THE EPIDEMIOLOGY OF CHILDHOOD TUBERCULOSIS AND CLINICAL OUTCOMES IN SOUTH AFRICA 2008 - 2012

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UNIVERSITY OF KWAZULU-NATAL DURBAN
SOUTH AFRICA

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ABSTRACT

Introduction

Tuberculosis (TB) in children, particularly in those under five years is regarded as an indicator of there being an infectious pool in the community. The World Health Organization (WHO) has focused on childhood tuberculosis, recognizing its contribution to the overall TB burden and to child survival. The Roadmap for Childhood Tuberculosis identifies the need to know the incidence of childhood TB in order to design and implement specific public health interventions to limit the spread of the disease and orientate health services in early TB detection, treatment and retention in care to prevent on-going transmission.

Aim

The aim of this research is to investigate the epidemiology of childhood TB in South Africa (SA) from 2008 to 2012 in order to inform TB control policy and practice.

Methods

An observational analytical cross sectional study design was used. The Electronic TB Register was used as the source of the data. Records from 1 January 2008 to 31 December 2012 were used. STATA and Excel were used to describe and analyse data.

Results

The proportion of children aged 0 to 14 years with TB in SA has fluctuated between 19.2% in 2008, reaching a high of 22.3% in 2009 and reducing to 18.8% in 2012. Testing children with TB for HIV has increased steadily from 17.9% in 2008 to 68.5% in 2012. The HIV prevalence in tested cases aged ten to fourteen years in 2012 was the highest at 42.6% with the lowest prevalence found in the zero to four year age group in 2012 of 16.7%. In analysing treatment outcomes, the children aged five to nine years had 21% (0.79) less risk of death compared to the children less than 5 years whereas the age group ten to fourteen had 1.33 times the risk of death.
Discussion

The WHO expects the proportion of childhood TB in high burden countries to be between ten and twenty percent. In SA the proportion of childhood TB has been above this level in 2009, it now falls within the upper limit of this expectation and has decreased annually since 2010. Given the large tuberculosis infectious pool in the country this is to be expected. Some progress is being made towards achieving the goal of HIV screening for all children with TB with the highest proportion tested being the age group ten to fourteen years.

Conclusion and Recommendations

Capacity building of clinicians in effective early TB case finding, appropriate management and better data recording and monitoring in children using the TB register is essential. Regular feedback of progress against programmatic targets would assist in focusing interventions to improve service delivery in TB in children. Youth friendly interventions for children that focus on screening, prevention, and retention in care are essential.
DECLARATION

I Jacqueline Robyn Smith declare that

The research reported in this dissertation, except where otherwise indicated, and is my original research.

This dissertation has not been submitted for any degree or examination at any other university. This dissertation does not contain other persons’ data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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Dr Stephen Knight February 16, 2017

J R Smith
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The co-investigator Dr S Moyo who helped conceptualise and develop the protocol on this study;

The co-authors of the article in the South African Health Review based on the same set of data;

The coaching assistance of Maanda Mudau in the initial STATA data file development; and

Dr. Stephen Knight, my supervisor, for his invaluable advice, support and guidance across all phases and processes in this study and the preparation of this dissertation.
The National Department of Health requested the Health Systems Trust (HST) to use the national TB dataset from the ETR.Net in order to conduct a more in depth analysis on tuberculosis in South Africa. Health Systems Trust has a TB team comprised of persons with expertise in the field of which I am a member. This team assessed the dataset to determine how the data could be used to inform the programme. A decision was taken to focus on tuberculosis in children as little has been published on this topic and in particular TB the burden of TB in HIV hotspots. I was asked to lead the analysis and writing of the chapter on childhood tuberculosis and co-author the chapter on HIV hotspots for the South African Health Review 2013/2014. I analysed the data and wrote the sections on case-finding and gave technical input to the sections on treatment outcomes which was written by Dr Moyo. The graphics were produced by Candy Day. The overall responsibility for the writing and analysis was mine.

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1. CHAPTER I: INTRODUCTION

1.1 BACKGROUND

The World Health Organization (WHO) declared tuberculosis (TB) a global emergency in 1993, with South Africa (SA) being one of 22 high burden countries. In 2012, South Africa had a TB incidence of 1003 per 100 000 population placing it amongst the highest in the world. Tuberculosis has increasingly been recognised as a major cause of morbidity and mortality among children in high TB burden settings. In a viewpoint article published in the Lancet in 2014, the importance of TB control in addressing child survival was highlighted, relating this to Millennium Developmental Goal 5. The Roadmap for Childhood Tuberculosis calls for strengthened reporting of TB cases occurring in children by national TB programmes, and among its ten key actions are inclusion of the needs of children and adolescents in research; policy development and clinical practice; and, collection and reporting of better data, including data on TB preventive measures directed at children.

Although the South African Children’s Act 38 of 2005 defines a child as being less than 18 years of age, WHO defines childhood TB as the form of the disease that affects those under the age of 15 years. Few countries report childhood TB incidence, as data is seldom available. The diagnosis of TB in children is difficult, usually based on history and clinical findings, and rarely supported by laboratory confirmation. In a best practice article in the Postgraduate Medical Journal, Hoskyns discusses the importance of childhood TB as a marker of recent TB transmission and a possible source of future TB disease. Children who have had TB are more likely to contract TB disease later in life.

In this study, we used data from all children reported with TB on the Electronic Tuberculosis Register (ETR.Net) in SA from 1 January 2008 to 31 December 2012. The purpose of the study was to describe the epidemiology of childhood TB in South Africa and assess whether demographic factors recorded in the ETR.Net are associated with TB outcomes.
The findings of this study can assist the Department of Health to determine if the national picture of childhood TB is similar to that found by Marais et al. in 2004, and to implement targeted child-appropriate TB interventions designed with a focus on prevention, early detection, treatment as well as improved recording in order to effectively manage the programme and decrease the burden of TB in children.

1.2 SPECIFIC OBJECTIVES

The specific objectives of this research are:

a. to describe TB incidence trends by age, sex and other demographic variables;

b. to compare the proportion of childhood TB cases in South Africa to the WHO estimated proportions for childhood TB cases in high burden countries; and

c. to determine if there are any associations between demographic variables and clinical outcomes of childhood TB.

1.3 DEFINITIONS

Electronic TB Register (ETR.Net)

The ETR.Net is an electronic TB register used in South Africa, designed for TB surveillance, programme monitoring and evaluation.

Childhood TB

Children under 15 years of age diagnosed with TB by means of bacteriological, radiological or clinical findings.

TB Outcomes

The health outcome of the patient at the end of the treatment as defined by the National Tuberculosis Management Guidelines 2014:

**Cure**: Patient who is smear-negative in the last month of treatment and on at least one previous occasion at least 30 days prior.
Treatment completed: Patient who has completed treatment but who does not meet the criteria to be classified as being cured or having failed treatment.

Treatment success: Patient who is cured or has completed treatment.

Treatment failure: Smear positive patient who remains or is again smear-positive at five months (for new) or seven months (for retreatment) after treatment start date or whose drug susceptibility test (DST) shows drug resistant TB (DR-TB) at two or three months.

Died: Patient who dies for any reason during the course of TB treatment.a

Treatment default: Patient whose treatment was interrupted for more than two consecutive months.

Transfer out: Patient who has been transferred to another reporting unit (e.g. district) and for whom the treatment outcome is not known 13

Cumulative TB Incidence in Children

The proportion of children under 15 years who developed active TB disease during the specified time period, reported for the age groups 0 to 4, 5 to 9 and 10 to 14 years against the district, provincial and national estimated populations for those age groups according to the 2011 census report produced by Statistics South Africa. 13

Childhood TB Prevalence

The total number of children with TB disease currently on treatment.

Drug Resistant TB

TB caused by strains of Mycobacterium tuberculosis that are resistant to isoniazid and/or rifampicin or any other first line drug.

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a The WHO defines TB deaths as all-cause mortality before completing anti-tuberculosis treatment
SUMMARY OF CHAPTER

Tuberculosis in children is accepted as an indicator of the burden of TB disease and the pool of TB infection in the community. Knowledge and understanding of the epidemiology of childhood TB will assist health service managers to plan efficiently to reduce the morbidity and mortality of children infected with TB. This chapter outlines the importance of establishing the epidemiological picture of childhood TB in South Africa.
2 CHAPTER II: LITERATURE REVIEW

2.1 INTRODUCTION

The focus on childhood TB has gained momentum in recent years. There is greater awareness that the increased incidence of childhood TB in a community is a reflection of the bigger burden of TB in adults in the same community. There is little recent literature available on the epidemiology of TB in children in South Africa, and studies available, other than a small study in the Western Cape, are based mostly in Europe and North America where the burden of TB is very low.

2.2 PURPOSE OF THE LITERATURE REVIEW

The purpose of this literature review was to look for similar countrywide studies on the demographic profiles and outcomes for childhood TB. Studies and other literature regarding TB in children globally, regionally and from South Africa were reviewed.

There are very few recent studies on the epidemiology of childhood TB, the most recent South African study was done by the Desmond Tutu TB Centre in 2004 in 2 communities in the Western Cape. The majority of the studies have been specifically related to the diagnosis and treatment of childhood TB.

2.3 SCOPE OF LITERATURE REVIEW

The literature review is limited to studies on children aged 0 to 14 years. The review will describe the available literature on the demographic profile of childhood TB in South Africa. The proportion of cases in South Africa will be compared to the WHO estimated proportions expected in a high TB burden countries.

2.4 LITERATURE REVIEWED

The electronic databases PubMed and Google Scholar were searched for studies on the epidemiology of childhood TB. The keywords and phrases, “childhood TB”, “epidemiology of childhood TB”, “targeting interventions for TB”, “incidence of childhood TB” and “outcomes for childhood TB” were used with or without the
Boolean operators “and” and “or”. Relevant citations in the identified literature were also used to search for further information.
2.4.1 Burden of TB

The WHO Global Taskforce on TB Impact Measurement uses the measures of incidence, prevalence and mortality to estimate the burden of TB. For the purposes of this study, we will use only incidence and prevalence. Incidence is defined as “the number of new and recurrent (relapse) episodes of TB (all forms) occurring in a given year”, prevalence as “the number of TB cases (all forms) at a given point in time”.

According to the WHO, TB remains the second leading cause of death in the world and substantially affects the health of millions of people. The Centers for Disease Control (CDC) defines TB infection as those persons that have been exposed to the mycobacterial bacillus and have become infected as shown by a positive Tuberculin Skin Test (TST) but are not ill. TB disease, however applies to those who are infected by the M.tb and have become ill and present with symptoms of active TB.  

Globally, there were 10.4 million people diseased with TB in 2015. Of these 1 million were children. South Africa was one of 6 countries who together accounted for 60% of the global TB burden. The African Region accounted for 26% (estimated 2.7 million cases) of the global TB burden with an estimated incidence of 275 per 100 000 (95% Confidence Interval (CI): 239 to 315) in 2015. South Africa had an estimated 454 000 cases (95% CI: 294 000 to 649 000) and an estimated prevalence of 834 per 100 000 (95% CI: 539 to 1190) in 2012. The prevalence of TB infection is not routinely measured due to the resource requirements of conducting large-scale cohort studies, the expense involved of performing TST and because where the Bacillus Calmette-Guerin (BCG) vaccine is routinely used, most children should have a positive TST.

In a WHO policy paper, it is stated that a country’s notification system is considered a satisfactory proxy indicator for incidence of TB. In South Africa notification of TB is compulsory and is legislated under the National Health Act 63 of 2003 as amended. Due to the vast number of TB cases in South Africa, the Electronic TB Register is felt to be a more reliable method than using the Notification of Medical Conditions surveillance system used for other notifiable medical conditions. The data from the
ETR.Net system informs South Africa’s TB data reporting to the WHO. It is reported that in 2012 there were 530 000 (95% CI: 430 000 to 630 000) new cases of
TB in South Africa. The cumulative incidence of 1000 per 100 000 population (95% CI: 827 to 1190) is the highest reported from amongst the high burden countries globally. 17

2.4.2 Demographic profile of childhood TB

Very few studies have been published on demographic profiles of children with TB. A prospective observational study conducted over an 18-month period by Marais et al. in a high burden community in Cape Town found that children under the age of 13 years comprised 14% of the total TB caseload, which is close to the WHO estimate of 15% for high burden countries. 20 The proportion of children less than 3 years was 54%. The sex ratio in these children was equal, 65% of the children had been tested for HIV, and 8.8% were HIV positive.

