Unmasking the hidden epidemic
The process of theory-guided intervention design to improve case detection of tuberculosis in hospitalised children in Kenya
Oliwa, J.N.

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UNMASKING THE HIDDEN EPIDEMIC

The process of theory-guided intervention design to improve case detection of tuberculosis in hospitalised children in Kenya

JACQUIE NAROTSO OLIWA
This thesis was prepared at the Faculty of Medicine, Academic Medical Center of the University of Amsterdam, Amsterdam, The Netherlands and at The KEMRI-Wellcome Trust Research Programme, Nairobi.

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Lay out: Frank Fieseler, IPSKAMP

Front cover: Mark Mutiso Mutinda

As Jacquie does, I too would like to make a positive contribution to fighting TB in children. My tool is visual art: to express beauty, to inspire emotion, to make a statement, or in this case to illustrate the most vulnerable in this greatest of fights, the children of this earth. It is my hope that my art draws others to the cause Jacquie fights for, and inspires them to do more in support of science, research and the body of medics committed to ending TB.

Paranymph: Jane Hassell

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Unmasking The Hidden Epidemic

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ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

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ten overstaan van een door het College voor Promoties ingestelde commissie,
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Table of Contents

<table>
<thead>
<tr>
<th>Abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chapter 1 General Introduction</td>
</tr>
<tr>
<td>Chapter 2 Variability in distribution and use of tuberculosis diagnostic tests in Kenya: a cross-sectional survey <em>BMC Infectious Diseases</em> 2018</td>
</tr>
<tr>
<td>Chapter 3 Tuberculosis as a cause or comorbidity of childhood pneumonia in tuberculosis-endemic areas: a systematic review <em>Lancet Respir Med.</em> 2015</td>
</tr>
<tr>
<td>Chapter 4 Diagnostic practices and estimated prevalence of tuberculosis among children admitted to 13 government hospitals in Kenya: An analysis of two years’ routine clinical data <em>PLoS One.</em> 2019</td>
</tr>
<tr>
<td>Chapter 5 Perspectives and practices of health workers around diagnosis of paediatric tuberculosis in hospitals in a resource-poor setting – modern diagnostics meet age-old challenges <em>BMC Health Services Research</em> 2020</td>
</tr>
<tr>
<td>Chapter 6 Improving case detection of tuberculosis in hospitalised Kenyan children– employing the Behaviour Change Wheel to aid intervention design and implementation <em>Implementation Science</em> 2020</td>
</tr>
<tr>
<td>Chapter 7 Policy Brief</td>
</tr>
<tr>
<td>Chapter 8 General Discussion</td>
</tr>
<tr>
<td>Chapter 9 Summary</td>
</tr>
<tr>
<td>PhD portfolio</td>
</tr>
<tr>
<td>Acknowledgements</td>
</tr>
</tbody>
</table>
Abbreviations

BCW: Behaviour Change Wheel
CFIR: Consolidated Framework for Implementation
CNR: Case Notification Rate (for Tuberculosis)
COM-B: Capability, Opportunity and Motivation Behavioural model
CT: Computer Tomography
DST: Drug Susceptibility testing
ERIC: Expert Recommendations for Implementing Change
GNI: Gross National Income
GNP: Gross National Product
HIV: Human Immunodeficiency Virus
IPT: Isoniazid Preventive Therapy
LMIC: Low- and middle-income countries
MRI: Magnetic Resonance Imaging
NTP: National TB Programme
PARIHS: Promoting Action on Research Implementation in Health
PCR: Polymerase-Chain Reaction
QUAL: Qualitative Data
QUAN: Quantitative data
RTI: Respiratory tract infection
TB: Tuberculosis
TWG: Technical Working Group
S/S: Signs and symptoms
SDGs: Sustainable Development Goals
TB: Tuberculosis
TDF: Theoretical Domains Framework
WHO: World Health Organisation
Chapter 1: General Introduction
Introduction

1. Overview of Tuberculosis in children

Epidemiology of tuberculosis in children: The hidden epidemic

Tuberculosis (TB) is the leading cause of death from an infectious disease. In the 2019 Global TB report, the World Health Organisation (WHO) estimated that there were 10 million new cases of TB in 2018 worldwide. Approximately 1.1 million cases (11%) were in children younger than 15 years, with 205,000 deaths (13.8% of all TB deaths) [1]. Most of these deaths (almost 80%) are in children younger than five years [2]. Under-detection of TB in children is especially important in low and lower middle-income settings, which also carry a high burden of TB, but unfortunately have limited surveillance data. Globally, low- and middle-income countries (LMICs) account for >90% of TB cases and deaths, indicating that TB incidence rates correlate with poor socio-economic conditions [3-5]. The population pyramids in many of these countries show that up to 50% of their populations may be young children [6, 7]. The relatively high number of children, potentially sharing crowded living spaces with adults (especially in informal settlements), is likely to lead to TB transmission at an early age in LMICs [6]. One would therefore expect greater numbers of children with TB in these settings- it is estimated that children should represent 10-20% of all TB cases in high burden countries [6, 8]. However, many of these countries often report child-adult case ratios of less than 5%, which is far less than what is expected [8].

Estimates suggest that the global incidence of TB is much higher than reported in the official notification data, with more than 60% of cases unreported and undiagnosed [2, 6, 9]. The greatest case detection failure is in children younger than five years, who probably account for around 50% of all paediatric TB cases [9, 10]. Until recently, paediatric TB estimates were obtained from data of smear-positive cases by age [11]. This has contributed to underestimation of the burden of TB in children especially because most children have pauci-bacillary and thus smear negative disease [8]. The true burden of TB in children is unknown due to several factors contributing to difficulty in making a diagnosis. First, is lack of standard case definitions; second, is lack of a proper gold standard diagnostic test; and third, is the fact that TB mimics many childhood illnesses like pneumonia, which is the leading cause of death in children[12]. Thus, the child TB cases being seen and reported represent a “tip of the iceberg”, supporting the assertion that TB is a hidden epidemic especially in young children [6, 8].

TB is curable and preventable, and most children respond well to treatment if started early. There is less than one percent mortality among children treated for TB [10, 13]. It is estimated that more than 90% of children who die from TB worldwide were untreated, a situation that is tantamount to
widespread neglect and a violation of children’s right to health [2, 13]. Children have historically been low priority for TB control programmes because they are less contagious than adults and this has contributed to the observed neglect of childhood TB and resultant preventable deaths [8, 13]. By ignoring TB in children, efforts at TB control will fail. This is because children with TB serve as a reservoir for future infections, thus elimination efforts will be ineffective if children are not treated [7]. It is therefore imperative to identify and treat children with TB not only from a human rights perspective, but also from a public health perspective.

Children with TB represent recent transmission and can be used as markers of ongoing disease transmission in a community and ineffective control measures [9]. The third Sustainable Development Goal (SDG 3) includes a global commitment to ending preventable deaths in children by 2030. Addressing childhood TB is key to achieving this goal. It is important to understand the epidemiology of TB in children to help clinicians make correct decisions about whom to test and treat for TB, as well as to enable TB programmes to allocate resources and services where they are needed most [7, 9].

Natural course of TB in children
To better understand the epidemiology of TB in children, it is important to reflect on the natural course of disease and how this influences diagnosis.

From exposure to infection
Tuberculosis is an airborne disease caused by the bacillus *Mycobacterium tuberculosis*. The mycobacterium bacilli are carried in droplet nuclei, usually 1-5 microns in diameter. Infectious droplet nuclei are generated when persons with pulmonary or laryngeal TB disease cough, sneeze, shout or sing. Young children generally lack the tussive force to effectively transmit TB. Very rarely, transmission can occur through unpasteurised milk into the gut or even the skin (injury with local infection). The source of infection for most children is an infectious adult within their proximity, usually in the household, although there have been cases of transmission outside the household in schools, vehicles and probably in hospitals too. Risk of transmission depends on: susceptibility of the child; infectiousness of the index case (higher smear positive cases with cavitatory disease); poorly ventilated/crowded spaces; duration and frequency of exposure [14, 15].

*Primary infection* occurs when an uninfected child inhales infectious aerosol droplets, and a few bacilli reach distal alveoli, where they are ingested by alveolar macrophages. A localised pneumonic inflammatory process occurs in the lung parenchyma called the Ghon focus or primary focus. From this focus, bacilli drain to the regional lymph nodes. The Ghon focus with the regional lymph nodes form the primary complex. From the regional lymph nodes, bacilli spread to the systemic circulation (occult haematogenous spread) occurs during the incubation period, before immune responses can
contain the disease [15]. The immune response develops approximately 4-6 weeks after the primary infection and this immune response stops the multiplication of *M. tuberculosis* at this stage. Thus, after dissemination, bacilli can survive in some privileged sites for long periods. This is latent TB infection. A child may be entirely asymptomatic or experience only mild self-limiting symptoms during the primary infection period. With progression to latent infection they remain well, the only evidence of infection being a positive tuberculin skin test or an incidental abnormality on chest radiograph [8, 16]. Pulmonary infection without progression to active disease implies successful containment of the organism.

**From infection to disease**

Further progression of disease will depend on the balance between the host’s immunity and the bacilli’s virulence. Host immunity is the major determinant of risk of progression from infection to disease. If the immune system fails to keep the bacilli under control at the point of primary infection, they multiply rapidly and spread through the lymphatics or the bloodstream to the rest of the body to cause TB disease in virtually any part of the body (*primary TB disease*). Most primary TB disease in children is pulmonary, although younger children are at greater risk of disseminated disease due to their inadequate innate and adaptive immunity [8, 17]. Persistent or non-remitting symptoms are usually indicative of disease progression. Progression of latent infection to active disease is called *secondary TB disease*.

Infants with immature immune systems have highest risk of developing active disease: 30-40% of infected infants develop pulmonary disease and 10-20% develop disseminated disease. For those infected in the second year of life, the risk of developing disease is 10-20%. This risk continues to fall as the child’s immunity matures, until adolescence where a second peak is observed [15, 17]. In most cases (>90%), active TB disease will occur within one year after primary infection, with greatest risk in young infants[17]. Additional risk factors for progression from infection to disease include HIV infection, not BCG vaccinated, recent TB infection, poorly treated previous TB, and immunosuppression due to causes like severe malnutrition, post measles, diabetes and malignancy [14].

**Diagnosis of TB in children: The challenges**

Diagnostic difficulties are the greatest challenge to childhood TB management and indeed in many cases, TB is often not even considered in a differential diagnosis in children [14]. Finding and correctly diagnosing childhood TB disease is uniquely challenging: the eyes see only what the mind knows. TB has many non-specific symptoms that overlap with other common childhood diseases like pneumonia, malnutrition or HIV [18, 19]. Pneumonia is of specific concern because it is the leading cause of death
in children [12], and some of these case could potentially be missed TB diagnoses. Cardinal symptoms include cough, failure to thrive, weight loss, fever and reduced playfulness, but these symptoms lack specificity particularly in younger children and those infected with HIV [16, 17]. None of the available diagnostic scoring systems have been found adequate, mostly due to lack of standard definitions adapted for different settings, poor sensitivity and specificity, causing them to be largely abandoned in practice [17, 20].

Chest radiography is valuable in the diagnosis of TB in children, it is the most widely used diagnostic test in clinical practice and classic hilar adenopathy is considered highly suggestive of TB [21]. Unfortunately, technical quality of radiographs hampers utility, alongside lack of expertise in interpreting the films in high endemic settings due to fewer radiologists and lack of competence amongst clinicians. And even amongst experts, agreement on interpretation of radiographical findings of TB in children is poor [22]. There is potential for ultrasound, computerised tomography (CT) and magnetic resonance imaging (MRI) to provide more sensitive imaging for TB in children, but these are often harder to access in lower resource settings where TB is endemic [17].

For laboratory diagnosis, sputum culture is considered the gold standard for bacteriological confirmation of TB, yet diagnostic yield is only 30-40% at best for TB in children [23]. The results take from 2-6 weeks to be available, contributing to delays in starting treatment and issues with loss-to-follow up in settings with limited resources, where access to health care is a challenge. Sputum microscopy is often the only diagnostic test available in resource-limited settings and has been the mainstay of bacteriological diagnosis of TB, but is positive in only 10–15% of children with probable tuberculosis [21].

The current recommended first-line bacteriological test for TB in children is the Xpert MTB/RIF® assay. It is an automated polymerase-chain reaction (PCR)-based test for tuberculosis and rifampicin resistance, recommended for its superior sensitivity compared to smear microscopy [24], and produces results much faster than liquid cultures [24]. There have been concerted efforts globally to increase access to this important diagnostic and its improved versions Xpert-Ultra®, Xpert-Omni® and Xpert-Xpand® are also being made available [25-27]. However, use of these diagnostics remains sub-optimal due to age-old implementation challenges including unreliable supplies of laboratory consumables, machine maintenance issues, poor access to the tests, technological challenges amongst health workers and inconsistent power supplies among others [27-32].

The main issue with bacteriological confirmation of TB in children remains the difficulty in obtaining suitable specimen. Children lack tussive force to expectorate and tend to swallow their sputum. Their
sputa specimen can be collected by gastric aspiration, naso-pharyngeal aspiration or sputum induction, but these need technical skill and patience when dealing with children. The yield tends to be low due to the pauci-bacillary nature of childhood TB disease (very few bacteria in sputa makes it harder to detect, although there have been reports of successful bacteriological confirmation in children as young as one month old) [33, 34]. Other specimens like cerebro-spinal fluid and aspirates from joints, cavities or stool can be collected for bacteriological confirmation with Xpert, but the sensitivity is low [35].

The other commonly used supportive tests for TB diagnosis in children are the immunological-based tuberculin skin test and interferon-gamma assays, but both lack sensitivity and specificity and are unable to distinguish between latent infection and disease [17].

In summary therefore, diagnosis of TB in children is restricted by a sequence of factors, from clinical oversight leading to lack of diagnostic work-up; lack of a sensitive point-of-care diagnostic test; irregular supplies of established diagnostic tests; poor uptake of available tests; difficulties obtaining specimens; frequent negative bacteriological test results; and variability in interpretation of chest radiographs [22, 36].

Importantly, a clinical diagnosis can be made presumptively, based on suggestive signs and symptoms of TB disease, an abnormal chest radiograph, a positive tuberculin skin test and documented exposure to an infectious contact [37]. Paediatric TB diagnostic capacity is however often centralized at secondary or tertiary levels of the health system and managed in a vertical way in many high burden countries [38]. Consequently, frontline health workers, often have limited capacity and confidence in preventing, diagnosing and managing childhood TB [36, 38].

Reliable childhood TB data will help identify more specific gaps in the care cascade from presentation with suggestive signs and symptoms to diagnosis and treatment and ultimately notification [39]. Better knowledge of these specific gaps will help in designing interventions to overcome them.

2. Overview of TB in Kenya

Burden of TB in Kenya

Kenya has a young population, with 73% of its approximately 48 million inhabitants under 30 years of age. It is classified as a low-middle-income country with a Gross National Income (GNI) per capita of $1,600, but 36.1% of the population lives below the poverty line [40]. Kenya is one of the 30 high burden TB countries (that together contribute to >80% of all the world’s TB cases) [1]. The prevalence of TB in Kenya from a recent survey was reported as 558 per 100,000 of the adult population (adjusted
after modelling calculations to 426 per 100,000 to include all age groups, as the survey only recruited people aged >15 years)[41, 42]. The annual incidence is estimated at 169,000 cases, but only 96,478 (64%) were notified to the TB programme in 2018 [42].

The true burden of TB in children in Kenya, like in the rest of the world, is unknown. In 2018, children aged <15 years comprised 10.4% of all notified TB cases, which is an improvement from recent years due to active case finding efforts by the National TB Programme (NTP), but the World Health Organisation (WHO) estimates that we are still missing >60% of childhood TB cases [42, 43]. From the 2018 Kenya annual programme report, children aged <5 years represented only 5.8% of all children reported, so there is still a persisting diagnostic gap in this age group, who face the greatest risk of severe disease and death due to their less mature immune systems [42]. Eighty-one percent of notified TB cases in children aged <15 years was pulmonary. Xpert® tests were done in 2,404 (24%) of children reported in 2018, which was also an improvement from previous years. Forty-one percent of Xpert®-tested cases were confirmed positive for \textit{M. tuberculosis}, the rest were treated based on clinical diagnosis [42]. Children showed good response to treatment, with an 87% cure rate [42].

Overview of paediatric TB care by the National TB Programme in Kenya

TB in children has been low priority for TB control efforts in Kenya until recently, as has been the case in other high burden settings [38, 44]. Historically, TB care in general has largely been provided vertically through the National TB Programme (NTP), with minimal linkage between the TB/chest clinics (run by specialist clinical officers) and other paediatric services in hospitals. This led to lack of confidence in diagnosing and managing TB in children by most frontline health care workers, who preferred to refer presumed childhood TB cases to the TB clinics or to higher level facilities to be seen by paediatricians, resulting in delay in diagnosis and poor outcomes [38]. Advocacy efforts by paediatricians led to more efforts to recognise TB in children as a serious public health concern, which saw the NTP set up a Childhood TB Technical Working Group (TWG) in 2010. The TWG led the development of child-specific guidelines and job aids (figure 1), training for health workers, disaggregation of notification data to include different child age bands and various policies to ensure more child-friendly TB services [38].
Kenya’s National TB Programme (NTP) is responsible for TB health policy and financing, quality assurance and standards, TB health information, communication and technology amongst other administrative roles that include TB in children. Childhood TB has been given prominence in the NTP’s National Strategic Plan, and TB care in general is recognised as a priority of the ongoing Universal Health Coverage efforts in Kenya [45]. Guidelines for paediatric TB clinical decision-making have been put in place, and the NTP conducts training on those guidelines every year, as part of its strategic plan [45-48]. The NTP has trained >600 workers from across Kenya’s 47 countries to-date, and has distributed various job aids and guidelines. Xpert® is the recommended first-line test for diagnosing TB in children, and was introduced in Kenya in 2011, with over 180 machines across the country, and the service is free for children in public hospitals [45].

Despite these efforts, there are still significant gaps in the case detection of TB in children and underuse of available TB diagnostics in Kenya [42, 49]. A patient-pathway analysis showed that up to three-quarters of adult patients visiting hospitals in Kenya with signs and symptoms suggestive of TB are never diagnosed, and this is probably also true for children [50].
Paediatric TB care in hospitals in Kenya and improving the quality gap

While a lot needs to be done to improve case detection of TB in children across the health care system, right from the community level to policy level, patients in hospitals represent “low-hanging fruit”, because they are already captured in formal healthcare settings and within easy reach of TB diagnostics. When patients present to hospitals with suggestive signs and symptoms of TB but fail to get investigated to aide diagnosis, this presents a missed opportunity and a gap in the quality of care given. As already discussed, delay in diagnosis in children leads to more severe disease and preventable deaths.

Most Kenyans receive hospital services they need from public health facilities. In Kenya, healthcare is organised in the following levels: i) Community health services - responsible for health promotion and early identification of cases to be managed at higher levels; Primary care services - dispensaries and health centres that carry out preventive and basic curative services; County referral services - hospitals that provide more comprehensive secondary level care; National referral services - hospitals that provide highly specialised services at tertiary referral level [51].

The National TB Programme supports all levels of care, from the community up to tertiary level. However, weak links and limited integration with maternal, child health, nutrition and other paediatric services still persist in many health facilities, exacerbating missed opportunities for diagnosis of TB in children [45].

3. A case for use of implementation science and behaviour change theories to better understand and improve case detection of TB in children

We have seen that considerable efforts have been made to implement evidence-based guidelines and new technologies to aid diagnosis of TB in general, but gaps remain in case detection and utilisation of diagnostic tests. Difficulties in diagnosis are reported to present the greatest challenge to childhood tuberculosis control efforts [14].

Implementation research is the scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services. It includes the study of influences on healthcare professional and organisational behaviour [52].

While acknowledging existence of wider system issues, we recognise that health workers are key in the step of diagnosis, and in adoption and utilisation of effective interventions [53]. Health workers need a high index of suspicion for TB, as it mimics many childhood diseases like pneumonia,
malnutrition and HIV. They need knowledge and skill to make the diagnosis with consistent availability of resources, and to be supported to adhere to best practices. Poor health worker practices may contribute to low uptake of health services by patients [53], and in our case, exacerbating missed opportunities to diagnose TB in children, leading to increased severity of disease and preventable deaths.

Changing health worker and organisational behaviour is challenging. It is important to understand factors that influence health worker practices in order to develop appropriate interventions to improve the quality of care provided in hospitals. Use of theory can help to inform the development and delivery of interventions, improve understanding of which elements of complex interventions are necessary and work together, inform adoption and spread of interventions and provide a guide to evaluate and explain potential causal mechanisms [54, 55].

A theory may generally be defined as a set of analytic principles designed to structure our observation, understanding and explanation of the world [56]. While it is highly encouraged to be explicit about use of theories when designing interventions, there is a bewildering range of theories to choose from varying disciplines including anthropology, sociology, psychology, behavioural economics etc. Eccles et al. [54] recommend that choice of theory needs to be pragmatic and most applicable to the stakeholders targeted for behaviour change. One needs to determine the origins of the theory, examine the meaning of the theory (concepts), analyse the logical consistency of the theory, consider the degree of generalisability and parsimony of the theory, and determine its testability and usefulness [54].

Several theories and frameworks have been advanced to explain factors likely to enhance or constrain uptake of new evidence or tools into clinical practice and to explain health worker practices. Some of the leading ones include the Consolidated Framework for Implementation Research (CFIR) [57]; Diffusion of Innovations [58]; Normalisation Process Theory [59]; The Promoting Action on Research Implementation in Health (PARIHS) [60]; and the Theoretical Domains Framework (TDF) [61]. Table 1 gives a description of each framework’s rationale and method adapted from Boulton et al [62].
Table 1 Summary of leading implementation frameworks

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<thead>
<tr>
<th>Framework</th>
<th>Theories/Discipline</th>
<th>Intended purpose</th>
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<tbody>
<tr>
<td>Consolidated Framework for</td>
<td>‘Meta-theoretical’: Comprises common constructs from published implementation theories</td>
<td>- Guide diagnostic assessments of implementation context</td>
</tr>
<tr>
<td>Implementation Research (CFIR)</td>
<td>- 5 major domains: intervention, inner and outer setting, individuals and the process of implementation</td>
<td>- Evaluate implementation progress</td>
</tr>
<tr>
<td>[57]</td>
<td></td>
<td>- Help explain findings in research studies or quality improvement initiatives.</td>
</tr>
<tr>
<td>Diffusion of Innovations [58]</td>
<td>‘Meta-narrative’; multi-disciplinary</td>
<td>- Provide a parsimonious and evidence-based model for considering the diffusion of innovations in health service organizations</td>
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<tr>
<td></td>
<td>- Marketing theory; general systems theory; Social network theory</td>
<td>- Provide a robust and transferable methodology for systematically reviewing complex research evidence</td>
</tr>
<tr>
<td></td>
<td>- Sociology, anthropology, psychology, ecology, literature, organization and management, systems, epidemiology, marketing, political science, economics, information and communications technology</td>
<td></td>
</tr>
<tr>
<td>Normalisation Process Theory</td>
<td>An action theory (concerned with explaining what people do)</td>
<td>- A sociological toolkit to understand the dynamics of implementing, embedding, and integrating some new technology or complex intervention</td>
</tr>
<tr>
<td>[59]</td>
<td>- Four constructs: Coherence, Cognitive Participation, Collective Action, and Reflexive Monitoring</td>
<td></td>
</tr>
<tr>
<td>The Promoting Action on Research</td>
<td>- Planned action theory</td>
<td>- Straddled between a planned action theory to guide implementation strategy and</td>
</tr>
<tr>
<td>Implementation in Health (PARIHS)</td>
<td>- Core elements: Evidence (codified &amp; non-codified sources of knowledge;</td>
<td>A classical model to describe/explain how change occurs</td>
</tr>
<tr>
<td>[60]</td>
<td>Context (environment/setting); Facilitation (support)</td>
<td></td>
</tr>
<tr>
<td>Theoretical Domains Framework</td>
<td>- Psychology/ behaviour change theories and synthesised constructs related to behaviour change and synthesised into a single framework</td>
<td>- Simplifies psychological theory and makes it accessible to those in evidence-based practice</td>
</tr>
<tr>
<td>(TDF) [61]</td>
<td>- 33 theories and 128 key theoretical constructs related to behaviour change and synthesised into a single framework</td>
<td>- To assess implementation and other behavioural problems and inform intervention design</td>
</tr>
<tr>
<td></td>
<td>- 14 domains: Knowledge, Skills, Social/Professional Role and Identity, Beliefs about Capabilities, Optimism, Beliefs about Consequences, Reinforcement, Intentions, Goals, Memory, Attention and Decision Processes, Environmental Context and Resources, Social Influences, Emotions, and Behavioural Regulation.</td>
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In efforts to explore the reasons for the gaps in case detection and utilisation of diagnostic tests in children, and to design a contextually appropriate intervention, I chose to explore the use of validated behaviour theories. I chose the Behaviour Change Wheel (BCW), which is based on the Theoretical Domains Framework (TDF)- recognising that individual and collective behaviour change is key to implementing new practices and to improving health outcomes [56, 61, 63, 64]. One of the strengths of the BCW is that it naturally incorporates context, which is key to effective design and implementation of interventions [63]. The TDF is one of the leading models of implementation science [62] and it has been used and validated in numerous studies in health and other sectors [61, 65-78]. The TDF is derived from 33 theories and 128 key theoretical constructs related to behaviour change and was developed to simplify and make theory usable by other disciplines [61]. How it has been used in the problem of childhood TB has been explained further in subsequent sections of this thesis.

4. Objectives and Thesis Outline

Thesis Objectives
The main study aim was to describe the epidemiology of childhood TB in Kenya and use of diagnostics, to determine the proportion of eligible children admitted to hospitals who have a clinical and laboratory evaluation for TB that is consistent with existing national guidelines. This work also sought to explore the influencers of TB case detection in children and adoption of Xpert® MTB/RIF in this population to see how employing an understanding of theory linked to a contextually appropriate intervention package might help promote better TB diagnostic work up.

The specific objectives were as follows:

i) To examine National TB Programme notification data for Kenya to describe notification rates by county and the distribution and determinants of use of Xpert® MTB/RIF assay comparing adults and children over a year

ii) To systematically review existing literature to describe the relationship between tuberculosis and pneumonia in children in high burden TB countries

iii) To describe the current status of childhood TB diagnosis in Kenya in order to estimate the gaps through the following steps:

a) developing a guideline-linked paediatric TB care cascade to explore clinician TB diagnostic practices;

b) estimating the prevalence of TB diagnosis in children admitted to Kenyan hospitals using various case-definitions; and
c) exploring associations with use of TB diagnostic tests that may help explain gaps in the cascade of paediatric TB care in Kenya.

iv) To explore health workers’ perspectives of the influencers of case detection and use of TB diagnostic tests in hospitalised children in Kenya guided by behaviour change theories using an embedded case study approach

v) To integrate quantitative and qualitative data to design a contextually-appropriate, theory guided behaviour change intervention to improve case detection of TB amongst children admitted in Kenyan hospitals, describing in detail what might work, how and why

**Study design**

A convergent parallel mixed methods approach was used, integrating findings from quantitative (objectives i & iii), the systematic review (objective ii) and qualitative studies (objective iv & v) to help design an intervention to improve case detection of tuberculosis in children in Kenya and other similar settings. This is summarised in the conceptual framework in Figure 2

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**Figure 2: Conceptual framework of mixed methods used in the PhD project**
Study Sites and Data Sources

Objective 1
For objective 1, data from all patients notified to the national TB programme with treatment outcomes who started TB treatment in 2015 were used to map health facilities, TB cases, facility specific TB incidence /100,000, and linked with capacity to do TB diagnostic tests (sputum smear microscopy, Xpert MTB/RIF®, culture/line probe assay and chest x-rays). Hierarchical regression models for adults and children were run to specifically establish determinants of use of Xpert MTB/RIF®, as per Kenyan guidelines.

Objective 2
Objective 2 was a systematic review and synthesis of 14 studies of children with pneumonia in high burden TB countries.

Objective 3
For objective 3, data used were from records of all children admitted in paediatric wards of hospitals participating in the Clinical Information Network (CIN), a partnership established in 2013 between Kenya Medical Research Institute (KEMRI), Ministry of Health (MoH) Kenya, Kenya Paediatric Association (KPA) and 13 public county referral hospitals [79, 80]. The network collects standardized routine data on paediatric admissions with the aim of promoting adoption of evidence-based interventions and improving quality of care. I analysed data for all paediatric admissions to the 13 hospitals from 1st November 2015-31st October 2016, and from 1st November 2017-31st October 2018 (24 calendar months), excluding Nov 2016-Oct 2017 because Kenya went through prolonged health worker strikes, which adversely affected admissions to public hospitals [81]. The national TB guidelines were used to develop a diagnostic cascade to estimate gaps in care.

Objective 4
For Objective 4, data used were from consenting health workers from various health facilities (public, private and faith-based) attending workshops and TB sensitisation meetings, those practising in CIN hospitals as well as policy makers/stakeholders involved in paediatric TB decision making. Data collection involved semi-structured interviews; small-group discussions; key informant interviews; observations of TB trainings, sensitisation meetings, policy meetings, hospital practices; desk review of guidelines, job aides and policy documents. The case study hospitals are large county hospitals selected because they are situated in high burden TB counties and had varying childhood TB case notification rates. Their paediatricians were keen to work together to improve care of children with probable tuberculosis. These hospitals additionally had moderate to high pneumonia admissions.
**Objective 5**

Objective 5 integrated findings from all the afore mentioned studies to guide development of the behaviour change intervention.

**Thesis Outline**

*Chapter 1* gives a general introduction, context and rationale to the thesis by exploring the literature around diagnosing TB in children in general, the situation in Kenya and the need for implementation science and behaviour change theories to help address the gaps.

*Chapter 2* is a cross-sectional survey of the national TB programme notification data that aimed to describe the characteristics and spatial distribution of notified TB cases by county, noting the differences between TB in adults and children in various counties in Kenya. We also report the distribution and determinants of use of Xpert® MTB/RIF assay and other TB diagnostic tests, again comparing adults and children. This was to start describing the hidden epidemic that is TB in children in Kenya (objective 1).

*Chapter 3* is a systematic review that explored the association between tuberculosis and pneumonia in high burden TB countries, with the hypothesis that some of the childhood TB cases in high endemic settings could be masked as pneumonia, which is the leading cause of admission in children (objective 2).

*Chapter 4* is a large longitudinal observational study of routine clinical data from 13 county hospitals in a clinical network in Kenya that aimed to describe clinician TB diagnostic practices through a guideline-linked TB care cascade and to quantify the magnitude of TB as a diagnosis amongst children admitted to Kenyan hospitals (objective 3).

*Chapter 5* is an exploratory qualitative study with an embedded case study approach that describes health workers’ perspectives of the influencers of case detection and use of TB diagnostic tests in hospitalised children in Kenya guided by behaviour change theories (objective 4).

*Chapter 6* describes how findings were analysed and integrated to design a contextually appropriate and theory-informed intervention to improve case detection of TB in children in Kenyan hospitals guided by the Behaviour Change Wheel. This was to develop a clear starting perspective to design an intervention that could feasibly be adopted, evaluated and scaled-up by the National TB programme (NTP), integrating information from the quantitative and qualitative studies, review of literature and discussions with key childhood TB stakeholders (objective 5).
Chapter 7 is a policy brief, developed to give a clear and concise summary of the findings in chapter 6 in a format that is easier for lay readers to understand, with recommendations to guide decision-making around childhood TB policies.

Chapter 8 provides a general discussion that integrates findings from across the various bodies of work undertaken, including reflections, future perspectives and implications for policy and practice.

Chapter 9 provides a high-level summary of all the work done, in English and Dutch.

References


Chapter 2: Variability in distribution and use of tuberculosis diagnostic tests in Kenya: a cross-sectional survey

Jacquie Narotso Oliwa, Joseph Maina, Philip Ayieko, David Gathara, Immaculate Anne Kathure, Enos Masini, Anja H van’t Hoog, Michael Boele van Hensbroek, Mike English

Abstract

Background
Globally, 40% of all tuberculosis (TB) cases, 65% paediatric cases and 75% multi-drug resistant TB (MDR-TB) cases are missed due to underreporting and/or under diagnosis. A recent Kenyan TB prevalence survey found that a significant number of TB cases are being missed here. Understanding spatial distribution and patterns of use of TB diagnostic tests as per the guidelines could potentially help improve TB case detection by identifying diagnostic gaps.

Methods
We used 2015 Kenya National TB programme data to map TB case notification rates (CNR) in different counties, linked with their capacity to perform diagnostic tests (chest x-rays, smear microscopy, Xpert MTB/RIF®, culture and line probe assay). We then ran hierarchical regression models for adults and children to specifically establish determinants of use of Xpert® (as per Kenyan guidelines) with county and facility as random effects.

Findings
In 2015, 82,313 TB cases were notified and 7.8% were children. The median CNR/100,000 amongst 0-14yr olds was 37.2 (IQR 20.6, 41.0) and 267.4 (IQR 202.6, 338.1) for ≥15yr olds respectively. 4.8% of child TB cases and 12.2% of adult TB cases had an Xpert® test done, with gaps in guideline adherence.

There were 2,072 microscopy sites (mean microscopy density 4.46/100,000); 129 Xpert® sites (mean 0.31/100,000); two TB culture laboratories and 304 chest X-ray facilities (mean 0.74/100,000) with variability in spatial distribution across the 47 counties. Retreatment cases (i.e. failures, relapses/recurrences, defaulters) had the highest odds of getting an Xpert® test compared to new/transfer-in patients (AOR 7.81, 95% CI 7.33-8.33). Children had reduced odds of getting an Xpert® (AOR 0.41, CI 0.36-0.47). HIV-positive individuals had nearly twice the odds of getting an Xpert® test (AOR 1.82, CI 1.73-1.92). Private sector and higher-level hospitals had a tendency towards lower odds of use of Xpert®.

Conclusions
We noted under-use and gaps in guideline adherence for Xpert® especially in children. The under-use despite considerable investment undermines cost-effectiveness of Xpert®. Further research is needed to develop strategies enhancing use of diagnostics, including innovations to improve access (e.g. specimen referral) and overcoming local barriers to adoption of guidelines and technologies.

Keywords: Tuberculosis, diagnostics, tests, distribution, use, adults, children
Background

Globally, there is a significant TB case detection gap: 40% of all tuberculosis (TB) cases, 65% paediatric cases and 75% multi-drug resistant TB (MDR-TB) cases are missed due to a mixture of underreporting and under diagnosis [1-3]. Rapid and accurate diagnosis of TB is critical for timely initiation of treatment to prevent death [4-6]. A recent prevalence survey in Kenya found higher rates of TB than previously thought (558/100,000), with up to 55% of cases being missed probably due to under-detection [7]. Three quarters of the positive TB cases identified in the survey reported seeking care for TB-like symptoms but were not diagnosed. The survey recruited ≥15yr olds, but extrapolation from adult data showed that two thirds of paediatric TB cases were missed [7]. Notification data may underestimate child TB incidence, which may be explained in part by poor reporting of diagnosed paediatric cases [8]; and challenges of diagnosing TB in children due to paucibacillary disease and difficulty obtaining suitable samples [9, 10].

Quicker, more sensitive TB diagnostic technologies are being introduced globally [4, 11]. In 2010, Xpert MTB/RIF® was initially endorsed by the World Health Organisation (WHO) for children, the HIV infected and suspected MDR-TB cases [12], but is now recommended as the first line diagnostic test for all presumed TB cases [13, 14]. Kenya introduced Xpert® in 2011. According to the guidelines used in Kenya in 2015 (when this study was done), all presumptive paediatric, HIV-infected smear negative, drug resistant (DR) cases, or retreatment cases i.e. relapse (recurrence)/defaults/treatment failures should have had at least one Xpert® assay as part of their diagnostic work up (Additional File 1) [15, 16]. By 2015, there were 129 machines distributed throughout the country (146 machines to date), with more expected [17]. Optimal use of Xpert® is important for TB case detection [18, 19]. Few studies have specifically reviewed spatial distribution and practices in the utilisation of bacteriological TB diagnostic tests like Xpert® comparing adults and children, in countries that carry a high TB/MDR burden like Kenya.

A multi-country study on gaps in reporting paediatric TB found children were rarely considered for testing [20]. Age, gender, poverty and literacy are known to influence general health care utilisation and demand for services [21, 22]. One study found socioeconomic status and prior anti-TB treatment were strong determinants of utilisation of bacteriological tests [23]. Behavioural or health system issues may also play a role where services are available but underutilised- perhaps due to patients’ lack of awareness or perceived poor quality [22, 24-26].

Seeking to understand and improve TB case detection in Kenya, we set out to: describe the characteristics and spatial distribution of TB cases reported to the TB programme; the availability, distribution and patterns of use of TB diagnostic tests as per Kenyan guidelines [15, 16]; and to
establish the determinants of use of Xpert®, noting differences in adults and children in the various counties. To the best of our knowledge, this is the first attempt to describe in detail the utilisation of TB diagnostics in Kenya, comparing adults and children to try to unmask the “hidden epidemic” of TB [27]. Findings will hopefully help guide policy makers on where the greatest needs are, how well guidelines are being implemented and offer suggestions to mitigate gaps identified. As new tests emerge [28], understanding patterns and determinants of use could help reduce TB deaths by guiding early diagnosis and linkage to appropriate treatment.

Methods

Setting

Kenya is administratively divided into 47 counties, that are now largely responsible for health care since devolution in 2013 [29]. Health services are provided by public, private, non-profit non-governmental organisations (NGO) and faith based organisations (FBO). The healthcare system is structured in a hierarchical manner, starting with primary healthcare in the community and complicated cases referred upwards to secondary and tertiary levels of healthcare [29]. According to the Kenyan Master Facility List, there are approximately 10,000 health facilities in the country and just about half are TB treatment sites [30-32]. For this analysis, we aggregated TB health facilities into two: lower level (dispensaries, health centres, and maternity/nursing homes) for primary care; and higher level (county hospitals and national referral facilities) that provide secondary and tertiary referral services.

Study Population

We included patients of all ages who were notified to the Kenya National TB programme and started TB treatment in 2015.

Study variables

We wished to explore the possible influence on use of Xpert MTB/RIF® of variables in three hierarchical levels: county, health facility and individual. Individual level co-variates included: age; gender; HIV status; nutritional status; and type of TB patient i.e. new/transfer-in or retreatment cases (relapse/defaults/treatment failures). An age cut-off of 15yrs for children is used locally and internationally for TB programming [14], therefore “child” here refers to 0-14yr olds. For nutrition status, weight-for-age Z (WAZ) scores were computed for those aged 0-23yr and body mass index (BMI) truncated at -5 to +5SD for those ≥10yr, and patients classified as underweight according to the scores. Those 10-23yr who met criteria of underweight by either criterion were also classified as underweight. Health facility level co-variates included: sector of care (public, private, or FBOs), level
of care provided (higher vs lower level) and whether they were an Xpert® site or not. County level co-
variates included: poverty; maternal education levels; travel time to nearest health facilities; and
availability of Xpert® facilities per 100,000. All co-variates were determined for each of the 47 counties
for 2015. These factors were decided upon a priori following review of literature on drivers of use of
TB and health care services in general and data availability [21, 22].

The primary outcome of interest was evidence of Xpert® being done in patients who had been started
on TB treatment. According to the 2015 Kenyan guidelines, all presumptive paediatric, HIV-infected
smear negative, drug resistant (DR) cases, or retreatment cases i.e. relapse (recurrence)/defaults/treatment failures should have had at least one Xpert® assay as part of their
diagnostic work up (Additional File 1) [15, 16].

Data sources
We considered the best data sources for the three levels of variables of interest. For the individual
level, de-identified data from the Kenya National TB Programme patients’ treatment register for 2015
were used (patients who were notified and/or started treatment in 2015). TB case definitions were as
per Guidance for National TB programmes (Additional File 1) [33]. Health facility level data were from
the Kenya Master Health Facility list [30] and Kenya Services Availability and Readiness Assessment
Mapping Report (SARAM) 2014 [34]. Health facilities in the national TB register were geocoded using
KEMRI-Wellcome Trust’s Kenya Health Facilities Database, which was last updated in 2016 using online
digital place-name gazetteers and Global Positioning System (GPS) sources. County level data were
from each county governments’ integrated development plans for 2015 [35]. The projected 2015
Kenya gridded population distribution surface at 100m spatial resolution was obtained from the
WorldPop project [36, 37].

Statistical and Spatial Analysis
Stata version 15MP (StataCorp.2017, College Station, TX, USA) and ArcGIS 10.5 (ESRI, Redlands, CA,
USA) were used for statistical analysis, and mapping and spatial analysis respectively. We described
the proportion of adults and children reported to the TB programme, their socio-demographic
characteristics, use of TB diagnostic tests and outcomes. We used the 2015 Kenya National TB
programme data to construct maps for each TB case notification rate (CNR) in different counties and
linked this with their capacity to perform diagnostic tests (chest x-rays, smear microscopy, Xpert®,
culture and line probe assay) from the SARAM report [34].

For adherence to guidelines, we only had data for those who had tests done, and used these patients
to describe patterns of use of TB diagnostic tests. Co-variates of theoretical and/or statistical
significance were used to build hierarchical logistic regression models to establish determinants of use of Xpert® in adults and children. Possible collinearity was assessed using the variance inflation factor (VIF). Variables with VIF less than 10 were considered for analysis. The models converged at five integration points for complete case analysis, with county and health facility as random effects [38]. Models were built for the 0-14yrs and ≥15yrs separately and a model for the total population, with likelihood ratio tests, exploration for interactions in pre-specified covariates (HIV and nutrition status) and quantile-quantile plots of residuals used to determine best fit as seen in Additional File 5 [38, 39].

