Childhood tuberculosis in Pakistan

The role of the private sector in TB-control

Aashifa Yaqoob

Thesis for the Degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
2023

UNIVERSITY OF BERGEN

Childhood tuberculosis in Pakistan

The role of the private sector in TB-control

Aashifa Yaqoob

Thesis for the Degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defence: 28.03.2023

Year: 2023

Title: Childhood tuberculosis in Pakistan

Name: Aashifa Yaqoob

Print: Skipnes Kommunikasjon / University of Bergen

List of Abbreviations:

BHU	Basic Health Unit
BMU	Basic Management Unit
CXR	Chest X-Ray
DHQ	District Head Quarter
DOTS	Directly Observed Treatment Short-Course
DTC	District TB Coordinator
HIV	Human Immunodeficiency Virus
IMCI	Integrated Management of Childhood Illnesses
IPT	Isoniazid Preventive Therapy
LHW	Lady Health Worker
LTBI	Latent TB Infection
MDR	Multidrug-resistant
MTB	Mycobacterium tuberculosis
NTP	National Tuberculosis Control Program
PHC	Primary Health Care
PLHIV	People living with HIV
PMDT	Programmatic Management of Drug Resistant Tuberculosis
PPM	Public-Private Mix
RHC	Rural Health Centre
TB	Tuberculosis

THQ	Tertiary Head Quarter
WHO	World Health Organization
XDR	Extensively drug-resistant

Scientific environment

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

This thesis is based on the project entitled “National inventory study to estimate child TB underreporting”. The project was implemented by NTP Pakistan. It was funded by UNITAID, while funding was channelled through the STOP TB program which was led by the TB Alliance and World Health Organization (WHO) in 2016. The project was implemented in twelve districts: Attock, Chiniot, Hafizabad, Vehari, Shikarpur, Hyderabad, Karachi, Buner, Peshawar, Pallundary, Jhal Magsi, & Ghizer.

A surveillance system among all eligible non-NTP providers was established in the selected 12 districts from April - June 2016. Record linkage was conducted by generating lists of child TB patients for the research study duration from all the selected facilities for the study. Then these lists were compared against the list of those child TB patients notified to the national TB surveillance system from the same districts, for the period two quarter before and one quarter after the study period. This research project estimated the underreporting of child TB cases that were diagnosed by the private health sector but not reported to national TB surveillance system.

The grant funded large project, with nested sub-studies were included in this thesis. This thesis includes four research papers that have been published in peer reviewed international journals. These research studies were done at the NTP Islamabad Pakistan, with technical support from NTP and CIH.

Acknowledgements

First and foremost, I would like to thank ALLAH, the Almighty, for letting me through all obstacles and guided me day by day till the accomplishment of my PhD degree.

I am privileged to have had Professor. Sven Gudmund Hinderaker who provided the opportunity to carry out and complete PhD at University of Bergen with the most flexibility that I could continue my professional work and family life too. This process has been extensive and has added value in my career. Professor. Sven Gudmund Hinderaker: Thank you very much for your gentle supervision and guidance who made this work possible. I also want to thank the University of Bergen, Centre for International Health for providing me the opportunity to complete my education.

I would like to acknowledge and extend my sincere gratitude to my co-supervisor, Dr. Razia Fatima, who encouraged, guided, and supported me throughout the entire process, from the conception of the idea to its conclusion. Dr. Razia Fatima: Thank you for paving the way for me to do the PhD at the UiB and for being my co-supervisor. I'm also grateful to Dr. Ejaz Qadeer, (of then NTP Manager), for giving me the permission and encouragement to enrol in UiB.

Professor. Tehmina Mustafa: Thank you so much for arranging funds for our visit to UiB for thesis writing when I needed it the most. Academic and support staff at UiB: I appreciate your assistance every time. Many thanks to Gunhild, Olga, Terese, and Daniel in particular for their prompt administrative and logistical support whenever I needed it.

I would like to thank many valuable people in my life who have prayed, supported and encouraged me to accomplish this difficult task especially Rashida Bhabhi & Aleem, and a special thanks to my sister Saadia and friend Nadia for their unceasing prayers and wishes.

Finally, I want to extend my sincere gratitude to my wonderful husband cum friend "Rizwan" for his commitment, compassion, and support in making this work a reality. Hubby Thanks for being my pillar of support. I am incredibly grateful for my kids' perseverance throughout the process. Inaya, Anas, and Ifrah, I want to thank you, sweethearts, for being so understanding while I was studying. I also guarantee that moving future, we'll achieve a better balance.

I want to dedicate my PhD Work to my parents who has a great desire for me to complete my highest level of education, all the academic excellence I achieved is because of their Prayers and Struggles for me. Thank you, Abu and Ammi (I miss you terribly), for instilling in me a tremendous enthusiasm for learning, especially determination and honesty. Words cannot describe how important you are to me.

Abstract in English

Worldwide, it is estimated that about 650 children (age 0-14 years) die on daily basis due to TB which is a preventable and treatable. TB among children is commonly not correctly identified due to absence of specific symptoms and difficulties in diagnosis. This has made it challenging to measure the actual magnitude of the disease burden. The private health sector in Pakistan caters for the health care needs of 75% of the general population, but only <5% of them are engaged with National TB Control Program (NTP). Therefore, it is anticipated that many child TB cases were not reported in the national TB surveillance system from the private health sector in spite of notification being mandatory.

In paper I, to estimate the extent of underreporting of child TB cases, a child TB inventory study was conducted in 12 randomly selected districts across Pakistan. A surveillance system was established among all eligible non-NTP providers in the study districts. The mapping was carried out of those health facilities engaged in diagnosis and treatment of childhood TB cases. All child TB cases from all facilities were listed for the study period (April-June 2016) and matched with the list of those child TB cases notified to the national TB surveillance system from the same districts during the same time duration. Amongst the children with TB 11% were bacteriologically confirmed and 89% clinically diagnosed. Only 4% cases among them were reported to the National TB Control Program. The underreporting was estimated about 78% of total child TB cases. The study confirmed that underreporting of child TB is very high in Pakistan. A particular attention needs to be paid in engaging and guiding the general practitioners as well as paediatricians to report their child TB patients to national TB surveillance system.

In paper II, we assessed the investigation and management practices of the private health care providers for managing presumptive TB patients by using child TB inventory study database. Private health care providers relied on chest X-ray in 46.1% patients, while tuberculin skin test and Gene-Xpert MTB/RIF testing was utilized to a limited number of patients. Bacteriological confirmation was present in 7.6%, and

clinical evaluation was the only basis for diagnosis among 39.3% of cases. Among the children diagnosed with presumptive TB, private providers diagnosed and treated only 955 (14.6%) children. Among all those referred, 3,812 (68.5%) were sent for investigations to District TB Centre (NTP). This study showed that many private providers use to refer children suspected having TB to the laboratories for further diagnosis, but the TB cases identified by these private health providers were often not notified to the NTP. This problem could be resolved by strengthening the referral linkages between private health providers, NTP laboratories and treatment centres.

In paper III, the child inventory study database was used to evaluate the adherence to the national guidelines by private health providers for the diagnosis of childhood TB. A total of 5,193 children were diagnosed with TB by Non-NTP private health providers. Only 47.8% of cases were diagnosed in line with the NTP guidelines. However, children age <5 years with a history of TB contact had a higher chance of being diagnosed according to the NTP guidelines. There is an urgent need to focus on awareness about the NTP guidelines may be through public-private partnership to address specific gaps in diagnosis, and treatment.

In paper IV, the study determined the health care services access to child TB services in Pakistan. The geospatial analysis was conducted using open-source database to calculate the distance from the nearest public health facility to the catchment population. The population living within the World Health Organization's recommended 5 km distance, was estimated. About, 74% of the population had geographical access to the general primary health care facilities within 5km radius, compare to 33.5% had geographical access to secondary and tertiary level health facilities within 5km radius. The average distance from a settlement to a facility for diagnosis of childhood TB was estimated at 26 km. This study indicated that access of catchment population to the specialized child TB facilities is limited. Geographical accessibility can be improved by involving lady health workers to create a closer link to higher level facilities through referral system particularly for distant communities.

Abstract in Norwegian

Globalt dør omkring 650 barn (0-14 år) daglig på grunn av tuberkulose (TB), som kan både forebygges og behandles. TB hos barn blir ofte oversett siden de mangler typiske symptomer, og diagnostikk er vanskelig. Dermed er det også vanskelig å beregne den faktiske sykdomsbyrden. Helsetjenester fra privat sektor i Pakistan dekker 75% av behovet, men bare 5% av privat sektor samarbeider med det nasjonale TB programmet NTP, og man ville anta at mange barn diagnostisert med TB av privat sektor blir aldri rapportert til NTP, selv om det er meldeplikt.

I **Paper-I** undersøkte vi rapportering av barnetuberkulose i 12 distrikter i Pakistan. I studieområdet ble et overvåkingssystem etablert ved helsetjenester utenfor selve NTP. Kartlegging ble gjort av de helseinstitusjonene som diagnostiserte og behandlet barnetuberkulose. Alle tilfeller av barnetuberkulose som ble listet i studieperioden ble sammenholdt med listen av barna som var rapportert å ha TB i samme perioden. Av alle barna med TB var 11% diagnostisert bakteriologisk og 89% klinisk, og bare 4% var meldt til den nasjonale TB programmet. Det var betydelig underrapportering på 78% av alle antatte tilfeller. Studien bekrefter at underrapportering av barnetuberkulose er et stort problem i Pakistan. Man bør rette oppmerksomhet både på barneleger og privatpraktiserende allmennleger for å bedre rapporteringen av barnetuberkulose til det nasjonale overvåkingssystemet.

I **Paper-II** studerte vi hvordan undersøkelser og behandling ble utført hos private helsetjenester for barn som hadde mistenkt tuberkulose. Privat sektor brukte røntgen i 46.1% av tilfellene, mens Mantoux tuberculin test or GeneXpert MTB/RIF ble brukt til et begrenset antall. Det var 7.6% som hadde bakteriologisk bekreftet TB, og 39.3% var diagnostisert bare klinisk. Blant barn med mistenkt TB ble 955(4.6%) diagnostisert og behandlet i privat sektor. Av de barna med mistenkt TB som ble henvist videre kom 3812(68.5%) til NTP for undersøkelser. Studien viste at mange private leger henviser barn til undersøkelser ved laboratorier, men selv om de blir diagnostisert blir de ofte ikke meldt til NTP. Dette kunne bedres ved å styrke kontakten mellom privat sektor, NTP laboratorier og behandlingssentre.

I **Paper-III** ble prosjektdata brukt til å se hvordan nasjonale retningslinjer for barnetuberkulose blir fulgt av privat sektor. Det var 5195 barn som ble diagnostisert med TB av privat sektor; bare 47.8% fulgte retningslinjene. Barn under 5 år hadde større sjanse for å bli diagnostisert i følge retningslinjene. Det er behov for å bedre kjennskap til NTP retningslinjene for diagnose og behandling kanskje via PPP, initiativet for samarbeid mellom privat og offentlige helsetjenester.

Paper IV studerte tilgjengeligheten av helsetjenester for barnetuberkulose i Pakistan. Geografiske analyser ble gjort med frie programvarer for å måle distanse fra et offentlig helsetilbud til nedslagsfeltet for folk som bodde innenfor 5km radius. Omtrent 74% hadde tilgang innen 5 km fra primærhelse tjeneste, mens 34% hadde tilgang nærmere enn 5km på sekundær og tertiær helsetjenester. I gjennomsnitt var distansen fra et tettsted til et sted som kunne stille diagnostisere barnetuberkulose 26km. Vi fant at tilgang på diagnostiske muligheter for barnetuberkulose er begrenset. Tilgang kan forbedres ved å involvere 'lady-health-workers' for å styrke henvisnings systemet særlig i fjerne distrikter.

List of Publications

Fatima, R., Yaqoob, A., Qadeer, E., Hinderaker, S. G., Ikram, A., & Sismanidis, C. (2019). Measuring and addressing the childhood tuberculosis reporting gaps in Pakistan: The first ever national inventory study among children. PloS one, 14(12), 1-11.

Yaqoob, A., Hinderaker, S. G., Fatima, R., & Najmi, H. (2021). How do private practitioners in Pakistan manage children suspected having tuberculosis? A cross sectional study. BMC Public Health, 21(1), 1-9.

Yaqoob, A., Hinderaker, S. G., Fatima, R., Shewade, H. D., Nisar, N., & Wali, A. (2021). Diagnosis of childhood tuberculosis in Pakistan: Are national guidelines used by private healthcare providers?. International Journal of Infectious Diseases, 107, 291-297.

Yaqoob A, Alvi MR, Fatima R, Najmi H, Samad Z, Nisar N, Haq AU, Javed B, Khan AW, Hinderaker SG. Geographic accessibility to childhood tuberculosis care in Pakistan. Global Health Action. 2022 Dec 31;15(1):2095782.

Table of Contents

List of Tables:

List of Figures:

1. Introduction

1.1 What is Tuberculosis:

Tuberculosis (TB) is a communicable disease caused by a pathogen Mycobacterium tuberculosis (MTB). It mostly affects the lungs and other organs in the human body such as kidneys, spine, or brain can also affect. TB spreads through air droplets from person to person, when infected person with pulmonary TB disease coughs, sneeze and laughs. Broadly, there are two types of TB infections i.e., active and latent. In active tuberculosis, TB transmits from a patient's lungs containing large amount of pus full of TB bacteria. When patient coughs a huge amount of bacteria transmit in the air. This greatly increases the chances to infect other persons in the surrounding, even if they inhale only a few drops of these pathogens. After exposure and infection, a person may develop TB disease immediately (primary disease), with the symptoms of productive cough, fever, weight loss, night sweat and sickness. Usually the infected person may control the bacteria that may go into latency.[1] A rare form of active TB is called Miliary, that occurs when TB bacteria enter into the bloodstream and spread throughout the body affecting multiple organs simultaneously, which can be potentially life threatening for the patient.[2]

People with latent TB disease, usually remain asymptomatic and non-infectious. In such cases, the immune system of host's body keeps TB bacteria under control without causing any TB symptoms. Mostly, the latent TB patients, have a positive TB skin or blood test. However, these people remain at risk to develop TB disease in their later in life. Many people who have latent TB infection (LTBI) never develop the disease, and the TB bacteria may stay inactive in the body for the rest of their life. However, people with weak immune system or those with Human Immunodeficiency Virus (HIV) infection, are at higher risk of bacterial activation resulting in the contraction of TB disease compared to those with normal immune systems.[1]

1.2 TB Etiology and Transmission

For Adults: About one-quarter of the world's population suffer from LTBI. However, infected people with TB have a 5–10% lifetime risk of contracting TB.[3] The risk of infection is determined by an intrinsic combination of factors related to the social and behavioural practices including smoking, alcohol, and indoor air pollution. In overcrowded settings, the chances for transmission and contraction of TB disease will be high. Similarly, conditions where prolonged exposure to an infectious patient, increases the risk of contracting TB. It also includes factors related to cascade of health care system such as delay in diagnosis, treatment, and compliance to medication.

The contributing factors of acquiring TB infection, developing disease or deaths due to TB may be associated with poverty, malnutrition, HIV infection, smoking and diabetes [4]. An estimated 95% of the TB cases and deaths are occurring in the developing countries. Moreover, the risk of developing active TB is 18 times high in HIV infected people and 3 times high in under-nutrition person and suffering from other medical conditions that can impair their immune system [3,5]. Globally in 2020, 1.9 million new TB cases were reported that were attributable to under nutrition. [3] The risk of TB also increases with the use of alcohol and tobacco smoking by 3.3 and 1.6 times, respectively. [3] Moreover, an exposure to tobacco smoke also considered as an important predictor for TB infection among children irrespective of their age.

For Children: Several studies conducted in low and middle-income countries have confirmed the associations of childhood TB with age <5 years, poverty, over-crowded living, under-nutrition and use of contaminated drinking water. [3] Ample evidence exists [6–8] that children in low-income countries usually have a frequent contact with a TB infected adult. On the other hand, the contact investigation is either weak or does not consider as the primary means of case finding in such settings. Hence, such children are at high risk of developing TB who are living in a household with an index TB case or other caregivers providing Directly Observed Treatment Short-Course (DOTS) to the TB patients. HIV-infected children are more likely to

contract TB infection from a close contact of smear-positive TB patient in comparison to the non-HIV infected children. Many of the HIV infected persons belong to reproductive age hence many of them are living in close proximity to young children. This suggests that more children worldwide may be exposed to tuberculosis due to TB-HIV co-infection. Countries with high burden of multidrug-resistant TB (MDR-TB) faced an extreme situation with common feature, such as poor previous case management and treatment compliance. Moreover, risk of TB in adolescents is high particularly due to lack of access to diagnosis and treatment services.[1,9] The predisposing factor in transmission of TB disease include lack of parental education, low household income, and overcrowded living.[10,11] Key differences between adults and children TB cases, are summarized in table 1 adopted from the article by Marais 2014.[12]

Table 1: Tuberculosis: Differences between adults and children

Aspect	Adults [a]	Children [a]
Epidemiology	Massive global disease burden that is well quantified; excellent awareness	Massive global disease burden that is poorly quantified; minimal awareness
TB control	Main focus of TB control programs	Not recognized as a TB control program priority
Pathogenesis	Usually "adult-type" lung disease	Usually intra thoracic lymph node disease, but extra pulmonary disease common
Infection control	Multibacillary; high infection risk	Paucibacillary; low infection risk, unless cavities or extensive lung involvement; epidemiologic marker of transmission
Drug resistance	Difficult to differentiate acquired from primary drug resistance	Nearly always primary drug resistance indicating recent transmission
Exposure history	Important, but often neglected [b]	Essential part of diagnostic work up
Risk of progression to disease	Relatively low risk of progression to disease following TB exposure / infection unless immune- compromised	Highly variable risk of progression to disease following TB exposure/ infection—greatest in the very young and/or immune-compromised
Preventive therapy	Limited value, except in immune compromised adults	Definite value in young (5 yr of age) and/ or immune-compromised children
Imaging studies	Chest radiographs (CXRs) not routinely required, unless sputum negative for mycobacterial investigations	CXRs (with both anteroposterior and lateral views, of good quality, and competently read) are the most informative study to perform
Disease classification	Pulmonary versus extra pulmonary Distinction Post primary TB is a confusing concept	Diverse spectrum of pathology that requires accurate classification
Microbiological studies	Relatively easy to collect adequate respiratory specimen and confirm presence of mycobacteria	Difficult to collect adequate respiratory specimens (young children cannot expectorate); smear microscopy has very low yield
Treatment (drug susceptible TB)	With four drugs in intensive phase	With three or four drugs depending on likely organism load and severity of disease in intensive phase
Prognosis	Excellent outcomes achievable with timely and appropriate treatment	Excellent outcomes achievable; potentially grave outcome with delayed diagnosis of especially tuberculosis meningitis

Table adapted Marais 2014 and Data from supplementary material in Perez-Velez and Marais 2014.
a Typical characteristic in the absence of HIV infection and/or severe immune compromise.
b Taking a careful contact history is often neglected in adults, but it has relevance to identify drug-resistant TB suspects.
The distinction between primary and post primary TB obscures the fact that adult-type (post primary) TB frequently results from recent reinfection and may also occur within months of documented primary infection (particularly in adolescents) [12].

1.3 Global burden of Tuberculosis

Globally, TB is considered as the second leading infectious killer and 13th leading cause of death. According to latest Global TB report [3], in 2020, an estimated 10 million people developed TB and 1.3 million TB deaths are reported among HIV-negative people. Additionally, 214, 000 deaths were estimated among people living with HIV. Adults accounted for 88% and children age less than 15 years for 12% of all reported TB cases. The highest TB burden was observed in adult men which was 56% of TB cases reported globally. In 2020, the 30 high TB burden countries accounted for 86% of new TB cases. Eight countries such as 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%), accounted for two thirds of all TB cases worldwide.

MDR-TB is still a public health issue and a security risk to health. In 2020, just around one third of the people with drug-resistant TB had access to the treatment. Globally, a decline in TB incidence has been noticed by 11% between 2015 and 2020 with a 2% rate of decline per year. While this progress is over half way of achieving the End TB Strategy milestone as target was 20% reduction between 2015 and 2020. However, an estimated 66 million people were saved between 2000 and 2020 by bringing improvements in TB diagnosis and treatment services. Each year, an estimated 30,000 children develop MDR -TB, yet only a small number of these cases are identified and treated. [13]

Currently, many high TB burden countries are not on track to reach End TB Strategy milestones i.e., 20% reduction in the TB incidence, 35% reduction in the number of TB deaths and zero catastrophic costs due to TB as compared to the levels in 2015. Globally, only 9.2% reduction in number of TB deaths was estimated from 2015 to 2020. The increase in number of deaths due to TB in 2020 was a result of disruptions of TB services for diagnosis and treatment due to COVID-19 pandemic. At regional level, only the WHO European Region nearly achieved the milestone with a

reduction of 26%. Among the top 5 high TB burden countries, only Bangladesh is on track.[4]

1.4 Tuberculosis burden in Pakistan

Pakistan is currently facing many challenges including a double burden of communicable and non-communicable diseases, an unregulated private sector, limited funds available for provision of health services through public sector, and a rapidly increasing population. TB is one of the major health problems in Pakistan, and the country ranked fifth among 22 TB high burden countries in 2020. Despite substantial improvements in case detection and treatment success rates since 2001, TB remained a serious public health issue. Pakistan piloted and implemented the DOTS strategy in 2001 and TB was declared as a national public health emergency through the "Islamabad Declaration",[14] significant progress in TB control was made. The provincial TB programmes and district health authorities are in charge of implementation, while the National TB Control Program (NTP) function under the federal ministry is responsible for general coordination, policy directives, and technical guidance for TB control.

TB remained 13th leading cause of death in Pakistan and the second most lethal infectious disease after COVID-19 (above HIV/AIDS). Total number of notified cases were 272, 990 in 2020 with an estimated incidence rate of 259 per 100,000 of the population. Among the notified TB cases, 49% were bacteriologically confirmed and 14% were children age 0-14 years. The treatment coverage in Pakistan remained 48% with 8% TB case fatality ratio. The TB epidemic in Pakistan is compounded by MDR-TB. Almost 2, 689 laboratory confirmed MDR-TB cases and 831 cases of pre-Extensively drug-resistant (XDR) or XDR-TB reported in year 2020. Of 2018 cohort, 70% MDR-TB and 49% XDR-TB cases had started second-line drugs. In 2020, 29% of new and relapse TB cases had a known HIV result and 556 (<1%) were tested positive; 364 (65%) initiated ART. Furthermore, 5% of those children age under 5 years with household contacts of bacteriologically-confirmed TB cases, put on

preventive treatment. Five major attributable risk factors for cases reported in 2020 were undernourishment, smoking, diabetics, HIV and alcohol use disorder. [3]

1.5 TB Control

1.1.1 History

Since the 1880s, sputum smear microscopy was used for TB diagnosis. Traditional TB treatment in the 19th century was bed rest in sanatoria or sometimes sunbath in addition to good food and rest. A hundred years ago, surgery also considered as a common treatment of TB but had no impact on the epidemiological situation. The BCG vaccine against TB was developed in early 1900 and introduced in Europe before the last world war. BCG became part of the global expanded programme of immunization (EPI) from 1974. When treatment of TB became available in 1950, more efforts were made to find TB cases. Mass TB screening was conducted in Europe after the World War II and chest x-ray was used as screening tool which contributed in decline of the TB epidemic in Europe.

From DOTS to END TB strategy:

In 1980s, TB affected mostly low and middle income countries while in Europe it has emerged as an epidemic of multidrug resistant TB. Tuberculosis control package DOTS was developed by Dr. Styblo in 1980s. This program was successfully piloted by Dr. Styblo in selected poor countries like Tanzania and Malawi. In 1993, the WHO declared TB a global emergency and launched five elements' DOTS strategy developed by Dr. Styblo. In 2000, 148 countries including all 22 highest burden countries (HBC) had adopted the DOTS strategy. Over the decade, DOTS made remarkable progress to control of TB worldwide. However, statistics suggested that DOTS alone was not sufficient to achieve TB related Millennium Development Goals (MDG) and Stop TB Partnership targets. In 2005, Global DOTS Expansion Plan was developed with a strong focus on concentrated preventative efforts to control the

influence of TB risk factors such HIV, smoking, under nutrition, alcoholism, diabetes, crowding and indoor air pollution.

The post-2015 global TB strategy, called as the “End TB Strategy” was developed under the Sustainable Development Goals agenda. It requires a mix implementation approach involving biomedical, public health, and socioeconomic interventions along with research and innovation. The vision of strategy is to make the world free of TB, zero deaths, disease, and suffering due to the disease. The End TB Strategy is based on a package of interventions using three pillars approach. The pillars are; care of TB patients, research to bring improvements, policies and support systems.

1.1.2 Strategies for TB Control

The Stop TB Strategy recommend patient-centred approach as a fundamental principle to control TB. It focuses on patient care, their management and reduction of risk to community. To reduce TB transmission and risk , following prevention strategies [15] are suggested in specific activities of TB control programmes:

i. Case detection

The current TB case detection framework suggests two pathways, passive case finding and active case finding. In passive case finding, individual with presumptive TB visits health care facility for further investigation of disease through different diagnostic algorithm to confirm TB diagnosis. On the other hand, active case finding is described as the systematic identification of people with TB suspicion in a specific target population through tests, examinations, or other quick procedures. Screening in active case finding may target different groups of people such as TB contacts, people living with HIV (PLHIV) etc. in different settings by applying different strategies and activities like health promotion and training of lady health workers etc.

The process of finding TB cases is very complex because any errors at any level lead to delays in detection or result in an incorrect diagnosis. Timely identification of presumptive TB cases and early initiation of treatment could help to reduce the TB infection in the community.

The DOTS strategy was adopted by Pakistan in 1995. However, major progress in TB control was made after 2001, when TB was declared a national public health emergency in Pakistan [14]. The mandate of program is to strengthen TB control efforts through effective partnerships, mobilization of necessary resources, availability of quality diagnostic and treatment services for all people in Pakistan defined in End TB Strategy. There are more than 1,313 Basic Management Units (BMUs) with a robust TB laboratory network that is present at national, provincial, district and peripheral level in 155 districts of Pakistan. GeneXpert has been rolled out in 2010, up till now 445 facilities were equipped with GeneXpert accessible to all districts. NTP started implementation of Public-Private Mix (PPM) initiative in 2010.About 420 private health sector laboratories are also providing microscopy facilities. There has been tremendous progress towards controlling spread of TB in Pakistan. TB cases notification increased by 22% from 2012 to 2019. Although, coverage of national TB efforts increased with various case detection strategies, which showed a slightly a downward trend in 2020 during COVID-19 pandemic but again started increasing afterward.

ii. NTP Treatment of tuberculosis patients

The WHO recommends the use of fixed-dose combinations of drugs for the treatment of all TB patients. This could reduce prescription errors over individual medicines. The fixed-dose combinations may encourage adherence to treatment as the patient has to ingest less tablets. With these measures and bringing improvements in treatment strategies, Pakistan witnessed a little improvement in treatment coverage from 63% for drug susceptible TB in 2015 to 64% in 2018, whereas drug resistant TB treatment coverage remained same since 2016 [16].

iii. Recording and reporting

The WHO TB recording and reporting system is an integral part of the general health information system which is based on different forms, registers and reports that systematically gauge the patient's progress and treatment outcomes, along with monitoring of overall programme performance.

World Health Organisation supported the NTP to establish a paper-based surveillance system since its inception till 2016. However, the NTP, with the support from Global Fund and University of Oslo implemented an electronic surveillance system for recording TB cases and reporting using DHIS-2 (aggregate model) in 2017 to augment the paper-based TB data generated at BMUs. However, the aggregate DHIS-2 model could not address the challenges of delayed data entry at district level and duplications in data. Recently, to capture real time data from TB health facilities, online case-based data collection is being piloted in Islamabad with target to rollout across country during the year 2023.

iv. Tuberculosis in children

Children are at increased risk of rapid disease development once infected with MTB. Therefore, they can be considered as a target group for preventive TB treatment. Primary TB can also affect children more frequently compared to adults. The existing NTP guidelines and strategies should incorporate effective prevention measures, TB disease management in children, and introduce standardize approaches. Moreover, the engagement of all health care providers including paediatricians and other clinicians, is crucial to manage child TB incidence.

The proportion of child TB cases in national case notification remained very low. Overall, child TB contributed 14% of total country level TB caseload in year 2020. A significant variation exists in child TB notification across provinces and regions of Pakistan starting from 10% in Punjab to 40% in Gilgit-Baltistan. Although NTP paediatric guidelines were developed in 2006-7 but not implemented yet. Most of the public sector hospitals do not have digital X-rays. Likewise, there is no mechanism exists for tracing the children lost to follow-up. The active contact investigation is not properly conducted to trace child TB cases. Therefore, an under-detection gap of more than 50% in Punjab needs urgent attention. Beside this, several sites in the Pakistan have shown evidence of clear over diagnosis of extra pulmonary TB, particularly abdominal TB. A significant underreporting especially from the private

sector is evident as 78% child TB cases were not reported to the national surveillance system [17].

v. Contact investigation

The process of identifying, examining, assessing, and treating everyone who may recently remain in contact with a newly diagnosed or presumptive case of pulmonary, laryngeal, or pleural TB is known as a contact investigation. [18] The findings of a study conducted in 20 TB high burden countries during 2019 estimated that 38 million people lived in a household with a contact person of pulmonary TB. [19] Under five children made up12% of those with household exposure, compared to 65% of adults. The major proportion of people who experienced household exposure belonged to Zimbabwe, Mozambique, Zambia, and Pakistan. In low-income countries where full implementation of contact investigations may not be practical, WHO and the International Union Against Tuberculosis and Lung Disease proposed targeting children age under 5 years for contact investigation and treatment of LTBI. The implementation of the contact investigation is also crucial in those low incidence countries, which are close to eliminate TB.

In Pakistan the contact investigation was made part of national guidance for over a decade but not yet fully implemented [20]. The contact investigation is not routinely under taken therefore it's relatively a small source of TB cases. According to routine surveillance data of 2015 to 2017, approximately 10% of the identified contacts were screened for TB, among them, 2-4% had active TB, and contact investigation contributed to hardly 1% of TB notifications. Ample evidence exists in favour of contact tracing among high risk groups with positive results in identification of TB cases in Pakistan [21,22]. The main causes of poor contact investigations in the country are a lack of guidelines, absence of training materials in healthcare facilities and a lack of capacity building for frontline physicians and nurses.

vi. Infection control in health-care settings

The increasing focus on drug-resistant TB, also having the impact of HIV infection, has led to reconsider the importance of infection control in health-care and other

congregate settings. The presence of many HIV-infected and immunocompromised patients in the hospitals, in the absence of appropriate infection control policy and practices create a favourable environment for transmission and spread of TB to the population comprised of hospital patients, health care workers and the community. This situation emphasizes on an urgent need to refocus attention on TB infection control, particularly in high-risk settings.

In 2013–15, a comprehensive TB inflectional control strategy was introduced, with a primary focus on the PMDT (Programmatic Management of Drug Resistant Tuberculosis) sites rather than the facilities managing drug susceptible TB or TB/HIV co-infections. With the help of this plan, the infrastructures of thirty PMDT hospitals were upgraded along with capacity building of nurses and doctors on the infection control practices. Informational material was also disseminated at these sites. TB infection control guidelines for households, monitoring tools, videos for patients and communities, guidelines for drug resistant TB patients, and posters were also developed to communicate preventive measures according to the intended audience. At present, there is no designated funding for the implementation of TB infection control practices in Pakistan. The country lacks a national committee and staffing to move this agenda further [23].

vii. Isoniazid preventive therapy

The preventive therapy, also referred as chemoprophylaxis, with isoniazid which reduces the risk of (i) a first episode of TB in people who have been exposed to infection or who have latent infection and (ii) a recurring episode of TB. Although isoniazid is beneficial for everyone with LTBI, however, the greatest decrease in infection has been observed in HIV-negative patients, TST- and HIV-positive individuals. The preventive therapy has primarily been adopted because of its positive effect at the individual level. Mathematical modelling of community-wide preventive therapy in settings with high burden of both HIV and TB also suggests that this strategy may help to lower the incidences of TB at the population level.[15]

The main groups for preventive therapy under programmatic conditions are those at the risk of TB disease progression. These are (i) PLHIV, (ii) infants and children in contact with TB patients and (iii) recent TST converters, since the risk of developing active TB increases in the first few years.[24]

Contact evaluation and IPT provision in children under 5 years (with no disease) is part of Pakistan national guidelines but its full implementation is lacking [20]. IPT is provided, at a limited scale where paediatricians are involved in the management of childhood TB cases. But many health care providers are reluctant to prescribe ITP due to the fear of anti TB drug resistance. Additionally, NTP guidelines doesn't include any algorithm for screening and assessing household contacts. Moreover, the guidance doesn't specify that contacts with HIV (PLHIV) who have been exposed to index TB cases must receive IPT for 6 months. Typically, IPT is not given to PLHIV who are exposed to index TB cases for this reason in Pakistan [25].

viii. BCG vaccination

Primary TB and meningitis/septicaemia which was 100% deadly is rarely seen now, due to high BCG vaccination. In high burden countries BCG vaccine is recommended both for infants and adults. In countries, where the BCG vaccine is part of the national childhood vaccination programme, coverage of neonates and infants with the vaccine has reached more than 80%. The BCG vaccine in children has a confirmed 86% protective efficacy against TB meningitis and miliary disseminated illness. It does not prevent primary infection or reactivation of latent pulmonary infection, and the principal source of bacillary spread in the community but prevents primary TB disease. Therefore, there is little effect of BCG vaccination on M. tuberculosis transmission. According to WHO recommendation, in countries having a high TB burden, a single dosage of BCG vaccine must be provided to all infants shortly after the birth.

In order to protect young children in Pakistan from measles, poliomyelitis, diphtheria, pertussis, tetanus, and childhood TB, the Expanded Programme on Immunization (EPI) was introduced in 1978. The overall coverage of BCG vaccination is 91%

across Pakistan [26]. "*Pakistan's Expanded Programme on Immunization (EPI) performance has a significant impact on global and regional immunization indicators such as poliomyelitis eradication, maternal and neonatal tetanus, measles elimination and coverage of BCG to control childhood TB*".

ix. Prevention through addressing risk factors

Trends in the incidence of TB may be strongly influenced by changes in exposure to various risk factors. Preventive measures to decrease chances of population's exposure to risk factors like HIV, smoking, diabetes, under nutrition and overcrowding is primarily the responsibility of other public health programmes as well as stakeholders outside the health sector.

In general, the implementation of bi-directional screening of TB & HIV and TB & diabetic are recommended. In Pakistan, program activities TB & HIV remained low. Moreover, the collaboration with diabetic prevention and care program is also not evident. Recently, smoking cessation trial is concluded in Pakistan which indicated that a brief behaviour support remained effective in achieving tobacco quit rate of more than 40% across Pakistan.[27] Based on this, a related question has been added in TB surveillance tools to assess status of smoking in TB patient.

1.1.3 TB Diagnosis

Presumptive TB refers to a person, with symptoms or signs suggestive of TB i.e., cough >2 weeks, fever >2 weeks, weight loss, haemoptysis, or those with chest x-ray findings suggestive of active TB (previously known as a TB suspect).

The traditional method for diagnosing TB is based on microscopy. It has been replaced in recent years, with various new methods and tools that are based on the detection of mycobacterial antigens or DNA. Recently, after recognizing the emerging needs, WHO developed and consolidated the guidelines and recommendations on TB, by combining five different sets of previously published guidelines between 2016 to 2020 into one document.[28]

According to latest WHO consolidated guidelines on diagnosis [28], recommended GeneXpert MTB/RIF as an initial diagnostic test for pulmonary TB and rifampicin-resistance detection in adults presumptive TB cases from the general population rather than smear microscopy/culture and phenotypic DST. The use of GeneXpert MTB/RIF is suggested in lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens for extra pulmonary TB. In TB meningitis, GeneXpert MTB/RIF or GeneXpert Ultra recommended in cerebrospinal fluid (CSF). In HIV-positive adults and children with presumptive disseminated TB, GeneXpert MTB/RIF may be used in blood.

Infants, young children under five years and HIV patients are more prone to develop TB meningitis / disseminated TB disease, the most severe forms of TB. Signs and symptoms of TB disease in children include: cough; feelings of sickness or weakness, lethargy, or reduced playfulness; weight loss or failure to thrive; fever; or night sweats. All children with a positive test for TB infection, symptoms of TB, or a history of contact with a TB patient should undergo a medical evaluation.