In 1998, Van Rie et al., in another Cape Town based study reported that childhood TB represented 37 to 58% of the total TB caseload. 14 Children aged 0 to 4 years comprised 25 to 49% of the total childhood TB caseload. A longitudinal study of 93 children with TB in Solapur City, India in 2012 by Bandichhode ST et al. 21 found that 37% were aged 1 to 5 years, 29% 5 to 10 years and 29% were in the 10 to 15 year age group.

Infants comprised 5% of the childhood TB in this study. These proportions are similar to those reported from Cape Town. In addition, the sex distribution was equal.

In a larger retrospective descriptive study also in India that comprised 541 children with TB, from 2000 to 2010, 39 were 13 to 14 years old, which differs from most other studies. 24 Females comprised 65% of the cases, also differing from other studies. These children were not tested for HIV. Only 3.8% of the children were under 5 years of age.

2.4.3 World Health Organization estimated proportions for childhood TB

The WHO estimates that in high burden settings, it is expected that TB in children will comprise 10 to 20% of the total TB caseload. 22 Globally childhood TB is on the increase in many countries although 75% of childhood TB cases notified in 2000 were from high TB burden countries. In the same year, (2000) in unpublished National TB Programme data, Botswana reported an increased number and proportion (12%) of
children (< 15 years) with TB. A study done by Van Rie et al. in two urban communities in Cape Town in 1998 reported that according to TB case notification data, childhood TB comprised 45% (95% CI: 37% to 58%) of the total TB burden in these communities. The number of childhood TB cases aged 0 to 4 years (n=1383) comprised 36% of the total TB caseload, while the 5 to 14 year age group had 9% of the total reported cases of TB. As this study was confined to two peri-urban communities in Cape Town the findings cannot be generalised to the whole South African population. This study was located in two small communities in the Western Cape, which is one of the highest burden areas in South Africa. The results may have been affected by sampling bias as this study was not a representative sample of the country burden of disease.

2.4.4 Bacteriological Coverage

Few countries report indicators of childhood TB incidence, as data is seldom available. The absence of a “gold standard” for diagnosis of TB in children continues to complicate diagnosis which is therefore usually based on history and clinical findings, and rarely supported by laboratory confirmation. Obtaining a suitable sputum sample from children as well as the frequency of low bacillary counts found in children, makes a bacteriological diagnosis difficult. Obtaining suitable specimens would require procedures such as gastric lavage, nebulization, or broncho-alveolar lavage, which all require overnight hospitalisation, in a facility with good infection control and suitably trained staff. No data could be found on bacteriological coverage in children less than 7 years of age for comparison. Other bacteriological coverage data for children older than 7 years is aggregated with adult data and therefore could not be determined.

The problem of obtaining a firm diagnosis of TB in children is further complicated by “the increased presence of extra-pulmonary disease in young children [and] the lower public health priority previously given to childhood TB.”

While culture remains the gold standard for diagnosing TB in children, recent advances like GeneXpert MTB/RIF assays have improved the turnaround time for diagnosis.
These tests can also be used for testing gastric aspirate and urine and once fully validated will aid in improved diagnosis. 27
2.5 SUMMARY OF CHAPTER

The reviewed literature in this chapter reflects the small number of studies and data available on the epidemiology of childhood TB globally and in South Africa or other high burden countries. Studies that have been conducted in other countries are not in the same high burden setting and not typical of the South African context.
3 CHAPTER III: METHODS

3.1 INTRODUCTION

The importance of understanding the epidemiology of TB in children is key to managing the TB epidemic. The paucity of studies in South Africa of TB in children has made this difficult. This study describes the demographic profile of childhood TB in South Africa between 2008 and 2012. In Chapter Three, the research methods used in this study are described, including the study design, study population and sampling, data collection, and analysis. Ethical considerations, which apply to this study, are also described.

3.2 CONCEPTUAL FRAMEWORK

The conceptual framework for this study has its foundation in the outcome of the treatment as this influences the future health of the child. The clinical outcomes of children 0 to 14 years diagnosed with TB through the lens of various demographic factors like age, sex and HIV status is reported, in an attempt to identify possible associations for the TB incidence and outcomes in different age groups.
3.3 TYPE OF RESEARCH

This study involves epidemiological research, which will be applied at a public health level, in order to assist in informing the design of appropriately targeted community based interventions to reduce the burden of childhood TB in SA.

3.4 STUDY DESIGN

An observational analytical cross sectional study design was used.

3.5 TARGET POPULATION

The results of this study are generalizable to all children aged less than fifteen years in South Africa as well those in other low to middle income countries in Africa with a similar demographic profile and burden of HIV infection.

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2 This conceptual framework is self-designed based on personal experience in the TB programme
3.6 STUDY POPULATION

The study population comprised all children reported with TB, and diagnosed by means of bacteriological, radiological or clinical findings and recorded in the ETR.Net in South Africa for the 5-year period from 2008 to 2012. A census was used of all records of TB patients aged 0 to 14 years between 2008 and 2012. (N=235 836).

Inclusion Criteria:

All children in the age groups 0 to 4, 5 to 9 and 10 to 14 years reported on TB treatment in the ETR.Net with drug sensitive TB between 2008 and 2012, irrespective of the diagnostic method or the site of the disease were included in the study population.

Exclusion Criteria:

The following criteria were applied for excluding study participants from the study:

1. TB patients 15 years and older; and
2. Children aged 0 to 14 years with drug resistant TB.

3.7 DATA SOURCES

The Electronic TB Register was used as the source of the data. Records from 1 January 2008 to 31 December 2012 were used. The ETR.Net is the software used by the South African National Department of Health to capture routine patient level data for drug sensitive TB in all public health facilities.

3.8 VARIABLES

3.8.1 Reliability and Validity of Data Source

The ETR.Net was used as the data source. While it is acknowledged that there are data quality issues with any clinician-recorded data, it remains the most reliable source of data on childhood TB in South Africa.
3.9 BIAS AND LIMITATIONS

To minimize selection bias all records were included and duplicate records were removed. Information bias has been minimized by automatic importing of the data from the electronic TB database into the statistical software thereby minimizing human capture error. It is acknowledged that there is potential for information bias with any clinician-recorded data. The database has incomplete data records for certain reporting variables and for some reporting periods. This was taken into account during analysis.

3.10 STATISTICAL PROCESSING

3.10.1 Descriptive statistics

A descriptive summary of the age groups and demographic factors as well as the outcomes per province is presented in Chapter Four.

3.10.2 Analytic statistics

The data, which was available in a Structured Query Language (SQL) database, was exported into MS Excel and imported into a statistical software package (STATA 13) for processing and analysis. Chi square analysis was used to determine odds ratios and risk ratios and logistic regression was used to control for confounding. Pearson’s Chi squared test was used for trend analysis. The results of this analysis of the data are presented in Chapter Four.
3.11 LIST OF ASSOCIATIONS ASSESSED

Various associations between variables have been measured as per Table 1 below.

Table 1: List of possible associations

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<tr>
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<td>Clinical Outcomes, HIV status</td>
</tr>
<tr>
<td>HIV status</td>
<td>Clinical Outcomes, Age</td>
</tr>
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3.12 ETHICS AND PERMISSIONS

3.12.1 Institutional Review Board

Application for expedited ethical approval was made to the Biomedical Research Ethics Committee at University of KwaZulu-Natal (UKZN). This was granted on 26 March 2015 (BE 271/14) (Appendix 7.4).

3.12.2 Permissions

Permission for the use of this ETR.Net data and to conduct this study was obtained from the National Department of Health on 19 March 2015 (Appendix 8.5).

3.12.3 Study registered

This study was registered with the School of Nursing and Public Health Higher Degrees and Research Committee towards completion of the Master of Public Health degree at UKZN.
3.13 SUMMARY OF CHAPTER

This study investigated the epidemiological profile of children aged 0 to 14 years with TB in South Africa from 2008 to 2012, as well as association of some demographic variables with possible outcomes. In this chapter the study design, study population and sampling, data collection and analysis that were employed in the study are described.

Measures to ensure validity and dependability, and ethical considerations, are also described.
4 CHAPTER IV: RESULTS

4.1 INTRODUCTION

Data was extracted from the ETR.Net and imported into STATA 13. Frequency distribution tables were generated and bivariate analysis performed to measure associations between exposure and outcome variables. Microsoft Excel was used to generate graphs. The database has incomplete records for certain reporting units and for some reporting periods. This has been noted in detail and analysis has been controlled to minimize the effect on the results.

4.2 PRESENTATION OF DATA

4.2.1 Age of children with TB

There were 384 936 children (< 15 years) diagnosed with TB and recorded in the ETR.Net in the five year period (Table 2). More than two-thirds of the children with TB (266 987 - 69%) were in the 0 to 4 year old age group.

Table 2: 4.1 Age groups of children recorded with TB in SA, 2008-2012

<table>
<thead>
<tr>
<th>Age Group</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 4 years</td>
<td>266 987</td>
<td>69</td>
</tr>
<tr>
<td>5 to 9 years</td>
<td>76 138</td>
<td>20</td>
</tr>
<tr>
<td>10 to 14 years</td>
<td>41 811</td>
<td>11</td>
</tr>
<tr>
<td>All children</td>
<td>384 936</td>
<td>100</td>
</tr>
</tbody>
</table>
This data was then categorized per year in order to determine trends in the number of children diagnosed with TB within the three age group categories (Table 3). The proportion reported from the ETR.Net within each age group remained consistent across the study period. It ranged from 67% to 71% in the 0 to 4 age group, from 19% to 22% in the 5 to 9 age group and from 10% to 11% in the 10 to 14 year old age group. No obvious trend was observed in the data.

Table 3: Age of children <15 years recorded with TB in SA per year, 2008-2012

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>0 to 4</td>
<td>47 381</td>
<td>67</td>
<td>65 460</td>
<td>71</td>
<td>53 574</td>
</tr>
<tr>
<td>5 to 9</td>
<td>15 425</td>
<td>22</td>
<td>17 315</td>
<td>19</td>
<td>14 892</td>
</tr>
<tr>
<td>10 to 14</td>
<td>7933</td>
<td>11</td>
<td>9215</td>
<td>10</td>
<td>8278</td>
</tr>
<tr>
<td>Total</td>
<td>70 739</td>
<td>100</td>
<td>91 990</td>
<td>100</td>
<td>76 744</td>
</tr>
</tbody>
</table>
4.2.2 Distribution of males to females

The distribution of males to females in the age groups 0 to 4 years and 5 to 9 years consistently had a slightly higher proportion of males than females. In the age group 10 to 14 years, the opposite was found with a higher proportion of females reported than males. Both patterns appear consistent over the five-year period (Table 4).

