of index case in addition to household screening

Figure 2: Map of Pakistan showing four selected districts for extended contact screening of tuberculosis (2013-15).

The Pakistan NTP implemented a project funded by TB-REACH wave III, which intended to facilitate detection of more TB cases (48).

All people, living within a radius of 50-meter (ascertained using geographic information system, GIS) from the households of known TB patients, were contacted and screened for TB by the trained project staff. A 50-meter radius was selected based on data from the electronic TB surveillance system that revealed the presence of many cases coming from the same family, same address, or close community suggesting high rates of geographical clustering. An estimated number of households in this radius was considered feasible to be covered by NTP under close community screening. Mobile phones enabled with ARC GIS (version 10) software were used to identify households within a 50-meter radius of the index case and collected data by the trained project staff. All the available people permanently living within a 50-meter radius were contacted. All the participants were informed about a TB patient in their neighbourhood (50-meter radius) but the information was provided without disclosing the name of the patients. Measures were taken to protect the confidentiality of the index patient. A 'presumptive TB case' was defined as, any person with a productive cough for more than two weeks. On spot sputum sample was collected from the presumptive TB patient and transported to the nearest BMU for diagnostic testing. The same diagnostic algorithm (as mentioned in Figure 1) was followed for presumptive TB case except the use of Xpert MTB/RIF (if available) assay among sputum smear microscopy negative. Patients with bacteriologically confirmed were contacted by the project staff and referred to the nearest BMU for registration and treatment initiation. Presumptive TB cases with age less than 15 years were referred to specialist paediatric care for further diagnosis and management. Those people who were negative on both sputum test, microscopy and X-pert MTB/RIF were referred to the nearest BMU for follow-up according to national guidelines. All the patients detected through ECS were marked "TB REACH" in the TB register (TB03).

3.3 Study area

Four districts with high number of slums were selected as intervention areas which included Lahore, Rawalpindi, and Faisalabad from Punjab province while Islamabad, the federal capital.

The target population was considered having limited access to TB services of the public sector. With a population of 176 million, of which 36% lives in urban areas of Pakistan that has been described by UN Habitat as a country with already high proportions of slum facing rapid and sustained slum growth rates. It is estimated that one in every three living in city in Pakistan dwells in a slum (49). The migrants usually get employment in informal sector, due high costs of living in the cities; they settle to squatter colonies by building some kind of temporary or permanent shelters. Consequently, slums and peripheral settlements came into being within most urban localities. In Pakistan, 35%-50% urban population lives in katchi abadi (desolate buildings without government permission). The total population of target areas selected for this project was 18 million out of which half of the population is living in slums (49). The slums in four selected areas include Lahore, Rawalpindi, Faisalabad, and Islamabad. Lahore, the second largest city of Pakistan considered an economic hub of Punjab. According to the population survey, about ten million people live in this glorious and magnificent city. More than 50% of the people are living in the slums, where they do not have proper sanitation, health, home, food and education facilities. Faisalabad is another big city in Punjab with many slums. The city is characterized by rapid spatial growth coupled with industrial growth, which led to attraction of people from other parts of country and rural areas; thus, the practice of living in unplanned shanty town and slums began in the city. The socioeconomic and physical conditions of these slums /kachi abadis are very poor as these are mostly located in low lying areas (50).

The people living in slums have three main characteristics such as living in congested and crowded homes, low-nutritional status, and prone to communicable diseases. The housing conditions are poor without civic amenities such as; clean water, proper sanitation, and access to subsidised public health services. Overcrowding, low nutritional status, and delay in access to health care make them prone to communicable diseases particularly TB. Limited availability of public sector health facilities, unorganized and poorly trained health providers pose further challenge access to quality TB care. There is no referral linkage between the health facilities located in slums and service providers both public and private. Though many CBO and NGO are working in these areas to support health and education projects; however, the community awareness, ownership, and coalitions for targeting TB are not yet properly addressed.

3.4 Data collection

For the ECS data collection, around 60 field officers were trained and were supervised by district supervisor, project coordinator, and project focal person. A web-based system was developed to collect data on mobile phones which was uploaded in real-time to a centralized server enabled with GIS technology. The web-based interface allowed comprehensive daily real-time supervision of field staff performance without losing any data. The online database was password protected and only the authorized persons were allowed access to the data for monitoring and analysis purposes.

Initially, the technology encountered many issues including problems in cell phones, software issues, and the use of technology by field officer; however, repeated field tests and trainings resolved these problems.

Case based patients' data (ECS and PCF) are being maintained in a facility based TB03 register which is being validated at district level, provincial level, and then at national level.

For paper 2, additional data was collected from the community using a structured questionnaire. Since this information is not being routinely collected, it was collected prospectively by the project staff from routine patients with TB who consented to participate.

3.5 Data validity

In overall, TB data recording system starts from the health facility outdoor register. Presumptive TB cases are identified among the patients visiting OPD and are referred to the laboratory for sputum smear microscopy or Xpert testing. Basic personal information and test results are recorded in the laboratory register (TB04). Results are sent back to physician who decides about the patient diagnosis. The diagnosed TB case is referred to TB DOTS section (a section where a trained health care worker provides the prescribed TB drugs and counselling services to patients according to national policies and international standards) after making relevant records in OPD register. The DOTS facilitator receives the patient who prepares patient's file by completing Patient facility card (TB01) & Patient Card indicating follow up visit dates (TB02) in the DOTS section. Then the information is translated to the facility based TB register (TB03).

The Monitoring and supervision (M&S) is conducted through structured checklists in accordance with national, provincial, and district monthly plans that cover all the dimensions and various interventions of the program. The M&E officers check the records of patients in TB03 and validate it with the TB04 register. They also randomly select a few patients and call them on their contact number for confirmation. After validation, the data is reported to provincial level. The process of validation is also done at district level by the district TB focal persons with the technical support of provincial Program Officer (PPO) or a technical officer at national or provincial level.

A series of quarterly review and surveillance meetings has been scheduled through the program to validate data at the district level and to review the progress at district, provincial, and federal level. The main objectives, process and outcomes of these meetings are described below.

- Intra-district meetings for all BMUs: Mainly these meetings are designed for data validation. The TB physicians, paramedics (DOTS facilitator) and lab technicians from each BMU of the district come to district TB focal person or district health officer office for one-day meeting. They bring the recording tools i.e. TB01, TB03 & TB04 and two reports i.e. TB07 & TB09. These tools and reports are validated by the District TB Focal person with the technical support of PPO/ expert at provincial level. The District Health Officer (DHO) chairs the meetings at the district level and appraises the achievements and shortcomings. The DHO is supposed to support the all the BMUs in the district in case of any administrative problems.

• Inter-district meetings for all districts: this meeting is conducted quarterly at provincial headquarter after completion of intra-district meetings in all the districts. The Provincial Technical Officer presents aggregated data of the province and individual data of each district. Updates and trend analysis are shared. The main purpose of this meeting is to review the performance of the districts in the previous quarters.

• Inter-Provincial meeting: This meeting is conducted after the completion of inter-district meetings in all the provinces at national level. The senior level management and technical person from NTP, PTP and partners attend this meeting. The aggregated data is shared with PTPs and partners. Trend analysis for national data and group work is done to address the programmatic shortcomings.

3.6 Ethics Approval

For Paper 1 the study protocol was reviewed and approved by the Ethics Advisory Group of International Union Against Tuberculosis and Lung Disease (The Union), Paris, France. The concerns of confidentiality and other ethical restrictions were imposed by the advisory group (eag@theunion) due to requirement of sharing the patient-wise data. Permission was obtained from NTP Pakistan for this operational research. As this research involved the analysis of secondary data, which is routinely collected under the national programme. Therefore, the ethics committee waived of the requirement for individual informed consent.

For Papers 2 and 3, ethical approval was taken from the Ethics Advisory Group of International Union Against Tuberculosis and Lung Disease, Paris, France (EAG number-58/16) and the Regional Committees for Medical and Health Research

Ethics in Norway (REK-Vest 2018/57). Administrative approvals were taken from the Provincial and National TB Control Program, Pakistan. For paper 3, a written informed consent was obtained from each participant and/or their legal representative, as appropriate.

3.7 Methods Paper I

Study design Paper I

This paper had a descriptive study design and outcome measurement was TB cases detected. A retrospective record review of TB patients identified through extended contact screening (ECS) by household and close community contacts investigation of pulmonary bacteriologically confirmed TB patients in the selected districts during 2013 to 2015, and compared with routine case detection in same area the year before.

Study participants Paper I

The participants in the study were all TB patients identified through ECS and all notified TB cases in the selected districts during the pre-intervention (July 2011-June 2013) and intervention period (July 2013-June 2015).

Study variables Paper I

The outcome variable was number of TB cases detected during this research project, and as comparison the number of notified TB cases in the same areas of the previous year. Exposure variables or risk factors were as follows. Number of people identified for screening; household and close community; age, sex; presumptive TB cases; sputum collection; result of sputum microscopy; result of Xpert MTB/RIF test; and treatment initiation (registration for treatment).

Analysis Paper I

Data was extracted from a central database and was analysed in STATA v12 (StataCorp, TX 2011). Descriptive aggregate data analysis was performed to assess the number of people screened in household and close community, to determine the number (proportion) with presumptive TB cases and were diagnosed as the TB cases among them. The number needed to screen to detect one TB patient (NNS—overall and stratified by household contacts and close community contacts) was calculated among total contacts screened and among presumptive TB cases. The increase in percentage of TB case notification in intervention districts was calculated between pre-intervention (Jul 2011-Jun 2013) and intervention periods (July 2013-June 2015).

3.8 Methods Paper II

Study design Paper II

A cross-sectional study design was used to assess determinants of case detection through ECS and routine PCF in the selected districts of Pakistan during 2015.

Study participants Paper II

The participants of paper 2 were all PTB patients diagnosed and reported through ECS and routine PCF, registered and treated at public or private health facilities engaged with NTP in the selected districts of Pakistan, between July 2013 and June 2015. For comparison, we used data about all PTB cases detected by the NTP

Study variables Paper II

The dependent (outcome) variable was case detection. Independent variables included patient characteristics such as; age, sex, city, TB category, bacteriological confirmation, marital status, education status, occupation, monthly family income, household members, type of house, residence, people sleeping in one room, ventilation, water source for drinking, smoking, and diabetes mellitus status.

Analysis of Paper II

The case-based data was entered from facility-based TB registers for clinical characteristics; whereas, the research data collected through interviews was entered into Microsoft Excel, validated and analysed using Stata (version 12.1; StataCorp LLC, College Station, TX, USA). For quality assurance and validation, our database was compared with aggregated data from the routine quarterly reports, and discrepancies were manually re-checked with the original TB registers. Demographic and clinical characteristics of patients identified through ECS and PCF were compared using 95% confidence intervals (CIs). We conducted logistic regression analysis to compare determinants of case finding by ECS, adjusting for potential confounders. Unadjusted and adjusted odds ratios (ORs) were reported. P-values of ≤0.05 were considered significant.

3.9 Methods Paper III

Study design Paper III

Paper 3 study had a cohort design and compared the treatment outcomes of PTB patients registered and received treatment at public or private health facility engaged with NTP in four selected districts of Pakistan, between July 2013 and June 2015 based on patients identified through ECS and routine PCF.

Study participants Paper III

Study participants of paper 3 were PTB patients detected through ECS and routine PCF and treated at public and private health facilities in the selected districts during 2013-15.

Study variables Paper III

The outcome variable was standard TB treatment outcomes, which were classified as favourable (treatment completed and cured) and unfavourable outcomes (treatment failure, lost to follow up, died or not evaluated). Determinants were patient characteristics including case detection strategy, age, sex, district, TB category, bacteriological confirmation and diabetes mellitus status

Analysis Paper III

Data were entered into Microsoft Excel (Microsoft, Redmond, WA, USA) and analysed using STATA (version 12.1, copyright 1985– 2011 Stata Corp LP USA). The comparison of demographic and clinical characteristics of patients detected through ECS and PCF was done using $\chi 2$ test. Our exposure of interest was the case finding strategy (ECS or PCF) and the treatment outcome (unfavourable or favourable) was our outcome of interest. To assess the association between ECS and unfavourable outcome, we used log binomial regression models after adjusting for potential confounders, giving crude and adjusted relative risk (95% CIs).

4. Results

In this section, we give a summary of the published papers that are part of this thesis, and the copies are given in the attachment section.

4.1 Results Paper I

Title: Extending 'Contact Tracing' into the Community within a 50-Metre Radius of an Index Tuberculosis Patient Using Xpert MTB/ RIF in Urban, Pakistan: Did It Increase Case Detection? ***PLOS ONE 2016; 11(11): e0165813.***

From July 2013 to June 2015, a total of 783, 043 contacts were screened for TB, of whom 89,222 were household and 693,821 were close community contacts. Among the contacts 23,741 (3.0%) presumptive TB cases were identified; of them 14,973 (63.1%) presumptive TB cases were examined for sputum microscopy and 5019 (21.1%) through chest X-ray. 4084 (20.4%) were bacteriologically confirmed TB patients. Of the 11064 who were smear-negative and required an Xpert test, only 6877 (62.2%) were tested using Xpert MTB/ RIF: 522 (7.6%) had TB and 44 (8.4%) had rifampicin resistance. Chest x-ray was done for 5019 presumptive TB cases, and based on the chest X-ray, 559 (11.1%) were clinically diagnosed as TB patient. Total 4710 TB patients were detected as a result of this intervention and out of them 4604 (97.7%) were initiated on treatment.

Overall, the yield of screening for all types TB patients among presumptive TB cases investigated was 19.8% where 22.3% among household and 19.1% among close community contacts. However, inter-district variation in case detection was observed, which was the highest in Lahore (42.9%) followed by Faisalabad (34.9%).

Overall, the number of notified TB patients increased by 8% during the intervention period. The increase was not different by age, sex and smear positive cases. However, there was a variation among districts and the increase in case detection was highest in the district Lahore (9.1%) and lowest (2.3%) in Islamabad. The intervention also increased the TB case notification.

4.2 Results Paper II

Title: Are patients with pulmonary tuberculosis identified by active and by passive case detection different? A cross-sectional study in Pakistan. *Int.J.Infect.Dis. 2022; 121:39-46.*

Total of 12,114 PTB patients were included in the study where 4,604 (38%) were detected by ECS, of whom 4,052 (88%) were bacteriological confirmed TB patients. Out of 74,827 patients (mean age 36 years, male = 49.6%) eligible in the routine TB registers in the study area and identified through PCF, we interviewed only 7,510 (10%) (Mean age 36 years, male = 49.7%), and they represented the comparison group designated as the PCF group.

