An evaluation of Isoniazid prophylaxis treatment and the role of Xpert MTB/RIF test in improving the diagnosis and prevention of tuberculosis in children exposed to index cases with pulmonary tuberculosis in Kigali, Rwanda

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Thesis submitted in fulfilment of the requirements for the degree
Doctor of Philosophy
(Public Health)
At the School of Public Health
University of the Western Cape

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Declaration

I, Birungi Mwayuma Francine, hereby declare that the work contained in this thesis is my original work, that neither this work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university. I further declare that all sources that I have cited or quoted have been indicated and acknowledged by complete references.

BirungiMwayuma Francine

Signature..  .....

Acknowledgments

First, I would like to thank God Almighty, my everything, my champion who gave me health, support, inspiration, knowledge and strength during my PhD journey. You have manifested your grace to me beyond what a human being can imagine. Yes, I saw your power and love day after day during this journey. May all honour and glory be given to Your Name.

The work presented in this thesis took place over a long period of time during which so many individuals and organizations contributed to its realization. This thesis is a set of stones that each person brought. From the bottom of my heart I would like to thank you and tell you how much I appreciated your effort, contribution and support to me.

May my special gratitude go to the following people:

The study participants and their parents or caregivers, TB diagnostic laboratory staff, TB focal points, head of Primary health care centres (PHCs), Community health workers and data enumerators involved in this study. Above all, I am delighted that the outcomes of this study will influence the change in the child contacts management practice in Rwanda.

Prof Brian van Wyk, my main supervisor, for sharing knowledge, experience with me and for being supportive throughout my doctoral education. Thank you for your trust that led you to accept to supervise me. Your availability, timely feedback, constructive criticism, optimism, consideration and friendliness to me during my stay in South Africa were much appreciated. Thank you for your administrative support to make my journey to South Africa possible. Your financial support is also greatly appreciated. I learned professional values from working with you.

Prof Stephen Graham, my co-supervisor, for being a very supportive co-supervisor, for your scientific contribution and constructive criticism. You have always been patient with me, provided a timely feedback and have been ready to check my analysis and syntax files when needed. I am grateful and appreciated working with you.

Dr Jeannine Uwimana Nicol, my co-supervisor, for your scientific contribution, encouragement and for being a person of contact with the SoPH. I am grateful and appreciated working with you.

Mr Gédéon Bahemuka, Dr Mary Nellima Ondiaka and **Ms Jean Fourie** for your kind help and support in editing the language of this thesis. Be blessed for your valuable support.

Aline Umubyeyi and Laetitia Nyirazinyoye, Dean of and CDC project coordinator at School of Public Health, College of Medicine and Health Sciences of the University of Rwanda respectively, for providing me with different kinds of support. You did your best to support all administrative matters related to my doctoral education and enabled my preparations and travel to go smoothly. I am sincerely grateful to you. May my God bless you.

Dr Paulin Basinga, for your time spent on writing the SPH CDC grant that supported my tuition fees, my travel to and stay in Belgium and South Africa. Your contribution was of great value and much appreciated.

Helen Schneider, Professor at SoPH of UWC, for your encouragement and financial support to translate my transcripts from Kinyarwanda to English, which was needed for my third and fourth papers to be accepted for publication. Your contribution was of great value and much appreciated.

Ferdinand C. Mukumbang, my co-author, for your scientific contribution, support, encouragement and availability. Your contribution was of great value and much appreciated.

Zandile J. Mchiza, Associate Professor at SoPH, University of Western Cape, for your support, availability and encouragement. Be blessed for your support.

Prof Jean Baptiste Kakoma and Prof Muganga Narcisse, former dean of Rwanda School of Public Health and former Head of the Paediatric Unit at Kigali University Teaching Hospital (UTH) respectively, for your support and trust when applying for the Sida grant. Without your help, I would not have got that fund which has partially contributed to the collection of data used in this thesis.

Wong Rex, former Director, Hospital Strengthening Initiative Yale Global Health Leadership Institute, for your support when writing the proposal of this thesis.

To my SOPH friends!!! **Neo Sematlane**, you have been my Aaron, usual available for me despite being yourself busy with your PhD!!! Thank you for your friendly support. Your constructive criticism has opened my mind. **WoldekidanKifle Amde**, my Uber, thank you for your support and kindness. Dr **Fidele K. Mukinda**, my Uber blackand IT, thank for your support and kindness.

The administrative staff of SoPH, for your support of any kind. My special gratitude to Corinne Carolissen to have always been there for me, for usually responding to my multiple emails with patience and professionalism. I am thinking of **Carnita Ernest**, **Theresa de Lima**, **Ntombonzi Buzani and Tamlin Petersen**. Thank you all for your support and kindness.

Rispa Tororrey and Dr Philomene (Maman Blaise) and family for your hospitality, prayers, support and encouragement. Your contribution is very much appreciated.

PastorsJohn and Clementine and Ms **Jacqueline Umutoniwase** and fellow pray group members, for your spirutual support. You have been my "Aaron" supporting me to raise my hands, so that the Lord may manifest His power during this hard journey. *Imana ibampere imigisha itagabanutse*.

My family (uncles, cousins and aunts) and in-laws, thank you for your prayers and encouragement. I express special gratitude to you, my uncle **Raphael Byakagaba,** for your support when I needed it. Special gratitude go to my brother **Lokpatchu Roger** for your support, encouragement, and hospitality. May my God bless all of you.

My **mother**, that special woman, who did a lot for me. Thank you for your love, encouragement and financial support to me and my family during my absence. You have been there to respond to our needs as much as you can during this hard period of my PhD study. May my God bless you abundantly.

My lovely husband, **Kugonza Jacques** and sons **Mugisa Daniel** and **Tumusime Kugonza Samuel**, thank you for your patience, support, love and care. My son **Samuel**, you have endured

a lot since your young age (mama no South Africa, no Kinshasa!!!!). Thank you for your patience. You did more than myself.

Dedication

To my God, Champion, Fellow-worker

To my sons, Tumusime Samuel and Mugisa Daniel.

To my husband, Kugonza Jacques.

To my mother, Akiki Louise Marie.

To Claude Bernier

To my late cousin, Mugisa Bahigani Amooti

To my grand-mother, Bamanyisa Ferlesi Amooti.

Acronyms/Abbreviation

ATLAS:	Automatically Tuned Linear Algebra Software
CDC:	Centres for Disease Control
CHW:	Community Health Workers
CXR	Chest X-ray
DR-TB:	Drug-resistant tuberculosis
FGD:	Focus group discussion
GL:	Gastric Lavage
HBC	High Burden Countries
HIV:	Human Immunodeficiency Virus
IPT:	Isoniazid preventive therapy
NISR:	National Institute of Statistics of Rwanda
NTP:	National Tuberculosis Programmes
PBF	Performance based financing
PHC:	Primary Health Centre
PTB:	Pulmonary Tuberculosis
SoPH:	School of Public Health
TB:	Tuberculosis
UWC:	University of the Western Cape
WHO:	World Health Organization

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Abstract

Background: Tuberculosis (TB) is a major cause of morbidity and mortality among children (<15 years) in resource-limited countries. The World Health Organization (WHO) identified active contact screening and isoniazid preventive therapy (IPT) as essential actions for detecting and preventing childhood TB. Despite their benefits and inclusion in the policy of most National TB Programme (NTP) guidelines of the resource-limited countries, there is still a wide gap between policy and implementation. The implementation of contact screening for active case finding might be improved by the decentralised use of the Xpert MTB/RIF test in gastric lavage (GL) specimens, but this has not been previously assessed. Furthermore, although the provision of IPT to eligible child contacts has been a focus for implementation by the NTP of Rwanda since 2005, implementation has not previously been evaluated. The assessment of IPT uptake and adherence as well as associated factors could be informative for the programme. Therefore, we aimed to assess the diagnostic yield of Xpert MTB/RIF in GL among child contacts with suspected pulmonary tuberculosis (PTB) and the uptake of and adherence to IPT by eligible child contacts to make recommendations towards strengthening TB diagnostic and prevention in children in Kigali, Rwanda.

Methods: The proposed study setting Kigali, the capital city of Rwanda, was the location for 30% of the national PTB case notifications in 2013-14.A conceptual framework based on ecological theory was used in this study. Quantitative, qualitative and mixed (using both quantitative and qualitative research methods in one study) research methods were applied, and various research designs were used depending on the research questions. The study involved a cross-sectional analysis of the diagnostic yield of Xpert MTB/RIF in GL among all child contacts with suspected TB. Across-sectional and prospective cohort study design was used to assess the uptake and adherence of IPT among eligible child contacts.

Results: During2015/6, over a 7-month period, we screened 216 child household contacts of 105 index cases with sputum smear-positive PTB, and 37 child contacts had TB-related symptoms at the time of screening. Only four(10.8%) children were clinically diagnosed with TB, and none had bacteriologically confirmed TB. While participants' family members and health care providers reported that Xpert MTB/RIF facilitated the early detection of PTB and

drug-resistant tuberculosis among older children (5-14 years old), the overall yield for diagnosing TB in children was perceived to be minimal. Several weaknesses in the utilisation of Xpert MTB/RIF were reported, the main ones being the inability to perform laboratory tests on samples other than sputum and health care providers' lack of awareness of the availability of the Xpert MTB/RIF test. The implementation challenges were also reported to have a negative impact on the effectiveness of IPT. These challenges included the interdiction of performing the GL at primary health centres (PHCs) to exclude active TB, lack of utilisation of Xpert MTB/RIF and informal system of sample transportation from PHCs to district hospitals. Of the 216 child contacts, 94 (44%) were younger than five years old, and uptake of IPT was high with 84 (89%, 95% CI 81-94) receiving IPT at the time of screening. The reasons for not initiating IPT in the remaining ten children were parents/caregivers' lack of information on the need for IPT, refusal to give IPT to their children, and poor-quality services offered at health centres. Factors associated with no uptake of IPT included children being more than three years old, unfriendly health care providers, HIV infected index cases and the index case not being the child's parent. Of the 84 child contacts who started IPT, 74 (88%) had complete adherence. There were no factors found to be significantly associated with IPT adherence. In the qualitative analysis, we identified factors relating to parents/caregivers, disease, household and health-care providers as major themes determining IPT adherence.

Conclusion: The yield from Xpert MTB/RIF in GL samples from symptomatic child contacts was low, but numbers evaluated were small and multiple implementation challenges were identified. There is a need for a more suitable diagnostic tool for TB in child contacts that would facilitate case detection and the implementation of preventive therapy for children without active TB. In this study, we found that IPT has been successfully implemented in Kigali. We also identified local interventions which contributed to that success, while identifying factors associated with non-initiation of IPT and incomplete adherence that health care providers can potentially use through counselling support and follow-up to further improve uptake and adherence.

Keywords: Pulmonary tuberculosis, Child, Active screening, Isoniazid preventive therapy, Adherence, Xpert MTB/RIF assay, culture, Gastric Aspiration, Sputum, Kigali Rwanda.

Definition of the concepts

Nota bene: The definitions given below apply to the terms as used in this thesis. The terms may have different meanings in other contexts. They have been adapted from the definitions given in the Guidance for National Tuberculosis programmes (NTP) on the Management of Tuberculosis (TB) in Children[1] and Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries[2].

Child contacts (also called Exposed children) are defined as children who shared the same household with index cases – adults diagnosed with sputum smear-positive pulmonary TB (PTB) in the 3 months prior to the diagnosis of the index cases.

Index cases are defined as the initially identified adult (>15 years old) with sputum smear-positive pulmonary TB to which children studied in this thesis have been exposed.

Active contact screening is defined as a systematic process for identifying children who have TB or are at high risk of developing TB. It includes an interview with the index cases or parent/caregivers of children (identified through the index cases) to obtain the names and ages of the child contacts and an assessment of child contacts' risk of having (generally based on symptoms suggestive of TB) or developing TB, to determine those for whom further investigation is indicated.

Symptoms suggestive of TB included one of the following symptoms:

- Persistent unexplained fever: a one-week unexplained fever of greater than 38^{o}C have been reported by parent or caregiver or at least once objectively recorded;

[1]WHO. Guidance for National Tuberculosis programmes on the Management of Tuberculosis in Children. Geneva , WHO 2014 (Second ed).

[2]WHO. Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva , WHO 2012.

- Cough for more than 2 weeks: a story of persistent, unremitting cough for more than two weeks not responding to the standard therapy;
- Documented weight loss or failure to thrive: unexplained weight loss for more than 5% compared with the highest weight recorded in last 3 months.

Further investigation (also called contact clinical evaluation): is a systematic process for diagnosis or exclusion of active TB among child contacts. In this thesis, it includes radiographic examinations, microbiological assessment using microscopy, culture and Xpert MTB/RIF in Gastric lavage.

Chapter 1: Introduction

1.1 Background

Tuberculosis (TB) has caused more deaths in human history than any other infectious disease, an estimated number of over one billion lives in the past two hundred years [1]. Currently, it is considered as the leading infectious cause of death worldwide. TB is a communicable disease caused mostly by *Mycobacterium tuberculosis(M.tb)* and rarely by *Mycobacterium bovis* [2,3]. Transmission is mostly through humans by means of fine droplets produced during coughing, sneezing or speaking in the case of pulmonary TB [2] or through other ways such as congenital transmission [4], and drinking raw and unpasteurized milk- in the case of *Mycobacterium bovis* [3]. In 90-95% of individuals with an unimpaired immune system, the infection with *M.tb* remains restrained because of host defence mechanisms, resulting in latent infection. About 5% of these individuals develop active TB called primary progressive TB. The lifetime risk of developing TB following the latent TB infection is 5% to 10% among individuals with an unimpaired immune system, with most of them doing so within the first five years after initial infection [5]. The risk of progression is higher among individuals with an impaired immune system such as individuals with HIV disease, diabetes mellitus, indoor air pollution, immunosuppressive medication, and young children [6,7].

Many advances have been made in the fight against TB resulting in an overall 47% drop in TB death rates since 1990 [8]. However, nowadays TB is still a major cause of morbidity and mortality among children in resource-limited countries [9]. The burden in children has been increased by the human immunodeficiency virus (HIV) epidemic for several reasons relating to the increased exposure and host immune-suppressants [10,11].

The occurrence of TB is subsequent to infection with *M.tb*. In young children (under 5-years old), this commonly happens because of exposure to an adult or older child with TB – known as an index case [12]. In studies, it has been have shown that "*child contacts, defined as children exposed to index cases with sputum smear-positive pulmonary TB"* (PTB) [12,13], are at high risk of infection [14–16]. Children generally have an 'immature'immune system and are not as able as adults to mount sufficient responses to fight infection and disease [17,18]. Without any

intervention, 30-40% of infected infants (<1-year old) and 10-20% of children between ages 1 and 2 years old or HIV-infected children are likely to develop active TB within one year [15,19–21]. In addition, a severe disseminated form of TB, such as TB meningitis and miliary TB, are particularly common in young children [21]. Furthermore, TB sometimes appears like acute pneumonia [22,23], which globally claims 19% of deaths in children [24].

Nevertheless, in most countries, childhood TB prevention and management have been neglected for decades [25–27] because childhood TB is less likely to be contagious than adult TB, as they have paucibacillary disease. Therefore, from the public health perspective, they have not been deemed to constitute a high risk of disease spread within the community. Nonetheless, the disease has nowadays attracted increased attention, as evidenced in 2012, when the WHO included an estimate for childhood TB in their annual TB report [28]. In 2013, the roadmap for childhood TB was launched with a comprehensive vision of what would be required for its eradication [29], and childhood TB was explicitly mentioned in the WHO's post 2015 End TB Strategy [30].

Despite the growing attention to childhood TB worldwide, it remains a concern because many child contacts with TB die before they can be diagnosed and treated [27,31]. Consequently, the burden is still the highest in many low-middle-income countries [31–33]. The high burden of TB in children may be explained by the fact that in recent years, the progress towards the development of improved tools for the TB in children was minimal when compared to similar progress in adult TB [34]. Additionally, most of the countries with a high incidence of TB have failed to implement effective interventions, such as active contact screening and TB preventive treatment that can reduce TB in children [35–38]. The high burden of TB among child contacts represents a missed opportunity for active screening and preventive treatment that could have led to early diagnosis and treatment or have prevented TB disease [35–38].

1.1.1 Burden of TB in children

The World Health Organization (WHO) estimates that there were at least 1,040,000 child TB cases, representing 10% of the 10.4 million TB incident cases, and 201,000 TB deaths among HIV-negative children, representing 16% of all deaths among HIV-negative people in 2016 [39]. Three-quarters of all childhood TB cases and high rates of under-five mortality worldwide were

reported by 22 TB high burden countries [33,40]. Despite this high reported incidence, it is deemed that the global magnitude and trends of incidence, morbidity and mortality of TB in children, are underestimated because of inadequate reporting systems [41] and undiagnosed children [10,39]. These are caused by the paucibacillary nature of the disease, difficulties in obtaining sputum samples, the ambiguity of chest X-ray (CXR) results and lack of a practical reference test (gold standard) [9,42,43]. The sensitivity of culture, considered as the gold standard, varies between 30% and 40% and sputum smear microscopy, often the only diagnostic test offered in endemic areas, is positive in less than 10-15% of children with probable tuberculosis [44,45]. The underestimation of the childhood TB has caused it be regarded as a problem of low public health importance, and its estimated burden has not been prioritised. Therefore, the global community has not set paediatric-specific targets for reducing the childhood TB burden.

Despite this underestimation, childhood TB remains a reality with its harmful consequences [9,31,32]. Thus, ending childhood TB epidemic requires interventions to reach at-risk children using simple tools for active screening and diagnosis, which lead to early initiation into TB treatment or IPT depending on the child contacts status [12]. In a study, it was suggested that half of the TB cases in young children could have been prevented by implementing the WHO guidelines for contact tracing and chemoprophylaxis [32].

1.1.2 Strategies by the WHO to address TB in child contacts

In 2012, the WHO identified active contact screening and isoniazid preventive therapy (IPT) as key actions for addressing childhood TB issues among child contacts. We describe each of these actions in turn.

1.1.2.1 Active contact screening

Active contact screening is a symptom-based screening approach recommended by the WHO [12] and carried out in the community. Two important roles include identifying symptomatic child contacts requiring further investigation of TB for early treatment and providing effective preventive therapy (usually IPT) to eligible contacts who do not have active TB, such as children under 5years or people living with HIV, of any age [46,47].