According to latest WHO consolidated guidelines management of TB in children and adolescents [29], the latest two recommendation are as follows:

i. Use of the GeneXpert Ultra assay: GeneXpert Ultra is recommended as the initial diagnostic test for TB and detection of rifampicin resistance on sputum, nasopharyngeal aspirate, gastric aspirate or stool.
ii. The use of integrated treatment decision algorithms for the diagnosis. A flow chart should be used which allocating evidence-based scores to clinical, microbiological, and radiological features.

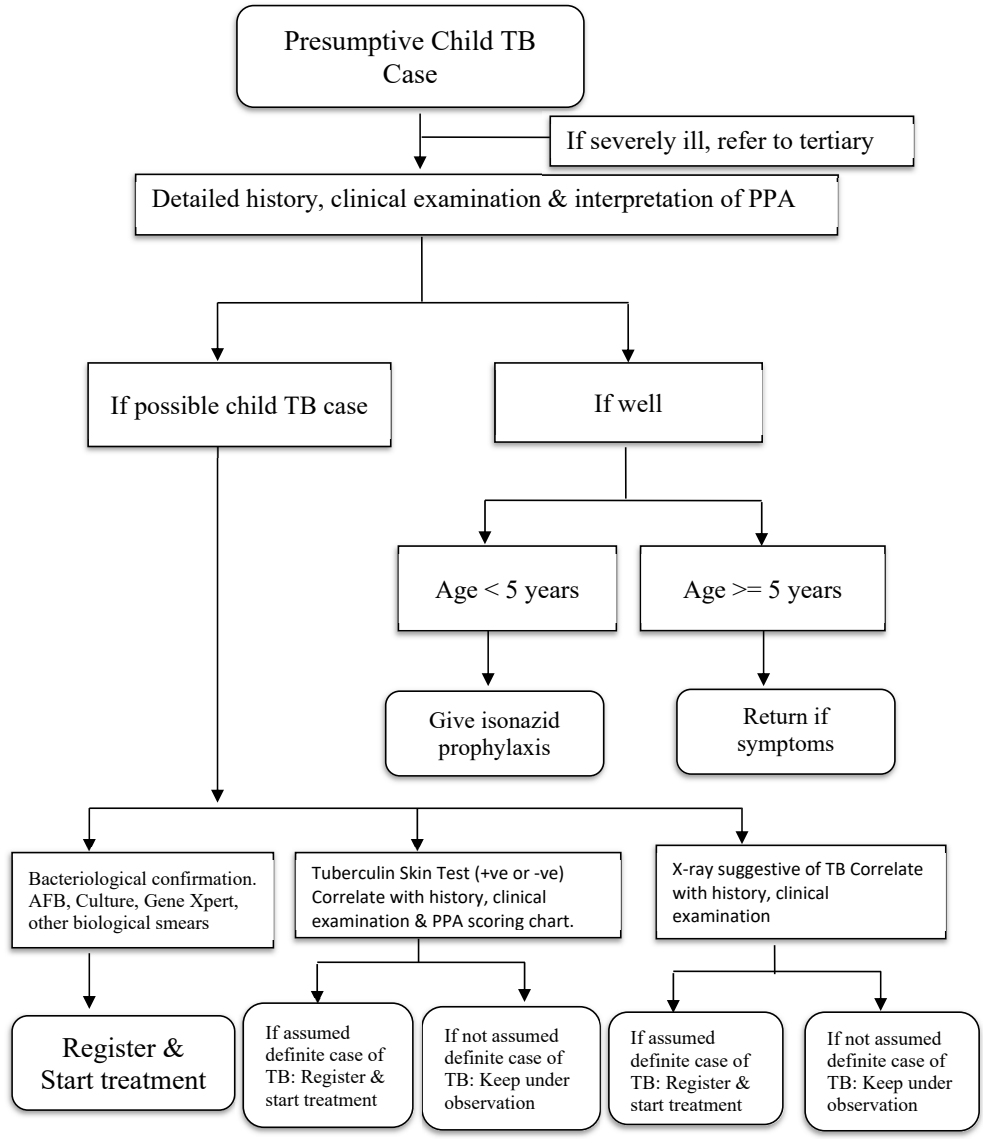
The WHO also recommend implementation of standardized approaches, by providing training to health care providers on diagnosis and management of childhood TB using international standards and national guidelines.

TB Diagnostic Strategy in Pakistan:

All adult presumptive TB patients with pulmonary TB whom chest radiograph findings are suggestive of TB, their sputum specimens should be examined in the NTP laboratory. The currently diagnostic algorithm in Pakistan, largely relies on symptom screening and sputum smear microscopy. The use of GeneXpert MTB-RIF test is confined to sputum smear positive cases for drug susceptibility testing.

In consultation with Pakistan Paediatric Association (PPA), NTP Pakistan developed first childhood TB diagnostic guidelines (Table 2) during 2006-07 with the aim to facilitate and standardize clinical practices of child TB health care providers for screening & diagnosis of presumptive child TB cases [30]. These guidelines categorized into unlikely, possible or probable TB cases by using clinical, histological, and radiological features. A diagnostic algorithm (revised 2019) [31] has been used in the NTP guidelines for child TB case management process in Pakistan (Figure 1).

Figure 1: Flow chart for evaluation of a child (<15 y) with presumptive TB, recommended by Pakistan National TB program



TB = Tuberculosis; PPA = Pakistan Paediatric Association**;** CXR = chest radiograph; TST = tuberculin sensitivity testing.

Table 2: Scoring chart for the diagnosis of childhood tuberculosis (<15 y) recommended by the Pakistan Paediatric Association (PPA) & National TB programme

Condition	Score 1	Score 2	Score 3	Score 4	Score 5
Age	<5 years				
Close contact[1]	TB suggestive	Clinically positive	Bacterio-logical positive		
PEM/SAM[2]	Yes	Not responding to nutritional rehabilitation for 2 months			
History of Measles, Whooping Cough	3-6 months	< 3 months			
HIV		Yes			
Immunocompromised[3]	Yes			Not improved	
Clinical Manifestation[4]		Suggestive		Strongly Suggestive	
Radio Diagnostic Imaging[5]	Non-specific	Suggestive	Strongly suggestive		
Tuberculin skin test	5 – 10 mm		> 10 mm		
GeneXpert MTB/RIF					Positive
Microscope examination of tissue	Non-specific				Positive

[1]Close contact defined as: History of cough for more than 2 weeks among the household member of the child

[2]PEM/SAM (Protein Energy Malnutrition/Severe acute malnutrition: Use WHO Recommended Z. scoring chart (1) & Not responding to Nutritional rehabilitation for 02 months (2)

[3]Immunocompromised status: Malignancies like leukaemia or lymphomas etc., Immunodeficiency diseases like agammaglobunemia etc.
Chemotherapy /Immuno- suppressive therapy such as steroids for more than 2 weeks.

[4]Clinical Manifestation: Suggestive of TB: Pulmonary Findings (unilateral wheeze, dullness, weight loss, Hepato-splenomegaly,
Lymphadenopathy, ascites etc. Strongly suggestive of TB: Matted lymph nodes, abdominal mass or doughy abdomen, sinus formation, gibbus formation, chronic mono arthritis, meningeal findings (bulging fontanel, irritability, choroid tubercle, papilloedema).

[5]Radio-Diagnostic/ imaging studies includes Chest X-ray, CT Chest/MRI. Non-specific signs: Ill-defined opacity or patchy infiltrates on chest X-Ray, Marked broncho-vacular marking. Signs suggestive of TB: Consolidation not responding to antibiotic therapy, Para-tracheal, or mediastinal Lymphadenopathy, Miliary Mottling, cavitation

Table 3: Interpretation of Pakistan Paediatric Association (PPA) scores for the diagnosis of childhood tuberculosis (<15 y)

Score	Interpretation	Suggested Actions
0 – 2	Unlikely TB	Investigate other reasons of illness
3 – 4	Possible TB	-Do not treat for TB -Manage the presenting symptom(s) -Monitor monthly the condition(s) for 3 months, using scoring chart
5 – 6	Possible TB	-Investigate and exclude other causes of illness -Investigation may justify therapy
7or more	Probable TB	- confirm (if possible)

National TB Control Program. Childhood TB Training Desk Guide. Islamabad, Pakistan: Ministry of Health; 2019.

1.1.4 TB Treatment

According to WHO guidelines on TB Treatment [32] in adults, new patients with pulmonary TB are recommended to receive a regimen containing 6 months of rifampicin: 2HRZE/4HR (isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months; and isoniazid plus rifampicin for 4 months) with fixed-dose combination tablets on daily dosing frequency. Same recommendation also applies to TB patients living with HIV and extra pulmonary TB except TB of the central nervous system, bone or joint, in this group longer therapy is suggested. An initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks is recommended in patients with TB meningitis. Pakistan is also following WHO recommended treatment regimen for adults in 2019.

According to WHO consolidated guidelines on management of TB in children and adolescents [29], between 3 months up to 16 years of age, a 4-month treatment regimen (2HRZ(E)/2HR) is recommended. In extra-pulmonary Children, standard six-month treatment regimen (2HRZE/4HR) is suggested. In bacteriologically confirmed or clinically diagnosed TB meningitis, a 6-month intensive regimen (isoniazid and rifampicin, pyrazinamide, and ethionamide (6HRZEto)) could be used. Pakistan follows the treatment for children given below in Table 4:

Table 4:Current regimen for treatment of TB in children< 15 years recommended by NTP, Pakistan [31]

TB Disease Category	Recommended Regimen	
	Intensive Phase	Continuation Phase
All forms of TB (Excluding TB meningitis and TB of bones & joints)	2 months HRZ (50, 75, 150) + E(100)	4 months HR (50, 75)
Re-treatment cases	3months HRZ (50,75,150) + E(100) + S = 20-40 mg/kg (if recommended by Paediatrician)	5 months HR (50, 75) + E (100)
TB meningitis, TB of the bones & joints	2months HRZ + E	10months HR

1.1.5 Monitoring

In Pakistan, the surveillance is integrated part of monitoring & evaluation plan which is based on national indicators used to assess program performance. Various monitoring strategies has been adopted to ensure treatment adherence, timely identification and management of adverse drug reactions, quality assurance of diagnostic services and reporting system.

i. Treatment Monitoring

It is advised by WHO to use a home or community based directly observed treatment (DOT). The administration of DOT by the trained community workers (LHWs) and family members is encouraged than an unsupervised treatment in Pakistan. Counselling and health education are provided on continuous basis by the health staff to patients and their relatives or attendants during treatment periods. All patients, their treatment supporters and healthcare professionals are instructed to report any adverse drug reactions, treatment disruptions, or persistence or reoccurrence of TB symptoms (including weight loss).

The TB Treatment Card (TB02) provides room for maintaining a record of all medications provided, bacteriological response and adverse effects for each patient. The health care workers are accountable to review patient treatment records, and

maintain the record of all the reasons for any interruptions. If any patient skips treatment for more than 2 consecutive days during intensive phase, they must be contacted through call or SMS, in no response scenario, health workers or the treatment supporter have to trace the patient. However, in the continuation phase, those patients who don't visit to receive medicines for up till one week after the medicines collection day, they should be contacted through calls or SMS, otherwise, health workers have to trace those patients.

ii. Surveillance activity for ensuring data quality and reporting

The National TB M&E Plan is based on systematic collection of information on the inputs, processes, outputs, outcomes and impact indicators while tracking the progress towards the set targets. Various surveillance activities include oversight monitoring visits, quality assurance monitoring, evaluation visits of warehouse and laboratories, Intra and inter district meetings for quality assurance of diagnostic services and reporting system.

iii. Patient Level monitoring system

To strengthen the national surveillance system for TB control activities, Pakistan's NTP has adopted "WHO recommended Revised Reporting & Recording Tools - 2013" for data collection. The NTP has developed an adequate information system to monitor TB notifications, implementation of TB prevention, care and treatment activities along with evaluation of their treatment outcomes. This system includes:

i) Presumptive register
ii) Prevention Treatment Register
iii) TB preventive Treatment Card
iv) TB Treatment Facility Card (TB-01)
v) TB Patient Card (TB-02)
vi) TB Treatment Register (TB-03)
vii) Lab Register (TB-04)
viii) TB Laboratory Request Form (TB-05)
ix) TB Case Notification (TB-07)
x) TB Outcomes (TB-09)
xi) Referral Transfer out (TB-10)

1.1.6 Outcome

The NTP is following the WHO revised guidelines for reporting of treatment outcome of TB patients [33]. The detail of treatment outcomes are explained in table 5. For analysis purposes a category of “Not evaluated” is added when there is no treatment outcome is assigned. The sum of “cured” and “treatment completed” is named as “treatment success".

Table 5: Outcomes of treatment of drug sensitive tuberculosis.

Cured	A smear-positive patient registered, completed the duration of treatment, became sputum smear negative at the end of the treatment and on at least one previous occasion.
Treatment completed	A smear positive patient who has completed the entire duration of treatment, have at least one follow-up smear negative results but none at the end of treatment period due to any reason. Smear negative and extra pulmonary cases complete six months of treatment successfully.
Treatment Failure	A sputum smears positive patient who remains or becomes sputum smear positive at fifth month or later.
Died	A patient who dies for any reason during the course of TB treatment.
Lost to follow up	A patient whose treatment was interrupted for two consecutive months or more after last medicine intake.
Not Evaluated	A TB patient for whom, no treatment outcome is assigned (includes “Transfer out” to another treatment unit and his/ her treatment outcome is unknown).

Pakistan achieved the WHO target of treatment success rates (both all forms & B+) >90% since 2015. Over the last five years, case holding practices have been

improved. However, a mismatch between case finding and case holding practices remained an issue from public health perspective and yet to be explored.

1.6 Rationale

TB is a curable and preventable disease but still children with TB die after every two minutes. According to Global TB report 2020, 11% TB incidence in children has been reported with 16% mortality rate. An estimated 80% deaths were recorded in children under-5 and 96% of them did not get access to the treatment either due to in correct diagnosis or not treated correctly [3]. TB is largely underestimated among children because of difficult bacteriological confirmation hence usually considered as common childhood illness. There is 72% case detection gap, which is widening in all age groups dramatically, especially in youngest ages i.e. 5-14 years (49%) and 0-4 years (65%). [3]

About 40% of total population of Pakistan is under the age of 15 years.[34] They are at risk of contracting TB disease, as the issue of childhood TB is of significance nature in the country. Lack of training of health staff, poor referral network, no tracking mechanism, lack of trained doctors, no access to quality diagnostics, and no access to shorter TB preventive treatment regimens are the major challenges for the paediatric TB care cascade in Pakistan.

The health care delivery system in Pakistan consists of both public and private health care sectors. Traditionally, public health care delivery has been jointly administered by the federal and provincial governments with districts mainly responsible for the implementation. The curative and rehabilitative services are being provided mainly at the secondary and tertiary care facilities. While preventive services, are mainly provided through various national programs; and community health workers' interfacing with the communities through primary healthcare facilities and outreach activities. Despite an elaborate and extensive public health infrastructure, the health care delivery suffers from some key issues such as high population growth, uneven distribution of health professionals, deficient workforce, insufficient funding and limited access to quality health care services.

Conversely, the private health care sector is large but unregulated, consisted of both qualified and unqualified health care providers in the categories of allopathic, homeopathic and tibb (Traditional Herbal Medicine). TB medicines are also freely available in private pharmacies. There are a number of large private teaching hospitals which are handling both communicable and non-communicable diseases. Private sector hospitals may extend better health care services and charge their patients ranging from low to high bills depending on the type of the private hospital. The patients on average spend between 50-100 $ per month on the health care.[35] However, the private sector provide primary health care services to approximately 75% of the population in Pakistan. [36].Only about 5% of the private providers are engaged with NTP. These health care providers are encouraged to refer patients to the NTP. As evident in other developing countries, this happens with varying comprehensiveness of notification. It is expected that many TB cases from the private sector are missing in the national TB surveillance system due to the fact that the NTP has not yet achieved 100% coverage of all health care providers. Unpublished data from adult inventory study indicated [37] that underreporting of TB cases was 2.5 times higher in children less than 15 years. It is expected that NTP is missing more child TB cases. **Thus, the first research question was: what is the level of under-reporting of child TB cases from non-engaged private sector in Pakistan?**

Private sector is the first point of contact for primary health services in 90% of the patients for various type of ailments in Pakistan. Many patients with presumptive TB seek health services from a wide range of private health providers outside the network of NTP services [38]. To understand the role of the private health sector in the diagnosis and treatment of childhood TB, limited evidences are available on the issue [39,40]. **Based on this the second research question was: how do health care providers in non-engaged private sector diagnose and manage child TB patients?**

During 2006-07, NTP Pakistan developed its national childhood TB policy guidelines aiming to facilitate the paediatricians, physicians and other health care workers to

improve and standardize clinical decisions for investigating presumptive child TB cases under 15 years of age [30]. NTP strongly recommends to all paediatricians and doctors who are dealing with children to use PPA scoring chart for the diagnosis and management of TB in children. A few studies in Pakistan provided evidence about utilization of the PPA scoring chart in public sector, claimed to be of particular value in detection of TB cases in children [41–43]. NTP guidelines for childhood TB includes use and interpretation of the PPA guide, but the practices and implementation among non-NTP private health providers for diagnosis of childhood TB have not been evaluated. Private sector is a very important part of the health care system as it provides general medical services to approximately 75% of general population in Pakistan [36]. They also manage a significant number of presumptive child TB cases and many among them refer cases to the NTP [17]. **The third research question was: what proportion of non-NTP health care providers adhere NTP diagnostic guidelines for TB diagnosis in children?**

One bottleneck in management of childhood TB in Pakistan is the lack of a systematic mechanism to refer children with presumptive TB from primary health care (PHC) facilities to the facilities where childhood TB diagnostic services are available. In such cases the distance is an important factor to access these services. Therefore, understanding the link between geographic distance, access to childhood TB diagnostic services and population coverage by the secondary & tertiary care hospital. There may be a useful to make evidence-based health policies that may reduce barriers to childhood TB care and improve their outcomes across Pakistan. **Thus, the fourth research question was: How much distance require from community centres to reach health facilities for childhood TB care in Pakistan. How much population is living within 5 km radius of PHC and childhood TB services to assess population coverage within facilities?**

2 Objectives

2.1 Aim

The aim of this thesis was to study child TB and its management by various services in Pakistan.

2.2 Specific Objectives

All specific objectives (1-III) relate to children under 15 years in 12 districts of Pakistan.

The specific objectives were to

1. Determine the extent of under reporting of child TB cases from non-NTP private health care providers in Pakistan. (Paper I)
2. Assess the diagnostic and management practices of non-NTP private health care providers for investigating presumptive child TB patients in Pakistan. (Paper II)
3. Evaluate adherence/use of national guidelines of Pakistan Paediatric Association (PPA) clinical scores by private providers to diagnose childhood TB in Pakistan. (Paper III)
4. Estimate distance from community centres to health facilities with childhood TB care and population coverage for primary health centres and childhood TB services in Pakistan. (Paper IV)

3 Methodology

3.1 Settings

3.1.1 Study area: Pakistan

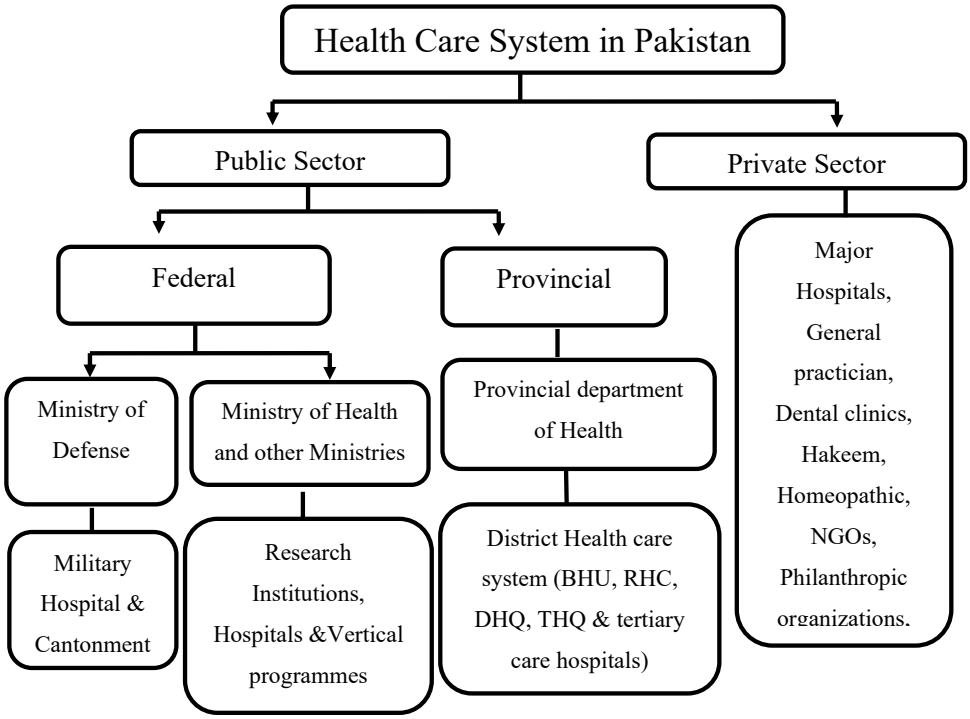
Pakistan is located in South Asia, covering 881,913 km2 (340,509 square mile) area and bordered by India, China, Iran and Afghanistan. Pakistan has four provinces: Balochistan, Khyber Pakhtunkhwa (KP), Punjab and Sindh and three regions or administrative areas Azad Jammu Kashmir (AJK), Gilgit Baltistan (GB), and Islamabad Capital Territory (ICT). Pakistan ranks fifth among most populous countries in the world. According to last population census in 2017, the overall population of Pakistan is 207 million. 35.1% of the population of Pakistan lives in urban areas and population density is 287 per km².

Pakistan is currently facing the double burden of communicable (38%), non-communicable diseases (51%) and injuries (11%) according to WHO NCD Country Profiles 2017. About 50% of all deaths are attributed to non-communicable diseases. Pakistan has considerably improved its health care sector over the past few decades by introducing many reforms. Life expectancy at birth was 60.1 years in 1990, which has been increased to 68 years in 2020. Similarly, under-5 mortality rate (per 1,000 live births) was 139 in the year 1990, which has been reduced to 65 in 2020. [44,45] The annual per capita health expenditures for Pakistan as per National Health Accounts 2014-15 is USD 39.4 and spending on the health sector is 2.6% of the gross domestic product (GDP) in contrast to the desired minimum expenditure of 6%. The government's contribution to total health expenditure in terms of GDP is about 1%. (IHME. http://www.healthdata.org/pakistan). Pakistan has seen improvement in healthcare access and quality index since 1990, the index increased from 26.8 in 1990 to 37.6 in 2016 [46]

3.1.2 Health Care System in Pakistan

Pakistan has a mixed health system, which includes government (public) infrastructure, parastatal health institutions, the private sector, civil society, philanthropic contributors and donor agencies. In Pakistan, health care delivery to the consumers is systematized through four modes of preventive, promotional, curative, and rehabilitative services. Traditionally, the health care delivery has been jointly administered by the federal and provincial governments with districts mainly responsible for implementation. The curative and rehabilitative services are being provided mainly at the secondary and tertiary care facilities. Whereas, preventive and promotional services are primarily provided by various vertical health care programs at national level. The outreach activities are being implemented through community health workers at community level under the primary healthcare program. The private sector consists of a diverse group of trained health care providers as well as traditional faith healers [47,48] . Additionally, both vertical and horizontal health care structures also exist in Pakistan. The Pakistan health care system is summarized in Figure 2.

Figure 2: Pakistan Health Care System



i. Public Sector

The public sector in Pakistan caters for the health care needs of only 25% of the general population by providing the curative care for minor ailments. Public sector health care system consists of a three-level healthcare delivery system with a range of public health interventions. The first level includes Basic Health Units (BHUs), Rural Health Centres (RHCs), Dispensaries and Maternity & Child Health Centres that provide primary healthcare services. The secondary level care covers referral of first level of facilities by providing acute, ambulatory and inpatient care through Tehsil Headquarter Hospitals (THQs) and District Headquarter Hospitals (DHQs). The third level of care is tertiary hospital that delivering full package of health care services including teaching hospitals. A major strength of the Pakistan public health care system is the outreach component of PHC that consists of one million LHWs, and an increasing number of community midwives (CMWs) and Lady Health Visitors (LHVs). The total number of trained health care providers have been increased over the time. Hence the availability of one doctor, dentist, nurse and one hospital bed shared by a certain number of population has been gradually improved. Despite an elaborative and extensive health infrastructure, the delivery of care stills facing challenges due to high population growth, uneven distribution of health professionals, deficient workforce, insufficient funding and limited access to quality health care services.

ii. Private Sector

In Pakistan, the private health care sector is very heterogeneous in nature that includes Hospitals, non-governmental organization (NGOs), pharmacies, solo qualified general practitioners, homeopaths, spiritual healers, traditional healers, herbalists, bonesetters and quacks. The private health sector is the main provider of health care services as it cater for 90% of initial outpatient visit for any illness.[38] Majority of the patients prefer to go to private health care providers for many reasons such as accessibility; less waiting time; availability in the evening; provides better attention, and maintains confidentiality. [20] Patients from low income segment of the society may spend between Rs.5000-10000 per month on health care [35]. The TB cases

diagnosed and managed by private sector are neither recorded nor reported due to the reasons cited above, therefore these are not part of consolidated national data.

iii. Informal health care providers

The literature shows that most of the patients in Pakistan visit at least 4-5 healthcare providers before reaching to TB diagnosis services, resulting in long treatment delays. [49] One study conducted in Pakistan showed that one of the first actions taken by the patient is to consult the health care provider within their own neighbourhood, which tends to be an informal medical practitioner. According to a small scale study conducted in Karachi Pakistan, the informal health care providers constitute of 50-60% of the private health care providers. [50] This is general perception that people prefer to visit them because they are easily accessible, relatively cheap in prescribing treatment and provide tailor made treatments, resulting in a higher level of trust and satisfaction from patients. Actually, patient's satisfaction is a key to patient's compliance with the prescribed treatment.

iv. Parastatal health institutions

Some government/ semi government organizations like parastatal institutes such as Pakistan International Airlines (PIA), the Water and Power Development Authority (WAPDA), K-Electric, Pakistan Steel Mills, Karachi Port Trust, Sui Southern Gas Company, Pakistan Petroleum Limited, Oil and Gas Development Corporation, Pakistan Railways, Fauji Foundation, armed forced hospital and the employees Social Security Institution provide health services to the employees and their families through the networks of health facilities, including hospitals, in many major cities. However, these collectively cover about 10% of the population.

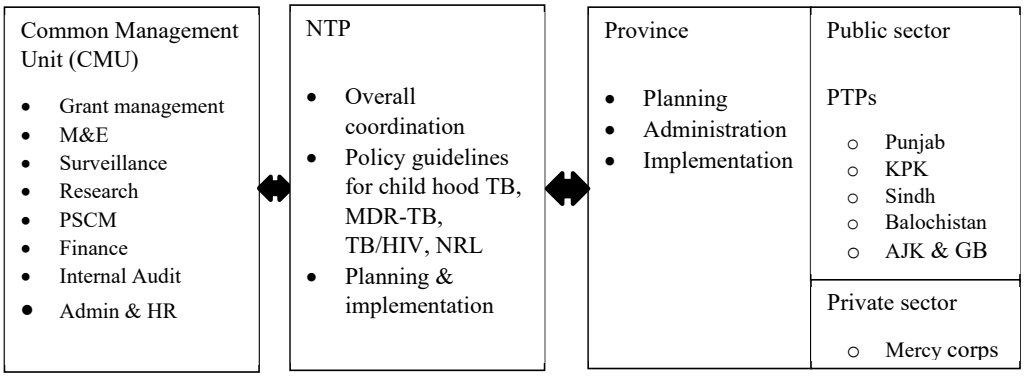
3.1.3 National Tuberculosis Control Program (NTP)

The National Tuberculosis Control Program in Pakistan has a stewardship role in TB control efforts across the country. NTP is a vertical program integrated into PHC. The program is responsible for overall management of the TB control activities in the country. The delivery and management of TB care is integrated within district

healthcare services so that health care can be provided close to the patient's home. Pakistan has achieved 100% DOTS coverage by engaging public health facilities such as all BMUs including BHUs, RHCs, DHQs, and Tertiary care hospitals. Since 2001, NTP is providing free of cost TB diagnostic and treatment services through a network of diagnostic and treatment centres all over Pakistan.

TB care in Private sector includes different intervention/models of care in Pakistan ranging from PPM-1-4 (GP clinics, NGO based facilities, Private Hospitals and facilities in non-health public sector respectively). TB care services are provided at the minimal cost to be bear by the facility as well as the support from the Global Fund in terms of diagnosis and treatment. Figure 3 showing the organizational chart (structure & functions) of TB control in Pakistan.

Figure 3: Organizational chart (structure & functions) of TB control in Pakistan



M&E = Monitoring & Evaluation, PSCM = Procurement and supply chain management, HR= Human Resource, MDR= Multi-drug Resistance, NRL= National Reference Laboratory, PTP= Provincial TB Programme, KPK= Khyber Pakhtunkhwa, AJK= Azad Jammu & Kashmir, GB= Gilgit Baltistan

Within the country PPM interventions have achieved some promising initial results, such as PPM contributed to 40% national case detection and treatment in 2020. 3500 private health facilities are providing TB DOTS services and over 1000 GPs are engaged with NTP. However, there is a critical need to enhance the degree of collaboration with those not currently engaged and reach out to a greater number and range of providers.

3.2 Study Population

In paper I (child TB inventory study), II (TB investigation practices by PP) & III (adherence of national guidelines to diagnose childhood TB), study population was all child presumptive TB patients brought to clinicians at a non-NTP private health facility, with a prolonged / unexplained illness more than 2 weeks from April – June, 2016. All participants were the private health care providers who were not engaged with the NTP such as paediatricians, pulmonologists, general practitioners and chest specialists working in private hospitals, NGOs or solo clinics. Of all the health care providers who were mapped and invited to participate in the study, 82% agreed. The same data set was used for Paper II (Private providers' investigation practices) and paper III (adherence of national guidelines to diagnose childhood TB).

In paper IV (access to child TB care), all population of Pakistan living in different settlements like a town, village, colony, small area in city, small community of people. All health facilities including primary, secondary & tertiary care level were included to estimate population coverage within 5km radius of health facilities and distance from settlements to general health facilities and child TB sites.

3.3 Study Design

In the child TB inventory study (paper I), the study design was a nationwide cluster-based cross-sectional study in 12 randomly selected districts across the country. A surveillance system was established for prospective collection of data for child TB cases diagnosed by all private health-care providers within selected districts from April – June, 2016, followed by record-linkage with case-based national NTP electronic database [51].

In paper II (TB investigation practices by PPs) & III (adherence of the national guidelines to diagnose childhood TB), we undertook a cross-study using data of child TB inventory study.

Paper IV (access to child TB care) followed a descriptive cross sectional study design to assess accessibility of general and child TB services in Pakistan using secondary data of different open sources.

3.4 Definition of Terms

Some important terms are defined below:

- Presumptive child TB case (previously called “TB suspects”: A presumptive child patient was defined in accordance with PPA scoring chart that any child under the age 15 years with an unexplained cough for more than 2 weeks or/and at least one other TB symptom. [31]
- Child TB case: A child less than 15 years, with confirmed diagnosis of either pulmonary, extra pulmonary TB or clinically diagnosed by health care provider
- Bacteriologically-confirmed: A bacteriologically confirmed TB case was consider the one who had a positive biological specimen through smear microscopy, Gene-Xpert MTB/RIF or culture
- Clinically-diagnosed: A clinically diagnosed TB case had no bacteriological confirmation but mainly diagnosed with active TB by a medical doctor or with X-ray abnormalities or suggestive histology and extra pulmonary cases with laboratory confirmation.
- Inventory Study: An inventory study is a study that determines level of under-reporting of existing TB cases by making comparison between number of cases meet standard case definition recorded in all or a sample of public and private health facilities with the records of cases notified in national TB surveillance system.
- Notified TB Cases: Refer to all TB patients registered with NTP
- Passive Case Finding: Passive case finding means identifying TB cases when they come to a clinic or health facility to get treatment for their TB symptoms.

- Active Case Finding: implies health care providers actively investigate for TB either through contact screening or otherwise.
- Private-Public-Mix (PPM): An international initiative to stimulate and assist collaboration between public and the private health sector.
- Under-Reporting: refers to the numbers of cases diagnosed but not notified to the TB surveillance system.
- Settlement: a village, colony, town, small area in city or any small segment of population in the community.
- Geographical access: according to WHO definition, health services geographical access is defined as percent of population living within five km radius of a health facility.[52]
- Child TB site: refers to secondary and tertiary care facilities where paediatricians and all diagnostic services are available to diagnose and managed child TB cases.

3.5 Study Outcomes

In paper I (child TB inventory study) the outcome was the level of under-reporting, which is define as proportion of child TB cases that are not notified to NTP.

In paper II (TB investigation practices by PP) the outcomes were management and referral practices of private health providers of patients to investigate presumptive child TB.

In paper III (adherence of national guidelines to diagnose childhood TB) the outcome was the proportions of presumptive patients diagnosed having TB according to national guidelines using PPA scoring chart.

In paper IV (access to child TB care) the outcomes were the population coverage of health facilities those living within five km radius and distance from settlement centres to general health facility and child TB site (secondary & tertiary care facilities).

3.6 Data collection Methodology

In paper (I-III) a total of 9,786 health facilities were providing health care services to child presumptive TB cases. These health facilities were mapped and invited to take part in the study. We used an electronic data collection technique and web interface for monitoring, mapping and data collection. In first phase all non-NTP facilities were mapped using electronic data collection application which was directly monitored by the central research team using web interface on daily basis. A report on uncovered areas was generated on basis of daily web monitoring and reported to field supervisor for further follow-up in the field. The supervisor paid monitoring visits to cross check mapping of health facilities. In 12 selected districts, all type of health care providers were included in the study such as paediatricians, general practitioners, pulmonologists and chest specialists working in private hospital, NGOs or solo clinics and private laboratories. Public health facilities include public primary, secondary & tertiary care hospitals, social security & railway hospitals, the army run hospitals, etc. Private health facilities include private large hospitals, teaching hospitals and universities, solo GPs clinic, health facilities run by NGOs, and informal health providers. Private laboratories were also included in this study.

In the child TB inventory study, OPD and laboratory registers were developed and provided to all non-NTP health care providers to record management of presumptive child TB cases patients without changing their routine practice from April—June 2016. The register included the information such as first, middle & last names of the patient, father name, mobile number, full address, age, sex, source of referral, type of test, results of the tests, diagnosis by the private providers and registration status at NTP. In tertiary care hospitals, these registers were placed at all entry points of child TB patients, such as paediatric specialist, chest physician and medical officer. These registers were filled out by health providers who are diagnosing child TB cases. A laboratory register was also provided to all laboratories in the selected districts to collect the information regarding the referral, type of tests suggested by the private

providers and result of the tests. All health care providers and laboratory personnel who consented to participate in the study were firstly briefed about capturing the required information on the registers. Field officers (FOs) and district TB coordinators (DTCs) were trained on the data collection and they were equipped with mobile phones to enter the data during their visits in the health facilities on a weekly basis. The mobile phones application was developed by "Zong 4G (Mobile network operator company)" with offline function of records the information. Field officers were instructed to upload all data to the server on daily basis to ensure timely monitoring and supervision by the research department at central level.

In paper IV (access to child TB care) multiple data sources were used in this study. The list of public health facilities in Pakistan was obtained from the District Health Information System [DHIS]. Geographical coordinates of all public health facilities were derived from publicly available data source "The Humanitarian Data Exchange" [https://data.humdata.org/organization/alhasan-systems-private-limited].
For Population density mapping, we used the grid population data from LandScan. [https://landscan.ornl.gov/]. Pakistan settlement data was obtained from publicly available on The Humanitarian Data Exchange website [https://data.humdata.org/dataset/pakistan-settlement].

3.7 Data Validation

In the child TB inventory study, following data validation techniques were used to ensure the quality and completeness of data at different levels:

- Electronic data collection and web interface for monitoring
  The data was collected using mobile phones enabled with GIS for mapping of all the private health facilities that were providing child TB services. A web-based system was developed to upload real-time data to the server to ensure timely monitoring and supervision to avoid any data loss.

- **Monitoring visits:**

  The collected data was reviewed by the field officers and crosschecked by the supervisor to verify diagnosis and confirm notification status before uploading to the server. A monitoring team comprised of field officers, district supervisor, were responsible to visit the health facilities on weekly basis to ensure the validity and completeness of data. The surprise visits were also conducted by the central research team, the provincial, district TB coordinators on a weekly basis at different sites in the selected districts.