**Results**

Data were available from 82,313 patients who started TB treatment in 2015. Table 1 gives the characteristics of these patients for the different age bands and overall population. There were 6,450 children aged 0-14yr, and they represented 7.8% of the total population. In the overall population, 62.4% (51,337) were male, and they were 3,406 (52.8%) in the 0-14yr group. Most of the patients were from the public sector. TB was pulmonary in approximately three quarters of all the patients. A quarter of patients 0-14yrs were HIV infected compared with a third of those ≥15yrs. Overall, close to half the patients were underweight. Close to 10% of those ≥15yrs needed TB retreatment (i.e. failures, relapses/recurrences, defaulters). Less than 5% (309/6,450) of patients 0-14yrs and 12.2% (9,224/75,863) of patients ≥15yrs had an Xpert® done. The proportion of positive Xpert® tests was 63.1% (195/309) for the 0-14yr and 81.2% (7,493/9,224) for the ≥15yrs old; while microscopy was positive in 36.7% (694/1,886) vs 67.1% (40,768/60,797) for 0-14yrs vs the ≥15yrs respectively. Overall case fatality was between 4-6% for both groups.
<table>
<thead>
<tr>
<th></th>
<th>0-14yrs, n (%)</th>
<th>≥15yrs, n (%)</th>
<th>Overall population, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(N = 6450)</td>
<td>(N = 75863)</td>
<td>(N = 82313)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3406 (52.8)</td>
<td>47931 (63.2)</td>
<td>51337 (62.4)</td>
</tr>
<tr>
<td>Female</td>
<td>3044 (47.2)</td>
<td>27932 (36.8)</td>
<td>30976 (37.6)</td>
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<td><strong>Sector</strong></td>
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<td>4938 (76.6)</td>
<td>59165 (78.0)</td>
<td>64103 (77.9)</td>
</tr>
<tr>
<td>Prisons</td>
<td>41 (0.6)</td>
<td>1349 (1.8)</td>
<td>1390 (1.7)</td>
</tr>
<tr>
<td>Private</td>
<td>1343 (20.8)</td>
<td>14010 (18.5)</td>
<td>15353 (18.7)</td>
</tr>
<tr>
<td>Faith based and others</td>
<td>128 (2.0)</td>
<td>1339 (1.8)</td>
<td>1467 (1.8)</td>
</tr>
<tr>
<td><strong>TB Type</strong></td>
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<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>4774 (74.0)</td>
<td>62964 (83.0)</td>
<td>67738 (82.3)</td>
</tr>
<tr>
<td>Extra-pulmonary</td>
<td>1676 (26.0)</td>
<td>12899 (17.0)</td>
<td>14575 (17.7)</td>
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<tr>
<td><strong>HIV testing</strong></td>
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<td></td>
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<tr>
<td>Negative</td>
<td>4517 (70.0)</td>
<td>49016 (64.6)</td>
<td>53533 (65.0)</td>
</tr>
<tr>
<td>Positive</td>
<td>1610 (25.0)</td>
<td>24980 (32.9)</td>
<td>26590 (32.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>323 (5.0)</td>
<td>1867 (2.5)</td>
<td>2190 (2.7)</td>
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<tr>
<td><strong>Anthropometry (BMI)</strong></td>
<td></td>
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<td></td>
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<td>Underweight*</td>
<td>2951 (45.8)</td>
<td>35274 (46.5)</td>
<td>38225 (46.4)</td>
</tr>
<tr>
<td>Normal</td>
<td>2777 (43.1)</td>
<td>31338 (41.3)</td>
<td>34115 (41.5)</td>
</tr>
<tr>
<td>Overweight/obese</td>
<td>22 (0.34)</td>
<td>2929 (3.9)</td>
<td>2951 (3.4)</td>
</tr>
<tr>
<td>Undocumented</td>
<td>700 (10.9)</td>
<td>6322 (8.3)</td>
<td>7022 (8.5)</td>
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<td><strong>Type of patient</strong></td>
<td></td>
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<tr>
<td>New</td>
<td>6233 (96.6)</td>
<td>68470 (90.3)</td>
<td>74703 (90.8)</td>
</tr>
<tr>
<td>Transfer in</td>
<td>40 (0.6)</td>
<td>788 (1.0)</td>
<td>828 (1.0)</td>
</tr>
<tr>
<td>Relapse (recurrence)</td>
<td>144 (2.2)</td>
<td>5383 (7.1)</td>
<td>5527 (6.7)</td>
</tr>
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<td>Default</td>
<td>33 (0.5)</td>
<td>999 (1.3)</td>
<td>1032 (1.3)</td>
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<td>Failure</td>
<td>0 (0)</td>
<td>223 (0.3)</td>
<td>223 (0.3)</td>
</tr>
<tr>
<td><strong>Chest-X-ray</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Done</td>
<td>3140 (48.7)</td>
<td>22141 (29.2)</td>
<td>25281 (30.7)</td>
</tr>
<tr>
<td>Not done</td>
<td>3310 (51.3)</td>
<td>53722 (70.8)</td>
<td>57032 (69.3)</td>
</tr>
<tr>
<td><strong>Smear Microscopy</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Done</td>
<td>1886 (29.2)</td>
<td>60797 (80.1)</td>
<td>62,683 (76.2)</td>
</tr>
<tr>
<td>Positive**</td>
<td>694 (36.7)</td>
<td>40768 (67.1)</td>
<td>41462 (66.1)</td>
</tr>
<tr>
<td>Negative**</td>
<td>1192 (63.2)</td>
<td>20029 (32.9)</td>
<td>21221 (33.9)</td>
</tr>
<tr>
<td><strong>Xpert MTB/RIF®</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Done</td>
<td>309 (4.8)</td>
<td>9224 (12.2)</td>
<td>9533 (11.6)</td>
</tr>
<tr>
<td>Positive (Rif-Sensitive)</td>
<td>195 (63.1)</td>
<td>7493 (81.2)</td>
<td>7688 (80.6)</td>
</tr>
<tr>
<td>Positive (Rif-Resistant)**</td>
<td>1 (0.3)</td>
<td>129 (1.4)</td>
<td>130 (1.4)</td>
</tr>
<tr>
<td>Negative**</td>
<td>113 (36.6)</td>
<td>1602 (17.4)</td>
<td>1715 (18.0)</td>
</tr>
<tr>
<td><strong>Culture/Line Probe Assay (LPA)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Done</td>
<td>5 (0.1)</td>
<td>444 (0.6)</td>
<td>449 (0.5)</td>
</tr>
<tr>
<td>Drug susceptible**</td>
<td>5 (100)</td>
<td>371 (83.6)</td>
<td>376 (83.7)</td>
</tr>
<tr>
<td>Drug resistant **</td>
<td>0 (0.0)</td>
<td>73 (16.4)</td>
<td>73 (16.3)</td>
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<tr>
<td><strong>Outcome</strong></td>
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<tr>
<td>Cured</td>
<td>537 (8.3)</td>
<td>31416 (41.4)</td>
<td>31953 (38.8)</td>
</tr>
<tr>
<td>Died</td>
<td>270 (4.2)</td>
<td>4391 (5.8)</td>
<td>4661 (5.7)</td>
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<tr>
<td>Treatment failure</td>
<td>1 (0.02)</td>
<td>429 (0.6)</td>
<td>430 (0.5)</td>
</tr>
<tr>
<td>Other***</td>
<td>5642 (87.5)</td>
<td>39627 (52.2)</td>
<td>45269 (55%)</td>
</tr>
</tbody>
</table>

*Underweight defined as either WAZ <-2SD or BMI<18.5 as appropriate for age
** Percentage in brackets represent proportions amongst those who got the test done
***Other included: treatment not completed; completed but not cured; defaulted; transferred out
Patterns of use of TB diagnostics tests

Figure 1 illustrates diagnostic practices amongst those patients who were started on anti-TB treatment. More than a third of children 0-14yr had no diagnostic test done, and were started on treatment based on clinical diagnosis only. Chest X-ray was the commonly used test in this age group (37.1%); while microscopy was the commonest amongst the ≥15yrs. Table 2 illustrates the patterns of use of bacteriological tests amongst those who had these tests done, relating them to the 2015 Kenyan guidelines (Additional File 1). Children 0-14yr represented <5% of those who had either Xpert® or Microscopy or Culture/LPA done. Those with extra-pulmonary TB also rarely got any of the tests done. Retreatment cases got a culture/LPA done more than any other test. Forty one percent of the patients got Xpert® as per guidelines, with better guideline adherence for culture/LPA (61.2%) and microscopy (97.8%), respectively.

Figure 1 Diagnostic practices amongst patients started on TB treatment in 2015
Table 3 Patterns of use of TB diagnostics and compared to recommended Kenyan TB guidelines in use in 2015

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Xpert® done*</th>
<th>Microscopy done**</th>
<th>Culture/LPA done***</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 9,553</td>
<td>N= 62,683</td>
<td>N = 515</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
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<tr>
<td>0-14yr</td>
<td>309 (3.2)</td>
<td>1886 (3.0)</td>
<td>5 (1.0)</td>
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<td>≥15yr</td>
<td>9224 (96.8)</td>
<td>60797 (97.0)</td>
<td>510 (99.0)</td>
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<tr>
<td><strong>Gender</strong></td>
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</tr>
<tr>
<td>Male</td>
<td>6152 (64.5)</td>
<td>40128 (64.0)</td>
<td>385 (74.8)</td>
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<td><strong>Type of TB</strong></td>
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<tr>
<td>Pulmonary</td>
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<td>61320 (97.8)</td>
<td>508 (98.6)</td>
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<td>Extrapulmonary</td>
<td>328 (3.4)</td>
<td>1363 (2.2)</td>
<td>7 (1.4)</td>
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<td><strong>Type of patient</strong></td>
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</tr>
<tr>
<td>New/transfer in</td>
<td>6774 (71.1)</td>
<td>56821 (90.7)</td>
<td>200 (38.8)</td>
</tr>
<tr>
<td>Retreatment</td>
<td>2759 (28.9)</td>
<td>5862 (9.3)</td>
<td>315 (61.2)</td>
</tr>
<tr>
<td><strong>Test done as per guideline</strong></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
| Excerpt from 2015 Kenyan guidelines: | * Xpert® recommended for all presumptive paediatric TB OR HIV-infected smear negative OR drug resistant cases OR retreatment cases i.e. relapse/defaults/treatment failures in adults OR suspected drug resistant TB
**Microscopy recommended for all pulmonary tuberculosis
*** Culture/LPA recommended for retreatment cases (i.e. relapse/defaults/treatment failures) regardless of age

Tuberculosis Case Notification Rates and distribution of TB cases in Kenya

Figures 2 and 3 and Additional files 3 and 4 show case notification rates (CNR) by age group and county, as well as variation in county use of Xpert® and microscopy. Median age was 32yr (IQR 24yr, 43yr). The highest CNR was amongst those 35-44yrs (455/100,000), and the lowest amongst the 5-9yrs (27/100,000)-Figure 2. The median CNR/100,000 amongst children 0-14yr old was 37.2 (IQR 20.6, 41.0) and 267.4 (IQR 202.6, 338.1) for ≥15yr olds respectively. Median use of Xpert® among 0-14yr olds was 1.45/100,000 (IQR 0.7, 2.1) and in ≥15yr olds was 29.9/100,000 (IQR 21.0, 42.8). Median use of microscopy among 0-14yr olds was 8.1/100,000 (IQR 6.6, 12.8) and 222/100,000 (IQR 169.8, 270.4) in ≥15yr olds. Xpert® use did not correlate with increase in county TB CNR/100,000 (Figure 3 and Additional File 4) and in this was also observed in the univariate analysis where counties with higher Xpert® density did not have significantly higher CNRs (Additional File 2). Microscopy use in the ≥15yr tended to be higher in counties with highest CNRs (Figure 3 and Additional File 4).
Figure 2 TB Case Notification Rates (CNRs) for different age group bands in Kenya

Figure 3 Chart showing variability of County TB CNRs and use of Xpert® and Microscopy per 100,000 population comparing adults and children (Full county names and variables in Appendix 3)
Figure 4 shows a panel of maps illustrating spatial distribution of TB patients in Kenya. The counties with two large cities had some of the highest CNRs, as did two counties serving the pastoralist communities of the northern and eastern frontiers (panel A). Panel B and C show the CNRs in the ≥15yr olds ("Adults") and in children 0-14yr old respectively, while D shows the ratio of adult to child TB cases. These maps highlight some of the adult hot spots with low child CNRs and ensuing differences in adult: child ratios highlighting the gaps in case detection for children.

Figure 4 Maps illustrating the spatial distribution of TB patients in various counties in Kenya by: Overall population CNR/100,000 (A); CNR/100,000 in "adults" i.e. ≥15yrs (B); CNR/100,000 in children 0-14yrs (C); and ratio of adult: child TB CNRs (D)
Figure 5 and Additional File 5 show the distribution of facilities with TB diagnostic facilities (Microscopy-Map A; Xpert MTB/RIF®-Map B; Culture and Line Probe Assay- Map C; and chest X Ray-Map D) overlaid with each county’s total population density. In 2015, there were 129 facilities providing Xpert® services (mean Xpert® density of 0.28/100,000); 304 chest X ray facilities (mean density 0.67/100,000); and 2,072 facilities with microscopy services (mean density 4.54/100,000). There were disparities noted in the distribution of Xpert® (panel B) and chest X-ray (panel D) facilities with some northern and eastern counties of Kenya having low facility densities/100,000 yet they carry a high burden of TB cases (Figure 4).

Figure 5 Maps illustrating the distribution of facilities with TB diagnostic facilities by: Microscopy (A); Xpert MTB/RIF® (B); Culture and Line Probe Assay Labs (C); and Chest X-ray (D), all overlaying each county’s population density in 2015 as the background.
Determinants of use bacteriological TB diagnostic tests comparing adults and children

Additional File 5 shows the univariate analysis of the factors that had been considered for the model building, and Table 3 shows the final adjusted hierarchical models of determinants of use of Xpert® in adults and children, with county and health facility as random effects. Amongst individual level factors, the retreatment cases (i.e. failures, relapses/recurrences, defaulters) had the highest odds of getting an Xpert® (total population AOR 7.81, 95% CI 7.33 to 8.33). From the model of the total population, children had reduced odds of getting an Xpert® test (AOR 0.41, CI 0.36 to 0.47), while being male was associated with increased odds in all age groups. Overall, the HIV positive individuals had nearly twice the odds of getting an Xpert® compared to the HIV negative. Nutrition status had a marginal effect, except in the 0-14yr olds where the underweight group had nearly twice the odds of getting an Xpert® compared with the well-nourished cases.

Examining factors at the facility and county levels, patients in private sector and from higher level facilities had a tendency towards lower odds of getting tested compared with those in public sector or lower level facilities, but this difference was not statistically significant for the 0-14yrs old. We also noted that counties with higher Xpert® density did not report significantly higher CNRs. From the intra-class correlation coefficients (ICC), county as a level explained approximately 4 & 7% and health facility 24 & 26% of the observed variability in each adjusted model.
Table 4 Determinants of use Xpert/MTB/RIF® in Kenya

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0-14yrs</th>
<th>≥15yrs</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Xpert® done</td>
<td>Xpert® done</td>
<td>0-14yrs adjusted OR (95% CI)</td>
<td>≥15yrs adjusted OR (95% CI)</td>
<td>Overall adjusted OR (95% CI)</td>
</tr>
<tr>
<td>N=309</td>
<td>n (column %)</td>
<td>n=9,224</td>
<td>N=6,450</td>
<td>N=75,845</td>
<td>N=82,295</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>140 (45.3)</td>
<td>3241 (35.1)</td>
<td>1 (base)</td>
<td>1 (base)</td>
<td>1 (base)</td>
</tr>
<tr>
<td>Male</td>
<td>169 (54.7)</td>
<td>5983 (64.9)</td>
<td>1.13 (0.88 to 1.45)</td>
<td>1.09 (1.03 to 1.14)</td>
<td>1.09 (1.03 to 1.14)</td>
</tr>
<tr>
<td><strong>HIV Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>164 (53.1)</td>
<td>4751 (51.5)</td>
<td>1 (base)</td>
<td>1 (base)</td>
<td>1 (base)</td>
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<tr>
<td>Positive</td>
<td>143 (46.3)</td>
<td>4372 (47.4)</td>
<td>2.00 (1.52 to 2.61)</td>
<td>1.83 (1.74 to 1.93)</td>
<td>1.82 (1.73 to 1.92)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (0.7)</td>
<td>101 (1.1)</td>
<td>0.19 (0.05 to 0.78)</td>
<td>0.81 (0.65 to 1.01)</td>
<td>0.76 (0.61 to 0.94)</td>
</tr>
<tr>
<td><strong>Nutrition Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>40 (12.9)</td>
<td>3379 (36.6)</td>
<td>1 (base)</td>
<td>1 (base)</td>
<td>1 (base)</td>
</tr>
<tr>
<td>Underweight</td>
<td>238 (77.0)</td>
<td>5132 (55.6)</td>
<td>1.97 (1.36 to 2.83)</td>
<td>1.13 (1.07 to 1.19)</td>
<td>1.15 (1.09 to 1.21)</td>
</tr>
<tr>
<td>Overweight/obese</td>
<td>3 (1.0)</td>
<td>360 (3.9)</td>
<td>0.94 (0.26 to 3.36)</td>
<td>0.88 (0.77 to 0.99)</td>
<td>0.88 (0.78 to 1.00)</td>
</tr>
<tr>
<td>Unknown</td>
<td>28 (9.1)</td>
<td>353 (3.8)</td>
<td>1.34 (0.79 to 2.27)</td>
<td>0.64 (0.56 to 0.73)</td>
<td>0.67 (0.59 to 0.76)</td>
</tr>
<tr>
<td><strong>Type of patient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New patient/transfer in</td>
<td>277 (89.6)</td>
<td>6497 (70.4)</td>
<td>4.19 (2.60 to 6.75)</td>
<td>7.97 (7.47 to 8.50)</td>
<td>7.81 (7.33 to 8.33)</td>
</tr>
<tr>
<td>Relapse/Default/Failure</td>
<td>32 (10.4)</td>
<td>2727 (29.6)</td>
<td>1.17 (0.74 to 1.85)</td>
<td>2.30 (1.86 to 2.82)</td>
<td>2.23 (1.82 to 2.74)</td>
</tr>
<tr>
<td><strong>Sector</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>242 (73.8)</td>
<td>7692 (83.4)</td>
<td>1 (base)</td>
<td>1 (base)</td>
<td>1 (base)</td>
</tr>
<tr>
<td>Private</td>
<td>62 (20.1)</td>
<td>1373 (14.9)</td>
<td>0.93 (0.63 to 1.37)</td>
<td>0.85 (0.75 to 0.97)</td>
<td>0.85 (0.75 to 0.97)</td>
</tr>
<tr>
<td>FBOs*</td>
<td>5 (1.6)</td>
<td>159 (1.7)</td>
<td>0.62 (0.19 to 2.11)</td>
<td>0.99 (0.67 to 1.46)</td>
<td>0.99 (0.68 to 1.45)</td>
</tr>
<tr>
<td><strong>Health Facility Level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower level**</td>
<td>174 (56.3)</td>
<td>5737 (62.2)</td>
<td>1 (base)</td>
<td>1 (base)</td>
<td>1 (base)</td>
</tr>
<tr>
<td>Higher level***</td>
<td>120 (38.8)</td>
<td>3165 (34.3)</td>
<td>1.18 (0.80 to 1.74)</td>
<td>0.91 (0.79 to 1.05)</td>
<td>0.91 (0.79 to 1.06)</td>
</tr>
<tr>
<td>Unknown</td>
<td>15 (4.9)</td>
<td>322 (3.5)</td>
<td>1.99 (1.01 to 3.92)</td>
<td>1.01 (0.82 to 1.26)</td>
<td>1.04 (0.84 to 1.28)</td>
</tr>
<tr>
<td><strong>Patient from an Xpert® site</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Not from Xpert® site</td>
<td>228 (73.8)</td>
<td>6778 (73.5)</td>
<td>1 (base)</td>
<td>1 (base)</td>
<td>1 (base)</td>
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<tr>
<td>From Xpert® site</td>
<td>81 (26.2)</td>
<td>2446 (26.5)</td>
<td>1.17 (0.74 to 1.85)</td>
<td>2.30 (1.86 to 2.82)</td>
<td>2.23 (1.82 to 2.74)</td>
</tr>
<tr>
<td><strong>County Poverty Levels (from poorest to richest)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quartile 1</td>
<td>53 (17.2)</td>
<td>1839 (19.9)</td>
<td>1 (base)</td>
<td>1 (base)</td>
<td>1 (base)</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>78 (25.2)</td>
<td>2875 (31.2)</td>
<td>0.85 (0.39 to 1.86)</td>
<td>1.22 (0.60 to 2.48)</td>
<td>1.19 (0.60 to 2.37)</td>
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<tr>
<td>Quartile 3</td>
<td>103 (33.3)</td>
<td>2802 (30.4)</td>
<td>1.04 (0.48 to 2.26)</td>
<td>1.34 (0.66 to 2.74)</td>
<td>1.32 (0.66 to 2.62)</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>75 (24.3)</td>
<td>1708 (18.5)</td>
<td>0.54 (0.25 to 1.18)</td>
<td>0.64 (0.32 to 1.27)</td>
<td>0.62 (0.32 to 1.21)</td>
</tr>
<tr>
<td><strong>Intra-class correlation coefficients (ICC)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>County</td>
<td>0.04 (0.02 to 0.11)</td>
<td>0.07 (0.04 to 0.11)</td>
<td>0.07 (0.04 to 0.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health facility</td>
<td>0.26 (0.18 to 0.37)</td>
<td>0.24 (0.21 to 0.27)</td>
<td>0.24 (0.21 to 0.27)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*FBOs= Faith Based Organisations **Primary referral facilities *** Secondary and tertiary referral facilities
Discussion

We set out to describe the spatial distribution of TB patients and TB diagnostic services, and patterns of use of TB diagnostic tests in Kenya as per the guidelines (with emphasis on Xpert MTB/RIF®), noting differences in children and adults. The TB case notification rate (CNR) in children 0-14yrs was nearly eight times less than that of those ≥15yrs, which may imply under detection. Children are thought to represent 10-20% of the total reported TB cases in high TB endemic settings like Kenya, but we observed only 7.8% in our data [40, 41]. Low CNR among children could additionally be explained by underreporting due to difficulties in confirming a diagnosis of TB in them and poor surveillance [2].

We observed wide county variation in distribution and use of TB diagnostic tests, as well as in case notification rates. Some of the northern and eastern counties had high TB CNRs, but a lower density/100,000 of facilities equipped with TB diagnostic services. Conversely, some counties had higher facility densities but reported lower rates of use. Kenya’s health system has been affected by devolution and decentralisation of health services, and this could be having a bearing on TB care [42]. A recently published patient pathway analysis in Kenya found distinct variation in diagnostic and treatment availability across counties and facility levels [32].

To comply with existing guidelines at the time, all presumed child TB cases, HIV infected adults and suspected MDR-TB cases and retreatment cases should have had at least an Xpert® done as part of the diagnostic work up [15, 16]. We noted underutilisation, with less than 5% of patients 0-14yrs and 12.2% of patients ≥15yrs having an Xpert MTB/RIF® test done, with gaps in guideline adherence. Many children, however, had smear microscopy done, on a specimen that presumably could have been used for Xpert®. The assay has much better sensitivity than smear microscopy and can identify rifampicin resistance with much faster turn-around time than traditional culture, and has been shown to be cost effective [43-46]. The Kenya prevalence survey found that when microscopy was used alone, up to 50% of TB cases were being missed, while Xpert MTB/RIF® detected 78% of TB cases [7]. While use of Xpert® is encouraged as the more sensitive test, it still misses approximately 22% of TB cases, and a negative Xpert®, especially in children does not rule out TB [43, 44]. However, if health workers can get sputum for microscopy especially in children, then they should ideally be able to send the sample for Xpert®, the recommended first-line test.

From the regression analysis, retreatment cases (i.e. failures, relapses/recurrences, defaulters) had the greatest odds of getting an Xpert® as expected from the guidelines, as did those who were HIV infected after adjusting for other covariates. Children had reduced odds of getting tested, despite the recommendation that all should have had an Xpert®. There is, however, no documentation of failed attempts to test.
Low utilisation of Xpert® has been illustrated in other low income, high TB burden countries both in adults and children [47-49]. From surveys of implementation in high TB burden countries including Kenya, reasons associated with low utilisation included operational issues like power outages and poor specimen referral; doubts about impact to TB morbidity and mortality; preference to trust clinical acumen; low sensitivity especially in children; challenges in getting good specimens and false negatives; and lack of awareness amongst health care workers and patients [45, 48, 50]. In Kenya, Xpert® sensitisation was initially done for lab staff only, which could have led to less demand for the test from clinicians. Some studies identified that training, workload, administrative support, staff motivation, role models and participation in the guideline development influence the implementation of TB guidelines in general [51-53].

Patients from higher level facilities had a tendency towards reduced odds of getting an Xpert® done. This could be because they get patients already being worked up from lower level facilities being referred to them to manage complications. The Kenya TB patient pathway analysis paper found that 58% of patients sought care in lower level facilities [32]. The Kenya SARAM report found only 60% of Kenya’s health facilities were ready to provide Kenya Essential Package for Health-defined TB services [34]. Readiness was found to be highest at the primary care facilities and in public facilities [34]. This is unlike in more well-resourced low TB burden countries, where TB care is at tertiary level facilities, and most patients have access to molecular diagnostic tests [54]. Private sector patients also had a tendency toward reduced odds of getting tested compared to public sector patients. This could be explained by private practice patients having to pay for tests to be done, and physicians may fail to comply with national guidelines, as seen in other settings [55-57].

Limitations

These data are from notification data which may be incomplete because an unknown number of cases may be treated but not reported. We additionally had no information on those in whom a test was done and not documented, or in whom a test was attempted but failed. A large proportion of relevant cases probably had no record of a test being done and no indication of why a test was not done.

This work, however, still provides much needed insights about the utilisation of diagnostic tests amongst those accessing health care who have been diagnosed and started on TB treatment. It also contrasts with the prevalence survey, where up to 40% of TB cases were missed and, thus, got no TB diagnostic tests. The guidelines recommend that all patients should have a bacteriological test prior to treatment. We evaluated, with the information available, how well the guidelines were being followed.
Our complete case analysis dropped approximately 3% of the cases due to missing data on facility, but this did not reduce our ability to make meaningful inferences. We also considered all the 0-14yrs old as a single group but there may be differences in the sub categories. Because the numbers of children were low, subgroup analysis could have been misleading. This analysis together with the prevalence survey still provide deep insights into the known TB cases and guideline adherence, which can aid in planning services to improve TB case detection, especially in children.

Conclusions
Underuse of Xpert® despite wide scale roll out and considerable investments undermines assertions of the cost-effectiveness of this technology. There is need to increase use of Xpert®, to ensure the correct patients are targeted for lengthy and potentially toxic TB treatment, and so that its potential advantages are realised and investments justified. Current focus on increasing access to Xpert® is insufficient and more attention needs to be given to service delivery models that involve and educate staff and that address potential challenges of patient and specimen referral, with consideration needed for the private sector. Further research can support such efforts by identifying barriers and testing strategies to overcome these.

List of Abbreviations
AOR: Adjusted Odds Ratios
BMI: Body Mass Index
CNR: Case Notification rate
DR: Drug-resistant
FBO: Faith-Based Organisations
HIV: Human Immune-deficiency Virus
IQR: Inter Quartile Ratio
LPA: Line Probe Assay
MDR-TB: Multidrug resistance Tuberculosis
NGO: Non-Governmental Organisations
SARAM: Services Availability and Readiness Assessment Mapping Report
TB: Tuberculosis
VIF: Variance Inflation Factor
WHO: World Health Organisation
WAZ: Weight-for-Age-Z score
Xpert®: Xpert MTB/RIF®
Declarations

Ethical considerations
Permission to analyse de-identified National TB programme data as part of a larger body of work to improve case detection for TB was granted by the KEMRI Scientific and Ethics Review Unit Committee (approval reference KEMRI/SERU/CGMR-C/076/3417) and the National TB programme.

Consent for publication
Not applicable

Authors' Contributions
All authors contributed to conception and design; JNO, JM, IAK and EM were responsible for acquisition of the data; JNO conducted the analysis with additional support from JM, DG and PA. IAK, EM, AVH, MBVH and ME reviewed and approved the interpretation of data. JNO drafted the manuscript and all the other authors were involved in revising it critically for important intellectual content and gave final approval of the version to be published.

Availability of Data and Materials
The datasets used and analysed for this study are stored in the KWTRP Research Data Repository, https://dataverse.harvard.edu/dataverse/kwtrp, and can be made available via written request to the corresponding author and to the National TB Programme, Ministry of Health, Kenya.

Competing interests
The authors declare that they have no competing interests.

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Acknowledgements
The authors acknowledge Dr Kadondi Kasera, Martin Githiomi and Dr Kamene Kimenye of the Ministry of Health/National TB Programme for providing data and technical support; Kasia Stepniewska for statistical support; Professor Bob Snow and the Population Health Group of KEMRI-Wellcome Trust for providing health facility geo-codes, county population level data and supporting spatial analysis; and Dr Ben Marais for reading the final manuscript and giving meaningful insights.
References


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Additional Files

Additional File 1: Guidelines and TB Case Definitions

Kenya Adult and Paediatric TB diagnostic algorithms in use for presumptive TB patients as per 2015 [26, 27]

Adult TB Diagnosis Guidelines

1. History of presenting complaints (history of cough is key)
2. Past medical illness (Diabetes, HIV)
3. History of contact with TB
4. Physical examination
5. Sputum AFB microscopy (all pulmonary TB suspects)
6. Other supportive investigation
7. Chest x-ray (supportive for smear negative TB)
8. Socialized bacteriological examination
   a) Culture (reserved for relapses, treatment failure, returnees, health care workers)
   b) Molecular tests (Xpert/MTB RIF 
   c) Drug susceptibility for anti-TB drugs

Pediatric TB Diagnosis Guidelines

1. History of presenting illness (cough, fever, poor weight gain, lethargy or reduced playfulness)-suspect TB if the child has two or more of these suggestive symptoms
2. History of contact with adult/adolescent with chronic cough or TB within the last 2 years
3. Physical examination temperature >37.5°C weight; respiratory exam and other systemic findings
4. Specimen for Xpert MTB/RIF® (and culture when indicated)
5. Chest X-ray (where available)
6. Mantoux test (where available)
7. HIV test
8. Other tests for extra-pulmonary TB (where suspected)

Bacteriologically confirmed TB: specimen positive Mycobacterium tuberculosis (MTB)
Clinically diagnosed:
• Two or more of persistent cough, fever, poor weight gain, lethargy
  PLUS
• Two or more of positive contact, abnormal respiratory signs, abnormal chest X-ray, positive Mantoux
  AND
• Absent or negative specimen for MTB

*Indications for Xpert MTB/RIF®

MDR TB Surveillance
- All retreatment cases: a) Failures b) Relapses c) Return after default
- Drug Resistant TB contacts
- smear positive returnees
- Health Care workers with TB

TB Diagnosis
- HIV positive Smear negative
- Diagnosis of TB in children
- TB screening for the symptomatic patients for and on IPT
### TB Case definitions and Treatment outcomes for Drug susceptible TB patients [34]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>A pulmonary TB patient with bacteriologically confirmed* TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion</td>
</tr>
<tr>
<td></td>
<td>* A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostics (such as Xpert MTB/RIF).</td>
</tr>
<tr>
<td></td>
<td>* A clinically diagnosed TB case is one who does not fulfil the criteria for bacteriological confirmation but who has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extra-pulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed</td>
</tr>
<tr>
<td></td>
<td>* Presumptive TB refers to a patient who presents with symptoms or signs suggestive of TB (previously known as a TB suspect)</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable</td>
</tr>
<tr>
<td>Treatment failed</td>
<td>A TB patient whose sputum smear or culture is positive at month 5 or later during treatment</td>
</tr>
<tr>
<td>Died</td>
<td>A TB patient who dies for any reason before starting or during the course of treatment</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more</td>
</tr>
<tr>
<td>Not evaluated</td>
<td>A TB patient for whom no treatment outcome is assigned. This includes cases “transferred out” to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.</td>
</tr>
<tr>
<td>Treatment success</td>
<td>The sum of cured and treatment completed</td>
</tr>
</tbody>
</table>
### Additional File 2: Univariate analysis and Model Diagnostics Charts

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>0-14yrs Xpert done n (%)</th>
<th>≥15yrs Xpert done n (%)</th>
<th>0-14yrs unadjusted OR (95% CI)</th>
<th>≥15yrs unadjusted OR (95% CI)</th>
<th>Overall unadjusted OR (95% CI)</th>
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<td>1.11 (1.06 to 1.17)</td>
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<td>1.89 (1.80 to 1.99)</td>
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<td>1.17 (1.11 to 1.23)</td>
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<td>360 (3.9)</td>
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<td>0.77 (0.69 to 0.87)</td>
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<td>0.94 (0.64 to 1.37)</td>
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<td>0.56 (0.28 to 1.12)</td>
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<td>≥15yrs</td>
<td>0-14yrs</td>
<td>≥15yrs</td>
<td>Overall</td>
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<td>N=82,295</td>
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<td>Short travel</td>
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<td>1.35 (1.30 to 1.41)</td>
<td>0.86 (0.52 to 1.42)</td>
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<td>Long travel</td>
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<td>1.44 (1.38 to 1.51)</td>
<td>0.57 (0.35 to 0.94)</td>
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<td>Health Facility Level</td>
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<td>Lower level**</td>
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<td>Higher level***</td>
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<td>1.19 (1.05 to 1.35)</td>
<td>1.17 (1.04 to 1.33)</td>
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<td>322 (3.5)</td>
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<td>1.02 (0.82 to 1.26)</td>
<td>1.03 (0.84 to 1.27)</td>
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<td>Patient from an Xpert site</td>
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<tr>
<td>Not from site</td>
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<tr>
<td>From site</td>
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<td>1.72 (1.64 to 1.81)</td>
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<td>Facility density of Xpert testing facilities/100,000</td>
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<tr>
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<td>1.26 (1.21 to 1.31)</td>
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<td>1.06 (1.01 to 1.12)</td>
<td>0.75 (0.46 to 1.20)</td>
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</table>

*% is column % except for age which is row % of the total

Quantile to quantile plot of the fully adjusted model to determine if well fit
Testing for collinearity amongst continuous variables
### Additional File 3: Distribution of TB cases by age group for the various counties

<table>
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<tr>
<th>County</th>
<th>Total TB Cases</th>
<th>% of Total TB cases</th>
<th>Cases in 0-14yrs</th>
<th>Cases in 0-14yrs % of county cases</th>
<th>Cases in ≥15yrs</th>
<th>Cases in ≥15yrs % of county cases</th>
<th>2015 County Population</th>
<th>2015 County CNR/100,000</th>
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Additional File 5: County Names, Case Notification Rates and use of Xpert® and Microscopy

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Chapter 3: Tuberculosis as a cause or comorbidity of childhood pneumonia in tuberculosis-endemic areas: a systematic review

Jacquie N Oliwa, Jamlick M Karumbi, Ben J Marais, Shabir A Madhi, Stephen M Graham

Abstract

Pneumonia is a major cause of morbidity and mortality in infants and children worldwide, with most cases occurring in tuberculosis-endemic settings. Studies have emphasised the potential importance of *Mycobacterium tuberculosis* in acute severe pneumonia in children as a primary cause or underlying comorbidity, further emphasised by the changing aetiological range with rollout of bacterial conjugate vaccines in high mortality settings. We systematically reviewed clinical and autopsy studies done in tuberculosis-endemic settings that enrolled at least 100 children aged younger than 5 years with severe pneumonia, and that prospectively included a diagnostic approach to tuberculosis in all study participants. We noted substantial heterogeneity between studies in terms of study population and diagnostic methods. Of the 3644 patients who had culture of respiratory specimens for *M tuberculosis* undertaken, 275 (7.5%) were culture positive, and an acute presentation was common. Inpatient case-fatality rate for pneumonia associated with tuberculosis ranged from 4% to 21% in the four clinical studies that reported pathogen-related outcomes. Prospective studies are needed in high tuberculosis-burden settings to address whether tuberculosis is a cause or comorbidity of childhood acute severe pneumonia.

Key messages

- Tuberculosis is not often reported in young children presenting with acute severe pneumonia in tuberculosis endemic settings
- Tuberculosis might be a direct cause of severe pneumonia or might be an underlying comorbidity that increases the risk of secondary bacterial pneumonia
- Clinical and autopsy studies have confirmed tuberculosis in children that have died with severe pneumonia
- Restrictions of tuberculosis diagnostic techniques in children hinder estimation of actual burden and improved case detection
- Data on tuberculosis in children with acute severe pneumonia are from a small number of studies in mainly large urban-based hospitals with marked heterogeneity in diagnostic approaches
- The non-specific clinical presentation of pulmonary tuberculosis in infants and young children highlights the urgent need for improved diagnostic instruments
Introduction

Pneumonia is the leading cause of death in children aged 1–59 months, accounting for an estimated 18% of under-5 mortality worldwide in 2011 [1]. In 2010, roughly 120 million episodes of pneumonia, 14 million severe pneumonia episodes, and 1·3 million deaths due to pneumonia in infants and children aged younger than 5 years were recorded [1–3]. Most (81%) of these deaths occurred in the first 2 years of life. The epidemiology of child pneumonia varies widely between different regions of the world in terms of disease incidence, severity, and associated mortality, and the contribution of causative pathogens and prevalence of risk factors (table 1, figure 1) [4,5]. Liu and colleagues [2] report that most pneumonia episodes in children younger than 5 years occurred in southeast Asia (39%) and Africa (26%), with sub-Saharan Africa accounting for 43% of pneumonia deaths, despite only constituting 19% of the world’s under-5 population.

An understanding of the common causative pathogens in high-burden settings is important to inform case-management and potential preventive strategies, such as vaccine development and delivery. Cases management and immunisation strategies have been informed by studies done in the 1980s which identified *Streptococcus pneumoniae* and *Haemophilus influenzae* as the most common bacterial pathogens causing pneumonia in children [6,7]. These studies also showed that most pneumonia-related deaths were due to bacterial rather than viral pneumonia, with the exception of measles. However, even in the case of measles-associated pneumonia deaths, 47–55% were associated with bacterial superinfection with *S pneumoniae* identified in 30–50% of confirmed bacterial co-infections [8]. The diagnostic techniques used in these studies restricted identification of pathogens to bacteria and known common viruses [7,9]. They did not use diagnostics specific to the identification of *M tuberculosis*, atypical bacteria, or opportunistic pathogens such as *Pneumocystis jiroveci* or cytomegalovirus. Furthermore, most previous studies did not highlight the potential importance of co-infections, as manifested by a high prevalence of pneumococcal-respiratory viral co-infections (roughly 33%), which has since been observed in children admitted to hospital with pneumonia in low-income, middle-income, and high-income settings [10,11]. Furthermore, the studies were done before the worldwide spread of the HIV epidemic.

The HIV epidemic has had a major effect on the burden and mortality of pneumonia in children; bacterial pneumonia is more common and more severe in HIV-infected children compared with uninfected children. *P jiroveci* pneumonia (PCP) is frequently fatal in HIV-infected infants not receiving co-trimoxazole preventive therapy and co-infections (concurrent bacterial, mycobacterial, fungal, or viral) are common in HIV-infected children [12]. Additionally, the HIV epidemic has substantially increased the incidence and transmission of tuberculosis in HIV endemic settings,
particularly in young women, greatly increasing the risk of tuberculosis in their infants [13]. Reversal of the burden of HIV in infants has been encouraging, with increasing coverage of prevention of mother-to-child transmission of HIV, early antiretroviral therapy, and co-trimoxazole prophylaxis for HIV-infected and HIV-exposed infants [14].

Table 1 Pneumonia disease burden estimates in children 0-4 years of age by WHO region*

<table>
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<tr>
<th>WHO Region</th>
<th>Estimated Pneumonia Disease Burden (2011)</th>
<th>Population &lt;5yrs (2010)</th>
<th>Incidence¹</th>
<th>Total Episodes (x10⁶)</th>
<th>Total Deaths (x10³)</th>
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<td>(18.2-84.4)</td>
<td>(43.8-627.3)</td>
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<td>(8.2-38.0)</td>
<td>(147.3-217.1)</td>
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<td>(14.7-23.4)</td>
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<td>(23.7-109.8)</td>
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<td>(0.05-0.24)</td>
<td>(6.2-28.2)</td>
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<td>(60.8-277.0)</td>
<td>(1053.2-1482.9)</td>
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</tr>
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</table>

WHO – World Health Organization

¹Incidence = episodes per child year

*Adapted from ²

Potential contribution of tuberculosis to childhood pneumonia

Although tuberculosis is a curable and preventable disease, it is the second leading cause of death from an infectious agent after HIV. In 2013, about 9.0 million new cases of tuberculosis occurred, with 1.5 million deaths worldwide, and most of the cases were from Asia and Africa [15]. Roughly 550,000 of the new cases were in children with 80,000 deaths in those who were HIV-uninfected [15,16]. This number might be an underestimate owing to the challenges of establishing the diagnosis of tuberculosis in children. There is a growing awareness that children have a high burden of tuberculosis-related disease that is often not reported as such [17].

Previous studies of pneumonia in infants and young children might also have underestimated the contribution of tuberculosis as a direct cause or comorbidity of acute community-acquired pneumonia in children because of the difficulties of microbiological confirmation in this age group, especially in
resource-restricted tuberculosis endemic settings [5]. These settings are the ones that have the highest incidence of childhood pneumonia and pneumonia-related mortality (figures 1, 2) [3,4,16]. Additionally, these settings have the highest prevalence of childhood malnutrition and HIV infection worldwide, both common comorbidities that increase the risk and the mortality of tuberculosis and of pneumonia in young children [17–19]. Furthermore, the relative interaction with tuberculosis as a cause or contributor to childhood pneumonia in tuberculosis endemic areas is likely to be changed with increasing global uptake of vaccines that protect against other causes of pneumonia, including measles vaccine, *H. influenzae* type b (Hib), and pneumococcal conjugate vaccines [17,20,21].

Tuberculosis needs specific treatment (in contrast to many respiratory viruses) and treatment outcomes in young children are usually excellent.

The contribution of tuberculosis to the burden of pneumonia and death in childhood as a direct cause or underlying contributing factor is still poorly quantified. Cause-specific mortality estimates are usually modelled from vital registration data with historical assumptions and allow only the reporting of a single cause of death, which in the context of respiratory disease is not pathogen-specific. Additionally, the fact that children with acute pneumonia symptoms might have microbiologically confirmed tuberculosis contradicts traditional teaching and standard case management, in which tuberculosis is only considered in children with prolonged persistent symptoms. The concept that tuberculosis might increase susceptibility to secondary bacterial pneumonia in young children is also not widely appreciated.

Figure 1: 2012 Incidence of clinical pneumonia in children less than 5 years of age [4]
Figure adapted from the World Health Organization (WHO) with permission. Small circles represent island populations.
To assess the association of tuberculosis with childhood pneumonia in tuberculosis-endemic areas, we did a systematic review of published literature reporting the causes of severe pneumonia in infants and young children that prospectively evaluated these children for multiple infectious causes, including *M. tuberculosis*. By reviewing the available data on prevalence, clinical presentation, diagnostic approaches, co-infection, and outcome, we aimed to provide an overview of knowledge gaps and a resource for future research and advocacy.

**Search strategy and selection criteria**  
We included studies of any design that were done in a tuberculosis-endemic setting (country incidence ≥50 new cases per 100 000 people per year at the time of the study); enrolled at least 100 children aged younger than 5 years who had a diagnosis of pneumonia or respiratory tract infection (defined as clinical evidence of severe or very severe pneumonia according to WHO criteria of acute respiratory infection [22], or radiological evidence of lobar or patchy consolidation); and included a tuberculosis diagnostic workup and described the diagnostic approach in sufficient detail. We included studies that reported additional comorbidities such as HIV or malnutrition as long as a lower respiratory tract infection provided the main point of entry into the study. Case reports or series, studies with older populations, and those done in high-income countries not endemic for tuberculosis (incidence <50 new cases per 100 000 people per year) were excluded. The primary outcomes considered were the...
numbers and proportions of tuberculosis cases diagnosed clinically or culture-confirmed in children aged younger than 5 years with pneumonia.

We recognised studies as potentially highly heterogeneous but did not exclude any because of perceived low quality (STROBE checklist) [23]. Heterogeneity included study population, study setting and diagnostic methods used to clinically diagnose or microbiologically confirm tuberculosis, and all recognised factors that have a risk of bias across studies for detection of the primary outcome of the review and for mortality. Assessment of the risk of bias of individual studies identified potential sampling bias in many of the clinical studies (appendix). The substantial heterogeneity and recognised risk of bias across and within studies did not allow for pooled estimates or meta-analysis of variables. Rather, the main characteristics of individual studies were listed. The gold standard for tuberculosis diagnosis is culture confirmation and so the principal summary measures that we aimed to report were the pooled numbers of culture-confirmed tuberculosis and as a proportion of those that had respiratory specimens cultured, with risk of bias explicitly acknowledged. We deemed the risk of bias of individual studies for reporting inpatient deaths negligible.

Findings

Study overview
Our search identified 14 articles that were eligible for the final analysis: 11 prospective clinical studies and three autopsy studies (figure 3, table 2) [24–37]. We noted substantial heterogeneity between studies in terms of factors that would potentially affect yield of tuberculosis diagnosis in children with pneumonia such as inclusion criteria, study setting, background tuberculosis incidence at the time of the study, prevalence of comorbidities such as severe malnutrition, and techniques used for sputum collection and microbiological confirmation. The 11 clinical studies of children treated in hospital included a total of 6504 infants and children with a clinical or radiological diagnosis of pneumonia that were aged younger than 5 years.

Six of these studies were done in large urban-based hospitals in South Africa and Malawi, which are very high-burden tuberculosis settings (reported incidence ≥300 cases per 100 000 population per year) with high rates of HIV infection [26,31–33,36,37]. The other five were studies of children treated in hospital from a wide range of high-burden tuberculosis settings (reported incidence 50–299 cases per 100 000 population per year) including rural Africa, and low-HIV-prevalence settings in Asia, namely Bangladesh and China [24,25,27,29,35]. The three autopsy studies were also from southern African countries with very high tuberculosis incidence (South Africa, Zambia, and Zimbabwe) [28,30,34].
949 records identified through database searching

4 records from other sources (experts in the field and bibliographies)

953 records from all relevant sources

825 records excluded after review of the title

128 abstracts reviewed

90 abstracts excluded
30 reviews
18 case reports
7 foreign languages
38 not relevant

38 full articles retrieved

7 full articles excluded
5 foreign language
2 duplications (same study population)

31 full articles assessed for eligibility

17 articles excluded based on inclusion criteria
(low sample size, low tuberculosis endemicity, high income settings)

14 studies included in the final review

Figure 3 Prisma flow diagram of studies included in the Review
**Tuberculosis diagnosis**

Studies were done in hospitals with varying capabilities to microbiologically confirm tuberculosis, and not all studies included mycobacterial culture for microbiological confirmation. Diagnostic approaches for each study are summarised in table 2. Potential sampling bias occurred within studies; four studies [25,27,31,33] collected samples for culture for *M tuberculosis* in all study participants, whereas four studies [24,26,32,35] collected samples for culture in a subset of participants, in which criteria for selection were not clearly mentioned. One study used Xpert MTB/RIF (Cepheid, CA, USA) additionally to culture in 214 children [27]. Most of the 3644 samples taken for culture or Xpert MTB/RIF were sputum samples obtained by induced sputum technique or gastric lavage, with an additional 94 samples from a direct lung aspirate. One study reported multiplex PCR results from a nasopharyngeal sample [29].

