CHILDHOOD TUBERCULOSIS: EVALUATION OF CLINICAL OUTCOMES AND TREATMENT COMPLIANCE IN MULTICENTER HOSPITALS OF SINDH, PAKISTAN

by

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LIST OF ABBREVIATIONS

ADRs	Adverse Drug Reactions
AFB	Acid- Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Transaminase
ART	Antiretroviral Therapy
AST	Aspartate Transaminase
ATDH	Anti-tuberculosis drug induced hepatotoxicity
ATT	Anti-Tuberculosis Treatment
BCG	Bacille Calmette-Guerin
B-cells	B-Lymphocytes
CI	Confidence Interval
CXR	Chest X-ray
DHQ	District Head Quarter Hospitals
DOTS	Directly Observed Treatment-Short Course
EMB	Ethambutol
EPTB	Extra-Pulmonary Tuberculosis
ESR	Erythrocyte Sedimentation Rate
HBC	High Burden Countries
HHC	House Hold Contacts
HIV	Human Immunodeficiency Virus
ICDK	Institute of Chest Diseases Kotri, Sindh
INH	Isoniazid
IPT	Isoniazid Preventive Therapy
IQR	Inter Quartile Range

IUATLD	International Union Against Tuberculosis and Lung Disease
LTBI	Latent Tuberculosis Infection
LFT	Abnormal Liver Function Tests
LUMHS-CHH	Liaquat University of Medical and Health Sciences Civil Hospital, Hyderabad.
M. bovis	*Mycobacterium bovis*
MDR	Multidrug Resistant
MGLS	Morisky Green Levine Medication Adherence Scale
MLR	Monocyte to Lymphocyte Ratio
MOH	Ministry of Health
MTB	Mycobacterium tuberculosis
NGOs	Non-Governmental Organizations
NK	Natural Killer
NLR	Neutrophil to Lymphocyte Ratio
NTP	National Tuberculosis Control Program
OR	Odd Ratio
PKRs	Pakistani Rupees
PPA	Pakistan Pediatric Association
PPD	Purified Protein Derivative,
PTB	Pulmonary Tuberculosis
PTBNS	Pulmonary Tuberculosis with no sputum examination
PTPs	Provincial TB Control Programs
PZA	Pyrazinamide
RBCs	Red Blood Cells
SBGH-LH	Shah Bhitai Government Hospital, Latifabad, Hyderabad
SBS-THM	Syed Baqadar Shah Taluka Hospital, Matiari

SD	Standard Deviation
SE	Standard Error
SGH-QH	Sindh Government Hospital Qasimabad, Hyderabad
SM	Streptomycin
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
Th	T Helper Cells
TST	Mantoux Tuberculin Skin Test
ULN	Upper Limit of Normal
UMC	The Uppsala Monitoring Centre
UNICEF	United Nations International Children's Emergency Fund
UK	United Kingdom
USA	United States of America
VAS	Visual Analog Scale
WHO	World Health Organization
Xpert MTB/RIF	Gene Xpert MTB/RIF
ZN	Ziehl-Neelsen

LIST OF UNITS

dL	Decilitre
g	Gram
hr	Hour
kg	Kilogram
Km	Kilometre
L	Litre
Mg	Milligrams
Ml	Milliliters
mm	Millimeters
U	Unit

LIST OF SYMBOLS

ß	Beta
°	Degree
=	Equal
>	Greater than
≥	Greater than or equal to
<	Less than
≤	Less than or equal to
-	Minus
×	Multiplication
±	Plus minus
+	Plus

TUBERKULOSIS KANAK-KANAK: PENILAIAN DAN DAPATAN KLINIKAL DAN PENETAPAN RAWATAN DI HOSPITAL-HOSPITAL SECARA MULTICENTER DI SINDH, PAKISTAN

ABSTRAK

Pakistan berada di kedudukan yang ke-11 dalam kalangan negara-negara yang mempunyai beban tuberkulosis (TB) yang tinggi di mana TB diberi nilai ke-6 dari 10 penyebab mortaliti. Walaupun garis panduan Kebangsaan bagi diagnosis dan pengurusan TB dalam kalangan kanak-kanak telah ditubuhkan pada tahun 2007, sedikit yang diketahui mengenai hasil pengurusan dan rawatan TB bagi kanak-kanak di Pakistan. Bagi tujuan ini, kanak-kanak yang dirawat di bawah Kursus Pendek Rawatan Pemerhatian Secara Langsung (DOTS) di lima buah hospital multicenter di Sindh telah direkrut sebagai kohort dalam kajian pemerhatian ini. Sejumlah 2,167 orang kanak- kanak telah didaftarkan semasa fasa retrospektif daripada tahun 2011 sehingga 2015 dan bagi fasa prospektif daripada 1 Jun 2016 sehingga 30 November 2016, 508 orang kanak-kanak telah didaftarkan dengan TB di tapak kajian. Semasa tempoh kajian, TB bagi kanak-kanak menyumbang sebanyak 12.2% daripada semua kes TB di daerah- daerah Hyderabad, Jamshoro dan Matiari. Dalam kajian ini, 12.1% adalah bakteria positif yang telah disahkan. Pada akhir fasa intensif, 79.3% pesakit mencapai penukaran lumuran dahak. Pesakit-pesakit yang mempunyai hubungan yang rapat dan yang berpengalaman dengan kesan-kesan yang buruk adalah dengan ketaranya berkemungkinan kurang untuk mendapat penukaran dahak dan lebih berkemungkinan menjadi positif dahak semasa rawatan. Sekitar 13.2% pesakit-pesakit mengalami kesan-advers yang buruk. Dalam analisis multivariat, kanak-kanak perempuan yang mendapat rawatan terdahulu dan yang tidak mempunyai parut BCG