- **Probabilistic record linkage**

  Three data sources were used for the analysis: i) NTP standard TB-registers TB-03; ii) Health facilities registers provided in private health facilities during the study; iii) Laboratory registers provided in private laboratories.

  At first stage; de-duplication was carried out through probabilistic matching for health facility mapping data and health facilities reporting databases by matching the following variables of each case: First name, last name, father's name, grandfather's name, district, sex, age, site of disease, hospital name, and type of health facility. Then a manual review of multi-matches (one case matching too many) was done by the research team & WHO consultant to remove duplicates.

  At second stage; the combination of the first name, father's name and family name in English language used as the identifiers for cross-checking the notifications of non-NTP facilities, comparison with official public district TB registers was made. In case, one of the identifier names was found missing then other available identifiers such as district, sex, age, site of disease, hospital name, and type of health facility were also compared. Presence or absence in the official district NTP register was recorded.

  At third stage; NTP registers were examined for the period between two quarters before and one quarter after the study period to correct possible misclassification. Then databases including notification data, and study

datasets were combined including both matched and unique records for final analysis.

- **Data Quality Audit**

After the data collection, data quality audit was conducted by a team of research assistants at NTP central unit. Every record was cross checked from the hard copies to remove inconsistencies between hard and soft records. The process of data quality audit for crosschecking registers was completed one quarter after the end of the study period.

In paper IV (access to child TB care) the database extracted from publicly available data source The Humanitarian Data Exchange. This data base was matched with list of health facilities available in DHIS and identified missed health facilities from the DHIS list which were later mapped manually using Google Maps. For population density mapping grid population data from LandScan was used. It considers community as standard for global population distribution and it provides an estimated population count up to approximately 1 km^2 with a spatial resolution of 30 arc-seconds. LandScan utilise census counts to estimate population and applies a spatial distribution model using roads, urban areas, location of villages, land cover, terrain, and provide high-resolution imagery analysis [53,54].

3.8 Sample Size

In child TB inventory study; different assumptions were investigated for the required sample size under different levels of expected under-reporting (p), its variability between clusters (captured by the coefficient of variation k), and the selected values of relative precision (d) and harmonic mean of cluster size m. Blow formula was used to determine the required sample size N for this study, in terms of the required number of clusters.

$$N = (\left[1 + (\mathrm{m} - 1)\frac{\mathrm{k}^2\mathrm{p}}{1 - \mathrm{p}}\right] * 1.96^2 \frac{(1-p)}{d^2 p})/m$$

The proportion of under-reporting from the previous inventory study among adults was used, at 0.27. By using the assumptions of precision of 25%, a coefficient of variation between 0.3-0.4 (similar levels to that from the previous study), and cluster size with harmonic mean between 33 and 77, It was estimated that 12 districts will be required to fulfil the objectives of the study.

3.9 Sample selection

A sample of 12 districts (clusters) out of total 131 districts across Pakistan excluding FATA was selected, with probability proportional to population size of provinces and regions (Table 6). At least one district was selected from each province and region to ensure national representation, while remaining 6 districts were distributed proportionately to province/region on the basis of the population size of children.

Table 6: Selection of districts by probability proportional to population size of provinces and regions

Strata	Number of districts	Population (0-14 years)	Percentage share of national	Number of clusters		
				All get one	*Additional* *	*Total*
Balochistan	30	2947212	5%	1	0	1
KPK	25	8239283	14%	1	1	2
Punjab	36	33027380	55%	1	3	4
Sindh	23	13712676	23%	1	2	3
AJK	10	1452889	2%	1	0	1
GB	7	412616	1%	1	0	1
National	131	59792055	100%	6	6	12

*Proportional to national share

In paper IV (access to child TB care), it was a national level study, covering all health facilities at primary, secondary & tertiary care and those engaged with NTP. Pakistan's settlement data was obtained from publicly available data on "The Humanitarian Data Exchange" which have approximately 261,217 geographical coordinates of the settlements covering 4 provinces and Islamabad Capital Territory in Pakistan.

3.10 Statistical Analysis

In Paper I of child TB Inventory Study, data from partially overlapping registers of TB in the community were analysed using capture-recapture methods [55], which examines the extent of overlap between different sources to estimate the total number of unobserved cases. The capture-recapture method involves cross-matching of records from at least three incomplete data sources covering the same population to identify the number of common cases in the paired lists. Then using the overlapping information, the number of TB cases not identified in any of lists were estimated [56–63]. Basic assumptions of capture-recapture analysis include: perfect record linkage; no migration/emigration/death (a "closed" population); and cases are independent [51].

The final dataset consisted of matched records from NTP public facilities, non-NTP private facilities or providers and private laboratories. Data from all sources was analysed using capture-recapture analysis to examine the extent of overlap between different sources to estimate total number of unobserved cases. Data analysis was carried out in STATA version 14.

In paper II (TB investigation practices by PP), the investigation, management and referral of presumptive children TB cases, by private providers were assessed using descriptive statistics. Differences in investigation practices between children 0–4, 5–11, and 12–14 years were identified by cross tabulation. The analysis was conducted in STATA version 14.

In paper III (adherence of national guidelines to diagnose childhood TB), descriptive analysis was carried out to assess characteristics of child presumptive TB cases. To measure the adherence of NTP guidelines for diagnosis of child TB, diagnosis of private providers was compared with PPA scoring chart. Agreement between diagnosis by the private provider and NTP guidelines using PPA scoring was evaluated by using the kappa statistic [64]. Adjusted prevalence ratios (95% CI) were calculated to determine the factors associated with non-adherence to the national

guidelines. The generalized linear model was used for the adjusted analysis by including age, gender, district and close contact of TB patient. We assessed programmatic significance (≥1.5 or ≤0.7) and interpreting statistical significance ($p<0.05$) with the study's large sample size [65]. For the analysis STATA version 14 was used.

In Paper IV (access to child TB care), the total population living within five km of public health facility [52] was determined by generating dissolved buffer from the health facilities to geographical accessibility catchment zone using open source GIS software [qGIS]. Using intersection tool in qGIS, the geographical accessibility catchment zone was overlaid with the district shapefile. Then, this output was intersected with the population grid map [Landscan] by using the Spatial Join and Summary Analyst Tool in qGIS. The total population within the five km of health facilities in each district was extracted and proportion of total population that lives within 5km of health facilities were calculated and choropleth maps (thematic map) were used to show summary of accessibility of health facilities.

Descriptive statistics was used to determine average distance from settlements/ communities to nearest health facility in term of median and interquartile range using the nearest neighbour analysis tool in qGIS.

3.11 Ethical Considerations

For child TB inventory study, the ethical clearance (registration # NBC 192 given in 2015) was obtained from the Pakistan Medical and Research Council at national level, REK Vest in Norway (# 2018/56) from University of Bergen, as well as the WHO Ethics Committee for the East Mediterranean region. As this study was based on record review without any intervention targeted for TB patients so the informed consent was taken from the health care providers but not from the patients. However, patient identifiers were required for record linkage. Data was maintained in electronic register with a password-protected code and only the principal investigator or an authorized person had access to the data for analysis purposes. Permission to use the

data was obtained from the program manager of the National TB control program, Islamabad, Pakistan.

In paper II (TB investigation practices by PP) and paper III (adherence of national guidelines to diagnose childhood TB), local ethical clearance was obtained from Institutional Review Board ethics committee, common management unit (TB, HIV/AIDS & Malaria). Informed consent was waived by the ethics committee, as all data used in this study had been previously collected during the child inventory study. Therefore, it did not pose any additional risks to the patients. However, the permission for using the data in this study was obtained from the program manager of the National TB control program, Islamabad, Pakistan.

In paper IV (access to child TB care), local ethical clearance was obtained from IRB, ethics committee, common management unit (TB, HIV/AIDS & Malaria). This study involved utilization and analysis of publicly available data of health facilities engaged with NTP, population density and settlements. The study did not involve any personal identifiers at individual level.

4 Result

Paper I: Measuring and addressing the childhood tuberculosis reporting gaps in Pakistan: The first ever national inventory study among children

Objectives This study aimed to estimate underreporting of diagnosed childhood TB cases by the private providers who were not engaged with NTP, in 12 selected districts in Pakistan.

Methods: The study design was cross sectional. It was conducted nationwide in 12 selected districts across Pakistan. Health facilities involved in diagnosis and treatment of childhood TB from all sectors were mapped and invited to participate. Lists of child TB cases were created during the study period (April-June 2016) from all selected health facilities and compared with the list of child TB cases notified to the national TB surveillance system for the same districts between the period two quarter before and one quarter after the study period.

Findings: In chid TB inventory study, a total of 7,125 children were identified with presumptive TB in 12 districts between Apr-Jun 2016. Of these, 6061 (73%) were recorded in NTP TB register. Of them, 5,258 were diagnosed with TB: 11% were bacteriologically-confirmed and 89% clinically-diagnosed; only 4% of them were notified to NTP. An additional 1,267 children with TB were also registered in the NTP. An underreporting of 78% was estimated with remarkable differences between provinces. The underreporting was higher in boys 84% (78% - 91%) than girls 68% (57% - 79%). The highest level of underreporting was found in the district Jhal Magsi, followed by Hafizabad and Pallundary. This study confirmed that childhood TB underreporting is very high in Pakistan. TB surveillance in the country must be strengthened to address the issue, particular attention is required to sensitize, guide, and support general practitioners and paediatricians to for notifying their TB cases in the national surveillance system.

Paper II: How do private practitioners in Pakistan manage children suspected having tuberculosis? A cross sectional study

Objectives: This study aimed to describe the investigation practices and management of child TB cases by the private health care providers in 12 selected districts in Pakistan.

Methods: This was a cross-sectional study based on retrospective review of database of child TB inventory study which was conducted in 12 selected districts of Pakistan from April–June, 2016. This study described the investigation and management practices of the private health care providers i.e., paediatricians, pulmonologists, chest specialists and general practitioners, who were mainly involved in the diagnosis and treatment of presumptive child TB cases under the age of 15 years.

Findings: A total of 5, 193 children suspected with TB were identified by the private health care providers in 12 selected districts during Apr-Jun, 2016. Majority of the presumptive child TB cases reported cough, fever, and retarded growth, and few had contacts with pulmonary TB patients. For the diagnosis, private providers mainly relied on chest X-ray in 46.1% cases, while tuberculin skin test and Gene- Xpert MTB/RIF testing was utilized in limited number of cases. 39.3% of children with presumptive TB were diagnosed and bacteriological confirmation was present in 7.6%. Private providers gave treatment to only 955 (14.6%) of these patients while the remaining patients were referred to others. Of whom 68.5% were referred to District TB Centre (NTP). There was a great variation between the districts in terms of referral rates (2.3–76.1%) and notifications (0–18.5%) of the child TB cases. This study showed that many private providers referred children suspected having TB to laboratories for further diagnosis, but the cases identified in these investigations were often not notified to the NTP. This problem could be resolved by strengthening the referral linkages between private health providers, NTP laboratories and treatment centres through capacity building and training of all private providers.

Paper III: Diagnosis of childhood tuberculosis in Pakistan: Are national guidelines used by private health care providers?

Objectives: This study aimed to assess the adherence of the NTP guidelines by private providers for diagnosis and management of child TB cases in Pakistan.

Methods: A cross-sectional study compared diagnosis of TB in children <15 years by non-NTP private providers with the NTP's paediatric scoring chart. A generalized linear model was used to determine the difference in adherence by non-NTP private providers to the NTP guidelines for childhood TB diagnosis by associated factors.

Findings: A total of 5193 (79.7%) of presumptive childhood TB cases identified in the selected districts during the study. The children were diagnosed with TB by Non-NTP private providers. Among them 34.3% of the children were diagnosed on chest x-rays and 17.3% of them on only clinical assessment. The Kappa score between non-NTP private providers and the NTP guidelines for diagnosis of TB was 0.152. The Kappa score showed weak agreement between the private providers' diagnosis and PPA chart diagnosis 0.152 (95% CI 0.140 - 0.165). Only 47.8% of the private providers followed the guidelines. The boys and the children < 5 years with a history of TB contact had a higher chance of being diagnosed according to the national guidelines. This study indicated a low adherence of NTP guidelines for diagnosing childhood TB by private providers in Pakistan. There is an urgent need to focus on advocacy at all levels and strengthen the public-private partnership. The NTP should regularly conduct training on the national guidelines and engage with the private sector to address specific gaps in diagnosis and treatment.

Paper IV: Geographic accessibility to childhood tuberculosis care in Pakistan

Objective: the study objective was to determine the geographical coverage and accessibility of child TB services in Pakistan.

Methodology: We used geospatial analysis to calculate the distance from the nearest public health facility to settlements, using qGIS, as well as the population living within the World Health Organization [WHO]'s recommended 5 km distance.

Findings: Out of all public health facilities, 1286 (20.5%) health facilities were engaged with NTP. Among the facilities the lowest engagement was found with basic health units (2.5%). 74% of the population had geographical access to general primary health care and live within 5km radius of these facilities. Geographical access to child TB sites was found limited. Moreover, only 33.5% of the population had geographical access to secondary- and tertiary-level health care within 5km radius. The average distance between a nearest TB facility for diagnosis of childhood TB and the settlement was equal to 26.3 km. The population of province Balochistan had to travel longer distances to access healthcare services. There was a high geographical accessibility to the general primary health services in Pakistan, compared to the specialised child TB. Consequently, catchment population have to cover longer distance to seek care in case of child TB cases. Geographic geographical accessibility can be improved by following the Integrated Management of Childhood Illnesses (IMCI) strategy by involving Lady Health Workers, and creating a closer link to higher level facilities to improve referral system particularly for distant communities.

5 Discussion

This section includes methodological issues, validity of the study, discussion of the major findings related to each paper, followed by some policy implication.

5.1 Methodological issues

5.1.1 Study Design

WHO suggests to evaluate the extent of under-reporting so that the strategies can be developed and implemented to improve national surveillance system, TB prevention, diagnosis and treatment services [51]. The inventory study has been used to measure underreporting in other resource-limited settings [51]. Compared to other population-based sampling techniques, the sampling method used in this study is less expensive.[66] In child TB inventory study (Paper I-III), the guidelines from WHO child inventory study were followed. This study also adheres to "STROBE" guidelines for observational studies [67,68].

A cross sectional study design was used in paper IV which defines the scope of a problem (descriptive), and captures its prevalence but can't identify the risk factors.

5.1.2 Validity of study

Any research's findings always depend upon the data quality, which might be impacted by study participants, the tools employed, and biological variance. Broadly, the term validity can be referred to the internal validity (study population) and external validity (general population). Bias, confounding and chance can affect the validity of study.

- **Internal validity**

The accuracy of measuring what a study is intended to measure is referred to as internal validity. This can be impacted by sample size, variability, attrition of the study sample, history, tools or instruments, and duration of the study [69]. The validity of a study can be influenced by the role of chance, selection or information bias, Hawthorne effect and confounding.

Chance can impact the accuracy. Statistically, it refers to the term random error (sampling variability). Confidence interval and tests for statistical significance are frequently used to assess the role of chance [70,71].

The WHO suggests that the geographical areas must be stratified according to a factor that is believed to be a good predictor of under-reporting.[51] Considering this guideline, the sample size was further stratified for provinces and regions to ensure national level representation which improved sampling efficiency. As appropriate sample size was required for validity, therefore a large sample size from all provinces and regions was used which would also reflect the diverse situation in Pakistan.

In paper IV (access to child TB care) it covers entire Pakistan, a huge sample size of health facilities (6,266) and settlements (261,217) were used to determine geographical access to health services.

Selection bias can happen if the study inadvertently includes or excludes groups of people in the target population. It should be avoided by adopting well-defined eligibility criteria in the design and execution of the study [69,71,72].
We used the electronic data collection technique and web interface for data collection, mapping and monitoring. All types of health care providers were included from the selected districts to ensure the completeness of data. However, there was no mechanism to include people who didn't have access to health care, those who were not under treatment and suffering at home for various reasons. Hence, Inventory study only included those persons seek health care from various providers during study duration. To include those who suffered at home and couldn't seek health care, there is need to conduct a household survey such as prevalence survey etc. [51].

Information bias is a distortion in the measure of association caused by inaccurate information or measurement, that can result from poor interviewing or measuring techniques, or differing level of recall by respondents [69,73]. To minimize information bias, the questionnaires were pre-tested and field officers were properly trained on study tools and use of mobile application. The validity of under-reporting estimates in

inventory study depends on underlying assumptions such as unique identifier, closed and homogeneous population and perfect record-linkage [74–81]. In our study, four names in Urdu were used as individual unique identifiers to assure perfect record linkage. The study period lasted for 3 months to minimize violation of closed population assumption by reducing population mobility. NTP registers were examined two quarters before and one quarter after study period to check and correct any misclassification of those patients not diagnosed during the study period or referred late for notification. Validity of the data was ensured in this study, through data quality audit by crosschecking every record with the hard copies to remove inconsistencies. Also using mobile phone for data collection, reduced data entry errors by eliminating one step for database creation. Mobile based data collection and web-interface for monitoring enhanced the validity of data.

Confounding can cause either an over or under estimation of outcomes when a variable associated to both exposure and outcome when distributed unevenly. However, it can be controlled during design phase with randomization, restriction; matching and during the analysis phase by stratification and multivariable modelling for adjustment. [71–73]

In these studies, randomization & stratification (Paper I-II) and generalized linear model (Paper III) was used to control the confounders. Randomization eliminates selection bias and control both known and unknown confounders. To further account for confounders in the analysis, the data was stratified by district, sex, and age. However, controlling for confounding factors was challenging in Paper IV due to the use of aggregate data.

Hawthorne effect refers to change in behaviour as a response to observation and assessment [82].
In Paper I (Child TB underreporting) close monitoring by the supervisor and DTC might affect reporting of child TB to NTP which was not routinely done hence reporting was improved.

In paper II: The study was done by the NTP and NTP data collectors visited the health facilities on weekly basis. There may have been an increase in referrals to NTP centres due to the Hawthorne effect that could affect referral practices of private providers.

In Paper III close monitoring by supervisors and DTCs could also affect the practices of private providers and adherence to the NTP guidelines for diagnosis of child TB cases. Probably, this would result in orientation of doctors on the guidelines and hence improved their adherence of the guidelines during the study period.

- **External Validity**

Generalizability of findings is referred to as external validity of the study [69,83]. In child TB inventory study (Paper I-III), clusters of 12 districts were randomly chosen from all the provinces and regions which were reasonably representative and reflect the diverse situation in this country. We think that this contributed to make the findings valid for the remaining districts and useful for Pakistan.

The study described in Paper IV covers almost all of Pakistan.

5.2 Discussion of main findings

5.2.1 Child TB underreporting in Pakistan

The paper I (child TB inventory study in Pakistan) revealed that a large proportion of children diagnosed with TB were detected by the private health care providers. After record linkage, it was found that there were a small number of child TB cases that were reported to NTP which yielded to a significant underreporting of 78%. A mathematical modelling study [84] conducted in 22 TB high-burden countries reported that the actual global TB burden is 25% more than the estimation for these high burden countries. Similar trends of TB underreporting were found in other similar studies [85–87]. Likewise, two studies listed various factors linked to under detection and underreporting including inadequate ability of medical professionals to identify paediatric TB and ineffective contact tracing [88,89].

A number of factors, including low socioeconomic status, accessibility to health care services, cultural beliefs and perspectives, a lack of knowledge, and lack of education, were also highlighted as the main causes of low utilization of public health services in paper I. There are many factors associated with low child TB case detection including poor record-keeping, no access to records on child TB cases and inability to produce sputum for many children. Various studies have shown that only 30% of child TB cases can be identified through smear microscopy [90–92]. To strengthen the basis for diagnosis in child TB patients, it is important to introduce some initiatives to increase the use of Gene Xpert MTB/RIF such as provision of transportation and establishment of a robust referral mechanism across Pakistan, especially in remote locations.

Although reporting TB cases is in principle mandatory but availability of anti- TB drugs over the counter in the private pharmacies [93] and presence of many large private teaching hospitals that are managing both infectious and non-infectious diseases, could be the causes for underreporting of child TB cases. A study in Viet Nam in 2020 showed that private sector is an initial health seeking point for 50-70%

of people with TB. [94] In Pakistan, the private providers manage child TB cases using private laboratories and private pharmacies hence, notification to NTP remains a missing piece. Since private providers are catering the health care need of a huge segment of population, it can be connected to NTP to improve the TB case detection perhaps by reminding them that NTP will cover the cost of TB diagnosis and medicines.

In 2006–07, National child TB guidelines was developed in collaboration with Pakistan Paediatric Association (PPA) [30]. The child TB inventory study showed an underutilization of these guidelines in diagnosis of child TB cases. Of total, majority 4,695 (89%) child TB cases were diagnosed clinically on the basis of clinical symptoms and chest X-rays. It is evident that a symptom-based approach is more feasible and cost effective for detection of child TB [94–96]. This may partially reflect on the limited availability of a better diagnostic choice for investigations like Gene Xpert, Tuberculin skin test (TST) and Gastric Lavage even IGRA in remote areas. In several TB high burden countries, the same challenges in diagnosis of child TB cases have been noted [97,98].

Few suggested actions might be helpful to improve the child TB reporting and diagnostic practices of private health providers such as widespread distribution of Pakistan Paediatric Association scoring guidelines; skills enhancement for Chest-X-ray reading with precision; frequent follow ups and linkage with further training opportunities for child TB case detection. These actions would support in strengthening the PPM approach in the country.

The suboptimal contact tracing and limited availability of appropriate diagnostic tools are among the biggest challenges in the diagnosis of childhood TB in Pakistan. This recommends for a better and sustainable public-private partnerships and a robust electronic surveillance system to record and notify all child TB cases using current District Health Management system. The contact tracing around bacteriological TB cases will be another potential strategy that could be adopted to find out more child TB cases and treat patients with latent TB infection.

At present, the child TB care diagnostic services are limited to secondary and tertiary care level in Pakistan. There is need to scale up the child TB services to primary care level and private sector to strengthen the diagnosis, treatment and reporting system within accessible distances, through skilled workforce. The Gastric lavage is mostly not available in many remote health care facilities; therefore, sputum induction; its transportation system for Gene Xpert, or smear microscopy and a proper referral linkage with peripheral centres should be ensured to bring improvements in the diagnosis of child TB cases. More studies on child TB care are needed in order to understand different aspects of child TB underreporting such as investigation practices, contact tracing and referral practices, level of engagement of tertiary care hospitals and role of informal providers. The findings of this study recommend, a proper training program for the private health providers for the diagnosis and referral of child TB cases to the National program for notifications. These steps would be helpful in reducing the observed underreporting of child TB cases.

5.2.2 Private practitioners' investigations of child patients with presumptive TB

The findings from this study indicated that the private providers mainly diagnose childhood TB on the basis of clinical symptoms, chest X-rays, smear microscopy, or rarely on TST, histopathology and Gene- Xpert MTB/RIF. Many other studies also proved that diagnosis of TB in children is often based on a combination of clinical symptoms and chest X-ray.[99–102] The availability of TB diagnostic tools varies across Pakistan. Chest X-ray and smear microscopy are the almost universally available and used tools for TB diagnosis at peripheral levels. Histopathology, tuberculin skin test, sputum culture and Gene-Xpert MTB/RIF are only available in the laboratories of public level tertiary care hospitals. Gene-Xpert MTB/RIF testing on stools is a good addition in TB diagnostic and a successful method for diagnosing TB cases.[103] However, availability of the advance diagnostic tools and tests is a big challenge in rural area in Pakistan. Therefore, some concrete actions would be required to improve the utilization of Gene Xpert MTB/RIF with provision of transport for the referred

presumptive TB cases especially from the remote areas to tertiary care level across Pakistan.

Important evidence from this study indicates that many non-NTP providers refer patients for diagnosis to NTP laboratories. One apparent reason could be the availability of free TB diagnostic services at NTP laboratories. On the other hand, the NTP registration process for diagnosed TB cases begins when treatment is started, not from the laboratory register. After the confirmtion of TB diagnosis from NTP laboratory, ideally these diagnosed patients should be directly registered to NTP register. There are numerous factors that may contribute to the significant gap in reporting of TB cases such as ineffective communication between the NTP laboratory and treatment facilities, insufficient counselling of TB patients by laboratory staff, and weak referral mechanism. [104–107] This emphasises the necessity of regular weekly visits by the district TB coordinator to the NTP laboratories in order to maintain efficient communication between NTP laboratories and treatment facilities. Also, it is important to contact referring private health providers to further guide them about NTP guidelines for TB case management and availability of free of cost TB diagnostic and treatment services at public health facilities. Across Pakistan, treatment services are also available in the public facilities with diagnostic arrangements. It has been noticed that there may be a lack of trust on quality of care in public sector, thus a large number of TB patients pursued their treatment and care in the private sector.[38] Additionally, it is possible that some referred TB patients might not actually go to NTP, rather preferred to seek care from the private sector. A study from Indonesia found similar type of results which indicate that only 2% of diagnosed child TB cases from different hospitals were reported to the NTP. [86] Child TB is managed by various health care providers at various levels of the private health care sector in Pakistan. It is important to improve linkages with private health providers by engaging the private sector with NTP. This can be done by building their capacity on NTP guidelines for management of child TB cases [108]. For instance, mHealth may be useful to engage and train non-NTP private providers. [109,110]

A larger percentage of adolescents experienced some respiratory problems, according to this study's findings. They underwent sputum testing, and had bacteriological confirmation. The infected adolescents can contribute to substantial transmission of TB in overcrowded settings such as schools, or other public places hence they could be an important segment of the target population for TB control program. The WHO recommends development of integrated family and community centred strategies for provision of comprehensive and effective services at the community level to bring improvements in child and adolescent notification [111]. Another possible explanation for the increased percentage of adolescent with TB is that adolescent can easily produce sputum than younger children. This study showed that failure to thrive and loss of body weight were more commonly reported symptoms in adolescent girls. This can be partly due to biological differences, effects of culture and under nutrition.[112] According to a study conducted in India, boys consume much more energy, iron, calcium, and protein than girls. [113] Moreover. the slightly higher absence of BCG scar in girls could be explained by less care for girls in Pakistan, where a boy is usually more valued.[114]

5.2.3 Adherence of national guidelines by private providers to diagnose childhood

This study also documents the practices of private health care providers in childhood TB diagnosis that highlights a low adherence to the NTP guidelines. Only 47.8% of the private health care providers, diagnosed child TB cases in accordance with national guideline PPA scoring chart. From other studies, it is evident that a feasible and cost effective method for screening of child TB cases is a symptom-based approach.[94–96] In Pakistan the national guideline PPA scoring chart are implemented in government sector, but the challenge is that almost 90% of patient's initiate care through the private sector and < 5% of private sector providers are effectively engaged with NTP.[38] Lack of awareness about the available services and guidelines, weak partnership and collaboration between private sector and NTP could be the reasons for not following the national guidelines properly. The findings highlight for an urgent need to improve linkages between NTP and private health sector through

engaging, providing them trainings and refreshers on NTP guidelines to improve the TB diagnosis and care in Pakistan.

According to the current study, adherence to NTP guidelines in diagnosis of child TB cases is diverse. In general, lower adherence of NTP guidelines could be due to a lack of knowledge. A systematic review on TB management practices of health care providers in Pakistan [115] also raises concerns about low standards of care and knowledge of health providers. Another explanation for variation in adherence to the NTP guidelines across the different districts might be due to no or limited availability of diagnostic services especially in the rural areas. Though tertiary care facilities have availability of diagnostic services but sometimes these are limited or not properly functional. Moreover, the referral mechanism for patient to the facility offering DOTS services has inherent flaws. There are gaps in capacities of many of the private and public health care providers. They are poorly trained in the diagnosis and treatment of TB. Along with trainings they require the communication and counselling skills to motivate the patient for better compliance.[116] The health system flaws indicated in this study are applicable to the entire country that can be addressed by the capacity building programs both for public and private health care providers through proper trainings on NTP guidelines, improved accessibility of recommended diagnostic tools, mandatory use of PPA scoring charts at all levels, and increased collaboration between public and private sectors.

5.2.4 Access to Child TB Care in Pakistan

According to this study, 74% of the population had geographic access to the main primary health care facilities, but secondary and tertiary care were less accessible. As per NTP guidelines [108], children with TB symptoms or severe unclear symptoms from primary health care level should be referred to higher level for further diagnosis and management. In Pakistan, child TB diagnostic tools and tests are often limited to secondary and tertiary care level. Majority of physicians at public health facilities are not properly trained in identification of TB cases, follow up, management, and NTP guidelines.[25] A study carried out in Ghana also reported findings of limited access to secondary [61.4%] and tertiary care level [14.3%].[117] Dedicated efforts would be

required to reach all levels of health care for better identification of child TB cases. The NTP must include a comprehensive training on childhood TB within its ongoing training program. The other step towards improvement of geographical access could be strengthening the referral mechanism between primary to secondary and tertiary care level. [25]

Generally, people have to travel up to 26 km on average to get child TB services in rural areas of Pakistan. The people living in Balochistan, AJK & GB are more likely to cover longer distances to access child TB services, which could lead to a significant burden in terms of time and money. The child TB inventory study in Pakistan revealed significant underreporting of 78% child TB cases from non-NTP private health care providers, which is obvious, keeping in view the long distances people have to travel to access a public child TB care facility. The childhood TB under-reporting was also highest in those provinces where people have to travel longer distances to seek TB care.[17] To remotely connect Primary Health Care facilities to child TB sites for prompt diagnosis and treatment of severe child TB cases, telemedicine may be an option. This could perhaps help with some of the difficulties caused by a the lack of physical healthcare infrastructure within accessible limits. [118,119]

In general, Basic Health Units (BHUs) in Pakistan are not engaged with NTP, representing a lost opportunity to bring TB services closer to the community and people affected with TB.[25] Many children in Pakistan still receive health care at home either from the traditional healers or informal sector. Studies consistently confirm that many sick children do not reach the health facilities, while children from poorer families are less likely to obtain care.[120] A community based approach to TB prevention, case detection, and supportive care platform labelled as "Integrated Management of Childhood Illnesses (IMCI) strategy" is recommended by the WHO for primary health care.[121] This strategy aims to ensure that all infants and children with TB receive high quality of care in order to eventually eliminate TB related mortality among children. In IMCI, the role of LHWs is evident for referral of presumptive TB cases from community to the designated TB care facility. [122,123] The

LHWs, are mainly connected with primary health care facilities located in their vicinity. In Public health care system of Pakistan, they are a crucial link for referral between the community and primary health care. LHWs can also assist in management of DOTS, report adverse reactions and household contact tracing in the community. Case studies from Malawi and Uganda also illustrated the successful experiences of increased case finding of child TB cases, improved treatment outcomes, successful implementation of contact screening and management by strengthening the child TB services at peripheral health facilities. [124,125] In order to improve geographic accessibility, focus on two areas is recommended. First, to improve identification and closer examination of children who may have approached PHC level for TB symptoms, secondly, improve referral pathways for children with TB from communities.

5.3 Public health use of the findings

This child TB inventory study is the first of its kind globally. This study estimated the extent of underreporting of child TB cases in Pakistan. The study was designed and conducted to address the need to determine child TB underreporting and investigate the challenges of undiagnosed child TB cases. The research was conducted within NTP setup using established NTP system with the advantage to influence policy and practice in a fast manner. In recent past, TB disease control was linked with various research initiatives in the country considering it a way out for good policy change and bringing improvements in practices [20]. NTP Pakistan has encouraged for the work done through this research project by considering the results and recommendations from all these studies for future policy planning. Results of paper I, II were already incorporated in National Strategic Plan vision 2021-2023 [20] and development of concept note for Global Fund Grant 2021-2023 which has been recently approved.

Recommendation for involvement of all health care providers, can significantly increase child TB case notifications. The finding of paper I (child TB Inventory study) was taken into account while planning a scale up of PPM approach in the country from 2018 onwards. Likewise, the evidence from paper II (private investigation practices) is of great value for the program in terms of devising

strategies to register those cases, referred to NTP for diagnosis that are not registered. To enhance the coverage of private providers for reporting child TB cases to NTP for diagnosis, by bringing improvements in referral from peripheral to tertiary care level and suggestions for involving LHWs at community level as highlighted in paper IV (access to child TB care). The timely evidence generated from Paper III (adherence of national guidelines to diagnose) will be helpful in upcoming Review of the Program in September 2022, to evaluate current training capacity and devise the training strategies to involve and train different health care providers during next grant period.

Furthermore, the results from these studies will contribute to various assessments such as the evaluation of the End TB Strategy targets [126] and the Sustainable Development Goals (SDGs) 2015-2030.[127] The SGDs aim to ensure healthy lives and well-being for all at all ages, achieving universal health coverage (UHC) and "ending epidemics," as well as action and collaboration across sectors. The studies are fully aligned with the goals and approach of the Global Strategy for Women's, Children's and Adolescents' Health (2016–2030). The strategy promotes optimal child and adolescent TB prevention and treatment services reaching the most vulnerable and neglected in any setting or society, where they can live without stigma and discrimination, and without experiencing financial hardships. [128]

5.4 Limitations & Strengths of study

This thesis and the studies embedded in it has several strengths. The child inventory study (Paper I-III) is as far as we are aware it is the first of its kind nationwide child inventory study to estimate under-reporting by all healthcare professionals as part of their routine practices without using any intervention. In this study, adequate analytical strategies were used to account for potential sampling and selection bias. There was a fairly representative coverage of the entire country, strong internal and external monitoring of field activities, no significant deviations from the survey protocol and SOPs, and an adequate participation rate.

The large total sample with participants from all provinces is one of its key strengths; we think that it may reflect the diverse situation of TB epidemic in Pakistan. The study was of great benefit for NTP as its findings provide evidence that will be used to plan scale up of PPM initiative on priority basis. The health care providers involved in the study are given an opportunity to develop linkages between the program and non-NTP private providers who would not have otherwise done so.

A strength of Paper IV is that it covers almost entire Pakistan, to estimate geographical access of catchment population to the health services in a way that was not done before in Pakistan. This can be helpful in identifying access related gaps in the health care services.

The study also has several limitations. Major difficulties in the study included a lengthy data collection tool that remained a challenge for many busy GPs who were unable to complete. Therefore, data collection was done by the data collectors or clinic staff using the mobile based questionnaires. Additionally, we were unable to determine the magnitude of a possible Hawthorne effect during the study, in which facilities included in the study were more likely to report cases than those not part of the study. Moreover, those who had no symptoms or no access to health care providers were not included in the study and they may have contributed to heterogeneity. Other assumptions include that record linkage was perfect, and the population was closed, i.e., impact of migration and deaths should be minimal. The risk of misclassification from delayed referrals or notifications was decreased by examining at NTP registries two quarters before and one quarter after the study period. Also, we did not conduct field evaluations or actual observations for our study. Therefore, the accuracy and completeness of the data could not be completely ensured. The study was closely related to NTP hence the data collectors from NTP visited the study sites on a weekly basis, this may have contributed to the high referral to NTP centres for diagnosis. This could have a Hawthorne effect on reporting. The proportion of people diagnosed with TB (79.7%) in this study was high compared to other settings ranged from 2.1% to 19%. [129–132] Due to workload constraints, private providers may have missed an unknown number of presumptive

TB cases from recording and may have recorded only the diagnosed child TB cases on the provided registers.

For Paper IV we lacked information about health care providers in the private sector, which is very huge in Pakistan. Only < 5% of private providers were engaged with NTP, even though many of these practitioners treat their patients without following the NTP guidelines. [20] Also, we did not have settlement data for the population of regions i.e., GB [0.5%] and AJK [2%]. The Humanitarian Data Exchange website provided information on settlements and healthcare facilities for this study, with figures based on 2018 records. Since then, it's possible that some adjustments have taken place. In an ecological study, we could analyse by groups even though we lacked the individual data for geographical access factors, such as distance and characteristics of population living within 5 km of healthcare services. The validity of the data cannot be assured because this study is a secondary analysis of several available data sources.

6 Conclusion

The aim of this research was to estimate child TB underreporting and its management by private health providers in Pakistan. The research has also evaluated the adherence of private providers to national guidelines for diagnosis of child TB cases. Furthermore, this research also determined the geographical accessibility of child TB services in Pakistan. Based on the findings the following conclusions are drawn, and recommendations are suggested.

1. The proportion of diagnosed child TB cases that have been reported to NTP is quite low. There is a massive under-reporting of child TB cases from private health care providers in Pakistan. A weak surveillance system could be a reason for this huge under-reporting.
2. The bacteriological confirmation was rarely done by the private health providers, mostly practitioners were mainly relying on clinical features, radiography and microscopy.
3. Despite relying on NTP laboratories for diagnosis, many private providers are treating child TB cases without notifying them in NTP.
4. There is low utilization of the national guidelines for childhood TB diagnosis by the private health providers as less than 50% of private healthcare providers followed the NTP guidelines.
5. The geographical access to specialised child TB sites is limited due to longer distance especially in remote areas of Pakistan.

