COMPLEMENTARY SURVEILLANCE STRATEGIES AND INTERVENTIONS TO INFORM A TUBERCULOSIS CARE CASCADE FOR CHILDREN

Dissertation presented for the degree of Doctor of Philosophy in the Faculty of Medicine and Health Sciences at Stellenbosch University

By

Karen du Preez

Supervisor: Professor Anneke Catharina Hesseling

Co-Supervisor: Professor Hendrik Simon Schaaf

Co-Supervisor: Dr Prenavum Naidoo

December 2020

The financial assistance of the National Research Foundation (NRF) towards this research is hereby acknowledged. Opinions expressed and conclusions arrived at, are those of the author and are not necessarily to be attributed to the NRF.

DECLARATION

By submitting this dissertation electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third-party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

This dissertation includes five original papers published in international peer-reviewed journals (Chapters 2 and 4-7), one paper accepted for publication (Chapter 2) and one unpublished paper submitted for publication (Chapter 3). The development and writing of the papers (published and unpublished) were the principal responsibility of myself. For the paper in chapter 2 ("Milestones and achievements in the response to tuberculosis and HIV in adults and children in South Africa"), I was joint first author with M. Osman. For each of the other papers, I was the sole first author and my role in each is declared in every paper. The nature and extent of the contributions of each of the co-authors is also presented in each paper and was disclosed to the journals to which the paper was submitted.

Two further papers are included as additional relevant outputs. For the paper in chapter 5 ("Timing of HIV diagnosis in children with tuberculosis managed at a referral hospital in Cape Town, South Africa"), I was joint first author with L.N. Byamungu. This data contributed towards her Master of Science in Clinical Epidemiology at Stellenbosch University in 2016. The paper in chapter 7 ("Incomplete registration and reporting of culture-confirmed childhood tuberculosis diagnosed in hospital"), was published prior to my PhD registration period.

Date: August 11, 2020

SUMMARY

Monitoring and evaluation is an integral component of tuberculosis (TB) control programmes. Children 0-14 years of age contribute substantially to the global TB epidemic, with an estimated 1 million cases and 233,000 deaths in 2017. The limited availability of age-disaggregated TB surveillance data for paediatric and adolescent populations and the lack of specific monitoring and evaluation approaches, hampers TB control efforts in these special populations. Challenges with the sources and the complexity of TB surveillance data in children compound the current limited monitoring and evaluation efforts for paediatric TB. Only 45% of the estimated number of children globally with TB were reported as diagnosed and treated by TB programmes in 2017. More than half of all paediatric TB cases globally were therefore either undiagnosed, or diagnosed but unreported to TB programmes. A TB care cascade framework has been used successfully in HIV and TB control efforts to identify specific gaps and to monitor the impact of targeted programmatic interventions and could also be useful for monitoring and evaluation of paediatric TB.

In an effort to address the lack of monitoring and evaluation approaches for paediatric TB, I investigated the role of diagnostic and treatment surveillance strategies to inform two pillars of a paediatric TB care cascade for South Africa. My research quantified the overall paediatric TB reporting gap in South Africa, showing that nearly a third of South African children with TB are undiagnosed, or diagnosed but unreported. Age- and HIV-stratified analyses of a large national routine TB treatment surveillance dataset, spanning a 13-year period (2004-2016), identified young, HIV-infected children (0-4 years) and adolescents (10-19 years) as populations who require additional targeted TB control interventions in South Africa.

Diagnostic surveillance conducted at a large tertiary referral hospital and a district-level hospital in Cape Town, South Africa, quantified the substantial burden and spectrum of paediatric TB routinely managed at these levels of care (~400 and ~170 children annually at each hospital, respectively). Surveillance of HIV-infected children and children with TB meningitis (TBM) proved valuable to monitor the impact of TB and HIV prevention strategies and of integrated TB/HIV care.

Finally, my research addressed the hospital-reporting gap in a prospective hospital-based study, where an intervention consisting of a simple TB referral service significantly improved recording and reporting as well as linkage to care of children with TB.

Including TB data from all hospitals in routine TB surveillance data will substantially reduce the hospital-reporting gap for paediatric TB in South Africa and improve the completeness of routine

TB surveillance data. Mandating hospitals to report TB data will also assist with improving the accuracy of reporting on the spectrum of TB disease and HIV data in routine TB surveillance data, increasing the utility of surveillance data for monitoring and evaluation approaches.

Together, this research highlights the importance of using multiple sources of data at different levels of health care to strengthen the accuracy and completeness of paediatric TB surveillance. The use of practical monitoring and evaluation approaches, such as a care cascade, can help to improve TB care and services for children and adolescents and will contribute towards achieving the ambitious global targets set for TB control.

OPSOMMING

Monitering en evaluasie is ‘n integrale komponent van progamme om tuberkulose (TB) te beheer. Kinders 0-14 jaar dra substantieël by tot die globale TB epidemie, met ‘n geraamde 1-miljoen gevalle en 233,000 sterftes in 2017. Die beperkte beskikbaarheid van ouderdoms-gestratifiseerde TB data vir kinders en adolessente en die afwesigheid van spesifieke benaderings tot monitering en evaluasie, belemmer huidige pogings om TB in hierdie spesiale populasies te beheer. Uitdagings rondom die bronne van en die kompleksiteit van TB oorsigdata in kinders vererger die huidige beperkte pogings tot monitering en evaluasie van pediatriese TB. In 2017 is slegs 45% van die geskatte aantal kinders wat wêreldwyd TB gehad het, deur TB programme as gediagnoseer en behandel gerapporteer. Meer as die helfte van alle pediatiese TB gevalle wêreldwyd word dus óf nie gediagnoseer nie, óf gediagnoseer maar nie aan TB programme gerapporteer nie. ‘n TB-sorgkaskade raamwerk is reeds suksesvol gebruik om spesifieke tekortkominge in TB en MIV-beheer te identifiseer, sowel as om die impak van geteikende intervensies te moniteer. ‘n Soortgelyke raamwerk kan ook waardevol wees vir die monitering en evaluasie van pediatriese TB.

In ‘n poging om die gebrek aan benaderings tot monitering en evaluasie van pediatriese TB aan te spreek, het ek die rol van diagnostiese en behandelings oorsigstrategieë ondersoek om twee pillare van ‘n Suid-Afrikaanse pediatriese TB-sorgkaskade toe te lig. My navorsing het die totale kinder-TB rapporteringsgaping in Suid-Afrika gekwantifiseer en aangetoon dat feitlik ‘n derde van Suid-Afrikaanse kinders met TB nie gediagnoseer, of wel gediagnoseer maar nie gerapporteer word nie. Ouderdoms- en MIV-gestratifiseerde analises op ‘n groot, nasionale TB behandelings en oorsigsdatastel wat strek oor ‘n 13-jaar periode (2004 - 2016), het jong MIV-geïnfekteerde kinders (0-4 jaar) en adolessente (10-19 jaar) geïdentifiseer as populasies wat addisionele geteikende beheerintervensies vir TB in Suid-Afrika benodig.

Diagnostiese oorsigstudies wat by ‘n groot tersiêre verwysingshospitaal en ‘n distrikshospitaal in Kaapstad, Suid-Afrika, uitgevoer is, het die noemenswaardige las en spektrum van pediatriese TB wat normaalweg by sulke fasiliteite behandel word, gekwantifiseer (~400 en ~170 kinders per jaar by die onderskeie hospitale). Oorsig van MIV-geïnfekteerde kinders en kinders met TB meningitis (TBM), was waardevol om die impak van TB en MIV-voorkomende stategieë, sowel as geintegreerde TB/MIV sorg, te moniteer.

Laastens het my navorsing die gaping in hospitaalraportering in ‘n prospektiewe hospitaal-gebaseerde studie aangespreek, waartydens ‘n intervensie wat die instel van ‘n eenvoudige TB

verwysingsdiens behels het, die dokumentering en rapportering van, asook die kontinuïteit van sorg vir kinders met TB betekenisvol verbeter het.

Deur TB data van alle hospitale in roetine TB oorsigdata in te sluit, sal die hospitaal-rapporteringsgaping van pediatriese TB in Suid-Afrika aansienlik verminder en die volledigheid van roetine TB-oorsigdata verbeter. Die verpligte rapportering van TB data deur hospitale sal ook help om die akkuraatheid van rapportering oor die spektrum van TB-siekte en MIV in die roetine TB-oorsigsdata te verbeter, sowel as die bruikbaarheid van TB oorsigsdata vir monitering en evalusie doeleindes.

Gesamentlik beklemtoon hierdie navorsing die belang van die gebruik van veelvuldige bronne van data van verskillende vlakke van gesondheidsorg om die akkurratheid en volledigheid van pediatriese TB oorsigdata te verbeter. Die gebruik van praktiese monitering- en evaluasiebenaderings, soos ‘n sorgkaskade, kan help om die TB sorg en dienste vir kinders en adolessente te verbeter, sowel as om tot die ambisieuese wêreldwye teikens vir TB beheer by te dra.

DEDICATION

I would firstly like to dedicate this research to my family – Gian, Anika and Jacques. Thank you for allowing me to take this journey, and for your never-ending love, encouragement and support. Gian, thank you for always believing in me, even when I didn't believe in myself. Your example of strength, rooted in faith, will always inspire me, and I am thankful for every day I can walk beside you.

Secondly, I would like to dedicate my research to all the children in South Africa, especially those who are suffering the burden and devastating consequences of tuberculosis and HIV. May I always remember that my pursuit to find better ways to provide health care to you is the only reason I am on this journey.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

aOR	Adjusted odds ratio
ARI	Annual risk of infection
ART	Antiretroviral therapy
BCG	Bacille Calmette-Guérin
CI	Confidence interval
CNR	Case notification rates
DR-TB	Drug-resistant tuberculosis
DS-TB	Drug-susceptible tuberculosis
DTTC	Desmond Tutu TB Centre
EDRWeb	Electronic drug-resistant tuberculosis register
EPI	Expanded programme on immunization
EPTB	Extra-pulmonary tuberculosis
ETR.Net	Electronic tuberculosis treatment register
HIV	Human immunodeficiency virus
ICD	International Classification of Disease
ILTFU	Initial loss to follow-up
IRR	Incidence rate ratio
KDH	Khayelitsha District Hospital
M.tb	*Mycobacterium tuberculosis*
NDOH	National Department of Health
NTP	National Tuberculosis Programme
OR	Odds ratio
PHC	Primary healthcare
PMTCT	Prevention of mother-to-child transmission of HIV
PTB	Pulmonary tuberculosis
TB	Tuberculosis
TBH	Tygerberg Hospital
TBM	Tuberculous meningitis
UNAIDS	Joint United Nations Programme on HIV and AIDS
UNHLM	United Nations General Assembly High-Level Meeting
WHO	World Health Organisation

CHAPTER 1: INTRODUCTION

1. BACKGROUND AND RATIONALE

This dissertation focusses on key epidemiological aspects of tuberculosis (TB) in children and adolescents in South Africa, specifically investigating the role of different types of surveillance at different levels of health care and in the context of the coinciding HIV epidemic. In the absence of any existing formal monitoring and evaluation framework for TB in children and adolescents, I then use the surveillance data obtained from my research and show how these contribute towards informing a paediatric TB care cascade as a useful theoretical framework.

The World Health Organisation (WHO) defines children as 0-14 years of age, and adolescents as those aged 10-19 years. For the purpose of this dissertation, the term *paediatric TB* includes children and adolescents, aged 0-19 years of age.

1.a. TB IN CHILDREN AND ADOLESCENTS – EPIDEMIOLOGY, PATHOGENESIS AND GLOBAL RELEVANCE

1.a.1. The global epidemiology of TB

TB, an infectious disease caused by *Mycobacterium tuberculosis (M.tb),* is mainly transmitted when a susceptible person inhales microscopic airborne respiratory droplets containing *M.tb* bacilli, produced when a person with infectious pulmonary TB speaks, coughs, sneezes or sings. TB remains a global, critical public health priority, with an estimated 10 million incident (new) cases of TB and 1.45 million TB deaths worldwide in 2018.[1] The global TB epidemic has been further fuelled by the coinciding HIV epidemic in many countries, especially in sub-Saharan Africa.[2] Despite the availability of effective treatment, TB remains the leading cause of death amongst people living with HIV and one of the top 10 causes of death globally in 2018.[1]

1.a.2. The pathogenesis and natural history of paediatric TB

The pathogenesis of paediatric TB has been well described from the literature during the pre-chemotherapy era. Most children, like adults, develop pulmonary TB (~75% of cases).[3, 4] Following pulmonary infection with *M.tb* in childhood, a localised, pneumonic inflammatory process results in a parenchymal (Ghon) focus.[3, 5] From the Ghon focus, lymphatic spread of bacilli will occur to the regional intra-thoracic lymph nodes, from where early haematogenous spread and dissemination of bacilli may occur.[3, 5] Haematogenous spread of *M.tb,* mainly during primary TB, establishes a meningeal, and sometimes a choroid plexus or ventricular wall caseating (Rich) focus.[6] Usually soon after such a focus is established, but in some cases much later, it caseates and discharges its content in the subarachnoid space, causing tuberculous

meningitis (TBM).[6] In rare cases a caseous lesion may extend from an adjacent structure such as a vertebrae or middle ear TB to involve the central nervous system.[6]

The risk of developing TB disease after primary infection is the highest in young children (<2 years of age), then declines with a nadir between the ages of 5 and 10 and thereafter increases again rapidly during adolescence (15-19 years).[3, 5] Accompanying these age-related differences in the risk of disease, are differences in the course and clinical features of disease. Pulmonary TB is the predominant form of TB in children and adolescents, as in adults. However, TB in children consists of a broad spectrum of disease manifestations ranging from non-severe pulmonary TB (a Ghon focus with or without hilar lymphadenopathy but without complications) at one extreme, to complicated and severe forms of pulmonary TB, to disseminated TB disease, including miliary TB and TBM , the latter with high morbidity and mortality.[7]

During adolescence, there is a clear shift in pathology, where features of pulmonary TB mirror adult-type disease with excessive tissue necrosis and parenchymal destruction.[3, 5] These observed changes are still not completely understood, but are likely related to changes in the host immune response to *M.tb* at key stages during the host-pathogen interaction.[8]

1.a.3. The age- and HIV-related risk of developing TB

The risk of developing TB varies substantially with age and HIV status. Changes in the risk of progression from *M.tb* infection to disease during childhood and adolescence are shown in Table 1.1.[3] Young children, especially those below 2 years of age, are also at highest risk of developing disseminated forms of disease, including TBM or miliary TB (Table 1.1).[3]

Table 1.1 The age-related risk of disease progression in HIV-uninfected children from natural history of disease studies, adapted from Marais et al. (reference 3).

Age at primary infection with *M.tb*	Risk of disease progression in immune competent children		
	No disease	Pulmonary disease	Disseminated disease (miliary or TBM)
<1 year of age	50%	30-40%	10-20%
1 – 2 years of age	75-80%	10-20%	2-5%
2-5 years of age	95%	5%	0.5%
5-10 years of age	98%	2%	<0.5%
>10 years of age	80-90%	10-20%	<0.5%

In infants, HIV infection increases this already high risk even further – the relative risk of culture-confirmed TB was 24.2 (95% confidence interval [CI]: 17–34) and of disseminated TB, was 17.1 (95% CI: 6–34) amongst HIV-infected infants compared to HIV-uninfected infants in a South African study, mostly in the absence of antiretroviral therapy (ART).[9] A recent systematic review

and meta-analysis found that HIV infection increased the risk of developing TB in children by approximately 8-fold, with ART reducing the risk by approximately 70%.[10]

The spectrum of TB disease in children also differs by HIV status. In a large study of 439 children treated for TB in the pre-ART era (2003-4), complicated Ghon foci or miliary disease manifestations were more frequent in HIV-infected children compared to HIV-uninfected children (odds ratio 10.9, 95%CI 3.2-35.9). [11] TBM and miliary TB were predominantly recorded in HIV-uninfected children below the age of 3 years.[11]

In settings with a high burden of TB and HIV like South Africa, the population pyramid is typically broad-based (i.e. a young population). Together with the high rate of TB transmission in TB endemic settings, children are exposed to *M.tb* at a young age and are therefore not only at high risk of developing TB, but also of developing severe forms of disease. Figure 1.1 shows the expected age-related TB incidence in both high and low TB incidence settings. It demonstrates the high TB incidence in young children, substantially dropping between 5-14 years of age, and then starting to increase again during puberty and adolescence, the pattern expected in high TB burden settings like South Africa.[12]

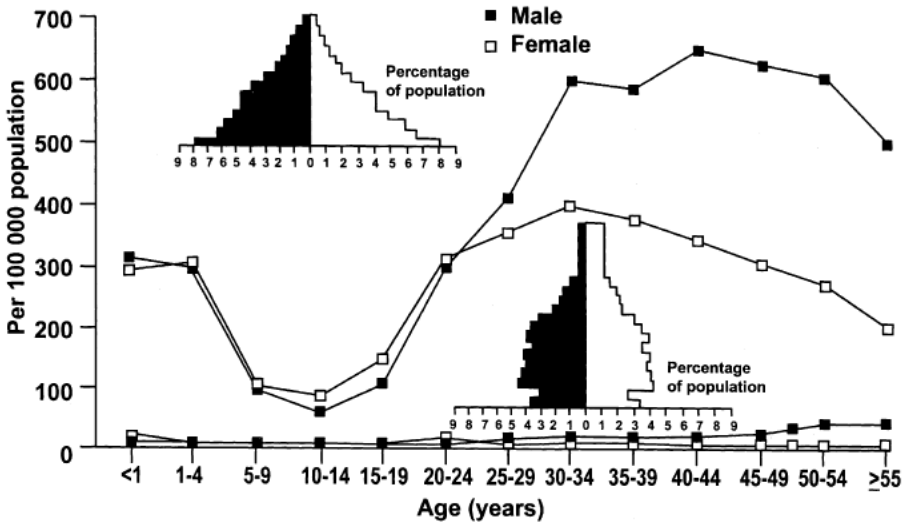


Figure 1.1 The age- and gender-related incidence of tuberculosis in a hypothetical high and low tuberculosis incidence community as published by Donald et al.[12]

The prevalence of HIV infection and the risk of HIV acquisition also changes with age. In young children, the risk of acquiring HIV is primarily through vertical transmission, either perinatally or during infancy (breastfeeding). It is thus directly linked to the antenatal (maternal) HIV prevalence and maternal access and adherence to ART or prevention of mother-to-child transmission of HIV (PMTCT).[13] During adolescence, the risk of HIV infection due to horizontal transmission rises into young adulthood, with adolescent females being at a higher risk of

becoming HIV-infected than their male counterparts.[14] With the widespread roll-out of ART to HIV-infected children, an increasing number of perinatally infected individuals, who would have been born in the early stages of the HIV epidemic, have survived into adolescence.[15] HIV-infected adolescents are at high risk of attrition in routine HIV care services,[16] which may increase their risk of developing TB and poor TB treatment outcomes as a result of poor adherence to ART.[10]

1.a.4. The epidemiological relevance of paediatric TB: contribution to burden of disease, morbidity and mortality

It is critically important to better understand epidemiological aspects of TB in addition to an improved understanding of the biology of the disease. Understanding the burden of TB disease over time and in the context of a specific population provides important perspectives which can inform improved TB control strategies.

Children and adolescents contribute a considerable, yet still under-appreciated proportion of the global TB epidemic, with high morbidity and mortality.[17-19] The WHO reported childhood TB estimates (0-14 years of age) for the first time only in 2012, and has subsequently estimated that of the 10 million TB cases globally, ~1.1 million children developed TB in 2018.[1] Despite effective treatment being available, TB remains one of the top 10 causes of under-5 mortality globally.[18] Children accounted for 14% of all HIV-negative TB deaths and an estimated 13% of TB deaths amongst people living with HIV.[1]

In addition to the significant contribution of paediatric TB to the overall burden of TB disease, severe forms of TB including TBM remain a major cause of morbidity and mortality, especially in young children living in high-burden settings, often resulting in lifelong disability or death.[20, 21] The long-term impact of pulmonary TB on lung health in children is still poorly understood, but an increasing body of evidence indicate significant impact of pulmonary TB on adult lung health even after successful cure.[22]

Adolescents have also been identified as a vulnerable population at high risk of developing TB,[23] and have been particularly neglected, resulting in poor surveillance data.[19, 24] An estimated 727,000 adolescents (10-19 years), 192,000 10-14 year olds and 535,000 15-19 year olds, developed TB in 2012.[25] This estimate was published in 2018, and no subsequent estimates or data are available. Adolescents are also at higher risk of unfavourable TB treatment outcomes [including treatment failure, loss to follow-up and mortality], especially if HIV-infected.[26, 27] Adolescents and older children (8-10 years) with TB are typically treated like adults in TB programmes in high-burden settings, with adult drug formulations, doses and anti-tuberculosis regimens, with limited targeted surveillance and additional treatment support.[19, 24]

1.b. TB SURVEILLANCE IN CHILDREN AND ADOLESCENTS

1.b.1. The importance of paediatric TB surveillance and monitoring and evaluation in the context of global TB control

Historically, TB control strategies and TB surveillance have focussed primarily on the group of patients who contribute the most to TB transmission – adults with infectious pulmonary TB.[12] Children typically develop paucibacillary TB disease, and due to their relative low contribution to the epidemic spread of the disease, they have historically been largely neglected in global TB control strategies and in TB surveillance.[28]

More than 90% of children who develop TB disease following infection with *M.tb,* will develop primary disease within the first 12 months following exposure.[29] TB in children, especially in those younger than 5 years of age, is therefore a sentinel epidemiological event and an indication of recent TB transmission.

Transmission of *M.tb* to young children (<5 years of age) frequently occurs in the household, although exposure in the wider community increases with age depending on the annual risk of *M.tb* infection (ARI). In a study conducted in Cape Town, South Africa, a setting with high burden of TB, nearly 50% of children under 5 years of age who were diagnosed with bacteriologically confirmed TB had documented household exposure to *M.tb*.[30] However, these data also indicate the high rate of background community transmission in addition to transmission in the household of *M.tb* under high burden epidemic conditions. TB in children remains a key marker of the success or failure of TB control programmes to reduce transmission of *M.tb* and to control TB.

1.b.2. Limited approaches currently exist for the monitoring and evaluation of paediatric TB care

Monitoring and evaluation of TB care is an integral part of all TB control programmes. These approaches have also been historically more focussed on adults with infectious TB. Limited approaches currently exist to monitor and evaluate TB care for children and adolescents. Currently, only three of the paediatric TB programme indicators recommended by the WHO are still useful: 1) children (0-14 years) as a percentage of the overall TB burden, 2) percentage of children treated for TB with a bacteriologically confirmed diagnosis, and 3) the proportion of paediatric cases that are younger than 5 years.[31] The other two indicators (proportion of paediatric cases that are smear-positive and that have extra-pulmonary TB (EPTB) are not useful anymore.[31] Xpert MTB/RIF has replaced smear as first-line diagnostic test in many counties, and the site of disease indicator has been changed to a binary variable, capturing all patients with pulmonary TB (irrespective of EPTB status) in one category, making it impossible to distinguish the total number of patients with EPTB.

1.b.3. The difference between burden of disease estimates for TB and case notifications

The reporting gap is the difference between the estimated number of cases and the number of TB case notifications (TB cases that had been recorded in a TB register and then reported [or notified] to national TB programmes).[31, 32] In 2017, only 45% of the estimated 1 million children with TB globally were reported to national TB programmes and were included in routine TB surveillance data (case notifications).[33]

The WHO estimates for paediatric TB were at first largely based on TB notification data. However, estimation techniques were revised in 2015 following publication of two mathematical modelling studies.[34, 35] These studies used additional complementary epidemiological estimates in combination with data from the published literature, and estimated the incident paediatric TB caseload (0-14 years of age) in 2010 to be 650,977 (95% CI 424,871–983,118)[34] in the 22 high TB-burden countries and 999,792 (95% CI: 938,000–1,055,000)[35] globally. A follow-up modelling study by Dodd et al. estimated 847 000 (inter-quartile range 558,000 – 1,280,000) children developed TB globally in 2014.[36] These dramatic variations substantiate the global concerns that routine notification data do not provide an accurate or a complete picture of the epidemiology of TB in children.

1.b.4. Limitations of current approaches to surveillance and reporting of paediatric TB

Unreliable and incomplete TB surveillance data for children has been noted as a key challenge in efforts to end the global TB epidemic in children. The first Roadmap for Childhood TB, published in 2013, urged countries to improve recording and reporting of paediatric TB as a key programmatic priority.[37] The reporting gap for paediatric TB remains a major concern. Both undiagnosed cases and incomplete notification and reporting of diagnosed cases contribute to this substantial gap.[31]

In addition to this reporting gap, current surveillance data for paediatric TB has several limitations. The WHO currently requires reporting of paediatric TB cases by two age bands only: 0-4 and 5-14 years of age. From these age bands, we are not able to distinguish two key groups: very young children (<2 years of age who are at highest risk of TB and disseminated disease) or adolescents (10-19 years of age). The current WHO-required reported data also does not routinely report on the spectrum and severity of disease (notably, TBM), and surveillance data from hospitals in high-burden settings are frequently not included.[38-41] Current TB surveillance data furthermore includes limited data on HIV and ART, not always allowing for the accurate capturing of HIV data in relation to the TB episode, for example the timing of TB diagnosis in relation to the diagnosis of HIV, the initiation of and adherence to ART in relation to the TB episode, ART adherence, efficacy and virologic suppression. The absence of key relevant HIV data aspects to complement TB surveillance data limits our current analytical ability to determine

many important clinical and epidemiological factors in TB patients co-infected with HIV. These aspects are relevant to identification of gaps in HIV care, to integration of TB/HIV services and are also relevant for TB treatment outcomes.

1.b.5. The impact of inaccurate and limited paediatric TB surveillance data

Without reliable estimates of the paediatric TB disease burden and spectrum of disease, the current understanding of the epidemiology of TB in children remains woefully inadequate.[31] This impacts negatively both on resource allocation for routine clinical care and on research, and hampers the measurement of the effectiveness of existing and new interventions.[31] These knowledge gaps further result in inaccurate estimates of market size for new anti-tuberculosis drugs and for TB diagnostics.[32] Evaluation of the efficacy of vaccination and other preventive control strategies, for example neonatal bacille Calmette-Guérin (BCG) vaccination, TB contact management and TB preventive therapy, HIV management, and potentially, novel TB vaccines, are also negatively affected by these gaps in knowledge.

Given the challenges in the diagnosis of paediatric TB and the more complex clinical care pathways in TB-affected children compared to adults, complementary sources of data are needed to enhance routine TB surveillance data. In turn, this will more comprehensively determine the burden and spectrum of TB in children and adolescents, and help inform local, national and international planning for TB management and surveillance in children and adolescents.

1.c. THE USE OF CASCADE ANALYSIS AS A FRAMEWORK FOR MONITORING AND EVALUATION OF TB CARE

1.c.1. A TB care cascade as an approach to monitoring and evaluation of services

The HIV community has clearly shown the value of adopting an HIV care cascade model, depicting several steps that need to be completed in order to achieve a desired health outcome relevant to HIV.[42] The HIV care cascade model can be used as a framework to visualize and measure not only a final target outcome, but also the sequential steps needed to reach the target outcome (for example diagnosis, linkage to care, retention in care, adherence to ART and viral suppression).[43, 44] Interventions can be focused to close specific, identified gaps along this HIV care continuum.

The TB community has been urged to also adopt a similar approach for TB care considering the potential impact this can have on TB elimination and the quality of TB care to patients.[45, 46] Reid and Goosby noted the need for integrating several strategic information systems in order to effectively implement such a strategy. Furthermore, the use of a care cascade approach for TB can assist with both programme evaluation and identifying gaps in the quality of care.[47] The TB care cascade starts with the estimated number of individuals with TB in a specific population, then the number of patients who accessed TB testing, of those the number who were diagnosed, followed

by the number who started anti-tuberculosis treatment and were reported/notified, the number who were successfully treated, and lastly, those who survived without recurrence.

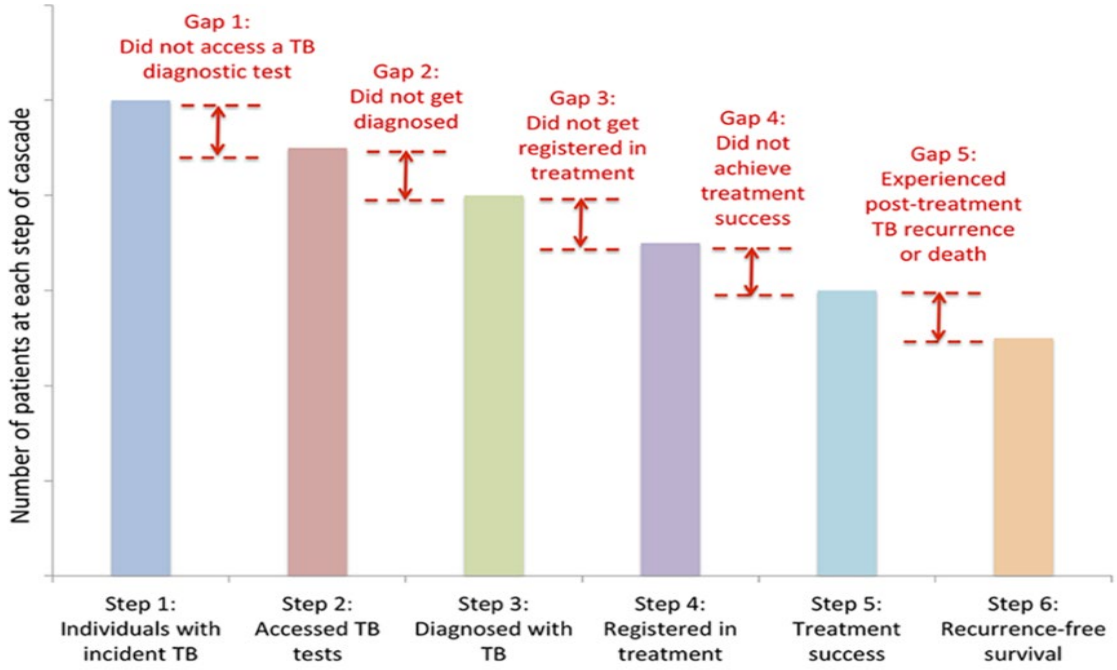


Figure 1.2 A generic model for a tuberculosis care cascade proposed by Subbaraman et al.[47]

Figure 1.2 shows a generic model of a TB care cascade and the gaps between each step, as proposed by Subbaraman et al. in 2019.[47] Adopting a TB care cascade approach holds several advantages for TB programmes.[46] It could also be a particularly useful tool in sub-populations to identify population-specific gaps, for example, in children and adolescents, TB/HIV co-infected patients, and pregnant women, which can inform targeted and tailored interventions.[46]

1.c.2. Consideration of differences between TB in adults and in children when constructing a paediatric TB care cascade

Paediatric TB differs from adult TB in several ways.[48] Symptoms, especially in young and HIV-infected children, tend to be more non-specific and of shorter duration compared to adults.[49, 50] Spontaneously expectorated sputum specimens from adults can be relatively easily obtained, compared to more invasive measures including gastric aspirates or induced sputa, which are typically required in young children given their inability to expectorate sputum, and which frequently result in hospital referral for TB investigation. Interpretation of paediatric chest radiographs, a cornerstone of TB diagnosis, remains challenging compared to adults.[51]

Children generally develop paucibacillary (smear and mostly culture-negative) disease, whilst adults with cavitary pulmonary TB generally have higher bacillary loads. Bacteriological diagnostic tests for TB based on the detection of *M.tb* therefore perform better in adults, and the

basis of diagnosis in children is mostly clinical (<30% of children are bacteriologically confirmed in routine care, depending on the spectrum of disease[52-54]), whilst approximately 60% of adults typically have a bacteriological confirmed diagnosis.[55-57] Culture remains the gold standard of TB diagnosis, but only detects *M.tb* in approximately 24% of children with TB.[54] The sensitivity of novel molecular tools including Xpert MTB/RIF (Cepheid, Sunnydale, CA), is limited in children, detecting approximately 60-70% of culture-confirmed cases only.[58] Despite rapid turnaround time and the ability to detect resistance to rifampicin with Xpert MTB/RIF, and resistance to both rifampicin and isoniazid with line-probe assays, these widely implemented molecular tools globally and in South Africa, will fail to detect *M.tb* in the majority of children, especially in children < 5 years of age.

Most children, like adults, will develop pulmonary TB (~75% of cases).[3, 4] The spectrum of pulmonary TB is however different from that of adults with mediastinal lymph node disease being the predominant manifestation in children, with or without complications, such as large airway compression and endobronchial spread.[3] In contrast, adults typically develop cavitary parenchymal disease. Children are also at higher risk of developing severe and disseminated forms of TB, including miliary TB and TBM, than adults.[3, 59]

In resource-limited settings, the complexity of diagnosing TB in young children compared to adults also results in differences between the level of health care accessed for TB diagnosis and care. The majority of children routinely managed in TB programmes will (appropriately) be diagnosed based on clinical grounds (symptoms, history, TB contact history, chest radiograph). Frontline healthcare workers at primary healthcare (PHC) level who are comfortable with diagnosing adult TB, are often not as comfortable and experienced in investigating, diagnosing or interpreting imaging of children with possible TB, especially in the very young children, who typically cannot expectorate sputum spontaneously. Children may also present with acute severe symptoms requiring hospitalisation.[60] Young children, who contribute the most to the paediatric TB disease burden, are therefore often referred to the next level of healthcare for further investigation, diagnosis or treatment. In contrast, the majority of adult TB patients in resource-limited settings are diagnosed at PHC level.

In addition, children's health seeking behaviour relies on their caregivers, who are often sick themselves with TB and/or HIV, which may also impact on their children's access to healthcare services. Furthermore, during TB treatment, children require regular dose adjustment of their medications to ensure adequate dosing and drug exposures as the child gains weight. Anti-tuberculosis medications frequently need to be halved and crushed, especially in young children, and HIV infection and ART complicates the treatment of TB in children and in adolescents, making treatment adherence challenging.

1.c.3. Consideration of levels of health care when constructing a paediatric TB care cascade

Due to the nature of paediatric TB and challenges in diagnosis and special investigations described above, children who present at a PHC facility to child and maternal health services are often referred to the next level of care for further investigation, diagnosis and treatment. A large proportion of TB in young children (<5 years of age) is therefore typically diagnosed at hospital level, especially those with severe forms of disease, including TBM, miliary TB, and drug-resistant forms of TB, or those with co-morbidities including HIV infection.

Children may also move back and forth between different levels of healthcare (PHC facilities, primary, secondary, tertiary or specialized hospitals, and medium-term care facilities) during the process of TB diagnosis and treatment given their different diagnostic care pathways and spectrum of disease. More severe paediatric TB cases, for example TBM and osteo-articular disease, may be admitted for long periods before being discharged from hospital to continue treatment as out-patients if they survive, contributing to the hospital-reporting gap for children in settings where hospitals do not function as TB reporting units.

TB surveillance data from hospitals therefore provide an important additional perspective on the overall burden, spectrum and mortality of TB in children with and without HIV, and are essential to provide a representative picture of paediatric TB. This is increasingly also being observed in adults with severe forms of TB and in TB/HIV co-infected adults.[61]

1.d. DEVELOPING A PAEDIATRIC TB CARE CASCADE

When constructing a paediatric TB care cascade, relevant paediatric-specific differences compared to adults and the adult TB care cascade need to be considered in order to develop a framework that is useful and relevant to paediatric TB control (Figure 1.3).

The first key difference relevant to paediatric TB lies in the second pillar, i.e. estimating the number of children who presented to health services, as opposed to the number of adults with TB who received a diagnostic test. In the adult TB care cascade, laboratory surveillance plays a major role in the second pillar, as the majority of adult TB patients are expected to have a specimen sent for bacteriological testing and ~60% are expected to have a bacteriologically confirmed diagnosis depending on the number and quality of specimens.[56] Laboratory surveillance has provided valuable information on the epidemiology and drug resistance patterns and impact of HIV on paediatric TB in South Africa.[62-67] However, due to the paucibacillary nature of paediatric TB and the challenges of obtaining suitable specimens from children, both bacteriological testing and bacteriological confirmation of disease are much lower than in adults.

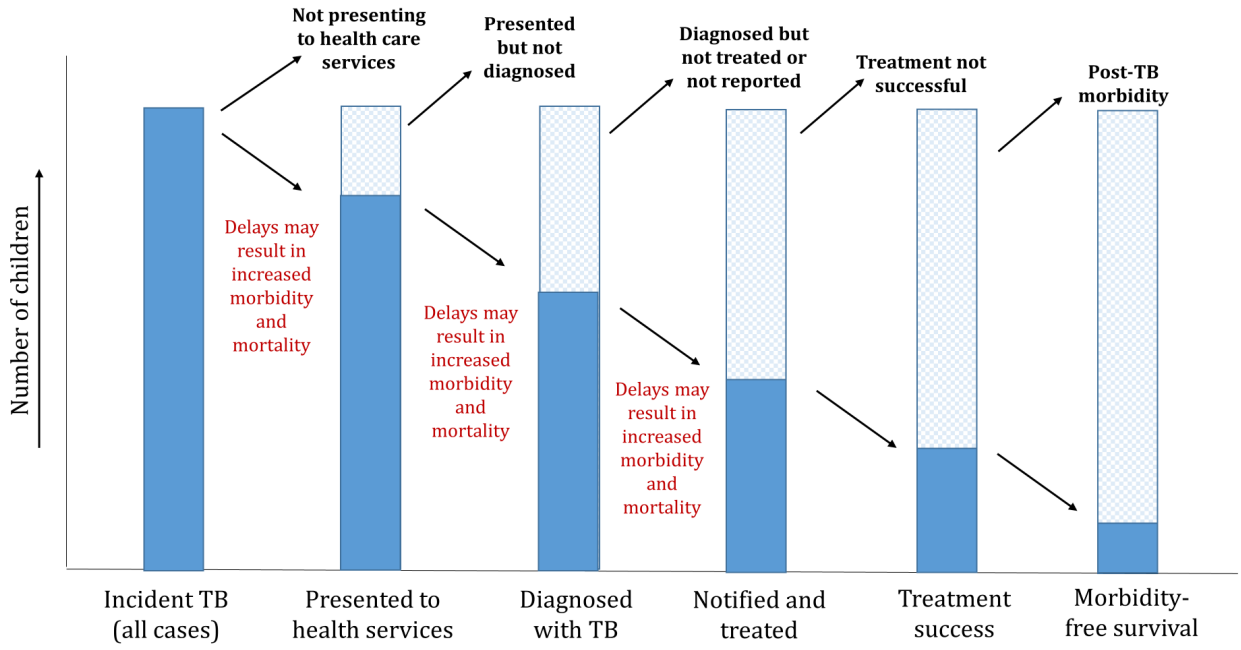


Figure 1.3 A proposed care cascade for paediatric TB

Bacteriological testing in young children is performed rarely in PHC facilities in high-burden settings, with the majority of children with TB at PHC level not having a sample taken for bacteriological testing.[68] Specimen collection and bacteriological confirmation of children will mostly occur in young children managed at hospital level, while older children and adolescents, who are able to spontaneously expectorate sputum, are more likely to have bacteriological testing done at PHC level.[68] These children are also more likely to have adult-type pulmonary TB, with higher bacillary burden (i.e. bacteriologically confirmation). Given the gaps in bacteriological investigation and the low yield of bacteriological tests in children with TB, laboratory surveillance alone will identify only a sub-set of paediatric TB patients. We therefore need to consider how and where children with TB access healthcare services and how they are diagnosed, to quantify the losses between pillars 1 & 2, and 1 & 3.

The second key difference affects pillars 2, 3 and 4, and lies in the difference in the movement between levels of healthcare for children and adults, respectively, and the impact this has on the source of surveillance data and how such data is captured and reported. A larger proportion of children with TB will either present, or will be diagnosed or treated at hospital level, compared to adults. It is therefore critically important that surveillance data for a paediatric TB care cascade includes data from multiple levels of health care, including hospital and PHC level, on the presentation, diagnosis and treatment of TB.

The third key difference lies in pillar 6 – this pillar captures recurrence-free survival in adults. For children, this pillar should in addition consider post-TB morbidity. Not only is it important

to understand post-TB lung health in children and adolescents, as it is in adults, but it also is critical to capture the neurological and social morbidity in children with severe forms of TB like TBM, which has a uniquely high incidence during early childhood.

1.d.1. Limitations of a care cascade approach for paediatric TB: the relevance of spectrum and severity of TB disease

Accurate TB surveillance should capture the full spectrum of disease in children in order to quantify both morbidity and mortality. Children below the age of 2 years are at high risk of developing TBM, a serious form of disseminated TB that affects the central nervous system.[3] Children with TBM suffer high morbidity and mortality, and often permanent neurological disability and poor long-term neurological outcomes if not diagnosed early.[20, 21]

International Classification of Disease 10 (ICD-10) codes are often poorly completed in routine TB surveillance data, and routine reporting does not distinguish TBM from other forms of TB. TBM frequently presents with non-specific symptoms, such as reduced playfulness and lethargy, failure to gain adequate weight, low-grade fever and vomiting, resulting in a delayed diagnosis, advanced presentation and severe morbidity.[20] The consequent lifelong neurological disability after TBM places a huge economic and social burden on families, communities and public health services. Early diagnosis and treatment are critical to improve TBM outcomes[69, 70] but in high TB burden settings, children are often diagnosed late or die undiagnosed.

A diagnosis of TBM may highlight missed opportunities for BCG vaccination or for TB preventive therapy following documented TB exposure, modifiable factors which could greatly reduce the burden and morbidity of TBM in children.[71] Surveillance of severe and distinct forms of paediatric TB, like TBM, is also a potential valuable source of surveillance data to identify health system challenges and solutions for children.

In summary, paediatric TB surveillance strategies need to utilise complementary data sources from multiple levels of health care to comprehensively report on the burden and spectrum of TB disease in children. Such surveillance strategies should include complete data on HIV co-infection and HIV-related data, and should address the age continuum and the care cascade relevant to children.

1.e. PAEDIATRIC TB IN SOUTH AFRICA

1.e.1. The burden of TB and HIV in South Africa

South Africa was one of only eight countries in the world that jointly accounted for 66% of the global TB burden in 2018, with an estimated 301,000 TB cases and an estimated TB incidence of 520 per 100,000 population.[1] Children (0-14 years of age), constituted an estimated 27,000 (9%) of the total national TB burden in 2018.[1] More than 95% of the national TB burden is drug-

susceptible TB (DS-TB), with drug-resistant TB (DR-TB) occurring in an estimated 11,000 (4%) of cases.[1]

South Africa also carries a high HIV burden with an estimated national HIV prevalence of 14.0% in 2017.[72] More than half of the national TB caseload in 2018 (177,000/301,000; 59%) was amongst people living with HIV.[1]

1.e.2. TB control and surveillance in South Africa in the context of the South African National TB programme

The South African National TB Programme (NTP) is responsible for the implementation, evaluation and reporting of all TB services within the public health sector in South Africa. Services for the treatment of DS-TB, and increasingly for DR-TB are decentralized, encouraging patients to be screened, diagnosed and treated at the PHC level.[73] Surveillance systems therefore focus primarily on capturing information on patients treated at PHC facilities. In the 1990's, South Africa implemented a standardised, paper-based TB reporting system across the country in all provinces. To strengthen the TB program, an electronic surveillance system, the electronic TB register (ETR.Net), was piloted and implemented during the early 2000's. This register focussed on capturing process and outcome indicators for all patients who had started TB treatment. Since 2004, South Africa has been using ETR.Net as the primary source of surveillance data for DS-TB. A separate register for surveillance of DR-TB cases (electronic drug-resistant TB register; EDRWeb) was implemented in 2009.

Following the diagnosis of TB, a patient should be started on TB treatment and recorded in the healthcare facility's paper-based register and captured in the relevant electronic TB treatment register. The facility where the patient receives treatment is then also responsible for recording and reporting the final TB treatment outcome, except if the patient was transferred to another facility during the course of TB treatment. Data for patients treated for DS-TB are captured into ETR.Net and for DR-TB into EDRWeb, either at facility or sub-district level, aggregated quarterly at district, provincial and national level, and used for annual national TB case finding and reporting cohort (outcome) data, which are reported directly to the WHO. Routine surveillance data in South Africa therefore only includes patients who were diagnosed, initiated on TB treatment and recorded and reported in ETR.Net or EDRWeb. Other sources of data are not included in routine TB surveillance or reporting.

TB is a notifiable medical condition in South Africa, and in parallel to the operational TB programme reporting described above, healthcare workers are required to complete formal notifications of all TB diagnoses. Merging the notification data with the operational TB surveillance data would require substantial data and information management infrastructure

and resources, as well as strong political will. Notification data in South Africa was therefore never included in the operational TB surveillance data used for national reporting.

Considerable heterogeneity exists in health services implementation at provincial level in South Africa, with provincial authorities deciding on how to implement national directives locally. In three of the four high TB-burden provinces in South Africa (Western Cape, Gauteng and Eastern Cape), hospitals do not currently function as TB reporting units. Hospitals in these provinces diagnose and treat patients with TB, but these cases are only reported if and when they access TB care at a PHC or another reporting facility upon hospital discharge and if they are captured in TB registers at these facilities. If not, they are excluded from national surveillance data and are not reported to the WHO. As a result, in-hospital TB deaths are also not included in TB reporting data in these provinces.

1.e.3. The South African TB care cascade

Following publication of the first national TB care cascade from India,[74] South Africa was the second country globally to publish estimates for a TB care cascade, in 2017.[75] Losses occurred at every step of the TB care cascade. It was estimated that only half (53%) of all TB patients in South Africa were successfully treated in 2013 (Figure 1.4). Results from this cascade analysis allowed the South African NTP to launch a dedicated and focussed response to reduce the estimated losses at each step of the cascade. However there are important considerations and gaps for children and adolecents affected by TB which require systematic investigation.

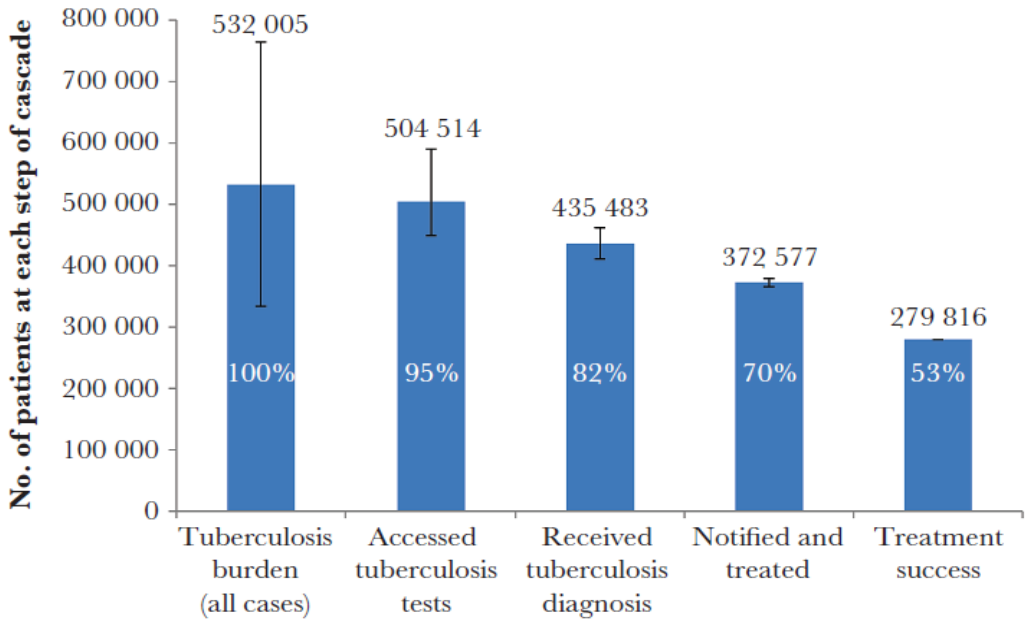


Figure 1.4 Care cascade for all patients with tuberculosis in South Africa, 2013[75]

1.e.4. How many South African children and adolescents are affected by TB and HIV?

In 2018, the WHO estimated that 27,000 children below the age of 15 in South Africa had developed TB. However, only 17,561 cases were reported to the WHO. Based on these numbers, only 65% of children with TB in South Africa were diagnosed, started on treatment and notified in 2018, leaving a third of children with TB in South Africa undiagnosed or unreported.[76]

The Joint United Nations Programme on HIV and AIDS (UNAIDS) estimated that 340,000 (260,000-420,000) children younger than 15 years were living with HIV in South Africa in 2019.[77] The maternal HIV prevalence in South Africa remains high with an estimated national HIV prevalence amongst pregnant women attending routine antenatal care services of 30.7% in 2017.[78] Despite effective PMTCT and low vertical HIV transmission rates (HIV prevalence amongst infants in 2017: 2.7%[72]), the high prevalence of maternal HIV infection results in a high risk of TB exposure to young children, even if children are HIV-exposed but uninfected.[79]

Case notification data on adolescents as a specific group of interest are not routinely reported in South Africa, and from the existing age-bands used in currently reported surveillance data, it is not possible to determine the number of national TB case notifications amongst adolescents (10-19 years of age). The WHO also does not report estimates of adolescent TB. The impact of the current limited reporting of paediatric TB by broad age-bands, does not allow for surveillance data to distinguish adolescents, and has been raised as a major concern.[19]

Other limitations of current reported TB surveillance data from South Africa include the lack of accurate data on the spectrum of disease, the limited data on HIV co-infection and relevant variables, and the lack of age-disaggregated treatment outcomes for paediatric and adolescent populations.

1.e.5. The hospital reporting gap for paediatric TB in South Africa

There are two factors contributing to patient losses between pillars 3 and 4 of the TB care cascade ('Diagnosed with TB' and 'Notified and treated'). The first contributing factor is initial loss to follow-up (ILTFU). This refers to patients who are diagnosed with TB but who are never started on treatment. Naidoo et al. estimated the proportion of TB patients who were ILTFU in South Africa to be 12% in 2013.[75] Considerable ILTFU (52% and 58%) has been documented among TB patients who are diagnosed at hospitals in South Africa.[61, 80] In South Africa, TB surveillance data are typically captured at treatment initiation, and patients who are ILTFU would therefore not be reported and are omitted from routine TB surveillance data.

The second contributing factor to patient losses between pillars 3 and 4 is the group of patients who are diagnosed and started on TB treatment, but who are never recorded in a TB treatment register at a TB reporting unit (health facility). In settings where hospitals do not report on TB

data, there can be many reasons for this hospital-reporting gap. Patients may be treated as in-patients for the entire duration of treatment or may die before hospital-discharge. Patients who are discharged to PHC facilities may not arrive at the next level of care, or patients may access care at the PHC facility but through poor communication do not receive the appropriate care or are not recorded and reported.

The successful linkage of TB care between hospital and PHC facilities is a well-recognised challenge.[81] Amongst patients who initiated TB treatment in South African hospitals, four studies from three different provinces between 2001 and 2009 found that successful linkage to PHC facilities did not occur in 12% to 31% of TB patients across the age spectrum.[61, 80, 82, 83] One study found that children younger than 15 years of age were at even higher risk than adults for discontinuing their TB care.[61] In settings where hospitals are not reporting units for TB cases, these patients, despite being diagnosed and initiated on treatment, are not included in routine TB surveillance data, and would therefore also contribute to the gap in TB cases captured between pillar 3 and 4. Large gaps in paediatric TB notifications from hospitals have also been reported from Indonesia,[39] India[40] and Benin.[41]

Poor continuity of TB care and linkages of data between different levels of healthcare services where children are diagnosed with TB (hospitals), and where they are commonly treated (PHC facilities), contribute to the hospital-reporting gap for paediatric TB and inaccurate routine surveillance data.

1.e.6. The potential impact of applying multiple surveillance strategies to inform monitoring and evaluation of paediatric TB control

A TB care cascade could be a useful approach for the monitoring and evaluation of TB care for children and adolescents in settings like South Africa and also globally. As for adults, a care cascade could be used to identify specific gaps that can be addressed by targeted interventions and track the impact of those interventions over time.

However, the development of a TB care cascade that comprehensively captures the burden of TB in children and adolescents, requires an in-depth understanding of the strengths and limitations of multiple surveillance strategies from several levels of healthcare and how each can inform estimates of the different pillars of the cascade. Complementary data sources to provide additional information on spectrum of TB disease are also essential for us to fully understand the true impact of the TB epidemic on children and adolescents.

2. PURPOSE AND SCOPE OF THIS PHD RESEARCH

Given the importance of an improved understanding of TB epidemiology in settings with a high burden of TB, this dissertation focussed on key epidemiological aspects of TB in children and

adolescents in South Africa, in the context of the HIV epidemic. The purpose of this PhD research was to address some of the critical knowledge gaps in the current understanding of TB surveillance strategies at different levels of health care and to inform estimates of the TB burden and spectrum of disease in children and adolescents in South Africa. I evaluated how these diagnostic and treatment surveillance strategies can contribute towards monitoring and evaluation of paediatric TB care using operational research and by informing two pivotal pillars of a paediatric TB care cascade. This dissertation specifically focused on addressing pillar 3 ('Diagnosed with TB') and pillar 4 ('Notified and treated') of the paediatric TB care cascade, using diagnostic and treatment surveillance data, and on reducing the hospital-reporting gap between these two pillars of the TB care cascade for paediatric TB through a linkage-to-care intervention.

Specific research gaps addressed in this dissertation included: 1) the current limited estimates of the burden and severity of paediatric TB, 2) uncertainty regarding the number of children lost between steps in the TB care cascade, 3) limited knowledge on how children with TB move between levels of healthcare, and 4) a lack of a standard framework to conduct systematic monitoring and evaluation of TB care in children and adolescents.

