

**CHILDHOOD TUBERCULOSIS CASE MANAGEMENT
IN PAKISTAN: ADDRESSING A PRIORITY**

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Dedication

This thesis is dedicated to the memory of my beloved father Dr Muhammad Safdar.

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LIST OF ABBREVIATION

AFB	Acid Fast Bacilli
BCG	Bacillus Calmette Guerin
CI	Confidence Interval
CXR	Chest X-Ray
DOTS	Direct Observation Therapy Short Course
DR	Drug Resistant
DTC	District Tuberculosis Coordinator
EMRO	Eastern Mediterranean Region Office
EPTB	Extrapulmonary Tuberculosis
FDC	Fixed Dose Combination
GDF	Global Drug Facility
GFATM	Global Fund for AIDS, Tuberculosis and Malaria
HIV	Human Immunodeficiency Virus
MCH	Maternal and Child Health
MDR	Multi-Drug Resistant
MDG	Millennium Development Goal
NBC	National Bioethics Committee
NGO	Non Government Organization
NTP	National Tuberculosis Control Programme
PCR	Polymerase Chain Reaction
PMRC	Pakistan Medical and Research Council
PPA	Pakistan Paediatric Association
PTB	Pulmonary Tuberculosis
R&R	Recording and Reporting
S+	Smear Positive
S-	Smear Negative
SPSS	Statistical Package for the Social Science
TB	Tuberculosis
TST	Tuberculin Skin Test
WHA	World Health Assembly
WHO	World Health Organization

LIST OF PAPERS

Paper I. N.Safdar, S.G.Hinderaker, N.A. Baloch, D.Enarson, M.A. Khan, O.Mørkve. Diagnosis and outcome of childhood tuberculosis: implementing public health policy in three districts of Pakistan. *Int J Tuberc Lung Dis* 2010, 14(7):872-877.

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SUMMARY

Childhood tuberculosis is considered a major cause of morbidity and mortality in high burden TB countries. It has had a low priority for research and development globally and was not given much attention in the past on ways and means to operationalize the case management strategies within the context of National TB Control Programmes.

The current thesis focuses on various cohorts of childhood TB and audit of the case management practices within the routine national TB control programme of Pakistan. The thesis also documents the lessons learned during this research and development. Our initial retrospective cohorts were based on the review of patient records, focused on the case notification, treatment outcomes and case management practices of patients registered during two complete years 2004 and 2005, when NTP had no particular emphasis on childhood TB and had recently expanded the DOTS strategy for adults. These results we compared with those of patients registered during 2006 and 2007, when new NTP childhood TB policy guidelines were implemented. Based on this we developed and piloted the intervention ‘childhood TB deskguide and structured monitoring’ with a purpose to increase case notification and improve treatment outcomes. This intervention was implemented in one district during the year 2008 and compared with the same district in 2007(pre-intervention) and we also compared the intervention district with the two control districts in 2008 (all post-intervention).

After the NTP introduced their childhood TB policy guidelines there was an increase in case notification ($p < 0.05$) from 1.4/100 000 (95% confidence interval [CI] 1.0-1.7) to 5.2/100 000 (95% CI 4.9-5.6) but the treatment outcomes varied across the sites. Paediatricians also began to follow parts of the national policy guidelines for management of childhood TB including the use of the tuberculin skin test, chest radiography and score chart, but the record keeping of case management practices including diagnosis and treatment outcomes was inadequate. Later, in the district with the intervention package of childhood TB ‘deskguide and structured monitoring’ there was an increase in case notification from 17 cases (0.6/100 000) before to 37 cases (1.3/100 000) after the intervention. During the same period control *District A* had a reduction of 6% and control *District B* had an increase of 30%. There were also better

outcomes (treatment success 100% compared to 18% in control *district A* and 72% in control *district B*) and it helped standardize the process of care and augmented the NTP policy.

In conclusion, our results show that the management of childhood TB is possible under routine National TB Control Programme circumstances in Pakistan. However, there is a need to refine the intervention package and develop a training package for the paediatricians, clinicians and paramedics who are to be involved in the scale-up process for childhood TB case management.

1. INTRODUCTION

1.1. Tuberculosis

Tuberculosis (TB) is an infectious disease caused by micro-organisms called *Mycobacterium tuberculosis*. It is an ancient disease and has claimed its victims throughout the history earning the sobriquet, “Captain Among these Men of Death” by reaching epidemic proportions in Europe and North American, in the 18th and 19th centuries [1]. The presence of TB has been detected in a 5400 years old Predynastic Egyptian skeleton [2]. Robert Koch isolated and described the organism, *Mycobacterium tuberculosis*; he announced his results on 24th March 1882, the day the world celebrates TB Day. Koch confirmed the communicable nature of TB leading towards a recognized need to fight it. It is estimated that more than two billion people or a third of the world’s population have been infected with mycobacterium tuberculosis. The World Health Organization (WHO) has estimated that globally in 2009 there were an estimated 9.4 million incident cases of tuberculosis (equivalent to 137 cases per 100000 population) [3]. It is among the major diseases in the world causing deaths, killing 1.8 million people worldwide in year 2008. It is a dilemma that even in 21st century with availability of effective anti-TB drugs and investigations such a high number of people are dying due to a curable disease.

1.1.1. Tuberculosis control strategy

The TB control we see today has passed through various stages including periods with particular emphasis on sanatorium treatment (rest and good nutrition), vaccination with Bacillus Calmette-Guerin (BCG) screening with chest x-rays, and after the second world war the use of antibiotics for the treatment of tuberculosis. In the 1970s and -80s Dr Karel Styblo piloted nationwide in 5 low resource countries what became the model of TB control based on a managerial approach to case-finding and treatment [4]. In 1993 the WHO declared TB as global emergency and promoted Styblo’s strategy as the brand-name DOTS “Directly Observed Therapy, Short course”. It had five key components including government commitment, case detection by sputum smear microscopy, standardized treatment directly observed, uninterrupted supply of anti-TB drugs and standardized recording and reporting

system [4]. It was demonstrated to be a cost effective TB control strategy [5, 6] having a combination of technical and managerial components. With the DOTS strategy fully applied, the problem of multi-drug resistant TB (MDR-TB) could probably have been prevented.

The DOTS strategy has been introduced in more than 200 countries around the world and has helped to improve TB control efforts. In 2006 the WHO implemented its Stop TB strategy with a goal to reduce dramatically the global burden of TB in line with the Millennium Development Goals (MGD number 6, target 8) stating that TB incidence should have “halted by 2015 and begun to reverse”. The six principal components of the STOP TB strategy include pursuing high quality DOTS expansion and enhancement, addressing TB/HIV, MDR-TB and other challenges, contributing to health system strengthening, engaging all care providers, empowering patients and communities and enabling and promoting research [7]. These components were meant to contribute towards the World Health Assembly (WHA) resolution in which a global target of “cure rate” of 85% of sputum-positive patients treated and detection of 70% of estimated incident cases was set to be achieved by the year 2000. It became apparent in 1998 that these targets would not be met by the specified date and therefore WHA postponed the target year to 2005. Between 1995 and 2008, a cumulative total of 36 million TB patients were successfully treated by DOTS programmes, and up to 6 million deaths may have been averted. The number of TB cases notified in 2008 was 5.7 million and among the patients in the 2007 cohort, 86% were successfully treated; this is the first time that the target of 85% (first set in 1991) has exceeded at global level [8]. Programme performance is reflected in the number of cases with unfavourable or unknown outcomes, which are “failure”, “defaulters” and “transfers”.

The most important indicator for the evaluation of a successful TB control initiative is to know the “proportion of all cases that have defaulted from treatment” with an objective to have a very low number of defaulters [9]. It reflects the organization and performance of case management by implying that patients find the services accessible and appropriate and reveals the attitude of the health care provider offering TB services. Figure 1 shows a map with the estimated TB incidence rates in 2009.

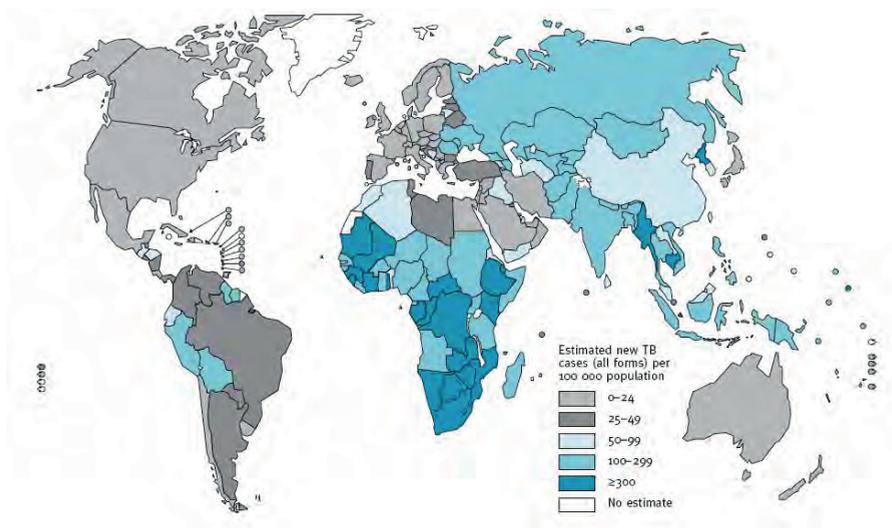


Figure 1: Estimated TB incidence rates, by country, 2009
(Global tuberculosis control: WHO report 2010)

1.1.2. Tuberculosis control in Pakistan

Pakistan ranks eighth highest in the world with regard to its burden of tuberculosis. The estimated prevalence, incidence and mortality of TB were 223, 181 and 29 per 100,000 populations respectively in year 2007 [10, 11]. The country is also facing a growing challenge of MDR-TB with 3.5% of new cases notified and 36.5% of re-treatment cases [12] and dealing with a huge private sector which is not very formally organized. The link of HIV infection increases the demands on global TB programmes, which are struggling to cope with the increased TB case load [13]. In the case of HIV, Pakistan has progressed from a low prevalence state to a concentrated epidemic country with estimated HIV prevalence among the general population currently less than 0.1% [14, 15].