7 Recommendations

Based on our findings, we suggest the following recommendations

1. The evidence generated from child TB Inventory study, clearly provides a roadmap for NTP Pakistan to scale up private-public-mix approach on priority basis to enhance child TB case detection to minimize under-reporting.
2. Mandatory notification should be implemented to register all diagnosed TB cases from private sectors across Pakistan. Over the counter sale of TB drugs should be discouraged and consider banning TB drug outside the NTP.
3. Regular weekly visits by district health coordinator to NTP laboratories, are highly recommended to bring improvements in communication between NTP laboratories & treatment centres.
4. Private providers should be engaged and linked with the NTP for proper training in order to improve utilization of national guidelines for management of child TB that will help to minimize TB case under-reporting as well control drug resistance in the community.
5. The staff working in the dispensaries and BHUs should be properly trained in the identification of child TB cases.
6. To improve geographical access for child TB services, referral networks between primary level facilities and those with diagnostic capacity at secondary and tertiary care levels need to be linked and strengthened.
7. The LHWs can play an important role by enhancing community referral of child presumptive cases to specialised child TB sites.

Source of data

1. Rieder HL. Epidemiologic Basis of Tuberculosis Control. 1st ed. Paris, France: International Union Against Tuberculosis and Lung Disease; 1999.

2. Kim JH, Langston AA, Gallis HA. Miliary Tuberculosis: Epidemiology, Clinical Manifestations, Diagnosis, and Outcome. Rev Infect Dis . 1990 Jul 1;12(4):583–90.

3. World Health Organization. Global Tuberculosis Report 2021. Geneva, Switzerland:WHO; 2021.

4. Chakaya J, Khan M, Ntoumi F, Aklillu E, Fatima R, Mwaba P, et al. Global Tuberculosis Report 2020 – Reflections on the Global TB burden, treatment and prevention efforts. Int J Infect Dis. 2021;113:S7–12.

5. Carwile ME, Hochberg NS, Sinha P. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases Undernutrition is feeding the tuberculosis pandemic : A perspective. J Clin Tuberc Other Mycobact Dis . 2022;27(March):100311.

6. Laghari M, Azhar S, Sulaiman S, Khan AH, Talpur BA, Bhatti Z. Contact screening and risk factors for TB among the household contact of children with active TB : a way to find source case and new TB cases. BMC Public Health. 2019;19:1–10.

7. Fatima R, Qadeer E, Yaqoob A, Haq M ul, 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? Chaturvedi V, editor. PLoS One . 2016 Nov 29 ;11(11):e0165813.

8. Saunders MJ, Wingfield T, Datta S, Montoya R, Ramos E, Baldwin MR, et al. A household-level score to predict the risk of tuberculosis among contacts of patients with tuberculosis : a derivation and external validation prospective cohort study. Lancet Infect Dis . 2020;20(1):110–22.

9. Caminero JA. Multidrug-resistant tuberculosis: Epidemiology, risk factors and case finding. Int J Tuberc Lung Dis. 2010;14(4):382–90.

10. Fradianto I, Nursasi AY. The group process in school-age children for tuberculosis prevention behaviour The group process in school-age children for tuberculosis prevention behaviour. Sri Lanka J Child Heal. 2020;49(3).

11. Pelissari DM, Diaz-quijano FA. Household crowding as a potential mediator of socioeconomic determinants of tuberculosis incidence in Brazil. PLoS One. 2017;12(4):1–13.

12. Marais BJ, Schaaf HS. Tuberculosis in children. Cold Spring Harb Perspect Med . 2014;4(9). Available from: /pmc/articles/PMC4143109/

13. Seddon JA, Johnson S, Palmer M, van der Zalm MM, Lopez-Varela E, Hughes J, et al. Multidrug-resistant tuberculosis in children and adolescents: current strategies for prevention and treatment. Expert Rev Respir Med . 2020;15(2):221–37.

14. Government of Pakistan. Twelfth SAARC Summit Islamabad 4-6 January 2004 Islamabad Declaration. Islamabad, Pakistan: Ministry of Health; 2004.

15. World Health Organization. Implementing the WHO Stop TB Strategy . Implementing the WHO Stop TB Strategy: A Handbook for National Tuberculosis Control Programmes. Geneva, Switzerland:WHO: World Health Organization; 2008.

16. National Tuberculosis Programme. Annual TB Report 2019. Islamabad, Pakistan. Goverment of Pakistan; 2019.

17. Fatima R, Yaqoob A, Qadeer E, Hinderaker SG, Ikram A, Sismanidis C. Measuring and addressing the childhood tuberculosis reporting gaps in Pakistan: The first ever national inventory study among children. PLoS One. 2019;14(12):e0227186.

18. World Health Organization. Recommendations for Investigating Contacts of Persons with Infectious Tuberculosis in Low- and Middle-Income Countries. World Heal Organ . 2012;28–41.

19. Ross JM, Xie Y, Wang Y, Collins JK, Horst C, Doody JB, et al. Estimating the population at high risk for tuberculosis through household exposure in high-incidence countries: a model-based analysis. EClinicalMedicine . 2021 Dec 1;42:101206.

20. National TB Control Program. National Strategic Plan 2020-2023. Government of Pakistan. Islamabad, Pakistan; 2020.

21. 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(11):e0165813.

22. Qadeer E, Fatima R, Haq MU, Yaqoob A, Thu N, Kyaw T, et al. Yield of facility-based verbal screening amongst household contacts of patients with multi-drug resistant tuberculosis in Pakistan. J Clin Tuberc Other Mycobact Dis . 2017;7:22–7.

23. National Strategic Plan “Vision 2020”. National TB Control Program, Government of Pakistan. Islamabad, Pakistan; 2014.

24. Marais BJ, Bernays S, Schaaf HS, Fox GJ. Increasing TB preventive treatment in children. Int J Tuberc Lung Dis . 2022 Oct 1;26(10):903–5.

25. National TB Control Program. The Pakistan TB Joint Program Review Mission, 2019. Islamabad, Pakistan: Ministry of Health; 2019.

26. Pakistan: WHO and UNICEF estimates of immunization coverage: 2020 revision. 2021.

27. Dogar O, Keding A, Gabe R, Marshall AM, Huque R, Barua D, et al. Cytisine for smoking cessation in patients with tuberculosis: a multicentre, randomised, double-blind, placebo-controlled phase 3 trial. Lancet Glob Heal. 2020 Nov 1;8(11):e1408–17.

28. World Health Organization. Consolidated Guidelines on Tuberculosis. Module 3 : Diagnosis -Rapid diagnostics for tuberculosis detection. Geneva, Switzerland:WHO; 2021.

29. World Health Organization. WHO consolidated guidelines on tuberculosis Module 5: Management of tuberculosis in children and adolescents. Geneva, Switzerland:WHO; 2022.

30. National TB Control Program. National guidelines for diagnosis and management of tuberculosis in children 2006-07. Islamabad, Pakistan; 2007.

31. National TB Control Program. Childhood TB Training Desk Guide. Islamabad, Pakistan: Ministry of Health; 2019.

32. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Geneva, Switzerland:WHO; 2020.

33. World Health Organization. WHO revised definitions and reporting framework for tuberculosis. Vol. 18. Geneva, Switzerland:WHO; 2013.

34. National Institute of Population Studies. Pakistan: Demographic and Health Survey 2017-18.Government of Pakistan. Islamabad, Pakistan: Ministry of Health; 2019.

35. Abro Z, AA J. Health care facilities and patients satisfaction: A case study of civil hospital Karachi. iijcrb . 2012;4(1).

36. Pakistan bureau of statistics. National Health Accounts Pakistan 2013-14 . Islamabad, Pakistan. Goverment of Pakistan; 2015.

37. Fatima R, Harris RJ, Enarson DA, Hinderaker SG, Qadeer E, Ali K, et al. Estimating tuberculosis burden and case detection in Pakistan. Int J Tuberc Lung Dis. 2014;18(March 2013):55–60.

38. Fatima R, Haq MU, Yaqoob A, Mahmood N, Ahmad KL, Osberg M, et al. Delivering Patient-Centered Care in a Fragile State: Using Patient-Pathway Analysis to Understand Tuberculosis-Related Care Seeking in Pakistan. J Infect Dis. 2017;216:S733–9.

39. Khan AJ, Khowaja S, Khan FS, Qazi F, Lotia I, Habib A, et al. Engaging the private sector to increase tuberculosis case detection: an impact evaluation study. Lancet Infect Dis . 2012 Aug;12(8):608–16.

40. Schwalbe NR, Wells WA, Geaneotes AP, Forcellina A, Lee MG, DiCola L, et al. Estimating the market for tuberculosis drugs in industrialized and developing nations. Int J Tuberc Lung Dis. 2008;12(10):1173–81.

41. Mehnaz A, Arif F. Applicability of scoring chart in the early detection of tuberculosis in children. J Coll Physicians Surg Pakistan. 2005;15(9):543–6.

42. Safdar N, Hinderaker SG, Baloch NA, Enarson DA, Khan MA, Morkve O. Are children with tuberculosis in Pakistan managed according to National programme policy guidelines? A study from 3 districts in Punjab. BMC Res Notes . 2010 Nov 30;3(1):1–7.

43. Ayesha Mehnaz. Tuberculosis in Children. JPMA . 2006;56(9):390–1.

44. Kurji Z, Premani ZS MY. View of analysis of the health care system of Pakisatn: Lessons learnt and way forward. J Ayub Med Coll Abbottabad . 2016;28(3):601.

45. Hassan B, Ahmed R, Li B, Noor A, ul Hassan Z. A comprehensive study capturing vision loss burden in Pakistan (1990-2025): Findings from the Global Burden of Disease (GBD) 2017 study. PLoS One . 2019 May 7;14(5):e0216492.

46. Fullman N, Yearwood J, Abay SM, Abbafati C, Abd-Allah F, Abdela J, et al. Measuring performance on the Healthcare Access and Quality Index for 195 countries and territories and selected subnational locations: A systematic analysis from the Global Burden of Disease Study 2016. Lancet. 2018 Jun 2;391(10136):2236–71.

47. Ghaffar A, Kazi BM, Salman M. Health care systems in transition III. Pakistan, Part I. An overview of the health care system in Pakistan. J Public Health Med . 2000 Mar;22(1):38–42.

48. Kumar S, Bano S, Khan A. Comparison and Analysis of Health Care Delivery Systems: Pakistan versus Bangladesh. J Hosp Med Manag . 2017 Jan 14;3(1):21–2.

49. Hussain A, Mirza Z, Qureshi F a., Hafeez A. Adherence of private practitioners with the national tuberculosis treatment guidelines in Pakistan: A survey report.

J Pak Med Assoc. 2005;55(1):17–9.

50. Qureshi H, Arif A, Alam E, Qadir N. Integration of informal medical practitioners in DOTS implementation to improve case detection rate. J Pak Med Assoc. 2010;60(1):33–7.

51. World Health Organization. Assessing tuberculosis Under-Reporting Through Inventory Studies. Geneva, Switzerland:WHO; 2012.

52. World Health Organization. Global Reference List of 100 Core Health Indicators (plus health-related SDGs). Geneva, Switzerland:WHO; 2018.

53. Tremblay JC, Ainslie PN. Global and country-level estimates of human population at high altitude. Proc Natl Acad Sci U S A. 2021 May 4;118(18):2102463118.

54. Home | LandScan™ . [cited 2021 Dec 11]. Available from: https://landscan.ornl.gov/

55. Mukerjee AK. Ascertainment of non-respiratory tuberculosis in five boroughs by comparison of multiple data sources. Commun Dis Public Health . 1999 Jun;2(2):143–4.

56. van Hest NAH, Smit F, Baars HWM, De Vries G, De Haas PEW, Westenend PJ, et al. Completeness of notification of tuberculosis in The Netherlands: how reliable is record-linkage and capture-recapture analysis? Epidemiol Infect . 2007 Aug;135(6):1021–9.

57. VAN Hest NAH, Story A, Grant AD, Antoine D, Crofts JP, Watson JM. Record-linkage and capture-recapture analysis to estimate the incidence and completeness of reporting of tuberculosis in England 1999-2002. Epidemiol Infect . 2008 Dec;136(12):1606–16.

58. Guernier V, Guégan JF, Deparis X. An evaluation of the actual incidence of tuberculosis in French Guiana using a capture-recapture model. Microbes Infect . 2006 Mar;8(3):721–7.

59. Bassili A, Grant AD, El-Mohgazy E, Galal A, Glaziou P, Seita A, et al. Estimating tuberculosis case detection rate in resource-limited countries: a capture-recapture study in Egypt. Int J Tuberc Lung Dis . 2010 Jun;14(6):727–32.

60. Huseynova S, Hashim DS, Tbena MR, Harris R, Bassili A, Abubakar I, et al. Estimating tuberculosis burden and reporting in resource-limited countries: a capture-recapture study in Iraq. Int J Tuberc Lung Dis . 2013 Apr;17(4):462–7.

61. Dunbar R, Lawrence K, Verver S, Enarson DA, Lombard C, Hargrove J, et al. Accuracy and completeness of recording of confirmed tuberculosis in two South African communities. Int J Tuberc Lung Dis . 2011 Mar;15(3):337–43.

62. Dunbar R, van Hest R, Lawrence K, Verver S, Enarson DA, Lombard C, et al. Capture-recapture to estimate completeness of tuberculosis surveillance in two communities in South Africa. Int J Tuberc Lung Dis . 2011 Aug;15(8):1038–43.

63. Bassili A, Al-Hammadi A, Al-Absi A, Glaziou P, Seita A, Abubakar I, et al. Estimating the tuberculosis burden in resource-limited countries: a capture-recapture study in Yemen. Int J Tuberc Lung Dis . 2013 Apr;17(4):456–61.

64. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. Biometrics. 1977;33(1):159–74.

65. Fonseca Martinez BA, Leotti VB, Silva G de S e., Nunes LN, Machado G, Corbellini LG. Odds ratio or prevalence ratio? An overview of reported statistical methods and appropriateness of interpretations in cross-sectional studies with dichotomous outcomes in veterinary medicine. Front Vet Sci. 2017;4(193).

66. Tejero Encinas S, Asensio Villahoz P, Vaquero Puerta JL. [Epidemiological surveillance of pulmonary tuberculosis treated at the specialized care level based on 2 data sources, Valladolid; Spain]. Rev Esp Salud Publica . Jan [cited 2015 Jan 7];77(2):211–20.

67. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and elaboration. PLoS Med. 2007;4(10):1628–54.

68. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495–9.

69. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology, 3rd Edition. 2008 Jan 1.

70. Boccia S, La Torre G, Persiani R, D'Ugo D, van Duijn CM, Ricciardi G. A critical appraisal of epidemiological studies comes from basic knowledge: a reader's guide to assess potential for biases. World J Emerg Surg . 2007 Jan;2(1):1–8.

71. Webb P, Bain C. Essential Epidemiology . New York: Cambridge University Press; 2010.

72. Charles H, Julie E. Epidemiology in Medicine . 1st ed. USA: Lippincott Williams and Wilkins; 1987.

73. Grimes DA, Schulz KF. Bias and causal associations in observational research.

Lancet. 2002;359:248–52.

74. van Hest NAH, Grant AD, Smit F, Story A, Richardus JH. Estimating infectious diseases incidence: validity of capture-recapture analysis and truncated models for incomplete count data. Epidemiol Infect . 2008 Jan ;136(1):14–22.

75. Hook EB, Regal RR. Capture-recapture methods in epidemiology: methods and limitations. Epidemiol Rev . 1995 Jan;17(2):243–64.

76. Zelterman D. Robust estimation in truncated discrete distributions with application to capture-recapture experiments. J Stat Plan Inference . 1988 Feb ;18(2):225–37.

77. Desenclos JC, Hubert B. Limitations to the universal use of capture-recapture methods. Int J Epidemiol . 1994 Dec;23(6):1322–3.

78. Cormack RM. Problems with using capture-recapture in epidemiology: an example of a measles epidemic. J Clin Epidemiol . 1999 Oct;52(10):909–14.

79. Papoz L, Balkau B, Lellouch J. Case counting in epidemiology: Limitations of methods based on multiple data sources. Int J Epidemiol. 1996;25:474–8.

80. Jarvis SN, Lowe PJ, Avery A, Levene S, Cormack RM. Children are not goldfish--mark/recapture techniques and their application to injury data. Inj Prev. 2000;6:46–50.

81. Tilling K. Capture-recapture methods--useful or misleading? Vol. 30, International journal of epidemiology. 2001. p. 12–4.

82. Sedgwick P, Greenwood N. Understanding the hawthorne effect. BMJ. 2015;351.

83. Eldridge S, Ashby D, Bennett C, Wakelin M, Feder G. Internal and external validity of cluster randomised trials: systematic review of recent trials. BMJ . 2008 Apr 19;336(7649):876–80.

84. Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: A mathematical modelling study. Lancet Glob Heal. 2014;2(8).

85. Hong SJ, Park YS, An H, Kang SM, Cho EH, Shin SS. Factors leading to under-reporting of tuberculosis in the private sector in Korea. Int J Tuberc Lung Dis. 2012;16(9):1221–7.

86. Lestari T, Probandari A, Hurtig AK, Utarini A. High caseload of childhood tuberculosis in hospitals on Java Island, Indonesia: A cross sectional study. BMC Public Health. 2011;11(1):1–7.

87. Coghlan R, Gardiner E, Amanullah F, Ihekweazu C. Understanding Market Size and Reporting Gaps for Paediatric TB in Indonesia , Nigeria and Pakistan : Supporting Improved Treatment of Childhood TB in the Advent of New Medicines. PLoS One. 2015;10(10):1–12.

88. Islam Z, Sanin KI, Ahmed T. Improving case detection of tuberculosis among children in Bangladesh: lessons learned through an implementation research. BMC Public Health. 2017;17(1):1–9.

89. Talukder K, Salim MAH, Jerin I, Sharmin F, Talukder MQK, Marais BJ, et al. Intervention to increase detection of childhood tuberculosis in Bangladesh. Int J Tuberc Lung Dis. 2012;16(1):70–5.

90. Linda M. Parsons, Akos Somoskovi, Cristina Gutierrez, Evan Lee CNP, Alash'le Abimiku, Steven Spector, Giorgio Roscigno and JN. Laboratory diagnosis of tuberculosis in resource-poor Countries: Challenges and opportunities. Clin Microbiol Rev . 2011;24(2):314–50.

91. Treatment Action Group. Tuberculosis Diagnostic Tools . New York; 2017 [cited 2018 Sep 28]. Available from: www.treatmentactiongroup.org

92. Oshi DC, Chukwu JN, Nwafor CC, Meka AO, Madichie NO, Ogbudebe CL, et al. Does intensified case finding increase tuberculosis case notification among children in resource-poor settings ? A report from Nigeria. Int J Mycobacteriology . 2015;5(1):44–50.

93. Rao NA, Irfan M, Hussain SJ. Primary drug resistance against Mycobacterium Tuberculosis in Karachi. J Pak Med Assoc. 2008;58:122–5.

94. Kruk A, Gie RP, Schaaf HS, Marais BJ. Symptom-Based Screening of Child Tuberculosis Contacts: Improved Feasibility in Resource-Limited Settings. Pediatrics . 2008;121(6):e1646–52.

95. Mandalakas AM, Hesseling AC, Gie RP, Schaaf HS, Marais BJ, Sinanovic E. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. Thorax. 2013;68(3):247–55.

96. Detjen A, Grzemska M, Sm G, Sismanidis C. Improving the estimates of childhood TB disease burden and assessing childhood TB activities at country level. Available from: http://www.tbcare1.org/publications/toolbox/tools/hss/Improving_the_estimates_of_childhood_TB.pdf

97. Donald PR. Childhood tuberculosis: The hidden epidemic. In: International Journal of Tuberculosis and Lung Disease. 2004. p. 627–9.

98. Marais BJ, Graham SM, Maeurer M, Zumla A. Progress and challenges in childhood tuberculosis. Lancet Infect Dis . 2013 Apr;13(4):287–9.

99. Shingadia D, Novelli V. Diagnosis and treatment of tuberculosis in children. Lancet Infect Dis. 2003;3(10):624–32.

100. Cruz AT, Starke JR. Clinical manifestations of tuberculosis in children. Paediatr Respir Rev. 2007;8(2):107–17.

101. Kumar MK, Kumar P, Singh A. Recent advances in the diagnosis and treatment of childhood tuberculosis. J Nat Sci Biol Med. 2015 Jul 1;6(2):314–20.

102. World Health Organization. best practices in child and adolescent tuberculosis care. Geneva, Switzerland:WHO; 2018.

103. MacLean E, Sulis G, Denkinger CM, Johnston JC, Pai M, Khana FA. Diagnostic accuracy of Stool Xpert MTB/RIF for detection of pulmonary tuberculosis in children: A Systematic Review and Meta-analysis. J Clin Microbiol . 2019 Jun 1;57(6):e02057-18.

104. Wali A, Kumar AM V., Hinderaker SG, Heldal E, Qadeer E, Fatima R, et al. Pre-treatment loss to follow-up among smear-positive TB patients in tertiary hospitals, Quetta, Pakistan. Public Heal Action . 2017;7(1):21–5.

105. Ram S, Kishore K, Batio I, Bissell K, Zachariah R, Satyanarayana S, et al. Pre-treatment loss to follow-up among smear-positive pulmonary tuberculosis cases: a 10-year audit of national data from Fiji. Public Heal Action. 2012;2(4):138–41.

106. Hinderaker SG, Fatima R. Lost in time and space: the outcome of patients transferred out from large hospitals [Editorial]. Public Heal Action . 2013 Mar 21;3(1):2–2.

107. Fatima R, Ejaz Q, Enarson DA, Bissell K. Comprehensiveness of primary services in the care of infectious tuberculosis patients in Rawalpindi, Pakistan. Public Heal Action. 2011;1(1):13–5.

108. National TB Control Program. Revised: Doctor's desk guide managment of childhood tuberculosis. Islamabad, Pakistan: Ministry of Health; 2017.

109. Hirsch-Moverman Y, Daftary A, Yuengling KA, Saito S, Ntoane M, Frederix K, et al. Using mhealth for HIV/TB treatment support in lesotho: Enhancing patient-provider communication in the start study. J Acquir Immune Defic Syndr . 2017 Jan 1;74(Suppl 1):S37–43.

110. Kundu D, Chopra K, Khanna A, Babbar N, Padmini TJ. Accelerating TB notification from the private health sector in Delhi, India. Indian J Tuberc. 2016;63(1):8–12.

111. World Health Organization. Roadmap towards ending TB in children and adolescents Second edition. Geneva, Switzerland:WHO; 2018.

112. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, et al. Sex and gender: modifiers of health, disease, and medicine. Lancet . 2020 Aug 22 [cited 2020 Aug 23];396(10250):565–82.

113. Kaur M, Kaur R, Walia P. Exploring Gender Disparity in Nutritional Status and Dietary Intake of Adolescents in Uttarkashi. Indian J Hum Dev. 2020;14(1):115–27.

114. Bugvi AS, Rahat R, Zakar R, Zakar MZ, Fischer F, Nasrullah M, et al. Factors associated with non-utilization of child immunization in Pakistan: Evidence from the Demographic and Health Survey 2006-07. BMC Public Health. 2014;14(1):1–7.

115. Braham CA, White PJ, Arinaminpathy N. Management of tuberculosis by healthcare practitioners in Pakistan: A systematic review. PLoS One. 2018;13(6):e0199413.

116. Mushtaq MU, Shahid U, Abdullah HM, Saeed A, Omer F, Shad MA, et al. Urban-rural inequities in knowledge, attitudes and practices regarding tuberculosis in two districts of Pakistan's Punjab province. Int J Equity Health . 2011;10(1):1–9.

117. Ashiagbor G, Ofori-Asenso R, Forkuo EK, Agyei-Frimpong S. Measures of geographic accessibility to health care in the Ashanti Region of Ghana. Sci African. 2020 Sep 1;9:e00453.

118. Bedard BA, Younge M, Pettit PA, Mendoza M. Using Telemedicine for Tuberculosis Care Management: a Three County Inter-Municipal Approach. J Med Syst. 2018 Jan 1;42(1):1–3.

119. Huang GKL, Pawape G, Taune M, Hiasihri S, Ustero P, O'Brien DP, et al. Telemedicine in Resource-Limited Settings to Optimize Care for Multidrug-Resistant Tuberculosis. Front Public Heal. 2019;7(222):1–5.

120. UNICEF & World Health Organization. Management of sick children by community health workers: Intervention models and programme examples. 2006.

121. The Union. A Framework for Integrating Childhood Tuberculosis into Community-based Child Health Care. 2013.

122. Hafeez A, Mohamud BK, Shiekh MR, Shah SAI, Jooma R. Lady health workers programme in Pakistan: Challenges, achievements and the way forward. J Pak Med Assoc. 2011;61(3):210–5.

123. Bechange S, Schmidt E, Ruddock A, Khan IK, Gillani M, Roca A, et al. Understanding the role of lady health workers in improving access to eye health services in rural Pakistan – findings from a qualitative study. Arch Public Heal

. 2021 Dec 1;79(1):1–12.

124. Zawedde-Muyanja S, Nakanwagi A, Dongo JP, Sekadde MP, Nyinoburyo R, Ssentongo G, et al. Decentralisation of child tuberculosis services increases case finding and uptake of preventive therapy in Uganda. Int J Tuberc Lung Dis . 2018 Nov 1;22(11):1314–21.

125. UNICEF. Strengthening community and primary health systems for tuberculosis. A consultation on childhood TB integration. 2016.

126. World Health Organization. Global strategy and targets for tuberculosis prevention, care and control after 2015 . Geneva, Switzerland:WHO; 2014.

127. United Nations System Staff College. The 2030 Agenda for Sustainable Development . Bonn, Germany; 2018 [cited 2019 Feb 4]. Available from: www.unssc.org

128. World Health Organization. Roadmap towards ending TB in children and adolescents. WHO: Geneva Switzerland; 2018.

129. Jaganath D, Zalwango S, Okware B, Nsereko M, Kisingo H, Malone LS, et al. Contact investigation for active tuberculosis among child contacts in Uganda. Clin Infect Dis. 2013;57(12):1685–92.

130. Fairlie L, Muchiri E, Beylis CN, Meyers T, Moultrie H. Microbiological investigation for tuberculosis among HIV-infected children in Soweto, South Africa. Int J Tuberc Lung Dis. 2014;18(6):676–81.

131. Tadesse Y, Gebre N, Daba S, Gashu Z, Habte D, Hiruy N, et al. Uptake of isoniazid preventive therapy among under-five children: TB contact investigation as an entry point. PLoS One. 2016;11(5):1–11.

132. Bonnet M, Kyakwera C, Kyomugasho N, Atwine D, Mugabe F, Nansumba M, et al. Prospective cohort study of the feasibility and yield of household child tuberculosis contact screening in Uganda. Int J Tuberc Lung Dis. 2017;21(8):862–8.

Published Papers

I

Paper I

PLOS ONE

RESEARCH ARTICLE

Measuring and addressing the childhood tuberculosis reporting gaps in Pakistan: The first ever national inventory study among children

Razia Fatima[1], Aashifa Yaqoob[1,2]*, Ejaz Qadeer[3], Sven Gudmund Hinderaker[2], Aamer Ikram[1,4], Charalambos Sismanidis[5]

1 Common Management Unit (HIV/AIDS, TB & Malaria), Islamabad, Pakistan, **2** University of Bergen, Bergen, Norway, **3** Pakistan Institute of Medical Sciences, Islamabad, Pakistan, **4** National Institute of Health, Islamabad, Pakistan, **5** Global TB Programme, World Health Organization, Geneva, Switzerland

* aashifa.yaqoob@gmail.com

OPEN ACCESS

Citation: Fatima R, Yaqoob A, Qadeer E, Hinderaker SG, Ikram A, Sismanidis C (2019) Measuring and addressing the childhood tuberculosis reporting gaps in Pakistan: The first ever national inventory study among children. PLoS ONE 14(12): e0227186. https://doi.org/10.1371/journal.pone.0227186

Editor: Sherri Lynn Bucher, Indiana University School of Medicine, UNITED STATES

Received: May 23, 2019

Accepted: December 13, 2019

Published: December 30, 2019

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: https://doi.org/10.1371/journal.pone.0227186

Data Availability Statement: Some data sharing restrictions are imposed by the program. Special permission for program is required for data

Abstract

Introduction

Tuberculosis in children may be difficult to diagnose and is often not reported to routine surveillance systems. Understanding and addressing the tuberculosis (TB) case detection and reporting gaps strengthens national routine TB surveillance systems.

Objective

The present study aimed to measure the percentage of childhood TB cases that are diagnosed but not reported to the national surveillance system in Pakistan.

Design

The study design was cross sectional. The study was nationwide in 12 selected districts across Pakistan, each representing a cluster. Health facilities that diagnose and treat childhood TB from all sectors were mapped and invited to participate. Lists of child TB cases were created for the study period (April-June 2016) from all study facilities and compared against the list of child TB cases notified to the national TB surveillance system for the same districts and the same period.

Results

All public and private health facilities were mapped across 12 sampled districts in Pakistan and those providing health services to child TB cases were included in the study. From all private health facilities, 7,125 children were found with presumptive TB during the study period. Of them, 5,258 were diagnosed with tuberculosis: 11% were bacteriologically-confirmed and 89% clinically-diagnosed; only 4% were notified to National TB Control Program. An additional 1,267 children with TB were also registered in the National TB Control Program. Underreporting was measured to be 78%.

availability request because of office policy restriction for data sharing. Data can be accessed by contacting IRC Ethics Committee [irb@ntp.gov.pk], Common Management unit (HIV/AIDS, TB & Malaria) to which data requests can be sent.

Funding: The study was carried out with funding from UNITAID, channeled through the STEPTB project that was led by the TB Alliance and WHO. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Conclusion

This is the first nationwide childhood TB inventory study globally and confirmed that childhood TB underreporting is very high in Pakistan. TB surveillance in the country must be strengthened to address this, with particular attention to guiding and supporting general practitioners and pediatricians to notify their TB cases.

Introduction

Every day globally up to 650 children (aged <15 years) lose their lives due to tuberculosis (TB), a preventable and curable disease [1]; children account for 10% of the new TB cases notified in 2017 [2]. In countries worldwide, the reported percentage of all TB cases occurring in children varies from 3% to more than 25% [3]. However, the estimates of child tuberculosis cases have been unreliable partly because of limited surveillance data of children in many countries; also very few epidemiological studies are done [4]. TB in children is often missed or overlooked due to non-specific symptoms and difficulties in diagnosis; this has made it difficult to assess the actual magnitude of the burden, [5]. Understanding and addressing the TB case detection and reporting gaps may strengthen national routine TB surveillance systems and allow for accurate monitoring of progress with TB prevention and care targets set by National Tuberculosis Programmes and their partners. An inventory study measuring the level of underreporting of child TB may show the gap between diagnosis and reporting of child TB cases [6].

During 2006–07, NTP Pakistan developed its national childhood TB policy guidelines in collaboration with Pakistan Pediatric Association (PPA) [7]. These guidelines for TB in children, including a scoring chart for helping diagnosis, were among the first of its kind in developing countries. The purpose of the guidelines was to help the pediatricians, physicians and other health workers to improve and standardize diagnosis and case management among children with TB. Currently, the PPA scoring chart is shared with all pediatricians to diagnose TB in children.

In Pakistan, TB accounts for 8–20% of all deaths in children [8]. According to TB notification 2018 in Pakistan, out of around 369,000 TB cases 13% were children. The private health sector in Pakistan is very big: 85% of patients choose to seek care in the private sector which is large and unregulated and is comprised of both qualified and unqualified service providers in the disciplines of allopathy, homeopathy and tibb (Traditional Herbal Medicine) [9]. TB drugs are available in private pharmacies and there are many large private teaching hospitals present in the country that are managing infectious and non-infectious diseases. In 2017, 28% of the TB notification in Pakistan was reported by private sector, [10] but the proportion of general practitioners (GPs) and paediatrician reporting is quite low. Therefore, it is expected that the national surveillance system is missing many child TB cases from the private sector. An inventory study carried out in 2012 showed that 27% of adult TB cases were not notified to the National Tuberculosis Program (NTP) in Pakistan [11]. Unpublished data from that study showed that underreporting was 2.5 times higher in age group < 15 years. One could hypothesize that the percentage of children could be even higher, since the study did not specifically include in its sampling frame facilities/private practitioners who would also diagnose TB in children. Therefore, the current study was done to assess the level of underreporting of child TB in Pakistan.

Materials and methods

Design

This was a nationwide cluster-based cross sectional study.

Study area

This study was a national cluster-based, prospective study targeting all facilities in the selected study areas that diagnose and treat childhood TB in Pakistan. To ensure national representation, at least one district was selected from each of the 6 provinces/regions, while the number of the remaining 6 districts were split proportional to province/region population size of children (Table 1). In these study areas we collected data on cases diagnosed by all health-care providers within these areas for a specified time period, followed by record-linkage to the electronic, case-based NTP database[6].

Districts were defined to be the study clusters and were randomly sampled from all four provinces (Balochistan, Khyber Pakhtunkhwa, Punjab and Sindh) and two regions (Gilgit Baltistan and Azad Jammu & Kashmir). All eligible facilities from sampled districts were enumerated and invited to participate in the study. Federally Administered Tribal Area districts were excluded from the sampling frame due to security concerns.

Sample size considerations

The required sample size *N*, in terms of number of districts, was determined using a standard equation for cluster-based studies that measure a single percentage.

$$N = \left(\left[1 + (\mathrm{m} - 1) \frac{\mathrm{k^2 p}}{1 - \mathrm{p}} \right] * 1.96^2 \frac{(1-p)}{d^2 p} \right) / m$$

Here ***p*** stands for the primary outcome of interest, the percentage of TB underreporting (assumed to be 27%, based on a previous such study in adults), precision (***d***) selected to be 25%, a coefficient of variation (***k***) between 0.3–0.4 (based on a previous such study in adults), and cluster size (***m***) with harmonic mean between 33 and 77 (based on case notification data from BMU's across the country inflated by the estimated 2014 case detection rate), the study requires 12 districts to fulfil its objectives.

Sample selection

The definition of a cluster in this study is the district, a well-defined geographical and administrative area, with low chances of broken linkages due to patients seeking health services from

Table 1. Selection of districts based on probability proportional to population size.

Strata	Number of districts	Population (≤14 years)	Percentage share of national	Number of clusters		
				All get one	*Additional* *	*Total*
Balochistan	30	2947212	5%	1	0	1
KPK	25	8239283	14%	1	1	2
Punjab	36	33027380	55%	1	3	4
Sindh	23	13712676	23%	1	2	3
AJK	10	1452889	2%	1	0	1
GB	7	412616	1%	1	0	1
National	**131**	**59792055**	**100%**	**6**	**6**	**12**

*Proportional to national share

https://doi.org/10.1371/journal.pone.0227186.t001

the private sector in neighbouring districts. Sampling of 12 districts (clusters) out of 144 across the country was done, with probability proportional to population size of provinces and regions (Table 1). Prospective collection of data for cases diagnosed by all health-care providers within these districts for a specified time period, followed by record-linkage with an electronic, case-based national NTP database [6].

A total of 9,786 health facilities that were providing health services to presumptive child TB cases were mapped and invited to participate in the study. Mapping of all health facilities and health care providers was done through mobile based GPS system in the 12 selected districts/clusters. Public providers include the NTP and non-NTP public health services (public hospitals, university hospitals, medical organizations, social security, the army, etc.). Private health services include private hospitals, teaching hospitals and universities, clinics of GPs, health facilities run by NGOs, and informal health providers. Private laboratories were also included in this study.

Case-definitions

A child TB case was aged less than 15 years, was diagnosed either pulmonary or extra pulmonary TB disease, and categorised either as a new case or retreatment. A child with presumptive TB was defined as someone with an unexplained cough for more than 2 weeks or/and at least one other TB symptom recommended by Pakistan Paediatric Association scoring chart [12].

Bacteriologically-confirmed. A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or rapid diagnostics like GeneXpert MTB/RIF. Data for all such cases was collected as part of study investigations, regardless of whether TB treatment has started. However, all diagnosed child TB cases were included in the analysis.

Clinically-diagnosed. A clinically diagnosed TB case has no bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner. This definition also includes child TB cases diagnosed with X-ray abnormalities or suggestive histology and extra pulmonary cases with laboratory confirmation. Data for all diagnosed cases was collected regardless of whether TB treatment had started.