The first two studies I present in the dissertation (chapter 2) provide background and context to the epidemiology of the intersecting TB and HIV epidemics in South Africa. The first manuscript provides an overview of the important milestones achieved in the South African public health response to TB and HIV in the context of the changing epidemiology of TB and HIV. The second reviews the current status of paediatric TB in South Africa, using the most recent WHO disease estimates, TB case notification data, and the South African targets set at the United Nations General Assembly High-Level Meeting (UNHLM) on TB in September 2018. Together, these two studies provide context to both the history of TB and HIV control and TB epidemiology in South Africa and highlight the need for better monitoring and evaluation frameworks for paediatric TB in order to achieve the ambitious global targets set for TB control.

Chapter 3 provides important data on the fourth pillar of the TB care cascade, 'Notified and treated'. Analysis of a uniquely large routine national TB treatment surveillance dataset from South Africa spanning a 13-year period (2004-2016) evaluate trends in the case notification rates and spectrum of DS-TB in children and adolescents. I further stratified these rates by age and HIV status, within the context of temporal programmatic TB and HIV changes in South Africa.

In Chapters 4 and 6, I examine the third pillar, 'Diagnosed with TB', from a hospital-based surveillance perspective. I characterize the burden, spectrum and care pathways of TB in children managed at both tertiary and district-level hospitals in the Western Cape province, South Africa.

In Chapter 5, I show how hospital-based surveillance data can be used for operational research to identify health system gaps. In a hospital-based cohort of HIV-infected children with TB, I evaluate the timing of a diagnosis of HIV in relation to the diagnosis of TB, highlighting the importance of integrated TB/HIV care in children. I also show the value of hospital-based epidemiological surveillance of severe forms of TB, specifically TBM, highlighting the ongoing need for preventive tools such as BCG.

Finally, in Chapter 6, I address ILTFU and the hospital-reporting gap between pillar 3 ('Diagnosed with TB') and pillar 4 ('Notified and treated') of the TB care cascade for children diagnosed at hospital level. I investigate the impact of a hospital-based intervention to support linkage of TB care between hospital and PHC level for children at a tertiary hospital. The aim of the intervention was to support continuation of clinical care, reduce ILTFU and improve reporting and thus surveillance of children with hospital-diagnosed TB. In this chapter, I present and discuss the results and impact of the intervention on the reporting gap for paediatric TB.

3. OVERALL AIM

The overall aim of this PhD dissertation was to evaluate the role of different surveillance strategies to inform estimates of the TB disease burden and spectrum focussed on two pillars ('Diagnosed with TB' and 'Notified and treated') of the paediatric TB care cascade in South Africa, a country with a high burden of TB and HIV. This research further evaluated the impact of an intervention to minimize losses between these two pillars of the TB care cascade for children managed at different levels of health care, to ensure continuity of care and improve paediatric TB surveillance data.

4. SPECIFIC OBJECTIVES

1. To map key programmatic changes in TB and HIV control and discuss the current status of paediatric TB in South Africa
2. To conduct in-depth analyses of trends in routine TB case notification rates, stratified by age and HIV status, in South African children and adolescents over a 13-year period
3. To characterise the burden and spectrum of TB and TB-HIV at a large tertiary referral hospital in South Africa
4. To characterise the burden and spectrum of TB and TB-HIV at a South African district level hospital in a sub-district with high burden of TB and HIV
5. To evaluate the impact of a hospital-PHC linkage-to-care intervention on the completeness of routine TB surveillance data in South Africa

CHAPTER 2: THE NATIONAL PUBLIC HEALTH RESPONSE TO TUBERCULOSIS AND HIV IN CHILDREN AND ADOLESCENTS IN SOUTH AFRICA

South Africa carries a very high burden of tuberculosis (TB) and HIV. In 2018, the estimated TB incidence in South Africa was 520 per 100,000 population, and it has been consistently greater than 500 per 100,000 population for the past 20 years.[1] In 2017, there were approximately 7.9 million people living with HIV in South Africa, with a national HIV population prevalence of 20.6% (95% confidence interval 19.2-22.0%) amongst adults 15-49 years of age.[72]

The interaction between TB and HIV has been well described, with HIV significantly increasing not only the risk of developing TB, but also altering the spectrum of TB disease and increasing TB-related mortality.[2, 10, 84] Amongst TB patients with a known HIV status in South Africa, nearly 60% were HIV-infected in 2018.[1]

Both TB and HIV are managed by disease-specific programmes established in the late 1990s within the National Department of Health of South Africa. Over the past two decades, several important changes have occurred in both these programmes. Clinical guidelines were updated as new diagnostics and treatment options became available for both TB and HIV. The availability and uptake of antiretroviral therapy (ART) has increased substantially over the past decade as ART eligibility criteria became progressively more inclusive, with all people living with HIV routinely being eligible for ART since 2016.

Milestones and achievements in the response to TB and HIV in adults and children in South Africa[85]

The first paper in this chapter provides an historical overview of TB and HIV health services in South Africa. It comprehensively reviews the combined key milestones in the South African public health response through the national TB and HIV programmes for adults and children over the 13 years from 2004 to 2016. Significant milestones in policy changes occurred in South Africa over this period and are presented in the context of the changing epidemiology of TB and HIV in South African adults, adolescents and children.

This overview provides critical background information to better understand the epidemiological and health services context of paediatric TB in South Africa since the early 2000s. This historical perspective also assists with interpretation of the data subsequently presented in this dissertation, helping to explain observed epidemiological changes and identify the possible impact of changes in health services on the paediatric TB care cascade over time.

Where are we in the battle of ending tuberculosis in children and adolescents in South Africa?[76]

The second paper provides a current perspective on paediatric and adolescent TB in South Africa. The analysis presented in this paper used data from the WHO Global TB database to show the difference between burden of disease estimates (2018) and current paediatric TB surveillance data (TB case notifications from 2015-2018) in South Africa. The current status in achieving the South African targets for 2018-2022 set at the United Nations General Assembly High-Level Meeting (UNHLM) on TB in September 2018 is discussed.

This paper highlights key gaps and opportunities to improve surveillance estimates for paediatric and adolescent TB and quantifies the large reporting gap (35%) between incident paediatric TB cases (pillar 1 of the TB care cascade) and those notified and treated (pillar 4 of the TB care cascade) in South Africa during 2018. This is an important first step towards developing a paediatric TB care cascade and understanding how well paediatric TB is currently being addressed in South Africa.

Citations

Osman M*, **du Preez K***, Naidoo P, Bock P, Rabie H, Dlamini SS, Hesseling AC. Key changes in the public health response to TB and HIV in South Africa. Int J Tuberc Lung Dis. 2020;24(8):857-9.

*Contributed equally – I jointly developed the concept with M. Osman, and contributed equally towards data extraction, data synthesis and the write-up of the manuscript.

Du Preez K, Seddon JA, Schaaf HS, Hesseling AC. Where are we in the battle of ending tuberculosis in children and adolescents in South Africa? S Afr Med J. 2020; Published online 26 March 2020. https://doi.org/10.7196/SAMJ.2020.v110i5.14728.

INT J TUBERC LUNG DIS 24(8):857–859

http://dx.doi.org/10.5588/ijtld.20.0147

LETTER

Key changes in the public health response to TB and HIV in South Africa

Dear Editor,

The link between HIV and TB has been well described and antiretroviral therapy (ART) is a critical tool for the prevention of HIV-associated TB in adults.[1] Similarly, in HIV-infected children, ART reduces the risk of TB, including morbidity and mortality.[2] In South Africa between 1999 and 2008, the approach to HIV and AIDS was marked by denialism, which led to a late and slow response to the emerging HIV epidemic.[3] This coincided with significant increases in TB rates in South Africa in the preceding years, resulting in calls for reappraisals of the TB control strategy, with South Africa reporting the third highest TB burden globally in 2008.[4] Changes in political leadership in 2009[5] resulted in increased access to ART and important changes to the TB programme for diagnostics, prevention and treatment for adults and children. Here, we present updated programmatic data on the epidemiology and key changes in the public health response to TB and HIV in South Africa between 2004 and 2016.

Since 2009, South Africa has embarked on a series of interventions to address the TB and HIV epidemics and progressively scaled up condom distribution, medical male circumcision and the prevention of mother-to-child transmission (PMTCT) programme.[3] The provision of ART to HIV-infected individuals was incremental, and significant progress was made after presidential commitment was made public in 2009.[3] In 2010, the country launched an aggressive HIV testing campaign to test 15 million people for HIV and offer a package of services to HIV-infected individuals.[6] Guidelines for the management of HIV in adults and adolescents, PMTCT and children were revised in 2010, with all HIV-infected infants being eligible for ART. Paediatric coverage was further expanded in 2012, when all HIV-infected children aged ≤5 years were eligible to start ART. Guidelines were revised again in 2013 and 2015 to increase access to ART for all adult and paediatric populations. In 2016, South Africa announced the provision of ART to all HIV-infected individuals under the Universal Test and Treat policy.[7]

The South African TB programme has made significant progress in the areas of prevention, diagnosis, treatment and monitoring. The electronic tuberculosis register (ETR.Net) provides case-based surveillance data on all drug-susceptible TB cases started on treatment since 2004. In 2011, South Africa published guidelines for the management of drug-resistant TB and a framework for decentralised care. At the same time, the use of Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) as an initial diagnostic test for all individuals with presumptive TB was initiated, and by 2016 South Africa was the global leading procurer of Xpert cartridges.[8] Drug susceptibility testing at diagnosis meant that the previous WHO regimen 2 (2 months of rifampicin (R), isoniazid (H), ethambutol (E), pyrazinamide (Z), streptomycin (S); followed by 1 month of HREZ, followed by 5 months of HRE)[9] was discontinued in 2012, i.e., streptomycin was no longer added to the first-line TB treatment regimen.[10] The availability of injectable-free multidrug-resistant TB regimens (including bedaquiline and delamanid), along with decentralised patient care, resulted in a dramatic shift towards a patient-centred approach to TB care. TB management in children, including contact management, had been included in the national TB guidelines since 2004, but in 2013 a specific childhood TB guideline was published.[11] In 2017, South Africa accounted for 39% of the nearly 1 million people infected with HIV receiving TB preventive therapy (TPT).[12] However, implementation in and uptake of TPT by child contacts have been sub-optimal, with multiple losses along the contact management cascade.[13]

We calculated annual TB case notification rates between 2004 and 2016 using the South African case finding cohort of drug-susceptible TB from ETR.Net. We used the published Thembisa model to ascertain population denominators stratified by age for each year.[14] The estimated TB incidence was extracted from the WHO global TB database,[15] and the estimated HIV prevalence and uptake of ART from the Thembisa model.[14] We constructed a comprehensive timeline, depicting major milestones in the TB and HIV public health programmes since the national roll-out of ART and the availability of credible data from ETR.Net (see Figure).

The estimated incidence of TB peaked in 2008, whereas TB case notifications for both adults and children peaked in 2009. The figures for adult TB case notifications in South Africa were higher than the WHO estimate of country incidence between 2008 and 2011. This is possibly due to the steeper increase in adult TB case notifications in 2008 and 2009. As the WHO incidence reflects the estimated incidence for the entire population, the disproportionate increase in case notification among adults compared to children may account for the higher case notification in adults than the estimated incidence for the country. The estimated HIV prevalence among adults aged 15–49 years progressively increased from 15.6% in 2004 to 18.9% in 2016. From 2009, South Africa showed a marked increase in ART uptake, coinciding with the expanded

MO and KDP are joint first authors.

Article submitted 13 March 2020. Final version accepted 14 March 2020.

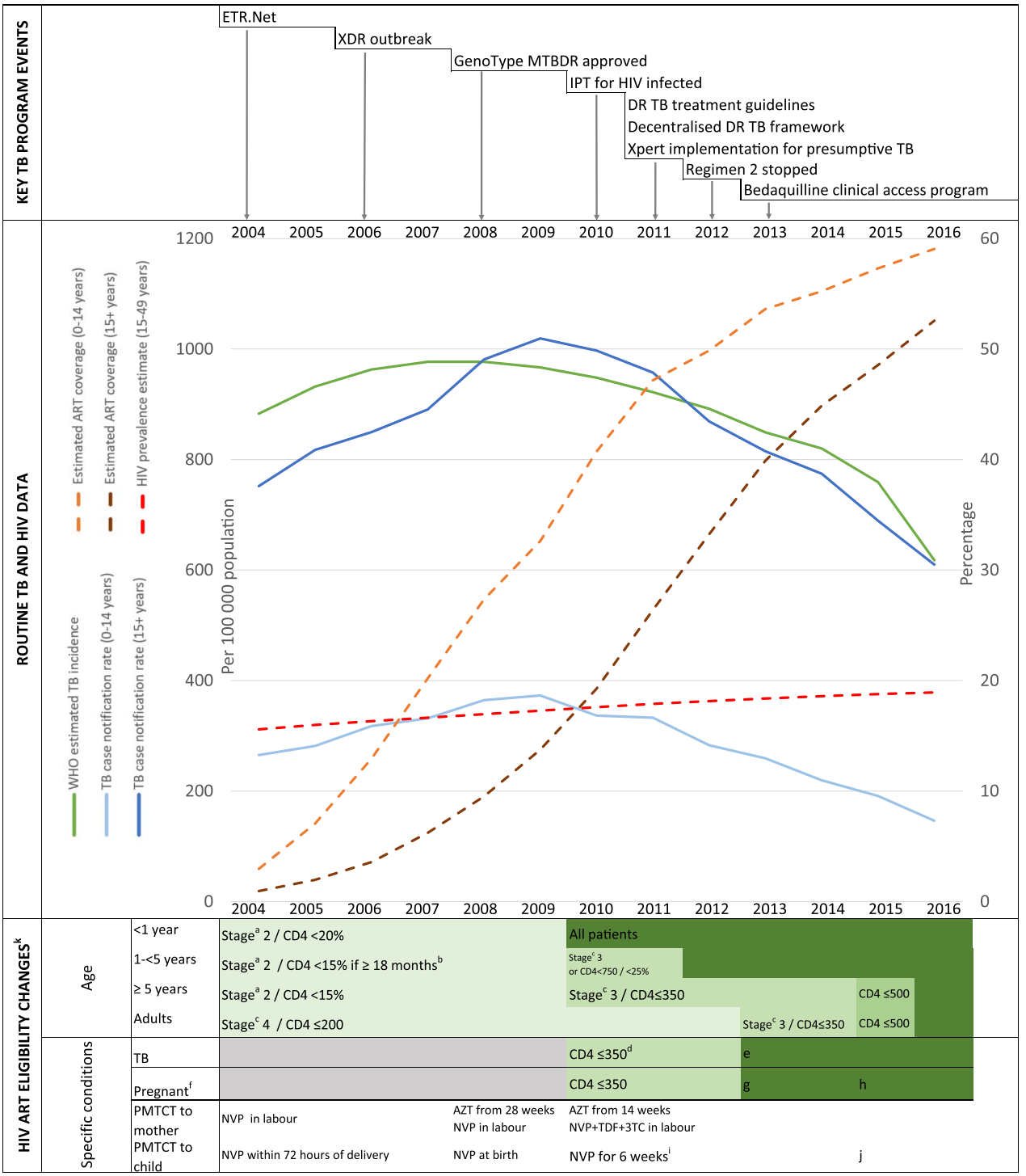


Figure Epidemiological changes in the adult and paediatric HIV and TB epidemics in South Africa in the context of key public health TB and HIV programme milestones, 2004–2016. [a]South Africa modified the WHO HIV clinical staging and excluded pulmonary TB from the classification of Stage 3 HIV. [b]Children between 12 and 18 months were eligible for ART with a CD4 <20%. [c]WHO clinical HIV staging. [d]Patients with MDR/XDR-TB were eligible irrespective of CD4 count. [e]Specific diseases mentioned extended from TB to include cryptococcal disease in 2013 and hepatitis B infection in 2015. [f]Includes pregnant or breastfeeding women. [g]In 2013 and 2014, pregnant women were eligible for ART, irrespective of CD4 count but women initiating ART with CD4 count > 350 cells/mm^3 and no other indication for ART were required to stop treatment 1 week after breastfeeding. [h]In 2015, pregnant or breastfeeding women were now eligible for lifelong ART and the definition of pregnant or breastfeeding women was expanded to include women up to 1 year post-partum. [i]The duration of NVP was determined by the maternal use of ART. NVP was given for 6 weeks or extended for the duration of breastfeeding if the mother was not on ART. [j]The duration of NVP was extended to 12 weeks or dual therapy (NVP/AZT) if maternal viral load suppression inadequate. [k]The HIV ART eligibility criteria are as documented in national guidelines. 3TC = lamivudine; ART = antiretroviral therapy; AZT = zidovudine; DR = drug resistance; ETR.Net = Electronic Tuberculosis Register; MDR = multidrug-resistant; NVP = nevirapine; PMTCT = prevention of mother-to-child transmission of HIV; TDF = tenofovir; XDR = extensively drug-resistant.

criteria for ART eligibility. Children had an earlier increase and overall greater ART uptake, possibly reflecting the lower numbers of children affected and initial eligibility criteria favouring the youngest children.

The HPTN 071 (PopART) trial, SEARCH in Kenya and the Botswana Combination Prevention Project in Botswana have shown equivocal results for the impact of universal test-and-treat strategies on HIV incidence at a population level.[16] As South Africa moves forward with a test-and-treat policy for HIV, the effect of this on the uptake of ART and national HIV and TB incidence will need to be carefully monitored. Ambitious 90-90-90 targets aim to have 73% of all HIV-infected patients virally suppressed and while the effectiveness and cost-effectiveness of this has been projected,[17] an evaluation of HIV trends over time, including ART adherence, will be critical as the policy is scaled up and sustained in South Africa.

TPT is a powerful tool to reach WHO's End TB Strategy of 90% reduction in TB incidence rate by 2035. As South Africa considers multiple preventive therapy regimens of shorter duration, the uptake and impact of TB preventive strategies in adults and children will need to be carefully evaluated.

Here, we have combined key milestones in the South African public health TB and HIV programmes for adults and children, and have used routine data to demonstrate the impact on the TB and HIV epidemics. Significant policy changes have taken place in South Africa, and these important milestones are presented in the context of the changing epidemiology of TB and HIV in South African adults and children.

M Osman[1]
K. du Preez[1]
P. Naidoo[1]
P. Bock[1]
H. Rabie[2]
S. S. Dlamini[3]
A. C. Hesseling[1]
[1]Desmond Tutu TB Centre
Department of Paediatrics and Child Health
Faculty of Medicine and Health Sciences, and
[2]Department of Paediatrics and Child Health
Tygerberg Hospital
Stellenbosch University
South Africa
[3]Research Information Monitoring
Evaluation & Surveillance (RIMES)
National TB Control & Management Cluster
National Department of Health
Pretoria, South Africa
e-mail: mosman@sun.ac.za

Acknowledgements

The authors would like to thank the South African Department of Health and the Research, Information, Monitoring, Evaluation and Surveillance (RIMES) unit of the National TB Programme, Pretoria, South Africa.

The work reported here was made possible through funding by the South African Medical Research Council (SA MRC; Cape Town, South Africa) through its Division of Research Capacity Development under the Bongani Mayosi National Health Scholars Programme from funding received from the Public Health Enhancement Fund/South African National Department of Health to MO. ACH is financially supported by the South African National Research Foundation (NRF) South African Research Chairs Initiative (SARChI). KDP is partly supported by this NRF SARChI grant to ACH. KDP also received salary support from the Fogarty International Center of the National Institutes of Health (Bethesda, MD, USA) under Award Number K43TW011006.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding bodies.

Conflicts of interest: none declared.

References

1 Suthar A B, et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. PLoS Med 2012; 9(7): e1001270.
2 Dodd P J, et al. The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis. Thorax 2017; 72(6): 559–575.
3 Simelela N P, Venter W D. A brief history of South Africa's response to AIDS. S Afr Med J 2014; 104(3 Suppl 1): 249–251.
4 Wood R, et al. Tuberculosis control has failed in South Africa - time to reappraise strategy. S Afr Med J 2011; 101(2): 111–114.
5 Kapp C. Profile Aaron Motsoaledi: South African Minister of Health. Lancet 2009; 374(9692): 776.
6 South African Government. Outline of the national HIV Counselling and Testing (HCT) campaign by Dr Aaron Motsoaledi, Minister of Health 2010. Cape Town, South Africa: Government of South Africa, 2010. https://www.gov.za/outline-national-hiv-counselling-and-testing-hct-campaign-dr-aaron-motsoaledi-minister-health. Accessed June 2020.
7 National Department of Health. Implementation of the universal test and treat strategy for HIV positive patients and differentiated care for stable patients. Pretoria, South Africa: NDoH, 2016.
8 World Health Organization. WHO monitoring of Xpert MTB/RIF roll-out 2016. Geneva, Switzerland: WHO, 2020. https://www.who.int/tb/areas-of-work/laboratory/mtb-rif-rollout/en/ Accessed June 2020.
9 World Health Organization. Implementing the WHO Stop TB Strategy: a handbook for national tuberculosis control programmes. WHO/HTM/TB/2008.401. Geneva, Switzerland: WHO, 2008.
10 Churchyard G J, et al. Tuberculosis control in South Africa: successes, challenges and recommendations. S Afr Med J 2014; 104(3 Suppl 1): 244–248.
11 Chiou S J, et al. Historical research into tuberculosis control strategies and the implications of mortality trends in Taiwan. Int J Tuberc Lung Dis. 2011; 15(8): 1033–1037.
12 World Health Organization. Global tuberculosis report, 2018. WHO/CDS/TB/2018.20. Geneva, Switzerland: WHO, 2018.
13 Szkwarko D, et al. Child contact management in high tuberculosis burden countries: A mixed-methods systematic review. PLoS One 2017; 12(8): e0182185.
14 Johnson L F, et al. Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: a mathematical modelling study. PLoS Med 2017; 14(12): e1002468.
15 World Health Organization. TB data: WHO's global TB database 2019. Geneva, Switzerland: WHO, 2019. https: // www.who.int/tb/data/en/. Accessed June 2020.
16 Abdool Karim S S. HIV-1 epidemic control — insights from test-and-treat trials. N Engl J Med 2019; 381(3): 286–288.
17 Walensky R P, et al. The anticipated clinical and economic effects of 90-90-90 in South Africa. Ann Intern Med 2016; 165(5): 325–333.

Where are we in the battle of ending tuberculosis in children and adolescents in South Africa?

To the Editor: Ambitious targets to end tuberculosis (TB) were set at the United Nations General Assembly High-Level Meeting (UNHLM) on TB in September 2018, with children and adolescents specifically noted as key populations deserving of more attention.[1] In addition, the World Health Organization (WHO) launched a revised 'Roadmap towards ending TB in children and adolescents',[2] outlining key actions that should be taken at country level to engage relevant stakeholders to optimally prevent and treat TB in these age groups.

In South Africa (SA), paediatric TB notifications (<15 years) declined steeply between 2015 and 2017 (29 137 in 2015, 20 546 in 2016 and 15 628 in 2017).[3] This fall could be due either to a true decline in cases or to a smaller proportion of cases being found. In 2018, SA reported 17 561 cases to the WHO,[3] a 12% increase from 2017 and probably due to the national 'finding the missing TB cases campaign' that was implemented in SA in 2018.

The WHO uses mathematical modelling to estimate the TB burden at both global and national level. In 2018, the WHO estimated that 27 000 children (<15 years; 95% confidence interval 18 000 - 36 000) developed TB in SA.[3] Despite the 2018 increase in notifications, these estimates suggest that the SA childhood TB case detection rate is still only 65%, leaving a third of children with TB in SA undiagnosed or unreported.

At the UNHLM, SA committed to diagnose and treat 95 500 children between 2018 and 2022 (Fig. 1).[4] Although SA achieved 96% of its target for 2018, services will need to be strengthened if it is to keep up with these commitments and improve case detection. To achieve this, the country will need better diagnostics for young children, non-invasive and point-of-care microbiological sampling and testing for all children, and more training to empower healthcare workers to make clinical diagnoses. Following diagnosis, it is also essential to ensure accurate and complete reporting of all cases. Sub-national analyses of routine TB data can additionally provide information on where interventions are most needed.

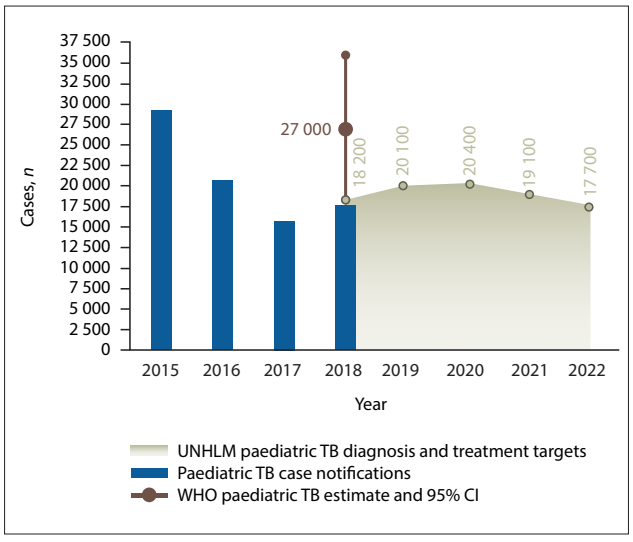


Fig. 1. National paediatric (<15 years) TB case notifications, WHO burden of disease estimates and committed UNHLM paediatric TB diagnosis and treatment targets for South Africa. (TB = tuberculosis; WHO = World Health Organization; UNHLM = United Nations General Assembly High-Level Meeting; CI = confidence interval.)

TB preventive therapy (TPT) is a safe and effective strategy to prevent TB disease in children following exposure.[5] At the UNHLM, SA committed to provide TPT to 206 510 child contacts aged <5 years.[4] SA is shortly to roll out shorter TPT regimens, and if this approach is coupled with strengthened TB contact management and PT implementation,[6] it could drastically reduce the burden of TB disease among children and adolescents.

The lack of surveillance data on adolescents (10 - 19 years) with TB remains a concern. Despite being recognised as a vulnerable group, they are 'missing' in the age bands currently reported, being included either with children in the 5 - 14-year age band or with adults in the 15 - 24-year age band.[7] SA has a strong TB surveillance system, allowing age-disaggregated reporting at a much more granular level. The country should either revise the current age bands or report adolescents separately if service provision to this age group is to be evaluated properly.

On 24 March, we commemorated World TB Day. Each year, this represents an opportunity to reflect on the promises made for children and adolescents, to evaluate progress, and to identify future priorities.

Author contributions. KdP and JAS developed the idea and produced the first draft. All authors reviewed the drafts and provided valuable input. All authors reviewed and approved the final version.

Funding. KdP is supported by the Fogarty International Center of the National Institutes of Health under Award No. K43TW011006. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. ACH is financially supported by the South African National Research Foundation (NRF) South African Research Chairs Initiative (SARChI). KdP is partly supported by this NRF SARChI grant to ACH. The financial assistance of the NRF towards this research is hereby acknowledged. The opinions expressed and conclusions arrived at are those of the authors and are not necessarily to be attributed to the NRF.

Conflicts of interest. None.

K du Preez
Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
karen_dupreez@sun.ac.za

J A Seddon
Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; and Department of Infectious Diseases, Imperial College London, UK

H S Schaaf
Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; and Department of Paediatrics and Child Health, Tygerberg Hospital, Cape Town, South Africa

A C Hesseling
Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

1. Political Declaration of the United Nations General Assembly High-Level Meeting on Ending TB. 26 September 2018, New York. Geneva: World Health Organization, 2018. https://www.who.int/tb/unhlmonTBDeclaration.pdf (accessed 16 March 2020).
2. World Health Organization. Roadmap towards ending TB in children and adolescents. 2nd ed. Geneva: WHO, 2018. http://apps.who.int/iris/bitstream/handle/10665/275422/9789241514798-eng.pdf?ua=1 (accessed 16 March 2020).
3. World Health Organization. TB Data: WHO's global tuberculosis database 2019. https://www.who.int/tb/data/en/ (accessed 30 March 2020).
4. United Nations High-Level Meeting on TB: Country targets for childhood TB diagnosis and treatment. http://www.stoptb.org/resources/countrytargets/ (accessed 16 March 2020).
5. Ayieko J, Abuogi L, Simchowitz B, Bukusi EA, Smith AH, Reingold A. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: A meta-analysis. BMC Infect Dis 2014;14:91. https://doi.org/10.1186/1471-2334-14-91
6. Szkwarko D, Hirsch-Moverman Y, du Plessis L, du Preez K, Carr C, Mandalakas AM. Child contact management in high tuberculosis burden countries: A mixed-methods systematic review. PLoS One 2017;12(8):e0182185. https://doi.org/10.1371/journal.pone.0182185
7. Snow KJ, Cruz AT, Seddon JA, et al. Adolescent tuberculosis. Lancet Child Adolesc Health 2020;4(1):68-79. https://doi.org/10.1016/S2352-4642(19)30337-2

S Afr Med J. Published online 26 March 2020. https://doi.org/10.7196/SAMJ.2020.v110i5.14728

CHAPTER 3: THE IMPACT OF THE EVOLVING HIV RESPONSE ON THE EPIDEMIOLOGY OF TUBERCULOSIS IN SOUTH AFRICAN CHILDREN AND ADOLESCENTS

The electronic tuberculosis (TB) treatment register (ETR.Net) and electronic drug-resistant register (EDRWeb) are the primary sources of routine TB surveillance data in South Africa, and are captured from TB treatment registers at TB reporting units, mostly primary healthcare (PHC) facilities, but also from hospitals in some provinces. Case notification data from ETR.Net and EDRWeb reflects TB treatment surveillance, and can therefore inform pillar 4 of the TB care cascade: 'Notified and treated', while TB treatment outcome data from these registers can be used to inform pillar 5: 'Treatment success'.

The Desmond Tutu TB Centre (DTTC) in the Department of Paediatrics and Child Health, Faculty of Medical and Health Sciences, Stellenbosch University has been collaborating closely with the National Department of Health (NDOH) to evaluate TB control from 2004 to 2016 in South Africa. As the majority (>95%) of TB cases in South Africa are treated for drug-susceptible (DS)-TB[1], the initial focus of this collaborative work has been on ETR.Net. As part of this work, the DTTC has been collaborating closely with the NDOH to develop standardised data management practices and to make national TB surveillance data more accessible. Serial ETR.Net data extractions were merged and underwent extensive cleaning and deduplication at the DTTC, resulting in a unique database of all patients reported as starting DS-TB treatment in South Africa from 2004 to 2016 (~4.5 million cases), with this database curated at the DTTC. This dataset also provided historical TB data as resource to the NDOH during the 2019 South African TB epidemiological review conducted by the World Health Organisation (WHO).

I was able to access this national ETR.Net dataset spanning 13 years of data (2004 to 2016) as a resource to characterize paediatric TB treatment surveillance. This very large, individual patient-level dataset provided a unique opportunity to investigate temporal trends of TB and HIV along the continuum of age in children and adolescents, and in the context of the evolving TB and HIV programmes in South Africa. My analysis was specifically aimed at informing pillar 4 ('Notified and treated') of the paediatric TB care cascade, and included 719,400 newly registered 0-19-year-olds. Both the risk of TB and the risk of HIV infection varies with age and by gender.[3, 8, 10] Given this intricate relationship between TB, HIV, age and gender, I also investigated the association between HIV co-infection, age and gender amongst children and adolescents treated for TB using multivariable logistic regression.

The burden of TB, TB case notification rates (CNRs) and the prevalence of HIV co-infection varied substantially by age. Incidence rate ratios (IRRs) of age- and HIV-stratified TB case notification rates are presented in table 3.1. TB CNRs in all age groups declined since 2009, but was largely driven by the trend observed in 0-4-year-olds. Both the decrease in HIV prevalence in this age group, and reduced *Mycobacterium tuberculosis (M.tb)* transmission to young children due to overall decreases in TB incidence following widespread roll-out of antiretroviral therapy (ART) likely contributed to the observed steep decline amongst 0-4-year-olds. The slow decline of TB CNRs in adolescents and young HIV-infected children is however concerning. Interventions are needed to improve TB control in these vulnerable sub-groups. Understanding how TB affects children beyond the current WHO-recommended broad age bands (<5 and 5-14 years of age) and by gender, can assist with paediatric TB monitoring and evaluation and inform more targeted TB control strategies in children and adolescents.

Table 3.1 Incidence rate ratios (IRRs) of age- and HIV-stratified TB case notifications in South Africa

	Overall 2016 vs. 2009		HIV-uninfected 2016 vs. 2013		HIV-infected 2016 vs. 2013	
	IRR	95%CI	IRR	95%CI	IRR	95%CI
0-4 years	0.41	0.40 - 0.42	0.66	0.64 - 0.67	0.90	0.85 - 0.95
5-9 years	0.28	0.27 - 0.29	0.56	0.53 - 0.58	0.57	0.53 - 0.61
10-14 years	0.54	0.52 - 0.57	0.80	0.75 - 0.84	0.68	0.64 - 0.73
15-19 years	0.73	0.71 - 0.74	0.89	0.86 - 0.92	0.84	0.80 - 0.88

Recording of International Classification of Disease-10 (ICD-10) codes and the level of the healthcare reporting unit (i.e. primary healthcare facility vs. hospital) at an individual level, also allowed me to start evaluating the spectrum of TB disease and the level of health care as the source of TB reporting within pillar 4 of the TB care cascade: 'Notified and treated'. Overall, 9% of children had only extra-pulmonary TB and only 2% had disseminated TB (TB meningitis or miliary TB). Hospitals reported 28% of all children and adolescents, but in KwaZulu-Natal, the only high TB burden provinces where all hospitals routinely report on TB data, 54% of all children and adolescents were reported from hospitals. This data highlight the high burden of paediatric TB cases diagnosed at hospital level, and the importance of ensuring that all hospital data are also included in routine TB surveillance data.

The recording of key HIV indicators in relation to the TB episode was not always captured consistently in ETR.Net. Small changes to standardise and improve the relevant HIV indicators, such as the date of HIV diagnosis, the timing and type of ART initiation and adherence (including viral load) in relation to the TB episode, could enhance monitoring and evaluation of TB control in HIV-infected children using routine surveillance data.

This study highlighted the value of evaluating epidemiological trends within one pillar of the TB care cascade and disaggregating TB incidence and HIV prevalence by using narrower age bands, in the context of the overall changes in TB and HIV programmes. I showed that stratified trends in CNRs provides a useful approach to monitoring and evaluation of paediatric TB, helping the programme to identify the most vulnerable groups and respond accordingly. The care cascade could also be a useful framework to evaluate data for specific paediatric sub-populations, such as very young children or adolescents, or by HIV infection status, if reliable data is available.

Future work should include age- and HIV-stratified analyses using data from KwaZulu-Natal, the only high-burden province where all hospitals currently report TB data, to determine estimates of the percentage of hospital-diagnosed cases in each age group and by HIV status. These estimates could inform estimates for pillar 3 ('Diagnosed with TB') in provinces where hospitals do not report TB data. EDRWeb cleaning and preparation is currently ongoing. Future work should also include evaluation of national epidemiological trends in drug resistant TB amongst children and adolescents. In addition, more in-depth analysis of TB treatment outcomes using this dataset will provide critical information on pillar 5 ('Treatment success').

Citation

Du Preez K, Osman M, Seddon JA, Naidoo P, Schaaf HS, Dunbar R, Mvusi L, Dlamini S, Hesseling AC. The impact of the evolving HIV response on the epidemiology of tuberculosis in South African children and adolescents. *Submitted to Clinical Infectious Diseases on 4 September 2020, and is currently under review*.

Title

The impact of the evolving HIV response on the epidemiology of tuberculosis in South African children and adolescents

Authors:

Karen du Preez (MSc)[1], Muhammad Osman (MSc)[1], James A. Seddon (PhD)[1,2], Pren Naidoo (PhD)[1], H. Simon Schaaf (PhD)[1], Zahn Munch (PhD)[3], Rory Dunbar (PhD)[1], Lindiwe Mvusi (MBChB)[4], Sicelo S. Dlamini (MPH)[5], Anneke C. Hesseling (PhD)[1]

Affiliations:

1. Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
2. Department of Infectious Diseases, Imperial College London, United Kingdom
3. Department of Geography and Environmental Studies, Stellenbosch University, Stellenbosch, South Africa
4. National TB Control & Management Cluster, National Department of Health, South Africa
5. Research Information Monitoring, Evaluation & Surveillance (RIMES), National TB Control & Management Cluster, National Department of Health, South Africa

Running head: Child and adolescent TB in South Africa

Abstract word count: 247/250 **Full text word count:** 2988/3000

Number of references: 32

Keywords: Tuberculosis; HIV; Children; Adolescents; South Africa

Corresponding author email and full address:

Dr Karen du Preez, MBChB, MSc (Epi)

E-mail: karen_dupreez@sun.ac.za; Telephone: +27219389173; +27845811785

Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie van Zijl Drive, Parow, 7505, South Africa.

Alternative contact author:

Dr Muhammad Osman

Email: mosman@sun.ac.za; Telephone: +27 83 556 9838

Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie van Zijl Drive, Parow, 7505, South Africa.

Summary: (40 words)

Tuberculosis surveillance data from South Africa provide a unique opportunity to study epidemiological trends and explore the association between age, HIV co-infection and sex in >700,000 children and adolescents (<20 years) in the context of an evolving HIV epidemic.

Abstract

Background

There are limited approaches to evaluate tuberculosis control in children and adolescents. Large-scale routine tuberculosis surveillance data provide a unique opportunity to evaluate trends over time and the relationship between tuberculosis, HIV, age and sex.

Methods

All children and adolescents (0-19 years) routinely treated for drug-susceptible tuberculosis in South Africa and recorded in a de-duplicated national electronic tuberculosis treatment register (2004-2016) were included. Age- and HIV-stratified tuberculosis case notification rates (CNRs) were calculated in four age bands: 0-4, 5-9, 10-14 and 15-19 years. The association between tuberculosis/HIV co-infection and age was evaluated using multivariable logistic regression.

Results

Of 719,400 children and adolescents included, 339,112 (47%) were 0-4-year-olds. The overall tuberculosis CNR for 0-19-year-olds declined by 54% from a peak in 2009 to 2016. Trends varied by age and HIV, with the lowest percentage-point reductions (2009-2016) observed in adolescents (aged 10-14: 46% and 15-19: 27%). Reductions in HIV-stratified tuberculosis CNRs (2013-2016) were the lowest in HIV-infected 0-4-year-olds (10%) and both HIV-infected (16%) and HIV-uninfected (11%) 15-19-year-olds. Sex disparity in adolescence was most pronounced in 15-19-year-olds: female:male ratio=1.84 (aOR[females]=2.49, 95%CI: 2.38-2.60] and aOR[males]=1.35, 95%CI: 1.29-1.42).

Conclusions

South Africa's national response to the HIV epidemic has made a substantial contribution to the observed declining trends in tuberculosis CNRs in children and adolescents. The slow decline of tuberculosis CNRs in adolescents and young HIV-infected children is concerning. Understanding how tuberculosis affects children beyond the conventional age bands and by sex, can inform targeted tuberculosis control strategies in children and adolescents.

Background

More than 1.5 million children and adolescents are estimated to develop tuberculosis (TB) each year.[1, 2] Despite TB being preventable and treatable, the World Health Organization (WHO) estimates that 233,000 children (<15 years), died from TB in 2017.[3] South Africa, one of the high TB burden countries, had an estimated TB incidence rate of 520/100,000 population in 2018[1] and an estimated national HIV prevalence of 14.0% in 2017.[4] Despite an initial slow response to the HIV epidemic in South Africa, substantial efforts were made from 2009 to reduce HIV transmission, including to children, with sequential changes to national guidelines leading to progressive roll-out of antiretroviral therapy (ART).[5] All HIV-infected infants became eligible for ART in 2010, and all young children (<5 years) in 2012.[6, 7] Since 2016, all HIV-infected individuals in South Africa have been eligible for ART under the universal-test-and-treat policy.[8]

The risk of developing TB varies substantially with age and HIV status. The risk of progression from *Mycobacterium tuberculosis* infection to disease is the highest in young children, falls to a nadir in pre-pubertal children, and then rises again through adolescence.[9] HIV infection increases this risk of developing TB by approximately 8-fold, with ART reducing the risk by approximately 70%.[10] Adolescents (10-19-year-olds) have also been identified as a vulnerable population, especially if HIV-infected.[2, 11, 12] In addition, there is some evidence that the age-related risk of TB in children and adolescents varies by gender.[13]

The prevalence of HIV and the risk of HIV acquisition also changes with age. For young children, the risk of acquiring HIV is primarily through vertical transmission, either perinatally or during infancy (breastfeeding). During adolescence, the risk of HIV infection due to horizontal transmission rises into young adulthood, with adolescent females being at higher risk of becoming HIV-infected than their male counterparts.[14] With the widespread roll-out of ART to HIV-infected children, an increasing number of perinatally-infected individuals, born during the early stages of the HIV epidemic, have survived into adolescence.[15] HIV-infected adolescents are at high risk of attrition in routine HIV care services,[16] which may further increase their risk of developing TB if not on ART.[10]

Given the intimate relationship between HIV and TB, it would be expected that the progressive roll-out of ART in South Africa would have produced a substantial decrease in TB case notification rates (CNRs) in children and adolescents, correlating with the decline in TB incidence in adults.

However, it is important to evaluate the interaction between TB, HIV, and age since both the risk of TB and HIV is influenced by age. One of the strengths of South Africa's National TB Programme was the implementation of an individual case-based, electronic TB register (ETR.Net) for surveillance of all treated drug-susceptible TB cases since 2004, allowing in-depth age-disaggregated analyses over time. This source of surveillance data provide a unique opportunity to evaluate the relationship between TB, HIV and age and review trends in TB notification rates (a proxy for TB incidence) over time. In this study, we undertook epidemiological analyses of TB trends in South African children and adolescents by four 5-year age bands in the context of routine programmatic changes in the HIV programme over more than a decade. We also investigated the relationship between HIV infection and age in children and adolescents with TB.

Methods

Study design

This was a retrospective cohort study of all newly registered children and adolescents (0-19 years) routinely recorded in the South African national ETR.Net as the drug-susceptible case-finding cohort from 2004 to 2016.

Setting

South Africa had an estimated population of 58 million people in 2018 and is divided into 9 provinces. In 2017, the estimated national HIV prevalence among pregnant women attending routine ante-natal services was 30.7%[17], and amongst infants 2.7%.[4]

Electronic TB treatment register

Routine data for drug-susceptible TB have been captured electronically in the ETR.Net from paper-based TB treatment registers at all designated TB reporting units, allowing facility, district, provincial and national reporting on case-finding, sputum conversion and treatment outcome cohorts since 2004.[18, 19] These data are also used for annual reporting of national TB surveillance data to WHO.

During the study period, TB data were collected and managed by the National Department of Health through the Research, Information, Monitoring, Evaluation and Surveillance (RIMES) unit. Back-end data from ETR.Net were extracted for the period 2004 to 2016 and underwent a systematic data cleaning and de-duplication process.

Definitions

Children and adolescents were divided into four 5-year age-bands (0-4, 5-9, 10-14 and 15-19), to determine the burden of TB and HIV amongst children and adolescents across the age spectrum. HIV status was classified as HIV-uninfected, HIV-infected, and HIV-unknown, constructed using documented HIV testing results, CD4 results, and cotrimoxazole or ART use from the ETR.Net. The term 'newly treated' refers to TB patients who had never been reported to have been previously treated, or who had previously received <4 weeks of TB treatment. The site of TB disease was categorised by treating clinicians as per national guidelines and distinguished only between any pulmonary TB (PTB; with or without extra-pulmonary TB [EPTB]), or EPTB exclusively. Intra-thoracic lymphadenopathy, common in children, is considered PTB in the national programme.[20] International classification of disease (ICD) 10 codes referring to miliary TB and central nervous system TB, including TB meningitis, were combined and classified as 'disseminated TB'. A bacteriologically confirmed TB diagnosis included any positive smear/culture/Xpert MTB/RIF (Xpert; Cepheid, Sunnyvale, CA) result on at least one specimen prior to treatment initiation.

Statistical Analyses

Population estimates from the Thembisa model (a mathematical model of the South African HIV epidemic and a publicly available data source containing both age-disaggregate HIV and general population statistics)[21] were used to calculate 1) age-disaggregated TB CNRs overall and by HIV status, and 2) national age-specific HIV prevalence estimates. All HIV analyses were restricted to years where >80% of patients had a known HIV status in all age groups. HIV-stratified TB CNR calculations excluded TB cases with an unknown HIV status, and were expressed as per 100,000 population using the HIV-infected and HIV-uninfected Thembisa model population estimates.[21] Overall and HIV-stratified percentage-point reductions in TB CNRs were calculated for each age group.

Univariable and multivariable logistic regression were used to calculate odds ratios (ORs), adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of the relationship between clinical characteristics and HIV infection, excluding patients with HIV-unknown status. We completed age- and sex-stratified analyses of the prevalence of HIV co-infection, and included an interaction term in the multivariable model to account for the observed effect modification of sex and age on the risk of HIV infection. All variables with an independent association in univariable analyses were included in the multivariable model. Due to the collinearity between 1) site of TB disease and the presence of disseminated disease, and 2) bacteriological investigation and bacteriological confirmation status only, the variable with the strongest association of each was included in the multivariable model. Analyses were completed using STATA SE version 14 (StataCorp, College Station, TX, USA).

Ethics

Stellenbosch University Health Research Ethics Committee provided ethics approval (N16/07/088); permission for the use of ETR.Net data was provided by the National Department of Health of South Africa.

Results

Clinical characteristics stratified by age

A total of 719,400 children and adolescents with drug-susceptible TB were treated and reported in South Africa during 2004-2016 (Table 1). Overall, differences by sex were not observed, with 368,885 (51.3%) of TB cases occurring amongst females. However, the proportion of females increased with age. HIV status was only recorded for 339,177 (47.1%) cases and a low proportion reported previous TB treatment (35,566; 4.9%). Most had PTB (654,533; 91.0%) while 2.0% (13,057) had disseminated TB. Bacteriological investigation was recorded in 221,771 (30.8%) of whom 154,255 (69.6%) had a confirmed diagnosis. The proportion who had bacteriological investigations performed and who had bacteriologically confirmed TB increased with age.

Table 1. Patient characteristics stratified by age group for all children and adolescents (0-19 years) with newly registered drug-susceptible tuberculosis reported in the ETR.Net 2004-2016 *(*n=719 400*)*

	0-4 years		5-9 years		10-14 years		15 - 19 years		Total	
	339 112	%	131 536	%	72 824	%	175 928	%	719 400	%
Sex[1]										
Male	177 439	52.3	66 458	50.5	32 558	44.7	74 056	42.1	350 511	48.7
Female	161 669	47.7	65 078	49.5	40 266	55.3	101 872	57.9	368 885	51.3
HIV status										
HIV-uninfected	116 141	34.2	34 535	26.3	19 244	26.4	66 655	37.9	236 575	32.9
HIV-infected	33 490	9.9	22 959	17.5	17 388	23.9	28 765	16.4	102 602	14.3
HIV unknown	189 481	55.9	74 042	56.3	36 192	49.7	80 508	45.8	380 223	52.9
TB treatment history[1]										
New	331 005	97.6	124 317	94.5	67 629	92.9	160 880	91.4	683 831	95.1
Retreatment	8 105	2.4	7 218	5.5	5 195	7.1	15 048	8.6	35 566	4.9
Site of TB Disease[1]										
PTB with/without EPTB	317 815	93.7	119 293	90.7	62 089	85.3	155 336	88.3	654 533	91.0
EPTB only	21 296	6.3	12 241	9.3	10 735	14.7	20 592	11.7	64 864	9.0
Disseminated TB[1]										
None	299 727	98.4	114 676	97.7	62 420	96.8	152 884	97.8	629 707	98.0
Present	4 966	1.6	2 671	2.3	2 036	3.2	3 384	2.2	13 057	2.0
Bacteriological investigation										
Not completed	314 031	92.6	104 536	79.5	31 048	42.6	48 014	27.3	497 629	69.2
Completed	25 081	7.4	27 000	20.5	41 776	57.4	127 914	72.7	221 771	30.8
Bacteriological status										
Bacteriologically confirmed	10 473	3.1	12 940	9.8	27 113	37.2	103 729	59.0	154 255	21.4
Clinically diagnosed	328 639	96.9	118 596	90.2	45 711	62.8	72 199	41.0	565 145	78.6

[1] Missing values for the following variables: sex (n=4), TB treatment history (n=3), site of disease (n=3) and disseminated TB (n=76,636)

ETR.Net=electronic tuberculosis treatment register; EPTB=Extra-pulmonary tuberculosis; PTB=Pulmonary tuberculosis; TB=Tuberculosis.

Burden and trends of TB and HIV co-infection over time

A similar trend was seen in the total number of TB cases and the overall national TB CNR in those <20 years, peaking in 2009 with a steady decline thereafter. The 0-4-year age group consistently contributed the most cases each year, followed by the 15-19-year-olds (Figure 1). TB CNRs were highest in the 0-4-year-olds (peak 2008: 635/100,000 population) and peaked in all age groups between 2008 and 2009 (Figure 2).

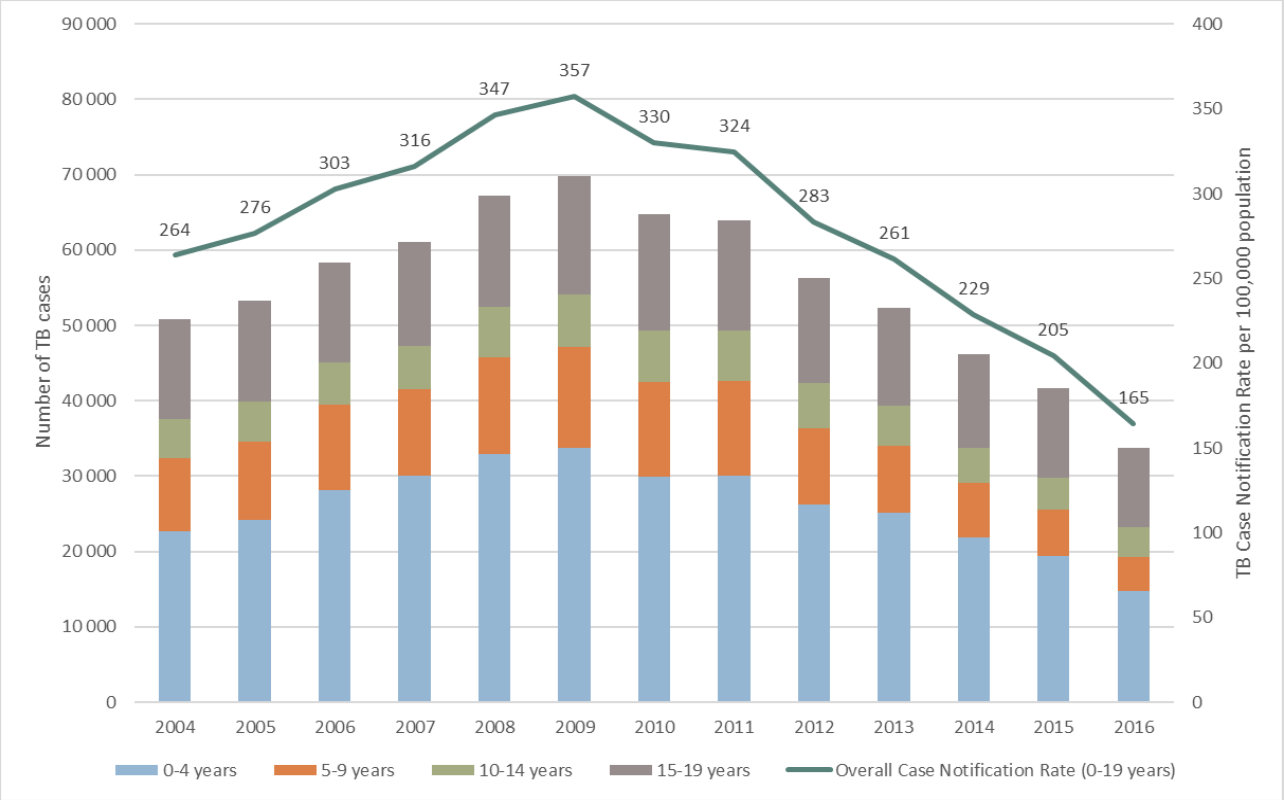


Figure 1. Overall tuberculosis case notification rate (0-19 years) and total number of reported childhood and adolescent tuberculosis cases in South Africa over time

TB=Tuberculosis

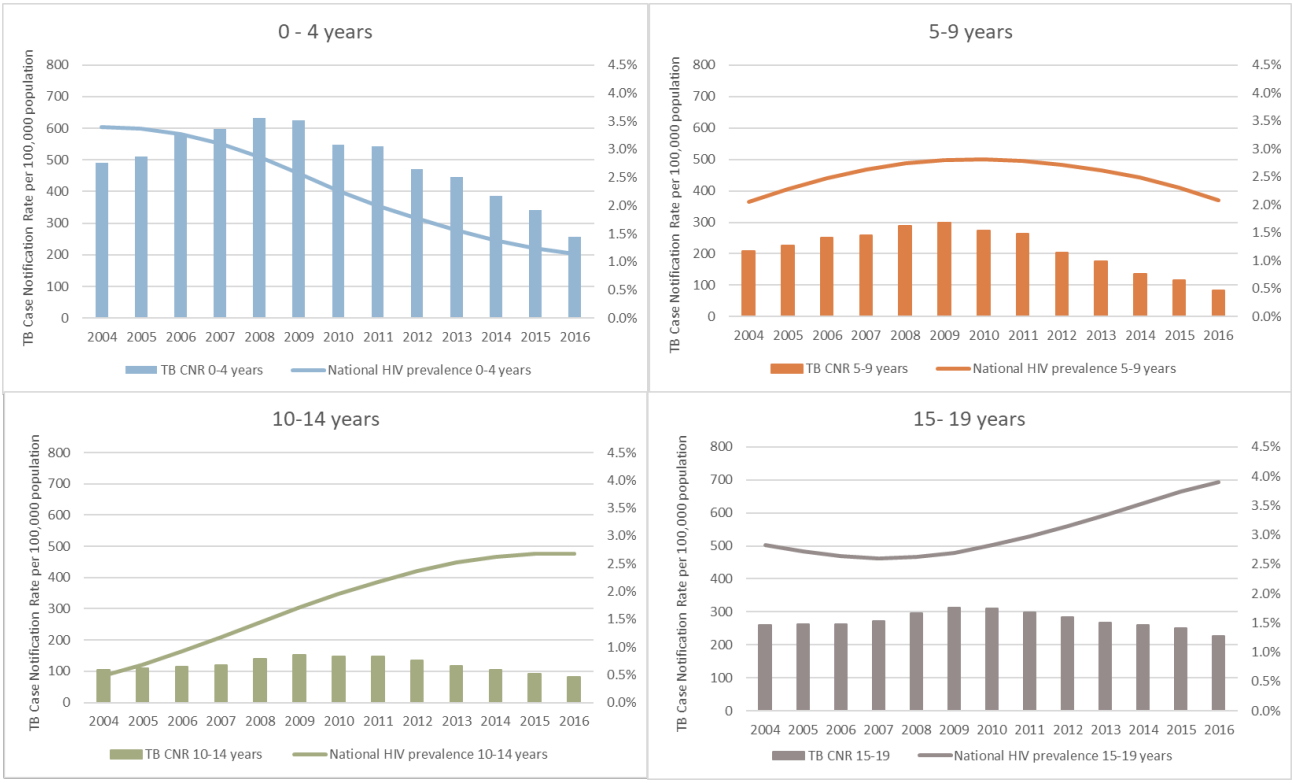


Figure 2. Tuberculosis case notification rates and estimated national HIV prevalence[1] in South Africa for each age band over time (2004-2016)

[1]HIV prevalence is calculated from the THEMBISA model and estimates HIV prevalence across the total population (reference nr 21). CNR=Case notification rate; TB=Tuberculosis.