The National TB Control Programme Pakistan (NTP) was rejuvenated in year 1999 and since then has constantly been expanding and sustaining TB control activities country wide using the DOTS strategy. In the early years the programme faced a major challenge to offer standardized TB care services to sputum smear positive cases

(mainly adults) in the country. To address this challenge the NTP was instrumental in gathering the required political commitment at all levels including evolving mechanisms to integrate TB services into primary health care, developing guidelines and training materials for managers and the various levels of health care providers and using national and international resources for procurement of anti-TB drugs and materials. In the recent past more initiatives in the country were introduced by the NTP, including TB control through public-private mix, external quality assurance system to enhance peripheral laboratories' performance through a system of national and regional reference laboratories, managing difficult to diagnose TB, hospital DOTS linkage (HDL) and MDR-TB control.

1.2. Childhood tuberculosis

It is estimated that among the 9 million cases each year, about 1 million (11%) occur in children (under 15 years of age) making tuberculosis one of the leading infectious diseases causing death among children. In countries worldwide, the reported percentage of all TB cases occurring in children varies from 3% to more than 25% [16] whereas the surveillance data from children in many countries is lacking with very few epidemiological studies [17]. During 2007 in Pakistan 3460 cases (4%) were notified in the age group 0-14 years out of a total of 88747 new smear positive TB cases, keeping in mind that in this age group often TB cases are not detectable by smear microscopy. This age group represents around 38% of the population in Pakistan.

In the absence of preventive chemotherapy, the burden of childhood TB is a reflection of the level of TB control achieved within a particular community, because TB in children results from recent transmission [18]. There is an identifiable source case in over 70% of cases, usually a relative or a friend [19]. Most of the children acquire the organism from adults [20] and congenital TB has also been observed [21]. Many experts feel that children have been neglected in the worldwide effort to control TB mostly due to the fact that most of them are less infectious, difficult to diagnosis and have been relatively neglected by paediatricians and researchers [22].

Few cases of childhood tuberculosis can be detected by sputum smear microscopy particularly the younger age groups, as the bacteriological population in case of childhood tuberculosis is often lower and children rarely develop pulmonary cavities. There are no reliable data or estimates for the incidence, prevalence, and mortality rates of childhood tuberculosis in most regions of the world. The natural history of disease in children studied during pre-chemotherapy era indicates that more than 95% of children who develop TB do so within 12 months after infection. Primary infection before 2 years of age may progress to a serious condition whereas that which occurs between 2 and 10 years of age rarely progresses to serious disease and if so it is associated with more significant clinical symptoms, whereas after 10 years of age it frequently progressed to an adult-type disease [23]. Infection in children is usually due to exposure to *Mycobacterium tuberculosis* from an adult or an older child who has sputum smear-positive PTB and often a family member [24] and the risk of progression to disease is up to 20% [13], which is greatest in infants (younger than 4 years) and which declines slowly reaching its lowest point at age 5-10 years[25]. The incidence of childhood TB rises in tandem with adult incidence and there is geographical clustering of child and adult TB cases. A child with drug resistant TB usually has primary rather than acquired resistance and previous drug treatment is easier to exclude [26]. A growing number of multi-drug resistance cases (MDR-TB) among adult TB cases with child contacts poses a future challenge in efforts to control childhood TB in high burden countries. The presence of HIV makes the diagnosis of TB in children more difficult for several reasons: a) several HIV-related diseases including TB may present in similar ways, b) the interpretation of the TST becomes less reliable and c) HIV-infected household contacts, especially parents, increase the chance of that child being infected with HIV[13].

Children will continue to suffer from TB as long as adults do. The huge burden of childhood TB in developing countries alerts us to the fact that the pandemic remains out of control and each case of tuberculosis in a child represents recent transmission in the community [27]. The WHO in its STOP TB Strategy emphasizes ensuring equitable access to care according to international standards for all TB patients, infectious and non-infectious, adults and children, with and without HIV, with and without drug-resistant TB [7]. For the successful implementation of childhood TB control NTPs need to standardize the care process by engaging all who provide care to

children and incorporating these approaches in their national guidelines and strategies [16].

1.3. Childhood TB case management

There are recognized difficulties with confirmation of childhood tuberculosis, which perhaps have contributed towards an erroneous thinking that the diagnosis of childhood TB is always difficult [28]. Several principles and issues related to the management of child with TB follow the same structure as for adults. However, the actual care delivery process for childhood TB is coupled with certain challenges.

1.3.1. Diagnostic challenges in children with tuberculosis

There are various diagnostic approaches and methods for diagnosing a child with TB in resource poor settings, but few are validated [29]. Also there are variable case definitions for childhood TB based on clinical symptoms and contact history, tuberculin skin testing (TST) and chest radiography. However, in the absence of simple criteria in a case of childhood TB the diagnostic task is challenging for a clinician. Establishing accurate diagnoses in children and access to the effective treatment will reduce morbidity and mortality in endemic TB setting [30]. To improve TB control among children, their management should be in line with the STOP TB strategy, considering the epidemiology and clinical presentation of TB in children. The key features that suggest a case of childhood TB may include; chronic symptoms suggestive of TB (such as prolonged cough, failure to thrive, enlarged cervical lymph nodes), physical signs highly suggestive of TB, a positive tuberculin skin test, chest X-ray suggestive of TB. The presence of three or more of the above mentioned features should strongly suggest a diagnosis of TB [16].

Contact with an adult index case:

A child should be suspected of being infected by *Mycobacterium tuberculosis* if there has been close contact with a person with TB. A contact is defined in a situation where “a child living in the same household or in regular contact with a person (e.g. care giver, grand parent) with highly infectious smear positive TB” [31]. The child

with TB disease usually presents with vague symptoms and signs which resemble other chronic diseases [32]. A history of having close contact with a sputum smear positive patient is therefore very important when considering a diagnosis of childhood TB, which is often a difficulty to obtain within a busy clinical care setting. The screening of children who have household contact adult patients who have smear positive TB is also a key to increase childhood TB case detection. To establish a contact history one could do special enquires about any symptoms, especially regarding cough, among living or recently deceased household members to identify previously undiagnosed or undocumented cases [24].

Contact screening should always be accompanied by a plan for starting preventive therapy in those found to have infection but do who have not yet developed disease. In order to improve the diagnosis of TB in children it is recommended by the WHO that all children aged 0-4 (whether sick or well) and children aged 5 and above who are symptomatic and in close contact with smear-positive TB cases must be screened for both TB infection and disease. This can be done with a simple clinical assessment in a routine outpatient setting. It has been the policy of NTPs, but rarely happens in high burden and resource poor settings including Pakistan. The constraints could relate to care provider ability including skills and dedication to manage prophylactic treatment, logistics constraints including adequate supply of isoniazid (INH) for prophylactic treatment, recording and reporting of such cases, follow-up arrangements and social issues related to initiation of preventive therapy. The INH prophylaxis recording and reporting is currently not happening in the context of TB control programme Pakistan.

Sputum smear microscopy

Sputum smear microscopy is a specific, cost effective, fairly quick and reliable test for the diagnosis of the most infectious forms of adult pulmonary TB. Sputum smear microscopy can be performed conveniently in a peripheral laboratory with a person trained on standard procedure, provided with a light microscope and reagents. The proper functioning of such arrangements does require an effective supportive supervision and external quality assurance system. The diagnosis of tuberculosis in children is difficult especially in infants and small children because the disease is

often non-specific [33] and paucibacillary, in which case the bacterial population is either too small to be directly detected under the microscope or is not collected in cavities in the lung (which are rarely present in pulmonary TB in small children) from which it is expelled in sputum. Moreover, children under 5 years of age rarely expectorate sputum. Due to limited resources, training of personnel, lack of time and priority, bacteriological diagnosis of TB in children is difficult and among the main reasons for usually under reporting of the cases [17]. In case of young children where it is difficult to get expectorate other techniques can be employed such as gastric aspirate, induced sputum, nasopharyngeal aspiration, broncho-alveolar lavage, urine/ stool and blood/ bone marrow [34]. With the techniques such as acid-fast smear of sputum or gastric contents, fewer than 20 percent of children with TB have a positive result [35] and even the culture yield is low (30-40%).

There are advantages and limitations with the application of these methods in resource poor settings. Children who are more than 7 years of age can usually produce sputum and with encouragement a good quality sputum sample could be collected. The WHO has recommended among the diagnostic approaches to have bacteriological confirmation wherever possible [16], but not mandatory for children. It is also recommended that children should be regarded as infectious if they show smear-positive pulmonary TB or have a cavity on chest X-ray. It is well documented that sputum induction is safe and useful for confirmation of TB in young children and is applicable in diagnosing pulmonary TB in both HIV-infected and HIV-uninfected infants and children [36]. These techniques can be used in high burden settings but require training and support to obtain good quality samples. A technique such as broncho-alveolar lavage is extremely invasive and should be used with caution. The samples from urine and blood require novel techniques which are currently less available in poor-resource settings.