adalah berisiko tinggi untuk mengalami kesan advers ubat anti-TB. Kadar kejayaan rawatan keseluruhan telah direkodkan sebanyak 93%. Penduduk-penduduk luar bandar, positif lumuran dahak, kanak-kanak dengan rawatan sebelumnya, mereka yang mempunyai ADR dan hubungan isi rumah dengan TB telah muncul sebagai peramal-peramal bagi hasil rawatan yang tidak berjaya. Sehingga kini, penyelidikan untuk pematuhan terhadap rawatan TB dalam kalangan kanak-kanak adalah terhad. Bagi tujuan ini, pematuhan telah diukur menggunakan Skala Analog Visual (VAS) dan Skala Pematuhan Perubatan Morisky Green Levine (MGLS). Pematuhan rawatan dalam kalangan penjaga-penjaga dalam kajian ini telah direkodkan sebanyak 86% ke atas MGLS dan 90.7% dengan VAS. Analisis komponen utama dalam kajian semasa telah menunjukkan bahawa MGLS yang telah diubahsuai adalah satu dimensi dan 4 perkara-perkara telah dimuatkan dengan baik ke atas faktor tunggal. Hubungan VAS dengan MGLS-U adalah 0.572 yang menunjukkan persamaan yang baik antara kedua-dua skor dan instrumen-instrumen telah dilaksanakan dengan baik dalam kalangan penjaga-penjaga dengan pendidikan yang lebih rendah. Penjaga-penjaga lelaki, mereka yang berumur $\geq$ 45 tahun, tanpa pendidikan formal, mempunyai kekangan kewangan, dilaporkan mempunyai kaunseling yang tidak mencukupi oleh pekerja-pekerja penjagaan kesihatan serta doktor dan sikap tidak ambil peduli terhadap professional penjagaan kesihatan telah diperhatikan sebagai faktor penyumbang kepada ketidakpatuhan dalam kalangan penjaga-penjaga di tapak kajian. Kelaziman keseluruhan TB dalam kalangan hubungan isi rumah adalah 1.5%. Kanak-kanak yang mempunyai hubungan isi rumah dengan TB dan merokok telah diperhatikan dengan risiko yang lebih tinggi untuk membangunkan TB. Hanya 33.8% kanak-kanak yang diberi terapi pencegahan isoniazid (IPT) (26/77) dengan berjaya telah menyelesaikan kursus enam bulan tersebut. Sebagai kesimpulan, kadar 12.2% TB kanak-kanak yang diberitahu dalam kajian semasa adalah membimbangkan. Faktor penting yang berkaitan dengan (P < 0.05) (isi rumah yang mempumyai kontek dengan TB dan mengalami kesan advers), kesan advers (wanita dan kanak-kanak dengan rawatan terdahulu), hasil rawatan yang tidak berjaya (Penduduk luar bandar, positif pundi pesakit, kanak-kanak dengan rawatan terdahulu, kenalan dengan TB), dan tidak mematuhinya (penjaga lelaki, mereka yang berumur ≥ 45 tahun, tanpa pendidikan formal, mempunyai masalah kewangan, melaporkan kaunseling yang tidak mencukupi oleh pekerja penjagaan kesihatan dan juga para doktor dan sikap tidak ambil peduli terhadap profesional penjagaan kesihatan) boleh dibuktikan secara praktikal sebelum atau tepat pada masa dalam rawatan. Kadar kejayaan rawatan adalah memberangsangkan tetapi dapat dipertingkatkan lagi dengan memberi perhatian yang penting dan memberikan pengurusan klinikal yang lebih baik kepada pesakit berisiko tinggi.

CHILDHOOD TUBERCULOSIS: EVALUATION OF CLINICAL OUTCOMES AND TREATMENT COMPLIANCE IN MULTICENTER HOSPITALS OF SINDH, PAKISTAN

ABSTRACT

Pakistan is ranked 11 among the high tuberculosis (TB) burden countries where TB is rated 6^{th} of top 10 causes of mortality. Although, the national guidelines for the diagnosis and management of TB in children were established in 2007, but little is known about the management and treatment outcomes of childhood TB in Pakistan. For this purpose, children treated under Directly Observed Treatment Short course (DOTS) at (5) multicentre hospitals of Sindh were recruited as cohort in this observational study. Total 2,167 children were registered during retrospective phase from 2011 to 2015 and for prospective phase from 1^{st} June 2016 to 30^{th} November 2016, 508 children were enrolled with TB at the study site. During the study period, childhood TB accounted 12.2% of all TB cases in Hyderabad, Jamshoro and Matiari districts. In the present study, 12.1% were bacteriologically confirmed sputum smear positive cases. At the end of intensive phase, 79.3% of patients achieved sputum smear conversion. Patients who had household contacts with TB and experienced adverse effects were significantly less likely to achieve sputum conversion and were more likely to become sputum positive during the treatment. Around 13.2% of patients came across with adverse effects. In multivariate analysis females and children with previous treatment were at greater risk to develop adverse effects due to anti-TB drugs. The overall treatment success rate was recorded as 93%. Rural residents, sputum smear positive, children with previous treatment, those who had ADRs and household contacts with TB emerged as predictors for unsuccessful treatment outcomes. Treatment adherence among the caregivers using Visual analog scale (VAS) and

Morisky Green Levine Medication Adherence Scale (MGLS) in the present study was recorded as 86% on MGLS and 90.7% with VAS. The principal component analysis in the current study indicated that the modified MGLS was one-dimensional and the 4 items loaded well onto the single factor. The correlation of VAS with MGLS-U was 0.572 that demonstrates good association between the two scores and the instruments performed well in caregivers with lower education. Male caregivers, those aged ≥ 45 years, with no formal education, had financial barrier, reported insufficient counselling by health care workers as well as clinicians and ignorant attitude of health care professional were observed as contributing factor to non-adherence among caregivers at the study site. The overall prevalence of TB among household contacts was 1.5%. Children who had household contacts with TB and smoking were observed at significantly higher risk for developing TB. Only 33.8% of children who were given isoniazid preventive therapy (IPT) (26/77) successfully completed the six-month course. In conclusion, the proportion of 12.2% childhood TB notified in the current study is alarming. The positively significant associated factors ($P < 0.05$) of sputum non-conversion (household contacts with TB and experienced adverse effects), adverse effects (females and children with previous treatment), unsuccessful treatment outcomes (Rural residents, sputum smear positive, children with previous treatment, those who had ADRs and household contacts with TB), and non-adherence (Male caregivers, those aged ≥ 45 years, with no formal education, had financial barrier, reported insufficient counselling by health care workers as well as clinicians and ignorant attitude of health care professional) are practically detectible before or timely in the course of treatment. The rate of treatment success was promising but can be further improved by giving significant attention and granting enhanced clinical management to the high risk patients.

CHAPTER ONE

INTRODUCTION

1.1 Background

Tuberculosis (TB) is expected to have affected humans for most of their history and remains a major reason of death worldwide regardless of the discovery of its effective and affordable therapy more than 50 years ago (Holloway *et al.*, 2011). According to the World Health Organization (WHO) about one third of the global population is infected by *Mycobacterium tuberculosis* (MTB).

In 2016, TB was one of the top 10 reasons of death at global level, ranking over Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) as one of the foremost causes of death from an infectious disease. During same year, 10.4 million new TB cases were estimated worldwide which comprise 90% adults and 65% male (WHO, 2017). According to WHO reports, the continuous rise has been seen in case detection rate of childhood TB worldwide with a parallel increase in the death toll in children with TB. In 2014, 136,000 children died from TB worldwide and the rate increased significantly to 210,000 deaths in 2015.

1.2 Childhood TB

TB in children has traditionally been deserted by practitioners, researchers and expounders partially, with the notion that children are rarely infectious and therefore add little to the dissemination of disease. A confirmed diagnosis is often challenging in children because of a low bacillary load and difficulties in specimen collection. Thus, diagnosis of TB is repeatedly completed presumably on the basis of a combination of clinical symptoms (Marais *et al.*, 2005) and radiological findings (Dodd *et al.*, 2014). In addition to the diagnostic uncertainties, a major challenge for estimating burden is under-reporting. The challenges of confirming diagnosis are more in less than 5 years age; additionally, this age group also has an increased risk of severe disease and TB-related mortality (Seddon *et al.*, 2015). Because of the difficulty in diagnosis of TB in children and insufficient data recording, little accurate information regarding childhood TB is available from countries with a high TB incidence (Donald *et al.*, 2007).