The uptake of HIV testing improved in all age groups over time, with HIV status reported for >80% of children and adolescents with TB in each age group from 2013. The HIV prevalence amongst children and adolescents with TB varied substantially between the 4 age groups, with the overall percentage HIV co-infected in 2016 being 15% in 0-4-year-olds, 27% in 5-9-year-olds, 43% in 10-14-year-olds and 30% in 15-19-year-olds (Figure 3).

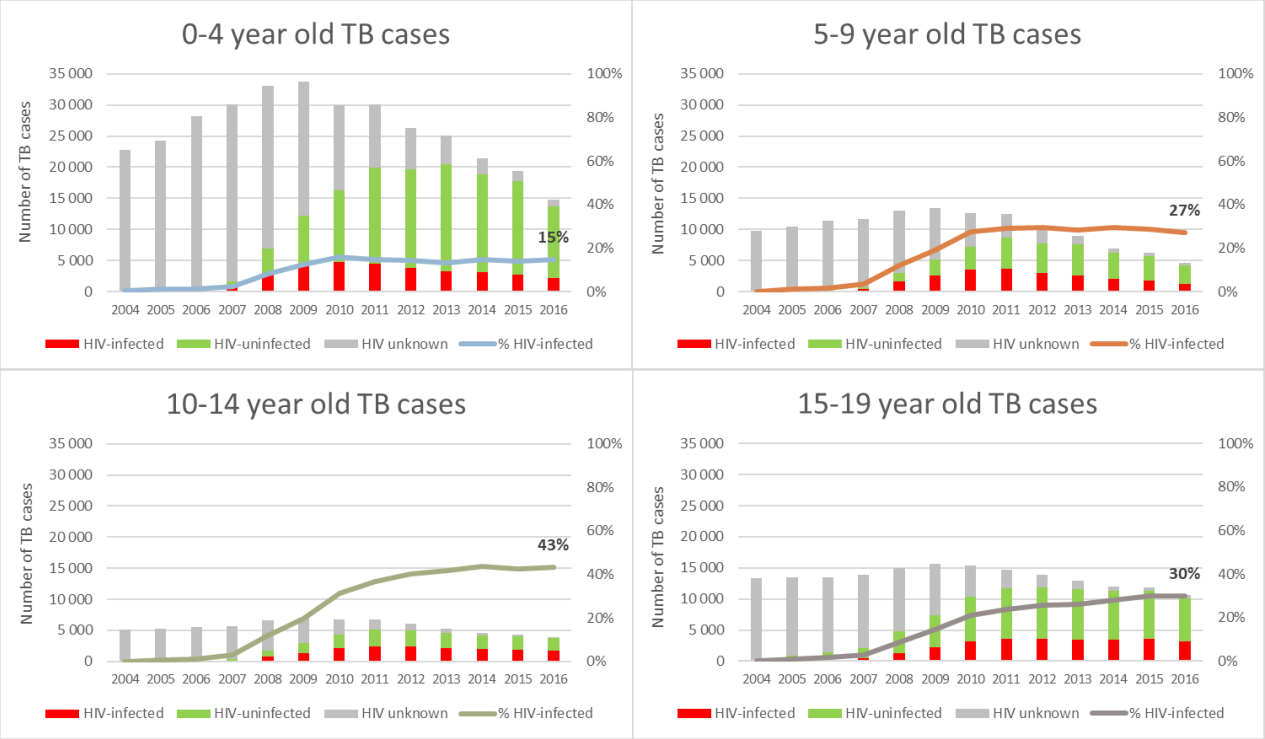
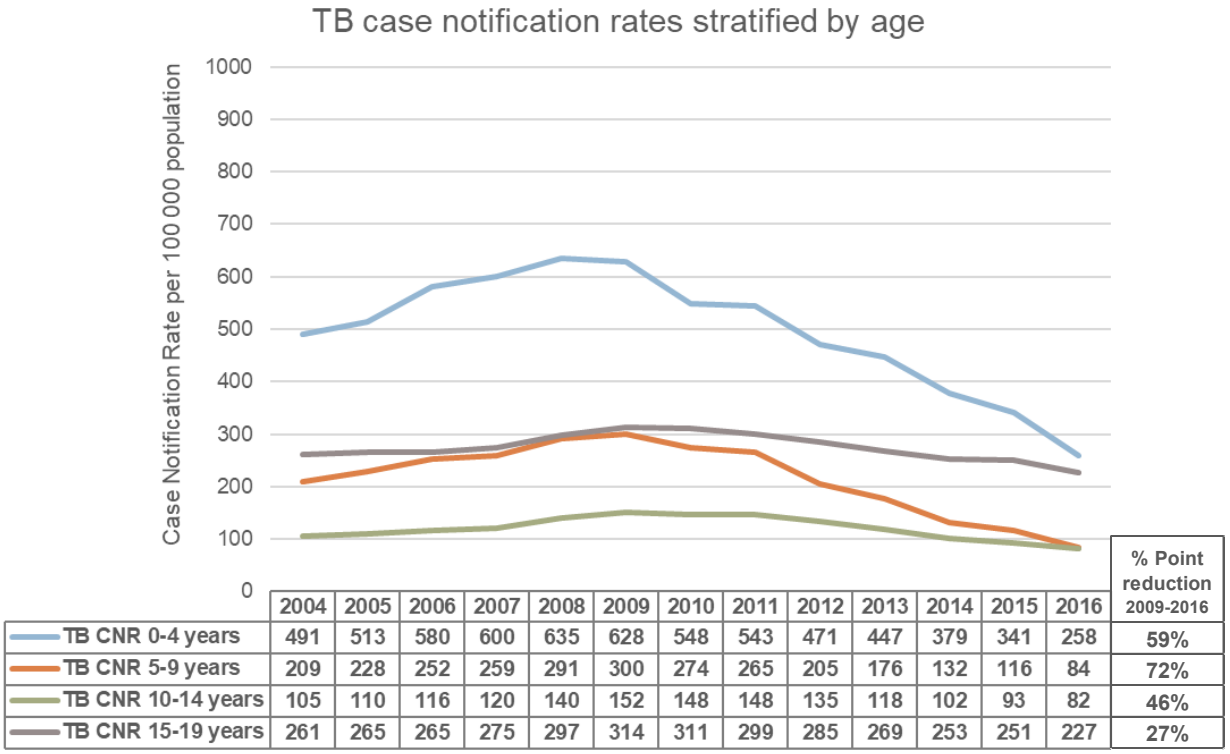


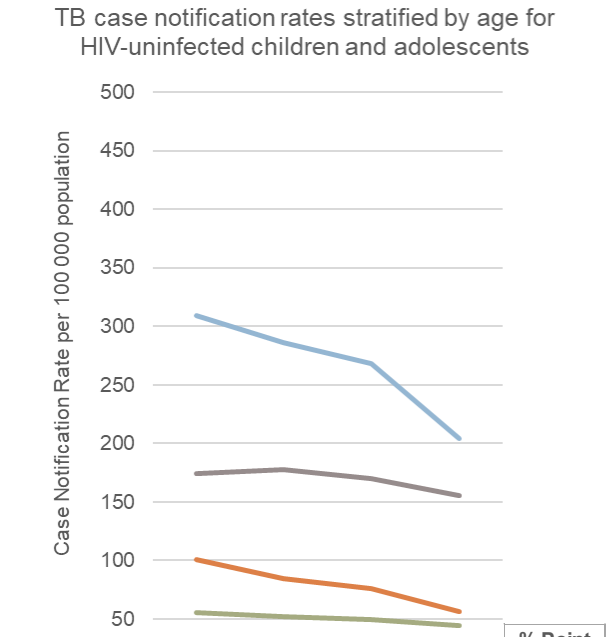
Figure 3. Uptake of HIV testing, HIV status and overall percentage HIV co-infected amongst children and adolescents treated for drug-susceptible tuberculosis in South Africa over time

TB=Tuberculosis

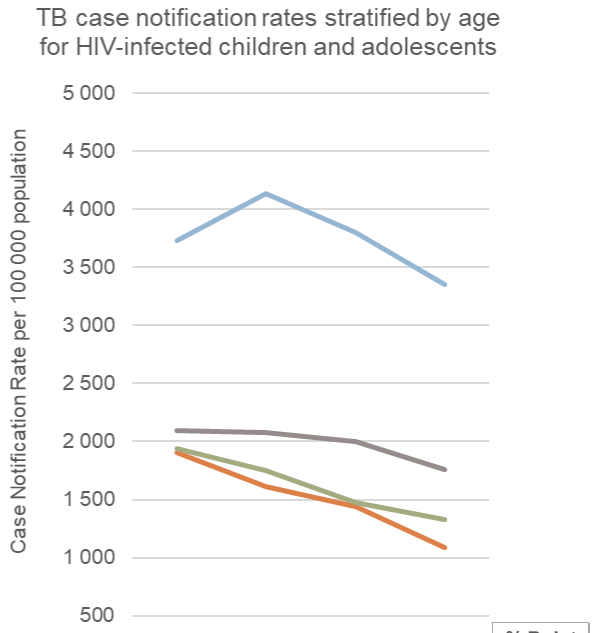
The percentage-point reduction in TB CNRs between 2009 and 2016 was the largest in 5-9-year-olds (72%) and smallest in 15-19-year-olds (27%) (Figure 4). The largest percentage-point reduction in HIV-stratified TB CNRs between 2013 and 2016 was also observed in 5-9-year-olds (HIV-uninfected: 44%; HIV-infected: 43%). Both HIV-uninfected and HIV-infected 15-19-year-olds experienced small percentage-point reductions in TB CNRs (11% and 16% respectively). The percentage-point reduction in TB CNR amongst HIV-uninfected 0-4-year-olds was more than three times the percentage-point reduction of TB CNR in HIV-infected 0-4-year-olds (34% vs. 10%).



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	% Point reduction 2009-2016
TB CNR 0-4 years	491	513	580	600	635	628	548	543	471	447	379	341	258	59%
TB CNR 5-9 years	209	228	252	259	291	300	274	265	205	176	132	116	84	72%
TB CNR 10-14 years	105	110	116	120	140	152	148	148	135	118	102	93	82	46%
TB CNR 15-19 years	261	265	265	275	297	314	311	299	285	269	253	251	227	27%



	2013	2014	2015	2016	% Point reduction 2013-2016
0-4 HIV-	310	286	268	204	34%
5-9 HIV-	101	85	76	56	44%
10-14 HIV-	56	52	50	44	20%
15-19 HIV-	175	177	170	156	11%



	2013	2014	2015	2016	% Point reduction 2013-2016
0-4 HIV+	3 731	4 133	3 799	3 352	10%
5-9 HIV+	1 901	1 608	1 441	1 085	43%
10-14 HIV+	1 940	1 747	1 473	1 327	32%
15-19 HIV+	2 094	2 081	2 002	1 760	16%

Figure 4. Tuberculosis case notification rates over time overall and stratified by HIV status and age[1]

[1]HIV-stratified TB CNRs excluded cases with an unknown HIV status

Percentage-point reduction = ((2009 CNR - 2016 CNR)/2009 CNR)%

**HIV-stratified percentage-point reduction = ((2013 CNR-2016 CNR)/2013 CNR)*%

CNR=Case notification rate; TB=Tuberculosis.

The association between HIV infection, age and sex

Since 2013, 173,909 children and adolescents were treated for TB: 40,422 (23.2%) HIV-infected and only 17,511 (10.1%) with an unknown HIV status (Table 2).

Table 2. Patient characteristics stratified by HIV status for all children and adolescents (0-19 years) with newly registered drug-susceptible tuberculosis reported in the ETR.Net 2013-2016 (*n=173 909*)

	HIV-uninfected		HIV-infected		HIV unknown		Total	
	n=115 976	%	n=40 422	%	n=17 511	%	n=173 909	%
Sex								
Male	58 411	50.4	18 384	45.5	8 929	51.0	85 724	49.3
Female	57 565	49.6	22 038	54.5	8 582	49.0	88 185	50.7
Age bands								
0 - 4 years	59 699	51.5	11 426	28.3	10 032	57.3	81 157	46.7
5 - 9 years	16 330	14.1	7 645	18.9	2 968	16.9	26 943	15.5
10 - 14 years	8 948	7.7	7 747	19.2	1 388	7.9	18 083	10.4
15 - 19 years	30 999	26.7	13 604	33.7	3 123	17.8	47 726	27.4
TB treatment history								
New	113 261	97.7	38 027	94.1	17 166	98.0	168 454	96.9
Retreatment	2 715	2.3	2 395	5.9	345	2.0	5 455	3.1
Site of TB Disease								
PTB with/without EPTB	107 912	93.0	35 665	88.2	16 119	92.1	159 696	91.8
EPTB only	8 064	7.0	4 757	11.8	1 392	7.9	14 213	8.2
Disseminated TB[1]								
None	104 263	98.6	34 672	96.7	15 477	98.0	154 412	98.1
Present	1 427	1.4	1 186	3.3	317	2.0	2 930	1.9
Time								
2013	32 720	28.2	11 384	28.2	8 197	46.8	52 301	30.1
2014	30 738	26.5	10 922	27.0	4 503	25.7	46 163	26.5
2015	28 988	25.0	9 816	24.3	2 845	16.2	41 649	23.9
2016	23 530	20.3	8 300	20.5	1 966	11.2	33 796	19.4
Bacteriological investigation								
Not completed	78 162	67.4	22 100	54.7	13 560	77.4	113 822	65.4
Completed	37 814	32.6	18 322	45.3	3 951	22.6	60 087	34.6
Bacteriological status								
Bacteriologically confirmed	28 319	24.4	9 871	24.4	2 577	14.7	40 767	23.4
Clinically diagnosed	87 657	75.6	30 551	75.6	14 934	85.3	133 142	76.6

[1]Missing values for ICD-10 classification: 16 567/173 909 (9.5%)

EPTB=extra-pulmonary tuberculosis; PTB=pulmonary tuberculosis; TB=Tuberculosis.

There was a strong association between age and HIV co-infection (Table 3). Sex was also associated with HIV status, but in age-stratified analyses the association disappeared in

children aged 0-9 years and became more pronounced in the adolescent groups (10-19-year-olds). Previous TB treatment history, EPTB only, disseminated TB, bacteriological investigation completed, and bacteriological confirmation were all associated with HIV co-infection.

Table 3. Univariable and age-stratified results of the association between HIV co-infection and age, sex and other clinical characteristics for all children and adolescents (0-19 years) with newly registered drug-susceptible tuberculosis and a known HIV status reported in the ETR.Net 2013-2016 (n=156 398)

	Odds of HIV co-infection		
	OR	95% CI	p-value
Age bands			
0 - 4 years	Reference		
5 - 9 years	2.45	2.36 - 2.53	<0.001
10 - 14 years	4.52	4.36 - 4.69	<0.001
15 - 19 years	2.29	2.23 - 2.36	<0.001
Sex			
Female vs. male (ref)	1.22	1.19 - 1.24	<0.001
Sex stratified by age:			
0-4-year-old females vs. males (ref)	1.00	0.96 - 1.04	0.969
5-9-year-old females vs. males (ref)	0.97	0.92 - 1.02	0.218
10-14-year-old females vs. males (ref)	0.76	0.71 - 0.8	0.000
15- 19-year-old females vs. males (ref)	1.80	1.73 - 1.88	0.000
TB treatment history			
Retreatment vs. New (ref)	2.63	2.48 - 2.78	<0.001
Site of TB Disease			
EPTB only vs. PTB with/without EPTB (ref)	1.78	1.72 - 1.85	<0.001
Disseminated TB[1]			
Disseminated disease vs. None (ref)	2.50	2.31 - 2.70	<0.001
Year			
2013	Reference		
2014	1.02	0.99 - 1.05	0.176
2015	0.97	0.94 - 1.00	0.090
2016	1.01	0.98 - 1.05	0.412
Bacteriological investigation			
Completed vs. Not completed (ref)	1.71	1.67 - 1.75	<0.001
Bacteriological status			
Confirmed vs. Clinically diagnosed (ref)	1.00	0.97 - 1.03	0.994

[1]ICD10 data available for n=141 548 (90.5%)

OR=odd's ratio; CI=confidence interval; EPTB=extra-pulmonary tuberculosis; PTB=pulmonary tuberculosis; ref=reference; TB=tuberculosis.

In multivariable analysis (Table 4), the association with HIV co-infection increased with age, being the strongest in 10-14-year-old compared to 0-4-year-old males (males: aOR=4.66 [95%CI: 4.39-4.94]; females: aOR=3.47 [95%CI: 3.28-3.67]). Variation by sex was the most pronounced amongst 15-19-year-olds (female:male ratio=1.84: aOR (females)=2.49 [95%CI: 2.38-2.60] and aOR (males)=1.35 [95%CI: 1.29-1.42]). The association between HIV co-infection and previous TB treatment history, having disseminated TB and bacteriological investigation remained in the multivariable model, with all aORs being slightly lower than in the univariable model.

Table 4. Multivariable model of the association between HIV co-infection, and age, sex and other clinical characteristics, including an interaction term for effect modification between age and sex in children and adolescents treated for drug-susceptible tuberculosis in South Africa during 2013-2016 and reported in ETR.Net (n=141 548[1])

	Adjusted Odds Ratio of HIV co-infection	95% CI	p-value	Female:Male ratio
Age and Sex (including an interaction term)				
0-4 Males	Reference			0-4-year-olds:
0-4 Females	0.99	0.95 - 1.04	0.738	0.99
5-9 Males	2.36	2.24 - 2.48	<0.001	5-9-year-olds:
5-9 Females	2.31	2.19 - 2.43	<0.001	0.98
10-14 Males	4.66	4.39 - 4.94	<0.001	10-14-year-olds:
10-14 Females	3.47	3.28 - 3.67	<0.001	0.74
15-19 Males	1.35	1.29 - 1.42	<0.001	15-19-year-olds:
15-19 Females	2.49	2.38 - 2.60	<0.001	1.84
TB treatment history				
Retreatment vs. New (ref)	2.23	2.10 - 2.37	<0.001	
Disseminated TB				
Disseminated disease vs. None (ref)	2.37	2.19 - 2.57	<0.001	
Bacteriological investigation				
Completed vs. Not completed (ref)	1.20	1.17 - 1.24	<0.001	

[1]Excluding patients with an unknown HIV status (n=17 511) and a missing ICD10 code (n=14 850)

CI=confidence interval; ref=reference; EPTB=extra-pulmonary tuberculosis; PTB=pulmonary tuberculosis; TB=tuberculosis.

Discussion

We evaluated age-stratified trends in TB CNRs in the context of HIV in a very large cohort of nearly 720,000 children and adolescents routinely treated for drug-susceptible TB in South Africa over a 13-year period. Overall, TB CNRs among children and adolescents declined by 54% from 2009 to 2016. This decline was largely driven by young children 0-4 years of age, who accounted for 47% of the total burden and consistently experienced the highest CNRs. This is consistent with what is expected in a high TB incidence setting with a broad-based population pyramid.[9, 22] However, we found important differences in TB CNRs over time when dis-aggregating data by age and HIV status. Adolescents aged 15-19 years experienced the slowest decline in TB CNRs, irrespective of HIV infection status. In this age group, females with TB had a considerably higher risk of HIV co-infection than males.

When evaluating disease trends over time in different age groups and in the context of the changes in health policies, it is important to consider the birth cohort effect. In South Africa, prevention-of-mother-to-child-transmission (PMTCT) options were initially limited with slow implementation and uptake prior to 2008,[23] and HIV-infected children would have been at high risk of both TB and of early mortality.[10, 24] As the roll-out and uptake of PMTCT increased, children born from 2008 onwards would have a reduced risk of perinatal HIV infection. This effect is evident in the stark reduction in national HIV prevalence amongst 0-4-year-olds during the study period (figure 2). HIV-infected children born before 2008 and who survived then had increased access to ART and subsequently moved into the 5-9 and 10-14-year-old age groups. This explains the transitioning peak in the national HIV prevalence curves through the age groups as children aged and started surviving. Early sexual debut could further contribute to the increasing HIV prevalence amongst 15-19-year-olds, especially amongst females.[25]

Amongst children 0-9 years old, the reduction in HIV prevalence was mirrored by a stark reduction in TB CNRs (59% in 0-4-year-olds and 72% in 5-9-year-olds) between 2009 and 2016. This is likely due to a reduction in vertical transmission resulting in lower HIV prevalence

and subsequent reduced risk of developing TB, as well as early diagnosis and access to ART for those HIV-infected. The change also reflects the high susceptibility of children to TB and the indirect effect of a reduced risk of TB transmission as the adult TB epidemic followed the same downward trajectory since 2009, primarily driven by ART roll-out and uptake.[5] However, HIV prevalence has been increasing amongst 10-19-year-olds. In 10-14-year-olds, this was likely still the result of the higher vertical transmission rates prior to and during the earlier years of the PMTCT programme in these HIV survivors. These perinatally-infected children may have accessed ART before, or as they transitioned into adolescence and experienced the protective effect of ART. In 15-19-year-olds, horizontal HIV transmission drives new HIV infections. A recent study showed that only 66% of 140,028 15-19-year-olds seeking HIV care in South Africa before or during 2016, started ART.[26] Nearly a third of this vulnerable population therefore remains at high risk of developing TB.

The relatively small reduction in TB CNRs of only 27% amongst 15-19-year-olds between 2009 and 2016 is concerning, and remained in the HIV-stratified TB CNRs between 2013 and 2016 (16% drop in HIV-infected and 11% drop in HIV-uninfected). Adolescents are an important and challenging group to engage in TB and HIV services, and are at high risk of unfavourable TB and HIV treatment outcomes.[12, 16, 27, 28] The success of HIV prevention strategies relies on how well health services accommodate the needs of adolescents. As the population of HIV-infected adolescents infected perinatally is also growing, these individuals are at high risk of being lost in the transition between paediatric and adult care, especially in high-burden settings.[29] TB prevention strategies and treatment should not only consider young children, but also adolescents.

During 2013-2016, TB CNRs for HIV-infected 0-4-year-olds declined much less than for their HIV-uninfected peers (10% vs 34%, respectively). Young children acquiring HIV infection despite a well-functioning and widely implemented national PMTCT programme likely represent an extremely vulnerable at-risk sub-set of children. These may be children who had undiagnosed perinatal HIV infection or who did not access PMTCT services, and TB may

have been the event that led to the diagnosis of HIV.[30] Unfortunately, we did not have good data on the timing of HIV diagnosis or ART initiation in this routine dataset, and we therefore do not know how many of these children were ART naïve. HIV-infected children in this age group should be prioritised for ART and healthcare workers should have a low threshold to re-test children born to HIV-infected mothers for HIV. TB exposure in these children should be actively verified at each contact with health services, as TB preventive therapy substantially reduces the risk of TB in this age group, irrespective of HIV status.[31]

Our study found an association between TB, HIV co-infection and age that differed by sex in adolescents. Amongst younger adolescents (10-14-year-olds), slightly more boys were co-infected than girls (female:male ratio: 0.74). The reason for this observation is unclear. Sex disparity was most pronounced in 15-19-year-olds, with the odds of HIV co-infection nearly double in older adolescent females (female:male ratio: 1.84). This is consistent with the observed higher HIV prevalence amongst adolescent females compared to their male counterparts globally and in sub-Saharan Africa.[14, 28] In South Africa, 301,242/342,443 (88%) 15-19-year-olds who entered HIV care during 2005-2016 were female.[26] More data are needed to fully understand the sex disparity seen for TB and HIV during adolescence and explore how this can be addressed in TB services.

Routine TB surveillance data in South Africa rely on health care access, diagnosis, treatment initiation and reporting of TB by routine public services. Thus, children and adolescents who were not diagnosed, who were lost-to-follow-up prior to initiating TB treatment, or were not reported, would have been excluded from this study. HIV data in the earlier years was poorly recorded, resulting in a short time-series of HIV-stratified TB data and which does not comprehensively report on pre-TB access to ART. The Thembisa HIV model was the only available source of age-disaggregated population estimates and HIV prevalence but estimates for children lack 95% confidence intervals. Furthermore, the quality of routine data relies on how accurate and complete frontline healthcare workers recorded and captured the data. Excluding cases with a missing HIV status from HIV-stratified CNRs reduced the number of

TB cases, and therefore resulted in more conservative estimates of HIV-stratified TB CNRs. Our findings therefore rather underestimate than overestimate the true burden of TB during the study period when stratified by HIV status.

With all HIV-infected patients in South Africa being eligible for ART, and with the imminent roll-out of shorter TB preventive therapy regimens, it will be important to evaluate the impact of these control strategies on TB CNRs in HIV-infected and uninfected children and adolescents beyond the broad age bands currently recommended by WHO. Such data will help to better understand how we can plan services to improve TB prevention and treatment for children and adolescents in high TB and HIV burden settings. A successful PMTCT programme in South Africa has resulted in very low HIV prevalence in younger children. However, the maternal antenatal HIV prevalence remains high. Future research should also continue to evaluate the risk of TB in HIV-exposed uninfected children and adolescents. Research that is responsive to local programme considerations and the epidemiological context for TB and HIV is needed to inform the design and implementation of child and adolescent-friendly TB and HIV services to better support care in affected children and in adolescents.

Acknowledgements

We would like to acknowledge the South African Department of Health, National TB program and the Research, Information, Monitoring, Evaluation and Surveillance (RIMES) unit. We would also like to acknowledge Mr. Dewald van Deventer for initial data management.

Funding

Initial data extraction and cleaning was funded by URC through the TB Care II Project (USAID Co-operative Agreement No. AID-OAA-A-10-00021).

KDP is supported by the Fogarty International Center of the National Institutes of Health under Award Number K43TW011006. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ACH is financially supported by the South African National Research Foundation (NRF) South African Research Chairs Initiative (SARChI), and KDP received grant-holder linked student support. The financial assistance of the NRF towards this research is hereby acknowledged. Opinions expressed, and conclusions arrived at, are those of the authors and are not necessarily to be attributed to the NRF.

MO is supported through funding by the South African Medical Research Council (SA MRC) through its Division of Research Capacity Development under the Bongani Mayosi National Health Scholars Program from funding received from the Public Health Enhancement Fund/South African National Department of Health. The contents are solely the responsibility of the authors and do not necessarily represent the official views of the SA MRC or the funders.

JAS is supported by a Clinician Scientist Fellowship jointly funded by the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID Concordat agreement (MR/R007942/1).

Conflict of Interest

The authors has no conflict of interest to declare.

Author contributions

KDP, MO, JAS, PN and ACH conceptualised the study. RD was responsible for data management, including cleaning and preparation. KDP, MO and ZM completed data analysis. All authors contributed towards interpreting the study results. KDP completed the first draft of the manuscript, and all authors provided input on the manuscript drafts. All authors critically reviewed and approved the final version of the manuscript.

References

1. Global tuberculosis report 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.
2. Snow KJ, Sismanidis C, Denholm J, Sawyer SM, Graham SM. The incidence of tuberculosis among adolescents and young adults: a global estimate. Eur Respir J 2018; 51(2): 1702352. Published 2018 Feb 21. doi:10.1183/13993003.02352-2017.
3. World Health Organisation. Roadmap towards ending TB in children and adolescents. Geneva, 2018. Licence: CC BY-NC-SA 3.0 IGO. Available at http://apps.who.int/iris/bitstream/handle/10665/275422/9789241514798-eng.pdf?ua=1 [accessed 10 August 2020].
4. Simbayi LC, Zuma K, Zungu N, et al. South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017. Cape Town: HSRC Press. Available at http://www.hsrc.ac.za/uploads/pageContent/10779/SABSSM%20V.pdf [accessed 10 August 2020].
5. Osman M, Du Preez K, Naidoo P, et al. Milestones and achievements in the response to tuberculosis and HIV in adults and children in South Africa. Int J Tuberc Lung Dis 2020 (in press).
6. National Department of Health. Guidelines for the management of HIV in children. South Africa, 2010. Available at https://sahivsoc.org/Files/Guidelines_for_Management_of_HIV_in_Children_2010.pdf [accessed 21 May 2020].
7. National Department of Health. Circular Minute No 2 of 2012: Initiation of anti retroviral treatment (ART) to all HIV positive children aged 5 years and under regardless of CD4 count and/or WHO clinical staging. South Africa, 2012. Available at https://sahivsoc.org/Files/Rx%20of%20children%20under%205-Circular%20Minute%20No%202%20of%202012%20-%20ART.pdf [accessed 10 August 2020].

8. National Department of Health. Implementation of the universal test and treat strategy for HIV positive patients and differentiated care for stable patients. South Africa, 2016. Available at https://sahivsoc.org/Files/22%208%2016%20Circular%20UTT%20%20%20Decongestion%20CCMT%20Directorate.pdf [accessed 10 August 2020].

9. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004; 8(4): 392-402.

10. Dodd PJ, Prendergast AJ, Beecroft C, Kampmann B, Seddon JA. The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis. Thorax 2017; 72(6): 559-75.

11. Snow K, Hesseling AC, Naidoo P, Graham SM, Denholm J, du Preez K. Tuberculosis in adolescents and young adults: epidemiology and treatment outcomes in the Western Cape. Int J Tuberc Lung Dis 2017; 21(6): 651-7.

12. Snow KJ, Cruz AT, Seddon JA, et al. Adolescent tuberculosis. Lancet Child Adolesc Health 2020; 4(1): 68-79.

13. Seddon JA, Chiang SS, Esmail H, Coussens AK. The wonder years: what can primary school children teach us about immunity to Mycobacterium tuberculosis? Front Immunol 2018; 9: 2946.

14. Abdool Karim Q, Baxter C, Birx D. Prevention of HIV in Adolescent Girls and Young Women: Key to an AIDS-Free Generation. J Acquir Immune Defic Syndr 2017; 75 Suppl 1: S17-S26.

15. Sohn AH, Hazra R. The changing epidemiology of the global paediatric HIV epidemic: keeping track of perinatally HIV-infected adolescents. J Int AIDS Soc 2013; 16: 18555.

16. Kranzer K, Bradley J, Musaazi J, et al. Loss to follow-up among children and adolescents growing up with HIV infection: age really matters. J Int AIDS Soc 2017; 20(1): 21737.

17. Woldesenbet SA, Kufa T, Lombard C, et al. The 2017 National Antenatal Sentinel HIV Survey, South Africa, National Department of Health, 2019.

18. Nadol P, Stinson KW, Coggin W, et al. Electronic tuberculosis surveillance systems: a tool for managing today's TB programs. Int J Tuberc Lung Dis 2008; 12(3 Suppl 1): 8-16.

19. Coggin W. Overview of the Electronic TB Register ETR.Net: CDC South Africa. Available from: https://www.who.int/tb/err/coggin.pdf [accessed 14 July 2020].

20. National Department of Health South Africa. National Tuberculosis Guidelines 2014. Pretoria, South Africa, 2014. Available at https://sahivsoc.org/Files/NTCP_Adult_TB%20Guidelines%2027.5.2014.pdf [accessed 10 August 2020].

21. Johnson LF, May MT, Dorrington RE, et al. Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study. PLoS Med 2017; 14(12): e1002468.

22. Donald PR. Childhood tuberculosis: the hidden epidemic. Int J Tuberc Lung Dis 2004; 8(5): 627-9.

23. Burton R, Giddy J, Stinson K. Prevention of mother-to-child transmission in South Africa: an ever-changing landscape. Obstet Med 2015; 8(1): 5-12.

24. Newell ML, Coovadia H, Cortina-Borja M, et al. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. Lancet 2004; 364(9441): 1236-43.

25. Zuma K, Setswe G, Ketye T, Mzolo T, Rehle T, Mbelle N. Age at sexual debut: a determinant of multiple partnership among South African youth. Afr J Reprod Health 2010; 14(2): 47-54.

26. Maskew M, Bor J, MacLeod W, Carmona S, Sherman GG, Fox MP. Adolescent HIV treatment in South Africa's national HIV programme: a retrospective cohort study. Lancet HIV 2019; 6(11): e760-e8.

27. Berry KM, Rodriguez CA, Berhanu RH, et al. Treatment outcomes among children, adolescents, and adults on treatment for tuberculosis in two metropolitan municipalities in Gauteng Province, South Africa. BMC Public Health 2019; 19(1): 973.

28. Slogrove AL, Mahy M, Armstrong A, Davies MA. Living and dying to be counted: What we know about the epidemiology of the global adolescent HIV epidemic. J Int AIDS Soc 2017; 20(Suppl 3): 21520.

29. Mapesi H. Challenges for HIV-infected adolescents during transition from paediatric to adult HIV clinics in Africa. Int J Public Health 2020.

30. Byamungu LN, du Preez K, Walters E, Nachega JB, Schaaf HS. Timing of HIV diagnosis in children with tuberculosis managed at a referral hospital in Cape Town, South Africa. Int J Tuberc Lung Dis 2018; 22(5): 488-95.

31. Ayieko J, Abuogi L, Simchowitz B, Bukusi EA, Smith AH, Reingold A. Efficacy of isoniazid prophylactic therapy in prevention of tuberculosis in children: a meta-analysis. BMC Infect Dis 2014; 14: 91.

CHAPTER 4: COMPLEMENTARY SURVEILLANCE STRATEGIES ARE NEEDED TO BETTER CHARACTERISE THE EPIDEMIOLOGY, CARE PATHWAYS AND TREATMENT OUTCOMES OF TUBERCULOSIS IN CHILDREN

In the previous chapter, I explored the use of routine tuberculosis (TB) surveillance data and the interlinking effects of age and HIV on TB. I used data from the electronic TB treatment register (ETR.Net) and focussed on trends in case notifications (the fourth pillar of the TB care cascade: 'Notified and treated').

In this chapter, I investigate diagnostic surveillance for paediatric TB, addressing pillar 3 of the TB care cascade – 'Diagnosed with TB'. Here, I characterize the burden, spectrum and care pathways between different levels of health care for children with TB managed at Tygerberg Hospital (TBH), a tertiary referral hospital in Cape Town, Western Cape province, South Africa,[86] which serves approximately 40% of the provincial paediatric population. In chapter 1, I reviewed challenges with obtaining paediatric specimens and with the diagnosis of TB in children, especially in young and HIV-infected children, and the reasons why many children are usually referred to hospital for investigation, diagnosis or treatment. Surveillance data from hospitals therefore provide an important perspective on the diagnosis of paediatric TB, especially in settings where hospitals do not report TB data to the TB programme.

At TBH, surveillance of all bacteriologically confirmed paediatric TB cases has been ongoing since 2003, and has provided valuable data on the changing epidemiology and drug resistance patterns and impact of HIV on paediatric TB.[62-67] Due to the paucibacillary nature of paediatric TB, bacteriological confirmation of disease is much lower than in adults, and typically varies between 15-40%, depending on the extent and spectrum of disease, timing, quality and number of specimens, and the bacteriological tests used.[87-90] The majority of children, even those managed in hospitals, are therefore clinically diagnosed, and bacteriological surveillance alone will identify only a sub-set of hospital-managed paediatric TB cases. More comprehensive surveillance data on all children routinely diagnosed with TB at referral hospital level, specifically including clinically diagnosed cases, would therefore provide more accurate and representative data on the burden and spectrum of TB disease, and will help address gaps in the reporting of TB in children.

I therefore designed and implemented a prospective cohort study, using both study-specific clinical surveillance in addition to the existing ongoing laboratory surveillance, to consecutively identify all children (< 13 years) routinely diagnosed and managed for TB at TBH from 1 January through 31 December 2012. In-hospital paediatric services only include children 0-<13 years age in non-TB public hospitals in South Africa. Adolescents (≥13 years) access adult services in these

hospitals and were therefore excluded. Children identified through prospective surveillance accessed the linkage-to-care intervention described in chapter 7, but the intervention did not impact the routine clinical processes around case ascertainment. Univariate analysis compared characteristics between children identified through the two hospital-based surveillance strategies (laboratory vs. clinically diagnosed) to characterise the group of children missed by the existing hospital-based laboratory surveillance.

The burden and spectrum of paediatric TB diagnosed and managed at referral hospital level in this setting was substantial, and included 395 children diagnosed in one year, with almost half (46%) younger than 2 years of age. The young observed age indicates the low threshold of referring children to the hospital for TB investigation and diagnosis and highlights the challenges in bacteriological investigation and clinical diagnosis in very young children, as well as the high burden of TB in the youngest age groups. One in four children (24%) were HIV-infected and almost a third (30%) was severely underweight for age. Care pathways and the movement of children between different levels of care were complex. Nearly a quarter of children (23%) were admitted with an established diagnosis of TB, the majority of them (84%) having been diagnosed and referred from another hospital. Only 63% of children were discharged to a primary healthcare facility for completion of treatment, 7% were scheduled to follow-up at the TBH outpatient department and 21% were referred to a TB hospital for further management.

Even in a tertiary hospital setting, nearly two thirds (60%) of the children would not have been identified by bacteriological surveillance, highlighting the importance of clinical surveillance strategies to complement laboratory surveillance for paediatric TB. Laboratory surveillance more frequently detected older children (5-<13 years of age; odds ratio [OR] 1.7, 95% confidence interval [CI] 1.0–2.8), children with extra-pulmonary TB (EPTB; OR 2.3; 95% CI 1.5–3.6) and miliary TB (OR 6.3, 95% CI 2.3-17.8) and children who died in hospital (OR 5.4, 95% CI 1.1–26.9). HIV-infected children were less likely to be identified through laboratory surveillance (OR 0.3, 95% CI 0.2–0.5).

In contrast to the national routine TB surveillance data presented in chapter 3, where only 9% of paediatric cases had only EPTB, and only 2% had documentation of severe disseminated TB, there was a higher proportion of children with only EPTB (18%) and severe disseminated TB (20%) in this hospital cohort. Another important difference between these two studies was the percentage of children with a confirmed diagnosis: in this hospital cohort, 40% of all children had a bacteriologically confirmed diagnosis, compared to only 9% of 0-14-year-olds in the national routine TB surveillance data. Amongst children 0-4 years of age, 38% of the hospital cohort had a confirmed TB diagnosis compared to only 3% of children in this age group in the routine surveillance data, where the vast majority (93%) had no record of any sampling and

bacteriological investigation undertaken. Overall, the proportion HIV-infected amongst those with a known status was similar between the two studies – 24% in the hospital cohort (0-12 years) and in the routine TB surveillance data (0-14 years). Age-stratified analyses on the hospital cohort and how this compare to the routine surveillance data is presented in chapter 5.

This hospital-based study quantified the substantial burden of paediatric TB and the large proportion of children with disseminated TB, bacteriologically confirmed TB and TB-HIV co-infection managed at tertiary hospital level in South Africa, providing important data on pillar 3 of the care cascade ('Diagnosed with TB'). Clinical and bacteriological hospital-based surveillance is therefore important in addition to routine TB surveillance data to provide a more complete picture of the burden, age and disease spectrum of paediatric TB, especially in settings where hospitals do not routinely report TB data to the programme.

Citation

Du Preez K, Schaaf HS, Dunbar R, Walters E, Swartz A, Solomons R, Hesseling AC. Complementary surveillance strategies are needed to better characterise the epidemiology, care pathways and treatment outcomes of tuberculosis in children. BMC Public Health. 2018;18(1):397.

du Preez et al. BMC Public Health (2018) 18:397
https://doi.org/10.1186/s12889-018-5252-9

BMC Public Health

RESEARCH ARTICLE Open Access

Complementary surveillance strategies are needed to better characterise the epidemiology, care pathways and treatment outcomes of tuberculosis in children

Karen du Preez[1*], H. Simon Schaaf[1,2], Rory Dunbar[1], Elisabetta Walters[1], Alvera Swartz[3], Regan Solomons[2] and Anneke C. Hesseling[1]

Abstract

Background: Tuberculosis (TB) in young and HIV-infected children is frequently diagnosed at hospital level. In settings where general hospitals do not function as TB reporting units, the burden and severity of childhood TB may not be accurately reflected in routine TB surveillance data. Given the paucibacillary nature of childhood TB, microbiological surveillance alone will miss the majority of hospital-managed children. The study objective was to combine complementary hospital-based surveillance strategies to accurately report the burden, spectrum and outcomes of childhood TB managed at referral hospital-level in a high TB burden setting.

Methods: We conducted a prospective cohort study including all children (< 13 years) managed for TB at a large referral hospital in Cape Town, South Africa during 2012. Children were identified through newly implemented clinical surveillance in addition to existing laboratory surveillance. Data were collected from clinical patient records, the National Health Laboratory Service database, and provincial electronic TB registers. Descriptive statistics were used to report overall TB disease burden, spectrum, care pathways and treatment outcomes. Univariate analysis compared characteristics between children identified through the two hospital-based surveillance strategies to characterise the group of children missed by existing laboratory surveillance.

Results: During 2012, 395 children (180 [45.6%] < 2 years) were managed for TB. Clinical surveillance identified 237 (60%) children in addition to laboratory surveillance. Ninety (24.3%) children were HIV co-infected; 113 (29.5%) had weight-for-age z-scores <− 3. Extra-pulmonary TB (EPTB) was diagnosed in 188 (47.6%); 77 (19.5%) with disseminated TB. Favourable TB treatment outcomes were reported in 300/344 (87.2%) children with drug-susceptible and 50/51 (98.0%) children with drug-resistant TB. Older children (OR 1.7; 95% CI 1.0–2.8), children with EPTB (OR 2.3; 95% CI 1.5–3.6) and in-hospital deaths (OR 5.4; 95% CI 1.1–26.9) were more frequently detected by laboratory surveillance. TB/HIV co-infected children were less likely to be identified through laboratory surveillance (OR 0.3; 95% CI 0.2–0.5).

(Continued on next page)

* Correspondence: karen_dupreez@sun.ac.za
[1]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
Full list of author information is available at the end of the article

(Continued from previous page)

Conclusions: The burden and spectrum of childhood TB disease managed at referral hospital level in high burden settings is substantial. Hospital-based surveillance in addition to routine TB surveillance is essential to provide a complete picture of the burden, spectrum and impact of childhood TB in settings where hospitals are not TB reporting units.

Keywords: Tuberculosis, Children, Surveillance, Hospital, Burden, Disease spectrum, Care pathways, Outcomes, HIV

Background

In 2016, South Africa remained the country with the highest estimated total tuberculosis (TB) incidence globally (781 per 100,000 population) with an estimated total of 438,000 TB cases, 58,000 occurring in children < 15 years [1]. The South African National TB Programme (NTP) has a decentralized model of TB care, supporting adult and paediatric patients to primarily receive diagnostic and treatment services at community-based primary healthcare (PHC) facilities [2]. Routine TB recording and reporting tools, including TB treatment registers, are therefore typically located at community-based PHC facilities. Data from the TB registers are captured and aggregated into two electronic registers used routinely for reporting NTP TB surveillance data: ETR.Net (drug-susceptible TB [DS-TB]), and EDRWeb (drug-resistant TB [DR-TB]). In the Western Cape Province, general hospitals do not function as TB reporting units therefore inclusion of adults and children in routine TB surveillance data rely on patients accessing treatment at PHC facilities.

In the absence of TB preventive therapy, young children (< 5 years of age) have a high risk of progressing to TB disease and to severe forms of TB once infected with *Mycobacterium tuberculosis (M. tb)* [3]. Young children are also frequently diagnosed with TB at the referral healthcare level (secondary or tertiary hospital) due to diagnostic challenges, including the ability to obtain adequate samples for TB microbiological testing. Children may frequently move between community and hospital-based healthcare services during the course of TB diagnosis and treatment [4]. A previous audit at a large referral hospital in this setting, Tygerberg Hospital (TBH) found that only 62% of children with culture-confirmed TB were included in routine TB surveillance data during 2007–2009, and that children with TB meningitis and children who died in hospital were more likely not to be included in NTP surveillance data [5]. In settings where hospitals do not function as TB reporting units, hospital-based surveillance data is critical to supplement NTP surveillance data in order to have an accurate reflection of the burden and spectrum of TB in children.

Hospital-based laboratory surveillance of childhood TB has provided valuable insight into the epidemiology and trends in drug resistance in the Western Cape Province since 2003 [6–10]. However, given the paucibacillary nature of TB in children with only 25–40% of children treated for TB expected to have bacteriologically confirmed disease [11–13], laboratory surveillance in isolation will miss the majority of children with TB managed at hospital-level. Hospital-based clinical surveillance strategies are therefore needed to identify children with an unconfirmed, clinical TB diagnosis.

In order to document the true burden and spectrum of childhood TB managed at a large referral hospital in a TB endemic setting we conducted a prospective one-year, hospital-based surveillance study at TBH, Cape Town. We implemented new clinical surveillance activities in addition to existing laboratory surveillance to identify all children routinely diagnosed with or treated for TB. We compared TB disease spectrum, clinical characteristics, care pathways and treatment outcomes between children identified through the two complementary hospital-based surveillance strategies, to characterise the group of children that would otherwise be missed by existing laboratory surveillance.

Methods

Setting

The Western Cape Province reported the third highest TB incidence rate (681 per 100,000 population) of the nine provinces in South Africa in 2015 [14]. During 2013, 34,880 newly diagnosed patients including 5,919 (17.0%) children < 15 years of age, with DS-TB were reported in routine provincial TB surveillance data [15]. Prevalence of HIV co-infection increased with age, from 5% amongst children < 5 years of age and reaching a high of 46% amongst adults ≥25 years [15].

TBH is a tertiary referral hospital in the Western Cape Province and serves approximately 50% of the paediatric population in the province. TBH has 10 paediatric wards with 268 general and neonatal beds, and had 15,133 admissions with an overall bed occupancy of 80% during 2012 [16]. TBH serves as referral hospital for uncomplicated and complicated TB cases from surrounding high-burden communities and complicated TB cases from more remote areas, and provides secondary level paediatric care to children living in adjacent communities. Children who are medically stable, but require prolonged hospitalisation for medical or social reasons, are referred to dedicated TB hospitals/care facilities.

Children with pulmonary DS-TB are routinely treated for 6 months with a standard first-line drug regimen, consisting of isoniazid, rifampicin and pyrazinamide with or without ethambutol, depending on disease severity [2]. Children with osteoarticular TB are treated for 9–12 months, while children with TB meningitis are treated with four drugs (ethionamide replacing ethambutol) for 6 months if HIV-uninfected and 9 months if HIV-infected [17]. DR-TB regimens are individualized for children based on the drug susceptibility test (DST) results of the child's *M.tb* isolate, or in the case of clinically diagnosed TB, of the adult source case's isolate, with treatment ranging from 12 to 24 months.

Study design and population

A prospective cohort study design was used to identify all children < 13 years of age (based on paediatric admission criteria at TBH) routinely diagnosed with or treated for TB at TBH during 2012.

Surveillance strategies

Prospective hospital-based surveillance activities conducted as part of this study provided the foundation for a health system strengthening intervention for paediatric TB at TBH. In addition to active clinical and laboratory surveillance activities, support of TB referral services between hospital and community-based PHC facilities was provided. This included TB education to parents/caregivers, supporting ward personnel with the referral process, and telephonic follow-up with parents and PHC facilities following discharge to ensure continuity of care. All health system strengthening activities were implemented as part of an integrated package of TB care for children at TBH.

Clinical hospital-based surveillance: a dedicated research team including a nurse practitioner and lay healthcare worker, conducted daily clinical surveillance (Monday-Friday) in all 10 medical and surgical paediatric wards to identify children diagnosed with or treated for TB during 2012. A paper-based childhood TB tracking system (register) was implemented in all paediatric wards, outpatient services and emergency department, to serve as a communication tool between clinical and research personnel. Detailed information regarding clinical surveillance was communicated to all clinical service personnel at the start of the study, and regular feedback and training was given at paediatric departmental meetings.

Laboratory hospital-based surveillance: a dedicated laboratory-based surveillance officer identified all specimens culture-positive for *M. tb* at the microbiology laboratory at TBH. Laboratory protocols for TB culture during this time period have been described previously [10]. This study was implemented prior to the rollout of Xpert MTB/RIF (Cepheid, Sunnydale, CA) for children in this setting. Information on culture-positive specimens was communicated weekly by the laboratory to the clinical team.

Data collection

Clinical information was captured on standard case report forms following review of clinical patient records and laboratory data. Children re-admitted during the study period were only included once. Information on TB treatment outcomes was obtained through probabilistic record linkage [18] with the 2 provincial electronic TB registers (2011–2013) using 4 variables (name, surname, gender and date of birth). All matches were manually reviewed before inclusion. If outcome information was not found in the TB registers, additional information was obtained from repeated reviews of medical records and telephonic contact with the healthcare facilities where children were discharged to (TB hospitals and PHC facilities). The National Health Laboratory Service database was also systematically surveyed for follow-up TB microbiological investigations in study participants with a culture-confirmed diagnosis. Data were dual captured in an access-controlled database and de-identified as soon as record linkages were completed.

Definitions

Hospital visits resulting in overnight admission were classified as in-patient visits. Care pathways included both TB diagnosis pathways in relation to presentation to TBH as well as referral pathways to continue TB care on hospital discharge.

The spectrum of TB disease was classified as follows: pulmonary TB (PTB) only, EPTB only, or both PTB and EPTB. Intra-thoracic lymphadenopathy was classified as PTB. Large/loculated pleural effusions and/or miliary TB were classified as both PTB and EPTB.

We applied standard TB treatment outcome definitions as per NTP guidelines [2]: *Cured:* Children who were sputum smear-positive for acid-fast bacilli pre-treatment and who were sputum smear-negative in the last month of treatment and on at least one previous occasion, at least 30 days apart. For study purposes, we also included children with a positive culture for *M. tb* (even if smear-negative), and who had at least one follow-up negative culture before the end of treatment. *Completed treatment:* Children who had completed treatment, but did not meet the criteria for either cure or treatment failure. This category included children with bacteriological confirmation at diagnosis, but no documented follow-up bacteriological sample. Children who had documentation of having received their last month of treatment in hospital were also included, even if no further follow-up was documented. *Lost to follow-up:* Children whose treatment was interrupted for at least 2 consecutive months. For study purposes, all children who did not have follow-up information

after hospital-discharge and who did not complete treatment in hospital, or where no formal outcome was assigned, were also classified as lost to follow-up. *Died*: Children who died for any reason during the course of TB treatment. For study purposes we also included in-hospital deaths prior to initiation of treatment (e.g. if TB was culture-confirmed only after the child died). *Treatment failure*: Children who remained bacteriologically positive at 5 months or later after starting treatment. *Transferred out:* Children who were transferred to another district and for whom the treatment outcome was not known. Favourable treatment outcomes were combined as cured or treatment completed. Unfavourable treatment outcomes included lost to follow-up (including not evaluated), died, treatment failure, and transferred out.

Statistical analysis

Given the long-standing history of hospital-based laboratory surveillance at TBH, the primary aim was to characterise the cohort of children with a clinical/presumed diagnosis of TB, who would not be identified by existing microbiological laboratory surveillance. Children were therefore grouped into those identified through laboratory surveillance and those identified through clinical surveillance only, acknowledging that a proportion of children identified through laboratory surveillance would have also been identified through clinical surveillance.

Descriptive and summary statistics were used to calculate numbers and percentages of the overall disease burden, spectrum, clinical characteristics, referral pathways and TB treatment outcomes. The following variables were included in analysis: demographics (age and sex), TB treatment and exposure history, HIV status and related variables, nutritional status, spectrum and type of TB disease, referral care pathways, and TB treatment outcomes. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated in univariate analysis to investigate and quantify differences between children identified through the two hospital-based surveillance strategies explained above (laboratory vs clinical only). Weights were transformed to z-scores using reference data available from the 1990 British Growth Reference [19]. Statistical analysis was completed using STATA SE version 14 software (StataCorp LP, Texas, USA).

Ethical considerations

Ethics approval was obtained from Stellenbosch University Health Research Ethics Committee (N11/09/28) and provincial and municipal authorities. As the study was implemented as part of standard clinical care, a waiver of individual informed consent was granted. The STROBE guidelines for reporting of cohort studies were followed [20].

Results

During 2012, 395 children (< 13 years of age) were managed for TB at TBH. Figure 1 provides an overview of the yield of clinical and laboratory hospital-based surveillance strategies. Although the majority of children (349, 88.4%) were identified through clinical surveillance, laboratory-based surveillance identified 158 (40.0%) children with culture-confirmed TB. Laboratory surveillance identified 46 (11.6%) children who were not detected by clinical ward-based surveillance. Clinical surveillance identified 237 (60%) of children that would have been missed by existing laboratory hospital-based surveillance.