Role of chest radiography

Chest radiography (CXR) is one of the frequently used investigations when investigating the child TB suspect. Chest radiographs with typical changes suggestive of tuberculosis should always be interpreted in conjunction with the proof of infection and symptoms of tuberculosis, TST and microbiological investigations in order to

avoid errors in diagnosis [37]. Some signs derived from reading a CXR which could indicate tuberculosis include lymphadenopathy (hilar or mediastinal) and lung parenchymal changes [29]. Furthermore while reading a CXR close attention should be given to observe; miliary mottling (mainly seen in cases that have disseminated TB), enlargement of lymph nodes (usually of hilar, mediastinal, or subcarinal glands), lung parenchymal changes (atelectasis, consolidation and effusion), pleural effusion, cavitation, parenchymal infiltrates and calcification. However, reading a CXR to diagnose intrathoracic TB in children has its own inherent problems in interpretation.

Children with tuberculosis and with non-tuberculosis pneumonia have many common features, with very few recognized distinguishing features of tuberculosis other than lymphadenopathy [38]. In some situations, the interpretation of CXR is difficult and clinicians while interpreting the findings of a CXR may give opinion based on their knowledge and practice, which in many cases may prove to be inconsistent. Based on the lack of specificity related to CXR it is suggested to be performed on children who are not responding to the anti-microbial treatment [39].

To help the clinicians in improving their skills in reading CXR, an illustrative atlas has been developed by the International Union Against TB and Lung Disease (The Union) for the health workers involved with childhood TB care which could provide an aid for the diagnosis of childhood TB [32]. The main purpose of this atlas is not to replace the opinion of a radiologist or specialist, but to assist those health workers where there is limited access to these services.

Tuberculin Skin Test (TST)

A positive tuberculin skin reaction is an indicator of past or present primary infection with *Mycobacterium tuberculosis* [29], but does not necessary indicate that the person has the disease tuberculosis. A negative TST does not rule out TB disease. A number of factors also contribute to false negative reactions of TST which may include; TST performed immediately after infection, overwhelming TB, children with debilitating or immunosuppressive illness, malnutrition and viral or bacterial infections (e.g. measles, varicella, typhoid or pertussis).

The Mantoux method is the recommended TST test for use in developing countries [16]. The most common technique used for the TST uses either 5 tuberculin units of purified protein derivatives (termed PPD-S and used in North America) or 2 tuberculin units (termed RT23 and obtained from Europe). A positive TST result may be seen in children and adults who have been given BCG as part of immunization. There are important limitations related to the use of TST in diagnosing the *M.tuberculosis* infection. Some of these limitations include; the conversion may be delayed up to three months after infection [23], its inability to differentiate when the primary infection has occurred [40], its limited value in HIV-infected children [41] and its reduced specificity in countries where TB is endemic and BCG is given during the neonatal period [42]. It is therefore very important that a stand alone positive TST test should not be considered as confirmation of TB in children. Several associated signs and symptoms, contact history and suggestive chest X-ray, need to be considered while interpreting the results of TST for making a childhood TB diagnosis.

The two major techniques currently used for carrying out TST include the intracutaneous Mantoux test and the multi-puncture method such as the Heaf and Tine tests [29]. The TST result should be read after 48-72 hours with an induration recorded in millimetres. A positive TST is designated when the induration in a non-contact is ≥ 10 mm and with a contact is ≥ 5 . Figure 3 shows the various steps involved in administering and reading a TST. In Pakistan any child with induration of more than 10mm should be considered as having positive TST.



Figure 3: Steps in tuberculin skin test (*Administering TST skin test NTP/ASD/ COMDIS Poster, 2009*)

Scoring Chart

The scoring chart (matrix) has been developed and tested in many part of the world including Zambia, Papua New Guinea, and Pakistan to support the diagnosis of children with TB. The purpose of the scoring chart is to simplify and standardize the scoring of clinical features (i.e. history and examination) and investigation results for making the diagnosis of child hood TB. In the scoring chart the conditions (i.e. mainly the clinical features and investigation results) are listed in the rows, whereas the individual score to these conditions are given in the columns. The score to any particular condition, ranging from '0' to '5', is determined on the basis of a pre-decided scale. Once all the conditions listed in the scoring chart are considered and individual scores are given, then the cumulative score (i.e. total of the scores for individual conditions) helps making the diagnosis.

The scoring charts have rarely been evaluated or validated and should be only used as screening tools [16] and perform poorly in children suspected with pulmonary TB and in children who are also HIV infected. One of the major limitations in these scoring systems is the poor symptom definitions [43]. A study conducted on the evaluation of the WHO criteria to assist diagnosis of TB in children has shown that the combination of three criteria has a positive predictive value of 63% in detecting cases of confirmed or probable TB.

Condition	Scores				
	1	2	3	4	5
Age	< 2 yrs				
Close contact in last 2 years	TB patient S -ve		TB patient S +ve		
BCG scar	Absent				
Low immune status	Yes				
PCM grade-3	Yes		Not improve		
Physical examination findings		Suggest TB		Strongly suggest TB	
Chest X-ray	Non-specific	Suggest TB			
Tuberculin skin test	5 – 10 mm		> 10 mm		
Granuloma	Non-specific				TB
H/o measles & whooping cough in the last:	3 – 6 months	< 3 months			

Figure: 4 Score chart: conditions and scores (*Childhood TB deskguide Pakistan 2008*)

However no useful value was obtained from the presence of only one or two individual criteria [44]. In resource poor countries these simple screening tools can be utilized at the health care facilities to help improve the TB diagnosis among children [45] and provide a model for epidemiological differences between target populations and help to select children for further investigation by radiography and bacteriology [46]. Figure 4 shows the score chart with its conditions and probable scores.

Other investigations:

Lymph node aspirates and biopsies, pleural aspirates and biopsies, histology and lumbar puncture are among the common investigation procedures to help diagnose extra-pulmonary TB. In many cases more technically sophisticated and expensive equipment is required such as use of PCR (polymerase chain reaction) and CT scan. Diagnosing tuberculosis in HIV-positive children or infants is even more difficult [9], if the HIV status is not confirmed. Simple and rapid HIV tests are recommended in such situations so that the diagnosis could be supported.

Some rapid culture methods have been developed and tested and are commercially available, but are still difficult to be implemented in the field settings. One of such test is rapid liquid TB culture medium (BACTEC MGIT 960) which is automated and standardized reading of samples giving positive result in seven days, but the equipment is expensive and requires regular technical support. There are commercially available rapid diagnostic tests (RDTs) but most of them vary widely in their performance. Antigen detecting techniques are also developed, such as LAM urine test and antigen-based detection test. The nucleic acid amplification (NAA) test includes amplified mycobacterium tuberculosis direct test, AMPLICOR MTB tests, Real time PCR, but they also have problems with costs and technical issues.

Recently the WHO has advised that implementation of the new rapid test i.e. Xpert MTB/RIF technology be phased in the context of NTPs and MDR-TB strategic plan [47]. This test has provided sensitive detection of tuberculosis and rifampicin resistance within minimal time [48]. It is found effective in the early diagnosis of TB, as well as MDR-TB and TB complicated by HIV infection, which are more difficult

to diagnose. The NTP Pakistan is also testing out this new test in its programme condition and likely will be available for implementation in near future.

1.3.2. Prescription of treatment and follow-up

A child who is a TB patient must be treated with the anti-tuberculosis drug regimens recommended by National TB Control Programme (NTP). The NTP recommended drug regimens are very effective and can treat successfully almost all cases of tuberculosis if used in the right dosage and for the right duration and provided that the disease is not caused by drug resistant organisms. It is very important to give the child a full course of treatment, which lasts 6 or 8 months (depending upon the category and the policy of the NTP). If the patient does not take the full course of treatment, the disease may recur and has a higher chance to be drug-resistant.

There were formerly challenges related to the anti-TB drug preparations of proven quality for the children, making the prescription option more difficult for the clinicians and also cumbersome for the intake by the patients. Recently with the availability of quality-assured child friendly anti-TB drugs and also the inclusion of them by the Global Drug Facility (GDF) in its product portfolio [49], many of the challenges related to prescription are addressed. The expected advantages of prescribing fixed dose combination drugs include: a) less prescription errors, mainly due to simple and easy dosage recommendation and adjustment, and b) better patient adherence, due to lesser number and types of tablets to ingest. The potential disadvantages include difficulty: a) to maintain optimum dosage of individual drugs across various patient-weight categories, and b) to manage patients who need to exclude one particular drug due to adverse reactions or side effects.

It is important to treat TB with the correct dosage of recommended drugs and to document the treatment. TB drugs are not effective if they are not given in the correct dose and according to the weight group of the patient. If the dose prescribed is less than the recommended dose, the TB bacteria may survive and become resistant to the drugs. If the dose is higher than recommended, the drugs may cause severe toxic effects. The revised childhood TB recording and reporting tools for the NTPs now carry a more detailed section to document and report the information on the children

being registered with TB, which may facilitate the process of follow-up of care to a child [50].