Chest radiographs were done as part of the diagnostic evaluation for pneumonia in all the studies but only three of the studies [27,30,31] compared radiological findings with those with a diagnosis of tuberculosis and those without. In a study of severely malnourished children in Bangladesh [27], no differences were noted except that one of the 27 confirmed tuberculosis cases had a miliary pattern. In the South African autopsy study of HIV-infected children [30], no differences were noted in radiological patterns between those with tuberculosis and those with other HIV-related lung diseases [30]. The clinical study by Zar and colleagues reported that hilar or mediastinal adenopathy was significantly more common in children with tuberculosis than in those without (43% vs 12%) [31].

**Contribution of tuberculosis to pneumonia**

The proportion of pneumonia cases that were diagnosed with tuberculosis ranged from 1% to 23%. The proportion of culture-confirmed tuberculosis in children with pneumonia also varied widely between the nine studies that included *M tuberculosis* culture, with five studies [25–27,31,32] reporting culture-confirmed rates of 5–8%. One study reported culture-confirmed rates of 15% [33]. Overall, of the infants and young children with pneumonia who had culture of respiratory specimens for *M tuberculosis* performed, 7.5% (275 of 3644) were culture positive. The proportion of culture positive cases was higher in settings with a very high tuberculosis burden at the time of the study (incidence of ≥300 cases per 100 000 population per year; 232 (8%) of 2800 pneumonia cases in which samples were available for culture) than in studies done in high tuberculosis burden settings (incidence of 50–299 cases per 100 000 people per year; 43 (5%) of 844 pneumonia cases in which samples were available for culture).
Relation to vaccine coverage
The national immunisation programme in six of the study sites included Hib conjugate vaccine in early infancy [24–27,33,37]. The only study [26] that included children who received a pneumococcal conjugate vaccine reported follow up of a randomised placebo-controlled trial of the nine-valent pneumococcal conjugate vaccine in South African infants. The main aim of the study was to assess protective efficacy against invasive pneumococcal disease and all-cause radiological confirmed pneumonia during the first 2 years of life. A post-hoc vaccine-probe analysis from this study [26] estimated that 43–47% of treatment in hospital for culture-confirmed tuberculosis in HIV-infected and HIV-uninfected children in this setting could be due to superimposed pneumococcal co-infection.

Symptoms associated with tuberculosis
The duration of respiratory symptoms such as cough before admission was acute in most patients with tuberculosis when this feature was reported in the study (table 2) [26,27,31–33], with the exception of the Ugandan study [25] that reported persistent cough of more than 2 weeks’ duration was more common in pneumonia cases with tuberculosis compared with those without. One study noted that 49% of patients with tuberculosis responded to first-line empirical antibiotic treatment for community-acquired pneumonia and were well enough to discharge with anti-tuberculosis treatment started later once culture results became available [26].

Association with HIV infection
HIV co-infection was common (28–89%) in children diagnosed with tuberculosis in the HIV-endemic settings of eastern and southern Africa [25,26,32,33,36,37,39]. One study [32] reported a 23-fold (95% CI 13–48) higher incidence of admission to hospital with culture-confirmed tuberculosis presenting as acute severe pneumonia in HIV-infected children aged younger than 2 years (1470 cases per 100 000 per year) than in HIV-uninfected children (65 per 100 000 per year). However, the proportion of patients that were culture positive for *M tuberculosis* was similar between HIV-infected and HIV-uninfected children treated in hospital for acute pneumonia in studies in HIV-endemic settings [25,26,32,33,39].

Mortality
Mortality in children with pneumonia and diagnosis of tuberculosis was not consistently reported. In those studies that reported inpatient deaths in tuberculosis cases from HIV-endemic African settings, case-fatality rates ranged from 4% to 21% [26,31,33,37]. The study of severely malnourished Bangladeshi children27followed all children until 12 weeks after discharge and reported deaths in four (four of 86 [5%] patients with tuberculosis that were discharged; note, one patient died of tuberculosis in hospital) of the patients with tuberculosis. Autopsy studies provide additional data on the
contribution of tuberculosis to pneumonia-related deaths in children. This contribution ranged from 4% to 20% in children who died from respiratory disease in three settings with very high tuberculosis incidence rates [28,30,34]. These autopsy studies were also done at the peak of the HIV epidemic and before the rollout of preventive measures, such as co-trimoxazole preventive therapy and universal antiretroviral therapy for HIV-infected children. The selection criteria in these studies were highly variable and only one study [30] provided antemortem clinical data (table 2). Disseminated tuberculosis was common, as were co-infections of tuberculosis with pyogenic pneumonia in children (most were younger than 5 years of age) dying from respiratory disease. Polymicrobial infections were also noted to be common and associated with a worse outcome in one of the clinical studies [33], with \( M \) \( {\text{tuberculosis}} \) identified in 18% of HIV-infected and 29% of HIV-uninfected infants with acute pneumonia who failed empirical first-line antibiotic therapy.

Discussion

Pneumonia is a major cause of under-5 mortality worldwide, and tuberculosis is a treatable and preventable disease in young children that most often presents as a lower respiratory tract disease. This Review provides evidence of the prevalence of tuberculosis in infants and young children admitted to hospital with predominantly acute pneumonia in a range of tuberculosis-endemic settings. The findings of this Review should, however, be interpreted with caution because of the heterogeneity of study populations and diagnostic approaches between studies, the sampling bias for diagnosis within some studies, and the acknowledged difficulties of diagnosis of tuberculosis in children. In view of the poor specificity of clinical features of tuberculosis in young children,40 the most robust data are provided by studies that sought culture confirmation. An important finding was that 275 of 3644 (7.5%) of patients with severe pneumonia in whom respiratory specimens were collected for \( M \) \( {\text{tuberculosis}} \) culture had culture-confirmed disease (especially because culture has low diagnostic sensitivity in young children with intrathoracic tuberculosis at about 30–60%, dependent on the specific disease manifestation) [41,42]. Our findings also show that tuberculosis might be an important contributor to pneumonia-related deaths in young children because of under-diagnosis or comorbidity predisposing to bacterial co-infection [11,26,31,33,34].

The findings from these studies are not likely to be representative of the epidemiology of childhood pneumonia in tuberculosis-endemic areas in general. First, four of the studies were from large urban hospitals in South Africa [26,31–33], a country that is highly endemic for tuberculosis and HIV, with routine access to conjugated Hib and pneumococcal vaccines at the time of the studies. Second, the studies from Bangladesh and The Gambia focused on tuberculosis diagnosis in malnourished children with respiratory symptoms [27,35]. Although the bidirectional association between tuberculosis and
malnutrition is well recognised, surprisingly few data on the prevalence of tuberculosis in malnourished children have been reported, with or without respiratory disease, and clinical diagnosis is especially challenging in this group [43]. Third, many of the studies were in HIV-endemic settings before the rollout of interventions that have substantially reduced HIV prevalence in young children in those settings and reduced the susceptibility to tuberculosis of children that are living with HIV. Although we noted the prevalence of tuberculosis in patients with pneumonia being similar between HIV-infected and HIV-uninfected children [25, 26, 31–33], the risk of tuberculosis was increased in HIV-infected children not receiving antiretroviral therapy [32, 44]. Finally, the two studies from Malawi relied on clinical suspicion, such as a positive contact history and poor response to antibiotics, and reported the lowest prevalence of tuberculosis of studies from the highly endemic countries [36, 37]. Relying solely on clinical criteria for the diagnosis of tuberculosis might overestimate rather than underestimate the prevalence of the disease [45]; however, this issue might not be the case in children with tuberculosis who present to hospital when they have an acute bacterial pneumonia because they might respond to antibiotics and the underlying tuberculosis might be missed, as noted in the study that followed the pneumococcal conjugate vaccine study cohort [26].

Case-management guidelines often advise health workers to consider the diagnosis of tuberculosis in infants and children with chronic cough. Tuberculosis is known to be common in studies of children with persistent cough in tuberculosis-endemic settings [46, 47]. However, in this Review we noted that many of the confirmed tuberculosis cases presented with acute cough [25–27, 31–33]. Furthermore, many of the study participants were infants. Although tuberculosis can directly cause severe pneumonia and disseminated disease, especially in infants, many of these children are likely to present to hospital with a bacterial pneumonia complicating underlying pulmonary tuberculosis. Many of the studies reported bacterial–tuberculosis co-infection [28, 29, 32–35]. One study reported that 10% of culture-confirmed tuberculosis cases also had bacteria isolated from blood culture, despite this being a test of low sensitivity (5–15%) for bacterial pneumonia [32]. Furthermore, tuberculosis cases improved with antibiotics for community-acquired pneumonia, and admission to hospital with tuberculosis was significantly less common in children who had received the pneumococcal conjugate vaccine compared with placebo [26]. A seasonal correlation between invasive pneumococcal disease and tuberculosis cases that is particularly pronounced in HIV-infected individuals has been reported by the same group in Johannesburg [48]. On the basis of the results from the pneumococcal conjugate vaccine-probe design and clinical response to empirical antibiotic treatment against bacterial pneumonia, the scarce evidence shows that almost half the children with culture-confirmed tuberculosis were admitted to hospital because of bacterial (and particularly pneumococcal) pneumonia [26].
The mortality associated with a diagnosis of tuberculosis is a concern. In view of the high prevalence of comorbidities and co-infections in these children, differentiation between children that died with underlying tuberculosis, which was complicated by concurrent or superimposed infections, from those that died directly because of tuberculosis is not possible. The autopsy studies suggest that bacterial co-infections are important causes of death in children with tuberculosis [28,30,34]. The autopsy studies included in this Review all had large sample sizes but did not necessarily represent the full range of children dying with pneumonia, because consent for autopsy was less than 25% in the studies in Zambia and Zimbabwe [28,34], whereas the South African study only included HIV-infected children. Only one study reported antemortem clinical data [30]. Small autopsy studies were not included in this Review, such as a study from Botswana that reported tuberculosis prevalence of 21% in children dying with respiratory disease in Francistown [49]. Additionally, an autopsy study from Bangladesh reported tuberculosis prevalence of 3% in children who died from pneumonia [50]. A review of autopsy studies of deaths due to respiratory infections in Africa reported that about 8.5% of all cases in children had pulmonary tuberculosis, which was statistically more prevalent in HIV-uninfected cases [51]. This Review shows the need for improved diagnostics for tuberculosis in infants and young children, including those presenting with acute severe pneumonia. The clinical presentation and radiological features frequently overlap and even a clinical response to antibiotics does not necessarily exclude a diagnosis of tuberculosis, which might be the underlying cause predisposing to susceptibility for acute bacterial pneumonia treatment in hospital. If an infant develops tuberculosis, infection of the infant by a close contact who has tuberculosis (which might or might not have been diagnosed) is very likely, and so this information should always be carefully sought after.

The first step is for clinicians managing infants and young children with severe pneumonia in tuberculosis-endemic countries to be aware that tuberculosis might be a cause or contributor. At present, this recognition is not the case and an aim of this Review is to improve awareness. Improved diagnosis will probably depend on the future development of a point-of-care test that does not rely on sputum sampling. This test is now an important focus of research [52,53]. Studies also need to be done in a wider range of settings than has been the case so far, such as rural based, secondary-level care settings that include a sufficient period of follow up after discharge to appropriately manage suspected or culture-confirmed tuberculosis.

In conclusion, this Review suggests that tuberculosis is important in the pathogenesis of acute childhood pneumonia in countries with a high incidence of tuberculosis, either as a direct cause or as an underlying risk factor that increases susceptibility to bacterial pneumonia. Interpretation of
findings from previous studies is restricted by recognised diagnostic challenges and substantial
heterogeneity between studies with risk of bias. Prospective studies from several epidemiological
settings that use optimum diagnostic techniques are needed to better understand the contribution of
tuberculosis to child pneumonia and to improve clinical management.

Contributors
All authors contributed to the concept and plan for this Review. JNO and JMK did the literature review
and analysis with input from BJM and SMG. JNO, BJM, and SMG developed the first draft and all
authors provided major contributions to the final manuscript. JNO abstracted the data and JMK, BJM,
SAM, and SMG verified accuracy. JNO and JMK independently screened the titles and abstracts of all
papers identified by the search and applied the predefined study selection criteria to identify eligible
studies.

Declaration of interests
SAM has received honoraria, but not linked to this work, from GlaxoSmithKline, Pfizer, Novartis, and
Sanofi Pasteur. The other authors declare no competing interests.

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helpful review of the manuscript

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findings from several developing countries. Coordinated Data Group of BOSTID Researchers. Rev Infect
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10 Michelow IC, Olsen K, Lozano J, et al. Epidemiology and clinical characteristics of community-


Table 2. Studies assessing the contribution of tuberculosis to pneumonia in children less than five years of age in tuberculosis-endemic areas

<table>
<thead>
<tr>
<th>Lead author, year of study</th>
<th>Country, setting</th>
<th>Tuberculosis' population incidence</th>
<th>Number (age range)</th>
<th>Duration of symptoms on presentation for tuberculosis cases</th>
<th>Inclusion criteria</th>
<th>Tuberculosis diagnosis</th>
<th>Tuberculosis cases n (% of enrolled)</th>
<th>Case-fatality rate and other characteristics of tuberculosis cases</th>
<th>%HIV prevalence (number of tuberculosis cases tested for HIV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very High Burden settings (Tuberculosis incidence ≥300 cases per 100,000 population)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graham 37 2005-6</td>
<td>Malawi urban and peri-urban</td>
<td>328</td>
<td>288 (2–59 months)</td>
<td>Not reported</td>
<td>WHO severe and very severe pneumonia Hospitalization for lower respiratory tract infection</td>
<td>Clinical only Culture of sputum in select cases</td>
<td>5 (1.7%)</td>
<td>1 (20%) died: aged 5 months</td>
<td>40% (5)</td>
</tr>
<tr>
<td>Moore 26 1998-2006</td>
<td>South Africa urban</td>
<td>406</td>
<td>2439 (3-59 months)</td>
<td>77% of cases had cough of &lt;10 days duration</td>
<td>WHO severe and very severe pneumonia</td>
<td>Culture of sputum in 1334 children when tuberculosis clinically suspected</td>
<td>421 (32%) 90 (7%) culture confirmed of 1334</td>
<td>376 first and 45 recurrent episodes 4 (4%) of 90 culture-confirmed died in hospital; 49% of cases discharged following response to empiric antibiotics and not initiated on tuberculosis treatment</td>
<td>64% (376)</td>
</tr>
<tr>
<td>McNally 33 2001-2</td>
<td>South Africa urban</td>
<td>780</td>
<td>358 (1-59 months)</td>
<td>85% of cases had symptoms &lt;2 weeks</td>
<td>WHO severe and very severe pneumonia</td>
<td>Culture of sputum</td>
<td>53 (15%) All culture</td>
<td>15 (30%) aged &lt;1 year 11 (21%) died Maternal tuberculosis associated with poorer outcomes</td>
<td>72% (53)</td>
</tr>
<tr>
<td>Zar 31 1998</td>
<td>South Africa urban</td>
<td>406</td>
<td>250 (3-16 months)</td>
<td>Enrolment criteria: cough &lt;14 days duration</td>
<td>WHO severe and very severe pneumonia</td>
<td>Culture of sputum</td>
<td>20 (8%) All culture</td>
<td>3 (15%) died</td>
<td>55% (19)</td>
</tr>
<tr>
<td>Madhi 32 1997-8</td>
<td>South Africa, urban</td>
<td>406</td>
<td>1215 (2-59 months)</td>
<td>Enrolment criteria: cough &lt;14 days duration</td>
<td>WHO severe and very severe pneumonia</td>
<td>Culture of sputum in 858 children when tuberculosis clinically suspected</td>
<td>69 (6%) 69 (8%) culture confirmed of 858</td>
<td>58 (84%) aged &lt;2 years 7 (10%) also had bacteremia</td>
<td>52% (69)</td>
</tr>
<tr>
<td>Graham 36 1996</td>
<td>Malawi urban and peri-urban</td>
<td>479</td>
<td>150 (2-59 months)</td>
<td>Not reported</td>
<td>WHO severe and very severe pneumonia</td>
<td>Clinical only</td>
<td>9 (6%)</td>
<td>All cases had close tuberculosis contact and poor response to antibiotics</td>
<td>89% (9)</td>
</tr>
</tbody>
</table>
### High Burden settings (Tuberculosis incidence 50-299 cases per 100,000 population)

| Location        | Year | Country       | Number | Age Range | Median Duration of Cough | WHO Severe and Very Severe Pneumonia | Clinical Indicator | Culture of Sputum | Clinical Indicator | Culture of Lung Tissue | Culture of Lung Aspirate | Culture of Lungs | Contact History | Case Fatality | HIV Prevalence Setting | HIV-Related | Other Medical Conditions |
|-----------------|------|---------------|--------|-----------|--------------------------|---------------------------------------|-------------------|------------------|-------------------|---------------------|------------------------|---------------------|----------------|--------------|----------------|--------------------------|----------------|--------------------------|
| Nantongo 25     | 2011 | Uganda, urban | 193    | 231       | (2 months - 5 years)     | 37% of cases had cough < 2 weeks      | WHO severe and very severe pneumonia | Clinical        | Culture of sputum | Clinical          | Culture of sputum     | WHO severe and very severe pneumonia | 24 (65%) aged < 2 years | Young age (<1 year) and contact history associated with confirmed tuberculosis | 28% (51) |
| Chisti 27       | 2011-2 | Bangladesh, urban | 225    | 385       | (2-59 months)           | Median (IQR) duration of cough for cases: 7 (4-8) days Not reported | WHO severe and very severe pneumonia | Clinical        | Culture of sputum | Clinical          | Culture of sputum     | WHO severe and very severe pneumonia | 87 (23%) | 4 (5%) died within 3 months | Not tested; low HIV prevalence setting |
| Hammitt 24      | 2010 | Kenya, rural   | 298    | 810       | (1-59 months)           | WHO severe and very severe pneumonia | Clinical        | Culture of sputum | Clinical          | Culture of sputum     | WHO severe and very severe pneumonia | 108 investigated for tuberculosis were selected from 810 severe pneumonia cases | Not reported for tuberculosis cases; 10% for severe pneumonia cases | Not tested; low HIV prevalence setting |
| Wang 20         | 2004-5 | China, urban | 92     | 100       | (1-60 months)           | Not reported | Radiological evidence of pneumonia | Multiplex PCR*** of nasopharyngeal specimens; Culture not done | Clinical        | Culture of sputum | Clinical          | Culture of sputum     | WHO severe and very severe pneumonia | 1 (1%) | S. pneumoniae and M. tuberculosis identified in same specimen | Not tested; low HIV prevalence setting |
| Adegbola 35     | 1990-2 | The Gambia, urban and peri-urban | 189    | 278       | (3-58 months)           | Not reported | WHO severe and very severe pneumonia; and radiological consolidation | Culture of lung aspirate (n=94) or induced sputum (n=26) | Clinical        | Culture of sputum | Clinical          | Culture of sputum     | WHO severe and very severe pneumonia | 5 (1-7%) | 2 (2%) culture confirmed of 120 sampled | All 5 cases were severely malnourished | 2% (3/159) of malnourished |

### Autopsy Studies

<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>Country</th>
<th>Number</th>
<th>Age Range</th>
<th>Median Duration of Cough</th>
<th>Cause of Death</th>
<th>Histopathology</th>
<th>Culture of Lung Tissue</th>
<th>Case Fatality</th>
<th>HIV Status</th>
<th>Other Medical Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chintu 34</td>
<td>1997-2000</td>
<td>Zambia, urban and peri-urban</td>
<td>645</td>
<td>264</td>
<td>(1-192 months)</td>
<td>Death from respiratory disease in hospital</td>
<td>Histopathology including Ziehl-Neelsen stain</td>
<td>PTB**** in 42 and miliary tuberculosis in 12 cases</td>
<td>54 (20%)</td>
<td>35 (65%) aged &lt;18 months</td>
<td>All HIV-infected</td>
</tr>
<tr>
<td>Rennert 30</td>
<td>1998-9</td>
<td>South Africa</td>
<td>406</td>
<td>103</td>
<td>(2-70 months)</td>
<td>HIV-related death with ante-mortem lung disease</td>
<td>Histopathology including Ziehl-Neelsen stain and culture</td>
<td>1 case &lt; 1 year age</td>
<td>4 (4%)</td>
<td>12 cases had concurrent pyogenic pneumonia</td>
<td>All HIV-infected</td>
</tr>
<tr>
<td>Ikeogu 28</td>
<td>1992-1993</td>
<td>Zimbabwe, urban and peri-urban</td>
<td>362</td>
<td>184</td>
<td>(1-55 months)</td>
<td>Death on arrival or shortly thereafter</td>
<td>Microscopy and culture of lung tissue</td>
<td>8 (4%)</td>
<td>4 disseminated and 4 PTB****</td>
<td>All severely malnourished</td>
<td>75% (8)</td>
</tr>
</tbody>
</table>
Chapter 4: Diagnostic practices and estimated prevalence of tuberculosis among children admitted to 13 government hospitals in Kenya: An analysis of two years’ routine clinical data

Jacquie Narotso Oliwa, David Gathara, Morris Ogero, Michaël Boele van Hensbroek, Mike English, Anja van’t Hoog and the Clinical Information Network^  

^ Membership of the Clinical Information Network is provided in the Acknowledgements section

Abstract

Background
True burden of tuberculosis (TB) in children is unknown. Hospitalised children are low-hanging fruit for TB case detection as they are within the system. We aimed to explore the process of recognition and investigation for childhood TB using a guideline-linked cascade of care.

Methods
This was an observational study of 42,107 children admitted to 13 county hospitals in Kenya from 01Nov 15-31Oct 16, and 01Nov 17-31Oct 18. We estimated those that met each step of the cascade, those with an apparent (or “Working”) TB diagnosis and modelled associations with TB tests amongst guideline-eligible children.

Results
23,741/42,107 (56.4%) met step 1 of the cascade (≥2 signs and symptoms suggestive of TB). Step 2 (further screening of history of TB contact/full respiratory exam) was documented in 14,873/23,741 (62.6%) who met Step 1. Step 3 (chest x-ray or Mantoux test) was requested in 2,451/14,873 (16.5%) who met Step 2. Step 4 (≥1 bacteriological test) was requested in 392/2,451 (15.9%) who met Step 3. Step 5 (“Working TB” diagnosis) was documented in 175/392 (44.6%) who met Step 4. Factors associated with request of TB tests in patients who met Step 1 included: i) older children [AOR 1.19 (CI 1.09-1.31)]; ii) co-morbidities of HIV, malnutrition or pneumonia [AOR 3.81 (CI 3.05-4.75), 2.98 (CI 2.69-3.31) and 2.98 (CI 2.60-3.40) respectively]; iii) sicker children, readmitted/referred [AOR 1.24 (CI 1.08-1.42) and 1.15 (CI 1.04-1.28) respectively]. “Working TB” diagnosis was made in 2.9%(1,202/42,107) of all admissions and 0.2%(89/42,107) were bacteriologically-confirmed.

Conclusions
More than half of all paediatric admissions had symptoms associated with TB and nearly two-thirds had more specific history documented. Only a few amongst them got TB tests requested. TB was diagnosed in 2.9% of all admissions but most were inadequately investigated. Major challenges remain in identifying and investigating TB in children in hospitals with access to Xpert MTB/RIF and a review is needed of existing guidelines.

Key words
Tuberculosis; Quality of TB care; diagnosis; diagnostic practices; children; hospital; care cascade
Introduction

The true burden of TB in children is unknown, but modelling estimates suggest it could be a leading cause of death in children, a “hidden epidemic”, with up to 65% of paediatric TB cases potentially missed each year [1-3]. Difficulties in accurately identifying cases of TB in children and lack of good surveillance data have made it challenging to quantify the actual burden of childhood TB [4]. According to World Health Organisation (WHO) estimates, there are 21,000 new childhood TB cases in Kenya, but only 7,648 (36%) are notified [5, 6]. The recent Kenya TB prevalence survey with participants >15yrs revealed 75% of TB cases had presented to health facilities with suggestive symptoms but were never diagnosed [7]. The proportion of younger children who present to health facilities and go undiagnosed in Kenya is presently unknown, but is presumed to be as high [6, 8, 9]. Data on burden of TB amongst paediatric admissions and clinicians’ diagnostic practices in resource-limited settings are also sparse, and where they exist, they mostly present data from single tertiary hospitals in better-resourced settings [10-12]. However, where TB is prevalent in the population one might expect to see TB more commonly amongst admissions.

In efforts to improve TB case detection and treatment, the WHO develops guidelines that national TB programmes adapt [13, 14]. According to Kenyan TB guidelines, diagnosing TB in children relies on careful history and physical examination to identify suggestive signs and symptoms of cough, fever, lethargy and growth faltering, followed by investigations including chest x-ray, tuberculin skin test (Mantoux), Xpert MTB/RIF and/or culture [13]. Unfortunately, TB diagnosis in children is complicated by low sensitivity and specificity of symptoms and lack of appropriate point-of-care diagnostic tests [15, 16]. Guidelines provide clinical decision support, therefore assessing how well health workers adhere to these guidelines provides opportunity to evaluate quality of TB care. Guidelines suggest clinicians should follow a series of steps spanning assessment, diagnosis and treatment, which can be represented in a care cascade. Cascades have been extensively used in HIV studies to describe quality of care [17-21], and are now increasingly used in TB care [22-25]. We identified one study using the cascade concept in paediatric TB [26] and another in adolescent TB [27] but none specifically looking at paediatric in-patient care.

This paper explored the process of recognition and investigation for childhood TB using a large longitudinal observational data set of hospitalised children in Kenya, a high burden TB country. Specifically, it aimed to: i) describe a guideline-linked paediatric TB care cascade (Fig 1) to audit clinician TB diagnostic practices; ii) to explore associations with use of TB diagnostic tests among children who entered the cascade; and iii) to estimate burden of TB diagnosis made in children admitted to Kenyan hospitals using various case-definitions. Findings may help explain a major gap in
the cascade of paediatric TB care in Kenya. This understanding could help develop targeted strategies to improve paediatric TB case detection and care.

![Figure 1 Panel showing guideline-recommended diagnostic steps and clinical case-definitions of TB in the study](image)

| Step 1: | History of suggestive TB symptoms: (cough, fever, weight loss/faltering, lethargy) |
| Step 2: | Further screening for TB risk: (History of TB contact, and abnormal respiratory signs) |
| Step 3: | Investigations to support clinical diagnosis: (chest x-ray and Mantoux) |
| Step 4: | Investigations for bacteriological confirmation of TB (Xpert or smear microscopy or culture) |
| Step 5: | Got a clinician TB diagnosis documented or anti-TB started (Working TB Dx) |

N/B Only patients who met the preceding step were included in the numerator for the subsequent step

**Clinical case definitions:**

- **Met guideline criteria for clinical TB diagnosis:** met two or more of: (persistent cough or fever or weight loss/faltering or lethargy) and two or more of: (positive TB contact or abnormal respiratory signs or abnormal chest x-ray or positive Mantoux) (steps 1-3)
- **Bacteriologically confirmed TB:** had a positive Xpert MTB/RIF or smear microscopy or culture for *Mycobacterium tuberculosis* (step 4)
- **Clinician decision-TB diagnosis:** documented clinician diagnosis of TB i.e. TB was recorded as either a primary or secondary differential diagnosis at admission/discharge (step 5)
- **Working TB diagnosis (Dx):** TB was documented either a primary or secondary differential diagnosis at admission/discharge and/or anti-TB medication was prescribed at admission/discharge (step 5). It includes those in whom anti-TB medication was prescribed, but clinician failed to document the TB diagnosis in the chart. We made an assumption that the TB drugs were given because of a TB diagnosis.

**Methods**

**Study design and setting**

We report findings from an observational study using data from the Clinical Information Network (CIN), a partnership established in 2013 between Kenya Medical Research Institute (KEMRI), Ministry of Health (MoH) Kenya, Kenya Paediatric Association (KPA) and 13 public county referral hospitals [28, 29]. The network collects standardized routine data on paediatric admissions with the aim of promoting adoption of evidence-based interventions and improving quality of care. Data are abstracted from a standard paediatric admission record (PAR) form (see S1 Chart) linked to national clinical guidelines defining key symptoms, signs, investigations, diagnostic formulations and treatment
plans for the most common childhood illnesses [30]. The data are then used to provide feedback every 2-3 months on patient process of care and outcomes to participating CIN sites to guide quality improvement activities. Over time, these audit and feedback processes have helped improve documentation practices and guideline adoption for common childhood illness like pneumonia, malnutrition and diarrhoea [31-33]. A detailed description of the CIN and data management processes have been documented in earlier publications [28, 29].

The data available within this network provided an opportunity to do a clinical audit of the extent to which the Kenya paediatric TB diagnostic guidelines are followed for children admitted to typical government county referral hospitals. All sites had access to an Xpert MTB/RIF machine and smear microscopy for bacteriological tests, all had X-ray facilities, but reagents for Mantoux testing were sporadically available nationwide throughout, and there was a shortage of Xpert MTB/RIF cartridges for some months in 2018. None of the study hospitals have been receiving feedback specific to TB from CIN. Table 1 summarises CIN study hospitals’ characteristics that we used in the exploration of hospital level characteristics and how they may influence case detection of TB in children.
Table 1 Hospital and respective county characteristics

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Paediatric Wards</th>
<th>Bed Capacity</th>
<th>County level parameters</th>
<th>Xpert MTB/RIF sites /county</th>
<th>TB CNR /100,000 $^a$</th>
<th>Proportion of TB cases among &lt;15yr $^b$ (%)</th>
<th>Proportion of HIV cases $^c$ (%)</th>
<th>Proportion of Stunting in &lt;5yr $^d$ (%)</th>
<th>Malaria Transmission rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>32</td>
<td>4</td>
<td>219</td>
<td>10</td>
<td>6.7</td>
<td>22</td>
<td>Moderate-high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H2</td>
<td>29</td>
<td>2</td>
<td>265</td>
<td>13</td>
<td>3.3</td>
<td>27</td>
<td>Very low-low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H3</td>
<td>35</td>
<td>4</td>
<td>120</td>
<td>10</td>
<td>4.0</td>
<td>28</td>
<td>Moderate-high</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H4</td>
<td>24</td>
<td>2</td>
<td>167</td>
<td>11</td>
<td>3.4</td>
<td>15</td>
<td>Very low-low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H5</td>
<td>63</td>
<td>2</td>
<td>227</td>
<td>13</td>
<td>3.1</td>
<td>17</td>
<td>Very low-low</td>
<td></td>
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<tr>
<td>H6</td>
<td>67</td>
<td>5</td>
<td>236</td>
<td>7</td>
<td>5.6</td>
<td>16</td>
<td>Very low-low</td>
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<tr>
<td>H7</td>
<td>29</td>
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<td>214</td>
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<td>19.9</td>
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<tr>
<td>H8</td>
<td>38</td>
<td>1</td>
<td>120</td>
<td>9</td>
<td>5.2</td>
<td>29</td>
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<tr>
<td>H9</td>
<td>35</td>
<td>3</td>
<td>205</td>
<td>5</td>
<td>4.5</td>
<td>27</td>
<td>Very low-low</td>
<td></td>
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</tr>
<tr>
<td>H10</td>
<td>41</td>
<td>15</td>
<td>304</td>
<td>7</td>
<td>6.1</td>
<td>17</td>
<td>Very low-low</td>
<td></td>
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</tr>
<tr>
<td>H11</td>
<td>42</td>
<td>15</td>
<td>304</td>
<td>7</td>
<td>6.1</td>
<td>17</td>
<td>Very low-low</td>
<td></td>
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<tr>
<td>H12</td>
<td>32</td>
<td>2</td>
<td>167</td>
<td>11</td>
<td>3.4</td>
<td>15</td>
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</tr>
<tr>
<td>H13</td>
<td>21</td>
<td>2</td>
<td>131</td>
<td>7</td>
<td>4.7</td>
<td>24</td>
<td>Moderate-high</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ County TB Case Notification Rates (CNR) from 2017 National TB Programme Annual Report [6]


$^c$ County HIV prevalence/proportions from National AIDS and STI Control County estimates for 2016 [34]

$^d$ County Malnutrition levels from KDHS 2014 [35]

Study participants, study size and data sources

We included routine hospital data for all paediatric admissions to CIN hospitals between from 1$^{st}$ Nov 2015-31$^{st}$ Oct 2016, and from 1$^{st}$ Nov 2017-31$^{st}$ Oct 2018 (24 calendar months), which gave us a total of 50,466 records. We excluded Nov 2016-Oct 2017 because Kenya went through prolonged health worker strikes, which adversely affected admissions to public hospitals [36]. We opted to use data for one calendar year prior to and after strikes when the health care system was relatively stable. We also excluded: i) surgical and burns patients, as they had little to no data on process of care; ii) those who were less than a month old, as tuberculosis in the neonatal age manifests differently and uses a
different diagnostic approach; and iii) patients whose admission was not recorded in structured record forms (see flowchart Fig 2). The Kenya Medical Research Institute (KEMRI) Scientific and Ethical Review Committee (SSC Number 2465) approved the CIN study enabling use of de-identified data without individual patient consent.

Figure 2 Flowchart of inclusion and exclusion criteria

Study variables and statistical methods

To describe diagnostic practices and explore associations with use of TB diagnostic tests, we used the Kenya National paediatric TB guidelines (S1 Fig) [13], to develop variables to demonstrate documentation of signs and symptoms suggestive of TB and use of investigations conceptualised in a cascade i.e. where only those who met the preceding step were included in the numerator for the next step (Fig 1 and S1 Table). We also described cases who partially met criteria for each step by missing one or more of the preceding steps.

The main outcome for exploratory modelling was documentation of request for any one of the TB diagnostic tests (chest X-ray, Mantoux test, smear microscopy, Xpert MTB/RIF or culture) in those admitted with two or more signs and symptoms of TB (step 1 of the cascade), chosen pragmatically because the guidelines are unclear as to when investigations should be done and for which category of patients. Explanatory variables chosen a priori in models exploring use of tests included: child’s age; gender; presence of a danger sign of severe illness; whether they were a readmission or referral case; and whether they had co-morbidities of HIV, malnutrition or pneumonia. Hospital level factors included whether patients came from facilities that were: i) busy (high admissions)- mean number of admissions was 3,239, so those admitting more were considered busy and included H1, H3, H6, H8,
H10, H12; ii) low or high malaria transmission sites (high transmission sites were H1, H3, H7, H8, H13); iii) and whether they were from high HIV prevalence counties i.e. above the group average of 5.9%, and included H1, H7, H10, H11. We also divided data into time periods (monthly, quarterly, bi-annually and annually) to explore effect of time on use of TB tests in study hospitals. S1 Table shows definitions of variables of interest.

To estimate the burden of TB amongst admissions to paediatric wards, we developed case definitions for clinician TB diagnosis, “Working TB” diagnosis and those who met guideline-recommended criteria for clinical TB or bacteriologically-confirmed TB (see panel in Fig 1 and S1 Fig).

We present summary statistics including frequencies, proportions, means, medians and ranges for categorical and continuous variables as appropriate for descriptive analysis. Variables of interest were used in both univariate and multivariate hierarchical models to explore possible factors that could explain the greatest identified gap in the cascade of TB care (use of TB investigations in children who entered the cascade) with hospital as a random effect. Backward selection was used to build the multivariate model, iteratively removing the least significant predictors at a time. We did not impute missing data as missingness of clinical information is itself an aspect of the cascade itself, which we needed to note, as part of the audit of clinical care.

Likelihood ratio tests and quantile-quantile plots of residuals were then used to determine best fit. Odds ratios were reported with 95% confidence intervals for explanatory variables, exploring for interactions in pre-specified covariates to determine effect modification. The final adjusted model converged at five integration points using a complete case analysis.

**Results**

Table 2 shows patient characteristics from the two-time periods pre- and post-strikes separately and pooled, with the last column showing data not documented/information missing from patients’ files as part of the clinical audit. The footnote in Table 2 and S1 Table shows definitions of variables. We ended up with 42,017 patients pooled from the two-time periods. Median age was 19 months (IQR 9, 47 mth) and 55.3% of all these admissions (N=42,107) were male. Fever was the most common presenting complaint followed by cough in 66.6% (28,032/42,107) and 50.8% (21,408/42,107) respectively. Nearly a third (12,485/42,107) were reported to have growth faltering, while 17.2% (7,400/42,107) had lethargy-defined by AVPU scale < Alert OR not able to drink. 30% (12,485/42,107) had a danger sign while nearly half (19,849/42,107) had an abnormal respiratory sign. Most had an acute illness presentation with median pre-admission history of illness being three days (IQR 1, 5 days). Approximately 10% (4,234/42,107) were readmissions and 16% (6,846/42,107) were referrals from...
lower-level facilities. Nearly 2% (778/42,107) were either HIV infected or sero-exposed; while 19,018/42,107 (45.2%) had an admission diagnosis of pneumonia or respiratory tract infection. Median stay in hospital was three days (IQR 2, 6 days). 2,448 (5.8%) of patients died during their hospital stay.

Table 2: Descriptive characteristics of patients admitted to CIN hospitals in the study period

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Pooled Data</th>
<th>Not documented /missing information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Admissions</td>
<td>Admissions</td>
<td>All admissions</td>
<td>(from pooled data)</td>
</tr>
<tr>
<td></td>
<td>N=23,194</td>
<td>N=18,913</td>
<td>N=42,107</td>
<td></td>
</tr>
<tr>
<td>Age in months: Median (IQR)</td>
<td>20 (9, 48)</td>
<td>18 (9, 43)</td>
<td>19 (9, 47)</td>
<td>433 (1.0)</td>
</tr>
<tr>
<td>Male</td>
<td>12,683 (54.7)</td>
<td>10,593 (56.0)</td>
<td>23,274 (55.3)</td>
<td>161 (0.4)</td>
</tr>
<tr>
<td>Any cough</td>
<td>11,586 (50.0)</td>
<td>9,822 (51.9)</td>
<td>21,408 (50.8)</td>
<td>3,789 (9.0)</td>
</tr>
<tr>
<td>Cough &gt;2weeks</td>
<td>756 (3.3)</td>
<td>836 (4.4)</td>
<td>1,592 (3.8)</td>
<td>21,078 (50.1)</td>
</tr>
<tr>
<td>Fever</td>
<td>15,522 (66.9)</td>
<td>12,510 (66.1)</td>
<td>28,032 (66.6)</td>
<td>3,916 (9.0)</td>
</tr>
<tr>
<td>History of TB contact</td>
<td>228 (1.0)</td>
<td>320 (1.7)</td>
<td>548 (1.3)</td>
<td>11,546 (27.4)</td>
</tr>
<tr>
<td>Underweight (-2SD WAZ)</td>
<td>5,809 (25.0)</td>
<td>4,927 (26.1)</td>
<td>10,736 (25.5)</td>
<td>4,629 (11.0)</td>
</tr>
<tr>
<td>Growth Faltering c</td>
<td>6,859 (29.6)</td>
<td>5,990 (31.7)</td>
<td>12,849 (30.5)</td>
<td>-</td>
</tr>
<tr>
<td>Lethargic d</td>
<td>4,143 (17.9)</td>
<td>3,256 (17.2)</td>
<td>7,400 (17.6)</td>
<td>3,790 (9.0)</td>
</tr>
<tr>
<td>Any danger sign (severe disease)e</td>
<td>6,653 (28.7)</td>
<td>5,831 (30.8)</td>
<td>12,485 (30.0)</td>
<td>3,444 (8.2)</td>
</tr>
<tr>
<td>Any abnormal respiratory sign f</td>
<td>10,763 (46.4)</td>
<td>9,086 (48.0)</td>
<td>19,849 (47.1)</td>
<td>3,442 (8.2)</td>
</tr>
<tr>
<td>Length of illness (median, IQR)</td>
<td>3 (1, 5)</td>
<td>3 (1, 5)</td>
<td>3 (1, 5)</td>
<td>5,133 (12.2)</td>
</tr>
<tr>
<td>Readmission</td>
<td>2,644 (11.4)</td>
<td>1,590 (8.4)</td>
<td>4,234 (10.1)</td>
<td>7,244 (17.2)</td>
</tr>
<tr>
<td>Referral</td>
<td>4,015 (17.3)</td>
<td>2,831 (15.0)</td>
<td>6,846 (16.3)</td>
<td>7,201 (17.2)</td>
</tr>
<tr>
<td>HIV infected/exposed</td>
<td>488 (2.1)</td>
<td>290 (1.5)</td>
<td>778 (1.9)</td>
<td>-</td>
</tr>
<tr>
<td>Pneumonia/RTI</td>
<td>10,382 (44.8)</td>
<td>8,637 (45.7)</td>
<td>19,018 (45.2)</td>
<td>-</td>
</tr>
<tr>
<td>Length of stay-days (median, IQR)</td>
<td>3 (2, 6)</td>
<td>4 (2, 7)</td>
<td>3 (2, 6)</td>
<td>32 (0.08)</td>
</tr>
<tr>
<td>Died</td>
<td>1,302 (5.6)</td>
<td>1,146 (6.1)</td>
<td>2,448 (5.8)</td>
<td>3 (0.01)</td>
</tr>
</tbody>
</table>

\(^a\) Period 1: 1\(^{st}\) November 2015 to 31\(^{st}\) October 2016
\(^b\) Period 2: 1\(^{st}\) November 2017 to 31\(^{st}\) October 2018
\(^c\) Growth Faltering: Either WAZ <-2SD OR admission diagnosis of malnutrition/failure to thrive OR had a prescription for supplementary feeds
\(^d\) Lethargic: AVPU < Alert OR not able to drink
\(^e\) Any danger sign: Central cyanosis OR AVPU < Alert OR not able to drink OR grunting OR received oxygen
\(^f\) Any abnormal respiratory sign: High respiratory rate (for age) OR received oxygen OR central cyanosis OR indrawing OR grunting OR acidic breathing OR crackles OR wheeze
Paediatric TB Diagnostic practices

Using the conceptualised paediatric TB care cascade (panel Fig 1) to examine diagnostic practices amongst paediatric admissions with results in Fig 3 (with blue bars illustrating those who met the criteria for each step, and the orange bars illustrating those who only partially met criteria, because they missed one or more of the preceding cascade steps). 23,741/42,107 (56.4%) of all admissions met step 1 of the cascade, with two or more signs and symptoms suggestive of TB (i.e. cough, fever, weight loss/growth faltering, lethargy). Step 2, further screening by documenting history of TB contact or full respiratory exam was done in 14,873/23,741 (62.6%) of those who met Step 1 (Fig 3 blue bar). An additional 5,125 patients were assessed in line with Step 2 guidance but had not met criteria for Step 1 (Fig 3 orange bar). Step 3, having a chest x-ray or Mantoux test was met in 2,451 (16.5%) of the 14,873 who met Step 2 (Fig 3 blue bar), while 1,484 only partially met Step 3 (Fig 3 orange bar). Step 4 of having at least one bacteriological test done was noted in 392 (15.9%) of the 2,451 who met Step 3 (Fig 3 blue bar); while an additional 592 patients only partially met Step 4 (Fig 3 orange bar). In Step 5, getting a Working TB diagnosis was observed in 175 (44.6%) of the 392 patients who met Step 4 (Fig 3 blue bar). There were an additional 1,177 patients who got a Working TB diagnosis, but missed one or more of the preceding cascade steps (Fig 3 orange bar). S2 Table and S2 Fig show the absolute numbers and full patient flow chart of the clinician decision making process.

Figure 3 Paediatric TB Care Cascade across the 13 hospitals
We further explored use of TB tests, and from Fig 4, we found majority 20,392 (85.9%) of those who had two or more suggestive signs of TB (cascade step 1, n=23,741) had no evidence of TB tests being requested. Chest X-ray was the most commonly requested TB test in 10.9% (2,576) of these patients, while 1.1% (261) had at least one bacteriological test requested with guideline recommended 1st line Xpert/MTB RIF only requested in 1.0% (226) of these patients who met Step 1.

**Figure 4 Use of TB tests in eligible patients**

**Factors explaining TB test requests among patients who had two or more suggestive signs of TB (Step 1)**

Table 3 shows associations between *a priori* specified variables and use of TB tests amongst patients admitted in paediatric wards in Kenya who had two or more suggestive signs of TB (step 1). In the unadjusted models (with hospital as random effect), patients who had greatest odds of having TB tests requested included: HIV infected/sero-exposed (OR 4.44, 95%CI 3.67 to 5.36); as those who had malnutrition (OR 2.72, 95%CI 2.49 to 2.97); severe pneumonia (OR 2.03, 95% CI 1.85 to 2.22); children >5yr (OR1.37, 95% CI 1.22 to 1.53); readmissions (OR 1.28, 95% CI 1.14 to 1.44); and referrals (OR 1.23, 95% CI 1.12 to 1.35). Male children had lower odds of getting TB tests compared to female patients (OR 0.90, 95% CI 0.83 to 0.97). Patients from hospitals in malaria endemic areas also had lower odds (OR 0.33, 95%CI 0.14 to 0.79).