Data collection tools and procedure

A health facility register for individuals with presumptive child TB cases was introduced in each NTP public and Non-NTP (public and private) health facilities in which all information regarding all such individuals and their management was recorded. This included full name of the patient, full contact address (with mobile number), age, sex, source of referral, number of specimens examined, results of the tests, final diagnosis and treating physician. In tertiary care hospitals, these registers were placed at all entry points of child TB patients, such as pediatric specialist, chest physician and medical officer. These forms were filled out by health providers who are diagnosing child TB cases in their ordinary work. All these health providers were asked to fill information, without any intervention to change their practice, for 3 months (1 quarter) during data collection from April—June 2016. A laboratory register was introduced to all laboratories to gather the information regarding the tests done for diagnosis and result of tests. All health care providers who consented to participate in the study were first trained to capture the required information in the registers, and also the laboratory personnel was trained. The data was collected through cell phones (using the application developed by "Zong"). Then all data was uploaded to the server. At central level, NTP, research department accessed the data on daily basis for monitoring and supervision.

Monitoring and supervision

The health facilities were visited weekly by field officers, provincial coordinators, district tuberculosis coordinators and a district supervisor to ensure the quality (completeness, correctness) of data collected, to conduct cross-checking the status of registration at NTP, and to contact the unregistered cases in NTP registers to verify the diagnosis made by NTP & non-NTP providers. Any case with doubtful diagnosis (based on existing data from medical records) was captured as part of the study but classified according to study case definitions.

Data quality audit (DQA)

To ensure the validity of data, every record was cross checked from the hard copies to remove inconsistencies between hard and soft records. The process of DQA for crosschecking registers was completed one quarter after the end of the study period.

Data analysis and management

Three sources of information were used: I) standard NTP TB-registers; 2) Patient registers in private health facilities; 3) Patient registers in private laboratories. The study was based on two databases: health facility mapping and health facilities reporting. At first stage; de-duplication on both databases was done through probabilistic matching by comparing the following variables of each case: First name, last name, father's name, grandfather, district, sex, age, site of disease, hospital name, type of health facility. Then a manual review of multi-matches (one case matching to many) was done by research team to remove duplicates, this was done for 450 cases. Lacking unique identifiers of patients record linkage was carried out as outlined in guidance issued by WHO [6], by cross-checking the notifications of non-NTP facilities, compared with official public district TB registers, using the combination of the first name, father's name and family name in English language as identifiers. In case one of the names was missing other available identifiers were also compared. Presence or absence in the official district NTP register was recorded. To correct for possible misclassification (between notified and un-notified cases to NTP) the NTP registers were examined for the period between two quarters before and one quarter after the study period. Then databases were combined e.g. notification/study dataset including matched and unique records for final analysis.

Ethical considerations

Ethical clearance (registration # NBC 192 given in 2015) was granted from the Pakistan medical and Research Council before execution of the study as well as the WHO Ethics Committee for the East-Mediterranean region. Informed consent was taken from the NTP and non-NTP providers but not from the patients as this study was based on record review and no intervention was targeted on TB patients and ethics committee waived the need for informed consent from patients for their data to be used in research. However, patient identifiers were required for record linkage. Data was maintained in electronic register with a password-protected code and only the principal investigator or an authorized person had access to the data for analysis purposes.

Results

A total of 7,125 presumptive child TB cases were detected by all participating health facilities between April—June, 2016, where 6,519 were diagnosed in the private health services, and 606 in private laboratories (Table 2). The age group 10-14y was largest (41%) and girls dominated (64%). From these children with presumptive TB, 5258 were diagnosed as TB and put on

Table 2. Characteristics of children with presumptive tuberculosis in the study: Apr—Jun 2016.

	Private Health Facility	Laboratory	Total
	n (%)	n (%)	
Age (in year)			
<1	113 (1.7)	2 (0.3)	115 (1.6)
1–4	1578 (24.2)	61 (10.1)	1639 (23.0)
5–9	2240 (34.4)	197 (32.5)	2437 (34.2)
10–14	2,588 (39.7)	346 (57.1)	2934 (41.2)
Gender			
Male	2,320 (35.6)	220 (36.3)	2540 (35.6)
Female	4,199 (64.4)	386 (63.7)	4585 (64.4)
Total	6519	606	7125

https://doi.org/10.1371/journal.pone.0227186.t002

treatment (Table 3); in private health facilities 498 child TB cases were bacteriological positive while 4,695 child TB cases were clinically diagnosed; in laboratories only 65 were diagnosed bacteriological confirmed.

The record linkage indicated that 5193 (5006+187) child TB cases were identified by the private health providers and 65 (64+1) by the laboratories in the 12 study districts (Fig 1). Of these, 188 (187+1) were recorded in the NTP TB register, with an additional 1,267 cases registered only among the NTP sites. The level of underreporting nationally was 78%, with marked differences between provinces. The highest level of underreporting was found in Jhal Magsi, followed by Hafizabad and Pallundary (Table 4).

Table 5 shows the potential risk factors and uncertainty interval of underreporting. The underreporting was higher in boys 84% (78%–91%) than girls 68% (57%–79%). The underreporting was 76% (65%-87%) for bacteriologically confirmed TB cases and 78% (68%–88%) for clinically diagnosed cases.

Table 3. Identified child TB cases by the private health providers & laboratories in selected districts of Pakistan: Apr—Jun, 2016.

Province	District	Health Facility		Laboratory	Total
		Bacteriological positive	Clinically Diagnosed	Bacteriological positive	
Punjab	Attock	31	411	1	443
	Chiniot	108	229	1	338
	Hafizabad	15	540	0	555
	Vehari	30	303	0	333
Sindh	Shikarpur	8	386	0	394
	Hyderabad	10	828	5	843
	Karachi	130	812	26	968
KPK	Buner	11	137	0	148
	Peshawar	126	873	32	1031
AJK	Pallundary	6	108	0	114
Baloschistan	Jhal Magsi	19	8	0	27
GB	Ghizer	4	60	0	64
Total		**498**	4695	65	5258

AJK = Azad Jammu & Kashmir, KPK = Khyber Pakhtunkhwa, GB = Gilgit Baltistan

https://doi.org/10.1371/journal.pone.0227186.t003

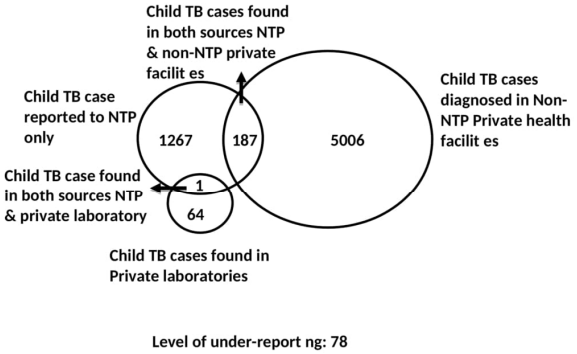


Fig 1. Venn diagram showing child TB cases by source of identification. NTP = National Tuberculosis Control Programme.

https://doi.org/10.1371/journal.pone.0227186.g001

Discussion

In this child TB inventory study in Pakistan we found that a substantial proportion of children diagnosed TB were detected by private providers, and the majority (89%) of child TB cases were clinically diagnosed. The proportion of notified child TB cases after record linkage was quite low and a massive underreporting (78%) was found. There was a marked difference between the provinces, and we notice that the highly populated Punjab contributed 64% of country TB case notification, and had a high level of underreporting. Proper training of private health providers and encouraging a "public-private-mix" approach to diagnosis and referral of

Table 4. Child tuberculosis detected and notified in Pakistan, by district: Apr—Jun, 2016.

Districts	Child TB cases notified to NTP Only Q2 2016	TB inventory study		Underreporting
		Cases reported to NTP	Cases not reported to NTP	
	(a)	(b)	(c)	[c/(a+b+c)]
Attock	50	34	409	83%
Buner	32	43	105	58%
Chiniot	34	4	334	90%
Ghizer	11	0	64	85%
Hafizabad	5	12	543	97%
Hyderabad	69	35	808	89%
Jhal maghsi	0	0	27	100%
Karachi	584	12	956	62%
Pallundary	9	2	112	91%
Peshawar	339	37	994	73%
Shikarpur	54	2	392	88%
Vehari	80	7	326	79%
Total	1267	188	5070	78%

https://doi.org/10.1371/journal.pone.0227186.t004

Table 5. Underreporting (overall and by risk factor) estimated taking into consideration the sampling design.

	Underreporting	
	Best estimate	**95% C.I**
Overall	78%	68%–87%
Gender		
• Boys	84%	78%–91%
• Girls	68%	57%–79%
Case Type		
• Bacteriological confirmed	76%	65%–87%
• Clinically diagnosed	78%	68%–88%

C.I = confidence Interval

https://doi.org/10.1371/journal.pone.0227186.t005

child TB cases to the National program for notifications could reduce the observed underreporting.

Underreporting has been described before, and a mathematical modelling study by Dodd in 22 high-burden countries predicted that the incidence of child TB is much higher than the number of notifications, and the global burden is perhaps 25% higher than the prediction for these countries Similar trends in under reporting of childhood TB cases have been reported elsewhere [13–15]. Effective household contact tracing through intensified case finding and engaging private providers who manage child TB could find more of these undetected or unreported cases.[16,17].

Factors associated with low case detection among children include poor record-keeping, lack of access to records on child TB cases for reporting. and inability to produce sputum for many children (only 30% of child TB cases can be detected through smear microscopy [16,18,19]. Other factors include limited capacity of healthcare providers to diagnose childhood TB and ineffective contact tracing [20,21]. A variety of factors have been identified as the leading causes of poor utilization of public health services, including poor socio-economic status, distance and accessibility to tertiary care level, cultural beliefs and perceptions, and low awareness and education.

During 2006–07, NTP Pakistan developed its national child TB guidelines in collaboration with Pakistan Paediatric Association [12]. Our study showed that these guidelines were underutilized in diagnosing child TB cases by the private providers across Pakistan. From other studies, it is evident that screening for child TB is feasible and cost effective using a symptom-based approach [22–24]. To improve the child TB case diagnostic practices of private health providers, wide dissemination of Pakistan Paediatric Association scoring guidelines, including chest-X-ray reading, needs to be properly followed and linked to further training of health care providers; this might strengthen the public-private mix approach. Its use should not be limited to tertiary care hospitals. The high proportion of children found in this study who were diagnosed with TB but not reported to the NTP confirms the potential significance of the non-NTP health providers. TB case notification is in principle mandatory, and private providers can be linked with NTP to increase the TB notification perhaps by reminding them that NTP will provide drugs free of cost. Contact tracing around index cases will find more cases of child TB and latent TB infection, and should be treated. There is also need to devise some strategies to increase utilization of GeneXpert MTB/RIF or develop some transportation referral mechanism across Pakistan especially in remote areas to improve the basis for diagnosis.

In our study, under-reporting was higher in males (84%) than females (68%). The Detected -to-notified case ratio was 70% higher in men than women. Other TB prevalence surveys in Asia have also shown higher such ratios for men than women [25].

Our study showed that a total of 4,695 (89%) child TB cases were diagnosed clinically, often based solely on clinical signs and chest X-ray. This may partly reflect the limited availability in remote areas of diagnostic investigations like GenXpert, TST (Tuberculin skin test) and Gastric Lavage. The same obstacles diagnosing child TB cases has been observed elsewhere [26,27]. A chest x-ray may give the clinicians a good indication that the patient suffers from TB, but bacteriological confirmation by rapid diagnostic tests to increase proportion of bacteriological confirmed child TB cases is highly recommended whenever available [28]. In children induced sputum, nasopharyngeal and gastric aspirates provide alternative respiratory samples in children who cannot expectorate. Fine needle aspiration biopsy could be an excellent option in children with peripheral lymphadenitis. Still, even such investigations some cases will still need to be diagnosed without clear evidence.

Suboptimal contact tracing and limited availability of appropriate diagnostic tools are big challenges in diagnoses of childhood TB in Pakistan. There is a need for better and sustainable public-private partnerships and robust electronic surveillance system to capture all child TB cases reported by strengthening child TB surveillance system, using current District Health Management system. Currently, child TB care services are confined to only tertiary care hospitals in Pakistan; so the services should be considered in other health facilities in public and private sectors, based on skills. Gastric lavage is often not available in many settings; sputum induction may be encouraged; sputum transportation system for Xpert/smear and proper referral linkages with peripheral centres should be ensured. In order to understand more about underreporting there is also need for research on child TB care delivery issues, like investigation practices, contact investigation and referrals, engagement of tertiary care hospitals and informal providers.

This study is as far as we know the first national inventory study in the world to assess underreporting of child TB cases. Major challenges in the study was a lengthy data collection tool, and many busy GPs didn't have time to fill themselves, so either the data collectors or clinic staff entered the data, enhanced by the use of electronic questionnaires by the data collectors. Also, we can not assess the size of a potential Hawthorne effect during the study, where facilities in the study were more likely to report cases than those not studied.

Conclusion

This is the first national TB inventory study globally among children, and it has provided much needed data to improve our understanding of TB burden among this vulnerable subpopulation. The study confirmed that childhood TB is seriously underreported in Pakistan. TB surveillance in the country should be strengthened to address this collaborating with GPs and paediatricians.

Acknowledgments

We are thankful to WHO headquarters and country office Pakistan for providing technical support for this study. We thank Kunju Shaji from Public Health England who supported record linkage. We are grateful to all survey field, central staff (research unit) and NTP management for continued support. We are thankful to all health care providers participated in this study. We highly acknowledge the corporation and facilitation of PTP Managers and PTOs from provisional TB control programs of Punjab, Sindh, Khyber Pakhtunkhwa, Balochistan, Azad Jammu & Kashmir and Gilgit Baltistan. University of Bergen provided a good academic background.

Author Contributions

Conceptualization: Razia Fatima, Aashifa Yaqoob, Ejaz Qadeer, Charalambos Sismanidis.

Data curation: Aashifa Yaqoob, Charalambos Sismanidis.

Formal analysis: Aashifa Yaqoob, Charalambos Sismanidis.

Funding acquisition: Razia Fatima, Charalambos Sismanidis.

Investigation: Razia Fatima, Aashifa Yaqoob, Charalambos Sismanidis.

Methodology: Razia Fatima, Aashifa Yaqoob, Charalambos Sismanidis.

Project administration: Razia Fatima, Aashifa Yaqoob, Ejaz Qadeer.

Resources: Razia Fatima, Aashifa Yaqoob, Charalambos Sismanidis.

Software: Aashifa Yaqoob, Charalambos Sismanidis.

Supervision: Razia Fatima, Aashifa Yaqoob, Sven Gudmund Hinderaker.

Validation: Razia Fatima, Aashifa Yaqoob, Charalambos Sismanidis.

Visualization: Razia Fatima, Aashifa Yaqoob, Charalambos Sismanidis.

Writing – original draft: Razia Fatima, Aashifa Yaqoob.

Writing – review & editing: Razia Fatima, Aashifa Yaqoob, Ejaz Qadeer, Sven Gudmund Hinderaker, Aamer Ikram, Charalambos Sismanidis.

References

1. World Health Organization. Roadmap towards ending TB in children and adolescents. WHO: Geneva Switzerland; 2018.
2. WHO. Global tuberculosis report 2018. Geneva: World Health Organization; 2018.
3. World Health Organization. WHO | Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva, Switzerland:WHO: World Health Organization; 2014.
4. World Health Organization. Estimating TB incidence among children. WHO: Geneva, Switzerland; 2018.
5. World Health Organization. Roadmap for childhood tuberculosis towards zero deaths. Geneva, Switzerland:WHO; 2013.
6. World Health Organization. Assessing tuberculosis Under-Reporting Through Inventory Studies. Geneva, Switzerland:WHO; 2012.
7. National TB Control Program. Revised: DOCTOR'S DESK GUIDE MANAGEMENT OF CHILDHOOD TUBERCULOSIS. Islamabad, Pakistan; 2017.
8. National TB Control Program. National guidelines for diagnosis and management in Children. Islamabad, Pakistan; 2006.
9. Fatima R, Haq MU, Yaqoob A, Mahmood N, Ahmad KL, Osberg M, et al. Delivering Patient-Centered Care in a Fragile State: Using Patient-Pathway Analysis to Understand Tuberculosis-Related Care Seeking in Pakistan. J Infect Dis. 2017; 216: S733–S739. https://doi.org/10.1093/infdis/jix380 PMID: 29117348
10. World Health Organization. Global Tuberculosis Report 2017. Geneva, Switzerland:WHO; 2017.
11. Fatima R, Harris RJ, Enarson DA, Hinderaker SG, Qadeer E, Ali K, et al. Estimating tuberculosis burden and case detection in Pakistan. Int J Tuberc Lung Dis. 2014; 18: 55–60. https://doi.org/10.5588/ijtld.13.0198 PMID: 24365553
12. National TB Control Program. National guidelines for diagnosis and management of tuberculosis in children 2006–07. Islamabad, Pakistan; 2007.
13. Hong SJ, Park YS, An H, Kang SM, Cho EH, Shin SS. Factors leading to under-reporting of tuberculosis in the private sector in Korea. Int J Tuberc Lung Dis. 2012; 16: 1221–1227. https://doi.org/10.5588/ijtld.11.0782 PMID: 22794136

14. Lestari T, Probandari A, Hurtig AK, Utarini A. High caseload of childhood tuberculosis in hospitals on Java Island, Indonesia: A cross sectional study. BMC Public Health. 2011; 11.
15. Coghlan R, Gardiner E, Amanullah F, Ihekweazu C. Understanding Market Size and Reporting Gaps for Paediatric TB in Indonesia, Nigeria and Pakistan: Supporting Improved Treatment of Childhood TB in the Advent of New Medicines. PLoS One. 2015; 10: 1–12.
16. Oshi DC, Chukwu JN, Nwafor CC, Meka AO, Madichie NO, Ogbudebe CL, et al. Does intensified case finding increase tuberculosis case notification among children in resource-poor settings? A report from Nigeria. Int J Mycobacteriology. 2015; 5: 44–50.
17. Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: A mathematical modelling study. Lancet Glob Heal. 2014; 2.
18. Parsons Linda M., Somoskovi Akos, Gutierrez Cristina, Lee Evan P CN, Abimiku Alash'le, Spector Steven, Roscigno Giorgio and N J. Laboratory diagnosis of tuberculosis in resource-poor countries: Challenges and opportunities. Clin Microbiol Rev. 2011; 24: 314–350. https://doi.org/10.1128/CMR.00059-10 PMID: 21482728
19. Treatment Action Group. Tuberculosis Diagnostic Tools. New York; 2017.
20. Islam Z, Sanin KI, Ahmed T. Improving case detection of tuberculosis among children in Bangladesh: lessons learned through an implementation research. BMC Public Health. 2017; 17: 1–9.
21. Talukder K, Salim MAH, Jerin I, Sharmin F, Talukder MQK, Marais BJ, et al. Intervention to increase detection of childhood tuberculosis in Bangladesh. Int J Tuberc Lung Dis. 2012; 16: 70–75. https://doi.org/10.5588/ijtld.11.0060 PMID: 22236849
22. Kruk A, Gie RP, Schaaf HS, Marais BJ. Symptom-Based Screening of Child Tuberculosis Contacts: Improved Feasibility in Resource-Limited Settings. Pediatrics. 2008; 121: e1646–e1652. https://doi.org/10.1542/peds.2007-3138 PMID: 18519467
23. Mandalakas AM, Hesseling AC, Gie RP, Schaaf HS, Marais BJ, Sinanovic E. Modelling the cost-effectiveness of strategies to prevent tuberculosis in child contacts in a high-burden setting. Thorax. 2013; 68: 247–255. https://doi.org/10.1136/thoraxjnl-2011-200933 PMID: 22717944
24. Detjen A, Grzemska M, Sm G, Sismanidis C. Improving the estimates of childhood TB disease burden and assessing childhood TB activities at country level.
25. Onozaki I, Law I, Sismanidis C, Zignol M, Glaziou P, Floyd K. National tuberculosis prevalence surveys in Asia, 1990–2012: an overview of results and lessons learned. Trop Med Int Health. 2015.
26. Donald PR. Childhood tuberculosis: The hidden epidemic. International Journal of Tuberculosis and Lung Disease. 2004. pp. 627–629. PMID: 15137546
27. Marais BJ, Graham SM, Maeurer M, Zumla A. Progress and challenges in childhood tuberculosis. Lancet Infect Dis. 2013; 13: 287–289. https://doi.org/10.1016/S1473-3099(13)70031-8 PMID: 23531386
28. Marais BJ, Graham SM. Childhood tuberculosis: A roadmap towards zero deaths. J Paediatr Child Health. 2016; 52: 258–261. https://doi.org/10.1111/jpc.12647 PMID: 24923706

II

Paper II

Yaqoob *et al. BMC Public Health* (2021) 21:71
https://doi.org/10.1186/s12889-020-10053-4

BMC Public Health

RESEARCH ARTICLE Open Access

How do private practitioners in Pakistan manage children suspected having tuberculosis? A cross sectional study

Aashifa Yaqoob[1,2*], Sven Gudmund Hinderaker[2], Razia Fatima[1], Hina Najmi[3] and Anwar-ul-Haq[4]

Abstract

Background: In Pakistan, private providers provide a large portion of health care, including for tuberculosis (TB). All TB patients are supposed to be reported to the National Tuberculosis Program (NTP), which provides drugs free of charge in addition to monitoring, supervision, and support. However, diagnosis of TB in children is difficult. We aimed to assess the private health care providers' investigation practices and management of childhood TB.

Methods: We used a cross-sectional study, which was based on a national survey measuring under-reporting of children with TB in 12 selected districts in Pakistan from April–June, 2016. We explored the practices of the private health care providers, including the health care workers i.e. general practitioners, pediatricians, pulmonologists and chest specialists, who were involved in the diagnosis of TB in children under 15 years for investigating and managing children suspected having TB.

Results: Among 6519 presumptive child TB cases, a total of 5193(79.7%) children under 15 years were diagnosed as TB by private health care providers during second quarter, 2016. Only 187(2.9%) were notified to NTP. The majority of presumptive child TB cases reported cough, fever, and failure to thrive; few had TB contacts with pulmonary TB patients. Failure to thrive, loss of body weight and absence of BCG (Bacillus Calmette–Guérin) scar was more common in female children. Private providers relied on chest X-ray in 46.1%, while tuberculin skin test and Gene-Xpert MTB/RIF testing was little utilized. Bacteriological confirmation was present in 7.6%, and clinical assessment was the only basis for diagnosis in 39.3%. Of children with presumptive TB, only 955(14.6%) children were treated by private provider, while 3121(47.9%) cases were referred for diagnosis and 2443(37.5%) were referred after diagnosis for treatment; among all the referred, 3812(68.5%) were sent for investigations to District TB Centre (NTP).

Conclusion: This study showed that many private providers referred children suspected having TB to laboratories for further diagnosis, but the cases identified in these investigations were often not notified to the NTP. This problem could be resolved by strengthening the referral linkages between private health providers, NTP laboratories and treatment centres through capacity building and training of their staff.

Keywords: Children, Tuberculosis, Private providers, Management practices, Referral, Diagnosis, Presumptive, Pakistan

* Correspondence: aashifa.yaqoob@gmail.com
[1]Common Management Unit (HIV/AIDS, TB & Malaria), Block F, EPI Building, Near National Institute of Health (NIH) (Prime Minister's National Health Complex), Park Road, Islamabad, Pakistan
[2]University of Bergen, Bergen, Norway
Full list of author information is available at the end of the article

Background

Tuberculosis (TB) among children is a significant global challenge affecting mainly low- and middle income countries. In 2018, 1.1 million children fell ill with TB, and 205,000 (18%) of them died [1]. Of the childhood cases, 75% occur in 22 high-burden countries that together account for 80% of the world's estimated incident cases [2, 3]. In terms of global TB control measures, children have a lower priority because they are considered to be less contagious and, therefore, a less important source of infection [3]. Globally, childhood TB cases are under-reported. This is probably due to the difficulty of confirming the diagnosis. Some of the challenges related to assessing the actual magnitude of TB in children include poor implementation of the national guidelines, inappropriate diagnoses, inadequate drug regimens and lack of knowledge about case management [4]. As a notifiable disease in most countries, all diagnosed cases must be recorded and reported.

In Pakistan, it is estimated that over 562,000 people were infected with TB in 2018, of whom 369,548 TB cases were notified; and among these 13% were children under 15 years. Private health care providers in Pakistan contributed 32% of all TB notifications [1]. During 2006–07, NTP Pakistan developed its national childhood TB policy guidelines in collaboration with Pakistan Pediatric Association (PPA), aiming to facilitate the pediatricians, physicians and other health workers to improve and standardize clinical decisions for investigating presumptive child TB cases (< 15 yrs) in Pakistan. In these guidelines, a score chart evaluates the likelihood of pulmonary and extra pulmonary TB based on clinical, histological and radiological features [5]. Currently, the PPA score chart is recommended by NTP to all pediatricians to help diagnose children with suspected TB, when presenting with prolonged or unexplained illness of more than 2 weeks. A flow chart for evaluation of a child with suspected TB is given in Fig. 1.

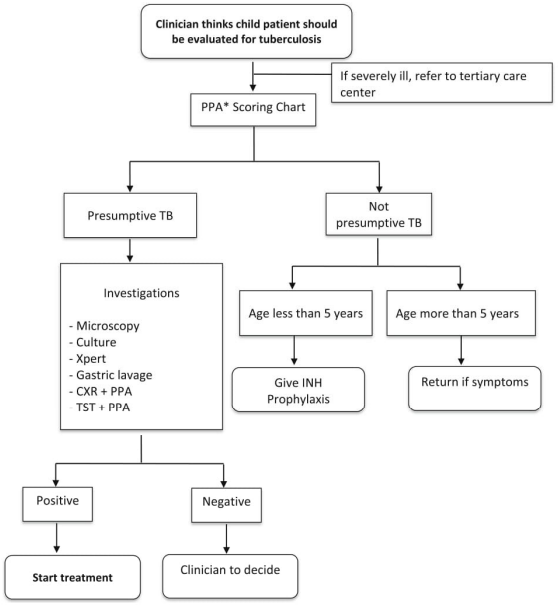


Fig. 1 NTP Flow chart for evaluation of a child with suspected TB. *PPA = Pakistan Paediatric Association

A recent patient-pathway analysis in Pakistan confirmed the important role of the private sector in providing TB care in Pakistan, and highlighted the extent of utilization of private sector (85%) by the patients as entry points to care [6]. This is crucial for understanding the role of the private sector in the diagnosis and treatment of pediatric TB, but limited evidence is available on this issue [7, 8]. Therefore, we aimed to assess the practices of private health care providers in investigation of children suspected having TB. Our target group was patients under 15 suspected having tuberculosis in Pakistan, and our specific objectives were 1) to assess signs and symptoms that private health providers record; and 2) to assess investigation and referral practices.

Methodology

Design

This is a descriptive cross sectional study based on a national child TB inventory involving a surveillance system that was established among all non-NTP facilities in a sample of 12 districts across Pakistan from April–June, 2016 [9].

Setting

Pakistan is the sixth most populous country of the world with an estimated population of 208 million in 2017. Approximately 64% live in rural areas [10]. The public sector is the main source of preventive health care, and has primary, secondary and tertiary levels of care. Quality-assured diagnosis and treatment for TB is provided by NTP free of charge to patients through general facilities in all public and selected private sector facilities. TB services in Pakistan are integrated into the primary health care system at the district level, and are coordinated at this level by the district TB coordinator who is responsible for monitoring, supervising and supporting all clinics in the given district. The data from the districts is monitored and evaluated at provincial and national levels. Patients are reported from rural health centres and sub district hospitals to district hospitals, where the TB coordinator is usually based. Other large private clinics engaged with NTP should report cases directly to Provincial TB Program.

Wealth distribution in Pakistan is highly skewed, with a larger proportion of lowest wealth quintile living in rural settings. In rural Punjab, 18% of population are in the lowest quintile, while these account for only 1% in urban Punjab. In rural Sindh, 69% are in the lowest quintile, while only 6% live in urban Sindh. In rural KPK (Khyber Pakhtunkhwa), 20% are in lowest quintile, while 2.3% live in urban KPK. In rural AJK (Azad Jammu & Kashmir), 15% are in lowest quintile, while 2% live in urban AJK. In rural Balochistan, 36% are from the lowest quintile, while in urban Balochistan 11% are from the lowest quintile [11].

Study site

We selected 12 districts in Pakistan, with representation from all four provinces (Balochistan, KPK, Punjab and Sindh) and two regions (GB (Gilgit Baltistan) and AJK). The selection of the districts was partly based on needing to have a sample proportional to the population size of the children [9]. Districts where security is an issue were excluded from the sampling process. The study was carried out in all private health facilities that manage childhood TB in the 12 selected districts across Pakistan [9]. All non-NTP private facilities in the selected districts were mapped and consenting private health providers managing childhood TB in 12 districts across Pakistan were enrolled. Non-NTP private facilities refer to private facilities that have no formal collaboration with NTP.

Study population

The study population was all children brought to a clinician at a non-NTP private facility who considered tuberculosis a potential diagnosis, because of a prolonged or unexplained illness lasting more than 2 weeks. All participants were identified by health care providers who were not engaged with the NTP i.e. general practitioners, pediatricians, pulmonologists and chest specialists who were involved in child TB inventory study April – June, 2016. Of all the health care providers who were mapped and invited to participate in the study, 82% agreed.

Data collection

A register for presumptive child TB cases was introduced to health facilities diagnosing childhood TB in order to record all information regarding history of presumptive TB cases as well as to facilitate investigation and management. All of the health care providers who consented to participate in the study were briefed on how to capture the required information in the registers. Immediately following these instructions, and without direct mentoring but with close follow up, the health care providers undertook the data collection for the period of 3 months (second quarter of 2016) and the management of child TB patients by the non-NTP health care providers was recorded without having them change their routine practice. To improve the accuracy and validity of the data, a mobile based data collection tool was used in this survey [12]. Data entry was done directly on site on mobile phones using an application developed by "Zong 4G (Mobile network operator company)". Field officers were provided mobile phones to enter the data when visiting the health facilities on a weekly basis. In addition, participants were visited every

2 weeks by the district TB coordinators along with a provincial coordinator, a supervisor and field officer to ensure the quality of data collected (completeness, correctness) for accurate record linkage, and for cross-checking the status of the NTP registration.

Variables and data collection tools

The data collection tool was based on all information regarding the diagnosis and management practices by private healthcare providers concerning children with presumptive TB. Variables included age, sex, place, symptoms, investigations, recommendations given, and referral decision. Data quality auditing of every record was conducted to ensure the validity of data by crosschecking from the hard copies.

Data analysis

Descriptive statistics were used to summarize the investigation, management and referral of children with presumptive TB by private providers. Cross tabulation was done to identify any differences between children 0–4, 5–11, and 12–14 years. Analyses were done in STATA version 14.

Results

Table 1 shows that 5193 children were diagnosed as having TB in 12 selected districts of various population sizes. Many doctors (37.5%) referred diagnosed TB cases to NTP for further management, but few notified NTP if they initiated treatment themselves. There was great variation between the districts in terms of referral rates (2.3–76.1%) and notifications (0–18.5%) of the child TB cases.

Table 2 shows the signs and symptoms of the children suspected having TB, by age group. We noticed many had coughs (92.1%), fever (89.0%), and failure to thrive (64.8%). Few reported contacts with a TB patient (11.9%). A BCG-scar was absent in 19.6% of children 0–4, 28.3% of children 5–11 and 37.4% of children 5–14, P = <.0001.

Table 3 shows signs and symptoms of children suspected having TB, by gender. Out of 6519 presumptive child TB cases, 6006 (92.1%) had reported having a history of coughing for more than two weeks i.e. 3904 (93.0%) males and 2102 (92.1%) females. Of the girls, a BCG-scar was absent in 742 (32.0%) compared to 1101 (26.2%) boys ($P < 0.0001$). Moreover, the differences in coughing, failure to thrive, enlarged lymph nodes and absence of BCG scar in male and female children were statistically significant ($P > 0.05$).

Table 4 shows investigations done on the 6519 children suspected having TB, by age group; 1564 (92.4%) children under five, 2545 (79.2%) children 5–11 and 1084 (67.2%) were diagnosed with tuberculosis: 4695 (72.0%) clinically and 498 (7.6%) bacteriologically verified. The most common investigation was chest X-ray (46.1%). Sputum smear was done on 14.3% among participants 0–4 years, 28.3% among participants 5–11 years, and 723 (44.8%) among 12–14 years. Clinical assessment was the only investigation done on 49.8% of the children below 5 and bacteriological confirmation was more in children 5–11 years (6.3%) and children 12–14 (14.0%), < 0.0001. Many children with presumptive TB were referred to the district TB

Table 1 Presumptive tuberculosis patients under 15 years identified by private health providers in selected districts in Pakistan, 2016

Province	District	Population (< 15 yrs) N	CNR[a] 2016 per 100,000	Presumptive child TB cases n	Diagnosed TB[a] n (%)	Referred to NTP[a] n (%)	Notified to NTP (Project notification) [a] n (%)
All sites		8,643,221	193	6519 (0.08)	5193 (79.7)	2443 (37.5)	187 (2.9)
Punjab	Attock	483,575	175	497 (0.10)	442 (88.9)	97 (19.5)	34 (6.8)
	Chiniot	362,756	232	671 (0.18)	337 (50.2)	139 (20.7)	4 (0.6)
	Hafizabad	317,804	219	874 (0.28)	555 (63.5)	32 (3.7)	12 (1.4)
	Vehari	837,748	225	376 (0.05)	333 (88.6)	223 (59.3)	7 (1.8)
Sindh	Shikarpur	390,208	126	623 (0.16)	394 (63.2)	128 (20.5)	2 (0.3)
	Hyderabad	650,492	149	838 (0.13)	838 (100)	638 (76.1)	35 (4.2)
	Karachi	4,366,147	143	1041 (0.02)	942 (90.5)	737 (70.7)	12 (1.2)
KPK[a]	Buner	211,496	157	232 (0.11)	148 (63.8)	89 (38.4)	43 (18.5)
	Peshawar	843,278	244	1034 (0.13)	999 (96.6)	340 (34.0)	36 (3.5)
AJK[a]	Pallundary	97,553	89.2	118 (0.12)	114 (96.6)	15 (12.7)	2 (1.7)
Balochistan	Jhal Magsi	46,011	29	44 (0.10)	27 (61.4)	1 (2.3)	0 (0.0)
GB[a]	Ghizer	36,153	133	171 (0.47)	64 (37.4)	4 (2.3)	0 (0.0)

[a] **Footnotes:** *KPK* Khyber Pakhtunkhwa, *AJK* Azad Jammu & Kashmir, *GB* Gilgit Baltistan, *CNR* Case Notification Rate (Routine Notification to NTP all forms) "Diagnosed TB by PP" with proportion out of all presumptive patients ("yield"). "Referred to NTP" with proportion out of all diagnosed patients. "Notified to NTP" with proportion out of all presumptive child TB patients

Table 2 Signs and symptoms of children with presumptive tuberculosis by age groups, recorded by private health care providers in 12 selected districts in Pakistan, 2016

History and investigations		Total n(%)	0–4 years n(%)	5-11 years n(%)	12-14 years n(%)	*p*-value
Total	All presumptive cases	**6519 (100)**	**1691 (100)**	**3214 (100)**	**1614 (100)**	< 0.0001
	Girls	2320 (35.6)	639 (37.8)	1063 (33.1)	618 (38.3)	
	Boys	4199 (64.4)	1052 (62.2)	2151 (66.9)	996 (61.7)	
Chest	Cough more than two weeks	6006 (92.1)	1560 (92.3)	2959 (92.1)	1487 (92.1)	0.974
	Failure to thrive	4210 (64.8)	1129 (66.8)	1947 (60.6)	1134 (70.3)	< 0.0001
Systemic	Fever	5794 (89.0)	1538 (91.0)	2836 (88.2)	1420 (88.0)	0.038
	Loss of body weight	504 (7.7)	115 (6.8)	237 (7.4)	152 (9.4)	0.011
	Enlarged cervical lymph nodes	785 (12.1)	147 (8.7)	389 (12.1)	249 (15.4)	< 0.0001
	BCG scar absent	1843 (28.2)	331 (19.6)	908 (28.3)	604 (37.4)	< 0.0001
Meningitis	Signs of slow onset meningitis[a]	658 (10.1)	115 (6.8)	330 (10.3)	213 (13.2)	< 0.0001
Contacts	Known pulmonary tuberculosis patient	778 (11.9)	234 (13.8)	391 (12.2)	153 (9.5)	< 0.0001

[a]Symptoms regarded as slow meningitis include headache, vomiting, irritability, lethargy, neck stiffness, bulging fontanella, coma

centre for diagnosis and treatment: 62.3% of children 0–4 years, 69.9% of children 5–11 and, 71.8% of children 5–14. Few children were notified to the NTP (187 children, 2.9%), more girls than boys (4.9% vs.1.8%,). Out of the girls referred for diagnosis, patients notified to NTP were 16 (14.2%) 0-4y, 54 (47.8%) 5-11y, and 43 (38.1%) 12-14y. Among the boys referred for diagnosis those notified were 19 (25.7%) 0-4y, 36 (48.6%) 5-11y, and 19 (25.7%) 12-14y.