1.4. Programmatic developments in childhood TB control

Historically, childhood TB control has had a low programme priority in low-income countries with high TB burden. There is limited experience at international level regarding developing and implementing programme interventions for effective childhood TB control activities in routine NTP arrangements, especially high TB burden countries. Most of the NTPs seem to be inadequately strengthened to meet the challenge of tackling the problem of childhood TB.

1.4.1. International guidelines on childhood TB control

In the recent past encouraging progress has been made in the area of childhood TB control. International agencies and global experts by reorganizing the public health importance of this issue have started encouraging NTPs to respond to the childhood TB control needs and address its related programmatic issue.

The WHO has made childhood TB a part of their global STOP TB strategy [7]. The formulation of technical expert sub-groups on childhood TB in WHO and in The Union were also the signs of prioritizing childhood TB by the international agencies. The WHO with the support of its expert group in 2006 has developed the guidelines for NTP on the management of tuberculosis in children [16]. These guidelines were meant to fill gaps in the existing national and international materials and provide recommendation based on the best available evidence. The key set of WHO recommendations includes:

- All children should be managed under the Stop TB Strategy as part of routine NTP operations;
- Basic tools for diagnosis should be available, including chest X-ray and tuberculin skin tests;

- Children who are close contacts of smear-positive TB cases should have contact investigations;
- The diagnosis and treatment of TB in children infected with HIV merits special considerations, and in settings of high HIV prevalence, all children with TB should be offered HIV testing and counselling, and HIV-infected children should be offered the full range of available HIV services;
- Special care is needed in the diagnosis and management of children with drug-resistant TB;
- In line with the Expanded Programme of Immunization, BCG vaccination should be given to all neonates in countries with a high TB prevalence.

The International Union against TB and Lung Diseases (The Union) published a Guide in 2005 on management of the child with cough or difficult breathing containing sections on childhood TB [31]. There is also guidance from The Union on assisting the health care workers in low income countries to interpret chest radiographs of children suspected of having TB [32]. In addition there are specialized courses internationally on the management of childhood TB.

There is now a revised recording and reporting information system (TB R&R) recommended internationally and very recently adopted in Pakistan which has sections on childhood TB. The purpose of these revisions is to capture the crucial new elements of the STOP TB strategy in order to ensure standardization of data collection [51]. It is recommended that all children managed for TB should be included in the routine NTP R&R. This will help in getting the number of cases identified, registered for treatment and with treatment outcomes. The children should be recorded and reported in two age groups i.e. 0-4 years and 5-14 years. These age groups are helpful in assessing the anti-TB drug need and monitoring trends among children [50].

The uninterrupted availability of free-of-cost anti-TB drugs to the patients is one of the key elements of the DOTS strategy within NTPs in high TB burden countries. The equation is the same when we talk about childhood TB. The Global Drug Facility (GDF) has included the paediatric anti-tuberculosis drugs in its product portfolio. The GDF since its establishment in 2001 has supplied over 12 million anti-TB treatment mainly in the high TB burden countries [49]. The average cost of treating one patient

is estimated around US\$ 20 through GDF, which is substantially lower than the cost of the same drugs through other channels. Since 2006 around 115000 child-friendly treatments have been provided free of cost to various TB high burden countries. This had helped advocating NTPs to produce manuals that include a section on the diagnosis and management of childhood TB. In addition support from donors such as Global Fund against TB, Malaria and AIDS (GFATM) is also pooling into the NTPs for the implementation of childhood TB control interventions.

1.4.2. Childhood tuberculosis in Pakistan

So far there are no exact epidemiological figures of childhood TB for Pakistan. The NTP data for year 2002-04 reveals that 4.4% of registered cases were children of 0-14 years of age [52]. These figures represent an underestimation of the actual number of childhood TB cases that exist in the country. There are several reasons to believe this under-reporting of the registered cases. The NTP recording and reporting system previously used to capture all patients but only new smear positive were reported by age and children in most of the cases are sputum smear negative or unable to expectorate. Secondly, childhood TB care was not propagated in the mainstream TB control programme nationally due to challenges such as unavailability of child friendly anti-TB drugs, low coverage and diagnostic difficulties.



Figure 5: Diagnosing child with suspected TB in a district hospital of Pakistan (picture taken during the field visit at district hospital by *N.Safdar*)

1.4.3. Rationale: Childhood TB Control initiative NTP Pakistan

Since the year 2000 the public sector in Pakistan, including the hospitals, has been offering core TB DOTS services including diagnosis and free of cost treatment to TB patients with the NTP collaboration. The focus of this care has mainly remained on the management of adult TB cases a high proportion of whom are smear positive and infectious. After achieving 100% DOTS coverage in 2005 (which means that DOTS services are available in every district of the country), the NTP expanded its scope of activities including standardized care to the children. The NTP Pakistan worked in collaboration with Pakistan Pediatric Association (PPA) during 2006-07 and developed its national childhood TB policy guidelines [53]. The guidelines were then implemented in ten districts at district and sub-district level hospitals in the public sector, before scaling up to other districts. These separate guidelines for TB in children 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. The NTP also supported the basic strengthening of these hospitals by providing training, anti-TB drugs for the children and tuberculin skin test.

The rationale of our study was to understand the impact from the implementation experience of the NTP childhood care and to help finding solution(s) to some of the challenges related to childhood TB control in the context of national tuberculosis programmes in high TB burden and resource constrained settings.

2. OBJECTIVES OF THE STUDY

The *general objective* was to study the diagnosis and treatment outcomes among children with tuberculosis in Pakistan.

The *specific objectives* were to;

- 2.1.** Compare the case notification and treatment outcomes of children with TB before and after the implementation of the NTP childhood TB policy guidelines in 2006
- 2.2.** Compare the documented case management practices of pediatricians and its impact on the outcome before and after implementing the NTP childhood TB policy guidelines
- 2.3.** Assess the impact on case finding and treatment outcome with and without an intervention package (guidance document i.e. childhood TB deskguide and structured monitoring) comparing intervention and control districts in 2008
- 2.4.** Assess the impact on case finding and treatment outcome before and after an intervention package (guidance document i.e. childhood TB deskguide and structured monitoring) in intervention district in 2007-2008
- 2.5.** Describe the programme experience of developing and testing an intervention package, outlining lessons learned that augmented NTP policy to scale-up childhood TB control

3. MATERIALS AND METHODS

3.1. Study design

The study was an observational study with a cohort design. We studied the case finding and treatment outcomes retrospectively and prospectively with an intervention in one district having control and intervention districts (prospective) embedded in routine programme operations. The process of development and implementation was described as lessons learned from the field (policy into practice). It incorporated various aspects of programme related to inputs (guidelines, anti-TB drugs, materials, monitoring, etc), implementation of services (case management practices), evaluation of the outputs and seeing the impact of services based on the outcomes. Figure 6 illustrates the study design and its components based on study objectives. The design was adapted from the framework of the management model for the NTP [54]. The review of the regular NTP records allowed the evaluation of treatment activities which could be done by comparing the performance with the neighbouring areas (with almost similar epidemiological, socio-economic and environment situations) based on trends over time [9].

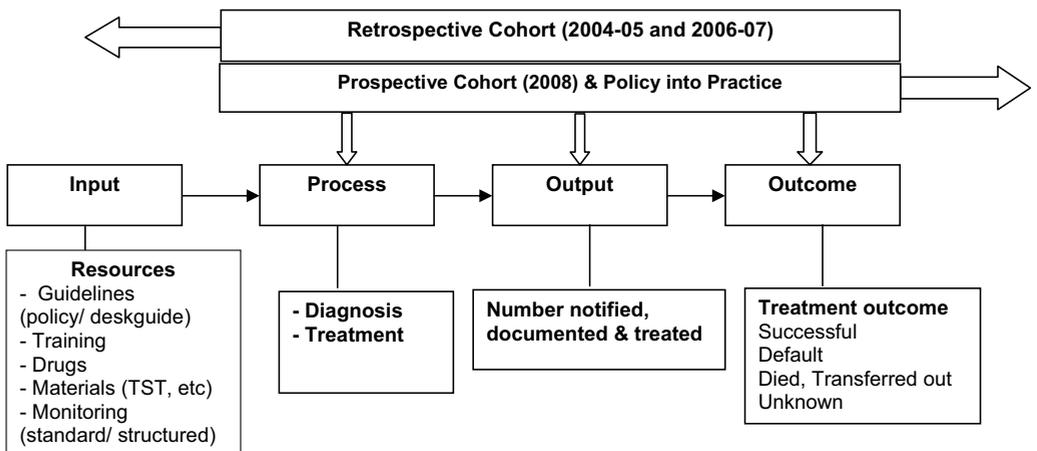


Figure 6: Flow diagram: Study components

3.1.1. Cohort study (historical)

The first part of the study was a historical cohort study based on review of patient records and focused mainly on case notification and treatment outcome. It also provided the audit of the case management practices with the same cohort of cases. We used two cohorts of childhood TB cases i.e. the first cohort was patients registered during two complete years 2004 and 2005, when NTP had no particular emphasis on childhood TB and had recently expanded the DOTS strategy for adults. The second cohort was patients registered during 2006 and 2007, when new NTP childhood TB policy guidelines were being implemented. In these studies we used the definition of NTP/WHO for childhood TB diagnosis, case management and treatment outcomes [53], which are explained in section 3.4.