In the ECS group, the proportion of males was 56.2% (95% CI 54.8–57.6) and 49.7% (95% CI 48.6–49.2) in the PCF group. The proportion of bacteriologically confirmed TB cases was higher in the ECS than in the PCF group. Similarly, the proportion of no schooling among patients aged < 15 years was higher in the ECS than in the PCF group, and there were fewer students in the ECS than in the PCF group. There were some differences in location, type of house and rural-urban habitation.

The characteristics of patients identified through household contact (HH) investigation and close community contacts screening were compared. The mean age of PTB patients identified through close community contact investigation was 37.0 years (95% CI 36.4–37.6), and 33.1 years (95% CI 32.1–34.2) in the HH group. The HH group had a higher proportion of TB patients aged 15–44 years and lower proportion of patients aged 45–64 years compared to the close community contacts group. There was no significantly different in the proportions of males and females. ECS contributed 5.8% of the total case finding, but this population was slightly different from the routine cases.

Compared to the patients aged 15–44 years, the children younger than 15 years were more likely to be identified through ECS than PCF (adjusted OR 2.69; 95% CI 2.21–3.28). TB patients in Faisalabad had higher chances of being identified through ECS than PCF (adjusted OR 2.57; 95% CI 2.01–3.29) as compared to those in Islamabad. For other factors, adjustment had little effect on the proportion of case finding by ECS.

4.3 Results Paper III

Title: 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? *Int.J.Infect.Dis. 2021; 104:634-640.*

Total of 79,431 persons with PTB were included in the study of whom 4604 (5.8%) were detected through ECS; of them 4052 (88%) were bacteriologically confirmed PTB patients, with a similar proportion in both household (3058/3477=87.9%) and close community contacts (994/1127=88.2%). Of 4052 bacteriologically confirmed PTB patients, 3573 (88.2%) were positives on smear microscopy alone, 172 (4.2%) on Xpert alone (of these 160 were microscopy negative and 12 had no microscopy result) and 307 (7.6%) were positive on both tests. For the PCF group, we do not have similar information.

For both groups, the mean age was 36 years and standard deviation 18 years with were more males (56.2%) in the ECS group than in the PCF group (49.6%, $P < 0.001$). Bacteriological confirmation was higher (88.0%) in the ECS group 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%, $P < 0.001$). The treatment outcomes were depicted for all PTB patients, bacteriologically confirmed, clinically diagnosed, and patients stratified by case finding strategy (ECS & PCF). On crude analysis, in all the three groups, the proportion with unfavourable outcomes was lower in the ECS group when compared to PCF, but it was significantly lower among bacteriologically confirmed PTB cases in the ECS group (9.9%) compared to PCF (11.6%; ($P < 0.05$). There was a higher contribution of cure to treatment success in the ECS group (48.1%) when compared to PCF (18%) in all PTB patients. Among the bacteriologically confirmed PTB patients in the ECS group; those detected in the index household had similar unfavourable outcomes (85 of 994; 9%) to those detected in the community (316 of

3058; 10%) (P = 0.06). In clinically diagnosed PTB 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.

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

5. Discussion

This thesis evaluates the impact of a big contact screening project. There was screening of all households and close community contacts living within 50-meter radius of pulmonary bacteriologically confirmed TB patients using GIS technology. Sputum samples from the presumptive TB cases were collected and carried to the closest health facility for TB diagnostic testing by the trained field staff. Confirmed cases were contacted and referred to the closest health facilities for registration and initiation of TB treatment. Field staff was provided with cell phones having GIS and internet based technology to collect data. An internet (web based) system was developed for data collection through mobile phones. The data was uploaded in real-time to a central server at the national level (NTP office). This was enabled through GIS technology, which captured the exact coordinates of the location of index case households along with the household and close community contacts. The online web based data was password protected which was accessible to only the authorized persons for the purpose of monitoring and analysis.

5.1 Discussion of Methodological issues

Study design

For paper I, a cross sectional study design was considered. It was a suitable design because we were studying the number of TB cases among screened (household and close community contacts) and their characteristics. A cross sectional study examines the association between disease and other variables of interest as they occur in a defined population at a single point and is used to measure the burden of a specific disease. Thus, it was the best study design because we were looking for the prevalence/burden of TB disease amongst the contacts of a positive TB patient. Furthermore, we obtained the data at a single point which were already collected and measured prevalence for all factors.

In paper II we employed a cross sectional design to make comparison between the characteristics of TB patients identified through ECS and those identified through routine PCF. No follow up information was needed to answer the research question, hence, this design was appropriate. Although the risk in cross-sectional studies is not easy to estimate as in the cohort design; where the subgroups of a study can be compared and the odds ratio can be calculated. Therefore, this is an overall assessment to measure the risk factors as part of cross-sectional analytics design.

In Paper III, a follow up was done to compare the treatment outcomes of pulmonary PTB cases identified through ECS with those identified by routine PCF. The longitudinal nature of research design helped us to see the impact of intervention on treatment outcomes.

Selection of districts

For the main project implementation during 2013-15, NTP Pakistan selected three districts from Punjab province and the capital territory (Islamabad). These districts were selected based on the characteristics such as urban slums having limited access to TB services of the public sectors, high population size and TB cases (except Islamabad). It would have been more useful for the generalizability of our study results if we had randomly selected a cluster-sample from all the five provinces and the regions that would be representative of the entire country. Hence, keeping in view the available resources, time and access limitations we focused on the three districts of Punjab province and the federal capital (ICT).

5.2 Discussion on validity

The findings quality largely depends on the data quality. Validity is applied to assess whether the collected information, accurately answers the research question.

Internal validity

Internal validity is the degree to which the observed findings leads to correct identification of inference regarding the phenomena taking place in the study. If the study measures what it was designed to measure, then we say it has internal validity. It can be compromised of by chance, by bias and by confounding.

Bias

Selection bias

Selection bias introduces through the selection of respondents, clusters, or data for analysis without proper randomization; therefore, failing to guarantee that the selected sample is representative of the population to be studied.

In the main project, all bacteriologically positive PTB patients were mapped and visited by trained field staff for household, and close community contact screening was done after the informed consent. To ensure the compliance, the data was obtained from the TB03 register of all health care facilities, both public and private engaged with NTP. However, during the process, some patients might have been missed in the selected districts; particularly those registered with non-NTP engaged health care providers, unregistered health practitioners, hakims, traditional healers, and homeopaths. This may effect generalization of the study findings. Moreover, there was no system to include those individuals who had no access to health care, who were not going through any treatment, and those suffering at home for numerous reasons. Additionally, details of duration to diagnosis from onset of TB symptoms and visiting a health care facility for any kind of TB symptoms were not recorded in this study. There are other factors that can contribute to selection bias; such as during the ECS intervention, the screening was carried out in the morning so working individuals who were not present at the time of screening could be missed as it is usually their working time. However, field staff was instructed to make a second visit not to miss presumptive TB cases.

Seasonal difference in incidence and TB case notification is well recognised that may have an impact on measuring changes in case identification. However, the study continued for over two years and total number of TB cases reported in the study districts increased gradually for each calendar quarter during the project period. Hence, seasonal variation had no direct impact on the results.

In paper II, we used convenience sampling; a subset of around 10% for the routinely detected cases (PCF). This might have introduced bias as we mostly studied those cases which were easily approachable, and their characteristics might be different from those of other patients. However, sampling was carried out to make sure that the study sample was true representative of the PCF group. Moreover, the inclusion and exclusion of passively identified cases had similar distributions of age and gender, favouring a fairly unbiased sample selection.

Recall bias

Recall bias refers to an error when the information is collected from the study participants in the same way, irrespective of the status of the exposure, existence of a measurement error, or both. In paper II, the responses were provided by the participants retrospectively, after their registration for TB treatment. Failure to recall the information could have led to recall bias; however, the information collected was mostly based on socio-demographic characteristics. We tried to minimise this bias with questioning and re-confirmation of their responses. Monthly family income is also subject to recall bias. The bias could overestimate or underestimates the family monthly income however, use of a structured face-to-face interview is an effective way of information collection. To minimise error in the information gathered, and our staff was trained and the questionnaires were piloted. Moreover, to minimize information bias, the data collection tool was pilot tested and on the basis of lessons learned, measures were taken to enhance validity.

Social desirability bias

There could be some information provided by the respondents are inaccurate or underreported. For example, the respondent could have provided inaccurate answer asking about smoking status because it is socially undesirable.

Confounding

All the patients detected through ECS were marked in the TB03 registers and checked whether these TB patients are better cared. Marking their names in the registers may be confounded due to close monitoring by the district TB staff and field staff because it was not a routine arrangement moreover, it might remind the doctors to improve follow-up.

In paper III, there might be some predictors of TB treatment outcomes in the study setting that could not be measured, as those were not routinely collected by the NTP during the study period; for examples severity of disease, nutritional status, socioeconomic status, and cigarettes smoking. Thus, residual confounding might not be ruled out. We handled the challenges of confounding at the time of analysis by using logistic regression to analyse the potential effect of a variable by controlling the effect of the other factors.

External validity

The studies are conducted in four districts with highest population size and urban slums; therefore, the findings are relevant and likely valid to be generalized for other large city slums in Pakistan. A strong system of monitoring and evaluation was established, and all TB patients, who were identified were confirmed by NTP Pakistan.

5.3 Discussion of main findings

5.3.1 Extending contact screening to increase TB notifications

In paper I, we found that extended contact screening strategy, that includes household and close community contact screening, resulted in identification of additional TB cases and increased TB case notification of around 8% in Pakistan during the intervention period.

WHO recommends that household and close contacts with patients suffering from TB are at higher risk of getting TB infection and developing the disease. Therefore, they should be screened for TB systematically (20). A systematic review indicated the weighted pooled prevalence of TB disease was 3.6% (95% confidence interval [CI]: 3.3–4.0), with a median NNS of 35 (95% CI: 17–65) among all close contacts of TB patients. Systematic screening of contacts of people with TB disease has strongly been recommended since 2012 (51).

Globally, different Randomize controlled trials show the the effectiveness of contacts screening. A trial conducted in Viet Nam on household conatct screening showed that the intervention resulted in an increase of 2.5-fold in the notification of diagnosed TB contacts (relative risk [RR]: 2.5; 95% CI: 2.0–3.2). In addition, there was a reduction of 40% in all-cause of mortality within household contacts (RR: 0.6; 95% CI: 0.4–0.8) (39). A contact screening trial conducted in South Africa and Zambia showed that screening household members could reduce the TB prevalence in a larger community. He year after 4 years, when the contacts were investigated; statistical significance was not reached (prevalence ratio: 0.82; 95% CI: 0.64–1.04). A recommendation showed that the intervention resulted in decline in TB transmission, that was estimated by the incidence of TB infection among school children (RR: 0.45 95 ؛% CI: 0.20–1.05) (52).

Contact screening is a proven strategy for detection of infected individuals, hence can be consider as a vital component of any TB control strategy (53). Such strategy among contacts screening of TB patient particularly in urban slums showed an increase in case identification and notification, thus it can be considered as an approach to reduce diagnostic delays (24,27,28,31–33). Community level screening programmes in those countries having high TB burden, mainly depended on TB symptom screening, sputum smears microscopy and culture, due to the challenges of mass CXR screening related to logistics and operations (52,54).

Although WHO recommends TB symptom screening as initial TB evaluation and similarly our project used TB symptoms for further investigation of these TB contacts; however, we could have missed all those TB patients who had no TB symptoms or no complaint. A study shows that 79.2% of people reported with TB disease were asymptomatic at the time of diagnosis indicating the weakness of symptoms based screening mostly in high risk and vulnerable population (55). Globally, around 20 prevalence survey conducted on TB showed that more than 50% of active TB patients would be missed with only a symptom screening method (19). Furthermore, a study conducted on the immigrants in the United State (56) showed that being asymptomatic was not associated with clinical signs of being less infectious, indicating absence of symptoms does not mean that those persons cannot initiate extensive outbreaks. On the other side, the absence of TB symptoms, or being unaware of TB symptom could mean the person would remain in contact with others for longer time, transmitting TB disease to wider clusters.

In routine PCF, we miss those TB patients who do not consult the health care facility regardless of having symptoms; they may be detected by ACF. Several ACF strategies within high risk population have shown positive results in TB identification (24,26). Nevertheless, there are weak evidence of ACF having any impact on epidemiology of TB. The ZAMSTAR assessed two different interventions (TB household visits and community-wide case identification) and reported a significant decline in undiagnosed TB at community level from the household intervention (52). A study in Cambodia provided the evidence of reduction in TB case notifications within individuals who passed through intensive screening for TB for more than 2 years of follow-up. Though, the study indicates that mass screening through WHO recommended a method combined with a routine DOTS program with good treatment outcomes. It resulted in a rapid reduction in incidence though mass screening by CXR in developing countries has been discouraged due to its high costs and uncertain impact (57). However, a study conducted in Zimbabwe found that the increase in TB case notification rates during the study period, resulted in a 41% decline in TB prevalence after 3 years of implementation of community-based TB case finding (54). Studies in a systematic review reported that screening of TB contacts contributed not more than 9% of all notified TB cases (22). In this current study, among all the bacteriologically confirmed TB patients diagnosed during the intervention period, 75% were contributed by close community contact screening. It has been noted by our study that NNS to find out one TB patient was 90 for the household contacts and 225 community contacts. Another systematic review indicated that overall NNS to find a TB patient was 100 individuals within community contacts in the high TB burden countries (58). The high screening yield within presumptive TB cases among household contacts remained (22.3%) while neighbours beyond the household (19.1%) support the intervention. Likewise, a study conducted in Sindh province of Pakistan showed, active TB case detection within household contact investigation have found 22.7% yield of TB patients (59). Other research studies involving active case findings has found additional yields of TB patients among those referred ranged from 4% in South Africa (60), 13% in Ethiopia (61) and 15.5% in Pakistan (24). One possible reason for the variation could be a small sample size in some of these studies. 297 additional children having TB were identified as result of intervention. This provided the evidence that the project resulted in an overall increase in child TB case detection hence the NNS for child TB case finding was more than adults recommends that the project might missed child TB patients that should be taken care of while scaling-up this intervention.

5.3.2 Characteristics of TB patients identified through ECS and PCF

This study compares the characteristics of PTB patients identified through ECS and standard routine PCF in Pakistan. A significant difference observed in age, sex, laboratory confirmation of TB, occupation, and monthly family income of the patients. The study found no significant variations in the level of education, marital status, household size, numbers of people sleeping in a room, ventilation, source of drinking water, smoking and diabetes.