Childhood TB is an indication for on-going transmission of TB within a community. Because the young children spent most of the time with their households, TB transmission is therefore supposed to be absolutely from adults in the household, particularly with smear positive adult cases (Kompala *et al.*, 2013; Middelkoop *et al.*, 2014). Level of exposure and contact hours with TB case indicates the severity of infection (for instance interaction of an infant with mother or any other caregiver in the household). The risk of developing TB disease subsequent to infection is hence greater for children under 5 years of age (WHO, 2014).

1.3 Diagnosis

Diagnosis of PTB in children can be challenging due to radiological changes, difficulty of making a definitive microbiologic diagnosis and nonspecific signs and symptoms (Zar *et al.*, 2015). These challenges create difficulties for understanding the risk factors for childhood TB and the poor outcomes from disease (Nelson and Wells, 2004). Depending on local epidemiology, various algorithms and scoring systems have been developed to foresee TB in patients with negative sputum (Siddiqi *et al.*, 2003). The scoring system is possibly a valuable diagnostic method of TB, particularly in resource limited and HBC.

The use of definite symptoms significantly improves diagnostic accuracy of PTB. It has been reported that presence of 3 symptoms at presentation can provide good diagnostic accuracy (sensitivity 82.3%, specificity 90.2%, positive predictive value 82.3%) in immune competent children $\geq$ 3 years of age, i.e. persistent non-remitting cough more than 2 weeks, failure to thrive during the foregoing 3 months and fatigue (Marais *et al.*, 2006b).

Until recently, TST was the only commercially available immunologic test for diagnosis of LTBI (Bua *et al.*, 2013) and is considered as standard method for detecting asymptomatic infection of MTB. A standard dose of 5 tuberculin units (TU) (0.1mL) is injected intradermal and the reaction is measured as millimetres (mm) of in duration after 48 to 72 hours. TST has low specificity as the antigen used for the test purified protein derivative, (PPD), is a mixture of more than 200 mycobacterial antigens also present in non-*Tuberculous mycobacteria* and in the BCG vaccine strains.

CXR is of great significance in sputum and culture negative TB (Kaguthi *et al.*, 2014) or inability of the patient to produce sputum (Bhalla *et al.*, 2015). Despite its many limitations, the CXR remains the most practical and helpful test (Marais *et al.*, 2006c) in abnormal findings among children with TB (Swingler *et al.*, 2005).

Microscopy is rapid, inexpensive and less labour intensive than other technologies. Detection of AFB using smear microscopy is the primary diagnostic method of TB in DOTS based programmes in low and middle income countries, (WHO, 2009a) providing results within hours. Culture is not performed in resource poor settings consistently but used for purposes of surveillance, treatment failure, or detection of drug resistance.

In December 2010, Gene Xpert MTB/RIF (Xpert MTB/RIF) assay was endorsed by WHO and then recommended that it needs to be evaluated in childhood

TB (WHO, 2010c). The Xpert MTB/RIF assay is a rapid molecular assay that can be used by operators with minimal technical expertise, enabling diagnosis of TB and simultaneous assessment of RIF resistance to be completed within 2 hours (Lawn and Nicol, 2011).

1.4 BCG vaccine

BCG is a live attenuated vaccine derived from *Mycobacterium bovis* and has been given to children since the 1920s (Rekha and Swaminathan, 2007). The only licensed vaccine for the prevention of TB and leprosy is BCG. More than 100 million doses of BCG are given each year. It is accepted that BCG vaccine protects young children (< 5 years) against more dangerous forms of EPTB and thus, is given as a routine vaccination in many countries, as recommended by the WHO. Though the efficacy of BCG vaccine against PTB is doubtful (Beresford and Sadoff, 2010) and differs geographically. A meta-analysis on the efficacy of BCG vaccination in new born and infants in the prevention of TB demonstrated that BCG vaccine provided a protective effect of 71% against TB deaths and 64% against TB meningitis (Colditz *et al.*, 1995). A further meta-analysis revealed a BCG protective effect of 86% against miliary or meningeal TB in randomized controlled trials and 75% in case- control studies (Rodrigues *et al.*, 1993). In 2004, WHO recommended a single dose of BCG vaccine after birth in HBC, unless the child presented with symptomatic HIV infection (WHO, 2004a). This is because serious immunodeficiency states like AIDS are associated with increased incidence of local as well as systemic disseminated BCG infection after vaccination (Goraya and Virdi, 2002).

1.5 Geography of Pakistan

Pakistan is located in the Middle East near the Gulf of Oman and the Arabian Sea. It is the country with 6^{th} number largest population in the world and the second largest Muslim population. The country is a developing nation with an underdeveloped economy. Pakistan is divided into five provinces and one capital territory for local administration.

1.5.1 Provinces

1) Sindh: Land Area: 140,915 square kilometer, Population: 47,886,051.Rural: 22,975,593, and Urban: 24,910,458.
2) Balochistan: Land Area: 347,190 square kilometer, Population: 12,344,408, Rural: 8,943,532, and Urban: 3,400,876.
3) Punjab: Land Area: 205,345 square kilometer, Population: 110,012,442, Rural: 69,625,144, and Urban: 40,387,298, Islamabad is capital city of Pakistan which is considered a separate Federal administrative area rather than a province but its population was given separate in census report 2017. Total population: 2,006,572, Rural: 991,747, and Urban: 1,014,825.
4) Khyber-Pakhtunkhwa (KPK): Land Area: 74,521 square kilometer, Population: 30,523,371, Rural: 24,793,737, Urban: 5,729,634.
5) Federally Administered Tribal Areas (FATA): The tribal belt adjoining KPK northern territory of Pakistan managed by the Federal Government and is named Federally Administered Tribal Areas. Land Area: 72,971 square kilometer, Population: 5,001,676. Rural: 4,859,778, Urban: 141,898 (Govt. Pakistan 2007).

1.6 Health care system in Pakistan

The health system in Pakistan is comprised of public and private sectors. Development of national policies and strategies for intact population comes under the major responsibility of Ministry of Health (MOH) at the Federal level. Apart from the federally administrated areas, health is first and foremost accountability of the provincial government under Pakistan constitution. Although Pakistan's health sector is basically a provincial subject, health care delivery is generally administered by the federal and provincial governments together with districts mainly responsible for implementation. There are 1,142 hospitals, 5,499 dispensaries, 5,438 basic health units (BHU) and 671 maternity and child health centres. A BHU is an extended framework consists of lady health visitor, mid-wives and communicable disease control. Immunization, family planning, providing experienced birth attendants in delivery, antenatal and post-natal care, nutritional counselling, management of reproductive tract infection and sexually transmitted infection comes under services of BHUs (Noureen, 2017). TB services are provided by chest clinics in tertiary (including public and private) district and sub-district hospitals, rural health centres and BHU (Fatima *et al.*, 2014).