The management practices of child TB patients stratified by gender is given in Table 5. Out of presumptive cases, 80.6% of girls and 79.2% of boys were diagnosed with TB. Bacteriological confirmation was noted for 244 girls and 254 boys, but the proportion of bacteriologically positives out of all the suspected cases was higher among girls (10.5%) than boys (6.0%). The NTP was notified about only a few of the children (187 children, 2.9%), with more girls than boys (4.9% vs.1.8%,). A higher proportion of girls (35.8%) with presumptive TB than boys (24.9%) were examined for sputum smear. However, referral for diagnosis was more common for boys (50.6%) than girls (43.0%).

Discussion

Our study found that almost half of the private health care providers investigating children for TB had used chest X-ray. Once suspected for TB, many were diagnosed (79.7%). Many doctors referred presumptive TB cases to NTP for further diagnosis and management. Private doctors who started TB treatment rarely (2.9%) reported the cases to NTP if they initiated treatment themselves.

This study indicated that the diagnosis of childhood TB by private providers was mainly based on clinical features, radiography and microscopy, and rarely on tuberculin skin tests, histopathology and Gene- Xpert MTB/RIF. Results from other settings has also shown that TB

Table 3 Signs and symptoms of children with presumptive tuberculosis by gender, recorded by private health care providers in 12 selected districts in Pakistan, 2016

History and investigations		Total n(%)	Female n(%)	Male n(%)	p-value
Total	All presumptive cases	**6519**	**2320**	**4199**	
Chest	Cough more than two weeks	6006 (92.1)	2102 (90.6)	3904 (93.0)	0.001
	Failure to thrive	4210 (64.8)	1644 (70.9)	2566 (61.1)	< 0.0001
Systemic	Fever	5794 (89.0)	2039 (87.9)	3755 (89.4)	0.075
	Loss of body weight	504 (7.7)	196 (8.4)	308 (7.3)	0.110
	Enlarged cervical lymph nodes	785 (12.1)	322 (13.8)	463 (11.0)	0.001
	BCG scar absent	1843 (28.2)	742 (32.0)	1101 (26.2)	< 0.0001
Meningitis	Signs of slow onset meningitis[a]	658 (10.1)	228 (9.8)	430 (10.2)	0.607
Contacts	Known pulmonary tuberculosis patient	778 (11.9)	258 (11.1)	520 (12.4)	0.121

[a]Symptoms regarded as slow meningitis include headache, vomiting, irritability, lethargy, neck stiffness, bulging fontanella, coma

Table 4 Management by private practitioners of children with presumptive tuberculosis, by age groups, in 12 selected districts in Pakistan, 2016

Practice of private health care providers		Total	0–4 years	5-11 years	12-14 years	p-value
		n(%)	n(%)	n(%)	n(%)	
Presumptive child TB		**6519**	**1691**	**3214**	**1614**	
Diagnosed TB	All	5193 (79.7)	1564 (92.4)	2545 (79.2)	1084 (67.2)	< 0.0001
	Bacteriologically positive	498 (7.6)	68 (4.0)	204 (6.3)	226 (14.0)	
	Clinically diagnosed	4695 (72.0)	1496 (88.5)	2341 (72.8)	858 (53.1)	
Notified	Notified to NTP	187 (2.9)	35 (2.1)	90 (2.8)	62 (3.8)	< 0.0001
Investigation practices	Tuberculin Skin/PPD testing	219 (3.4)	45 (2.7)	112 (3.5)	62 (3.8)	0.1464
	Sputum Smear	1875 (28.8)	242 (14.3)	910 (28.3)	723 (44.8)	< 0.0001
	X-ray	3005 (46.1)	683 (40.4)	1499 (46.6)	823 (51.0)	< 0.0001
	X-pert test	324 (5.0)	34 (2.0)	146 (4.5)	144 (8.9)	< 0.0001
	Granuloma/Histopathology	837 (12.8)	175 (10.4)	406 (12.6)	256 (15.9)	< 0.0001
	Culture	152 (2.3)	13 (0.8)	73 (2.3)	66 (4.1)	< 0.0001
Number of tests done*	Only clinical assessment	2559 (39.3)	842 (49.8)	1219 (37.9)	498 (30.9)	< 0.0001
	1 test	2217 (34.01)	574 (33.9)	1165 (36.3)	478 (29.6)	
	2 tests	1270 (19.5)	223 (13.2)	617 (19.2)	430 (26.6)	
	3 tests or more	473 (7.3)	52 (3.1)	213 (6.6)	208 (12.9)	
Management practices	Referred for TB diagnosis	3121 (47.9)	842 (49.8)	1578 (49.1)	701 (43.4)	< 0.0001
	Diagnosed and referred	2443 (37.5)	494 (29.2)	1293 (40.2)	656 (40.6)	
	Treated	955 (14.6)	355 (21.0)	343 (10.7)	257 (15.9)	
Place of referral ($n = 5564$)	District TB Centre (NTP)	3812 (68.5)	832 (62.3)	2006 (69.9)	974 (71.8)	< 0.0001
	Private laboratory	1190 (21.4)	388 (29.0)	561 (19.5)	241 (17.8)	
	Private specialist hospital/GP	562 (10.1)	116 (8.7)	304 (10.6)	142 (10.5)	

*indicates how many tests were performed to reach final diagnosis

diagnosis in children is often based on a combination of clinical symptoms and chest X-ray; this could be due to the lack of a simple and precise diagnostic tool, especially at the local level, or due to inadequate training and capacity of health care workers [8, 13–16]. In Pakistan, the availability of diagnostic tools varies across the country. Chest X-ray sand smear microscopy are almost universally available and used for TB diagnosis at peripheral levels. Histopathology, tuberculin skin test, sputum culture and Gene-Xpert MTB/RIF are only available at tertiary care hospital laboratories. Gene-Xpert MTB/RIF testing of patient stools has been shown to be a useful technique for identifying children with TB [17], and could be a good addition to traditional tests. However, in Pakistan the limited availability of such tests in rural areas makes it currently less universal.

An important finding of the study was that private health care providers referred many children with presumptive TB: 3121 (47.9%) for diagnosis and 2443 (37.5%) for treatment. They only initiated treatment in 14.6% of the diagnosed cases. Of all the referred presumptive TB cases, 3812 (68.5%) were referred for diagnosis to district NTP centres. However, only 2.9% of the referred cases were registered in the NTP registers. This large gap in reporting treatment outside the NTP system could be due to several factors: poor interdepartmental coordination between the laboratory and the treatment centres; inadequate counselling of presumptive TB patients by the laboratory technicians; and weak referral mechanisms [18–21]. The communication between laboratories and treatment centres could be improved by having regular weekly visits by district health coordinator to the laboratories, and by contacting the referring private doctor to discuss further management of cases according to the NTP guidelines. Across Pakistan, treatment services are also available in the public facilities that have diagnostic capacity. It has been reported that there may be a lack of trust in public sector to provide quality care, and thus few patients sought care in the public sector [6]. It is also possible that some referred TB patients might not actually go to NTP, and perhaps received treatment in the private sector. A similar finding is also reported in a study from Indonesia, where only 2% of childhood TB cases recorded in hospitals were reported to the NTP [22]. In Pakistan, childhood TB is managed by various providers and various levels of

Table 5 Management by private practitioners of children with presumptive tuberculosis, by gender, in 12 selected districts in Pakistan, 2016

Practice of private health care providers		Total	Female	Male	p-value
		n(%)	n(%)	n(%)	
Presumptive child TB		**6519**	**2320**	**4199**	
Diagnosed TB	All	5193 (79.7)	1869 (80.6)	3324 (79.2)	< 0.0001
	Bacteriologically positive	498 (7.6)	244 (10.5)	254 (6.0)	
	Clinically diagnosed	4695 (72.0)	1625 (70.0)	3070 (73.1)	
Notified	Notified to NTP	187 (2.9)	113 (4.9)	74 (1.8)	< 0.0001
Investigation practices	Tuberculin Skin/PPD testing	219 (4.7)	106 (4.6)	113 (2.7)	< 0.0001
	Sputum Smear	1875 (28.8)	830 (35.8)	1045 (24.9)	< 0.0001
	X-ray	3005 (46.1)	1127 (48.6)	1878 (44.7)	0.003
	X-pert test	324 (5.0)	154 (6.6)	170 (4.1)	< 0.0001
	Granuloma/Histopathology	837 (12.8)	331 (14.3)	506 (12.1)	0.010
	Culture	152 (2.3)	67 (2.9)	85 (2.0)	0.03
Number of tests done*	Only clinical assessment	2559 (39.3)	844 (36.4)	1715 (40.8)	< 0.0001
	1 test	2217 (34.01)	699 (30.1)	1518 (36.1)	
	2 test	1270 (19.5)	543 (23.4)	727 (17.3)	
	3 tests or more	473 (7.3)	234 (10.1)	239 (5.7)	
Management practices	Referred for TB diagnosis	3121 (47.9)	997 (43.0)	2124 (50.6)	< 0.0001
	Diagnosed and referred	2443 (37.5)	857 (36.9)	1586 (37.8)	
	Treated	955 (14.6)	466 (20.1)	489 (11.7)	
Place of referral (n = 5564)	District TB Centre (NTP)	3812 (68.5)	1260 (68.0)	2552 (68.8)	0.136
	Private laboratory	1190 (21.4)	386 (20.8)	804 (21.7)	
	Private specialist hospital/GP	562 (10.1)	208 (11.2)	354 (9.5)	

*indicates how many tests were performed to reach final diagnosis

the health care sector. There is an urgent need to improve communication between the NTP and other health care providers by increasing engagement in the private sector through training and capacity building on the national guidelines for managing childhood TB cases [23]. For example, mHealth could potentially accelerate TB notification from the part of private sector that is not collaborating with NTP [24, 25].

Almost all children had coughs and fever, and most had failure to thrive, which is consistent with the guidelines [23]. BCG vaccination is associated with decreased severity of tuberculosis [26] and BCG is part of the child immunization program in Pakistan A lack of a BCG scar was more common in older children, which may reflect the improved Expanded Program on Immunization (EPI) performance from 2012 to 2018. The percentage of fully immunized children aged 12–23 months increased from 54% in 2012–13 to 66% in 2017–18 [11]. Vaccination coverage inequalities exist at sub district levels, ranging from 58 to 85% in rural to urban areas and from 60 to 80% in lower to higher income quintiles [27].

In this study, we found that a higher proportion of adolescents reported respiratory symptoms, underwent sputum testing, and had bacteriological confirmation. Adolescents are important for TB control and can contribute to substantial transmission in settings such as schools. WHO suggests efforts to develop integrated family- and community-centered strategies to provide comprehensive and effective services at the community level to improve child and adolescent notification [28]. Another potential reason for this higher proportion is that adolescents are easier to test for sputum than younger children.

This study showed that failure to thrive and loss of body weight was more common in girls. This can be partly a biological difference and effect of culture and nutrition [29]. A study in India showed that the dietary intake of energy, iron, calcium and protein was significantly higher in boys than girls [30]. The slightly higher absence of BCG scar in girls could be explained by less care for girls in Pakistan, where a boy is usually more valued than a girl [31]. Similar differences in non-utilization of child immunization are reported elsewhere [32, 33].

Our study had several strengths. A major strength of this study is the large total sample with participants

from all provinces, and we believe it may reflect the diverse situation in this country. In this study, validity of the data was ensured though data quality audit by cross-checking every record from the hard copies to remove inconsistencies. Also using mobile phone for data collection reduced data entry errors by eliminating one step for database creation. This study adheres to "STROBE" guidelines for observational studies [34, 35].

The study also had some limitations. Although it had a large total sample, the number of clusters was limited to the number of provinces, giving lower precision. Despite this, it probably reflects fairly well the different situations in the country. Also, our study did not include actual observations through field assessments. so the accuracy and completeness of the data could therefore not be totally ensured. High referral to NTP centres for diagnosis may be partly because the study was closely related to NTP, and data collectors from NTP visited the study sites twice a month, and this could affect reporting, like a Hawthorne effect. The levels of childhood TB (79.7%) in this study were high compared to other settings ranging from 2.1 to 19% [36–39]. One possible reason for this is that private providers may have recorded mostly already diagnosed child TB cases on the provided registers due to their workload constraints and they may have missed an unknown number of other presumptive TB cases. The levels varied among the districts, and this may reflect variations in completeness, with different compliances with reporting all "suspects". Future research is recommended to further assess and verify these findings in the field.

Conclusion

This study showed that many private health care providers rely on NTP supported laboratories for diagnosis, but they often do not report the children diagnosed with TB to NTP. The private health providers often rely on chest X-ray in addition to clinical symptoms for diagnosis TB in children. Communication between private providers, laboratory and NTP treatment centres could and should be strengthened through training.

Abbreviations

AJK: Azad Jammu & Kashmir; BCG: Bacillus Calmette–Guérin; GB: Gilgit Baltistan; KPK: Khyber Pakhtunkhwa; NTP: National TB Control Program; PPA: Pakistan Pediatric Association; TB: Tuberculosis

Acknowledgements

We are grateful to all health care providers who participated in this study. We are thankful to the survey team in the field for their efforts and to the University of Bergen, Norway for providing a good academic background, and to the World Health Organization Eastern Mediterranean Office for funding for the main survey. We gratefully acknowledge the corporation and facilitation of National TB Control Program, Provincial TB Program Managers and Provincial Technical Officer of Punjab, Sindh, Khyber Pakhtunkhwa, Balochistan, Azad Jammu & Kashmir and Gilgit Baltistan. We thank Elinor Bartle for providing helpful input.

Authors' contributions

Conceptualization: AY; Designing of the work: AY, SGH, RF; Acquisition: AY, SGH, RF, HN, AH; Analysis of data: AY, SGH, RF, HN; Interpretation of data and results: AY, SGH, RF, HN, AH; Creation of data collection form used in the work: AY, RF, Drafted and revised the work: AY, SGH, RF, HN, AH. All authors read and approved the final version.

Funding

World Health Organization Eastern Mediterranean Office funded the main survey. No specific funding was available or obtained from any organization for this study. The publication fee for publication in an international journal is covered by University of Bergen.

Availability of data and materials

The datasets analyzed during the current study are not publicly available due to maintaining the confidentiality of participants keeping in view the ethical consideration for stigmatized infectious diseases i.e. TB, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The ethical clearance (registration # NBC 192 given in 2015) was obtained from the Pakistan Medical and Research Council, REK Vest in Norway (# 2018/56), as well as the WHO Ethics Committee for the East-Mediterranean region. Informed consent was waived by the ethics committee, as all data used had been previously collected during the child inventory study and did not pose any additional risks to the patients. Permission to use the data was obtained from the program manager of the National TB control program, Islamabad, Pakistan.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Common Management Unit (HIV/AIDS, TB & Malaria), Block F, EPI Building, Near National Institute of Health (NIH) (Prime Minister's National Health Complex), Park Road, Islamabad, Pakistan. [2]University of Bergen, Bergen, Norway. [3]Health Services Academy, Islamabad, Pakistan. [4]Ministry of National Health Services Regulation & Coordination, Government of Pakistan, Islamabad, Pakistan.

Received: 28 March 2020 Accepted: 10 December 2020
Published online: 07 January 2021

References

1. World Health Organization. Global Tuberculosis Report 2019. Geneva: WHO; 2019.
2. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd ed. Geneva: WHO; 2014.
3. Hamzaoui A, Yaalaoui S, Cherif FT, Saidi LS, Berraies A. Childhood tuberculosis: a concern of the modern world. Eur Respir Rev. 2014;23:278–91.
4. World Health Organisation. Engaging private health care providers in TB care and prevention: a landscape analysis. Geneva: WHO; 2018.
5. National TB Control Program. National guidelines for diagnosis and management of tuberculosis in children 2006–07. Islamabad, Pakistan; 2007.
6. Fatima R, Haq MU, Yaqoob A, Mahmood N, Ahmad KL, Osberg M, et al. Delivering patient-centered Care in a Fragile State: using patient-pathway analysis to understand tuberculosis-related care seeking in Pakistan. J Infect Dis. 2017;216:S733–9.
7. Khan AJ, Khowaja S, Khan FS, Qazi F, Lotia I, Habib A, et al. Engaging the private sector to increase tuberculosis case detection: an impact evaluation study. Lancet Infect Dis. 2012;12:608–16.
8. Detjen A, M G, Sm G, C S. Improving the estimates of childhood TB disease burden and assessing childhood TB activities at country level. Geneva: WHO; 2018.
9. Fatima R, Yaqoob A, Qadeer E, Hinderaker SG, Ikram A, Sismanidis C. Measuring and addressing the childhood tuberculosis reporting gaps in

Pakistan: The first ever national inventory study among children. PloS one. 2019;14(12):e0227186.
10. Pakistan Bureau of Statistics. 6th Population and Housing Census 2017. Islamabad: Government of Pakistan; 2017.
11. National Institute of Population Studies. Pakistan: Demographic and Health Survey 2017–18.Government of Pakistan. Islamabad: Ministry of Health; 2019.
12. Yu P, de Courten M, Pan E, Galea G, Pryor J. The development and evaluation of a PDA-based method for public health surveillance data collection in developing countries. Int J Med Inform. 2009;78:532–42.
13. Shingadia D, Novelli V. Diagnosis and treatment of tuberculosis in children. Lancet Infect Dis. 2003;3:624–32.
14. Cruz AT, Starke JR. Clinical manifestations of tuberculosis in children. Paediatr Respir Rev. 2007;8:107–17.
15. Kumar MK, Kumar P, Singh A. Recent advances in the diagnosis and treatment of childhood tuberculosis. J Nat Sci Biol Med. 2015;6:314–20.
16. World Health Organization. best practices in child and adolescent tuberculosis care. Geneva: WHO; 2018.
17. MacLean E, Sulis G, Denkinger CM, Johnston JC, Pai M, Khan FA. Diagnostic accuracy of stool Xpert MTB/RIF for detection of pulmonary tuberculosis in children: a systematic review and meta-analysis. Journal of clinical microbiology. 2019;57(6).
18. Wali A, Kumar AMV, Hinderaker SG, Heldal E, Qadeer E, Fatima R, et al. Pre-treatment loss to follow-up among smear-positive TB patients in tertiary hospitals, Quetta, Pakistan. Public Heal Action. 2017;7:21–5.
19. Ram S, Kishore K, Batio I, Bissell K, Zachariah R, Satyanarayana S, et al. Pre-treatment loss to follow-up among smear-positive pulmonary tuberculosis cases: a 10-year audit of national data from Fiji. Public Heal Action. 2012;2:138–41.
20. Hinderaker SG, Fatima R. Lost in time and space: the outcome of patients transferred out from large hospitals. Public Heal Action. 2013;3:2–2.
21. Fatima R, Ejaz Q, Enarson DA, Bissell K. Comprehensiveness of primary services in the care of infectious tuberculosis patients in Rawalpindi, Pakistan. Public Heal Action. 2011;1:13–5.
22. Lestari T, Probandari A, Hurtig AK, Utarini A. High caseload of childhood tuberculosis in hospitals on Java Island, Indonesia: a cross sectional study. BMC public health. 2011;11(1):784.
23. National TB Control Program. Revised: DOCTOR'S DESK GUIDE MANAGEME NT OF CHILDHOOD TUBERCULOSIS. Islamabad: Ministry of Health; 2017.
24. Hirsch-Moverman Y, Daftary A, Yuengling KA, Saito S, Ntoane M, Frederix K, et al. Using mhealth for HIV/TB treatment support in Lesotho: enhancing patient-provider communication in the start study. J Acquir Immune Defic Syndr. 2017;74:S37–43.
25. Kundu D, Chopra K, Khanna A, Babbar N, Padmini TJ. Accelerating TB notification from the private health sector in Delhi, India. Indian J Tuberc. 2016;63:8–12.
26. Hasan Z, Irfan M, Khan JA, Jahangir SK, Haris M, Ashraf M, et al. BCG vaccination is associated with decreased severity of tuberculosis in Pakistan. Int J Mycobacteriology. 2012;1:201–6.
27. Khowaja AR, Zaman U, Feroze A, Rizvi A, Zaidi AKM. Routine EPI coverage: subdistrict inequalities and reasons for immunization failure in a rural setting in Pakistan. Asia-Pacific J Public Heal. 2015;27:1050–9.
28. World Health Organization. Roadmap towards ending TB in children and adolescents Second edition. Geneva: WHO; 2018.
29. Mauvais-Jarvis F, Bairey Merz N, Barnes PJ, Brinton RD, Carrero J-J, DeMeo DL, et al. Sex and gender: modifiers of health, disease, and medicine. Lancet. 2020;396:565–82.
30. Kaur M, Kaur R, Walia P. Exploring gender disparity in nutritional status and dietary intake of adolescents in Uttarkashi. Indian J Hum Dev. 2020;14:115–27.
31. Bugvi AS, Rahat R, Zakar R, Zakar MZ, Fischer F, Nasrullah M, Manawar R. Factors associated with non-utilization of child immunization in Pakistan: evidence from the Demographic and Health Survey 2006-07. BMC public health. 2014;14(1):232.
32. Pande RP. Selective gender differences in childhood nutrition and immunization in rural India: the role of siblings. Demography. 2003;40:395–418.
33. Taiwo L, Idris S, Abubakar A, Nguku P, Nsubuga P, Gidado S, Okeke L, Emiasegen S, Waziri E. Factors affecting access to information on routine immunization among mothers of under 5 children in Kaduna State Nigeria, 2015. Pan African Medical Journal. 2017;27(1).
34. Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. PLoS Med. 2007;4:1628–54.
35. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg. 2014;12:1495–9.
36. Jaganath D, Zalwango S, Okware B, Nsereko M, Kisingo H, Malone LS, et al. Contact investigation for active tuberculosis among child contacts in Uganda. Clin Infect Dis. 2013;57:1685–92.
37. Fairlie L, Muchiri E, Beylis CN, Meyers T, Moultrie H. Microbiological investigation for tuberculosis among HIV-infected children in Soweto, South Africa. Int J Tuberc Lung Dis. 2014;18:676–81.
38. Tadesse Y, Gebre N, Daba S, Gashu Z, Habte D, Hiruy N, et al. Uptake of isoniazid preventive therapy among under-five children: TB contact investigation as an entry point. PLoS One. 2016;11:1–11.
39. Bonnet M, Kyakwera C, Kyomugasho N, Atwine D, Mugabe F, Nansumba M, et al. Prospective cohort study of the feasibility and yield of household child tuberculosis contact screening in Uganda. Int J Tuberc Lung Dis. 2017;21:862–8.

Publisher's Note

III

Paper III

International Journal of Infectious Diseases 107 (2021) 291–297

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Diagnosis of childhood tuberculosis in Pakistan: Are national guidelines used by private healthcare providers?

Aashifa Yaqoob[a,b,*], Sven Gudmund Hinderaker[b], Razia Fatima[a], Hemant D. Shewade[c,d], Nadia Nisar[e], Ahmed Wali[f]

[a] Common Management Unit (TB, HIV/AIDS and Malaria), Islamabad, Pakistan
[b] University of Bergen, Bergen, Norway
[c] Centre for Operational Research, International Union Against Tuberculosis and Lung Disease (The Union), Paris, France
[d] The Union South-East Asia Office, New Delhi, India
[e] Public Health England, Islamabad, Pakistan
[f] Provincial TB Control Program, Quetta, Pakistan

ARTICLE INFO

Article history:
Received 31 January 2021
Received in revised form 12 April 2021
Accepted 15 April 2021

Keywords:
Tuberculosis
Children
Diagnosis
Guidelines
PPA scoring chart
Private providers
Pakistan

ABSTRACT

Background: The National Tuberculosis Control Program (NTP) in Pakistan developed, with the Pakistan Paediatric Association, a pediatric scoring chart to aid diagnosis of childhood tuberculosis (TB). Our study compared the diagnostic practice of private healthcare providers in Pakistan with the NTP guidelines.
Methods: A cross-sectional study comparing diagnosis of TB in children <15 years by Non-NTP private providers with the NTP's pediatric scoring chart. A generalized linear model was used to determine the difference in adherence by Non-NTP private providers to the NTP guidelines for childhood TB diagnosis by associated factors.
Results: A total of 5193 (79.7% of presumptive childhood TB cases identified in the selected districts during the study) children were diagnosed with TB by Non-NTP private providers. A strong clinical suspicion of TB was present in 17.3%, and chest x-ray was suggestive of TB in 34.3%. The Kappa score between Non-NTP private providers and the NTP guidelines for diagnosing TB was 0.152. Only 47.8% of cases were diagnosed in line with the NTP guidelines. Children <5 years old with a history of TB contact had a higher chance of being diagnosed according to the NTP guidelines.
Conclusion: This study indicates a low adherence of NTP guidelines for diagnosing childhood TB by private providers in Pakistan.

Introduction

Globally, nearly 600 children die of tuberculosis (TB) each day. Of the 1 million children estimated to have developed active TB in 2019, approximately 70% were either undetected or incorrectly diagnosed by healthcare providers (World Health Organization, 2020). The management of TB in children <15 years remains a challenge due to non-specific symptoms and difficult diagnosis. Despite advances in TB diagnosis, no diagnostic tool has been proven to be sufficiently sensitive and specific for childhood TB (Cartaxo et al., 2014; Coghlan et al., 2015; Detjen et al., 2018). The use of Xpert MTB/RIF© assay in stool samples has been explored to diagnose pulmonary TB in children (Kabir et al., 2020). Because of the challenges in diagnosing childhood TB, different diagnostic approaches, such as point-scoring systems, diagnostic classifications and diagnostic algorithms, have also been used; however, none are used routinely (Cartaxo et al., 2014; Pearce et al., 2012).

The diagnosis of TB in children is more difficult and challenging in resource-constrained countries like Pakistan. It is primarily based on a history of contact with a TB case, in addition to clinical and radiological findings, often without microbiological confirmation. Challenges in diagnosis are compounded by under-reporting by private healthcare providers (Non-NTP private providers), with estimates that 78% of childhood TB cases are not reported to the National TB Control Program (NTP) by Non-NTP private providers (Fatima et al., 2019).

The present study aimed to evaluate the practices of Non-NTP private providers in 12 districts across Pakistan in the diagnosis of childhood TB against the diagnostic guidelines recommended by the NTP. Our objectives were to describe: (1) the proportion of diagnosed patients among presumptive cases; (2) the Pakistan

* Corresponding author at: Department of Global Public Health and Primary Care, University of Bergen, Norway.
E-mail address: Aashifa.Yaqoob@uib.no (A. Yaqoob).

https://doi.org/10.1016/j.ijid.2021.04.055

Paediatric Association (PPA) scores in the presumptive cases; (3) the Non-NTP private providers adherence to the NTP guidelines for the diagnosis of childhood TB.

Methods

Study design

We undertook a cross-sectional descriptive study involving secondary data.

Study setting

General setting

Pakistan ranks 5th globally in countries with the highest TB burden. In 2018, Pakistan had approximately 562 000 active TB cases, and TB was the 9th leading cause of death in Pakistan (WHO, 2018). Approximately 361 000 TB cases (all ages, all forms) were notified in Pakistan in 2018, with 32% of notifications coming from the Non-NTP private providers. Administratively, Pakistan (population: 208 million in 2017) is divided into four provinces (Balochistan, Khyber Pakhtunkhwa, Punjab and Sindh) and two regions (Gilgit Baltistan and Azad Jammu, and Kashmir), which are subdivided into 144 districts (Pakistan Bureau of Statistics, 2017). The private healthcare sector is large and unregulated in Pakistan. The sector includes teaching hospitals and universities, general practitioner clinics, polyclinics, health facilities run by various charitable groups, and informal health providers. Less than 1% of Non-NTP private providers are engaged with the NTP.

Diagnostic tools for childhood tuberculosis in Pakistan

During 2006–7, the NTP developed its national childhood TB policy guidelines in collaboration with the PPA (National TB Control Program, 2007). The PPA scoring chart (see Table 1) aims to facilitate and standardize clinical decisions for screening children with presumptive TB. Scoring was based on clinical, histological and radiological features, categorized into TB unlikely, possible or probable. The NTP presented a diagnostic algorithm (revised 2019) in the guidelines to facilitate the case management process (Figure 1).

Study population

For national representation, 12 districts in Pakistan were randomly selected based on probability proportional to population size of annual notified children per million population in the districts of all provinces and regions (Fatima et al., 2019). Districts with security concerns were excluded from the sampling frame. All private healthcare facilities that managed childhood TB in the 12 selected districts were included (Fatima et al., 2019); practitioners, including pediatric specialists, general practitioners, chest physicians and medical specialists, were mapped, and those in the consenting facilities were enrolled in the study.

The study period was April to June 2016, and the study population included all children <15 years in the 12 selected districts suspected of having TB after consulting with a PP. The data formed part of the national childhood TB inventory study (Fatima et al., 2019).

Data collection and variables

Under the national childhood TB inventory study (April–June 2016), a surveillance system was established among all PP facilities (Fatima et al., 2019).

To capture case history, investigation and management of presumptive TB cases by Non-NTP private providers, a register was introduced in health facilities diagnosing childhood TB to record information without changing their practices. All healthcare providers who participated in the study were trained to enter the required information in the provided registers. To reduce data entry errors, data from paper-based registers were captured through a mobile phone application developed by a mobile service provider (Yu et al., 2009). Field officers were asked to capture this data when visiting the health facilities every week. Data included PPA score, diagnosis by PP, district, and baseline characteristics of presumptive childhood TB cases. As shown in the Box 1, the PPA

Table 1
Scoring chart for the diagnosis of childhood tuberculosis (<15 y) recommended by the Pakistan Paediatric Association (PPA) & National TB programme.

Condition	Scores				
	1	2	3	4	5
Age	<5 years				
Close contact[a]	TB suggestive	Clinically positive	Bacteriological positive		
PEM/SAM[b]	Yes	Not responding to Nutritional rehabilitation for 02 months			
H/O Measles, Whooping Cough	3–6 months	<3 months			
HIV		Yes			
Immunocompromised[c]	Yes			Not improved	
Clinical Manifestation[d]		Suggestive		Strongly Suggestive	
Radio Diagnostic Imaging[e]	Non-specific	Suggestive	Strongly suggestive		
Tuberculin skin test	5–10 mm		>10 mm		
GeneXpert MTB/RIF					Positive
Microscope examination of tissue	Non-specific				Positive

[a] Close contact: History of cough for more than 2 weeks among the household member of the child.
[b] PEM/SAM (Protein Energy Malnutrition/Severe acute malnutrition: Use WHO Recommended Z. scoring chart (1) & Not responding to Nutritional rehabilitation for 02 months (2).
[c] Immunocompromised status: Malignancies like leukemia or lymphomas etc, Immunodeficiency diseases like agammaglobunemiaetc. Chemotherapy /Immunosuppressive therapy such as steroids for more than 2 weeks.
[d] Clinical Manifestation: Suggestive of TB: Pulmonary Findings (unilateral wheeze, dullness, weight loss, Hepato-splenomegaly, Lymphadenopathy, ascites etc. Strongly suggestive of TB: Matted lymph nodes, abdominal mass or doughy abdomen, sinus formation, gibbus formation, chronic mono arthritis, meningeal findings (bulging fontanel, irritability, choroid tubercle, papilloedema).
[e] Radio-Diagnostic/ imaging studies includes Chest X-ray, CT Chest/MRI. Non-specific signs: Ill-defined opacity or patchy infiltrates on chest X-Ray, Marked bronchovacular marking. Signs suggestive of TB: Consolidation not responding to antibiotic therapy, Para-tracheal, or mediastinal Lymphadenopathy,Miliary Mottling, cavitation.

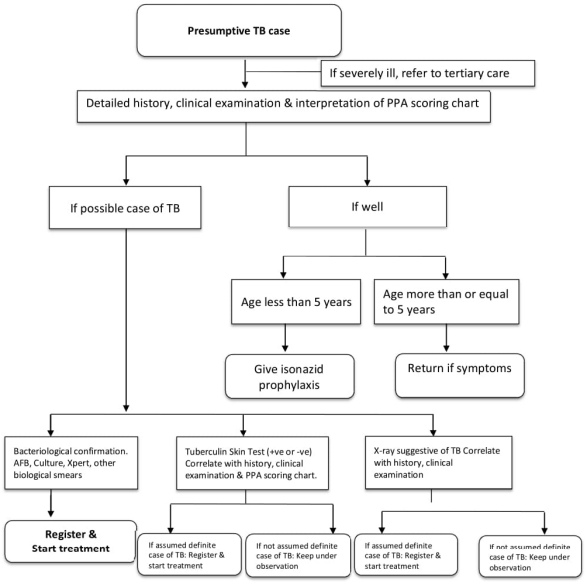


Figure 1. Flow chart for evaluation of a child (<15 y) with presumptive tuberculosis, recommended by the National TB programme.
TB = Tuberculosis; PPA = Pakistan Pediatric Association; CXR = chest radiograph; TST = tuberculin sensitivity testing.

Box 1. Interpretation of Pakistan Paediatric Association (PPA) scores for the diagnosis of childhood tuberculosis (<15 y).

Score	Interpretation	Suggested Actions
0–2	Unlikely TB	Investigate other reasons of illness
3–4	Possible TB	-Do not treat for TB -Manage the presenting symptom(s) -Monitor monthly the condition(s) for 3 months, using scoring chart
5–6	Possible TB	-Investigate and exclude other causes of illness -Investigation may justify therapy
7 or more	Probable TB	- Confirm (if possible)

score is based on various items, including levels of clinical suspicion. The district TB coordinators undertook monitoring visits with a provincial coordinator, supervisor and field officer to ensure the quality of data collected (completeness, correctness) for accurate record linkage and cross-checking of the NTP registration status.

Data analysis

We described the baseline characteristics of presumptive childhood TB cases and the proportion of those diagnosed as TB by Non-NTP private providers. PPA scores were compared with TB diagnosis by Non-NTP private providers. The kappa statistic was calculated to evaluate the agreement between diagnosis by the Non-NTP private providers and the NTP guidelines using PPA scoring (Landis and Koch, 1977). Analysis was done to describe the PPA scores to diagnose childhood TB. The diagnosis of the Non-NTP private providers was compared with the PPA scoring chart to measure the adherence to NTP guidelines for the diagnosis of childhood TB. The factors associated with non-adherence to the national guidelines were summarized using adjusted prevalence ratios (95% CI). Adjusted analysis was done using a generalized

Table 2
Children with presumptive and diagnosed tuberculosis identified by private health providers in 12 districts of Pakistan, 2016.

Province	District	Presumptive TB	Diagnosed TB	
		N	n	(%)[a]
All sites		6519	5193	(79.7)
Punjab	Attock	497	442	(88.9)
	Chiniot	671	337	(50.2)
	Hafizabad	874	555	(63.5)
	Vehari	376	333	(88.6)
Sindh	Shikarpur	623	394	(63.2)
	Hyderabad	838	838	(100)
	Karachi	1041	942	(90.5)
KPK	Buner	232	148	(63.8)
	Peshawar	1034	999	(96.6)
AJK	Pallundary	118	114	(96.6)
Balochistan	Jhal Magsi	44	27	(61.4)
GB	Ghizer	171	64	(37.4)

KPK = Khyber Pakhtunkhwa, AJK = Azad Jammu & Kashmir, GB = Gilgit Baltistan.
[a] "Diagnosed TB" with proportion out of all presumptive patients.

linear model. Age, gender, district and being a close contact of a TB patient were included in the model. With our large sample size, we assessed for programmatic significance ($\geq$1.5 or $\leq$0.7) and interpreting statistical significance ($P < 0.05$) (Fonseca Martinez et al., 2017). Analysis was done in STATA version 14.

Results

Table 2 shows that among 6519 presumptive childhood TB cases were identified by Non-NTP private providers in our study area during the study period, 5193 (79.7%) were diagnosed as TB by the Non-NTP private providers; this varied from 37.4%–100% across districts. Characteristics of children suspected of having TB who were assessed with the PPA scoring chart are given in Table 3. Of 6519 presumptive childhood TB cases, 32.1% were <5 years of age. Strong clinical suspicion of TB was present in 17.3%; chest x-ray was suggestive of TB in 34.3%. Table 4 shows the comparison of the PPA score categories and the diagnosis set by Non-NTP private providers indicating 30% of children were highly possible or probable TB cases according to their PPA score. A large proportion of those with a PPA score of 1–4 were diagnosed with TB. Table 5 presents a comparison of diagnostic practices of Non-NTP private providers with the PPA scoring chart. According to the PPA scoring chart, 1910 (36.8%) were categorized as TB cases. The Kappa score between the Non-NTP private providers diagnoses and PPA-scored diagnoses was 0.152 (95% CI 0.140–0.165). Table 6 describes some factors associated with adherence to the NTP guidelines. Only 47.8% of the Non-NTP private providers followed the guidelines. Children <5 years old with a history of TB contact had a higher chance of being diagnosed according to the NTP guidelines.