While the microbiological confirmation of TB is usually possible in the adult population with PTB, this is not the case for children. The microbiological confirmation of TB is a critical challenge given the widely recognised limitations of current diagnosis technique, especially in young children with paucibacillary disease and often unable to provide a sputum sample [47,48]. Therefore, the diagnosis of a child with symptoms suggestive of TB is made based on a combination of (i) the positive history of contact with an index case, (ii) clinical symptoms, (iii) radiological findings, and (iv)a tuberculin skin test. However, the sensitivity and specificity of the clinical diagnosis are limited by several diseases which have overlapped the clinical presentation of TB, leading clinicians to be increasingly faced with a diagnostic dilemma [49]. Additionally, the over-reliance on the clinical diagnosis limits the possibility of diagnosing drug-resistant TB (DR-TB) [50]. These diagnostic challenges, mostly the unavailability of an accurate, rapid test often leads to microbiological confirmation not being endeavoured [51,52]. Often, it is essential to have microbiological confirmation of TB to support a definitive diagnosis, to make the best decision about TB treatment, and to facilitate the epidemiological tracing of isolates [53].

The Xpert MTB/RIF, a new approach in TB diagnosis, offers advantages over smear microscopy for acid-fast bacilli [54]. This approach is three times more sensitive than sputum smear and its sensitivity compared to culture is lower in outpatient children than in inpatients (48% versus 70%) [55]. Furthermore, it can be implemented in a peripheral laboratory because of its simplicity [51] and detect resistance to rifampicin in less than two hours [47,56]. Hence, it can potentially overcome several constraints experienced with active screening including the reduction of the transportation cost and complexity of health services such as referring a child from primary health centres (PHCs) to district hospitals for further investigation, which may delay the diagnosis health facilities because of a lack of communication between the two levels [46,57]. Additionally, Xpert MTB/RIF has been endorsed by the WHO as an initial test for diagnosing TB in children since 2013, but the quality of the evidence has been very low [12,54]. Moreover, to date, a few studies have assessed the performance of the Xpert MTB/RIF for contact screening in children. Conversely, many studies have been conducted to assess the accuracy of Xpert MTB/RIF in diagnosing TB in children [48,58–61]; only a few have evaluated

its strength, weaknesses and challenges of its implementation from the programmatic perspective [62,63].

Furthermore, despite multiple advantages of Xpert MTB/RIF, its use requires sputum, which has been one of its limitations in diagnosing TB among children, mostly young children unable to expectorate. Therefore, to overcome that limitation, the use of other specimens collected through gastric lavage (GL), nasopharyngeal aspiration and induced sputum techniques are required and have been reported to be useful in diagnosing TB in children [53,64–66].

Nevertheless, GL has multiple limitations, which requires 4-6 hours fasting, repeated specimens and the admission of children to inpatient care. The procedure is unpleasant for the child and the health care provider [53]. However, its biological confirmation in young children has widely been relying on specimens from GL [43]. Despite its multiple limitations, GL is preferred in the diagnosis of TB in children than induce sputum [67]. The induced sputum method requires having access to isolation rooms with negative pressure which is not available in many health care facilities [68]. The GL method can be performed at all health facilities with a trained health care provider.

1.1.2.2 Isoniazid preventive therapy

In 2006, the WHO [69] recommended active contact screening, a symptom-based approach, that can be implemented in the community by providing IPT to at-risk asymptomatic contacts. IPT is one of the infection control strategies which consists in offering a six-month isoniazid (10 mg/kg/day) to children younger than 5-years old who have close contact with an index case after excluding TB disease [69,70]. IPT is also recommended for any HIV-infected person regardless of her/his age given the high risk of TB in HIV infection [71]. Several studies have highlighted the effectiveness of IPT in treating latent TB in adults and children [72–74]. Full adherence to IPT reduces the risk of developing TB up to 92% [72,75]. However, despite the benefits of active contact screening and IPT and that they have been integrated into the policy of most National Tuberculosis Programme (NTP) guidelines of resource-limited countries [69], the active contact screening is rarely conducted and IPT is not systematically offered to eligible children [76–78]. Also, where IPT is offered to eligible children, it is unsupervised, and its uptake and adherence are often inadequate [16,78–80].

Rwanda, a country devastated by the 1994 genocide which has currently built a strong health system [24,25], established the IPT policy in 2005 using the algorithm shown in figure 1.1. The algorithmic approach can easily be applied in any setting by any health care provider, as well as the community health care workers at the community level, as indicated in figure 1.1. The only information needed is age, HIV status and presence or absence of TB symptoms [69]. Access to district or referral levels is not needed, except for symptomatic contacts who may need to be referred for further investigation.

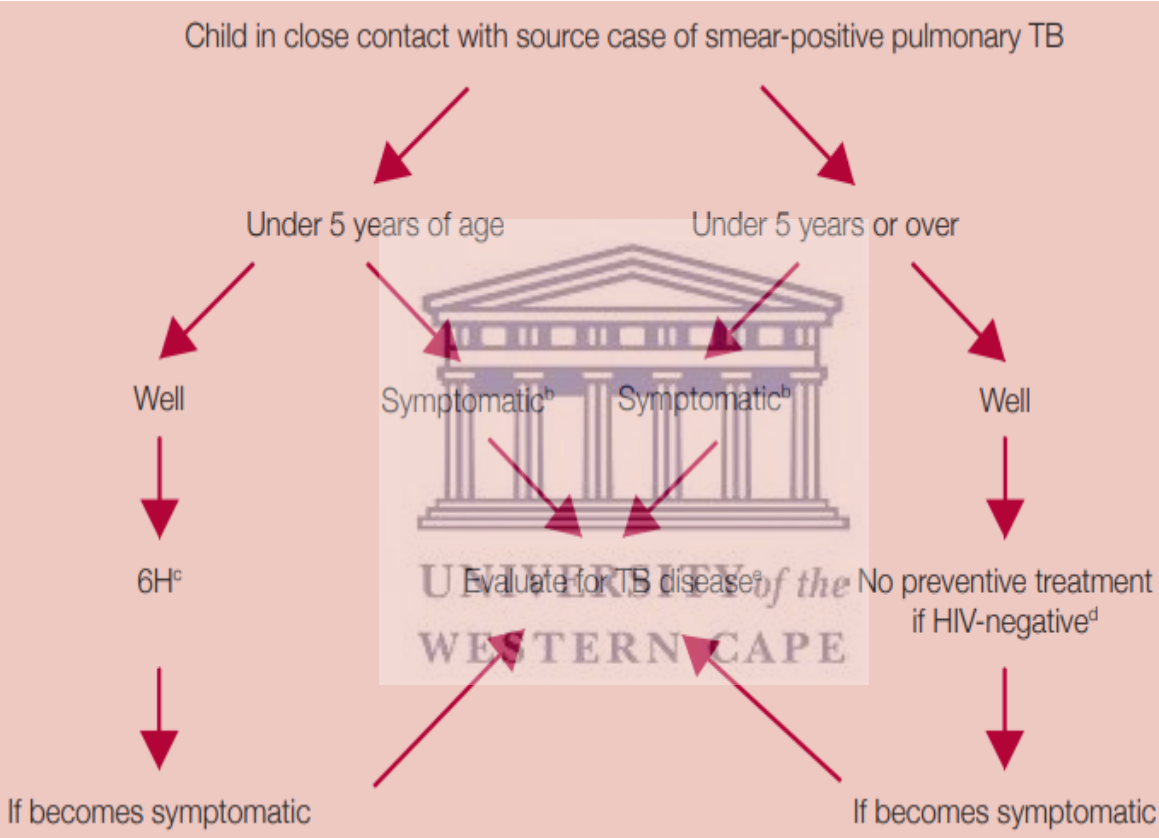


Figure 1.1: Symptom-based screening approach to child contact management [12]

[b]If TB disease is suspected, the need for further investigation

[c] Isoniazid 10 mg/kg (7−15 mg/kg) daily for 6 months

[d] If HIV-positive, isoniazid daily for 6 months is indicated regardless of age.

[e]If the child is diagnosed with TB disease, anti-TB treatment is started, and the child is registered with the NTP

The child needs to be considered for eligibility for IPT if TB disease is excluded.

1.1.3 Rwanda health system and tuberculosis

Rwanda located in central and East Africa has around 12.5 million inhabitants according to the last estimation of the United Nations [81]. Rwanda's history is affected by the 1994 genocide against Tutsis, which led to the deaths of about one million people, and the displacement of more than one million of the population. These events were followed by a devastated economy and health system [82]. Shortly after the genocide of 1994, the Government created a national development plan, called Vision 2020 that was launched in 2000 and focused on moving the country from the disaster toward becoming a middle-income country by 2020 [83]. The central point of this vision was health equity. The Rwandan economy has grown over the years at about 8% per year since 2001 [84], as evidenced by the gross domestic product per capita tripling from 201 United States Dollar (USD) in 2001 to USD 719 in 2014 [85].

Rwanda has put in place a decentralised health system with community-based health insurance and performance-based financing (PBF) as key components, which resulted in a significant improvement in the health status of the Rwandan population [86,87]. Community-based health insurance was piloted in 1999, extended countrywide in 2000 and made mandatory for all Rwandans in 2006. In 2012, 90.6% of the population was enrolled with 7% registered with other health insurance programmes [86]. The PBF – a strategy whereby health services are funded based on their performance in increasing the quantity and quality of the preventive and curative health care for the population based on the norms [88] - was piloted and adopted by the government of Rwanda in 2001 and 2005, respectively. In 2008, it was deployed in the general health system [89]. The effectiveness of PBF in improving the quality of health care service in Rwanda has been demonstrated [87,90,91].

In Rwanda, health care delivery is organised around a decentralised referral system with a pyramidal structure (figure 1.2) which varies according to the administrative level. At the top of the system are the National Referral Hospitals including University Teaching Hospitals and the Provincial Referral Hospital, which provide tertiary care. The next level is district hospitals, followed by health centres and health posts, which provide primary health care. Health posts are implemented far from the health centres and a way of reaching out to those distant communities. These posts receive oversight from the health centres and offer a reduced package of activities

including curative outpatient care, vaccination, growth monitoring for <5-year-old children, antenatal care and family planning counselling, health education and a few laboratory tests (usual rapid test). At the bottom, community level, there are community health workers (CHW), who are trained to deal with basic illnesses or preventive treatment. They can assess, classify, and treat or refer cases of diarrhoea, pneumonia, malaria, and malnutrition in children younger than 5 years old. They can also provide contraceptives, and directly observed treatment, short-course (DOTS) for TB. They can sensitise the population for behaviour change [92].

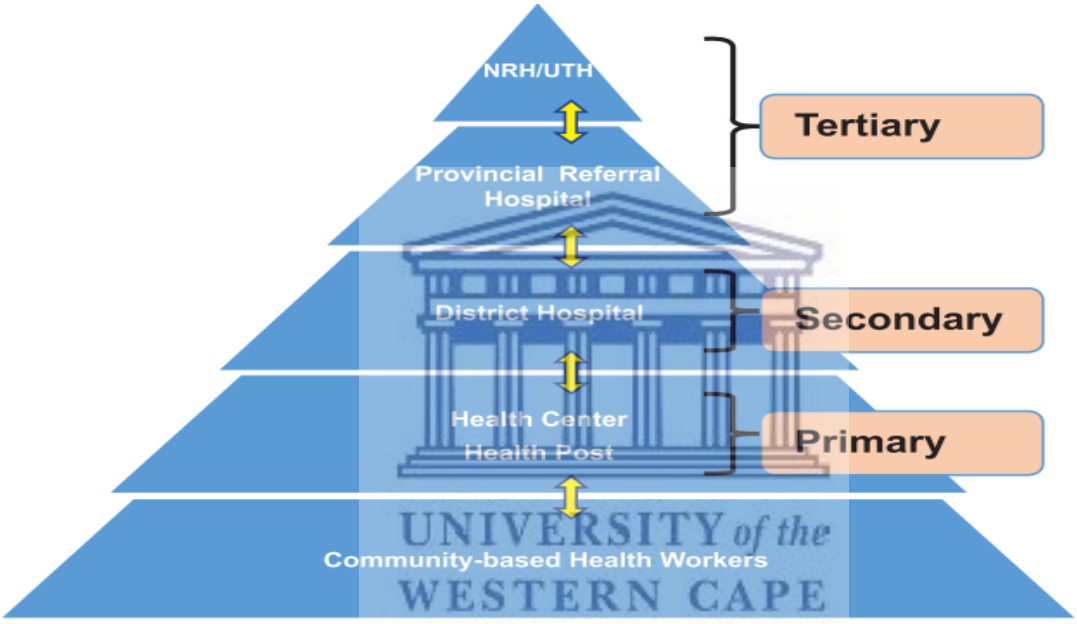


Figure 1.2: Levels of services provided within the public health care system in Rwanda[92]

The management of the NTP in Rwanda is modelled on the health care system shown in figure 1.2. Most of the TB patients (80%) are managed at the primary level. Additionally, the country has set up a well-functioning TB programme with accurate, complete, internally and externally reliable data that provide a good overview of its situation [93]. The policies are made based on evidence. Over the past decade, Rwanda demonstrated an excellent treatment success rate of 90% and 87% among sputum smear positive and DR-TB patients, respectively, approximately

reaching the global plan target of 90% [30]. Thus, Rwanda is a developing country where the fight against TB has been a success for years.

The use of Xpert MTB/RIF has contributed to the increase of early case detection of TB and DR-TB in Rwanda [94]. The involvement of CHW in the fight against TB has also contributed to the early diagnosis of TB and an increase in the treatment success rate in Rwanda. In 2016, 44.5% among the 167,941 persons with presumptive TB and 25.4% among the 3,493 people diagnosed with sputum smear-positive TB cases were referred by CHW [95]. Of worth noting is that all care services relating to the prevention and treatment of TB are free of charge. Thus, Rwanda has made progress in reducing the incidence of TB among its population, with a gradual decline from 100 cases per 100,000 persons in 2006 to 50 cases per 100,000 persons in 2016 [96].The trend of TB incidence from 2006 to 2016 is presented in figure 1.3.

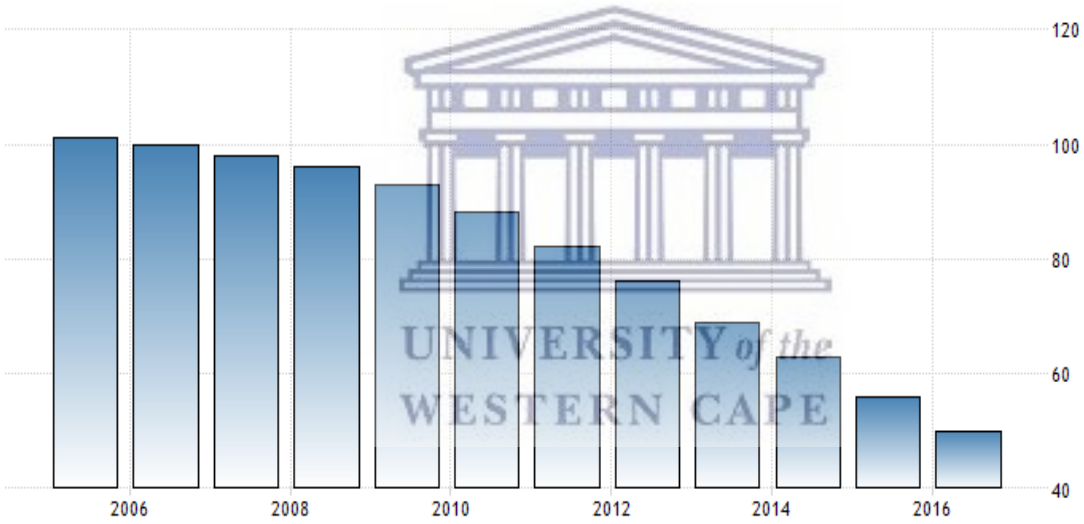


Figure 1.3: Rwanda - incidence of tuberculosis (per 100,000 persons) [96].

1.1.4 Childhood tuberculosis in Rwanda

1.1.4.1 Burden of TB in children in Rwanda

The Rwandan 2013-2014 NTP annual report indicated that the proportion of child TB cases among all forms of TB cases was 6-8%, while the national target was set at 12%. Among these cases, 65-77% were paediatric PTB, and only 22% were bacteriologically confirmed cases. In 2016, among all-forms TB cases reported, children under 15years represented only 5.3%, among

whom 77% had PTB of which 27.3% were bacteriologically confirmed cases [95]. These data suggest under-detection of TB in children in Rwanda, especially the bacteriological diagnosed cases. In 2015, the WHO estimated that 840 children under 15 years, developed TB in 2015, but only 331 were reported [97]. Thus, demonstrating the inability of the health system to confirm TB cases bacteriologically.

1.1.4.2 Addressing childhood TB in Rwanda

The Rwanda NTP pays particular attention to childhood TB, which is in line with the Rwandan government priority intervention consisting of preventing and treating the most important causes of child mortality [9,10]. As evidence, the TB active contact screening among children was initiated in 2008, and in 2014, a specific national child TB guideline was developed. The Xpert MTB/RIF was also introduced as a diagnostic tool for all children suspected of having TB in Rwanda. In 2015, TB investigation was integrated into the integrated management of childhood illnesses (IMCI) register. Additionally, NTP Rwanda strategies were developed to strengthen more than 30 indicators in the PBF. PBF indicators related to TB are redefined considering achieved targets and indicators in need of being improved. Since 2009 "number of children eligible to IPT who received it" and "number of the under-5 [years child] contacts who completed IPT" have been included as indicators.

However, despite the attention given to childhood TB in Rwanda, challenges remain. The case detection is low (40%). Therefore, active case finding and the use of the Xpert MTB/RIF test in diagnosing or excluding TB among symptomatic child contacts are some of the strategies developed by the National Strategic Plan. These strategies, in particular, are to increase the case detection in child contacts (those most at risk for developing TB disease) and among children in general. Thus, there is a need to assess the performance of the Xpert MTB/RIF for contact screening in children, its strength, weakness and challenges from the programmatic perspectives. Such a study, to our knowledge, has not yet been done in Rwanda.

1.1.4.3 Active contact screening and IPT in Rwanda

Rwanda is one of the resource-limited countries where active contact screening and IPT are integrated into the policy of NTP and National Strategic Plan [98]. However, there are

discrepancies between the actual implementation and the policy. The main case detection strategy is limited to passive screening, i.e. screening conducted at the health facilities to detect TB in individuals who are already ill enough to seek medical care [12]. Although the IPT guideline has been in use in Rwanda since 2005, its implementation and added value to the NTP have not been assessed. Recently, it has been identified by the NTP as a research priority on the National Health Research Agenda 2014-2018 [100].