3.1.2. Intervention study (prospective cohort)

The second part of the study was an intervention in which package of a specific guidance document ‘childhood TB deskguide and structured monitoring’ was added in one district during year 2008, along with the on-going NTP childhood guidelines implementation.. The outcomes of the intervention district were compared with control districts (same months, 2008), and were compared with historical outcomes in the intervention district (same months, 2007). All districts enrolled patients in the year 2007 when the policy on childhood TB was implemented by NTP. Then one district introduced the specific guidance document ‘desk guide and structured monitoring’ during 2008 (May-Dec).

The intervention was implemented early in the process, which refers to the implementation of intervention where inputs and circumstances were kept close to routine programme arrangements for future replication. The intervention package was tested with the ongoing childhood TB care in a district and evaluates the effectiveness by comparing different time periods and also other districts.

The guidance document of childhood TB case management deskguide combined with structured monitoring was developed on the concept of an adult TB deskguide [55]. It was meant to be integrated into the general TB care delivery process within the

hospitals. The childhood TB deskguide (*Appendix-A*) was developed through a consultative process, as an operational care delivery tool for the children suspected of having tuberculosis. It was based on national and international guidelines and literature for managing childhood TB [16, 53, 56]. The short statements and decision tables, covering technical and operational details of case management tasks, made the deskguide a handy aid for health care workers.

The monitoring of services always plays a pivotal role in the success of a health intervention. Since the integration of TB control services into the routine district health system in Pakistan, there was a designated district TB coordinator (DTC) in each district looking after the TB control activities. A structured monitoring tool (*Appendix-B*) was developed for the DTC so that he could use it during his routine monitoring visits to a hospital. The tool consisted of inputs indicators including the base line supply of anti-TB drugs, TST, print materials, etc. It also took into account the availability status of the care providers trained on the guidelines on monthly basis to address the issues related to staff attrition. The tool also included a tabulated version of the output indicators including the number of suspects, case registered and their categories and follow-up information. The tool was made the part of the DTC regular monitoring events to facilitate him making timely decisions.

3.1.3. Policy into practice (lessons learned)

The last part of the study describes the programme experience of developing and testing an guidance document, outlining lessons learned that augmented NTP policy to scale-up childhood TB control. It explains the translation of childhood TB case management research into operational policies following an operational research approach.

Operational research has begun to be appreciated in the global scientific and donor communities. There are many definitions of operational research. However, from a health programme perspective a pragmatic definition is as follow: the search for knowledge on interventions, strategies, or tools that can enhance the quality, effectiveness, or coverage of programmes in which the research is being done [57]. Retrospective and prospective cohort analysis is among the methods employed in

operational research. The operational research is important in improving the programme outcomes in relation to medical care or prevention, assessing the feasibility of a new strategy or intervention and to advocate the policy change.

3.1.4. Inclusion and exclusion criteria

The study data was extracted based on following criteria;

Inclusion criteria of children with TB:

- Districts participated in NTP childhood TB management pilot
- Geographic location (three districts of province of Punjab, Pakistan i.e. Jhelum, Kasur and Muzaffargarh)
- Age less than 15 years (male and female)
- Government hospitals registered TB patients (district and sub-district)
- Time period years 2004-2007 and May-Dec, 2008

Exclusion criteria:

- Private sector (general practitioners, homeopathic and traditional healers)
- Para-government run hospitals (serving railways, social security, army; government owned but not serving the general public)
- Maternal and child health centres
- Primary health care centres

The key co-determinants in the study are age, sex, and geographic location. The outcome measures were the TB case notification including the type of disease (pulmonary and extra-pulmonary) and treatment outcomes (cured, treatment completed, died, transfer out, failure, default and unknown).

Diagnosis by clinicians was based on the combination of history and examination suggestive of TB, history of close contact with an adult case of TB, bacteriological examination, chest X-ray, TST and histopathology of tissue samples. In addition there was a scoring chart to help in making diagnostic decisions. The prescription was based on body weight of the patient and the category of disease. The outcome was

based on the investigation results, duration of treatment, and death during treatment and transfer to other district.

3.2. Study sites

The NTP selected a total of ten districts in Pakistan representing all four provinces of the country, to introduce the implementation of the policy guidelines about childhood TB care. The selection of districts by the NTP was based primarily on evidence of functioning adult TB care in the district, geographic distribution and access, and willingness of districts to participate. For our study we selected the province of Punjab for the intervention study because of the availability of continued programme support, including drugs and materials, which made implementation more feasible under programme circumstances. For the historical cohort studies three districts in Punjab in which the NTP strategy was being first implemented, with all nine district and sub-district level hospitals, were included. Figure 7 presents the study locations in the province of Punjab. The three districts represent southern, central and northern parts of the province. The district Kasur had a population of 2.9 million whereas the district Jhelum had a population of 1.2 and Muzaffargarh 3.2 million respectively. All childhood TB cases registered at these hospitals [58] during the period under review were included in the study.

For the intervention study the same three districts (in which the historical cohort study was conducted) were selected among which one district was the intervention district and the two other were control districts.

In principle this was a pilot of a deskguide and as such needed no sample size calculations. Furthermore, the selection of districts and the inclusion of cases were restricted due to its inherent circumstances i.e. the research arrangements were kept close to the routine programme arrangements for an early implementation phase. Figure 8 presents the overall research setting in which the study was conducted.

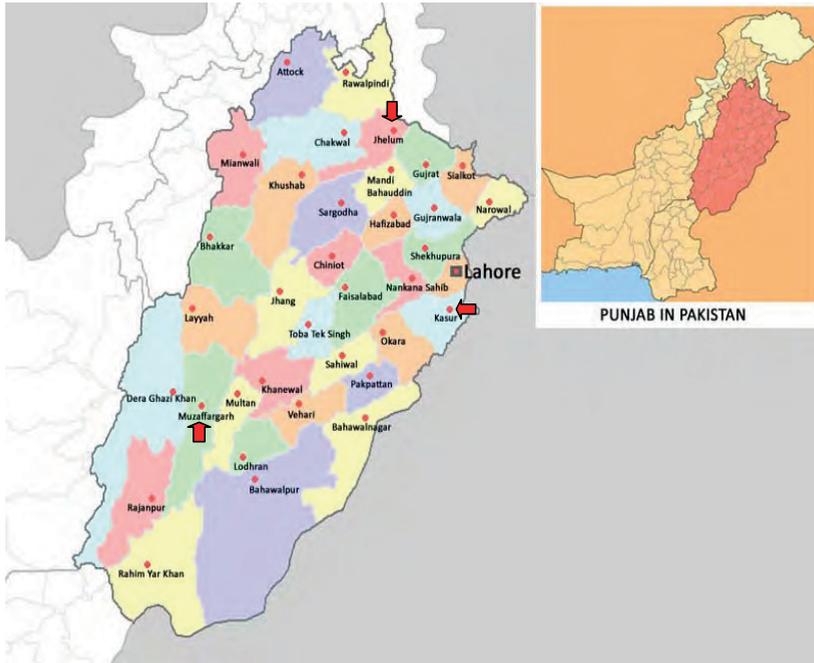


Figure 7: Location of three study districts in province of Punjab-Pakistan

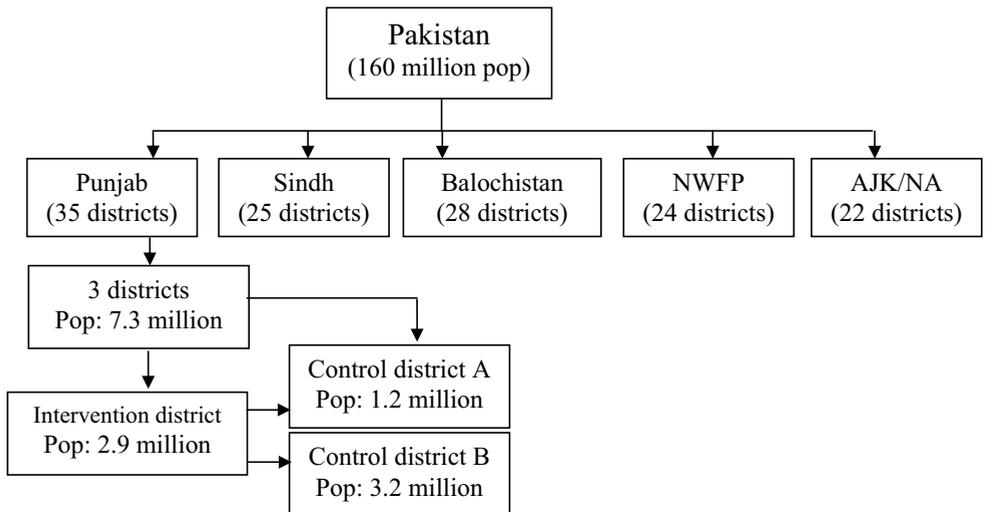


Figure 8: Research setting (historical cohort and intervention study)

3.3. NTP Pakistan arrangements

Health care in Pakistan is a provincial responsibility and the district is responsible for offering health care services to urban and rural communities [59]. Within each district there are public sector district and sub-district level hospitals having specialized services. They are the urban health facilities but have ill defined catchment area and are responsible for routine and referral health care services. The first level of primary health care to the rural communities is mainly through the rural and basic health units. There is also a set up of maternal and child health centres (MCH) and population and welfare centres. In addition to these facilities, a typical district also has other sources of health care including; a) private sector which mainly consists of general practitioners, hakeems and homeopaths, b) non-government organization (NGO) run hospitals and clinics, c) government hospitals that serve special government institutions, mainly social security, army, railway and energy authorities.