1.7 National TB Control Program in Pakistan

The National TB Control Program (NTP) was implemented in 1995 and after descending, it was revitalized in 2001 (Chughtai *et al.*, 2013). The mission of NTP was to attain TB control at national level by Directly Observed Treatment, Short Course (DOTS) strategy and by certifying quality TB care through public sector health services together with private sector and Non-Governmental Organizations (NGOs) (NTP, 2004). In addition to this, major concern of NTP was to reduce the levels of underreporting by: increased cooperation of public and private sector, obligatory notification of childhood TB cases and efforts to assemble data on diagnosed cases from amenities not consistently reporting to national surveillance systems. In Pakistan, health care is a liability of provincial government whereas the district presents health care services to urban and rural regions. In NTP, the TB control services in the district health system, operates in the course of diagnostic centres and treatment centres. The diagnostic centre diagnoses the TB case having its individual laboratory with a laboratory technician to carry out the sputum smear microscopy. A treatment centre is responsible to distribute the anti-tuberculosis treatment (ATT) to the patients. Furthermore, the treatment support is offered to the patients by a network of community health workers. The ATT are principally promoted by the NTP and supervised through district health authorities. Once the cases are registered, the quarterly reports on case findings and treatment outcomes are sent to the district TB coordinator office, who integrates these reports and pass on a quarterly consolidated district reports to the provincial TB control office. Regular quarterly intra and inter district meetings are held to fortify the reports to avoid errors and to further improve the program.

NTP, working under the Ministry of National Health Services, Regulation & Coordination, is fighting against TB to lessen the mortality, morbidity and spread of TB infection in the country. NTP is incorporated with Primary Health Care system implemented by the district health authorities with the support of Provincial TB Control Programs (PTPs). The NTP is responsible for overall TB Control Activities in the country including Policy Guidelines, Technical Support, Coordination, Monitoring, Evaluation and Research whereas the PTPs and Districts are responsible for the actual care delivery processes including program planning, training of care providers, case detection, case management, monitoring and supervision. Since 2001, over 2.1 million TB patients have been diagnosed and treated with quality assured free of cost ATT in both public and private sector across the country in the course of 1,500 qualities assured microscopy and 5,000 treatment centres. Approximately 300,000 TB cases were notified to NTP and Treatment Success Rate remained at 91% during 2013 (NTP, 2013).

1.8 Directly observed treatment

The Directly observed treatment (DOT), a critical aspect of the DOTS strategy, is an effort to improve adherence to TB treatment (Wright *et al.*, 2015). DOTS supervisors encourage and supervise patients swallowing each and every dose of their anti-TB drugs during the treatment course (Wright *et al.*, 2004). A DOTS supervisor can be a medical staff member, a family member, any health worker, a teacher, or any volunteer from community (Dick *et al.*, 1996). Supervision of TB treatment through DOT at health clinics can put extra burden on health care systems, mainly in high TB burden and resource limited settings. Beside this, it is tiresome for patients to visit a health clinic daily for treatment supervision, in terms of traveling and waiting times (Wright *et al.*, 2015). Community-based DOT is intended to reduce the strain of patient care on health facilities in high TB burden countries in terms of cost effectiveness and control over TB transmission (Nardell and Dharmadhikari, 2010). Family member as DOTS supervisor for TB patients has also proven as an efficient and cost effective technique in different studies (Maciel *et al.*, 2008). Study conducted in Pakistan found no statistically significant difference in cure rate for DOTS with direct observation by health workers, DOTS with direct observation by family members and DOTS without direct observation (Khan *et al.*, 2002). Similarly, a controlled trial in Nepal revealed that family members are as proficient as health care staff in treatment administration (Newell *et al.*, 2006). While evaluating the effectiveness of DOTS, treatment completion rates for the patients supervised by their family members was significant in contrast to the supervision by health professionals (Okanurak *et al.*, 2007). Despite of these results, no conformity about the use of family members as treatment supervisors by TB control programs is endorsed in the TB guidelines.

1.9 TB in Pakistan

TB is an endemic and foremost public health problem in Pakistan. Despite its high prevalence in the country, it had been a deserted area in the past. TB control was nearly fictional in the country until the NTP was reinforced in 2001 (Vermund *et al.*, 2009). In 1962, the first TB survey in Pakistan led to foundation of collaborative efforts for TB control between MOH, WHO and United Nations International Children Emergency Fund (UNICEF). The main focus was set to develop specialized TB centres and wards at the district head quarter hospitals (DHQ). But, UNICEF departed in 1985 and pull out its financial support. In 1993, WHO announced TB as a global emergency and the Government of Pakistan administered the DOTS strategy to have the effective TB control. In 1994 the TB control policy, national policy and technical guidelines were revised by the MOH in collaboration with WHO. Later on, in 1996 the Directorate for TB Control of Pakistan was eliminated and the Medical superintendent (MS) of the TB Centre was made responsible for NTP, with no any additional support. Accordingly, in 1998, Pakistan was stated as one of the 16 countries without an appropriate NTP (De Muynck *et al.*, 2001).

The primary features of TB epidemiology consist of socioeconomic dissimilarities, rapid urbanization and population growth at the global level. All these features lead to lack of food, starvation, poor housing and socio-economic, geographic and cultural hurdles to approach the health care. Crowdedness in homes and localities raise the chances of exposure to TB infection, whereas poverty and scarcity of food may possibly enhance the vulnerability to TB infection (Hargreaves *et al.*, 2011). People are moving from the rural to urban areas in search of better livings and access to rather better education and healthcare services, thus growing the number of people living in substandard housing called slums. The millions of people living in slums do not have access to the education and health services, affecting the children and females most. In urban areas, increased rate of death is reported in children ≤ 5 years of poorer as compared to rich people. Practically 8% of the global burden of deaths < 5 children occurred in Pakistan due to insufficient nutrition and health care support (UNICEF, 2016). Living conditions in many urban slums are worst. The bulk of people in areas with inadequate provision of water, sanitation, garbage collection and health care produce the conditions where infectious diseases can spread at greater rate. Infectious disease in Pakistan is thought to be correlated to the poor sanitation and unsafe potable water (WHO, 2007).

Pakistan currently stands as 5th highest burden of TB together with the 4th highest burden of drug resistant TB globally and is one of the 6 countries that stand out as having the largest number of incident cases in 2014 (NTP, 2015; WHO, 2015). In 2016, of total estimated incidence of 518,000 TB cases notified in Pakistan, 51,000 were cases of children aged ≤ 14 years (WHO, 2017). Pakistan is one of the 6 countries accounting 60% of new TB cases (WHO, 2016). Pakistan adds approximately 44% of TB burden in the Eastern Mediterranean Region and 5.1% of the total national disease burden is accounted with TB (Vermund *et al.*, 2009). TB ranked as 6th of top 10 causes of motility in Pakistan (WHO, 2007).