1.1.5 Problem statement

TB is a major cause of mortality and morbidity in children [101]. The burden remains the highest in many low- and middle-income countries [31–33] and mostly among child contacts – those exposed to an adult with smear-positive PTB – who are at higher risk of developing TB than no contacts [14–16]. In 2012, active contact screening was recommended by the WHO as a key action for addressing childhood TB issues [12,13]. The effectiveness of active screening of the child contact has been established for more than 60 years [102,103] as a way to initiate either TB treatment or IPT once active TB has been excluded. The active screening allows the health care providers to determine whether a child is symptomatic or not and to act accordingly.

The management of asymptomatic child contacts is straightforward as it entails offering IPT to those eligible (0–4 years) and surveillance of those not eligible (5–14years) [8]. However, the management of symptomatic child contacts has proven to be complex, with a need to refer them for further investigation at higher levels of care (district and referral hospitals). This referral is done to either confirm or exclude active TB to initiate either TB treatment or IPT (when a child is eligible).

The International Union Against TB and Lung Disease recommends that in each country the NTP should develop a clinical management strategy of symptomatic child contacts which should be accompanied by an evaluation plan that assesses its overall effectiveness [76,104]. The WHO endorsed the Xpert MTB/RIF for use in children in 2013 [54], as an initial diagnostic test for all children with symptoms suggestive of TB [12]. Subsequently, the Xpert MTB/RIF was introduced and adopted as a diagnostic tool for all children with symptoms suggestive of TB in Rwanda in 2014. In a few studies, Xpert MTB/RIF performance in the context of contact screening in child contacts has been evaluated [58–61]. Thus, children detected with TB as

outpatients were likely to have an early paucibacillary disease compared to hospital-based advanced cases who presented themselves to seek care (passive detection) [58–61].

A study done in the context of contact screening used induced sputum as the sample given the difficulty of having sputum in young children known as a limit of the use of Xpert MTB/RIF in children [105]. To our knowledge, no study had ever utilised Xpert MTB/RIF in GL in the evaluation of symptomatic child contacts when we undertook this PhD project. Additionally, the evaluation of the efficacy and sensitivity of diagnostic tests and treatment protocols for common lung diseases is one of the priorities of the Rwanda National Health Research Agenda [100]. Therefore, there is a need to evaluate Xpert MTB/RIF in GL in symptomatic child contacts.

Also, it is known that the effectiveness of active screening partially relies on IPT initiation of eligible children once active TB has been excluded [69]. The WHO has for many years recommended IPT for at least six months for young (<5 years) children who are exposed to a TB index case and who do not have active TB disease [12,69]. However, less than 15% of eligible child contacts receive preventive therapy [39] suggesting the inability of implementing policies and intervention known to be highly effective in reducing childhood TB burden by countries with a high incidence of TB [76,106]. Rwanda established the IPT policy in 2005, yet no study to date has assessed its implementation. Moreover, referring to the recommendation of the Rwanda National Research Agenda, the assessment of the level of IPT implementation is one of the priorities [100].

Hence, in this thesis we seek to assess the effectiveness of Xpert MTB/RIF as an active screening tool (early detection) and the implementation of IPT among child contacts to inform the practice.

1.2 Literature review

1.2.1 Epidemiology of tuberculosis in Children

The understanding of the epidemiology of TB is a milestone in the fight against childhood TB since it helps to determine which children are at risk of developing TB, and when and why the

disease occurs. Also, it helps stakeholders involved in the management of childhood TB to set up specific strategies to reduce the burden of TB.

A child develops TB infection that leads to TB disease after his/her exposure to an infectious case of PTB, known as an index case [12]. The prevalence of TB in the community is the greatest factor that influences the risk of a child's exposure to TB. That risk becomes greater in the case where the child lives in a community with a high TB prevalence [107]. The population density, which increases physical contacts of a child among adults, multiple adults in a household and age of a child also influence the risk of exposure [107].

Older children are at higher risk of exposure than a child of pre-school age. The latter interacts with only a few adults, generally those with whom they live in the same household, while the former interact with adults in the community besides the members of their household. Moreover, environmental factors such as high outdoor temperatures and rainfall determine the time children spend indoors and the opening or the closing of windows and doors, which consequently influence the risk of their exposure [107–109].

Following exposure, the risk for a child to develop TB infection is influenced by many factors. These include the infectiousness of the index case, duration and intensity of the interaction with index cases, duration of a cough in the index case and low immunity of the child [14,110,111]. A child exposed to an index case with sputum smear-positive TB is at higher risk of developing TB infection than the one exposed to an index case with sputum smear-negative results [14,110,111]. The risk increases proportionally with the increase of the bacterial loads [112]. Additionally, close contact between children and index cases such as sharing of bedrooms and their relationships increase the risk of infection with TB. For instance, first degree relatives are more likely to transmit infection than distant relatives [14,113–116]. Exposure to an environment with tobacco, young age and severe malnutrition also increases the risk of developing TB infection [111].

The progression from TB infection to TB disease is influenced by multiple factors. A child is at high risk of developing TB if s/he has TB infection, HIV infection, malnutrition or other diseases that induce immune deficiency. Additionally, they develop TB disease if living in a crowded

household or are a passive smoker [116–119]. Individual factors, like age, play a big role in determining which child will develop TB disease. Without any intervention, children younger than 12 months old have a 50% risk of infection progressing to the disease. Those children from 1-2, 3-4, 5-10 and >10-14 years old have 20%, 30%, 5%, 2% and 5% risk of the infection developing into TB disease, respectively [6,120,121].

In 2010, in a model, it was estimated that 15,319,701 was the median number of children younger than 15-years old who lived in the same household with TB-positive adults in 22 high-burden countries. In the same year, the median number of *M.tb* infections in children was 7,591,759, of which 650,977 developed TB disease [32]. Knowledge of the epidemiology of childhood TB leads to putting in place strategies that target mostly child contacts who are at high risk of developing TB. The active contact screening is one of those strategies.

1.2.2 Impact of active contact screening and management of TB in children

Active contact screening is a means of improving TB control through early detection and treatment, which targets mostly children as well as adults who have been in contact with a smear-positive PTB case. Active contact screening of a child contact followed by effective management has the potential to reduce the burden of TB considerably. This reduction occurs through early diagnosis among all contacts of any age and by providing preventive therapy to those without the disease who are at risk for developing TB. The active contact screening, which leads to early detection of disease among child contacts, reduces the disease severity, thus improving outcome [46]. Also, it helps to prevent future TB transmission as infected children constitute a reservoir of future TB in the community [13,29].

In studies conducted in high-burden areas, active contact screening among households was shown to yield considerably more TB cases than passive case detection varying from 1.74-10% [19,46,122–124]. This approach detects 40-60% TB in patients who are not detected by the passive model mostly used by NTP [125].

1.2.3 The benefits of preventive therapy in child contacts

The effectiveness of active screening of child contacts relies on IPT initiation after excluding active tuberculosis. In the past, IPT was only offered to young child contacts (<5-years old) and

any HIV-positive person regardless of age [69,126,127]. However, in the most recent WHO guidelines for treatment of latent TB infection, consideration of older child contacts (≥5 years) without active TB for preventive therapy is now included [128]. The benefit of IPT has been recognised since 1950 [129]. IPT has the potential of reducing the risk of (i) developing TB infection among exposed children, and (ii) developing TB disease among infected children. Also, it helps to prevent future TB transmission as infected children constitute a reservoir of future TB in the community [13,29,72,130]. However, the effectiveness of IPT varies according to the level of the adherence [131,132]. Adherence of 90% or more is recommended for effectiveness of the treatment [133]. Additionally, without IPT, 20% of child contacts under 5-years old can develop active TB within one or two years [6,134].

In another study, using predictive modelling process based on data from Sub-Saharan Africa suggested that 90% of TB cases could be avoided if for a decade 30% of persons with TB infection were given an effective preventive treatment [135]. Furthermore, in another modelling study to eradicate TB by 2050, it was shown that TB programmes, along with treatment targeting TB patients, should include preventive measures for treating TB infection cases [136]. IPT is the most broadly adopted preventive treatment and is safe and cost-effective [137,138]. However, despite the benefit of IPT and that the WHO recommends it for eligible child contacts [69], implementation remains challenging in most low-and middle-income countries [106]. Several studies have reported poor uptake [35,80,139–141] and IPT adherence among child contacts under 5-years old [16,79,142–145]. Furthermore, the WHO Global TB Report 2017 revealed that less than 15% of eligible child contacts receive preventive therapy [39]. The poor uptake and adherence of IPT represent a missed opportunity to prevent future TB cases, thus constraint to reach the End TB global strategy target [30].

1.2.4 Constraints on active contact screening and IPT

Despite the known effectiveness of active contact screening [102,103], it is rarely conducted in resource-limited countries. In the past, many barriers limited the implementation of active contact screening in resource-limited countries. Among those barriers were a lack of tuberculin and X-ray, lack of trained staff to interpret diagnostic results, the need for multiple visits to a hospital to complete screening, parents/caregivers' limited time and mobility (e.g. transport

costs), lack of human resources (sufficient and trained staff), and difficulty of implementing the IPT guideline by health care providers [46,57,78]. Those barriers led to poor compliance of active contact screening, hence poor IPT initiation.

In several studies, conducted in resource-limited countries to assess the extent of active contact screening compliance it varied between 8% and 52% [139,146,147]. Even when IPT was initiated, transport costs remained an obstacle for adherence [143–145]. Other challenges included lack of knowledge and time for health workers to understand and explain the rationale for screening and IPT, health service experience, and the belief that IPT is needless and even harmful to healthy children [106,145].

To overcome those barriers, the WHO introduced an approach called symptom-based screening. This approach can be implemented in the community and does not require tuberculin skin testing or CXR for asymptomatic child contacts in 2006 guidelines [69]. The approach is based on the first screening; asymptomatic child contacts eligible to IPT are promptly initiated, whereas symptomatic child contacts of any age require further investigation to confirm or exclude TB, then initiate TB treatment or IPT depending on their results and age [12,69]. The approach was proven to be safe [148,149] and effective [105], and overcame several barriers experienced by active contact screening. However, most of the barriers to uptake and adherence of IPT that are not related to active contact screening persist. Those barriers may be a refusal to initiate IPT by parents/caregivers, transport costs, relocation, child refusal to take medicine, lack of food, stigma with lack of disclosure, and a lack of adequate communication with health professionals [79,143,144,150]. Additionally, the management of symptomatic child contacts remains a challenge as it needs further evaluation using diagnostic tools that are not available at the primary health care level.

1.2.5 Effectiveness of early diagnosis using Xpert MTB/RIF test in reducing child TB burden

The WHO recommended the use of a symptom-based approach in 2006, which has made the management of asymptomatic child contacts at the PHC possible and easy [151]. However, the management of symptomatic child contacts is complex, with the need to refer them for further

investigation at higher levels of care (district and referral hospitals). The complexity of managing the symptomatic child contacts depends upon several factors. First, it is further aggravated by the structural and communication disconnect between the primary health care level (where active screening is conducted) and the higher level of care causing significant delays in TB diagnosis or IPT initiation. In some instances, child contacts may be lost because of a lack of communication feedback between the primary health care and a higher level of care. Second, the effectiveness of diagnostic tools that are available at the health facilities is limited to diagnosing TB among children because of the paucibacillary nature of TB in children, especially those with HIV. There is also difficulty in obtaining diagnostic expectorated sputum samples, the ambiguity of CXR results and lack of a practical reference test (gold standard) [43,44,66,149,152–155]. Also, when a child contact is referred for symptoms suggestive of TB, health care providers usually think about diseases other than TB. The reason for that is the clinical overlap of TB with other widespread diseases such as severe pneumonia and malnutrition [22,156–159]. These constraints lead to the increase of undiagnosed TB cases [39,160,161].

The high number of undiagnosed TB cases remains a public health problem [31,39] as it increases the burden of TB in children and the rate of TB transmission in the community. In the 2013-2014 Annual Report of Tuberculosis in Rwanda, childhood TB cases represented 6% of all notified TB cases, which is half of the national estimate of 12% [162]. Among these notified TB cases, 68% were PTB, and 22% were bacteriological confirmed cases. These data suggest under-detection of TB in children in Rwanda and the health system's inability to confirm cases bacteriologically.

Subsequent to its endorsement by the WHO in 2013 [163] as an initial diagnostic test [12], Rwanda introduced and adopted the Xpert MTB/RIF as a diagnostic tool for all children with symptoms suggestive of TB in 2014. Xpert MTB/RIF is easy to implement in a peripheral laboratory and offers more advantages than other diagnostic tools (microscopy, culture, CXR) available at the health facilities [46,54,56,57]. Despite those multiple advantages and the fact that Xpert MTB/RIF has proved its effectiveness in diagnosing children in inpatient care settings [58–61,164], its effectiveness remains questionable for children in outpatient care settings [43,98].

In a systematic review, using 15 studies which included 4768 respiratory samples of 3640 children, the pooled sensitivities and specificities of Xpert MTB/RIF were found to be 62% (95% CI 51-73%) and 98% (95% CI 97-99%), respectively in comparison with culture using expectorated or induced sputum samples [55]. Using samples from GL, the pooled sensitivities and specificities were 66% (95% CI 51-81%) and 98% (95% CI 96-99%), respectively [55]. Also, the sensitivity of Xpert MTB/RIF reported in this systematic review was found to be 36-44% higher than the sensitivity of microscopy. Additionally, Xpert MTB/RIF's pooled sensitivity and specificity to detect rifampicin resistance was 86% (95% CI 53-98%) and 98% (95% CI 94-100%), respectively. The pooled sensitivity of outpatients whose parents/caregivers seek care themselves was 48% (95% CI 31-65%).

However, in comparison with hospital-based studies of more advanced and passively detected cases, a few have evaluated the performance of the Xpert MTB/RIF in the context of contact screening in outpatient TB-positive children likely to have an early disease, known as the paucibacillary disease [18,23,24]. To our knowledge, no previous studies have utilised GL in the evaluation of symptomatic child contacts. Therefore, there is a need for evidence of its performance among symptomatic child contacts. Furthermore, the implementation of the Xpert MTB/RIF encountered multiple challenges that limited its impact in diagnosing TB [62,63,166]. Among those challenges, there were a lack of awareness of programme guidelines, problems with cartridge supply management, a lack of local repair options for Xpert MTB/RIF machines, and poor sample quality which increased the probability of negative results. There is a need for each country to identify its challenges in finding strategies to solve these, and thus improve the Xpert MTB/RIF impact.

1.2.6 Study questions

To address the knowledge gaps highlighted in the literature in this thesis, we endeavoured to answer the following questions:

1. What is the diagnostic yield of using Xpert MTB/RIF in GL among symptomatic child contacts?

2. What are the perceptions and perspectives of various stakeholders (laboratory staff, health care workers and programme managers) on the strength, weakness and challenges of Xpert MTB/RIF, especially using GL as sample, in diagnosing TB among child contacts in Rwanda?

3. What is the uptake of isoniazid preventive therapy by eligible child contacts in Kigali, Rwanda, and its associated factors?

4. What is isoniazid preventive therapy adherence and what are its facilitators and barriers in Kigali, Rwanda?

1.2.7 Aims

To determine the diagnostic yield of Xpert MTB/RIF in sputum collected by GL in symptomatic children, who are contacts of index cases with sputum smear-positive TB, and to perform a mixed-methods evaluation of the implementation of IPT.

1.2.8 Specific objectives

The specific objectives and the corresponding papers are presented in Table 1.1.

Table 1.1: Specific objectives and corresponding studies

Specific Objectives	Corresponding Paper
1. To assess the diagnostic performance of the Xpert MTB/RIF assay in sputum collected by GL in symptomatic children who are contacts of index cases with sputum smear-positive TB.	**Paper 1:** Xpert MTB/RIF assay did not improve diagnosis of pulmonary tuberculosis among child contacts in Rwanda
2. To explore the perceptions of and challenges experienced by various stakeholders (laboratory staff, health care workers and programme managers) on the use of Xpert MTB/RIF in diagnosing TB among child contacts.	**Paper 4:** Perceptions Using the Xpert MTB/RIF to diagnose pulmonary tuberculosis in children in Rwanda: Stakeholders' perspectives
3. To assess the uptake of isoniazid preventive therapy by eligible children in Kigali, Rwanda, and associated individual, households and health care systems' characteristics.	**Paper 2:**Assessment of the isoniazid preventive therapy uptake and associated Characteristics: a cross-sectional study
4. To assess the isoniazid preventive therapy adherence and explore its facilitators and barriers in Kigali, Rwanda.	**Paper 3**: Adherence to isoniazid preventive therapy among child contacts in Rwanda: A mixed methods study

1.3 Methodology

1.3.1 Study setting

The study site, Kigali, is the capital city of Rwanda. Kigali covers an area of 730 square kilometres (km^2) and has a high population density (1,552 people/km^2), with an internal migration rate of 6.5% (NISR, 2014a). The city is divided into three Districts, Gasabo, Kicukiro and Nyarugenge of which 70% is urban.

The demographics show a low percentage of residents with no education (7% and 10% among men and women, respectively). Only 14% of women were not exposed to any form of media. Kigali has the largest percentage (73%) of households in the highest wealth quintile. However, it has the lowest percentage of working women (65%) and men (18%) [168]. Additionally, Kigali has the lowest rate of food insecurity compared to other regions in the country [169].

Kigali is served by four referral hospitals, four district hospitals and 35 PHCs. Among these PHCs, 23 are TB detection centres and entry points of all TB cases. Therefore, data were collated from the PHCs that provide TB detection services and hold detailed information on TB patients. The criterion used to select the PHCs from the 23 PHCs was a record of at least ten sputum smear-positive PTB cases reported between January and June 2015. This was to increase the possibility of finding complete information on index cases. Thirteen PHCs met these criteria and are presented in the Table 1.2. Additionally, three district hospitals and one referral hospital, all equipped with Xpert MTB/RIF machine and based in Kigali, were involved in this study as health facilities that received samples from 13 selected PHCs.

Kigali is congested with private health facilities. However, they do not submit their reports to the Rwanda Health Management Information System and do not offer TB care services. Therefore, they were not included in this thesis. Among the 13 PHCs selected for this study, nine (69%) were public-funded, and four were faith-based (public and private funded). Of the 13 PHCs, three had each two staff members and ten (77%) one staff member working in TB services. All the staff members were trained in TB management and provided counselling to parents/caregivers on IPT before their children started the regimen. In Rwanda, medication for TB is provided free-of-charge. Moreover, all TB index cases are offered the opportunity to choose the nearest health care facility from which they wish to receive TB treatment or IPT.