Table 4: Distribution across age groups of males and females less than 15 years reported with TB from 2008 to 2012

<table>
<thead>
<tr>
<th>Year</th>
<th>0 to 4 years</th>
<th>5 to 9 years</th>
<th>10 to 14 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>2008</td>
<td>22</td>
<td>48%</td>
<td>24 501</td>
</tr>
<tr>
<td>2009</td>
<td>31</td>
<td>49%</td>
<td>33 661</td>
</tr>
<tr>
<td>2010</td>
<td>26</td>
<td>49%</td>
<td>27 543</td>
</tr>
<tr>
<td>2011</td>
<td>26</td>
<td>49%</td>
<td>28 403</td>
</tr>
<tr>
<td>2012</td>
<td>22</td>
<td>49%</td>
<td>23 277</td>
</tr>
<tr>
<td>Total</td>
<td>129 599</td>
<td>49%</td>
<td>137 385</td>
</tr>
</tbody>
</table>

4.2.3 Proportion of children diagnosed with TB

A total of 1 882 139 cases of TB were reported in South Africa from 2008 to 2012, of which 384 936 (21%) were aged 0 to 14 years (Table 4). The proportion of TB in children aged 0 to 14 years remained consistent at 19% over the five-year period.
Table 5: Children diagnosed with TB as a proportion of all TB cases reported in the same period, 2008 to 2012

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 4</td>
<td>47 831</td>
<td>13%</td>
<td>65 460</td>
<td>16%</td>
<td>53 574</td>
<td>15%</td>
<td>55 219</td>
<td>14%</td>
<td>45 353</td>
<td>13%</td>
</tr>
<tr>
<td>5 to 9</td>
<td>15 425</td>
<td>4%</td>
<td>17 315</td>
<td>4%</td>
<td>14 892</td>
<td>4%</td>
<td>15 814</td>
<td>4%</td>
<td>12 692</td>
<td>4%</td>
</tr>
<tr>
<td>10 to 14s</td>
<td>7933</td>
<td>2%</td>
<td>9215</td>
<td>2%</td>
<td>8278</td>
<td>2%</td>
<td>8713</td>
<td>2%</td>
<td>7472</td>
<td>2%</td>
</tr>
<tr>
<td>All children</td>
<td>71 189</td>
<td>19%</td>
<td>91 990</td>
<td>22%</td>
<td>76 744</td>
<td>21%</td>
<td>79 746</td>
<td>20%</td>
<td>65 517</td>
<td>19%</td>
</tr>
<tr>
<td>Total 15+ years</td>
<td>297 457</td>
<td>81%</td>
<td>319 734</td>
<td>78%</td>
<td>282 217</td>
<td>79%</td>
<td>313 468</td>
<td>80%</td>
<td>284 077</td>
<td>81%</td>
</tr>
<tr>
<td>Total TB</td>
<td>368 646</td>
<td>100%</td>
<td>411 724</td>
<td>100%</td>
<td>358 961</td>
<td>100%</td>
<td>393 214</td>
<td>100%</td>
<td>349 594</td>
<td>100%</td>
</tr>
</tbody>
</table>

4.2.4 Treatment category

A total of 292 185 children were newly diagnosed with TB in the five year period (Table 6). The proportion of children with TB that were not classified according to disease history ranged from 12% to 19% over the five-year period. The proportion in children reported having had previous TB remained largely unchanged. Knowing the previous TB history of the child is important to assess risk of possible drug resistance and to determine the regimen of treatment for the child.

Table 6: History of previous TB of reported cases from 2008 to 2012

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>New</td>
<td>59590</td>
<td>84%</td>
<td>66659</td>
<td>73%</td>
<td>55104</td>
<td>72%</td>
<td>59825</td>
<td>75%</td>
<td>51007</td>
<td>78%</td>
<td>292185</td>
<td>76%</td>
</tr>
<tr>
<td>Re-treatment</td>
<td>2607</td>
<td>4%</td>
<td>2609</td>
<td>3%</td>
<td>2368</td>
<td>3%</td>
<td>2593</td>
<td>3%</td>
<td>1968</td>
<td>3%</td>
<td>12145</td>
<td>3%</td>
</tr>
<tr>
<td>Not</td>
<td>8542</td>
<td>12%</td>
<td>22722</td>
<td>25%</td>
<td>19272</td>
<td>25%</td>
<td>17328</td>
<td>22%</td>
<td>12742</td>
<td>19%</td>
<td>80606</td>
<td>21%</td>
</tr>
<tr>
<td>Total</td>
<td>70739</td>
<td>100%</td>
<td>91990</td>
<td>100%</td>
<td>76744</td>
<td>100%</td>
<td>79746</td>
<td>100%</td>
<td>65717</td>
<td>100%</td>
<td>384936</td>
<td>100%</td>
</tr>
</tbody>
</table>
Between 2008 and 2009, there was a huge increase in the proportion of children with TB whose previous history of TB was not categorised. Since 2009, this proportion has shown a decreasing trend from 25% in 2009 to 19% in 2012 (Figure 2).

Figure 2: Children with TB whose previous history of TB was not classified from 2008 to 2012.

4.2.5 Bacteriological Coverage

Bacteriological coverage varied between the age groups with the highest coverage found in the 10 to 14 year old age group. The coverage in the 5 to 9 year old age group ranged between 21% in 2008 and 33% in 2012. This is very low as most children in this age group could be expected to produce a sputum sample.
4.2.6 Type of TB

The majority (284 556 -93%) of children classified according to the type of TB, in the five-year period had pulmonary TB (PTB). There were 19 757 (7%) of children with extra pulmonary TB (EPTB) reported over the five year period. This ranged from 4156 (7%) children in 2008 to 3351 (6%) in 2012. The downward trend trend of children reported with EPTB was significant, (0.035) (Table 7). In the case of HIV positive children reported with EPTB, it is noted that in the age groups 0 to 4 years, there is a significant trend in the decrease in the proportion of children with EPTB (p=<0.0001).

This decrease is mirrored in the 5 to 9 year age group (p <0.0001) and less strongly in the age group 10 to 14 years, although the trend is still significant (p = 0.003) (Table 8).

Table 7: Type of TB for childhood TB cases registered 2008 to 2012

<table>
<thead>
<tr>
<th>TB Type</th>
<th>EPTB</th>
<th>No.</th>
<th>%</th>
<th>PTB</th>
<th>No.</th>
<th>%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td></td>
<td>4156</td>
<td>7%</td>
<td></td>
<td>58 028</td>
<td>93%</td>
<td>62 184</td>
</tr>
<tr>
<td>2009</td>
<td></td>
<td>4385</td>
<td>6%</td>
<td></td>
<td>64 880</td>
<td>94%</td>
<td>69 265</td>
</tr>
<tr>
<td>2010</td>
<td></td>
<td>3746</td>
<td>6%</td>
<td></td>
<td>53 725</td>
<td>94%</td>
<td>57 471</td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td>4119</td>
<td>7%</td>
<td></td>
<td>58 299</td>
<td>93%</td>
<td>62 418</td>
</tr>
</tbody>
</table>

Figure 3: Bacteriological coverage of children reported with PTB from 2008 to 2012

Table 7: Type of TB for childhood TB cases registered 2008 to 2012
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>6%</th>
<th></th>
<th>94%</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>P value</td>
<td>0.035</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>19,757</td>
<td>7%</td>
<td>284,556</td>
<td>94%</td>
<td>304,313</td>
</tr>
</tbody>
</table>

EPTB = extra pulmonary TB, PTB = pulmonary TB
<table>
<thead>
<tr>
<th>Year</th>
<th>0 to 4 years</th>
<th>5 to 9 years</th>
<th>10 to 14 years</th>
<th>All children &lt;15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive %</td>
<td>CI 95%</td>
<td>Positive %</td>
<td>CI 95%</td>
</tr>
<tr>
<td>2008</td>
<td>202 49%</td>
<td>42 - 56</td>
<td>198 59%</td>
<td>52 - 66</td>
</tr>
<tr>
<td>2009</td>
<td>452 52%</td>
<td>47 - 57</td>
<td>363 61%</td>
<td>56 - 66</td>
</tr>
<tr>
<td>2010</td>
<td>396 41%</td>
<td>36 - 46</td>
<td>437 59%</td>
<td>54 - 64</td>
</tr>
<tr>
<td>2011</td>
<td>406 35%</td>
<td>30 - 40</td>
<td>463 56%</td>
<td>52 - 61</td>
</tr>
<tr>
<td>2012</td>
<td>322 32%</td>
<td>27 - 37</td>
<td>348 48%</td>
<td>43 - 53</td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.000</td>
<td>&lt;0.000</td>
<td>0.003</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Total</td>
<td>1778 40%</td>
<td>1809 56%</td>
<td>1803 48%</td>
<td>5390 32%</td>
</tr>
</tbody>
</table>
4.2.7 HIV testing

The proportion of children with TB who were tested for HIV increased progressively from 22% (15 478) in 2008 to 72% (47 379) in 2012 (Table 10), which increased across all age groups during the period (Figure 4).

Table 9: Proportion of children diagnosed with TB who were tested for HIV in South Africa, 2008 to 2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Reported cases</th>
<th>HIV tested No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>70 739</td>
<td>15 478</td>
<td>22%</td>
</tr>
<tr>
<td>2009</td>
<td>91 990</td>
<td>31 468</td>
<td>34%</td>
</tr>
<tr>
<td>2010</td>
<td>76 744</td>
<td>38 950</td>
<td>51%</td>
</tr>
<tr>
<td>2011</td>
<td>79 746</td>
<td>50 770</td>
<td>64%</td>
</tr>
<tr>
<td>2012</td>
<td>65 717</td>
<td>47 379</td>
<td>72%</td>
</tr>
<tr>
<td><strong>5 Year Total</strong></td>
<td><strong>384 936</strong></td>
<td><strong>184 045</strong></td>
<td><strong>48%</strong></td>
</tr>
</tbody>
</table>

*Figure 4: Proportion of children with TB who were tested annually for HIV, 2008-2012*
During the five-year study period 184 045 (48%) children with TB were tested for HIV, of which 58 876 (32%, 95% CI: 31.8 to 32.2) tested positive (Table 10). A Pearson’s Chi squared test was used to determine if there is a significant change in the data over time. The trend in HIV prevalence is increasing in each of the three age group category. In the 10 to 14 year category HIV prevalence increased from 33% (95% CI 31.7 - 35.1) in 2008 to 51% (95% CI 49.9 - 52.3) in 2012 and the increase is statistically significant (p= <0.000). There were decreases in both the children aged 0 to 4 years and 5 to 9 years (Table 10).

**Table 10: Trends in HIV prevalence in children <15 years diagnosed with TB from 2008 to 2012**

<table>
<thead>
<tr>
<th>Year</th>
<th>No.</th>
<th>0 to 4 years</th>
<th>95% CI</th>
<th>5 to 9 years</th>
<th>95% CI</th>
<th>10 to 14 years</th>
<th>95% CI</th>
<th>All children &lt;15</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>3150</td>
<td>37%</td>
<td>35 - 38</td>
<td>1879</td>
<td>48%</td>
<td>46 - 50</td>
<td>1029</td>
<td>33%</td>
<td>30 - 36</td>
</tr>
<tr>
<td>2009</td>
<td>6138</td>
<td>32%</td>
<td>30 - 33</td>
<td>3618</td>
<td>49%</td>
<td>47 - 51</td>
<td>2087</td>
<td>43%</td>
<td>41 - 45</td>
</tr>
<tr>
<td>2010</td>
<td>6394</td>
<td>27%</td>
<td>25 - 28</td>
<td>4521</td>
<td>50%</td>
<td>49 - 52</td>
<td>2832</td>
<td>50%</td>
<td>48 - 52</td>
</tr>
<tr>
<td>2011</td>
<td>6438</td>
<td>20%</td>
<td>19 - 21</td>
<td>4968</td>
<td>44%</td>
<td>43 - 45</td>
<td>3414</td>
<td>50%</td>
<td>48 - 52</td>
</tr>
<tr>
<td>2012</td>
<td>5193</td>
<td>17%</td>
<td>16 - 18</td>
<td>3947</td>
<td>40%</td>
<td>39 - 42</td>
<td>3268</td>
<td>51%</td>
<td>49 - 53</td>
</tr>
</tbody>
</table>

P value<0.000 <0.000 <0.000 <0.000

Total 27313 24% 24 - 25 18933 45% 44 - 46 12630 47% 46 - 48 58876 32% 32 - 32
The percentage of children with TB that were tested for HIV rose consistently while the prevalence of HIV leveled off in the age groups 0 to 4 years and 5 to 9 years but continued to rise in the children aged 10 to 14 years (Figure 5).

Figure 5: HIV testing (%) and prevalence per age group of children reported for TB from 2008 to 2012
4.2.8 Treatment Outcomes

Tuberculosis outcomes are categorised as “treatment success”, “default”, “death”, and “failure”. Outcomes of “transferred” and “moved” and “not evaluated” have been removed from the denominator. The proportion of children who successfully completed treatment increased from 90% (95% CI 89.5 - 90.1) to 93% (95% CI 92.8 - 93.4) from 2008 to 2012. This is statistically significant if measured against a combination of unsuccessful outcomes (\(p<0.0001\)). The proportions of those who died and those who defaulted treatment showed slight decreases while the proportion who failed treatment remained unchanged (Table 11).