There are many reasons why TB rates are still higher in Pakistan. In the absence of health insurance and social protection, it is hard for the poorest to access health services while they are sick. This contributes to undiagnosed TB, sustained transmission in the community and poor treatment outcomes in diagnosed TB cases. As definite connection between poverty and TB is previously reported (Oxlade and Murray, 2012), majority of TB cases are found in people with low income, mostly uneducated and limited resources. In Pakistan, malnutrition is common among all ages. According to the National Nutrition Survey 2011, one-third of all children are underweight because of existing poverty and food insecurity; not only increasing the risk of morbidity and infections but also impede the growth and mental development of a child. Beside this, poor are living in substandard overcrowded and poor ventilated houses and polluted communities, expected to boost the risk of TB transmission (Marais *et al.*, 2009).

1.10 Management of childhood TB in Pakistan

1.10.1 Diagnosis of childhood TB

Children with TB registered in five selected hospitals were diagnosed according to algorithm presented by NTP (Figure 1.1) and treated under the DOTS program where a paediatrician, i.e. child or TB specialist, DOTS facilitator, laboratory technician and field officer were working as a team for DOTS. The recording and reporting (R & R) of routine TB cases was the liability of a DOTS facilitator. Children presented to the hospitals with clinical symptoms including cough lasting for ≥ 2 weeks, fever, night sweat, dyspnea, weight loss and sputum production were examined. TST was done using standard of 5 tuberculin units (TU in 0.1 mL), during the initial visit and read at 48-72 hours. Since children were being evaluated for TB, a

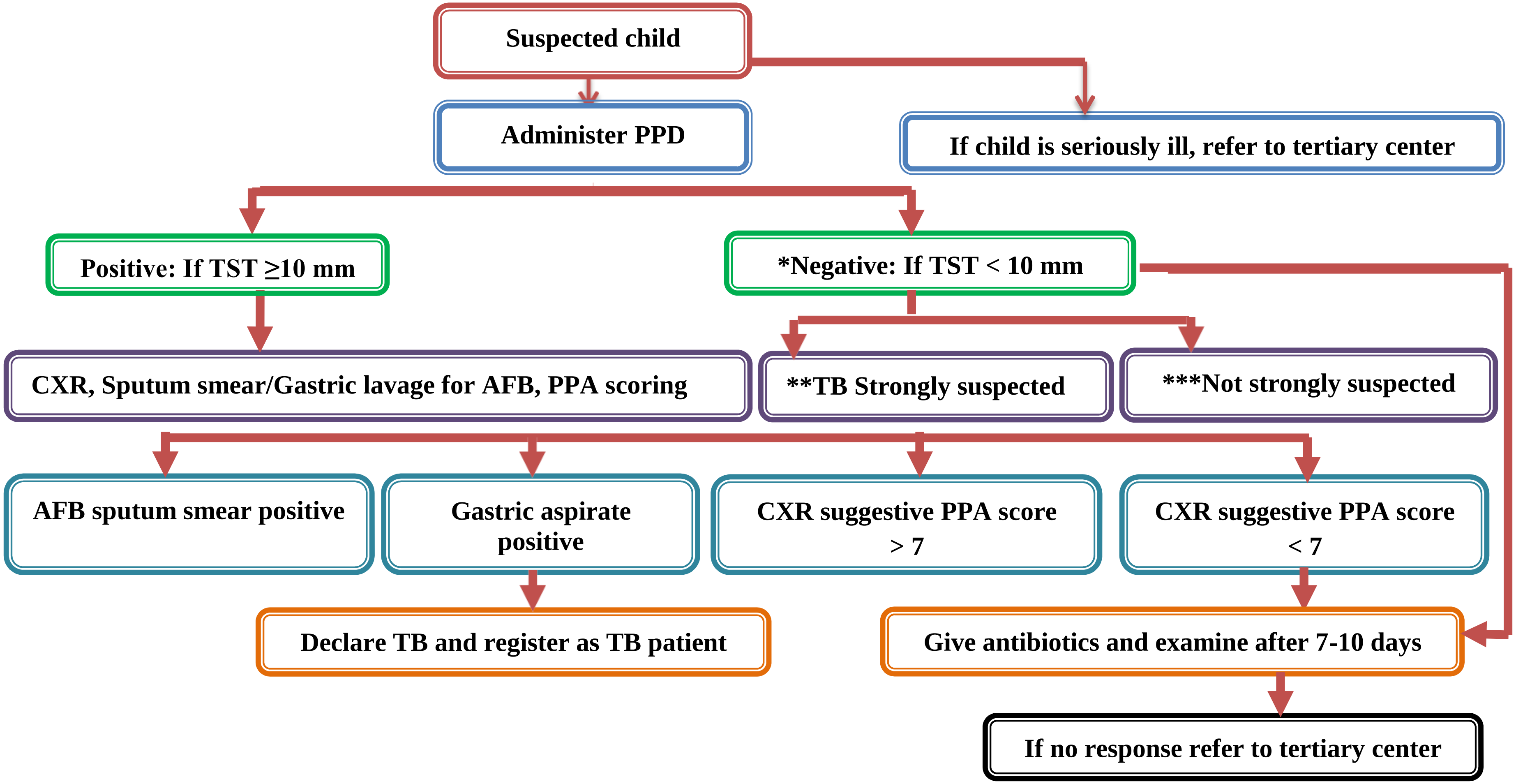
TST $\geq$ 10 mm was considered positive (WHO, 2014). Antero- posterior view was performed in all children. The CXR was read by a local paediatrician and a general physician. CXRs were evaluated for the presence and location of hilar lymphadenopathy, opacification (consolidation), nodular images, pleural effusion, cavitation, calcification or vertebral spondylitis. If at least one of the above features is found, the CXR was classified as persistent with TB. An abnormal CXR with symptoms suggestive of TB were referred for sputum microbiological examination including smear and Xpert MTB/RIF. In the absence of symptoms with an abnormal CXR a course of antibiotics was given and a repeat CXR was performed two weeks later to rule out persisting abnormality. Children with a normal CXR, but with persisting symptoms were evaluated for EPTB. Fluorescence microscopy was being used for sputum smear samples for the presence of AFB. In addition, Xpert MTB/RIF assay was routinely done in PTB- and PTB+ patients for further confirmation of MTB and drug resistance TB. For EPTB, diagnostic tests were performed depending on the sites involved. X-ray was done in all cases of EPTB so as to exclude the concomitant pulmonary involvement. Fine Needle Aspiration Cytology (FNAC) was the first-line diagnostic technique for the peripheral lymphnodes. However, if the FNAC examination results were indecisive, excision biopsy was done for definitive diagnosis. Fluid specimens (pleural, cerebrospinal fluid, gastric aspirate, synovial) were subjected to microscopy, culture, Xpert MTB/RIF and biochemical analysis. Diagnosis of skin TB was more complex and hence multiple tests were performed to ascertain the diagnosis including microscopy, tissue culture and skin biopsy with histological analysis. For children who cannot expel sputum, the diagnosis was confirmed on clinical basis.