We included 18,282 children in a complete case multivariable analysis and after adjusting for other variables and with hospitals as a random effect, patients diagnosed with malnutrition now had nearly five times the odds of getting TB tests requested compared to those without this diagnosis (AOR 4.68, 95% CI 3.95 to 5.54), with evidence of interaction between malnutrition and those who had...
pneumonia which increased the odds of getting TB tests. Effects of readmission, referral, having an HIV diagnosis and older age were all still associated with greater odds of getting TB tests in the adjusted model, while effect of gender was no longer statistically significant (Table 3). Patients from malaria endemic areas still had reduced odds of getting TB tests done. From the intraclass correlation coefficient (ICC), hospital as a level explained approximately 12% of the variability observed in the data.

**Estimated burden of TB amongst all paediatric admissions to Kenyan hospitals**

Using our pre-specified case definitions, we provide a range of estimates for TB burden (Table 4). Clinicians documented a diagnosis of TB in 1,100/42,107 (2.6%) paediatric admissions, with highest reported in H5 (142/2,346, 6.1%) and lowest in H4 (16/1,954, 0.8%). This number increased by 102 patients to 1,202/42,107 (2.9%) when we included those who got anti-TB prescription but TB diagnosis was not documented. Only 234/42,107 (0.6%) of the admissions were documented to have met the guideline criteria for clinical TB diagnosis (met Steps 1-3 of the cascade), while only 89/42,107 (0.2%) patients from 13 hospitals over two calendar years had documented evidence of bacteriologically confirmed TB. Overall, 4,245/42,107 (10.1%) of all admissions had evidence of at least one TB test being requested.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Full cohort who met step 1 N=23,741</th>
<th>Proportion who met step 1 criteria with TB tests requested N= 3,350 (row %)</th>
<th>Unadjusted odds of getting TB tests requested (95% CI) N=23,741</th>
<th>Adjusted odds of getting TB tests requested (95% CI) N=18,282</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients admitted in each time period</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period 1 (01st Nov 15 to 31st Oct 16)</td>
<td>12,698</td>
<td>1,581 (47.2)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Period 2 (01st Nov 17 to 31st Oct 18)</td>
<td>10,773</td>
<td>1,769 (52.8)</td>
<td>1.22 (1.13 to 1.31)</td>
<td>1.19 (1.09 to 1.31)</td>
</tr>
<tr>
<td><strong>LEVEL 1: INDIVIDUAL LEVEL FACTORS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under 5yr</td>
<td>20,319</td>
<td>2,851 (14.0)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Over 5yr</td>
<td>3,257</td>
<td>477 (14.7)</td>
<td>1.37 (1.22 to 1.53)</td>
<td>1.70 (1.55 to 2.05)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10,467</td>
<td>1,551 (14.8)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Male</td>
<td>13,202</td>
<td>1,787 (13.5)</td>
<td>0.90 (0.83 to 0.97)</td>
<td>0.91 (0.83 to 1.00)</td>
</tr>
<tr>
<td>Readmission cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>17,404</td>
<td>2,413 (13.9)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>2,463</td>
<td>471 (19.1)</td>
<td>1.28 (1.14 to 1.44)</td>
<td>1.24 (1.08 to 1.42)</td>
</tr>
<tr>
<td>Referral cases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15,601</td>
<td>2,004 (12.8)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Yes</td>
<td>4,444</td>
<td>871 (20.5)</td>
<td>1.23 (1.12 to 1.35)</td>
<td>1.15 (1.04 to 1.28)</td>
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<tr>
<td>Admission diagnosis of HIV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not HIV infected</td>
<td>23,193</td>
<td>3,117 (13.4)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>HIV infected or exposed</td>
<td>548</td>
<td>44 (24.5)</td>
<td>4.44 (3.67 to 5.36)</td>
<td>3.81 (3.05 to 4.75)</td>
</tr>
<tr>
<td>Pneumonia with WHO guideline severity classification [37]</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No pneumonia (cold/URTI)</td>
<td>10,633</td>
<td>973 (9.2)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Pneumonia (non-severe)</td>
<td>5,080</td>
<td>848 (16.7)</td>
<td>1.83 (1.65 to 2.03)</td>
<td>2.50 (2.14 to 2.91)</td>
</tr>
<tr>
<td>Severe pneumonia</td>
<td>8,028</td>
<td>1,529 (19.1)</td>
<td>2.03 (1.85 to 2.22)</td>
<td>2.98 (2.60 to 3.40)</td>
</tr>
<tr>
<td>Admission diagnosis of malnutrition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No malnutrition</td>
<td>19,749</td>
<td>2,164 (11.0)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>3,992</td>
<td>1,187 (29.7)</td>
<td>2.72 (2.49 to 2.97)</td>
<td>2.98 (2.69 to 3.31)</td>
</tr>
<tr>
<td>Effect of admission diagnosis of malnutrition interacting with pneumonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No malnutrition + no pneumonia</td>
<td>19,748</td>
<td>2,163 (11.0)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Malnutrition + no pneumonia</td>
<td>1,869</td>
<td>445 (23.8)</td>
<td>3.92 (3.39 to 4.53)</td>
<td>4.67 (3.94 to 5.54)</td>
</tr>
<tr>
<td>Malnutrition + non-severe pneumonia</td>
<td>875</td>
<td>308 (35.2)</td>
<td>6.31 (5.30 to 7.50)</td>
<td>7.08 (5.76 to 8.70)</td>
</tr>
<tr>
<td>Presence of any danger sign</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13,558</td>
<td>1,698 (12.5)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10,183</td>
<td>1,652 (16.2)</td>
<td>1.21 (1.12 to 1.31)</td>
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</tr>
<tr>
<td><strong>LEVEL 2: HOSPITAL LEVEL FACTORS (ICC 0.12, 95% CI 0.06 to 0.24)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients from hospitals in malaria transmission areas</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low malaria transmission</td>
<td>14,933</td>
<td>2,705 (18.1)</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>High malaria transmission</td>
<td>8,808</td>
<td>645 (7.3)</td>
<td>0.33 (0.14 to 0.79)</td>
<td>0.41 (0.19 to 0.89)</td>
</tr>
<tr>
<td>Patients from hospitals with high admissions (mean = 3239)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low admissions</td>
<td>11,165</td>
<td>1,962 (17.6)</td>
<td>1 (ref)</td>
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<tr>
<td>High admissions</td>
<td>12,576</td>
<td>1,388 (11.0)</td>
<td>0.89 (0.32 to 2.50)</td>
<td></td>
</tr>
<tr>
<td>Patients from hospitals in counties with high HIV prevalence</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower HIV prevalence</td>
<td>15,512</td>
<td>2,160 (13.9)</td>
<td>1 (ref)</td>
<td></td>
</tr>
<tr>
<td>Higher HIV prevalence</td>
<td>8,229</td>
<td>1,190 (14.5)</td>
<td>0.55 (0.19 to 1.62)</td>
<td></td>
</tr>
</tbody>
</table>

89
Table 4 Hospital level characteristics and estimated burden of TB amongst admissions over 24 calendar months

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Paediatric Admissions n (col%)</th>
<th>Clinician TB Diagnosis* n (row%)</th>
<th>Working TB Diagnosis* n (row%)</th>
<th>Clinical TB Diagnosis* n (row%)</th>
<th>Bacteriologically confirmed TB* n (row%)</th>
<th>TB tests requested* n (row%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1</td>
<td>3,429 (8.1)</td>
<td>34 (1.0)</td>
<td>35 (1.0)</td>
<td>8 (0.2)</td>
<td>0 (0)</td>
<td>187 (5.5)</td>
</tr>
<tr>
<td>H2</td>
<td>3,128 (7.4)</td>
<td>128 (4.1)</td>
<td>138 (4.4)</td>
<td>41 (1.3)</td>
<td>4 (0.1)</td>
<td>378 (12.1)</td>
</tr>
<tr>
<td>H3</td>
<td>4,154 (9.9)</td>
<td>70 (1.7)</td>
<td>72 (1.7)</td>
<td>11 (0.3)</td>
<td>2 (0.1)</td>
<td>284 (6.8)</td>
</tr>
<tr>
<td>H4</td>
<td>1,954 (4.6)</td>
<td>16 (0.8)</td>
<td>17 (0.9)</td>
<td>7 (0.4)</td>
<td>3 (0.2)</td>
<td>114 (5.8)</td>
</tr>
<tr>
<td>H5</td>
<td>2,346 (5.6)</td>
<td>142 (6.1)</td>
<td>155 (6.6)</td>
<td>17 (0.7)</td>
<td>2 (0.1)</td>
<td>352 (15.0)</td>
</tr>
<tr>
<td>H6</td>
<td>5,186 (12.3)</td>
<td>55 (1.1)</td>
<td>56 (1.1)</td>
<td>6 (0.1)</td>
<td>8 (0.2)</td>
<td>237 (4.6)</td>
</tr>
<tr>
<td>H7</td>
<td>3,135 (7.5)</td>
<td>33 (1.1)</td>
<td>37 (1.2)</td>
<td>6 (0.2)</td>
<td>4 (0.1)</td>
<td>21 (0.7)</td>
</tr>
<tr>
<td>H8</td>
<td>3,773 (9.0)</td>
<td>61 (1.6)</td>
<td>61 (1.6)</td>
<td>21 (0.6)</td>
<td>9 (0.2)</td>
<td>266 (7.1)</td>
</tr>
<tr>
<td>H9</td>
<td>2,479 (5.9)</td>
<td>124 (5.0)</td>
<td>139 (5.6)</td>
<td>33 (1.3)</td>
<td>37 (1.5)</td>
<td>368 (14.8)</td>
</tr>
<tr>
<td>H10</td>
<td>3,731 (8.9)</td>
<td>90 (2.4)</td>
<td>95 (2.6)</td>
<td>19 (0.5)</td>
<td>3 (0.1)</td>
<td>221 (5.9)</td>
</tr>
<tr>
<td>H11</td>
<td>3,180 (7.6)</td>
<td>172 (5.4)</td>
<td>183 (5.8)</td>
<td>45 (1.4)</td>
<td>16 (0.5)</td>
<td>1,008 (31.7)</td>
</tr>
<tr>
<td>H12</td>
<td>3,583 (8.5)</td>
<td>151 (4.2)</td>
<td>185 (5.2)</td>
<td>18 (0.5)</td>
<td>1 (0.03)</td>
<td>695 (19.4)</td>
</tr>
<tr>
<td>H13</td>
<td>2,029 (4.8)</td>
<td>24 (1.2)</td>
<td>29 (1.4)</td>
<td>2 (0.1)</td>
<td>0 (0)</td>
<td>115 (5.7)</td>
</tr>
<tr>
<td>Total</td>
<td>42,107</td>
<td>1,100 (2.6)</td>
<td>1,202 (2.9)</td>
<td>234 (0.6)</td>
<td>89 (0.2)</td>
<td>4,245 (10.1)</td>
</tr>
</tbody>
</table>

*N/B Denominator for columns is the total number paediatric admissions in each hospital for pooled time period

Discussion

We explored TB diagnostic practices amongst paediatric admissions in Kenya using a conceptualised care cascade based on clinical guidelines, and found 56.4% of all admissions met step 1 of the cascade, with two or more signs and symptoms suggestive of TB. Step 2, further screening of history of TB contact or full respiratory exam was done in 62.6% who met Step 1. Step 3, a chest x-ray or Mantoux test was requested in 16.5% who met Step 2. Step 4, at least one bacteriological test was requested in 15.9% who met Step 3. In Step 5, a Working TB diagnosis was documented in 44.6% who met Step 4. Factors associated with requests of TB tests amongst patients who entered the cascade included: i) older age; ii) co-morbidities of HIV, malnutrition or pneumonia; iii) and severe disease, with sicker children, or those being readmitted or referred. The estimated burden of TB in children admitted to Kenyan hospitals by “Working TB Diagnosis” was 2.9%, and only 0.2% all admissions had bacteriologically confirmed TB.

If more than half of all admissions went on to get TB tests as implied by guidelines, this could potentially put a strain on stretched hospital resources due to time, cost and effort to test every eligible patient. We noted similar findings in an analysis of Kenya national TB programme data, with underuse of TB diagnostic tests both in children and adults and a preference for clinical diagnosis [8]. This has been observed in other high burden settings, which report the greatest gap in the TB care
cascade being failure to get investigations [26, 38]. Clinicians appear to resort to their own judgement, selecting patients who are malnourished, HIV infected, referrals/readmissions, probably due to how non-specific guidelines seem to be.

TB symptoms of cough, fever, weight loss and lethargy mimic many other childhood diseases including malaria, pneumonia, malnutrition and HIV [39-41]. The investigations are also difficult to interpret in children who have pauci-bacillary disease, non-specific radiology findings and scanty sputum samples all contributing to reduced sensitivity and specificity of tests, which is compounded by lack of an appropriate gold-standard [15, 39]. Diagnostic criteria or scoring systems using constellations of clinical, radiological and laboratory findings are recommended by some to support clinical decision making [42]. The WHO criteria on which Kenyan guidelines are based, are widely in use and do not promote use of scoring systems [13, 43]. Our study however revealed that clinicians seem to prefer their own acumen, which begs the question: are guidelines helping? Clinicians’ preferences are probably influenced by other nuanced factors like co-morbidities or severity of illness, even in patients who met guideline criteria for further investigations.

Guidelines ideally should help improve effectiveness, reduce variations in clinical practice as well as mistakes and adverse events, and are key in quality of care [44]. Studies have shown even though TB diagnostic criteria and scoring systems have been widely used since the 1960’s, their reliability and validity remain unclear, especially in low resource settings where other co-morbidities like HIV, malnutrition and pneumonia are common [45, 46]. This contributes to the difficulty of understanding the true burden of TB in children. We used a case definition of “Working TB Diagnosis” and found TB represented 2.9% of all admissions. If clinicians adhered strictly to the guidelines, there might be much more testing and probably more TB diagnoses documented. As such, we are still uncertain about the true burden of TB in admitted children in Kenya.

The proportion of tuberculosis amongst admitted children in high burden countries has scarcely been reported, and case definitions vary widely from setting to setting. In Papua New Guinea, they reported TB in 8% of admitted children, and this was based on a clinical score system [12, 47]. A Ugandan study found a TB occurrence of 18.9% in children admitted with pneumonia, using confirmed or probable case definitions [48]- this translated to a proportion of 1.1% amongst all admissions (51 TB cases/4,774 admissions). [49]. Our study found a slightly higher proportion than was noted in Uganda when we considered the “Working TB” diagnosis, probably because this definition included those who got anti-TB medication prescribed despite undocumented diagnosis. However, due to earlier reported issues of under-reporting and under-detection of TB in children in Kenya, and lack of adherence to
guidelines, we believe our estimates are likely to be conservative, with a good number of cases still
undetected [7, 8].

More work is required to continue to understand the complex epidemiology of TB in children, with a
need for better surveillance/reliable data [9, 50, 51]. Understanding the epidemiology will guide
clinicians especially in high burden settings like ours to develop a higher index of suspicion for TB. A
review showed most TB patients are diagnosed after several weeks or months and multiple visits to
health facilities [52]. Improved guidelines should provide clarity as to which patients should be
investigated when, the order of doing investigations, including what to do in case tests are negative
but one has a high index of suspicion for TB, as can be seen in the example of the Indian diagnostic
algorithm [53]. A trade-off is needed between sensitivity and specificity, our data from clinician
practice suggest that they weigh heavily on specificity and thus reject guideline recommendations.

A recent review suggested using existing tools and improving quality of care could potentially reduce
TB deaths by half, but this all depends on having good clinical tools and investigations to identify cases
that clinicians can rely on [54, 55]. We need to continuously review quality of care in our facilities, as
several TB deaths occur despite patients seeking medical care [54]. This was seen in the Kenya national
TB prevalence survey where three quarters of the patients went to health facilities with signs and
symptoms suggestive of TB, but were never diagnosed [7]. Our results give the best estimates we have
at present of the burden of TB in hospitalised children in Kenya and an audit of quality of care given
to children with probable tuberculosis by using the cascade model to describe diagnostic practices,
highlighting gaps in use of investigations that could be targeted in future quality improvement
activities.

Limitations
We observed some missing data, especially of laboratory results, and therefore could not infer if tests
requested were done and what results were, despite efforts to trace back results. We did not impute
missing data as missingness of clinical information is itself an aspect of the cascade itself, which we
needed to note, as part of the audit of clinical care. There is also no unique identifier to link in-patient
and out-patient records, which are often paper based, so we did not have access to follow-up post-
discharge information for our study population. We however only included patients in whom a
structured admission record form (PAR) was used, previous CIN analyses have shown more than 90%
documentation in sites where these forms are used, so we are reasonably certain of documentation
of test requests.
Data were collected around a time of civil strikes that caused disruptions in the health system and may have affected health seeking behaviour and health-worker morale. We dealt with this by taking calendar years before and after the strikes, and found admission characteristics were similar in the two study periods and therefore used pooled data for analysis. Our patient sample was large (more than 40,000 admissions), and from diverse sites. We are confident that we present the best available estimates of TB burden from routine paediatric inpatient data in Kenya as well as diagnostic practices [56].

Unlike other cascade studies, we did not have information on whether the patients completed TB treatment and what their outcomes were after, which would have required longer follow up of these patients. Our study how ever presents the first attempt in our knowledge to describe the burden of paediatric TB and diagnostic practices in a large group of in-patients over a two-year period, highlighting gaps that can aid in planning future interventions and studies as described by Ramnath Subbaramann et al, who describe potential uses of the TB care cascade [57].

Conclusions: Generalisability/application
This work helps contribute to much-needed information on the burden of TB in children. With global efforts being harnessed to find the missing TB cases in the WHO END TB Strategy [58], patients already accessing health care are a potential low-hanging target for improving case detection. We need a better understanding of which children may have TB in our setting and how they present with clearer guidelines to help clinicians better select which patients to investigate, and how to interpret test results considering low sensitivity/specificity of available tests. A cascade approach was useful to visualise critical gaps so that interventions can be targeted to improve quality of care.

Further qualitative work is needed to understand reasons behind health workers’ diagnostic practices despite existing national guidelines and availability of diagnostic tests in these facilities. Economic analyses could also shed more light onto resource implications of implementing the guidelines that recommend investigations for potentially more than half the admissions who had suggestive signs and symptoms of TB. More sensitive criteria would be helpful to discriminate those patients who would benefit from investigations including positive history of contact with a suspected/known TB patient or chronicity of cough both of which were poorly documented in our data. Clinicians therefore need additional support to improve their index of suspicion of TB amongst the admissions they see, in a high burden TB country like ours.
Acknowledgements

We would like to thank the Ministry of Health who gave permission for this work to be developed and have supported the implementation of the CIN together with the county health executives and all hospital management teams. We are grateful to the Kenya Paediatric Association, the Kenya Ministry of Health and the University of Nairobi for promoting the aims of the CIN and the support they provided through their officers and membership. We also thank the hospital clinical teams on all the paediatric wards who provide care to the children for whom this project is designed. This work is published with the permission of the Director of KEMRI.

The Clinical Information Network author group who contributed to the design of the data collection tools conduct of the work, collection of data and data quality assurance that form the basis of this report include: Victor Juma (Vihiga County Hospital); Nick Aduro, Boniface Nyumbile, & Rozzie Malangachi (Kakamega County Hospital); Loice Mutai, Christine Manyasi & David Kimutai (Mbagathi County Hospital); Caren Emadau, Cecilia Mutiso & Celia Muturi (Mama Lucy Kibaki County Hospital); Charles Nzioki & Supa Tunje (Machakos County Hospital); Francis Kanyingi & Agnes Mithamo (Nyeri County Hospital); Magdalene Kuria (Kisumu East County Hospital); Sam Otido & Esther Mukami Njiru (Embu County Hospital); Peninah Muthoni (Kerugoya County Hospital); Rachel Inginia & Melab Musabi (Kitale County Hospital); Emma Sarah Namulala (Busia County Hospital); Grace Akech & Lydia Thuranira (Kiambu County Hospital); Mercy Chepkirui, Abraham Lagat, Cynthia Khazenzi, Basil Okola, Sam Akech, Ambrose Agweyu and Grace Irimu (KEMRI-Wellcome Trust Research Programme). Jacquie Oliwa had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
References


Supporting Information

S1 Chart. Paediatric Admission Record (PAR)

<table>
<thead>
<tr>
<th>Examination</th>
<th>Temp.</th>
<th>Resp.</th>
<th>HR.</th>
<th>O2 Sat.</th>
<th>BP.</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Examination</td>
<td>Oral thrush Y □ N □</td>
<td>Lymph N &gt; 1 cm Y □ N □</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finger Clubbing Y □ N □</td>
<td>Jaundice</td>
<td>0</td>
<td>+</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Oedema</td>
<td>None □</td>
<td>Foot □</td>
<td>Knee □</td>
<td>Face □</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Stridor</td>
<td>Y □</td>
<td>N □</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Central Cyanosis</td>
<td>Y □</td>
<td>N □</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Indrawing</td>
<td>Y □</td>
<td>N □</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grunting</td>
<td>Y □</td>
<td>N □</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acidotic breathing</td>
<td>Y □</td>
<td>N □</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wheeze</td>
<td>Y □</td>
<td>N □</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Crackles</td>
<td>Y □</td>
<td>N □</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Circ. & Dehy. | | | | |
| | Blood Pressure | | | | |
| | Mental status | AVPU | | | |
| | | A | V | P | U |
| | | Can drink / breastfeed? | Y □ | N □ | | |
| | | Stiff neck | Y □ | N □ | | |
| | | Bulging fontanelle | Y □ | N □ | | |

| Infant < 2 ym | Intable | Reduced movement / tone | | | |
| | Y □ | N □ | | | |
### ENT Exam
- **Rt Ear**
- **Lt Ear**
- **Nose**
- **Throat**

### Neurological Examination
- **Rt**
- **Lt**

### Investigations Ordered
- **Blood slide**
- **Rapid Test**
- **Glucose**
- **Stick test**
- **Laboratory**
- **Hb**
- **HCT**
- **Full hemogram**
- **Chemistry**
- **Na + K + U & C**
- **Ca + Alb**
- **LFT**
- **Rapid test**
- **PCR**
- **Lumbar Puncture**
- **Blood Culture**
- **HIV**

### X-Ray
- **CXR**
- **AVS**
- **Other**

### TB Test
- **Microscopy for AFB**
- **Xpert MTB/RIF**
- **Mycobacterial TB culture**

### Summary of Presentation & Problems

### Admission Diagnosis
- **Select One primary diagnosis (tick box indicating "1") and ANY secondary diagnoses (tick box indicating "2"), then indicate level of severity or type of disease if required**

<table>
<thead>
<tr>
<th>Malnutrition</th>
<th>Severe</th>
<th>Non-severe</th>
<th>Acute</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehydration</td>
<td>Positive</td>
<td>Exposed to PMTCT</td>
<td>Negative</td>
<td>Declined test</td>
<td>Asthma</td>
</tr>
<tr>
<td>TB</td>
<td>Kwaish</td>
<td>Malaria</td>
<td>M. Kwaish</td>
<td>Moderate risk</td>
<td>HIV</td>
</tr>
</tbody>
</table>

### Treatment/Supportive Care & Observations
- **Oxygen**
- **Clinician Name & Sign**

### Review status
- **Medical + notes**
- **Priority Nursing Observations**

### Date
- **1/1/2023**

### Time
- **am/pm**
S1 Fig. Excerpt from the Kenya Paediatric TB Guidelines

<table>
<thead>
<tr>
<th>History of presenting illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>For all children presenting to a health facility ask for the following suggestive symptoms: (Cough, fever, poor weight gain, lethargy or reduced playfulness) Suspect TB if child has two or more of these suggestive symptoms Ask for history of contact with adult/adolescent with chronic cough or TB within the last 2 years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Examine the child and check for:</td>
</tr>
<tr>
<td>- Temperature &gt;37.5 (fever)</td>
</tr>
<tr>
<td>- Weight (to confirm poor weight gain, weight loss) - check growth monitoring curve</td>
</tr>
<tr>
<td>- Respiratory rate (fast breathing)</td>
</tr>
<tr>
<td>- Respiratory system examination - any abnormal findings</td>
</tr>
<tr>
<td>Examine other systems for abormal signs suggestive of extra-pulmonary TB</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
</tr>
</thead>
</table>
| Obtain specimen* for Xpert MTB/RIF (and culture when indicated**)
Do a chest Xray (where available)
Do a Mantoux test*** (where available)
Do a HIV test
Do other tests to diagnose extra-pulmonary TB where suspected |

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bacteriologically confirmed TB:</strong> Diagnose if specimen is positive for MTB</td>
</tr>
</tbody>
</table>
| **Clinically diagnosed TB:**
Child has two or more of the following suggestive symptoms:
- Persistent cough, fever, poor weight gain, lethargy PLUS two or more of the following:
- Positive contact, abnormal respiratory signs, abnormal CXR, positive Mantoux |
Note: if the child has clinical signs suggestive of EPTB, refer to EPTB diagnostic table* |
S1 Table. Definitions of key variables of interest

<table>
<thead>
<tr>
<th>Variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; -2SD Weight for age Z score (using CDC charts for 0-20yrs)</td>
</tr>
<tr>
<td>Growth faltering</td>
<td>Either WAZ &lt;-2SD OR admission diagnosis of malnutrition/failure to thrive OR had a prescription for supplementary feeds</td>
</tr>
<tr>
<td>Lethargic</td>
<td>AVPU &lt; Alert OR not able to drink</td>
</tr>
<tr>
<td>Danger signs</td>
<td>Central cyanosis OR AVPU &lt; Alert OR not able to drink OR grunting OR received oxygen</td>
</tr>
<tr>
<td>Abnormal respiratory sign</td>
<td>High respiratory rate (for age) OR received oxygen OR central cyanosis OR indrawing OR grunting OR acidotic breathing OR crackles OR wheeze</td>
</tr>
<tr>
<td>Severe chest signs (as per Kenya Guidelines)</td>
<td>Oxygen saturation &lt;90% OR central cyanosis OR not able to drink OR AVPU &lt; Alert OR grunting</td>
</tr>
<tr>
<td>Severe pneumonia</td>
<td>Had cough/difficulty breathing AND at least one of the severe signs</td>
</tr>
<tr>
<td>Non-severe chest signs</td>
<td>Indrawing OR high respiratory rate for age</td>
</tr>
<tr>
<td>Non-severe pneumonia</td>
<td>Had cough/difficulty breathing AND none of the severe signs AND at least one of the none severe signs</td>
</tr>
</tbody>
</table>

S2 Table. Absolute patient numbers in the cascade of care

<table>
<thead>
<tr>
<th>Step</th>
<th>N= 42,107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1. Two or more suggestive signs and symptoms (cough, fever, lethargy, growth faltering)</td>
<td>23,741 (100)</td>
</tr>
<tr>
<td>Step 2. Further screening done for TB risk done in those who met step 1 (checked for positive TB contact or abnormal respiratory signs)</td>
<td>14,873/23,741 (62.6)</td>
</tr>
<tr>
<td>Step 3: Initial investigations to support clinical TB diagnosis requested for those who met step 1 and 2 (chest x-ray or Mantoux test requested)</td>
<td>2,451/23,741 (10.3)</td>
</tr>
<tr>
<td>Step 4. Patients who met steps 1-3 and had at least one bacteriological investigation requested (Xpert® or microscopy or culture)</td>
<td>392/23,741 (1.7)</td>
</tr>
<tr>
<td>Step 5. Patients who met steps 1-4 and got a Working TB diagnosis</td>
<td>175/23,741 (0.7)</td>
</tr>
</tbody>
</table>
S2 Fig. Patient Flow according to the cascade of care

**KEY**

- Partly meet all the cascade steps
- Fully meet all the cascade steps
- Partially meet the cascade steps

Flowchart depicting patient flow according to the cascade of care.
Chapter 5: Perspectives and practices of health workers around diagnosis of paediatric tuberculosis in hospitals in a resource-poor setting – modern diagnostics meet age-old challenges

Jacquie Narotso Oliwa, Sabina Adhiambo Odero, Jacinta Nzinga, Michaël Boele van Hensbroek, Caroline Jones, Mike English, Anja van’t Hoog

Abstract

Background Detection of tuberculosis (TB) in children in Kenya is sub-optimal. Xpert MTB/RIF® assay (Xpert®) has the potential to improve speed of TB diagnosis due to its sensitivity and fast turnaround for results. Significant effort and resources have been put into making the machines widely available in Kenya, but use remains low, especially in children. We set out to explore the reasons for the under-detection of TB and underuse of Xpert® in children, identifying challenges that may be relevant to other newer diagnostics in similar settings.

Methods This was an exploratory qualitative study with an embedded case study approach. Data collection involved semi-structured interviews; small-group discussions; key informant interviews; observations of TB trainings, sensitisation meetings, policy meetings, hospital practices; desk review of guidelines, job aides and policy documents. The Capability, Opportunity and Motivation (COM-B) framework was used to interpret emerging themes.

Results At individual level, knowledge, skill, competence and experience, as well as beliefs and fears impacted on capability (physical & psychological) as well as motivation (reflective) to diagnose TB in children and use diagnostic tests. Hospital level influencers included hospital norms, processes, patient flows and resources which affected how individual health workers attempted to diagnose TB in children by impacting on their capability (physical & psychological), motivation (reflective & automatic) and opportunity (physical & social). At the wider system level, community practices and beliefs, and implementation of TB programme directives impacted some of the decisions that health workers made through capability (psychological), motivation (reflective & automatic) and opportunity (physical).

Conclusion We used comprehensive approaches to identify influencers of TB case detection and use of TB diagnostic tests in children in Kenya. These results are being used to design a contextually-appropriate intervention to improve TB diagnosis, which may be relevant to similar low-resource, high TB burden countries and can be feasibly implemented by the National TB programme.

Key words: Perspectives, health workers, influencers, case detection, diagnostics, TB, children, Kenya
**Background**

The World Health Organisation (WHO) recommends Xpert MTB/RIF® assay (Xpert®) as the first-line test for bacteriological confirmation of tuberculosis (TB) in children. It provides results fast (ideally within 2-4hr) compared to the 4-6weeks of traditional bacteriological culture [1]. Despite the potential of Xpert® to improve case detection of TB, several studies, including those undertaken in Kenya, have shown that adoption and utilisation has been low [2-5]. Kenya introduced Xpert® in 2011 and now has 156 machines, with more coming, including the newer improved Ultra® [6, 7]. Although most Kenyan county hospitals now have the machines, there is a wide policy-practice gap. Many TB patients (especially children) do not seem to benefit-over 80% have a clinical diagnosis alone and only around 1% have documented use of Xpert® [4, 5]. Given its potential to improve diagnosis due to same day results, and the effort and resources put into making it available, it is important to try to understand the reasons for underuse of Xpert®, and to identify challenges relevant to the use of it and other newer diagnostics.

Alongside the underuse of Xpert® for the diagnosis of TB in Kenyan county referral hospitals, studies have found a general problem with the diagnosis of TB among children-very few children with suggestive symptoms get a proper history and examination as per the TB guidelines [5, 8]. Documented constraints to diagnosing TB in children include the fact that TB mimics many other childhood illnesses; difficulty in obtaining suitable specimens; and low sensitivity of available tests leading to low adoption and poor utilisation [4, 5, 9-12]. A qualitative study from Peru (a high TB burden, low-resource setting) also identified constraints to diagnosing TB in children related to ignorance and stigma; limited access to diagnostic tests; inadequately trained health centre staff; and provider shortages [13]. While several studies have highlighted the challenges of implementing Xpert® among adults, data addressing constraints to the use of this diagnostic among children are sparse [3, 14-17].

New diagnostics like Xpert® are introduced into “old systems” which have established patterns of practice/behaviour that influence technology adoption [18]. Understanding these “old systems”-the context into which the new equipment is introduced, is essential to identifying practices and behaviours that are likely to enhance or constrain uptake and use. This study built on quantitative descriptions of TB detection and management in Kenyan public hospitals [4, 5] and aimed to understand how context influences/shapes TB case detection and use of TB diagnostic tests including Xpert® in children within these hospitals. It was undertaken as part of a larger body of work describing the epidemiology, adherence to clinical guidelines and use of diagnostics for childhood TB in Kenya to...
develop theory-driven contextually-appropriate interventions to address the gaps in detection of TB in children by targeting potentially modifiable influencers (Additional File 1).

Methods

Study setting
In Kenya, healthcare is organised in the following levels: i) Level 1 (Community health services) - responsible for health promotion and early identification of cases to be managed at higher levels; ii) Level 2 (Primary care services) - dispensaries and health centres that carry out preventive and basic curative services; iii) Level 3 (County referral services) - hospitals that provide more comprehensive secondary level care: where TB ideally should be confirmed as they have Xpert® machines; iv) Level 4 (National referral services) - hospitals that provide highly specialised services at tertiary referral level [19]. The National TB Programme (NTP) is responsible for TB health policy and financing; quality assurance and standards; TB health information, communication and technology amongst other administrative roles and these include paediatric TB. The NTP supports all levels of care, from the community up to tertiary level. The NTP is also responsible for training and capacity building on TB for health workers and the child TB training they offer is mainly didactic and runs for three days covering 10 modules covering epidemiology, diagnosis, treatment, HIV co-infection, drug resistant-TB, nutrition, monitoring and evaluation. This study focused on county hospitals and the National TB programme.

Study design
This was an exploratory qualitative study using an embedded case study approach [20], where the broader ‘case’ of TB policy implementation (investigated at national level), and individual case studies (in-depth studies at the hospitals) are embedded within the study. It was designed to provide an understanding of the reasons for the low case detection of TB in children and minimal use of available diagnostic tests including Xpert® in Kenya [4, 5].

Study process, sampling and data collection
The study ran from November 2017 to August 2018 in two phases.

Phase 1: Data were collected during regional paediatric TB sensitisation meetings; national level paediatric training workshops; meetings involving 13 hospitals that are part of a Clinical Information Network (CIN); and interviews with purposively selected staff from the 13 CIN hospitals as well as national level stakeholders. The CIN is a partnership established in 2013 between the Kenya Medical Research Institute (KEMRI), Ministry of Health (MoH) Kenya and the Kenya Paediatric Association (KPA) [21, 22]. The network collects standardized routine data on paediatric admissions from
participating hospitals with the aim of promoting adoption of evidence-based interventions and improving quality of care, with documented successes over time [23-25].

Data collection involved face-to-face semi-structured interviews, small group discussions, face-to-face key informant interviews and observations of child TB trainings, sensitisation meetings and policy meetings, as well as desk review of relevant guidelines, job aides and policy documents.

There were two regional paediatric TB sensitisation meetings during the study period (day long, with 20-30 health workers from various counties sharing guideline updates and discussing diagnostic challenges) and two paediatric TB trainings (three days long, 20 participants each). The lead investigator (JNO) was both a participant and observer in these sessions and both she and SAO recorded notes from observations of the discussions during and after the sessions.

Two regularly scheduled CIN meetings to discuss quality of care in the network hospitals were also held during the study period (each was half a day with 20 participants) and JNO and SAO attended these meetings and recorded notes from the discussions. Data on reported TB diagnostic practices and adherence to guidelines were obtained from interviews with health workers from the 13 CIN hospitals and national level TB stakeholders. Interviewees were purposively selected from among mid-level and senior managers from the CIN hospitals and officers from the National TB programme. They included paediatricians, medical officers, nurse managers and public health officers, selected due to their roles in management to explore perspectives of heads of wards/mid-level managers in the care of children with tuberculosis in Kenyan hospitals.

**Phase 2:** Based on emerging quantitative findings from the broader TB study [4,5], and to further explore issues identified in Phase 1, an in-depth study of health care provider perceptions and practices was undertaken in two purposively selected busy CIN hospitals (paediatric admissions > 1000/year). Both hospitals were in counties with a high burden of TB but one hospital had low numbers while the other had high numbers of TB cases identified [7], and were selected to explore common and unique issues influencing diagnosis of TB in children. Data collection during phase 2 involved interviews, group discussions and observations of hospital practices. Different cadres of front line staff working in the two study hospitals were purposefully selected to elicit diverse perspectives from the different groups including: medical officers; clinical officers; nursing officers; medical officer interns; clinical officer interns; nursing officer interns and laboratory technologists.

Data collection involved JNO and SAO spending two weeks in each hospital attending and observing ward rounds, visiting outpatient departments, making observations to orientate to the context, as
well as having informal discussions and semi-structured interviews with staff to describe what typically happens to children presumed to have TB in their hospitals.

Each formal interview took on average between 30-45 minutes. The topic guide was flexible to allow deeper exploration of issues as they arose within an interview and in subsequent interviews (see Additional File 2). The questions sought explanations/different perspectives from the different settings, freely exploring various health workers’ perceptions and experiences in diagnosing TB in children and use of TB diagnostic tests including Xpert®. Data collection proceeded until no new concepts emerged (theoretical saturation). Both JNO and SAO conducted the interviews and discussions in English, singly and sometimes in pairs. Sessions were audio-recorded using encrypted digital recorders after obtaining informed consent. Interviews and discussions were transcribed verbatim, and transcriptions reviewed for accuracy by JNO, SAO and JN. Fieldwork notes, reflections and summaries were written by both JNO and SAO to capture insights and used to understand the context, and to triangulate findings from the interviews, observed meetings, informal conversations and observations at the hospitals.

Analysis process
JNO reviewed all the interview and field notes’ transcripts to gain a sense of the data, then used an iterative, framework analysis approach [26] to code. Descriptive open codes were used initially and these were subsequently grouped into broad emerging themes. Charting was used to organise the emerging themes into analytic categories guided by a theoretical framework (see Figure 1 and Additional File 3). SAO and JN also independently coded 30% of the documents to ensure consistency as part of primary coding. Using an iterative process, the investigators met over the study period to review the coding framework, resolve any discrepancies and to reach consensus. JNO identified sets of illustrative quotes for each analytic category from the coded segments and discussed with co-investigators to select the most salient. The whole team was also involved in discussions moving from descriptive to analytic coding and they approved the final groupings. The data were organised using QDA Miner® vs 5 to help with the coding and grouping and Microsoft Excel® for charting.

Theoretical Framework
We used the Capability, Opportunity, Motivation- Behavioural model (COM-B) framework [27] to help guide in the interpretation of the data. COM-B posits that three essential conditions interact to generate a desired behaviour/action (figure 1). Capability represents the aptitude to engage and has physical (e.g., strength, skills, stamina) and psychological (e.g., knowledge, memory) domains. Opportunity represents environmental factors that affect one’s capacity to perform and has physical (e.g., time, physical environment) and social (e.g., interpersonal influences, social cues, cultural
norms) domains. **Motivation** represents internal factors that allow one to employ **capability** and **opportunity** to perform, and has **automatic** (e.g., wants, needs, impulses, habits) and **reflective** (e.g., beliefs, intentions, choices) domains. COM-B has been widely used in various contexts, both as a lens to analyse implementation barriers and facilitators and to help design interventions [28-48]. It was used in this work to interpret the factors that influence diagnostic practices, in a way that will enable design of interventions that might change behaviours to increase TB case detection in children and to help policy makers and health workers (key target audiences) understand the issues being explored.

**Figure 1 COM-B model elements, influences and outcomes**

**Assurance of analytic rigour**

There was active engagement with participants before and over the study period. Informal discussions during clinics and ward rounds and observations of practices during the two-week hospital visits helped to triangulate findings from the formal interviews, offering explanations for observed convergence and divergence of opinions. The quantitative data from earlier work [4, 5] helped identify divergent hospitals as cases and highlighted problem areas in the cascade of paediatric TB care that were used to guide interviews. Theory was used for interpretive analysis of the data. Common and contrasting issues from different cadres of health workers were identified, noting any deviant cases. Notes were kept of observations and reflections. The Principal Investigator (JNO) being a paediatrician, member of the Ministry of Health paediatric TB technical working group and a paediatric TB trainer had an insider perspective of child TB activities in the country and found that her position made it easier to enter spaces and to get people to open up about their experiences; while SAO was a research
assistant with a background in environmental health and she had a more open mind going in to interview and asking more questions for her own understanding that made the data richer. Regular peer debriefing with senior co-investigators and social science experts in the research team at various stages of data collection and analysis helped ensure reflexivity. Preliminary results were fed back to some of the participants and to child TB stakeholders during network meetings and technical working group meetings for member checking. The Consolidated criteria for reporting qualitative studies (COREQ) checklist [49] was used for further quality assurance.

Results

Between November 2017 and August 2018, we conducted 29 semi-structured interviews with frontline health workers and mid-level managers. We also held three small group discussions and five key informant interviews with policy makers and senior health service administrative staff (Additional File 4 for summary of participants). Observation notes were obtained from the two day-long paediatric TB sensitisation meetings, two CIN meetings, two paediatric TB trainings and two-week visits to the two hospitals of interest. In our interviews and discussions with the various cadres of health-workers about their experiences diagnosing TB in children and using diagnostics including Xpert®, participants described at length the challenges they faced but also provided some suggestions on what could potentially be done to improve the situation.

Context: Our observations helped provide an understanding of the context of typical Kenyan county hospitals. In brief, the hospitals selected were both very busy (>1,000 paediatric admissions a year) and came from counties that reported a high incidence of TB. We noted that they had similar constraints in terms of low staffing, periodic stock-out of Xpert® cartridges and reagents and bottlenecks in work flows. The main distinguishing factor in the hospital that detected more TB cases was their localized norms and culture of teaching, mentorship and teamwork. Our observations also helped describe the flow that a patient presumed to have TB would be processed in a typical county hospital (Additional File 5).

Findings were summarised into 25 themes, representing the factors that influence TB case detection in children (chart in Additional File 3). These themes were then grouped into eight broad analytic categories, illustrating how the emerging themes had potential to impact Capability, Motivation and/or Opportunity to diagnose TB in children, and whether the influences were at individual, hospital or community level and are further described in the subsection that follows.
Individual level influences

i) Knowledge and skills

Knowledge/awareness of paediatric TB did not appear to be a major challenge: most health workers across the cadres were aware of the manifestations of TB in children and how to arrive at a TB diagnosis. Most were also aware of the Kenyan paediatric TB guidelines and had had some form of TB-specific training, either from medical school or on-the-job training:

“... So, after you’ve enquired everything, contact with the person, loss of weight, see those things actually lead you to TB...since they have a cough and all that you’ll do a chest x-ray. A chest x-ray might actually show ...you might get a miliary picture or something like that. So, after that you can do the skin test but here we don’t do it, but we do sputum for Xpert. So, we do the sputum and if it comes back positive we treat the baby for tuberculosis...” Clinical Officer Intern_SSI_21

Many participants, both junior and senior however reported difficulties in actual specimen collection, as illustrated in the following comment:

“...the biggest problem is specimen collection. It’s invasive, whether you are doing gastric, bronchoalveolar, because most of them...those are the things.... it’s not very easy...” Paediatrician_SSI_10

According to most participants and what we observed, training provided by the National TB programme and other partners was mainly didactic with little opportunity to gain competence in specimen collection. Some participants therefore suggested a review of the content of paediatric TB training and how it is delivered, and this feedback was given to the National TB programme representatives.

ii) Experience, confidence and competence

Where TB was more commonly detected in children, the health workers were not only knowledgeable but seemed more alert to the possibility of the disease, possibly because they had increased confidence and greater individual experience of investigating and diagnosing TB in children. Interestingly, this pattern seemed self-reinforcing, helping sustain efforts to identify TB as a shared local norm among health workers in that hospital:

“It all boils down to...if you provide exposure to as many cases as possible then you’ll see actually day becoming...being as clear as day and night... it comes with experience [[okay]] it comes with skills, it comes with seeing many patients...” Paediatrician_SSI_01
In most places however, TB was rarely a differential diagnosis until the child had been seen several times for un-resolving diseases like pneumonia:

“And you know when I get a first contact, like it will not hit to me that this is TB initially, I will treat first then from there the second time she comes...that is when I will think like, ooh this kid has been seen in the clinics outside, has been treated probably twice or thrice with antibiotics, I have also treated with antibiotics, but this is the fourth time the baby is back with a cough and a fever.” Clinical Officer_SSI_23

Where health workers experienced marked improvement in children in whom they decided to start anti-TB medication, this affirmed their decision, making them more likely to consider TB as a diagnosis in the future (positive feedback):

“Positive experiences...getting a child who’s doing very bad, send to nutrition, child not improving.... the moment you initiate anti-TBs, the third week, the fourth week the child is good, putting on weight. You see that child and you feel so encouraged and you’d really want to see, even if it’s a hundred and one you’ll still see tomorrow...” Clinical Officer_SSI_31

Reflecting on their experience in using Xpert® in children, many health workers from the meetings and the various hospitals reported to have never actually never seen a positive test result:

“I have never gotten a positive GeneXpert...All of them. In my many years by the way, I have never gotten a positive GeneXpert in our work place...” Paediatrician_SSI_09

Consequently, the clinicians both junior and senior, had little faith in the diagnostic test leading them to rely on their clinical acumen and treat presumptively:

“...especially even that GeneXpert I’ve told you it usually doesn’t help much but we have also had, you know, those x-rays sometimes you are not sure...But when you are in that dilemma you do...you give treatment and see what happens...” Paediatrician_SSI_07

“...Never, never...I don’t know if it’s our samples that don’t have enough bacteria, I don’t know what the problem is, but it’s never positive. Even in someone who you are so sure this can’t be anything else...this is TB. Lakini [but] Xpert is showing you negative. We usually just continue treating as a presumptive...” Medical officer_SSI_24

iii) Fears and Beliefs

Alongside perceived competencies, some individuals also held certain beliefs or fears that influenced their practices, including the fear of acquiring TB:
“...one of the things people [health workers] fear is getting sick. Because, you know, once you see how the TB patients struggle, finishing the 6-month medication, if you fail you have to roll over and get in your drug resistant medication. It’s crazy...” Public Health Officer_KII_02

In addition, for some, there was a reluctance to diagnose and treat TB in children linked to a fear of the side effects of the drugs:

“...We didn’t treat because we were afraid that...the liver was an issue. I think we learnt that we should treat regardless...” Medical Officer_SSI_32

Relatedly, the reluctance to diagnose was often linked to underlying beliefs that children do not usually get TB as shown below;

“To be honest, I think I have been a bit reluctant. I’ve not been that vigilant to identify this child[ren] with TB, which I’ll start from now... We are so reluctant on our part. Or maybe we may overlook these children; maybe we may think...we may not suspect a child may be having TB...” Nursing Officer_SSI_30

However, as described above, fears were allayed as health workers observed children improving with treatment:

“I don’t think I have that fear anymore in terms of saying yes, start this child on anti-TB. I think our confidence levels with time and having observed children, you know there are some you see, you start on anti-TB then the improvement within a month or two is like magical...” Paediatricians_SGD_11

These examples show that at individual level, experiences affect one’s knowledge, skill and competence and can increase or decrease one’s perceived capability (psychological) to make a child TB diagnosis. This is often reinforced by positive experiences of improvement where treatment had been initiated and in other cases discouraged by negative test results. Positive experiences therefore contribute to the health worker’s motivation (reflective) to keep trying to diagnose TB in children, especially if they can see or receive news of the clinical results of their practice. This in turn affects their opportunity (social), because no culture of Xpert® use is established and so they fail to gain competence. Strongly held fears and beliefs about TB possibly affected motivation (reflective & automatic) negatively.
Hospital influences

i) Hospital norms

In the hospital that reported higher numbers of child TB cases, established localized norms guided work practices. Senior clinical leads offered teaching and mentoring, fostered multi-professional teamwork, with every member having shared responsibility for ensuring patient well-being; and National TB guidelines used as standard practice. These local working practices enhanced individual capabilities as they created a conducive environment where good practices were taught and encouraged:

“When you get to the ward you are trained and now you are the one who will be getting it...They definitely teach us...Clinical officer [X] is very helpful...he’s the one who taught us how to collect the sputum after Dr [M] had taught us...he also repeated the whole thing as in physically...” Clinical Officer Intern_SSI_21

A key feature of this conducive environment was facilitative teamworking where team members relied on each other, for example, in making a diagnosis:

“...then since us we are interns we have people who are more experienced than us...the clinical officers...and the MO [Medical Officer] who is in paediatrics and also Dr. K so you just talk to...your immediate-most senior like an MOI [Medical Officer Intern] if he’s unable...we talk to our MO and then maybe them they can do it [specimen collection] ...” Clinical Officer Intern_SSI_21

Of note in several hospitals, leadership and mentorship was missing as some senior clinicians were not at-ease doing specimen collection procedures themselves. This lack of competence by seniors consequently lead to challenges in diagnosing TB in children:

Interviewer: “Have you ever participated in the sample collection process?”