Our study provides the evidence that, the ECS group had a higher proportion of diagnosed child TB cases as compared to the routine PCF group. This finding is same as in another study related to active case finding conducted in Myanmar (62). The findings recommend that the routine program may have missed child TB patients that should be taken care of during scale-up phase of this intervention. Within the ECS group, more patients aged 15–44 years were found from household-contact screening as compared to close community contacts, and a lower proportion aged 45–64 years. The findings of our study are consistent with a study conducted in Peru screening household contacts and close community contacts (63).

This study also detected a higher proportion of males in ECS than in PCF. A prevalence survey conducted in Pakistan during 2010-11 found that the prevalence of TB was approximately double among men in comparison to women (17), hence we expect that TB notification to be noticeably higher too, about equal to two thirds male. The percentage of men identified and notified during 2015 ranged between 49% in Sindh 59% in GB province. This show that more men are missed than women for TB notification and treatment (64). This has been validated through a study conducted in Karachi, Pakistan also found that higher TB notification rates among women as compared to those of men (65). In almost all other countries in the world, a higher prevalence of TB has been reported among men (5,34,66), also indicated by TB prevalence surveys conducted in Asia (35). A systematic review and meta-analysis recommended that men might be less likely compared with women to seek or access health care in many settings (67). This conclude that a higher proportion of men who were missed in routine PCF, but identified through ACF; and this is the finding from our study.

Our study found that the patients, who were identified through ECS, had 88% bacteriologically confirmed TB cases as compared to only 50% who were identified through the routine PCF. To a large extent, we think this can be attributed to the algorithm utilized for detection of the TB cases. Mostly, Xpert MTB/RIF testing was done in the ECS group resulted in most of the bacteriologically confirmed TB patients. In routine TB patients, a much higher proportion of TB patients were clinically diagnosed and treated following the standard guidelines for diagnosis of TB. This is found consistent with the results from a study in Zambia used ACF (68).

The study results also showed that TB cases detected using ECS were more likely belong to the lowest income class compared to those in PCF group. Moreover, patients identified through ECS were living in kacha houses. For example, TB cases identified through ECS are more often poor than passively identified TB cases; they have limited resource to consult a clinic on their own initiative, however, they are likely to be identified during home visits. TB cases found through ECS were more often from urban area compared with the PCF group. The burden of TB disease is usually considered to be in urban areas in comparison to rural settings most probably due to crowded living and occupational transmission of disease (69). The poor peri-urban sites in developing countries, where living conditions are not satisfactory due to overcrowding, poor hygiene and insufficient sanitation are usually more affected with TB (70,71). Such type of living conditions coupled with limited access to health-care with poor health care seeking behaviours would result in promoting transmission of TB (70,72). Though, a large prevalence survey conducted in Pakistan found that bacteriologically confirmed TB was more common within rural than urban dwellers in Pakistan (17).

5.3.3 Treatment outcomes of TB cases identified by different strategies

In this large study conducted in four districts of Pakistan, we found that the treatment outcomes among PTB patients detected through ECS were same as to those detected through routine PCF. However, ECS group was associated with a slightly lower risk of unfavourable treatment outcomes among bacteriologically confirmed TB cases, but this was not observed among those clinically diagnosed.

Our study recommends that the treatment outcomes of TB patients in ECS group are not inferior compared to the PCF group. The slightly better outcomes in bacteriologically confirmed TB patients may be with better follow-up of cases in the ECS group (reflected by the small proportion of patients not evaluated for treatment outcomes) and perhaps better exclusion of rifampicin resistance prior starting treatment. Overall, our feeling is that these differences are marginal and though statistically significant (due to the large sample size), but these are programmatically insignificant.

The findings from this study are comparable with recent studies conducted in India and Myanmar, which found no variation in treatment outcomes; evidence from the in India showed that the proportion of unfavourable outcomes were 10.2% in the ACF group and 12.5% in the PCF group, $p = 0.468$, while in Myanmar's study (12.4% vs 14.6%) means no significant differences were observed between ACF and PCF (40,41). A systematic review conducted in 2013 also reported no variation in TB treatment outcomes in both the groups (22). However, in contrast, another study conducted in India during 2017-18 reported worst TB treatment outcomes in ACF than PCF. A high rate of initial loss to follow up (25% vs 0%) in ACF than PCF was found. The unfavourable TB treatment outcomes were 33% in ACF group as compared to 14% in PCF (42). However, these research studies used smaller sample size and Xpert MTB/RIF was not used for smear negative contacts, as we did in this study.

5.4 Strength and limitations

Strength of the study

The overall strength of this study is, that the main project was implemented by NTP, Pakistan targeting a very large sample size in the selected districts having the highest urban slums. The project focused on a major challenge for Pakistan NTP, which is the undetected and un-notified TB cases. The finding of this project can easily be incorporated by NTP Pakistan into policy guidelines and practice. The intervention was conducted under the stewardship of NTP Pakistan through routine program settings, therefore it's feasible, if scale-up is considered. The Xpert tools belonging to NTP were utilized on many TB cases.

Paper I has several strengths; this was an innovative ACF strategy based on household and close community contact (within 50 metres radius) investigation has not been found in the literature as per our knowledge. Additionally, the intervention was implemented on a large set of population in urban area of Pakistan as narrated above, so it's generalizable to similar settings and TB epidemics. Extending the contact circle (within 50 metres) looks obvious in areas with high population density, and equally easy to implement. A web-based interface with GIS software was used that allowed comprehensive real-time monitoring and supervision for data collection on daily basis, and helped us to ensure accurate and complete data. Finally, the study followed the STROBE guidelines for reporting purposes. (73).

Strength of Paper III is, it's the first study as per our knowledge in Pakistan to measure the treatment outcomes of PTB patients identified through the ECS strategy in comparison with standard PCF. Multiple studies exit that have evaluated the yield and impact of ACF on TB case notification.

Study limitations

At the implementation stage of the ECS intervention, the addresses of the index cases were not completely recorded in BMU TB03 registers, thus tracing those patients was a challenge. Initially, the community people were reluctant of screening for TB. The sensitization of the community to convince them for TB screening took a long time. For example, an innovative GIS and web-based system was established to capture data using mobile phones, that was later uploaded to a central server at NTP in real-time. During deployment of this technology, many issues encountered that include problems in cell phones, software issues and understanding of the technology by field officers however, repeated field tests and trainings resolved these issues.

In the routine data, incomplete, duplicate, or incorrect patient data could have introduced as bias and misrepresented. There was no unique identification for patients therefore duplication in the record and incorrect linkage might be persist. Single-site patient identification errors are more likely to occur in the high burden settings, especially when workers lack resources or the proper training on the importance of capturing the accurate data. The other possible limitation could be unreadable handwriting, exclusion of data fields in the TB registers during the time of patient registration could have led to duplication of patients' record and incorrect linking of data. Furthermore, the routine data might not be properly validated because of the factors such as data validation, supervision of staff, systems for monitoring of data rely on funding, availability of designated monitoring staff, and program prioritization of data quality. Moreover, migration could have occurred in the selected districts due to employment opportunities, political instability, family visits, and cultural customs.

Paper I has several limitations. There was no data collected for the respondents who did not consented or unavailable during the field visit in the intervention areas. It is likely that the sample participating in this study was not representative and had different characteristics. However, it was not feasible operationally to visit them in the community for the second time. The details of time to diagnosis from onset of TB symptoms, and consultation visit to health care facility for TB related symptoms (if any) were not captured in this study. Findings from clinical trials are lacking and more data is required to inform international policy. In most of the cases, the TB diagnosis was based on a single smear without any culture that could lead to false positive TB cases which remains a common concern with regards to ACF (22).

Paper II also has several limitations. First of all, the data was several years old, and there have been some changes to routine PCF since then, such as the introduction of routine GeneXpert test at many health facilities. The selected population for this study area has a slightly higher socioeconomic status compared to the average population in Pakistan, therefore careful consideration would be required when generalizing the results. Rest of the limitations are recall bias as the study participants provided responses retrospectively, after they were registered for TB treatment. We tried to reduce this bias by questioning and re-confirming participants' responses. Another weakness in the study is that we employed convenience sampling methodology for the passively identified TB cases. This could have resulted into bias as we mainly studied the TB cases that were easily approachable, and their characteristics might have been different than those of other patients. However, the inclusion and exclusion of passively identified cases had a similar distribution of age and sex, favouring a fairly unbiased sample selection.

Paper III also had various limitations. Some cases detected by ECS might have been mistakenly categorized as PCF in TB registers available at the health facility, but not a vice versa. We see no reason why these few incorrectly categorized cases should have different outcomes, therefore, bias our results. By a slight reduction in the sample size of the smallest group it might slightly reduce the statistical power. We believe in our study setting, that there were other predictors of TB treatment outcomes that could not be assessed, as these were not routinely collected by the NTP during the study period; examples might be disease severity, smoking, nutritional status and socioeconomic status. Hence, residual confounding cannot be ruled out. The recording and reporting system for TB cases had no data related to TB patient's HIV status. According to Integrated Biological Behavioural Surveillance Survey (IBBS) in 2016, the prevalence of HIV in Pakistan is low (0.12%) and limited to specific risk groups, such as sex workers and intravenous drug users. We included only those TB patients who were initiated on TB treatment therefore, the impact of pre-treatment loss to follow-up on overall outcomes could not be assessed in this study. There is a possibility that the ECS might have experienced different rates of pre-treatment losses than PCF groups and this may have influenced the TB treatment outcomes. This is one limitation and we are not able to assess its impact on overall results. Another limitation may be related to the differences in the way Xpert testing was done in both the groups. Whereas approximately 12% of TB patients in the ECS group received an Xpert test (and thus excluded rifampicin resistance), we are not aware what proportion of TB patients in the PCF group had received Xpert test and had rifampicin resistance excluded before first-line TB treatment. This may have introduced a bias that makes the two groups different and may have effected TB treatment outcomes.

6. Conclusion and Recommendations

6.1 Conclusion

An innovative tuberculosis active case finding strategy funded by Stop TB Partnership involved screening of household and close community contacts (within 50 meters' radius) of TB patients, identified TB patients which were previously undetected through routine passive case finding and led to a substantial increase in TB case notification.

The project identified more men and children than routine TB program, the groups that are more often missed by routine TB program. The use of Gene Xpert testing for smear negative TB cases gave a yield; previously, Gene Xpert was never used for further investigation of smear negative cases in routine practice as per NTP/WHO guidelines.

The treatment outcomes among the cases detected in the project were not inferior to those for patients detected by routine TB program.

6.2 Recommendations

The current National Strategic Plan (2020) has adopted several strategies like active and systematic screening of high-risk populations to increase detection of TB cases. The widening circle approach is actually important for the program since there is weak focus on the contact screening. and there is need to enhance the yield of smear positive cases. This strategy of widening circle is simple and can be adopted as a routine program activity. Therefore, the NTP plans to incorporate the lesson learnt from this research project to sustainable program activities, is probably initially funded by Global Fund Grant and then by the local government.

ECS should be considered as an important addition to standard case finding as the findings encourage stakeholders in Pakistan. The adaptation of this approach will help in TB case finding projects within household and close community contacts and treat missed TB cases, to complement the essential routine standard PCF.

Policy implication

The close community contacts investigation is feasible after considering the main operational implications include the requirement for additional human resources and access to Xpert MTB/RIF test for diagnosis of TB. The obvious question will be, how much does it cost? Once the long term impact and cost effectiveness of close community contact investigation is established, and the feasibility of implementation during routine activities is considered, the national and provincial programme managers may consider scaling up the proposed intervention across the country. As of now, the current study provides robust findings for short-term impact of close community contact investigation for TB case finding.

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8. Published papers

8.1 Paper I

PLOS | ONE

RESEARCH ARTICLE

Extending 'Contact Tracing' into the Community within a 50-Metre Radius of an Index Tuberculosis Patient Using Xpert MTB/RIF in Urban, Pakistan: Did It Increase Case Detection?

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Data Availability Statement: The study protocol was reviewed and approved by the Ethics Advisory Group of International Union Against Tuberculosis and Lung Disease (The Union), Paris, France. It will not be possible to share the patient-wise data due to concerns of confidentiality and other ethical restrictions imposed by the advisory group. However, data will be available upon request. Interested researchers may contact "eag@theunion".

Abstract

Background

Currently, only 62% of incident tuberculosis (TB) cases are reported to the national programme in Pakistan. Several innovative interventions are being recommended to detect the remaining 'missed' TB cases. One such intervention involved expanding contact investigation to the community using the Xpert MTB/RIF test.

Methods

This was a before and after intervention study involving retrospective record review. Passive case finding and household contact investigation was routinely done in the pre-intervention period July 2011-June 2013. Four districts with a high concentration of slums were selected as intervention areas; Lahore, Rawalpindi, Faisalabad and Islamabad. Here, in the intervention period, July 2013-June 2015, contact investigation beyond household was conducted: all people staying within a radius of 50 metres (using Geographical Information System) from the household of smear positive TB patients were screened for tuberculosis. Those with presumptive TB were investigated using smear microscopy and the Xpert MTB/RIF test was performed on smear negative patients. All the diagnosed TB patients were linked to TB treatment and care.

Results

A total of 783043 contacts were screened for tuberculosis: 23741(3.0%) presumptive TB patients were identified of whom, 4710 (19.8%) all forms and 4084(17.2%) bacteriologically

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Competing Interests: Author Robert Stevens is affiliated with Mott MacDonald. Mott MacDonald was contracted by Stop TB (which author Jacob Creswell is affiliated with) to provide independent monitoring and evaluation of TB REACH projects. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

confirmed TB patients were detected. The contribution of Xpert MTB/RIF to bacteriologically confirmed TB patients was 7.6%. The yield among investigated presumptive child TB patients was 5.1%. The overall yield of all forms TB patients among investigated was 22.3% among household and 19.1% in close community. The intervention contributed an increase of case detection of bacteriologically confirmed tuberculosis by 6.8% and all forms TB patients by 7.9%.

Conclusion

Community contact investigation beyond household not only detected additional TB patients but also increased TB case detection. However, further long term assessments and cost-effectiveness studies are required before national scale-up.

Introduction

Pakistan ranks fifth amongst the 22 high burden tuberculosis (TB) countries with TB incidence rate of 270 per 100,000 population and prevalence of 341 per 100,000 population; however, only 62% of these cases are detected and reported to the National TB Program (NTP) [1]. Eighteen national prevalence surveys in high TB burden countries have demonstrated that more than half of TB patients remain undetected [2]. Progress towards achieving national and global TB targets requires detecting these 'missed' cases. To achieve this, the current strategy of passive case finding (PCF) will not be sufficient. There has been renewed interest and investment in for systematic screening / intensified case finding strategies for TB [2].