Table 1.1 shows the NTP and PPA scoring chart for screening of TB in children used as diagnostic algorithm during the study as per recommendations of NTP (NTP, 2006). Patients with PPA score ≥ 5 were suggestive of TB contrary to the NTP where PPA score ≥ 7 is standard (NTP, 2015). Children who were diagnosed with TB disease were initiated on ATT. At the end of treatment, outcomes were recorded as per WHO criteria. Patients who were stated "cured" and/or "completed treatment" were recorded as "treatment success", and all those patients who were defaulted, died, or practiced treatment failure were reported under category of "unsuccessful treatment". A *cured* patient was a bacteriologically confirmed PTB patient and became smear negative in the last month of treatment and on at least one previous occasion. Treatment completed included TB patients who completed treatment with no record to show smear negative in the last month of treatment and on at least one previous occasion (WHO, 2014).

Table 1.1: NTP and PPA scoring chart for screening of TB in children at DOTS centers in Pakistan.

Condition	**Scores***				
	1	**2**	**3**	**4**	**5**
Age	< 2 years				
Close contact in last 2 years	PTB- patient		PTB+patient		
BCG scar	Absent				
Low immune status	Yes				
PCM grade-3	Yes		Notimprove		
Physical examination findings		Suggest TB		Strongly suggest TB	
CXR	Non-specific	Suggest TB			
TST	5-10 mm		>10 mm		
Granuloma	Non-specific				TB
History of measles and whooping cough	3-6 months	<3 months			

PCM = Protein calorie malnutrition, *0-2=Unlikely TB, 3-6= possible TB, and ≥ 7 probable.



Negative TST does not rule out TB, evaluate further if strongly suspected. **prolong illness like cough, fever, weight loss, abdominal mass, lymphadenopathy etc., and history of contact with TB case in family. ***Absence of above.

Figure 1.1: NTP flow chart for assessment of a child with suspected TB.

1.10.2 Treatment of children with TB

All PTB and EPTB cases were treated with the same standardized first-line anti-TB regimen. Treatment was free and was only provided by the DOTS program for all TB patients. The treatment of all new TB cases (Category-I, with no previous history of TB treatment) was comprised of INH, RIF, and PZA for 2 months intensive phase followed by INH and RIF for 4 months continuation phase. For category-II patients (relapse, failure and default), INH, RIF, PZA and EMB were given for 3 months intensive phase and INH and RIF during 5 months continuation phase. Based on the pre-treatment weight, children were assigned to one of 4 pre- treatment weight bands (5 to 7 kg, 8 to 14 kg, 15 to 20 kg and 21 to 30 kg). They were treated on the basis of pre-fixed weight band dosage. Patients weighing less than 5 kg were treated with individualized dosages while those weighing more than 30 kg were treated using adult dosages. As improvement in weight was observed during monthly visits, dose of ATT was then adjusted accordingly. During follow- up, sputum microscopy was performed for PTB+ and PTB- patients and those with EPTB and no sputum examination (PTBNS) were monitored clinically.

1.11 Sindh province

Sindh is the 2nd largest populated province of Pakistan located at west corner of South Asia. Geographically, Sindh is 3rd largest province of Pakistan, about 579 km from north to south and 281 km from east to west, with an area of 140,915 square km (54,408 square miles) of Pakistani territory. Generally, Sindh is known as the lower valley of Indus (Encyclopedia, 2017). There are 3 well defined parts of Sindh: The Siro (Head), The vicholo (Middle) and The Lar (Descent). Locally, Sindh, province is also known as Mehran. Sindh's climate is noted for hot summers and mild winters.

Karachi, Pakistan's largest city and financial hub, is provincial capital of this province. Sindh is divided into 6 divisions and 29 districts. Hyderabad division has total 9 districts including Hyderabad, Jamshoro and Matiari.

In 2010, the Sindh province had an estimated population of 42.4 million people with approximately equal rural (51.2%) and urban (48.8%) natives (Khan, 2017). Sindh is a multicultural province of Pakistan and is portrayed by an extensive gap between rich and destitute individuals with unequal access to health services. Inhabitants of low-wage neighbourhoods, for instance, suffer from overcrowding and malnutrition. Consequently, they are susceptible to developing TB (Akhtar *et al.*, 2007). The uncertain NTP framework frequently brings about confusions and false beliefs among TB patients in Pakistan, particularly in rural zones of Sindh. These myths have transformed TB into a social shame. This defamation negatively affects patients and makes them uncertain to look for treatment. Extremely restricted learning about Bacillus Calmette-Guerin (BCG) as a preventive measure against TB has been accounted for among provincial occupants in Sindh. Be that as it may, a significant number of rural populations had little information of how to secure against TB (Khan, 2017).

1.12 Problem statement

To restraint childhood TB in Pakistan, NTP developed its guidelines in 2006 to 2007 in collaboration with the Pakistan Paediatric Association (PPA). The guidelines included the protocols with a principle to get better care of children with TB (NTP, 2006). Nevertheless, the program has met with considerable success; Pakistan is however far-off from attaining its target. It is prerequisite to give enough importance to diagnosis and management of TB in children in DOTS program being executed in Pakistan. TB is treated with a multi-drug regimen, and is thus exceptionally vulnerable to incidences of adverse effects, unacceptable patient compliance and slow improvement of patients (Prabakaran *et al.*, 2004). The reporting of ADRs is still frequently disregarded by medical professionals and has yet not grasped the meriting significance in Pakistan (Khan *et al.*, 2015b). It is realized that making mindfulness on the significance of ADRs monitoring is a confirmation for setting up and maintaining a thorough ADRs reporting system (Iffat *et al.*, 2014). The duration and complexity of treatment result in non-adherence to treatment. This leads to suboptimal response (failure and relapse), the emergence of resistance and continuous spread of the disease. TB patients who are non-adherent or not cured are the common scourge not only for individuals and community, but pose a challenge to effective TB control as well (Tesfahuneygn *et al.*, 2015). In high burden countries (HBC) like Pakistan, ensuring treatment adherence and reaching a high treatment success rate hence regularly gets less consideration (D"Souzaa *et al.*, 2017). WHO has developed DOTS strategy to optimize response and adherence to TB treatment (Van den Boogaard *et al.*, 2009). Monitoring the outcome of treatment is essential in order to evaluate the effectiveness of the DOTS program. Furthermore, understanding the specific reasons for unsuccessful outcomes is important in order to improve treatment systems (Vasankari *et al.*, 2007; WHO, 2009b).

As per WHO recommendations, children must be considered as infectious if they are sputum smear positive or have cavitation on chest X-ray (CXR). When the index case is a child, it is recommended that contact screening should be done to pinpoint the source case (WHO, 2014). Contact investigation is an approach to identify active disease or Latent Tuberculosis infection (LTBI) among the contacts of known TB patients (Rieder, 2003).