Respondent: “No. I am used to giving instructions and go. Maybe now I should participate to see how it is being done. Because I am now suspecting, could it be the sample collection which is causing the issue?” Paediatrician_SSI_07

ii) Organisational processes and resource management

In the hospitals we visited, we noted there was poor patient flow, no designated procedure on when or where investigations should be done for children seen in the outpatient department of both
hospitals (patient flow process map Additional File 5). Consequently, as reported by some of the participants, this led to a lack of continuity of care:

“...So, I was feeling the challenge that is there in making the diagnosis of TB is that when the child leaves here, you don’t know when...if the child is going to the next...will get to the next place, and if they are going to have a Mantoux [TB skin test] done, is the report going to come back to you? You know if it doesn’t come back to you directly, you’ll find...the child might get lost somewhere along the way...because if you are not the same person seeing that same patient again, you don’t know what the decision of the next person will be. And you’ve sent them for a Mantoux, the interpretation, who will interpret it and are they going to use the same thought that you had?” Clinical Officer_SSI_24

The lack of proper post-discharge follow-up was common in most of the other hospitals:

“Now there is a gap in this child at out-patient at this level, once treatment is initiated in the ward the child is discharged. Linking them to a TB clinic sometimes becomes an issue, so they may fall by the way side, they may not end up in the TB clinic, or they may interrupt TB treatment because of that...” Public Health Officer_KII_01

Where key resources were available (equipment; reagents; skilled manpower; guidelines/job aides), clinicians could more comfortably make a TB diagnosis (psychological capability and motivation), like in the following example:

Respondent 2: “...yes, yes, yes. There are some charts even in the nursing station I think you’ve seen one. There is a chart on the wall. Yeah, but basically as she has said, these are things we do almost every day so most of them actually stick...”

Respondent 2: “...any time you think you have forgotten something. You know there is the paediatrics bible, that is the paediatrics protocol...” Small group discussion with interns

However, where there were resource shortages, health workers struggled:

“Against us again is the X-rays, because X-rays are a mainstay of diagnosis for TB in children. Unfortunately, they have not been readily available all over the country. They are available in very few sites and in those sites, there is a cost implication to the children which sort of acts as a deterrent or a limitation to the same...” Public Health Officer_KII_01

For the diagnostic tests, commonly reported issue was frequent stock-out of Xpert® cartridges and reagents (nation-wide) which in turn led to delays in making a diagnosis and reinforced a reluctance
in ordering the tests in future. This shows how age-old system issues like stock-outs potentially affect adoption of new diagnostics:

“...Most times no coz sometimes we have stock outs of Xpert... when there are stock outs you might want to send the patient to another place, where... maybe a private facility where they have to pay for it out of pocket...” Medical Officer_SSI_14

The influences of hospital capacities in diagnosing TB therefore span hospital norms including multi-professional teamwork, leadership and mentorship; as well as processes and resource management. The hospital environment thus affected both group and individual work practices around diagnosing TB in children by influencing opportunity (physical & social) which in turn affects psychological capability as well as motivation (reflective) to keep at it.

Community influences and implementation of policies and directives

Beyond individual and hospital levels, we identified themes spanning two aspects of the broader health system: the policy level and characteristics of the population seeking care.

i) Community beliefs and practices

Stigma, health-seeking behaviour and community awareness of TB manifestations in children made some health workers reluctant to test and treat for TB as illustrated in this example:

“...in a few instances you tell the parent the child has TB and they get very mad. They don’t want to believe it, ‘You can’t say my child has TB, kwetu hakuna TB [there is no TB where come from]’ ...in fact there are some who even refuse treatment arguing that their place people don’t get TB, especially the rich people ...” Paediatrician_SSI_07

Of note, TB is stigmatised in this setting due its presumed association with HIV, which increased reluctance by health workers to give a TB diagnosis, as health workers feared it may lead to emotional burden for their patients as seen in this illustration:

“...And then there is that thing people thinking TB is equal to HIV, so when now someone has been told that they have TB now everyone thinks that they are HIV positive, so there is that even being shunned by the family. I have a mother right now who was actually chased away by her extended family because of the TB diagnosis...” Paediatrician_SSI_03

ii) Implementation processes by the National TB programme

At policy level, we found that that some of the National TB programme implementation decisions affected health workers’ capacity to use TB diagnostic tools. For instance, when Xpert® was being
introduced in Kenya, the selection of participants to take part in trainings inadvertently left out key actors like clinicians, resulting in low demand for use of the diagnostic reported here:

“...We realized that when we rolled out Xpert, we focused a lot of our training on the lab personnel, thereby leaving out the drivers of the service use. So, the clinicians initially were not part of the target population for training and so what we have realized as a programme is that therefore the demand for the service is skewed and is not actually being availed to the people who need the service...” Public Health Officer_KII_01

Policy-related directives from the National TB programme that encourage data use for audit purposes could subsequently motivate quality improvement initiatives in hospitals which lead to increased number of children diagnosed with TB:

“...But in terms of feedback... we do data quality audits and they are done together with the health care workers so it is a participatory sort of quality audit. And the feedback [about performance] is given on the spot...” Public Health Officer_KII_02

We therefore found that health worker practices are influenced by what was happening in the wider communities and from policy implementation processes led by the National TB programme which affect the opportunity (physical) and motivation to diagnose TB in children.

In summary, we have described influencers of diagnosing TB in children at different levels: (individual, hospital and the wider community and policy level) and shown how these factors interact to influence the behaviour of health workers through impacting capability, opportunity and motivation (illustrated in figure 2 and chart in Additional File 3). At individual level, knowledge, skill, competence and experience, as well as beliefs and fears impacted on capability (physical & psychological) to diagnose TB in children and use diagnostic tests, and eventually their motivation (reflective then automatic) to keep doing it will lead to sustained practice. Most of the issues of processes and resources at hospital level we thought had potential to impact capability (physical & psychological) and opportunity (physical & social), because of breaks in the care, and this in turn could influence motivation (reflective and eventually automatic) through impaired decision making. Community beliefs and practices as well as policies, we thought influenced capability (psychological), motivation (reflective & automatic) and opportunity (physical) and because of these, the health workers seemed hesitant/reluctant to make a TB diagnosis in children.
Discussion

We set out to document experiences of Kenyan health workers in Kenyan county hospitals, describing the context and influencers of TB case detection and use of TB diagnostic tests in children. This was to explore reasons for gaps noted in earlier studies from the same setting [4, 5, 50] and to identify potentially modifiable influencers, guided by the COM-B framework. At individual level, notable factors included knowledge, skills and competence, which were influenced by past experiences and confidence (mainly drawn from experiential knowledge and strongly held fears and beliefs about TB) and these affected capability (physical & psychological). Guided practice and positive experiences of success seemed likely to contribute to health workers’ motivation (reflective) to keep trying to diagnose TB in children, findings consistent with ideas around ‘trialability’ in the wider implementation literature and dissemination of innovations [51-53]. A notable example was consistent negative Xpert® results leading to loss of faith in the diagnostic, which probably contributed to its underuse. Difficulties in obtaining specimen and bacteriological confirmation of TB in children is recognised age-old dilemma [54]. Although knowledge seemed adequate and most participants had had some form of paediatric TB training, this on its own was not enough to translate into changes in practice, and this supported by various other studies [55, 56]. While formal education and training of health workers is key to ensuring competence and capability, it is now apparent that diagnosing TB in children is mostly reliant on “embodied” or tacit knowledge, developed through observing empathetically and hands-on...
experience, described by various authors [57, 58]. Improving the quality of training by the National TB Programme to make it more practical and ensuring continued mentorship and sensitisation or other sustaining strategies such as supervision or group problem solving after training could potentially address some of these gaps, as described by Rowe et al [56, 59].

At the hospital level, the influences of hospital capacities in diagnosing TB in children spanned hospital norms including multi-professional teamwork, leadership and mentorship; as well as processes and resource management. The hospital environment affected both group and individual work practices around diagnosing TB in children by influencing physical and social opportunity as well as motivation to keep at it. While resources may not be immediately modifiable, they do have great impact and should be available for anything else to work well. We saw how frequent stock-outs of Xpert® cartridges and reagents were a hindrance to developing a culture of its use. Lack of availability of resources and staffing issues are some of the age-old challenges in lower-income settings like ours, and these hinder adoption of new policies and health interventions [60]. Patient flows and processes are however potentially modifiable. We observed lengthy procedures and bottlenecks that ended up frustrating both health workers and patients. Poor patient flow has been recognised elsewhere as an impediment to quality of care given to patients [61] and simple care redesign strategies can improve patient flows using existing capacity efficiently, leading to improved physical opportunities to diagnose TB in children. We also noted in the facility with high TB case detection, the existence of positive hospital cultures and norms like teamwork, mentorship and shared responsibility for patient care provided social opportunity, an environment conducive to routine diagnosis of TB in children including improved processes. Schein describes organizational culture as a pattern of basic assumptions held by a group that has worked well enough to be considered valid and therefore is taught to new members as the correct way to perceive, think, and feel [62]. The cumulative way in which health-workers experience their jobs and lives at the organization is therefore a key factor in quality improvement and can potentially be leveraged to improve case detection of TB in children: mid-level managers are key [63-66].

At community level, a notable influencer was stigma, which seemed to reduce willingness to diagnose TB in children. Stigma arose from local communities—some caregivers believed that TB was a disease of poor people. Health workers themselves sometimes perpetuated TB stigma—some did not look for TB in children and seemed unwilling to diagnose it due to their own fears and beliefs. Various studies reveal the main reason for TB stigma is fear of infection (although in our case, it seemed to be mainly due to the association of TB with HIV), and that TB stigma increased diagnostic delays and treatment noncompliance [67, 68]. Addressing stigma is fundamental to delivering quality healthcare in general.
and needs to be factored in efforts to improve TB case detection. It is an example of how the “outer setting” i.e. the social context as described by Damschroder, influences what happens at hospital and individual level [53]. Strategies to address stigma and patient beliefs need to be multi-level (from patient-level, to the community, to policy level, to the institutions and to individual health workers) to be effective and may include structural/policy changes, patient empowerment, education, and counselling amongst others [69, 70]. Policies are also part of the outer setting. We found that some of the National TB programme implementation decisions affected health workers’ capacity to diagnose TB in children using diagnostics. We saw for instance how training directives (i.e. who gets selected for trainings) impacted hospital practices and ultimately on the individual health worker’s knowledge, skill and competence in diagnosing TB in children by providing opportunity and therefore impacting their capability and motivation to keep at it. Human resources for health literature suggest that even in settings like Kenya where it may be challenging to increase staff numbers, smart policies like those aimed at strengthening retention, education, training, job-protection for staff can still achieve good health outcomes [71].

Our study had several strengths. We employed various strategies to ensure rigour, including purposive selection of cases to allow comparison and a wide range of perspectives; triangulation of findings from interviews, discussions and observations; clear records of all processes; member checking; and debriefing and support from colleagues. The research was embedded in theory that helped get a better understanding of the problem of TB case detection in children as a part of a larger mixed methods study, which will help guide development of contextually appropriate interventions. This work helps extend the body of literature in which the COM-B models has been used to understand health systems and to better explain the complex problem of diagnosing TB in children.

We had some limitations. As this was baseline formative work, to be useful it needs to progress to inform plans for testable interventions. Our data collection was cross-sectional, but we still managed to delve deep into the issues by using rich and varied data collection methods. There was a lot of disruption caused by prolonged industrial action by the health workforce during the study period [72]. This influenced who was available to interview and how much time we could spend at each site. We however leveraged on good relationships from long standing quality improvement work by our group that eased participants’ willingness to work with us despite being disgruntled.

Conclusions

We used comprehensive approaches to identify modifiable influencers of TB case detection and use of TB diagnostic tests in children in Kenya, which is a high burden setting and few children get notified to the TB programme. At individual level, knowledge, skill, competence and experience, as well as
beliefs and fears impacted on *capability* (physical & psychological) as well as *motivation* (reflective) to diagnose TB in children and use diagnostic tests. Hospital level influencers included hospital norms, processes & patient flows and resources which affected how individual health workers attempted to diagnose TB in children by impacting on their *capability* (physical & psychological), *motivation* (reflective & automatic) and *opportunity* (physical & social). At the wider system level, community practices, beliefs, and implementation of TB programme directives impacted some of the decisions that health workers made through *capability* (psychological), *motivation* (reflective & automatic) and *opportunity* (physical). These results are being used to design a contextually-appropriate intervention to improve TB diagnosis, which may be relevant to similar low-resource, high TB burden countries and can be feasibly implemented by the National TB programme.

**Abbreviations**

Anti-TB: Anti-tuberculosis medication  
CIN: Clinical Information Network  
COM-B: *Capability, Opportunity, Motivation*- Behavioural model  
COREQ: Consolidated criteria for reporting qualitative studies  
DST: Drug Susceptibility Testing  
IPT: Isoniazid preventive Therapy  
KEMRI: Kenya Medical Research Institute  
KPA: Kenya Paediatric Association  
MoH: Ministry of Health  
MO: Medical Officer  
NTP: National Tuberculosis Programme  
RTI: Respiratory Tract Infection  
Rx: Treatment  
S/S: Signs and Symptoms  
TB: Tuberculosis  
WHO: World Health Organisation
Additional Files

Additional File 1: Mixed Methods Conceptual Framework

Additional File 2: Interview guides

KEMRI-WELLCOME TRUST RESEARCH PROGRAMME: HEALTH WORKERS INTERVIEW GUIDE

UNDERSTANDING AND IMPROVING CASE DETECTION AND CARE FOR CHILDREN WITH TUBERCULOSIS IN KENYA

Tuberculosis (TB) is a major global public health challenge, and diagnosis in children remains a challenge. The Kenyan health care system requires all cadres of health workers to be equipped to suspect, diagnose and treat children with TB, but their capacity to diagnose childhood TB is unknown. I will ask you some questions around care provision for children with suspected TB in your facility, and would request you answer as honestly as possible. Thank you

1. Gender

   • Male
   • Female

2. Educational background as a health care provider

   • Other (specify)
• Nurse
• Pediatrician
• Laboratory technician
• Medical Officer
• Clinical Officer
• Intern
• TB Clinic MO/CO

3. Type of facility/level of care e.g County referral, sub county etc

4. Which department do you work in?

• Chest clinic
• MCH
• Outpatient – IMCI
• Paediatric ward
• Other, specify...........................

5. How many cases of children suspected of having TB do you see on average in a:

• Day?  • Week?  • Month?

6. You get a child admitted with cough, difficulty in breathing, cyanosis and severe lower chest wall indrawing referred from a lower level facility after having been on Amoxil for 3 days without improving.

Please talk me through how you would provide care for such a child

7. Probe: what further history would you ask for?

    i. Why would you ask for the particular factors you have stated?
    ii. How would you establish if this child has a history of TB contact?
    iii. How has your experience been in trying to determine if a child has had a history of contact?

8. If there are challenges (e.g. stigma) in establishing contact history, how do you deal with them?

• duration of cough
• fever
• poor weight gain
• lethargy or reduced playfulness

125
• Ask for history of contact with adult/adolescent with chronic cough or TB within the last 2 years.
• Contact includes frequency and duration of contact e.g. sleeping in the same room, caregiver etc

9. What would you look for in his physical exam?

Probe: Find out what they usually check for in terms of abnormal respiratory findings. List should include: cyanosis, chest wall indrawing, fast breathing (tachypnoea), wheeze, crackles, low oxygen saturation (SPO2), acidic breathing

• Temperature >37.5 (fever)
• Weight (to confirm poor weight gain, weight loss) - check growth monitoring curve
• Respiratory rate (fast breathing)
• Respiratory system examination - any abnormal findings

10. Following these history and examination findings, what differentials would you consider for this child, and why?

• URTI
• Pneumonia
• TB
• Allergic reaction
• Foreign body inhalation
• Heart disease

11. You suspect this child could be having tuberculosis from the history and physical examination and you need to investigate further to confirm

Probe: What investigations or tests would you do?

• Xpert MTB/RIF
• Chest x-ray
• Microscopy
• Culture
• Mantoux

Probe further for Xpert. Does their hospital have a machine? Have they ever sent specimen for children? How many times past 3 months? Any positive result past 3 months? How quickly do they get results? Hours/days/weeks? Pos/Neg experience using it?)
12. Which tests are available in your hospitals to test for TB? Which one do you prefer using?

13. At what point would you ask for the specific investigations along the evaluation process?

14. What has been your experience using each of the TB investigations?

15. When does the child get the test in patient (during admission or how many days after?) vs out patient.

16. Who orders the tests? Where do they document? can an intern order?

17. Does the test result come with a report? who reads the report

Probe: are the interviewees themselves comfortable reading the x-rays and interpret results for this and other TB tests (based on which they say they use)?

18. Which type of sample would you ask for?

19. How would you determine the type of specimen to collect for testing? How frequently are they collected?

- Sputum (probe for specimen)
- Other specimen e.g. FNA, bronchoscopy and bronchoalveolar lavage (BAL), biopsy, CSF, Joint aspirate, stool, urine

How would you obtain this sample? (explore other methods apart from sputum induction)

20. Who collects the specimen (here ask also if they have champions for the sample collection procedures)?

21. What are some of the highlights/downsides to these sample collection procedures?

- Sputum expectoration
- Gastric aspiration
- Sputum induction
- Tuberculin skin test (TST)
- Nasopharyngeal aspirate
- Gastric aspirate

22. What has been your experience with these sample collection procedures?

23. Which methods have you personally carried out?

How long did it take you?

What were the good, the bad experiences?

24. How would you arrive at a final diagnosis of TB in Moses? When and how do you arrive at a final diagnosis of TB??
25. Probe how they interpret the guidelines to make:

a) clinical TB diagnosis, what combination of signs, symptoms and tests would they use?

b) Bacteriologically confirmed TB, what tests would they do?

• Bacteriologically confirmed TB: Diagnose if specimen is positive for MTB

• Clinically diagnosed TB: diagnose if child has two or more of the following suggestive symptoms: Persistent cough, fever, poor weight gain, lethargy PLUS two or more of the following: Positive contact, abnormal respiratory signs, abnormal CXR, positive Mantoux

26. Show them a chart of the guidelines and probe for their experience in using these guidelines. Which areas do they find challenging and why?

27. Who makes the final TB Diagnosis decision? Can interns/medical/clinical officers make decisions to start treatment or do they have to wait for someone more senior like a paediatrician?

28. What treatment would you start, and when would you change and why?

29. What has your experience been with diagnosis of childhood TB?

   i. Please tell me of the negative or positive experiences you have had
   ii. What lessons have you learnt from these experiences?
   iii. What would you do differently?

30. From this discussion, these seem like a lot to remember. What strategies do you use/have in place to help you decide if a child has TB or not? How frequently do you refer to these aides?

31. We looked at one-year data from your medical records. In this period, we found the following:

   • Admissions to children’s wards = 3,018
   • Admissions with a respiratory tract infection/pneumonia = 1,495 (49%)
   • Children with 2 or more suggestive signs and symptoms of TB amongst the RTIs = 941 (62.9% of all RTIs)
   • Children with a working diagnosis of TB (i.e. either admission/discharge Dx or were started on anti-TB) = 33 (1.08% of all admissions)
   • Children with a missed diagnosis of TB (i.e. had 2 or more suggestive symptoms, but did not get a TB test or get a working TB Dx) = 1,356 (44.4%)
Amongst those with a working TB Dx, 7 (21.2%) had an Xpert test; 8 (24.2%) had a chest x-ray, and no children had documentation of culture, smear or Mantoux test being done.

Why do you think there were so many potential missed diagnoses?

What can be done to improve this situation?

In your opinion, why do you think there so few investigations carried out?

What can be done to improve this situation?

KEMRI-WELLCOME TRUST RESEARCH PROGRAMME: KEY INFORMANTS INTERVIEW GUIDE

UNDERSTANDING AND IMPROVING CASE DETECTION AND CARE FOR CHILDREN WITH TUBERCULOSIS IN KENYA

Tuberculosis (TB) is a major global public health challenge, and diagnosis in children remains a challenge. The Kenyan health care system requires all cadres of health workers to be equipped to suspect, diagnose and treat children with TB, but their capacity to diagnose childhood TB is unknown. I will ask you some questions around your experiences surrounding care provision for children with suspected TB, and would request you answer as honestly as possible. Thank you.

1. Educational background as a health care provider and what additional training have you received? _____________________________
2. Type of facility/level of care e.g County referral, sub county etc
3. Which department do you work in and what does your role entail with regards to TB in children?
4. How long have you served in this capacity?
5. What have been some of your experiences (good and bad) around case detection of TB in children as you serve in your role?
6. What is your opinion on the priority given to child TB by the Ministry of Health? Why is it a priority or not? How are resources allocated for your docket? What are your thoughts on this? Explain reasons why?
7. What targets have been set to achieve control in TB in children in your county? How far have we gotten in meeting these targets? What has been your experience in this?
8. We looked at one-year data from medical records. In this period, we found the following:
1. Admissions to children’s wards = 3,018
2. Admissions with a respiratory tract infection/pneumonia = 1,495 (49%)
3. Children with 2 or more suggestive signs and symptoms of TB amongst the RTIs = 941 (62.9% of all RTIs)
4. Children with a working diagnosis of TB (i.e. either admission/discharge Dx or were started on anti-TB) = 33 (1.08% of all admissions)
5. Children with a missed diagnosis of TB (i.e. had 2 or more suggestive symptoms, but did not get a TB test or get a working TB Dx) = 1,356 (44.4%)
6. Amongst those with a working TB Dx, 7 (21.2%) had an Xpert test; 8 (24.2%) had a chest x-ray, and no children had documentation of culture, smear or Mantoux test being done.

9. Why do you think there were so many potential missed diagnoses? Why do you suppose there might be clinician reluctance to suspect TB, even to order tests? (from interviews, TB Dx only comes after several Rx of pneumonia)
10. What can be done to improve this situation?
11. In your opinion, why do you think there so few investigations carried out?
12. Some health workers have reported that getting negative results even in cases where clinically they can make a diagnosis of TB. Any idea of the numbers of negative Xpers in children? What do you think might be causing this situation? How can the situation be improved?
13. What specimen collection methods have you observed people here mainly use? Who is responsible for specimen collection? Decision to start TB treatment?
14. What is the average Turn-around time for tests? Reasons for this? Any idea of proportions of loss to follow up? Is it an indicator you track?
15. Who procures reagents? How do they get feedback on stock outs? What are service contracts like for broken down Xpert machines?
16. How well do clinical teams work together to diagnose and start TB treatment in children? Positive and negative experiences and reasons why?
17. Let’s talk through the process a child goes through in a typical district hospital. How they would be processed up to start of TB treatment?
18. Probe with an example of a process map. What are some of the bottle necks in your opinion? Why? The hospital is a complex system with a number of different departments that are involved in the care for children with TB. How can we ensure that these departments are able to appropriately manage TB in children?
19. How do you ensure that guidelines get embedded in to the institutions and in to daily practice by individual health workers? How do you in practice ensure that this get done? Any M/E? how is communication/awareness about them generated? Any feedback to and from the health care workers on the same?

20. For child TB training, please expound/describe the training, who is selected, where are the trainings done, by whom, how often, where, how are sites selected etc. In your opinion, what are some of the gaps?

21. Any form of supervision/mentorship specifically for child TB? How is it done? By whom, where, how often etc. Do health care workers ever get feedback on the cases detected, data quality, lab specimen quality? How often? By whom? In your opinion, what are some of the gaps?

22. Finally, in your role, what is working well, what is not working well and why? what support is in place to make sure your role is effective, do you feel supported, and who supports you? What tools/structures are in place for this support. (e.g. guidelines/frameworks)? What would you like to see happen, that would improve things e.g. staffing?

23. Probe further, to give specifics to see how each step will address the problem.
Additional File 3: Influencers of case detection and use of TB diagnostic tests in children
(N/B shaded area shows which domain of COM-B each theme occupies)

<table>
<thead>
<tr>
<th>INFLUENCERS</th>
<th>ILLUSTRATIVE QUOTES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physical and psychological capacity to engage in activities to diagnose TB in children, including the necessary knowledge and skills</strong></td>
<td><strong>Factors lying outside the individual that make it possible for them to diagnose TB in children</strong></td>
</tr>
</tbody>
</table>
| **Physical capability**
  - Strength, skills, stamina | **Physical Opportunity**
  - Time, physical environment |
| **Psychological Capability**
  - Knowledge, memory | **Social Opportunity**
  - Interpersonal influences, social cues, norms |
| **Reflective Motivation**
  - Beliefs, intentions, choices | **Automatic Motivation**
  - Wants, needs, impulses, habits |

**INDIVIDUAL-LEVEL INFLUENCERS**

**Confidence, Competence & Experience:**

- Frequent exposure to cases
  - "I would say maybe suspected TB maybe 2 a week and at minimum 1 a week..." Paed_SSI_06

- Index of suspicion of TB in children
  - "this kid...has been treated probably twice or thrice with antibiotics, I have also treated with antibiotics, but this is the fourth time the baby is back..." CO_SSI_23

- Reinforcement by positive/negative experiences
  - "you start on anti-TB then the improvement within a month or two is like magical..." CO_SSI_05

**Knowledge and Skill:**

- Of TB manifestations in children
  - "There’s cough, there’s fever, there’s less playfulness so I think of TB..." CO_SSI_05

- Of how and when to do procedures
  - "for adults it’s obvious...sputum you will be able to get...For children getting the specimen is usually the most challenging thing." Paed_SSI_13
### Fears & Beliefs:

**- Self-efficacy**

> "gastric aspirate… I’ve learnt how to do it. I think now am confident I can do it…" CO_SSI_31

**- Stigma**

> "people are still afraid even those already on treatment…afraid to be stigmatized…" MO_SSI_032

**- Value of guidelines & investigations**

> "The guidelines, fine they are there, but sometimes...you don't use them...Most times actually..." MO_SSI_25

### Hospital/Institutional Level Influencers

#### Hospital norms:

**- Professional roles & leadership**

> "we train interns so they are usually...the people who do most of these investigations...the intern and the medical officer" Paed_SSI_12

**- Information sharing & data for decision making**

> "you might get cases whereby maybe you are not really comfortable making the diagnosis for TB, but through sharing of knowledge you might get people who've had the same experience and you want to share and they also want to share of how they have been able to go through the same cases..." Paed_SSI_02

**- Teamwork & shared patient responsibility**

> "But at least in KR I think we are doing well. We have a really good team that is very good at really detecting some cases..." Paed_SSI_08

**- Routine use of guidelines & best practices**

> "Once they [guidelines] are launched, they take a bit of time to get there but eventually we do..." KII_1

### Processes & Patient Flow:

**- Poor selection of participants for trainings**

> "people in the office are the ones who go for TB training, job group P, Q and they are not the ones who are seeing the patients, and they never come and give us the information." CO_SSI_31
- Large patient numbers & poor flow & delays
  “sometimes we are overwhelmed by the workload here... as you can see... Chest [clinic]... there is the TB lab guys, sometimes they do [specimen collection]... if a child is really sick... they are usually done the gastric lavage, from the ward” CO_SSI_23

- Lack of dedicated spaces for specimen collection
  “Sample collection is usually done at the lab... sometimes the children are sent to the paediatrics ward [from OPD] for collection...” NO_SSI_19

Resources:

- Skilled manpower
  “I’m not comfortable, I request for radiologist’s report which can take you even up to two weeks” CO_SSI_31

- Equipment & reagents
  “Most times no coz sometimes we have stock outs of Xpert...” MO_SSI_14

- Guidelines & job aides
  “No, we don’t have charts. In my place we don’t have charts...” Paed_SSI_09

WIDER HEALTH SYSTEM (COMMUNITY & POLICY) INFLUENCERS

Implementation of TB programme directives:

- On training
  “We realized that when we rolled out Xpert we focused a lot of our training in the lab personnel, thereby leaving out the drivers of the service use...” KII_01

- On resources
  “government or the hospital is very supportive. Because for like chest x-rays and such it’s not very expensive. But like we have said for Xpert it’s free. You don’t pay for it...” Interns SGD

- On processes e.g. referrals, decentralisation, case finding, many registers/forms to fill
  And those forms are very annoying to fill [...] They are very long, they are very long... You get here you are tired... you have a kiform to fill and you are not just filling one...” COI_SSI_21

- On data use for audit, supervision
  “we do data quality audits and they are done together with the health care workers so it is a participatory sort of quality audit. And the feedback is given on the spot...” KII_01
<table>
<thead>
<tr>
<th>Community Beliefs &amp; Practices:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>- Awareness of TB manifestations in children</strong></td>
</tr>
<tr>
<td>&quot;we encourage them that if you are having a child who is not growing, as a child should be... please bring the baby to the... to be checked... to be screened&quot; KII_02</td>
</tr>
<tr>
<td><strong>- Health-seeking behaviour</strong></td>
</tr>
<tr>
<td>&quot;...parent believes that the child has been bewitched... coz she went to the hospital several times, she found there was no improvement... so would give herbs...&quot; Paed_SSI_03</td>
</tr>
<tr>
<td><strong>- Stigma</strong></td>
</tr>
<tr>
<td>&quot;people thinking TB is equal to HIV, so when now someone has to... been told that they have TB now everyone thinks that they are HIV positive... shunned by the family.&quot; Paed_SSI_03</td>
</tr>
</tbody>
</table>
### Additional File 4: Summary of interviewees

<table>
<thead>
<tr>
<th>Code</th>
<th>Gender</th>
<th>Designation/Cadre</th>
<th>County</th>
<th>Interview type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PHASE 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paed_SSI_001</td>
<td>M</td>
<td>Paediatrician</td>
<td>H</td>
<td>Semi-structured interview</td>
</tr>
<tr>
<td>Paed_SSI_002</td>
<td>F</td>
<td>Paediatrician</td>
<td>B</td>
<td>Semi-structured interview</td>
</tr>
<tr>
<td>Paed_SSI_003</td>
<td>F</td>
<td>Paediatrician</td>
<td>K1</td>
<td>Semi-structured interview</td>
</tr>
<tr>
<td>Paed_SSI_004</td>
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<td>Paediatrician</td>
<td>K2</td>
<td>Semi-structured interview</td>
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<tr>
<td>CO_SSI_005</td>
<td>F</td>
<td>Clinical officer</td>
<td>V</td>
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<td>Paed_SSI_006</td>
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<td>Paediatrician</td>
<td>N1</td>
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<td>K3</td>
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<td>E</td>
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<td>Paediatrician</td>
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<td>Paed_SGD_011</td>
<td>M</td>
<td>Paediatrician</td>
<td>V</td>
<td>Small group discussion</td>
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<tr>
<td></td>
<td>M</td>
<td>Paediatrician</td>
<td>M2</td>
<td></td>
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<td><strong>PHASE 2</strong></td>
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<tr>
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<tr>
<td>INT_SDG_027</td>
<td>M</td>
<td>Medical &amp; Clinical officer Interns</td>
<td>N1</td>
<td>Small group discussion</td>
</tr>
</tbody>
</table>
Additional File 5: Patient Flow in a typical Kenyan county hospital

Legend
DOT: Drug Susceptibility testing
PT: Isolated Preventive Therapy
RIT: Respiratory tract infection
S1: Signs and symptoms

Child gets to hospital and gets triaged and registered

Clinician/healves history and physical exam and screens for TB

S1 of TB

Managed for other RIT/Respiratory disease (start on PT)

Yes

No

Managed for other RIT/Respiratory disease (start on PT)

No

Clinical criteria?

Yes

No

Started on A/T and follow up

Sample X

Sent for chest X-ray

Culture DOT

Phlebotomist wanted

Medical clinical officer returns history and physical exam

Suggestive of TB?

No

Taxed done?

Yes

No

Clinical criteria?

Yes

No

Started on A/T and discharged through chest clinic once stable

Started on A/T and antibiotics to return for

Clinician requests Mantoux test

Yes: contacts sample for AFB MTB, NAP, etc. - Culture
Declarations

Ethical approval and consent to participate
The Kenya Medical Research Institute (KEMRI) Scientific and Ethical Review Committee (SSC Number 2465) approved the study. Participants were given a brief introduction to who the researchers were, reasons for doing the research and what the study entailed. They were reassured that their confidentiality would be maintained by omitting personal identifiers. They gave written consent for formal interviews and for audio-recording. Data were stored electronically in password-protected laptops only accessed by the research team. Consent forms and notes were filed and stored in a locked cabinet at the KEMRI-Wellcome Trust Research Programme Nairobi offices, where only JNO and SAO had access.

Consent for publication N/A

Availability of data and materials
The datasets (interview transcripts and observation notes) generated and analysed during the current study are not publicly available due to maintaining confidentiality of the study participants but are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Authors’ Contributions
All authors have read and approved the final manuscript.

JNO, ME and AVH conceived the paper. JNO, SAO, JN contributed to data analysis, while CJ, ME, MVH and AVH helped in interpretation of data. JNO drafted the initial form and all revisions of this paper while all other authors (SAO, JN, CJ, MVH, ME, AVH) made significant contributions to the conceptual framework and revision of the drafts. All authors read and approved the final manuscript and have
agreed to its content and are accountable for all aspects of the accuracy and integrity of the
manuscript.

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Chapter 6: Improving case detection of tuberculosis in hospitalised Kenyan children– employing the Behaviour Change Wheel to aid intervention design and implementation

Jacquie Narotso Oliwa, Jacinta Nzinga, Enos Masini, Michaël Boele van Hensbroek, Caroline Jones, Mike English, Anja van’t Hoog

Abstract

Background
The true burden of tuberculosis in children remains unknown, but approximately 65% go undetected each year. Guidelines for tuberculosis clinical decision-making are in place in Kenya and the National Tuberculosis programme conducts several trainings on them yearly. By 2018, there were 183 GeneXpert® machines in Kenyan public hospitals. Despite these efforts, diagnostic tests are underused and there is observed under detection of tuberculosis in children. We describe the process of designing a contextually appropriate, theory-informed intervention to improve case detection of TB in children and implementation guided by the Behaviour Change Wheel.

Methods
We used an iterative process, going back and forth from quantitative and qualitative empiric data to reviewing literature, and applying the Behaviour Change Wheel guide. The key questions reflected on included: i) what is the problem we are trying to solve; ii) what behaviours are we trying to change and in what way; iii) what will it take to bring about desired change; iv) what types of interventions are likely to bring about desired change; v) what should be the specific intervention content and how should this be implemented?

Results
The following behaviour change intervention functions were identified: i) training: imparting practical skills; ii) modelling: providing an example for people to aspire/imitate; iii) persuasion: using communication to induce positive or negative feelings or stimulate action; iv) environmental restructuring: changing the physical or social context; and v) education: increasing knowledge or understanding. The process resulted in a multi-faceted intervention package composed of redesigning of child tuberculosis training; careful selection of champions; use of audit and feedback linked to group problem solving; and work flow restructuring with role specification.

Conclusion
The intervention components were selected for their effectiveness (from literature), affordability, acceptability and practicability and designed so that TB programme officers and hospital managers can be supported to implement them with relative ease, alongside their daily duties. This work contributes to the field of implementation science by utilising clear definitions and descriptions of underlying mechanisms of interventions that will guide others to do likewise in their settings for similar problems.

Key words: Tuberculosis; child; case detection; diagnostics; hospitalised; implementation; intervention; behaviour change
Contributions to literature

- Implementation studies have been criticised for lack of conceptual/theoretical clarity and inconsistent use of terminologies, making them difficult to replicate.
- We used the Expert Recommendations for Implementing Change (ERIC) taxonomy to ensure consistent language in our intervention design, which adds to the body of work that can be comparable in future reviews of implementation studies.
- We also used theory guided by the Behaviour Change Wheel to propose how change should occur and to describe the underlying mechanisms of change that will guide others proposing to do likewise in their settings. This was particularly helpful for the complex longstanding problem of diagnosing tuberculosis in children, for which using behavioural approaches provided a range of insights that guided development of an intervention.
- We demonstrated the use of theory to describe intervention components and to explain how they will achieve their effects that will enhance transferability of our findings to other settings that grapple with same issues as we do in diagnosing TB in children.
- We demonstrated the importance of the use of local empiric data to ensure the intervention is designed for the context: any existing efforts for paediatric TB in Kenya have been adaptations of WHO recommendations by local experts.

Background

Tuberculosis (TB) is a leading cause of morbidity and mortality in children. According to the World Health Organisation (WHO), there were approximately 1.12 million incident child TB cases in 2018 and 205,000 deaths [1]. The true burden remains unknown due to challenges in diagnosis, but it is estimated that up to 65% of TB cases in children <5yrs go undetected each year [2-4]. In Kenya, 75% of TB cases identified in a recent population based survey had visited health facilities with suggestive symptoms but were never diagnosed [5]. Our work has shown that failure to detect tuberculosis in children who are already admitted in hospital represents a missed opportunity [6]. Guidelines for TB clinical decision-making are in place in Kenya, adapted from global resources, and the National TB programme (NTP) conducts training on those guidelines every year, as part of its strategic plan [7-10]. WHO recommends use of Xpert® MTB/RIF (Xpert®) as a first-line TB diagnostic test and by 2018 there were 183 machines in Kenya in public hospitals across the country [10]. Despite these efforts by the NTP of training and making machines available, underuse of TB diagnostic tests in Kenya is quite high [6, 11].
Research on factors that are likely to enhance or constrain the uptake of new evidence or tools into clinical practice is becoming more common [12-18]. Implementation science looks at the best approaches to move research into practice to improve quality and effectiveness of health services, and focuses a lot on changing healthcare professional and organisational behaviour [19]. Implementation studies have however been criticised for lack of conceptual/theoretical clarity and inconsistent use of terminologies, making them difficult to replicate [20, 21]. Theory is important to guide the process of implementation, to explain what influences implementation outcomes and evaluate implementation [22]. The linkage of theory with intervention design is recommended by the Medical Research Council (MRC) guidance on the development and evaluation of complex interventions [23, 24]. Systematic use of theory aids delivery of evidence informed strategies adapted to the local context [21, 25, 26]. However, programmatic interventions in low-resource settings are still often only input focused, for example the major focus of the Kenya TB programme has been increasing provision of GeneXpert® machines, training more staff, and distributing more guidelines [10].

We describe the process we undertook to design a contextually appropriate and theory-informed intervention to improve case detection of TB in children in Kenyan hospitals guided by the Behaviour Change Wheel (BCW)[27]. We chose the BCW, recognising that individual and collective behaviour change is key to implementing new practices and to improve health outcomes [22, 28-30]. One of the strengths of the BCW is that it naturally incorporates context, which is key to effective design and implementation of interventions [29]. The BCW is anchored on the Theoretical Domains Framework (TDF), an integrative framework of 33 psychological theories related to behaviour change, synthesised in a way that enables systematic assessment of implementation issues to inform intervention design, and is explained further in subsequent sections [30]. We also used the Expert Recommendations for Implementing Change (ERIC) taxonomy to ensure consistent language [20]. This work thus aimed to develop a clear starting perspective to design an intervention that could feasibly be adopted, evaluated and scaled-up by the National TB programme (NTP). We used information from our empiric data [6, 11, 31, 32], literature and discussions with key stakeholders to gain a deep understanding of context to support choice of intervention strategies. While focused on Kenya, we hope this work will be of value to others in similar contexts working to improve effectiveness of TB care for children.
Methods

Setting
Kenya has a young population, 73% of its approximately 48 million inhabitants are below 30 years of age. It is classed as a low-middle-income country with a Gross National Income (GNI) per capita of $1,600 but 36.1% of the population lives below the poverty line [33]. Kenya is one of the 30 TB high-burden countries, with a prevalence of 426 per 100,000 and case detection rate of 64%, with children representing 9-10% of the notified cases [34]. Most Kenyans receive inpatient hospital services from public health facilities. These are classified in three tiers (Levels 4 to 6) with lower tiers (Levels 1 – 3) offering community and primary care. Sub-county hospitals (level 4) may be run by a clinical officer or a medical officer or a specialist medical practitioner. County hospitals (level 5) may be run by a medical officer or a specialist. National referral hospitals (level 6) are run by fully qualified specialist medical practitioners. The focus of the work that has led to this paper is the management of children hospitalised in Kenyan county and sub-county hospitals, all of which have at least one GeneXpert® machine, or access via specimen referral. The process map derived from previous work [31] and replicated in Figure 1 shows how children with possible tuberculosis are processed within these hospitals, and illustrates the local context. Our earlier work helped to identify bottlenecks within this context and contributing factors to these bottlenecks are the starting points for the intervention design described in this paper.
Figure 1 Process map showing patient flow of a probable TB case through typical county hospital.
Using the Behaviour Change Wheel to guide intervention design

The Behaviour Change Wheel (BCW) is a framework that supports systematic development of interventions [27, 29]. It is designed to facilitate systematic, evidence-based progression from behavioural analysis of a problem to intervention design employing behaviour change theory to bring about desired change in three stages as shown in Figure 2.