Table 11: Trends in treatment outcomes of children with TB reported from 2008 to 2012

<table>
<thead>
<tr>
<th>Year</th>
<th>Treatment Success</th>
<th>Default</th>
<th>Died</th>
<th>Failed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>95% CI</td>
<td>No.</td>
</tr>
<tr>
<td>2008</td>
<td>41 413</td>
<td>90%</td>
<td>89.5 - 90.1</td>
<td>2971</td>
</tr>
<tr>
<td>2009</td>
<td>44 653</td>
<td>91%</td>
<td>90.2 - 90.8</td>
<td>2984</td>
</tr>
<tr>
<td>2010</td>
<td>35 452</td>
<td>91%</td>
<td>90.3 - 90.9</td>
<td>2348</td>
</tr>
<tr>
<td>2011</td>
<td>41 583</td>
<td>93%</td>
<td>92.7 - 93.1</td>
<td>2005</td>
</tr>
<tr>
<td>2012</td>
<td>34 843</td>
<td>93%</td>
<td>92.8 - 93.4</td>
<td>1673</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>197 944</td>
<td>91%</td>
<td>91.3 - 91.5</td>
<td>11 981</td>
</tr>
</tbody>
</table>
Using the age group 0 to 4 years as the reference group, risk ratios were calculated for clinical outcomes of successful treatment. The age group 0 to 4 years was used because it is the largest group. It was found that all children had a significant chance (p<0.01) of treatment success irrespective of age, 1.01 for 5 to 9 years and 0.99 for 10 to 14 years (Table 12).

Table 12: Risk ratio for the outcome successful treatment per age group from 2008 to 2012

<table>
<thead>
<tr>
<th>Age group</th>
<th>Treatment success</th>
<th>Total with outcome</th>
<th>Proportion with successful outcome</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 4 years</td>
<td>121 138</td>
<td>132 890</td>
<td>0.912</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 9 years</td>
<td>50 505</td>
<td>54 653</td>
<td>0.93</td>
<td>1.014</td>
<td>1.011-1.017</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>10 to 14</td>
<td>26 301</td>
<td>29 220</td>
<td>0.9</td>
<td>0.987</td>
<td>0.983-0.992</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total</td>
<td>197 944</td>
<td>216 763</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In terms of the clinical outcome of death, the children aged 5 to 9 years had 21% (0.79) less risk of death compared to the children less than 5 years (p<0.01) whereas the age group 10 to 14 had 1.33 times the risk of death (P<0.01) (Table 13).

Table 13: Risk ratio for the clinical outcome of death per age group for children reported with TB from 2008 to 2012

<table>
<thead>
<tr>
<th>Age group</th>
<th>Died</th>
<th>Total with outcome</th>
<th>Proportion who died</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 4 years</td>
<td>3812</td>
<td>132 890</td>
<td>0.029</td>
<td>Reference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 9 years</td>
<td>1246</td>
<td>54 653</td>
<td>0.023</td>
<td>0.79</td>
<td>0.75-0.85</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>10 to 14</td>
<td>1115</td>
<td>29 220</td>
<td>0.038</td>
<td>1.33</td>
<td>1.25-1.42</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Total</td>
<td>6173</td>
<td>216 763</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Both children aged 5 to 9 and children aged 10 to 14 have a significantly greater risk of testing positive for HIV, 1.9 times (p<0.01) and 2.0 times (p<0.01) respectively (Table 14).

Table 14: Risk ratio for testing HIV positive per age group from 2008 to 2012

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Positive</th>
<th>Negative</th>
<th>Total</th>
<th>Tested positive</th>
<th>Risk ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 4 years</td>
<td>27 313</td>
<td>88 135</td>
<td>115</td>
<td>0.237</td>
<td>Ref group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 9 years</td>
<td>18 933</td>
<td>22 817</td>
<td>41 750</td>
<td>0.453</td>
<td>1.92</td>
<td>1.89-1.95</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
4.3 SUMMARY

The results of the analysis show clearly the demographic picture of childhood TB in each age group over the five-year period as well as changes in trends of HIV testing for childhood TB as well as HIV prevalence trends.
CHAPTER 5: DISCUSSION

5.1 INTRODUCTION

In this chapter, the results of this study looking at the epidemiology of childhood TB cases reported in South Africa from 2008 to 2012 is discussed. Associations between variables are examined to identify any that may be of statistical significance. The results are compared to existing knowledge, and possible explanations for the findings are provided. The study findings are also considered in light of the possible biases and limitations of the study design, the data collection process and results obtained in the study.

5.2 AGE GROUPS

Most (69%) of reported cases of childhood TB in South Africa from 2008 to 2012 were younger than 5 years old and only 11% were from the 10 and 14 years aged group.

This is consistent with two studies from the Western Cape where the burden of childhood TB was also in the youngest age group. Van Rie et al. 14 found that children aged 0 to 4 years comprised 79% of the total cases of childhood TB during the period 1985 to 1994 and Marais reported that 5% of children with TB were less than 3 years old. All three South African studies found higher proportions than those of the two Indian studies where Mazta and Bandichhode reported proportions of 3.9% and 37% respectively in this age group. Data comparison is made difficult by the use of slightly different age groupings in each of these reported studies.

The studies by Van Rie et al. examined data from 1744 cases of TB in children from two communities. Mazta et al. studied data from 541 cases, Bandichhode et al. 93 cases and Marais et al. 443 cases. These studies were limited to small communities or district areas where factors such as health policy or health staff competency and capacity may have influenced the results. Our study examined data from 266 987 cases reported from the whole country. There could be random variation when the sample population is small, which could be a reason for the difference in proportions reported across the different studies.
5.3 TREATMENT CATEGORY

Most of the children with TB were reported to be the first episode of disease. The proportion being first episode cases ranged from 84% of the total cases in 2008 to 78% in 2012. This is not remarkable considering these were all young children. There was however, an increasing trend in the proportion of childhood TB who were non-classified. These cases increased from 12% in 2008 to 19% in 2012. Non-classification may be attributed to poor history taking skills or poor recording of data in the patient files and Electronic TB registers, which is the basis of the dataset used in this study.

5.4 BACTERIOLOGICAL COVERAGE

The proportion of childhood TB with a bacteriological diagnosis varied between the age groups. The 10 to 14 year old age group had the highest bacteriological coverage. The coverage in the 5 to 9 year old age group ranged between 21% in 2008 and 33% in 2012, which is very low as most children in this age group could be expected to produce a sputum sample. Failure to implement TB guidelines, lack of knowledge of the health staff and lack of patient education may have contributed to this low proportion with bacteriological coverage. In poor resource settings, anecdotal data indicates that laboratory transport systems are irregular and samples often are leaked or spoiled by the time specimens arrive at the laboratory.

5.5 TYPE OF TB

Poor data quality and missing data is reflected in the analysis of the type of TB in children in the ETR.Net. In 21% of the 384,936 cases, the site of disease was not classified. The highest proportion (30%) of childhood TB cases not classified occurred in the children in the under 5-year age group. Incomplete recognition of the type of TB may be due to a lack of understanding of the International Classification of Disease 10th revision (ICD 10) codes used to record the type of TB disease in the registers. Most (284,556 - 94%) of children in this study were classified as having pulmonary TB (PTB). This finding is similar to other studies reported in SA. Van Rie reported that 98% of children with TB in the Western Cape reported having had PTB. However, both Indian studies reported lower proportions (55%) and (68%) with PTB and higher proportions with extra-pulmonary TB (EPTB).
There were 19,757 (7%) children with EPTB reported over the five year period. This ranged from 4,156 (7%) children in 2008 to 3,351 (6%) in 2012. The trend of EPTB registrations showed significant decrease (p = 0.035) over the five year period. In children reported to be living with HIV reported with EPTB, it is noted that in the age groups 0 to 4 years, there is a significant decreasing trend in the proportion of children with EPTB (p = <0.0001 for trend). This decrease is mirrored in the 5 to 9 year age group (p < 0.0001 for trend) and less strongly in the age group 10 to 14 years, although the trend is still significant (p = 0.0029). A study in India reported EPTB in 15 to 20% of HIV-negative children with TB and 20 to 70% of those HIV infected, while in a Thai study, 40% of HIV-infected children with TB reported as having EPTB. 28,29

5.6 HIV TESTING AND COUNSELING (HTC)

South Africa has actively promoted HIV testing and counselling for patients with TB with particular emphasis since the HTC campaign launched in 2010. 30 As a result, the trends in the proportion tested annually increased from 18% in 2008 to 68% in 2012. The largest increase in the proportion tested was in the children aged 10 to 14 years. Using the age group 0 to 4 years as a reference group, it was found that children aged 5 to 9 years had 1.27 times higher probability of being tested for HIV, while those aged 10 to 14 had a 1.48 times higher probability of accessing HTC. This is encouraging as it appears that implementation of national HTC policy has increased access to HIV care for children with TB. Children aged 0 to 4 years should have been tested as part of the Prevention of Mother-to-Child Transmission programme (PMTCT), where mothers are tested during pregnancy and children born to HIV infected mothers are tested at 2 months and 18 months of age.

5.7 HIV PREVALENCE IN TESTED CASES

During the five-year study period 184,045 (48%) children with TB were tested for HIV, of which 58,876 (32%, 95% CI: 31.8% to 32.2%) tested positive. A Pearson’s chi squared test was used to determine if there is a significant change in the data over time.

The trend in HIV prevalence in the 10 to 14 year category HIV prevalence increased from 33% (95% CI 31.7 - 35.1) in 2008 to 51% (95% CI 49.9 - 52.3) in 2012 and the increase is statistically significant (p = <0.0001). There were decreases in the HIV prevalence both the
children aged 0 to 4 years and 5 to 9 years. The proportion of HIV positive cases over the whole sample has steadily decreased over the five year period from 39% in 2008 to 26% which is statistically significant (p<0.001). It is unclear if this is due to fewer children being infected with HIV, or poorer implementation of Department of Health policy requiring 100% HIV screening and therefore reduced HIV testing of symptomatic or ill children only.

In looking at the data broken into age groups it can be observed that in the age group 5 to 9 years the proportion of children with TB tested for HIV increased from 26% to 78% over the five-year period while the proportion of those HIV positive decreased from 48% to 40% over the same period. In the age group 10 to 14 years however, while HIV testing increased from 39% to 83%, the proportion of HIV positive cases increased from 33% to 51%. No comparative studies could be found to compare these findings.

The high numbers of HIV positive cases in the age group 10 to 14 years in SA is of concern. Some of these children would not have had access to the PMTCT programme and therefore the virus may have been transmitted from mother to child during pregnancy and birth or breastfeeding, or it may indicate HIV infection at a young age due to early debut into sexual intercourse. Using the age group 0 to 4 years as the reference group, it was found that children aged 5 to 9 years had 1.92 times higher risk of being HIV positive while children aged 10 to 14 years had almost double the chance of being HIV infected (1.99). The proportion of children tested for HIV over the five-year period (48%) was lower than that reported by Marais in 2006 for children with TB in the Western Cape where 65% had been tested. In the Western Cape, this had reached 83% by 2012 indicating a nationwide improvement in access to HTC. The prevalence of HIV in children with TB was 32% nationally, which was much higher than that found by Marais in the Western Cape of 8.8%.

5.8 TREATMENT OUTCOMES

The outcomes of “successful treatment” and “death” were analysed in children with TB who had outcomes recorded at the end of treatment. Outcomes of “transferred out” “moved out” and “not evaluated” were removed from the denominator. Over the five-year period, the treatment success for children with TB was 91%, which is above the national target of 85%. Successful TB outcomes reported ranged from 90% in the age group 10 to 14 years to 92% in the 5 to 9 year olds. Hailu et al. found that the treatment success was 85%, which was similar to this study and above the
target of the WHO. Once again, the incompleteness of the data meant that there was a high proportion of outcomes that could not be evaluated. In terms of the reliability of the results of this study, this is of concern. Lack of reported TB outcomes is of particular concern in the under-5 age group where 33% of outcomes could not be evaluated. This is much higher than that of the Ethiopian study where only 4.9% of the records had no treatment outcome recorded. This potentially skews the proportions and makes it difficult to assess the true performance of the TB programme in South Africa.