A systematic review of 62 studies concluded that screening increased the number of TB patients found in the short term and found patients earlier with less severe disease [3]. ACF strategies include mobile screening units, contact investigation, public-private collaborative activities, and mass community screening. Indiscriminate mass screening of communities for TB is not recommended due to concerns of cost and lack of evidence of effectiveness [4–6]. Many ACF initiatives among high risk groups including household and close contacts and people living in urban slums have shown promising results [4,7–10]. However, the evidence of impact on TB transmission and epidemiology (incidence, prevalence and mortality) is insufficient as there is dearth of studies with long term follow up and the availability of a control group [3]. Operational research on well planned ACF interventions should be conducted to measure the impact of ACF and inform NTPs and policy makers.

Recognizing the need to screen high risk groups, the Pakistan NTP adopted several novel strategies [11]. One such innovative strategy was TB screening among close community contacts living within a radius of 50 metres of index TB cases in addition to household contact investigation. All contacts were screened for TB symptoms and investigated using smear microscopy, Xpert MTB/RIF (for smear-negatives) and chest radiography. A similar concept of radius contact screen has previously been tried successfully in patients of smallpox [12]. The NTP implemented this with the support of TB-REACH wave III in four districts of Punjab province, Pakistan, from July 2013 to June 2015.

This operational research is the first systematic assessment of the impact of close community contact screening on TB case detection in Pakistan. **Specific objectives** were i) To assess the number of household and community contacts of sputum smear-positive TB patients screened in intervention districts between July 2013—June 2015; and among them, to determine the number (proportion) of presumptive TB patients identified, TB patients detected and number initiated on treatment and ii) to determine the percentage increase in TB case detection relative to baseline (July 2011 –June 2013) in the intervention districts.

Methods

Ethics Approval

The study protocol was reviewed and approved by the Ethics Advisory Group of International Union Against Tuberculosis and Lung Disease (The Union), Paris, France. Sharing of the patient-wise data due to concerns of confidentiality and other ethical restrictions is imposed by the advisory group (eag@theunion). Permission was taken from NTP, Pakistan to conduct this operational research. As this research involved analysis of secondary data collected routinely under the national programme, the need for individual informed consent was waived by the ethics committee.

Study design and population

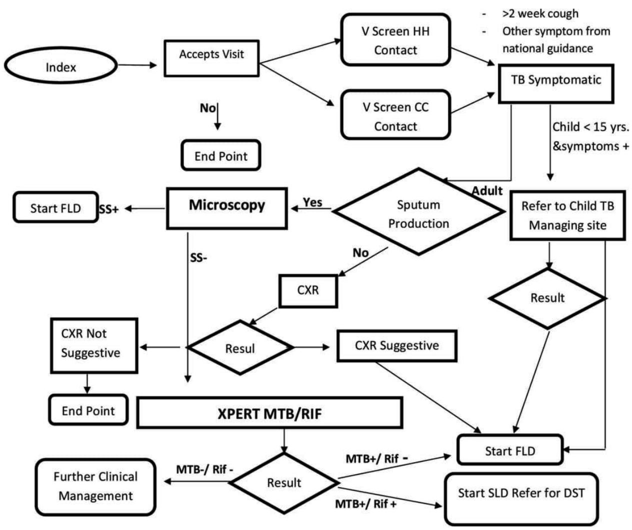
This research involved a retrospective record review of a cohort of community contacts living within 50 metre radius of infective tuberculosis patients in intervention districts. For the first objective, study participants were all the community contacts within 50 metre radius of a sputum smear-positive TB patient registered for treatment in intervention districts from July 2013 to June 2015. For the second objective, study participants were all notified TB patients in intervention districts during pre-intervention (July 2011-June 2013) and intervention period (July 2013-June 2015).

Setting

General. Thirty-six percent of Pakistan's 182.5 million people live in urban areas. Pakistan is a country with high and growing proportion of people living in urban slums[13]. People living in these overcrowded settings are more likely to have low nutritional status and are vulnerable to communicable diseases, in particular TB. The Basic Management Unit (BMU) is a health facility providing primary health care, TB diagnosis with sputum smear microscopy, patient registration and treatment. The Xpert MTB/RIF test is available at Programmatic Management Drug Resistant Tuberculosis (PMDT) sites for Multi Drug Resistance MDR contacts and treatment failure (all category II patients). Household contact investigation of smear positive index TB patients is routinely implemented by the NTP.

Study setting. Four districts with a high concentration of slums were selected as intervention areas which included Lahore, Rawalpindi, Faisalabad and Islamabad. These districts have a total population of 18 million half of whom live in slums.

Intervention. All people staying within a radius of 50 metres from the household of index patient were contacted and screened for TB. A cut-off of 50 metres was chosen based on the data from the electronic TB surveillance system which revealed the presence of many patients coming from the same family, same address or neighbouring areas and suggested high rates of epidemiological (geographical) clustering of TB patients. Additionally, the approximate number of household in this radius (5–50) was deemed feasible to be covered under close community screening by the NTP. Mobile phones enabled with Geographic information system (GIS) technology were used by field workers to identify households within a 50 metre radius of the index patient and collect data. All people permanently residing within a radius of 50 metres, available at the time were contacted and screened for TB. Measures were taken to maintain the index patient's confidentiality in front of contact persons. Any person with productive cough for more than two weeks was defined as 'presumptive TB patient'. Initially, one spot sputum



V screen: Verbal screening, HH: Household, CC: Community contact, SS +: sputum smear positive, SS-: Sputum smear negative, CXR: chest X-ray, MTB +: Mycobacterium tuberculosis detected, MTB -: Mycobacterium tuberculosis not detected, Rif +: resistance to rifampin, Rif -: No resistance to rifampin, FLD: First line drug, SLD: Second line drug, DST: Drug susceptible test

Fig 1. Flow chart to explain the flow of patients in TB Reach project, Pakistan

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sample was collected and transported to the BMU for diagnostic testing. If it was found negative, another visit was made to collect second sample for Xpert MTB/RIF. The project diagnostic algorithm is displayed in Fig 1. According to project algorithm, smear-positivity was defined as at least one smear containing at least one acid-fast bacillus, which is in tune with WHO guidelines. All patients with a positive smear, or M. tuberculosis detected by Xpert were considered bacteriologically positive TB. Clinical TB was defined as active TB diagnosed by a physician who decided to give a full course of TB treatment based on clinical, radiology and/or histology findings but without bacteriological confirmation.

Patients that were bacteriologically positive for TB were contacted by the project Field Officer (FO) and referred to the nearest BMU for registration and treatment initiation. All presumptive child TB patients aged less than 15 years were referred to hospitals with availability of specialist paediatric care for diagnosis and treatment and were followed-up. People who were negative on both sputum microscopy and Xpert MTB/RIF were referred to the nearest BMU for follow-up according to national guidelines.

Xpert MTB/RIF testing was funded by the project and provided free of cost. Sixty Field Officers (FOs) were trained under this project and allocated to BMUs. Primary and maternal health workers called Lady Health Workers (LHW) from respective BMUs accompanied the FOs during the house to house visits. The activity of LHW was incentivized by the project. FOs were provided two wheeler transport facility to transport the sputum to the BMU. FOs were equipped with mobile phones enabled with GIS and web interface technology for data collection. Web-based system was developed to capture data on mobile phones which were uploaded real-time to a centralized server. This was enabled by GIS technology which captured the co-ordinates of the location of the households of the index case as well as the household and community contacts. The web-based interface permitted comprehensive daily real-time supervision of field officers' performance, with no data loss. The online database was password protected and only authorized persons were permitted to access the data for monitoring and analysis purposes.

Data collection and variables

For the first objective, aggregate district-wise (quarter-wise) data was collected: number of persons identified for screening; stratified by household and community; age and sex distribution; presumptive TB patients (yes/no); sputum collection (yes/no); result of sputum microscopy (positive, negative and pending); outcome of Xpert MTB/RIF test (MTB detected/ rifampicin resistance/ MTB not detected/ No result or error or invalid); TB status (yes/no); and treatment initiation (yes/no). For the second objective the following aggregate data was collected: total number of TB patients notified during pre-intervention and intervention period, stratified by district, type of TB, age distribution and sex distribution.

Data Analysis

Data was extracted out of the centralized database and analysed in STATA v12 (StataCorp, TX 2011). Descriptive aggregate data analysis was done to assess the number of people screened in household and community and among them, to determine the number (proportion) with presumptive TB and diagnosed as TB. Number needed to screen (NNS—overall and stratified by household contacts and close community contacts) to detect one TB patient was calculated among total contacts screened and among presumptive TB patients. The percentage increase in case notification in intervention districts was calculated between pre-intervention (Jul 2011-Jun 2013) and intervention periods (July 2013-June 2015).

Results

A total of 783043 contacts were screened for tuberculosis symptoms, of whom 89222 were household contacts and 693821 were close community contacts. A total of 23741 (3.0%) presumptive TB patients were identified and of whom, 14973 (63.1%) presumptive TB patients were investigated for sputum microscopy and 5019 (21.1%) underwent chest X-ray. Among investigated, 4084 (20.4%) were bacteriologically confirmed TB patients. Of 11064 found to be smear-negative and requiring an Xpert test, only 6877 (62.2%) were tested using Xpert MTB/RIF. Of them, 522 (7.6%) were found to have TB and among them, 44 (8.4%) had rifampicin resistance (Table 1). A total of 5019 presumptive TB patients were examined through chest X-rays and among them 559 (11.1%) were clinically diagnosed as TB patient based on chest X-ray. Of the 4710 TB patients detected as a result of this intervention, 4604 (97.7%) were initiated on treatment.

NNS to detect one bacteriologically confirmed TB among total contacts screened was 192 overall: 90 among household contacts and 225 among close community contacts. NNS to detect one confirmed TB (all forms) among total contacts screened was 166 overall: 77 among household contacts and 195 among close community contacts. The screening yield for all

Table 1. Screening Yield and Number Needed to Screen among household contacts and Close community contacts of index patients in intervention* districts, Pakistan.**

Contacts screening	Index household	Close community within 50m radius of index HH	Total
Total screened	89222	693821	783043
Presumptive TB patients	5173 (5.8%)	18568 (2.7%)	23741 (3.0%)
Investigated for sputum smear microscopy	3356/5173 (64.9%)	11617/18568 (62.6%)	14973/23741 (63.1%)
Number smear positive	932 /3356 (27.8%)	2977/ 11617 (25.6%)	3909/14973 (26.1%)
Number smear negative eligible for Xpert testing	2424/3356 (72.2%)	8640/ 11617 (74.4%)	11064/14973 (73.9%)
Number tested using Xpert	1476/2424 (60.9%)	5401/8640 (62.5%)	6877/11064 (62.2%)
Number of TB positive on Xpert	160/1476 (10.8%)	362/5401 (6.7%)	522/6877 (7.6%)
Number of Rifampicin Resistant positive	14/160 (8.8%)	30/362 (8.3%)	44/522 (8.4%)
Number who underwent Chest X-ray	992/5173 (19.2%)	4027/18568 (21.7%)	5019/23741 (21.1%)
Number clinically diagnosed as TB based on Chest X-ray	133/992 (13.4%)	426/4027 (10.6%)	559/5019 (11.1%)
Bacteriologically confirmed TB	996/5173 (19.3%)	3088/18568 (16.6%)	4084/23741 (17.2%)
NNS among total screened	90	225	192
NNS among presumptive TB	5	6	5.8
All forms of TB	1154/5173 (22.3%)	3556/18568 (19.1%)	4710/23741 (19.8%)
• Lahore	479 (41.5)	1540 (43.3)	2019 (42.9)
• Faisalabad	363 (31.5)	1279 (36.0)	1642 (34.9)
• Rawalpindi	277 (24.0)	668 (18.8)	945 (20.0)
• Islamabad	35 (3.0)	69 (1.9)	104 (2.2)
NNS among total screened	77	195	166
NNS among presumptive TB	5	5	5.0
Treatment initiated	1126 (97.6%)	3478 (97.8%)	4604 (97.7%)
Child TB patients among child presumptive	84/1269 (6.6%)	213/4596 (4.6%)	297/5865 (5.1%)
NNS among total child screened	358	1143	921
NNS among presumptive child TB patients	15	22	20

*Community screening in addition to household screening within 50 meter radius of index house

** Lahore, Faisalabad, Rawalpindi and Islamabad

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forms TB patients among investigated presumptive TB patients was 19.8% overall: 22.3% among household contacts and 19.1% among close community contacts. However, there was inter-district variation in case detection, which was highest in Lahore (42.9%) and Faisalabad (34.9%).

NNS to detect one child TB patient among total child contacts (<15 years) screened were 921 overall: 358 among household contacts and 1143 among close community contacts. The screening yield for child TB patients among investigated presumptive child TB patients was 5.1%.

Table 2. Numbers of tuberculosis patients reported in the pre-intervention and intervention period of the project (Close community contact screening) in Pakistan.

	Pre-intervention (July 11–June 13)	Intervention (July 13 –June 15)	Increase in TB case detection
	n	n	%
Lahore	49778	54325	9.1
Faisalabad	20576	22220	8.0
Rawalpindi	27181	28881	6.3
Islamabad	2849	2915	2.3
0–4 yrs	1487	1591	7.0
5–14 yrs	11019	11697	6.2
> = 15 yrs	87878	95143	8.3
Male	51013	55178	8.2
Female	49371	53263	7.9
Bacteriological positive	28159	30066	6.8
Total all forms	**100384**	**108341**	**7.9**

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Table 2 shows age, sex and bacteriologically positive status of TB patients notified during the intervention period and compared with the pre-intervention period. Overall, there was an eight percent increase in notified TB patients during the intervention period. This was consistent among males or females, children or adults and sputum positive TB. However, there was inter-district variation and the increase in case detection was highest in Lahore district (9.1%).

Fig 2 demonstrates that there was an increase in new sputum positive (NSP) case notifications during the project above than the expected linear trend in the intervention districts.