Kigali bears 30% of the country's PTB cases according to the 2015–2016 NTP Report [95]. Since 2012, 50 Xpert MTB/RIF machines have been installed in Rwanda, of which nine are based in Kigali. Their use was limited to the diagnosis of TB and MDR TB in adults. Only in 2014 was it considered as a TB diagnostic tool for all children suspected of having TB. A sample transportation system that uses vehicles to access each district hospital weekly is in place to facilitate the transfer of samples from district hospitals to the National Reference Laboratory

(NRL). However, the transfer of the samples from the PHCs without an Xpert MTB/RIF to another health facility with the equipment is not formal. That means each PHC uses its resources to assure sample transportation. The frequency of reference is determined by the availability of the resources. Samples that are rifampicin (RIF) indeterminate are sent to the NRL for confirmation on a weekly basis. Sample transportation service is provided free of charge to the patient. The calibration and maintenance of Xpert MTB/RIF machines are done at the national level by NRL.

Table 1.2: Eligible primary health centres and health facilities with Xpert MTB/RIF receiving samples from eligible primary health centres

Number	Primary health centres	District
1	Biryogo*	Nyarugenge
2	Cor-unum	Nyarugenge
3	Gitega	Nyarugenge
4	Kabusunzu	Nyarugenge
5	Kabuye*	Gasabo
6	Kacyuru	Gasabo
7	Kibagabaga	Gasabo
8	Remera (former Kimironko)*	Gasabo
9	Kinyinya	Gasabo
10	Muhima	Nyarugenge
11	Busanza	Kicukiro
12	Kicukiro	Kicukiro
13	Gikondo	Kicukiro
14	Kanombe military hospital**	Kicukiro
15	Masaka district hospital**	Kicukiro
16	Kibagabaga district hospital**	Gasabo
17	Kigali teaching hospital**	Nyarugenge

* Primary health centres with Xpert MTB/RIF

** Hospitals with Xpert MTB/RIF receiving samples from eligible primary health centres

1.3.2 Conceptual framework for the study

This study used a conceptual framework adapted from the one proposed by Bronfenbrenner [170], which is based on the ecological theory that demonstrates the direct and indirect influence of individual, social and physical environmental factors, and policy (norms and values of society) on human behaviours. The framework offers possibilities of investigating factors contributing to the transmission of infections or diseases to susceptible individuals [171]. The factors contributing to infections and progression of TB in children are a complex combination of individual factors (age, HIV status, nutritional status, contacts' history), household factors (number of people and adults in a household, mode of cooking, number of smokers, residence mobility, parents/caregivers' knowledge on the benefit of IPT), physical environment (duration and intensity of the interaction with index cases, sputum smear-positive index cases) and health policy in the place (active screening, IPT, early diagnostic which led to early treatment). These factors are the main ones under investigation in this study. For instance, the research has found that age of the child contact, an individual factor, is positively correlated to the development of TB infection and disease [20,111]. Also, it has been demonstrated that there is a strong correlation between TB infection and active TB disease with ecological factors connected to the household, such as enclosed space, poor ventilation, duration of exposure, household size (crowding), temperature, rainfall, the degree of shared activities with index cases and urban milieu [14,106,172]. This adapted conceptual framework (figure 1.4) illustrates four circles that start with individual level, followed by household, physical environment and health policy levels respectively. The four circles indicate the interrelationship between different levels for a child to develop TB infection and disease.

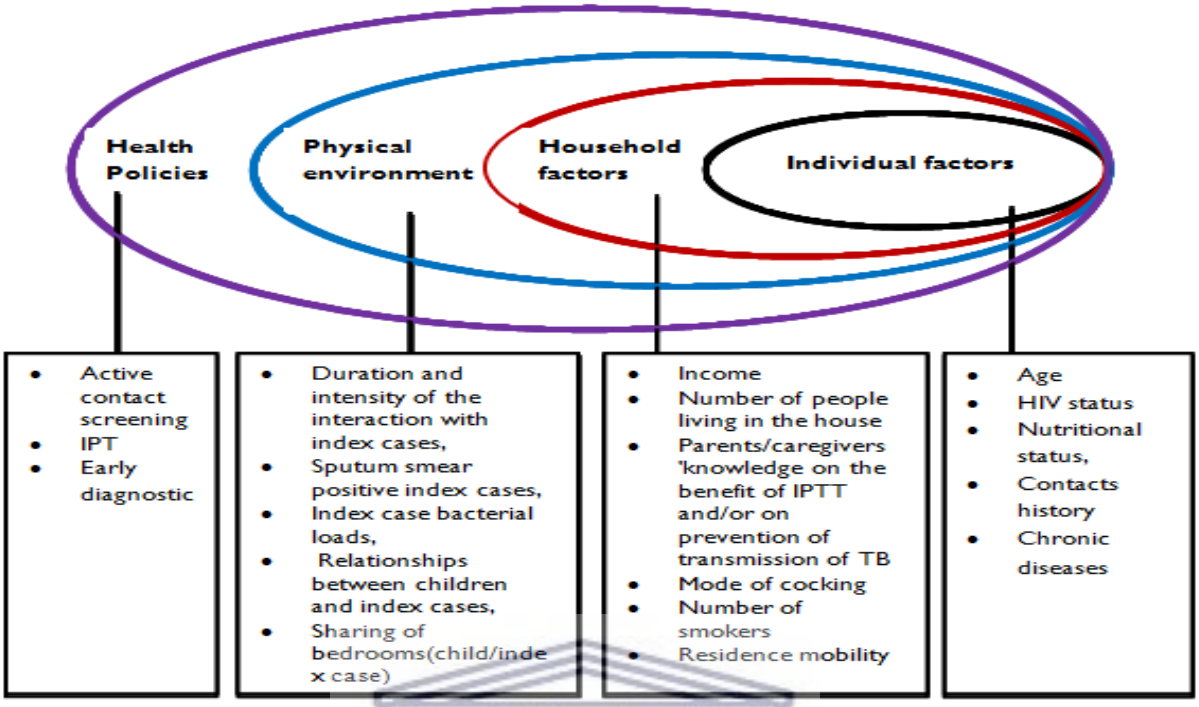


Figure 1.4: An ecological model of four factors that interact in the development of TB infection or disease in child contacts. Source: Adapted from Bronfenbrenner [170]

1.3.3 Overview of the methodology

The studies conducted in this thesis assess IPT and the role of Xpert MTB/RIF test in improving the diagnosis and prevention of tuberculosis in children exposed to index cases with PTB in Kigali, Rwanda. Quantitative **(Studies 1 and 2)**, qualitative **(Study 4)** and mixed-method **(Study 3)** approaches were used in this thesis. The choice of the methodological approach was informed by the research objectives. An overview of the main aims, the study types and design, the data collection methods, the study samples and the main analyses for each study are provided in Table 3. Details on the sampling, data collection methods and data analysis are presented for each study.

Table 1.3: Overview of the method used in different studies

	Study I	**Study II**	**Study III**	**Study IV**
Main aim	To assess the diagnostic performance of the Xpert MTB/RIF assay in sputum collected through GL in symptomatic children who are contacts of index cases with sputum smear-positive TB	To assess the uptake of isoniazid preventive therapy by eligible children in Kigali, Rwanda, and associated individual, household and health care systems' characteristics	To assess the isoniazid preventive therapy adherence and explore its facilitators and barriers in Kigali, Rwanda	To explore the perceptions of and challenges experienced by various stakeholders (laboratory staff, health care workers and programme managers) on the use of Xpert MTB/RIF in diagnosing TB among child contacts
Type of study	Quantitative	Quantitative	Mixed methods	Qualitative
Design	Cross-sectional	Cross-sectional	• Prospective cohort study • Descriptive qualitative [173]	Descriptive [173]
Data collection method	• Face-to-face structured interview with parents/caregivers of selected child contacts. • Record of results from TB registers, index case folders, child contacts screening, X-ray and laboratory tests results (Xpert MTB/RIF, culture and microscopy)	• Face-to-face structured interview with parents/caregivers of selected child contacts*. • Record of results from TB registers, index case folders	• Focus group discussions • Records review Face-to-face structured interviews with parents/caregivers of selected child contacts*.	In-depth interviews

Data collections tools	• Standardised data collection forms • Structured questionnaire	• Standardised data collection forms • Structured questionnaire	• Standardised data collection forms • Structured questionnaire • Interview guides	Interview guides
Study sample	All child contacts of index cases with sputum smear-positive pulmonary tuberculosis who attended selected primary health centres over a 7-month period, from 1 August 2015 to 29 February 2016 (n=216).	All under five-year-old child contacts from the study I who were eligible to isoniazid preventive treatment (n=94)	All under five-year-old child contacts from the study II who started isoniazid preventive treatment (n=84) Purposely selected parents/caregivers whose child contacts had complete adherence (n=15) All parents/caregivers whose child contacts has incomplete adherence (n=6) Purposely selected TB focal persons (n=10) Three focus group discussions (8 persons/each)	Twenty-one stakeholders purposively selected and involved in involvement in using Xpert MTB/RIF: • National TB Programme managers (n=4) • Laboratory staff (n=9) • Health care providers (n=8)
Main analysis	Descriptive statistics, univariate and multivariate logistic regression	Descriptive statistics, univariate and multivariate logistic regression	• Descriptive statistics, univariate and multivariate logistic regression • Thematic analysis	Framework analysis[174]

*The interview was done when collecting data for Study I.

1.3.4 Reliability and validity of the study

The terms reliability and validity were applied for quantitative data, and the terms trustworthiness and credibility were used for qualitative data. Validity refers to the extent to which an instrument is supposed to measure and draws conclusions that are appropriately applicable to the universe outside the study [175]. Therefore, the questionnaire, interview and focus discussion guides used in this study were initially designed in English then translated into Kinyarwanda, and back-translated from Kinyarwanda into English for corroboration of the contents. They were tested using participants and environment similar to what we used during the study. Furthermore, the questionnaire was adapted from different studies including the International Expert Panel in childhood TB [13,176]. Finally, all the data collection tools were revised before adopting finals versions.

Reliability refers to the degree in which results are consistently measured using any data collection instrument [175]. Data enumerators were rigorously selected among people who were trained in how to use the questionnaire and familiar with collecting health-related data in Rwanda to ensure reliability. Furthermore, during data collection of the quantitative data, researchers checked if enumerators were conducting the interviews consistently.

A triangulation approach was used to ensure the validity of the qualitative and quantitative data. Triangulation refers to the use of two or more theories, methods or sources of data to develop a comprehensive understanding of a topic [177]. Validity supports the accuracy, consistency, trustworthiness, and strength of the study. The analysis of a focus group discussion (FGD) and individual interviews from different stakeholders helped with contrast and allowed for the comprehensive design of the situation.

To ensure trustworthiness and credibility of qualitative data, we used the procedures described by Mays and Pope [178] such as to prolong engagement with the participants and constant follow up – the same participants and research team were involved throughout the study. This procedure helped participants to develop a sense of ownership and involvement in the outcome of the research and build the quality of their commitment to this study. Also, we use a triangulation approach of qualitative data to ensure the "Respondent validation" method, the procedure described by Roberts and Priest [179]. This method consists of sharing results with

research participants for allowing them to check, amend and provide feedback based on the response provided.

1.3.5 Ethics considerations

The Biomedical Research Ethics Committee of the University of the Western Cape and the Ethics Review Board of the University of Rwanda, College of Medicine and Health Sciences approved the study protocol. Permission was obtained from Rwanda NTP to collect data from the eligible PHCs.

Written informed consent (Appendix 1) was obtained from parents/caregivers after they were informed about the details of the study (Annexure2– Information Sheet). If they agreed to their participation assent was obtained from older children. Parents or caregivers were provided with all information such as the purpose and nature of the study in their language of choice before signing the consent form (Appendix1). Their anonymity and confidentiality were assured. They were informed about voluntary participation and that they could withdraw from the study at any time without providing reasons. Parents or caregivers were also told that refusal or acceptance to participate would not influence the treatment and counselling of the index cases (when they were still under treatment). All collected data were kept in a safely locked cabinet at the College of Medicine and Health Sciences/School of Public Health (CMHS-SPH) to preserve the confidentiality of all participants. Data were accessed only by the researcher of this study.

1.4 Outline of the thesis

The overall thesis and its different chapters are outlined under this section. In Chapter 2, the yield of Xpert MTB/RIF in GL in diagnosing TB among child contacts is presented.
[Paper 1: *Xpert MTB/RIF assay did not improve* [the] *diagnosis of pulmonary tuberculosis among child contacts in Rwanda*.]

In Chapter 3, the perceptions and perspectives of various stakeholders (laboratory staff, health care workers and programme managers) on the strengths, weaknesses and challenges of Xpert

MTB/RIF in diagnosing TB among child contacts in Rwanda. The Xpert MTB/RIF in GL diagnosing TB among child contacts is particularly targeted.

[Paper 4: *Perceptions of stakeholders on the use of Xpert MTB/RIF for the diagnosis of pulmonary tuberculosis in children in Rwanda: A qualitative study*.]

In Chapter 4, the rate of IPT uptake among eligible children in Kigali, Rwanda is given along with the associated socio-demographic characteristics of child contacts and index cases as well as household and health care system characteristics.

[Paper 2: *Assessment of the Isoniazid Preventive Therapy Uptake and Associated Characteristics: a cross-sectional study*.]

For Chapter 5 the rate of child contacts who have completed the six months of IPT in Kigali, Rwanda is displayed. The facilitators and barriers to IPT adherence are also explored.

[Paper 3: *Adherence to isoniazid preventive therapy among child contacts in Rwanda: A mixed methods study*.]

Finally, in Chapter 6, the summary, main findings and discussion, conclusion, and future perspectives are presented.

The details on the four studies and how they are linked to this thesis are illustrated in figure 1.5.

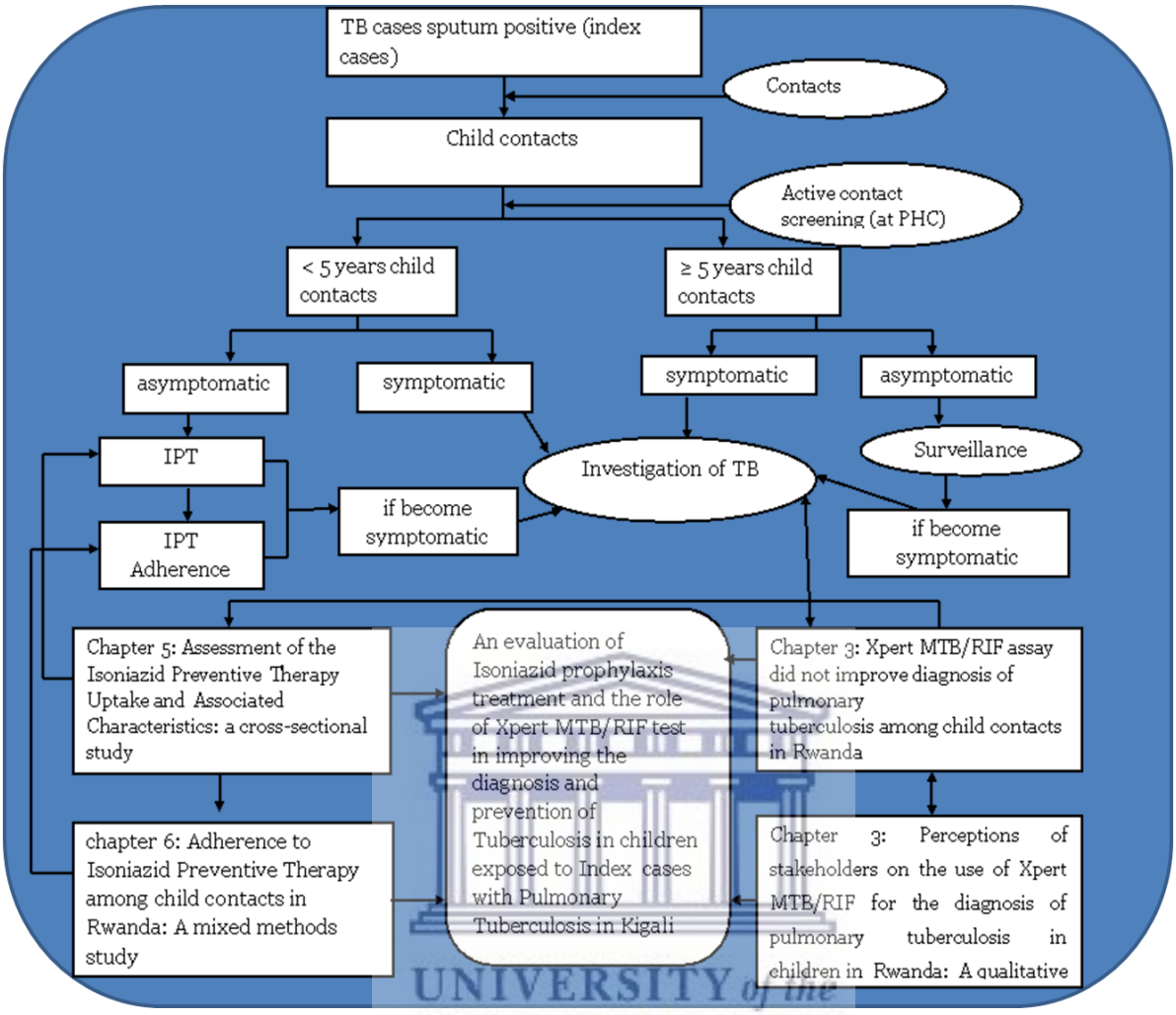


Figure 1.5: Schematic representation of the thesis

Chapter 2

Paper 1

Xpert MTB/RIF assay did not improve diagnosis of pulmonary tuberculosis among child contacts in Rwanda.

Birungi MF, Van Wyk B, Uwimana J, Ntaganira J, Graham MS. Xpert MTB/RIF assay did not improve diagnosis of pulmonary tuberculosis among child contacts in Rwanda. Panafrican Med J. 2018;2018:30–9. doi: 10.11604/pamj.2018.30.39.12600.

Abstract

Objectives: To report on the diagnostic yield using the Xpert MTB/RIF assay on gastric lavage samples from children (<15 years) who were household contacts of tuberculosis (TB) cases in Kigali, Rwanda.