Demographic and clinical characteristics for all children are presented in Table 1. The median age was 2.4 years (interquartile range [IQR] 1.0–5.1) with 180 (45.6%) children less than 2 years of age; 213 (53.9%) were male. Hospital admission was required for 361 (91.4%) children, of whom 238 (65.9%) was admitted for > 1 week. Twenty-six (7%) children had a history of previous TB treatment. A history of TB exposure was reported in 213 (55.5%), of which 143 (73.3%) occurred in the household. HIV status was documented in 370 (93.7%), with 90/370 (24.3%) HIV-infected and 24/90 (26.7%) diagnosed with HIV during hospital admission. Of the 66 children known to be HIV-infected at the time of admission, 44 (66.7%) were already on antiretroviral therapy (ART). By 2 weeks following TBH discharge, 83 (92.2%) were receiving ART. Of all TB cases, 113 (29.5%) children had a weight-for-age Z-score < − 3. PTB only was diagnosed in 207/395 (52.4%), both PTB and EPTB in 117 (29.6%) and the remaining 71 (18.0%) children had only EPTB. TB meningitis and miliary TB were diagnosed in 62 (15.7%) and 24 (6.1%) children, respectively; 9 children had both. Of 393 children started on treatment, 342 (87.0%) were treated for DS-TB, 9 (2.3%) for isoniazid mono-resistant TB, 4 (1.0%) for rifampicin mono-resistant TB, 34 (8.7%) for multidrug-resistant TB, 3 (0.8%) for pre-extensively drug-resistant TB and 1 (0.2%) for extensively drug-resistant TB. Nine (2.3%) children died during hospital admission; 2 with culture-confirmed DS-TB (results available only after death) died before TB treatment was initiated.

Ninety-one (23.0%) children had been diagnosed with TB prior to admission at TBH (Table 2); of these, 76 (83.5%) were diagnosed with TB at hospital level and 41 (45.1%) were diagnosed less than 2 weeks before admission to TBH. At the time of discharge (n = 386 children), multiple referral pathways to continue TB care were followed: 244 (63.2%) were discharged to community-based PHC facilities, 82 (21.2%) were transferred to dedicated TB hospitals, 28 (7.3%) were discharged home with monthly outpatient follow-up visits at TBH, 23 (6.0%) were down-referred to secondary hospitals, 8 (2.1%) were referred to medium-term care facilities and 1 (0.3%) child

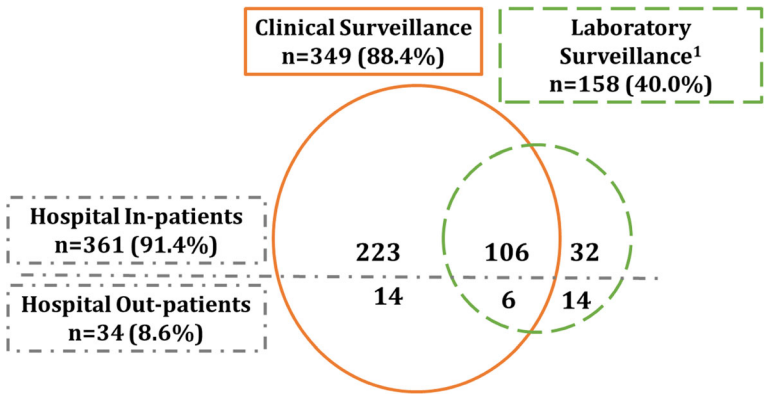


Fig. 1 Overview of the yield of complementary hospital-based surveillance strategies to identify children with tuberculosis. [1]Of the 46 children identified only through laboratory surveillance, 27 children were started on TB treatment prior to TBH discharge but missed by clinical hospital surveillance; 19 were only started on TB treatment at a follow-up visit

completed TB treatment during a non-TB related admission at TBH.

Final TB treatment outcomes overall were excellent, with favourable treatment outcomes in 300/344 (87.2%) children treated for DS-TB, and 50/51 (98%) treated for DR-TB (Table 2). Despite the overall favourable outcomes, mortality was substantial amongst children diagnosed with DS-TB (17; 4.9%).

Results of the analysis comparing characteristics between children identified through the two hospital-based surveillance strategies (laboratory culture-confirmed vs. clinical diagnosis only), are presented in Table 3. Laboratory surveillance was more likely to identify older children (5–<13 years of age) compared to children < 2 years of age (OR 1.7; 95% CI 1.0–2.8; $p = 0.042$), children with EPTB (OR 2.3; 95% CI 1.5–3.6; $p < 0.001$) especially in the presence of miliary TB (OR 6.3; 95% CI 2.3–17.8; $p < 0.001$), and children who died during hospital admission (OR 5.4; 95% CI 1.1–26.9; $p = 0.033$). TB/HIV co-infected patients (OR 0.3; 95% CI 0.2–0.5; $p < 0.001$) and in-patients (OR 0.4; 95% CI 0.2–0.9; $p = 0.019$) were less likely to be detected by laboratory surveillance. No significant differences were observed for sex, duration of hospital admission, TB history, documentation of HIV status, weight-for-age Z-score < − 3, presence of TB meningitis, type of TB treatment, discharge referral pathways and TB treatment outcomes.

Discussion

In this TB-endemic setting, our study identified a very large burden of childhood TB managed at referral hospital level, with almost 400 children during a one-year period at a single hospital. Clinical surveillance identified 237 (60%) children in addition to the existing laboratory surveillance. Despite the majority of children being young (74.9% < 5 years of age), the diagnosis was bacteriologically (culture) confirmed in 40% of children. Such a high proportion of confirmed diagnoses is probably the result of appropriate specimen collection (standard of care is at least 2 respiratory specimens in children < 5 years of age or other indicated specimens for EPTB) and the high proportion of severe forms of TB, which is associated with higher yield by culture [11]. Nearly 20% of children had disseminated TB (TB meningitis or miliary TB), associated with high morbidity and mortality [21–23]. Almost a quarter of children were already on TB treatment at the time of admission, and only 63% of children were referred to community-based PHC facilities on discharge. This reflects both the complexity of TB disease in children with TB managed at referral hospital level, as well as the as-yet under-appreciated movement of children between different levels of healthcare services during the course of their TB diagnosis and treatment. The high proportion of children with drug-resistant TB (12.9%) reflects that TBH is a provincial centre of expertise for the management of DR-TB in children with a dedicated paediatric DR-TB outpatient service and clinical experts.

To our knowledge, this is the first study to characterize the TB disease burden, spectrum, clinical care pathways and final TB treatment outcomes of childhood TB (including both confirmed and clinically diagnosed cases) managed within routine health care services at a large referral hospital in South Africa. This study therefore comprehensively captured the true burden and spectrum of paediatric TB in a large hospital in a high TB burden setting. We also identified important clinical and care pathway differences between children identified through existing laboratory surveillance at this hospital and those with a presumed diagnoses identified through additional clinical surveillance.

There are some studies reporting on childhood TB at tertiary/referral hospitals in Africa. An Ethiopian study reported 491 children treated from 2009 to 2014, and also found a high proportion (49.4%) of EPTB [24]. However,

Table 1 Demographic and clinical characteristics of children with tuberculosis managed at Tygerberg Hospital during 2012

	Number (%)[a] *n* = 395
Demographics and characteristics at hospital admission	
Age (years)	
0 - < 2	180 (45.6)
2 - < 5	116 (29.4)
5 – < 13	99 (25.1)
Male sex	213 (53.9)
In-patient admissions	361 (91.4)
Duration of hospitalisation for in-patients (*n* = 361)	
≤ 1 week	123 (34.1)
2–3 weeks	168 (46.5)
≥ 4 weeks	70 (19.4)
TB history	
Previous TB treatment reported	26/371 (7.0)
Any TB exposure reported	213/384 (55.5)
Household TB exposure reported (level of TB exposure documented; *n* = 195)	143/195 (73.3)
HIV and nutritional status	
HIV status documented	370 (93.7)
HIV-infected	90/370 (24.3)
Diagnosed with HIV before hospital admission	66/90 (73.3)
On ART at hospital admission	44/66 (66.7)
Median CD4 percentage[b] (inter-quartile range)	17.0 (11.6–23.0)
Median CD4 absolute value[b] (inter-quartile range)	593 (274–1,150)
On ART within 2 weeks after hospital discharge	83/90 (92.2)
Weight-for-Age Z-score < −3[c]	113/383 (29.5)
TB disease characteristics	
Bacteriologically confirmed TB (culture-positive for *M. tb*)	158 (40.0)
Spectrum of disease	
Pulmonary TB (PTB) only	207 (52.4)
Both PTB and extra-pulmonary TB (EPTB)	117 (29.6)
EPTB only	71 (18.0)
Disseminated TB (TB Meningitis and Miliary TB)	77 (19.5)
Spectrum of EPTB	
TB Meningitis[d]	62 (15.7)
Miliary TB[d]	24 (6.1)
TB pleural effusion/empyema[e]	35 (8.9)
Abdominal TB only	16 (4.1)
Central Nervous System TB (not TB meningitis)	8 (2.0)
Musculoskeletal TB	19 (4.8)
Pericardial effusion	3 (0.8)
Cutaneous TB	1 (0.3)
Renal TB	1 (0.3)
Peripheral lymphadenitis	28 (7.1)
Type of TB treatment[f]	
First-line regimen (drug-susceptible TB) [f]	342/393 (87.0)
INH mono-resistant treatment regimen	9/393 (2.3)
Rif mono-resistant treatment regimen	4/393 (1.0)
MDR treatment regimen	34/393 (8.7)
Pre-XDR treatment regimen	3/393 (0.8)
XDR treatment regimen	1/393 (0.2)
Deaths during hospital admission	9 (2.3)

[a]The denominator was 395, unless otherwise specified due to missing data
[b]Median value of available CD4 laboratory result within 2 weeks before and after hospital admission (not available for 32/90 HIV-infected children)
[c]Weights were transformed to z-scores using the reference data available from the 1990 British Growth Reference
[d]Includes 9 children that had both miliary TB and TB meningitis
[e]TB pleural effusion/empyema includes 4 children with abdominal TB as well
[f]Excludes two children who died in hospital before any treatment was started, but subsequently had a drug-susceptible mycobacterial culture
TB Tuberculosis, *HIV* Human immune-deficiency virus, *ART* Antiretroviral treatment, *M. tb* = *Mycobacterium tuberculosis*, *INH* Isoniazid, *Rif* Rifampicin, *MDR* Multidrug-resistant, *XDR* Extensively drug-resistant

children in that study were considerably older, with only 107 (21.8%) children < 5 years of age. In the Ethiopian study, 82 (28%) children were HIV-infected, but the HIV status was unknown in a large proportion (41%) [24]. Another study from Kinshasa, Democratic Republic of Congo, reported similar proportions of children with EPTB (159/283; 56.1%) and 32/97 (33%) were culture-positive for *M. tb* during 2005–2011 [25]. However, cultures were only performed on a third of children, and similar to the Ethiopian study, the age distribution of children was older with only 87 (30.7%) less than 7 years of age. In this study only 2.5% of children were HIV-infected, but in 75% the status was not known [25]. The burden of childhood TB reported at these hospitals was considerably lower than what we have observed in our study (491/5 years; 283/7 years; 395/1 year).

Younger and HIV-infected children were less likely to be identified by existing laboratory surveillance, i.e. they were less likely to have culture-confirmed TB. This may reflect clinicians' lower threshold to diagnose TB in children at high risk of developing more severe forms of TB. Older children, and those with EPTB and disseminated disease were more likely to be bacteriologically confirmed, possibly reflecting a higher likelihood to develop adult-type pulmonary disease, with a higher bacillary burden and the ability to produce and expectorate sputum [3]. Laboratory surveillance also identified a

Table 2 Care pathways and treatment outcomes[a] of children with tuberculosis managed at Tygerberg Hospital during 2012

TB diagnosis pathways in relation to Tygerberg Hospital (TBH) presentation	*n* = 395 (%)
TB diagnosis made during/following current presentation to TBH	304 (77.0)
TB diagnosis made prior to TBH admission	91 (23.0)
Duration of TB treatment at time of TBH admission (*n* = 91)	
0–14 days on TB treatment	41 (45.1)
15–60 days on TB treatment	23 (25.3)
> 60 days on TB treatment	27 (29.7)
Level of care at which TB diagnosis was made (*n* = 91)	
Diagnosed at hospital level	76 (83.5)
Diagnosed at a community primary health care (PHC) facility	15 (16.5)
Discharge referral pathways to continue TB care[b]	
Community-based TB services (PHC facilities)	244/386 (63.2)
Hospital-based outpatient follow–up at TBH	28/386 (7.3)
TB hospitals	82/386 (21.2)
Other[c]	32/386 (8.3)
TB treatment outcomes for children treated as drug-susceptible TB[d]	*n* = 344 (%)
Favourable treatment outcomes (Total)	*300 (87.2)*
Cured	12 (3.5)
Treatment completed	288 (83.7)
Unfavourable treatment outcomes (Total)	*44 (12.8)*
Died[d]	17 (4.9)
Lost to-follow up[e]	23 (6.7)
Treatment failure	1 (0.3)
Transferred out	3 (0.9)
TB treatment outcomes for children treated as drug-resistant TB[f]	*n* = 51 (%)
Favourable treatment outcomes (Total)	*50 (98.0)*
Cured	14 (27.5)
Treatment completed	36 (70.6)
Unfavourable treatment outcomes (Total)	*1 (2.0)*
Died	0
Lost to-follow up	1 (2.0)
Treatment failure	0
Transferred out	0

[a]Outcome information was firstly collected through probabilistic record linkage with electronic TB treatment registers. If information was not found in the registers, additional follow up information on outcomes were obtained from repeated reviews of medical records, telephonic contact with the facilities patients were discharged to (TB hospitals and community PHC facilities), as well as the National Health Laboratory Service database
[b]Excludes children who died during hospital admission (*n* = 9)
[c]Includes referrals to secondary hospitals (*n* = 23), chronic medium term care facilities (*n* = 8) and one child that completed TB treatment during a non-TB related admission
[d]Includes two children that died during hospital admission before TB treatment was initiated, but subsequently had a positive culture for drug-susceptible TB
[e]Includes 10 children (2.9%) for whom no follow up documentation could be found in any available data sources
[f]Includes 9 children with isoniazid mono-resistant TB, 4 with rifampicin mono-resistant TB, 34 with multidrug-resistant TB, and 4 with extensively drug-resistant TB
TB Tuberculosis, *TBH* Tygerberg Hospital, *PHC* Primary healthcare

large proportion of children with EPTB where pathological specimens are more readily obtained (e.g. peripheral lymphadenitis). However, laboratory surveillance in isolation is likely to still miss certain types of EPTB, especially TB meningitis (extremely paucibacillary in the absence of additional PTB), TB in HIV co-infected children and in very young children.

Multiple studies have shown that adult and paediatric TB patients are at risk of loss to follow-up when moving between different levels of health care, especially if they

Table 3 Comparing clinical characteristics, referral pathways and TB treatment outcomes of children by two complementary hospital-based surveillance strategies

	All identified through laboratory surveillance *n* = 158 (40.0%)[a]	Identified through clinical surveillance only *n* = 237 (60.0%)[a]	Odds Ratio (95% CI)	*p*-value
Demographics and admission characteristics				
Age (years)				
0 - < 2	63 (39.9)	117 (49.4)	Reference	
2 – < 5	48 (30.4)	68 (28.7)	1.3 (0.8–2.1)	0.269
5 – < 13	47 (29.8)	52 (21.9)	1.7 (1.0–2.8)	0.042
Male sex	77 (48.7)	136 (57.4)	0.7 (0.5–1.1)	0.092
In-patient admissions	138 (87.3)	223 (94.1)	0.4 (0.2–0.9)	0.019
Duration of hospitalisation				
≤ 1 week	46 (33.3)	77 (34.5)	Reference	–
2–3 weeks	68 (49.3)	100 (44.8)	1.1 (0.7–1.8)	0.595
≥ 4 weeks	24 (17.4)	46 (20.6)	0.9 (0.5–1.6)	0.666
TB History				
Previous TB treatment reported	7/150 (4.7)	19/221 (8.6)	0.5 (0.2–1.3)	0.146
Any TB exposure reported	77/154 (50.0)	136/230 (59.1)	0.7 (0.5–1.0)	0.078
Household TB exposure reported	50/69 (72.5)	93/126 (73.8)	0.9 (0.5–1.8)	0.781
HIV and nutritional status				
HIV status documented	146 (92.4)	224 (94.5)	0.7 (0.3–1.6)	0.400
HIV-infected (of those tested)	18/146 (12.3)	72/224 (32.1)	0.3 (0.2–0.5)	< 0.001
Weight-for-Age Z-score < – 3[b]	53/153 (34.6)	60/230 (26.1)	1.5 (1.0–2.3)	0.073
TB disease characteristics				
Spectrum of TB disease				
PTB only	63 (39.9)	144 (60.8)	Reference	
ETPB with/without PTB	95 (60.1)	93 (39.2)	2.3 (1.5–3.6)	< 0.001
Disseminated TB				
TB Meningitis[c]	20 (12.7)	42 (17.7)	0.7 (0.4–1.2)	0.176
Miliary TB[c]	19 (12.0)	5 (2.1)	6.3 (2.3–17.8)	< 0.001
Type of TB treatment				
First-line regimen	134/156 (85.9) [d]	208/237 (87.8)	Reference	–
Any drug-resistant regimen	22/156 (14.1) [d]	29/237 (12.2)	1.2 (0.7–2.1)	0.591
Deaths during hospital admission	7 (4.4)	2 (0.8)	5.4 (1.1–26.9)	0.033
Discharge referral pathway for continuation of TB care[e]				
Community-based PHC facilities	93/151 (61.6)	151/235 (64.3)	Reference	
Hospital-based outpatient follow-up	9/151 (6.0)	19/235 (8.1)	0.8 (0.3–1.8)	0.537
TB hospitals	37/151 (24.5)	45/235 (19.2)	1.3 (0.8–2.2)	0.263
Other[f]	12/151 (8.0)	20/235 (8.5)	1.0 (0.5–2.1)	0.946
TB treatment outcomes (DS-TB)				
Favourable	119/136 (87.5)	181/208 (87.0)	1.0 (0.5–2.0)	0.896
Unfavourable	17/136 (12.5)	27/208 (13.0)	Reference	

Table 3 Comparing clinical characteristics, referral pathways and TB treatment outcomes of children by two complementary hospital-based surveillance strategies *(Continued)*

	All identified through laboratory surveillance $n = 158$ (40.0%)[a]	Identified through clinical surveillance only $n = 237$ (60.0%)[a]	Odds Ratio (95% CI)	*p*-value
TB treatment outcomes (DR-TB)				
Favourable	22/22 (100)	28/29 (96.6)	–	1.000
Unfavourable	0/22 (0.0)	1/29 (3.5)		

[a]The denominator was 158 or 237 respectively, unless otherwise specified due to missing data
[b]Weights were transformed to z-scores using the LMS method and the reference data available from 1990 British Growth Reference; missing admission weights ($n = 10$)
[c]Inlcudes 9 children that had both miliary TB and TB meningitis
[d]Excludes two children that died during hospital admission before TB treatment was initiated, but subsequently had a positive culture for drug-susceptible TB
[e]Excludes children who died in-hospital ($n = 9$)
[f]Includes referrals to secondary hospitals ($n = 23$), chronic medium term care facilities ($n = 8$) and one child that completed TB treatment during a non-TB related admission
TB Tuberculosis, *CI* Confidence interval, *HIV* Human immune-deficiency virus, *ART* Antiretroviral treatment, *PHC* Primary healthcare, *DS* Drug-susceptible, *DR* Drug-resistant

access care at large hospitals [5, 26, 27]. Our study found considerable movement of children between community PHC facilities, general hospitals and TB hospitals during their TB episode, possibly increasing the risk of unfavourable outcomes and incomplete NTP surveillance data. Almost half of the children received in-patient tertiary care for 2–3 weeks, and a fifth of the children were referred to TB hospitals for specialized care after discharge. Only approximately two-thirds were referred for community TB care. An additional advantage of hospital-based surveillance for paediatric TB, is to provide information on hospital admissions and to inform resource allocation to improve management of children with TB. Despite the relative resource intensity of clinical surveillance in a large hospital, a major advantage is the ability to complete linkage to care and real-time follow-up, which is not feasible when using laboratory-based surveillance only due to long turn-around time in culture results. This will be only partially addressed by the shorter turn-around time of new microbiological methods such as Xpert MTB/RIF, as current molecular diagnostic methods are less sensitive than culture in paucibacillary TB [28].

Overall TB treatment outcomes were very good despite the young age and the high proportion of children with severe TB and co-morbidities (HIV co-infection and malnutrition), especially in children with DR-TB. The higher proportion of favourable outcomes amongst children with DR-TB is likely partly a function of the established high-quality clinical program for the management of children with DR-TB in this setting and the more complete follow-up data available in this group of children. The treatment outcomes observed in the drug-resistant group are similar to those described previously in this setting (92% favourable treatment outcomes; $n = 149$) [29]. We report favourable outcomes similar to those observed in a study evaluating routine community-based surveillance data for children treated for DS-TB in this setting (85.9%), where children typically would have limited/uncomplicated disease [30]. However, mortality among children with DS-TB (4.9%) was considerably higher than reported from routine community-based NTP surveillance data (0.7%) from the same setting. Laboratory hospital-based surveillance identified the majority of children who died from TB during hospitalization (two never started TB treatment), and can potentially provide important information on paediatric mortality. This highlights the importance of hospital-based surveillance strategies to better capture TB mortality in children. However, TB treatment outcome data do not provide information on morbidity, hospital admission requirements, healthcare costs and the lifelong disabilities suffered by children and families resulting from severe forms of TB like TB meningitis, osteoarticular disease (especially spinal TB), and chronic lung disease from PTB. A long-term outcome study evaluating children with TB meningitis found that only 1 in 5 children functioned normally at long-term follow-up (median follow-up time after completion of anti-tuberculosis therapy: 6 years 6 months), with 80% suffering cognitive impairment, highlighting the extreme morbidity and life-long implications of TB meningitis [31]. Hospital-based surveillance data can therefore provide important information to the NTP to guide appropriate planning and resource allocation.

Our study had several limitations. All children diagnosed with or managed for TB by routine healthcare services clinicians were included. Over-diagnosis in the clinically diagnosed group was therefore possible, especially among very young and HIV-infected children. However, given the high proportion of children with a confirmed diagnosis in this cohort, and the specialised nature of clinical services at the tertiary referral hospital, we expect the proportion of children who did not truly have TB to be low. Operational implementation of ongoing clinical surveillance in a hospital with 10 paediatric wards, several outpatients and an emergency unit, staffed with more than a 100 clinicians was challenging.

Study personnel had to rely on hospital clinicians to record all children diagnosed over weekends and evaluated as out-patients in paper-based registers, and clinical surveillance may have missed some patients. The documented burden of disease in our study would therefore represent the minimum burden of paediatric TB managed at TBH.

Conclusion

Complementary hospital-based surveillance strategies are essential to provide a comprehensive picture of the burden, spectrum, referral pathways and outcomes of children with TB managed at referral hospital level. It is important to understand setting-specific and epidemiological differences when interpreting NTP TB data from different sources of surveillance. Integration of electronic patient management systems, including hospital data, could simplify and improve the accuracy of TB reporting in future. In settings where hospitals do not function as TB reporting units, the inclusion of hospital surveillance data within NTP surveillance data should be prioritised.

Abbreviations

ART: Antiretroviral therapy; CI: Confidence interval; DR-TB: Drug resistant TB; DS-TB: Drug susceptible TB; EPTB: Extra-pulmonary TB; *M.tb*: *Mycobacterium tuberculosis*; NTP: National Tuberculosis Program; OR: Odds ratio; PHC: Primary healthcare; PTB: Pulmonary TB; TB: Tuberculosis; TBH: Tygerberg Hospital; WHO: World Health Organisation

Acknowledgements

This operational research was funded by Fogarty International Centre Grant (3U2RTW007370-05S1). The authors would like to acknowledge Ms. Daphne Leukes, Ms. Klassina Zimri, Ms. Elizabeth Viljoen and Mr. Corne Bosch for their contribution to study activities and data collection. KDP's salary was supported by a South African National Research Foundation SARchi Chair in Paediatric Tuberculosis grant to ACH. Ms. K. Zimri was supported by National Research Foundation grant to HSS.

Funding

This research was funded through an operational and epidemiological research fellowship awarded to KDP by Fogarty International Centre Grant (3U2RTW007370-05S1). The funding body did not have any role in study design, data collection, analysis, interpretation of data or in writing the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KDP, HSS and ACH conceptualised the study and contributed towards protocol development. KDP, HSS, EW, RS and AS assisted with surveillance and data collection. KDP and RD was involved with data management, data cleaning and linkage between electronic data sources. KDP completed data analysis, and prepared the first draft of the manuscript. All authors (KDP, HSS, RD, EW, RS, AS and ACH) were involved with interpretation of the results, and provided critical input during manuscript preparation. All authors approved of the final version of the manuscript.

Ethics approval and consent to participate

Ethics approval was obtained from Stellenbosch University Health Research Ethics Committee (N11/09/28). Research approval was also obtained from the relevant provincial and municipal health authorities. As the study was implemented as part of standard clinical care, a waiver of individual informed consent was requested, and granted by the ethics committee.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Author details

[1]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa. [2]Tygerberg Hospital, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa. [3]Western Cape Department of Health, Cape Town, South Africa.

Received: 22 August 2017 Accepted: 2 March 2018
Published online: 23 March 2018

References

1. World Health Organisation. Global Tuberculosis Report 2017. Geneva: WHO/HTM/TB/2017.23; 2017.
2. Department of Health: South Africa. Guidelines for the management of tuberculosis in children 2013. DOH, Pretoria, South Africa, 2013. www.health.gov.za/index.php/shortcodes/2015-03-29-10-42-47/2015-04-30-08-18-10/2015-04-30-08-23-21?download=577:tb-in-children-guidelines. [Accesssed 12 Mar 2018].
3. Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Starke JJ, Enarson DA, Donald PR, Beyers N. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. 2004;8(4):392–402.
4. Marais BJ, Hesseling AC, Gie RP, Schaaf HS, Beyers N. The burden of childhood tuberculosis and the accuracy of community-based surveillance data. Int J Tuberc Lung Dis. 2006;10(3):259–63.
5. du Preez K, Schaaf HS, Dunbar R, Swartz A, Bissell K, Enarson DA, Hesseling AC. Incomplete registration and reporting of culture-confirmed childhood tuberculosis diagnosed in hospital. Public Health Action. 2011;1(1):19–24.
6. Schaaf HS, Marais BJ, Hesseling AC, Gie RP, Beyers N, Donald PR. Childhood drug-resistant tuberculosis in the western Cape Province of South Africa. Acta Paediatr. 2006;95(5):523–8.
7. Schaaf HS, Marais BJ, Hesseling AC, Brittle W, Donald PR. Surveillance of antituberculosis drug resistance among children from the Western Cape Province of South Africa–an upward trend. Am J Public Health. 2009;99(8):1486–90.
8. Seddon JA, Hesseling AC, Marais BJ, Jordaan A, Victor T, Schaaf HS. The evolving epidemic of drug-resistant tuberculosis among children in Cape Town, South Africa. Int J Tuberc Lung Dis. 2012;16(7):928–33.
9. Schaaf HS, Hesseling AC, Rautenbach C, Seddon JA. Trends in childhood drug-resistant tuberculosis in South Africa: a window into the wider epidemic? Int J Tuberc Lung Dis. 2014;18(7):770–3.
10. Schaaf HS, Garcia-Prats AJ, du Preez K, Rautenbach C, Hesseling AC. Surveillance provides insight into epidemiology and spectrum of culture-confirmed mycobacterial disease in children. Int J Tuberc Lung Dis. 2016;20(9):1249–56.
11. Marais BJ, Hesseling AC, Gie RP, Schaaf HS, Enarson DA, Beyers N. The bacteriologic yield in children with intrathoracic tuberculosis. Clin Infect Dis. 2006;42(8):e69–71.
12. Rachow A, Clowes P, Saathoff E, Mtafya B, Michael E, Ntinginya EN, Kowour D, Rojas-Ponce G, Kroidl A, Maboko L, et al. Increased and expedited case detection by Xpert MTB/RIF assay in childhood tuberculosis: a prospective cohort study. Clin Infect Dis. 2012;54(10):1388–96.
13. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. Lancet. 2005;365(9454):130–4.
14. Massyn N, Peer N, English R, Padarath A, Barron P, Day C. District health barometer 2015/16. Durban: Health Systems Trust; 2016.

15. Snow K, Hesseling AC, Naidoo P, Graham SM, Denholm J, du Preez K. Tuberculosis in adolescents and young adults: epidemiology and treatment outcomes in the Western Cape. Int J Tuberc Lung Dis. 2017;21(6):651–7.
16. Western Cape Government. Annual Report: Tygerberg Hospital. 2012. https://www.westerncape.gov.za/your_gov/153/documents/annual_reports/2012. [Accessed 12 Mar 2018].
17. van Toorn R, Schaaf HS, Laubscher JA, van Elsland SL, Donald PR, Schoeman JF. Short intensified treatment in children with drug-susceptible tuberculous meningitis. Pediatr Infect Dis J. 2014;33(3):248–52.
18. Sayers A, Ben-Shlomo Y, Blom AW, Steele F. Probabilistic record linkage. Int J Epidemiol. 2016;45(3):954–64.
19. Cole TJ. The LMS method for constructing normalized growth standards. Eur J Clin Nutr. 1990;44(1):45–60.
20. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007;335(7624):806–8.
21. Nataprawira HM, Ruslianti V, Solek P, Hawani D, Milanti M, Anggraeni R, Memed FS, Kartika A. Outcome of tuberculous meningitis in children: the first comprehensive retrospective cohort study in Indonesia. Int J Tuberc Lung Dis. 2016;20(7):909–14.
22. Bang ND, Caws M, Truc TT, Duong TN, Dung NH, Ha DT, Thwaites GE, Heemskerk D, Tarning J, Merson L, et al. Clinical presentations, diagnosis, mortality and prognostic markers of tuberculous meningitis in Vietnamese children: a prospective descriptive study. BMC Infect Dis. 2016;16(1):573.
23. Chiang SS, Khan FA, Milstein MB, Tolman AW, Benedetti A, Starke JR, Becerra MC. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. Lancet Infect Dis. 2014;14(10):947–57.
24. Tilahun G, Gebre-Selassie S. Treatment outcomes of childhood tuberculosis in Addis Ababa: a five-year retrospective analysis. BMC Public Health. 2016;16:612.
25. Aketi L, Kashongwe Z, Kinsiona C, Fueza SB, Kokolomami J, Bolie G, Lumbala P, Diayisu JS. Childhood tuberculosis in a sub-saharan tertiary facility: epidemiology and factors associated with treatment outcome. PLoS One. 2016;11(4):e0153914.
26. Edginton ME, Wong ML, Phofa R, Mahlaba D, Hodkinson HJ. Tuberculosis at Chris Hani Baragwanath hospital: numbers of patients diagnosed and outcomes of referrals to district clinics. Int J Tuberc Lung Dis. 2005;9(4):398–402.
27. Loveday M, Thomson L, Chopra M, Ndlela Z. A health systems assessment of the KwaZulu-Natal tuberculosis programme in the context of increasing drug resistance. Int J Tuberc Lung Dis. 2008;12(9):1042–7.
28. Detjen AK, DiNardo AR, Leyden J, Steingart KR, Menzies D, Schiller I, Dendukuri N, Mandalakas AM. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis. Lancet Respir Med. 2015;3(6):451–61.
29. Seddon JA, Hesseling AC, Godfrey-Faussett P, Schaaf HS. High treatment success in children treated for multidrug-resistant tuberculosis: an observational cohort study. Thorax. 2014;69(5):458–64.
30. Osman M, Lee K, Du Preez K, Dunbar R, Hesseling AC, Seddon JA: Excellent treatment outcomes in children treated for tuberculosis under routine operational conditions in Cape Town. Clin Infect Dis 2017, cix602, https://doi.org/10.1093/cid/cix602.
31. Schoeman J, Wait J, Burger M, van Zyl F, Fertig G, van Rensburg AJ, Springer P, Donald P. Long-term follow up of childhood tuberculous meningitis. Dev Med Child Neurol. 2002;44(8):522–6.

CHAPTER 5: THE EPIDEMIOLOGICAL VALUE OF HOSPITAL-BASED SURVEILLANCE OF TUBERCULOSIS IN HIV-INFECTED CHILDREN AND IN CHILDREN WITH SEVERE TUBERCULOSIS

In the previous chapter I highlighted the importance of using both bacteriological and clinical surveillance to more accurately capture the true burden and spectrum of paediatric tuberculosis (TB) diagnosed and managed at a large, tertiary referral hospital (pillar 3 of the care cascade: 'Diagnosed with TB'). In this chapter, I conduct further in-depth research to determine the value of hospital-based surveillance for the diagnosis of TB in two important paediatric sub-populations who are most likely to be diagnosed and managed at hospital level: HIV-infected children with TB, and TB meningitis (TBM), the most severe form of paediatric TB.

Study 1: The timing of HIV diagnosis in children with tuberculosis managed at a referral hospital in Cape Town[91]

HIV-infected children are at very high risk of developing TB. A recent systematic review showed an 8-fold increase (incidence rate ratio [IRR]=7.9, 95% confidence interval [CI] 4.5-13.7) in risk of TB amongst HIV-infected children compared to HIV-uninfected children in the absence of antiretroviral therapy (ART).[10] ART lowered this risk by approximately 70% and even more over the first 12 months.[10] The risk of TB in HIV-infected infants (<1 year of age) is even higher – they are approximately 24 times more likely to develop TB than their HIV-uninfected peers.[9] In the previous chapter, I quantified the substantial burden of paediatric TB managed at Tygerberg Hospital (TBH) in Cape Town, South Africa. Of this cohort of 395 children with TB routinely diagnosed over a period of one year, 90 (24.3%) were HIV co-infected.

The timing of a diagnosis of HIV in children with TB is critically important. For some children, their TB symptoms might have prompted HIV testing, resulting in a relative late diagnosis of HIV within a healthcare system which has a strong focus on HIV prevention, including a widely implemented prevention-of-mother-to-child-transmission (PMTCT) programme, early HIV diagnosis initiatives and rapid introduction of ART. In South Africa, all infants were eligible for ART since 2010, all children 1-4 years of age since 2012, and all people living with HIV in South Africa since 2016.[92-94] In children already known to services with HIV infection, it is important to verify whether they have been started on ART, whether their ART has failed, or whether their ART has been interrupted. All of these possible scenarios are related to very different clinical or health system challenges, which require different solutions. Data on the specific scenarios outlined could help in the identification of specific gaps and targeted interventions. HIV

surveillance data in children with TB should therefore allow for distinguishing between these different groups of patients to inform the most suitable interventions. However, in South Africa, the current method of capturing HIV data in TB treatment registers has several limitations, including inadequate information on the timing of HIV diagnosis in relation to a diagnosis of TB, and limited data on the timing of initiation, the duration of ART and adherence.

This retrospective cohort study, nested in the larger surveillance study described in chapter 4, investigated the prevalence of and factors associated with a simultaneous diagnosis of TB and HIV in children routinely diagnosed or treated for TB at TBH in 2012. A simultaneous diagnosis of TB and HIV was defined as an HIV diagnosis made within 7 days before or after a diagnosis of TB was made.

Approximately 40% of the children co-infected with HIV and TB had a delayed diagnosis of HIV with an HIV diagnosis made at or after the time of their TB diagnosis. Amongst the children already known to be HIV-infected at the time of their TB diagnosis, missed opportunities for ART initiation were identified in nearly half of all ART-naïve children, and ART interruptions were reported amongst almost 30% of those who were initiated on ART before their TB diagnosis.

In this hospital cohort, nearly three-quarters (74%) of HIV-infected children with TB were <5 years of age. The prevalence of HIV infection in all young children with TB (0-4 years of age) was significantly higher in this hospital cohort compared to the routine TB treatment surveillance data presented in chapter 3. During 2012, 65 of all 296 (22%) 0-4 year olds at TBH were HIV-infected compared to 3,751 of 26,294 (14%) 0-4 year olds in the ETR.Net database ($p<0.001$).

Children whose maternal HIV infection status was not known or whose mothers were HIV-negative during pregnancy or at the time of their birth, had a nearly 3-times higher odds (odds ratio [OR] 2.7, 95% CI 1.0–7.2) of having a simultaneous diagnosis of TB and HIV. This finding emphasizes the importance of repeated maternal HIV testing, not only antenatally, but also at birth and during breastfeeding, and the need for a low threshold for testing or re-testing breastfed and/or HIV-exposed infants and children in settings with high burden of TB and HIV.

The study also identified remaining gaps in PMTCT implementation, with almost a third of children born to known HIV-infected mothers not receiving or reporting having received PMTCT. This is an important missed opportunity for HIV prevention and may reflect lack of access, or other barriers to access the well-established antenatal care and PMTCT services in the study setting. Children co-diagnosed with TB and HIV had a higher risk of disseminated TB (including TBM; OR 5.7, 95%CI 1.0-31.2) and having an unfavourable TB treatment outcome (OR 5.9, 95% CI 1.4–25.2). All in-hospital deaths (n=3) also occurred in the group where HIV was diagnosed simultaneously with TB. In total, nearly three quarters (65/88; 74%) of all HIV-infected children

with incident TB in this hospital cohort were not on effective ART at the time of TB diagnosis. These data further highlights the importance of an early diagnosis of HIV and rapid initiation of ART, to prevent TB including progression to more severe forms of TB. Young children often access healthcare services for immunisations or other routine child care ("well child services"), and every encounter is a potential opportunity to screen and test the mother and child for HIV and for TB.

The diagnosis of TB provides an important opportunity to test for HIV in children. All children evaluated for TB should therefore should be tested for HIV, especially in settings with high burden of TB and HIV. A TB diagnosis is also an opportunity to verify ART adherence and support re-initiation of ART. Following the completion of this study, missed opportunities for ART initiation would likely have been reduced since South Africa adopted a universal-test-and-treat-policy in 2016, allowing universal access to ART for all people living with HIV. This study is an example of how the rich clinical data captured through hospital surveillance can be used for operational research as a monitoring and evaluation approach for paediatric TB and emphasizes the importance of integration of TB and HIV services in children.

Study 2. Global shortages of BCG vaccine and the impact on tuberculous meningitis in children[95]

TBM is the most devastating form of TB, with high morbidity and mortality.[20] Lifelong physical disability and intellectual impairment is common in child survivors,[21] resulting in substantial social, physical, and economic burden to children, families, and health services. Children with TBM are mostly diagnosed at hospital level and in the Western Cape province, often complete their treatment as hospital inpatients. A previous study from TBH found that children with TBM were significantly less likely to be included in routine reported TB surveillance data compared to children with other forms of TB.[38]

Detailed information on the spectrum of TB disease, including the burden of TBM, is not part of the currently required routine TB indicators reported to the World Health Organisation (WHO) by national TB programmes. In South Africa, International Classification of Disease 10 (ICD-10) codes are meant to be captured in the ETR.Net for the primary and secondary TB diagnoses of each patient. However, this data is often not accurately captured and does not include hospital data from several provinces. Cases with severe forms of TB carry a disproportionately large burden of the mortality and morbidity of paediatric TB, making them an important sub-group of children with TB. TBM, despite its epidemiological, clinical and health systems relevance, is

currently not reported on separately, and the TB care cascade is therefore not able to fully represent the TB disease spectrum observed in children.

For several decades, bacille Calmette-Guérin (BCG) vaccination has been an integral part of routine WHO-recommended Expanded Programme on Immunization (EPI) childhood immunisation programmes in high TB burden countries. Two systematic reviews found a consistent protective effect of BCG vaccination against miliary TB and TBM in young children.[96, 97]

Since 2013, the global availability and procurement of BCG has been challenging due to problems with vaccine production and a limited number of suppliers.[98] Local vaccine shortages were experienced in the Western Cape province from 2015, presenting a unique opportunity to document the effect of these shortages on the burden of TBM.

This study investigated trends in the number of children with TBM admitted to TBH during 2008-2017, before and during the time that these BCG shortages were experienced. Poisson regression was used to model the count of admissions for 10 years and estimated a specific incidence rate ratio (IRR) for 2017 compared to the preceding 2 years (2014-2016), where there were no BCG vaccine shortages. Birth cohort analyses were completed to evaluate the relationship between the years the BCG shortages were experienced and the incidence of TBM.

This study found an alarming increase in the number of admissions for TBM and/or tuberculomas during 2017, with the number of admissions increasing from a mean of 32.7 in 2014–2016 to 70 in 2017 (IRR 2.2, 95% CI 1.6–2.9; p<0·0001). Admissions for TBM and or tuberculomas before the age of 2 years, were almost three times higher in children born during 2015 (the period during which BCG stock-outs started in the study setting), compared to the mean number of those born during the preceding 3 years (IRR=2.7, 95% CI 1.3-5.5, p=0.005).

This study highlights the importance of monitoring trends of TBM in children as part of monitoring and evaluation for paediatric TB, and the importance of this data for monitoring the impact of TB prevention strategies. This study again confirmed the role of neonatal BCG vaccination as a critical component of TB control especially in the prevention of severe forms of TB in young children. Strategies should be put in place to prevent disruption in vaccine supply, allowing for uninterrupted BCG vaccination at birth for children born in high TB burden settings. This study also highlights the importance of epidemiological surveillance of severe forms of TB in children, typically not captured in routine TB surveillance data, and the utility of TBM as a sensitive indicator of the effectiveness of TB prevention strategies.

Citations:

Byamungu LN*, **Du Preez K***, Walters E, Nachega JB, Schaaf HS. Timing of HIV diagnosis in children with tuberculosis managed at a referral hospital in Cape Town, South Africa. Int J Tuberc Lung Dis. 2018;22(5):488-95. doi: 10.5588/ijtld.17.0613. PubMed PMID: 2966395.

*Contributed equally – I jointly led the design of the study with LN Byamungu, assisted with study implementation and data collection, led the statistical analysis, contributed equally to the interpretation of the study results and write-up of the manuscript.

(This data contributed towards LN Byamungu's MSc in Clinical Epidemiology at Stellenbosch University in 2016 and was included as additional relevant output only)

du Preez K, Seddon JA, Schaaf HS, Hesseling AC, Starke JR, Osman M, Lombard CJ, Solomons R. Global shortages of BCG vaccine and tuberculous meningitis in children. Lancet Glob Health. 2019;7(1):e28-e9. doi: 10.1016/S2214-109X(18)30474-1. PubMed PMID: 30554756.

INT J TUBERC LUNG DIS 22(5):488–495

http://dx.doi.org/10.5588/ijtld.17.0613

Timing of HIV diagnosis in children with tuberculosis managed at a referral hospital in Cape Town, South Africa

L. N. Byamungu,* K. du Preez,† E. Walters,† J. B. Nachega,‡§¶ H. S. Schaaf†

*Department of Global Health, †Desmond Tutu TB Centre, Department of Paediatrics and Child Health, ‡Department of Medicine and Centre for Infectious Diseases, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; §Departments of Epidemiology, Infectious Diseases and Microbiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, ¶Departments of Epidemiology and International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA

SUMMARY

SETTING: Tygerberg Hospital, Western Cape Province, Cape Town, South Africa.

OBJECTIVE: To investigate the prevalence of and factors associated with simultaneous tuberculosis (TB) and human immunodeficiency virus (HIV) diagnoses in children.

DESIGN: Retrospective cohort study in TB-HIV co-infected children aged <13 years admitted to Tygerberg Hospital in 2012. Data were collected from medical records, laboratory results and electronic TB treatment registers. A simultaneous TB-HIV diagnosis was defined as an HIV diagnosis made within 7 days before or after a diagnosis of TB.

RESULTS: Of 88 children with TB-HIV co-infection, 37 (42%) had a simultaneous TB-HIV diagnosis; 51 children had been known to have HIV before their TB diagnosis. Interruption of antiretroviral therapy (ART) was reported in 9/32 (28%) children with known HIV infection at TB diagnosis, while missed opportunities for ART initiation were identified in 8/19 (42%) ART-naïve children. Simultaneous TB-HIV diagnosis was more likely if maternal HIV infection was unknown at the time of the child's birth (OR 2.7, 95%CI 1.0–7.2), and was associated with unfavourable TB treatment outcomes (OR 5.9, 95%CI 1.4–25.2).

CONCLUSION: TB diagnosis provides an important opportunity to test children for HIV. Missed opportunities for HIV prevention, earlier diagnosis and ART initiation were identified.

KEY WORDS: TB-HIV co-infection; infants; children; ART; missed opportunities

HUMAN IMMUNODEFICIENCY VIRUS (HIV) infection is among the strongest risk factors for developing tuberculosis (TB) after infection with *Mycobacterium tuberculosis*. HIV-infected infants aged <1 year who are not on antiretroviral therapy (ART) are 24 times more likely to develop TB than their non-HIV-infected counterparts.[1] TB-HIV co-infected children also have a six times higher risk of death than HIV-infected children without TB.[2,3] Almost 9% of all HIV-infected children in a high HIV burden country live in South Africa.[4] In Western Cape Province, one of the three provinces in South Africa with the highest incidence of TB, approximately 0.7% (95% confidence interval [CI] 0.2–2.1) of children aged 2–14 years were HIV-infected in 2012.[5,6]

Evidence from the Children with HIV Early Antiretroviral Therapy (CHER) trial showed that early ART reduced all-cause mortality by up to 76% and progression to HIV disease by 75% in childhood.[7] These findings prompted an update to the World Health Organization (WHO) guidelines in 2010 recommending ART for all HIV-infected infants aged <1 year, and according to CD4 percentage thresholds for children aged 1–5 years. South Africa included these recommendations in its updated 2010 national ART guidelines, recommending treatment for all HIV-infected children aged <1 year, irrespective of clinical stage or CD4 count; for children aged 1–5 years if WHO clinical Stage 3 or 4, or CD4 count ⩽25% or 750 cells/μl; and for those aged >5 years if WHO clinical Stage 3 or 4 or CD4 count ⩽350 cells/μl.[8]

In Western Cape Province, only 65% of all children who tested HIV-positive using polymerase chain reaction (PCR) were linked to ART services using

LNB and KdP contributed equally to the study and manuscript. HSS and JBN co-supervised the study as senior authors.

Correspondence to: Jean B Nachega, Faculty of Medicine and Health Sciences, Department of Medicine & Centre for Infectious Diseases, Stellenbosch University, Francie van Zijl Drive, Parow 7505, Cape Town, South Africa. e-mail: jnachega@sun.ac.za

Article submitted 3 September 2017. Final version accepted 3 January 2018.

viral load testing performed before ART initiation as a marker.[9] Access to ART is even lower in many low- and middle-income countries, where ART coverage in children is estimated to be 23%.[10] In 2013, South African national guidelines were again updated to recommend treatment of all HIV-infected children aged <5 years regardless of CD4 count.[11] Western Cape Province consolidated these guidelines 1 year later, and in addition promoted HIV-PCR testing within 48 h after birth for all infants antenatally exposed to HIV.[12]

Mother-to-child transmission of HIV in Western Cape Province decreased from 8.7% in 2003 to 1.6% in 2012.[13,14] At the time of the present study, the 2010 South African HIV guidelines were in practice.[8] ART initiation was recommended within 2 weeks of HIV diagnosis if children were aged <1 year at the time of HIV diagnosis, WHO HIV Stage 4, or co-infected with multidrug-resistant or extensively drug-resistant TB. The 2010 national guidelines for the prevention of mother-to-child transmission (PMTCT) of HIV recommended testing all pregnant women for HIV at their first antenatal visit, and again at around 32 weeks gestation if the first test was negative, to detect late seroconversion.[15]

South Africa remains among the 21 African countries with the highest rates of HIV infection in pregnant women; however, only 49% of these exposed infants received early infant testing for HIV and only 31% of HIV-infected children aged <15 years received ART in 2014.[16] Diagnostic and treatment delays increase the risk of developing TB and other opportunistic infections and jeopardise clinical outcomes.[17] We investigated the prevalence of and risk factors associated with a simultaneous HIV diagnosis in children managed with TB at a referral hospital in Western Cape Province, South Africa.

STUDY POPULATION AND METHODS

Setting and context

We conducted a retrospective cohort study of all TB-HIV co-infected children aged <13 years (paediatric ward admission criteria) managed at Tygerberg Hospital (TBH), Cape Town, South Africa, during 2012. All children with presumed or confirmed TB were identified through active daily surveillance in the paediatric wards by dedicated research personnel as part of a health system strengthening intervention to improve linkage to care between hospital and community clinics for children with TB. TBH is a referral hospital that provides secondary and tertiary level care to approximately a third of the population of Western Cape Province. During 2012, 9802 children were admitted to TBH and 14 178 children were seen as out-patients in the general paediatrics service.[18]

Variables and data management

Clinical and laboratory information were extracted retrospectively onto a standard case report form through hospital chart review and from the National Health Laboratory Service (NHLS) database. Documentation of referral to social worker and receipt of a child support grant at the time of hospital presentation were used as indicators of the social support needed by the families.

TB treatment outcomes were obtained using probabilistic record linkage[19] with extracted copies of the provincial electronic TB registers (ETR.Net for drug-susceptible TB; EDRweb for drug-resistant TB) and then manually reviewed. Additional information on TB treatment outcome was obtained from hospital chart review and telephone contact with the receiving health care facilities to which the children had been discharged. Standard WHO definitions for TB treatment outcomes were used according to South African National TB Programme guidelines.[20]

We searched laboratory records to clinically verify the recorded date of HIV diagnosis. The main outcome variable was based on the timing of HIV diagnosis in relation to TB diagnosis. We compared children for whom the diagnosis or symptomatic presentation of TB led to HIV testing and the diagnosis of HIV infection (as a proxy for a late diagnosis of HIV) with those who had been diagnosed with HIV before developing TB. All children were therefore categorised into one of two groups: HIV diagnosed simultaneously with or after TB, or HIV diagnosed before TB. All children who were diagnosed with HIV on the same day or after the date of TB diagnosis were classified as 'HIV diagnosed with/after TB'. A medical chart review was performed among all children who were diagnosed with HIV within 7 days before the TB diagnosis. If signs or symptoms consistent with TB disease were recorded at the time of HIV diagnosis, children were classified as 'HIV diagnosed with/after TB'. If there was no evidence of TB symptoms at the time of HIV diagnosis, or if HIV was diagnosed >7 days before the TB diagnosis, children were classified as 'HIV diagnosed before TB'. We wanted to distinguish between children for whom TB was the event leading to an HIV diagnosis and those with newly diagnosed HIV infection who were diagnosed with TB as part of routine investigation before ART initiation. Children diagnosed with HIV before TB were further classified into those who were started on ART before TB diagnosis and those who were not receiving ART at the time of TB diagnosis.

We calculated the age of children at HIV diagnosis to determine eligibility for ART initiation according to the 2010 South African guidelines. If children were diagnosed with HIV >4 weeks before their TB diagnosis and were eligible to start ART according

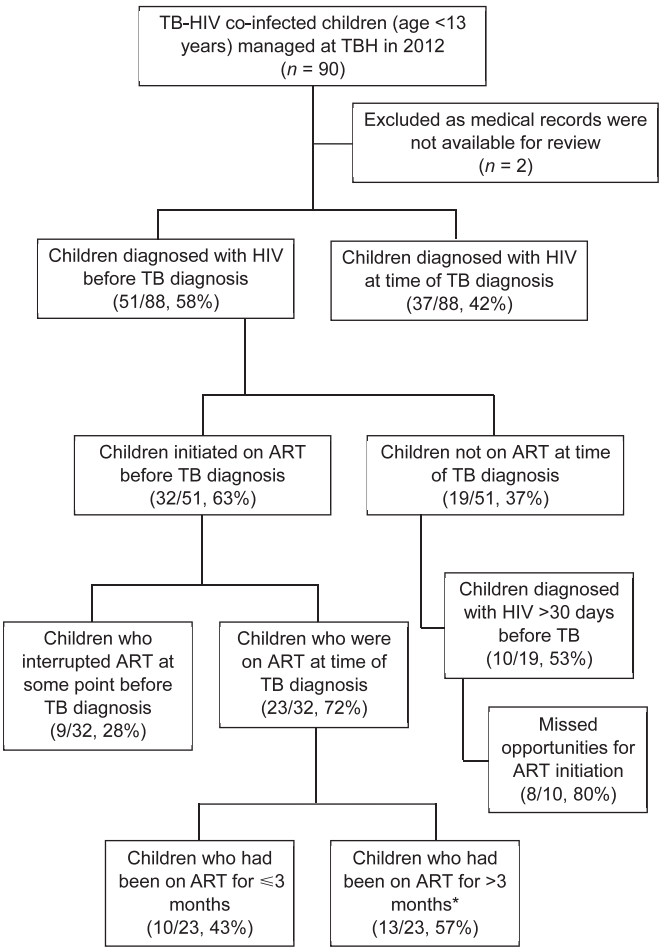


Figure Timing of HIV diagnosis and initiation of ART in children with TB managed at TBH in 2012. *Of the 11 children with an available viral load result who had been on ART for >3 months, only one child had an undetectable viral load result at the time of TB diagnosis. TB = tuberculosis; HIV = human immunodeficiency virus; TBH = Tygerberg Hospital; ART = antiretroviral therapy.

to the guidelines, they were classified as missed opportunities for ART initiation. Advanced HIV disease at the time of hospital admission was based on WHO HIV staging guidelines taking into account age and immunological criteria based on CD4 count results obtained within a 6-week window before/after the TBH admission date.[21]

Data were entered into a password-protected database using Excel™ 2016 (MicroSoft, Redmond, WA, USA). Personal identifying information was removed on completion of matching, and 11-digit barcodes were used as unique identifiers.

Statistical analysis

We used STATA v14 (StataCorp, College Station, TX, USA) for analyses. Baseline characteristics recorded at the time of presentation at TBH were stratified by the timing of HIV diagnosis in relation to TB diagnosis using frequencies and percentages for categorical data and medians with interquartile ranges (IQRs) for continuous data. Proportions were compared using the χ^2 or Fisher's exact test, while crude odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate effect size.