In NTP Pakistan the TB control services after integration into the routine district health system, functions through diagnostic centres (average 12-15 in public sector in a district) and treatment centres. The diagnostic centre diagnoses and manages a TB case including follow-up and reporting. It needs to have its own laboratory with a laboratory technician who will perform the sputum smear microscopy. A treatment centre delivers the anti-TB drugs and is accessible to the patients. In addition there is a network of community health workers under the primary health care who are involved in the treatment support component related to the patients. The anti-TB drugs and materials are mainly facilitated by the TB control programme and managed through district health authorities by a designated DTC.

The diagnostic centres after registering the TB cases send their quarterly reports on case finding and treatment outcome reports to the district TB coordinator office. The district TB coordinator office then consolidates these quarterly reports and transmits a quarterly consolidated district reports on case finding and treatment outcome to the provincial TB control office. There are regular quarterly intra- and inter- district meetings to consolidate reports to avoid errors and to facilitate the progress. The new smear positive cases are reported in 7 age bands and children are in band 0-14 years.

The new 0-4 and 5-14 age band for the children was not used at the time of the study in the regular reporting system.

3.4. Definitions used in the study

3.4.1. Case definitions

In our study we used the definitions of the NTP and WHO to designate a case of childhood TB [53]. A ‘new case’ of TB is a patient who has never before been treated for tuberculosis or who has previously been treated for less than four weeks. ‘Transferred-in’ is a patient who has been transferred from a TB register in another district to continue treatment. ‘Treatment after failure’ is any patient who returns with symptoms to another treatment after having been declared a failure during a previous course of treatment (see definition below). ‘Treatment after default’ is a patient who returns to treatment after interrupting previous treatment for two months or more. ‘Relapse’ is any patient who requires treatment again after being previously documented to have been cured of a previous episode of TB. However recently in 2009 the WHO has updated its definitions [60].

3.4.2. Regimens of anti-TB drugs

The regimen prescribed was based on the category assigned. The four treatment categories are as follow: Category- I is new smear positive pulmonary TB, severe forms of new extra-pulmonary TB, new severe concomitant HIV disease and TB meningitis. Category-II is previously treated smear positive pulmonary TB (relapse, treatment after interruption and treatment failure). Category-III is new smear negative pulmonary TB and less severe forms of extra-pulmonary TB. Category-IV is chronic and MDR-TB. The drugs prescribed to a child diagnosed with TB always have an intensive phase of 2 to 3 months duration and a continuation phase of 4 to 6 months duration. The anti-TB drugs dosage depends on body weight and category of patient [53]. Category I is 2 months of Isoniazid (H) plus Rifampicin (R) plus Pyrazinamide (Z) plus Ethambutol (E) followed by 4 months of H and R (abbreviated 2HRZE/4RH), for category II Streptomycin (S) is also added, it is 2HRZES/ 1HRZE/

5HRE, for category III, it is 2HRZ/ 4HR and for category IV, treatment is individualized.

3.4.3. Treatment outcomes

The treatment outcomes used in this study follow the NTP Pakistan definitions [53] which NTP has adapted from the WHO guidelines of that period. ‘Cured’ is defined as initial positive chest x-ray (CXR) (with or without gastric or other specimen AFB smear or culture positive) of a child who has completed the treatment and responded clinically with or without full radiological improvement at the end of treatment. ‘Completed’ is initial positive CXR (with or without gastric or other specimen AFB smear or culture positive) of a child who has completed the treatment and responded well but had no radiological examination at the end of treatment or any child who received a full course of treatment (6-8 months). ‘Failure’ is initial positive CXR (with or without gastric or other specimen AFB smear or culture positive) of a child who has remained, or became again, smear positive or demonstrated a worsening CXR two or more months after commencing treatment, or smear negative found smear positive or worsening of CXR at the end of 2nd month with or without clinical symptoms compatible with TB. ‘Defaulted’ is a child who at any time after registration had not collected drugs for two consecutive months or more. ‘Transferred out’ is a child transferred from one facility to another and the outcome is not known. ‘Died’ is a child who is reported to have died for any reason during the course of treatment. There were cases where documented outcome was not available and hence were categorized as ‘Unknown’.

3.4.4. Other definitions

The term ‘practice’ in this study is the paediatrician’s documented record of case management, which should be based on NTP childhood TB policy guidelines. The absence of such records was termed as ‘missing information’. The *missing* in terms of diagnosis includes missing information on the use of TST, chest X-ray or score charts. In the case of prescribing anti- TB treatment *inadequacy* was used to denote prescriptions that were not correct for all drugs according to category and dose.

3.5. Data collection and analysis

The NTP has introduced its standard TB recording and reporting registers and forms with unique patient number and specific purpose in all of its diagnostic centres in the country. The prime sources of the data collection for our study were the TB registers, TB treatment cards and quarterly reports. The details on period of data collection were already described in the section 3.1.1 and 3.1.2 above. A researcher visited each hospital to review the patient records and extract relevant data, using a specially designed manual tool (appendix B). The quality of data extraction was ensured by another researcher by cross-checking the extracted data for missing information and inconsistency. Data were entered and analyzed mainly using the SPSS version 12 and 15 software package (Statistical Package for the Social Science, Chicago, IL, USA). The Pearson's χ^2 test was used to compare group differences of categorical variables. The student *t*-test was used for continuous variables. The level of significance was set at $P < 0.05$.

In Paper I we compared notification and treatment outcomes retrospectively before and after the implementation of a Child TB policy guideline by the NTP. In Paper II we compared management practices of the same cohorts. In Paper III we compared notification and outcomes in a district with an intervention and two districts without it. In Paper IV the process and development and lessons learnt are outlined.

3.6. Ethical clearance

Ethical clearance was obtained from the National Bioethics Committee (NBC) Pakistan which is managed by the Pakistan Medical and Research Council (PMRC) in Islamabad under the Ministry of Health, Government of Pakistan (*Appendix-C*).

4. SUMMARY OF THE RESULTS

The key findings related to paper I-III are described in the section below. Paper IV was based on the summary of the lesson learned and recognition related to the previous three papers.

4.1. Diagnosis and outcome of childhood tuberculosis: implementing public health policy in three districts of Pakistan (*Paper I*)

This was a retrospective cohort study following all children aged <15 years placed on TB treatment in public hospitals under the National TB Control Programme (NTP) in the districts studied. The objective was to determine case notification of children with tuberculosis (TB) and the outcome of their treatment. The study period was 2 years before and 2 years after the implementation of new NTP policy guidelines for childhood TB. Data were collected from all nine public sector hospitals in three districts of Pakistan from hospital TB registers, patient treatment cards and quarterly reports. The study showed that with the introduction of the new NTP policy, case notification of childhood TB increased from 189(2004–2005) to 731 for the 2 years 2006–2007. The annual notification rate of childhood TB cases increased from 1.4 (2004–2005) to 5.2 per 100 000 population (2006–2007). Of the total 920 childhood TB cases registered, 610 were pulmonary, 202 extra-pulmonary and the remaining 108 unclassified. The three-fold increase in case notification was accompanied by a lack of follow up, resulting in an increase in unknown treatment outcomes from 21.7% to 73.3%. We concluded that managing children with TB in routine NTP practice is possible, but without adequate operational guidelines and careful monitoring, expanding services and follow-up, it can lead to suboptimal results.

4.2. Are children with tuberculosis in Pakistan managed according to National programme policy guidelines? A study from 3 districts in Punjab (*Paper II*)

An audit of case management practices of a historical cohort was carried out in children below 15 years of age who were put on anti-tuberculosis treatment at all nine public hospitals in three districts in province of Punjab. The objective was to compare the documented case management practices of pediatricians and its impact on the

outcome of treatment before and after introducing NTP childhood TB policy guidelines. The study period was two years before the guidelines (2004-05) and two years (2006-07) after implementation of new NTP policy guidelines for childhood TB. The study showed that among 920 childhood TB cases registered during four years, 189 before and 731 after the guidelines, the practices changed significantly in terms of the use of the tuberculin skin test (63% of pulmonary cases, 19% of extrapulmonary cases and 67% for site unknown), and for the use of chest x-ray (69% of pulmonary cases, 16% of extrapulmonary cases and 74% for site unknown). Diagnostic scores were recorded for only a minority of cases (18%). The proportion of correct drugs and their dosages before and after guidelines remained the same. There were unknown treatment outcomes in 38 (27%) of 141 cases before guidelines and 483 (87%) of 551 cases after guidelines, all among the 692 cases without documented treatment supporter. We concluded that paediatricians have started following parts of the national policy guidelines for management of childhood TB. The use of diagnostic tools increased but record keeping of case management practices remained inadequate. This seemed to increase case finding substantially but the treatment outcomes were poor mainly due to poor recording (unknown outcomes). Development and implementation of standardized operational tools and regular monitoring system may improve the services.

4.3. Childhood tuberculosis deskguide and monitoring: An intervention to improve case management in Pakistan (*Paper III*)

An intervention study was conducted with cohort design within a routine TB control programme comparing case findings and treatment outcomes before and after the intervention, and in districts with and without intervention. The objective of the study was to measure effectiveness of an intervention package of guidance document i.e. deskguide and monitoring tool by comparing tuberculosis (TB) case finding and treatment outcomes among districts in 2008, and performance assessment in intervention district. We enrolled all children below 15 years registered at public hospitals in three districts. The data was collected from public sector hospital TB records. The results showed that in eight months during 2007 there were 164 childhood TB cases notified, and after intervention in 2008 a total of 194 cases were notified. In the *intervention district* case finding doubled (110% increase) and correct

treatment practice significantly increased over the eight months. Successful outcomes were significantly higher in *intervention district* (37,100%) compared to *control district A* (18, 18%, $p<0.05$) and *control district B* (41, 72%, $p<0.05$). We concluded that the childhood TB deskguide and structured monitoring was associated with improved case management and it augmented NTP policy. More development and implementation in all health services of the district are indicated.