Methods: A cross-sectional study was conducted among 216 child contacts of index cases with sputum smear-positive TB over a 7 month period, from 1st August 2015 to 29th February 2016. Child contacts with tuberculosis-related symptoms or abnormal CXR had sputum collected by gastric lavage on two consecutive days, and samples were examined by smear microscopy, Xpert MTB/RIF assay and solid culture.

Findings: Of the 216 child contacts, 94 (44%) were less than 5 years old. Most of them 84 (89%) were receiving isoniazid preventive therapy at the time of screening. Thirty-seven out of 216 children had TB-related symptoms; their median age was 4 years (interquartile range: 2-13) and 59% were under 5 years old. Only 4 (10.8) were clinically diagnosed with TB. None of the 37 symptomatic child contacts had bacteriologically confirmed tuberculosis and none of these contacts less than 5 years old was diagnosed with tuberculosis.

Conclusions: The use of Xpert MTB/RIF assay did not contribute to bacteriological confirmation of active TB in child contacts in this study. The low prevalence of tuberculosis in child contacts in this study may reflect the high coverage of preventive therapy in young (<5 years old) child contacts. The low sensitivity of Xpert MTB/RIF assay in contacts may also suggest the likely reflection of paucibacillary disease.

Background

Tuberculosis (TB) is a major cause of morbidity and mortality among children (0-14 years) in resource-limited countries [33]. The World Health Organisation (WHO) estimated that 10% of the 9 million TB incident cases occurred in children in 2015 and that there were 210,000 TB-related deaths in children, including 170,000 in Human Immunodeficiency Virus (HIV)-uninfected children [97]. The annual report of Rwanda's 2013-2014 NTP indicated that child TB cases represented 6% of all notified TB cases, below the national target of 12% [162]. Among these cases, 68% were pulmonary TB and 22% were bacteriologically confirmed. These data suggest under-detection of TB in children in Rwanda, especially the clinically diagnosed cases. There are well recognised challenges with detection and diagnosis, particularly in young children (<5 years old) with paucibacillary disease, difficulty in obtaining samples and clinical overlap of TB with other common diseases such as severe pneumonia and malnutrition [22,156,157,180].

Young children (< 5 years old) who develop active TB subsequent to infection with *Mycobacterium tuberculosis* usually do so within one year of infection [102]. Children who are close to a TB index case are at high risk of TB infection [14,78,111,181]. Without any intervention, 5-10% of infected children will develop active TB within one year, with the highest prevalence of TB at the time of screening being in young children (< 5 years old) [19,102]. Screening of child contacts of TB cases, prioritising index cases with sputum smear-positive pulmonary TB, is almost universally recommended and plays two important roles that include identification and evaluation of symptomatic contacts of any age requiring further diagnostic assessment of TB for early treatment (i.e. active case finding), and the provision of preventive therapy to "high-risk" contacts that do not have active TB [182]. Since 2006, WHO has recommended a symptom-based screening approach that allows the initiation of contact

management and the provision of preventive therapy for asymptomatic young child contacts at the household or primary care level [12,69]. However, symptomatic contacts need further evaluation for TB, and this remains challenging at the primary or secondary care level given the widely recognized limitations of current diagnostic tools especially in young children.

In 2013, the WHO endorsed the Xpert MTB/RIF assay for use in children [12,54] since the Xpert MTB/RIF assay offers advantages over smear microscopy for acid-fast bacilli. Research studies reported Xpert MTB/RIF assay to be three times more sensitive than sputum smear but with lower sensitivity in outpatient children than in inpatients (48% versus 70%) when compared to culture [55]**.** Under programmatic conditions in a large study in India, Xpert MTB/RIF assay had twice the yield of smear with similar yield from sputum collected by gastric aspirate or induced sputum [183].

The Xpert MTB/RIF assay can be implemented in a peripheral laboratory with a result in less than two hours that includes information on rifampicin resistance [54,56]. Hence, the Xpert MTB/RIF assay can potentially improve case detection among child contacts compared to smear while overcoming other constraints to active screening that include reducing the time, cost and complexity to the individual, family and health services incurred by the requirement of multiple visits to a hospital to complete the TB evaluation [46,57].

Few studies have evaluated the performance of the Xpert MTB/RIF assay in the context of contact screening in children where the children with TB are outpatients and likely to have early disease that is paucibacillary compared to hospital-based studies of more advanced cases passively detected [55,61,105]. Furthermore, no previous studies have utilised GL in the evaluation of symptomatic child contacts.

The Xpert MTB/RIF assay was introduced as a diagnostic tool for all children suspected of having TB in Rwanda in 2014. However, only samples from self-expectorated sputum have been used. This study aims to evaluate the diagnostic performance of the Xpert MTB/RIF assay in sputum collected by GL in symptomatic children who are contacts of index cases with sputum smear-positive TB.

Methods and materials

Study design and setting

This is a cross-sectional study of child contacts of sputum smear-positive index cases who were detected between 1st August 2015 and 29th February 2016 at 13 PHCs based in Kigali, the capital city of Rwanda. Kigali reports the highest prevalence of TB in Rwanda and around 30% of Rwanda's total PTB cases [95]. Kigali city has four referral hospitals, four District hospitals which are all TB diagnostic and treatment centres and 35 PHCs. Among those PHCs, 23 provide TB diagnostic and treatment services; thus, they are potential entry points for TB cases. A PHC was selected for inclusion in this study if it reported an average of at least 10 sputum smear-positive PTB cases during the first half (January to June) of 2015.

Study population

Index cases diagnosed with sputum smear-positive PTB between August 2015 and February 2016 who had at least one child less than 15 years old, but who were not a member of a household to which a previous selected index case belonged and still living in Kigali city, were eligible for inclusion in the study. Identified index cases were requested, either via telephone calls or through a trained CHW, to bring the children with whom they live to their PHC on a specific day to coincide with the data enumerators' visits to that PHC. Child contacts were defined as being less than 15 years old and having shared the same household with a selected index case within the 3 months prior to the diagnosis of the index case. Therefore, all child contacts born after the index cases had started treatment or who were not leaving with the index cases before the diagnosis of the latter were excluded. Eligible children were enrolled after the signing of the informed consent by their parents or caregivers, or after the signing of an assent form in the case of seven or more years old children.

Data collection and management

A structured questionnaire adapted from screening guidelines [13,176] was pre-tested and modified during a pilot study in two selected sites. Twelve data enumerators were trained to conduct interviews with parents/caregivers of selected child contacts and to collect data from TB

registers and index case folders, using standardised data collection forms. We also trained 20 CHW to explain the study to the parents/caregivers and sensitise them to bring child contacts for screening at the PHC. Data of the index case included: result of smear microscopy, demographic data, address of residence and telephone number. The uptake of IPT among child contacts subsequent to diagnosis of the index case was also recorded. The recorded data were validated by the index case, parents or caregivers of selected children once they were identified in order to ensure the accuracy of the data.

The demographics and medical history of index cases were recorded; and all eligible children underwent clinical screening including nutritional assessment and CXR. The clinical screening focussed on symptoms suggestive of TB: cough for ≥ 2 weeks, haemoptysis, fever, failure to gain weight, absence of appetite, fatigue, and the presence of lymphadenopathy. Anteroposterior and lateral CXR were also performed on all the 216 children; and read by two independent experienced general practitioners who were trained in interpreting CXR and blinded to the clinical details of participants and proofread by an experienced radiologist. Children with symptoms suggestive of TB and/or CXR "consistent with active TB", as described in table 2.1, were given antibiotics for seven days as recommended by the current TB diagnostic algorithm in the country. Those children were thereafter reassessed. Children with persistent symptoms despite appropriate treatment were referred to a district hospital as outpatients for sputum collection through GL.

Table 2. 1: Characteristics of child contacts

	1. Symptoms suggestive of tuberculosis:
a)	Persistent unexplained fever: a one-week unexplained fever of greater than 38^{o}C have been reported by parent or caregiver or at least once objectively recorded.
b)	Cough for more than 2 weeks: a story of persistent, unremitting cough for more than two weeks not responding to the standard therapy.
c)	Documented weight loss or failure to thrive: unexplained weight loss for more than 5% compared with the highest weight recorded in last 3 months.
d)	Malnourished: weight for height Z score (see definition four below)
	2. CXR "consistent with active TB" if there is a positive response to any of the radiographic features, at the same location, by at least 2 independent radiologist reviewers
	a) Air compression and/or tracheal displacement;
	b) Soft tissue density suggestive of lymphadenopathy;
	c) Air space opacification;
	d) Nodule picture (miliary or larger widespread) and bilateral;
	e) Pleural effusion;
	f) Cavities;
	g) Calcified parenchyma; and
	h) Vertebral spondylitis
	3. Tuberculosis disease; if the child met the following criteria
a)	Confirmed TB: Presence of one or more symptoms suggestive of TB, a chest radiography "consistent" with active TB and microbiological confirmation (in this study Xpert MTB/RIF assay test and/or culture positive).
b)	Unconfirmed TB: as our study is constituted by child contacts, we will consider in this category a child who will display at least one of the symptoms suggestive of TB, CXR consistent with active TB.
c)	Unlikely TB: symptomatic child contacts suspected of TB whose symptoms and/or CXR consistent with active TB spontaneously improved after seven days of antibiotics without receiving any TB treatment.
	4. Nutritional assessment using Weight-for-Height
a)	Normal : Z score ≥ -2 of the WHO median
b)	Moderate malnutrition: Z score -3 to < -2 of the WHO median
c)	Severe malnutrition: Z score < -3
	Abbreviation WHO: World Health Organisation; CXR: Chest X-ray

A trained nurse, under the supervision of a senior paediatrician, collected a sputum sample (3-4ml) through GL technique from the children after six hours of fasting on two consecutive mornings. The samples were directly transported to Kigali teaching hospital laboratory, a qualified high performance diagnostic mycobacteriology laboratory, where they were processed by trained technicians and investigated by smear microscopy, Xpert MTB/RIF assay and solid culture within two hours subsequent to their collection. Children diagnosed with TB were treated in accordance with the Rwanda NTP treatment guidelines [184]. The under 5 years old child contacts without any evidence of active TB were offered IPT for 6 months as per the national guidelines if they were not already receiving IPT at the time of screening.

Laboratory procedure

For Xpert MTB/RIF assay test, 2 ml of buffer, a tampon solution of Xpert MTB/RIF assay test, were added to 1 ml of fresh sample. The sample was then shaken and stood for 10 minutes and shaken again and stood for further 5 minutes and then, 2.5 ml of the mixed solution were transferred into the Xpert cartridge, scanned and tested. The result was read two hours later. For the solid culture, 2 ml of fresh sample were decontaminated with 2 ml of sodium hydroxide, and then the mixed solution was neutralized with hydrochloric acid before centrifuging at 3000xg for 15 minutes by using aerosol free centrifuge cups. The sediment was thereafter re-suspended in 2ml of sterile distilled water by 0.5 ml transfer pipette. At the end, 0.2 ml of sediment was inoculated onto solid media, Lowenstein Jensen media as per standard protocols [185]. The growth of *Mycobacterium tuberculosis* bacteria was checked every 7 days up to 8 weeks. For microscopy, a drop of sediment prepared for culture was used for fluorescent acid-fast smear microscopy following the standard procedure [185].

Data analysis

The clinical case definition categories for TB in children considered the standardised case definition recently published [186] and were based on clinical screening, X-ray and microbiological investigations. Children were categorized as follows: bacteriologically confirmed TB, unconfirmed TB and unlikely TB (Table 2.1). The categorical data were

interpreted through frequency table with median and interquartile range (IQR) for continuous data. The Chi square test or Fisher Exact test was performed to compare the proportion of the outcomes between the groups and 95% confidence intervals (CIs) were calculated for the proportion of an outcome using the binomial exact method. The diagnostic performance of Xpert MTB/RIF assay was compared with the culture method as the primary reference standard. All analyses were conducted using Stata statistical software version 13.1 for Windows [187]

Ethical approval

The Senate Research Committee of the University of the Western Cape and the Ethic Review Board of the University of Rwanda, College of Medicine and Health Sciences approved the study protocol. Permission was obtained from Rwanda NTP to collect data from the eligible PHCs.

Results

Figure 2.1 outlines the study flow chart. There were 346 cases of sputum smear-positive PTB diagnosed and treated in Kigali during the study period, that is, from 1st August 2015 and 29th February 2016. Of these 346 index cases, 136 (39%) had at least one child contact and of these 136 index cases, 105 (77%) had a child contact that met the inclusion criteria. The other 31 (23%) index cases with a child contact did not meet inclusion criteria as the child was born after the diagnosis of the index case. Among the 233 child contacts of the 105 eligible index cases, 216 (93%) children met the inclusion criteria of child contacts. The other 17 (17%) were not living with the index case within the 3 months preceding the diagnosis of the index case. Among these 216 child contacts, 37 (17%) children from 28 index cases had symptoms suggestive of TB and/or CXR "consistent with active tuberculosis" at the time of screening.

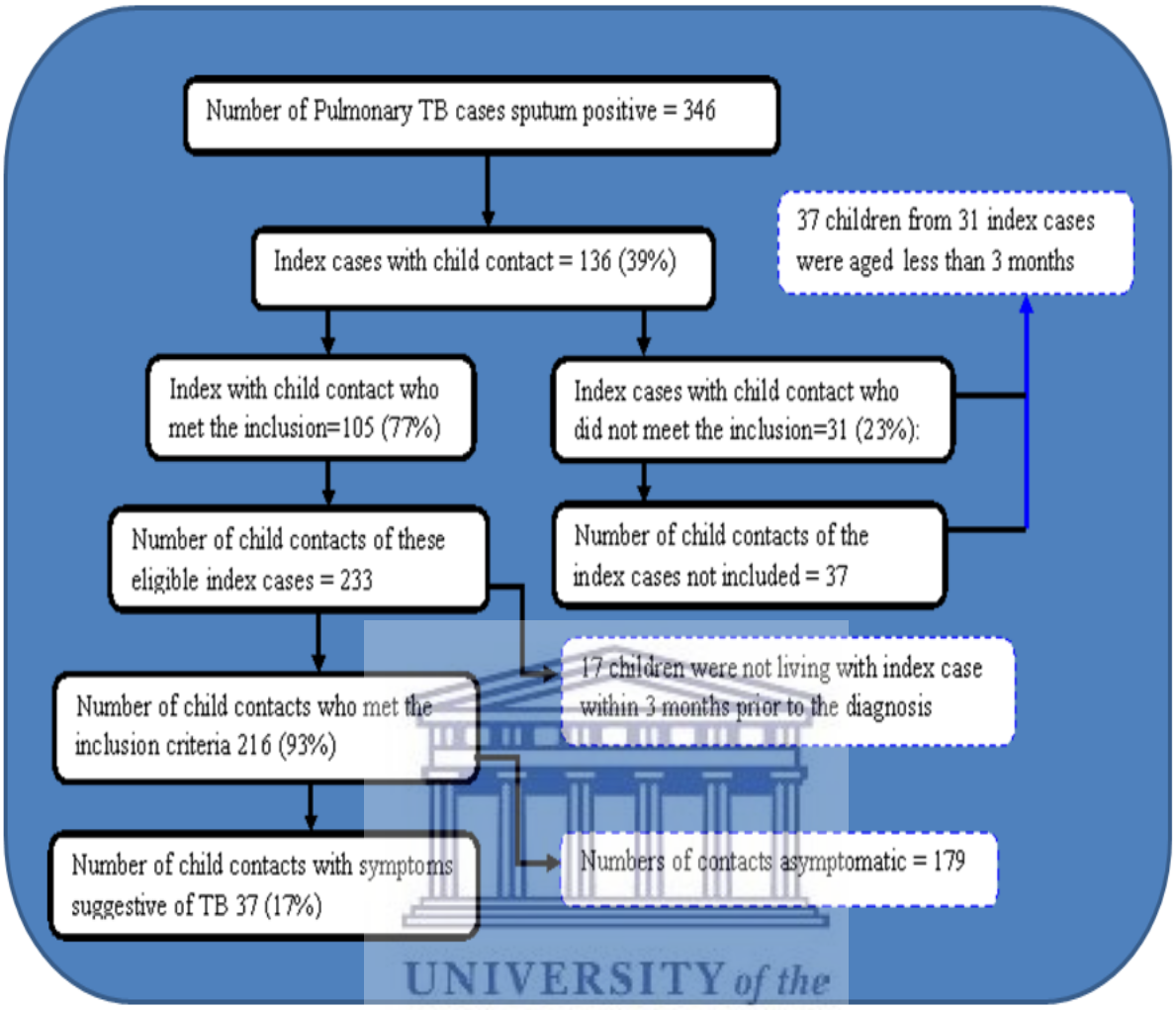


Figure 2. 1: Flow of child contacts recruitment

Tables 2.2 and 2.3 show the demographic characteristics of the eligible index cases and child contacts, respectively. The results reveal that median age of index cases was 35 years (IQR: 18-65); HIV test was done for 95 (90%) index cases and HIV prevalence was 27%. The findings show that 71 (68%) of all index cases had not yet completed TB treatment. The median age for symptomatic child contacts was 4 years (IQR: 2-13). Among those 37 children, 59% were under five years old, 54% were female; the HIV test was done for 31 (84%) of them, 3% were HIV positive, and 97% had the evidence of BCG vaccination recorded. IPT had previously been commenced in 84 (89%) of 94 young child contacts without active TB at the time of evaluation.

Table 2. 2: Characteristics of the index cases of child contacts

Characteristics	All index cases (n=105) No (%)	Index cases with symptomatic children (n=28), No (%)
Age median (IQR)	35 (18-65)	33 (19-65)
Age group in years		
Female	51 (49)	13 (46)
Residence of children		
Nyarugenge	23 (22)	7 (25)
Kicukiro	27 (26)	8 (29)
Gasabo	55 (52)	15 (46)
Type of health facility		
Public	70 (67)	16 (57)
Faith based	35 (33)	12 (43)
Sputum smear		
Scanty	8 (7.6)	4 (14)
Positive 1	22 (20)	5 (18)
Positive 2	15 (14)	6 (21)
Positive 3	32 (30.4)	9 (32)
Positive 4	28 (27)	4 (14)
Not completed TB treatment	71 (68)	17 (61)
Index case tested for HIV	95 (90)	27 (96)
HIV positive	28 (27)**	6 (22)

Abbreviations: IQR: interquartile range; HIV: human immunodeficiency virus; **: only 95 persons were tested and this number is the denominator.