Regulatory approvals

The study protocol was approved by the Stellenbosch University Health Research Ethics Committee, Cape Town (S15/10/255), with a waiver for individual informed consent due to its retrospective nature. Approval was also obtained from TBH, Cape Town, and the Western Cape Province Department of Health, Cape Town.

RESULTS

During 2012, 90 children with TB-HIV co-infection were treated at TBH, 88 (98%) of whom had charts available for review (Figure). TB and HIV were diagnosed simultaneously in 37 (42%) children. In 51 (58%) children, HIV was diagnosed before TB, 19 of whom were not receiving ART, although 10/19 had been diagnosed with HIV infection >30 days earlier. Of these 10 children, eight were infants at the time of

Table 1 Demographic, birth history and social support characteristics of TB-HIV co-infected children managed during 2012 at Tygerberg Hospital, stratified by the relationship in timing of TB and HIV diagnoses ($n = 88$)

Variables	Total ($n = 88$)* *n/N* (%)	HIV diagnosed before TB ($n = 51$) *n/N* (%)	HIV diagnosed with TB ($n = 37$) *n/N* (%)	Univariate analysis OR (95%CI)	*P* value
Demographic factors					
Age at admission, years					
<1	30 (34.1)	18 (35.3)	12 (32.4)	Reference	
1–<5	35 (39.8)	19 (37.3)	16 (43.2)	1.3 (0.5–3.4)	0.643
5–<13	23 (26.1)	14 (27.5)	9 (24.3)	0.9 (0.3–2.9)	0.949
Sex					
Male	46 (52.3)	27 (52.9)	19 (51.4)	Reference	
Female	42 (47.7)	24 (47.1)	18 (48.7)	1.0 (0.5–2.5)	0.884
Maternal and birth history characteristics					
Documentation of maternal HIV status at the time of admission					
Documented as HIV-positive	82 (93.2)	48 (94.1)	34 (91.9)	Reference	
HIV status not documented	6 (6.8)	3 (5.9)	3 (8.1)	1.4 (0.2–7.5)	0.693
Documentation of maternal HIV status during pregnancy or at the birth of the child ($n = 75$)†					
HIV-positive	46/75 (61.3)	30/42 (71.4)	16/33 (48.5)	Reference	
HIV-negative	29/75 (38.7)	12/42 (28.6)	17/33 (51.5)	2.7 (1.0–7.1)	0.044
Any documentation that child received PMTCT if mother HIV-infected and status known at birth ($n = 45$)‡					
Yes	29/45 (64.4)	18/29 (62.1)	11/16 (68.8)	Reference	
No	16/45 (35.6)	11/29 (37.9)	5/16 (31.3)	0.7 (0.2–2.8)	0.658
Maternal breastfeeding ($n = 66$)					
Yes	51/66 (77.3)	30/37 (81.1)	21/29 (72.4)	Reference	
No	15/66 (22.7)	7/37 (18.9)	8/29 (27.6)	1.6 (0.5–5.3)	0.408
Type of feeding ($n = 60$)					
Exclusive§	23/60 (38.3	11/32 (34.4)	12/28 (38.3)	Reference	
Mixed	37/60 (61.7)	21/32 (65.6)	16/28 (57.1)	0.7 (0.2–2.0)	0.504
Socio-economic factors					
Child support grant					
Yes	55 (62.5)	31 (60.8)	24 (64.9)	Reference	
No/not recorded	33 (37.5)	20 (39.2)	13 (35.1)	0.8 (0.4–2.0)	0.698
Social work referral					
Yes	57 (64.8)	34 (66.7)	23 (62.2)	Reference	
No	31 (35.2)	17 (33.3)	14 (37.8)	1.2 (0.5–2.9)	0.664

* Denominator 88 unless otherwise specified due to missing/not recorded data.
† Of 82 HIV-positive mothers, details of the time of maternal HIV diagnosis in relation to the child's birth were not recorded for seven (all in HIV before TB group).
‡ Of 46 children with HIV-infected mothers whose status was recorded as known at birth, PMTCT information was not recorded for 1.
§ Eight children were breastfed and 15 were formula-fed.
TB = tuberculosis; HIV = human immunodeficiency virus; OR = odds ratio; CI = confidence interval; PMTCT = prevention of mother-to-child transmission.

HIV diagnosis and were therefore eligible for ART. Of the 23 children diagnosed with HIV >7 days before TB and who were on ART at the time of TB diagnosis, 10 (43%) had been on ART for ⩽3 months. Of the 11 children who had a viral load result available and had been on ART for >3 months, only one child had an undetectable viral load result at the time of TB diagnosis.

Table 1 provides an overview of the demographics, birth history and social support characteristics of all children with TB-HIV, stratified by time of HIV diagnosis in relation to TB diagnosis. The median age at hospital presentation was 1.6 years (IQR 0.8–5.2); 30/88 (34%) were aged <1 year. Maternal HIV infection was documented in 82 (93%) mothers at the time of the child's presentation with TB to TBH. Of the 82 HIV-infected mothers, 46 (56%) were known to be HIV-infected during pregnancy or at the birth of their babies, 29 (35%) were HIV-negative during pregnancy or at their baby's birth, and HIV status during pregnancy/at birth was not recorded in 7 (9%) charts. Children with mothers whose HIV infection status was negative during pregnancy were twice as likely to have an HIV diagnosis simultaneously with TB (OR 2.7, 95%CI 1.0–7.1, $P = 0.044$) as children whose maternal HIV infection was known during pregnancy/at birth. Of 46 children whose mothers were known to be HIV-infected at birth, provision of PMTCT had been documented for only 29 (64%). Care givers of 55 (63%) children were receiving a child support grant, and 57 (65%) required support from social services.

Clinical characteristics and TB treatment outcomes are given in Table 2. TB diagnosis was culture-confirmed in 18 (21%) children; 31 (35%) were diagnosed with extra-pulmonary TB and 9 (10%) had TB meningitis and/or miliary TB. Children with a simultaneous TB-HIV diagnosis were six times more likely (OR 5.7, 95%CI 1.0–31.2, $P = 0.032$) to present with disseminated TB than those with a previous diagnosis of HIV. All three (3%) children who died in hospital were diagnosed simultaneously with HIV and TB ($P = 0.071$). Overall favourable TB treatment outcomes were observed in 75 (85%) children. However, children diagnosed simultaneously with HIV and TB were six times more likely to have

Table 2 Clinical characteristics and TB treatment outcomes of TB-HIV co-infected children managed during 2012 at TBH, stratified by the relationship in timing of TB and HIV diagnoses ($n = 88$)

Variables	Total ($n = 88$)* *n/N* (%)	HIV diagnosed before TB ($n = 51$) *n/N* (%)	HIV diagnosed with TB ($n = 37$) *n/N* (%)	Univariate analysis OR (95%CI)	*P* value
TB-related clinical characteristics					
History of exposure to TB					
History of TB exposure	40/83 (48.2)	23/48 (47.9)	17/35 (48.6)	Reference	
No history of TB exposure	43/83 (51.8)	25/48 (52.1)	18/35 (51.4)	1.0 (0.4–2.5)	0.953
TB diagnosis					
Presumed	70 (79.6)	39 (76.5)	31 (83.8)	Reference	
Culture-confirmed	18 (20.5)	12 (23.5)	6 (16.2)	0.6 (0.2–1.9)	0.404
Site of TB disease					
PTB only	57 (64.8)	36 (70.6)	21 (56.8)	Reference	
EPTB with/without PTB†	31 (35.2)	15 (29.4)	16 (43.2)	1.8 (0.7–4.5)	0.183
Disseminated disease					
Yes (5 TB meningitis/3 miliary TB/ 1 both)	9 (10.2)	2 (3.9)	7 (18.9)	5.7 (1.0–31.2)	0.032
No	79 (89.8)	49 (96.1)	30 (81.1)	Reference	
In-hospital deaths	3 (3.4)	0	3 (8.1)	—	0.071
Type of anti-tuberculosis treatment					
Treatment for drug-susceptible tuberculosis	83 (94.3)	48 (94.1)	35 (94.6)	Reference	
Treatment for drug-resistant tuberculosis	5 (5.7)	3 (5.9)	2 (5.4)	0.9 (0.1–5.8)	1.000
HIV-related clinical characteristics					
CD4 laboratory results, median [IQR]‡					
CD4%	17.8 [12.0–24.6]	18.3 [11.9–25.5]	16.9 [12.0–23.0]		0.658§
CD4 cell count	547 [311–1050]	574 [337–1043]	521 [215–1203]		0.812§
Advanced HIV disease at time of TBH presentation¶					
No	18/65 (27.7)	11/36 (30.6)	7/29 (24.1)	Reference	
Yes	47/65 (72.3)	25/36 (69.4)	22/29 (75.9)	1.4 (0.5–4.2)	0.569
TB treatment outcomes					
Favourable	75 (85.2)	48 (94.1)	27 (73.0)	Reference	
Cured	2 (2.3)	1 (2.0)	1 (2.7)		
Completed	73 (83.0)	47 (92.2)	26 (70.3)		
Unfavourable	13 (14.8)	3 (5.9)	10 (27.0)	5.9 (1.4–25.2)	0.006
Died	6 (6.8)	1 (2.0)	5 (13.5)		
Transferred out	3 (3.4)	1 (2.0)	2 (5.3)		
Lost to follow-up/unknown	4 (4.6)	1 (2.0)	3 (8.1)		

* Denominator 88 unless specified otherwise due to missing data in folders/not recorded.
† 10 only EPTB, 21 both PTB and EPTB.
‡ 23 children did not have a CD4 result available within 6 weeks before/after hospital admission date, and therefore had missing data: 15 in those diagnosed before TB and 8 in those diagnosed simultaneously with TB and HIV. Results of stratified analyses of median CD4 (absolute and percentages with IQRs) if available by ART initiation in relation to TB diagnosis were as follows: children on ART with no reported ART interruptions ($n = 15/23$): CD4 absolute, 1036 (range 439–1594), CD4 percentage, 23.0% (IQR 16–27); children on ART with history of ART interruption ($n = 7/9$): CD4 absolute, 601 (range 331–1165), CD4 percentage 20% (IQR 14–48); children not yet on ART ($n = 14/19$): CD4 absolute, 391 (range 210–547), CD4 percentage 13% (IQR 9–17).
§ Mann-Whitney *U*-test was used for comparison between mean ranks.
¶ Defined according to age and immunological criteria based on CD4 results obtained within 6 weeks of TB admission date with advanced disease defined as (age, cut-off): <12 months, <30%; 12–35 months, <25%; 36–59 months, <20%; >5 years absolute <350.[21]
TB = tuberculosis; HIV = human immunodeficiency virus; TBH = Tygerberg Hospital; OR = odds ratio; CI = confidence interval; PTB = pulmonary TB; EPTB = extra-pulmonary TB; IQR = interquartile range; ART = antiretroviral therapy.

unfavourable TB treatment outcomes (OR 5.9, 95%CI 1.4–25.2, $P = 0.006$).

DISCUSSION

We found that 42% of TB-HIV co-infected children managed at a tertiary hospital had a late diagnosis of HIV infection (at or after TB diagnosis), despite a dedicated PMTCT and HIV programme in Western Cape Province.

In these children, the suspicion of TB disease likely prompted health care professionals to test for HIV. Unknown or negative maternal HIV infection status at the birth of the child significantly increased the risk of a TB-HIV co-diagnosis. Mother-to-child transmission is therefore likely to have occurred either at birth or postnatally through breastfeeding. This emphasises the importance of repeated maternal HIV testing in high HIV prevalence settings and early infant testing in HIV-exposed babies. In addition, clinicians should maintain a high index of suspicion and a low threshold for HIV testing among breastfed infants and children diagnosed with TB in a TB-HIV endemic area.

Provision of adequate PMTCT is an essential opportunity to prevent vertical HIV transmission from pregnant HIV-infected women.[22] The results of our study highlight gaps that remain in PMTCT implementation in Western Cape Province. In almost a third of children born to known HIV-infected mothers, PMTCT was not provided or not reported. These results are similar to those of other studies from

South Africa that report PMTCT uptake in only between 8.5% and 35% of pregnancies.[23–27] One study in 2013 found that gaps in PMTCT steps contributed to 34% of infant HIV infections in South Africa.[26] In addition, among children diagnosed with HIV before TB, we identified missed opportunities for ART initiation, all in infants. Retaining mothers in post-delivery care is critical for the health of both mothers and their infants, and strategies to close gaps in the continuity of care between antenatal and postnatal services, as well as improved integration of maternal and child health care programmes, are critical. Based on the 2015 Western Cape Province consolidated PMTCT guidelines calling for universal lifelong ART regardless of CD4 count ('Option B+'), theoretically many women with known HIV status may be on ART preconception onward. Option B+, if fully implemented, will likely increase the number of women getting PMTCT in the future.[12] Nearly two thirds of children in our study required social support, which further emphasises the importance of following an integrated approach to optimally support vulnerable families affected by TB-HIV.

In our study, children diagnosed simultaneously with HIV and TB had a higher risk of disseminated TB disease. All in-hospital deaths occurred in this group, and they were also at greater risk of unfavourable TB treatment outcomes. Similar to our results, a large cohort study of HIV-infected children enrolled in sub-Saharan African HIV care programmes found that children with advanced HIV disease presentations (including TB) had increased mortality and loss to follow-up rates.[17] The rate of favourable TB treatment outcomes was slightly higher in our study than in a large, multinational cohort of 386 HIV-infected children diagnosed with TB from 2012 to 2014 (85% vs. 80%).[28] This difference could have been a reflection of our study's urban setting, and the relatively good health care services in Western Cape Province; however, it may also have been due to the hospital-community linkage intervention that was part of the health systems strengthening study implemented during the time of this study. This intervention supported the continuity of TB care between hospital discharge and referral to local community clinics to continue anti-tuberculosis treatment.

Our results have important clinical and public health implications. In our study, children who were diagnosed with TB while on ART developed TB either within the first 3 months of ART (consistent with other literature supporting the early high incidence of TB unmasking with ART[29,30]) or in the context of an unsuppressed viral load. A recent systematic review showed the importance of an early diagnosis of HIV and initiation of ART, with TB incidence reduced by more than two thirds in HIV-infected children on ART (hazard ratio 0.30, 95%CI 0.21–0.39).[31] There is an urgent need to reinforce guidelines for early infant HIV diagnosis and treatment and to address the modifiable barriers to care identified above. Improved strategies to promote the integration of maternal and child health and improved access to TB-HIV services are essential to reduce the morbidity and mortality associated with TB-HIV co-infection.

Our study limitations included a small sample size owing to the availability of only a single year of comprehensive TB surveillance data and, as with any retrospective study, data collection relied on routinely recorded information in hospital records. Furthermore, rapid diagnostic HIV testing results were not consistently included in NHLS records; however, we included information from the medical records of the attending clinician during hospital admission, as well as any additional documentation found in the hospital folders (copies of Road-to-Health cards or antenatal records), as well as any laboratory tests that might be indicative of HIV infection to confirm the date of HIV diagnosis; we therefore do not expect this to have had substantial impact on our results. Laboratory data were limited to the results of tests performed as part of standard of care: testing was therefore not completed in a standardised manner. Reported laboratory results thus included CD4 results if available within a 6-week window around TBH admission. Finally, TB-HIV co-infected children admitted to a referral-level hospital are a very specific sub-population, and may not necessarily be representative of the larger population of co-infected children in Western Cape Province.

In conclusion, despite comprehensive national ante- and post-natal HIV testing guidelines, HIV co-infection was frequently diagnosed late, at the time of presentation with TB symptoms, in a large proportion of children. These children were at an increased risk of unfavourable TB treatment outcomes and death. Opportunities for earlier HIV diagnosis through adequate PMTCT provision and appropriate ART initiation were missed in many children in this high TB-HIV burden setting. These are modifiable factors that, if guidelines are followed appropriately, could substantially improve outcomes for TB-HIV co-infected children in this setting. Future implementation research should aim to identify modifiable factors contributing to delays in HIV diagnosis among mothers and children, and missed opportunities for early ART initiation in infants. Public health programmes in settings with a high HIV burden should offer repeat HIV testing for women testing HIV-negative at birth and during or after breastfeeding. These recommendations have been put to policy in Western Cape Province since 2015.[12] Future studies should evaluate the impact of this policy on early HIV diagnosis and ART initiation in mothers and children. Given the current gaps in health care delivery for children due to socio-economic and

health system factors, the diagnosis of TB in children in TB-HIV-endemic areas remains an important opportunity to test for HIV and provide appropriate care.

Acknowledgements

The authors thank R Dunbar for his contribution to record linkage and data management.

This operational research was partly funded by Fogarty International Centre (FIC), Bethesda, MD, USA (3U2RTW007370-05S1). HSS is supported by a National Research Fund (NRF, Pretoria, South Africa) grant. KdP's salary was supported by a South African NRF SARChI Chair in Paediatric Tuberculosis grant to ACH. JBN is supported by a research grant from the US National Institutes of Health (NIH)/National Institutes for Allergy and Infectious Disease, the AIDS Clinical Trial Group/Stellenbosch University Clinical Trial Unit (2UM1AI069521-08); and the Pittsburgh-Stellenbosch University AIDS-comorbidities Training Research Program (Pitt-SU AI-CoTRP; NIH/FIC 1D43TW010340-01).

Conflicts of interest: none declared.

References

1 Hesseling A C, Cotton M F, Jennings T, et al. High incidence of tuberculosis among HIV-infected infants: evidence from a South African population-based study highlights the need for improved tuberculosis control strategies. Clin Infect Dis 2009; 48: 108–114.
2 Swaminathan S. Tuberculosis in HIV-infected children. Paediatr Respir Rev 2004; 5: 225–230.
3 Palme I B, Gudetta B, Bruchfeld J, Muhe L, Giesecke J. Impact of human immunodeficiency virus 1 infection on clinical presentation, treatment outcome and survival in a cohort of Ethiopian children with tuberculosis. Pediatr Infect Dis J 2002; 21: 1053–1061.
4 Birx D. Analysis of the HIV epidemic in the highest burden countries. Atlanta, GA, USA: US Centers for Disease Control and Prevention, 2013. http://www.iapac.org/tasp_prep/presentations/TPSlon13_Closing_Panel_Birx.pdf. Accessed February 2018.
5 Soul City Institute for Social Justice. Tuberculosis in South Africa: literature review. Randburg, South Africa: Soul City Institute for Social Justice, 2015 http://www.soulcity.org.za/news/tuberculosis-in-south-africa-literature-review. Accessed February 2018.
6 Shisana O, Rehle T, Simbayi L C, et al. South African National HIV prevalence, incidence and behaviour survey, 2012. Cape Town, South Africa: Human Sciences Research Council, 2014. http://www.hsrc.ac.za/uploads/pageContent/4565/SABSSM IV LEO final.pdf. Accessed February 2018.
7 Cotton M F, Violari A, Otwombe K, et al. Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial. Lancet 2013; 382: 1555–1563.
8 Department of Health, South Africa. The South African antiretroviral treatment guidelines, 2010. Pretoria, South Africa: DoH, 2012. http://apps.who.int/medicinedocs/documents/s19153en/s19153en.pdf. Accessed February 2018.
9 Hsiao N-Y, Stinson K, Myer L. Linkage of HIV-infected infants from diagnosis to antiretroviral therapy services across the Western Cape, South Africa. PLoS ONE 2013; 8: e55308.
10 World Health Organization. Treatment of children living with HIV. Geneva, Switzerland: WHO, 2014. http://www.who.int/hiv/topics/paediatric/hiv-paediatric-infopage/en/. Accessed February 2018.
11 Department of Health, South Africa. The South African antiretroviral treatment guidelines 2013. Pretoria, South Africa: DoH, 2013. http://www.kznhealth.gov.za/medicine/2013_art_guidelines.pdf. Accessed February 2018.
12 Western Cape Government Department of Health. The Western Cape consolidated guidelines for HIV treatment: prevention of mother-to-child transmission of HIV (PMTCT), children, adolescents and adults. Cape Town, South Africa: Western Cape Government DoH, 2015. https://www.westerncape.gov.za/sites/www.westerncape.gov.za/files/the_western_cape_consolidated_guidelines_for_hiv_treatment_29032016.pdf. Accessed February 2018.
13 Western Cape Provincial AIDS Council. Annual progress report 2014/15. Cape Town, South Africa: Western Cape Government DoH, 2012. https://www.westerncape.gov.za/assets/departments/treasury/Documents/annual_report_2014-15.pdf. Accessed February 2018.
14 Stinson K, Giddy J, Cox V et al. Reflections on a decade of delivering PMTCT in Khayelitsha, South Africa. South Afr J HIV Med 2014; 15: 30–32.
15 Department of Health, South Africa. Clinical guidelines: PMTCT (prevention of mother-to-child transmission). Pretoria, South Africa: DoH, 2010. http://www.fidssa.co.za/Content/Documents/PMTCT_Guidelines.pdf. Accessed February 2018.
16 Ananworanich J, Abrams E J, Newell M, et al. Time to prioritise the UNAIDS 90-90-90 targets for infants. Lancet HIV 2016; 3: e241–243.
17 Bastard M, Poulet E, Nicolay N, Szumilin E, Balkan S, Pujades-Rodriguez M. Pediatric access and continuity of HIV care before the start of antiretroviral therapy in sub-Saharan Africa. Pediatr Infect Dis J 2016; 35: 981–986.
18 Tygerberg Hospital. Health annual report 2012. Cape Town, South Africa: Western Cape Government, 2012. https://www.westerncape.gov.za/your_gov/153/documents/annual_reports/2012. Accessed February 2018.
19 Sayers A, Ben-Shlomo Y, Blom A W, Steele F. Probabilistic record linkage. Int J Epidemiol 2016; 45: 954–964.
20 Health Systems Trust. National tuberculosis management guidelines 2014. Durban, South Africa: HST, 2014.
21 World Health Organisation. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva, Switzerland: WHO, 2007. http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf Accessed February 2018.
22 Goga A E, Dinh T-H, Jackson D J, et al. First population-level effectiveness evaluation of a national programme to prevent HIV transmission from mother to child, South Africa. J Epidemiol Community Health 2015; 69: 240–248.
23 Stinson K, Boulle A, Coetzee D, Abrams E J, Myer L. Initiation of highly active antiretroviral therapy among pregnant women in Cape Town, South Africa. Trop Med Int Health 2010; 15: 825–832.
24 Hussain A, Moodley D, Naidoo S, Esterhuizen T M. Pregnant women's access to PMTCT and ART services in South Africa and implications for universal antiretroviral treatment. PLoS ONE 2011; 6: e27907.
25 Stinson K, Boulle A, Smith PJ, Stringer EM, Stringer JSA, Coetzee D. Coverage of the prevention of mother-to-child transmission program in the Western Cape, South Africa using cord blood surveillance. J Acquir Immune Defic Syndr 2012; 60: 199–204.
26 Woldesenbet S, Jackson D, Lombard C, et al. Missed opportunities along the prevention of mother-to-child transmission services cascade in South Africa: uptake, determinants, and attributable risk (the SAPMTCTE). PLoS ONE 2015; 10: e0132425.
27 Horwood C, Butler L M, Haskins L, Phakathi S, Rollins N. HIV-infected adolescent mothers and their infants: low

coverage of HIV services and high risk of HIV transmission in KwaZulu-Natal, South Africa. PLoS ONE 2013; 8: e74568.
28 Carlucci J G, Blevins Peratikos M, Kipp A M, et al. Tuberculosis treatment outcomes among HIV/TB-coinfected children in the International Epidemiology Databases to Evaluate AIDS (IeDEA) Network. J Acquir Immune Defic Syndr 2017; 75: 156–163.
29 Walters E, Duvenhage J, Draper H R, et al. Severe manifestations of extrapulmonary tuberculosis in HIV-infected children initiating antiretroviral therapy before 2 years of age. Arch Dis Child 2014; 99: 998–1003.
30 Anígilájé E A, Aderibigbe S A, Adeoti A O, Nweke N O. Tuberculosis, before and after antiretroviral therapy among HIV-infected children in Nigeria: what are the risk factors? PLoS ONE 2016; 11: e0156177.
31 Dodd P J, Prendergast A J, Beecroft C, Kampmann B, Seddon J A. The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis. Thorax 2017; 72: 559–575.

RÉSUMÉ

CONTEXTE : Hôpital de Tygerberg, Province du Cap Ouest, Le Cap, Afrique.

OBJECTIF : Examiner la prévalence et les facteurs associés avec un diagnostic simultané de tuberculose (TB) et de l'infection par le virus de l'immunodéficience humaine (VIH) chez les enfants.

SCHÉMA : Etude rétrospective d'une cohorte d'enfants âgés de <13 ans coinfectés à l'hôpital Tygerberg en 2012. Les données ont été recueillies à partir de dossiers médicaux, de résultats de laboratoire et de registres électroniques de traitement de TB. Un diagnostic simultané de TB et de VIH a été défini comme un diagnostic de VIH établi dans les 7 jours précédant ou suivant le diagnostic de TB.

RÉSULTATS : Des 88 enfants avec une coinfection TB-VIH, 37 (42%) ont eu un diagnostic simultané de TB et de VIH ; 51 enfants ont eu un diagnostic de VIH avant celui de TB. Une interruption du traitement antirétroviral (ART) a été rapportée chez 9/32 (28%) enfants connus comme infectés par le VIH lors du diagnostic de TB, tandis que des opportunités manquées de mise en route de l'ART ont été identifiées chez 8/19 (42%) enfants n'ayant jamais eu d'ART. Un diagnostic simultané de TB-VIH a été plus probable si l'infection maternelle au VIH était inconnue lors de la naissance de l'enfant (OR 2,7 ; IC95% 1,0–7,2) et a été associé à des résultats défavorables du traitement de la TB (OR 5,9 ; IC95% 1,4–25,2).

CONCLUSION : Le diagnostic de TB constitue une opportunité majeure de tester les enfants pour le VIH. Des opportunités manquées de prévention, de diagnostic plus précoce du VIH et de mise en route de l'ART ont été identifiées.

RESUMEN

MARCO DE REFERENCIA: El Hospital Tygerberg de la Ciudad del Cabo en la Provincia Cabo Occidental de Suráfrica.

OBJETIVO: Investigar la prevalencia de diagnóstico simultáneo de infección por el virus de la inmunodeficiencia humana (VIH) y tuberculosis (TB) y los factores que se asocian este diagnóstico simultáneo en los niños.

MÉTODO: Fue este un estudio de cohortes retrospectivo de los niños de <13 años de edad aquejados de coinfección por el VIH y TB en el Hospital Tygerberg durante el 2012. Los datos se obtuvieron de las historias clínicas, los resultados de laboratorio y los registros electrónicos del tratamiento antituberculoso. Se definió el diagnóstico simultáneo de infección por el VIH y TB, como el diagnóstico de infección por el VIH ocurrido en un plazo de 7 días antes o 7 días después del diagnóstico de TB.

RESULTADOS: En 37 de los 88 niños con coinfección por el VIH y TB (42%) el diagnóstico de estas enfermedades había sido simultáneo; en 51 niños se conocía el diagnóstico de infección por el VIH antes de detectar la TB. Se notificó la interrupción del tratamiento antirretrovírico (ART) en nueve de 32 niños con diagnóstico conocido de infección por el VIH (28%), en el momento de diagnosticar la TB y se desaprovecharon oportunidades de iniciar el ART en ocho de 19 niños que nunca habían recibido ART (42%). El diagnóstico simultáneo de TB e infección por el VIH fue más probable cuando se desconocía la infección materna por el VIH en el momento del nacimiento del niño (OR 2,7; IC95% 1,0–7,2) y se asoció con desenlaces desfavorables del tratamiento antituberculoso (OR: 5,9; IC95% 1,4–25,2).

CONCLUSIÓN: El diagnóstico de TB ofrece una importante oportunidad de practicar la prueba diagnóstica de la infección por el VIH en los niños. El estudio reveló oportunidades desaprovechadas de prevención, diagnóstico más temprano e iniciación del tratamiento de la infección por el VIH.

Global shortages of BCG vaccine and tuberculous meningitis in children

The WHO estimates that 1 million children younger than 15 years developed tuberculosis globally in 2016, 58 000 of whom live in South Africa.[1] Vaccination with bacille Calmette-Guerín (BCG) has been an integral part of childhood immunisation programmes in countries with a high burden of tuberculosis for several decades. BCG traditionally has been considered to have limited efficacy in preventing tuberculosis disease in adults. However, BCG has consistently been shown to protect young children against miliary tuberculosis and tuberculous meningitis[2,3]—a devastating disease with high morbidity and mortality. Life-long disability is common in survivors,[4] resulting in substantial social, physical, and economic burden to children, families, and health services. WHO strongly recommends BCG vaccination be given to all neonates in settings with a high tuberculosis burden.[5]

Due to problems with vaccine production and limited supplier options in some countries, the global availability and procurement of BCG has been a challenge since 2013.[6] Concern was expressed in 2016 that this could lead to substantial increases in child mortality globally.[7] A mathematical model estimated that, globally, more than 100 000 deaths per birth cohort over the first 15 years of life could result from interrupted BCG vaccine supply.[8] To date, there have not been any empirical data to document the actual consequences of BCG shortages.

In the Western Cape province, South Africa, where BCG is routinely recommended at birth to all infants, BCG vaccine supply shortages were first experienced during 2015. Less than half the number of BCG vials were available for distribution in 2015 compared to the number of vials distributed annually in 2013 and 2014 (2013: 24 540 vials; 2014: 28 100 vials; 2015: 11 320 vials [personal communication: Sisanda Mtatambi, Biovac Institute]). Concerted efforts were made to reduce wastage of available stock, and the response of routine services resulted in only a 6% drop in reported BCG coverage (95% in 2014 to 89% in 2015 [personal communication: Sonia Botha, Western Cape Department of Health]).[9] However, some of these reported BCG doses included catch-up vaccinations for infants not receiving vaccinations at birth, and in high-burden tuberculosis settings, infants can be at risk of tuberculosis exposure before vaccination if not vaccinated at birth. In addition, contingency planning led to the procurement of a different BCG strain in 2016 (Danish strain, Serum Statens Institute Denmark replaced by Moscow strain, Serum Institute of India).

The number of children admitted to the paediatric neurology ward at Western Cape's Tygerberg Hospital, a large academic referral hospital, for diagnostic evaluation and management of tuberculous meningitis or tuberculomas showed an alarming increase during 2017 (figure). We reviewed hospital discharge summaries for these children to extract age and BCG vaccination status. Ethics approval was granted by Stellenbosch University Health Research Ethics Committee (numbers N11/01/006 and N16/11/142 to Regan Solomons). Unfortunately, BCG vaccination status was not recorded for the majority. We used Poisson regression to model the count of admissions for 10 years and estimated a specific incidence rate ratio (IRR) for 2017 compared to the preceding 3 years (2014–16),

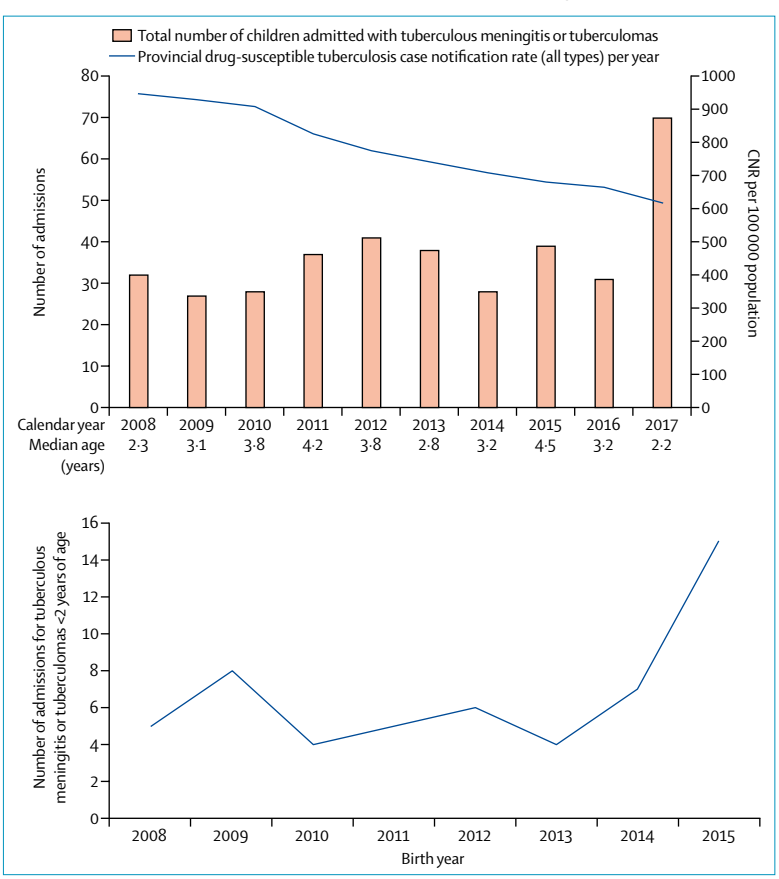


Figure: **Annual case load (top) and birth cohort analysis (bottom) of children admitted with tuberculous meningitis or tuberculomas to the paediatric neurology ward at Tygerberg Hospital, Cape Town, South Africa over a 10-year period**
Date of birth/age at admission not available for five children. CNR=case notification rate.

assuming a stable population at risk for these 4 years. The number of admissions for tuberculous meningitis or tuberculomas increased from a mean of 32·7 in 2014–16 to 70 in 2017 (IRR 2·2, 95% CI 1·6–2·9; p<0·0001). This increase cannot be explained by a concomitant increase in overall tuberculosis incidence, since the tuberculosis case notification rate in the province has been steadily declining since 2008 (figure; personal communication: Alvera Swartz, Western Cape Department of Health).[10] There were also no changes in the diagnostic algorithm used for tuberculous meningitis in this clinical setting over the 10 years of investigation, no changes in clinical care or hospital referral pathways during 2014–17, and no increase in the total number of general and specialised paediatric admissions at Tygerberg Hospital during 2017 (15 695 in 2017 *vs* a mean of 16 727 in 2014–16[11]).

We hypothesise that this sharp increase in the number of children with tuberculous meningitis is related to BCG shortages. To further evaluate the relation between BCG vaccination and tuberculous meningitis incidence, we completed birth cohort analyses. As surveillance data were only available until 2017, children were divided into birth cohorts by calendar year of birth (2008–15), with 2 years of follow-up time in each cohort (figure). Admissions for tuberculous meningitis or tuberculomas before the age of 2 years were almost three times higher in children born in 2015 compared to the mean number of those born in 2012–14 (n=15 *vs* n=5·7; IRR=2·7, 95% CI 1·3–5·5; p=0·005). Given that the median age of children with tuberculous meningitis in a large observational cohort over a period of 20 years at Tygerberg Hospital was 2·3 years,[12] it would be expected that the peak would occur just over 2 years after the actual BCG shortage occurred if shortages of BCG led to increased numbers of tuberculous meningitis cases. This was indeed the case. The median age of children with tuberculous meningitis in 2017 (2·2 years) was the lowest observed over the past 10 years (figure), further supporting this hypothesis.

These data serve as a stark warning that neonatal BCG vaccination remains a crucial component of tuberculosis control in children. Disruptions to vaccine supply can have multiple effects on the health system delivery of BCG. Strategies should be put in place to prevent such stockouts. Surveillance data on tuberculous meningitis from other settings affected by BCG shortages should be systematically collected and reported to investigate whether similar trends have been observed elsewhere. Given the paucity of current tools to combat this devastating form of tuberculosis in children, we, as a global community, must demand that supplies and quality of BCG vaccine remain secure.

KdP, JAS, and RS conducted data collection and prepared the first draft of the manuscript. KdP and CL conducted the statistical analyses. All authors critically reviewed the manuscript, provided input during preparation, and have approved the final version of the manuscript. KdP's salary is supported by a South African National Research Foundation (NRF) Chair grant to ACH. The financial assistance of the NRF towards this research is hereby acknowledged. Opinions expressed, and conclusions arrived at, are those of the authors and are not necessarily to be attributed to the NRF. MO was financially supported by the South African Medical Research Council National Health Scholars Programme from funds provided for this purpose by the National Department of Health Public health Enhancement Fund. We declare no competing interests.

**K du Preez, J A Seddon, H S Schaaf, A C Hesseling, J R Starke, M Osman, C J Lombard, R Solomons*

karen_dupreez@sun.ac.za

Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa (KdP, JAS, HSS, ACH, MO); Academic Department of Paediatrics, Imperial College London, London, UK (JAS); Tygerberg Hospital, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa (HSS, RS); Department of Pediatrics, Baylor College of Medicine, Houston, TX, USA (JRS); and Division of Epidemiology and Biostatistics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa (CJL)

1 World Health Organization. Global tuberculosis report 2017. Geneva: World Health Organization, 2017.

2 Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet* 2006; **367:** 1173–80.

3 Abubakar I, Pimpin L, Ariti C, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guerin vaccination against tuberculosis. *Health Technol Assess* 2013; **17:** 1–372.

4 Chiang SS, Khan FA, Milstein MB, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2014; **14:** 947–57.

5 World Health Organization. BCG vaccines: WHO position paper. February 2018. *Wkly Epidemiol Rec* 2018; **93:** 73–96.

6 UNICEF Supply Division. Bacillus Calmette-Guérin (BCG) vaccine supply & demand update, September 2013. https://www.unicef.org/supply/files/BCG_Supply_Status_Sept_2013.pdf (accessed June 28, 2018).

7 Marais BJ, Seddon JA, Detjen AK, et al. Interrupted BCG vaccination is a major threat to global child health. *Lancet Respir Med* 2016; **4:** 251–53.

8 Harris RC, Dodd PJ, White RG. The potential impact of BCG vaccine supply shortages on global paediatric tuberculosis mortality. *BMC Med* 2016; **14:** 138.

9 Statistics South Africa. Statistical release P0305—recorded live births, 2017. Pretoria: Statistics South Africa, 2018.

10 Massyn N, Peer N, English R, Padarath A, Barron P, Day C. District Health Barometer 2015/16. Durban: Health Systems Trust, 2016.

11 Western Cape Government. Annual report 2017: Tygerberg Hospital (in press).

12 van Well GT, Paes BF, Terwee CB, et al. Twenty years of pediatric tuberculous meningitis: a retrospective cohort study in the Western Cape of South Africa. *Pediatrics* 2009; **123:** e1–8.

CHAPTER 6: BURDEN, SPECTRUM AND OUTCOMES OF CHILDREN WITH TUBERCULOSIS DIAGNOSED AT A DISTRICT-LEVEL HOSPITAL IN SOUTH AFRICA

In the previous two chapters, I explored the burden, HIV status and disease spectrum of paediatric tuberculosis (TB) diagnosed and treated at a large South African tertiary referral hospital. I also described the complex clinical care pathways for tertiary-level hospital care for paediatric TB, and discussed the value of surveillance of specific vulnerable sub-sets of children with TB including HIV-infected children and children with TB meningitis (TBM). In this chapter, I continue to focus on the third pillar of the care cascade ('Diagnosed with TB'). However, here, I focus on surveillance strategies at a different level of health care - the district-level hospital.[99]

Hospital-based studies reporting on the diagnosis, management and outcomes of paediatric TB in sub-Saharan Africa have mostly presented data from tertiary or academic (referral) centres.[38, 66, 100-102] The most severe forms of TB or complicated cases would usually be referred to these centres. In contrast, the burden and spectrum of paediatric TB diagnosed and managed at the typical district-level hospital is expected to be different, with more children presenting with non-severe forms of TB and with potentially less complex care pathways. Understanding how the paediatric TB disease burden, spectrum of disease and HIV status vary at different levels of health care is important to ensure that adequate and appropriate resources are available at each level of health care providing services to children. It is also important to understand these factors when designing monitoring and evaluation approaches for paediatric TB services in national programmes.

The objective of this study was to characterise the burden and spectrum of disease, the clinical presentation, diagnostic investigations and outcomes of children with TB diagnosed at Khayelitsha District Hospital (KDH), a district-level hospital in Cape Town, South Africa, which serves the entire Khayelitsha health sub-district, an urban community with an exceptionally high burden of TB and HIV.

This retrospective cohort study included 99 children (age <13 years) routinely diagnosed with TB from 1 January through 31 July 2014 at KDH. Most children with TB were young (85% ≤ 2 years) and younger than those managed at the local tertiary level hospital (94% <5 years vs 75% <5 years). The prevalence of HIV infection was slightly lower than at the tertiary hospital (19% vs 24%), but as for the tertiary hospital, TB remained an important opportunity for HIV diagnosis, with 39% of HIV-infected children only diagnosed with HIV during their hospital admission for TB. Of the 7 children newly diagnosed with HIV, 5 (71%) were ≤18 months of age.

As expected given the less severe spectrum of disease in children presenting directly to district level hospital services, just 2 (2%) children had only extra-pulmonary TB, 3 (3%) of the children had disseminated TB (miliary TB or TBM) and there were no in-hospital deaths observed. Although respiratory specimens were submitted for bacteriological confirmation in the majority (at least 2 specimens obtained in 84%), only 13% had bacteriologically confirmed TB, potentially indicative of less extensive pulmonary disease, with a tendency for lower bacteriological yield.[87] Thus, laboratory surveillance alone in this context would have missed the large majority of children with TB.

Care pathways were simple at this district-level hospital compared to those observed at the tertiary referral hospital, with the majority of children referred from primary healthcare (PHC) facilities, admitted for diagnostic and treatment purposes and then referred directly back the local PHC facility to continue their TB treatment. During the study period, a lay healthcare worker provided simple referral and linkage-to-care support between hospital and PHC level at discharge. With this support, most children (96%) discharged to a PHC facility successfully continued their TB care, and 90% were recorded in the TB treatment register and reported in routine TB surveillance data (ERT.Net or EDRWeb).

In high TB burden settings, data on the burden and spectrum of paediatric TB managed at all relevant levels of healthcare services provides important information for hospital and public health managers. Clinical surveillance was very important at district level of care in addition to laboratory surveillance. This study provided a new perspective on hospital-based paediatric TB surveillance in a setting with very high burden of TB and HIV and quantified the burden and spectrum of paediatric TB at a district-level hospital for the first time in South Africa. This district-level hospital managed a large burden of paediatric TB cases (~100 children in a 7-month period). Although the spectrum of TB was less severe compared to the tertiary care level, children were young and had a high prevalence of HIV infection. To ensure accurate reporting, it is important that data from district hospitals are also included in routine TB surveillance data, especially in settings where hospitals are not currently reporting TB data.

Citation

Du Preez K, du Plessis L, O'Connell N, Hesseling AC. Burden, spectrum and outcomes of children with tuberculosis diagnosed at a district-level hospital in South Africa. Int J Tuberc Lung Dis. 2018;22(9):1037-43.

INT J TUBERC LUNG DIS 22(9):1037–1043

http://dx.doi.org/10.5588/ijtld.17.0893

Burden, spectrum and outcomes of children with tuberculosis diagnosed at a district-level hospital in South Africa

K. du Preez,* L. du Plessis,* N. O'Connell,† A. C. Hesseling*

*Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, †Western Cape Province Department of Health, Khayelitsha District Hospital, Cape Town, South Africa

SUMMARY

SETTING: The Khayelitsha subdistrict has the highest burden of reported tuberculosis (TB) cases in Cape Town, Western Cape Province, South Africa.

OBJECTIVES: To characterise the TB burden, spectrum and treatment outcomes among children managed at a district-level hospital, the Khayelitsha District Hospital.

DESIGN: Retrospective medical record review of all children (age <13 years) diagnosed with TB in January–July 2014. A lay health care worker completed daily surveillance and supported linkage to TB care. Symptoms and investigations at presentation, TB disease spectrum, referral pathways and outcomes were reported.

RESULTS: Most children were aged ⩽2 years (84/99, 85%), 18/96 (19%) were infected with the human immunodeficiency virus, 31/91 (34%) were malnourished and 80/99 (81%) had pulmonary TB only. The majority of the children (63/80, 79%) presented with cough of acute onset (<2 weeks). Only 5/36 (14%) eligible child contacts had documentation of receiving isoniazid preventive therapy. Twelve (13%) children had bacteriologically confirmed pulmonary TB. Overall, 93/97 (96%) children successfully continued TB care after hospital discharge. Favourable TB treatment outcomes were recorded in only 77 (78%) children.

CONCLUSIONS: Children with TB managed at this district-level hospital were young, and frequently had acute symptoms and substantial comorbidities. Missed opportunities for TB prevention were identified. Linkage to care support resulted in excellent continuation of TB care; however, treatment outcomes could be further improved.

KEY WORDS: diagnosis; HIV; pathways; presentation

THE 2016 WORLD HEALTH ORGANIZATION (WHO) global tuberculosis report indicated that South Africa remained one of the countries with the highest tuberculosis (TB) incidence in the world.[1] In 2015, children aged <15 years accounted for 29 137 (10%) cases of the overall national reported new and relapse TB case load ($n = 287\,224$) in South Africa.[1]

Children have a high risk of progressing to TB disease following infection with *Mycobacterium tuberculosis* and a high risk of developing severe forms of disease.[2] In settings with a high burden of TB and human immunodeficiency virus (HIV), such as South Africa, paediatric TB contributes significantly to TB-related morbidity and mortality.[3–5] HIV-infected children have higher rates of progression to TB disease and poorer TB treatment outcomes, even with the use of antiretroviral therapy.[6,7]

The paucibacillary nature of childhood TB disease in younger children and difficulties confirming diagnosis often result in children being managed on the basis of clinical symptoms and chest radiography (CXR) alone. This poses challenges, particularly in young children who may present with acute symptoms and atypical CXRs that may be difficult to interpret.[8] In addition, respiratory specimen collection in young children is time-consuming and invasive. Children presenting at primary health care (PHC) facilities are therefore often referred for investigation and diagnosis at hospital level.

Data in the literature regarding the diagnosis, management and outcomes in paediatric TB are frequently from tertiary academic hospitals.[9–13] Children managed at these centres are likely to have complicated or severe forms of disease, and possibly poor outcomes. The burden, spectrum and outcomes in children with TB managed at a district-level hospital might be very different, but these have not been well described in the literature. Insight into disease burden and spectrum managed at all levels of

KdP and LdP contributed equally to the study and the article.

Correspondence to: Karen du Preez, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie van Zijl Drive, Parow 7505, Cape Town, South Africa. e-mail: karen_dupreez@sun.ac.za

Article submitted 22 December 2017. Final version accepted 6 April 2018.

health care is important to ensure appropriate planning for resources at each level.

The objective of the present study was to characterise the burden and spectrum of disease, clinical presentation, diagnostic investigations and outcomes of children with TB diagnosed at a district-level hospital in a peri-urban, high TB-HIV burden setting in South Africa.

SETTING

In 2011, the estimated population of Khayelitsha was 391 748 people; nearly one third were aged <15 years and 74% of households had a monthly income of ⩽3200 South African rand.[14] The Khayelitsha health subdistrict contributed 3972 (17%) to the total TB caseload (23 846) in the City of Cape Town during 2016; 2378 (59.9%) were HIV-infected and 321 (8%) were children aged <15 years (unpublished data, City Health, City of Cape Town). TB services are provided at nine PHC facilities in the subdistrict.

KDH has been providing primary and secondary level paediatric health care to children aged <13 years in the Khayelitsha subdistrict since February 2012. At the time of the present study, the KDH Paediatric Department consisted of one paediatrician (Department Head), a shared family physician and five medical officers. The department has 38 dedicated paediatric beds, a paediatric emergency centre, a 12-bed neonatal nursery and a 10-bed Kangaroo Mother Care unit. A paediatric out-patient clinic (POPD) operates 3 days per week. In 2014, KDH had 4290 paediatric admissions and 25 607 POPD/emergency consultations. Children typically present to PHC facilities, and are referred to hospital for further investigations and management only if clinically indicated. Following a hospital diagnosis of TB, children are referred to their local PHC facility at discharge for treatment continuation. TB treatment outcome definitions are aligned with WHO recommendations, and outcomes are documented in the TB treatment registers.

The 2013 South African National TB Programme (SANTP) Childhood TB guidelines introduced a paediatric diagnostic algorithm based on one specimen sent for Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) testing in addition to smear and mycobacterial culture.[15] In addition, HIV testing, the tuberculin skin test (TST), CXR and clinical examination remained part of the diagnostic algorithm. Until September 2014, Western Cape provincial guidelines restricted the use of Xpert to sputum, induced sputum and tracheal aspirates.

METHODS

During 2013–2014, as part of a childhood TB health systems strengthening study in Khayelitsha (Kidcare), a lay health care worker completed hospital-based surveillance and linkage to care activities at KDH. Daily surveillance was implemented in the paediatric wards, POPD and the Emergency Department to identify all children diagnosed with or treated for TB. Linkage to care activities included structured disease-specific education for parents/care givers, referral support for clinical personnel and telephone follow-up after hospital discharge.

All children (age <13 years) routinely diagnosed with TB at KDH from January to July 2014 were included. Data on demographics, clinical, diagnostic and referral pathways were collected through a retrospective review of medical records by a trained study nurse, and recorded on a standard case report form. Bacteriological records were accessed via the National Health Laboratory Services (NHLS) website. TB treatment outcome information was collated from hospital records, paper-based TB treatment registers at PHC facilities and provincial electronic TB registers (ETR.Net and EDRweb).

Malnutrition included any nutritional deficiencies (wasted, underweight, stunted, marasmus, kwashiorkor, malnutrition, severe acute malnutrition or moderate acute malnutrition) documented in clinical notes.

All data were dual captured into a central database using unique study identifiers, and were de-identified before analyses.

Statistical analysis

Statistical analysis was descriptive, and was performed using STATA v14 (StataCorp, College Station, TX, USA). Numbers and percentages are reported for categorical variables.

Regulatory approvals

The study protocol was approved by the Western Cape Department of Health, Cape Town, and the Human Research Ethics Committee, Stellenbosch University, Cape Town (N14/10/135).

RESULTS

The hospital-based clinical surveillance strategy identified 113 children with TB managed at KDH during the 7-month study period. Eleven children diagnosed outside the study period or admitted with an already established TB diagnosis were excluded. Of the remaining 102 children, 99 (97%) hospital records were available for review.

Table 1 provides an overview of the clinical presentation and TB disease spectrum. Most children were aged ⩽2 years (84, 85%), and 69 (67%) were male. Of the 88 children admitted, 70 (81%) stayed in hospital for ⩾3 days. Cough (80, 81%) and failure to thrive/weight loss (78, 79%) were the most frequently reported symptoms. The majority of the

Table 1 Demographics, clinical presentation and type of disease among children with TB diagnosed at a district-level hospital, Cape Town, South Africa ($n = 99$)

	n (%)*
Age category, years	
<1	37 (37)
1–2	47 (48)
3–4	9 (9)
⩾5	6 (6)
Male sex	69/98 (67)
Admitted to hospital as in-patient†	88 (89)
Duration of hospitalisation, days	
<3	16/86 (18)
3–6	46/86 (54)
7–13	16/86 (19)
>14	8/86 (9)
More than 5	5/99
Symptoms and signs suggestive of TB recorded	
Cough, weeks	80 (81)
⩾2	17/80 (21)
<2	63/80 (79)
Failure to thrive or weight loss	78 (79)
Failure to thrive with/without weight loss	70/78 (90)
Only weight loss	8/78 (10)
Fever, weeks	62 (62)
⩾2	6/62 (10)
<2	56/62 (90)
History of TB contact	
TB exposure history documented	96 (97)
Exposure to an infectious TB source case documented	38/96 (40)
Documentation of IPT (in eligible children)‡	5/36 (14)
Nutritional status	
Any form of malnutrition documented§	31/91 (34)
Severe acute malnutrition	8/91 (9)
Type of TB disease	
PTB only	79 (80)
EPTB only	2 (2)
Both PTB and EPTB	18 (18)
Disseminated TB	18 (18)
TB meningitis	1 (1)
Miliary TB	2 (1)
Abdominal TB¶	15 (15)

* The denominator is 99, except where otherwise indicated due to missing data.
† 11 (10%) children were seen and followed up at the KDH Paediatric Out-Patient Department only. All 11 had full work-up, including bacteriological testing.
‡ Of 38 children with a history of TB exposure, 36 (95%) were aged <5 years or HIV-infected and therefore eligible for IPT according to the 2013 SANTP guidelines.
§ 31/91 children were diagnosed with some form of nutritional deficiency during hospitalisation. We included all children clinically described by attending physicians as wasted, underweight, stunted, SAM, MAM, or diagnosed with marasmus, kwashiorkor or malnutrition.
¶ Children with abdominal TB mostly had uncomplicated abdominal lymph nodes (12/15) detected on ultrasound; splenic micro-abscesses were seen in 2/15, and pericardial effusion on 1/15 ultrasounds.
TB = tuberculosis; IPT = isoniazid preventive therapy; PTB = pulmonary TB; EPTB = extra-pulmonary TB; SAM = severe acute malnutrition; MAM = moderate acute malnutrition; KDH = Khayelitsha District Hospital; SANTP = South Africa National TB Programme; HIV = human immunodeficiency virus.

children with cough reported symptoms for <2 weeks (63/80, 79%). Most children presenting with fever also reported acute onset of <2 weeks (56/62, 90%). History of TB exposure was documented in 96 (97%) children; 58 (60%) had no known TB exposure, and 38 (40%) had household or other close contact TB exposure. Among children with reported TB exposure, 36/38 were aged <5 years or were HIV-infected and therefore eligible for TB preventive therapy. However, only 5/36 (14%) had documentation of receiving isoniazid preventive therapy (IPT) before hospital admission.

Malnutrition was documented in 31/91 (34%) children, 8 (9%) with severe acute malnutrition. The spectrum of TB included 79 (80%) children with only pulmonary TB (PTB), 2 (2%) with only extra-pulmonary TB (EPTB) and 18 (18%) with both PTB and EPTB. Two children were diagnosed with miliary TB and one with TB meningitis.

Table 2 provides an overview of TB diagnostic investigations. HIV status was documented in 96 (97%) children, of whom 18 (19%) were HIV-infected. Of the 18 HIV-infected patients, 10 (56%) were known to be infected before hospital admission (6 were on antiretrovirals at the time of hospital admission), and 7 (39%) were newly diagnosed at the time of hospital presentation, including 5 (71%) who were aged ⩽18 months.