Discussion

Community contact investigation within 50 metres of an index patient as an ACF strategy which included household contact investigation and contact investigation beyond household resulted in detection of additional TB patients and increased case notification during

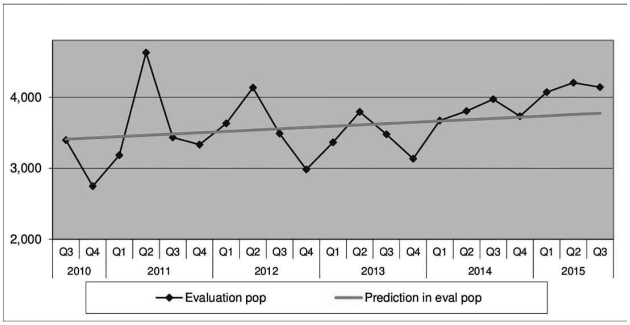

Fig 2. New sputum positive TB case notifications (NSP) compared with projected baseline linear trends

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intervention period by about 7.9% in Pakistan. This research had several strengths. First, community contact investigation within 50 metres is a novel ACF intervention that to our knowledge has not been reported in literature. Second, the intervention was conducted on a large population in urban Pakistan, hence generalizable to similar settings and TB epidemics. Extending the contact circle seems obvious in overcrowded areas, and fairly easy to perform. Third, this was the first time the Xpert MTB/RIF test was implemented in contact screening in Pakistan. Fourth, the GIS web-based interface was used for data collection which permitted comprehensive daily real-time monitoring and supervision and ensured accuracy and completeness of data. Fifth, despite being implemented by project staff, the intervention was conducted routinely under the stewardship of Pakistan NTP and thus feasible, if considered for scale up. Finally, the study adhered to the STROBE guidelines for reporting [14].

The study had several limitations. No data was collected on participants who did not consent or were not available at the time of field visit in intervention areas; and it was possible that this participant sample was not representative and had different characteristics. However, it was not operationally feasible to make a second visit. Details of time to diagnosis from onset of symptoms and visit to a health care facility for TB symptoms (if any) were not collected in this study. Treatment outcomes were not compared among those detected through the intervention. This is being studied and will be reported in a separate paper. However, a recent systematic review has found no difference in treatment outcomes between TB patients found by screening and those found through PCF [3]. Evidence from clinical trials is lacking and more data are needed to inform international policy. Most of TB diagnoses were based on a single smear with no culture that could lead to false positive TB cases which is a common concern with regards to ACF [15].

Xpert MTB/RIF offers a new possibility for diagnosis of bacteriological positive TB among those initially negative on sputum examination [16]. TB yield from Xpert MTB/RIF was lower in intervention, but more absolute numbers of MDR TB diagnosed; which has benefit in stopping transmission if linked to treatment and care.

Contact tracing is a proven strategy to identify infected individuals, and a vital component of any tuberculosis (TB) elimination strategy [17,18]. Community based screening programmes in high burden TB countries have mainly relied on symptom screening, sputum smears and culture, due to the logistical and operational challenges of mass CXR screening [5,19]. Various ACF strategies among high risk groups have shown positive results in identification of TB [7–9]. Nonetheless, the evidence that ACF impacts on TB epidemiology remains weak. The ZAMSTAR evaluated two different interventions (respectively TB household visits and community-wide case finding) and reported a significant reduction in undiagnosed TB at community level from the household intervention [19]. A study from Cambodia provided evidence of reduced TB notifications among individuals who underwent intensive screening for TB over 2 years of follow-up [20]. However, a study from Zimbabwe showed increased case notification rates during the study period, with a 41% reduction in TB prevalence in 3 years of implementation of community-based TB case finding [5]. A systematic review reported that screening contacts does not contribute to more than 9% of all notified patients [3]. In current study, of all the bacteriologically confirmed TB patients diagnosed in the intervention period, 75% were contributed by close community screening. NNS to find one patient of TB was 90 in household contacts and 225 in community contacts, where a systematic review reported the NNS was reported 100 in community contacts in high burden TB countries [21].

The high screening yield among presumptive TB patients in beyond household contacts (19.1%) and in household contacts (22.3%) justified the intervention. Similarly in another study in Sindh, Active case detection through household contact investigation have found 22.7% yield of TB patients [22]. Other studies on active case detection have found yields of TB patients among those referred ranging from 4% in South Africa [23], 13% in Ethiopia [24] and 15.5% in Pakistan [7]. 297 additional children with TB were detected due to intervention and this generated the evidence that the project contributed to the overall increase in child case detection but the NNS was greater than adults, this suggested that the project may have missed child patients that should be addressed while scaling-up this intervention. Increase in patients notified was only 2.3% in Islamabad district which needs to be further explored.

Policy implication

The close community investigation is feasible to conduct though the main operational implications are the need for additional human resources and access to Xpert MTB/RIF for TB diagnosis. Once the long term impact and cost effectiveness of close community investigation is established, and the feasibility of implementation in to routine activities is considered [25], national programme managers may consider scaling up this intervention nationwide. As of now, the current research provides robust evidence for short term impact of close community investigation on TB case detection.

In conclusion, an innovative strategy involving close community contact tracing using Xpert MTB/RIF led to increase in TB case detection suggesting the value of expanded contact investigation into the community beyond the household. Further studies are needed to establish feasibility and cost-effectiveness before scale-up and assess long-term epidemiological impact.

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8.2 Paper II

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Are patients with pulmonary tuberculosis identified by active and by passive case detection different? A cross-sectional study in Pakistan.

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A R T I C L E I N F O

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Objectives: Our objective was to compare the characteristics of patients with pulmonary tuberculosis (TB) identified through "extended contact screening" (ECS) with those of patients identified through routine passive case finding (PCF).
Methods: Active TB case finding by ECS was tested from 2013–2015. This was a cross-sectional study based on data collected from ECS and routine program data from Lahore, Faisalabad, and Rawalpindi districts, and Islamabad in 2015. Characteristics of patients identified through ECS and PCF were compared.
Results: Of the 12,114 patients with pulmonary TB in the study, 4604 (38%) were identified through ECS, of whom 4052 (88%) had bacteriological confirmation. Male patients comprised 56.2% (95% confidence interval [CI] 54.8–57.6) of patients with pulmonary TB identified through ECS and 49.7% (95% CI 48.6–50.8) of those identified through PCF. The proportion of bacteriologically confirmed cases was 88.0% (95% CI 87.1–88.9) in the ECS group and 50.3% (95% CI 49.2–51.4) in the PCF group. By regression analysis we found that compared with patients aged 15–44 years, children aged <15 years had higher chances of being identified through ECS (adjusted odds ratio 2.69; 95% CI 2.21–3.28). There was a higher chance of cases being detected by ECS in Faisalabad (adjusted odds ratio 2.57; 95% CI 2.01–3.29) than in Islamabad.
Conclusion: ECS identified a higher proportion of male and child patients with pulmonary TB than routine case finding; both of these groups are more often unidentified through routine TB control.

Introduction

Globally, out of the estimated 9.9 million new tuberculosis (TB) cases, approximately 4.3 million (41%) were not identified and registered during 2020. Pakistan had an estimated 0.6 million TB cases in 2020, with 272,990 (48%) reported and about 300,000 (52%) "missing," unreported, or undetected cases (World Health Organization, 2021). In most countries, the prevalence of TB is higher among men than among women (Borgdorff et al., 2000; Onozaki et al., 2015; Qadeer et al., 2016), and higher among the poor. Patients with TB who are "missed" may not seek health care, may have no symptoms or may not recognize them, or may face barriers to health care (World Health Organization, 2013a). These missing cases may remain sources of TB transmission and sustain the global TB epidemic (World Health Organization, 2015), and therefore represent an obstacle for meeting the ambitious global targets of 90% reduction in TB incidence and mortality by 2035 (World Health Organization, 2013b).

Global TB control is mainly based on "passive case finding" (PCF), in which patients with symptoms visit health facilities on their own initiative and are identified by the health system as patients with presumptive TB and followed up. In "active case finding" (ACF), the health system initiates active screening of population groups (World Health Organization, 2013a). ACF is often focused on populations with known high prevalence of undetected TB, or on marginalized and vulnerable populations with poor access to health services (World Health Organization, 2012).

The characteristics of patients identified through ACF may differ from those of patients identified through PCF. In India, ACF identified more female patients with TB (Shewade et al., 2019);

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Table 1
Basic population characteristics of Pakistan in 2015.

Characteristics	Value
Population, total (millions)	199.43
Population growth (annual %)	2.1
Surface area (sq. km) (thousands)	796
Population density (people per sq. km of land area)	258.7
Poverty headcount ratio at national poverty lines (% of population)	24.3
Income share held by lowest 20%	9
Life expectancy at birth, total (years)	67
Fertility rate, total (births per woman)	3.66
Primary school completion rate, total (% of relevant age group)	65
School enrollment, primary (% gross)	85
School enrollment, secondary (% gross)	40
School enrollment, primary and secondary (gross), gender parity index (GPI)	0.83
Urban population growth (annual %)	2.7
GDP growth (annual %)	4.7

Source: World Development Indicators database.

similar studies conducted in Eastern Nepal and Cambodia showed that ACF detected more TB cases among older adults and women (Cassels et al., 1982; Eang et al., 2012); a combination of ACF and PCF was more common in detecting TB cases among males and people aged >15 years in Vietnam (Fox et al., 2018).

The strategies of most national TB programs are based on PCF, but often include special risk groups (e.g., household contacts, patients with HIV infection) and actively try to identify them. Pakistan's National TB Control Program (NTP) tested an innovative ACF strategy, called "extended contact screening" (ECS), from 2013–2015 in four selected districts. This involved investigating community contacts in addition to the routinely investigated household contacts. All neighbors in households within a 50-m radius of the home of a smear-positive patient with TB were investigated on the basis of reported TB symptoms. This strategy increased case notification in the districts of intervention by approximately 8%, which was more than expected in relation to usual annual increases reported through routine TB control (Fatima et al., 2016). The treatment outcomes were not inferior to those of routine treatment in the NTP (Ul Haq et al., 2021). Other TB REACH projects also found increased TB case findings (Malik et al., 2020).

The question arose: were these additional cases similar to those routinely detected, or was there a higher proportion of "missing" classic risk groups? The aim of this study was to investigate if patients identified through ECS and PCF in four selected districts of Pakistan from 2013–2015 were different, and to compare their sociodemographic and clinical characteristics.

Methods

Study design

This cross-sectional study investigated the difference between ECS and routine PCF in the characteristics of detected pulmonary TB (PTB) cases, on the basis of data collected during 2015 in four selected districts in Pakistan.

Setting

According to the World Bank Annual Report 2015, Pakistan is among the world's most populous countries, with a population of nearly 200 million, 64% of which constitutes the rural population. The population characteristics are shown in Table 1.

The health system in Pakistan includes government (public) and parastatal health institutions (Pakistan Armed Forces, Sui Gas, Water & Power Development Authority, Pakistan Railways, Fauji Foundation) and the private sector. Public health care is delivered mainly through a network of primary, secondary, and tertiary-level health facilities. The primary healthcare facilities include civil dispensaries, basic health units, rural health centers, mother-child health care centers, urban health units, and urban health centers. The secondary-level healthcare facilities comprise sub-district hospitals and district hospitals. Tertiary-level health care is provided through teaching and specialized hospitals. Private health services include private-sector hospitals, teaching hospitals and universities, clinics of general practitioners, polyclinics, health facilities run by various charitable groups, informal health providers, and private laboratories. Some of these private enterprises work under the "PPM" (private-public mix) model in a national network with the NTP, and have units supported by supervision, training, and free drugs from the NTP; all TB cases must be reported quarterly to the NTP. However, most of the private sector in Pakistan is not involved with this system and is encouraged to refer patients with TB symptoms to a basic management unit (BMU) for further management, but this is often not done because of busy schedules.

TB BMUs are located at the district and sub-district levels, consisting of hospitals, rural health centers, and some basic health units. A BMU has a laboratory staff performing smear microscopy, with some also performing Xpert MTB/RIF assays, and a doctor/qualified medical staff trained to diagnose and initiate TB treatment. TB treatment involves six to eight months of treatment provided under daily direct observation by a healthcare provider, a community volunteer, or a family member. The BMU is also a facility where patients with TB 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, 2020). Sputum microscopy, Xpert MTB/RIF testing, and TB treatment services are provided free of cost.

All patients are diagnosed and treated in accordance with the national TB guidelines under direct observation (National Tuberculosis Programme, 2019).

The Pakistan NTP had a project funded by TB REACH Wave 3, intended to facilitate the detection of more TB cases (Fatima et al., 2016). From 2013–2015, ECS was implemented in four districts of Pakistan, namely Lahore, Rawalpindi, Faisalabad, and Islamabad. 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 socioeconomic status of the districts' population is higher than the national average because of better jobs and business opportunities. However, half of the population live in slums with poor socioeconomic conditions.

ECS was done as follows. Patients of all ages receiving TB treatment were identified through TB registers from BMUs. All people staying within a 50-m radius (ascertained using geographic information system [GIS]) of the households with known patients with

TB were contacted and screened for TB by trained project staff. A 50-m radius was chosen on the basis of data from the electronic TB surveillance system, which revealed the presence of many cases coming from the same family, same address, or neighboring areas, and suggested high rates of geographic clustering. The approximate number of households in this radius was deemed feasible for close community screening by the NTP. Mobile phones enabled with ArcGIS (version 10) software were used by field workers to identify households within the 50-m radius of the index case and collect data. All available people permanently residing within the 50-m radius were contacted. The participants were informed about a patient with TB in the neighborhood (50-m radius), but measures were taken to safeguard the index patient's anonymity and the confidentiality of their personal information. Any person with a productive cough for more than two weeks was defined as a patient with presumptive TB. Initially, one spot sputum sample was collected and transported to the closest BMU for diagnostic testing. The same diagnostic algorithm was used except among sputum smear microscopy–negative cases of presumptive TB, for which the Xpert MTB/RIF assay was used if available. Patients bacteriologically positive for TB were contacted by the project staff and referred to the nearest BMU for registration and treatment initiation. All patients with presumptive TB aged <15 years were referred to specialist pediatric care for diagnosis and management. People whose sputum tested negative on both microscopy and Xpert MTB/RIF were referred to the nearest BMU for follow-up according to the national guidelines. Patients identified through ECS were marked "TB REACH" in the TB register.

Study population and sampling technique

The study population were patients with PTB of all ages and sexes diagnosed and reported in the study districts. These patients were classified on the basis of case detection strategy: patients detected by routine PCF or by ECS, registered and treated at public or private facility, and engaging with the NTP in four districts of Pakistan, namely Lahore, Rawalpindi, Faisalabad, and Islamabad, between July 2013 and June 2015. The cases identified through ECS were marked as such in the TB registers at facility level. All patients were considered as identified through PCF unless referred by ECS field staff. This was confirmed by reviewing the project records. Patients with known rifampicin resistance and treated with second-line drugs were not included. Only one person from the same family was invited to participate. Patients were excluded if they already had a family member registered for TB treatment through ECS and included in the study.