4.4. Translating childhood tuberculosis case management research into operational policies (*Paper IV*)

We summarized the lessons learned based on our three studies to outline programme experience of developing and testing policy guidelines and subsequently the guidance document that augmented NTP policy to scale-up childhood TB control. The National Tuberculosis programme (NTP) in Pakistan has been instrumental in providing policy guidelines for the management of childhood TB and later a guidance document of ‘childhood TB case management deskguide and structured monitoring’. The NTP Pakistan has demonstrated the implementation of childhood TB interventions in the routine programme context based on systematic development. The initial results were encouraging however more development in order to improve the quality is the key area where further programme attention is required.

5. DISCUSSION

This section describes the methodological issues including the strengths and limitations of the studies. It also discusses the major findings related to each of the papers.

5.1. Methodological issues

5.1.1. Study design

The study was an observational study with a cohort design. It was designed to review various aspects of programme performance with and without intervention, and to examine trends over time related to selected indicators. This objective could have been addressed by a randomized controlled trial based on cluster-sample, but the purpose was to keep the research close to the routine programme arrangements being at an early implementation phase. This would provide a basis for future refinement and scale-up under routine programme conditions.

5.1.2. Selection of study districts

We selected three districts, all from Punjab province from the ten districts chosen by NTP to start the implementation of NTP childhood TB policy in year 2006. The ten districts represent the four provinces of the country and are from Punjab (3), Sindh (3), NWFP (2) and Baluchistan (2). The selection of these ten districts by NTP was based primarily on the evidence of functional adult TB care in the district, geographical distribution and willingness of the districts to participate. It would have been more useful for the generalisability of our study results if we had randomly selected a cluster-sample from all the four provinces representative of the entire country. Due to the available resources, time and access limitations we focused on the districts of Punjab province by selecting all the three districts.

5.1.3. Analysis

Papers I and II addressed research questions by collecting data from similar sites and comparing two years each i.e. two years before and two years after the NTP implementation of policy guidelines. In paper III the time period was limited to eight months for the inclusion of cases during the intervention period. In order to avoid an influence of seasonal variation, the study focused on the same months in the intervention year and in the previous year both in the intervention and control districts. As this study was an early implementation experience we had no sample size calculations.

5.1.4. Definitions and bias

The definitions related to case management and treatment outcomes were based on the NTP/WHO policy guidelines which existed during the study period. Recently new definitions of NTP/WHO have been introduced which will be considered during the process of scale-up of these guidance documents.

There might have been a few cases that had died after being diagnosed but their outcomes were not reported in the routine data in the hospitals. We were also unable to trace them in the community which may have resulted in some increase in numbers of cases reported as unknown treatment outcome. We were also not able to include the private sector and all types of public sector facilities in our study. This would have provided a better figure on the notification of childhood TB cases in the study districts. The bias that would have been related to the research arrangements in the intervention district termed as Hawthorne effect has been explained in the section 5.3.2.

5.2. Discussions of major study findings (paper I-IV)

5.2.1. Case notification trends in different periods

Papers I and paper III focused on the case notification trends observed in different study periods of childhood TB implementation in the three districts of Pakistan. A

historic cohort of children with TB diagnosed and registered during 2004-05 (i.e. before implementation of NTP guidelines) was studied through record review. A second historic cohort of children with TB diagnosed and registered during 2006-07 (i.e. after implementation of NTP guidelines) was also studied. After the introduction of the guidance document comprising a desk guide and a monitoring tool - a prospective cohort of children diagnosed and registered during May – December 2008 was studied in one intervention and two control districts, and also compared with same months in 2007. After the implementation of policy guidelines for childhood TB there was a marked increase in case notification rate, from 1.4 to 5.2 per 100000 population. There was also significant improvement in case notification associated with the implementation of a childhood TB deskguide and structured monitoring in the intervention district which doubled in eight months, from 17 (0.6/100000) before to 37 (1.3/100000) after the intervention. The intervention district showed 110% increase in case notification whereas in the *control district A* the case finding was reduced by 6% whereas in the *control district B* an increase of 30% in case notification was observed during the same eight months. The deskguide being a case management tool provided an additional opportunity to the care givers in the intervention district to be sensitized and have access to a quick reference to attend a child TB suspect.

The results of the studies reported in paper I and III do not represent the total number of childhood TB cases which may have occurred during these months in the three districts studied, because the study focused on only public district level hospitals. The absence of exact national childhood TB incidence and prevalence statistics [53] and also the exclusion of the intervention from other public health outlets and private health sector, makes it difficult to estimate the proportion of childhood TB cases currently being dealt with by the NTP policy guideline implementation and subsequently the deskguide and structured monitoring intervention in these districts. Given the low rate of childhood TB case notification, the high TB incidence and the pattern of public health sector utilization, more childhood TB cases probably occur than those that are notified to the NTP. In Pakistan health sector is very diverse and only around 20% of all care is provided by public sector doctors [61]. They may be managed by the private sector which includes general practitioners and homeopathic and traditional healers. In the public sector care may be given by primary health care

centres and government-run hospitals and may also be informally referred to specialized and tertiary care hospitals in the adjoining districts. In the case of Malawi where TB care is mainly through the public sector, there is a more representative picture of case notification of children (11.9% of total cases) [62]. Similarly, in Papua New Guinea the 2005-06 data shows that childhood TB contributed to 31% of total case load in the four provinces studied [63].

The purpose of the studies reported in papers I and III was not to have an intra-hospital or intra-district comparison of case notification. However, the enhanced childhood TB case finding did show variation across three districts. This variation seems more related to difference in the practice of individual paediatricians and also the phase of DOTS expansion rather than the difference in disease occurrence and programme inputs. One of the districts, indeed a single hospital, showed a remarkable increase in case notification in the first year of programme intervention. There were few cases notified in the age group 0-5 years as compared to the age group 6-14 years. This low case finding reflects the diagnostic challenge for the paediatrician in Pakistan.

5.2.2. Case management practices in childhood tuberculosis

Papers II and III examined the case management practices observed in different study periods. The improvement in case management practices is among the priorities in childhood TB control [64]. There is now a revised recording and reporting information system (TB R&R) which has sections on childhood TB. Children should be registered separately for age 0-4 and 5-14 years [51]. It is recommended that all the children managed for TB should always be included in the routine NTP R&R. This will help in getting the number of cases identified, registered for treatment and with treatment outcomes [50]. The NTP has provided the training and logistic support including TST and anti-TB drugs to initiate the childhood TB care in the public sector district level hospitals.

The results of paper II revealed that the use of tuberculin skin test after implementation of the NTP guidelines increased. The TST was not initially available from the programme and after the implementation of the new policy its use by the

pediatricians in the programme conditions was encouraging. The TST as a tool to support diagnosis of TB among children is well established and still considered to be the best available method to detect TB infection [65]. It can be used as an adjunct in diagnosing TB disease [66] and a regular stock of tuberculin should be maintained in hospitals involved with managing childhood TB [67]. The documented use of chest radiographs to assist in diagnosis increased among both pulmonary and extra-pulmonary TB cases. The use of CXR in making the diagnosis of children with TB has been supported internationally and a majority of cases with children with pulmonary TB have CXR changes suggestive of TB [66]. The CXR should always be read by a trained health care provider. Since NTP adopted the DOTS strategy in 1995 the emphasis remained on the use of sputum smear microscopy which downplayed the importance of CXR in supporting the diagnosis of smear negative TB. In a study in Malawi over 80% of the childhood TB cases the CXR findings were consistent with TB [68]. The increased use of CXR emphasizes the need of structured training of health care providers on reading the CXR among children with TB; if not done it may have consequences on the quality of diagnosis and care. The NTP policy guidelines on childhood TB had a section on the use of X-ray to help the paediatrician diagnose a child with suspected TB. The quality control mechanism was not well defined with a possibility of missed cases or over-diagnosis. To address this limitation the NTP Pakistan has recently developed a training module having sections on reading chest X-ray in children, adapted from international literature, which will address this important issue related to case management. There are also international guidelines available to assist the health care workers in low income countries to interpret chest radiographs of children suspected of having TB [32]. The diagnosis of TB in low-income countries needs to be improved based on the available technology and resources [67].

In our study some children had sputum smear done, although this proportion did not increase with implementation of the new policy guidelines. Very few of the cases below 5 years of age had sputum smears done, which shows the challenge faced by the health care providers in getting smear done in very young children within routine programme conditions. The NTP childhood TB case management policy and involving pediatricians in TB control activities are recent activities. We observed an increase in case notification during post guideline implementation phase but the

linkage between various facilities to operationalize diagnostic algorithms within the hospital was limited. The role of laboratory services in childhood TB diagnosis including sputum smear microscopy and specimen collection by gastric lavage was not well defined. The operational linkages between the pediatricians and laboratory services need to be strengthened in order to enhance sputum microscopy among children suspected of having TB. Similar operational issues are relatively common in the start of a new initiative and gradually improve with programme implementation. More training is required regarding introduction of techniques such as gastric lavage and induced sputum within routine programme situation in order to increase sputum smear microscopy among children. The use of the score chart was introduced by the new guidelines. The score chart helps suspect screening [16] and the NTP policy-aim is to have a score of each case diagnosed. The use of a score chart has been suggested in the situations where accurate diagnosis of childhood TB is complicated by the lack of diagnostic tools and facilities [69]. The diagnostic criteria documented in the score chart are simple and well structured and can be applied in resource poor settings like the health facilities we have in Pakistan. More attention should be paid by the health care workers to document the use of score charts.