Treatment outcomes have lower than expected reported proportions of defaulting from therapy and treatment failures, but these may be hidden in the large proportion of cases with no recorded outcomes. Using the age group 0 to 4 years as a reference group, children aged 5 to 9; and 10 to 14 years have no significant difference in probability of successfully completing treatment. This differs from a retrospective data analysis of 2708 records by Hailu et al. \textsuperscript{31} conducted in Ethiopia from 2007 to 2011. The Ethiopian study found that the age group 5–9 years [AOR= 2.5 (95% CI 1.7-3.7)] and 10–14 years [AOR = 2.7 (95% CI 1.9-3.9)] were independently associated with successful treatment outcomes.

In the case of those who died, children aged 5 to 9 have a 21% lower risk of dying while the age group 10 to 14, have a 1.33 times higher risk of dying. In this study the proportion of children with TB who were reported to have died was 3% which was the same proportion found by Hailu. \textsuperscript{31}

### 5.9 BIAS AND CONFOUNDING

#### 5.9.1 Bias

**Selection bias**

Selection bias was minimized by the identification and management of duplicate records and the fact that a census of all records was used. The database had incomplete records for certain reporting units and for some reporting periods. This has been noted in the discussion and has been controlled for in the analysis to minimize the effect on the results.

**Information bias**
Information bias was minimized by automatic importing of the information from the electronic TB database into the analysis software thereby minimizing human capture error. Poor data quality in terms of incomplete records has been noted and discussed. These incomplete records may result in skewed results for those periods or reporting units.

5.9.2 Confounding

Confounding variables have been identified and controlled for by stratifying into age groups to minimise effect on the results.

5.10 EFFECT MODIFICATIONS

Effect modification was controlled for by stratification into age groups to ensure that positive associations for specific subgroups were not disguised within the whole.

5.11 LIMITATIONS OF RESULTS AND STUDY DESIGN

This study used routine data and therefore patients that are not reported but that may have been on treatment were not included e.g. those being treated in the private sector. The study was limited by the quality of the routine records used. There was a large number of incomplete records for some reporting units as well as for some reporting periods, which was a major limitation. Due to the large number of records, it was not possible to verify data from individual patient files.

5.12 SUMMARY OF CHAPTER

This study describes the epidemiology of childhood TB in South Africa over a five-year period with respect to several variables. Analysis of the caseload per age group revealed that the South African profile follows the trends experienced in other countries. The data reveals an implementation of national policy and a rising proportion of HIV positive cases particularly in the age group 10 to 14 years.
6 CHAPTER VI: CONCLUSIONS AND RECOMMENDATIONS

6.1 INTRODUCTION

The proportion of childhood TB cases is a recognised indicator for the size of the infectious pool of TB in a population. It is also seen as an indicator of the quality of TB control. As a high burden TB country, understanding the epidemiology of childhood TB in South Africa has become increasingly important to enable better management of the TB epidemic. In particular, the age group 10 to 14 years are seen as a vulnerable group and this study provides important insight into their epidemiological profile.

6.2 CONCLUSIONS

The study has revealed that the proportion of childhood TB cases is within the upper limit of the range of WHO’s expected proportion for high burden countries of 10 to 20%. It can also be seen that while advances have been made in the implementation of the policy for 100% HIV testing for all TB cases, this is still lagging behind the target in terms of children with TB. The poor quality of recording and incompleteness of recording has the potential to skew the results as well as undermine the health outcomes of the patients who may be lost to follow up. The high numbers of HIV positive cases in the age group 10 to 14 years is of concern. It is clear that this subgroup will need particular attention. Treatment outcomes are difficult to establish as the large proportion of cases with no recorded outcome may hide the true picture.

6.3 RECOMMENDATIONS

Based on the findings of this study the following recommendations are made:

1. Case finding is below expected
   - Improve antenatal care for pregnant women to include TB screening and identification of household contacts particularly those under 5 years.
   - Screening of infants with mothers having TB
   - Include routine TB screening in all contacts with children.
   - Ensure school health teams are providing TB screening at schools and preschools.
2. Bacteriological coverage is low
   - Implement training programmes for health staff on gastric lavage and other methods for encouraging the production of sputum in children.

3. Routine HIV testing for children
   - Capacity building of nurses in adherence to the national TB guidelines with regard to HIV screening for all TB cases.
   - Ensure that all HIV exposed infants (those born to HIV positive mothers) are tested for HIV at 2 months and at 18 months of age.
   - Ensure that all children attending a public health facility are screened for HIV.

4. Specific prevention programmes for children aged 10 to 14 years

5. Targeted youth friendly interventions for adolescents aged 10 to 14 years focusing on screening, prevention, retention in care

6. Poor recording and reporting
   - Monitoring and supervision by the operational managers at facilities with regard to data quality and completeness of recording.
   - Capacity building of clinicians in ICD-10 codes, reporting, and recording in the TB register is essential to correct the poor completeness of records.
   - Regular feedback on progress towards targets in order to focus interventions on areas of poor performance and thus improve service delivery and programmatic performance.

7. Implement practical training on other methods of diagnosing TB in children. E.g. the utilisation of the triad approach of the triad of (1) known contact with an adult index case, (2) a positive tuberculin skin test (TST) as evidence of latent tuberculosis infection (LTBI), and (3) suggestive signs on chest x ray (CXR) is used for use in clinical practice.
7. REFERENCES


15. Centers for Disease Control (CDC). Fact Sheet: Tuberculosis: General

8 ADDENDA

8.1 PUBLICATIONS OR PRESENTATIONS


8.2 PROTOCOL

8.3 RESEARCH PROJECT APPROVAL BY POSTGRADUATE EDUCATION COMMITTEE

8.4 RESEARCH PROJECT APPROVAL FROM BIOMEDICAL RESEARCH ETHICS COMMITTEE

8.5 GATE KEEPER PERMISSION
8.1 PUBLICATIONS
A review of tuberculosis in children and adolescents in South Africa 2008-2012: Analysis of data from ETR.net

Smith J1
Moyo S2
Day C1

1Health Systems Trust
2HIV/ AIDS, STI and TB Research Programme, Human Sciences Research Council

1 Abstract

Childhood tuberculosis has gained increasing focus in recent years due to the recognition of the contribution of the disease to morbidity and mortality in children. Previous studies have shown that the burden of TB disease in South Africa may mirror the high burden of the adult epidemic, although systematic reporting on childhood TB has been absent.

This chapter looks at an analysis of data from the Electronic TB Register to examine the characteristics of childhood TB (0-19 years) in South Africa over the five-year period 2008-2012.

Childhood cases represented 15.3% of all TB cases in South Africa in 2012, with the majority of cases in the 0-4 years age group, similar to trends found in the majority of countries. The five-year trends reflect the influence of national HIV Counselling and Testing policies implemented during the same period. The basis for diagnosis has historically leaned towards radiology due to the difficulty of obtaining microscopy specimens; while this still holds true for children aged 0 to 4 years, there has been a consistent increase in the proportion of children with microscopy results.

Clinical outcomes are generally better than for adult TB patients, with all age groups achieving a successful completion rate in excess of 80%. The defaulter rates are correspondingly lower than in adults, with the 15 to 19 years age group having the highest defaulter rates.

2 Introduction

Tuberculosis (TB) has increasingly been recognised as a major cause of morbidity and mortality among children in high TB-burden settings. Graham et al poignantly highlighted the importance of TB control in addressing child survival, relating this to Millennium Developmental Goal 5. Although there are limited data on TB adolescents, they are noted to be an important group at risk for TB infection. A cross-sectional study in a high TB-burden setting in Cape Town reported that the force of infection with mycobacterium tuberculosis increased from 3.96 at age 10 years to 6.63 at 19 years, indicative of a high TB burden, even in this age group. The Child TB Roadmap calls for strengthened reporting of TB cases occurring in children by national TB programmes, and among its 10 key actions are (i) inclusion of the needs of children and adolescents in research, policy development and clinical practice, and (ii) collection and reporting of better data, including data on preventive measures.
This chapter presents selected trends in TB in children and adolescents (0-19 years) in South African provinces from 2008 to 2012. Data were derived from the national drug-sensitive TB electronic database (ETR.net). As expected from routine data, there are concerns about certain aspects of data quality. Data were known to be incomplete for 2008 (Mpumalanga and KwaZulu-Natal) and 2010 (Gauteng) due to database management problems which resulted in the loss of some patient records. This impacts primarily on case-finding numbers, and to a lesser extent on treatment outcomes and results presented in percentage form.

Data on the demographic profile of TB across the country are presented, followed by a report on case-finding and treatment outcome data.

3 Demographic profile

3.1 Age group distribution

In Figure 1 it can be seen that the distribution of cases in the age groups 0-4 years, 5-9 years, 10-14 years and 15-19 years has remained fairly constant between 2008 and 2012, with the largest distribution being in the 0-4 year age group and the lowest distribution being in the 10-14 year age group, as expected.

Figure 1: Age distribution of TB case finding, 0-19 years, as a percentage of total cases

The distribution of cases by age group aligns closely with the general provincial picture for all TB case-finding, with the high-burden provinces of KwaZulu-Natal (KZN), Eastern Cape (EC) and Western Cape (WC) also having the highest load of cases in the age group 19 years and under (Figure 2). The data losses experienced by the provinces can be seen on these graphs; Gauteng Province (GP) is clearly illustrated, while Mpumalanga Province (MP) and KZN are less obvious.

Figure 2: Percentage of cases by province for children (0-19) and all other ages, 2008-2012
3.2 Distribution of males to females:
Table 1 shows the distribution of males and females. In the age groups 0-4 and 5-9, there are more males than females being diagnosed, whereas this balance shifts in the 10-14 and 15-19 year age groups. This pattern may be attributed to the increased risk of HIV infection as the child gets older and hence a more typical pattern following the trend of the more female-driven HIV and AIDS epidemic. This could also reflect health-seeking behaviours in males who are known to attend health facilities to a lesser degree than do females.\textsuperscript{v,vi} The pattern remains constant in 2008 and 2012 as shown in Figure 3. Males do outnumber females in all these age groups in the population, however the pattern of slightly higher incidence (TB case-finding per 100 000 population) among males in the 0-4 and 5-9 age groups remains, as does the shift to higher incidence in females in the 10-14 and 15-19 age groups (Table 2).

Table 1: Distribution of case finding by gender in children, 2008-2012

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
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</tr>
<tr>
<td>0-4</td>
<td>16 0</td>
<td>14 97</td>
<td>17 4</td>
<td>15 97</td>
<td>13 8</td>
</tr>
<tr>
<td>5-9</td>
<td>6 03</td>
<td>7 6 032</td>
<td>6 75</td>
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<td>6 601</td>
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<tr>
<td>10-14</td>
<td>2 78</td>
<td>0 3 320</td>
<td>3 07</td>
<td>6</td>
<td>3 889</td>
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<tr>
<td>15-19</td>
<td>5 62</td>
<td>9 8 304</td>
<td>6 22</td>
<td>1</td>
<td>9 321</td>
</tr>
</tbody>
</table>

Table 2: Incidence of TB (case finding per 100 000 population) by gender in children, 2008 and 2012

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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<tr>
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<td>---------------</td>
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</tr>
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<td>0-4</td>
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</tr>
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<td>5-9</td>
<td>2 567 947</td>
<td>2 551 336</td>
</tr>
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<td>10-14</td>
<td>2 607 728</td>
<td>2 592 210</td>
</tr>
<tr>
<td>15-19</td>
<td>2 516 392</td>
<td>2 495 721</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Incidence</th>
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<th>Female</th>
<th>Male</th>
<th>Female</th>
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<td>0-4</td>
<td>617.3</td>
<td>582.7</td>
<td>484.0</td>
<td>457.5</td>
</tr>
<tr>
<td>5-9</td>
<td>235.1</td>
<td>236.4</td>
<td>189.2</td>
<td>184.2</td>
</tr>
<tr>
<td>10-14</td>
<td>106.6</td>
<td>128.1</td>
<td>102.9</td>
<td>120.0</td>
</tr>
<tr>
<td>15-19</td>
<td>223.7</td>
<td>332.7</td>
<td>213.6</td>
<td>299.7</td>
</tr>
</tbody>
</table>

Source: Stats SA mid-year estimates times series (released with 2013 estimates) and ETR.net.