For the PCF group, we selected a subset of approximately 10% of the total population identified through PCF, so that the sample was almost twice that of the ACF group. Sampling was done to ensure that the sample was representative of the PCF group with regard to sex, age, facility, and city (appended Table).

Data collection, variables, and sources

The main outcome variable was the detection method: PCF or ECS. The data were collected through a structured questionnaire by trained project staff in the community and case-based data were obtained from a centralized database, entered into Microsoft Excel (Microsoft, Redmond, WA, USA), and validated in 2015. This information was prospectively collected from routine patients with TB who consented to participate because this information was not collected routinely.

Independent variables included patient characteristics such as age, gender, district, TB category, bacteriological confirmation, marital status, education status, occupation, family income, household members, type of house, residence, people sleeping in one room, ventilation, water source for drinking, smoking, and diabetes mellitus status.

Analysis and statistics

For clinical characteristics, case-based data were entered from facility-based TB registers, whereas the research data collected through interviews were entered into Microsoft Excel and validated and analyzed using Stata (version 12.1; StataCorp LLC, College Station, TX, USA). For quality assurance, our database was compared with aggregated data from the routine quarterly reports, and disparities were manually re-checked with the original TB registers. Demographic and clinical characteristics of patients identified through ECS and PCF were compared using 95% confidence intervals (CIs). We conducted logistic regression analysis to compare determinants of case finding by ECS, adjusting for potential confounders. Unadjusted and adjusted odds ratios (ORs) were reported. *P*-values of ≤0.05 were considered significant.

Results

We included 12,114 patients with PTB in the study; 4604 (38%) were identified through ECS, of whom 4052 (88%) had bacteriological confirmation. Out of 74,827 patients (mean age 36 years, male = 49.6%) eligible in the routine registers in the study area and identified through PCF, we interviewed 7510 (10%) (mean age 37 years, male = 49.7%), and they represented the comparison group designated as the PCF group.

Table 2 shows the characteristics of patients in the ECS and the PCF groups. The mean age was 36 years (95% CI 35.5–36.6) in the ECS group and 37 years (95% CI 36.9–37.7) in the PCF group. The proportion of males was 56.2% (95% CI 54.8–57.6) in the ECS group and 49.7% (95% CI 48.6–49.2) in the PCF group. The proportion of bacteriologically confirmed cases was higher in the ECS than in the PCF group. Regarding education, the proportion of no schooling among patients aged <15 years was higher in the ECS than in the PCF group, and there were fewer students in the ECS than in the PCF group. Similarly, there were more unemployed patients aged <15 years in the ECS than in the PCF group. There were some differences in house type, rural-urban habitation, and location.

Table 3 shows the characteristics of patients in the ECS group, comparing those identified through household contact (HH) investigation with those identified through neighborhood screening. The mean age of patients with PTB identified through close community contact investigation was 37.0 years (95% CI 36.4–37.6), and 33.1 years (95% CI 32.1–34.2) in the HH group. The HH group had a higher proportion of patients with TB aged 15–44 years and lower proportion of patients with TB aged 45–64 years than the close community contacts group. The proportions of males and females with PTB were not significantly different.

ECS contributed to 5.8% of the total case finding, but this population was slightly different from the routine cases. Table 4 shows that, compared with patients aged 15–44 years, children aged <15 years had higher chances of being identified through ECS than PCF (adjusted OR 2.69; 95% CI 2.21–3.28). Patients in Faisalabad had higher chances of being identified through ECS than through PCF (adjusted OR 2.57; 95% CI 2.01–3.29) compared with those in Islamabad. For other factors, adjustment had little effect on the proportion of case finding by ECS.

Discussion

This study compared the characteristics of patients with PTB identified through a new method of ACF and routine program in Pakistan. There were significant differences in age, gender, laboratory confirmation of TB, occupation, and family income among the

Table 2
Characteristics of patients with tuberculosis identified through extended contact screening[a] versus passive case finding[a] in four selected districts, Pakistan, 2013–2015.

Variable	Passive case finding(N = 7510)		Extended contact screening(N = 4604)	
	n	% (95% CI)	n	% (95% CI)
Age in years				
<15	172	2.3 (2.0–2.6)	391	8.5 (7.7–9.3)
15–44	4654	62 (60.9–63.1)	2613	56.8 (55.4–58.2)
45–64	1971	26.2 (25.2–27.2)	1192	25.9 (24.6–27.2)
≥65	713	9.5 (8.8–10.2)	408	8.9 (8.1–9.7)
Gender				
Male	3731	49.7 (48.6–50.8)	2587	56.2 (54.8–57.6)
Female	3779	50.3 (49.2–51.4)	2017	43.8 (42.4–45.2)
City				
Lahore	3324	44.3 (43.2–45.4)	1994	43.3 (41.9–44.7)
Faisalabad	1983	26.4 (25.4–27.4)	1619	35.2 (33.8–36.6)
Rawalpindi	1913	25.5 (24.5–26.5)	899	19.5 (18.4–20.6)
Islamabad	290	3.9 (3.5–4.3)	92	2 (1.6–2.4)
Classification by laboratory				
Bacteriologically confirmed	3778	50.3 (49.2-51.4)	4052	88 (87.1-88.9)
Clinically diagnosed	3732	49.7 (48.6-50.8)	552	12 (11.1-12.9)
Marital status				
Married	5105	68 (66.9–69.1)	3135	68 (66.7–69.3)
Single	2405	32 (30.9–33.1)	1469	32 (30.7–33.3)
Education status				
No schooling in <15 yrs	109	1.5 (1.2–1.8)	180	4 (3.4–4.5)
No schooling in ≥15 yrs	3799	50.5 (49.5–51.7)	2222	48 (46.8–49.7)
Primary	1879	25 (24–26)	1146	25 (23.7–26.3)
Secondary	1049	14 (13.2–14.8)	648	14 (13–15)
Tertiary	376	5 (4.5–5.5)	226	5 (4.4–5.6)
Madrassah	298	4 (3.6–4.4)	182	4 (3.4–4.6)
Occupation				
Not working in <15 yrs	112	1.5 (1.2–1.8)	287	6.1 (5.6–7.0)
Not working in ≥15 yrs	2821	37.6 (36.5–38.7)	1744	37.9 (36.5–39.3)
Agriculture	693	9.2 (8.5–9.9)	406	8.8 (8–9.6)
Student	1303	17.4 (16.5–18.3)	600	13 (12–14)
Labor	1735	23.1 (22.1–24.1)	1100	24 (22.8–25.2)
Govt. service	344	4.6 (4.1–5.1)	174	3.8 (3.2–4.4)
Business	502	6.7 (6.1–7.3)	293	6.4 (5.7–7.1)
Family income				
<20,000	5828	77.6 (76.7–78.5)	3737	81.2 (80.1–82.3)
21,000–50,000	1091	14.5 (13.7–15.3)	579	12.6 (11.6–13.6)
>50,000	591	7.9 (7.3–8.5)	288	6.3 (5.6–7)
Total household members				
<5	1803	24 (23–25)	1147	25 (23.7–26.3)
>5	5707	76 (75–77)	3457	75 (73.7–76.3)
Type of house				
Kutcha	1622	21.6 (20.7–22.5)	1563	34 (32.6–35.4)
Pucca	5888	78.4 (77.5–79.3)	3041	66 (64.6–67.4)
Residence				
Urban	5653	75.3 (74.3–76.3)	3712	80.6 (79.5–81.7)
Rural	1857	24.7 (23.7–25.7)	892	19.4 (18.3–20.5)
People sleeping in one room				
Single	75	1 (0.8–1.2)	47	1 (0.7–1.3)
Double	140	2 (1.7–2.3)	92	2 (1.6–2.4)
More than 2	7295	97 (96.6–97.4)	4465	97 (96.5–97.5)
Ventilation				
Window	5820	77.5 (76.6–78.4)	3591	78 (76.8–79.2)
Ventilator	1690	22.5 (21.6–23.4)	1013	22 (20.8–23.2)
Water source for drinking				
Tube well	781	10.4 (9.7–11.1)	410	8.9 (8.1–9.7)
Borehole	3230	43 (41.9–44.1)	2027	44 (42.6–45.4)
Filter plant	879	11.7 (11–12.4)	653	14 (13–15)
Public supply	2620	34.9 (33.8–36)	1514	33 (31.6–34.4)
Smoking status				
Non-smoker	7273	96.8 (96.4–97.2)	4435	96.3 (95.8–96.8)
Smoker	237	3.2 (2.8–3.6)	169	3.7 (3.2–4.2)
DM status				
Diabetic	323	4.3 (3.8–4.8)	192	4.2 (3.6–4.8)
Non-diabetic	7187	95.7 (95.2–96.2)	4412	
				95.8 (95.2–96.4)

CI = confidence interval; DM = diabetes mellitus; TB = tuberculosis.
[a] Extended contact screening is close community contact screening. Passive case finding is identifying patients with TB through routine TB program.

Table 3
Characteristics of patients with tuberculosis identified through household contact screening and neighborhood screening in four selected districts, Pakistan, 2013–2015.

Variable	Community contacts (N = 3477)		Household contacts (N = 1127)	
	n	% (95% CI)	n	% (95% CI)
Age in years				
<15	283	8.1 (7.5-8.7)	108	9.6 (8.7-10.5)
15–44	1928	55.5 (54.4-56.6)	685	60.8 (59.4-62.2)
45–64	925	26.6 (25.6-27.6)	267	23.7 (22.5-24.9)
≥65	341	9.8 (9.1-10.5)	67	5.9 (5.2-6.6)
Gender				
Male	1952	57 (55.9-58.1)	635	56.3 (54.9-57.7)
Female	1525	44 (42.9-45.1)	492	43.7 (42.3-45.1)
City				
Lahore	1517	43.6 (42.5-44.7)	477	42.3 (40.9-43.7)
Faisalabad	1262	36.3 (35.2-37.4)	357	31.7 (30.4-33)
Rawalpindi	639	18.4 (17.5-19.3)	260	23 (21.8-24.2)
Islamabad	59	1.7 (1.4-2)	33	3 (2.5-3.5)
Classification by laboratory				
Bacteriologically confirmed	3058	88 (87.3-88.7)	994	88 (87.1-88.9)
Clinically diagnosed	419	12 (11.3-12.7)	133	12 (11.1-12.9)
Marital status				
Married	2350	67.6 (66.5-68.7)	785	69.7 (68.4-71)
Single	1127	32.4 (31.3-33.5)	342	30.3 (29-31.6)
Education status				
No schooling in <15 yrs	131	3.8 (3.2-4.5)	49	4.4 (3.2-5.8)
No schooling in ≥15 yrs	1680	48.3 (46.7-50)	542	48 (45.2-51)
Primary	867	25 (24-26)	279	24.8 (23.6-26)
Secondary	490	14 (13.2-14.8)	158	14 (13-15)
Tertiary	171	5 (4.5-5.5)	55	4.9 (4.3-5.5)
Madrassah	138	4 (3.6-4.4)	44	3.9 (3.3-4.5)
Occupation				
Not working in <15 yrs	226	6.5 (5.8-7.4)	61	5.4 (4.2-6.9)
Not working in ≥15 yrs	1293	37.2 (35.6-38.9)	451	40 (37.2-43)
Agriculture	308	9 (8.4-9.6)	98	8.7 (7.9-9.5)
Student	485	14 (13.2-14.8)	115	10.2 (9.3-11.1)
Labor	834	24 (23-25)	266	23.6 (22.4-24.8)
Govt. service	118	3.4 (3-3.8)	56	5 (4.4-5.6)
Business	213	6 (5.5-6.5)	80	7 (6.3-7.7)
Family income				
<20,000	2821	81 (80.1-81.9)	916	81 (79.9-82.1)
21,000–50,000	435	12.5 (11.8-13.2)	144	13 (2.5-3.5)
>50,000	221	6.5 (5.9-7.1)	67	6 (5.3-6.7)
Total household members				
<5	871	25 (24-26)	276	24.5 (23.3-25.7)
>5	2606	75 (74-76)	851	75.5 (74.3-76.7)
Type of house				
Kutcha	1168	33.6 (32.5-34.7)	395	35 (33.6-36.4)
Pucca	2309	66.4 (65.3-67.5)	732	65 (63.6-66.4)
Residence				
Urban	2755	79 (78.1-79.9)	895	79.4 (78.2-80.6)
Rural	722	21 (20.1-21.9)	232	20.6 (19.4-21.8)
People sleeping in one room				
Single	35	1 (0.8-1.2)	12	1 (0.7-1.3)
Double	69	2 (1.7-2.3)	23	2 (1.6-2.4)
More than 2	3373	97 (96.6-97.4)	1092	97 (96.5-97.5)
Ventilation				
Window	2711	78 (77.1-78.9)	880	78 (76.8-79.2)
Ventilator	766	22 (21.1-22.9)	247	22 (20.8-23.2)
Water source for drinking				
Tube well	319	9.2 (8.5-9.9)	91	8 (7.2-8.8)
Borehole	1509	43.4 (41.9-44.1)	518	46 (44.6-47.4)
Filter plant	515	14.8 (14-15.6)	138	12 (11.1-12.9)
Public supply	1134	32.6 (31.5-33.7)	380	34 (32.6-35.4)
Smoking status				
Non-smoker	3352	96.4 (96-96.8)	1083	96 (95.4-96.6)
Smoker	125	3.6 (3.2-4)	44	4 (3.4-4.6)
DM status				
Diabetic	129	3.7 (3.3-4.1)	63	5.6 (4.9-6.3)
Non-diabetic	3348	96.3 (95.9-96.7)	1064	94.4 (93.7-95.1)

CI = confidence interval; DM = diabetes mellitus; TB = tuberculosis.

Table 4
Determinants of extended contact screening among patients with pulmonary tuberculosis in four selected districts, Pakistan 2013–2015.