Table 3
Baseline assessment and PPA score of children with presumptive tuberculosis identified by private health providers in 12 districts of Pakistan, 2016.

Characteristics of children	n	(%)*
Total	6519	(100)
Age (year)		
0–4	2090	(32.1)
5–14	4429	(67.9)
Close contact of TB patient in last 2 years		
TB patients Bacteriological positive	778	(11.9)
TB patients Bacteriological Negative	709	(10.9)
No TB contact	2611	(40.1)
Missing	2421	(37.1)
Loss of body weight		
Yes	504	(7.7)
Missing	6015	(92.3)
H/O Measles, Whooping Cough		
Missing	6519	(100)
HIV		
Missing	6519	(100)
Immunocompromised		
Missing	6519	(100)
Clinical Manifestation		
Suggestive	3352	(51.4)
Strongly suggestive	1128	(17.3)
Not suggestive	2039	(31.3)
Radio Diagnostic imaging		
Suggestive of TB	2235	(34.3)
Non-TB specific	770	(11.8)
Missing	3514	(53.9)
Tuberculin skin test		
5–10 mm	155	(2.4)
More than 10 mm	64	(1.0)
Missing	6300	(96.6)
Sputum (or induced sputum or gastric lavage) smear microscopy		
Positive	545	(8.4)
Negative	1330	(20.4)
Missing	4644	(71.2)
Xpert MTB/RIF		
NAAT MTB detected	130	(2.1)
Not detected	194	(3.1)
Missing/not applicable	6195	(95.0)
Culture		
Positive	36	(0.6)
Negative	116	(1.8)
Missing / not applicable	6367	(97.7)
Histopathology Examination		
Non-TB specific	296	(4.5)
Consistent with TB (microscope examination of tissue)	541	(8.3)
Missing / not applicable	5682	(87.2)
PPA score		
Unlikely TB (0–2)	3068	(47.1)
Possibly TB (3–4)	1443	(22.1)
Highly Possibly TB (5–6)	839	(12.9)
Probably TB ($\geq$7)	1169	(17.9)

NAAT = Nucleic Acid Amplification Testing.

Discussion

This study documents practices among Non-NTP private providers of childhood TB diagnosis, highlighting low adherence to the NTP guidelines in Pakistan. Results indicated that a strong clinical suspicion of TB was present in 17.3% of the children, and chest x-ray was suggestive of TB in 34.3%. According to the PPA score, 30% of the children were suspected as highly possible or probable TB cases. Only 47.8% of the Non-NTP private providers diagnosed childhood TB in accordance with the PPA scoring chart. Children <5 years old with a history of TB contact had a higher chance of being diagnosed according to the national guidelines.

In 2006, the NTP, in collaboration with PPA, prepared guidelines for early diagnosis and management of TB in children. A few studies in Pakistan provide evidence on the effectiveness of the PPA scoring chart to identify cases of childhood TB at an early stage (Ayesha Mehnaz, 2006; Mehnaz and Arif, 2005; Safdar et al., 2010). In the public health sector, these guidelines were implemented; however, in Pakistan, almost 90% of patients initiate care in the private sector. Less than 5% of Non-NTP private providers are effectively engaged with the NTP, accounting for only 15% of the facilities with capacity for TB diagnosis and treatment (Fatima et al., 2017). The current study revealed that utilization of the national guidelines was low nationally. There is an urgent need to improve linkages between the NTP and the private sector through engaging, training and capacity building on the national guidelines for managing childhood TB cases to improve TB care in Pakistan.

An important finding of the study was that Non-NTP private providers often diagnosed childhood TB but were not following the NTP guidelines. Reasons for this non-adherence were not identified

Table 4
Diagnosis by private health care providers and the corresponding PPA scores for children (0–15 y) with presumptive tuberculosis in 12 districts of Pakistan, 2016.

	PPA score				
Diagnosis by private providers	Unlikely TB (0–2)	Possible TB (3–4)	Highly possible TB (5–6)	Probable TB (>6)	Total
Childhood TB case	2,122 (69.5)	1,161 (81.2)	769 (91.7)	1,141 (97.6)	5193
Not a TB case	931 (30.5)	269 (18.8)	70 (8.3)	27 (2.4)	1297
Total	3,053 (100)	1,430 (100)	839 (100)	1,168 (100)	6,519

Table 5
Diagnosis recorded by private providers versus diagnosis based on PPA score on children with presumptive tuberculosis identified in 12 districts of Pakistan, 2016.

	TB based on PPA score		
TB diagnosis	Yes (≥5)	No (0–4)	Total
Yes	1910 (95.2)[c] (36.8)[r]	3,283 (73.2)[c] (63.2)[r]	5,193 (X%) (100)
No	97 (4.8)[c] (7.5)[r]	1,200 (26.8)[c] (92.5)[r]	1297 (x%) (100)
Total	2007 (100) (Y%)	4483 (100) (Y%)	6519

[c] column percentage.
[r] row percentage.

in this study; however, we speculate that a lack of awareness and a weak partnership/collaboration between the Non-NTP private providers and the NTP are potential reasons. A misdiagnosis of childhood TB could be challenging for the individuals and their community. At an individual level, there may be adverse impacts from treating patients and taking the drugs every day is a burden for the family. At the community level, a misdiagnosis could increase the financial burden and stigma due to unnecessary investigation and traveling to healthcare facilities for investigation and/or treatment. Communication between the NTP and Non-NTP private providers needs to be improved in both directions: guidelines and training for childhood TB need to reach all stakeholders, and providers outside the NTP need to implement the guidelines and report childhood TB cases to the program. It may be included in the regular visits of the District TB coordinators to facilities that report TB cases for discussion with the responsible person.

Our study indicates that adherence to the NTP guidelines in the diagnosis of childhood TB cases varied and was generally inadequate in the study area, which may be due to a lack of knowledge. A systematic review of the management of TB by healthcare practitioners in Pakistan (Braham et al., 2018) also suggested poor standards of care and knowledge. Another reason for variation in adherence to the guidelines across the different districts is that treatment facilities available at health centers, especially in the rural areas, are limited and ineffective. There are inherent problems with the system of patient referral to a facility with directly observed treatment short-course services (DOTS), and the private sector is not fully involved in the implementation of these services. However, many private practitioners and government health workers are poorly trained in diagnosing and treating TB and lack the communication skills required to motivate patients towards increased compliance (Mushtaq et al., 2011). We believe the shortcomings shown in this study represent the whole country and improvement could be achieved through better training of practitioners, greater availability of recommended diagnostic tools and PPA scoring charts, and expansion of public-private partnerships.

The study had several strengths. The study area was reasonably representative of Pakistan, involving all provinces, and included all children with presumptive TB who approached Non-NTP private providers for diagnosis and treatment. To improve the study's validity, data quality was audited, removing inconsistencies by

Table 6
Generalized linear model for factors associated with adherence to national guidelines for the diagnosis of childhood TB by private health providers in 12 districts of Pakistan, 2016.

Variables		Presumptive childhood TB	Adherence of guidelines n (%)	Adjusted prevalence ratio	(95% CI)
Overall		**6519**	**3110 (47.8)**		
Sex	Male	4199	1903 (45.3)	Ref.	
	Female	2320	1207 (52.0)	1.10	(1.04–1.15)
Age group	0–4	1691	1020 (60.3)	1.23	(1.15–1.31)
	5–11	3214	1341 (41.7)	0.95	(0.89–1.00)
	12–14	1614	749 (41.7)	Ref.	
Area					
Punjab	Attock	497	118 (23.7)	0.75	(0.64–0.88)
	Chiniot	671	448 (66.8)	1.81	(1.64–1.98) *
	Hafizabad	874	363 (41.5)	1.12	(1.00–1.25)
	Vehari	376	149 (39.6)	0.99	(0.85–1.16)
Sindh	Shikarpur	623	484 (77.7)	1.92	(1.74–2.12) *
	Hyderabad	838	100 (11.9)	0.30	(0.25–0.37) *
	Karachi	1041	728 (69.9)	1.75	(1.59–1.92) *
KPK	Buner	232	165 (71.1)	1.94	(1.73–2.18) *
	Peshawar	1034	330 (31.9)	Ref.	
AJK	Pallundary	118	71 (60.2)	1.58	(1.34–1.86) *
Baloschistan	Jhal Magsi	44	35 (79.6)	2.18	(1.88–2.53) *
GB	Ghizer	171	119 (69.6)	1.80	(1.58–2.05) *
Close contact of TB patient	TB patient	1487	992 (66.7)	1.39	(1.32–1.47)
	No TB contact	5032	2118 (42.1)	Ref.	

cross-checking every record from the hard copies; a mobile phone application was used for data entry to avoid input errors. The study also has several limitations. All demographic, clinical and radiographic data of presumptive childhood TB patients were collected from registers, and diagnostic practices of Non-NTP private providers were retrospectively assessed so that the accuracy and completeness of the data could not be ensured. The proportion of examinees diagnosed with TB (79.7%) in this study was high compared to other settings, where they ranged from 2.1% to 19% (Bonnet et al., 2017; Fairlie et al., 2014; Jaganath et al., 2013; Tadesse et al., 2016). One possible reason for this high yield is that Non-NTP private providers may have recorded most cases on the provided registers post x-ray or when there was already a strong suspicion of childhood TB; this may have missed an unknown number of other presumptive TB cases. The proportion of TB among examined patients varied among the districts, which may reflect a variation in the completeness of reporting of "suspects". Future research is recommended to further assess and verify these findings in the field. Further research is also required into treatment practices, including the drug dosages being prescribed by practitioners.

Although scoring systems with a moderate case yield are less prone to extreme diagnostic error, in the absence of a gold standard, the predictive value of any one system cannot be determined (Hatherill et al., 2010; The Union, 2016). However, the findings of this study should not undermine confidence in existing national guidelines using the PPA scoring chart. Instead, innovative research and critical analysis should be encouraged to search for improved diagnostics for childhood TB.

Conclusion

This study highlights the low utilization of the NTP guidelines by Non-NTP private providers for the diagnosis of childhood TB in Pakistan. There is an urgent need to focus on advocacy at all levels and strengthen the public-private partnership. The NTP should regularly conduct training on the national guidelines and engage with the private sector to address specific gaps in diagnosis and treatment.

Funding source

World Health Organization's headquartersfunded the main survey. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of this manuscript. No specific funding was available or obtained from any organization for this study. The publication fee for publication in an international journal is covered by the University of Bergen.

Conflict of interest

None to declare

Ethics

Ethical clearance (registration # NBC 192 given in 2015) was obtained from the Pakistan Medical and Research Council, as well as the World Health Organization Ethics Committee for the East-Mediterranean region, from the ethics committee in Norway (2018/56/REK vest), and local ethical clearance was also obtained from Institutional Review Board ethics committee, common management unit (HIV, TB and Malaria). Informed consent was waived by the ethics committee, as all data used had been previously collected during the child inventory study and did not pose any additional risks to the patients.

Acknowledgments

We highly acknowledge the role and contribution of the University of Bergen, Norway, for providing a good academic background and developing the research capacity. We are thankful to the World Health Organization's headquarters and Pakistan national office for providing technical support and funding the main project. We are grateful to all healthcare providers who participated in this study. We are grateful to all survey field and central staff (research unit) and NTP management for continued support. We highly acknowledge the cooperation and facilitation of the National TB Control Program, Provincial TB Program Managers and Provincial Technical Officers of Punjab, Sindh, Khyber Pakhtunkhwa, Balochistan, Azad Jammu and Kashmir and Gilgit Baltistan.

References

Mehnaz Ayesha. Tuberculosis in children. JPMA 2006;56:390–1, doi:http://dx.doi.org/10.1016/j.pcl.2017.03.010.

Bonnet M, Kyakwera C, Kyomugasho N, Atwine D, Mugabe F, Nansumba M, et al. Prospective cohort study of the feasibility and yield of household child tuberculosis contact screening in Uganda. Int J Tuberc Lung Dis 2017;21:862–8, doi:http://dx.doi.org/10.5588/ijtld.16.0889.

Braham CA, White PJ, Arinaminpathy N. Management of tuberculosis by healthcare practitioners in Pakistan: a systematic review. PLoS One 2018;13:, doi:http://dx.doi.org/10.1371/journal.pone.0199413.

Cartaxo CGB, Rodrigues LC, Braga CP, Ximenes RA de A. Measuring the accuracy of a point system to diagnose tuberculosis in children with a negative smear or with no smear or culture. J Epidemiol Glob Health 2014;4:29–34, doi:http://dx.doi.org/10.1016/j.jegh.2013.10.002.

Coghlan R, Gardiner E, Amanullah F, Ihekweazu C. Understanding market size and reporting gaps for paediatric TB in Indonesia, Nigeria and Pakistan: supporting improved treatment of childhood TB in the advent of new medicines. PLoS One 2015;10:1–12, doi:http://dx.doi.org/10.1371/journal.pone.0138323.

Detjen A, M G, Sm G, C S. Improving the estimates of childhood TB disease burden and assessing childhood TB activities at country level. Geneva, Switzerland: WHO; 2018.

Fairlie L, Muchiri E, Beylis CN, Meyers T, Moultrie H. Microbiological investigation for tuberculosis among HIV-infected children in Soweto, South Africa. Int J Tuberc Lung Dis 2014;18:676–81, doi:http://dx.doi.org/10.5588/ijtld.13.0839.

Fatima R, Haq MU, Yaqoob A, Mahmood N, Ahmad KL, Osberg M, et al. Delivering patient-centered care in a fragile state: using patient-pathway analysis to understand tuberculosis-related care seeking in Pakistan. J Infect Dis 2017;216:S733–9, doi:http://dx.doi.org/10.1093/infdis/jix380.

Fatima R, Yaqoob A, Qadeer E, Hinderaker SG, Ikram A, Sismanidis C. Measuring and addressing the childhood tuberculosis reporting gaps in Pakistan: the first ever national inventory study among children. PLoS One 2019;14:e0227186, doi:http://dx.doi.org/10.1371/journal.pone.0227186.

Fonseca Martinez BA, Leotti VB, Silva G de Se, Nunes LN, Machado G, Corbellini LG. Odds ratio or prevalence ratio? An overview of reported statistical methods and appropriateness of interpretations in cross-sectional studies with dichotomous outcomes in veterinary medicine. Front Vet Sci 2017;4:, doi:http://dx.doi.org/10.3389/fvets.2017.00193.

Hatherill M, Hanslo M, Hawkridge T, Little F, Workman L, Mahomed H, et al. Sistemas estructurados de cribado y diagnóstico de la tuberculosis infantil en una región de alta prevalencia de Sudáfrica. Bull World Health Organ 2010;88:312–20, doi:http://dx.doi.org/10.2471/BLT.09.062893.

Jaganath D, Zalwango S, Okware B, Nsereko M, Kisingo H, Malone LS, et al. Contact investigation for active tuberculosis among child contacts in Uganda. Clin Infect Dis 2013;57:1685–92, doi:http://dx.doi.org/10.1093/cid/cit645.

Kabir S, Rahman SMM, Shakil Ahmed, Islam MS, Banu RS, Shewade HD, et al. Xpert ultra assay on stool to diagnose pulmonary tuberculosis in children. Clin Infect Dis 2020;, doi:http://dx.doi.org/10.1093/cid/ciaa583.

Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159, doi:http://dx.doi.org/10.2307/2529310.

Mehnaz A, Arif F. Applicability of scoring chart in the early detection of tuberculosis in children. J Coll Physicians Surg Pakistan 2005;15:543–6 https://doi.org/09.2005/JCPSP.543546.

Mushtaq MU, Shahid U, Abdullah HM, Saeed A, Omer F, Shad MA, et al. Urban-rural inequities in knowledge, attitudes and practices regarding tuberculosis in two districts of Pakistan's Punjab province. Int J Equity Health 2011;10:, doi:http://dx.doi.org/10.1186/1475-9276-10-8.

National TB Control Program. National guidelines for diagnosis and management of tuberculosis in children 2006-07 Islamabad, Pakistan. 2007.

Pakistan Bureau of Statistics. 6th population and housing census 2017. Islamabad, Pakistan: Government of Pakistan; 2017.

Pearce EC, Woodward JF, Nyandiko WM, Vreeman RC, Ayaya SO. A systematic review of clinical diagnostic systems used in the diagnosis of tuberculosis in children. AIDS Res Treat 2012;2012:, doi:http://dx.doi.org/10.1155/2012/401896.

Safdar N, Hinderaker SG, Baloch NA, Enarson DA, Khan MA, Morkve O. Are children with tuberculosis in Pakistan managed according to National programme policy guidelines? A study from 3 districts in Punjab. BMC Res Notes 2010;3:324, doi: http://dx.doi.org/10.1186/1756-0500-3-324.

Tadesse Y, Gebre N, Daba S, Gashu Z, Habte D, Hiruy N, et al. Uptake of isoniazid preventive therapy among under-five children: TB contact investigation as an entry point. PLoS One 2016;11:1–11, doi:http://dx.doi.org/10.1371/journal.pone.0155525.

The Union. The union's desk guide for diagnosis and management of TB in children. third edition 2016 Paris, France: 2016.

WHO. Global tuberculosis report 2018. Geneva: World Health Organization; 2018 2018. Licence: CC BY-NC-SA 3.0 IGO.

World Health Organization. Global Tuberculosis Report 2020. Geneva, Switzerland: WHO; 2020.

Yu P, de Courten M, Pan E, Galea G, Pryor J. The development and evaluation of a PDA-based method for public health surveillance data collection in developing countries. Int J Med Inform 2009;78:532–42, doi:http://dx.doi.org/10.1016/j.ijmedinf.2009.03.002.

IV

Paper IV

GLOBAL HEALTH ACTION
2022, VOL. 15, 2095782
https://doi.org/10.1080/16549716.2022.2095782

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

OPEN ACCESS Check for updates

Geographic accessibility to childhood tuberculosis care in Pakistan

Aashifa Yaqoob [a,b], Muhammad Rizwan Alvi[c], Razia Fatima[a], Hina Najmi[d], Zia Samad[e], Nadia Nisar[f], Anwar Ul Haq[g], Basharat Javed[e], Abdul Wali Khan[h] and Sven Gudmund Hinderaker[b]

[a]Research Unit, Common Management Unit [TB, HIV/AIDS & Malaria], Islamabad, Pakistan; [b]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; [c]Digital Security & Intelligence, Inbox Business Technologies, Islamabad, Pakistan; [d]Maternal Newborn and child Health, Health Services Academy, Islamabad, Pakistan; [e]M & E and Surveillance, Common Management Unit (TB, HIV/AIDS & Malaria), Islamabad, Pakistan; [f]International Health Regulations Strengthening project, Public Health England, Islamabad, Pakistan; [g]Directorate of Central Health, Ministry of National Health Services Regulation & Coordination, Government of Pakistan, Islamabad, Pakistan; [h]National TB Control Program, Common Management Unit (TB, HIV/AIDS & Malaria), Islamabad, Pakistan

ABSTRACT

Background: Tuberculosis (TB) in children is difficult to detect and often needs specialists to diagnose; the health system is supposed to refer to higher level of health care when diagnosis is not settled in a sick child. In Pakistan, the primary health care level can usually not diagnose childhood TB and will refer to a paediatricians working at a secondary or tertiary care hospital. We aimed to determine the health services access to child TB services in Pakistan.
Objective: We aimed to determine the geographical access to child TB services in Pakistan.
Method: We used geospatial analysis to calculate the distance from the nearest public health facility to settlements, using qGIS, as well as population living within the World Health Organization's (WHO) recommended 5-km distance.
Result: At primary health care level, 14.1% of facilities report child TB cases to national tuberculosis program and 74% of the population had geographical access to general primary health care within 5-km radius. To secondary- and tertiary-level health care, 33.5% of the population had geographical access within 5-km radius. The average distance from a facility for diagnosis of childhood TB was 26.3 km from all settlement to the nearest child TB sites. The population of one province (Balochistan) had longer distances to health care services.
Conclusion: With fairly good coverage of primary health care but lower coverage of specialist care for childhood TB, the health system depends heavily on a good referral system from the communities.

ARTICLE HISTORY
Received 13 April 2022
Accepted 24 June 2022

RESPONSIBLE EDITOR
Stig Wall

KEYWORDS
Tuberculosis; children; access; secondary; tertiary care level; public sector; distance; health facilities; settlements

Background

Every day, more than 650 children are estimated to die from tuberculosis (TB); 96% of them do not get TB treatment [1]. Children with TB are often not diagnosed and reported due to multiple factors like limited capacity of health care providers, unavailability of child health services, lack of trained clinician, non-specific symptoms overlapping with other common childhood diseases, complex diagnostic algorithms, lack of a sensitive point-of-care test, and limited contact-tracing activities [2,3].

Pakistan ranks sixth among countries with the largest contributions to the global shortfall in TB notifications in 2020 and reported incidence of 259 per 100,000 new TB cases annually with 48% of them getting treatment [4]. Of the total load of TB cases, children accounts 11%, with 9.9 million incidence rate [4]. Majority of the population in Pakistan has geographical access to primary health care (PHC), and a child with presumptive TB is recommended referral to a secondary or tertiary care hospital with diagnostic services and paediatricians [5].

Geographical distance to health care has been linked to treatment delay and poor adherence to TB management plans [6–9]. One bottleneck in the management of childhood TB in Pakistan is the lack of a systematic mechanism to refer children with presumptive TB from PHC facilities to the facilities where childhood TB diagnostic services are available. Therefore, understanding the link between geographic distance and coverage of childhood TB services may be useful to make evidence-based health policies that could reduce barriers to childhood TB care and improve their outcomes across Pakistan. A number of studies have explored access to health facilities in Pakistan with different perspectives [10–14]. Empirical quantitative information on health care distribution, geographical accessibility, and equity of general and child TB care remains generally scare. Therefore, this study aimed to measure the distance from community centres to health facilities with childhood TB care in Pakistan by using spatial analytical techniques. Our specific objectives were as follows: 1) to measure the distance from community centres to PHC facilities and to childhood TB services and 2) to measure

CONTACT Aashifa Yaqoob aashifa.yaqoob@gmail.com Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

the population coverage within 5 km for PHC and for childhood TB services.

Methods

Study design

This was an ecological study design based on retrospective record of different source to determine the health services geographical access to general and child TB services in Pakistan using secondary data.

General setting

Pakistan is the sixth largest country of the world having 207 million population with an annual growth rate of 2.4% [15]. Out of this, 37% live in urban areas, while a significant portion (63%) resides in rural areas. The country is administratively divided into the Islamabad Capital Territory (ICT); four provinces: Balochistan (with 33 districts), Khyber–Pakhtunkhwa (KP, with 34 districts), Punjab (36 districts), and Sindh (29 districts) and two regions: Gilgit-Baltistan (GB with 10 districts) and Azad Jammu and Kashmir (AJK with 10 districts)], and the Federally Administered Tribal Areas (FATA) are merged with KP from 31 May 2018. The four provinces, capital territory, and two autonomous territories of Pakistan are subdivided into 37 administrative 'divisions', which are further subdivided into districts, tehsils, and finally union councils. The divisions do not include the ICT or the FATA, which were counted at the same level as provinces.

Pakistan has a mixed health system, which includes government (public) infrastructure, parastatal health institutions, the private sector, civil society, and philanthropic contributors. Public health care is delivered in the provinces mainly through a chain of primary-, secondary-, and tertiary-level health facilities. PHC facilities include civil dispensaries, basic health units (BHU), rural health centres, maternal and child health centres, urban health units, and urban health centres. The secondary-level health care facilities comprise taluka (tehsil-sub-district level) hospitals and district hospitals. Tertiary-level health care is provided through teaching and specialized hospitals. The private health sector is large and unregulated, comprising qualified and unqualified service providers; it is estimated that 75% of general curative services are from private sector [16].

Specific setting

The Pakistan National TB Control Program (NTP), with the support of provincial TB programs (PTPs), is responsible for TB care and control activities that are integrated into PHC at district level. This integration has made it possible to plan and carry out TB control in a district without the addition of TB-specific care delivery staff. The district TB team is primarily responsible for advocating, planning, financing, implementing, and monitoring TB care services in their respective districts. In Pakistan, facilities where children with TB can be diagnosed and managed (Child TB sites) are secondary and tertiary care facilities.

Data sources and collection

a. The list of public health facilities in Pakistan was obtained from the District Health Information System (DHIS) and matched with number of health facilities reported by provincial health department. Of these, 1283 health facilities engaged with NTP (Table 1). Geographical coordinates of all public health facilities were derived from publicly available data source The Humanitarian Data Exchange (https://data.humdata.org/organization/alhasan-systems-private-limited). This database was matched/cross-verified with list of public health facilities reported in DHIS, and missed health facilities were mapped manually using Google Maps. Distribution of health facilities in Pakistan is shown in Figure 1.
b. Population density mapping: Since there is no official source available accounting for the population in the cities and sub-districts level, we used the grid population data from LandScan. This provides gridded population

Table 1. Number of public health facilities and their engagement with NTP in Pakistan, by province or region, 2021.

	Primary Health Care Level											
	Public Health Facilities			Basic Health Units (BHUs)			Rural Health Centres (RHCs)			Secondary and Tertiary Care Level		
		Engaged with NTP			Engaged with NTP			Engaged with NTP			Engaged with NTP	
Province/region	Total	n	(%)	Total	n	(%)	Total			Total		
Punjab	3062	516	(17.0)	2500	6	(0.24)	358	332	(92.7)	204	178	(87.3)
Sindh	1010	330	(32.7)	710	48	(6.7)	204	186	(91.2)	96	96	(100.0)
KPK	976	222	(22.7)	738	10	(1.3)	111	96	(86.5)	127	116	(91.3)
Balochistan	839	109	(13.0)	688	39	(5.7)	106	26	(24.5)	45	44	(97.8)
AJK	297	59	(19.8)	227	12	(5.3)	46	26	(56.5)	24	21	(87.5)
GB	59	40	(67.8)	13	6	(46.2)	14	14	(100)	32	20	(62.5)
Islamabad	23	10	(43.4)	16	3	(18.7)	3	3	(100)	4	4	(100.0)
Total	6266	1286	(20.5)	4892	124	(2.5)	842	683	(81.1)	532	479	(90.0)

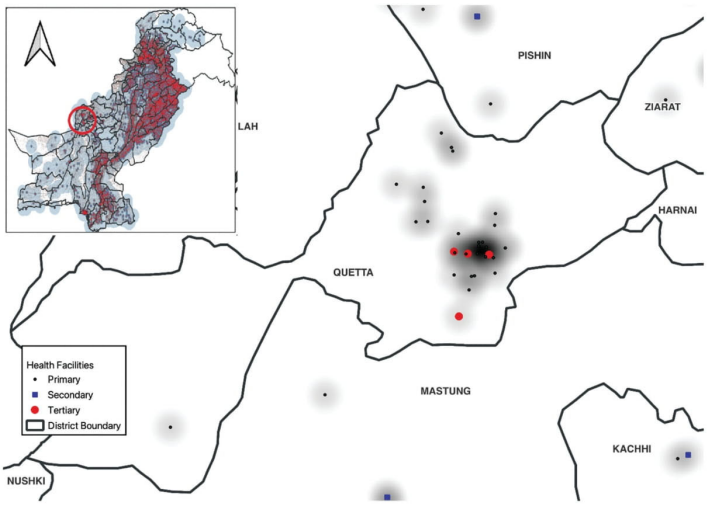


Figure 1. Distribution of primary, secondary, and tertiary health facilities in Pakistan.

estimates range in size from 30 × 30 mm to 1 × 1 km; it is freely available for researchers (https://landscan.ornl.gov/). These estimates are generated through spatial modelling and image analysis with inputs from census data, high-resolution imagery, land cover, and other spatial data such as various boundaries, coastlines, elevations, and slopes [17].

c. Spatial geographical accessibility analysis: Pakistan settlement data were obtained from publicly available dataset on The Humanitarian Data Exchange website (https://data.humdata.org/dataset/pakistan-settlement). The dataset contains the settlements/locations across Pakistan with Province-, District-, and Tehsil-level details; there are approximately 261,217 geographical coordinates of settlements covering four provinces and ICT in Pakistan. GB and AJK settlements are not covered in this dataset. The source of the dataset is World Gazetteer – National Geospatial-Intelligence Agency. Settlement defines as a colony, a town, a village, some small area in city, or any small community of people.

Outcome measurement

The WHO defines health services geographical access as per cent of population living within 5 km of a health facility and recommends everyone should have geographical access to a health facility within a 5-km radius [18]. The main primary outcome was the population living within 5-km radius from a health facility engaged with NTP (all vs child TB sites). Secondary outcome was summarising the distance from settlement centres to health facility engaged with NTP (all vs child TB sites).

Analysis

To determine the total population living within 5 km of a health facility engaged with NTP [19], 5 km dissolved buffer from the health facilities shapefile was generated using open source GIS software (qGIS) to create a geographical accessibility catchment zone (Figure 2 and 3). The geographical accessibility catchment zone was overlaid with the district shapefile using intersection tool in qGIS. The output of this operation was then geographically intersected with the population grid map (Landscan) using the Spatial Join and Summary Analyst Tool in qGIS. The total population in each district within 5 km of health facilities was extracted. The percentage of the total population that fell in the geographical access area was calculated and a choropleth map was created from the results. We repeated the same analysis with different subsets of health facilities (health facilities engaged with NTP that were child TB sites [secondary and tertiary health care facilities]).

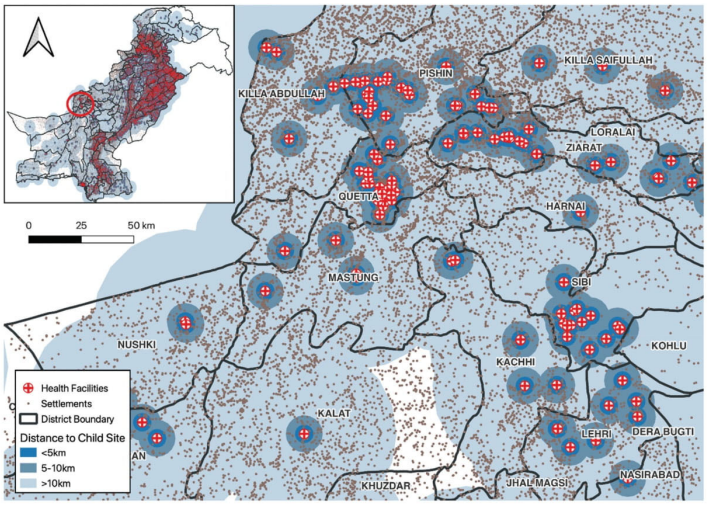


Figure 2. A geographical accessibility catchment zone (5-km buffer) of all health facilities in Pakistan.

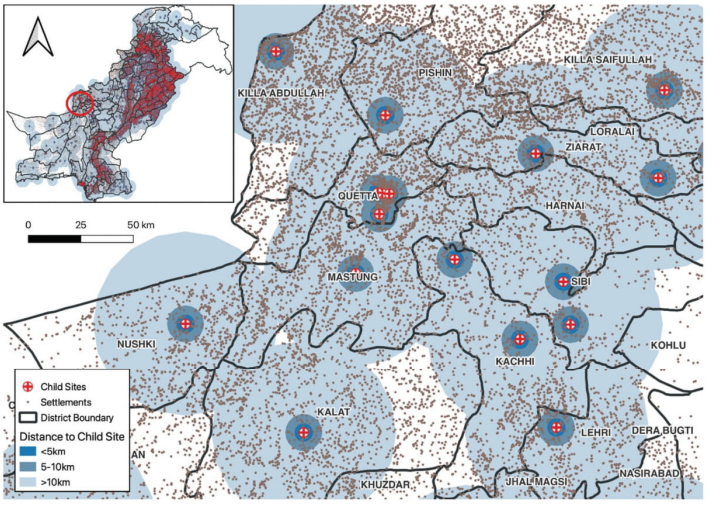


Figure 3. Distribution and geographical accessibility catchment zone (5 km buffer) of child sites (secondary and tertiary facilities) in Pakistan.

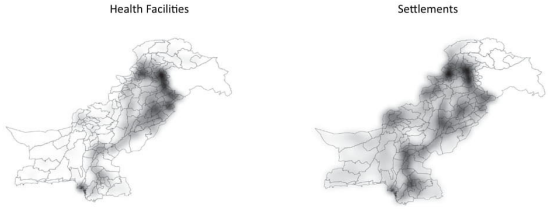


Figure 4. Heat map: Distribution of Health Facilities and Settlements in Pakistan.

Proximity information (median and interquartile range [IQR] distance) between settlements/communities and the nearest health facility engaged with NTP was calculated using the nearest neighbour analysis tool in qGIS which takes number of nearest settlements as input parameter and return mean max and summary of all nearest point to health facilities. We repeated the analysis, calculating distance between settlements/communities and health facilities engaged with NTP that were child TB sites.

Results

Table 1 shows the number of public health facilities in Pakistan and those reporting and engaged with the NTP, by region and type of facility. Out of all public health facilities, 1286 (20.5%) were engaged with NTP. In primary care, NTP was primarily involved at rural health centres, whereas BHU level was very limited, except in the capital areas of Islamabad and the less populated GB province. At secondary and tertiary care level, NTP engagement was at 90%. PHC-level engagement with NTP was low except for Gilgit-Baltistan.

Table 2 shows the proportion of community centres living closer than 5 km from a health facility. On average, in Pakistan, 74% lived closer than 5 km from health services. The province of Balochistan had longer distance to health facilities than all the other provinces; GB had the lowest proportion of its population living closer than 5 km from a health centre (26.5%), followed by Balochistan (51.8%). The overall average distance of all settlements to the nearest health facility in the study was estimated as 9.4 km. The province with the highest average distance to a health facility was Balochistan with 32.1 km, whereas for Punjab province, it was 5.9 km and for Islamabad, it was 3.6 km. A map of Pakistan showing health facilities and settlement is shown in Figure 4.

Table 3 shows the median distance to the closest health facilities giving childhood TB services in Pakistan, which are secondary and tertiary care hospitals. The total population within the 5-km buffer of child TB sites (secondary and tertiary) health facilities in Pakistan was estimated to be 69 million, representing 33.5% of the total population. The average distance of all settlement to the nearest child TB sites was estimated as 26.3 km. The median distance from communities to nearest facility to manage childhood TB was below 30 km in Punjab, Sindh, and KPK but almost 60 km in Balochistan.

Table 2. Distance from geographical centre of communities to nearest public health facility, and proportion of communities closer than 5 km from a health facility, in Pakistan, 2020.

Province/ region	Population	Population within 5 km*	(%)	Distance to nearest health facilities (km) ** Median	IQR
Punjab	107,389,208	84,799,769	(79.0)	5.9	3.8
Sindh	47,915,702	35,282,065	(73.6)	9.6	11.8
KPK	33,963,627	22,893,206	(67.4)	9.3	19.6
Baloschistan	9,586,794	4,967,299	(51.8)	32.1	30.2
AJK	4,831,880	3,045,826	(63.0)	-	-
GB	1,008,820	267,631	(26.5)	-	-
Islamabad	2,402,966	1,989,367	(82.8)	3.6	2.4
Pakistan	207,098,997	153,245,163	(74.0)	9.4	286.2

*Per cent of population living within 5 km of a health facility.
**Distance from geographical centre of community to health facilities. AJK and GB had no settlement data.

Table 3. Distance from geographical community centre to the nearest health facility for childhood TB* in Pakistan, 2021.

Province/ region	Population	Population within 5 km**	(%)	Distance of all communities*** to nearest child TB sites (km) Median	IQR
Punjab	107,389,208	32,722,162.00	(30.5)	19.6	12.0
Sindh	47,915,702	21,671,105.00	(45.2)	25.8	23.1
KPK	33,963,627	9,363,649.00	(27.6)	23.1	28.5
Baloschistan	9,586,794	2,921,308.00	(30.5)	58.7	33.5
AJK	4,831,880	1,107,448.00	(22.9)	-	-
GB	1,008,820	260,320.00	(25.8)	-	-
Islamabad	2,402,966	1,239,151.00	(51.6)	8.6	7.8
Pakistan	207,098,997	69,285,143.00	(33.5)	26.3	449.2

*Child TB sites comprise secondary- and tertiary-level facilities where paediatrician and child TB diagnostic services are available.
**Per cent of population living within 5 km of a health facility.
***Distance from geographical centre of community to health facilities. AJK and GB had no settlement data.