Our study has shown that the proportion of cases with a correct treatment regimen did not change from before to after policy guideline implementation. There was wide variation in the practices of paediatricians regarding prescribing anti-TB drugs to the diagnosed children and none of the doses prescribed were found to be recorded correctly. To have good treatment outcomes the application of standardized treatment regimen needs to be according to the relevant diagnostic category [70]. The findings in paper III showed that the recording and reporting of the notified cases improved in the intervention district after the deskguide and structured monitoring and was associated with a documented improvement in correct treatment practices.

5.2.3. Treatment outcomes

Paper I discussed the treatment outcomes observed before (2004-2005) and after (2006-2007) the implementation of NTP policy guidelines. The study clearly indicates that in the absence of adequate case follow-up measures in place, the potential gain from increased case finding is lost by an increase in proportion of cases with

treatment outcomes unknown. In Malawi and Papua New Guinea an unknown outcome was reported in 21% and 23 % of notified cases [62, 63]. This is an important programme implementation issue and must not be ignored. Experiences with adult TB care show that similar operational issues are relatively common in the beginning of a programme and then gradually settle down with improvement in programme implementation. We observed a decrease in the default rate over the time from 16.9 % before to 4.6 % after the intervention. An example of decrease in default rate is the province of Punjab, where default changed from 21% in 2002 to 6% in 2006 (unpublished NTP reports). However, assessing the default separately among children and adult TB cases has not been possible from routine quarterly programme reports. In a study from Brazil, a default rate of 24.4% was observed among children with 42.4% among those above 1 year [71]. Multiple studies have identified factors contributing to default of TB patients including inadequate knowledge, lack of family support, economic factors, medicine side effects, availability of medicines [72-74]. Various studies have shown improvement in treatment outcomes achieved with late patient tracers and reminders [75], motivation [76], and patient support. The implementation of DOTS strategy among pulmonary childhood TB patients in India has shown success rate up to 95.4% with time [77]. However, operational research has been limited on determinants of childhood TB default and its reduction strategies.

Paper II revealed that the treatment support and treatment outcome were recorded in a low proportion of the children during the period 2004-2007, and that the proportion of cases documented as cured was even lower in the post guideline implementation than in the pre guideline period. To have good treatment outcomes the application of standardized treatment regimen needs to be according to the relevant diagnostic category [70]. This suggests that NTP could benefit from more stringent process monitoring of the childhood TB care to improve practices. Improving the care delivery process among children also requires more emphasis by NTP on the treatment support component.

Paper III revealed that the deskguide and structured monitoring helped to improve treatment outcomes in the intervention district during 2008. The comprehensiveness of reporting of treatment outcome was also improved. The global interventions such as revised TB recording and reporting system (TB R&R) is among recent measures to

promote high standard of individual patient care, adherence to treatment regimen and transfer of information between health facilities [78]. Our study also supported the concept of operational research in which the research determines how such interventions are translated into benefit in the heterogeneous setting of routine care [57].

5.2.4. Implications on policy and practice

The operational research within the context of national disease control programmes may enhance programme effectiveness. Key factors that enable operational research in our setting include addressing the constraints to TB control, planning within the NTP setup, using the established NTP system and being able to move fast to help influence policy and practice [79]. In the recent past there has been a stronger emphasis on linking disease control with various research initiatives in the country [80] considered a way to bring policy change and improvement in practice [81]. The NTP Pakistan has demonstrated the implementation of childhood TB interventions in a routine programme context. The results of studies on childhood TB case management in Pakistan were encouraging. The systematic development of guidelines and application of research to guide the development of policy was followed by better results. The interventions to bring evidence into practice have not been developed and tested extensively in developing countries, and the need to put ‘what works’ into practice is particularly important in resource-poor countries [82]. There are arguments related to the process of development of guidelines and if they are not developed in a rigorous way, it could affect the process of actual care [83]. However, there is substantial evidence that guidelines are a repository of information and contribute to the practice of medicine, the quality of care and patient outcomes [84].

It is of crucial importance to understand the health services context in the country while developing public health research into interventions and while evaluating guidelines within a disease control programme. The guidelines need to address the local needs including quality of care and patient outcomes. One of the key steps is to ensure that the existing evidence is translated into a context-specific and user friendly format including deskguides and then adopted in routine clinical practice [85]. In China a study on the adaptation and scale-up process of generic TB operational

guidelines had showed its usefulness in the daily practice of country TB doctors [86]. The results of our studies provided assistance before the scale-up process of childhood TB control activities in the country. The lead role taken by the NTP Pakistan provided the framework for translating the research into policy and practice. The programme vision and commitment were two key elements that steered the intervention development through a consultative process whereas the researchers contributed as the catalyst to the entire process.

The programme arrangements for staff training, regular supply of drugs and materials (in particular TST) and ongoing monitoring of implementation quality are key areas where further programme attention is required. The NTP Pakistan has already started responding to these requirements by developing staff trainings, addressing supply and quality issues, and refining monitoring guidelines for nationwide implementation of childhood TB interventions. These early programme products (i.e. childhood TB materials) have been recognized internationally by experts and programmes for potential future reference and are freely available, on request, from the NTP Pakistan.

5.3. Strengths and limitations

5.3.1. Strengths of the study

One strength of the study was that it was based on the review of available patient records under routine programme conditions in collaboration with NTP in the three districts with previous TB care experience, experience of implementation of NTP childhood TB policy and later childhood TB deskguide. The paediatrician, doctors and paramedics responsible for providing childhood TB care in these district and sub-district hospitals were from the regular district health system and were not offered incentives.

Strength related to paper III was the development of the intervention based on the standardized NTP integrated model of TB care, within the context of scale-up process in the country. In the intervention phase with childhood TB deskguide and structured monitoring, the supply of anti-TB drugs and TST was channelled through the TB control programme and none of the supplies were purchased through our research

arrangement. The data collection was included as part of the TB monthly cluster monitoring meeting lead by the DTC. An additional strength of the study was its inherent opportunity to collect the data and share the information and results, and hence ensure impact of the results.

5.3.2. Study limitations

Our study has shown various limitations which are described below.

Data issues

One major limitation related to papers I, II and III was that the patient records were incomplete in the hospitals. In the DOTS expansion phase of the childhood TB the recording and reporting was based on the NTP format which has limited flexibility related to capture all the required information related to a management of a child with TB. Furthermore, it was not possible to follow-up patients by visiting their homes to get more information to determine treatment outcomes. The incomplete record gives compromised results of a cohort but provided information related to on-the-ground practices. Our study being an operational research and not a trial, we had to document the findings based on the routine programme arrangements and not as an exclusive research arrangement.

Generalisability

Another limitation particular to paper III was that we had only one intervention district, and that the private sector and health facilities below sub-district level were not included. This made it difficult to generalise the intervention findings based on early implementation experience. In Pakistan there is limited coverage of health care services through the public sector, whereas most of the people seek private sector, which includes general practitioners and homeopathic and traditional healers. Our study was focused on the NTP implementation arrangements of childhood TB in the context of public sector so for the study purpose inclusion of all types of health care structure was not possible. In addition we had time and resource limitations. Due to the time limitations we had to stop the inclusion of cases after eight months in the

intervention district. The intervention district started at a very low number of cases, so the increase observed after the intervention was also not big in numbers but seen as the doubling in case notification.

Hawthorne effect

In a retrospective study there cannot be any Hawthorne effect. In the case of the prospective intervention we anticipated that the behaviour of the intervention group might modify in response to the fact that they were being studied. We tried to control this effect by making our district visits for data collection part of the regular district monitoring process.

6. CONCLUSIONS AND RECOMMENDATIONS

- 6.1.** The implementation of national policy guidelines for the management of childhood TB in Pakistan led to an increase in childhood TB case notification, which varied across the sites.
- 6.2.** Many paediatricians started following parts of the national policy guidelines for management of childhood TB. In the diagnosis of childhood TB the documented use of TST, CXR and score chart increased but the same was not observed for sputum smear examination.
- 6.3.** Record keeping of case management practices including diagnosis and treatment outcomes was inadequate in this study. Development and implementation of standardized operational tools and a regular monitoring system is required to improve the performance and quality of services.
- 6.4.** The early implementation experience of an intervention package of childhood TB with deskguide and structured monitoring was associated with improved case management and augmented NTP policy. There was an increase in case notification, better record keeping and better treatment outcomes. This improvement helped standardizing the process of care.
- 6.5.** Our research assisted the national programme developing useful intervention for public health. There is a need to refine the intervention package and develop a training package for the paediatrician, clinicians and paramedics to be involved in the childhood TB implementation scale-up process in the country.
- 6.6.** We have documented development and testing of an intervention package, and the lessons learned from the process which can augment NTP scale-up of childhood TB control in Pakistan. The programme arrangements for quality childhood TB care need further attention.

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