	OR	95% CI		aOR	95% CI	
Age in years						
<15	2.82	1.88	4.3	2.69	2.21	3.28
15–43	Ref			Ref		
45–64	0.89	0.79	1	1.03	0.95	1.12
≥65	0.47	0.39	0.56	0.97	0.86	1.1
Sex						
Female	Ref			Ref		
Male	1.7	1.54	1.88	1.3	1.21	1.4
City						
Islamabad	Ref			Ref		
Lahore	1.54	1.16	2.04	1.89	1.49	2.4
Faisalabad	2.02	1.52	2.68	2.57	2.01	3.29
Rawalpindi	1.4	1.05	1.87	1.48	1.16	1.9
Classification by laboratory						
Bacteriologically confirmed	Ref			Ref		
Clinically diagnosed	0.03	0.03	0.04	0.14	0.12	0.15
Marital status						
Married	Ref			Ref		
Single	1.11	0.97	1.26	1	0.93	1.09
Education status						
No schooling in <15 yrs	0.3	0.14	0.63	2.7	2.1	3.5
No schooling in ≥15 yrs	4.65	3.98	5.44	0.96	0.88	1.05
Primary	Ref			Ref		
Secondary	0.95	0.82	1.09	1	0.9	1.15
Tertiary	0.91	0.73	1.14	0.98	0.82	1.18
Madrassah	0.99	0.74	1.32	1	0.82	1.2
Occupation						
Not working in <15 yrs	44	21.66	90	4.1	3.3	5.2
Not working in >15 yrs	Ref			Ref		
Agriculture	0.99	0.8	1.23	0.95	0.83	1.08
Student	0.4	0.33	0.47	0.75	0.66	0.83
Labor	0.74	0.64	0.85	1.02	0.93	1.13
Govt. Service	0.51	0.4	0.65	0.82	0.68	0.99
Business	0.58	0.47	0.71	0.94	0.81	1.1
Family income						
<20,000	Ref			Ref		
21,000–50,000	0.84	0.73	0.97	0.83	0.74	0.92
>50,000	0.84	0.70	1.01	0.76	0.66	0.88
Total household members						
<5	Ref			Ref		
>5	0.68	0.61	0.77	0.95	0.87	1.04
Type of house[a]						
Kutcha	Ref			Ref		
Pucca	1.1	0.97	1.25	1.87	1.72	2.03
People sleeping in one room						
Single	Ref			Ref		
Double	1	0.60	1.7	1.05	0.67	1.64
More than 2	1.15	0.75	1.76	0.98	0.68	1.41
Water source for drinking						
Public supply	Ref			Ref		
Tube well	0.29	0.23	0.36	0.91	0.79	1.04
Borehole	0.89	0.79	1	1.08	0.99	1.18
Filter plant	0.96	0.83	1.12	1.29	1.14	1.45
Smoking						
Non-smoker	Ref			Ref		
Smoker	1.0	0.76	1.34	1.17	0.96	1.43
DM						
Non-diabetic	Ref			Ref		
Diabetic	1	0.81	1.27	0.97	0.81	1.16

Aor = adjusted odds ratio; CI = confidence interval; DM = diabetes mellitus; TB = tuberculosis.

[a] Kutcha houses are made of raw materials that are easily available such as stone, wood, mud, or straw. Pucca houses are built using materials such s iron, cement, bricks, and steel.

patients. We found no significant differences in education, marital status, number of persons in the household, number of persons sleeping in one room, ventilation, water source for drinking, smoking, and diabetes mellitus status.

In our study, the ECS group had a higher proportion of children with PTB compared with the routine PCF group. This is similar to the findings of a study on ACF conducted in Myanmar (Aye et al., 2018), and suggests that the routine program may have missed child patients, which should be addressed while scaling up this intervention. Within the ECS group, there were more patients aged 15–44 years and a lower proportion of patients aged 45-64 years identified through household-contact tracing than through neighborhood screening. Our findings are consistent with a study from Peru that screened household contacts and members of neighborhood (Becerra et al., 2005).

We observed a higher proportion of males identified through ECS than through PCF. The prevalence survey conducted in Pakistan in 2011 showed that TB prevalence among men was almost double that of women (Qadeer et al., 2016), thus we expected TB notification to also be markedly higher for men (approximately two-thirds male). The proportion of male patients identified and reported in 2015 ranged from 49% (Sindh) to 59% (Gilgit-Baltistan Province), thus it seems more men than women remain unidentified and untreated (National Tuberculosis Programme Pakistan, 2016). A study conducted in Karachi, Pakistan also showed higher TB notification rates in female than in male patients (Codlin et al., 2011). A higher prevalence of TB among men has been reported from almost all other countries in the world (Borgdorff et al., 2000), as well as from TB prevalence surveys in Asia (Onozaki et al., 2015). A systematic review and meta-analysis suggested that men may be less likely than women to seek or access care in many settings (Horton et al., 2016). From this we would expect a higher proportion of men among those missed in routine PCF but identified through ACF, which is what we observed in our study.

Of the patients identified through ECS, 88% had bacteriologically confirmed TB, compared with only 50% of those identified through routine PCF. This may be to a large extent attributed to the algorithm used for identifying patients with TB: the ECS was mostly performed using the Xpert MTB/RIF testing, resulting in most patients being confirmed bacteriologically, while a much higher proportion of routine patients with TB were clinically diagnosed and treated following standard guidelines for TB diagnosis. This is also consistent with the findings of a study from Zambia that used ACF (Kagujje et al., 2020).

There were more patients in the lowest-income category and patients living in kutcha houses in the group identified through ECS than in the group identified through PCF. Given that patients with TB identified through ECS are more often of low socioeconomic status than those identified through PCF, they have less resources to visit a clinic on their own initiative, but are likely to be identified during home visits. TB cases detected by ECS were more often from urban settings compared with the PCF group. The burden of TB disease is generally considered to be higher in urban settings than rural settings because of crowding and occupational transmission (Kapata et al., 2016). The poor peri-urban areas of developing countries, where living conditions are unsatisfactory, with overcrowding, poor hygiene, and inadequate sanitation, are usually more affected by TB (Banerjee et al., 1999; Tupasi et al., 2000b). Such living conditions of lack of access to health care and poor health-seeking behavior may promote transmission of TB (Tupasi et al., 2000a, 2000b). However, a large prevalence survey in Pakistan showed that bacteriologically positive TB was more common among rural than urban residents in Pakistan (Qadeer et al., 2016).

ACF has been widely recommended as an important strategy in addition to standard PCF for the control of TB in low- and middle-income countries with high disease burden (Reid et al., 2019). Studies conducted in different countries confirmed the obvious fact that ACF is more cost-effective in high-burden settings. A study conducted in Pakistan found that the incentive-based ACF program was more effective and less expensive than PCF (Hussain et al., 2019). Another study in Pakistan also showed that active approaches to contact investigation effectively identify additional patients with TB among household contacts at a relatively modest cost (Hussain et al., 2021). However, a study from Russia showed that ACF has low yield and high cost in low-burden settings (Bogdanova et al., 2019). Given the limited evidence on cost efficiency in high-burden and resource-limited settings, significant scale-ups of ACF should be rationally planned (Dobler, 2016; Lung et al., 2019).

This study had several strengths. There was a large sample size, enabling fairly precise estimates and using a sensitive and specific test for examining sputum. The study also had several limitations. The data were several years old, and some changes in routine PCF have occurred since then, such as the introduction of routine GeneXpert examination at many health facilities. The population of the selected study area has a somewhat higher socioeconomic status than the average in Pakistan, thus care must be taken when generalizing results. Other limitations include recall bias because participants provided responses retrospectively, after they had been registered for TB treatment. We aimed to reduce this bias by questioning and re-confirming participants' responses. Another weakness is that we used convenience sampling for the passively detected cases. This could have introduced bias because we studied mainly the cases that were easy to approach, and their characteristics may have been different from those of other cases. However, the included and excluded passively detected cases had similar distributions of age and sex, favoring a fairly unbiased selection.

In conclusion, our innovative ACF strategy identified a higher proportion of men and children with PTB than routine case finding; both of these groups are more often missed by routine TB control. ACF should be considered as an important addition to standard case finding.

Declarations of competing interest

The authors have no competing interests to declare.

CRediT authorship contribution statement

Mahboob Ul Haq: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Sven G. Hinderaker:** Conceptualization, Formal analysis, Methodology, Resources, Software, Visualization, Writing – original draft, Writing – review & editing. **Razia Fatima:** Conceptualization, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Ejaz Qadeer:** Conceptualization, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Hammad Habib:** Data curation, Methodology, Resources, Visualization, Writing – original draft, Writing – review & editing. **Kashif Hussain:** Data curation, Resources, Visualization, Writing – original draft, Writing – review & editing. **Abdul Wali Khan:** Data curation, Methodology, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Ethical approval

Ethical 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 Committees for Medical and Health Research Ethics in Norway (REK-Vest 2018/57). Administrative approvals were obtained from the National and Provincial TB Control Program, Pakistan. A written informed consent was obtained from each participant and/or their legal representative, as appropriate.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.04.055.

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8.3 Paper III

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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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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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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

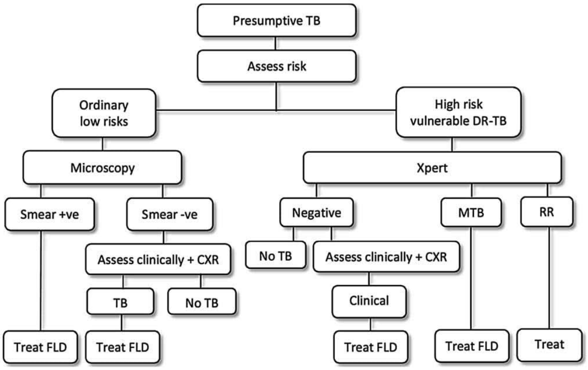

Figure 1. Algorithm used by Pakistan NTP for assessing a patient with presumptive tuberculosis in routine (PCF) program (2013–15).
TB = tuberculosis, sm+ve = Smear positive, sm-ve = Smear negative, FLD = First Line Drug, CXR = Chest X-ray, MTB = Mycobacterium tuberculosis, RR = Rifampicin resistant,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

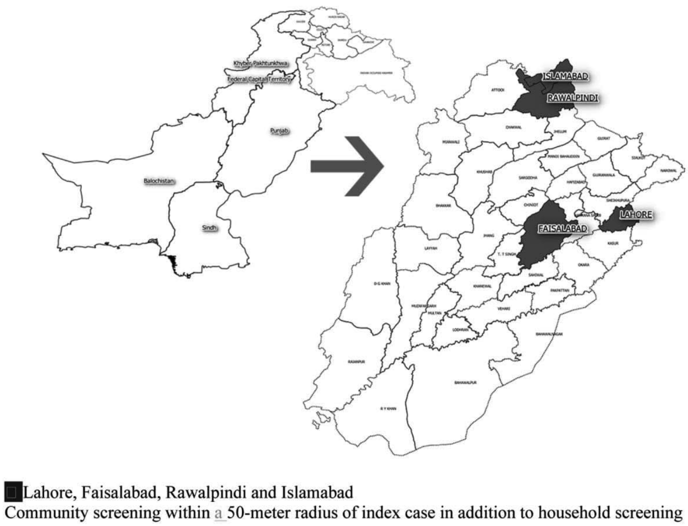

Figure 2. Map of Pakistan showing the 4 selected districts for extended contact screening for tuberculosis (2013–15).

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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List of Appendices

9. Appendices

9.1 Appendix 1: Data collection Tools;

TUBERCULOSIS SCREENING QUESTIONNAIRE

Name; ____________Father Name; __________ ID_____ Sex; ____ Age; ________ Marital Status; ________ Education status; _____ Occupation; ___________ Monthly income (family); _______ Total household members; ____ Type of house; _________ Residence; _______ People sleeping in one room; ______ Ventilation; ________Water source for drinking; ________ Address; _____ City; _____Today Date; _______ DOB; _____ Contact No; _______________________

Please indicate if you are having any of the following problems for more than 2 weeks or longer:

Part I

1. Chronic Cough (greater than 2 weeks). Yes _____ No _____
If yes, then go to Part II

2. Cough less than 2 weeks with any of the following

a. Production of Sputum Yes _____ No _____
b. Blood-Streaked Sputum Yes _____ No_____
c. Unexplained Weight Loss Yes _____ No_____
d. Fever Yes _____ No _____
e. Fatigue/Tiredness Yes _____ No _____
f. Night Sweats Yes _____ No _____
g. Shortness of Breath Yes _____ No _____
h. Have you been in contact with someone who has TB disease? Yes____ No______

3. Associated co morbidities

a. Diabetes Yes____ No _____
b. Smoking Yes ____ No _____
c. Other (Specify) ____

If "YES" to cough and "YES" to one-or-more of the other TB symptom questions, then:
Part II

- Enter into electronic suspect register within GIS enabled mobile phone and maintain a central data base.
- Collect sputum sample on spot for microscopy in the nearest BMU and get the result of smear microscopy latest on next day.
- Give a sputum cup and request to submit morning sample the next day in the nearest BMU using a referral form

Register of Household TB Contacts

Name Index case	TBMU Number of index case	Diagnosis of index case	Age	Gender	Nationality	TBMU No	Name of contact [1]	Address of contact	Symptoms	Date of onset of symptoms	Method of screening (tick)			Result of screening 2			Action taken 3	Results of Pv treatment 4
											DSM	x-Ray	G X-pert	DSM	x-Ray	G X-pert		

1 List all contacts consecutively under the name of the index case. (Definition of contact is to be included.)

2 NEG; POS; ND

3 Action: *Registration for treatment, Referred, Defaulted, none*

4 Result: *Completed, Defaulted, NA*

Register of Non-Household Contacts (widened circle)

Addresses based on GIS mapping	House number	Contact ID No	Contact name(first, father, grandfather)	Age	Gender	Nationality(N/NN)	Already diagnosed TB case (Y/N)	If yes, TBMU no	Symptoms	Date of onset of symptoms	Result of screening			Action taken		
											DSM	X-Ray	G X-pert	DSM	X-Ray	G X-pert
	1															

Treatment register

Registration No.	Sex (M/F)	Age	Date of diagnosis	Year of enrollment	Date of start treatment	Treatment Category (cat I/II)	Disease Classification P/EP	Site of EPTB **	Type of TB*	Date treatment stopped	Treatment Outcome#	Smoking Yes/no	Diabetes Yes/no

***1= New, 2= Relapse, 3= Treatment failure, 4= Treatment after loss to follow-up, 5= Transferred in, 6= others**
#1= Cured, 2= Treatment completed, 3=Died, 4=Failure, 5=Loss to follow-up, 6=Transferred out
**** 1=Pleura, 2= Lymph nodes, 3= Abdomen, 4= Genito-urinary tract, 5= Skin, 6= Joints, 7= Bones, 8= Meninges, 9= "Not Applicable"**

9.2 Appendix 2; Information sheet and Consent form

Information Sheet

Effectiveness of widening circle of contact tracing on case finding through outreach using GIS

You are being invited to take part in a study. Before you decide to take part, it is important for you to understand why the project is being done and what it will involve. Please read the following information carefully (If illiterate then please read out loud to the individual). Take your time, ask questions if it is not clear to you, and discuss it with others if you wish.