Figure 2 Steps in intervention design [27]

The BCW is made up of three layers as shown in figure 3, and fully described in the Guide to Designing Interventions and accompanying article [27, 29]. The core is formed by the Capability, Opportunity and Motivation Behavioural (COM-B) theoretical model. Capability is defined as one’s psychological capacity (knowledge, memory) and physical capacity (strength, skills, stamina) to engage in an activity/behaviour. Opportunity represents factors that lie outside the individual that affect one’s capacity to perform, and include time, physical environment, interpersonal influences, social cues and cultural norms. Motivation represents internal factors (brain processes) that allow one to employ capability and opportunity to perform a behaviour, and include wants, needs, impulses, habits, beliefs, intentions and choices [29]. COM-B model thus explains conditions internal to individuals and within their social and physical environment necessary for them to enact a desired behaviour, which in our case is to correctly diagnose TB in children [29]. COM-B is the starting point used by the Behaviour Change Wheel for understanding behaviour in the context in which it occurs. Surrounding the core are interventions which mainly target individuals e.g. education, coercion; or act at policy level e.g. guidelines, fiscal measures.
Each of the COM-B components maps onto the Theoretical Domains Framework (TDF)—a synthesis of 33 theories and 84 theoretical constructs of behaviour change organized into 14 domains [21]. The domains thought to be relevant to health workers’ change in behaviour include: knowledge; skills; memory, attention and decision processes; behavioural regulation; social/professional role and identity; beliefs about capabilities; optimism; beliefs about consequences; intentions; goals; reinforcement; emotion; environmental context and resources; and social influences [28, 35]. The TDF therefore provides a theoretical basis for implementation research, to aid understanding of which interventions are likely to work and why. Behaviour Change Techniques (BCTs) are the active, observable and replicable components of an intervention designed to change behaviour i.e. the proposed mechanism of change and commonly used examples include: problem solving, feedback on outcomes, instruction on how to perform a behaviour, restructuring the physical environment, prompts and cues etc [36]. COM-B/BCW have been used successfully for behavioural analysis and to design interventions in both health and non-health-related fields [26, 37-56], but to our knowledge, has been used in only one study of TB on contact tracing in a low-resource setting, to identify barriers and facilitators and to tailor interventions to improve contact investigation in Kampala [26].

**Data Collection (Stage 1: Understanding the behaviour)**

We used a mixed-methods strategy (Additional File 1) to collect empirical data to identify challenges in case detection of TB in children to enable behavioural analysis. For the quantitative arm, we analysed national TB programme data as well as data from children admitted to 13 county hospitals.
in Kenya to describe the burden of childhood TB and diagnostic practices and these have been reported elsewhere [6, 11]. Results show at national level, there is under-detection of TB in children and underuse of available TB diagnostic tests. At hospital level, we found more than half of all paediatric admissions in Kenyan county hospitals had signs and symptoms suggestive of TB, but in most, TB was not considered as a differential diagnosis. Only 1% of these children meeting criteria for diagnostic testing had an Xpert® MTB/RIF assay performed, which was available in all the hospitals.

In the qualitative arm, to understand the challenges in recognising and testing for TB in admitted children we analysed data from: i) semi-structured interviews, small-group discussions and key informant interviews with front line health workers and mid-level managers; ii) observations of TB trainings, sensitisation meetings, policy meetings, and hospital practices, and iii) desk review of guidelines, job aides and policy documents, which have been reported elsewhere [31]. We used the COM-B framework to interpret emerging themes. At individual level, we found that knowledge, skill, competence and experience, as well as beliefs and fears impacted on capability (physical & psychological) as well as motivation (reflective) to think of TB as a differential diagnosis in children and use diagnostic tests. Hospital level influences included hospital norms, processes & patient flows and resources which affected how individual health workers attempted to diagnose TB in children by impacting on their capability (physical & psychological), motivation (reflective & automatic) and opportunity (physical & social). At the wider system level, community practices & beliefs, and implementation of TB programme directives impacted some of the decisions that health workers made through capability (psychological), motivation (reflective & automatic) and opportunity (physical).

Behavioural Analysis and intervention design: Identifying intervention options, content and implementation options (Stage 2 & 3)

As a study team, we used an iterative brainstorming process over several meetings during the study period (an average of weekly for the lead investigator and research assistant, and monthly for the larger study team, with increased frequency during study onset and analysis). During discussions at these meetings, we went back and forth from the quantitative and qualitative empiric data to reviewing literature, and applying the BCW guide [27]. We used frameworks, charting, spreadsheets and note taking to organise the data. The key questions reflected on included: i) what is the problem we are trying to solve; ii) what behaviours are we trying to change and in what way; iii) what will it take to bring about desired change; iv) what types of interventions are likely to bring about desired change; v) what should be the specific intervention content and how should this be implemented?
The empiric data helped identify gaps in case detection of TB in children and use of diagnostic tests in Kenya. We used COM-B and TDF to map out these gaps in behavioural terms i.e. to identify and specify what actions need to change and by who to address the gaps. Behavioural analysis involves the consideration of conditions internal to individuals and in their social and physical environment that need to be in place for a particular target to be achieved [29], and was done by the study team, led by the lead investigator (JNO).

Panel illustrating a worked example of behavioural analysis

<table>
<thead>
<tr>
<th>What is the problem from empiric data</th>
<th>gaps in the evaluation of children for TB.</th>
</tr>
</thead>
<tbody>
<tr>
<td>What behaviour needs to change</td>
<td>better documentation of signs and symptoms suggestive of TB in children</td>
</tr>
<tr>
<td>By who</td>
<td>all clinicians seeing sick children. When: at each patient encounter</td>
</tr>
<tr>
<td>Examples of some relevant COM-B elements, TDF constructs, intervention functions, policy functions, behaviour change techniques and mode of delivery (as per BCW guide steps)</td>
<td></td>
</tr>
<tr>
<td>i) Capability: clinicians need to know the importance of correctly identifying TB in children, and the skills to identify the key signs and symptoms;</td>
<td></td>
</tr>
<tr>
<td>TDF construct: Knowledge- awareness of the steps in diagnosing TB in children</td>
<td></td>
</tr>
<tr>
<td>Intervention function: Training to impart skills; modelling to provide a credible example</td>
<td></td>
</tr>
<tr>
<td>Policy function: Guidelines - to ensure availability and access to child TB protocols</td>
<td></td>
</tr>
<tr>
<td>Behaviour change techniques: Instruction on how to perform the behaviour (Training); Demonstration of the desired behaviour (Modelling)</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery: Face-face to individuals &amp; groups (training); print media (guidelines)</td>
<td></td>
</tr>
<tr>
<td>ii) Opportunity: the time to do proper assessment, structured forms that prompt documentation, culture of providing quality care;</td>
<td></td>
</tr>
<tr>
<td>TDF construct: Social influences: group conformity to good clinical practices</td>
<td></td>
</tr>
<tr>
<td>Intervention function: environmental restructuring to ensure availability of structured forms; Modelling- providing credible examples</td>
<td></td>
</tr>
<tr>
<td>Policy function: Regulation (establishing principles of best practice)</td>
<td></td>
</tr>
<tr>
<td>Behaviour change techniques: adding objects to the environment (structured forms); demonstration of the behaviour (champions)</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery: Face-face to individuals and groups</td>
<td></td>
</tr>
<tr>
<td>iii) Motivation: belief that failure to correctly evaluate children could lead to missed diagnosis and death</td>
<td></td>
</tr>
<tr>
<td>TDF construct: Beliefs about consequences</td>
<td></td>
</tr>
<tr>
<td>Intervention function: Persuasion- using audit and feedback of missed diagnosis, adverse outcomes</td>
<td></td>
</tr>
<tr>
<td>Policy: Regulation- requirement of regular audits</td>
<td></td>
</tr>
<tr>
<td>Behaviour change techniques: Feedback on behaviour</td>
<td></td>
</tr>
<tr>
<td>Mode of delivery: Face-face to individuals and groups</td>
<td></td>
</tr>
</tbody>
</table>
We used the BCW to link the gaps to evidence-based intervention functions like education, persuasion, environmental restructuring and these were in turn linked to policy categories. The panel illustrates a worked example of this process and Additional files 2-4 have lengthier descriptions of the steps we followed during behavioural analysis as illustrated in Figure 2 and 3 from the BCW guide [36].

We used the experience of the research team including implementation scientists, epidemiologists, social scientists, clinicians and clinician educators, together with feedback from clinical colleagues to select potential interventions (Table 1). We focused on those behaviour change techniques and modes of delivery that would yield results at low cost and that could feasibly be taken up by the National TB programme.

Using information gathered from our empirical data, literature on interventions likely to be successful, [57, 58], our understanding of the context and taking the perspective of what would be feasible for hospital managers and NTP officers to implement, we came up with a list of possible interventions to address the gaps in diagnosing TB in children. We then further selected options linked to the predicted mechanism of change according to the TDF constructs and used the APEASE criteria¹ and reflections of the context from our observations and process mapping to rationalise in terms of affordability, practicability, effectiveness, acceptability, safety and equity [27]. We presented findings to key paediatric TB stakeholders (including NTP officials, developmental partners, paediatricians and academic staff). We had informal discussions during technical working group meetings (there were two during the study period) to gain their perspectives on what could work, after considering our local context.

Table 1 summarises the process of linking the gaps in empiric data through the major behaviour change wheel design steps. The first column gives a summary of the key findings from our previous studies, and these were linked to the various COM-B elements and TDF constructs, and proposed intervention functions from the BCW guide.

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¹ APEASE Criteria
A- Affordability
P- Practicability (can be delivered as designed through the means intended to target population)
E- Effectiveness and cost-effectiveness
A- Acceptability (judged to be appropriate by relevant stakeholders)
S- Side-effects/Safety- minimal unintended consequences
E- Equity (reduces or increases disparities in standard of living or wellbeing)
Relevant aspects of The Standard for Reporting Implementation Studies (STaRI) tool [59] were used to help ensure key elements needed when developing and evaluating implementation strategies have been covered to enhance adoption and sustainability (see Additional File 5).

Results

From the behavioural analysis, the following behaviour change intervention functions were identified: i) training: imparting practical skills conducted by the National TB Programme (NTP); ii) modelling: providing an example for people to aspire/imitate by champions/clinical leaders; iii) persuasion: using communication to induce positive or negative feelings or stimulate action via audit & feedback by the ward clinical leaders and/or TB programme staff; iv) environmental restructuring: changing the physical or social context e.g. availability of record forms for better documentation; and v) education: increasing knowledge or understanding by the champions. From these, the following policy categories were identified: i) guidelines: ensuring availability and access to child TB diagnostic protocols by the NTP; ii) regulation: establishing principles of best practice by the NTP; and iii) communication/marketing: conducting mass media campaigns to educate the public on TB by the NTP and mass marketing to target health workers on need to scale up TB testing.

From discussions with the various child TB stakeholders, a multi-faceted intervention package composed of redesigning of training to focus on practical skills, selection of champions, better use of audit and feedback and work flow restructuring was proposed. Table 2 summarises the process that was followed in linking our intervention package with theory. The intervention components are defined using ERIC taxonomy, after considering the BCW guide intervention functions. The logic model (figure 4) conceptualises the theory of change of how the intervention package might work.

The subsequent section looks at each component in turn, elucidating selected BCW interventions functions using the definitions as per the Expert Recommendations for Implementing Change (ERIC) taxonomy [20], briefly reviewing available evidence for how each may impact health worker practice and how they would be delivered in our context.
Problem Statement

There are gaps in identification and investigating of tuberculosis in children in Kenya

Goal

Improved case detection of TB and appropriate use of TB diagnostics in hospitalised children in Kenya

Rationale

- Gaps identified in QUANT
  - Under-detection & under-reporting of TB in children
  - Under use of diagnostic tests especially Xpert®

- Gaps identified in QUAL
  - Knowledge, skills, competence & experience
  - Hospital norms & workflows
  - Resources
  - Community beliefs & policies

3. Theory-driven, contextually appropriate intervention to address modifiable gaps

Intervention & TDF Mechanism

1. Training Programme Redesign
   Physical skills; knowledge; memory, attention & decision processes; intentions

2. Selecting Champions
   (Mid-level managers)
   Social influences; professional role & identity; behavioural regulation; reinforcement

3. Audit & Feedback of child TB indicators
   Reinforcement; goals; belief about capabilities; knowledge; behavioural regulation

4. Redesigning work flows and role specification
   Environmental context & resources; reinforcement

Outputs

- Health workers reporting confidence in diagnosing TB
- Champions with defined roles supported by admin and NTP
- Regular audit and feedback with ongoing quality improvement (QI) activities
- Clear plans for diagnosis & testing; designated space & time; reduced turnaround times

Intermediate Outcomes

- Improved documentation and regular quality improvement meetings supported by data
- Improved time spent from diagnosis to starting treatment
- Increased number of children correctly evaluated for TB

Short-Term Outcomes

- Increased understanding of good documentation & use of data for improvement
- Increased understanding on role modelling and working as a team to improve work flows
- Increased knowledge, skill and confidence on collecting specimen for TB, use of diagnostic tests to diagnose TB in children

Long Term Outcome

To increase the number of appropriately investigated children reported to the TB programme in Kenya

Figure 4 Theory of change for a multi-faceted intervention to improve case detection of tuberculosis in children in Kenya
Redesigning of Training

Training is defined as giving instruction and/or actual demonstration of the desired action and works to improve physical and psychological capabilities of health workers, and with time, their reflective and automatic motivation [20]. The theoretical constructs through which training work are physical skills; memory, attention & decision processes [27]. The child TB training has traditionally been didactic/classroom based, usually away from the providers’ facility (to remove interruptions from work) and NTP has trained hundreds of health workers in this way. Training is a key component of the NTP national strategic plan and receives a considerable budget every year [10]. Feedback from Kenyan health workers was that they felt they still lacked competence in specimen collection in children and how to interpret test results. There was also concern about the selection of participants for training—key frontline actors were often left out [31].

ERIC recommend that training should be made dynamic i.e. vary the information delivery methods to cater to different learning styles and work contexts, and shape the training to be interactive [20]. The evidence however shows that training on its own has modest effects on health worker performance and propose that it should be combined with other strategies like supervision and group problem solving [58]. We recommend that child TB training be made more hands-on, with skills being demonstrated and participants given opportunities to practice under supervision until competence is attained. The mode of delivery should be both to individuals and groups, preferably at their work places, initially using video demonstrations and then with actual patients. Ongoing training in the form of continuous medical education/refresher sessions can be arranged ideally led by the champions. Training can be supplemented with educational outreach visits- having a trained person meet with providers in their practice settings to educate providers about TB in children with the intent of changing their practice. Redesign and distribution of printed material like guideline booklets and posters to remind health workers of the correct steps and procedures are an additional suggested mode of delivery of training as an intervention.

Champions/Local Opinion Leaders

Champions are usually local opinion leaders, individuals perceived as credible and trustworthy and disseminate and implement best evidence, for instance through informal one-to-one teaching [60]. According to ERIC, these are individuals who dedicate themselves to supporting, marketing, and driving through an implementation, overcoming indifference or resistance that the intervention may provoke in an organisation [20]. They provide clinical leadership, mentorship and supervision through modelling/demonstrating the correct procedures and this should impact health workers’ reflective and automatic motivation positively- important in places where leadership is largely lacking [31]. The
main theoretical construct through which champions work to improve health worker practices is through social influence and reinforcement. A recent Cochrane review found that local opinion leaders alone or in combination with other interventions probably improve health workers’ compliance with evidence-based practice but effect on patient outcomes is uncertain [60]. Another review found that combining training and supervision had somewhat larger effects than use of either strategy alone [58]. We recommend selection of willing mid-level managers like paediatricians, senior medical or clinical officers and nurse managers in county hospitals to perform this champion role, together with the TB clinic teams. Our work found that paediatricians in particular are often left out of child TB trainings and policy decisions, and yet a final decision to start TB treatment in difficult to diagnose patients is often left to them [31]. The NTP now recognises them as opinion leaders and has had several sensitisation meetings to update them on the latest guidelines and engage them as partners in improving care. The champions should be supported with leadership training to enable them to perform their roles.

**Audit and Feedback with Group Problem Solving**

Audit and feedback involves collecting and summarising clinical performance data over a specified time period and giving it to clinicians and administrators to monitor, evaluate and modify provider behaviour [20]. We found that the NTP regularly collect data from patients started on treatment but the hospital teams were not consumers of these data. The audit is done at county level, but feedback is mainly given to the county TB co-ordinators and clinicians at the TB clinics, excluding those on the wards [31].

Audit and feedback has been widely used based on the belief that healthcare workers will be prompted to modify their practice when given feedback showing their behaviour is inconsistent with a desirable target [12]. Ivers et al showed that audit and feedback generally leads to small but potentially important improvements in professional practice [12]. The effectiveness depends on baseline performance and how the feedback is provided. We propose that feedback from national level Could be given by the TB county co-ordinators or by the champions to all the clinical teams on quality of care given to children with possible TB. This then sets the stage for local audits and group problem solving led by the champions/clinical leads or TB co-ordinators. Audit and feedback will target health workers’ psychological capability and eventually their reflective and automatic motivation. The theoretical constructs through which audit and feedback work include reinforcement and behavioural regulation.

Group problem solving has been shown to have moderate to large effects on improving health worker practices [58]. According to ERIC, group problem solving could work through clinician implementation
team meetings. Initiating these may require some coaching and they would require protected time to reflect on the implementation effort, share lessons learned and support one another’s learning [20]. These teams should ideally bring together representation from clinicians from the TB clinic, laboratory personnel, biomedical teams and clinicians in the wards and out-patient departments, as our work showed gaps in team work leading to bottlenecks in patient flows [31]. For feedback to work well, there needs to be credible data, and this requires good documentation as the initial step. Good documentation requires environmental restructuring to ensure consistent availability of structured record forms, laboratory forms and other records.

**Work flow restructuring**

We observed several bottlenecks in patient flow and processes that were a hindrance to identifying potential TB patients in hospitals, as illustrated in the following vignette:

**Workflow vignette**

An example is given of a child with possible TB in a busy outpatient department. The patient was sent to the laboratory with a request form for investigations, as the clinician was alone with long queues and had no designated space or time to collect specimens. The laboratory technician said it was not his job to collect samples and he was also alone, so the patient was sent to the ward to request the junior doctor to assist. Unfortunately, she was new in the ward and had never done specimen collection for TB in children and was busy with other procedures for the ward admissions and could not help. After spending the whole day in and out of various departments, the child and the caregiver were sent back where they started, only to find their clinician left for the day, and a new clinician had started a shift.

ERIC describe an intervention strategy of changing physical structure and equipment. This requires one to evaluate current configurations and adapt as needed the physical structure and/or equipment e.g. changing the layout of a room, adding equipment to best accommodate the targeted innovation [20]. Reorganising patient flow and processes targets physical & social opportunity as well as reflective & automatic motivation and works through TDF constructs of reinforcement, knowledge and behavioural regulation. Work flow also encompasses social restructuring with clear definition of roles and expectations e.g. who should collect samples, where and when. We propose that work flow restructuring be done with the local clinical implementation teams, as part of earlier described group problem solving activities, where they restructure and keep adapting until they reach the best local solutions. The use of process maps such as Figure 1 can help with this. It is important to ensure holistic care of all patients, so that improved TB care for children is done in tandem with improving quality of
care for all. Work flow restructuring has been shown to improve health worker practices as they are based on local problem analysis and generation of solutions. The health workers get empowered because they gain control over their own work [61].

Implementation and Evaluation

This intervention is considered complex due to the number of interacting components, number of behaviours being targeted, range of possible outcomes and the need to adapt implementation to the local settings- which has implications for evaluation, especially in assessing fidelity. Guided by the Medical Research Council Framework for designing and evaluating complex interventions [62], we present a plan for evaluation and implementation of the intervention (see figure 5).

![Figure 5 An adaptation of the MRC Framework for implementation and evaluation of complex interventions](image)

We propose to select four hospitals as learning sites/case studies to test feasibility and acceptability of the intervention. The hospitals will be selected from counties that have different TB case
notification rates (high vs low), in which we are able to collect reliable estimates of the outcomes of interest (see figure 4). We propose to choose hospitals from the Clinical Information Network where we started the preliminary work, as they have already shown readiness and willingness to improve care for children with TB and have reliable medical records. All the hospitals will undergo a sensitisation to the project and a process of getting champions to emerge with a strategy to further support them including leadership training. All will also receive the redesigned child TB training, followed by regular audits of performance in the care given to children with possible TB. Two hospitals will receive feedback with supervision by the hospital TB champion and the other two will receive feedback with supervision by outreach from TB programme officers. This will test feasibility of these two strategies with qualitative determination of differences in preference for supervisors.

Mechanisms for delivery of feedback i.e. how frequently, to groups or individuals, written or verbal feedback, will be allowed to adapt to each site, guided by the champions/supervisors, with each team deciding how they will go about problem solving, frequency of meetings, what goals to set for improvement etc. The data for feedback will however be standard, reporting on similar variables for the quality of care given. Workflow restructuring will be site dependent, and will evolve from the group problem-solving efforts. External support and mentorship will be available from the TB programme and the research team, who will be responsible for documenting the implementation process. The intervention will initially be delivered over six months in all the participating hospitals, to learn what aspects of the intervention work as intended, what are the resource costs, are the processes acceptable, practical while causing minimal disruption. Aspects that need refinement will go back to the development stage, and those that are effective will be adopted for implementation, learning and refining iteratively over an 18-month period.

After feasibility has been established, evaluation will be done to establish effectiveness of the intervention, understand the change process and assess cost-effectiveness. Simultaneous quasi-experimental interrupted time series studies will be conducted with data prospectively collected from medical records of all paediatric admissions in the selected hospitals. Quantitative data outcomes as outlined in the logic model (Figure 4) will include proportion of paediatric admissions including pneumonia cases with suggestive signs of TB who get correctly evaluated for TB; number of TB tests done and results; proportion of patients who get a documented differential diagnosis of TB; proportion who get started on treatment; and time spent from diagnosis to treatment. While a cluster randomised control trial would have been a more robust approach, this interrupted time series design is chosen for feasibility and to enable learning and refining of the intervention with local adaptations. Conduct of parallel studies in two sets of case study hospitals powered for effect will explore
replication and provide effect estimates for interventions that share major components but differ in supervision, feedback and activities prioritised for problem solving. Consistent results will increase plausibility that effects are attributable to the intervention.

The quasi-experimental design will be strengthened by qualitative work which will explore the intervention process, the pathway to effect, validity of the pre-specified theory while describing the modifying effect of differences in context. We will collect data on the health workers’ experiences, their confidence levels, their beliefs about capabilities, decision processes etc as guided by the logic model, to assess how well the BCW intervention functions explain what works about the intervention. For process evaluation, we will document the quality of delivery of the intervention at each site and any variabilities, assess how well the champions take up their roles, frequency of feedback and group problem solving, goals set and how all these contribute to the desired outcomes of interest, and whether there are any unintended disruptions to other clinical services. We will be looking to identify how well the starting theory explains the causal mechanisms of the outcomes, and whether other contextual factors can explain variation at the case study sites.

We also propose to also carry out an economic evaluation that will be of great use to policy makers when planning for scale up. We will document the time and effort as well as material resources used to deliver the intervention, compared to status quo. We propose to use participant observation by the champions and TB programme supervisors, and non-participant observation by the research team, all of whom will be documenting their reflections in diaries. For analysis, we will use the theoretical domains framework to assess theoretical fidelity (to what extent the intervention was delivered in tandem with the intervention theory). We will also borrow from realist philosophies [63], to learn and document: “what works for whom, in what respects, in what contexts and how?” This will be important for predicting the outcomes and translating and adapting interventions for other contexts.

Discussion

We set out to describe the process we undertook to design a contextually appropriate and theory-informed intervention to improve case detection of TB in children in Kenyan hospitals, guided by the Behaviour Change Wheel [27] and using standard intervention taxonomies as recommended by Expert Recommendations for Implementing Change (ERIC) project [20]. The behaviour change interventions identified included: training; ii) modelling; iii) persuasion; iv) environmental restructuring; and v) education; with the following policy categories- guidelines, regulation and communication/marketing. The process thus resulted in a multi-faceted intervention package composed of: i) redesigning of child TB training; ii) careful selection of champions; iii) use of audit and feedback linked to group problem solving; and iv) work flow restructuring with role specification. The intervention components were
selected for their effectiveness (from literature), affordability, acceptability and practicability and designed so that NTP officers and hospital managers can be supported to implement them with relative ease, alongside their daily duties. We also provide for how the proposed intervention package can be implemented and evaluated, guided by the MRC framework for complex interventions and the Theoretical Domains Framework/Behaviour Change Wheel.

There are several implementation frameworks in literature, including those by Sheikh et al [64], Greenhalgh et al [65], Murray et al [66], Damschroder et al [67] amongst others. They all have concepts demonstrating connections between the individual and the context (organisation and wider environment, inner vs outer settings). Choice of framework often needs trade-offs between being complex enough to represent reality while being simple enough to be useful for policy making, planning and research. The behaviour change wheel served the purpose of providing an intuitive approach to designing an intervention to improve case detection of tuberculosis and use of TB diagnostic tests in children that seems relevant to county hospital settings in Kenya.

This approach has various strengths including the use of local empiric data to ensure the intervention is designed for the context; using consistent implementation terminologies; and use of theory to describe intervention components and explain how they are intended to achieve their effects. The process further provides the opportunity to evaluate intervention delivery and effects linked to a logic model/conceptual framework. The merits of combining the BCW and ERIC taxonomy is that it enhances understanding and generalisability of the study findings. The intervention design process considered perspectives of individual health workers and the institutions expected to deliver the intervention over the long-term and is based on a well-developed understanding of existing problems from an insider perspective, which increases chances of intervention success [68]. A major assumption is that all the other structures and processes in the health system consistently function well and are in support of the proposed intervention, e.g. resources need to be consistently available, staff should be sufficient and the environment in the hospitals, community and policy space should be conducive for the intervention to work well. The major limitation is that we are yet to pilot test the intervention, and the next steps will include implanting and evaluating the process.

Conclusion

We have designed a contextually appropriate theory-driven intervention to help address gaps in case detection of tuberculosis in children in Kenya. The intervention components were selected for their effectiveness (from literature), affordability, acceptability and practicability and designed so that TB programme officers and hospital managers can be supported to implement them with relative ease, alongside their daily duties. This work is relevant to policy and practice because it calls for a revaluation
of the strategies adopted by the existing NTP especially its approach to identifying children with TB. There is need to review the approach to training in terms of its goals, content, pedagogy and participants with a suggestion that training should be conducted at hospitals themselves. Other practice implications include using champions and establishing social norms like teamwork and mentorship, as well as group problem solving for quality improvement and to restructure work flows in the hospitals. This work contributes to the field of implementation science by utilising clear definitions (from ERIC) and descriptions of underlying mechanisms of interventions (from the BCW) that will guide others to do likewise in their settings for similar problems.

**Abbreviations**

BCW: Behaviour Change Wheel

COM-B: *Capability, Opportunity and Motivation* Behavioural model

DST: Drug Susceptibility testing

ERIC: Expert Recommendations for Implementing Change

IPT: Isoniazid Preventive Therapy

NTP: National TB Programme

QUAL: Qualitative Data

QUAN: Quantitative data

RTI: Respiratory tract infection

S/S: Signs and symptoms

TDF: Theoretical Domains Framework

WHO: World Health Organisation
Declarations

Ethical approval and consent to participate
The Kenya Medical Research Institute (KEMRI) Scientific and Ethical Review Committee (SSC Number 2465) approved the quantitative arm of the study enabling use of de-identified data without individual patient consent. For the qualitative arm, participants were given a brief introduction to who the researchers were, reasons for doing the research and what the study entailed. They were reassured that their confidentiality would be maintained by omitting personal identifiers. They gave written consent for formal interviews and for audio-recording. Data were stored electronically in password-protected laptops only accessed by the research team. Consent forms and notes were filed and stored in a locked cabinet at the KEMRI-Wellcome Trust Research Programme Nairobi offices, where only JNO and SAO had access.

Consent for publication N/A

Availability of data and materials
The datasets (interview transcripts and observation notes) generated and analysed for the qualitative study published elsewhere [31] are not publicly available due to maintaining confidentiality of the study participants but are available from the corresponding author on reasonable request.

The summary data and underlying findings for the quantitative studies are freely available in the published papers and their supporting information files [6, 11]. Access to raw data may require additional approval from the Ministry of Health, Kenya. Requests can be facilitated by contacting the KEMRI-Wellcome Trust Research Programme’s Data Governance Committee through this email: dgc@kemri-wellcome.org.

Competing interests
The authors declare that they have no competing interests.

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The views expressed in this publication are those of the author(s) and not necessarily those of AAS, NEPAD Agency, Wellcome Trust or the UK government. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors’ Contributions
JNO, ME and AVH conceived the paper. JNO, AVH, ME and JN contributed to data analysis, while EM, CJ and MVH helped in interpretation of data. JNO drafted the initial form and all revisions of this paper while all the other authors (AVH, JN, EM, CJ, MVH, ME) made significant contributions to the conceptual framework and revision of the drafts. All authors read and approved the final manuscript and have agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript.

Acknowledgements
We would like to thank Sabina Adhiambo Odero, an exceptional research assistant who contributed to the qualitative work that later fed into the intervention design. We would also like to acknowledge the Kenya National TB Programme, The Paediatric TB Technical Working Group, The Clinical Information Network and participating staff of the hospitals all of whom shared freely of their experiences and perspectives with the aim of improving care of children with TB in Kenya.
References


Table 5: Linking gaps in empiric data for behavioural analysis to intervention design (Stages 1 & 2).

<table>
<thead>
<tr>
<th>Summary of gaps identified in empiric data from our previous studies</th>
<th>COM-B</th>
<th>TDF constructs linked to COM-B</th>
<th>Relevance of the theoretical domain</th>
<th>Proposed intervention function from the BCW guide [36]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under-detection of TB in children, 60-70% thought to be missed (QUAN)</td>
<td>Capability-psychological</td>
<td>Knowledge</td>
<td>Awareness of steps in diagnosing TB in children; of the available tests. Do they know what they should do and when and why?</td>
<td>Training: Imparting skills on how to correctly diagnose TB in children</td>
</tr>
<tr>
<td>Nearly 60% of all paediatric admissions met guideline-criteria for suspected TB but &lt;3% got a diagnosis (QUAN)</td>
<td>Behavioural regulation</td>
<td>Self-monitoring; how to break a habit e.g. missed diagnosis. Anything in place to prompt them to make a diagnosis and to self-monitor?</td>
<td>Modelling: Providing an example for people to aspire/imitate e.g. via champions/clinical leaders</td>
<td></td>
</tr>
<tr>
<td>Some reported that they did consider a TB differential diagnosis but sometimes forgot to document (QUAL)</td>
<td>Capability-psychological</td>
<td>Memory attention and decision processes</td>
<td>Ability to retain information, to consistently remember to document what is done</td>
<td>Persuasion: Using communication to stimulate action e.g. via audit &amp; feedback</td>
</tr>
<tr>
<td>Some reported they do tests but forgot to document (QUAL)</td>
<td>Behavioural regulation</td>
<td>Self-monitoring; how to break a habit e.g. failure to document. Anything in place to prompt them to always document?</td>
<td>Environmental restructuring: Changing the physical context e.g. availability of record forms for better documentation, job aides</td>
<td></td>
</tr>
<tr>
<td>Some health workers fear/are reluctant to make a diagnosis of TB in children sometimes due to stigma in caregivers of TB-HIV association (QUAL)</td>
<td>Capability-psychological</td>
<td>Knowledge</td>
<td>Awareness of steps in diagnosing TB in children; of the available tests. Do they know what they should do and when and why?</td>
<td>Education: Increasing knowledge or understanding of TB in children</td>
</tr>
<tr>
<td></td>
<td>Motivation-automatic</td>
<td>Reinforcement</td>
<td>Anything to motivate or demotivate them?</td>
<td>Persuasion: Building communication skills to better counsel families</td>
</tr>
<tr>
<td></td>
<td>Emotion</td>
<td>Emotion</td>
<td>Does it evoke an emotional response e.g. some got uncomfortable when babies cried during specimen collection; some were reprimanded harshly by caregivers</td>
<td>Modelling: by the champions to demonstrate how best to de-stigmatise</td>
</tr>
<tr>
<td>Underutilisation of TB diagnostic tests, 1% get Xpert done (QUAN)</td>
<td>Capability - psychological</td>
<td>Knowledge</td>
<td>Awareness of steps in diagnosing TB in children; of the available tests. Do they know what they should do, when and why?</td>
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<tr>
<td>Health workers generally seem to have a challenge in collecting specimen for children (QUAL)</td>
<td>Capability - physical</td>
<td>Physical skills</td>
<td>Are they physically able/proficient in diagnosing TB; collecting specimen; using diagnostic tests? Acquired through practice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motivation - reflective</td>
<td>Beliefs about capability</td>
<td>Are they confident diagnosing TB in children; collecting specimen? How difficult or easy?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motivation - automatic</td>
<td>Reinforcement</td>
<td>Increasing likelihood of TB tests being used appropriately</td>
<td></td>
</tr>
<tr>
<td>Training: Imparting skills to use available diagnostic tests and specimen collection</td>
<td>Modelling: Champions/clinical leaders demonstrating correct procedures</td>
<td>Environmental restructuring: identifying who is responsible for ensuring TB tests get done; job aides to serve as reminders of procedures</td>
<td></td>
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</tr>
<tr>
<td>Health workers report consistently negative Xpert test results (QUAL)</td>
<td>Capability - psychological</td>
<td>Knowledge</td>
<td>Do they know how to respond to negative test results? How and when to make a clinical diagnosis?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motivation - reflective</td>
<td>Beliefs about consequences</td>
<td>Do they believe doing it or not makes a difference?</td>
<td></td>
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<tr>
<td>Education: increasing understanding on making a clinical diagnosis and the epidemiology and natural course of TB in children</td>
<td>Persuasion: communication to pass on the value of TB tests</td>
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<tr>
<td>Some facilities had good teamwork and mentorship that helped model the correct way to diagnose TB in children (QUAL)</td>
<td>Opportunity - social</td>
<td>Social/professional role &amp; identity</td>
<td>Do they think it is part of their job e.g. to collect specimen (senior doctors struggled)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Motivation - reflective</td>
<td>Optimism</td>
<td>Do they think it’s something that can be done? How confident are they of this?</td>
<td></td>
</tr>
<tr>
<td>Modelling and social environment restructuring: Providing an example for people to aspire/imitate and encouraging teamwork</td>
<td>Persuasion: communication to pass on the value of diagnosing TB in children</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Most facilities had long and unclear processes that contributed to TB being missed in children (QUAL) Some reported frequent stock-outs of some reagents and Xpert cartridges (QUAL)</td>
<td>Opportunity - physical</td>
<td>Environmental context &amp; resources</td>
<td>Organisational processes and patient flows; resources like job aides, PPE, reagents. Aspects of the environment that influence whether or not they diagnose TB in children</td>
<td></td>
</tr>
<tr>
<td>Environmental restructuring: Changing the physical context to ensure better work flows and availability of equipment, reagents</td>
<td></td>
<td></td>
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<tr>
<td>Aspect</td>
<td>Opportunity</td>
<td>Environmental context</td>
<td>Aspects of the environment that influence whether or not they diagnose TB in children</td>
<td>Environmental restructuring: e.g. job aides to guide clinical diagnosis; remote decision-support for X-ray interpretation</td>
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<tr>
<td>Lack of skilled human resource to interpret some test results like Chest X-rays (QUAL)</td>
<td>Physical Capability-psychological Knowledge</td>
<td>Awareness of steps in diagnosing TB in children; of the available tests. How to make a clinical diagnosis?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Some policies and directives including selection of participants for training disadvantaged front-line health workers (QUAL)</td>
<td>Physical Motivation-automatic</td>
<td>Aspects of the environment that influence whether or not they diagnose TB in children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education: increasing policy makers’ understanding of the need of rethinking how TB training is done</td>
<td>Persuasion: Using communication to stimulate action e.g. feedback to policy makers on the impact of training</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB programme policy of doing quarterly audits and supervisory visits helped (QUAL)</td>
<td>Reflective Intentions Goals</td>
<td>Feedback to enable health workers to make a conscious decision to improve case detection Visualise what they want to achieve</td>
<td></td>
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</tr>
</tbody>
</table>
Table 6 Linking interventions with behaviour change techniques and mode of delivery

<table>
<thead>
<tr>
<th>Intervention (as defined by ERIC taxonomy)</th>
<th>Target behaviour</th>
<th>Behaviour Change Technique</th>
<th>Mode of delivery</th>
<th>Major gaps using APEASE criteria</th>
</tr>
</thead>
</table>
| Training Programme Redesign               | On-job training HCWs in child TB (specimen collection, interpreting CXRs) | Instruction on how to perform the behaviour  
Demonstration of the behaviour | Face-face to individuals and groups  
Print media (guidelines) | Low Practicability: Needs skilled staff to train and time off busy schedules |
| Purposeful selection of Champions         | Providing clinical leadership, mentorship and supervision  
Building teamwork to ensure best practices | Demonstration of the behaviour  
Credible source  
Social support  
Goal setting  
Feedback on the behaviour | Face-face to individuals and groups | Low Practicability: low where staff are few and stretched and none willing to take up role |
| Audit & Feedback                          | Encourage better documentation of history and physical signs and symptoms suggestive of TB  
Encourage better documentation of tests ordered and date done  
Encourage better documentation of samples collected, when and test results | Adding objects (record forms) to the environment  
Feedback on the behaviour  
Prompts/cues | Face-face to individuals and groups  
Individually accessed computer-generated reports | Low Acceptability: may resist if not part of their culture  
Practicability: low where staff are few and stretched |
| Work flow restructuring                   | Reorganising patient flow and processes  
Ensuring samples get to the lab on time  
Ensuring results get back to each patients’ file and gets reviewed by clinician | Restructuring of the physical & social environment  
Feedback on the behaviour  
Prompts & cues  
Demonstration of the behaviour | Group | Low Practicability and acceptability: may be low where staff are few and stretched |
| Resources                                 | Ensuring availability of reagents, cartridges, specimen bottles, safety masks  
Ensuring availability and use of guidelines/job aides  
Providing personal protective equipment and encouraging consistent use | Restructuring of the physical environment  
Adding objects to the environment  
Feedback on the behaviour  
Demonstration of the behaviour  
Prompts & cues | Group  
Individual—in-charge: using reports | Low Affordability: cost prohibitive  
Low Acceptability: using masks  
Low Effectiveness: of procurement  
Low Availability: dependent on TB programme  
Low Acceptability: low where people prefer to use their acumen |
Additional Files

Additional File 1: Mixed Methods Conceptual Framework

- **QUALITATIVE:** Preliminary Interviews, meetings, document reviews *(Phase 1)*
- **QUALITATIVE:** Structured interviews and observations *(Phase 2)*
- **QUANTITATIVE:** Analysis of National TB programme data
- **QUANTITATIVE:** Analysis of CIN hospitals data

**INTERPRETATION**
Integration of Qualitative & Quantitative findings to guide development of a contextually appropriate intervention

Understanding gaps in case detection of TB in children
Additional File 2 Behavioural Analysis

Intervention Aim: Improving TB case detection and use of TB diagnostic tests in children in Kenya

Behavioural target (what needs to be done and by whom?)