Fifty-eight (59%) children received a TST. Of 41 (71%) children with a documented result, 20 (49%) were TST-positive (⩾5 mm in HIV-infected and ⩾10 mm in HIV-negative children). All children underwent CXR, with documented clinician reviews reported in 97/99 (98%). CXR was reported as 'suggestive of TB' in 95/97 (98%) children. Of these, 78/95 (82%) had 'typical CXR signs', defined in the SANTP guidelines as hilar nodes, expansile pneumonia, compression/collapse, pleural effusions, miliary TB, apical infiltrates or cavities. Hilar adenopathy was the most common finding on CXR (61/78, 78%). Respiratory specimens from 92 (93%) children were sent for bacteriological investigation; most of the specimens ($n = 84$, 91%) were gastric aspirates, 10 of which were collected successfully from out-patients in POPD. TB diagnosis was bacteriologically confirmed on respiratory specimens in 12 (13%) children (Xpert-positive specimens, 2/10 [20%]; MGIT [BD, Sparks, MD, USA] mycobacterial culture-positive specimens, 11/90 [12%]).

Type of TB treatment, referral care pathways and treatment outcomes are given in Table 3. During initial presentation at hospital, 83 (84%) children were started on anti-tuberculosis treatment. Of the 16 children followed up after the initial presentation without starting anti-tuberculosis treatment,12 started treatment within 30 days and only 4 (25%) had a >30-day delay in treatment initiation from initial presentation. Two of these children had positive mycobacterial cultures (culture took >30 days) and two did not improve clinically after oral antibiotics and follow-up. Most children (96, 97%) were started on first-line drug regimens. The three children who started second-line multidrug-resistant TB (MDR-TB) regimens either had bacteriologically confirmed resistance ($n = 2$) or reported MDR-TB exposure ($n = 1$).

Table 2 Diagnostic investigations completed for children diagnosed with TB at a district-level hospital, Cape Town, South Africa ($n = 99$)

	n (%)
HIV testing ($n = 99$)	
HIV status documented	96 (97)
HIV-negative	78/96 (81)
HIV-infected	18/96 (19)
Timing of HIV diagnosis in relation to hospital admission ($n = 18$)	
Known to be with HIV infection before hospital admission*	10/18 (56)
Diagnosed with HIV infection during hospital admission†	7/18 (39)
Time of HIV diagnosis not documented‡	1/18 (5)
TST	
Recorded that TST had been performed	58 (59)
Documentation of TST result	41/58 (71)
TST-positive§	20/41 (49)
CXR	
Number of children recorded to have undergone CXR	99 (100)
CXR findings recorded by clinician	97/99 (98)
CXR reported as suggestive of TB¶	95/97 (98)
One or more typical CXR signs of TB reported according to SANTP guidelines#	78/95 (82)
Bacteriological testing on respiratory samples	
Children with results of respiratory bacteriological investigations at NHLS	92 (93)
Type of respiratory specimens sent for TB microbiological testing	
First specimen gastric aspirate	84/92 (91)
First specimen sputum	8/92 (9)
Number of respiratory specimens per child sent for TB investigations	
1	16/92 (16)
2	52/92 (57)
⩾3	24/92 (25)
Xpert ($n = 92$)	
Total number of patients who underwent Xpert	10/92 (11)
Positive Xpert	2/10 (20)
RIF resistance detected on Xpert result	1/10 (10)
Mycobacterial culture (MGIT™) ($n = 92$)	
Total number of patients who underwent culture	90 (98)
Positive *M. tuberculosis* culture	11/90 (12)
No susceptibility results available**	5/11 (45)
Drug resistance identified on culture††	1/11 (9)
Total bacteriologically confirmed cases	12/92 (13)

* 6/10 children known to be HIV-infected were on ART before hospital admission, 3 children not on ART were diagnosed within 1 month before admission.
† Of the 7 diagnosed during admission, 5 were aged ⩽18 months.
‡ No information relating to HIV diagnosis documented in folder or available on NHLS.
§ According to SANTP guidelines: HIV-negative ⩾10 mm; HIV-infected ⩾5 mm.
¶ CXR was reported as not being suggestive of TB ($n = 2$). Both children had extra-pulmonary TB only.
# Typical CXR signs defined as hilar nodes (61/78, 78%), expansile pneumonia (27/78, 35%), pleural effusions (2/78, 3%), miliary TB (2/78, 3%), cavities (2/78, 3%). Atypical CXR reported as suggestive of TB included lobar/paratracheal infiltrates or paratracheal nodes. CXR was only reported as suggestive of TB with no specific signs documented in 6.
** Culture-positive specimens were subject to drug susceptibility testing only if specifically requested by the clinician.
†† Drug resistance pattern identified as isoniazid monoresistance.
TB = tuberculosis; HIV = human immunodeficiency virus; TST = tuberculin skin test; CXR = chest radiograph; SANTP = South Africa National TB Programme; NHLS = National Health Laboratory Service; RIF = rifampicin; MGIT™ = Mycobacteria Growth Indicator Tube; ART = antiretroviral treatment.

Most children 89 (90%) were discharged to community PHC facilities for further treatment, and 79/89 (89%) were scheduled for hospital follow-up at the POPD, although 63/89 (80%) had already been started on anti-tuberculosis treatment. Attendance of hospital follow-up visits was good (67/79, 85%). Of 10 children (10%) referred for tertiary care, eight were referred back to KDH and eventually to a PHC facility for treatment completion. Of 97 children referred to PHC facilities, 93 (96%) were successfully linked to community-based TB care following hospital diagnosis. Overall, 89/99 (90%) were included in routine TB surveillance data (ETR.Net/EDRWeb). Favourable TB treatment outcomes were recorded in 77 (78%) children. Unfavourable outcomes included 11 (11%) children lost to follow-up, 9 (9%) not evaluated and 2 (2%) transferred out.

DISCUSSION

Based on the data presented here, surveillance of paediatric TB at a district-level hospital provides important insights into the burden and spectrum of disease, including the basis for diagnosis in children managed for TB at this level of health care. The study identified a large burden of children diagnosed with

Table 3 Type of anti-tuberculosis treatment, referral care pathways and TB treatment outcomes of children diagnosed with TB at a district-level hospital, Cape Town, South Africa (n = 99)

	n (%)
Type of anti-tuberculosis treatment initiated	
Treated for drug-susceptible TB	96 (97)
Treated for drug-resistant TB*	3 (3)
Referral pathways at hospital discharge	
Discharged to PHC facilities with a hospital POPD follow-up†	79 (80)
Discharged to PHC facilities with no hospital follow-up	10 (10)
Referred to tertiary hospital‡	10 (10)
Continuity of TB care between hospital and PHC facilities	
TB care successfully linked with PHC facility following hospital discharge	93/97 (96)
TB treatment outcomes§	
Cured	1 (1)
Treatment completed	76 (77)
Transferred out	2 (2)
LTFU¶	11 (11)
Not evaluated#	9 (9)

* Two cases were bacteriologically confirmed (1 culture-positive, isoniazid monoresistance; 1 Xpert-positive with rifampicin resistance); 1 treated due to history of exposure to MDR-TB.
† Mainly for verification of culture results; 67/79 (85%) attended their scheduled follow-up.
‡ Characteristics of referred children were as follows: 3 HIV-infected (1 with disseminated MDR-TB, 1 with tuberculous meningitis and 1 with PTB) and 7 HIV-negative children (5 with PTB and 2 with disseminated TB). All these children had other comorbidities such as malnutrition and sepsis.
§ Outcomes of 89/99 (90%) of children were obtained from routine TB surveillance sources (ETR.Net and EDR.Web).
¶ Included 7 children with an LTFU outcome in ETR, and 4 children LTFU after hospital discharge before accessing care at the PHC clinic.
# Included children with no documented outcomes, as well as one child with an illegible outcome in the PHC register.
TB = tuberculosis; PHC = primary health care; POPD = Paediatric Out-patient Department; LTFU = lost to follow-up; MDR-TB = multidrug-resistant TB; HIV = human immunodeficiency virus; PTB = pulmonary TB.

TB at a district-level hospital in a high TB-HIV burden community, nearly 100 in a 7-month period. Children were very young (85% were aged <2 years), and mostly presented with acute symptoms of short duration (<2 weeks). There was a high prevalence of HIV infection (19%) and malnutrition (34%), while significant missed opportunities for TB prevention were identified. Simple linkage to care activities successfully supported clinical continuity of TB care between district hospital and community-based health care services for nearly all children.

According to our study findings, children diagnosed with TB at this district hospital were thoroughly investigated for TB, with almost all undergoing HIV testing, CXR and bacteriological investigations. The diagnostic process followed was appropriate based on national guidelines, with the exception of bacteriological testing.[15] Provincial guidelines were only revised after the study at the end of 2014, allowing Xpert testing on gastric washings. Current guidelines recommend one Xpert test in addition to culture in all paediatric respiratory specimens. Although Xpert has lower sensitivity than culture to detect *M. tuberculosis* in children, it does allow for more rapid confirmation in acutely ill children.[16,17] Most children in our study were investigated using culture, and given the lower sensitivity of Xpert we do not expect its roll-out to impact significantly on confirmation rates in this setting; it could, however, potentially reduce the time to diagnosis/confirmation.

Given the paucibacillary nature of paediatric TB, bacteriological confirmation of diagnosis in children treated for TB varies between 25% and 40%.[18–20] In our study, only 13% of children had a bacteriologically confirmed diagnosis, potentially indicating the lower proportion of children with complicated forms of intrathoracic (pulmonary) TB and disseminated TB. CXR was an important diagnostic tool for paediatric TB at this hospital. However, CXR interpretation, particularly in young children, can be challenging, even for experts.[21–23] Taking into account the young age of children managed at this hospital, the associated comorbidities and the extremely high burden of TB in the surrounding community, one would expect a high index of suspicion for TB among clinicians. Some degree of overdiagnosis would therefore be expected and even acceptable, given the high risk of disease progression and severe forms of TB in young and HIV-infected children.[2,6] Verification of diagnostic accuracy was beyond the scope of this study. Our results, however, highlight the urgent need for new, improved diagnostic tests that are child-friendly, more sensitive, specific and capable of informing real-time clinical management to reduce over- and underdiagnosis of TB in young children in high-burden settings.

TB care remains an important opportunity for HIV care in children. We observed that 7/18 (39%) HIV-infected children were diagnosed with HIV after presenting to hospital with symptoms of TB (5 of them were aged ⩽18 months). This is of concern, as there has been a long-standing local Prevention of Mother-To-Child Transmission (PMTCT) programme, which reported only 2.6% vertical transmission in 2012–2013.[24] A national review, however, has identified multiple losses in the implementation of the PMTCT service cascade in South Africa.[25]

We also identified missed opportunities for initiating TB preventive therapy in children with documented TB exposure, similar to findings from other studies in South Africa.[26–28] As highlighted by a recent systematic review of child contact management in high-burden countries, high TB burden settings continue to face many challenges in the implementation of TB preventive therapy in child contacts.[29] Strategies to support the implementation of preventive therapy should be prioritised to improve child contact management and prevention of TB in children.[30]

The majority of children diagnosed at this district hospital did not require further specialist/tertiary-

level care, and were referred to community-based PHC facilities for further management and continuation of anti-tuberculosis treatment. However, the majority were admitted for >3 days, possibly reflecting the considerable severity of respiratory disease in this young cohort. Underpinned by the acute presentation of many children in our study, this highlights the need to better understand the role that TB plays in childhood pneumonia in high-burden settings.[31] It also emphasises TB-related morbidity in young children and the need for adequate resource allocation at this level of health care.

Our results also showed successful follow-up in the majority of the children who were asked to attend out-patient hospital follow-up after discharge, mainly to facilitate verification of culture results. For patients for whom the decision to treat for TB had already been taken, follow-up could potentially have been more feasibly done at the PHC facilities. However, in those patients for whom the decision to treat was not yet established, hospital follow-up provided a valuable opportunity for a review of clinical and culture results.

Linkage to care activities resulted in 96% of children successfully continuing TB care after hospital discharge and 90% included in routine TB surveillance data (ETR.Net/EDRWeb). This is considerably higher than previously reported (62%) by the large, tertiary-level hospital that serves KDH; however, the tertiary-level hospital also caters to a larger catchment area.[10] Favourable TB treatment outcomes were observed in nearly 80% of children. A study evaluating routine TB treatment register data in the City of Cape Town found a higher proportion of children (85.9%) with favourable outcomes.[32] The large proportion of children lost to follow-up during anti-tuberculosis treatment and with no evaluated outcome in our study is worrying. Interventions to strengthen treatment support and completeness of documentation could further improve outcomes.

This retrospective study had several limitations. Reliable surveillance data were only available for a fixed time period, resulting in a limited sample size. Data collection was limited to clinical documentation by routine health services staff. As an additional identification strategy, laboratory surveillance could have identified children missed by clinical hospital surveillance. However, as the paediatric department consists of a small team of clinicians, with one paediatric consultant conducting daily ward rounds and standardising care, we do not expect the lack of laboratory surveillance to substantially affect our results. Verification of diagnostic accuracy was beyond the scope of the study, but should be considered in future research. Despite these limitations, these routine data provide valuable insights into TB epidemiology in children at a district hospital, and give a more complete picture of the true burden of TB in South African children, complementary to data from PHC facilities and referral hospitals.

CONCLUSIONS

Investigation into the burden and spectrum of paediatric TB managed at all levels of health care services in high TB burden settings provides important information for hospital and public health managers. Our study provides a new perspective, characterising the epidemiology of paediatric TB at a district-level hospital. In our study, children with TB managed at a district-level hospital were very young, with substantial comorbidities. New diagnostic tools that can improve diagnostic accuracy in young children will greatly assist clinicians working in high-burden settings. Missed opportunities for TB prevention in child contacts were identified. Although most children successfully continued with TB care with simple linkage support activities, further research is needed to explore specific support interventions to improve TB treatment outcomes.

Acknowledgements

The authors thank the Harry Crossley Foundation, Cape Town, for supporting this study financially, the Paediatric Department at the Khayelitsha District Hospital, Cape Town, and D Bester and L Mafu from the Desmond Tutu TB Centre, Cape Town. KdP is supported by a South African Research Chairs Initiative grant to ACH. The Kid-care project and linkage to care activities was funded by the University Research Co Grant Agreement (FY2013-G87-4740) under the US Agency for International Development (674-C-00-09-00121-00; TB Programme in South Africa).

Conflicts of interest: none declared.

References

1 World Health Organization. Global tuberculosis report, 2016. WHO/HTM/TB/2016.13. Geneva, Switzerland: WHO, 2016.
2 Marais B J, Gie R P, Schaaf H S, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004; 8: 392–402.
3 Jenkins H E, Yuen C M, Rodriguez C A, et al. Mortality in children diagnosed with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis 2017; 17: 285–295.
4 Starke J R. Mortality in childhood tuberculosis: has there been progress? Lancet Infect Dis 2017; 17: 239–241.
5 Seddon J A, Shingadia D. Epidemiology and disease burden of tuberculosis in children: a global perspective. Infect Drug Resist 2014; 7: 153–165.
6 Hesseling A C, Cotton M F, Jennings T, et al. High incidence of tuberculosis among HIV-infected infants: evidence from a South African population-based study highlights the need for improved tuberculosis control strategies. Clin Infect Dis 2009; 48: 108–114.
7 Hesseling A C, Westra A E, Werschkull H, et al. Outcome of HIV infected children with culture confirmed tuberculosis. Arch Dis Child 2005; 90: 1171–1174.
8 Hesseling A C, Schaaf H S, Gie R P, Starke J R, Beyers N. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. Int J Tuberc Lung Dis 2002; 6: 1038–1045.

9 Schaaf H S, Garcia-Prats A J, du Preez K, Rautenbach C, Hesseling A C. Surveillance provides insight into epidemiology and spectrum of culture-confirmed mycobacterial disease in children. Int J Tuberc Lung Dis 2016; 20: 1249–1256.
10 du Preez K, Schaaf H S, Dunbar R, et al. Incomplete registration and reporting of culture-confirmed childhood tuberculosis diagnosed in hospital. Public Health Action 2011; 1: 19–24.
11 Frigati L, Maskew M, Workman L, et al. Clinical predictors of culture-confirmed pulmonary tuberculosis in children in a high tuberculosis and HIV prevalence area. Pediatr Infect Dis J 2015; 34: e206–210.
12 Aketi L, Kashongwe Z, Kinsiona C, et al. Childhood tuberculosis in a sub-saharan tertiary facility: epidemiology and factors associated with treatment outcome. PLOS ONE 2016; 11: e0153914.
13 Tilahun G, Gebre-Selassie S. Treatment outcomes of childhood tuberculosis in Addis Ababa: a five-year retrospective analysis. BMC Public Health 2016; 16: 612.
14 Statistics South Africa. Provinicial profile: Western Cape. Census 2011.Pretoria: South Africa, SSA, 2014. http://www.statssa.gov.za/publications/Report-03-01-70/Report-03-01-702011.pdf Accessed May 2018.
15 Department of Health, South Africa. Guidelines for the management of tuberculosis in children 2013. Pretoria, South Africa: DOH, 2013. www.health.gov.za/index.php/shortcodes/2015-03-29-10-42-47/2015-04-30-08-18-10/2015-04-30-08-23-21?download=577: tb-in-children-guidelines Accessed May 2018.
16 Detjen A K, DiNardo A R, Leyden J, et al. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis. Lancet Respir Med 2015; 3: 451–461.
17 Walters E, van der Zalm M M, Palmer M, et al. Xpert MTB/RIF on stool is useful for the rapid diagnosis of tuberculosis in young children with severe pulmonary disease. Pediatr Infect Dis J 2017; 36: 837–843.
18 Marais B J, Hesseling A C, Gie R P, Schaaf H S, Enarson D A, Beyers N. The bacteriologic yield in children with intrathoracic tuberculosis. Clin Infect Dis 2006; 42: e69–71.
19 Rachow A, Clowes P, Saathoff E, et al. Increased and expedited case detection by Xpert MTB/RIF assay in childhood tuberculosis: a prospective cohort study. Clin Infect Dis 2012; 54: 1388–1396.
20 Zar H J, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. Lancet 2005; 365: 130–134.
21 Hatherill M, Hanslo M, Hawkridge T, et al. Structured approaches for the screening and diagnosis of childhood tuberculosis in a high prevalence region of South Africa. Bull World Health Organ 2010; 88: 312–320.
22 Kaguthi G, Nduba V, Nyokabi J, Onchiri F, Gie R, Borgdorff M. Chest radiographs for pediatric tb diagnosis: interrater agreement and utility. Interdiscip Perspect Infect Dis 2014; 2014: 291841.
23 Swingler G H, du Toit G, Andronikou S, van der Merwe L, Zar H J. Diagnostic accuracy of chest radiography in detecting mediastinal lymphadenopathy in suspected pulmonary tuberculosis. Arch Dis Child 2005; 90: 1153–1156.
24 Goga A, Jackson D, Singh M, Lombard C, for the SAPMTCTE study group. Early (4–8 weeks postpartum) population-level effectiveness of WHO PMTCT Option A, South Africa, 2012–2013. Pretoria, South Africa: South African Medical Research Council and National Department of Health of South Africa, 2015.
25 Woldesenbet S, Jackson D, Lombard C, et al. Missed opportunities along the prevention of mother-to-child transmission services cascade in South Africa: uptake, determinants, and attributable risk (the SAPMTCTE). PLOS ONE 2015; 10: e0132425.
26 Osman M, Hesseling A C, Beyers N, et al. Routine programmatic delivery of isoniazid preventive therapy to children in Cape Town, South Africa. Public Health Action 2013; 3: 199–203.
27 van Wyk S S, Reid A J, Mandalakas A M, et al. Operational challenges in managing isoniazid preventive therapy in child contacts: a high-burden setting perspective. BMC Public Health 2011; 11: 544.
28 Du Preez K, Hesseling A C, Mandalakas A M, Marais B J, Schaaf H S. Opportunities for chemoprophylaxis in children with culture-confirmed tuberculosis. Ann Trop Paediatr 2011; 31: 301–310.
29 Szkwarko D, Hirsch-Moverman Y, Du Plessis L, Du Preez K, Carr C, Mandalakas A M. Child contact management in high tuberculosis burden countries: a mixed-methods systematic review. PLOS ONE 2017; 12: e0182185.
30 Hill P C, Rutherford M E, Audas R, van Crevel R, Graham S M. Closing the policy-practice gap in the management of child contacts of tuberculosis cases in developing countries. PLOS MED 2011; 8: e1001105.
31 Oliwa J N, Karumbi J M, Marais B J, Madhi S A, Graham S M. Tuberculosis as a cause or comorbidity of childhood pneumonia in tuberculosis-endemic areas: a systematic review. Lancet Respir Med 2015; 3: 235–243.
32 Osman M, Lee K, Du Preez K, Dunbar R, Hesseling A C, Seddon J A. Excellent treatment outcomes in children treated for tuberculosis under routine operational conditions in Cape Town. Clin Infect Dis 2017; 65: 1444–1452.

RÉSUMÉ

CONTEXTE : Le sousdistrict de Khayelitsha a le taux le plus élevé de cas de tuberculose (TB) rapportés au Cap, Province du Cap Ouest, Afrique du Sud.
OBJECTIF : Caractériser le poids, le spectre et l'évolution de la TB pédiatrique prise en charge dans l'hôpital de district de Khayelitsha.
SCHÉMAY : Revue rétrospective des dossiers médicaux de tous les enfants (<13 ans) ayant eu un diagnostic de TB de janvier à juillet 2014. Un agent de santé de base a noté la surveillance quotidienne et la liaison au soutien des soins de TB. Les symptômes et investigations lors de la présentation, le spectre de la maladie TB, les parcours de référence et les résultats sont rapportés.
RÉSULTATS : La majorité des enfants (84/99 ; 85%) avaient <2 ans, 18/96 (19%) étaient infectés par le virus de l'immunodéficience humaine, 31/91 (34%) étaient malnutris et 80/99 (81%) avaient seulement une TB pulmonaire. La majorité des enfants se sont présentés avec une toux de début brutal (<2 semaines) (63/80 ; 79%). Seulement 5/36 (14%) enfants contacts éligibles avaient la preuve d'un traitement préventif par isoniazide. Douze (13%) enfants avaient une TB pulmonaire bactériologiquement confirmée. Dans l'ensemble, 93/97 (96%) enfants ont poursuivi avec succès le traitement de TB après la sortie de l'hôpital. Seulement 77 enfants (78%) ont eu des résultats favorables du traitement de la TB.
CONCLUSION : Les enfants atteints de TB pris en charge dans cet hôpital de district ont été jeunes, ont fréquemment eu des symptômes aigus et des comorbidités importantes. Des opportunités manquées de prévention de la TB ont été identifiées. Le lien avec le soutien au traitement a abouti à une excellente continuité de la prise en charge de la TB, mais les résultats du traitement pourraient être améliorés.

RESUMEN

MARCO DE REFERENCIA: El subdistrito de Khayelitsha notifica la más alta carga de morbilidad por tuberculosis (TB) en Ciudad del Cabo, en la Provincia Cabo Occidental de Suráfrica.
OBJETIVO: Describir la carga de morbilidad, los tipos de TB y los desenlaces terapéuticos en los casos de TB pediátrica tratados en el hospital distrital del distrito de Khayelitsha.
MÉTODO: Se llevó a cabo una revisión retrospectiva de las historias clínicas de todos los niños (<13 años) con diagnóstico de TB tratados de enero a julio del 2014. Un trabajador de salud lego completaba la vigilancia diaria y reforzaba la vinculación al servicio de atención de la TB. Se describen los síntomas y las investigaciones iniciales, los tipos de enfermedad tuberculosa, los mecanismos de remisión y los desenlaces clínicos.
RESULTADOS: La mayoría de los niños (84/99; 85%) tenía ⩽2 años de edad, 18/96 (19%) sufrían infección por el virus de la inmunodeficiencia humana, 31/91 (34%) presentaban malnutrición y 80/99 (81%) presentaban TB de localización pulmonar exclusiva. La mayoría de los niños (63/80; 79%) acudió con tos de presentación aguda (<2 semanas). En solo cinco de los 36 contactos pediátricos (14%) se pudo documentar que habían recibido tratamiento preventivo con isoniazida. En 12 niños (13%) se obtuvo la confirmación bacteriológica del diagnóstico de TB pulmonar. En general, 93/97 niños (96%) continuó de manera satisfactoria el tratamiento de la TB después del alta hospitalaria. Se registraron desenlaces favorables del tratamiento antituberculoso en solo 77 niños (78%).
CONCLUSION: Los niños tratados por TB en este hospital distrital eran pequeños, con frecuencia presentaban síntomas agudos e importantes enfermedades concurrentes. Se reconocieron oportunidades desaprovechadas de prevenir la TB. La vinculación a los servicios de atención dio lugar a una excelente continuación del tratamiento de la TB, pero aún es posible mejorar los desenlaces terapéuticos.

CHAPTER 7: QUANTIFYING AND CLOSING THE HOSPITAL-REPORTING GAP FOR CHILDHOOD TUBERCULOSIS IN SOUTH AFRICA

In the previous three chapters, I investigated the value of different surveillance strategies to determine the burden and spectrum of paediatric tuberculosis (TB) referred to, diagnosed and managed in hospitals at two different levels of care. I also explored care pathways to better understand the movement of children with TB between different levels of health care, in order to better inform the current understanding of pillar 3 of the paediatric TB care cascade ('Diagnosed with TB'), and to determine the most appropriate surveillance strategies for paediatric TB.

In chapter 7, I quantify the hospital-reporting gap for children with TB and describe a prospective cohort study conducted at a large tertiary referral hospital. This study aimed to investigate the impact of a hospital-primary healthcare (PHC) linkage to care intervention to address the observed hospital-reporting gap between pillar 3 ('Diagnosed with TB') and pillar 4 ('Notified and treated') of the paediatric TB care cascade for children diagnosed at hospital level. The goal of the intervention was not only to improve the reporting of paediatric TB in the Western Cape, a province where hospitals do not routinely report TB cases, but also to reduce initial loss to follow-up (ILTFU) and improve hospital-PHC linkage of TB treatment following hospital discharge.

As explained in chapter 1 (section 1.e.5 The hospital reporting gap for paediatric TB in South Africa), there are two factors that contribute to patient losses between pillars 3 and 4 of the TB care cascade: 1) ILTFU (patients who are diagnosed with TB but who are never started on treatment) and 2) patients who are diagnosed, started on treatment but never recorded in a TB treatment register at a TB reporting unit. Both of these factors have been recognised as important challenges that contribute to the hospital-reporting gap in South Africa and in several other countries.[39-41, 61, 80-83]

Study 1. Incomplete registration and reporting of culture-confirmed childhood tuberculosis diagnosed in hospital[38]

In the first study I present in this chapter, I quantified the hospital-reporting gap for children with TB in South Africa for the first time. I completed a retrospective audit of children routinely diagnosed with culture-confirmed TB at Tygerberg Hospital (TBH) during 2007–2009.[38] Of 267 children, 101 (38%) were not included in routine TB surveillance data (i.e. were not captured in the electronic TB treatment register; ETR.Net). Furthermore, children with TB meningitis (TBM) and those who died in hospital were significantly less likely to be reported.[38] Children who were diagnosed with TBM at TBH were either treated as out-patients in an established TBM home-

based care programme with monthly hospital follow-up and received treatment at this hospital, or completed their treatment as in-patients at one of the two provincial TB hospitals.

Due to the retrospective nature of this study, I was not able to determine whether children discontinued their TB care, or whether they were not recorded and reported at the facility they had been referred to for completion of their TB treatment. However, large numbers of children with TB are routinely managed at referral hospitals,[86] and underestimation of the burden and spectrum of paediatric TB at hospitals can result in large gaps in surveillance for paediatric TB and impact significantly on service delivery and resource allocation. This was one of my first research projects and was undertaken as part of an international operational research fellowship funded by the International Union Against Tuberculosis and Lung Disease. The large hospital reporting gap identified and its substantial impact on the completeness and the quality of paediatric TB surveillance data, sparked my interest in further pursuing research to explain and address this finding. I subsequently designed and implemented study 2, described below.

Study 2. Closing the reporting gap for childhood tuberculosis in South Africa: improving hospital referrals and linkages[103]

Despite several studies clearly indicating the challenges and losses with continuity of TB care when patients are discharged from hospitals, there is a paucity of data on the impact of interventions to address this reporting and linkage to care gap for children with TB. Only three previous studies, two from South Africa and one from Pakistan, have reported on interventions supporting hospital referrals to improve continuity of TB care following hospital discharge.[104-106] None has specifically focussed on children.

I designed and implemented a dedicated TB referral service in all the paediatric wards at TBH during 2012 to reduce initial loss to follow-up among children with TB discharged from hospital and to improve on the completeness of routine TB surveillance data. Study-specific personnel provided TB education and counselling, referral support for TB services and weekly telephonic follow-up after hospital discharge for all children discharged home to continue their TB care at their local PHC facility or at the TBH out-patient department. Similar to the initial audit, probabilistic record linkage was used to match all children identified to routine national electronic TB treatment registers (ETR.Net for drug-susceptible TB [DS-TB] and EDRWeb for drug-resistant TB [DR-TB]). Primary study outcomes were successful TB referral and reporting. Multivariable logistic regression was used to compare the reporting of culture-confirmed and DS-TB cases before (2007–2009) and during (2012) the intervention, using an intention-to-treat analysis.

During 2012, a total of 272 children with TB were discharged from TBH to continue their TB care. Similarly to the larger cohort described in chapter 4, 75% of children were <5 years of age, 22% were HIV infected, 17% had only extra-pulmonary TB, 13% had disseminated TB, 38% had bacteriologically confirmed TB and 95% were treated for DS-TB.

The majority of children (n=244; 90%) were discharged to continue their care at PHC facilities and 28 (10%) were followed at the paediatric out-patient department at TBH, including all 26 children with TBM who were part of the established TBM home-based care programme. Overall, successful referral resulting in linkage to care was confirmed in 267/272 (98%) of children and successful reporting was confirmed in 227/272 (84%) children.

Children with culture-confirmed DS-TB were significantly more likely to be included and reported in routine TB surveillance data (ETR.Net) during the intervention period than during the pre-intervention period (adjusted odds ratio [aOR] 2.62; 95% confidence interval [CI] 1.31–5.25). A diagnosis of TBM remained strongly associated with not being reported (aOR 0.18; 95% CI 0.07-0.48) in the multivariable model.

This study found that a simple TB referral service could minimize initial loss to follow-up and significantly improve recording and reporting of children with TB managed at a large referral hospital in South Africa. This study did not address the completeness of reporting of in-hospital deaths, but this is important to consider in future research to improve the quality and completeness of reporting on paediatric TB mortality.

The highly significant association between a diagnosis of TBM and not being reported in the TB register is very likely a reflection of the difference in place of attendance (i.e. follow-up visits) for monthly follow-up for children with TBM. All of these children were followed monthly at TBH, with their TB medications dispensed by the hospital, and despite the study team's effort to facilitate their recording in the paper-based TB register at their local PHC facility, they were still significantly less likely to be reported compared to the children who followed at their PHC facility.

These data highlight the importance of hospital reporting of TB data to ensure the accuracy and completeness of routine TB surveillance data in children. This could be accomplished through paper-based or electronic TB treatment registers at hospitals, and would feasibly address the hospital-reporting gap and improve surveillance data. Electronic and automated information systems could improve communication between hospitals and other levels of health care without increasing staff work load. However, similar to findings reported from qualitative research with healthcare providers at TBH,[107] it is recommended that existing referral systems be strengthened to include patient-centred discharge planning and disease-specific education to better support TB patients with successful continuation of TB care after hospital discharge.

Citations

Du Preez K, Schaaf HS, Dunbar R, Swartz A, Bissell K, Enarson DA, Hesseling AC. Incomplete registration and reporting of culture-confirmed childhood tuberculosis diagnosed in hospital. Public Health Action. 2011;1(1):19-24. doi: 10.5588/pha.11.0010. (This manuscript was published prior to my PhD registration period, and is included as additional relevant output only)

Du Preez K, Schaaf HS, Dunbar R, Swartz A, Naidoo P, Hesseling AC. Closing the reporting gap for childhood tuberculosis in South Africa: improving hospital referrals and linkages. Public Health Action. 2020;10(1):38-46.

Public Health Action

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

VOL 1 NO 1 PUBLISHED 21 SEPTEMBER 2011

Incomplete registration and reporting of culture-confirmed childhood tuberculosis diagnosed in hospital

K. du Preez,[1] H. S. Schaaf,[1] R. Dunbar,[1] A. Swartz,[2] K. Bissell,[3] D. A. Enarson,[3] A. C Hesseling[1]

http://dx.doi.org/10.5588/pha.11.0010

Setting: The South African National Tuberculosis Programme (NTP) recommends the registration of tuberculosis (TB) patients at community clinics. TB in children is often diagnosed at referral hospitals, and there are concerns as to whether these children are accurately reflected in routine NTP reporting.

Objective: To assess the completeness of registration of children with culture-confirmed TB diagnosed in a referral hospital, in the routine provincial electronic TB register (ETR.Net), and to describe TB treatment outcomes.

Design: A retrospective cohort study including children aged <13 years diagnosed with culture-confirmed TB at Tygerberg Children's Hospital from July 2007 to June 2009. Data on demographic, clinical and referral factors were collated from hospital data sources. Electronic matching was used to identify children in the provincial ETR.Net.

Results: Only 166 of 267 (62%) children were registered in ETR.Net. Children with TB meningitis and death prior to referral were significantly less likely to be registered. Treatment outcome data were available for only 70% of children; favourable outcomes were reported in 56%.

Conclusions: A large proportion of children diagnosed with confirmed TB at a referral hospital were not registered, resulting in underreporting of the burden and severity of childhood TB. Routine surveillance of childhood TB should include linkage of hospital data.

Routine surveillance is required by national tuberculosis programme (NTP) managers for decision-making and planning. If the quality of data is poor or incomplete, the burden and extent of tuberculosis (TB) may be inaccurately estimated, leading to poorly informed decisions and planning for TB prevention and treatment.

The South African NTP has adopted a decentralised model for TB care, encouraging routine diagnosis and treatment at community primary health clinics (PHCs).[1] In the Western Cape Province, South Africa, TB registers are kept at community clinics and at selected specialised TB hospitals where case-finding services are provided. Based on NTP guidelines,[2] TB patients should be registered and recorded at this level, irrespective of where the diagnosis was made. Health facility-based paper TB registers are captured monthly in electronic form (ETR.Net). Provincial and national reporting of TB surveillance data in South Africa has used ETR.Net since 2004.

Following diagnosis at a referral hospital, TB patients are usually referred to their local PHC for treatment, where they should be recorded in the TB register. Two previous studies from South Africa showed high rates of unsuccessful hospital-to-clinic down-referrals—21% in Gauteng and 31% in KwaZulu-Natal[3,4]—but these studies did not focus specifically on children. A study at five local PHCs in the Western Cape Province showed that 54 of 354 (15.3%) children with TB were not recorded in the facility-based TB registers. All of these children were diagnosed at the adjacent referral hospital and a high proportion had disseminated disease.[5] The nature of incomplete reporting and treatment outcomes was not documented in that study.

We were concerned about larger scale underreporting of hospital-diagnosed TB in children, and specifically whether reported provincial data underestimate the true burden and severity of childhood TB.

The aim of this study was to assess the completeness of registration in children with culture-confirmed TB diagnosed at a tertiary referral hospital in the provincial electronic TB register, and to describe their TB treatment outcomes.

METHODS

This was a review of routine information from health services collated through different sources using a retrospective cohort design.

Study setting

The Tygerberg Children's Hospital (TCH) in Cape Town, Western Cape Province, serves as a referral hospital for a large surrounding geographic area (30–40% of the provincial population). In 2007, the TB notification rate in the province was 994.2 per 100 000; children aged 0–13 years were reported to have contributed 17.1% of the burden, with a TB notification rate of 620/100 000 (unpublished data, Western Cape Department of Health). Bacille Calmette-Guérin (BCG) vaccination is routinely given at birth; coverage in 2005 was 99%.[6]

There is no routine in-hospital administered system or register to record children diagnosed with TB. A senior paediatrician at TCH (HSS) maintains a database of all children routinely diagnosed with culture-confirmed TB as part of ongoing TB surveillance, drug susceptibility testing (DST) surveillance and to ensure comprehensive clinical care.

Sources of laboratory and clinical surveillance data

All requests for *Mycobacterium tuberculosis* culture are sent to the in-hospital division of the National Health

AFFILIATIONS
1 Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, Cape Town, South Africa
2 Western Cape Department of Health, Cape Town, South Africa
3 International Union Against Tuberculosis and Lung Disease, Paris, France

CORRESPONDENCE
Karen du Preez
Desmond Tutu TB Centre
Department of Paediatrics and Child Health
Stellenbosch University
PO Box 19063
Francie van Zyl Drive
Parow 7505, Cape Town, South Africa
Tel: (+27) 21 938 9177
Fax: (+27) 21 938 9719
e-mail: karen_dupreez@sun.ac.za

ACKNOWLEDGEMENTS
The authors sincerely thank the local health authorities, E Playandi (Desmond Tutu TB Centre study nurse) for her substantial contribution with the data collection, N Titus (Tygerberg Children's Hospital [TCH] administration department) for her efficient help with providing administration data from TCH, and Professor Schoeman and Dr Springer for allowing access to TBM home-based care records and treatment outcomes.
This research was supported through an operational research course jointly developed and run by the Centre for Operational Research (COR), International Union Against Tuberculosis and Lung Disease (The Union), Paris, France, and the Operational Research Unit, Médecins Sans Frontières, Brussels. KdP is an operational research fellow at the Desmond Tutu Tuberculosis Centre, supported by the COR at The Union, Paris, France. The project received financial support from the Harry Crossley Foundation, Stellenbosch University.

KEY WORDS
surveillance; electronic register; referral

Received 16 June 2011
Accepted 26 August 2011

PHA 2011; 1(1): 19–24

Laboratory Service (NHLS). Mycobacterial culture is routine (Mycobacterial Growth Indicator Tube liquid culture medium [MGIT] 960, BD, Sparks, MD, USA). All positive paediatric culture results are routinely labelled and stored by designated NHLS laboratory personnel, and communicated on a weekly basis to HSS. The folders of these children are routinely reviewed to collect relevant clinical and demographic data.

Following bacteriological diagnosis in the hospital, children are typically referred to other health care facilities for initiation or continuation of TB treatment and recording. Referrals are mostly to PHCs, but also to TB hospitals, secondary hospitals (down-referral) and, infrequently, medium-term chronic care facilities. All children who are referred to a PHC for TB treatment should receive an official referral letter to the clinic at discharge. A copy of the letter should be left in the child's TCH hospital folder. In most cases, culture results are only available weeks after discharge and referral. As part of hospital surveillance, HSS performs active surveillance for those children with positive mycobacterial isolates when a clinical diagnosis has not been made prior to discharge from hospital, to ensure initiation of appropriate anti-tuberculosis treatment, typically by a nurse practitioner at the local PHC.

Based on NTP guidelines, facility-based TB register data should be updated on a daily basis and the register quality validated before capture in ETR.Net. ETR data updates are performed monthly, and data are aggregated for quarterly reports. All patients who are diagnosed and started on drug-susceptible TB treatment regimens should therefore be recorded in the TB registers, and captured in ETR.Net. Patients diagnosed with multidrug-resistant TB (MDR-TB) from the outset are not entered into ETR.Net, as they have a separate surveillance system. If a patient is recorded in the TB register and started on first-line treatment, but is later found to have MDR-TB, the NTP guidelines state that the patient's treatment outcome should be documented as 'failed', and that the 'MDR-TB patient' column in the register should be filled in. In addition, such patients should be recorded in a separate paper MDR register that is also captured electronically.

Study population and eligibility

All children aged <13 years routinely diagnosed with culture-confirmed *M. tuberculosis* disease at TCH from 1 July 2007 to 30 June 2009 were included in the study. Although the World Health Organization (WHO) international guidelines recommend reporting TB in children aged 0–14 years,[7] we used 0–13 years as this is the classification used for paediatric care at our hospital. Following initial inclusion in routine clinical-laboratory surveillance, exclusion criteria were a diagnosis of MDR-TB prior to referral from TCH and referral to a different province for management. The rationale for exclusion of children with MDR-TB is that additional surveillance and specialised care services are required for this subpopulation (studies ongoing).

Summary of data sources, variables and definitions

The following sources were used for data collection: TCH electronic laboratory-based hospital surveillance database, TCH administrative department data, TCH hospital folders, available TCH notification records, TCH TB meningitis (TBM) home-based care programme records, discharge summaries of the local TB referral hospital (Brooklyn Chest Hospital) and the provincial electronic TB register (ETR.Net).

A comprehensive database was compiled that collated clinical, demographic and referral-process hospital data. A second electronic source of data was then obtained from the provincial health department, containing all TB patients registered in the provincial ETR.Net during 2007–2010. We used electronic probabilistic linking[8–11] software (Registry Plus™ Link Plus, Centers for Disease Control and Prevention, Atlanta, GA, USA) to identify all possible matches between the comprehensive hospital database and the database extracted from ETR.Net using an inclusive approach. The software was configured to use four demographic variables: name, surname, sex and age. Names and surnames were converted using the New York State Identification and Intelligence System (NYSIIS),[12] a phonetic coding system that allows for inconsistencies and variations in spelling.

All matches were manually and independently reviewed by two investigators, initially for correlation of demographic details, and second to review the accuracy of the TB episode data. If there was agreement on three of the four demographic variables, records were included for further review. Further comparison of dates was then completed for all matched records to ensure identical treatment episodes, again using an inclusive approach. If one of the dates in ETR.Net (registration, treatment start or treatment outcome date) matched the hospital consultation or culture dates, the child was included, allowing a window period of 2 months prior to the admission date and of 6 months after the date the culture results became available.

Data regarding age, human immunodeficiency virus (HIV) status, sex, reported household TB contact and current TB treatment were recorded from the hospital folders. TB cases were classified as pulmonary TB (PTB), including hilar and mediastinal lymphadenopathy; extra-pulmonary TB (EPTB); or both PTB and EPTB. We report separately on disseminated TB (miliary TB and TB meningitis).

TB treatment outcomes are reported according to international recommendations.[13] Treatment outcomes were classified as favourable (treatment completed/cured) or unfavourable (treatment failure, transferred out, died or defaulted). For the purposes of the present study, an additional category, 'not evaluated', was included. This category included treatment outcomes that were not recorded in ETR.Net, as well as children who were not registered in ETR.Net and for whom no treatment outcome data were available from additional hospital surveillance sources.

Statistical considerations

Analyses were descriptive, presenting actual numbers and percentages for categorical variables and median and interquartile ranges (IQRs) for continuous variables. Hypothesis testing was performed using the χ^2 or Mann-Whitney *U*-tests. $P < 0.05$ was considered statistically significant. We used the STROBE (strengthening the reporting of observational studies in epidemiology) guidelines for reporting.[14]

Ethical considerations

Ethical approval was obtained from the Research Ethics Committee of the Stellenbosch University (waiver obtained for informed consent), the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, the study hospital and the provincial and metropolitan health services.

RESULTS

During the study period, 291 children were diagnosed with culture-confirmed TB at TCH. Twenty-four were excluded: 22 were diagnosed with MDR-TB disease before discharge and two were referred to PHCs in another province. Evidence of registration in the provincial ETR.Net was found for only 166 (62%) of the 267 children. Demographic, clinical and referral process factors in relation to ETR.Net registration are summarised in Table 1. There was no

association between evidence of registration and the demographic variables age or sex.

The only clinical factors that were significantly associated with lack of registration were disseminated TB and death prior to referral. In a sub-analysis of children with disseminated TB this finding was retained in children with TB meningitis, but not in those with miliary TB. TB meningitis remained significantly associated with lack of registration even when children who died prior to registration were excluded from the analysis ($P < 0.01$). Ten children died before referral for treatment; all were absent from the ETR.Net and hospital notification records.

The type of consultation and duration of hospital admission were borderline significant as risk factors for non-registration. None of the other clinical factors considered, i.e., HIV status, type of TB disease (non-disseminated), reported TB contact history, current TB treatment at time of investigation or drug resistance, was associated with presence of registration in ETR.Net. Some referral process factors showed only borderline association (presence of clinic referral letter in the hospital folder, and hospital notification done), but the type of health care centre to which the child was referred was not associated with ETR.Net registration.

Table 2 describes TB treatment outcomes, first showing all outcomes for registered children as documented in ETR.Net and second, showing treatment outcome data on all identified children, including outcome data on non-registered children from additional surveillance sources (TCH surveillance database, TBM

TABLE 1 Demographic, clinical and referral process factors in relation to electronic registration of children with culture-confirmed TB at a tertiary hospital in Cape Town ($n = 267$)

	Not registered ($n = 101$) *n* (%)	Registered ($n = 166$) *n* (%)	*P* value
Demographic factors			
Age, months, median [IQR]*	25 [13–51]	23 [12–73]	0.870
Male sex	51 (50.5)	97 (58.4)	0.200
Clinical factors			
HIV status			
Tested	79 (78.2)	124 (74.7)	0.514
HIV-infected	21/79 (26.6)	35/124 (28.2)	0.798
HIV-infected, on HAART	8/21 (38.1)	15/35 (42.9)	0.726
Type of TB			
PTB only	39 (38.6)	71 (42.8)	0.612
EPTB only	21 (20.8)	27 (16.8)	
PTB and EPTB	41 (40.6)	68 (41.0)	
Disseminated TB	29 (28.7)	27 (16.3)	0.015
Miliary TB	12 (11.9)	16 (9.6)	0.562
TB meningitis	22 (21.8)	13 (7.8)	0.001
Deaths prior to referral†	10 (9.9)	0	<0.001
Reported TB contact history‡			
Household contact	42 (41.6)	77 (46.4)	0.099
Parent on TB treatment	24 (23.8)	40 (24.1)	0.918
On TB treatment at the time of consultation	5 (4.9)	5 (3.0)	0.419
Drug resistance			
INH monoresistance	5 (4.9)	7 (4.2)	0.928
RMP monoresistance	1 (0.9)	1 (0.6)	
Multidrug resistance	2 (2.0)	5 (3.0)	
Type of consultation			
Out-patient	16 (15.9)	41 (24.7)	0.087
In-patient	85 (84.2)	125 (75.3)	
Duration of hospitalisation, days, median [IQR]*§	16 [5–29]	3 [9–20]	0.052
Referral process factors			
Presence of referral letter in folder¶	17/31 (54.8)	68/93 (73.1)	0.058
Referral decision at discharge to#			
Community Health Clinic	58 (63.7)	125 (75.3)	0.100
TB hospital	26 (28.6)	28 (16.9)	
Secondary hospital	3 (3.3)	9 (5.4)	
Chronic medium-term care facility	4 (4.4)	4 (2.4)	
Hospital notification done	7 (6.9)	23 (13.9)	0.082

*Mann-Whitney *U*-test used for hypothesis testing.
†9 children died in hospital and 1 child died after discharge before culture results were available.
‡Known TB contact reported for 140/267 (52%) children.
§Data missing for 9/210 children admitted as in-patients.
¶Only for those children who were referred to PHCs for TB treatment at discharge from TCH 151/183; 21 folders were not available for review, and six children were already on TB treatment.
#The denominator here is 257 and not 267, due to the 10 children who died in hospital prior to a referral decision.
TB = tuberculosis; IQR = interquartile range; HIV = human immunodeficiency virus; HAART = highly active anti-retroviral therapy; PTB = pulmonary TB; EPTB = extra-pulmonary TB; INH = isoniazid; RMP = rifampicin.

TABLE 2 TB treatment outcomes of children diagnosed with culture-confirmed TB at a tertiary hospital in Cape Town, South Africa

	Treatment outcomes as documented in the provincial ETR.Net (n = 166) n (%)	Treatment outcomes for all children, including outcome data from additional hospital surveillance sources (n = 267)* n (%)
Completed/cured	134 (81)†	149 (56)
Defaulted	13 (8)	13 (5)
Failed	3 (2)	4 (2)
Transferred out	6 (4)	6 (2)
Died	2 (1)	14 (5)
Not evaluated	8 (5)‡	81 (30)§

*Additional treatment outcomes included for 28 non-registered children.
†Actual recorded breakdown: completed = 120, cured/completed = 10, cured = 4.
‡Treatment outcomes not recorded in ETR.Net (n = 8).
§Includes children with no recorded treatment outcome in ETR.Net (n = 8), and children not registered in ETR.Net for whom no outcome data were available from additional hospital surveillance sources (n = 73).
TB = tuberculosis; ETR.Net = electronic TB register.

home-based care programme records and discharge summaries of the local TB hospital [Brooklyn Chest Hospital]). Treatment outcomes were available for only 70% of the children, and favourable treatment outcomes were documented in only 56%. Clinical characteristics, referral process factors and mortality data are described in Table 3.

TABLE 3 Clinical and referral process factors among children with culture-confirmed TB and documentation of death (n = 14)

	Deaths (n = 14) n (%)
Age, months, median [IQR]	26 [9–84]
HIV-infected*	4 (29)
HIV-infected on HAART	0
Drug resistance	
Rifampicin monoresistance	1 (7)
Multidrug resistance	2 (14)
Type of TB	
PTB only	4 (29)
EPTB only	1 (7)
Both	9 (64)
Disseminated TB†	7 (50)
Miliary TB	4 (29)
TB meningitis	5 (36)
Referral decision at discharge to	
Community health clinic	2 (14)
TB hospital	1 (7)
Secondary hospital	1 (7)
Deaths prior to referral‡	10 (71)
Source of mortality recording	
Hospital surveillance	13 (93)
ETR.Net	2 (14)
Recorded in both	1 (7)

*HIV status unknown (n = 2).
†Children with both miliary TB and TB meningitis (n = 2).
‡Nine children died in hospital and one child died after discharge before culture results were available.
TB = tuberculosis; IQR = interquartile range; HIV = human immunodeficiency virus; HAART = highly active antiretroviral therapy; PTB = pulmonary TB; EPTB = extrapulmonary TB; ETR.Net = electronic TB register.

DISCUSSION

This study confirmed our hypothesis that a large proportion of children with culture-confirmed TB diagnosed at a large tertiary level hospital are not recorded and registered in ETR.Net, and are thus not included in provincial, national and, consequently, international TB reporting. Children who were not registered more frequently had serious forms of disease and were more likely to have died. This implies underestimation not only of the burden of childhood TB in this setting, which is already high, but also of TB-related morbidity and mortality in children. The study further indicates that reported TB treatment outcomes in children may be inaccurate. Although treatment outcomes were favourable in more than 80% of those recorded, it does not take into account that data on approximately 40% of children were not captured, and that these children may be a group at high risk for unfavourable TB outcomes.

To our knowledge, no other studies in South Africa have accessed ETR.Net data at the provincial level and used electronic matching to evaluate the completeness of registration of childhood TB.[3,4,15,16] We used the actual source electronic data routinely used for TB reporting in our province, and were not limited in accessing only selected facilities and their registers. We were therefore able to identify all children who were registered, irrespective of the facility where they accessed care.

As the data collected at TCH form part of ongoing clinical care and research, the quality of this source of routine data was good, with negligible missing data. Unfortunately, data from ETR.Net are captured from TB registers, and there are some concerns regarding quality. Examples of problems identified were inconsistencies between treatment duration and treatment outcome (e.g., recorded treatment duration of only 2 months, with a treatment outcome documented as cured/completed), and incorrect classification of treatment outcomes (e.g., children with MDR-TB who were not classified as 'failed'). We were not able to verify true outcome data in this retrospective study; future prospective studies should address this aspect systematically.

It is important to note that our data do not necessarily reflect poor individual clinical care, but demonstrate limitations in the existing surveillance systems linking key data from a large hospital with recording and registration to the decentralised model. On the pathway from diagnosis at hospital level to registration in ETR.Net, we have to consider three processes. First is the hospital-to-clinic referral process, second is accurate recording of registration and treatment outcome data in the TB register at facility level, and third, accurate capture of the information recorded in the paper register into ETR.Net. Further studies are required to assess these individual components of the surveillance cascade.

Although our study could not identify any specific factors associated with non-registration in relation to the hospital-to-clinic referral process, previous literature has shown that this process is likely to be responsible for a substantial amount of non-registrations. Two previous studies from South Africa showed significant loss specifically during this process.[3,4] As a diagnosis of TB is made in, and the referral done from hospital, it should be the responsibility of the hospital personnel to ensure access to care at the PHC. Thereafter, PHC personnel are responsible for care, including accurate registration as part of monitoring and evaluation in the NTP. Improved systems to capture hospital-to-clinic referral and continuity of care for childhood TB are therefore critically important.

In our setting, children diagnosed with TB meningitis follow a different treatment path after the initial months of treatment. Some are referred to TB hospitals for the first few months

of treatment, while others are enrolled in a home-based care programme. These children are discharged home, but receive their treatment and clinical follow-up on a monthly basis from TCH until completion of treatment. Although these children are treated as out-patients, most of them will never attend a PHC for registration as they are treated only at the hospital. This highlights an additional gap in the processes linking hospital management and provincial registration systems. A possible way to solve this is to implement a hospital-based register specifically for children who are not likely to attend a PHC for treatment.

The association between a longer duration of admission and non-registration was interesting. We speculate that children with longer hospitalisation are likely to be more ill, with more severe forms of TB disease, and treatment is most likely started during hospital admission. This implies a lower probability of clinic-based management during the initial months of treatment and thus, possibly, also of clinic-based registration. It is possible that clinic staff might assume that children who were started on treatment in the hospital had already been registered. In contrast, children with a short period of hospitalisation will probably not start treatment in hospital but will be referred directly to a clinic for initiation of treatment.