The study determines the effectiveness of widening circle of contact tracing on case finding through outreach using GIS.

Why have I been chosen for the study?

We are conducting a project on tuberculosis in which all individuals having the symptoms of TB will take part. Tuberculosis is an infectious bacterial disease caused by Mycobacterium tuberculosis, which most commonly affects the lungs. It is transmitted from person to person via droplets from the throat and lungs of people with the active respiratory disease. The symptoms of active TB of the lung are coughing more than 2 weeks, sometimes with sputum or blood, chest pains, weakness, weight loss, fever and night sweats. Tuberculosis is treatable with a six-month course of antibiotics.

The field officer will collect sputum for test along with home address. They might the individual for further investigation or treatment to the nearest TB centre.

What happens if I agree to take part?

Participation is completely voluntary; you may choose not to participate or to withdraw from the study at any time.

The laboratory tests and medicines you receive are the same if you do or do not agree to participate. If you participate you will help us find out the best way to provide that treatment

You will be registered with us if diagnosed and receive information on the treatment for TB. Some tests will be done in order to decide on the most appropriate medication for you. You will visit this hospital once a month for tests, for the doctor to check your progress and to find out if you have any drug side effects.

If you do not participate, you are also likely to visit once a month. This is usual care.

All **tests and medicines are free-of-charge** to you if you do or do not participate and will be paid for by the National Tuberculosis Control programme (NTP) of Pakistan.

What are the benefits of taking part?

Full free treatment will be provided if diagnosed. This study also hopes to improve the care of patients like you in the future.

What are the possible disadvantages and risks of taking part?

There are no added risks involved in participating in this study. Whether you agree or not to participate you will have the same tests and treatment.

Will my participation in the study be kept confidential?

Yes. The information will be stored by a number, not by your name. The information will only be available to your doctors and researchers working on the study.

What will happen to the results of the project?

They will be used to improve TB care across the country. The results will also be published in medical journals. You will not be identified or identifiable in any reports of publications.

For further information please contact **Dr Ejaz Qadeer**, National Manager, National TB Control Program, 23 West, Zakia Aziz Plaza, Fazl-e-Haq Road,Islamabad, Pakistan. Ph: (92-51) 8438077-80 Fax: (92-51) 8438081. Email: ntpmanager@ntp.gov.pk

Consent Form

Effectiveness of widening circle of contact tracing on case finding through outreach using GIS

Name of the person taking consent: ____

Read out the following statements to the participant, one by one, and record their response (√ or X)in the boxes provided on the right side.

1	I understand the information sheet *[insert date]* explaining the project, and I have had the opportunity to ask questions about the project.	☐
2	I understand that my participation is voluntary, that I can change my mind and am free to withdraw at any time. If I withdraw, I will continue to get my treatment and there will not be any negative consequences. In addition, should I not wish to answer any particular question or questions, I can say no if I wish.	☐
3	I understand that my responses will be kept strictly confidential. I give permission for members of the project team to look at the test results and my responses to questions. I understand that the information will be recorded using a number and not my name, so that I will not be identified or identifiable in the report or reports that result from the research.	☐
4	I agree for the information collected from me to be used in the project.	☐
5	I agree to take part in the above project and will inform the field officer if my contact details change.	☐

_________________________ _________________ _____________________

Name of participant Date Signature

(*or legal representative*)

_________________________ _________________ _____________________

Name of person taking consent Date Signature

To be signed and dated in presence of the participant

9.3 Appendix 3; Ethical approvals

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Jessica Svärd	55978497	30.04.2018	2018/57/REK vest
			Deres dato:	Deres referanse:
			07.04.2018	

Vår referanse må oppgis ved alle henvendelser

Sven Gudmund Hinderaker
Senter for internasjonal helse ved Institutt for Global helse og Samfunnsmedisin

2018/57 Identifisering av tuberkulosepasienter ved undersøkelse av nære kontakter

Forskningsansvarlig: Universitetet i Bergen, National Tuberculosis Program
Prosjektleder: Sven Gudmund Hinderaker

Vi viser til tilbakemelding for ovennevnte forskningsprosjekt. Tilbakemeldingen ble behandlet av leder for Regional komité for medisinsk og helsefaglig forskningsetikk (REK vest) på fullmakt. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 11.

Prosjektomtale
TB programmet prøver å identifisere TB pasienter ved å spørre naboer de har symptomer på TB: et eget prosjekt kalt TBREACH drevet av programmet. Prosjektet bruker bare eksisterende helsesystem. Med dette prosjektet i bakgrunnen er våre forskningsspørsmål: Kan man finne flere TB pasienter med den nye metoden? Hvem er TB pasientene som identifiseres med denne metoden? Er behandlingsresultat like godt? Kan denne metoden brukes av TB programmet i hele landet? Paper1 bruker aggregerte data av personer som har vært i kontakt med TB pasienter. Data finnes i rapporter fra distriktene som er utvalgt. Paper2 er en tverrsnittsstudie som sammenligner pasientene identifisert med ny og gammel metode. Paper3 er en oppfølgingsstudie for å sammenligne behandlingsresultater hos pasienter identifisert med de to metodene. Paper4 har kvalitativt design for å undersøke gjennomførbarhet og akseptabilitet av den nye metoden. Forskningen har fått lokal godkjenning. REKVEST bør kanskje fokusere på paper4?

Vurdering
REK vest ønsket tilbakemelding på følgende:

- Informasjon om prosjektleders involvering i tidligere studier om tuberkulose i Pakistan, spesielt med tanke på artikkel 1.
- En klargjøring om hvordan prosjektdeltakere skal rekrutteres.
- Et nytt og forbedret informasjonsskriv.
- Forklaring på hvorfor det mangler spørreskjema for andre enn TB pasienter.
- En plan for hva som skal gjøres med data ved prosjektslutt.

Tilbakemelding fra prosjektleder

Besøksadresse:
Armauer Hansens Hus (AHH), Tverrfløy Nord, 2 etasje. Rom 281. Haukelandsveien 28

Telefon: 55975000
E-post: post@helseforskning.etikkom.no
Web: http://helseforskning.etikkom.no/

All post og e-post som inngår i saksbehandlingen, bes adressert til REK vest og ikke til enkelte personer

Kindly address all mail and e-mails to the Regional Ethics Committee, REK vest, not to individual staff

Informasjon om prosjektleders involvering i tidligere studier om tuberkulose i Pakistan. Spesielt med tanke på artikkel 1.
Prosjektleder (SGH) har tidligere veiledet PhD for den lokale veileder i Pakistan (Dr Razia Fatima) og har publisert 4 papers med henne. En annen PhD kandidat fra Pakistan (Dr Nauman Safdar) har også publisert fire papers sammen med prosjektleder SGH. Artikkel 1 («Extending 'contact tracing into community…» i PLoS One) var ferdig før kandidaten startet å planlegge sitt PhD arbeid, og kandidaten er medforfatter på denne artikkelen. Han var aktivt med i alle faser av publikasjonen, og den er svært relevant for hans PhD tema som ble definert ETTER at han publiserte; den brukes ikke i noen andre PhD theses. Han hadde nasjonal ethics clearance i Pakistan. Prosjektleder SGH var IKKE involvert i arbeidet på denne tiden.

En klargjøring om hvordan prosjektdeltakere skal rekrutteres.
For den kvalitative studien, paper 4, er protokollen med metoder forbedret. Det trengs om lag 25 IDI dybdeintervjuer. Det blir om erfaringer fra prosjektet, og ikke om deltakers egen helse. Det blir fra TB pasienter, fra familiemedlem av TB pasienter, og fra helsearbeidere i prosjektet. Rekruttering er beskrevet bedre i det nye dokumentet med protokoll for Paper 4. Man bruker TB registeret til å lage liste av alle TB pasienter som ble identifisert av i prosjektet, og bruker systematisk sampling ved å velge hver femtiende pasient i registeret. Man velger 7-8 deltakere fra listene av pasienter 7-8 deltakere til dybdeintervju. Man velger 7-8 deltakere familiemedlemmer til pasientene som ble valgt Men velger 7-8 deltakere blant helsearbeidere som har arbeidet i prosjektet ved conveninet sampling. Man vil velge blant leger, DOTS facilitators, farmasøyter, feltassistenter som identifiserer kontakter som må undersøkes for TB.

Et nytt og forbedret informasjonsskriv.
Nye informasjonsskriv er vedlagt, med endringer ifølge kommentarene. Det nye skrivet vil bli oversatt til Urdu. De er i tre versjoner, en til pasient, en til familiemedlem, en til helsearbeidere.

Forklaring på hvorfor det mangler spørreskjema for andre enn TB pasienter.
Det var en feil. Spørreskjema er nå vedlagt for pasient, for familiemedlem, og for helsearbeidere.

En plan for hva som skal gjøres med data ved prosjektslutt
Ved prosjekt slutt blir alle data anonymisert. De blir lagret lokalt ved NTP Pakistan og ved Universitetet i Bergen.

REK vest ved leder har vurdert tilbakemeldingen.

Vurdering
Ettersom prosjektleder og UiB ikke var involvert i artikkel 1 så vurderes søknaden ikke å være en søknad om ettergodkjenning. REK vest har kun vurdert de deler av studien som ikke er gjennomført ennå.

REK vest forstår det slik at TB-pasientene som ble identifisert i det tidligere intervensjonsprosjektet og som nå skal rekrutteres til intervju gjennom sampling i TB-registeret har samtykket til at deres opplysninger er registrert i registeret. Rekrutteringsmetoden og prosjektet i sin helhet vurderes som forsvarlig.

REK vest har ingen merknader til vedlagte spørreskjemaer, men REK vest har en mindre merknad til vedlagte informasjonsskriv. Disse mangler UiB-logo.

Vilkår

Informasjonsskrivene må revideres ved at logo for forskningsansvarlig, UiB, påføres. Reviderte skriv sendes REK vest på post@helseforskning.etikkom.no.

Vedtak
REK vest godkjenner prosjektet på betingelse av at ovennevnte vilkår tas til følge.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK vest på eget skjema senest 30.06.2021, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK vest dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK vest. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK vest, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Marit Grønning
professor, dr.med.
Komitéleder

Jessica Svärd
rådgiver

Kopi til: post@uib.no; drraziafatima@gmail.com

Sven Gudmund Hinderaker

From: Sven Gudmund Hinderaker
Sent: 07 October 2022 07:56
To: Sven Gudmund Hinderaker
Subject: FW: REK vest 2018/57 Identifisering av tuberkulosepasienter ved undersøkelse av nære kontakter

Vår ref. nr.: 2018/57
Prosjekttittel: "Identifisering av tuberkulosepasienter ved undersøkelse av nære kontakter"
Prosjektleder: Sven Gudmund Hinderaker

Til Sven Gudmund Hinderaker.

Vi viser til Annet/Generell henvendelse innsendt 09.05.2018. Komiteen tar dette til orientering uten ytterligere merknader.

Med vennlig hilsen
Anna Stephansen
sekretariatsleder
post@helseforskning.etikkom.no
T: 55978496

Regional komité for medisinsk og helsefaglig forskningsetikk REK vest-Norge (REK vest)
http://helseforskning.etikkom.no

Government of Pakistan
Ministry of National Health Services, Regulations and Coordination
NATIONAL TB CONTROL PROGRAM

27 September 2017

SUBJECT: **Approval for Mahboob Ul Haq, to use the TB Reach Wave III project data for PhD thesis**

National TB Control Program conducted TB REACH Wave III project with the title "Effectiveness of widening circle of contact screening from within the household to 100 m around the house of index case on case finding through outreach using GIS software" from 1st July 2013 to June 2015. The project introduced active contact investigation into 3 cities in Punjab Province and the Capital Territory utilizing all SS+ notified cases as index cases.
These districts were Islamabad, Lahore, Faisalabad and Rawalpindi. Household contacts, i.e. those normally resident or sharing the same airspace, were verbally screened initially, followed by a widening circle of close community contacts. The project tested additional yield by Gene-Xpert among smear negatives and chest X-ray suggestive.
A total of 4,710 TB patients including 4,084 bacteriologically confirmed TB cases were detected as a result of this intervention.
The main paper of project has been published in Plos-one Journal in which Mahboob Ul Haq is a co-author however, further scientific publications /studies need to be prepared from the project. It is expected that up to 5 peer reviewed papers could be written using the project data follow by some prospective data collection (For Qualitative & Quantitative studies) in the above mentioned districts.
Mahboob Ul Haq (Research Associate) who is PhD candidate in University of Bergan, Norway, will be responsible and allow for the remainder scientific publications from the above mentioned project data.

It will provide the necessary evidence for National TB Programs to consider scaling up ACF intervention nationwide if found successful.
I ensure that proper time and support will be provided by the NTP to carry out his PhD research and I also ensure about the support to adhere the timelines of the PhD program and also permit him to publish the work as first author.

I wish him all the best for his successful completion of PhD with some interesting findings.

Dr Razia Fatima

Chief Data

National TB Control Program, Block E&F, EPI building, Near National Institute of Health (NIH)
(Prime Minister's National Health Complex), Park Road, Islamabad, Pakistan
Tel: +92 51 843 8077 – 80, Fax: +92 51 843 8081, Email: ntpmanagerpak@ntp.gov.pk, Web: http://www.ntp.gov.pk

International Union Against
Tuberculosis and Lung Disease
Promoting lung health in low- and middle-income countries

Ethics Advisory Group

31st March 2014

To **Aashifa Yaqoob**

Title of research project:

Expanding the contact screening beyond the household: Did it increase detection of tuberculosis in Punjab, Pakistan?

EAG number : 11/14

Investigators:

PI: Aashifa Yaqoob, National TB Control Program, Pakistan

Co-investigators:
Ejaz Qadeer, National TB Control Program, Pakistan
Razia Fatima, National TB Control Program, Pakistan
Ajay MV Kumar, The Union, South East Asia Regional Office, New Delhi
Suman Majumdar, Centre for International Health, Burnet Institute, Australia

Thank you for your application to the Ethics Advisory Group of the Union. Your study has our formal approval.

- Any changes to the approved protocol need to be sent to the EAG, using the form for **extension/modification** of proposals (to be found on the Union website under EAG)
- **Final report :** The EAG requires the executive summary or the abstract of all study reports or papers within 90 days of the completion of the study

We trust that your study proceeds well and that it will be productive.

With best wishes,

Prof. Mary Edginton
Chairperson

Union Internationale
Contre la Tuberculose
et les Maladies Respiratoires

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