Table 2. 3: Characteristics of child contacts

Characteristics	All child contacts (n=216) No (%)	Symptomatic child contacts (n=37) No (%)
Age median (IQR)	6 (2-13)	4 (2-13)
Age group in years		
< 5 years	94 (44)	23 (62)
≥ 5 years	122 (56)	15 (41)
Sex child contact		
Female	104 (49)	20 (54)
Sputum smear of index cases		
Scanty	23 (11)	8 (22)
Positive 1	36 (17)	6 (16)
Positive 2	33 (15)	7 (19)
Positive 3	58 (26)	10 (27)
BCG scar	196 (90)	36 (97)
Nutritional status (Weight for age)		
Severe malnutrition	0 (0)	0 (0)
Moderate Malnutrition	15 (7)	7 (19)
Normal	201 (93)	30 (81)
HIV positive/tested (%)	5/83 (6)	1 (3)
Receiving IPT /eligible (%)	84/94 (89)	19/23 (82)
Relationship to Index case		
Grandchild	15 (7)	5 (14)
Sibling	27 (13)	4 (11)
Child	150 (70)	23 (64)
Others	21 (10)	4 (11)
CXR "consistent with active TB"	4 (1.8)	4 (11)
Spends ≥ 8 hours per day in the same room as the index case	144 (67)	30 (81)
Shares a bed with the index case	150 (69)	15 (41)

Sleeps in the same room as the index case	77 (36)	16 (44)
Number of people living in the house at the time of the diagnosis		
One person	36 (17)	7 (19)
Two persons or more	180 (83)	30 (819)
Number of bedrooms in the house at the time of interview		
One bedroom	181 (84)	29 (78)
Two bedrooms	27 (13)	8 (22)
Three bedrooms	7 (3)	0 (0)
Indoor air pollution exposure (to tobacco or biomass cooking)	159 (74)	37 (100)
Abbreviations: IQR: interquartile range; BCG: Bacille calmette guerin; IPT: isoniazid preventive therapy		

Data of uptake and adherence to IPT were presented separately once the follow-up of the cohort was completed.

The majority of child contacts selected in the study were asymptomatic at the time of screening: 179/216 or 83% (95% CI, 77% - 87%). All symptomatic child contacts (100%) were exposed to air pollution (tobacco smoke or burning wood) and the majority (64%) had their parents as index cases with 81% in contact with index cases for more than 8 hours per day. In addition, the majorities (81%) of these children were living in the households with more than two people and 78% of those households had just one bedroom. Among the 37 symptomatic child contacts, 92% had at least one symptom suggestive of TB (Table 1.1) and 10.8% had a CXR "consistent with active tuberculosis". The most commonly reported symptoms
were cough (65%), fever (24%), moderate malnutrition (19%) and enlarged cervical, axillary or inguinal lymph nodes (5%). The CXR was normal in 212 (98%) of all 216 children, whereas 33 (89%) of 37 symptomatic child contacts had a normal CXR. All four abnormal CXRs were reported as “air space opacification”. No asymptomatic child had an abnormal CXR.

Of the 37 symptomatic child contacts, 33 or 89% (95% CI, 73-96) were classified as unlikely TB children and 4 or 10.8% (95% CI, 3.9-26.4) had a clinical diagnosis of TB. This represented 1.8 % (95% CI, 0.06-0.4) of TB cases among all 216 child contacts. All clinically diagnosed TB cases had at least one symptom suggestive of TB and a CXR consistent with active TB. All these children, who were ≥5 years of age, were initiated on TB treatment for six months according to the national guidelines [184] and all completed the TB treatment. None of the symptomatic contacts was bacteriologically confirmed by smear, Xpert MTB/RIF assay or culture on two GL samples.

Discussion

No child contacts were detected with bacteriologically confirmed TB, including those who were symptomatic at the time of screening. Only four (10.8%) children of all symptomatic child contacts were treated for TB based on clinical diagnosis. The very low overall yield (1.8%) of children diagnosed with TB in our study following contact screening is in sharp contrast to the high yield recently reported from Uganda where 10% of 761 contacts were diagnosed with TB of whom 71% were bacteriologically confirmed [180]. A study conducted in Indonesia among 269 child contacts using two separate samples obtained by induced sputum that also included Xpert MTB/RIF assay for *M. tuberculosis* diagnosed TB in 8% of 269 child contacts, but as in our study, none was bacteriologically confirmed [105]. Contrasting findings have been reported in adult household contacts in Ethiopia [188] where the Xpert MTB/RIF assay in sputum yielded a high percentage of cases (9/14 or 64%) but the numbers were small. A possible explanation for a low yield from Xpert MTB/RIF assay is that contact screening may select children with early disease as hospital based studies of children with presumptive TB have had much higher yields [55,58–61]. It has been demonstrated that the detection limit of Xpert MTB/RIF assay is low, showing only 131 colony forming unit (CFU) [95% CI: 106–176] /ml of specimen [56,188,189].

Our study also shows that none of the under-five years old child contacts had TB at the time of screening, despite being deemed to be an "at-risk" group with a high yield of active TB (around 10%) at the time of screening [19,78,102]. This is likely because a large proportion (89%) of

child contacts ≤5 years old were already on IPT at the time of screening. In the studies in Uganda and Indonesia, only 1.5% (7/490) and 0% (0/99), respectively, of eligible child contacts who started on IPT developed active TB [105,180]. Furthermore, there was a time delay between diagnosis of the index case and contact screening of up to 5 months.

There was a low yield from Xpert MTB/RIF assay in sputum collected through GL technique in this study from two sputum samples, which suggests the need to evaluate resource implications and cost-benefit of the policy that recommends Xpert assay for children with presumptive TB who are household contacts [105].

Our study has a number of major limitations. The absence of any confirmed TB cases prevented us from making conclusive remarks about the performance of Xpert MTB/RIF assay as a diagnostic tool in child contacts in sputum collected through GL technique and there was no comparison with other collection methods. Moreover, the small number of TB cases observed could lead to the reduction of the power to detect small differences in the yield between Xpert MTB/RIF assay and clinical diagnosis, microscopy and solid culture.

Conclusion

The use of Xpert MTB/RIF assay did not contribute to bacteriological confirmation of tuberculosis in child contacts in this study in Rwanda, a setting where there was a high uptake of preventive therapy among eligible child contacts. The low sensitivity of Xpert MTB/RIF assay in contacts may also suggest likely reflection of paucibacillary disease because of early case detection.

What is already known on this topic:

- Performance of the Xpert MTB/RIF assay in inpatient and outpatient children (passive case detection)
- Performance of the Xpert MTB/RIF assay in induced sputum in symptomatic contacts children

What this study adds:

- Performance of the Xpert MTB/RIF assay in the context of contact screening in child contacts already on IPT
- Performance of the Xpert MTB/RIF assay in sputum collected through GL in symptomatic child contacts (early case detection)

Chapter 3

Paper IV

Using the Xpert MTB/RIF to diagnose pulmonary tuberculosis in children in Rwanda: Stakeholders' perspectives

Francine Mwayuma Birungi,' Brian Eduard van Wyk, Ferdinand C. Mukumbang

Under review with BMC Health Services Research. Submission ID: BHSR-D-19-00343

Abstract

Background: Xpert MTB/RIF was introduced as a diagnostic tool for all children with presumptive TB in Rwanda in 2014. However, its use in outpatient care settings remains questionable. We explored the perceptions and perspectives of various stakeholders (laboratory staff, health care workers and programme managers) on the strengths, weaknesses and challenges of Xpert MTB/RIF in diagnosing TB among child contacts in Rwanda.

Methods: We conducted an exploratory qualitative study to capture the perceptions and experience of various stakeholders on the use of Xpert MTB/RIF in gastric lavage among child contacts in Kigali, Rwanda. We conducted 21 semi-structured interviews with nine laboratory staff, eight health care providers, and four programme managers purposively sampled. These interviews were audio-recorded, transcribed verbatim in *Kinyarwanda*and translated to English by professional translators. We analysed the data using thematic content analysis to identify emerging themes and trends.

Results: Our findings showed that although Xpert MTB/RIF facilitated early detection of pulmonary TB and drug resistant TB among older children (5-14 years old) at the primary health care (PHC) level, its over-all contribution to TB diagnoses among younger children (0-5 years

old) was very minimal, special when using GL as sample. Nevertheless, evidence from referral hospitals revealed that Xpert MTB/RIF contributed substantially to TB diagnosis in young child contacts than to microscopy owing to the availability of skilled staff. We also unveiled other weaknesses regarding the utilisation of Xpert MTB/RIF such as the challenges around performing laboratory tests on samples other than sputum and health care providers' lack of awareness on the availability of Xpert MTB/RIF test. Further implementation challenges were noted around the restriction of performing the gastric lavage at PHC and the absence of a reliable system of sample transportation from the PHC to the district hospital.

Conclusion: Xpert MTB/RIF contributed little to improve the diagnosis of TB in child contacts in Kigali because of its low yield, and numerous implementation challenges at the PHC. There is a need to integrate the gastric lavage technique and strengthen clinical diagnosis and management of child contacts at PHC through training health care providers and community health workers at the PHC level to improve TB diagnosis among child contacts.

Keywords: Tuberculosis, children, Xpert MTB/RIF, diagnosis, qualitative research

Background

Tuberculosis (TB) is a major cause of morbidity and mortality among children (0-14 years old) in resource-limited countries [32,33]. The World Health Organization (WHO) estimated that 10% of the 10.4 million TB incident cases worldwide occurred in children in 2016; with 201,000 TB-related deaths in HIV-negative children and 52,000 in HIV-infected children [39]. In 2015, WHO introduced the goal to end the global TB epidemic by 2035 by reducing the incidence of TB by 90% and TB deaths by 95% [30]. Most deaths from TB can be prevented with early diagnosis and appropriate treatment. To achieve this goal, there is a need to reduce the number of undiagnosed TB cases [39,160,161]. The high number of undiagnosed TB cases remains a public health problem because it increases the burden of TB and the rate of TB transmission in the community [31].

The annual report of Rwanda's 2013-2014 NTP indicated that childhood TB cases represented 6% of all notified TB cases, which is half of the national estimate of 12% [162]. Among these notified TB cases, 68% were pulmonary TB, and 22% were bacteriological confirmed cases. These data suggest under-detection of TB among children in Rwanda, and the health system's inability to confirm cases bacteriologically. The high prevalence of undiagnosed TB in children could be explained by the lack of accurate diagnostic tools and the poor implementation of diagnostic guidelines [190].

Current tools for TB diagnosis in children have widely recognized limitations such as the difficulty to obtain paucibacillary respiratory samples from children, especially those with HIV, and the difficulty to obtain diagnostic expectorated sputum samples [66]. In 2013, WHO endorsed the use of Xpert MTB/RIF for the diagnosis of TB in children [12,54] owing to the fact that it is easy to implement in a peripheral laboratory, provides rapid results and produces information on rifampicin resistance in less than two hours [54,56]. It can also help overcome challenges to active screening resulting from the need for multiple visits to complete TB diagnosis by reducing time, cost and complexity to the individual, family and health service [46,57]. Although Xpert MTB/RIF has proven its effectiveness in diagnosing children in inpatient care settings, nevertheless, where induced sputum or gastric lavage (GL) techniques can be used [58–61], its effectiveness remains questionable for children in outpatient care settings [48,105,165]. In addition to the limitations inherent to the test itself, the implementation of the Xpert has also encountered multiple challenges that limited its impact [62,166,191].

Rwanda introduced the Xpert MTB/RIF as a diagnostic tool for children suspected of having TB in 2014. Although sputum samples are required to conduct a TB test using the Xpert MTB/RIF, children, especially the under-fives with pulmonary TB are often unable to provide sputum samples [53]. For this reason, GL exudates are used as an alternative approach to obtain sputum samples for testing TB in children [53]. GL is a technique in which a nasogastric tube is introduced into the stomach of the child and fluid is collected through a syringe for the microbiological confirmation of TB [192]. GL has several limitations including four to six hours of fasting, repeated specimens, and admission of children to inpatient care. Additionally, the

procedure is reported to be unpleasant for both the child, parents/caregivers and the health care provider [53]. In this study, we explore the perceptions and perspectives of various stakeholders (laboratory staff, health care workers and programme managers) on the strength, weakness and challenges of Xpert MTB/RIF, specially using GL as sample, in diagnosing TB among child contacts in Rwanda.

Methods

This study is part of a larger research project that was conducted in Kigali, the capital city of Rwanda by a consortium of researchers from South Africa, Australia and Rwanda between the August 2015 and February 2016 [165]. The project evaluated the diagnostic performance of the Xpert MTB/RIF assay in sputum collected by GL technique from symptomatic child contacts. Kigali has 35 PHCs that offer TB diagnosis and treatment. Thirteen of these facilities were selected for inclusion in the main study based on a recording of at least ten sputum smear-positive PTB between January and June 2015.

Since 2012, 50 Xpert MTB/RIF machines have been installed in Rwanda, nine of them are based in Kigali. Their use was limited to the diagnosis of TB and MDR TB in adults. It is only in 2014 that it was considered as a TB diagnostic tool for all children suspected of having TB. A sample transportation system is in place to facilitate the transfer of samples from health facilities without an Xpert MTB/RIF machine to those equipped with the machines. Samples that are rifampicin (RIF) indeterminate are sent to the NRL for confirmation on a weekly basis. This service is provided free of charge to the patient. The calibration and maintenance of Xpert MTB/RIF machines are done at the national level by NRL.

Study design

We conducted an exploratory qualitative study from January to May 2018 in Kigali, Rwanda. The study design allows the researcher to report on the experience of study participants in relation to a specific phenomenon under study [173].

Participant selection

We recruited various stakeholders involved in the use of Xpert MTB/RIF: laboratory staff, health care providers, and National TB Programme (NTP) managers. We purposefully selected participants according to their involvement in using Xpert MTB/RIF at the selected health facilities. A health facility was selected if it was based in Kigali City, had an Xpert MTB/RIF machine and received samples from 13 PHCs described in the main research project [165]. There was no predetermined number of participants – the acquired number of interviews was determined by data saturation – no new data emerged or new findings were accommodated by existing themes [193].

We contacted 21 participants who all accepted to be interviewed. These included nine laboratory staff, eight health care providers and four NTP managers. Their work experience in TB ranged from 5 to 15 years (Table 3.1).

Table 3.1: Characteristics of participants

Type of institutions	n
Laboratory staff	9
Health care providers	8
Programme managers	4
Gender	
Male	15
Female	6
Profession	
Microbiologist	4
Laboratory technicians	5
Nurse	4
Paediatricians	4
Programme managers	4
Type of facilities	
National Referral Laboratory	2
Referral hospital	7
District hospitals	6
Primary Health Centres	2
National TB Programme	4
Work experience (years)	
5-10	11
11-15	10

Data collection

Three experienced qualitative fieldworkers (all female senior nurses) were recruited and trained to conduct semi-structured interviews in the local language, *Kinyarwanda*, using an interview guide. Two days debriefing sessions were held with the fieldworkers before the fieldwork started. In the debriefing session, the principal investigator discussed each question with the fieldworkers explaining the nature of the response that each of the questions is meant to elicit. Discussions on how to probe for further explanations were also held. An interview guide was

developed and pretested. The interview guides elicited information on the experience and perceptions of the stakeholders on the use of Xpert MTB/RIF in paediatric populations. The pre-test was done using two laboratory staff working in a non-participating district hospital. No further modification was needed after pre-test.

Laboratory staff, health care providers and programme managers were recruited at their workplace. After a brief explanation of the project and obtaining informed consent, fieldworkers conducted semi-structured interviews with the participants at their respective places of work.

Each interview lasted between 20–45 minutes. All interviews were audio-recorded after obtaining participants' consent. For quality control, at the end of each interview session, the fieldworkers summarized the salient points of the interviews with confirmation or adjustments from the participants when necessary. Thereafter, the fieldworkers transcribed the interviews verbatim in *Kinyarwanda*. The principal investigator checked the transcriptions and addressed the necessary alterations before analysis. A professional translator then translated the transcripts into English. A bilingual member of the research team verified the English transcripts to ensure that the English version was clear and accurately represented the information in the original language.

Data analysis

We employed a framework analysis to analyse the data. Two of the authors developed an analytical framework - Strength, Weakness, and Challenges – to guide the analysis, as described by Braun *et al*. [174]. We read the transcripts several times for familiarisation and understanding. We then applied a deductive thematic analysis to the transcripts by coding sections and portions of the text linked to the categories of strength, weakness and challenges. These codes where then classified to formulate subthemes, which were further collated to form themes under the identified categories. We managed the data analysis using Atlas.ti software [194]. Two authors coded portions of the transcripts independently. Discrepancies were discussed and resolved by consensus. Thereafter, the codes were grouped into sub-themes and further aggregated into themes.

Ethics considerations

The study protocol was submitted to and approved by the Biomedical Research Ethics Committee (BIMREC) of the University of the Western Cape and the Ethics Review Board of the University of Rwanda, College of Medicine and Health Sciences. Written informed consent was obtained from all participants prior to data collection. Participants' anonymity and confidentiality were assured: during transcription, pseudo-names were used to make the identity of the participants anonymous. All records were stored in a password-protected folder in the computer and the hard copies of the data (printed transcripts) were clocked in a cupboard accessible only to the research team.

Results

We classified our findings under three main categories: the strengths, weaknesses and challenges of using Xpert MTB/RIF for diagnosing PTB in children. Under each category, we identified sub-themes and themes (Figure 3.1).