Figure 3: Age pyramids of TB case finding in children, 2008 and 2012
Age Pyramid TB Casefinding
2012

- 0-4
- 5-9
- 10-14
- 15-19

Males
Females
3.3 HIV status
The testing of TB patients for HIV has gained momentum in recent years following changes in the National Department of Health policies. This is reflected in the decreased percentage of cases where the HIV status is unknown from 2008 to 2012 as shown in Figure 4. Cases where HIV status is unknown have dropped by more than half across all age groups 0-19 years.

Figure 4: Percentage of cases with HIV status unknown by age group, 2008-2012

The positivity rate has increased proportionally by more than double across all age groups, as seen in Figure 5, as a result of the substantial improvement in testing for HIV status.

Figure 5: Tree-map showing the number (size) and percentage (label) of TB cases according to HIV status by age group, 2008 and 2012
The greatest increase in TB-HIV cases was found in the age group 10-14 years (11.9% of all cases in this age group in 2008 to 39.9% in 2012). When considering only the cases where the HIV status was known, the highest HIV prevalence was also in the 10-14 year age group in 2012 (Table 3). The trends are difficult to interpret due the change in the proportion of cases with known HIV status over the period.

Table 3: Percentage HIV+ of those with known HIV status, by age group, 2008-2012

<table>
<thead>
<tr>
<th></th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>36.54%</td>
<td>34.40%</td>
<td>29.32%</td>
<td>22.42%</td>
<td>19.39%</td>
</tr>
<tr>
<td>5-9</td>
<td>45.50%</td>
<td>46.33%</td>
<td>47.02%</td>
<td>41.68%</td>
<td>38.45%</td>
</tr>
<tr>
<td>10-14</td>
<td>30.76%</td>
<td>39.21%</td>
<td>47.10%</td>
<td>47.59%</td>
<td>49.10%</td>
</tr>
<tr>
<td>15-19</td>
<td>18.57%</td>
<td>25.36%</td>
<td>29.86%</td>
<td>29.74%</td>
<td>30.67%</td>
</tr>
</tbody>
</table>
4 Case-finding

The WHO estimates that in high-burden settings, childhood TB cases comprise 10-20% of the total TB caseload. Until the last decade, TB reporting has largely been focused on smear-positive cases known to drive transmission. Hence childhood TB was overlooked and data on childhood TB were limited since most cases are smear-negative. Age-specific estimates of TB incidence (including an adjustment for smear-negative cases) based on TB data for 2000 attributed 10.7% of incident cases globally to children aged 0-14 years. In the same analysis in South Africa, 16.1% of TB was estimated to have occurred in children younger than 15 years old, with a case rate of 501 per 100 000 population in this age group. Seventy-five per cent of all childhood TB cases globally were recorded for high TB-burden countries, with an increase in childhood TB cases noted in many regions of the world, including America and Europe.

In a study that reviewed TB notifications over a 10-year period (1985-1994) in two urban communities in Cape Town in 1998 (high TB burden and antenatal HIV prevalence 0.37% in 1991), among all childhood cases the proportion occurring in children aged 0-4 years ranged from 25 to 49% and from 7-12% in those in the 5-14 year age group (n=1 744) in that period. The TB case notification rate among children aged 0-5 years was 3.5 times that in adults, highlighting the high burden of childhood TB in that setting. Although this study might have only been representative of similar urban settings, it nonetheless served as an early indicator of the burden of childhood TB in high TB-burden settings in South Africa. The limitation of this study was that it was confined to two peri-urban communities in Cape Town at the beginning of the HIV epidemic, and therefore the findings cannot be extrapolated to the general South African context.

Childhood TB case notifications in South Africa have declined slightly from 63 151 cases in 2008 to 53 331 in 2012. This mirrors somewhat the decrease in TB case-finding for cases older than 20 years, which decreased from 305 495 cases in 2008 to 296 263 cases in 2012. The proportion of cases under 20 years commenced on treatment showed a slight decline, from 17.1% of total cases in 2008 to 15.3% of all cases in 2012 (Table 4). The proportion of cases by age group varied widely at the district level, which may be due to different population age structures and the completeness of case-finding, among other factors (Figure 6).
Table 4: Number and percentage of TB cases by age group, 2008-2012

<table>
<thead>
<tr>
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<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
</tr>
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<tbody>
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<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>0-4</td>
<td>31</td>
<td>9 8.4%</td>
<td>3339</td>
<td>5 8.1%</td>
<td>2674</td>
</tr>
<tr>
<td>5-9</td>
<td>12</td>
<td>9 3.3%</td>
<td>1335</td>
<td>7 3.2%</td>
<td>1148</td>
</tr>
<tr>
<td>10-14</td>
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<td>1.7%</td>
<td>6965</td>
<td>1.7%</td>
<td>6190</td>
</tr>
<tr>
<td>15-19</td>
<td>1393</td>
<td>3 3.8%</td>
<td>1554</td>
<td>2 3.8%</td>
<td>1425</td>
</tr>
<tr>
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<td>6315</td>
<td>1 17.1%</td>
<td>6925</td>
<td>9 16.8%</td>
<td>5867</td>
</tr>
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<td>20+ years</td>
<td>305</td>
<td>4 82.9%</td>
<td>3424</td>
<td>4 83.2%</td>
<td>3002</td>
</tr>
<tr>
<td>All ages</td>
<td>368</td>
<td>6 100.0%</td>
<td>4117</td>
<td>7 100.0%</td>
<td>3589</td>
</tr>
</tbody>
</table>

Figure 6: Age distribution of TB case finding, 0-19 years, as a percentage of total cases, 2012
4.1 Basis for diagnosis:
The challenges faced by clinicians in determining a definitive diagnosis of TB in young children are well described in the literature, and most persist to this
This is mainly due to the difficulties in obtaining sputum samples, the paucibacillary nature of disease in young children, the lack of a standard case definition, and the difficulties of interpreting radiological features that is pivotal for diagnosis in the absence of bacteriological confirmation. This is further complicated by “the increased presence of extra-pulmonary disease in young children [and] the lower public health priority previously given to childhood TB”.

Bacteriological coverage rates (percentage of cases of PTB for which sputum microscopy results were available) improved with each age group, as expected, but all age groups showed increases between 2008 and 2012 (Figure 7), suggesting an overall increase in cases with microscopy results. However, bacteriological coverage remained very low in the age group 5-9 years (24.3% in 2012) even though these children should be able to provide sputum samples with encouragement.

Figure 7: Bacteriologic coverage (% PTB cases with smear results available) by age group, 2008-2012

4.2 Site of Disease:
Although pulmonary disease comprises the bulk of TB cases, children, particularly in the 10-19 year age groups, experience a substantial proportion of extrapulmonary disease.
Data from the ETR.net show that extrapulmonary TB (EPTB) cases make up between 3.9% and 14.5% of all cases aged 0-19 years, with the proportion of EPTB cases highest in the 10-14 year age group (Figure 8).

Figure 8: Percentage of TB cases that are EPTB by age group, 2008-2012

A study in India reported EPTB in 15-20% of HIV-negative cases and 20-70% of HIV-positive cases, while in a Thailand study, 40% of HIV-infected patients had EPTB. The data in Figure 9 indicate higher proportions of EPTB in HIV-positive children, as has been observed in adults. The largest difference in proportions between the HIV-positive and HIV-negative EPTB cases was in the 15-19 year age group (16.6% of TB cases are EPTB in those known to be HIV-positive, compared to 9.4% with EPTB in those with known HIV-negative status).

Figure 9: Percentage of TB cases that are classified as EPTB by age group and HIV status, 2012
5 Treatment outcomes

Outcome data among children and adolescents aged 0-19 years were analysed and are presented in this section. Outcome data for the years 2008-2010 were not included due to quality concerns described in the case-finding section, while data for 2012 were incomplete at the time of this analysis.

Treatment outcome definitions in children and adolescents with TB are reported in the same categories applied to adult cases, and are generally defined as follows (based on revised WHO definitions): xviii

Cured A pulmonary TB patient with bacteriologically confirmed tuberculosis at the beginning of treatment and who was smear- or culture-negative in the last month of treatment and on at least one previous occasion

Treatment completed A TB patient who completed treatment without evidence of failure BUT there is no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because they were not done or because results were not available.

Treatment failed A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.

Died A TB patient who dies for any reason before starting or during the course of treatment.

Lost to follow-up A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more. (This was previously called default. The term default is used in this chapter.)

Not evaluated A TB patient for whom no treatment outcome is assigned. This includes cases ‘transferred out’ to another treatment unit and where the treatment outcome is unknown to the
reporting unit. Patients who were transferred out are recorded as a separate category in the system-generated outcomes from ETR.net and are therefore reported in this chapter.

5.1 National profile
Outcome data were available for 62,454 children and adolescents aged 0-19 years in 2011. Of these, 69.9% completed treatment, 15.3% were cured, 5.1% defaulted, 2.25% died on treatment, 0.5% experienced treatment failure, and 7.0% were transferred out or not evaluated. Analysis of outcomes by age categories showed successful outcomes (cure and treatment completion) reaching 80% in all the age groups (86.6% – 0-4 year, 88.0% – 5-9 years, 85.2% – 10-14 years and 80.0% – 15-19 years). Figure 10 shows treatment outcomes by age group in 2011.

Figure 10: Treatment outcomes by age group in children and adolescents in South Africa 2011

The proportion of defaulters was relatively similar in the 0-4, 5-9 and 10-14 year age groups, with the greatest percentage observed in older adolescents (15-19 years, 8.2%), a value twice that in the 10-14 year age group (4.1%). Similarly, older adolescents also had the largest mortality and failure treatment percentages (3.2% and 1.3% in 15-19 years respectively). Overall, mortality was generally low in all the age groups, ranging from 1.6% in the 0-4 year age group, 1.7% in those aged 5-9 years, 2.9% in those aged 10-14 years, and 3.2% in the 15-19 year age group. Tuberculosis is generally severe in the youngest children with poorly developed immune systems, hence a greater proportion of mortality would be expected in the 0-4 year age group. However, in this analysis, mortality in the 15-19 year age group was significantly greater than that seen in children aged 0-4 years (p<0.001). This could be due to HIV-associated mortality, a poorer prognosis associated with poor adherence to treatment among adolescents, or other causes of mortality in adolescents who are on treatment for tuberculosis.

Various analyses have shown high levels of injury- and trauma-related mortality in young people. Studies have also shown that adolescents struggle to adhere to chronic medication due to various factors attributed to and associated with the period
However, a more detailed analysis taking into account a range of clinical, social and other factors is required to fully explain this observation.

In all the age groups, more than 6% of cases were either transferred out or not evaluated. HIV-associated mortality was high in all age groups, with the highest proportion (7.3%) being in the 15-19 year age group (Figure 11). Mortality percentages among those aged 0-4 and 5-9 years were similar (1.6% and 1.7% respectively) but higher in children aged 5-9 years who generally have a lower risk and burden of TB. Although massive strides have been made with regard prevention of mother-to-child transmission (PMTCT) of HIV and antiretroviral treatment provision in general in South Africa, this high proportion of mortality could be partially attributed to the impact of HIV infection, as illustrated by the substantially higher death rates in cases known to be HIV-positive (Figure 11). Outcomes did not differ much by gender (Figure 12).