1. Better clinical evaluation of possible TB patients by health workers in hospitals
   - Better documentation of history and physical signs and symptoms suggestive of TB (evidenced by ticked boxes in the PAR)

2. Better use of TB diagnostic tests by health workers in hospitals
   - Better documentation of:
     - Test ordered (CXR, Mantoux, Xpert, culture), date done
     - Samples collected, and when
     - Results documented (plus date)

3. Increase in documentation of TB as a primary or secondary differential diagnosis, from the current 2.9% to double by health workers in hospitals

4. Quality improvement meetings: reflection and goal setting to improve paediatric TB care by health workers in hospitals
   - Role of champion
   - External supervision
   - Teamwork, norms, best practices
   - Improve patient flows/processes; documentation

Possible other linked behaviours

- Ensuring availability of paediatric admission record forms
- Ensuring availability of reagents, cartridges, specimen bottles, safety masks
- Ensuring availability of guidelines/job aides
- Designating a safe space for specimen collection
- Ensuring samples get to the lab on time
- Ensuring results get back to each patients’ file and gets reviewed by clinician
- Providing personal protective equipment
- Increasing number of HCWs trained in child TB (specimen collection, interpreting CXRs)
- Making data available for audit and feedback, and to track improvement
### Behavioural analysis: Defining the gaps in behavioural terms

<table>
<thead>
<tr>
<th>What behaviour</th>
<th>Where &amp; when does the behaviour occur</th>
<th>Who is involved in performing the behaviour</th>
<th>Likely impact of the behaviour if changed</th>
<th>How easy it is to change</th>
<th>Likely spill-over effect</th>
<th>Ease of measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better documentation of history and physical signs and symptoms suggestive of TB</td>
<td>Out-patient departments and hospital wards Each visit</td>
<td>Clinicians, Doctors, Nurses (triage)</td>
<td>Very promising, better documentation enables audit</td>
<td>Promising, needs reinforcing and availability of resources</td>
<td>Very promising, if everyone does it</td>
<td>Promising, review of documents</td>
</tr>
<tr>
<td>Better documentation of Tests ordered (CXR, Mantoux, Xpert, culture), date done</td>
<td>Out-patient departments and hospital wards Each visit</td>
<td>Clinicians, Doctors</td>
<td>Very promising, better documentation enables audit</td>
<td>Promising, needs reinforcing and availability of resources</td>
<td>Very promising, if everyone does it</td>
<td>Promising, review of documents</td>
</tr>
<tr>
<td>Encourage better documentation of samples collected, and when (NPA, GA, IS)</td>
<td>Out-patient departments and hospital wards Each visit</td>
<td>Clinicians, Doctors</td>
<td>Very promising, better documentation enables audit</td>
<td>Promising, needs reinforcing and availability of resources</td>
<td>Promising</td>
<td>Promising, review of documents</td>
</tr>
<tr>
<td>Encourage better documentation of TB test results, date positive or negative</td>
<td>Out-patient departments and hospital wards Each visit</td>
<td>Clinicians, Doctors, Lab staff Radiology staff</td>
<td>Very promising, better documentation enables audit</td>
<td>Promising, needs motivation to follow results &amp; availability of resources</td>
<td>Promising</td>
<td>Promising, review of documents</td>
</tr>
<tr>
<td>Encourage better documentation of TB as a primary or secondary differential diagnosis, from the current 2.9% to double?</td>
<td>Out-patient departments and hospital wards Each visit</td>
<td>Clinicians, Doctors</td>
<td>Very promising, better documentation enables audit</td>
<td>Promising, needs reinforcing</td>
<td>Very promising, if everyone does it</td>
<td>Promising, review of documents</td>
</tr>
<tr>
<td>Ensuring availability of paediatric admission record forms/structured forms</td>
<td>Out-patient departments and hospital wards Each visit</td>
<td>Ward-in-charge Administration</td>
<td>Very promising, it will improve documentation</td>
<td>Promising, needs to be prioritised: policy, hospital supplies</td>
<td>Promising</td>
<td>Promising</td>
</tr>
<tr>
<td>Ensuring availability of reagents, cartridges, specimen bottles, safety masks</td>
<td>Out-patient departments, hospital wards, (? Labs) Each visit</td>
<td>Lab in charge Administration Ministry of Health</td>
<td>Very promising, it will ensure people can do tests when needed</td>
<td>Promising, needs</td>
<td>Promising will to be prioritised</td>
<td>Promising, review of documents</td>
</tr>
<tr>
<td>What behaviour</td>
<td>Where does the behaviour occur</td>
<td>Who is involved in performing the behaviour</td>
<td>Likely impact of the behaviour if changed</td>
<td>How easy it is to change</td>
<td>Likely spill-over effect</td>
<td>Ease of measurement</td>
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<tr>
<td>Ensuring availability of guidelines/job aides</td>
<td>Out-patient departments, hospital wards, (? Labs) Each visit</td>
<td>Administration Ministry of Health</td>
<td>Very promising, it will reinforce Promising practice</td>
<td>Promising, the guidelines as they stand are vague. May need revision</td>
<td>Promising</td>
<td>Promising</td>
</tr>
<tr>
<td>Designating a safe space for specimen collection</td>
<td>Out-patient departments, hospital wards, (? Labs) Each visit</td>
<td>Administration</td>
<td>Promising but people still need to want to do it</td>
<td>Promising-hard Might need restructuring, consider cost</td>
<td>Unpromising but worth considering-Promising</td>
<td>Promising</td>
</tr>
<tr>
<td>Ensuring samples get to the lab on time</td>
<td>Out-patient departments, hospital wards Each visit</td>
<td>Clinicians, Doctors, Nurses</td>
<td>Promising, Promising for sample quality</td>
<td>Promising, requires reinforcing</td>
<td>Promising</td>
<td>Unpromising but worth considering Needs time to be documented</td>
</tr>
<tr>
<td>Ensuring results get back to each patients’ file and gets reviewed by clinician</td>
<td>Labs, radiology, Hospital wards, Outpatient departments Each visit</td>
<td>Clinicians, Doctors, Nurses Lab &amp; radiology</td>
<td>Promising, will allow audit</td>
<td>Promising, requires reinforcing</td>
<td>Promising</td>
<td>Promising</td>
</tr>
<tr>
<td>Providing personal protective equipment and encouraging consistent use</td>
<td>Labs, radiology, Hospital wards, Outpatient departments Each visit</td>
<td>Administration, Ministry of Health</td>
<td>Promising, people still need to use them</td>
<td>Promising-hard, cost implication</td>
<td>Promising</td>
<td>Promising</td>
</tr>
<tr>
<td>Training HCWs in child TB (specimen collection, interpreting CXRs)</td>
<td>Hospitals Ministry of Health (when to be decided by NTP)</td>
<td>Administration, Ministry of Health</td>
<td>Very promising if made practical &amp; done for the right staff</td>
<td>Promising-hard, cost implication</td>
<td>Very promising</td>
<td>Promising</td>
</tr>
<tr>
<td>Making data available for audit and feedback, and to track improvement</td>
<td>Hospitals Ministry of Health ? Monthly or every two months or quarterly</td>
<td>Health records staff Ministry of Health</td>
<td>Very promising, allows for reflection and action planning</td>
<td>Easy, just need to pick indicators to track</td>
<td>Very promising</td>
<td>Promising</td>
</tr>
<tr>
<td><strong>What behaviour</strong></td>
<td><strong>Where does the behaviour occur</strong></td>
<td><strong>Who is involved in performing the behaviour</strong></td>
<td><strong>Likely impact of the behaviour if changed</strong></td>
<td><strong>How easy it is to change</strong></td>
<td><strong>Likely spill-over effect</strong></td>
<td><strong>Ease of measurement</strong></td>
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<tr>
<td>Providing clinical leadership, mentorship and supervision</td>
<td>Hospitals Ministry of Health Monthly or every two months or quarterly</td>
<td>Administration, Ministry of Health</td>
<td>Very promising</td>
<td>Promising, needs the right people</td>
<td>Very promising</td>
<td>Promising</td>
</tr>
<tr>
<td>Building teamwork to ensure best practices</td>
<td>Hospitals Daily</td>
<td>Staff and admin</td>
<td>Very promising</td>
<td>Promising, before team cohesion builds</td>
<td>Very promising</td>
<td>Promising</td>
</tr>
<tr>
<td>Reorganising patient flow and processes</td>
<td>Hospitals Every QI cycle</td>
<td>Staff &amp; admin</td>
<td>Very promising</td>
<td>Promising, needs work to ID bottlenecks</td>
<td>Very promising</td>
<td>Promising</td>
</tr>
</tbody>
</table>
## Additional File 3 Identifying what behaviour needs to change linked to COM-B

<table>
<thead>
<tr>
<th>What behaviour</th>
<th>Physical capability</th>
<th>Psychological capability</th>
<th>Physical opportunity</th>
<th>Social opportunity</th>
<th>Reflective motivation</th>
<th>Automatic motivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Encourage better documentation of history and physical signs and symptoms suggestive of TB</td>
<td>Physical skill of history taking and physical exam</td>
<td>Know the correct patients to triage for TB screening</td>
<td>Have PAR forms</td>
<td>Be part of a team keen on TB detection</td>
<td>Hold beliefs that it is possible to Dx TB in children</td>
<td>Have established routines and habit of considering TB as a DDx in sick children</td>
</tr>
<tr>
<td>Encourage better documentation of Tests ordered (CXR, Mantoux, Xpert, culture), date done</td>
<td>Physical skill of documenting requests &amp; results</td>
<td>Know who &amp; when to investigate</td>
<td>Have space for requests and results in structured forms</td>
<td>A culture of documenting requests and results</td>
<td>Hold beliefs that it is important to document</td>
<td></td>
</tr>
<tr>
<td>Encourage better documentation of samples collected, and when (NPA, GA, IS) and tests results</td>
<td>Physical skill of correctly collecting appropriate specimen and documenting</td>
<td>Know which specimen collection method to choose and when</td>
<td>Availability of resources and dedicated space and time for specimen collection</td>
<td>Be part of a team keen on TB detection</td>
<td>Hold beliefs that it is important to document</td>
<td>Have established routines and habits of good documentation</td>
</tr>
<tr>
<td>Ensuring availability of paediatric admission record forms/structured forms</td>
<td>Physical skill of ordering PAR forms before they stock out</td>
<td>Know when and how many forms to order</td>
<td>Have funds to regularly print PAR forms</td>
<td>Be part of a team keen on good documentation.</td>
<td>Hold beliefs that it is important to document</td>
<td>Have established routines and habits of good documentation</td>
</tr>
<tr>
<td>What behaviour</td>
<td>Physical capability</td>
<td>Psychological capability</td>
<td>Physical opportunity</td>
<td>Social opportunity</td>
<td>Reflective motivation</td>
<td>Automatic motivation</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>------------------------------------------</td>
<td>----------------------------------------</td>
<td>-----------------------------</td>
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</tr>
<tr>
<td>Ensuring availability of guidelines/job aides</td>
<td>Physical skill of ordering resources before they stock out</td>
<td>Know when and how to order resources</td>
<td>Have funds to ensure availability job aides</td>
<td>Have clinical leads who ensure consistent availability of resources</td>
<td>Hold beliefs that it is important to ensure availability of resources</td>
<td>Have established routines and habits of good stock keeping</td>
</tr>
<tr>
<td>Ensuring samples get to the lab on time</td>
<td>Physical ability to get samples to lab as soon as collected or safely store</td>
<td>Know when specimen should get to lab and how to appropriate store</td>
<td>Ensuring there’s a mechanism for prompt transport to lab and appropriate conditions for storage</td>
<td>Be part of a team that is comfortable in specimen transport &amp; storage</td>
<td>Hold beliefs that it is important to ensure appropriate transport &amp; storage of specimen</td>
<td>Have established routines and habits of specimen transport and storage</td>
</tr>
<tr>
<td>Ensuring results get back to each patient’s file and gets reviewed by clinician</td>
<td>Physical skill of correctly documenting results in patient files</td>
<td>Know when results should be of concern</td>
<td>Ensuring there’s a mechanism for prompt transfer of results to patient files and reviewed by clinicians</td>
<td>Be part of a team that routinely reviews patient results</td>
<td>Hold beliefs that it is important to document and review results</td>
<td>Have established routines and habits of review of results</td>
</tr>
<tr>
<td>Providing personal protective equipment and encouraging consistent use</td>
<td>Physical ability to ensure use of PPE</td>
<td>Know when and how PPE should be used</td>
<td>Resources available to buy PPE</td>
<td>Culture of using PPE</td>
<td>Holds beliefs that it is important to use PPE</td>
<td>Have routines and habits of using PPE</td>
</tr>
<tr>
<td>On-job training HCWs in child TB (specimen collection, interpreting CXRs)</td>
<td>Physical ability to provide on-job training for child TB</td>
<td>Know how and why to provide OJT</td>
<td>Resources available to provide OJT (time, space, equipment, skilled staff)</td>
<td>Culture of knowledge sharing</td>
<td>Holds beliefs that it is important to share knowledge</td>
<td>Have routines and habits of knowledge sharing</td>
</tr>
<tr>
<td>What behaviour</td>
<td>What needs to change in terms of COM-B, in order for hospital staff to improve case detection of TB and use of TB diagnostic tests in children</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>---------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physical capability</strong></td>
<td><strong>Psychological capability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Providing clinical leadership, mentorship and supervision</td>
<td>Physical ability to provide clinical leadership and mentorship</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Know how and when to provide leadership and mentorship</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Have dedicated processes and people to provide clinical leadership</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Culture of supportive supervision</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Hold beliefs that it is important to have good clinical leadership and mentorship</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Have routines and habits of clinical leadership and mentorship</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Building teamwork to ensure best practices</td>
<td>Physical ability to organise staff into clinical teams</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Know how to use teamwork to ensure best practices</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Have structures in place to ensure good teamwork like communication, handing over etc</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Culture of working together as a team</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hold beliefs that it is important to work as a team</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have routines and habits of working together as a team</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reorganising patient flow and processes</td>
<td>Physical ability to reengineer patient flow</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Know how and why and when to reorganise patient flows</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have space to be able to reorganise patient flows</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Culture of quality improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hold beliefs that it is important to reduce bottlenecks and redundancies in the system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Have routines and habits of improvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Additional File 4 Using the TDF to expand on COM-B components identified in the behavioural diagnosis**

<table>
<thead>
<tr>
<th>COM-B</th>
<th>TDF linked to COM-B</th>
<th>Relevance of the domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychological capability</td>
<td>Knowledge</td>
<td>Awareness of steps in diagnosing TB in children; of the available diagnostic tests. Rationale. Do they know what they should do and when and why?</td>
</tr>
<tr>
<td></td>
<td>Cognitive &amp; interpersonal skills</td>
<td>Proficiency in diagnosing TB; using diagnostic tests. Acquired through practice</td>
</tr>
<tr>
<td></td>
<td>Memory attention and decision processes</td>
<td>Ability to retain information, to consistently remember to order TB tests to do, and when</td>
</tr>
<tr>
<td></td>
<td>Behavioural regulation</td>
<td>Self-monitoring; how to break a habit e.g. missed diagnosis. Anything in place to prompt them to make a diagnosis and to monitor whether or not they have</td>
</tr>
<tr>
<td>Physical capability</td>
<td>Physical skills</td>
<td>Are they physically able/proficient in diagnosing TB; collecting specimen; using diagnostic tests. Acquired through practice</td>
</tr>
<tr>
<td>Social opportunity</td>
<td>Social influences</td>
<td>Social norms/group conformity to good clinical practices; group identity; modelling/role models. How might the views/opinions of colleagues/patients influence their decision to diagnose TB in children</td>
</tr>
<tr>
<td>Physical opportunity</td>
<td>Environmental context &amp; resources</td>
<td>Organisational processes and patient flows; resources like job aides, PPE, reagents. Aspects of the environment that influence whether or not they diagnose TB in children</td>
</tr>
<tr>
<td>Reflective motivation</td>
<td>Social/professional role &amp; identity</td>
<td>Do they think it is part of their job e.g. to collect specimen (seniors struggled with this)</td>
</tr>
<tr>
<td></td>
<td>Beliefs about capability</td>
<td>Are they confident diagnosing TB in children; collecting specimen? How difficult or easy?</td>
</tr>
<tr>
<td></td>
<td>Optimism</td>
<td>Do they think it’s something that can be done? How confident are they of this?</td>
</tr>
<tr>
<td></td>
<td>Intentions</td>
<td>Have they made a decision (not) to do it?</td>
</tr>
<tr>
<td></td>
<td>Goals</td>
<td>How much do they want to do it?</td>
</tr>
<tr>
<td></td>
<td>Beliefs about consequences</td>
<td>DO they believe doing it or not makes a difference?</td>
</tr>
<tr>
<td>Automatic motivation</td>
<td>Reinforcement</td>
<td>Anything to motivate or demotivate them?</td>
</tr>
<tr>
<td></td>
<td>Emotion</td>
<td>Does it evoke an emotional response e.g. uncomfortable when babies cry during specimen collection; fear of reprimand from rich relatives</td>
</tr>
</tbody>
</table>

186
### Additional File 5: Standards for Reporting Implementation Studies: the StaRI checklist

<table>
<thead>
<tr>
<th>Checklist item</th>
<th>Reported on page #</th>
<th>Implementation Strategy</th>
<th>Reported on page #</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Title</td>
<td>1</td>
<td>1</td>
<td>“Implementation strategy” refers to how the intervention was implemented</td>
<td>“Intervention” refers to the healthcare or public health intervention that is being implemented.</td>
</tr>
<tr>
<td>Abstract</td>
<td>2</td>
<td>2</td>
<td>Identification as an implementation study, including a description of the implementation strategy to be tested, the evidence-based intervention being implemented, and defining the key implementation and health outcomes.</td>
<td></td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td>3</td>
<td>3-4</td>
<td>Description of the problem, challenge or deficiency in healthcare or public health that the intervention being implemented aims to address.</td>
<td></td>
</tr>
<tr>
<td>Rationale</td>
<td>4</td>
<td>3-4</td>
<td>The scientific background and rationale for the implementation strategy (including any underpinning theory/framework/model, how it is expected to achieve its effects and any pilot work).</td>
<td>3-4</td>
</tr>
<tr>
<td>Aims and objectives</td>
<td>5</td>
<td>4</td>
<td>The aims of the study, differentiating between implementation objectives and any intervention objectives.</td>
<td></td>
</tr>
<tr>
<td><strong>Methods: description</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Design</td>
<td>6</td>
<td>7</td>
<td>The design and key features of the evaluation, (cross referencing to any appropriate methodology reporting standards) and any changes to study protocol, with reasons</td>
<td></td>
</tr>
<tr>
<td>Context</td>
<td>7</td>
<td>4</td>
<td>The context in which the intervention was implemented. (Consider social, economic, policy, healthcare, organisational barriers and facilitators that might influence implementation elsewhere).</td>
<td></td>
</tr>
<tr>
<td>---------</td>
<td>---</td>
<td>---</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Targeted ‘sites’</td>
<td>8</td>
<td>9</td>
<td>The characteristics of the targeted ‘site(s)’ (e.g. locations/personnel/resources etc.) for implementation and any eligibility criteria.</td>
<td>9</td>
</tr>
<tr>
<td>Description</td>
<td>9</td>
<td>13-18</td>
<td>A description of the implementation strategy</td>
<td>18</td>
</tr>
<tr>
<td>Sub-groups</td>
<td>10</td>
<td>N/A</td>
<td>Any sub-groups recruited for additional research tasks, and/or nested studies are described</td>
<td></td>
</tr>
<tr>
<td><strong>Methods: evaluation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>11</td>
<td>18</td>
<td>Defined pre-specified primary and other outcome(s) of the implementation strategy, and how they were assessed. Document any pre-determined targets</td>
<td>N/A</td>
</tr>
<tr>
<td>Process evaluation</td>
<td>12</td>
<td>18</td>
<td>Process evaluation objectives and outcomes related to the mechanism by which the strategy is expected to work</td>
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<tr>
<td>Economic evaluation</td>
<td>13</td>
<td>N/A</td>
<td>Methods for resource use, costs, economic outcomes and analysis for the implementation strategy</td>
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</tr>
<tr>
<td>Sample size</td>
<td>14</td>
<td>N/A</td>
<td>Rationale for sample sizes (including sample size calculations, budgetary constraints, practical considerations, data saturation, as appropriate)</td>
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<td>Analysis</td>
<td>15</td>
<td>N/A</td>
<td>Methods of analysis (with reasons for that choice)</td>
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<tr>
<td>Sub-group analyses</td>
<td>16</td>
<td>N/A</td>
<td>Any a priori sub-group analyses (e.g. between different sites in a multicentre study, different clinical or demographic populations), and sub-groups recruited to specific nested research tasks</td>
<td></td>
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<tr>
<td>Characteristics</td>
<td>17</td>
<td>N/A</td>
<td>Proportion recruited and characteristics of the recipient population for the implementation strategy</td>
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</tr>
<tr>
<td>----------------</td>
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<td>--------------------------------------------------</td>
<td>-----</td>
</tr>
<tr>
<td>Outcomes</td>
<td>18</td>
<td>18</td>
<td>Primary and other outcome(s) of the implementation strategy</td>
<td>N/A</td>
</tr>
<tr>
<td>Process outcomes</td>
<td>19</td>
<td>18</td>
<td>Process data related to the implementation strategy mapped to the mechanism by which the strategy is expected to work</td>
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<tr>
<td>Economic evaluation</td>
<td>20</td>
<td>N/A</td>
<td>Resource use, costs, economic outcomes and analysis for the implementation strategy</td>
<td>N/A</td>
</tr>
<tr>
<td>Sub-group analyses</td>
<td>21</td>
<td>N/A</td>
<td>Representativeness and outcomes of subgroups including those recruited to specific research tasks</td>
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</tr>
<tr>
<td>Fidelity/adaptation</td>
<td>22</td>
<td>N/A</td>
<td>Fidelity to implementation strategy as planned and adaptation to suit context and preferences</td>
<td>N/A</td>
</tr>
<tr>
<td>Contextual changes</td>
<td>23</td>
<td>N/A</td>
<td>Contextual changes (if any) which may have affected outcomes</td>
<td>N/A</td>
</tr>
<tr>
<td>Harms</td>
<td>24</td>
<td>N/A</td>
<td>All-important harms or unintended effects in each group</td>
<td>N/A</td>
</tr>
<tr>
<td>Discussion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured discussion</td>
<td>25</td>
<td>13-18</td>
<td>Summary of findings, strengths and limitations, comparisons with other studies, conclusions and implications</td>
<td></td>
</tr>
<tr>
<td>Implications</td>
<td>26</td>
<td>19-20</td>
<td>Discussion of policy, practice and/or research implications of the implementation strategy (specifically including scalability)</td>
<td>19-20</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statements</td>
<td>27</td>
<td>20-22</td>
<td>Include statement(s) on regulatory approvals (including, as appropriate, ethical approval, confidential use of routine data, governance approval), trial/study registration (availability of protocol), funding and conflicts of interest</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 7: Policy Brief

Jacquie Oliwa, Alex Njeru, Joy Kiptim

KEMRI | Wellcome Trust

POLICY BRIEF 2020
IMPROVING CASE DETECTION OF TUBERCULOSIS IN HOSPITALISED CHILDREN IN KENYA

Key Messages

- Tuberculosis is a leading cause of illness and death in children. The World Health Organization estimates that there were over 1.12 million incident child TB cases and over 205,000 deaths in 2018.
- Kenya is one of the 30 TB high-burden countries, with a prevalence of 426 per 100,000 with children representing 9-10% of the notified cases.
- The true burden of TB in children remains unknown partly due to challenges in diagnosis. It is estimated that 65% of TB in under-five children remains undetected each year.
- Despite the availability of TB testing kits, guidelines to guide TB clinical decision-making and regular periodic training on these guidelines by the National TB Programme every year; under detection of TB in children and underuse of TB diagnostic tests in Kenya remains quite high.
- For example, though half of all paediatric admissions in Kenyan county hospitals exhibit signs and symptoms suggestive of TB, it was rarely considered as a differential diagnosis. Only 1% of children meeting the criteria for diagnostic testing had a TB test carried-out.
- To remedy the above situation, there is need to re-evaluate the strategies adopted by the existing National TB Programme especially its approach to identifying children with TB.
- There is need to review the approach to training; we suggest a shift to practical child TB training as it addresses difficulties with specimen collection; in addition, this training should be preferably conducted in the hospitals.

Introduction

The World Health Organization recommends use of Xpert® MTB/RIF (Xpert®) as a first-line TB diagnostic test. By 2018 there were 183 machines in Kenya in public hospitals across the country. However, despite the availability of these testing kits and efforts by the National TB Programme to provide training and guidelines; under detection of TB in children and underuse of TB diagnostic tests in Kenya is still quite high. For example, 75% of TB cases identified in a recent survey had visited health facilities in Kenya with suggestive symptoms but were never diagnosed. The failure to detect tuberculosis in patients who are already admitted in hospital represents a missed opportunity to provide optimal care.
Researchers at KEMRI-Wellcome carried out a study to design a contextually appropriate and theory-informed intervention to improve case detection of TB in children in Kenyan hospitals. The study employed the Behaviour Change Wheel (BCW), due its recognition that individual and collective behaviour change is key to implementing new practices and to improve health outcomes. In addition, it naturally incorporates context, which is key to effective design and implementation of interventions.

**Methods**

The Behaviour Change Wheel process involves evidence-based progression from behavioural analysis of a problem to intervention design employing behaviour change theory to bring about desired change. The BCW is made up of three layers as shown in **figure 1**. The core is formed by the **Capability, Opportunity and Motivation** Behavioural (COM-B) theoretical model which explains conditions internal to individuals and within their social and physical environment necessary for healthcare workers to enact a desired behaviour, which in this case was to correctly diagnose TB in children. COM-B is the starting point used by the BCW for understanding behaviour in the context in which it occurs. Surrounding the core are interventions which mainly target individuals e.g. education, coercion; or act at policy level e.g. guidelines, fiscal measures.

*Figure 1 The Behaviour Change Wheel (Source: Michie et al, 2011)*
Identifying intervention options, content and implementation options

An iterative process was used, going back and forth from the quantitative and qualitative empiric data to reviewing literature, and applying the BCW guide. The guiding questions were:

1. what problem are we trying to solve;
2. what behaviours are we trying to change and in what way;
3. what will it take to bring about desired change;
4. what types of interventions are likely to bring about desired change;
5. what should be the specific intervention content and how should this be implemented?

Findings

Understanding the behaviour around TB Case Detection

Within the BCW framework, quantitative and qualitative data was collected in three main stages, stage one involved understanding behaviour and challenges with cases detection; while stage two and three entailed, identifying intervention options, content and implementation options. The study found that at national level, there was under-detection of TB in children and underuse of available TB diagnostic tests. At hospital level, more than half of all paediatric admissions in Kenyan county hospitals had signs and symptoms suggestive of TB, but in most, TB was not considered as a differential diagnosis. Only 1% of these children meeting criteria for diagnostic testing had an Xpert® MTB/RIF assay performed, which was available in all the hospitals.

Qualitative interviews found that there were 25 themes, representing the factors that influence TB case detection in children. These themes were then grouped into eight broad analytic categories, illustrating how they had potential to impact Capability, Motivation and/or Opportunity to diagnose TB in children, and whether the influences were at individual, hospital or community level. Knowledge, skill, competence and experience, as well as beliefs and fears impacted on capability (physical & psychological) as did motivation (reflective) to think of TB as a differential diagnosis in children and use diagnostic tests at individual level as indicated in figure 2. On the other hand, hospital level influences included hospital norms, processes & patient flows and resources which affected how individual health workers attempted to diagnose TB in children by impacting on their capability (physical & psychological), motivation (reflective & automatic) and opportunity (physical & social). At the wider system level, community practices & beliefs, and implementation of TB programme directives impacted some of the decisions that health workers made through capability (psychological), motivation (reflective & automatic) and opportunity (physical).
Proposed Behaviour Change Interventions

Discussions with the various child TB stakeholders, gave rise to a multi-faceted intervention package composed of: i) redesigning of training to focus on practical skills; ii) selection of champions; iii) better use of audit and feedback; and, iv) workflow restructuring was proposed. Table 1 summarises the process that was followed in linking the proposed intervention package with theory while the logic model (Figure 2) conceptualises the theory of change of how the intervention package might work.
<table>
<thead>
<tr>
<th>Proposed Intervention</th>
<th>Target behaviour</th>
<th>Behaviour Change Technique</th>
<th>Mode of delivery</th>
<th>Major gaps using APEASE criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training Programme Redesign</td>
<td>On-job training HCWs in child TB (specimen collection, interpreting CXRs)</td>
<td>Instruction on how to perform the behaviour, Demonstration of the behaviour</td>
<td>Face-face to individuals and groups, Print media (guidelines)</td>
<td>Low Practicability: Needs skilled staff to train and time off busy schedules</td>
</tr>
<tr>
<td>Purposeful selection of Champions</td>
<td>Providing clinical leadership, mentorship and supervision, Building teamwork to ensure best practices</td>
<td>Demonstration of the behaviour, Credible source, Social support, Goal setting, Feedback on the behaviour</td>
<td>Face-face to individuals and groups</td>
<td>Low Practicability: low where staff are few and stretched and none willing to take up role</td>
</tr>
<tr>
<td>Audit &amp; Feedback</td>
<td>Encourage better documentation of history and physical signs and symptoms suggestive of TB, Encourage better documentation of tests ordered and date done, Encourage better documentation of samples collected, when and test results</td>
<td>Adding objects (record forms) to the environment, Feedback on the behaviour, Prompts/cues</td>
<td>Face-face to individuals and groups, Individually accessed computer-generated reports</td>
<td>Low Acceptability: may resist if not part of their culture, Practicability: low where staff are few and stretched</td>
</tr>
<tr>
<td>Workflow restructuring</td>
<td>Reorganising patient flow and processes, Ensuring samples get to the lab on time, Ensuring results get back to each patients’ file and gets reviewed by clinician</td>
<td>Restructuring of the physical &amp; social environment, Feedback on the behaviour, Prompts &amp; cues, Demonstration of the behaviour</td>
<td>Group</td>
<td>Low Practicability and acceptability: may be low where staff are few and stretched</td>
</tr>
</tbody>
</table>
**Problem Statement**

There are gaps in identification and investigating of tuberculosis in children in Kenya

**Goal**

Improved case detection of TB and appropriate use of TB diagnostics in hospitalised children in Kenya

**Rationale**

Gaps identified in QUANT
- Under-detection & under-reporting of TB in children
- Under use of diagnostic tests especially Xpert®

Gaps identified in QUAL
- Knowledge, skills, competence & experience
- Hospital norms & workflows
- Resources
- Community beliefs & policies

3. Theory-driven, contextually appropriate intervention to address modifiable gaps

**Intervention & TDF Mechanism**

1. Training Programme Redesign
   - Physical skills; knowledge; memory, attention & decision processes; intentions

2. Selecting Champions (Mid-level managers)
   - Social influences; professional role & identity; behavioural regulation; reinforcement

3. Audit & Feedback of child TB indicators
   - Reinforcement; goals; belief about capabilities; knowledge; behavioural regulation

4. Redesigning work flows and role specification
   - Environmental context & resources; reinforcement

**Outputs**

- Health workers reporting confidence in diagnosing TB
- Champions with defined roles supported by admin and NTP
- Regular audit and feedback with ongoing quality improvement (QI) activities
- Clear plans for diagnosis & testing; designated space & time; reduced turnaround times

**Intermediate Outcomes**

- Improved documentation and regular quality improvement meetings supported by data
- Improved time spent from diagnosis to starting treatment
- Increased number of children correctly evaluated for TB

**Short-Term Outcomes**

- Increased understanding of good documentation & use of data for improvement
- Increased understanding on role modelling and working as a team to improve work flows
- Increased knowledge, skill and confidence on collecting specimen for TB, use of diagnostic tests to diagnose TB in children

**Long Term Outcome**

To increase the number of appropriately investigated children reported to the TB programme in Kenya

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**Figure 3 Theory of change for a multi-faceted intervention to improve case detection of tuberculosis in children in Kenya**
Summary and Recommendations

1. There is need to review the approach to training in terms of goals, content, pedagogy and participants with a suggestion that training should be conducted at hospitals themselves.

2. In addition to training, the National TB Programme should consider the following:

   I. using child TB champions;

   II. the establishment of social norms like teamwork and mentorship

   III. group problem solving for quality improvement and to restructure workflows in the hospitals.

About this Research

Related Publication
This is brief is adapted from a research paper published under the title, “Improving case detection of tuberculosis in hospitalised children in Kenya – employing the Behaviour Change Wheel to aid intervention design” [https://implementationscience.biomedcentral.com/articles/10.1186/s13012-020-01061-4]

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Chapter 8: General Discussion
General Discussion

It is increasingly being recognised that tuberculosis is a leading cause of mortality and death in children. The World Health Organisation estimates that there were over 1 million new cases of TB and over 200,000 deaths in children <15yrs in 2018 [1]. The true burden of TB in children however remains unknown- a hidden epidemic- due to various challenges in establishing a diagnosis. These include lack of standard case definitions, lack of proper gold standard diagnostic tests and the fact that TB mimics many childhood illnesses like pneumonia, malnutrition and HIV. Approximately 60% of TB cases in children go unreported and undiagnosed [1], a missed opportunity that contributes to childhood deaths, from a disease that is curable and preventable. Missed diagnosis is particularly unfortunate for children who present with suggestive signs and symptoms to health facilities, but do not get investigations to rule out TB.

Considerable efforts have been made to implement evidence-based guidelines and new technologies to aid diagnosis of TB in general, but gaps remain in case detection and utilisation of diagnostic tests. Difficulties in diagnosis present the greatest challenge to childhood tuberculosis control efforts [2]. Health workers, especially those on the frontline, often have little capacity and confidence in preventing, diagnosing and managing childhood TB [3, 4]. It is important to understand factors that influence health worker practices in order to develop appropriate interventions to improve the quality of care provided in hospitals in high burden TB countries like Kenya. At the time of this study, very little was known about childhood TB in Kenya, other than what was reported to the National TB programme. The main aim of this work was to better describe the epidemiology of childhood TB in Kenya and use of diagnostics, to determine the proportion of eligible children admitted to hospitals who have a clinical and laboratory evaluation for TB that is consistent with existing national guidelines. We also sought to explore the influencers of TB case detection in children and of adoption of Xpert® MTB/RIF in this population, to see how employing an understanding of behavioural theory linked to a contextually appropriate intervention package might help promote better TB diagnostic work up.

Reflections and Positionality

When I started thinking about this work, nearly four years ago, I had brave ambitions to develop, implement and evaluate an intervention that would increase case detection of TB in children. My work involved a planned time-series analysis to document the changes over time and develop plausibility arguments to explain what could have worked. As I started, I realised that I needed to first describe the epidemiology and the burden of disease, in order to have a baseline from which to evaluate
improvements on. This involved looking at large volumes of data from the national TB programme (almost 90,000 patients) and from 13 county hospitals (nearly 50,000 patients), with the attendant issues of cleaning and shaping the data for meaningful inferences. I had to rely on what was documented to infer clinician practices, but both data sets revealed under-detection and underutilisation of TB diagnostic tests, and clinical decisions that did not seem in line with the existing national guidelines. We observed some missing data, especially of laboratory results, and therefore could not infer if tests requested were done and what some of the results were, despite efforts to trace back results. We however only included in the analyses patients in whom a structured admission record form (PAR) was used, and previous analyses have shown more than 90% documentation of patient information in sites where these forms are used, so we are reasonably certain of documentation of test requests.

While planning the next phase, the country entered widespread industrial action by health workers, that lasted the better part of a year. I was not going to be able to implement my proposed intervention as planned, and lack of continuous data points meant a time-series analysis would not be possible. My background in clinical medicine and epidemiology meant that I was mainly viewing my work from a post-positivist approach as described by Creswell and Poth - elements of being reductionist, logical, empirical and deterministic [5]. Disruptions in my data flow led me to take a more pragmatic stance and utilise mixed methods, integrating both my quantitative and qualitative data to triangulate findings and explain the “whys” behind the data and observed practices and “how” a proposed intervention might work.

As I developed my qualitative interrogation, my position as a Paediatrician, a member of the Kenyan Ministry of Health Paediatric TB Technical Working Group and a clinical practice trainer/educator for the Kenyan NTP meant that I had an insider’s perspective of childhood TB activities in the country and this made it easier to enter spaces and to get people to open up about their experiences in a collegial manner, with the shared desire to improve gaps in detection of TB in children. I was familiar to several of the clinicians in participating hospitals as I had trained them during some of the National TB Programme childhood TB trainings. I participated in ward rounds, helped think through with clinicians about challenging cases that they thought might have TB and demonstrated correct procedures for specimen collection. I believe these working relationships engendered trust in me as a credible colleague and peer, who wanted to work with them to help improve things for TB in children.

To further develop my understanding of the context and challenges for TB diagnosis, I had a research assistant with a background in environmental health who conducted some of the interviews. She
tended to ask more questions and delved deeper, for her own understanding, and this provided richer data. We had regular peer debriefing with research colleagues at various stages of data collection and analysis to help ensure reflexivity in the process of making analytic inferences. We also fed back some of our preliminary results to clinicians and other key childhood TB stakeholders for member checking to verify what we had observed.

To develop the intervention, I spent a lot of time reflecting on the data collected and delving into implementation and behaviour change literature to come up with what might be contextually appropriate and feasible.

Integration of the Research Done

This subsequent section integrates the research findings from the various studies that contributed to this PhD thesis.

From analysis of the national TB programme data for patients who started TB treatment in 2015 (Chapter 2), we identified probable under-detection and underreporting of TB in children <15 years. The TB case notification rate (CNR) in children 0-14yrs was nearly eight times less than that of those ≥15 years, and it is known that young children are particularly vulnerable to primary TB disease. Factors contributing to underreporting and resultant low CNR among children include difficulties in confirming a diagnosis of childhood TB and poor surveillance [6]. We also found widespread inter-county variation in distribution and use of TB diagnostic tests, with underutilisation of Xpert® despite its widescale roll-out. Less than 5% of patients aged 0-14 years and 12.2% of patients ≥15 years who met criteria for TB testing had an Xpert® test done, with gaps in guideline adherence. Low utilisation of Xpert® has been illustrated in other low income, high TB burden countries both in adults and children [7-9]. Reported factors associated with low utilisation include operational issues like power outages and poor specimen referral; doubts about impact on TB morbidity and mortality; preference to trust clinical acumen; low sensitivity especially in children; challenges in getting good specimens and false negatives; and lack of awareness amongst health care workers and patients [8, 10, 11]. We concluded that more work needs to be done to understand reasons for under-detection of TB in children and to enhance appropriate use of diagnostics.

In trying to further unmask the hidden epidemic, we hypothesised that some of the cases being managed for pneumonia could potentially be missed TB cases, especially since TB mimics pneumonia and other childhood disease like malnutrition and HIV. We carried out a systematic review to explore the association between tuberculosis and pneumonia in high burden TB countries (Chapter 3). The
countries studied included: Malawi, South Africa, Uganda, Bangladesh, Kenya, China, The Gambia, Zambia and Zimbabwe. We found that the proportion of children with pneumonia who ended up with a TB diagnosis ranged from 1-23% (the highest proportion was seen in Bangladesh); while on average, up to 8% of children admitted with severe pneumonia had culture-confirmed TB disease (South Africa had the highest proportion at 15%). This is important especially since culture is known to have low yield in children. The findings suggest that tuberculosis is important in the pathogenesis of acute childhood pneumonia in countries with a high incidence of tuberculosis, either as a direct cause or as an underlying risk factor that increases susceptibility to bacterial pneumonia. Many of the cases were young infants, and a good number died, with case fatality ranging from 4-21% in children with pneumonia and a diagnosis of TB obtained later. This work suggests that clinicians managing infants and young children with severe pneumonia in tuberculosis-endemic countries need to be aware that tuberculosis might be a cause or contributor.

We decided to have a closer look at what was happening to children admitted in Kenyan hospitals. The recent Kenya TB prevalence survey with participants from the general population aged >15 years revealed 75% of newly identified TB cases during the survey had presented to health facilities earlier with suggestive symptoms but were never diagnosed during their visits [12]. The proportion of younger children undiagnosed in Kenyan hospitals was unknown, but presumed to be as high [13-15].

Chapter 4 is a large longitudinal observational study of routine clinical data from 13 county hospitals in a clinical network in Kenya. It aimed to describe clinician TB diagnostic practices through a guideline-linked TB care cascade and to quantify the magnitude of TB as a diagnosis amongst children admitted to Kenyan hospitals. We found that more than half of all paediatric admissions had two or more symptoms associated with TB (cough, fever, weight loss, lethargy), but very few of them got TB diagnostic tests requested. TB was diagnosed in 2.9% of all admissions and most were inadequately investigated. The considerable underuse of TB diagnostic tests in hospitals was consistent with what we noted in the national TB programme data. This has been reported in other high burden settings, whereby the greatest gap in the TB care cascade is failure to get investigations [16, 17]. There is need to review the applicability of existing Kenyan paediatric TB guidelines, to provide further clarity as to which children should be investigated for TB and when, as it may not be feasible to investigate more than half of admissions. Clinicians probably realise this and make their own implicit decisions on who to treat for TB, that may not necessarily be related to the guidelines.

Further qualitative work was needed to understand reasons behind health workers’ diagnostic practices despite existing national guidelines and availability of diagnostic tests in these facilities. We
carried out a study to explore health workers’ perspectives of the influencers of case detection and use of TB diagnostic tests in hospitalised children in Kenya guided by behaviour change theories (Chapter 5). The emerging themes and their relationship with each other and COM-B elements has been illustrated in figure 1 (reproduced from Chapter 5). At individual level, we found that knowledge, skill, competence and experience, as well as beliefs and fears impacted on capability (physical & psychological) as well as motivation (reflective) to diagnose TB in children and use diagnostic tests. While formal education and training of health workers has been the primary focus of the TB programme, and is indeed key to ensuring competence and capability, our work found that diagnosing TB in children is mostly reliant on “embodied” or tacit knowledge, developed through observing empathetically and hands-on experience under supervision/guided by an experienced practitioner, as described by various authors [18, 19]. Hospital level influencers included hospital norms, processes and patient flows and resources which affected how individual health workers attempted to diagnose TB in children by impacting on their capability (physical & psychological), motivation (reflective & automatic) and opportunity (physical & social). The cumulative way in which health-workers experience their jobs and lives at the organisation is a key factor in quality improvement and can potentially be leveraged to improve case detection of TB in children: mid-level managers are key as they could be the potential change-agents or champions if well-supported [20-23]. At the wider system level, community practices, beliefs, and implementation of TB programme directives impacted some of the decisions that health workers made through capability (psychological), motivation (reflective & automatic) and opportunity (physical). Human resources for health literature suggest that smart policies like those aimed at strengthening retention, education, training, job-protection for staff can still achieve good health outcomes and could potentially be leveraged to improve TB care in children [24].
With the information gathered from the quantitative and qualitative studies, we gained a deeper understanding of some of the issues underlying the under-detection of TB in children in Kenya, and sought to use validated behaviour change theories to help inform the development of a contextually appropriate intervention (Chapter 6). We chose the Behaviour Change Wheel (BCW) anchored on the Theoretical Domains Framework (TDF), recognising that individual and collective behaviour change is key to implementing new practices and to improving health outcomes [25-28]. One of the strengths of the BCW is that it naturally incorporates context, which is key to effective design and implementation of interventions [27]. We identified the following behaviour change intervention functions: training (impacting practical skills); modelling (credible examples for the others to aspire/imitate); persuasion (to stimulate action); environmental restructuring (to avail necessary resources and opportunities); and education (to increase awareness). The process resulted in a multi-faceted intervention package composed of redesigning of child tuberculosis training; careful selection of champions; use of audit and feedback linked to group problem solving; and workflow restructuring with role specification. The intervention components were selected for their effectiveness (from literature), affordability, acceptability and practicability and designed so that NTP officers and hospital managers can be supported to implement them with relative ease, alongside their daily duties. We used our findings to develop a policy brief (Chapter 7) that will be shared with childhood TB
stakeholders, and some of our suggestions are already being used to help support the development of smart policies for TB in children.

**Strengths and Limitations**

This thesis had several strengths. Using a mixed methods approach, we triangulated findings from several data sources including national TB programme data, patient records, interviews, discussions and observations, achieving a holistic understanding of into the context and the state of tuberculosis in children in Kenya. We employed various strategies to ensure rigour, including data cleaning for the quantitative data, purposive selection of cases and participants to allow comparison and to ensure a full range of voices was captured for the qualitative data; triangulation of findings from national TB programme data, patient records, interviews, discussions and observations; clear records of all processes; member checking; and debriefing and support from colleagues to ensure reflexivity.

The research was embedded in behaviour change theory that helped get a better understanding of the problem of TB case detection which helped guide development of a contextually appropriate intervention and to explain the underlying mechanisms by which the intervention might work. The use of local empiric data will ensure that the interventions are designed for the context. We used consistent implementation terminologies and theory to describe intervention components and explain how they are intended to achieve their effects. We also developed a logic model which provides an opportunity to later evaluate the implementation of our proposed intervention.

Some limitations include the cross-sectional nature of the work the fact that the hospitals we chose to work with may not be representative of smaller hospitals in Kenya where routine documentation may not be as good, and that may not be staffed by Paediatricians. These factors could potentially have led us to under-estimate of the hidden burden of childhood TB in Kenya and to overlook issues pertinent to smaller hospitals in designing our intervention. Nonetheless, we managed to delve deep into the issues by using rich and varied data collection methods, and our qualitative data will make transferability to other settings easier due to the linkage with theory.

There was a lot of disruption caused by prolonged industrial action by the health workforce in Kenya during the study period. This influenced our planned data collection and analysis. There was also missing data as we relied on what was documented in patient records and notification data. However, we leveraged on the rich data we were still able to obtain, using mixed methods to tell the previously unclear story of TB in children in Kenyan hospitals, and give a detailed plan for implementation and evaluation.
A major assumption for this work is that all the other structures and processes in the health system consistently function well and are in support of the proposed intervention, e.g. resources need to be consistently available, staff should be sufficient and the environment in the hospitals, community and policy space should be conducive for the intervention to work well. Whilst unfortunately these conditions may not always be true within our public healthcare system, our strong established relationships with the National TB programme and other key developmental partners make us ideally placed to advocate and ensure that appropriate resources are in place to support the efforts to improve case detection of TB in children in Kenya

Future Perspectives

Implementation and Evaluation of the Proposed Intervention

Our intervention is considered complex, due to the number of interacting components, the number of behaviours being targeted, the range of possible outcomes and the need to adapt implementation to local settings [29]. This has implications for evaluation, especially assessing the fidelity (i.e. was the intervention delivered exactly as proposed). An initial key question for us will be to evaluate practicability- whether the intervention will work effectively in routine practice without too much disruption of other clinical services. The next will be to explain whether the intervention works in ways proposed by the theory of change (see figure 1 of logic model from chapter 6).

The Medical Research Council proposes a framework for evaluating complex interventions [29, 30] which we propose to adopt to guide our thinking for evaluation and implementation of the proposed intervention (see figure 1).
**i) Development**

The first step outlined in the MRC Framework is development of the intervention. We first identified the evidence base, reviewed literature on improving health worker performance and adoption of technologies and guidelines into practice, and carried out empiric studies to help understand the gaps in case detection of TB in children. Next, we identified and developed the theory. We used the Theoretical Domains Framework embedded within the Behaviour Change Wheel to identify behaviour change techniques that may help solve our problem. We also considered interventions supported by literature that are likely to be effective if combined, and would be affordable, practical, effective, acceptable, practical, with minimal disruptions while ensuring equity. We then built a logic model with a theory of change, conceptualising how we believe the intervention would work and the underlying mechanisms, defining the outputs and the intermediate and long-term outcomes (see figure 2 from Chapter 6).

We will work with key stakeholders to redesign the childhood TB training to make it more practical and standardise how it will be delivered, plus develop accompanying supporting material like posters.
and booklets. We propose to select four hospitals as learning sites/case studies to test feasibility and acceptability of the intervention to health workers, and the consistency of delivery. The facilities will be selected from counties that have different TB case notification rates (compare high and low), in which we are able to collect reliable estimates of the outcomes of interest. We propose to select the facilities from the Clinical Information Network in which we started the preliminary work, as they have already shown readiness and willingness to improve care for children with TB and they have a proven/established track record in routine clinical data collection and audit.

Each facility will undergo a sensitisation to the project, followed by a process of getting champions to emerge (ideally these will be hospital mid-level managers), with a strategy to further support them including leadership training. All the facilities will receive the redesigned training on paediatric TB, followed by regular audits of their performance, coupled with formal feedback and structured supervision aiming to identify and overcome barriers to detecting TB in children. Two hospitals will receive feedback with supervision by the hospital TB champion and the other two will receive feedback with supervision by expert outreach from National TB Programme officers. We will assess the feasibility of these two strategies with qualitative determination of differences in preference for supervisors.

Mechanisms for delivery of feedback i.e. how frequently, to groups or individuals, written or verbal feedback, will be allowed to adapt to each site, guided by the champions/supervisors with each team deciding how they will go about group problem solving, how frequently to meet, what goals to set for improvement etc. The data to be used for feedback will however be standard, reporting on similar variables for the quality of care given. Workflow restructuring will also be site dependent, and will evolve from the group problem-solving efforts. External support and mentorship will be available from the National TB Programme and the research team, who will be responsible for documenting the implementation process.

ii) Feasibility

The next step is assessing how far the intervention can be delivered as intended, acknowledging its complex nature and need to allow local adaptation of some aspects. The intervention will initially be delivered over a six-month period in the four case study hospitals, initially aiming to learn what aspects of the intervention are working as intended, estimate what are the resource costs involved, and evaluate whether the processes acceptable, practical and causing minimal disruption to other services. Aspects that need refinement will go back to the development stage, and those that are
effective will be adopted for implementation, learning and refining iteratively over an 18-month period.

**iii) Evaluation**

After feasibility has been established, we will proceed with evaluation to establish effectiveness of the intervention, to understand the change process and to assess cost-effectiveness. Best practice for assessing effectiveness should involve randomisation, as it is the most robust method of preventing selection bias [29]. This may however not always be possible especially for complex interventions due to technical challenges and ethical or political problems associated with randomisation, especially when there may be some pre-implementation evidence of effectiveness [29]. Evaluation must still be done with the best available methods, not least to ensure that the costs of such interventions are justified.

Simultaneous quasi-experimental interrupted time series studies will be conducted with data prospectively collected from medical records of all paediatric admissions in the selected hospitals, guided by the logic model (figure 3). Quantitative data outcomes will include the proportion of paediatric admissions with suggestive signs of TB who get correctly evaluated for TB; the proportion who get a documented differential diagnosis of TB; the proportion who get started on treatment; and the time spent from diagnosis to treatment outlined in Figure 3. The quasi-experimental design will be strengthened by qualitative work which will explore: the intervention process; the pathway to effect; and validity of the pre-specified theory while describing the modifying effect of differences in context. We will collect data on the health workers’ experiences, their confidence levels, their beliefs about capabilities, decision processes et cetera as guided by the logic model, to assess how well the Behaviour Change Wheel intervention functions explain what works (figure 2).