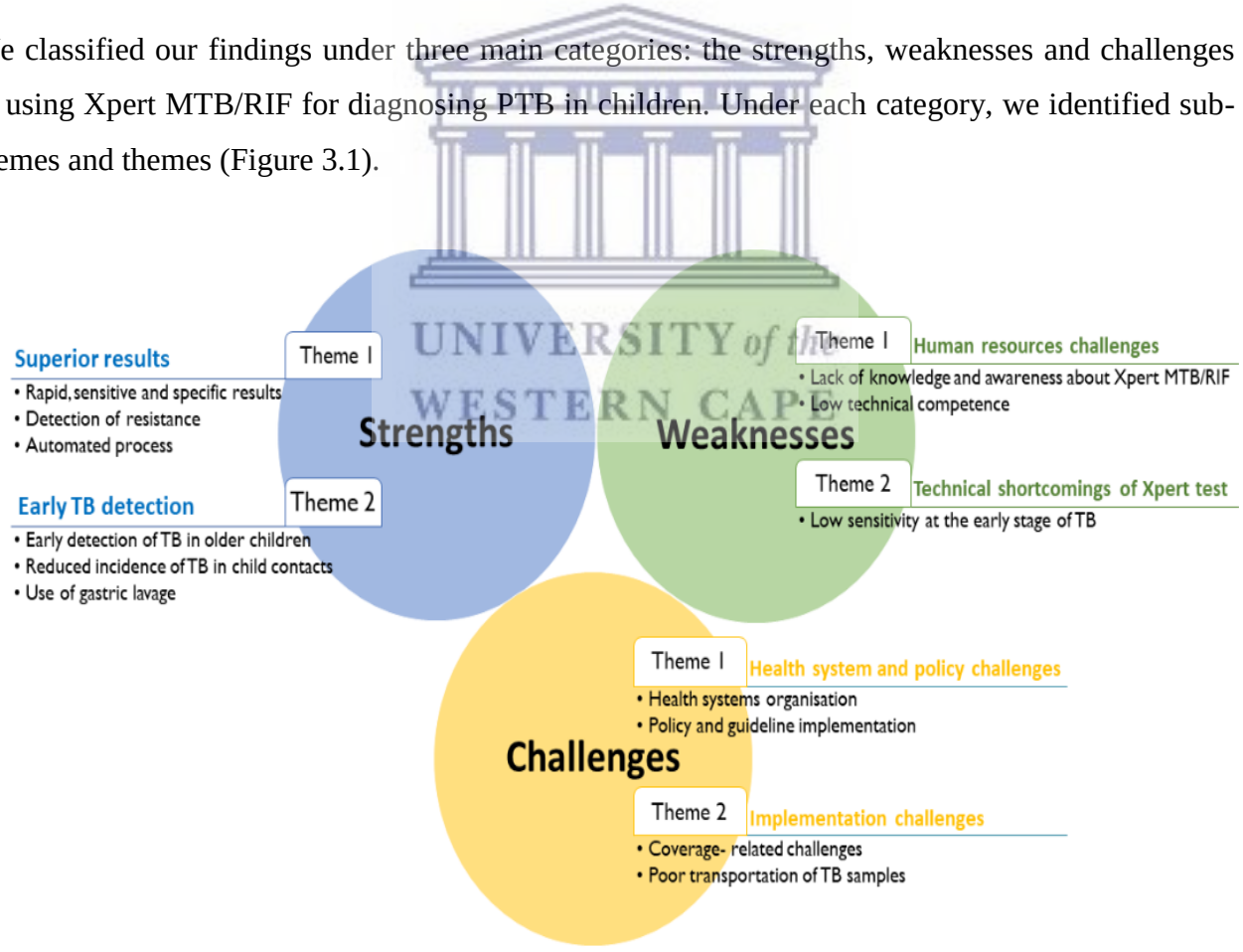


Figure 3. 2: Overview of categories, themes and sub-themes identified in this study

Strengths of using Xpert MTB/RIF

The strengths of using Xpert MTB/RIF were identified under two themes: *superior results* and *early detection of TB.*

Superior results

The study participants acknowledged the advantages of Xpert MTB/RIF in yielding rapid, sensitive and specific results, showing superiority over sputum smear testing. Participants also highlighted the additional advantage of Xpert MTB/RIF to detect resistance to rifampicin in less than two hours.

> *I think that Xpert MTB/RIF test increases the yield of TB detection in children due to its high sensitivity compared to other tests we were familiar with like smear microscopy. Additionally, this test has a shorter processing time, two hours only for detecting Mycobacterium tuberculosis than other tests do. It also detects resistance to rifampicin (one of the four first-line drugs for tuberculosis treatment) and, therefore, helps doctors to choose the appropriate treatment regimen for the patient.* – **Laboratory technician 1, District hospital.**

> *It [Xpert MTB/RIF] helped in confirming TB in patients with suggestive symptoms, meaning that it showed which child was sick or not and in a very short time* – **Nurse, Referral hospital.**

Participants also commended Xpert MTB/RIF as an automatic equipment with less diagnostic errors than microscopy. The 'automatic equipment' means that, except for the sputum liquefaction and inactivation process, following the transfer of the sputum on the cartilage, all other processes are automated.

> *Xpert MTB/RIF also has a higher specificity than smear microscopy does, which [smear microscopy] can give false negative results due to its lower specificity or errors in its operating procedures. Xpert MTB/RIF is an automated diagnostic test and has a high accuracy (precision). While doing the test manually [using smear microscopy], you are subject to human errors. So, I think Xpert MTB/RIF has*

helped us a lot by reducing the likelihood of human-associated error.–**Laboratory technician 2, District hospital.**

Early detection of TB

Participants reported that Xpert MTB/RIF contributed to early detection of PTB and DR-TB among older children (5 -14 years old) who are able to produce quality spontaneous or induced sputum. To this end, it contributes to the reduction of TB incidence through prompt detection.

In my opinion, Xpert MTB/RIF is useful because when used to test a sample of a child attending a school and provides a positive result, we are sure that the child has tuberculosis. Further, when they test other children of the same school, they can know those who have tuberculosis or not. This helps a lot in the sense that it can reduce TB incidence. – **Laboratory technician 3, District hospital.**

I can say that this test has helped a lot in increasing the yield of TB detection bearing in mind that we had children whose sputum smear microscopy result was negative. However, when you use Xpert MTB/RIF, the result becomes positive; though it's not all cases. Xpert MTB/RIF provides the yield of TB detection as we expected – **Paediatrician 1, Referral hospital.**

Since we started using these machines, we have been able to detect DR TB in the under 15-year-old children; but before 2015 we did not have a paediatric case among DR TB notified cases, all were adult cases. From 2015 to date, we have registered seven cases of DR TB among children aged between five and 14. This demonstrates the contribution of Xpert MTB/RIF. No child was diagnosed with DR TB before Xpert MTB/RIF, that did not mean that no child had DR TB; but the reason was that the tests we had could not easily detect DR TB. – **Programme manager 1.**

Participants also reported that the use of GL in Xpert MTB/RIF substantially contributes to TB diagnosis in children than microscopy, specially children in advanced stage of the disease.

When gastric lavage technique has been well carried out and Xpert MT/RIF test done, the yield of TB detection in children, specially inpatient children, has increased, but the yield remains still low. – **Paediatrician 1, Referral hospital.**

Participants also reported that Xpert MTB/RIF assay has indirectly reduced the incidence of TB in child contacts through early detection and prompt treatment of adults with TB who live with them.

With microscopy, if you have a low bacillary load in the sample, you could miss the MTB bacilli and tell the patient that she/he has no tuberculosis while she/he has it. In this case, during the period she/he is not diagnosed yet, that person would continue to transmit TB to others and particularly to children. Currently, with the accurate diagnostic tool such as Xpert MTB/RIF, you cannot miss the diagnosis. This is stopping early the spread of TB in the community. Therefore, we witness a reduction in the number of TB cases." **- Laboratory technician 3, District hospital.**

Weakness of using Xpert MTB/RIF

Two themes were identified under this category: human resources challenges and Xpert MTB/RIF test technique-related weakness.

Human resource challenges

We identified two sub-themes under this theme: *lack of knowledge and awareness* about Expert MTB/RIF and *low technical competence* of health workers.

Lack of knowledge and awareness

Some participants reported that the health care providers lack knowledge about and awareness of the availability of Xpert MTB/RIF test and its indications, and therefore make little demands for the test for children. Consequently, it remained under-used.

A Weakness in using Xpert MTB/RIF has existed since its introduction. I believe that many health care providers have not been aware of its existence or its use as a

routine initial diagnostic test for easier and faster TB detection among children - **Paediatrician 2, Referral hospital.**

Low technical competence

It was reported that health workers had low technical competence to perform quality TB screening using the GL technique and Xpert MTB/RIF test when samples other than sputum are to be used.

We started using this gastric lavage liquid recently; I cannot say it is the weakness of Xpert MTB/RIF test, but it is because our laboratory technicians don't know, maybe they know that it's possible to use samples other than sputum; but they are not able to perform Xpert MTB/RIF test in samples other than sputum for TB diagnostics. - **Programme manager 2.**

Participants reported the inability of PHC providers to presume TB in child contacts, mostly among young child contacts with symptoms suggestive of TB led to their delayed referral and TB diagnosis as explained by one of the programme managers.

I can say the weakness lies in the incapacity of health facilities to presume TB in children and their referral to hospitals where they can benefit from a gastric lavage collection and rapid testing of liquid gastric which can contain the bacilli.– **Programme manager 1.**

Participants reported the inability of some health care providers to collect quality GL samples, thus increasing the probability of negative results even though a child has TB as a technical competency weakness.

The challenge is that sometimes the sputum sample you get is not of good quality; and when the gastric liquid sample is not of good quality, you cannot be sure 100% to get a positive result. – **Nurse 2, Referral hospital.**

When the sample is saliva and of insufficient quantity, you can get a negative (absence of the Mtb bacilli) or undetermined result. –**Laboratory technician1, Referral hospital.**

Technical shortcomings of Xpert MTB/RIF test

This theme refers to the inability of Xpert MTB/RIF to detect TB among child contacts with presumptive TB due to its low sensitivity at the early stage of TB disease. Most participants have reported that Xpert MTB/RIF has contributed little to increase TB diagnosis in children in their practices even when using spontaneous sputum samples; and its contribution was even less when GL exudates were used.

> *Xpert MTB/RIF did not really meet our expectations: it was not very successful on samples obtained from presumptive TB children; and it performed poorly in GL* - **Laboratory microbiologist 2, Referral hospital.**

> *Referring to my experience, I have not seen patients [children] with positive Xpert MTB/RIF results. It has not increased the yield of positivity very much. I can't tell how much it has increased the yield of TB detection in children; I have not seen such a case.* – **Paediatrician 2, District hospital.**

> *In general, based on the numbers of TB cases among adults, it is clear that Xpert MTB/RIF has helped in increasing diagnoses; nevertheless, we have not seen a substantial increase in the number of cases in children particularly among those below five years since the Xpert MTB/RIF was introduced.* –**Programme manager2.**

Challenges of using Xpert MTB/RIF

We identified two themes under this category: Health system organisation and implementation-related challenges.

Health system and policy related challenges

Health system organisation

Although most child contacts with presumptive TB receive care at PHC, participants reported the restrictions on to performing GL at PHC, as a challenge to using Xpert MTB/RIF. Therefore,

most young children with presumptive TB are referred to the district or referral hospitals when GL is indicated.

> *Not all health facilities can perform gastric lavage; it can't be done at the PHC level where we know that 80% of children get the primary care. This can show you the existing weakness.* –**Programme manager 3.**

The organisational restriction of conducting TB tests at the PHC where the majority of cases enter the health system poses challenges to the efficient use of Xpert MTB/RIF.

Non-compliance with Policy Guidelines

This sub-theme concerns challenges related to non-compliance with TB diagnostic guidelines.

Participants have identified non-compliance with TB diagnostic guidelines as a challenge of using Xpert MTB/RIF in child contacts with presumptive PTB. This led to the under-use of Xpert MTB/RIF, which could minimize the impact of Xpert MTB/RIF.

> *At the laboratory, we have observed that there is little demand of Xpert MTB/RIF assay test in children, mostly young children – less than 5 years old, by health care providers* –**Laboratory technician, District hospital.**

Another challenge reported by the participants was the lack of a clear indication of when GL is to be used. A programme manager explained:

> *Firstly, they don't do it [GL] in all children; secondly, it requires team discussion to decide which child is eligible for GL.* –**Programme manager 2.**

Implementation challenges

Two sub-themes were identified under this theme: Poor transportation of TB samples and lack of infrastructure.

Poor transportation of TB samples

This sub-theme relates to the non-availability of the Xpert MTB/RIF machines at several PHC and speaks to the absence of a formal system and means of sample transportation from a site without Xpert MTB/RIF (usual PHC) to another equipped with it.

> *This situation [Absence of machines at PHCs] requires transportation of samples collected from children at the PHC level to the hospital for Xpert MTB/RIF testing. The challenge here is that the sample transportation system is not optimal to ensure a timely delivery of the samples.* –**Programme manager 1.**

> *I can't tell whether Xpert MTB/RIF has increased the numbers of cases or not given that its coverage is not nationwide. Although we say that all children under 15 years old with suggestive symptoms of TB should be tested with Xpert MTB/RIF, we know that all are not tested with this technique. This makes it hard to tell with confidence whether it helped or not.* –**Programme manager2.**

Coverage related challenges:

According to our data, only seven Xpert MTB/RIF were installed in the Kigali region. A participant confirmed that these machines are only installed at the secondary and tertiary health care level.

> *Xpert MTB/RIF machines are installed at district hospitals and referral hospitals. We don't test tuberculosis at this level [PHC] using Xpert MTB/RIF machines despite that 80% of presumptive cases are screened at this level*–**Programme manager 1.**

It is understandable that the Xpert MTB/RIF is only installed at the district and referral hospitals because they are very expensive and the microscopic approach is effective as screening tool at the PHC level.

Discussion

The aim of this study was to explore the perceptions and perceptions of various stakeholders on the strengths, weaknesses and challenges of the use of Xpert MTB/RIF in diagnosing TB among child contacts in Rwanda. The findings of this study showed that the yield of Xpert MTB/RIF in diagnosing TB in children was dependent on the type of samples used and on the age of the child. We learnt that Xpert MTB/RIF facilitated early detection of PTB and DR-TB among older children (5 -14 years old) and that its yield increased more in child contacts aged between 10 and 14 years old as they can provide quality sputum nearly like adults. Our findings corroborated the findings of a study conducted in Kenya, where the proportion of bacteriological confirmed cases were higher among older children than others [195]. However, our study indicates that even though the use of Xpert MTB/RIF was effective among older children, it contributed minimally to the overall TB diagnosis in the paediatric population.

Our findings also suggested that in addition to the age of the child contacts, the yield of Xpert MTB/RIF depends on the stage of TB in child contacts. The yield of Xpert MTB/RIF increased in diagnosing TB among young child contacts at the referral hospital compared to those who were diagnosed at the district hospital or PHCs. This can be explained by the fact that children at the referral hospital are inpatients, mostly at the advanced stage of TB disease. However, patients at the district hospital are outpatients who are likely child contacts with symptoms suggestive of TB identified through active screening and referred from PHCs to the district hospital for further investigation. This is assertion is confirmed by findings from others studies, which found that the sensitivity of Xpert MTB/RIF was lower among child contacts who are outpatients identified through active screening [105,196] than among inpatients or outpatients children whose parents/caregivers seek care themselves (passively detected) [55,58–61]. Our study findings are consistent with the results from a quantitative study conducted in Kigali, Rwanda, which showed that Xpert MTB/RIF assay did not improve the diagnosis of PTB among child contacts [165]. Therefore, the diagnosis of TB in symptomatic child contacts should not only depend on Xpert MTB/RIF but has shown its effectiveness in increasing the diagnosis of TB among child contacts in combination with a clinical evaluation, especially at the primary health care level [105,197].

In spite of the above strengths of Xpert MTB/RIF, our study also identified weaknesses in the use and implementation of Xpert MTB/RIF. Although some of the weaknesses of Xpert MTB/RIF are directly related to the actual test – i.e. low sensitivity to detect TB among child contacts – other weaknesses are related to the human resources capacity. Those weaknesses were the inability of PHC providers to presume TB in a child contact, the inability of some district or referral hospital health care providers to collect quality GL samples and laboratory staff to perform Xpert MTB/RIF test in samples other than sputum. Another weakness identified was the health care providers' lack of information on the availability of Xpert MTB/RIF test and its indications. All the identified weaknesses can reduce the yield of the Xpert MTB/RIF test by contributing to its underutilization or lowering its sensitivity by the use of poor quality samples. For instance, it is known that the sensitivity of a test depends on the quality of the sample used [63,197]. Most of those weaknesses have been reported by a study conducted in Mongolia and India [62,63]. Likely, the weaknesses identified by our study are easily manageable and could be addressed through the training of health care providers, staff awareness on the availability and indication of Xpert MTB/RIF, training of health care providers on performing GL technique. Also, the training of laboratory staff on the use of Xpert MTB/RIF in samples other than sputum and make the standard of procedure of using Xpert MTB/RIF in samples other than sputum available could address some identified weaknesses.

Our study also identified some challenges in the implementation and use of Xpert MTB/RIF which may limit its impact in diagnosing TB in child contacts. A major challenge herein reported was related to organisation of the diagnosis process of TB and the distribution of Xpert MTB/RIF at the different levels of health care. Indeed, the level of a health care (primary, secondary or referral) determines the extent of techniques or services that its health care providers can perform [198]. We found guideline restrictions of performing the GL at the PHC, where the majority of child contacts with symptoms suggestive of TB are managed. Therefore, most of the young child contacts (0-5 years old) with symptoms suggestive of TB and unable to expectorate were referred to the district hospitals. These referrals causes significant delay in TB diagnosis or Isoniazid preventive therapy initiation. In some instances, child contacts may be lost due to lack of feedback between the PHC and higher level of care or because children did not

reach the health facilities where they were referred because of financial constraints – parents/caregivers had to pay fare to the district hospitals, consultation and admission fees as the child had to be admitted for early morning collection of sample. These referral challenges lead to missed opportunities to young child contacts with a higher risk of contracting TB than old ones, thus the increase of child contacts' TB burden. There is a need for the NTP to advocate for the inclusion of GL practice at PHC level at national policy level.

Our study also unveiled the non-implementation of Xpert MTB/RIF at the PHC due to a small number of Xpert MTB/RIF machines in the country and the existence of an informal structure of sample transportation from PHC to district hospital. Each PHC uses its own resources, either a motorbike or public transport for transporting samples to the district hospital and the frequency of the sample transfer is not predetermined. There is a delay in handling samples at the district hospital as it receives samples from all its PHC networks, causing delays of results cascading to delays in initiation of TB treatment and IPT. Additionally, the non-implementation of Xpert MTB/RIF to the PHC increases the need for multiple visits to the hospital for parents/caregivers to complete their children screening, thus causing delays in or non-initiation of TB treatment and IPT [46,148]. There is a need for guidelines stipulating how samples should be channelled, and the frequency of reference per week. There is also the need to increase the number of Xpert MTB/RIF in circulation to reduce the backlog of TB samples to be tested.