As this was an operational study focusing on routine data, the study had several limitations. We only had access to data on children diagnosed with culture-confirmed TB, which represents only 30–40% of all children diagnosed with TB at TCH. Although we included all provincial records, we do not know if non-registered children sought care in a different province or from private practitioners. With record matching the most important consideration was not to miss true registrations, and thus an inclusive approach was used. Children aged 13–14 years were excluded due to local classification systems, but this could have resulted in further underestimation of the burden of disease. The natural history of disease shows that adolescents (especially girls) are at high risk of disease progression.[17] This study was not able to establish the specific reasons for non-registration or verify data sources between PHCs and ETR.Net, and future research is needed to evaluate these processes.

Our findings have implications for all three data-linking processes in the surveillance cascade. The hospital-to-clinic referral system could be improved by implementing a dedicated monitoring and follow-through service in the hospital. An in-hospital TB Care Centre has been shown to significantly improve referral success in Johannesburg.[18] NTP managers should monitor the quality of recording and registration regularly by verifying data using clinic records, TB registers and ETR.Net entry to ensure that accurate data are collected for TB reporting.

In conclusion, we found that almost 40% of the children diagnosed with culture-confirmed TB at a tertiary referral hospital were not included in ETR.Net, resulting in underreporting of the burden and severity of TB and TB deaths in South African children. Routine surveillance of childhood TB should include linkage of hospital data.

References

1 Department of Health. Tuberculosis strategic plan for South Africa, 2007–2011. Pretoria, South Africa: Ministry of Health, 2010. http://www.info.gov.za/view/DownloadFileAction?id=72544 Accessed August 2011.
2 Department of Health. South African national tuberculosis management guidelines. Pretoria, South Africa: Ministry of Health, 2008. http://www.sasohn.org.za/images/TBGUIDELINES2008SFINALFORPRINTINGMARCH09.pdf Accessed August 2011.
3 Edginton M E, Wong M L, Phofa R, Mahlaba D, Hodkinson H J. Tuberculosis at Chris Hani Baragwanath Hospital: numbers of patients diagnosed and outcomes of referrals to district clinics. Int J Tuberc Lung Dis 2005; 9: 398–402.
4 Loveday M, Thomson L, Chopra M, Ndlela Z. A health systems assessment of the KwaZulu-Natal tuberculosis programme in the context of increasing drug resistance. Int J Tuberc Lung Dis 2008; 12: 1042–1047.
5 Marais B J, Hesseling A C, Gie R P, Schaaf H S, Beyers N. The burden of childhood tuberculosis and the accuracy of community-based surveillance data. Int J Tuberc Lung Dis 2006; 10: 259–263.
6 Corrigal J. Western Cape provincial EPI vaccination survey. Cape Town, South Africa: University of Western Cape, 2005. http://www.capegateway.gov.za/Text/2007/6/cd_volume_7_childhood_diseases_overview.pdf Accessed August 2011.
7 World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. WHO/HTM/TB/2006.371. Geneva, Switzerland: WHO, 2006.
8 Dunn H L. Record linkage. Am J Public Health 1946; 36: 1412–1416.
9 Fair M, Cyr M, Allen A C, Wen S W, Guyon G, MacDonald R C. An assessment of the validity of a computer system for probabilistic record linkage of birth and infant death records in Canada. The Fetal and Infant Health Study Group. Chronic Dis Can 2000; 21: 8–13.
10 Meray N, Reitsma J B, Ravelli A C, Bonsel G J. Probabilistic record linkage is a valid and transparent tool to combine databases without a patient identification number. J Clin Epidemiol 2007; 60: 883–891.
11 Newcombe H B. Handbook of record linkage: methods for health and statistical studies, administration and business. Oxford, UK: Oxford University Press, 1988.
12 Black P E. 'NYSIIS'. In: US National Institute of Standards and Technology. Dictionary of algorithms and data structures. Gaithersburg, MD, USA: NIST, 2009. http://www.nist.gov/dads/HTML/nysiis.html Accessed August 2011.
13 World Health Organization, International Union Against Tuberculosis and Lung Disease, Royal Netherlands Tuberculosis Association. Revised international definitions in tuberculosis control. Int J Tuberc Lung Dis 2001; 5: 213–215.
14 von Elm E, Altman D G, Egger M, Pocock S J, Gotzsche P C, Vandenbroucke J P. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007; 370: 1453–1457.
15 Botha E, den Boon S, Lawrence K A, et al. From suspect to patient: tuberculosis diagnosis and treatment initiation in health facilities in South Africa. Int J Tuberc Lung Dis 2008; 12: 936–941.
16 Dunbar R, Lawrence K, Verver S, et al. Accuracy and completeness of recording of confirmed tuberculosis in two South African communities. Int J Tuberc Lung Dis 2011; 15: 337–343.
17 Marais B J, Gie R P, Schaaf H S, et al. The natural history of childhood intrathoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis 2004; 8: 392–402.
18 Edginton M E, Wong M L, Hodkinson H J. Tuberculosis at Chris Hani Baragwanath Hospital: an intervention to improve patient referrals to district clinics. Int J Tuberc Lung Dis 2006; 10: 1018–1022.

Contexte : Le Programme National contre la Tuberculose (PNT) de l'Afrique du Sud recommande l'enregistrement des patients tuberculeux dans les dispensaires de la collectivité. C'est dans les hôpitaux de référence que le diagnostic de la tuberculose (TB) est souvent porté chez les enfants et des préoccupations existent concernant le fait que ces enfants soient ou non inclus de manière précise dans les déclarations de routine du PNT.
Objectif : Evaluer le caractère complet de l'enregistrement des enfants atteints d'une TB confirmée par la culture et diagnostiquée dans un hôpital de référence vers le registre provincial électronique de routine (TB) (ETR.Net), et d'autre part décrire les résultats du traitement de la TB.
Schéma : Etude rétrospective de cohorte comportant des enfants âgés de <13 ans chez qui une TB confirmée par la culture a été diagnostiquée à l'Hôpital des Enfants de Tygerberg entre juillet 2007 et juin 2009. On a rassemblé les données démographiques, cliniques et les facteurs de référence à partir des sources de données de l'hôpital. On a utilisé la corrélation électronique pour identifier les enfants dans le réseau ETR.net de la province.
Résultats : N'ont été enregistrés dans le réseau ETR.Net que 166 des 267 enfants (62%). On a noté que les enfants atteints de méningite TB et décédés avant leur transfert étaient enregistrés de manière significativement moins fréquente. Les données de résultats du traitement ont été disponibles chez 70% des enfants seulement. On a signalé des résultats favorables chez 56% d'entre eux.
Conclusions : Une proportion importante des enfants chez qui une TB confirmée a été diagnostiquée dans un hôpital de référence n'ont pas été enregistrés, ce qui entraîne des sous-déclarations du fardeau et de la gravité de la TB infantile. La surveillance de routine de la TB infantile devrait inclure un lien avec les données hospitalières.

Marco de referencia: El Programa Nacional contra la Tuberculosis de Sudáfrica recomienda el registro de los pacientes tuberculosos en los consultorios comunitarios. En el caso de los niños, el diagnóstico de tuberculosis (TB) se suele establecer en los hospitales de referencia y existen dudas sobre su inclusión en los informes corrientes del programa nacional.
Objetivo: Se buscó evaluar la exhaustividad del registro electrónico corriente de TB de la provincia (ETR.Net), con respecto a los casos de niños con TB confirmada por cultivo que se diagnostica en un hospital de referencia y se describió además el desenlace del tratamiento antituberculoso.
Método: Fue este un estudio retrospectivo de cohortes, en el cual se incluyeron los niños con diagnóstico de TB confirmada por cultivo en el Hospital Infantil de Tygerberg entre julio del 2007 y junio del 2009. Se recogieron los datos personales, los datos clínicos y los criterios de remisión a partir de las fuentes hospitalarias de datos. Mediante una comparación informatizada de los datos se verificó la notificación de estos casos en el registro ETR.Net de la provincia.
Resultados: Solo 166 de los 267 niños (62%) estaban notificados en ETR.Net. La probabilidad de registro de los casos de meningitis tuberculosa y de los niños que fallecieron antes de la remisión fue significativamente menor. Se obtuvo información sobre el desenlace terapéutico de solo 70% de los niños; se notificó un desenlace favorable en el 56% de los casos.
Conclusiones: Una gran proporción de los niños con diagnóstico confirmado de TB en el hospital de referencia no se encuentra notificada en ETR.Net, por lo cual existe una subestimación de la carga de morbilidad por TB y de la gravedad de la enfermedad en los niños. La vigilancia corriente de la TB de los niños debería comportar un vínculo con los datos hospitalarios.

Public Health Action (PHA) The voice for operational research.
Published by The Union (www.theunion.org), PHA provides a platform to fulfil its mission, 'Health solutions for the poor'. PHA publishes high-quality scientific research that provides new knowledge to improve the accessibility, equity, quality and efficiency of health systems and services.

e-ISSN 220-8372
Editor in Chief: Donald A Enarson, MD, Canada
Contact: pha@theunion.org
PHA website: http://www.theunion.org/index.php/en/journals/pha
Article submission: http://mc.manuscriptcentral.com/pha

Public Health Action

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

VOL 10 NO 1 PUBLISHED 21 MARCH 2020

Closing the reporting gap for childhood tuberculosis in South Africa: improving hospital referrals and linkages

K. du Preez,[1] H. S. Schaaf,[1,2] R. Dunbar,[1] A. Swartz,[3] P. Naidoo,[4] A. C. Hesseling[1]

http://dx.doi.org/10.5588/pha.19.0053

Setting: A referral hospital in Cape Town, Western Cape Province, Republic of South Africa.
Objective: To measure the impact of a hospital-based referral service (intervention) to reduce initial loss to follow-up among children with tuberculosis (TB) and ensure the completeness of routine TB surveillance data.
Design: A dedicated TB referral service was established in the paediatric wards at Tygerberg Hospital, Cape Town, in 2012. Allocated personnel provided TB education and counselling, TB referral support and weekly telephonic follow-up after hospital discharge. All children identified with TB were matched to electronic TB treatment registers (ETR.Net/EDRWeb). Multivariable logistic regression was used to compare reporting of culture-confirmed and drug-susceptible TB cases before (2007–2009) and during (2012) the intervention.
Results: Successful referral with linkage to care was confirmed in 267/272 (98%) and successful reporting in 227/272 (84%) children. Children with drug-susceptible, culture-confirmed TB were significantly more likely to be reported during the intervention period than in the pre-intervention period (OR 2.52, 95%CI 1.33–4.77). The intervention effect remained consistent in multivariable analysis (adjusted OR 2.62; 95%CI 1.31–5.25) after adjusting for age, sex, human immunodeficiency virus status and the presence of TB meningitis.
Conclusions: A simple hospital-based TB referral service can reduce initial loss to follow-up and improve recording and reporting of childhood TB in settings with decentralised TB services.

Inaccurate surveillance data for childhood tuberculosis (TB; age <15 years) has been noted as a critical concern globally, and one which limits our ability to appropriately manage paediatric TB.[1,2] Since 2013, the World Health Organization (WHO) has been urging countries to prioritise improving the quality of TB surveillance data in children;[3] however, only 45% of the estimated 1 million childhood TB cases worldwide were reported to the WHO in 2017.[4,5] Under-detection of cases and incomplete reporting of detected cases both contribute to this large deficit.[1]

In 2017, South Africa reported only 40% of the 39 000 estimated child TB caseload.[4] South Africa follows a decentralised model of TB care, and the primary sources of TB surveillance data are two electronic TB treatment registers: ETR.Net for drug-susceptible (DS)-TB and EDRWeb for drug-resistant (DR)-TB. Both registers are used for TB case notification at local, national and international levels.[6,7]

Naidoo et al. estimated that 12% of the total TB burden in South Africa in 2013 was lost between diagnosis and treatment initiation (initial loss to follow-up [ILTFU]).[8] Substantial ILTFU (52% and 58%) has been documented among hospital-diagnosed TB patients in South Africa.[9,10] As TB surveillance data are typically captured at treatment initiation, ILTFU contributes to the reporting gap in South Africa. Successful linkage of TB care between hospital and community-based PHC facilities is another recognised challenge.[11] Following TB treatment initiation in South African hospitals, unsuccessful linkage to PHC care occurred in respectively 12% (Western Cape, 2008/2009),[9] 21% (Gauteng, 2001),[12] 23% (Gauteng, 2009)[13] and 31% (Kwa-Zulu Natal, 2005)[10] of TB patients, with children (age <15 years) being at even higher risk than adults for discontinuing TB care.[9] In provinces in South Africa where general hospitals are not required to report TB case-notification data, such as the Western Cape, TB patients who started treatment in-hospital but are not successfully linked to care, contributes to the reporting gap.

Childhood TB, especially TB in young children, is often diagnosed at hospital level due to challenges faced in specimen collection and diagnosis.[14,15] A retrospective audit of children diagnosed with culture-confirmed TB during 2007–2009 at a large tertiary hospital in Cape Town, Western Cape Province, South Africa, found an overall reporting gap of 38% (101/267); 32% (58/183) among children discharged home to continue TB care.[16] Given the large number of children with TB managed at this hospital (approximately 400 per year)[14] and other referral centres, this underestimation of the burden and spectrum of TB disease can have a considerable impact on resource allocation and service delivery. An evaluation of community-based TB surveillance data in one health sub-district in Cape Town found frequent omission of severe cases and a reporting gap of 15% (54/354) among children, all of whom had been diagnosed at the referral hospital.[17]

Similar challenges with hospital notification of childhood TB cases have been reported in other settings. A study from Indonesia found a large reporting gap in children, with only 75/4821 (1.6%) child TB cases managed in hospitals being recorded and reported to the National TB Programme.[18] At a private, tertiary hospital in India during 2015/2016, only 24/264 (9.1%) of child TB cases were notified.[19] In Cotonou, Benin, the hospital contributed 29 (16%) of the total child TB burden, of which none had been reported.[20] Although data on the gap in hospital report-

AFFILIATIONS
1 Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
2 Department of Paediatrics and Child Health, Tygerberg Hospital, Cape Town, South Africa
3 Western Cape Department of Health, Cape Town, South Africa
4 Public health management consultant, Cape Town, South Africa

CORRESPONDENCE
Karen du Preez, Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Francie van Zijl Drive, Parow, Cape Town 8001, South Africa.
e-mail: karen_dupreez@sun.ac.za

KEY WORDS
paediatric; TB; initial loss to follow-up; reporting; notification

Received 30 July 2019
Accepted 8 November 2019

PHA 2020; 10(1): 38–46

ing for childhood TB are available, there is a paucity of data on interventions to address this.

Continuation of TB care from hospital to community-based PHC facilities and accurate reporting is essential to reduce ILTFU and accurately capture the true burden and spectrum of TB in children. Dedicated TB referral support interventions in hospitals has been previously shown to improve hospital-community linkage to care and TB reporting in Gauteng, South Africa.[21,22] We implemented a hospital-based intervention to support referral and linkage of children with TB from the hospital to community-based PHC facilities and evaluated the impact of this intervention on the completeness of routine TB reporting data.

METHODS

Study design and population

Prospective hospital surveillance activities identified 395 children (age 0–<13 years) routinely managed with either confirmed or clinically diagnosed TB at Tygerberg Hospital (TBH) during 2012.[14] Surveillance methods, clinical characteristics, care pathways and treatment outcomes have been previously reported.[14] Prospective enhanced surveillance provided the foundation for an intervention to support linkage to care focussed on children with TB who were discharged home to continue routine TB care at either community-based PHC facilities or as an outpatient at TBH.

All eligible children during the intervention period (January–December 2012) contributed to a prospective cohort. To assess the intervention impact on the completeness of reported data, a before-and-after study design was used to compare prospective cohort data from the intervention period with data from a previous retrospective cohort study of children with culture-confirmed TB at the same hospital (July 2007–June 2009).[16]

Setting

South Africa remains one of the highest TB burden countries globally, with an estimated annual TB incidence rate of more than 500 per 100 000 population per year since 2000.[4] Of the 296 996 new TB case notifications that were reported in 2012 to the WHO, 38 578 (13%) were children aged <15 years.[23] TBH is one of two tertiary referral hospitals in Cape Town, serving the paediatric population in the Western Cape Province. During 2012, the hospital had 268 paediatric beds and a staff complement of more than 100 clinical personnel.[24] It serves as a referral hospital for both uncomplicated and complicated TB cases from surrounding high-burden communities, and for complicated TB cases across the province. The majority of the paediatric TB cases are discharged home to continue TB care, and others are referred to TB hospitals, secondary-level hospitals or chronic, medium-term care facilities.[14,16] Following a diagnosis of TB meningitis (TBM), eligible children can enter a home-based care programme with monthly outpatient follow-up at TBH until treatment completion.[25]

An electronic register for DR-TB (EDRWeb) was piloted and implemented in South Africa from 2009. In addition to the changes in surveillance and reporting, paediatric DR-TB care was decentralised in 2011 at provincial level. Xpert MTB/RIF (Cepheid, Sunnydale, CA) was only routinely implemented for paediatric TB after 2012.

Linkage to care intervention

A hospital-based TB referral service, staffed by a dedicated full-time nursing officer and a lay healthcare worker, was established in the paediatric wards and outpatient clinics at TBH in 2012. The Figure provides an overview of the intervention. In-hospital support for children routinely diagnosed with TB by TBH clinical staff included TB education and counselling of parents/caregivers (by telephone if not possible in person), and supporting completion of routine TB referral stationary. During study implementation, paediatric hospital personnel received ongoing training and feedback regarding appropriate TB referral procedures. All intervention activities were implemented as part of an integrated package of TB care for children at TBH. Following discharge, intervention support included weekly follow-up by telephone with TB staff at the receiving PHC to confirm whether the child had accessed care, and with parents/caregivers if necessary. TB nurses at the PHCs were reminded to record all children into the PHC-based paper TB register. Parents/caregivers of children who were followed up monthly at the TBH outpatient department were asked to attend their community-based PHC facility upon hospital discharge and at the end of treatment to ensure recording of the child and their TB treatment outcome in the PHC-based TB treatment registers.

Data collection, definitions and outcome measures

Demographic and clinical information were extracted from routine patient records. Based on standard of care diagnostic testing in this setting (chest radiography and at least two respiratory specimens), the duration of admission was divided into two categories—1–3 days or ⩾4 days—to distinguish between uncomplicated and more complicated admissions. Referral information was captured through telephonic follow-up with healthcare providers and parents/caregivers, as well as patient record reviews. A successful referral outcome required telephonic (with a healthcare provider) or paper-based confirmation of attendance at a community-based PHC facility or outpatient clinic following hospital discharge.

Standard case report forms were completed and dual-captured in an access-controlled database with restricted access. Probabilistic record linkage was used to match identified TBH patients to an extracted TB surveillance database (ETR.Net and EDRWeb; 2011–2013).[26] Following electronic linkage, demographic and TB episode data were manually reviewed for accuracy. Previously described methods and criteria were used to determine successful matching, consistent with methods used in the baseline/pre-intervention as-

ACKNOWLEDGEMENTS

The authors would like to acknowledge D Leukes, E Viljoen, L du Plessis and R Solomons for their contribution to study activities and data collection. This operational research was funded by the Fogarty International Centre (Bethesda, MD, USA) Grant (3U2RTW007370-05S1). The funding body did not have any role in study design, data collection, analysis, data interpretation or in writing the manuscript. KDP is supported by a South African National Research Foundation (NRF) South African Research Chairs Initiative (SARCHI) grant to ACH. HSS received a NRF grant. The financial assistance of the NRF towards this research is hereby acknowledged. Opinions expressed, and conclusions arrived at, are those of the authors and are not necessarily to be attributed to the NRF. Conflicts of interest: none declared.

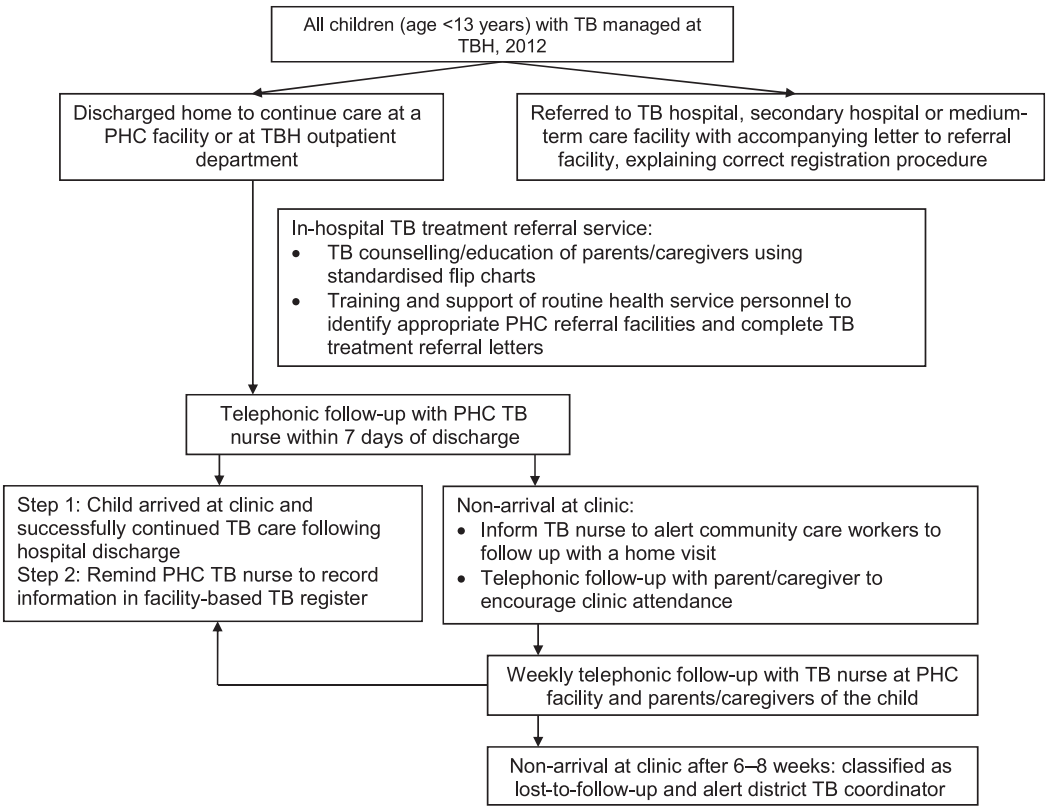


FIGURE Hospital intervention to support successful referral and reporting of childhood TB, Tygerberg Hospital, Cape Town, Western Cape Province, Republic of South Africa, January–December 2012. TB = tuberculosis; TBH = Tygerberg Hospital; PHC = primary health care.

sessment.[16] Data were de-identified upon completion of matching procedures.

Statistical analysis

Results are reported as numbers and percentages for categorical variables, and median and inter-quartile ranges (IQRs) for continuous variables. Statistical comparisons were made to assess differences between children who had successfully received the intervention vs. those who did not, and to evaluate associations between primary outcome measures and in-hospital intervention activities, relevant admission and referral factors. Odds ratios (ORs) and 95% confidence intervals (CIs) are reported. The χ^2 test or Fisher's Exact test was used for hypothesis testing.

To measure the impact of the intervention on TB case notification, data from the intervention period (2012) were compared with data from the pre-intervention period (baseline; 2007–2009) at the same hospital using an intention-to-treat analysis approach. Baseline data were limited to children with culture-confirmed TB. Therefore, analysis of the intervention period included only children with culture-confirmed TB, although analysis with the total intervention group was also performed. Demographic, admission and clinical factors were compared to assess comparability between the groups from the two periods. Univariable and multivariable logistic regression were used to measure the impact of the intervention on reporting, and to identify and adjust for possible confounders. Data are reported as ORs and adjusted odds ratios (aORs). Due to the changes in reporting for children with DR-TB over the total study period, primary analysis included only children treated for DS-TB during both periods. The multivariable model included age, sex and HIV status *a priori*, and variables that were significantly associated with outcomes, at $P < 0.05$, in univariable analyses. Analyses were completed using Stata SE version 14.0 (StataCorp, College Station, TX, USA).

Ethics approval was obtained from the Stellenbosch University Health Research Ethics Committee, Tygerberg, South Africa (N11/09/287), and provincial (RP143/2011) and municipal authorities (ID 10266)). A waiver of individual informed consent was granted since the intervention was implemented as part of standard paediatric clinical care.

RESULTS

During 2012, 272 children with TB (102 [38%] culture-confirmed) were discharged to continue TB care at a community-based PHC facility (n = 244) or at the TBH outpatient department (n = 28). TB education and counselling were completed with parents/caregivers of 230 (85%) children, and referral documentation was completed for 220 (81%) children. Table 1 gives the associations between demographic, clinical, care pathway and admission factors and the completion of in-hospital intervention activities. Bacteriological confirmation, diagnosis after discharge and hospital admission ⩽3 days were associated with not completing TB education. Extrapulmonary TB (EPTB) only, bacteriological confirmation and a pre-admission or post-discharge TB diagnosis were associated with incomplete TB referral documentation.

Referral and reporting outcomes are shown in Table 2 in relation to the in-hospital intervention activities, clinical and TB care pathway factors. Of the 272 children, successful referral was confirmed in 267 (98%), and successful reporting in 227 (84%

TABLE 1 Characteristics of children with TB discharged from Tygerberg Hospital, Cape Town, Western Cape Province, Republic of South Africa, by completion status of in-hospital linkage-to-care intervention activities, January–December 2012 (n = 272)

	TB education		Referral documentation	
	Completed (n = 230, 84.6%) n/N (%)	P value	Completed (n = 220, 80.8%) n/N (%)	P value
Demographic/clinical factors				
Age, years				
0–<2	103/119 (86.6)		97/119 (81.5)	
2–<5	74/85 (87.1)		73/85 (85.9)	
5–13	53/68 (77.9)	0.218	50/68 (73.5)	0.151
Sex				
Male	130/155 (83.9)		131/155 (84.5)	
Female	100/117 (85.5)	0.718	89/117 (76.1)	0.079
HIV status				
Positive	51/59 (86.4)		48/59 (81.4)	
Negative	166/195 (85.1)		161/195 (82.6)	
Unknown	13/18 (72.2)	0.316	11/18 (61.1)	0.086
TB disease type				
PTB only	130/154 (84.4)		132/154 (85.7)	
Both PTB and EPTB	62/72 (86.1)		62/72 (86.1)	
EPTB only	38/46 (82.6)	0.874	26/46 (56.5)	0.001
Diagnostic status				
Culture-confirmed *M. tuberculosis*	80/102 (78.4)		76/102 (74.5)	
Clinical diagnosis	150/170 (88.2)	0.030	144/170 (84.7)	0.038
TB treatment regimen				
DS-TB regimen	216/258 (83.7)		209/258 (81.0)	
DR-TB regimen*	14/14 (100)	0.137†	11/14 (78.6)	0.735†
TB care pathway/admission factors				
TB diagnostic pathway				
Diagnosed before admission	50/56 (89.3)		36/56 (64.3)	
Diagnosed during admission	174/203 (85.7)		178/203 (87.7)	
Diagnosed after discharge‡	6/13 (46.2)	<0.001	6/13 (46.2)	<0.001
Level of health care accessed before diagnosis§				
Primary health care	11/13 (84.6)		9/13 (69.2)	
Other hospital	39/43 (90.7)	0.615†	27/43 (62.8)	0.752†
Duration of hospital visit/admission				
Outpatients	28/34 (82,4)		28/34 (82.4)	
1–≤3 days	23/39 (59.0)		30/39 (76.9)	
≥4 days	179/199 (90.0)	<0.001	162/199 (81.4)	0.787

*Includes all types of drug resistance.
†Fisher's Exact test used if χ^2 assumptions were not met.
‡12 of 13 children who were diagnosed only after discharge were diagnosed based on a culture-positive result that became available only after discharge.
§Including only children diagnosed before hospital admission.
TB = tuberculosis; HIV = human immunodeficiency virus; PTB = pulmonary TB; EPTB = extrapulmonary TB; DS-TB = drug-susceptible TB; DR-TB = drug-resistant TB.

matched with the routine TB surveillance data [ETR.Net/EDRWeb]). Receiving education/counselling was associated with successful referral. Children who were followed as hospital outpatients, including all children with TBM, as well as children with DR-TB, were less likely to be reported.

Table 3 compares demographic, admission and clinical characteristics of children with culture-confirmed TB who were discharged to continue TB care by time period: baseline (2007–2009; n = 183[16]) and intervention (2012; n = 102). Children from the two periods were similar regarding age distribution, sex, patient category, duration of admission, TB disease spectrum, TBM, miliary TB and drug resistance. The proportion of children with unknown HIV status decreased substantially over time from 59 (32%) to 11 (11%), and documented HIV infection decreased from 29 (16%) to 12 (12%).

Table 4 provides results of the univariable and multivariable analyses to assess the impact of the intervention on reporting of children with DS-TB. During the intervention period, children discharged home to continue TB care were 2.52 times (95%CI 1.33–4.77, P= 0.004) more likely to be recorded in the ETR.Net than during the baseline period. The intervention effect remained consistent in the multivariable model, adjusting for age, sex, HIV status and TBM (aOR 2.62, 95%CI 1.31–5.25; P = 0.006). In the multivariate model adjusting for the effect of the intervention, the odds of children with TBM being reported remained significantly lower than children without TBM (aOR 0.18, 95%CI 0.07–0.48; P = 0.001). Although data are not presented, multivariable analyses of the culture-confirmed baseline group and the total intervention group (culture-confirmed plus clinically diagnosed cases) adjusted for the same variables,

TABLE 2 Referral and reporting outcomes of a hospital-community linkage to care intervention for children with TB discharged from Tygerberg Hospital, Cape Town, Western Cape Province, Republic of South Africa, January–December 2012 (*n* = 272)

		Referral outcomes		Reporting outcomes	
	Overall (*n* = 272) *n* (%)	Accessed clinical care (*n* = 267, 98.2%) *n* (%)	*P* value	Recorded in ETR.Net/EDRWeb (*n* = 227, 83.5%) *n* (%)	*P* value
In-hospital intervention activities					
TB education/counselling					
Completed*	230 (84.6)	229 (99.6)		188 (81.7)	
Not possible†	42 (15.4)	38 (90.5)	0.002‡	39 (92.9)	0.075
Relationship with counselled caregiver					
Parent	214/228 (93.9)	213/214 (99.5)		176/214 (82.2)	
Other	14/228 (6.1)	14/14 (100)	1.000‡	10/14 (71.4)	0.297‡
Appropriate referral documents					
Completed	220 (80.9)	217 (98.6)		187 (85.0)	
Not completed	52 (19.1)	50 (96.2)	0.244‡	40 (76.9)	0.162
Demographic/clinical factors					
Age, years					
0–<2	119 (43.7)	115 (96.6)		95 (79.8)	
2–<5	85 (31.3)	85 (98.8)		70 (82.4)	
5–13	68 (25.0)	68 (25.5)	0.324‡	62 (91.2)	0.126
Sex					
Male	155 (57.0)	153 (98.7)		127 (81.9)	
Female	117 (43.0)	114 (97.4)	0.655‡	100 (85.5)	0.437
HIV status					
Positive	59 (21.7)	58 (98.3)		49 (83.1)	
Negative	195 (71.7)	191 (98.0)		164 (84.1)	
Unknown	18 (6.6)	18 (100)	1.000‡	14 (77.8)	0.784
TB disease type					
PTB only	154 (56.6)	150 (97.4)		128 (83.1)	
Both PTB and EPTB	72 (26.5)	71 (98.6)		62 (86.1)	
EPTB only	46 (16.9)	46 (100)	0.835‡	37 (80.4)	0.710
Disseminated TB					
TBM	26 (9.6)	26 (100)	1.000‡	16 (61.5)	0.004‡
Miliary TB	10 (3.7)	10 (100)	1.000‡	8 (80.0)	0.673‡
Diagnostic status					
Culture-confirmed *M. tuberculosis*	102 (37.5)	100 (98.0)		86 (84.3)	
Clinical diagnosis	170 (62.5)	167 (98.2)	1.000‡	141 (82.9)	0.768
TB treatment regimen					
DS-TB treatment	258 (94.9)	253 (98.1)		219 (84.9)	
Any DR-TB treatment	14 (5.2)	14 (100)	1.000‡	8 (57.1)	0.016‡
TB care pathway/admission factors					
TB diagnostic pathway					
Diagnosed before admission	56 (20.6)	55 (98.2)		43 (76.8)	
Diagnosed during admission	203 (74.6)	199 (98.0)		172 (84.7)	
Diagnosed after discharge§	13 (4.8)	13 (100)	1.000‡	12 (92.3)	0.249
Duration of hospital visit/admission					
Outpatients	34 (12.5)	34 (100)		31 (91.2)	
1–≤3 days	39 (14.3)	37 (94.9)		35 (89.7)	
≥4 days	199 (73.2)	196 (98.5)	0.263‡	161 (80.9)	0.172
Location of monthly follow-up					
Community-based	244 (89.7)	239 (98.0)		209 (85.7)	
Hospital-based¶	28 (10.3)	28 (100)	1.000‡	18 (64.3)	0.012‡

*228 of the 230 education sessions were completed with the child's primary caregiver.
†Parent or caregiver not available or contactable for TB-specific education.
‡Fisher's Exact were used if χ^2 assumptions not met.
§12 of 13 children who were diagnosed only after discharge were diagnosed based on culture-positive result that became available only after discharge.
¶26/28 (92.9%) children who were followed up monthly at Tygerberg Hospital, Cape Town, Western Cape Province, Republic of South Africa, had TBM and were part of the established TBM home-based care programme.
TB = tuberculosis; ETR.Net = electronic TB register for drug-susceptible TB; EDRWeb = electronic TB register for drug-resistant TB; HIV = human immunodeficiency virus; PTB = pulmonary TB; EPTB = extrapulmonary TB; DS-TB = drug-susceptible TB; DR-TB = drug-resistant TB; TBM = TB meningitis.

TABLE 3 Characteristics of children with culture-confirmed TB discharged from Tygerberg Hospital, Cape Town, Western Cape Province, Republic of South Africa, during baseline and intervention periods (n = 285)

	Baseline 2007–2009 (n = 183) n (%)	Intervention 2012 (n = 102) n (%)	P value
Demographic and admission factors			
Age, years			
0–<2	89 (48.6)	39 (38.2)	
2–<5	49 (26.8)	30 (29.4)	
5–13	45 (24.6)	33 (32.4)	0.204
Sex			
Male	105 (57.4)	54 (52.9)	
Female	78 (42.6)	48 (47.1)	0.470
Patient category*			
Outpatients only	52/177 (29.4)	20 (19.6)	
Overnight admission	125/177 (70.6)	82 (80.4)	0.072
Duration of hospital admission*			
1–≤3 days	35/125 (28.0)	14/82 (17.1)	
≥4 days	90/125 (72.0)	68/82 (82.9)	0.070
Clinical factors			
HIV status			
Negative	95 (51.9)	79 (77.5)	
Positive	29 (15.9)	12 (11.8)	
Unknown	59 (32.2)	11 (10.8)	<0.001
TB disease type			
PTB only	86 (47.0)	43 (42.2)	
Both PTB and EPTB	58 (31.7)	40 (39.2)	
EPTB only	39 (21.3)	19 (18.6)	0.439
Disseminated TB			
TBM	15 (8.2)	8 (7.8)	0.916
Miliary TB†	8 (4.4)	5 (4.9)	1.000‡
Drug resistance (binary variable)	12 (6.6)	5 (4.9)	
INH monoresistance	5 (2.7)	3 (2.9)	
RMP monoresistance	2 (1.1)	1 (1.0)	
MDR-/XDR-TB	5 (2.7)	1 (1.0)	0.572

*Unknown for 6/183 (3%) children from the baseline period.
†Total number of patients with miliary TB who also had TBM: 2 and 2, respectively.
‡Fisher's Exact were used if χ^2 assumptions not met.
TB = tuberculosis; PTB = pulmonary TB; EPTB = extra-pulmonary TB; TBM = TB meningitis; INH = isoniazid; RMP = rifampicin; MDR = multidrug-resistant TB; XDR-TB = extensively drug-resistant.

yielded very similar results (n = 429: aOR 2.62, 95%CI 1.57–4.38, $P < 0.001$).

DISCUSSION

Our study shows that a simple linkage to care intervention can substantially reduce the hospital reporting gap for childhood TB. Children discharged home to continue TB care were nearly three times more likely to be reported and included in routine surveillance during the intervention period compared to the baseline period, after adjusting for age, sex, HIV status and TBM. In addition to the impact on reporting, the intervention allowed for confirmation of the continuity of clinical care for nearly all children (98.2%), resulting in <2% ILTFU.

Two referral hospitals in Gauteng Province have successfully implemented interventions to address challenges in linkage to care. A dedicated TB care and linkage service at a large tertiary referral hospital in Johannesburg, South Africa, reduced losses between hospital and PHC referrals for adults and children from 21% (2001) to 6% (2003–2005) and improved reporting of TB patients.[21] Age-stratified results were unfortunately not reported. Implementation of a TB Focal Point at another tertiary hospital decreased the proportion of TB cases failing to link to TB care from 23% in 2009 to 14% during 2012.[22] Our study showed similar improvement when dedicated staff were recruited to support TB patients with both the referral and reporting processes. However, interventions involving clinical personnel are costly and not always sustainable in resource-limited settings. At a district-level hospital, comparable results were achieved by only one dedicated lay health care worker for referral support and follow-up, provided surveillance was done by routine clinical personnel; 93 (96%) of child TB cases successfully accessed PHC care and 89 (90%) were matched in the ETR.Net/EDRWeb.[15]

In settings where information technology infrastructure is available, automated, electronic processes at hospital discharge could greatly assist with surveillance and linking of important referral processes, but will still rely on personnel at the referral hospital to provide sufficient information and the receiving facility to act on the information. Another potential solution to close this reporting gap would be to mandate all hospitals to report TB data.

TABLE 4 Impact of a hospital-community linkage to care intervention on completeness of TB reporting in children discharged with culture-confirmed, drug-susceptible TB during baseline and intervention, Tygerberg Hospital, Cape Town, Western Cape Province, Republic of South Africa (n = 268)

	Completeness of reporting		Univariable analyses		Multivariable analyses	
	Reported in ETR.Net (n = 199) n (%)	Not reported in ETR.Net (n = 69) n (%)	OR (95%CI)	P value	aOR (95%CI)	P value
Impact of intervention						
Baseline period (2007–2009)	117 (58.8)	54 (78.3)	Reference		Reference	
Intervention period (2012)	82 (41.2)	15 (21.7)	2.52 (1.33–4.77)	0.004	2.62 (1.31–5.25)	0.006
Covariates						
Age, years						
0–<2	90 (45.2)	33 (47.8)	Reference			
2–<5	49 (24.6)	22 (31.9)	0.82 (0.43–1.55)	0.536	0.83 (0.42–1.66)	0.604
5–13	60 (30.2)	14 (20.3)	1.57 (0.78–3.18)	0.209	1.51 (0.71–3.22)	0.283
Sex						
Male	116 (58.3)	37 (53.6)	Reference		Reference	
Female	83 (41.7)	32 (46.4)	0.83 (0.48–1.43)	0.500	0.85 (0.47–1.52)	0.579
Patient category and admission duration*						
Outpatients	52/196 (26.5)	16/67 (23.9)	Reference			
1–≤3 days	35/196 (17.9)	11/67 (16.4)	0.98 (0.41–2.36)	0.962		
≥4 days	109/196 (55.6)	40/67 (59.7)	0.84 (0.43–1.63)	0.605	—	
HIV status						
Negative	122 (61.3)	39 (56.5)	Reference		Reference	
Positive	30 (15.1)	9 (13.1)	1.07 (0.47–2.44)	0.880	1.01 (0.42–2.44)	0.974
Unknown	47 (23.6)	21 (30.4)	0.72 (0.38–1.34)	0.296	0.81 (0.40–1.61)	0.540
TB disease type						
PTB only	88 (44.2)	34 (49.3)	Reference			
Both PTB and EPTB	76 (38.2)	18 (26.1)	1.63 (0.85–3.12)	0.139		
EPTB only	35 (17.6)	17 (24.6)	0.80 (0.39–1.60)	0.523	—	
Disseminated TB						
TBM	8 (4.0)	12 (17.4)	0.20 (0.08–0.51)	0.001	0.18 (0.07–0.48)	0.001
Miliary TB†	10 (5.0)	2 (2.9)	1.78 (0.38–8.30)	0.737‡	—	

*Duration of admission unknown for 5 children from the baseline period.
†1/10 and 2/2 children with miliary TB also had TBM.
‡Fisher's Exact were used if χ^2 assumptions not met.
TB = tuberculosis; ETR.NET = electronic tb register for drug-susceptible TB; OR = odds ratio; CI = confidence interval; AOR = adjusted OR; HIV = human immunodeficiency virus; TBM = TB meningitis; PTB = pulmonary TB; EPTB = extra-pulmonary TB.

The logistics around surveillance and supporting paediatric TB patients and their families in a large referral hospital with multiple wards and a large staff complement is complex. Despite dedicated efforts and multiple attempts, TB counselling was not possible for 15% of patients and referral documentation was not completed for 19%. Furthermore, children managed at referral hospitals often have complex admission and care pathways and move between different levels of care.[14] It is therefore not surprising that children who were diagnosed only after hospital discharge, either due to non-resolving symptoms or a positive culture at follow-up, were less likely to receive counselling and correct referral documentation. Similarly, counselling was less frequently performed if the duration of the hospital visit was short (≤3 days), possibly due to the fact that patients were discharged before the study team could counsel the parent/caregiver or obtain reliable contact information. Irrespective of these challenges, we used an intention-to-treat analysis approach and the observed intervention effect is therefore a conservative estimate.

During the intervention period, approximately 10% (28/272) of the children who were discharged home were followed monthly as outpatients at the referral hospital. The majority had TBM (n = 26) and were treated as part of a dedicated TBM home-based care programme at TBH. As TBH was not required to report TB data, we encouraged the caregivers of these children to attend their community-based PHC facility at the beginning and end of treatment to facilitate appropriate recording in the TB register and allow for reporting. These extra visits place an additional burden on the families, and staff at the PHC facilities are often reluctant to include patients in their reporting data if they are not primarily responsible for the patients' TB treatment. Therefore, it was not unexpected that children who were followed up at the hospital during the intervention were significantly less likely to be reported than those who were followed up at their community-based PHC facility (P = 0.012). The highly significant association between TBM and incomplete reporting observed in univariable analysis became even more pronounced in multivariable analysis (aOR 0.18, 95%CI 0.07–0.48), and is likely a reflection of the difference in place of attendance for monthly follow-up for children with TBM.

To our knowledge, this was the first study to specifically evaluate the impact of a hospital-based linkage-to-care intervention on childhood TB case notification. Our intervention focussed on

children continuing TB care from home, and although this included almost two thirds of children diagnosed with TB, completeness of reporting of children discharged to TB hospitals, other general hospitals or medium-term care facilities, were not addressed. These children likely represent more severe cases of disease or social problems, and their reporting is critical to ensure accurate reflection of the full spectrum of TB disease in children. Completeness of reporting of in-hospital deaths is an important factor not addressed in our study, but one that needs to be considered in future interventions to improve TB mortality data. Another limitation was that our baseline data were limited to culture-confirmed children only. Therefore, we could only evaluate the impact of the intervention on children with culture-confirmed disease, although analyses of the total intervention group showed similar results. The only difference between the baseline and intervention groups was a decrease in unknown HIV status during the intervention period. HIV testing has improved substantially in the entire country, and an increase in the number of children with a known HIV status was therefore expected in the intervention period. HIV status was not associated with completeness of reporting in univariable analysis, but were included a priori in the multivariable model. Due to the changes in DR-TB care and surveillance between the baseline and intervention periods, we could not accurately evaluate the impact of our intervention on the small number of children with DR-TB (n = 26).

CONCLUSIONS

Adequately supporting linkage-to-care of children with TB between hospitals and community-based PHC facilities can minimise ILTFU and substantially improve hospital reporting of childhood TB. Mandating all hospitals to function as TB reporting units can comprehensively address and reduce the hospital reporting gap for childhood TB in South Africa. Future research should evaluate scale-up and cost-effectiveness of different approaches to improve TB reporting from hospitals and strengthen linkage and referrals of children with TB.

References

1 Seddon J A, Jenkins H E, Liu L, et al. Counting children with tuberculosis: why numbers matter. Int J Tuberc Lung Dis 2015; 19(12 Suppl 1): 9–16.
2 Marais B J. Quantifying the tuberculosis disease burden in children. Lancet 2014; 383(9928): 1530–1531.
3 World Health Organisation. Roadmap for childhood tuberculosis. Geneva, Switzerland: WHO, 2013. http://www.who.int/iris/bitstream/10665/89506/1/9789241506137_eng.pdf Accessed February 2020.
4 World Health Organisation. Global tuberculosis report, 2018. WHO/CDS/TB/2018.20. Geneva, Switzerland: WHO 2018.
5 World Health Organisation. Roadmap towards ending TB in children and adolescents. Geneva, 2018. http://apps.who.int/iris/bitstream/handle/10665/275422/9789241514798-eng.pdf?ua=1 Accessed 16 July 2019.
6 National Department of Health South Africa. National Tuberculosis management guidelines, 2008. Pretoria, Republic of South Africa: DoH, 2008.
7 National Department of Health South Africa. National tuberculosis guidelines, 2014. Pretoria, Republic of South Africa; DoH, 2014. https://sahivsoc.org/Files/NTCP_Adult_TB%20Guidelines%2027.5.2014.pdf=1 Accessed February 2020.
8 Naidoo P, Theron G, Rangaka M X, et al. The South African tuberculosis care cascade: estimated losses and methodological challenges. J Infect Dis 2017; 216(Suppl 7): S702–S713.
9 Dudley L, Mukinda F, Dyers R, Marais F, Sissolak D. Mind the gap! Risk factors for poor continuity of care of TB patients discharged from a hospital in the Western Cape, South Africa. PLoS One 2018; 13(1): e0190258.
10 Loveday M, Thomson L, Chopra M, Ndlela Z. A health systems assessment of the KwaZulu-Natal tuberculosis programme in the context of increasing drug resistance. Int J Tuberc Lung Dis 2008; 12(9): 1042–1047.
11 Hinderaker S G, Fatima R. Lost in time and space: the outcome of patients transferred out from large hospitals. Public Health Action 2013; 3(1): 2.
12 Edginton M E, Wong M L, Phofa R, Mahlaba D, Hodkinson H J. Tuberculosis at Chris Hani Baragwanath Hospital: numbers of patients diagnosed and outcomes of referrals to district clinics. Int J Tuberc Lung Dis 2005; 9(4): 398–402.
13 Voss De Lima Y, Evans D, Page-Shipp L, et al. Linkage to care and treatment for TB and HIV among people newly diagnosed with TB or HIV-associated TB at a large, inner city South African hospital. PLoS One 2013; 8(1): e49140.
14 du Preez K, Schaaf H S, Dunbar R, et al. Complementary surveillance strategies are needed to better characterise the epidemiology, care pathways and treatment outcomes of tuberculosis in children. BMC Public Health 2018; 18(1): 397.
15 du Preez K, du Plessis L, O'Connell N, Hesseling A C. Burden, spectrum and outcomes of children with tuberculosis diagnosed at a district-level hospital in South Africa. Int J Tuberc Lung Dis 2018; 22(9): 1037–1043.
16 du Preez K, Schaaf HS, Dunbar R, et al. Incomplete registration and reporting of culture-confirmed childhood tuberculosis diagnosed in hospital. Public Health Action 2011; 1(1): 19–24.
17 Marais B J, Hesseling A C, Gie R P, Schaaf H S, Beyers N. The burden of childhood tuberculosis and the accuracy of community-based surveillance data. Int J Tuberc Lung Dis 2006; 10(3): 259–263.
18 Lestari T, Probandari A, Hurtig A K, Utarini A. High caseload of childhood tuberculosis in hospitals on Java Island, Indonesia: a cross sectional study. BMC Public Health. 2011 Jan; 11: 784.
19 Siddaiah A, Ahmed M N, Kumar A M V, et al. Tuberculosis notification in a private tertiary care teaching hospital in South India: a mixed-methods study. BMJ Open 2019; 9(2): e023910.
20 Ade S, Harries A D, Trébucq A, et al. The burden and outcomes of childhood tuberculosis in Cotonou, Benin. Public Health Action 2013; 3(1): 15–19.
21 Edginton M E, Wong M L, Hodkinson H J. Tuberculosis at Chris Hani Baragwanath Hospital: an intervention to improve patient referrals to district clinics. Int J Tuberc Lung Dis 2006; 10(9): 1018–1022.
22 Jong E, Sanne I M, van Rie A, Menezes C N. A hospital-based tuberculosis focal point to improve tuberculosis care provision in a very high burden setting. Public Health Action 2013; 3(1): 51–55.
23 World Health Organisation. Global tuberculosis report, 2013. WHO/HTM/TB/2013.11. Geneva, Switzerland: WHO, 2013.
24 Western Cape Government. Tygerberg Hospital Annual report, 2012. Cape Town, Republic of South Africa: Western Cape Government, 2014. https://www.westerncape.gov.za/your_gov/153/documents/annual_reports/2012eng.pdf?sequence=1 Accessed February 2020.
25 Schoeman J, Malan G, van Toorn R, Springer P, Parker F, Booysen J. Home-based treatment of childhood neurotuberculosis. J Trop Pediatr 2009; 55(3): 149–154.
26 Sayers A, Ben-Shlomo Y, Blom A W, Steele F. Probabilistic record linkage. Int J Epidemiol 2016; 45(3): 954–964.

Contexte : Un grand hôpital de référence au Cap, Afrique du Sud.
Objectif : Mesurer l'impact d'un service de référence basé en hôpital (intervention) afin de réduire les pertes de vue initiales parmi les enfants atteints de tuberculose (TB) et améliorer l'exhaustivité des données de routine de surveillance de la TB.
Schéma : En 2012, un service de référence dédié de la TB a été créé dans le service de pédiatrie de l'hôpital Tygerberg. Le personnel dédié a fourni une éducation relative à la TB ainsi que des conseils, un soutien à la référence et un suivi téléphonique hebdomadaire après la sortie de l'hôpital. Tous les enfants identifiés comme atteints de TB ont été appariés aux registres électroniques de traitement de la TB (ETR.Net/EDRWeb). Une régression logistique multivariable a été utilisée pour comparer la notification des cas confirmés par la culture de TB pharmacorésistante avant (2007–2009) et pendant (2012) l'intervention.
Résultats : Une référence réussie avec un lien à la prise en charge a été confirmée chez 267/272 (98%) et une notification réussie chez 227/272 (84%) enfants. Pendant la période d'intervention, les enfants atteints de TB pharmacorésistante confirmée par la culture ont été significativement plus susceptibles d'être notifiés comparés à la période précédant l'intervention (OR 2,52 ; IC95% 1,33–4,77). L'effet de l'intervention est resté stable en modèle multi variable (ORa 2,62 ; IC95% 1.31–5,25) après ajustement sur l'âge, le sexe, le statut VIH et la présence d'une méningite tuberculeuse.
Conclusion : Un simple service de référence de la TB basé en hôpital peut réduire les pertes de vue initiales et améliorer l'enregistrement et la notification de la tuberculose de l'enfant dans un contexte de services de TB décentralisés.

Marco de Referencia: Un gran hospital de referencia de Ciudad del Cabo en Suráfrica.
Objetivo: Medir el impacto de un servicio hospitalario de remisiones (intervención) destinado a disminuir la pérdida durante el seguimiento inicial de los niños con tuberculosis (TB) y mejorar la exhaustividad de los datos de la vigilancia sistemática de la TB.
Método: En el 2012, se instauró un servicio dedicado a la derivación de los casos de TB en las unidades pediátricas del Hospital Tygerberg. Miembros designados del personal impartían educación y asesoramiento, apoyo a la derivación de los casos de TB y seguimiento telefónico semanal después del alta hospitalaria. Se emparejaron todos los niños detectados con TB con los casos de los registros electrónicos de tratamiento antituberculoso (ETR.Net/EDRWeb). Con un modelo de regresión logística multivariante se comparó la notificación de los casos de casos de TB normosensible confirmada por cultivo antes de la intervención (2007–2009) y durante la misma (2012).
Resultados: Se confirmó la remisión eficaz con vinculación a los servicios de atención en 267 de 272 niños (98%) y la notificación de 227 de los 272 (84%). La notificación de los niños con TB normosensible confirmada por cultivo fue mucho más probable durante el período de la intervención que antes de la misma (OR 2,52; IC95% 1,33–4,77). El efecto de la intervención permaneció constante en el modelo multivariante (aOR 2,62; IC95% 1,31–5,25) tras ajustar con respecto a la edad, el sexo, la situación frente al virus de la inmunodeficiencia humana y la presencia de meningitis tuberculosa.
Conclusión: Un servicio hospitalario sencillo de remisiones disminuye las pérdidas iniciales durante el seguimiento y mejora el registro y la notificación de los casos de TB en los niños de un entorno con servicios de TB descentralizados.

Public Health Action (PHA) The voice for operational research.
Published by The Union (www.theunion.org), PHA provides a platform to fulfil its mission, 'Health solutions for the poor'. PHA publishes high-quality scientific research that provides new knowledge to improve the accessibility, equity, quality and efficiency of health systems and services.

e-ISSN 2220-8372
Editor-in-Chief: Dermot Maher, MD, Switzerland
Contact: pha@theunion.org
PHA website: http://www.theunion.org/what-we-do/journals/pha
Article submission: http://mc.manuscriptcentral.com/pha

CHAPTER 8: CONCLUSIONS

In this dissertation, I investigated key aspects of the epidemiology of paediatric tuberculosis (TB) in South Africa which have not been systematically addressed before. I designed studies and investigated multiple relevant sources of paediatric TB surveillance data across different levels of health care with consideration of the full paediatric age spectrum (0-19 years), HIV status and the spectrum of TB disease observed in children. I reviewed the value and role of each surveillance strategy and its associated data in the context of the larger TB and HIV epidemics in South Africa and identified areas where interventions would improve the completeness and quality of data. Knowledge and data generated through these studies contributed towards informing two pivotal pillars of a paediatric TB care cascade ('Diagnosed with TB' and 'Notified and treated'), including representative data on the unique spectrum of TB in children and their point of health care access for TB services. Lastly, I implemented and evaluated the impact of an intervention that successfully improved the completeness of routine TB surveillance data and reduced losses between these two pillars by supporting linkage to care and improving reporting of paediatric TB. These are important requirements towards developing a comprehensive care cascade for children and adolescents affected by TB. This framework may be useful not only in South Africa, but also more globally, especially in other high TB-burden settings.