Figure 11: Mortality outcomes in children by age group and HIV status, 2011

Figure 12: Treatment outcomes by gender in children and adolescents in South Africa, 2011

5.2 Treatment outcome by facility type

Figure 13 shows that across the country, childhood TB is successfully managed at a primary care level, with the majority of children completing treatment or achieving cure. Poor outcomes (default, death and failure of treatment) occurred across all types of health facilities in all age categories in 2011. However, hospitals had higher levels of default and mortality. Higher levels of mortality would be expected from hospitals, since the sicker patients and more complicated cases with a greater likelihood of mortality are seen there. With regard to default, patients may fail to return to hospital because of difficulties in accessing the hospital, especially in rural areas where the hospital may be a long distance from where patients live and they might have rare or no means of transportation. It is also possible that as a result of access problems, some patients may choose to continue treatment at their local
clinic and be erroneously classified as defaulters. Notable also is the high level of transfers out from private care, which most likely reflects transfer to the public health sector where TB treatment is provided free of charge. Treatment failure cases were mainly recorded in specialised TB hospitals and were most frequent in the 10-14 and 15-19 year age groups.

Figure 13: Treatment outcomes in children by age group and facility type (number and percentage of cases), 2011

5.3 Treatment outcomes by province

Figure 14 shows treatment outcomes for the children and adolescents across the nine provinces in South Africa. The percentage achieving successful treatment outcomes (cure and treatment completion) in all age categories 0-4, 5-9, 10-14 and 15-19 ranged from 63.1% (age group 0-4 years in LP) to above 93% (age group 5-9 years in GP). However, across all provinces, there is a concerning proportion of young patients who did not complete treatment (defaulted), albeit largely confined to older adolescents aged 15-19 years (8.2% defaulter rate). The possible reasons for this observation have been discussed earlier. Default from treatment is a problem in
many TB programmes across all age groups. Given the long duration of treatment (at least six months), the drug side-effects and the fact that people feel better long before they complete the recommended course of treatment, many patients stop taking their medication prematurely. However, these patients require a longer course of treatment when they eventually return to care, and are at risk of mortality without adequate treatment. Therefore, greater efforts and innovative methods are needed to encourage adherence to and completion of treatment among TB patients. The highest defaulter rate overall was in North West Province (6.6% in children 0-19 years). The Eastern Cape and Northern Cape Provinces also had high defaulter rates.

Figure 14: Treatment outcomes in children by age group and by province, 2011

Mortality per province is shown in Figure 15 for each age group. Limpopo Province (LP) had the highest mortality, followed by Free State, while the WC and GP had the lowest mortality rates. The WC in particular has extremely low mortality in all age groups. While provinces vary greatly in socio-demographic, economic, disease-burden profiles and other factors, there is need to investigate how successful practices in GP and WC could be adapted and replicated in other provinces with higher mortality rates. Mortality was greater in the 10-14 year and 15-19 year age groups, as described for the national profile.

Figure 15: Mortality outcomes in children by age group and by province, 2011
All provinces recorded a proportion of children and adolescents who experienced treatment failure (Figure 16). The cases were concentrated in older adolescents: 1.3% in the age group 15-19 years recorded treatment failure. Mpumalanga Province recorded the highest failure rates of 2.2% in the 10-14 year age group, 2.0% in the 15-19 age group and 1.2% overall (age 0-19 years). Although the overall proportion is low, these data are concerning, given the increasing burden of drug-resistant tuberculosis in South Africa.

Figure 16: Treatment failure in children by age group and by province, 2011

5.4 Treatment outcomes by district

The proportion of children and adolescents achieving successful treatment ranged from a low of 61.3% in Capricorn (LP) to a high of 93.1% in Ekurhuleni (GP). In 30 districts, treatment success rates were ≥85% overall among children and adolescents. Default was highest in Waterberg (LP) at 10%, followed by Pixley ka Seme (NC) at 9.7% and then by Buffalo City and OR Tambo Districts (EC) with 8.7 and 8.2% default respectively. The mortality rate at district level ranged from 0.4% in Overberg (WC) to 7.2% Mopani (LP). Waterberg (LP) had the second-highest mortality rate at 6.4%. Other districts with high mortality rates in 2011 were Frances Baard (NC) with 5.6%, and T Mofutsanyana (FS) and Bojanala (NW) each reporting 4.9% mortality in the 0-19 year age group in 2011. Treatment failure was above 1% in 13 districts, with the highest proportions reported in Central Karoo (WC) at 1.8% and JT Gaetsewe (NC) with 1.7%.

Figure 17: Treatment outcomes in children by age group, by district, 2011
Figure 18: Treatment outcomes in children 0-19 years by district, 2011
<table>
<thead>
<tr>
<th>Province</th>
<th>District</th>
<th>n</th>
<th>Transferred Out</th>
<th>Treatment Success</th>
<th>Defaulted</th>
<th>Died</th>
<th>Failed</th>
<th>Not evaluated</th>
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<td>EC</td>
<td>A Nzo: DC44</td>
<td>1099</td>
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<td>0.7%</td>
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<tr>
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<td><strong>Total</strong></td>
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<td>0.6%</td>
<td>0.3%</td>
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<tr>
<td>Province</td>
<td>District</td>
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<td>KZN</td>
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<tr>
<td></td>
<td>Harry Gwala: DC43</td>
<td>900</td>
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<td>78.7%</td>
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<td>170</td>
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<td>Province</td>
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<td>Treatment Success</td>
<td>Defaulted</td>
<td>Died</td>
<td>Failed</td>
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<td>uThukela: DC23</td>
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<td>92.4%</td>
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<td>1.0%</td>
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<td>Zululand: DC26</td>
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<tr>
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<td>84.4%</td>
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<td>2.1%</td>
<td>0.5%</td>
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<td>61.3%</td>
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<tr>
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<td>79.8%</td>
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</table>
6 Conclusion:
This narrative presents important information on TB in children and adolescents in South Africa, and highlights the challenges of TB data management and its impact on reporting. As expected, the burden of childhood TB is high, with a large proportion concentrated in the 0-4 year and 15-19 year age groups. With momentum and focus on HIV counselling and testing (HCT) and a move towards integration of TB and HIV care, cases with unknown HIV status dropped significantly between 2008 and 2012. However, the proportion remains high, indicating a need for further effort to increase testing and recording of HIV status in all TB cases.

TB in children and adolescents accounted for 15.3% to 17.1% of all TB cases between 2008 and 2010. This is within the expected proportion for high TB burden countries. Given that the expected estimates are based on children aged 0-14 years, the cases recorded on ETR.net may be underestimating the total disease burden in this age group. This is supported by the fact that in very young children, TB can easily be misdiagnosed as being other respiratory tract infections, hence some cases may be undiagnosed. The same could apply to older adolescents, especially males, who may not readily present to healthcare facilities even when symptomatic. These concerns extend to drug-resistant TB, which also tends to be undiagnosed and poorly quantified in children.

Treatment outcomes present an encouraging picture, indicating successful treatment in the majority of cases. However, the proportion of defaulters, even though small, needs to be addressed given the negative consequences of defaulting from treatment. As expected, mortality was high among HIV-infected cases, with the highest proportion in those aged 15-19 years. Early initiation of ART has been shown to reduce mortality in HIV-infected patients and is thus recommended as soon as possible for HIV-infected children (0-14) and adults, regardless of CD4 count.

Implementation of this guideline should be assessed in all facilities.

The provincial and district outcome profiles vary due to many factors. In many areas, outcomes are favourable, requiring a small proportion of unfavourable outcomes to
be addressed. In other areas, more work is needed to reduce concerning burdens of default from treatment and mortality in children and adolescents.

Finally, this narrative serves as a useful review in the journey towards achieving the goals of reducing the burden of TB in children and adolescents in South Africa.
References


8.2 PROTOCOL
THE EPIDEMIOLOGY OF CHILDHOOD TUBERCULOSIS AND CLINICAL OUTCOMES IN SOUTH AFRICA 2008-2012

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Student No. : 213568251

Contact details: e-mail: Jackie.smith@hst.org.za Cell: 0834191168

Student’s signature: [Signature]

SUPERVISOR:

Name: Dr Stephen Knight

Discipline of Public Health Medicine

Tel.: 0312604508 e-mail: Knights@ukzn.ac.za Cell: 0827623123

Signature:

CO-INVESTIGATORS (if any) exact role of each co-Investigator to be stated:

Name: Dr Sizulu Moyo

Department: Medicins Sans Frontieres

Role: Co-investigator in the descriptive analysis as it is part of a chapter for the South African Health Review

Signature: [Signature]
Purpose of Protocol

This protocol is submitted for the purposes of a Master of Public Health at the School of Nursing and Public Health at the University of KwaZulu-Natal. The research project and dissertation comprises 50% of the qualification.

Abstract

Background:

Tuberculosis (TB) in children, particularly in those under five years is regarded as an indicator of there being an infectious pool in the community. The World Health Organization (WHO) has focused on childhood tuberculosis, recognizing its contribution to the overall TB burden and to child survival. The “Roadmap for Childhood Tuberculosis” identifies the need to know the incidence of childhood TB in order to design and implement specific public health interventions to limit the spread of the disease and orientate health services in early TB detection, treatment and retention in care to prevent unnecessary morbidity and mortality.

Purpose:

The purpose of this research is to investigate the epidemiology of childhood TB in South Africa from 2008-2012 using data recorded in the Electronic TB Register, in order to inform TB control policy and practice.

Objectives

The objectives of this study are:

a. To describe TB incidence trends by age, sex and other demographic variables;

b. To document the characteristics of childhood TB;

c. To determine the proportion of childhood TB; and

d. To compare the proportion of childhood TB cases in South Africa to the WHO estimated proportions for childhood TB cases in high burden countries.
An observational analytical cross-sectional study design will be used. Data from the Electronic TB register (ETR.Net) will be summarised and comparisons made to the expected WHO estimates. The study population will be all children registered with B on the ETR.Net in South Africa from 2008 to 2012.

Word count: 243
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### Acronyms & abbreviations

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immune Deficiency Syndrome</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>ETR.Net</td>
<td>Electronic Tuberculosis Register</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>YLL</td>
<td>Years of Life Lost</td>
</tr>
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</table>
1 Introduction

The World Health Organization (WHO) declared tuberculosis a global emergency in 1993, with South Africa being one of 22 high burden countries.\textsuperscript{1} In 2012, South Africa had a TB incidence of 1003 per 100 000 placing it amongst the highest in the world.\textsuperscript{2}

The WHO defines childhood tuberculosis as that tuberculosis affecting those under the age of 15 years. The South African Children’s Act 38 of 2005 defines a child as being less than 18 years of age. In this study a child would be under 15 years of age.

Childhood TB particularly in those under five years is an indicator of there being an infectious pool of TB in the community.\textsuperscript{3} In the past, the WHO did not emphasize childhood TB as more than 95% of children are smear negative and therefore are not part of the infectious pool.\textsuperscript{4} This mindset has changed in recent years with WHO reporting in 2013 that globally there were an estimated 530 000 children with TB, with more than 200 children dying of TB every day.\textsuperscript{5}

Few countries report the incidence of childhood TB as data is seldom available. The diagnosis of childhood TB is difficult and is rarely supported by laboratory confirmation\textsuperscript{6} In 2000, South Africa reported an incidence of childhood TB of 501 per 100 000 population from birth to 14 years.\textsuperscript{5}

This study will use data of all children registered with TB on the ETR.Net in South Africa from 2008 to 2012 in an attempt to describe the epidemiology of childhood tuberculosis in South Africa and assess whether demographic factors influence TB outcomes.

The findings of this study can assist the Department of Health to implement targeted TB interventions appropriate for children and design a range of health
interventions focussed on prevention, early detection and treatment in order to decrease the burden of childhood TB specifically.

2 Literature Review

2.1 Introduction

The focus on childhood TB has gained momentum in recent years. There is greater awareness that the increased incidence of childhood tuberculosis in a community is a reflection of the bigger burden of tuberculosis in adults in the same community. The study will describe the demographic profile of childhood TB in South Africa, looking at trends in sites of disease and diagnostic methods most commonly used. It will also compare the proportion of cases in South Africa to the WHO estimated proportions expected in a high TB burden countries. The study will also describe the outcomes for childhood TB over the last 5 years and determine if there are any associations between clinical outcomes and other demographic factors such as age, gender, HIV status and severity of the disease.