While a cluster randomised control trial would have been a more robust approach, the interrupted time series design was chosen for feasibility and to enable learning and refining of the intervention, and potentially to justify a larger step-wedge trial for scale-up. Conduct of parallel studies in a set of case study hospitals powered for effect will explore replication and provide effect estimates for interventions that share major components but differ in who the champions will be and what activities will be undertaken for problem solving. Consistent results will increase plausibility that effects are attributable to the intervention.

For process evaluation, it is important to assess implementation fidelity, which is the degree to which an intervention is delivered as intended in terms of content, coverage, frequency and duration [31].
Fidelity is important to determine whether a lack of impact may be due to poor implementation or inadequacies in the intervention itself. The fidelity with which an intervention is implemented affects how well it succeeds—the more detailed or specific an intervention is, the more likely that it will be implemented with high fidelity [31]. The nature of complex interventions however, calls sometimes for scope for variation in their delivery with adaptation to local context, and they may not always get implemented with strict fidelity as the goal is ideally for pragmatic effectiveness rather than efficacy [29, 31].

As a proxy for fidelity in its strictest sense, we will therefore document the quality of delivery of the intervention at each site and any variability, assess how well the champions take up their roles, frequency of feedback and group problem solving, goals set and evaluate how all these contribute to the desired outcomes of interest, and whether there are any unintended disruptions to other clinical services. We will be looking to identify how well the starting theory explains the causal mechanisms of the outcomes, and whether other contextual factors can explain variation at the case study sites.

We also propose to also carry out an economic evaluation that will be of great use to policy makers when planning for scale up. We will document and cost the time and effort as well as material resources used to deliver the intervention, compared to status quo. We propose to support our evaluations with Participant Observations by the champions and TB programme supervisors and Non-participant observations by the research team, all of whom will be documenting their reflections in diaries. We will analyse these reflections using the Theoretical Domains Framework to assess theoretical fidelity (to what extent the intervention was delivered in tandem with the intervention theory). We will also borrow from realist philosophies [32], to learn and document: “what works for whom, in what respects, in what contexts and how?” This will be important for predicting the outcomes and translating and adapting interventions for other contexts.

**iv) Implementation**

This phase will involve dissemination of what works to the other facilities, working in partnership with the Ministry of Health, to help establish adoption of lessons learnt into routine practice. Other than scientific manuscripts, we will ensure that the results are communicated in accessible formats like policy briefs with clear recommendations to help dissemination. There will be long-term follow up, including through routine surveillance and monitoring, to see if these efforts eventually contribute to increased case detection of tuberculosis in children in Kenya, and whether the effects persist after the active intervention has stopped.
Problem Statement

There are gaps in identification and investigating of tuberculosis in children in Kenya

Goal

Improved case detection of TB and appropriate use of TB diagnostics in hospitalised children in Kenya

Rationale

Gaps identified in QUANT
- Under-detection & under-reporting of TB in children
- Under use of diagnostic tests especially Xpert®

Gaps identified in QUAL
- Knowledge, skills, competence & experience
- Hospital norms & workflows
- Resources
- Community beliefs & policies

3. Theory-driven, contextually appropriate intervention to address modifiable gaps

Intervention & Theoretical Mechanism

1. Training Programme Redesign
   Physical skills; knowledge; memory, attention & decision processes; intentions

2. Selecting Champions
   (Mid-level managers)
   Social influences; professional role & identity; behavioural regulation; reinforcement

3. Audit & Feedback of childhood TB indicators
   Reinforcement; goals; belief about capabilities; knowledge; behavioural regulation

4. Redesigning work flows and role specification
   Environmental context & resources; reinforcement

Outputs

Health workers reporting confidence in diagnosing TB

Champions with defined roles supported by admin and NTP

Regular audit and feedback with ongoing quality improvement (QI) activities

Clear plans for diagnosis & testing; designated space & time; reduced turnaround times

Intermediate Outcomes

Improved documentation and regular quality improvement meetings supported by data

Improved time spent from diagnosis to starting treatment

Increased number of children correctly evaluated for TB

Short-Term Outcomes

Increased understanding of good documentation & use of data for improvement

Increased understanding on role modelling and working as a team to improve work flows

Increased knowledge, skill and confidence on collecting specimen for TB, use of diagnostic tests to diagnose TB in children

Long Term Outcome

To increase the number of appropriately investigated children reported to the TB programme in Kenya
Concluding remarks: Implications for Policy and Practice

This work contributes to much-needed information on the burden of TB in children. It is highly relevant to national policy and practice because it calls for a re-evaluation of the strategies adopted by the National TB Programme, especially its approach to identifying children with TB, with wider-reaching implications for efforts to address the global burden of childhood TB.

First, we have highlighted urgent need for a better understanding of which children may have TB in our setting and how they present, with clearer guidelines to help clinicians better select which patients to investigate, as well as how to interpret test results considering the low sensitivity and specificity of available tests. If national TB guidelines were uniformly adhered, to resulting in more than half of all paediatric hospital admissions undergoing testing, as our data imply would be the case, this could potentially put a strain on stretched hospital resources due to time, cost and effort to test every eligible patient. A reasonable step would be to start to focus on those with pneumonia, a recognised leading cause of child deaths worldwide [33], as our work shows that these could be potentially missed TB cases, who would be at high risk for adverse outcome without the correct treatment.

Second, we have identified the need to review the approach to national child TB training in terms of its goals, content, pedagogy and participants with a suggestion that training should be conducted at hospitals themselves. Other practice recommendations include using champions and establishing social norms like teamwork and mentorship, as well as group problem solving for quality improvement and to restructure work flows in the hospitals.

Finally, by using the Capability, Opportunity, Motivation-Behaviour (COM-B) model approach to better explain the complex problem of diagnosing TB in children, our work extends the body of literature in which COM-B has been used to understand health systems. It contributes to the field of implementation science by utilising clear definitions from Expert Recommendations for Implementing Change (ERIC) and descriptions of underlying mechanisms of interventions (from the Behaviour Change Wheel) that will hopefully guide others to do likewise in their settings for similar problems.

We have already prepared a national policy brief with clear recommendations from our work and have fed back to policy meetings, where we have been met with good will for uptake, as there is urgency to address the gaps in child TB in Kenya. We hope that ultimately our work will contribute to improved childhood TB detection and treatment in Kenya, other high-burden countries and worldwide.
References


Chapter 9: Summary
**English Summary**

Tuberculosis is a leading cause of morbidity and mortality in children. The true burden however, remains unknown. It is a hidden epidemic, mainly due to various challenges in establishing a diagnosis. Children that go unreported and undiagnosed represent a missed opportunity that contributes to childhood deaths, from a disease that is curable and preventable. This is particularly unfortunate for patients who present with suggestive signs and symptoms to health facilities, but do not get investigations to rule out TB. Considerable efforts have been made to implement evidence-based guidelines and new technologies to aid diagnosis of TB in general, but gaps remain in case detection and utilisation of diagnostic tests. It is important to understand factors that influence health worker practices to develop appropriate interventions to improve the quality of care provided in hospitals in high burden TB countries like Kenya. This thesis reports findings from five studies that described the epidemiology of childhood TB in Kenya, use of diagnostics and adoption of Xpert® MTB/RIF, the influencers of TB case detection in hospitalised children in Kenya, and finally described the process of developing a contextually appropriate intervention package to help improve case detection of TB in children.

*Chapter 1* gave an introduction to TB in children general, highlighting the diagnostic challenges that gave the rationale for this thesis. It also put in perspective the Kenyan context and justified the need for implementation science and behaviour change theories to help address the gaps.

*Chapter 2* was a cross-sectional survey of the National TB Programme notification data that described the characteristics and spatial distribution of notified TB cases and available TB diagnostic tests by county noting the differences between TB in adults and children in various counties in Kenya. The study found that there was probable under detection and underreporting of TB in children aged <15 years. There was also widespread inter-county variation in distribution and use of TB diagnostic tests, with underutilisation of Xpert® despite its widescale roll-out.

*Chapter 3* highlights findings from a systematic review that explored the association between tuberculosis and pneumonia in high burden TB countries. We found that nearly 8% of children admitted with severe pneumonia had culture-confirmed TB disease, which is of concern, especially since culture is known to have low yield in children. The findings suggest that tuberculosis is important in the pathogenesis of acute childhood pneumonia in countries with a high incidence of tuberculosis, either as a direct cause or as an underlying risk factor that increases susceptibility to bacterial pneumonia.
Chapter 4 reports findings from a large longitudinal observational study of routine clinical data from 13 county hospitals in a clinical network in Kenya. The study described clinician TB diagnostic practices through a guideline-linked TB care cascade and quantified the magnitude of TB as a diagnosis amongst children admitted to Kenyan hospitals. More than half of all paediatric admissions had two or more symptoms associated with TB (cough, fever, weight loss, lethargy), warranting further TB investigations, but very few of them got TB diagnostic tests requested. TB was diagnosed in 2.9% of all admissions and most were inadequately investigated. There were gaps in documenting TB as a differential diagnosis even in children who presented with suggestive signs and symptoms as per the guidelines. There was considerable underuse of TB diagnostic tests as was observed in the analysis of the national TB programme data. There is need to review the existing paediatric TB guidelines to provide further clarity as to which children should be investigated for TB and when, as it may not be feasible to investigate more than half of admissions. Clinicians probably realised this and made their own implicit decisions on who to manage for TB, that may not necessarily be consistent with the guidelines.

Chapter 5 was an exploratory qualitative study with an embedded case study approach that described health workers’ perspectives of the influencers of case detection and use of TB diagnostic tests in hospitalised children in Kenya, guided by behaviour change theories. At the individual level, knowledge, skill, competence and experience, as well as beliefs and fears impacted on capability (physical & psychological) as well as motivation (reflective) to think about a diagnosis of TB in children and to use diagnostic tests. Hospital level influencers included hospital norms, processes and patient flows and resources which affected how individual health workers attempted to diagnose TB in children by impacting on their capability (physical & psychological), motivation (reflective & automatic) and opportunity (physical & social). At the wider system level, community practices, beliefs, and implementation of TB programme directives impacted some of the decisions that health workers made through capability (psychological), motivation (reflective & automatic) and opportunity (physical).

Chapter 6 described the process of designing a contextually appropriate and theory-informed intervention to improve case detection of TB in children in Kenyan hospitals guided by the Behaviour Change Wheel. The behaviour change intervention functions included training, modelling, persuasion, environmental restructuring and education. The process resulted in a multi-faceted intervention package composed of: i) redesigning of child tuberculosis training; ii) careful selection of champions;
iii) use of audit and feedback linked to group problem solving; and iv) work flow restructuring with role specification.

**Strengths and Limitations**

We had several data sources including national level data, hospital level data and interviews and observations which enabled deep insights into the state of tuberculosis in children in Kenya. We employed various strategies to ensure rigour, including data cleaning for the quantitative data, purposive selection of cases to allow a wide range of perspectives for the qualitative data and triangulation of findings from diverse data sources. We kept clear records of all processes and had debriefing and support from colleagues to ensure reflexivity. The research project was embedded in theory that helped get a better understanding of the problem of TB case detection and helped guide development of a contextually appropriate intervention, explaining the underlying mechanisms by which the intervention might work. We also developed a logic model which provides an opportunity to later evaluate the intervention implementation.

Some limitations include the cross-sectional nature of the work, and the fact that the hospitals we chose to work with may not be representative of smaller hospitals in Kenya where documentation may not be as good, and may not be staffed by specialists. We still managed to delve deep into the issues by using rich and varied data collection methods. There was a lot of disruption caused by prolonged industrial action by the health workforce in Kenya during the study period. This influenced our planned data collection and analysis. There was also missing data as we relied on what was documented in patient records and notification data. We however leveraged on the rich data we were still able to obtain and mixed methods to tell the previously unclear story of TB in children in Kenya, and give a detailed plan for implementation and evaluation.

**Conclusion and Recommendations**

This work helps contribute to much-needed information on the burden of TB in children, using mixed methodology to generate a rich evidence base.

First, we call for re-evaluation of the strategies adopted by the Kenyan National TB Programme, especially its approach to identifying children with TB. Through our detailed quantitative analysis of national TB notification data and guideline adherence, we have demonstrated urgent need for better understanding of which children may have TB in our setting and how they present, including
development of clearer guidelines to help clinicians better select which patients to investigate and to interpret test results considering low sensitivity/specificity of available tests.

Second, our qualitative exploration of health worker perspectives highlights the need to review the approach to training by the National TB Programme in terms of its goals, content, pedagogy and participants, with a suggestion that training should be conducted at hospitals themselves. Practical recommendations include using training champions drawn from within recipient hospitals; establishing social norms like teamwork and mentorship; and using a collective problem-solving approach for quality improvement and to restructure work flows in the hospitals.

Finally, we integrate our data to design a contextually-appropriate, theory-guided behaviour change intervention to improve child TB case detection. We employ the Capability, Opportunity, Motivation-Behaviour (COM-B) model approach to better understand the complex problem of diagnosing TB in children, thus extending the body of literature which exemplifies the value of this model to understand health systems. We contribute to the field of implementation science by utilising clear definitions from Expert Recommendations for Implementing Change (ERIC) and descriptions of underlying mechanisms of interventions (from the Behaviour Change Wheel) that will guide others to do likewise in their settings for similar problems.

We have already prepared a national policy brief with clear recommendations from our work and have fed back to policy meetings, where we have been met with good will for uptake, as there is urgency to address the gaps in child TB in Kenya. We hope that our work will contribute to improved childhood TB detection and treatment, and ultimately to the reduction of TB-related childhood morbidity and mortality in Kenya and worldwide.
Dutch Summary

Tuberculose (tbc) is een belangrijke oorzaak van morbiditeit en mortaliteit bij kinderen. De werkelijke ziekteelast is echter onbekend. Het is een verborgen epidemie, die vooral te wijten is aan uitdagingen bij het stellen van een diagnose. Kinderen met tbc die niet worden aangegeven en niet worden gediagnosticeerd, vertegenwoordigen een gemiste kans die bijdraagt aan kindersterfte door een ziekte die te genezen en te voorkomen is. Dit geldt temeer voor patiënten die zich presenteren bij gezondheidsinstellingen met verschijnselen die verdacht zijn voor tbc, maar geen onderzoek krijgen om tbc uit te sluiten. Ondanks inspanningen om evidence-based richtlijnen en nieuwe diagnostische technologieën in te zetten, schiet het gebruik van diagnostische testen en de aangifte te kort. Om passende interventies te ontwikkelen ter verbetering van de kwaliteit van de zorg in ziekenhuizen in landen met een veel tbc, zoals Kenia, is beter inzicht nodig in factoren die de praktijken van gezondheidswerkers beïnvloeden. In dit proefschrift worden de bevindingen gerapporteerd van vijf studies naar de epidemiologie van tbc bij kinderen in Kenia, het gebruik van diagnostiek en de adoptie van Xpert® MTB/RIF, en naar factoren die tbc-detectie bij gehospitaliseerde kinderen in Kenia beïnvloeden. Tot slot wordt het proces beschreven om een contextueel passend interventiepakket te ontwikkelen om de opsporing van tbc bij kinderen te verbeteren.

Hoofdstuk 1 geeft een inleiding over tbc bij kinderen in het algemeen, met nadruk op de diagnostische uitdagingen die aanleiding gaven voor dit proefschrift. Ook wordt de situatie in Kenia geschetst en uitgelegd waarom implementatieonderzoek en gedragsveranderingstheorieën geschikt zijn om de hiaten te helpen opvullen.

Hoofdstuk 2 beschrijft een cross-sectionele studie waarin aangiftegegevens van het nationale tbc-bestrijdingsprogramma geanalyseerd worden. De kenmerken en de ruimtelijke spreiding van aangegeven tbc-gevallen en de beschikbare tbc-diagnostische testen worden beschreven, met nadruk op de verschillen tussen tbc bij volwassenen en kinderen in verschillende counties in Kenia. Uit het onderzoek bleek dat er waarschijnlijk sprake was van te lage opsporing en onderrapportage van tbc bij kinderen jonger dan 15 jaar. Er was aanmerkelijke spreiding tussen counties in de distributie en het gebruik van diagnostische tests voor tbc, en Xpert® MTB/RIF werd onderbenut ondanks de grootschalige invoering ervan.

In hoofdstuk 3 worden de bevindingen belicht van een systematisch literatuuronderzoek naar het verband tussen tuberculose en longontsteking in landen met veel tbc. We ontdekten dat bijna 8% van de kinderen die werden opgenomen met ernstige longontsteking kweek-positieve tbc had. Dat is
zorgwekkend, vooral omdat bekend is dat kweek een lage opbrengst heeft bij kinderen. De bevindingen suggereren dat tbc belangrijk is in de pathogenese van acute longontsteking bij kinderen in landen met een hoge tbc-incidentie, hetzij als een directe oorzaak, hetzij als een onderliggende risicofactor die de vatbaarheid voor bacteriële longontsteking verhoogt.

**Hoofdstuk 4** rapporteert de bevindingen van een grote longitudinale observationele studie op basis van routinematige klinische gegevens van 13 county ziekenhuizen in een klinisch netwerk in Kenia. De diagnostische praktijken van clinici m.b.t. het diagnosticeren van tbc worden beschreven aan de hand van een aan de richtlijnen gekoppelde tbc-zorgcascade. Het percentage tbc-diagnoses onder kinderen die opgenomen werden in de 13 Keniaanse ziekenhuizen is bepaald. De studie vond dat bij meer dan de helft van alle pediatrische opnames twee of meer symptomen aanwezig waren die kunnen wijzen op tbc (hoesten, koorts, gewichtsverlies, lethargie), en die verdere tbc-diagnostiek rechtvaardigen, maar bij slechts een klein percentage van hen werden de benodigde tbc diagnostische tests aangevraagd. Bij 2,9% van alle opnames werd tbc vastgesteld en meestal na incomplete diagnostiek. Er waren hiaten in het documenteren van tbc als differentiaaldiagnose, ook bij kinderen die volgens de richtlijnen voor tbc verdachte verschijnselen vertoonden. Ook hier werd onderbenutting van de diagnostische tbc-tests geconstateerd, net als bij de analyse van de nationale tbc-bestrijdingsprogramma gegevens. Om meer duidelijkheid te verschaffen over welke kinderen op tbc moeten worden onderzocht en wanneer, dienen de bestaande pediatrische tbc-richtlijnen herzien worden, ook omdat het mogelijk niet haalbaar is om meer dan de helft van de opnames aan tbc-diagnostiek te onderwerpen. De clinici realiseerden zich dit waarschijnlijk en namen hun eigen impliciete beslissingen over wie voor tbc te behandelen, die niet noodzakelijkerwijs in overeenstemming zijn met de richtlijnen.

**Hoofdstuk 5** beschrijft een verkennend kwalitatief onderzoek met een ingebedde casestudy benadering, naar de perspectieven van gezondheidswerkers op factoren die het detecteren van tbc gevallen en het gebruik van tbc-diagnostische tests onder gehospitaliseerde kinderen in Kenia beïnvloeden, aan de hand van gedragsveranderings-theorieën. Op individueel niveau hadden kennis, vaardigheid, competentie en ervaring, evenals overtuigingen en angsten invloed op de bekwaamheid (fysiek en psychisch) en de motivatie (reflectief) om tbc bij kinderen te diagnosticeren en om diagnostische tests te gebruiken. Op ziekenhuisniveau waren ziekenhuisnormen, processen en patiëntenstromen, en middelen de factoren die invloed hadden op hoe individuele gezondheidswerkers probeerden om tbc bij kinderen te diagnosticeren, door invloed op hun bekwaamheid (fysiek en psychologisch), motivatie (reflectief en automatisch) en kansen (fysiek en
sociaal). Op een breder systeemniveau hadden gemeenschapspraktijken, overtuigingen, en de implementatie van de richtlijnen van het tbc-bestrijdingsprogramma invloed op de beslissingen die gezondheidswerkers namen door middel van bekwaamheid (psychologisch), motivatie (reflectief en automatisch) en kansen (fysiek en sociaal).

In *hoofdstuk 6* wordt het ontwerpproces beschreven van op de context afgestemde en theoretisch onderbouwde interventie ter verbetering van de detectie van tbc bij kinderen in Keniaanse ziekenhuizen, aan de hand van de *Behaviour Change Wheel* methode. De functies van de gedragsveranderingsinterventie omvatten training, modellering, overtuigen, herstructurering van de omgeving en onderwijs. Het proces resulteerde in een veelzijdig interventiepakket bestaande uit het:

i) herontwerpen van het onderwijs over tbc bij kinderen; ii) zorgvuldig selecteren van kampioenen; iii) gebruik van audit en feedback gekoppeld aan probleem oplossen door de groep; en iv) herstructureren van de workflow met rolspecificatie.

**Sterke punten en beperkingen**

We hadden verschillende gegevensbronnen, waaronder gegevens op nationaal niveau, gegevens op ziekenhuisniveau, en interviews en observaties die diepgaande inzichten mogelijk maakten in de tbc-situatie bij kinderen in Kenia. We hebben verschillende strategieën toegepast om de nauwkeurigheid te waarborgen, waaronder het opschonen van gegevens voor de kwantitatieve analyses, doelgerichte selectie van *cases* voor kwalitatieve analyses om een breed scala aan perspectieven te verkrijgen, en triangulatie van bevindingen uit verschillende gegevensbronnen. We hielden duidelijke dossiers bij van alle processen, hielden debriefings, en kregen ondersteuning van collega’s om reflexiviteit te garanderen. Het onderzoek was ingebed in theorie wat hielp bij het verkrijgen van inzicht in de problemen t.a.v. detectie van tbc-gevallen. Ook gaf de theorie richting aan de ontwikkeling van een op de context afgestemde interventie, door inzicht in de onderliggende mechanismen waardoor de interventie zou kunnen werken. We hebben ook een logisch model ontwikkeld om later de implementatie van de interventie te kunnen evalueren.

De beperkingen zijn onder andere de cross-sectionele aard van het onderzoek, en het feit dat de door ons gekozen ziekenhuizen mogelijk niet representatief zijn voor kleinere ziekenhuizen in Kenia, waar documentatie mogelijk minder goed is, en waar geen medisch specialisten werkzaam zijn. We zijn er daarentegen wel in geslaagd om diep op het probleem in te gaan, door rijke en gevarieerde methoden van dataverzameling te gebruiken. Er was veel verstoring door langdurige vakbondsacties van gezondheidswerkers in Kenia tijdens de onderzoeksperiode. Dit beïnvloedde onze geplande gegevensverzameling en -analyse. Er ontbraken ook gegevens omdat we vertrouwden op wat was
gedocumenteerd in patiëntendossiers en aangiftegegevens. Het gebruik van de rijke gegevens die we konden verkrijgen en van mixed-methods hebben desondanks geleid tot een duidelijker beeld over tbc bij kinderen in Kenia, en een gedetailleerd plan voor implementatie en evaluatie.

**Conclusie en aanbevelingen**

Het onderzoek in dit proefschrift draagt bij aan de hoognodige informatie over de ziekte last van tbc bij kinderen, door toepassing van mixed-methods. Ten eerste pleiten we voor een herevaluatie van de strategie van het nationale tbc-bestrijdingsprogramma ten aanzien van het diagnosticeren van tbc bij kinderen. Door gedetailleerde kwantitatieve analyse van nationale tbc-aangifte gegevens en van de naleving van richtlijnen laten we zien dat beter inzicht nodig in welke kinderen in de Keniaanse setting mogelijk tbc hebben en wat hun klinische presentatie is. Ook zijn duidelijker richtlijnen nodig die clinici beter ondersteunen bij het selecteren van patiënten voor verdere diagnostiek, en bij de interpretatie van de resultaten van diagnostische testen, gezien de lage sensitiviteit en specificiteit van de beschikbare testen.

Ten tweede onderstreep onze kwalitatieve verkenning van de perspectieven van gezondheidswerkers dat de aanpak van trainingen door het Nationale TB Programma herzien dienen te worden, zowel de leerdoelen, de inhoud, de pedagogische methoden, en selectie van deelnemers. Het is aan te raden om trainingen op locatie in de ziekenhuizen te geven. Ander implicaties voor de praktijk zijn het inzetten van kampioenen, het tot stand brengen van sociale normen zoals teamwork en mentorschap, evenals groeps-probleem-oplossing ten behoeve van kwaliteitsverbetering, en het herstructureren van de workflow in de ziekenhuizen.

Ten slotte integreren we onze gegevens om een contextueel geschikte, theorie-gestuurde gedragsveranderingsinterventie te ontwerpen ter verbetering van de detectie van tbc bij kinderen. We gebruiken het Capability, Opportunity, Motivation-Behavior (COM-B) model om beter inzicht te krijgen in het complexe probleem van tbc-diagnose bij kinderen, en dragen daarmee bij aan de literatuur die de waarde van dit model voor het begrijpen van gezondheidssystemen illustreert. Het werk draagt ook bij aan de implementatiewetenschap door gebruik te maken van duidelijke definities uit Expert Recommendations for Implementing Change (ERIC) en door onderliggende mechanismen van interventies te beschrijven (d.m.v. de Behaviour Change Wheel methode), hetgeen een leidraad kan zijn voor anderen om soortgelijke problemen in hun omgeving aan te pakken.

We hebben al een nationale beleidsnota opgesteld met duidelijke aanbevelingen uit ons werk, en die teruggekoppeld op beleidsbijeenkomsten, waar ze met goede wil zijn ontvangen omdat er dringend
iets moet worden gedaan aan de lacunes in kinder-tbc in Kenia. We hopen dat ons werk zal bijdragen aan een betere opsporing en behandeling van tbc bij kinderen, en uiteindelijk aan de vermindering van tbc-gerelateerde morbiditeit en mortaliteit bij kinderen in Kenia en wereldwijd.
PhD Portfolio
**PhD portfolio**

**Name PhD student:** Jacquie Narotso Oliwa  
**PhD period:** April 2017- August 2020  
**Name PhD supervisors:** Prof Michaël Boele van Hensbroek  
Prof Mike English  
Ass. Prof Anja van’t Hoog  
Dr Caroline Jones

**PhD training**

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<tr>
<td>i) Introduction to Time series analysis</td>
<td>Feb 2017</td>
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<td>ii) Introduction to Social Science approaches, qualitative data analysis and Nvivo training</td>
<td>Mar 2017</td>
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<td>iii) Summer school University College London; Behaviour Change Principles and Practice</td>
<td>Aug 2017</td>
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<td>iv) 11th International Child TB Training Course: Stellenbosch University</td>
<td>Sep 2017</td>
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<td>v) WHO/TDR Implementation Research course (MOOC) with a focus on diseases of poverty</td>
<td>Apr-May 2018</td>
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<td>vi) Research Writing in the social sciences (MOOC)</td>
<td>Feb-Apr 2019</td>
<td>7 wks/28hr</td>
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<td>vii) Health Systems Strengthening (MOOC)</td>
<td>Jun-Jul 2019</td>
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<td>viii) Project Management in Global Health (MOCC)</td>
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### Seminars, workshops and master classes

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<tr>
<td>i) Weekly journal clubs/seminars at the Nairobi Programme</td>
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<td>ii) WHO-TDR/UoN/Makerere Trainer of Trainers Workshop on Evidence</td>
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<td>Informed Policy making</td>
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<td>iii) Clinical Information Network meeting: collected data on</td>
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<td>health worker challenges in diagnosing TB in children</td>
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<td>iv) National TB programme paediatricians’ sensitisation meeting</td>
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<td>v) Clinical Information Network meeting: presented results for</td>
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<td>respondent validation and feedback from qualitative work</td>
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<td>vi) Generic skills training: Writing &amp; Publication for PhD students</td>
<td>Feb 2019</td>
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<td>vii) Social Sciences Group workshop: Power and privilege</td>
<td>Feb 2019</td>
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<tr>
<td>viii) PhD students workshop (Oxford)</td>
<td>Jul 2019</td>
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### Presentations

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<td>i) Pre-registration seminar to present PhD proposal</td>
<td>Jan 2017</td>
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<td>ii) Theory-guided mixed methods approach in improving case</td>
<td>Apr 2017</td>
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<td>detection of tuberculosis in children</td>
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<td>iii) Seminar on preliminary results from National TB programme data</td>
<td>May 2017</td>
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<td>analysis</td>
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<td>iv) Childhood TB: Are we really doing enough to pick the children?</td>
<td>Jun 2017</td>
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<td>v) Factors associated with use of bacteriological tests for</td>
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<td>diagnosing TB in Kenya</td>
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<td>vi) Current issues in diagnosis and management of TB in children</td>
<td>Nov 2017</td>
<td>30 min</td>
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<td>vii) An estimate of the burden, potential missed care and</td>
<td>Oct 2018</td>
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<td>diagnostic practices for tuberculosis amongst children admitted</td>
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<td>to government hospitals in Kenya</td>
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<td>viii) Findings and recommendations from Health workers’</td>
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<td>perspectives on diagnosis of TB in children to child TB stakeholders</td>
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<td>ix) Seminar: Attempts at understanding the complex</td>
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<td>epidemiology of TB in children in Kenya</td>
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<tr>
<td>x) Seminar: Health worker perspectives on diagnosing TB in children</td>
<td>Jul 2019</td>
<td>30 min</td>
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Local conferences

i) Annual Kenya Paediatrics Association Conference (speaker and part of scientific committee)  
   Apr 2017  1 week

ii) Kenya Lung Health Conference (speaker)  
    Jun 2017  1 week

iii) Annual Kenya Paediatrics Association Conference (speaker & scientific committee)  
     Apr 2018  1 week

iv) Annual Kenya Paediatrics Association conference (speaker & scientific committee)  
    Apr 2019  1 week

v) Kenya Lung Health Conference (Speaker)  
   Jun 2019  1 day

International conferences

i) 48th Union World Conference on Lung Health (Guadalajara)  
   Oct 2017  1 week

ii) 49th Union World Conference on Lung Health (The Hague)  
    Oct 2018  1 week

iii) Crossing Boundaries Global Health Meeting (Oxford)  
     Dec 2018  3 days

Other: Policy engagement

i) Technical support for National TB programme strategic plan mid-term review  
   Mar 2017  2 days

ii) Development of New born guidelines for Kenya  
    Apr 2017  2 weeks

iii) Core TB Technical Working group  
    Feb 2018  1 day

iv) Paediatric TB Technical Working Group  
    Feb 2018  1 day

v) Paediatric TB Curriculum review  
   April 2018  2 weeks

vi) Paediatric TB stakeholders’ meeting  
    Mar 2019  1 day

vii) Paediatric TB Technical Working Group  
     April 2019  1 day

2. Teaching

Lecturing

i) East Africa Diploma in Tropical Medicine with the London School of Hygiene and Tropical Medicine  
   2017 & 2018  4 weeks

ii) University of Nairobi, School of Medicine Undergraduate & postgraduate students on child health  
    2017  2 semesters

iii) University of Nairobi postgraduate research methods course  
    2017-2019  2 weeks

iv) National TB Programme child TB trainings  
    2018 & 2019  3 weeks

v) Diagnosis of TB in children and advanced specimen collection (Malawi)  
   Aug 2019  2 weeks

Tutoring, Mentoring

i) Took part in “I am a Scientist, Get me out of here" mentorship programme for High School students on STEM  
   2017  2 weeks

ii) Mentored a postgraduate diploma student  
    2017-2018  2 years

iii) Mentored 3 MMed Paediatrics students  
    2016-2018  3 years
Supervising

i) Supervised 2 Masters students and a postgraduate diploma student 2016-2018 3 years

Parameters of Esteem

Grants

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<td>2017</td>
<td>Travel grant for Union conference to Guadalajara, Mexico</td>
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<tr>
<td>2018</td>
<td>Travel grant for Union Conference to The Hague, The Netherlands</td>
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</table>

Publications


8. Comparable outcomes among trial and nontrial participants in a clinical trial of antibiotics for childhood pneumonia: a retrospective cohort study. Agweyu A, Oliwa J, Gathara D, Muinga N,


Curriculum Vitae

Summary
Jacquie is a paediatrician, clinical epidemiologist, a lecturer and doctorate research fellow under the Initiative to Develop African research Leaders (IDEAL). Her research focus is in health systems and implementation science. Her current project is trying to understand the complex epidemiology of tuberculosis in children and optimising implementation of guidelines and diagnostic tests to improve case detection of tuberculosis in children. She has collaborated with the Kenyan Ministry of Health and government hospitals in various quality improvement projects, clinical trials and systematic reviews—all of which have contributed to building evidenced-based care and policies for sick children in Kenya. She serves on the Kenya Paediatric TB Technical Working Group, is a member of the International Union of Lung Health and the WHO Child TB subgroup providing technical expertise in policy development and advocacy for improved care for children with tuberculosis.

Jacquie has vast experience in medical education. She is a trainer of trainers for the Paediatric HIV Care Course; Paediatric TB; as well as Paediatric Life support courses. She lectures Paediatrics and Child Health at the University of Nairobi; and the Diploma in Tropical Medicine with the London School of Hygiene and Tropical Medicine. She has taken part in curriculum development/review of the mentioned courses and has trained/facilitated several courses in Kenya and the wider East Africa region. Jacquie’s expertise spans curriculum development and medical education; health systems research; clinical and observational studies; quality improvement; monitoring and evaluation; policy formulation and implementation. She is passionate about capacity building and use of evidence to improve quality of care in children.

Education and Training

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<tr>
<th>Qualification</th>
<th>Institution</th>
<th>Year of Study</th>
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<tr>
<td>Doctor of Philosophy</td>
<td>University of Amsterdam</td>
<td>Submitted</td>
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<tr>
<td>Master of Science Epidemiology</td>
<td>London School of Hygiene &amp; Tropical Medicine</td>
<td>2012-2014</td>
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<tr>
<td>Master of Medicine Paediatrics &amp; Child Health</td>
<td>University of Nairobi</td>
<td>2007-2010</td>
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<tr>
<td>Bachelor of Medicine and Surgery</td>
<td>University of Nairobi</td>
<td>2000-2005</td>
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Employment History

1. **Lecturer Paediatrics & Child Health** University of Nairobi (Feb 2016 to Date)

2. **Research Medical Specialist** KEMRI-Wellcome Trust Research Programme (April 2011-Jan 2016)

3. **Senior House Officer-Paediatrics & Child Health** University of Nairobi (Oct 2007- Dec 2010)

   We had several data sources including national level data, hospital level data and interviews and observations which enabled deep insights into the state of tuberculosis in children in Kenya

Grants Held

1. **Elizabeth Glaser Pediatric AIDS Foundation**: Catalyzing Pediatric Tuberculosis Innovations (CaP TB): Implementation and Integration of New TB Care and Treatment Models

   **Amount awarded**: 7,000 Euros. Duration 6 months

2. **Initiative to Develop African Research Leaders (IDEAL) PhD studentship**: Understanding and improving case detection and care for children with tuberculosis in Kenya

   **Amount awarded**: USD 135,248. Duration 45 months

3. **General Electric Foundation/Centre for Public Health Development**: Programme to Improve the Use of Medical Equipment and Best Clinical Practices in Maternal and Child Health in Five Hospitals in Nyanza-Kenya

   **Amount awarded**: USD 236,819. Duration 18 months

Committees, Boards and Technical Steering Groups

1. **Board member National TB Programme Paediatric TB Technical working group**: Provides technical expertise to the TB programme, conduct reviews, guide guideline development, conduct training for health workers, sensitisation meetings

2. **Member Kenya Paediatric Association Scientific Committee**: Responsible for helping to plan and co-ordinate medical education for paediatricians/child health workers as well as planning content for the annual scientific congress, reviewing abstracts and chairing sessions

3. **Kiwimbi Kenya Board Member**: Kiwimbi partners with underserved communities world-wide to create educational opportunities through locally run learning centres. Kiwimbi also supports education by running camp programmes and mentoring; trade-skills like tailoring and carpentry; exam revision; access to books, newspapers and e-resources in satellite libraries in villages. As a board member, I was responsible for planning and implementing the activities including fundraising, budgeting, accounting, reporting as well as advocacy for projects.
Acknowledgements
I would like to thank the following people for their invaluable support over the past few years.

Mike: mentor, supervisor, friend, father-figure all rolled into one. Thank you for taking a chance on a shy, introverted paediatrician almost a decade ago, and helping to groom me into a proficient scientist, a confident public speaker, author and a passionate advocate for quality of health care. Thank you for your support through the years, often throwing me into the deep end helped me learn that I am indeed capable of so much, indeed I learnt to swim with the big fish! Through you, I have learnt the importance of engaging with stakeholders, of quietly doing excellent work, and speaking up/letting my voice be heard. I learnt the only stupid question is the one never asked. And how to recognise “bad science”, the role of critical appraisal (haha I still have your copy of Ben Goldacre’s book!). You taught me to be a good scientist, one must read voraciously (I however never got around to the lofty goal of 20 articles a week!) I could go on, and on, and on…but suffice it to say I am glad our paths crossed, and grateful for the growth I have experienced under your tutelage.

Anja: thank you so much for being such an incredible supervisor, often going over and above the call of duty...this past year has been crazy, trying to write my thesis with a young baby in the midst of a pandemic, with a partner on the frontline! Our weekly calls became a lifeline, they kept me sane and helped me develop goals for each week till I finished writing up. Thank you for always giving constructive feedback on my writing drafts, even when time was running out for submissions. Thank you for helping me crystallise my thoughts, for being a good sounding board, for always giving such excellent advice, in work and life. Through you I have learnt qualities of a good mentor, and will be paying forward to my future students. I am eternally grateful for your support, and hope we get to work together again in the future.

Caroline: thank you for your help and direction in the field of qualitative science where I was so green starting off. Thank you for pointing me to the right resources, for listening and critiquing my work. For giving valuable feedback. For lending your voice to the battles I had to fight this year to complete my work. I have learnt and grown so much, and despite our different philosophical stances, we were able to produce amazing work that will hopefully positively impact the lives of children with tuberculosis.

Michael: thank you for being an amazing promotor. I remember when I was starting off, our conversation stayed with me when we met a few years back in Amsterdam. You told me, “you are the driver of this PhD...”. You reminded me to always take charge and own my work. Through this I learnt to find my voice when there was a lot of “noise” around. Thank you for providing leadership and direction, and teaching me to steer my ship. It has been a pleasure working with you the past four years.

To my exam committee members, thank you for taking the time to read and mark my thesis and for being present for my defence. I appreciate each and every one of you. Special thanks to Frank Cobelens for your encouragement during my mid-term review.

Linde Nieuwenhuys and Bettina Batista: thank you for your help throughout my PhD period, especially for helping me navigate the AMC bureaucracies as a Kenyan student in a Dutch system.
Judy Ng’ang’a, Liz Kyala and Metrine Saisi: thank you so much for providing great support, for going out of your way to make sure I had everything I needed when I needed it, for going out of your way to help sort out issues, for your friendship… I am eternally grateful.

IDEAL/DELTAS scheme and KWTRP finance and administrative team: thank you for funding my work and for the administrative support throughout my studies.

My colleagues turned dear friends at the KEMRI-Wellcome Trust: thank you for providing such an interactive and fun space for good science to happen. Thank you for providing feedback during seminars, for being available for me to pick your brains whenever I was stuck. For the long debates over coffee/lunch at the coffee room. Thanks Naomi for reading my drafts, slashing word counts, formatting my documents, bringing me chocolates from your travels. Special thanks to my deskies Naomi and Judy, and across neighbours, Michuki, Tim, Conrad, Lynda…I love and miss our little corner space, our conversations…this past year has been so hard working away from that camaraderie. Thank you Nay especially for your help in proofreading and formatting so many of my documents. And for your friendship and wise counsel over the years. Thank you also to Jacinta for teaching me how to do good qualitative work and for encouraging me as a fellow PhD mom. To David, Philip and Morris—my stats doctors asanteni. Ambrose, Edwine, Karis, Munge, Charlie, Herbert, Aluvaal-a-tumetoka mbali, na mbali tutaenda. Thank you for cheering me on, for listening when I needed to debrief, for sharing my struggles, for encouraging me, thank you. I am so proud of you my peers and all you have been able to achieve; Kenya’s future is quite bright with all of you leading in your various capacities. Sabina, my amazing research assistant and mentee, thank you! I know you will soar to great heights, I’ll be here cheering you on...

Thanks to Alex Njeru and Joy Kiptim for your help preparing the policy brief and bearing with the endless back and forth.

Victor SSempija, fellow mature PhD student and survivor, thank you for your friendship and encouragement and for your help with my statistics while we were in Amsterdam.

To my colleagues at the University of Nairobi, Department of Paediatrics, with a special mention to Fred Were, Lisa Obimbo, Dorothy Mbori-Ngacha, Aggrey Wasunna, Grace Irimu, Diana Marangu, and current chair Dalton Wamalwa. Thank you for giving me space and support to do my research, thank you for your mentorship and guidance over the years. I am looking forward to working together to continue to uplift the university’s profile and to mentor the next generation of paediatricians.

To all our colleagues in the Clinical Information Network and the National TB Programme, thank you for your support that made this work possible. Special thank you to Enos Masini, Maureen Kamene Immaculate Kathure and Kadoni Kasera. Colleagues at the Centre of Health Solutions: Brenda Mungai, Lorraine Mugambi-Nyaboga, Tessa Njoroge, Ann Masese—thank you for the opportunity to work together in the fight against TB in children.

Ben Marais, Steve Graham: thank you for responding with kindness when I reached about my ideas to study the links between pneumonia and TB, even though you did not know me. Thank you for giving me mentorship, direction, for collaborating with me on manuscripts which set me on course to do this PhD. Thank you.
Olubayi, my mentor and friend. Thank you for your guidance throughout the journey, for sharing snippets of wisdom, for illuminating the path. Thank you for reigniting my reading culture, I enjoyed our book club Thinks and Reads very much. For the opportunity to serve with you on the Kiwimbi board, thank you. Thank you also for taking the time to proofread my thesis and giving such valuable feedback.

Nick Gichu and Jane Hassell, thanks for taking the time to read my thesis and proofreading and believing in my work. True friends are hard to find, I am so very glad I have you in my corner.

Peace Masinde-Mutuma, my BFF...I missed you a lot during my final year with you in Geneva...but thanks for your friendship through the years, for being a shoulder I know I can always lean on...for making me the world’s coolest auntie to my amazing nephews. Your love and friendship have seen me through the darkest phases of my life, and I am so glad I have you on my team for life.

To my hiking family the Outdoor Ninjas: thank you for your friendship, for organising excursions that helped me find outlets for the stress of being a PhD student. For helping me reach great heights, this helped me develop the grit to go through this crazy final year!

To my family: Mom and Dad, thank you for always believing in my dreams, for supporting me, for being my #1 cheerleaders, for being the wind beneath my wings. I love you and hope I have made you proud. My siblings Dennis, Cyn, Dwayne...I know it’s not being easy always being compared to your crazy over-achieving big sister. Chart your own course and soar, knowing that you too have the DNA of high achievers...thank you for your love and support. For cheering me on always. I love you all, you are my rock. My bonus siblings Patti and Edwina, I am passing on the scholar baton to you...kazaneni...My very large extended family, my loving aunties and uncles, my cousins...I am blessed to be part of the Mak-Oliwa clan...thank you for your love and support through the years. Because of you, I know I will never walk alone.

To little Josh, without whom this PhD would likely have been completed a year ago...but I would not change a thing! Having you during my final year has stretched me to limits I did not know existed...writing a thesis, during a pandemic, sleep deprived and on gallons of coffee and still finding time to be present to watch you grow into this amazing bubbly little human being has been such a trip! You have been my amazing light during this crazy pandemic year. I love you Beans, you inspired me to finish strong, as my friend Jacinta reminded me, your little eyes will always be watching me...I could not bear to let you down, so I pressed on. I hope you get to do more, and go further. I’ll always be here cheering you on.

To my darling husband Mark...we became friends on a Kilimanjaro excursion when I had been going through grant proposal rejection and was very depressed. Our passion for the outdoors and traveling and good food and reading drew us together, and I am so blessed that I get to travel through this journey of life with such an amazing soul. Thank you for believing in me, for your friendship, for always uplifting me, for cheering me on...for feeding me, for spoiling me silly...I have not only survived but thrived in this crazy PhD season because of your love and support. My guardian angel, always looking out, giving me room to be me, pushing me to be the best I can be. Thank you for being invested in my work, for reading (and bashing!) my manuscripts and for giving creative input to my work. For spending countless days drawing the amazing illustrations that have helped to tell
this story. For being you. Thank you. Loving you always, in all ways. This doctorate is also yours, we surely have been in the trenches together, Dr Captain Mutinda!

And finally, I would like to give thanks God...my faith has been my anchor through the crazy ups and downs of this journey...I know many think it is crazy for a scientist trained to be a rationale thinker to have faith, but through my years of questioning and searching, when very little made sense and sometimes felt like I was close to losing my mind...I found my inner peace and I am grateful.

I dedicate this work to our patients, the little children whose faces inspired this work...we will continue to unmask each and every one, until all who need treatment get it. Here’s to zero child TB deaths in our lifetime!