In Pakistan, the increased risk of TB may be associated with highest proportion of poverty. Poor people are malnourished, living in overcrowded houses and mostly remain uneducated due to lack of resources (Figure 1.2) (Khan, 2017). Research contribution in childhood TB is still limited and only few studies have been conducted until now. Beside this, little is known in regard to the epidemiology, clinical outcome and adherence to ATT of the childhood TB. This study aimed to contribute to childhood TB management by investigating whether certain factors are associated with TB and poor treatment outcomes among children living in a developing country. It is worth mentioning that no study has been conducted to estimate the incidence and risk factors of TB among children, measure the treatment outcomes, assess and manage the adverse drug reactions (ADRs), determine risk factors for unsuccessful treatment outcome and incidence of ADRs, approximate the knowledge of adherence to ATT among the caregivers and evaluate contact screening among the household contacts (HHC) of TB children.

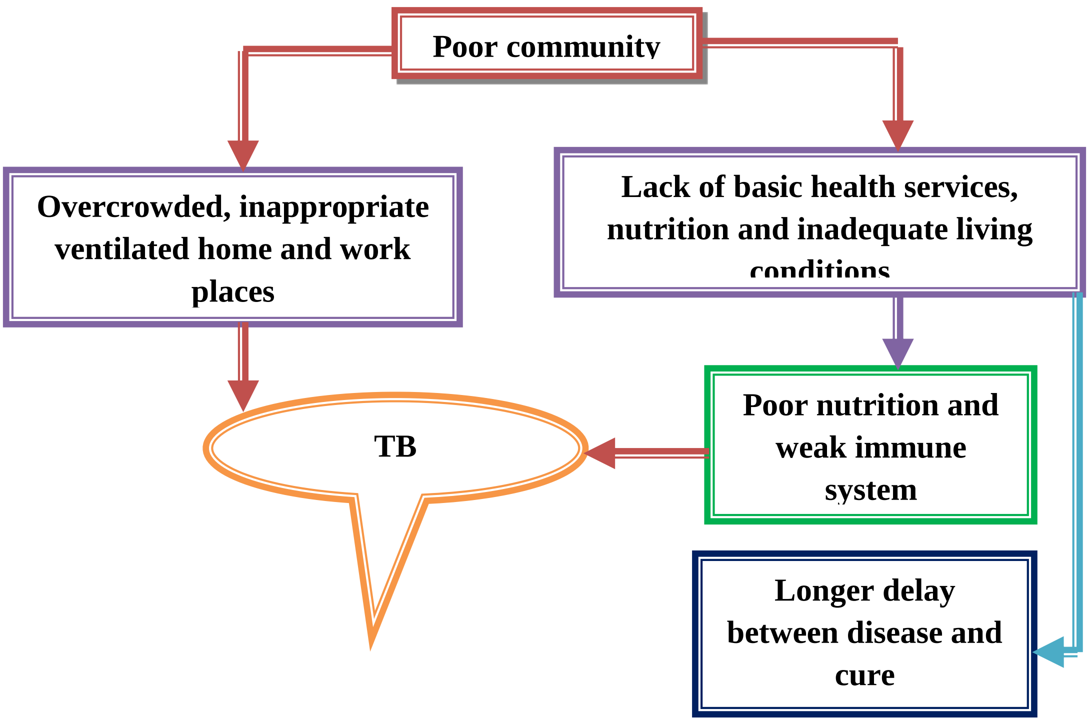


Figure 1.2: Relationship of poverty and TB.

1.13 Objectives

In general, the objective of the present study was to evaluate the proportion, management and treatment outcomes of children with TB in 3 districts (Hyderabad, Jamshoro and Matiari) of Sindh province, Pakistan. Due to the available resources, time and access limitations, the above said districts of Sindh province were focused in the present study.

1.14 Specific aims

The definite aims of the present study were to evaluate:

i. Socio-demographic and clinical characteristics of children with TB.

ii. Rate and predictors of delayed sputum conversion.

iii. Treatment outcomes and risk factors of unsuccessful treatment outcomes of TB regimen.

iv. Occurrence of ADRs in study population, using causality assessment scale (Naranjo) and severity assessment scale (Hartwig and Siegel), and their possible impact on ATT.

v. Treatment adherence among the caregivers of children under ATT using the Morisky Green Levine Medication Adherence Scale (MGLS-U) and Visual Analogue Scale (VAS).

vi. Contact screening among the HHC of TB children and risk factors of TB among the HHC.

1.15 Significance of study

Despite the increased global attention, findings and achievements in the control of TB over the past decade, children have been largely ignored and have not benefited from the advances in diagnosis and treatment. TB transmission to children not only indicates inadequate control in the community, but creates a pool of latently infected individuals who form the source of adult disease at some time in the future. Therefore, early detection of childhood cases is important in order to prevent further dissemination of TB in future. Data regarding childhood cases in Pakistan is scarce. This is the first study conducted in 3 districts (Hyderabad, Jamshoro and Matiari) of Sindh province of Pakistan. The current study will help pharmacists, clinicians and program managers to:

i. Reduce TB infection by controlling risk factors of TB.
ii. Increase in treatment success rate by looking into the predictors of unsuccessful treatment outcomes.
iii. Minimize noncompliance after giving knowledge regarding expected ADRs and their management.
iv. Improve treatment outcomes by educating the caregivers for adherence of ATT and assessing factors for non-adherence.
v. Decrease morbidity and mortality by early detection of TB cases among HHC by contact tracing.

CHAPTER TWO

LITERATURE REVIEW

2.1 Epidemiology of childhood TB

TB remains a disease of poor, over-burdened and vulnerable populations. Despite of effective treatment regimens, lack of proper diagnosis, non-adherent to treatment and barriers to infection control keep the constant transmission of TB. Globally, nearly one million children were affected with TB in 2015, accounted for 6.9% of the new cases notified in 2016 (WHO, 2017). Annually, 75% of total childhood TB cases are reported in 22 HBC, where they comprise 20 to 40% of total TB (Swaminathan and Rekha, 2010).

2.2 Prevalence and incidence of childhood TB

According to National Institute of Mental Health, “Prevalence” is the proportion of a population who have a specific illness, a condition or a risk factor in a given time period, usually expressed as a percentage or as the number of cases per 10,000 or 100,000 populations while “Incidence” is a measure of the number of new cases of an illness, a condition or a risk factor that occur in a population over a given period. Prevalence studies are done to evaluate the burden of disease in a population, to compare the frequency of disease in different populations and to study the trends of severity of disease over time (NIH, 2017).

A National surveillance study in England and Wales was conducted between 1999 and 2006 to estimate the incidence of TB in children younger than 16 years. Around 3,563 cases of TB were reported in children, giving an incidence rate of 4.3/100,000 in general. The highest incidence rate was found in 15 years old age group at 6.5/100,000 while 5 to 9 years old age group represented the lowest rate of

3.2/100,000 population. Beside this, black African and those born outside United Kingdom (UK) had the highest incidence rate of TB (87.6/100,000 and 37.3/100,000) comparatively to white population and those who were born in the UK (1.1/100,000 and 2.5/100,000). However, maximum numbers of cases were estimated from India, Pakistan, Philippines, Somalia, and Zimbabwe (Abubakar *et al.*, 2008).