Discussions

This study found that PHC facility is available within 5 km for 74% of the general population. Management of children with TB is limited to secondary and tertiary care facilities, and only a third of the population lives within 5-km distance from these facilities. The median distance to a facility for the management of childhood TB is 26.3 km from settlements (community centre). According to guidelines [20], at PHC level, children with symptoms compatible with TB or severe unclear symptoms should be referred to higher level for further management.

In Pakistan, geographical access to diagnostic tools is often concentrated at and limited to secondary and tertiary care level. The current study estimated that 74% of the population had geographical access to general PHC but low geographical accessibility to secondary and tertiary care level. According to latest review, WHO mission report, the majority of physicians in Pakistan are not trained in TB case identification, follow-up, management, or the guidelines of the NTP [21]. Similar findings are evident in a study conducted in Ghana that describes the limited geographical access to secondary (61.4%) and tertiary care level (14.3%) [22]. Efforts should be made to reach all levels for identification/recognition of child TB cases, and childhood TB training should be incorporated within ongoing NTP training activities. There is also a need to strengthen referral networks between primary level facilities and those with diagnostic capacity of child TB cases at secondary and tertiary care level to improve child TB care geographical access [21].

This study estimated that only one third of the population living within 5km distance to secondary and tertiary health care facilities, but a majority of the population have geographical access to PHCs that provide only basic preventive and curative services, and importantly to refer cases they cannot diagnose or handle. According to the latest WHO Joint Mission report [21], the health staff of these PHC facilities are not trained and involved in the provision of any TB service including identification and referral of presumptive cases. In Sindh Province, however, it was observed that BHUs, whose staff were trained on the identification of presumed TB and linked to the relevant BMUs, were able to identify patients with TB signs and symptoms, use the register of presumed TB cases, and refer them to the closest BMUs. This experience strongly suggests that the involvement of PHC facilities is feasible. Most of the presumed TB patients who seek care in the BMUs visited during the WHO Joint Review Mission had not been detected by health-provider-initiated screening and referral from a PHC level; they were usually self-referred. This suggests that the process of TB case-finding is not taking place in the existing PHC network in Pakistan. In addition, the staff of the dispensaries and BHUs have little training in the management of the TB patients. As we see in Table 1, less than 10% of BMUs deal with NTP on regular basis, except special regions.

On average, people will have to travel 26 km to geographical access child TB services. The people living in Balochistan, AJK, and GB are more likely to have longer distances to geographical access child TB services, and this could lead to a significant burden in terms of time and money. An inventory study in Pakistan highlighted that 78% child TB cases were diagnosed by the non-NTP private providers, which may not be surprising when distance is long to public child TB care; childhood TB under-reporting was highest in these provinces [23]. We think telemedicine could be used remotely to link PHC to child TB sites for timely diagnoses and management of serious child TB cases and this could address some of the challenges posed by lack of physical health care infrastructure [24,25].

In general, in Pakistan, below the level of the rural health centre is not currently involved in TB services, representing a lost opportunity to bring TB services closer to the community and people affected by tuberculosis [21]. Many children are treated at home through the informal sector or by traditional healers. Studies consistently confirm that many sick children do not reach health facilities, and children from poorer families are less likely to obtain care [26]. The WHO recommend Integrated Management of Childhood Illnesses (IMCI) strategy [27] to be used in PHC sites, a community approach to TB prevention, case finding, and supportive care platform to ensure that all infants and children with TB receive high-quality care, and to ultimately eliminate TB deaths in children. The role of Lady Health Workers (LHWs) in referring individuals with presumptive TB from communities to qualified public providers has been well documented [28,29]. The LHWs who are usually linked to PHC facilities and community can play an important to connect community with PHC LHWs to improve referral of persons suspected to have TB from the community to primary health facilities, to support DOTS and report adverse reaction and for household contact tracing in community. Case studies from Malawi and Uganda also illustrated the successful experiences of increase case finding of child TB cases, improve treatment outcomes, and the successful implementation of contact screening and management by strengthening of child TB services at peripheral health facilities [2,30]. IMCI should be involved to find and refer from community to child TB sites. In order to improve geographic accessibility, we think there needs to be improvements in two areas. First, to improve

identification of children who may have TB at PHC level and need closer examination. Secondly, to improve referral pathways for children with TB from community.

A strength of this study is that it covers almost all of Pakistan, measuring geographical access to health services in a way not done before in Pakistan. A limitation of this study was that we did not have any data on health care in private sector, which is very big in Pakistan. But only <5% of these private facilities are given roles in the national TB control program with diagnosis and management, even though many treat their patients not following the national guidelines [31]. Also, data on settlements and health facilities used in this study were extracted from the Humanitarian Data Exchange website with numbers from 2018, and some changes may have occurred since then. We did not have individual data for geographical access indicators, such as distance, population living within 5 km of health facilities, in order to do cross-sectional analysis, but we could analyse by groups in an ecological study. Finally, we did not have data for the population of provinces of GB (0.5%) and AJK (2%). This study is secondary analysis of different existing data sources; validity of data cannot be assured.

Conclusion

There was high geographical accessibility to general primary health services in Pakistan, while geographical access to specialised child TB is lower with consequent longer distance to care. Geographical accessibility can be improved by integrated IMCI approach involving Lady Health Workers, and creating a closer link to higher level to improve referral system particularly for distant communities.

Acknowledgments

We highly acknowledge the role and contribution of University of Bergen, Norway, for providing a good academic background and developing the research capacity. We highly acknowledge the corporation and facilitation of National TB Control Program, Provincial TB Program departments Punjab, Sindh, Khyber Pakhtunkhwa, Balochistan, Azad Jammu, and Kashmir and Gilgit-Baltistan.

Author contributions

AY conceived the paper idea and led the development of initial drafts of the paper. AY, RA, and SGH performed the analysis. All authors were engaged in the implementation of the course, provided insights into manuscript development, and reviewed and approved the manuscript for publication.

Disclosure statement

No potential conflict of interest was reported by the authors.

Ethics and consent

Local ethical clearance was obtained from IRB, ethics committee, common management unit (HIV, TB, and Malaria). This study involved utilization and analysis of publicly available data of health facilities engaged with NTP, population density, and settlements. The study did not involve personal identifiers at individual level.

Funding information

No specific funding was available or obtained from any organization for this study. The publication fee for publication in an international journal is covered by University of Bergen, Norway.

Paper context

Geographical access to child TB health care has direct impact on burden of TB. In Pakistan, child TB services are mainly limited to secondary/tertiary care level. We aimed to determine the geographical access to child TB services in Pakistan. This study reveals low coverage of specialist care for childhood TB with consequent longer distance to care. Integrated IMCI approach involving Lady Health Workers and improved referral system could improve geographical accessibility of child TB care.

ORCID

Aashifa Yaqoob http://orcid.org/0000-0002-5680-1507

References

[1] UNOPS. Every day more than 650 children die from TB. 2019
[2] UNICEF. Strengthening community and primary health systems for tuberculosis. A consultation on childhood TB integration. 2016.
[3] World Health Organization. Roadmap for childhood tuberculosis towards zero deaths. Geneva(Switzerland): WHO; 2013.
[4] World Health Organization. Global Tuberculosis Report 2021. Geneva, Switzerland:WHO; 2021.
[5] World Health Organization. Roadmap towards ending TB in children and adolescents. Geneva Switzerland: WHO; 2018.
[6] Fluegge K, Malone LL, Nsereko M, et al. Impact of geographic distance on appraisal delay for active TB treatment seeking in Uganda: a network analysis of the Kawempe community health cohort study. BMC Public Health. 2018 Jun 26;18:1–14.
[7] Robsky KO, Robsky KO, Hughes S, et al. Is distance associated with tuberculosis treatment outcomes? A retrospective cohort study in Kampala, Uganda. BMC Infect Dis. 2020 Jun 11;20:1–9.
[8] Tadesse T, Demissie M, Berhane Y, et al. Long distance travelling and financial burdens discourage tuberculosis DOTs treatment initiation and

identification of children who may have TB at PHC level and need closer examination. Secondly, to improve referral pathways for children with TB from community.

A strength of this study is that it covers almost all of Pakistan, measuring geographical access to health services in a way not done before in Pakistan. A limitation of this study was that we did not have any data on health care in private sector, which is very big in Pakistan. But only <5% of these private facilities are given roles in the national TB control program with diagnosis and management, even though many treat their patients not following the national guidelines [31]. Also, data on settlements and health facilities used in this study were extracted from the Humanitarian Data Exchange website with numbers from 2018, and some changes may have occurred since then. We did not have individual data for geographical access indicators, such as distance, population living within 5 km of health facilities, in order to do cross-sectional analysis, but we could analyse by groups in an ecological study. Finally, we did not have data for the population of provinces of GB (0.5%) and AJK (2%). This study is secondary analysis of different existing data sources; validity of data cannot be assured.

Conclusion

There was high geographical accessibility to general primary health services in Pakistan, while geographical access to specialised child TB is lower with consequent longer distance to care. Geographical accessibility can be improved by integrated IMCI approach involving Lady Health Workers, and creating a closer link to higher level to improve referral system particularly for distant communities.

Acknowledgments

We highly acknowledge the role and contribution of University of Bergen, Norway, for providing a good academic background and developing the research capacity. We highly acknowledge the corporation and facilitation of National TB Control Program, Provincial TB Program departments Punjab, Sindh, Khyber Pakhtunkhwa, Balochistan, Azad Jammu, and Kashmir and Gilgit-Baltistan.

Author contributions

AY conceived the paper idea and led the development of initial drafts of the paper. AY, RA, and SGH performed the analysis. All authors were engaged in the implementation of the course, provided insights into manuscript development, and reviewed and approved the manuscript for publication.

Disclosure statement

No potential conflict of interest was reported by the authors.

Ethics and consent

Local ethical clearance was obtained from IRB, ethics committee, common management unit (HIV, TB, and Malaria). This study involved utilization and analysis of publicly available data of health facilities engaged with NTP, population density, and settlements. The study did not involve personal identifiers at individual level.

Funding information

No specific funding was available or obtained from any organization for this study. The publication fee for publication in an international journal is covered by University of Bergen, Norway.

Paper context

Geographical access to child TB health care has direct impact on burden of TB. In Pakistan, child TB services are mainly limited to secondary/tertiary care level. We aimed to determine the geographical access to child TB services in Pakistan. This study reveals low coverage of specialist care for childhood TB with consequent longer distance to care. Integrated IMCI approach involving Lady Health Workers and improved referral system could improve geographical accessibility of child TB care.

ORCID

Aashifa Yaqoob http://orcid.org/0000-0002-5680-1507

References

[1] UNOPS. Every day more than 650 children die from TB. 2019
[2] UNICEF. Strengthening community and primary health systems for tuberculosis. A consultation on childhood TB integration. 2016.
[3] World Health Organization. Roadmap for childhood tuberculosis towards zero deaths. Geneva(Switzerland): WHO; 2013.
[4] World Health Organization. Global Tuberculosis Report 2021. Geneva, Switzerland:WHO; 2021.
[5] World Health Organization. Roadmap towards ending TB in children and adolescents. Geneva Switzerland: WHO; 2018.
[6] Fluegge K, Malone LL, Nsereko M, et al. Impact of geographic distance on appraisal delay for active TB treatment seeking in Uganda: a network analysis of the Kawempe community health cohort study. BMC Public Health. 2018 Jun 26;18:1–14.
[7] Robsky KO, Robsky KO, Hughes S, et al. Is distance associated with tuberculosis treatment outcomes? A retrospective cohort study in Kampala, Uganda. BMC Infect Dis. 2020 Jun 11;20:1–9.
[8] Tadesse T, Demissie M, Berhane Y, et al. Long distance travelling and financial burdens discourage tuberculosis DOTs treatment initiation and

from all provinces, and we believe it may reflect the diverse situation in this country. In this study, validity of the data was ensured though data quality audit by cross-checking every record from the hard copies to remove inconsistencies. Also using mobile phone for data collection reduced data entry errors by eliminating one step for database creation. This study adheres to "STROBE" guidelines for observational studies [34, 35].

The study also had some limitations. Although it had a large total sample, the number of clusters was limited to the number of provinces, giving lower precision. Despite this, it probably reflects fairly well the different situations in the country. Also, our study did not include actual observations through field assessments. so the accuracy and completeness of the data could therefore not be totally ensured. High referral to NTP centres for diagnosis may be partly because the study was closely related to NTP, and data collectors from NTP visited the study sites twice a month, and this could affect reporting, like a Hawthorne effect. The levels of childhood TB (79.7%) in this study were high compared to other settings ranging from 2.1 to 19% [36–39]. One possible reason for this is that private providers may have recorded mostly already diagnosed child TB cases on the provided registers due to their workload constraints and they may have missed an unknown number of other presumptive TB cases. The levels varied among the districts, and this may reflect variations in completeness, with different compliances with reporting all "suspects". Future research is recommended to further assess and verify these findings in the field.

Conclusion

This study showed that many private health care providers rely on NTP supported laboratories for diagnosis, but they often do not report the children diagnosed with TB to NTP. The private health providers often rely on chest X-ray in addition to clinical symptoms for diagnosis TB in children. Communication between private providers, laboratory and NTP treatment centres could and should be strengthened through training.

Abbreviations

AJK: Azad Jammu & Kashmir; BCG: Bacillus Calmette–Guérin; GB: Gilgit Baltistan; KPK: Khyber Pakhtunkhwa; NTP: National TB Control Program; PPA: Pakistan Pediatric Association; TB: Tuberculosis

Acknowledgements

We are grateful to all health care providers who participated in this study. We are thankful to the survey team in the field for their efforts and to the University of Bergen, Norway for providing a good academic background, and to the World Health Organization Eastern Mediterranean Office for funding for the main survey. We gratefully acknowledge the corporation and facilitation of National TB Control Program, Provincial TB Program Managers and Provincial Technical Officer of Punjab, Sindh, Khyber Pakhtunkhwa, Balochistan, Azad Jammu & Kashmir and Gilgit Baltistan. We thank Elinor Bartle for providing helpful input.

Authors' contributions

Conceptualization: AY; Designing of the work: AY, SGH, RF; Acquisition: AY, SGH, RF, HN, AH; Analysis of data: AY, SGH, RF, HN; Interpretation of data and results: AY, SGH, RF, HN, AH; Creation of data collection form used in the work: AY, RF, Drafted and revised the work: AY, SGH, RF, HN, AH. All authors read and approved the final version.

Funding

World Health Organization Eastern Mediterranean Office funded the main survey. No specific funding was available or obtained from any organization for this study. The publication fee for publication in an international journal is covered by University of Bergen.

Availability of data and materials

The datasets analyzed during the current study are not publicly available due to maintaining the confidentiality of participants keeping in view the ethical consideration for stigmatized infectious diseases i.e. TB, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The ethical clearance (registration # NBC 192 given in 2015) was obtained from the Pakistan Medical and Research Council, REK Vest in Norway (# 2018/56), as well as the WHO Ethics Committee for the East-Mediterranean region. Informed consent was waived by the ethics committee, as all data used had been previously collected during the child inventory study and did not pose any additional risks to the patients. Permission to use the data was obtained from the program manager of the National TB control program, Islamabad, Pakistan.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Common Management Unit (HIV/AIDS, TB & Malaria), Block F, EPI Building, Near National Institute of Health (NIH) (Prime Minister's National Health Complex), Park Road, Islamabad, Pakistan. [2]University of Bergen, Bergen, Norway. [3]Health Services Academy, Islamabad, Pakistan. [4]Ministry of National Health Services Regulation & Coordination, Government of Pakistan, Islamabad, Pakistan.

Received: 28 March 2020 Accepted: 10 December 2020
Published online: 07 January 2021

References

1. World Health Organization. Global Tuberculosis Report 2019. Geneva: WHO; 2019.
2. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2nd ed. Geneva: WHO; 2014.
3. Hamzaoui A, Yaalaoui S, Cherif FT, Saidi LS, Berraies A. Childhood tuberculosis: a concern of the modern world. Eur Respir Rev. 2014;23:278–91.
4. World I ealth Organisation. Engaging private health care providers in TB care and prevention: a landscape analysis. Geneva: WHO; 2018.
5. National TB Control Program. National guidelines for diagnosis and management of tuberculosis in children 2006–07. Islamabad, Pakistan; 2007.
6. Fatima R, Haq MU, Yaqoob A, Mahmood N, Ahmad KL, Osberg M, et al. Delivering patient-centered Care in a Fragile State: using patient-pathway analysis to understand tuberculosis-related care seeking in Pakistan. J Infect Dis. 2017;216:S733–9.
7. Khan AJ, Khowaja S, Khan FS, Qazi F, Lotia I, Habib A, et al. Engaging the private sector to increase tuberculosis case detection: an impact evaluation study. Lancet Infect Dis. 2012;12:608–16.
8. Detjen A, M G, Sm G, C S. Improving the estimates of childhood TB disease burden and assessing childhood TB activities at country level. Geneva: WHO; 2018.
9. Fatima R, Yaqoob A, Qadeer E, Hinderaker SG, Ikram A, Sismanidis C. Measuring and addressing the childhood tuberculosis reporting gaps in

List of Appendices

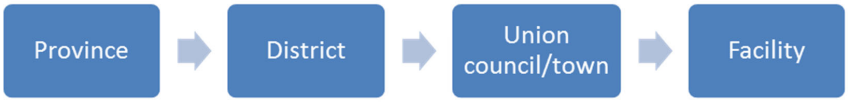
Appendix I. Sample size determination – different assumptions

Harmonic mean of cluster size	Coefficient of between-cluster variation	Under-reporting expressed as a proportion	Relative precision	Design effect	Number of patients	Number of clusters	Finite population	*After finite population correction*	
								Number of patients	Number of clusters
m	K	P	d	DEFF	N2=N1*DEFF	c1=N2/m	t	N3=N2/(1+(N2-1)/t)	c2=N3/m
33.5	0.3	0.27	0.2	2.08	541	16	10000	513	15
33.5	0.4	0.27	0.2	2.92	759	23	10000	706	21
33.5	0.5	0.27	0.2	4.01	1040	31	10000	942	28
33.5	0.3	0.27	0.25	2.08	346	10	10000	334	10
33.5	0.4	0.27	0.25	2.92	486	15	10000	463	14
33.5	0.5	0.27	0.25	4.01	666	20	10000	624	19
50	0.3	0.27	0.2	2.63	683	14	10000	640	13
50	0.4	0.27	0.2	3.90	1013	20	10000	920	18
50	0.5	0.27	0.2	5.53	1436	29	10000	1256	25
50	0.3	0.27	0.25	2.63	437	9	10000	419	8
50	0.4	0.27	0.25	3.90	648	13	10000	609	12
50	0.5	0.27	0.25	5.53	919	18	10000	842	17

77	0.3	0.27	0.2	3.53	917	12	10000	840	11
77	0.4	0.27	0.2	5.50	1428	19	10000	1249	16
77	0.4	0.27	0.25	5.50	914	12	10000	837	11
77	0.5	0.27	0.25	8.03	1334	17	10000	1177	15

Appendix II. Data collection tools

1. Health facility-level registration form: tablet-based data collection

Date of data collection		(*dd/mm/yyyy*)
Location of health facility		
Initial questions ask the data collector to choose the **province**, after which a list of districts in the study appears; after the **district** is chosen, a list of all **councils/towns** in the district appears. After selecting the council/town, a serial facility code is generated automatically from the system. 		
1.	Longitude of the facility	(*GPS coordinate*)
2.	Latitude of the facility	(*GPS coordinate*)
3.	Name of nearest BMU	
4.	Longitude of nearest BMU	(*GPS coordinate*)
5.	Latitude of nearest BMU	(*GPS coordinate*)
6.	Distance from nearest BMU	
7.	Estimated facility staff	
Identification of health facility		
S.No	**Question**	**Response**
8.	Name of facility	(*free entry*)
9.	Name of primary contact person	(*free entry*)
10.	Contact number of primary contact person	(*free entry*)
11.	Within NTP Network	1. Yes 2. No
12.	Facility Type	1. Tertiary care hospital a. Medicine OPD b. Pediatric OPD c. Pulmonology/chest OPD 2. Secondary health care facility 3. Primary health care facility 4. Ministry of defense 5. Parastatal 6. Private hospital

		a. Medicine OPD b. Pediatric OPD c. Pulmonology/chest OPD 7. Private clinic/GP 8. NGO clinic/hospital 9. Private laboratory 10. Informal provider
13.	Facility diagnosis and treats children (0-14 years)	1. Yes 2. No
14.	Specialty	1. Pediatric Specialist
		2. Practitioner (GP)
		3. Chest physician
		4. Medical specialist

2. Individual-level form for presumptive TB cases (<15 years): tablet-based data collection

S. No	Question	Response
Part 1. Identification of child with presumptive TB		
1.	Date of data collection	(*dd/mm/yyyy*)
2.	Date of consultation	(*dd/mm/yyyy*)
3.	Names	1. First: _____ 2. Father's: _____ 3. Grand-father's: _____ 4. Last: _____ 5. NA
4.	Date of birth *if unknown go to 5.*	(*dd/mm/yyyy*) 99. NA
5.	Age (*approximate*)	(*free entry*) 99. NA
6.	Gender	1. Male 2. Female 3. NA
		1. Non-Pakistan national 2. NA
7.	Pakistan National ID Number (*indicate whose: 1=Father, 2=Mother, 3=Guardian*)	(*free entry*) 99. NA
8.	Complete address	(*free entry*) 99. NA
9.	Mobile Number of Contact Person	(*free entry*) 99. NA
TB Symptoms		
10.	Cough more than two weeks	1. Yes 2. No
11.	Fever (usually low grade at evening)	1. Yes 2. No
12.	Enlarge cervical lymph nodes	1. Yes 2. No

13.	Failure to thrive	1. Yes 2. No	
14.	Signs of slow onset meningitis	1. Present 2. Absent 3. NA	
15.	Low Immune Status	1. Malignancies like leukemia or lymphomas 2. Immunodeficiency 3. Immunosuppressive therapy such as chronic steroids more than 2 weeks 4. NA	
16.	Protein calorie Malnutrition	1. Grade 3 or below 3% line on child card. 2. NA	
17.	Physical Examination	1. Suggestive of TB: i. Pulmonary findings (unilateral wheeze, dullness); ii. Hepatosplenomegaly; ascites 2. Strongly suggestive of TB i. Lymphadenopathy, matted lymph nodes; ii. Abdominal mass; gibbus formation; iii. Chronic monoarthritis; iv. Meningeal findings(bulging fontanel, irritability, papilledema) 3. NA	
18.	Status of Child	1. Presumptive TB case 2. Not Presumptive TB case	
Part 2. Available clinical and bacteriological evidence			
19.	Clinical Diagnosis	1. Close contact of TB patient in last 2 years	1=TB patient SS –ve, 2=TB patient

			SS +ve , 3=No contact 4=NA
		2. BCG scar	1=absent, 2=present, 3=NA
		3. Low immune status (check according to growth chart)	1=Yes, 2=No, 3=NA
		4. Physical examination findings (symptoms)	1=not TB, 2=suggestive of TB, 3=strongly suggestive of TB, 4=NA
		5. CXR	1=non-TB specific, 2=suggestive of TB, 3=not available, 4=NA
		6. Tuberculin skin test (mm)	1=5-10mm, 2= more than 10mm, 3=not available, 4=NA
		7. Histopathology Examination	1=non-TB specific, 2=consistent with TB (Granuloma) 3=NA
21.	Specimen used for bacteriological examination	1. Sputum 2. Gastric Lavage	

		3. Extra-pulmonary specimen		
22.	Requested bacteriological investigation ‘s results	1. Smear examination		1=positive, 2=negative, 3=not available, 4=NA
		2. NAAT (e.g. Gene-Xpert)	MTB	1=detected, 2=not detected, 3=not available, 4=NA
			Rifampicin Resistance	1=detected, 2=not detected, 3=indeterminate, 4=not available, 5=NA
		3. Culture		1=positive, 2=negative, 3=not available, 4=NA
Part 3. Action(s) taken and diagnosis by health facility				
23.	Action taken If treated for TB on site go to 14.	1. Treated for TB on site 2. Referred for TB treatment 3. Referred for TB diagnosis 4. Not treated for TB 5. NA		
24.	Place of referral	1. District TB Centre (NTP) 2. Private lab 3. Private specialist hospital/GP 4. NA 5. Not Applicable		
25.	Diagnosis	1. Bacteriologically-confirmed TB 2. Clinically-diagnosed TB 3. Not TB 4. NA		
26.	Site of TB	1. Pulmonary TB 2. Extra-pulmonary TB 3. NA		
27.	History of TB treatment	1. New 2. Relapse 3. NA		

Part 4. Final diagnosis at central study level		
28.	Final diagnosis	1. Confirmed TB 2. Probable TB 3. Possible TB 4. Not TB
29.	Date of initiation of anti-TB treatment at the NTP	(*dd/mm/yyyy*)

* NA=Not available

3. Laboratory register for presumptive TB cases (<15 years): tablet-based data collection

S. No	Question	Response
Part 1. Identification of child with presumptive TB		
1.	Date of data collection	(*dd/mm/yyyy*)
2.	Date of specimen received	(*dd/mm/yyyy*)
3.	Names	6. First: _____ 7. Father's: _____ 8. Grand-father's: _____ 9. Last: _____ 10. NA
4.	Date of birth *if unknown go to 5.*	(*dd/mm/yyyy*) 99. NA
5.	Age (*approximate*)	(*free entry*) 99. NA
6.	Gender	4. Male 5. Female 6. NA
7.	Nationality	3. Pakistan 4. Non-Pakistan national 5. NA
8.	Pakistan National ID Number/Passport Number for non-Pakistani (*indicate whose: 1=Father, 2=Mother, 3=Guardian*)	(*free entry*) 99. NA
9.	Complete address	(*free entry*) 99. NA
10.	Mobile Number of Contact Person	(*free entry*) 99. NA
Part 2. Available clinical and bacteriological evidence		
11.	Referred by	8. Self 9. Community treatment supporter. etc.

		10. Public provider 11. Private provider 12. Informal health provider 13. Drug store/pharmacies 14. Others		
12.	Type of referring facility	11. Public hospital 12. Private hospital/clinic/doctor 13. Ministry of defense 14. NGOs 15. Charity based 16. Others 17. NA		
13.	Specimen used for bacteriological examination	4. Sputum 5. Gastric Lavage 6. Extra-pulmonary specimen		
14.	Results of required investigations	4. Smear examination		1=positive, 2=negative, 3=not available, 4=NA
		5. NAAT (e.g. Gene-Xpert)	MTB	1=detected, 2=not detected, 3=not available, 4=NA
			Rifampicin Resistance	1=detected, 2=not detected, 3=indeterminate, 4=not available, 5=NA
		6. Culture		1=positive, 2=negative, 3=not available, 4=NA
15.	Other lab investigations	1. Tuberculin skin test (mm)		1=5-10mm, 2= more than 10mm, 3=not available, 4=NA
		15. Histopathology Examination		1=non-TB specific, 2=consistent with TB (Granuloma) 3=NA
Part 3. Final diagnosis at central study level				
16.	Final diagnosis	5. Confirmed TB 6. Probable TB		

		7. Possible TB 8. Not TB
17.	Date of initiation of anti-TB treatment at the NTP	(*dd/mm/yyyy*)

* NA=Not available

Appendix III. Consent form for health facility

Consent Form

Estimation of level of under-reporting of child TB cases in Pakistan

Principal Investigator
National TB Control Programme
Pakistan
sats.net.pk2-51) 925-7228

Sponsor
World Health Organization HQ Geneva

Information for participating health facility/GP

We are conducting a study to identify child TB cases that are diagnosed outside the national tuberculosis programme. We want to know how many children in Pakistan currently have tuberculosis. If you decide to participate in the study then you are requested to follow the procedure given below:

We request you to register all children with presumptive TB who routinely visit your facility, both pulmonary and extra-pulmonary, and complete the information in the study register. This consists of the names of the child, age, gender, requested investigations, action taken and your final diagnosis. This information will be kept confidential at the national TB control programme.

We have selected you in the study because you are managing childhood TB cases and are a practicing health professional in an area which has been randomly selected to be included in the study.

If you participate, it will not affect in any way the services that you are delivering in your clinic on a routine basis.

We would highly appreciate your participation in the study.

Certificate of consent

I have read the information sheet concerning the estimation of Under-reporting in child TB cases in Pakistan. I have had the opportunity to ask questions about the study and the questions that I have asked have been answered to my satisfaction. I now understand what will be required of me and what will or may happen to me if I take part.

I understand that I may withdraw from this study at any time without giving a reason and without my withdrawal affecting the usual care and treatment delivered in my facility.

I consent voluntarily to participate in this study.

Name_____

Signature_____ Date_____

Signature of field officer_____ Date_____

Appendix IV. Ethical Approvals

National Bioethics Committee (NBC) Pakistan

Ref: No.4-87/15/NBC-192/RDC/1181 **Date:** October 29, 2015

Dr Ejaz Qadeer
Programme Manager
National TB Control Program, Pakistan,
Block E & F, EPI Building,
Near National Institute of Health (NIH)
Park Road,
Islamabad.

Subject: **National Inventory Study in Pakistan to Measure TB Under-Reporting in Children (NBC192).**

Dear Dr Ejaz Qadeer,

I am pleased to inform you that the above mentioned project has been cleared by "Research Ethics Committee of the National Bioethics Committee".

Kindly keep the National Bioethics Committee Secretariat updated with the progress of the project and submit the formal final report on completion.

Yours sincerely

(Prof Dr. Aasim Ahmad)
Chairman
NBC-Research Ethics Committee

NBC Secretariat:
Pakistan Medical Research Council, Shahrah-e-Jamhuriat, Off Constitution Avenue, Sector G-5/2, Islamabad
nbcpakistan.org.pk, www.pmrc.org.pk, e-mail: pmrc.rdc@gmail.com Tel: 92-51- 8207386, 9216793, 9205480, Fax 9216774, 9204559

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

26 September 2017

SUBJECT: Approval for use of Child Inventory Study data for PhD Thesis

A nationally representative TB inventory study among children was carried out by National Tuberculosis Control Program, Pakistan in 2016. The project's main goal was generation of national-level empirical measurements among children, such as from TB inventory studies to measure TB under-reporting from the private sector. A surveillance system was established among all non-NTP providers in randomly selected 12 districts across Pakistan from April to June 2016 and record linkage was done. Across the mapped facilities, 8,056 children were enumerated in total of which 7,125 were considered presumptive TB cases. Of the 5,249 TB cases diagnosed from the health facilities only 188 were notified to the NTP that indicate 78% under-reporting of child TB cases among national surveillance system.

The main paper of project will be published in international peer reviewed journal in which Aashifa Yaqoob will be co-author however, further scientific publications /studies need to be prepared from the project. It is expected that up to five peer-reviewed papers could be written using the project data followed by some prospective study in the above-mentioned districts.

Aashifa Yaqoob (Senior Research Officer) who is PhD candidate in University of Bergan, Norway, will be responsible and allow for the scientific publications from the above-mentioned project data for pursual of her PhD. It will provide the necessary evidence for National TB Program to understand the burden and management of child TB cases in Pakistan.

I ensure that proper time and support will be provided by the NTP to carry out her PhD research and I also ensure about the support to adhere the timelines of the PhD program and permit her to publish the work as first author.

I wish her all the best for her successful completion of PhD and future endeavours.

Dr Razia Fatima
Chief Data (NTP)

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

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK vest	Jessica Svärd	55978497	30.04.2018	2018/56/REK vest
			Deres dato:	Deres referanse:
			27.03.2018	

Vår referanse må oppgis ved alle henvendelser

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

2018/56 Tuberkulose hos barn i Pakistan

Forskningsansvarlig: Universitetet i Bergen
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
Tuberkulose er et stort problem i Pakistan. Barn kan også få tuberkulose men er vanskelige å diagnostisere. Mange barn med TB blir identifisert av private leger og blir ikke rapportert. Rapportering av tilfeller til TB programmet er viktig for myndigheter for å gi medisiner (gratis fra myndigheten), og vite situasjonen i landet, og hvordan man kan bedre forholdene. For å hjelpe diagnostiseringen av TB hos barn er det utarbeider et hjelpemiddel (BBA) der klinikere gir score ut fra det de vet om pasienten, for å styrke diagnosen. Studiene har fått etisk klarering og godkjennelser i Pakistan. En forsker er valgt til å publisere, og ta en PhD med dette materialet.

Vurdering
REK vest ønsket tilbakemelding på følgende:

- Tidspunkt for når og hvordan UiB ble involvert i datainnsamlingen for de fire artiklene.
- En forklaring på hvilket samtykke som finnes og om de som har samtykket også har gitt tillatelse til deling av opplysninger til utlandet.
- Revidert informasjonsskriv.
- En klargjøring om fritaket fra samtykkekravet.
- En klargjøring om hva som skjer med data ved prosjektslutt.

Tilbakemelding fra prosjektleder:

Tidspunkt for når og hvordan UiB ble involvert i datainnsamlingen for de fire artiklene.
UiB ble formelt involvert i denne studien i 2017. endelig NOKUT klarering ble gitt 10.3.2017. Før dette var AY lokal leder av denne forskningen i Pakistan ved det nasjonale tuberkuloseprogrammet NTP; det ble

veiledet av forskningsleder ved NTP, Dr Razia Fatima, som har sin PhD fra Bergen, og brukte lignende metoder i sine studier. I starten var UiB ikke involvert, og tillatelse ble gitt nasjonalt i Pakistan før data ble samlet inn. På grunn av langvarig samarbeid mellom NTP Pakistan og UiB ble dette forskningsprosjektet gjort til et PhD prosjekt ved UiB, for å styrke forskningsenheten ved NTP.

En forklaring på hvilket samtykke som finnes og om de som har samtykket også har gitt tillatelse til deling av opplysninger til utlandet.
For paper 1+2+3+4 søkes samtykkefritak fordi dette er bare sekundære data fra rutinemessig vedlikeholdte tuberkulose registre. Imidlertid, det er også brukt et skjema for å få tillatelse/samtykke fra helseklinikken å bruke registerne, men dette angår ikke intervjuer: dette er ikke deltakersamtykke, men samtykke fra eier av registeret til å bruke det. For paper 5 trengs samtykke fra deltakere, alle helsearbeidere som intervjues med dybdeintervjuer.

Revidert informasjonsskriv.
Vedlagt infoskriv for paper 5, der det sier «If you do not participate…», viser lokal tillatelse, viser logo til NTP som driver studien, og viser når studien slutter.

En klargjøring om fritaket fra samtykkekravet.
Her var det for uklart i originalprotokollen vår. For deltakerne (barna) som er regisrert er det bare retrospektive data, og derfor søker vi om fritak for samtykkekrav. I denne typen studier (capture/recapture) er det viktig å kunne identifisere deltakerne for bl.a. å finne samme deltaker i ulike registre, og derfor trengs navn og adresse. Under analyser og skriving brukes ingen personidentifiserbare variabler. For papers 1-4 er det ingen kontakt med deltakerne, bare deres data.

En klargjøring om hva som skjer med data ved prosjektslutt.
Ved prosjektslutt vil alle data anonymiseres og lagres separat fra tuberkuloseregisteret.

REK vest ved leder har vurdert tilbakemeldingen.

Vurdering

Hovedparten av studien er en registerstudie på opplysninger om barn i tuberkuloseregisteret uten at det innhentes samtykke fra de som er registrert. I en delstudie skal helsearbeidere intervjues. Til denne delen innhentes samtykke fra deltakerne.

REK vest anser at formålet med studien er samfunnsnyttig og anser studien som forsvarlig å gjennomføre uten innhenting av samtykke for registerstudiene ettersom det er vanskelig å innhente samtykke fra så mange deltakere og ettersom deltakernes velferd å integritet er ivaretatt gjennom at data anonymiseres etter identifikasjon av deltakere i forskjellige register. Det skal søkes helseklinikk/registereier om tillatelse å bruke data i registrene.

Ettersom Universitetet i Bergen ikke var involvert i datainnsamlingen til tuberkuloseregisteret eller i arbeidet med artikkel 1 så er søknaden ikke en søknad om ettergodkjenning. REK har kun vurdert de deler som ikke er gjennomført.

REK vest har kun en mindre merknad til det vedlagte informasjonsskrivet til helsearbeidere som skal intervjues, dette mangler fremdeles UiB-logo.

Vilkår

Informasjonsskrivet må revideres slik at UiB-logo også finnes på skrivet. Revidert informasjonsskriv sendes til 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
dr.med.
Avdelingsdirektør, professor

Jessica Svärd
rådgiver

Kopi til:post@uib.no

Graphic design: Communication Division, UiB / Print: Skipnes Kommunikasjon AS

uib.no

ISBN: 978-82-308-7072-3 (PRINT)
978-82-308-7161-4 (PDF)