2.2 Burden of Tuberculosis

According to the WHO, TB remains the second leading cause of death in the world and substantially affects the health of millions of people. Globally, there were 8.6 million people who developed TB in 2012. Of these 530 000 were less than 15 years of age. The African Region accounts for 28% (estimated 2.3 million cases) of the global TB burden with an estimated prevalence of 303 per 100 000 (95% Confidence Interval (CI): 239 to 373) in 2012. South Africa had an estimated 450 000 cases (95% CI 160 000 to 880 000) and an estimated prevalence of 857 per 100 000 (95% CI 305 to 1680) in 2012. The prevalence of TB is not routinely measured due to the requirement of large cohorts and the expense involved.
The notification system is considered a satisfactory proxy indicator for incidence of TB. The World Health Organisation’s estimates the incidence of TB in South Africa is 530 000 (95% CI 430 000 to 630 000) cases in 2012. The incidence risk of 1000 per 100 000 population (CI 827 to 1190) is the highest incidence amongst the high burden countries.7  

2.3 Demographic Profile of Childhood Tuberculosis  

Very few studies have been published on demographic profiles of children with TB. The Nairobi Urban Health and Demographic Surveillance System, situated in two slum areas in Nairobi, Kenya, reported that AIDS and TB were ranked sixth on the list of premature mortality among children under the age of five years (609 year of Life Lost (YLL) out of 15129 YLL for under five mortality), but was the leading cause of death in those aged 5 years and above. This data did not consider the age categories used by the WHO as it divided the data into two age categories, zero to four years and those above 5 years, therefore it is not possible to determine the burden on children aged between 5 and 14 years.8  

2.4 WHO Estimated Proportions for Childhood Tuberculosis  

The WHO estimates that in high burden settings, it is expected that childhood TB cases will comprise 10 to 20% of the total TB caseload.5 Globally childhood TB is on the increase in many countries although 75% of childhood TB cases notified in 2000 were from high burden countries.6 In the same year, (2000) Botswana reported increases in cases as well as a proportion of 12% of all Tuberculosis cases being under the age of 15 years, as was the case in Malawi in 1998.6  

In a study by Rie et al, carried out in two urban communities in Cape Town in 1998, it was found that the 0 to 5 year age group comprised 25 to 49% of the total number of childhood TB cases (n=3588), and the 5 to 14 year age group comprised 7 to 12% of the total cases (n=1744) in that period. The limitation of this study was
that it was confined to two peri-urban communities in Cape Town and therefore the
data cannot be extrapolated to the general South African context.

Word Count = 641

3 Purpose of the Study

The purpose of this research is to investigate the epidemiology of childhood TB in
South Africa from 2008-2012 using data recorded in the Electronic TB Register, in
order to inform TB control policy and practice.

4 Specific Objectives

The objectives of this study are:
a. To describe TB incidence trends by age, sex and other demographic variables;
b. To show the characteristics of childhood TB;
c. To determine the proportion of childhood TB; and
d. To compare the proportion of childhood TB cases in South Africa to the WHO
   estimated proportions for childhood TB cases in high burden countries.

5 Type of Research

Epidemiological research, which will be applied at a public health level, in order to
assist in informing the design of appropriately targeted community based interventions.

6 Definitions

a. Tuberculosis
   Cases identified as TB by means of bacteriological, radiological or clinical
   findings.

b. Electronic Tuberculosis Register (ETR.Net)
   The ETR.Net ETR.Net is an electronic tuberculosis register used in South Africa,
designed for TB/HIV surveillance, program monitoring and evaluation
c. **Childhood TB**
   Persons diagnosed with TB by means of bacteriological, radiological or clinical findings that are 0 to 14 years of age

d. **TB Outcomes**
   The health outcome of the patient at the end of the treatment as defined by the National Tuberculosis Management Guidelines 2009.

   **Cure:** Patient who is smear-negative in the last month of treatment and on at least one previous occasion at least 30 days prior.

   **Treatment completed:** Patient who has completed treatment but who does not meet the criteria to be classified as cure or treatment failure.

   **Treatment success:** Patient who is cured or treatment completed

   **Treatment failure:** Smear positive patient who remains or is again smear-positive at 5 months (for new) or 7 months (for retreatment) after treatment start date or whose DST shows MDR-TB at 2 or 3 months.

   **Died:** Patient who dies for any reason during the course of TB treatment.

   **Treatment default:** Patient whose treatment was interrupted for more than two consecutive months

   **Transfer out:** Patient who has been transferred to another reporting unit (e.g. district) and for whom the treatment outcome is not known.⁹

f. **Childhood TB Incidence Risk**
   The proportion of children aged 0 to 14 who developed TB during the specified time period, reported for the age groups 0 to 4 years, 5 to 9 years and 10 to 14 years against the district, provincial and national estimated populations for those age groups according to the 2011 census.

f. **Drug Resistant TB**
TB caused by strains of *Mycobacterium tuberculosis* that are resistant to isoniazid and and/or rifampicin

7 Research Methods

7.1 Study Setting

This study will take place using the Electronic TB Register from all nine provinces of South Africa.

7.2 Study Design

An observational analytical cross sectional study design will be used.

7.3 Target Population.

The results of this study will be generalizable to the children aged 0-14 in South Africa as well those in other lower to middle income countries in Africa with a similar demographic and disease (HIV) profile.

7.4 Study Population

The study population will be all children registered with Tuberculosis, and diagnosed by means of bacteriological, radiological or clinical findings and recorded in the ETR.Net in South Africa from 2008 to 2012.

7.4.1 Inclusion / Exclusion Criteria

**Inclusion Criteria:**

- All children in the age groups 0 to 4, 5 to 9, and 10 to 14 years registered on TB treatment in the ETR.Net with drug sensitive TB between 2008 and 2012, irrespective of the diagnostic method or the site of the disease.

**Exclusion Criteria:**
• TB patients 15 years and older
• Children aged 0 to 14 years with drug resistant TB

7.5 Study Sample

7.5.1 Method of selecting sample

A census will be used of all records of TB patients aged 0 to 14 during 2008 to 2012

7.5.2 Size of sample

The ETR.Net database contains 235,836 records of children aged 0 to 14 fitting the inclusion criteria for this study.

7.6 Data Sources

The Electronic TB Register (ETR.Net) will be the source of the data. Records from 1 January 2008 to 31 December 2012 will be used. The ETR.Net is the software used by the South African National Department of Health to capture routine patient level data for drug sensitive TB in all public health facilities.

7.6.1 Measurement instruments and data collection techniques

The data is available in a Structured Query Language (SQL) database which is exported into MS Excel and will be imported into a statistical software package (STATA13) for processing and analysis.

7.7 Measures to Ensure Validity

7.7.1 Internal validity

7.7.1.1 Selection bias

Selection bias will be minimized by the identification of duplicate records and the fact that all records will be used. The database has incomplete records for certain
reporting units and for some reporting periods. This will have to be noted in detail and analysis controlled to minimize the effect on the results.

### 7.7.1.2 Information bias

Information bias will be minimized by automatic importing of the information from the electronic TB database into the analysis software thereby minimizing human capture error. It is acknowledged that there is potential for information bias with any clinician recorded data. The database has incomplete records for certain reporting units and for some reporting periods. This will have to be taken into account during analysis. These incomplete records may result in skewed results for those periods or reporting units.

### 7.7.2 External validity / generalizability

This study examines all cases over the study period and results will be available at a provincial and district level, therefore the results of this study will be generalizable to the TB population under 15 years in every district. The results may also be generalizable to other countries with a similar HIV and AIDS and TB burden.
### 7.8 List of Variables

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<td>HIV status</td>
<td>Clinical Outcomes Age</td>
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<td>Diagnostic methods</td>
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<tr>
<td>Outcomes</td>
<td>Age, diagnostic methods HIV status, site of disease</td>
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</tbody>
</table>

### 7.9 Plan for Data Handling/Processing

#### 7.9.1 Data Collection

Data from the national ETR.Net data set will be used for the study. The data that will be analyzed is aggregated to the 52 districts level and therefore contains no patient identifiers, thereby protecting the confidentiality of the TB patient.

#### 7.9.2 Data storage

1. Copies of all data files will be kept on an external hard drives and locked in a safe in a separate location. A further back up will be stored in an encrypted file on an external server.
2. Computers and files will be password protected with access limited to the researcher.
7.9.3 Back up of data

Data will be backed up as follows:

- Daily – The most recent backup will be kept off-site
- Weekly backups will be kept for a month
- Monthly backups will be kept for 6 months
- Quarterly backups will be kept for one year
- 6 monthly back-ups

7.10 Statistical Methods

7.10.1 Descriptive statistics

Descriptive methods will be used to analyze data. Modes, medians and ranges will be measured for a variety of categorical variables. Comparisons will be made between proportions of childhood TB in South Africa and the proportions estimated by WHO for high burden countries.

7.10.2 Analytic statistics

Appropriate Measures of association will be determined between clinical outcomes and demographic variables

7.11 Study Limitations

- This study will use routine data and therefore patients that are not registered but that may be on treatment will not be included e.g. those being treated in the private sector.

- The study will be limited by the quality of the routine records used. Where data is found to be missing, the patient’s individual record will be used to complete the missing data where possible.
8 Ethical Considerations

8.1.1 Institutional Ethical Review Board

Application for expedited ethical approval will be made to the Biomedical Research Ethics Committee at University of KwaZulu-Natal.

8.1.2 Permissions

Permission has been sought for the use of this data from the National Department of Health who are custodians of the data. This will only be granted once approval has been granted by BREC. The project will be registered for academic purposes with the School of Nursing and Public Health, Research Higher Degrees Committee.

8.1.3 Informed Consent and Participant Information

A waiver of written informed consent to access and use routine ETR data is requested. This study uses retrospective, routinely collected information. The number of records included is large, with an estimated 235 836 patients included. For these reasons, it is not feasible to get patient consent. No identifying patient information will be used in the analysis.
## 9 Work Plan

### 9.1 Budget

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### Study period / Time lines

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<td>Submission for ethics committee approval</td>
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<td>Register dissertation</td>
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<td>Obtain access to data</td>
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<td>Finalize manuscript and submit for marking</td>
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10 References


8.3 RESEARCH PROJECT APPROVAL FROM THE BIOMEDICAL RESEARCH ETHICS COMMITTEE
26 May 2014

Mrs JR Smith
Student No 213568251
Discipline of Public Health Medicine
School of Nursing & Public Health

Dear Mrs Smith

**MPH PROTOCOL:** "The Epidemiology of Childhood Tuberculosis and Clinical Outcomes in South Africa 2008-2012" JR Smith Student No 213568251

Your protocol has been given final approval of the abovementioned study, on the 23\textsuperscript{rd} May 2014. This will be noted at the next Postgraduate and Research & Higher Degrees Committee Meeting.

Please note:

- The Postgraduate Committee must review any changes made to this study.
- Please note that the study may not begin without the approval from the Biomedical Research Ethics Committee.

May I take this opportunity to wish you every success with the study.

Yours sincerely

Mrs Devi Anumugam
School of Nursing & Public Health

CC: Discipline of Public Health Medicine
8.4 BREC APPROVAL
26 March 2015

Mrs Jackie Smith
P O Box 644
Melmoth
3835
jackie.smith@hst.org.za

Dear Mrs Smith


EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 28 May 2014.

The study was provisionally approved pending appropriate responses to queries raised. Your responses received on 15 October 2014 to queries raised on 10 September 2014 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given full ethics approval.

This approval is valid for one year from 26 March 2015. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.


BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee’s decision will be RATIFIED by a full Committee at its meeting taking place on 14 April 2015.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee
8.5 GATEKEEPER PERMISSION
Ms Jackie Smith
Health Systems Trust
Email: jackie.smith@hst.org.za

Dear Ms Smith,

RE: PERMISSION TO USE ETR.NET DATA FOR MASTERS STUDY

The National Department of Health has reviewed your request and has granted permission to use the ETR.Net data supplied to the Health Systems Trust for the purposes of completion of the study "THE EPIDEMIOLOGY OF CHILDHOOD TUBERCULOSIS AND CLINICAL OUTCOMES IN SOUTH AFRICA 2008-2012".

Please ensure that a synopsis of the findings of the study is shared with this office.

Regards

[Signature]

DR YOGAN PILLAY
DEPUTY DIRECTOR-GENERAL: HIV/AIDS, TB AND MWCH.
DATE: 19/3/15