Menzies *et al*., (2010) retrospectively evaluated the incidence rate of TB among United States of America (USA) and foreign born children (less than 13 years) and adolescents (13 to 17 years) from 1994 to 2007. About 8% of total cases were reported for children and adolescents. Study findings suggested the highest TB rates for both USA and foreign born children younger than 5 years. TB rates declined from 2.1/100,000 population in 1994 to 1.1/100,000 in 2007 among USA born children and adolescents and also for foreign born children from 20.3/100,000 to 11.4/100,000 population. The number of TB cases among foreign born children and adolescents was highest in the starting year of study and finally declined to 33% in 2007. During the study, more or less 90% of children and adolescents completed treatment successfully.

The incidence rate of TB among the children under 16 years was calculated from 1998 to 2009 in Oslo. The overall incidence rate of TB among all children was 2.6/100,000 population per year. For non-Western and those from Somalia, the overall incidence rate was 8.1/100,000 and 52.5/100,000 population. PTB, hilar lymphadenopathy and cases of lymph node TB were most frequently seen during the study period. From 19 of culture positive cases, 1 patient was reported resistant to streptomycin (SM), 2 to isoniazid (INH) and 2 were found resistant to both INH and SM (Krogh *et al.*, 2010).

Moyo *et al*., (2010) conducted a retrospective study between 1999 and 2004 in Cape Town, South Africa to estimate the incidence and severity of TB in children less than 5 years old. Children aged ≤ 11 months had highest proportion of bacteriological confirmed TB cases. The incidence rate in this group of age was notified as 0.2%. The highest rate of incidence (1.2%) was reported in children aged 12 to 23 months. The cumulative incidence of definite and probable TB was 2.9% in children less than 5 years and those aged 12 to 35 months had the highest incidence rate of severe TB.

Another retrospective study conducted in Kilimanjaro region assessed the incidence of childhood TB and treatment outcomes for the period 2002 to 2006. During this time, detection rate was 147/100,000 for urban and 41.8/100,000 for rural populations, thereby constituting 13% of total TB burden. Around 75.2% had PTB; 5.8% of patients tested for AFB were sputum positive (PTB+). The remaining 94.2% were presumptively treated for TB. Treatment success rate was 79.9% with 10.9% of mortality and 7% of default rate. The proportion of childhood TB was presented as 13.9, 12.4 13.1, 11 and 13.6%, respectively from 2002 to 2006. The prevalence of childhood TB during the study time frame ranged from 41 to 59/100,000 population per year, at the average of 52.8/100,000 (Mtabho *et al.*, 2010). Hatleberg and his colleagues (2014) retrospectively illustrated the trends of epidemiology and treatment outcomes of TB among children aged less than 15 years in Denmark from 2000 to 2009. Nearly half of the cases were presented from ≤ 4 years and 10 to 14 years in Danes and immigrants. Resistance to any drug was found in 18 of 159 cases, tested for drug susceptibility. Thirteen children were presented with mono-resistant to INH, 2 with ethambutol (EMB) and 2 with pyrazinamide (PZA) mono-resistant. However, 1 case was found to be MDR-TB with resistant to rifampicin (RIF), INH and EMB. There was an increased trend of notification rate of TB from 0.5 to 0.6/100,000 for

Danish children during the study time. Conversely, the trend of TB for immigrant decreased from 94.1/100,000 to 35.1/100,000 during the same time.

To estimate the incidence of childhood TB in 22 HBC (Afghanistan, Bangladesh, Brazil, Burma, Cambodia, China, DR Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Nigeria, Pakistan, Phillipines, Russia, South Africa, Thailand, Uganda, Tanzania, Vietnam, Zimbabwe) for the year 2010, a mathematical model study was conducted by Dodd *et al.*, (2014) for children younger than 15 years. During the study year, almost 7,600,000 children became infected with MTB whereas 650,000 developed TB. However, calculated proportion of total TB burden in children for each country varied from 4 to 21%. In all children notified with TB, 14% of the cases were likely to be of EPTB.

Wobudeya *et al*., (2015) conducted a retrospective study in Kampala, Uganda to estimate the incidence of TB in children aged under 15 years during 2009 to 2010. Around 7.5% of all registered cases were presented with cases of childhood TB. Of these, half of the cases were accounted for children less than 4 years, 25% of cases were 10 to 14 years and 5 to 9 years represented 21% of the cases. Nearly 89% of the children had PTB; with 15% PTB+ and 11% had EPTB. The incidence of childhood TB in Kampala was 56/100,000 and 44/100,000 in 2009 and 2010, respectively.

In Pakistan, a retrospective study was carried out for children aged < 15 years treated under the NTP in public hospitals of 3 districts of Punjab province. Of total 920 child TB cases, only 189 were notified during 2004 to 2005, almost 3 times less than those reported in 2006 to 2007. The implementation of policy guidelines for childhood TB resulted in increased annual notification rate of childhood TB cases from 1.4/100,000 in 2004 to 2005 to 5.2/100,000 population in 2006 to 2007. About 66.3% children were recorded with PTB, 22% with EPTB while 11.7% remained uncategorized. Fifty-five cases of total PTB were found as PTB+ (Safdar *et al.*, 2010).

2.3 Sputum smear conversion during TB treatment and predictors of sputum non-conversion

Sputum conversion is worthwhile in monitoring the TB program performance and as an indicator for assessing the patients who remain smear positive (WHO, 2010a). Beside this, sputum smear conversion plays a vital role in monitoring the response to treatment of infectious cases of PTB (WHO, 2004b). The sputum conversion rate (SCR) is the percentage of PTB+ cases converted to smear negative (PTB-) after 2 months of treatment (Kayigamba *et al.*, 2012). Patients are expressed as non-infectious once the sputum smear turned into negative. The intensive phase is extended to additional 1 month for the patient who remains smear positive at the end of 2nd month of treatment (Banu *et al.*, 2007). If PTB+ patients do not become negative at the end of 5th month of ATT, treatment failure is declared in these patients (Azarkar *et al.*, 2016). It is estimated that 80 to 90% of PTB+ patients experience smear conversion in 2 to 3 months of treatment. Negative smears during and at the end of treatment are requisite to state a patient cured of TB (WHO, 2004b). Consistent sputum smear at the end of the intensive phase of treatment is likely to be associated with unfavourable outcomes, definitely with failure and default and drug resistance TB. Below are given the findings of studies estimating sputum conversion rate and predictors of delayed sputum smear conversion and its effect on outcomes among TB adults.

Kayigamba *et al.*, (2012) conducted a study in Rwanda to evaluate the completion rate of sputum smear examinations at the end of the intensive phase of ATT and to calculate the sputum conversion rate. Smear examination at 2nd month was done in 1,039 out of 1,299 PTB+ patients. Among these, 82% turned into smear