1. DEVELOPMENT OF A TB CARE CASCADE AS AN APPROACH TO MONITOR AND EVALUATE PAEDIATRIC TB CARE

In chapter 2 of the dissertation, I used data from the World Health Organisation (WHO) global TB database[108] to determine the paediatric TB burden of disease estimates and the paediatric TB case notifications reported for South Africa for 2018. This data informed pillars 1 and 4 of the paediatric TB care cascade for South Africa for 2018, and quantified the reporting gap for paediatric TB in South Africa.

During 2018, only 65% of the estimated 27,000 children (0-14 years) with TB were diagnosed, started on treatment and notified, leaving a third of children with TB in South Africa undiagnosed or unreported.[76] I presented these data in figure 8.1, showing the substantial reporting gap of 35% between the estimated number of TB cases (pillar 1) and the reported TB case notifications for children (pillar 4) in South Africa. Both undiagnosed cases and diagnosed but unreported cases contribute to this large gap.

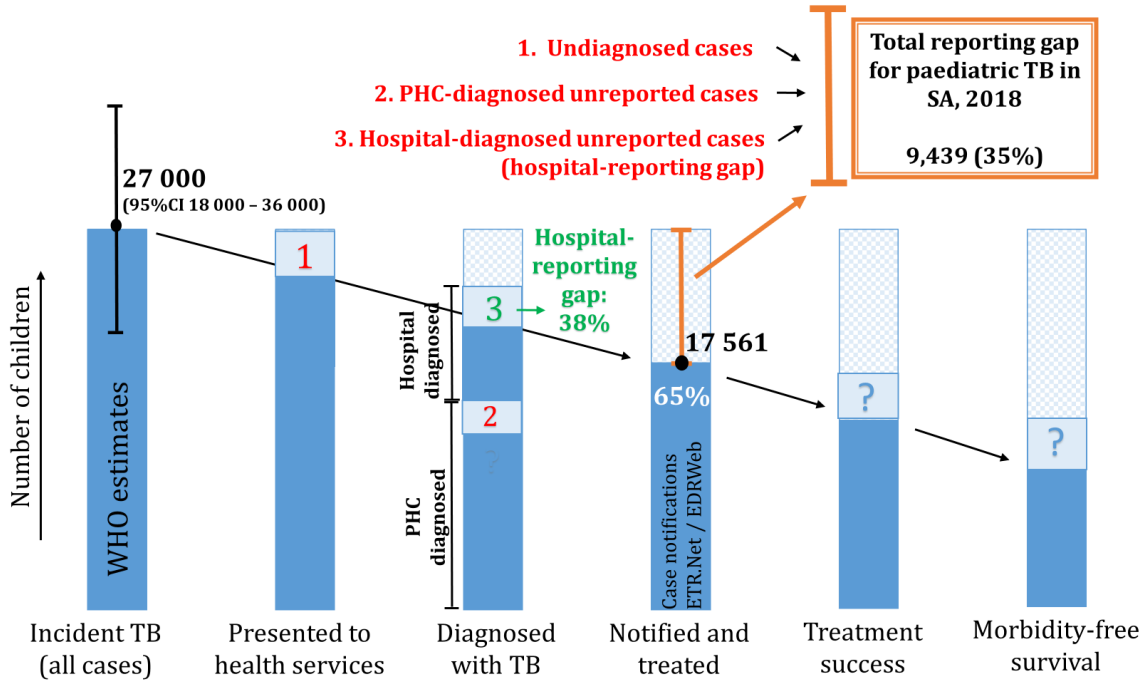


Figure 8.1. Paediatric TB care cascade for South Africa for 2018

Incident TB estimates and case notification data for 2018 were obtained from the WHO global TB database.[108] The estimated hospital-reporting gap was 38% (95% confidence interval 32%-44%)[38]

The research in this dissertation contributed in several ways towards an improved understanding of estimates of pillar 3 and pillar 4. Within pillar 3 ('Diagnosed with TB'), my research quantified the substantial burden of paediatric TB and the large proportion of children with disseminated TB and TB-HIV co-infection managed at public hospitals in South Africa for the first time (chapters 4 and 6). Surveillance of HIV-infected children and children with TB meningitis (TBM) proved valuable monitoring and evaluation strategies within pillar 3, specifically to monitor the impact of TB and HIV prevention strategies and of integrated TB/HIV care (chapter 5). Despite affecting fewer than 5% of children with TB, TBM is the major contributor to morbidity and mortality in paediatric TB. Within pillar 4, I used stratified and time-series analyses of treatment surveillance data and identified young HIV-infected children (0-4 year old), and adolescents (10-19 year olds) as particularly vulnerable groups to address in TB control efforts in South Africa (chapter 3). I further quantified the hospital-reporting gap for TB in provinces where hospital data are not reported to the TB programme, and identified that children with severe TB disease and those dying in hospital were more likely not to be reported (chapter 7).[38] This may have a profound negative impact on the completeness and accuracy of surveillance of TB-related morbidity and mortality in children. My research also clearly showed that the hospital-reporting gap plays an important role in the large overall paediatric TB reporting gap in South Africa, considering that more than half (54%) of all paediatric and adolescent cases were reported from hospitals in Kwa-Zulu Natal, the only high-TB burden

province where all hospitals currently report TB data. Quantifying the hospital-reporting gap for children with TB in provinces in South Africa where hospitals do not report TB data is a useful contribution towards the care cascade framework, and can help to improve estimates of TB diagnosis at sub-national level. These are important steps towards defining a paediatric TB care cascade within the South African context, building on the overall adult-focused South African TB care cascade published in 2017 (Naidoo et al).[75]

This work also contributes to the development of one of the first paediatric TB cascades initiated globally. To date, only two other paediatric TB care cascades have been developed and published.[27, 109] The first study constructed a TB care cascade for children (<15 years of age) for 32 rural communities in Kenya and Uganda, using routine programmatic TB surveillance data only from primary healthcare (PHC) centres (Figure 8.2).[109] The authors identified only 42 children reported in the TB treatment registry over a two and a half-year period. To determine the number of children with TB (pillar 1) they assumed a similar child case detection rate to the WHO estimate for Africa at the time of the study (27%; calculation: 42 x (100/27). Case notification in the study settings represented "treatment surveillance", and the authors assumed that the number notified was equal to the number diagnosed. Therefore, the authors did not quantify the gap between TB diagnosis and notification, assuming that the entire reporting gap between pillar 1 and 4 would be explained by undiagnosed TB cases. The authors also did not discuss whether hospital-diagnosed cases might have contributed to this gap. Understanding the level of health care access and the context of reporting practices is important in the interpretation of paediatric TB care cascade data using routine TB surveillance data.

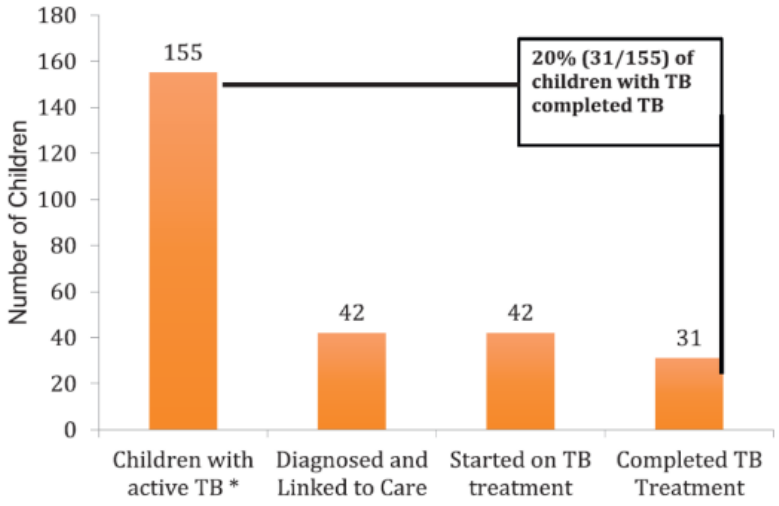
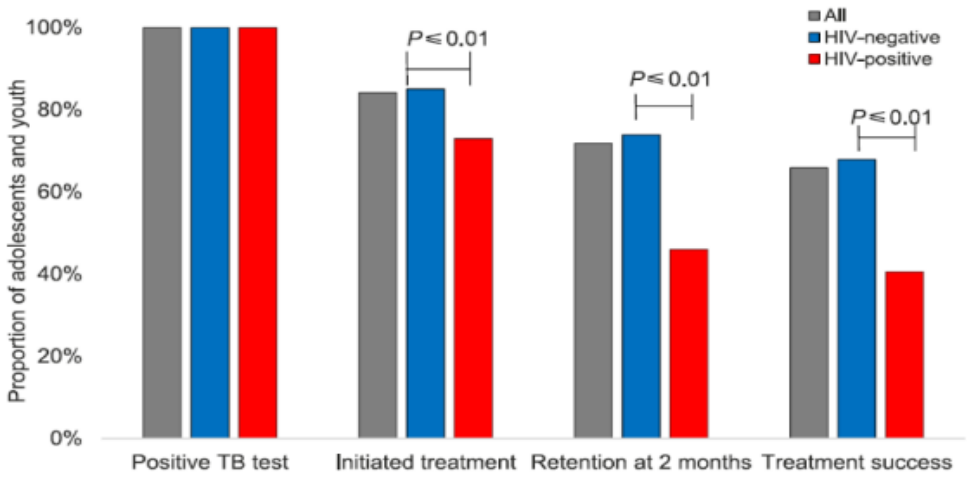


Figure 8.2 A paediatric TB care cascade developed from data on 32 rural communities in Kenya and Uganda[109]

The only other paediatric TB care cascade published to date evaluated adolescents and young adults (10-24 years) with bacteriologically confirmed TB diagnosed at PHC level in Haiti (Figure

8.3).[27] The cascade in this study started with a subset of cases in pillar 3 ('Diagnosed with TB' – bacteriologically confirmed). Clinical data was collected to determine the totals of each of the other pillars, and pillar 4 only evaluated treatment initiation and not whether cases were successfully notified to the TB programme. In this cohort diagnosed at a single PHC facility, 16% of adolescents (27% amongst HIV-infected) were lost between TB diagnosis and treatment initiation. Only 66% were successfully treated, with a higher risk of poor outcomes amongst HIV-infected cases. This study is an excellent example of showing the value of using a cascade analysis at sub-national level, in this case a single facility, using diagnostic surveillance to evaluate clinical care. Given the paucity of adolescent surveillance data globally, quantifying the reporting gap in this population would also have provided critical information, which is currently lacking.



All *N* (cumulative	1005 (100%)	846 (84%)	722 (72%)	662 (66%)
HIV-negative	931 (100%)	792 (85%)	688 (74%)	632 (68%)
HIV-positive	74 (100%)	54 (73%)	34 (46%)	30 (41%)

Figure 8.3. TB treatment continuum among adolescents and young adults aged 10-24 years with microbiologically confirmed TB in Haiti[27]

My research provided important additional knowledge on pillar 3 and 4 through comprehensively and systematically investigating and reporting TB across the age continuum, the disease spectrum, by HIV infection status and level of health care, in South African children with bacteriologically confirmed and clinically diagnosed TB.

2. THE IMPACT OF INTERVENTIONS ON THE TB CARE CASCADE: CLOSING THE HOSPITAL-REPORTING GAP FOR PAEDIATRIC TB

Despite the considerable evidence that hospital-diagnosed cases contribute to the global paediatric TB reporting gap,[38-41] there is a paucity of data on interventions to address this gap. Following on my initial study to quantify the reporting gap, I implemented and evaluated the

impact of a hospital-based intervention to support linkage of paediatric TB care to PHC level upon hospital discharge. In chapter 7, I showed how this intervention significantly decreased the hospital-reporting gap for paediatric TB. Using a TB cascade approach not only provides the ability to monitor data, but also to track the impact of targeted interventions over time.

In addition to the impact on reporting, the intervention I implemented showed that successful continuation of care for children with TB was possible with some dedicated referral support – nearly all children managed at both tertiary hospital (98%) and district hospital (96%) successfully continued clinical care after discharge from hospital.

3. MOVING FROM KNOWLEDGE TO ACTION: SPECIFIC RECOMMENDATIONS FOR IMPROVED PAEDIATRIC TB CONTROL IN SOUTH AFRICA

3.a. Recommendations for adolescents

I have identified South African adolescents as a particularly vulnerable sub-population within current TB control efforts. Adolescents have been identified as a population difficult to engage and retain in TB and HIV services. In order to develop adolescent-friendly TB and HIV health services, specifically targeted to address their needs, one needs to acknowledge that adolescents are neither children nor are they adults. Socio-behavioural research may help improve the understanding of how health services can encourage and support adolescents' engagement with TB services. Adolescents, especially if HIV-infected, may need additional treatment adherence support. HIV care also provides an opportunity for regular TB screening and education about TB. Prevention of both TB and HIV in this age group remain highly relevant given the high risk of acquisition of both disease during adolescence. New WHO-recommended[110] and South African TB preventive therapy guidelines (currently in draft format) now include all close contacts as eligible for TB preventive therapy, irrespective of age or HIV status, which could substantially reduce the TB burden in adolescents once implemented and if accessed. A systematic review of current evidence of HIV prevention in South African adolescents suggested addressing social risk factors for HIV, including gender norms, alcohol use and poverty, engaging schools to use participatory learning and changing social norms.[111] Lastly, strengthening TB surveillance of adolescents, including reporting routine TB data by two additional age bands in ages 10-14 and 15-19 years, would assist with monitoring and evaluation efforts of TB control in adolescence.

3.b. Recommendations for HIV-infected, young children

TB control in HIV-infected young children (0-4 year old) also requires additional action. My research showed that TB remains an important, albeit late, opportunity to diagnose HIV in children. Young children with TB who are diagnosed with HIV were missed by prevention-of-mother-to-child-transmission (PMTCT) efforts. Either the diagnosis of HIV was missed in the mother or the mom and/or infant received limited HIV care either antenatally or during the post-partum period whilst breastfeeding.

All children investigated for TB should be tested for HIV, and clinicians should have a low threshold to test or re-test breastfeeding mothers and their infants living in high HIV-burden communities, as well as children who were HIV-exposed but tested HIV negative at birth. Small changes to ensure capturing of key HIV indicators, such as the timing of HIV diagnosis, the timing and type of antiretroviral therapy (ART) initiation and adherence (including viral load) in relation to the TB episode, can significantly enhance monitoring and evaluation of TB control in HIV-infected children and will help to determine missed opportunities for HIV diagnosis or ART (re)-initiation.

3.c. Recommendations to strengthen TB surveillance and reduce the hospital-reporting gap for paediatric TB

To accurately capture the full burden and spectrum of paediatric TB in South Africa, it should be mandatory for all hospitals to report TB surveillance data, including TB deaths, to the TB programme. This will also allow for improved surveillance of children with TB-HIV and TBM, who carry a disproportionately large burden of morbidity and mortality and are mostly diagnosed and treated at hospitals. Hospitals could implement paper-based or electronic TB registers to facilitate TB reporting, but will require resources to strengthen and support the additional burden of implementing such surveillance. Optimizing the use of existing data sources and information systems should be the priority, rather than implementing additional or parallel surveillance systems. In settings where electronic data capturing and automated data notification at different levels of healthcare facilities are possible, this could greatly reduce the administrative burden on staff and electronic data capturing and data linkage should be pursued.

Combining patient-level healthcare data from multiple electronic data sources and at different levels of health care has already been completed successfully in the Western Cape Provincial Health Data Centre.[112] Using such data for TB reporting could impact substantially on closing the hospital-reporting gap and to facilitate linkage from hospital by allocating patients to specific PHC facilities. The success of linkage will however rely on healthcare workers or community care workers at the allocated facility to act on information when patients did not successfully link to

care or had positive bacteriology after hospital discharge (up to 20% of children with culture-confirmed TB are only diagnosed following hospital discharge[113]). The success of using combined surveillance data for linkage to care will further rely on the accuracy of routine capturing of personal contact details, otherwise patients who are lost to follow-up will not be traceable by healthcare workers.

A large scale demonstration study is currently being implemented in three high-burden provinces in South Africa to evaluate the impact of linking hospital data with routine TB surveillance data to reduce initial-loss-to-follow-up (ILTFU) amongst all TB patients diagnosed in hospital – adults and children (LinkedIn, PIs AC Hesseling/M Osman). Within this study, electronic linkage of data between different sources (laboratory, public healthcare facilities including hospitals, pharmacies and electronic TB registers [ETR.Net and EDRWeb]) is successfully being implemented in the Western Cape at the provincial health data centre and will pave the way for improved recording and linkage to care for hospital and PHC-diagnosed TB cases.[112] This could significantly reduce patient losses between pillar 3 and 4 of the TB care cascade.

In addition to surveillance, children and their caregivers will still need some additional referral support to ensure continuity of TB care following discharge from hospital. Adequate referral documentation is important, and a small amount of time from clinical staff is needed to educate the child and caregivers about the diagnosis of TB and what is expected of them following discharge. This communication could be standardised and facilitated through structured material, such as the material developed in our intervention described in chapter 7, to ensure adequate communication between patients and their healthcare providers about the continuation of their TB treatment. These recommendations are also supported by findings from qualitative research with healthcare providers at Tygerberg Hospital,[107] reporting the need to strengthen existing referral systems to include patient-centred discharge planning and disease-specific education to support successful continuation of TB care after hospital discharge. The practical referral tools developed in this intervention could be implemented at other tertiary hospitals in South Africa to further strengthen linkage-to-care for paediatric TB.

4. RECOMMENDATIONS TO IMPROVE MONITORING AND EVALUATION OF PAEDIATRIC TB IN SOUTH AFRICA AND BEYOND

TB programmes need better monitoring and evaluation strategies to ensure that adequate TB care is provided to children and adolescents. The existing indicators recommended by the WHO require revisions, and surveillance should be strengthened to ensure accurate reporting of all diagnosed paediatric cases. Moving the point of surveillance from TB treatment initiation to

diagnosis will result in more complete surveillance data and can assist the TB programme with identifying patients who are lost between diagnosis and treatment. In South Africa, the current information management systems already have the ability to merge electronic bacteriological surveillance data from laboratories with electronic clinical surveillance data from diagnostic centres, including hospitals and clinics. Clinical and laboratory diagnostic surveillance data will be captured in the newly implemented Notifiable Medical Condition surveillance system that is currently being rolled out in South Africa at a national level. This surveillance system will allow clinicians to notify TB patients using a mobile application, and will include laboratory data. Merging of this data with operational TB surveillance data could greatly strengthen TB surveillance in South Africa. South Africa is also in the process of rolling out a unique health identifier (PMI) across the country, which could further strengthen data linkage and deduplication processes for TB and other health indicators, resulting in better quality data.

Building on my research findings, I propose the following recommendations to improve monitoring and evaluation of paediatric TB:

- Using a TB care cascade approach at national and sub-national level for reporting of paediatric TB. This will allow for the quantification of specific gaps, inform targeted interventions and support monitoring of the impact of implemented interventions.
- Current age bands of paediatric case notifications (0-4, 5-14, 15-24 years) should be changed to allow for surveillance data to distinguish between children (0-4 and 5-9 years), adolescents (10-14 and 15-19 years) and adults (20+ years). This will greatly assist with monitoring and evaluation of TB control in adolescence.
- TB surveillance systems should be strengthened to include TB data from hospitals. This will be an important first step to reduce the large global reporting gap for paediatric TB.
- Stratified analyses by age and HIV status over time can greatly assist with monitoring and evaluation of paediatric TB control, specifically to identify vulnerable groups who may require targeted surveillance and interventions. Aggregate data should be accessible to TB programme managers, and in analysable format or in user-friendly standard interface formats to allow actionable TB and HIV data usage by the programme.
- Revision of existing paediatric TB programme indicators are needed to ensure relevance and include the reporting of severe forms of paediatric TB disease, such as TBM, from countries where this data is collected and available. The availability of surveillance data on severe forms of TB could improve the current understanding of the burden of this devastating disease in the paediatric population and could assist programmes with improved planning and resource allocation to better support children and their families. Given the high burden

of TBM in HIV-infected adults, this approach will also benefit overall TB control efforts, in addition to the paediatric population.[114]

Interventional studies are needed to address the multiple aspects of the TB care cascade and to address specific gaps. Future intervention studies in South Africa should focus on addressing TB control in HIV-infected, young children and adolescents, making the most of every opportunity to prevent TB and HIV. Interventions to strengthen the capacity of healthcare workers to investigate and diagnose paediatric TB at primary healthcare level, including collecting respiratory samples, will reduce the burden of paediatric TB managed at public hospitals and will facilitate linkage to care. An early diagnosis of TBM is strongly associated with better outcomes in children[20], and interventions to facilitate earlier diagnosis could substantially reduce morbidity and associated healthcare and societal costs. The observed ecological association with bacille Calmette-Guérin (BCG) shortages and admissions for TBM should be further investigated, preferably with individual-patient level analyses linked to prospective surveillance across multiple healthcare centres and provinces.

5. STRENGTHS AND LIMITATIONS

The hospital-based diagnostic surveillance studies presented in this dissertation provided rich clinical details of paediatric TB and provided the opportunity to implement and evaluate an intervention to improve TB care in children. However, paediatric services at public hospitals in South Africa only include children less than 13 years of age, and adolescents were therefore excluded from the hospital-based surveillance studies.

Routine TB treatment surveillance data provided a robust, large case-based national TB surveillance dataset, allowing in-depth and stratified time-series analyses to investigate the interaction between age, HIV, gender and TB. Limitations of this routine TB dataset, however, include the incompleteness of hospital data in some provinces, resulting in underreporting of TB deaths and severe TB cases. HIV data was also not captured consistently, resulting in substantial missing HIV data during the early years of the study. Finally, this treatment surveillance study was limited to drug-susceptible TB, as drug-resistant data from the EDRWeb only started collection later and is still in data cleaning and preparation phase.

All of the studies built on an existing collaboration between researchers at the Desmond Tutu TB Centre (DTTC) and government partners within the TB programme and Department of Health (DOH). The National DOH used the ETR.Net dataset as the primary source of historical TB data to inform the WHO national epidemiological review in 2019, in which I participated. I collaborated with provincial DOH colleagues to draft a circular on recording and reporting guidelines for adults and children diagnosed or managed with TB at general hospitals in the

Western Cape province. The TBM surveillance study at Tygerberg Hospital heightened awareness of the potential impact of the local shortages of BCG vaccine and the importance to monitoring stock. It also contributed to the development of TBM surveillance algorithms at the Western Cape Provincial Health Data Centre, to monitor local paediatric TBM trends.

6. FUTURE DIRECTIONS AND RESEARCH IMPLICATIONS

There are several remaining key considerations and future directions for a paediatric TB care cascade which are not addressed in this dissertation. These include the absence of national estimates of the adolescent TB burden or the burden of severe forms of TB such as TBM (pillar 1). Furthermore, there are limited data on how and where children with TB access healthcare services and how they were investigated (pillar 2). The reporting gap (including ILTFU) among children diagnosed at primary healthcare facilities (pillar 3) still needs to be quantified. Finally, there is a paucity of data on post-TB morbidity in children and adolescents successfully treated for TB (pillar 6). Time delays between steps in the TB care cascade remain an important consideration, and including time delays could further improve monitoring and evaluation efforts. Whilst it is relatively easy to quantify treatment delays, diagnostic delays may be more difficult to measure as data on the onset of symptoms is not routinely collected. These important considerations are beyond the scope of the research presented in this dissertation.

Current complementary research at the Desmond Tutu TB Centre is ongoing on TB treatment outcomes in South African children and adolescents (pillar 5, Work in progress PI M. Osman), as well as on post-TB health (pillar 6; Work in progress, PI M. van der Zalm). These results will continue to inform further development of the paediatric TB care cascade. Future research will include methods to better estimate the disease burden of TBM in South African children (pillar 1, PI K. du Preez, through an awarded K43 International Fogarty grant). Novel non-sputum based, more accurate diagnostic tests for paediatric TB hold great promise and several large studies are underway globally. Improved strategies to diagnose TB has been addressed through several studies of improved bacteriological diagnosis and biomarker studies.[90, 115-117]

Future useful work on estimates of the diagnostic pillar would include sub-national, HIV-stratified data from Kwa-Zulu Natal, the only high TB burden province where all hospitals currently report TB data. These results could be used to estimate the percentage of hospital-diagnosed cases in each age group and by HIV status. This, in combination with my estimate of the hospital reporting gap, could be used to produce an estimate of diagnosis (pillar 3) in the other high TB-burden provinces. However, data from diagnosis at PHC level will also be helpful to quantify (ILTFU) amongst paediatric cases diagnosed at this level of care.

Vital registration data could also provide important data to quantify undiagnosed TB cases, specifically evaluating pneumonia in young children as cause of death, as TB has been identified as an important underlying cause of acute severe pneumonia in young children.[60]

7. CONCLUSIONS

TB in children and adolescents remains a major problem in South Africa and contributes significantly to the overall disease burden. HIV remains a driving force behind the TB epidemic, and the impact of the widespread availability of ART in South Africa has not yet equally mitigated the negative impact of HIV on the TB epidemic in all age groups of children and adolescents. The spectrum of TB disease remains an important consideration for paediatric TB, especially disseminated forms of disease such as TBM, which occur predominately in very young children. Including clinical and bacteriological TB data from hospitals will ensure more complete and accurate paediatric TB surveillance data. All healthcare facilities who diagnose or manage TB should therefore also report on TB. Better quality surveillance data combined with improved monitoring and evaluation approaches for paediatric TB will inform better planning of services and improved TB control in children and adolescents. More complete surveillance data will also allow for measuring of the impact of interventions such as TB contact management and TB preventive therapy, HIV prevention services and TB vaccination strategies.

A paediatric TB care cascade provides a comprehensive picture of TB in children and adolescents and could contribute to improving monitoring and evaluation of paediatric TB. The TB care cascade, of which pillars 3 ('Diagnosed with TB') and 4 ('Notified and treated') were systematically addressed in this dissertation, is a helpful construct to frame gaps in epidemiological data and identify opportunities for intervention.

National TB programmes should adopt the use of practical monitoring and evaluation approaches, such as care cascades, as these can help to improve TB care and services for children and adolescents and will contribute towards achieving the ambitious global targets set for TB control.

CHAPTER 9: BIBLIOGRAPHY

1. Global tuberculosis report 2019. Geneva: World Health Organization; 2019, Licence: CCBY-NC-SA3.0IGO.

2. Harries AD, Zachariah R, Corbett EL, et al. The HIV-associated tuberculosis epidemic--when will we act? Lancet. 2010;375(9729):1906-19.

3. Marais BJ, Gie RP, Schaaf HS, et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. 2004;8(4):392-402.

4. Loddenkemper R, Lipman M, Zumla A. Clinical Aspects of Adult Tuberculosis. Cold Spring Harb Perspect Med. 2015;6(1):a017848.

5. Marais BJ, Donald PR, Gie RP, Schaaf HS, Beyers N. Diversity of disease in childhood pulmonary tuberculosis. Ann Trop Paediatr. 2005;25(2):79-86.

6. Donald PR, Schaaf HS, Schoeman JF. Tuberculous meningitis and miliary tuberculosis: the Rich focus revisited. J Infect. 2005;50(3):193-5.

7. Wiseman CA, Gie RP, Starke JR, et al. A proposed comprehensive classification of tuberculosis disease severity in children. Pediatr Infect Dis J. 2012;31(4):347-52.

8. Seddon JA, Chiang SS, Esmail H, Coussens AK. The wonder years: what can primary school children teach us about immunity to Mycobacterium tuberculosis? Front Immunol. 2018;9:2946.

9. Hesseling AC, Cotton MF, Jennings T, et al. High incidence of tuberculosis among HIV-infected infants: evidence from a South African population-based study highlights the need for improved tuberculosis control strategies. Clin Infect Dis. 2009;48(1):108-14.

10. Dodd PJ, Prendergast AJ, Beecroft C, Kampmann B, Seddon JA. The impact of HIV and antiretroviral therapy on TB risk in children: a systematic review and meta-analysis. Thorax. 2017;72(6):559-75.

11. Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Enarson DA, Beyers N. The spectrum of disease in children treated for tuberculosis in a highly endemic area. Int J Tuberc Lung Dis. 2006;10(7):732-8.

12. Donald PR. Childhood tuberculosis: the hidden epidemic. Int J Tuberc Lung Dis. 2004;8(5):627-9.

13. Desta ML, Saravanan M, Hilekiros H, et al. HIV prevalence and risk factors in infants born to HIV positive mothers, measured by dried blood spot real-time PCR assay in Tigray, Northern Ethiopia. BMC Pediatr. 2019;19(1):257.

14. Abdool Karim Q, Baxter C, Birx D. Prevention of HIV in Adolescent Girls and Young Women: Key to an AIDS-Free Generation. J Acquir Immune Defic Syndr. 2017;75 Suppl 1:S17-S26.

15. Sohn AH, Hazra R. The changing epidemiology of the global paediatric HIV epidemic: keeping track of perinatally HIV-infected adolescents. J Int AIDS Soc. 2013;16:18555.

16. Kranzer K, Bradley J, Musaazi J, et al. Loss to follow-up among children and adolescents growing up with HIV infection: age really matters. J Int AIDS Soc. 2017;20(1):21737.

17. Marais BJ. Quantifying the tuberculosis disease burden in children. Lancet. 2014;383(9928):1530-1.

18. Dodd PJ, Yuen CM, Sismanidis C, Seddon JA, Jenkins HE. The global burden of tuberculosis mortality in children: a mathematical modelling study. Lancet Glob Health. 2017;5(9):e898-e906.

19. Snow KJ, Cruz AT, Seddon JA, et al. Adolescent tuberculosis. Lancet Child Adolesc Health. 2020;4(1):68-79.

20. Chiang SS, Khan FA, Milstein MB, et al. Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis. Lancet Infect Dis. 2014;14(10):947-57.

21. Schoeman J, Wait J, Burger M, et al. Long-term follow up of childhood tuberculous meningitis. Dev Med Child Neurol. 2002;44(8):522-6.

22. Allwood B, van der Zalm M, Makanda G, Mortimer K, Steering Committee of the First International Post-Tuberculosis S. The long shadow post-tuberculosis. Lancet Infect Dis. 2019;19(11):1170-1.

23. Snow KJ, Nelson LJ, Sismanidis C, Sawyer SM, Graham SM. Incidence and prevalence of bacteriologically confirmed pulmonary tuberculosis among adolescents and young adults: a systematic review. Epidemiol Infect. 2018;146(8):946-53.

24. Garcia-Basteiro AL, Schaaf HS, Diel R, Migliori GB. Adolescents and young adults: a neglected population group for tuberculosis surveillance. Eur Respir J. 2018;51(2).

25. Snow KJ, Sismanidis C, Denholm J, Sawyer SM, Graham SM. The incidence of tuberculosis among adolescents and young adults: a global estimate. Eur Respir J. 2018;51(2):1702352.

26. Snow K, Hesseling AC, Naidoo P, Graham SM, Denholm J, du Preez K. Tuberculosis in adolescents and young adults: epidemiology and treatment outcomes in the Western Cape. Int J Tuberc Lung Dis. 2017;21(6):651-7.

27. Reif LK, Rivera V, Bertrand R, et al. Outcomes across the tuberculosis care continuum among adolescents in Haiti. Public Health Action. 2018;8(3):103-9.

28. den Boon S, Verver S, Marais BJ, et al. Association between passive smoking and infection with Mycobacterium tuberculosis in children. Pediatrics. 2007;119(4):734-9.

29. Marais BJ, Gie RP, Schaaf HS, et al. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung Dis. 2004;8(3):278-85.

30. Du Preez K, Hesseling AC, Mandalakas AM, Marais BJ, Schaaf HS. Opportunities for chemoprophylaxis in children with culture-confirmed tuberculosis. Ann Trop Paediatr. 2011;31(4):301-10.

31. Seddon JA, Jenkins HE, Liu L, et al. Counting children with tuberculosis: why numbers matter. Int J Tuberc Lung Dis. 2015;19 Suppl 1:9-16.

32. Coghlan R, Gardiner E, Amanullah F, et al. Understanding Market Size and Reporting Gaps for Paediatric TB in Indonesia, Nigeria and Pakistan: Supporting Improved Treatment of Childhood TB in the Advent of New Medicines. PLoS One. 2015;10(10):e0138323.

33. World Health Organisation. Roadmap towards ending TB in children and adolescents. Geneva; 2018. Licence: CC BY-NC-SA 3.0 IGO. Available at http://apps.who.int/iris/bitstream/handle/10665/275422/9789241514798-eng.pdf?ua=1 [accessed 10 August 2020].

34. Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. Lancet Glob Health. 2014;2(8):e453-9.

35. Jenkins HE, Tolman AW, Yuen CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. Lancet. 2014;383(9928):1572-9.

36. Dodd PJ, Sismanidis C, Seddon JA. Global burden of drug-resistant tuberculosis in children: a mathematical modelling study. Lancet Infect Dis. 2016.

37. World Health Organisation. Roadmap for childhood tuberculosis. Geneva, Switzerland.; 2013. Available at http://www.who.int/iris/bitstream/10665/89506/1/9789241506137_eng.pdf [accessed 10 Aug 2020].

38. du Preez K, Schaaf HS, Dunbar R, et al. Incomplete registration and reporting of culture-confirmed childhood tuberculosis diagnosed in hospital. Public Health Action. 2011;1(1):19-24.

39. Lestari T, Probandari A, Hurtig AK, Utarini A. High caseload of childhood tuberculosis in hospitals on Java Island, Indonesia: a cross sectional study. BMC Public Health. 2011;11:784.

40. Siddaiah A, Ahmed MN, Kumar AMV, et al. Tuberculosis notification in a private tertiary care teaching hospital in South India: a mixed-methods study. BMJ Open. 2019;9(2):e023910.

41. Ade S, Harries AD, Trebucq A, et al. The burden and outcomes of childhood tuberculosis in Cotonou, Benin. Public Health Action. 2013;3(1):15-9.

42. Levi J, Raymond A, Pozniak A, Vernazza P, Kohler P, Hill A. Can the UNAIDS 90-90-90 target be achieved? A systematic analysis of national HIV treatment cascades. BMJ Glob Health. 2016;1(2):e000010.

43. Kay ES, Batey DS, Mugavero MJ. The HIV treatment cascade and care continuum: updates, goals, and recommendations for the future. AIDS Res Ther. 2016;13:35.

44. Sidibe M, Loures L, Samb B. The UNAIDS 90-90-90 target: a clear choice for ending AIDS and for sustainable health and development. J Int AIDS Soc. 2016;19(1):21133.

45. Reid MJ, Goosby E. Lessons learned from the HIV care cascade can help End TB. Int J Tuberc Lung Dis. 2017;21(3):245-6.

46. Cazabon D, Alsdurf H, Satyanarayana S, et al. Quality of tuberculosis care in high burden countries: the urgent need to address gaps in the care cascade. Int J Infect Dis. 2017;56:111-6.

47. Subbaraman R, Nathavitharana RR, Mayer KH, et al. Constructing care cascades for active tuberculosis: A strategy for program monitoring and identifying gaps in quality of care. PLoS Med. 2019;16(2):e1002754.

48. Lamb GS, Starke JR. Tuberculosis in Infants and Children. Microbiol Spectr. 2017;5(2).

49. Marais BJ, Gie RP, Hesseling AC, et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. Pediatrics. 2006;118(5):e1350-9.

50. Jeena PM, Pillay P, Pillay T, Coovadia HM. Impact of HIV-1 co-infection on presentation and hospital-related mortality in children with culture proven pulmonary tuberculosis in Durban, South Africa. Int J Tuberc Lung Dis. 2002;6(8):672-8.

51. Swingler GH, du Toit G, Andronikou S, van der Merwe L, Zar HJ. Diagnostic accuracy of chest radiography in detecting mediastinal lymphadenopathy in suspected pulmonary tuberculosis. Arch Dis Child. 2005;90(11):1153-6.

52. Zar HJ, Connell TG, Nicol M. Diagnosis of pulmonary tuberculosis in children: new advances. Expert Rev Anti Infect Ther. 2010;8(3):277-88.

53. Marais BJ, Pai M. Recent advances in the diagnosis of childhood tuberculosis. Arch Dis Child. 2007;92(5):446-52.

54. DiNardo AR, Detjen A, Ustero P, Ngo K, Bacha J, Mandalakas AM. Culture is an imperfect and heterogeneous reference standard in pediatric tuberculosis. Tuberculosis (Edinb). 2016;101S:S105-S8.

55. Kunkel A, Abel Zur Wiesch P, Nathavitharana RR, Marx FM, Jenkins HE, Cohen T. Smear positivity in paediatric and adult tuberculosis: systematic review and meta-analysis. BMC Infect Dis. 2016;16:282.

56. Tavares e Castro A, Mendes M, Freitas S, Roxo PC. Diagnostic yield of sputum microbiological analysis in the diagnosis of pulmonary tuberculosis in a period of 10 years. Rev Port Pneumol (2006). 2015;21(4):185-91.

57. Horne DJ, Kohli M, Zifodya JS, et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra for pulmonary tuberculosis and rifampicin resistance in adults. Cochrane Database Syst Rev. 2019;6:CD009593.

58. Detjen AK, DiNardo AR, Leyden J, et al. Xpert MTB/RIF assay for the diagnosis of pulmonary tuberculosis in children: a systematic review and meta-analysis. Lancet Respir Med. 2015;3(6):451-61.

59. Forssbohm M, Zwahlen M, Loddenkemper R, Rieder HL. Demographic characteristics of patients with extrapulmonary tuberculosis in Germany. Eur Respir J. 2008;31(1):99-105.

60. Oliwa JN, Karumbi JM, Marais BJ, Madhi SA, Graham SM. Tuberculosis as a cause or comorbidity of childhood pneumonia in tuberculosis-endemic areas: a systematic review. Lancet Respir Med. 2015;3(3):235-43.

61. Dudley L, Mukinda F, Dyers R, Marais F, Sissolak D. Mind the gap! Risk factors for poor continuity of care of TB patients discharged from a hospital in the Western Cape, South Africa. PLoS One. 2018;13(1):e0190258.

62. Schaaf HS, Marais BJ, Hesseling AC, Gie RP, Beyers N, Donald PR. Childhood drug-resistant tuberculosis in the Western Cape Province of South Africa. Acta Paediatr. 2006;95(5):523-8.

63. Schaaf HS, Marais BJ, Hesseling AC, Brittle W, Donald PR. Surveillance of antituberculosis drug resistance among children from the Western Cape Province of South Africa--an upward trend. Am J Public Health. 2009;99(8):1486-90.

64. Seddon JA, Hesseling AC, Marais BJ, Jordaan A, Victor T, Schaaf HS. The evolving epidemic of drug-resistant tuberculosis among children in Cape Town, South Africa. Int J Tuberc Lung Dis. 2012;16(7):928-33.

65. Schaaf HS, Hesseling AC, Rautenbach C, Seddon JA. Trends in childhood drug-resistant tuberculosis in South Africa: a window into the wider epidemic? Int J Tuberc Lung Dis. 2014;18(7):770-3.

66. Schaaf HS, Garcia-Prats AJ, du Preez K, Rautenbach C, Hesseling AC. Surveillance provides insight into epidemiology and spectrum of culture-confirmed mycobacterial disease in children. Int J Tuberc Lung Dis. 2016;20(9):1249-56.

67. Schaaf HS, Garcia-Prats AJ, Draper HR, et al. Trends in Drug Resistance in Childhood Tuberculosis in Cape Town, South Africa. Pediatr Infect Dis J. 2020;39(7):604-8.

68. Detjen AK, Walters E. Editorial Commentary: Improving Children's Access to New Tuberculosis Diagnostic Tools Starts With the Collection of Appropriate Specimens. Clin Infect Dis. 2016;62(9):1169-71.

69. Lincoln EM, Sordillo VR, Davies PA. Tuberculous meningitis in children. A review of 167 untreated and 74 treated patients with special reference to early diagnosis. J Pediatr. 1960;57:807-23.

70. van Toorn R, Springer P, Laubscher JA, Schoeman JF. Value of different staging systems for predicting neurological outcome in childhood tuberculous meningitis. Int J Tuberc Lung Dis. 2012;16(5):628-32.

71. Solomons R, Grantham M, Marais BJ, van Toorn R. IMCI indicators of childhood TBM at primary health care level in the Western Cape Province of South Africa. Int J Tuberc Lung Dis. 2016;20(10):1309-13.

72. Simbayi LC, Zuma K, Zungu N, et al. South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017. Cape Town: HSRC Press. Available at

http://www.hsrc.ac.za/uploads/pageContent/10779/SABSSM%20V.pdf [accessed 10 August 2020].

73. National Department of Health South Africa. National Tuberculosis Guidelines 2014. Pretoria, South Africa. Available at https://sahivsoc.org/Files/NTCP_Adult_TB%20Guidelines%2027.5.2014.pdf [accessed 10 August 2020].

74. Subbaraman R, Nathavitharana RR, Satyanarayana S, et al. The Tuberculosis Cascade of Care in India's Public Sector: A Systematic Review and Meta-analysis. PLoS Med. 2016;13(10):e1002149.

75. Naidoo P, Theron G, Rangaka MX, et al. The South African Tuberculosis Care Cascade: Estimated Losses and Methodological Challenges. J Infect Dis. 2017;216(suppl_7):S702-S13.

76. Du Preez K, Seddon JA, Schaaf HS, Hesseling AC. Where are we in the battle of ending tuberculosis in children and adolescents in South Africa? S Afr Med J. 2020;Published online 26 March 2020. https://doi.org/10.7196/SAMJ.2020.v110i5.14728.

77. UNAIDS. HIV and AIDS estimates: South Africa, 2019. Available from: https://www.unaids.org/en/regionscountries/countries/southafrica [Accessed 10 August 2020].

78. Woldesenbet SA, Kufa T, Lombard C, et al. The 2017 National Antenatal Sentinel HIV Survey, South Africa, National Department of Health. 2019.

79. Cranmer LM, Draper HR, Mandalakas AM, et al. High Incidence of Tuberculosis Infection in HIV-exposed Children Exiting an Isoniazid Preventive Therapy Trial. Pediatr Infect Dis J. 2018;37(10):e254-e6.

80. Loveday M, Thomson L, Chopra M, Ndlela Z. A health systems assessment of the KwaZulu-Natal tuberculosis programme in the context of increasing drug resistance. Int J Tuberc Lung Dis. 2008;12(9):1042-7.

81. Hinderaker SG, Fatima R. Lost in time and space: the outcome of patients transferred out from large hospitals. Public Health Action. 2013;3(1):2.

82. Edginton ME, Wong ML, Phofa R, Mahlaba D, Hodkinson HJ. Tuberculosis at Chris Hani Baragwanath Hospital: numbers of patients diagnosed and outcomes of referrals to district clinics. Int J Tuberc Lung Dis. 2005;9(4):398-402.

83. Voss De Lima Y, Evans D, Page-Shipp L, et al. Linkage to care and treatment for TB and HIV among people newly diagnosed with TB or HIV-associated TB at a large, inner city South African hospital. PLoS One. 2013;8(1):e49140.

84. Gupta A, Wood R, Kaplan R, Bekker LG, Lawn SD. Prevalent and incident tuberculosis are independent risk factors for mortality among patients accessing antiretroviral therapy in South Africa. PLoS One. 2013;8(2):e55824.

85. Osman M, du Preez K, Naidoo P, et al. Key changes in the public health response to TB and HIV in South Africa. Int J Tuberc Lung Dis. 2020;24(8):857-9.

86. du Preez K, Schaaf HS, Dunbar R, et al. Complementary surveillance strategies are needed to better characterise the epidemiology, care pathways and treatment outcomes of tuberculosis in children. BMC Public Health. 2018;18(1):397.

87. Marais BJ, Hesseling AC, Gie RP, Schaaf HS, Enarson DA, Beyers N. The bacteriologic yield in children with intrathoracic tuberculosis. Clin Infect Dis. 2006;42(8):e69-71.

88. Rachow A, Clowes P, Saathoff E, et al. Increased and expedited case detection by Xpert MTB/RIF assay in childhood tuberculosis: a prospective cohort study. Clin Infect Dis. 2012;54(10):1388-96.

89. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. Lancet. 2005;365(9454):130-4.

90. Walters E, van der Zalm MM, Demers AM, et al. Specimen Pooling as a Diagnostic Strategy for Microbiologic Confirmation in Children with Intrathoracic Tuberculosis. Pediatr Infect Dis J. 2019;38(6):e128-e31.

91. Byamungu LN, du Preez K, Walters E, Nachega JB, Schaaf HS. Timing of HIV diagnosis in children with tuberculosis managed at a referral hospital in Cape Town, South Africa. Int J Tuberc Lung Dis. 2018;22(5):488-95.

92. National Department of Health. Guidelines for the management of HIV in children. South Africa; 2010. Available at https://sahivsoc.org/Files/Guidelines_for_Management_of_HIV_in_Children_2010.pdf [accessed 10 Aug 2020].

93. National Department of Health. Circular Minute No 2 of 2012: Initiation of anti retroviral treatment (ART) to all HIV positive children aged 5 years and under regardless of CD4 count and/or WHO clinical staging. South Africa; 2012. Available at https://sahivsoc.org/Files/Rx%20of%20children%20under%205-Circular%20Minute%20No%202%20of%202012%20-%20ART.pdf [accessed 10 August 2020].

94. National Department of Health. Implementation of the universal test and treat strategy for HIV positive patients and differentiated care for stable patients. South Africa; 2016. Available at https://sahivsoc.org/Files/22%208%2016%20Circular%20UTT%20%20%20Decongestion%20CCMT%20Directorate.pdf [accessed 10 August 2020].

95. du Preez K, Seddon JA, Schaaf HS, et al. Global shortages of BCG vaccine and tuberculous meningitis in children. Lancet Glob Health. 2019;7(1):e28-e9.

96. Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet. 2006;367(9517):1173-80.

97. Abubakar I, Pimpin L, Ariti C, et al. Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette-Guerin vaccination against tuberculosis. Health Technol Assess. 2013;17(37):1-372, v-vi.

98. Cernuschi T, Malvolti S, Nickels E, Friede M. Bacillus Calmette-Guerin (BCG) vaccine: A global assessment of demand and supply balance. Vaccine. 2018;36(4):498-506.

99. du Preez K, du Plessis L, O'Connell N, Hesseling AC. Burden, spectrum and outcomes of children with tuberculosis diagnosed at a district-level hospital in South Africa. Int J Tuberc Lung Dis. 2018;22(9):1037-43.

100. Frigati L, Maskew M, Workman L, et al. Clinical Predictors of Culture-confirmed Pulmonary Tuberculosis in Children in a High Tuberculosis and HIV Prevalence Area. Pediatr Infect Dis J. 2015;34(9):e206-10.

101. Aketi L, Kashongwe Z, Kinsiona C, et al. Childhood tuberculosis in a sub-saharan tertiary facility: epidemiology and factors associated with treatment outcome. PLoS One. 2016;11(4):e0153914.

102. Tilahun G, Gebre-Selassie S. Treatment outcomes of childhood tuberculosis in Addis Ababa: a five-year retrospective analysis. BMC Public Health. 2016;16:612.

103. du Preez K, Schaaf HS, Dunbar R, Swartz A, Naidoo P, Hesseling AC. Closing the reporting gap for childhood tuberculosis in South Africa: improving hospital referrals and linkages. Public Health Action. 2020;10(1):38-46.

104. Edginton ME, Wong ML, Hodkinson HJ. Tuberculosis at Chris Hani Baragwanath Hospital: an intervention to improve patient referrals to district clinics. Int J Tuberc Lung Dis. 2006;10(9):1018-22.

105. Jong E, Sanne IM, van Rie A, Menezes CN. A hospital-based tuberculosis focal point to improve tuberculosis care provision in a very high burden setting. Public Health Action. 2013;3(1):51-5.

106. Badar D, Ohkado A, Naeem M, Khurshid-ul-Zaman S, Tsukamoto M. Strengthening tuberculosis patient referral mechanisms among health facilities in Punjab, Pakistan. Int J Tuberc Lung Dis. 2011;15(10):1362-6.

107. Marais F, Kallon, II, Dudley LD. Continuity of care for TB patients at a South African hospital: A qualitative participatory study of the experiences of hospital staff. PLoS One. 2019;14(9):e0222421.

108. World Health Organization. TB Data: WHO's global tuberculosis database 2019. Available from: https://www.who.int/tb/data/en/ [accessed 10 August 2020].

109. Mwangwa F, Chamie G, Kwarisiima D, et al. Gaps in the Child Tuberculosis Care Cascade in 32 Rural Communities in Uganda and Kenya. J Clin Tuberc Other Mycobact Dis. 2017;9:24-9.

110. Latent tuberculosis infection: updated and consolidated guidelines for programmatic management. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

111. Harrison A, Newell ML, Imrie J, Hoddinott G. HIV prevention for South African youth: which interventions work? A systematic review of current evidence. BMC Public Health. 2010;10:102.

112. Boulle A, Heekes A, Tiffin N, et al. Data Centre Profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. International Journal of Population Data Science. 2019;4(2):6.

113. Engelbrecht AL, Marais BJ, Donald PR, Schaaf HS. A critical look at the diagnostic value of culture-confirmation in childhood tuberculosis. J Infect. 2006;53(6):364-9.

114. Thwaites GE, van Toorn R, Schoeman J. Tuberculous meningitis: more questions, still too few answers. Lancet Neurol. 2013;12(10):999-1010.

115. Walters E, Demers AM, van der Zalm MM, et al. Stool Culture for Diagnosis of Pulmonary Tuberculosis in Children. J Clin Microbiol. 2017;55(12):3355-65.

116. Walters E, van der Zalm MM, Palmer M, et al. Xpert MTB/RIF on stool is useful for the rapid diagnosis of tuberculosis in young children with severe pulmonary disease. Pediatr Infect Dis J. 2017.

117. Liu C, Lyon CJ, Bu Y, et al. Clinical Evaluation of a Blood Assay to Diagnose Paucibacillary Tuberculosis via Bacterial Antigens. Clin Chem. 2018;64(5):791-800.

APPENDIX A. ACKNOWLEDGEMENTS

I would firstly like to acknowledge all the children and families who participated in these research studies, and all the colleagues within the Department of Health for their tireless efforts to care for patients with TB in South Africa.

I am also especially grateful to my three supervisors, Anneke Hesseling, Simon Schaaf and Pren Naidoo – without you this would not have been possible. Thank you for being willing to give your time and knowledge to guide me on this journey.

Anneke, your mentorship has played an instrumental role throughout my career. Thank you for sharing your depth of knowledge and for teaching me the things that are not written in textbooks. Thank you for your never wavering commitment, the countless opportunities and for encouraging me to reach even higher.

Simon, your kindness, support and encouragement since I started at the Desmond Tutu TB Centre has been invaluable. Thank you for sharing your ideas and knowledge, and for never missing any details.

Pren, thank you for always challenging me to think about the operational relevance of my research and ways to translate research into policy and practice.

Being part of the Desmond Tutu TB Centre is an incredible privilege. Over the past decade, I have always felt inspired and encouraged by the work we do every day, and I feel truly blessed to be part of such a dynamic and caring team. A special word of thanks to all my friends and work colleagues for all your support and encouragement during this journey, particularly Rory Dunbar, for all his help with data management and record linkage.

To Anita Fourie, for always smiling and being willing to help, but especially for your help with formatting the dissertation.

On a personal note, my sincerest thanks to my friends who were always there, constantly praying for me, and who stepped in every time I needed help. Theresa and Igna, you were incredible and words cannot express my gratefulness for your wonderful friendships. Sanet, I will always treasure your special words of motivation and continued encouragement.

And finally, a very special thanks to my entire family, for your patience and your motivation, and the endless cups of coffee. To my parents, for always encouraging me to be the most I can be, and my Heavenly Father who gave me the strength to persevere.

APPENDIX B. FUNDING

This doctoral research was supported by a scholarship for doctoral studies from the South African National Research Foundation's SARCHI Chair in Paediatric Tuberculosis (PI: AC Hesseling). The financial assistance of the National Research Foundation (NRF) towards this research is hereby acknowledged. Opinions expressed and conclusions arrived at, are those of the authors and are not necessarily to be attributed to the NRF.

The doctoral research was also supported by funding from the Division of Research Development at Stellenbosch University (Early Research Development Grant) in 2017.

During the time of preparation and submission of this dissertation, I was supported by the Fogarty International Center of the National Institutes of Health under Award No. K43TW011006. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Funding support for the individual studies are described in each manuscript presented in this dissertation, and are also listed below:

- Initial data extraction and cleaning of the ETR.Net dataset was funded by URC through the TB Care II Project (USAID Co-364 operative Agreement No. AID-OAA-A-10-00021; PI P Naidoo)
- The surveillance and intervention research at Tygerberg Hospital (TBH; Chapters 4 and 7) was funded through an operational and epidemiological research fellowship awarded by Fogarty International Centre Grant (3U2RTW007370-05S1; PI K du Preez).
- The research at Khayelitsha District Hospital (KDH; Chapter 6) received project support through the Harry Crossley Foundation, Stellenbosch University. The Kid-care project and linkage to care activities at KDH was funded by the University Research Co Grant Agreement (FY2013-G87-4740) under the US Agency for International Development (674-C-00-09-00121-00; TB Programme in South Africa; PI K du Preez).
- The retrospective study at TBH (Chapter 7) was supported through an operational research course jointly developed and run by the Centre for Operational Research (COR), International Union Against Tuberculosis and Lung Disease (The Union), Paris, France, and the Operational Research Unit, Médecins Sans Frontières, Brussels. I was an operational research fellow at the Desmond Tutu Tuberculosis Centre, supported by the COR at The Union, Paris, France. This project also received financial support from the Harry Crossley Foundation, Stellenbosch University.