Our findings unveiled some challenges related to the non-compliance to the policy or guideline currently used in Rwanda. We identified challenges related to the limited demand for the Xpert MTB/RIF test by health care providers and non-existence of a clear guideline for using the GL method. This led to Xpert MTB/RIF being under utilised for TB confirmation in children. There is a need to raise awareness on the appropriate use of Xpert MTB/RIF through training of health care providers and making the guideline on the indication of GL available. The availability of policies and guidelines as well as training opportunities by an organisation increases the uptake of new technologies [199].

A limitation of this study was that it was only conducted in Kigali, Rwanda. Thus, the findings may not apparently represent the situation in the whole country. However, considering that the management of childhood TB in the whole country is under the NTP and the policies governing the management of TB in children are the same countrywide, we assume that our findings may be applicable to the rest of the country. Additionally, Kigali has two parts: an urban part and a rural part. So, it may reflect the reality of the rest of the country regarding the implementation of Xpert MTB/RIF.

Conclusion

Xpert MTB/RIF has contributed a little to the diagnosis of TB in child contacts in Kigali. Its contribution, although minimal, has mainly been observed in older children (5-14 years). The minimal contribution of Xpert MTB/RIF was also observed in young child contacts (0-5 years) at referral hospitals, where they were likely to be inpatients with an advanced stage of TB disease. However, Xpert MTB/RIF did not contribute to the diagnostic of young child contacts (0-5 years old) who attended district hospital, likely to be child contacts with early TB disease. In addition to its low sensitivity in diagnosing TB in child contacts, the implementation weaknesses and challenges have contributed to lowering its impact. There is a need to integrate the GL technique and strengthen clinical diagnosis and management of child contacts at PHC through the training of health care providers and community health workers at the PHC level to improve TB diagnosis among child contacts.

Chapter 4

Paper II

Assessment of the Isoniazid Preventive TherapyUptake and Associated Characteristics: a cross-sectional study

Birungi FM, Graham S, Uwimana J, Van Wyk B. Assessment of the Isoniazid Preventive Therapy Uptake and Associated Characteristics : A Cross-Sectional Study. Journal of Tuberculosis Research and Treatment. 2018;2018:1–9.doi.org/10.1155/2018/8690714

Abstract

Objective: To assess the uptake of isoniazid preventive therapy (IPT) by eligible children in Kigali, Rwanda, and associated individual, households and health care systems.

Methods: A cross-sectional study was conducted among child contacts of index cases having sputum smear-positive Pulmonary Tuberculosis. Data were collected from 13 selected primary health centres. Descriptive statistics were used to generate frequency tables and figures. Logistic regression models were performed to determine characteristics associated with IPT uptake.

Results: Of 270 children (under 15 years old), who were household contacts of 136 index cases, 94 (35%) children were less than 5 years old and eligible for IPT; and 84 (89%, 95% CI 81-94) were initiated on IPT. The reasons for not initiating IPT in the remaining 10 children were parents/caregivers' lack of information on the need for IPT, refusal to give IPT to their children, and poor quality services offered at health centres. Factors associated with no uptake of IPT included children being more than 3 years old, unfriendly health care providers, HIV infected index cases and the index case not being the child's parent.

Conclusion: The policy of the National Tuberculosis Programme on IPT delivery was effectively implemented. Future interventions should find strategies to manage factors associated with IPT uptake.

Introduction

In 2015, the World Health Organisation (WHO) estimates showed that 10% of the 9 million tuberculosis (TB) incident cases occurred in children, which resulted in 210,000 TB-related deaths including 170,000 in HIV-negative children [97]. Children exposed to index cases with TB, particularly sputum smear-positive PTB, are at risk of infection and, when infected, infants and young children (< 5 years old) are at high risk of developing the disease [20,111]**.** WHO recommends routine screening of child contacts in resource-limited settings through a symptom-based screening approach that can be implemented in the community and provision of preventive therapy for at-risk contacts after excluding TB [12]. The most widely recommended regimen is isoniazid preventive therapy (IPT) that is provided as a daily dose for at least 6 months. Notwithstanding the potential benefits of contact screening for active case detection and initiation of IPT, these activities are rarely implemented in TB endemic settings [76,106]. Furthermore, even when IPT is offered to eligible children, its uptake is often poor [79,146].

Rwanda is a TB endemic resource-limited country, which had an estimated 6.6 [95% IC:5.6-7.6] thousand new TB cases in 2015 [97]. According to the TB surveillance system, 5,763 TB cases, including 68.1% of new confirmed bacteriological pulmonary TB cases and 85.3% of sputum smear-positive PTB cases were reported in the period between 2015 and 2016. Children under 15 years old represented 5.3% of all TB cases reported [95]. The active contact screening and IPT are recommended by the NTP in Rwanda, but TB case detection strategy is limited to passive screening. Although guidelines for IPT have been in existence since 2005, their implementation has not been assessed. For a few years, particular attention has been given to TB in children by Rwanda's NTP since TB treatment is recognized as an opportunity that prevents and addresses an important cause of child mortality [99,100]. The NTP strategy has promoted the uptake and adherence of IPT as one of the 30 performance indicators since 2009. This paper reports about the uptake of IPT by eligible children in Kigali, the capital City of Rwanda, and evaluates the associated individual, households' and health care systems' characteristics.

Methodology

Site selection

A cross-sectional study was conducted at 13PHC providing TB diagnostic and treatment services in Kigali. Kigali, the capital city of Rwanda, reports the highest prevalence of TB in Rwanda and around 30% of Rwanda's total PTB cases [95]. Thus, Kigali was selected as case study site. There are 35 PHC in Kigali whence 23 PHC provide TB diagnostic and treatment services and represent entry points for TB cases. The criterion used to select 13 PHC from the 23 PHC providing TB diagnostic and treatment services was a record of at least 10 sputum smear-positive PTB cases reported between January and June 2015. Among the 13 PHC selected for this study, nine (69%) were public-funded and four were faith-based (public and private funded). Of the 13 PHC, three had two staff members, and ten (77%) had one staff member, working in TB services. All the staff members were trained in TB management and provided counseling to parents/caregivers on IPT before their children started the regimen. In Rwanda, medication for TB is provided free-of-charge. Moreover, all TB index cases are offered the opportunity to choose the nearest health care facility or community health worker they wish to receive TB treatment or IPT.

Study population

This study was conducted among household contacts of index cases with sputum smear-positive PTB in 13 selected PHC from 1st August 2015 to 29th February 2016. The criteria for selecting an index case of any gender were: having at least one child under the age of 5 years, not belonging to a household with a previously selected index case and providing proof of living in Kigali during the period of study. Identified index cases were requested, either through phone conversations or trained CHW, to bring their children to the nearest PHC on a specific day that coincided with data enumerators' visits to the PHC. In case the index cases were not parents/caregivers of the children needed at the PHC, they were requested to inform those children's parents/caregivers to do so.

Eligible child contacts were below 5 years old and shared the same household with a selected index case within 3 months prior to the diagnosis of the latter. The children were enrolled after the signing of written informed consent by parents or primary caregivers. Ineligible child

contacts included those born after the index cases were diagnosed and initiated on TB treatment, child contacts on TB treatment as well as those that were not living in the same household with the index cases before the diagnosis. Moreover, child contacts above 5 years old, including those infected with HIV, were also excluded in accordance with Rwanda's NTP policy.

Data collection and management

Data were collected from two sources, from patients' records at the PHC facilities and from parents/caregivers of eligible child contacts interviewed by trained enumerators using a structured questionnaire. The questionnaire was developed, pre-tested during a pilot study in two selected sites and modified for later use in data collection. Twelve selected data enumerators were trained to conduct interviews with parents/caregivers of selected child contacts. Additionally, 20 CHW were trained to identify and enumerate all eligible children in the households as well as to explain the study to parents/caregivers and to sensitize them to take child contacts to the nearest PHC for clinical evaluation and data collection. Furthermore, by screening each child and interviewing each parent/caregiver, data enumerators ensured that the child contact was eligible; otherwise he/she was excluded even if he/she has been declared eligible by CHW.

The uptake of IPT is defined as the proportion of children eligible to receive IPT according to the WHO recommendation [69]. The screenings conducted during this study identified all children as eligible for IPT according to the WHO recommendation [69]. To assess the uptake of IPT, every parent/caregiver of an eligible child was asked whether the child was initiated on the IPT or not. The IPT register at the PHC assisted to verify the information given by parents/caregivers. The socio-demographic characteristics and medical history of index cases, such as the result of smear microscopy, HIV status, residential address and telephone number were recorded. The data collected were validated by the index cases, parents or caregivers of the selected children once they were identified to ensure their accuracy. All children underwent a history, physical and CXR examination. Anteroposterior and lateral CXR were also performed on all children; and they were read by two independent experienced general practitioners, trained in interpreting CXR and blinded to the clinical details of participants; an experienced radiologist verified all CXR to rule out any discordance. The components of all reports were agreed on

before a final diagnosis was determined. Symptomatic children are treated with antibiotics for seven days as recommended by the current TB diagnostic algorithm in the country. Child contacts with persistent TB-related symptoms or abnormal CXR were referred to the District Hospital for further tests including smear microscopy, Xpert MTB/RIF assay and solid culture using sputum collected through gastric lavage following the standard procedure [185] in order to exclude TB disease.

The interview with eligible children's parents/caregivers helped identify the socio-demographic and economic characteristics of the index cases, their households, and knowledge on how to prevent TB in child contacts. A parent/caregiver was considered knowledgeable about, first, IPT prevention if he/she knew that administering INH for 6 months would protect the child contacts against TB; second, prevention of child contacts from contracting TB if he/she knew three of the following pieces of information: using a mask when breastfeeding, avoiding to kiss him/her, avoiding to sleep in the same room or bed with him/her, opening windows and doors for good ventilation, and using hand protection when coughing. The interview with eligible children's parents/caregivers also helped determine the characteristics of the health care facility such as quality of services provided and the attitude of health providers towards the patients. Those characteristics were assessed by asking parents/caregivers the level of satisfaction with the quality of services offered at the PHC and whether the health care service providers were friendly.

Data Analysis

The data collected were double-entered into a Microsoft Excel worksheet and exported to Stata Software for statistical analysis after checking their consistency. The data were analyzed using descriptive and multivariate statistics. Continuous variables were dichotomized using the median as the cut-off. Categorical variables were described using frequency tables and proportionate methods. Univariate and multivariate logistic regression was performed to determine characteristics associated with IPT uptake. Where appropriate, the Chi-square test or Fisher's exact test were performed to assess the association between two variables. Variables with a p-value < 0.2 in univariate analysis were included in the logistical regression model using backward stepwise method. The final model included those factors that retained statistical

significance. The odd ratios (OR) and adjusted OR (aOR) along with its 95% confidence interval were calculated using Stata Software (version 13). The associations were declared significant if p-value <0.05.

Ethical approval

The Biomedical Research Ethics Committee of the University of the Western Cape and the Ethics Review Board of the University of Rwanda, College of Medicine and Health Sciences approved the study protocol. The permission was obtained from Rwanda NTP to collect data from the eligible PHC.

Results

Figure 4.1 shows the flow of recruitment of child contacts with 136 (39%) of 346 sputum smear-positive PTB index cases diagnosed and treated at 13 PHC in Kigali during the period of 7months of the study. The index cases had at least one child contact aged between 0 and 14 years. Of the 136 index cases, 72 (53%) had at least a child contact who met the inclusion criteria. Of 94 (35%) children from 72 index cases who were eligible, 84 (89%) had started IPT.

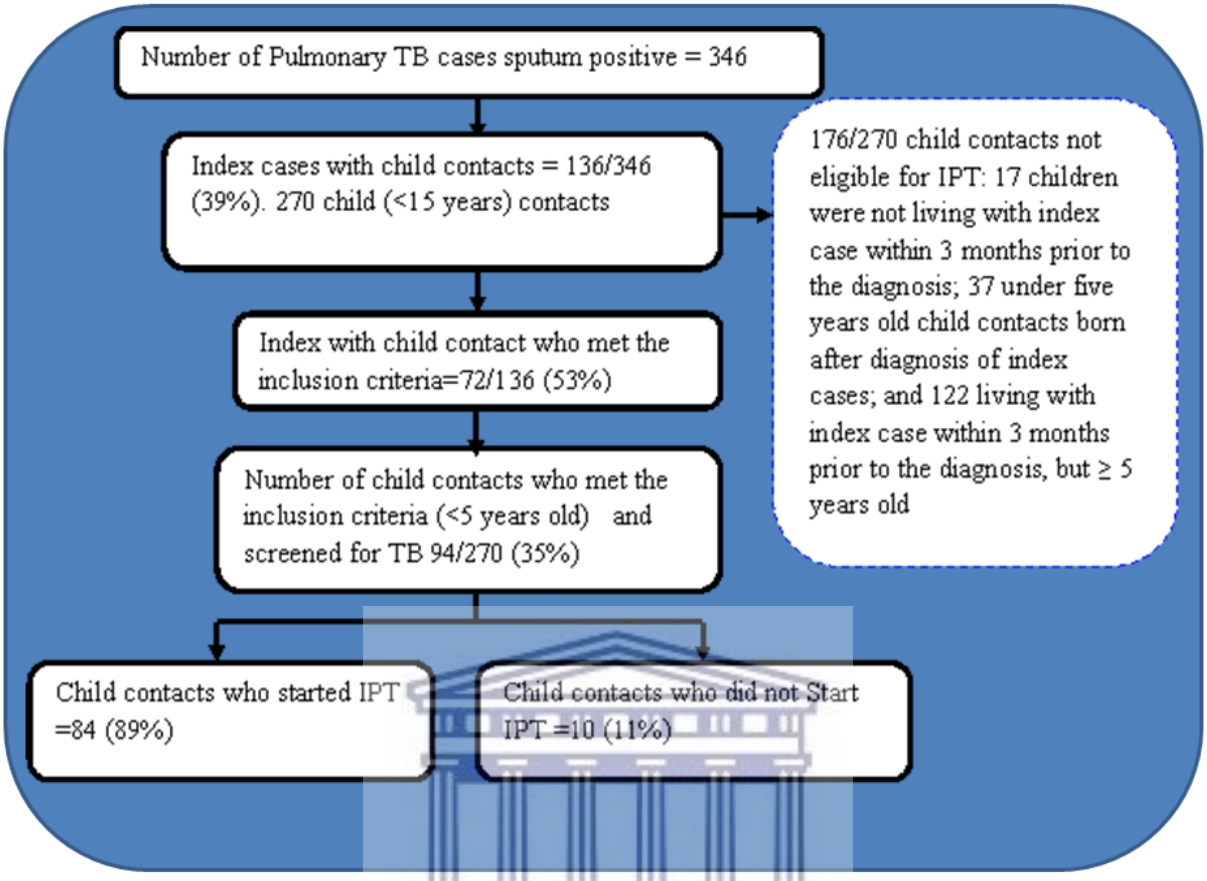


Figure 4. 1: Flow of recruitment of child contacts.

Tables 4.1, 4.2 and 4.3 show the characteristics of the eligible index cases, their households, and child contacts by IPT uptake, respectively. The results show no significant difference between children who started IPT and those who did not with regard to the characteristics of index cases (Table 4.1) and health care facilities (that are unfriendly versus friendly and satisfaction level of parents/caregivers on the quality of services offered). There were significant differences between children who started IPT and those who did not with regard to the sex of the head of the household (13/62 vs. 5/10, p=0.049) (Table 4.2) and the age of the child contact (≤3 vs. >3 years, p=0.007) (Table 4.3). Children living in households headed by female were more likely not to be initiated on IPT than those living in households headed by a male. Also, children aged > 3 years old were more likely not to be initiated on IPT than those ≤ 3 years old. Tuberculosis-related symptoms such as coughing, fever, and weight loss were reported by 25% (23/94) of child

contacts, and those cases reported responded to generic antibiotics recommended by the current TB diagnostic algorithm in the country. The screened children presented neither an abnormal CXR nor a diagnosed TB disease [69,184]**.** The majority of parents/caregivers of child contacts (66/72, 92%) had the knowledge of at least one method on how to prevent transmission of TB to children and 32% (23/72) had knowledge of IPT prevention (Table 4.2).

Table 4. 1: Characteristics of the Index Cases of the Child contacts by uptake of IPT

Characteristics	**Index cases (N=72) (%)**	**Index case whose children took IPT (N=62)(%)**	**Index case whose children did not take IPT (N=10)(%)**	**P-value**
Age group				0.716
=<35 years old	39 (54)	34 (55)	5(50)	
> 35 years old	33 (46)	28 (45)	5(50)	
Sex, female	33 (46)	28 (45)	5 (50)	0.776
Residence of the index case				0.641
Nyarugenge	12 (17)	11 (18)	1 (10)	
Kicukiro	20 (28)	16 (26)	4 (40)	
Gasabo	40 (55)	35 (56)	5 (50)	
Type of health facility used by index cases				0.262
Public	51 (71)	42 (68)	9 (90)	
Faith-based	21 (29)	20 (32)	1 (10)	
Marital Status				0.243
Never married	11 (15.5)	8 (13)	3 (30)	
Married	50 (69)	45 (73)	5 (50)	
Separated	11 (15.5)	9 (14)	2 (20)	
Index case Head of household	29 (40)	25 (40)	4 (40)	0.985
Index case tested for HIV	61 (85)	52(84)	9(90)	0.617
Result of HIV test Positive	18/61 (30)	13/52 (25)	5/9 (56)	0.063

IPT= Isoniazid Preventive Therapy; HIV = Human Immunodeficiency Virus

Table 4. 2: Characteristics of the household of Child contacts by uptake of IPT

Characteristics	Total (N=72) (%)	Child contact started IPT (N=62) (%)	Child contact did not start IPT (N=10) (%)	P-value
Head of household				
Age group				0.501
=<37 years old	38 (53)	34 (55)	4 (40)	
> 37 years old	34 (47)	28 (45)	6 (60)	
Sex, female	18 (25)	13 (21)	5 (50)	**0.049**
Household monthly income				0.149
=< 50.000 Rwandan Franc	47 (65)	38 (61)	9 (90)	
> 50.000 Rwandan Franc	25 (35)	24 (39)	1(10)	
Marital Status				0.967
Never married	7 (10)	6 (10)	1 (10)	
Married	56 (78)	48 (77)	8 (80)	
Separated	9 (12)	8 (13)	1 (10)	
Highest education level completed				0.625
Never attended school	9 (12)	7 (11)	2 (20)	
Primary school	43 (60)	38 (61)	5 (50)	
Secondary school and plus	20 (28)	17 (28)	3 (30)	
Household				
Number of people living in the house at the time of the diagnosis of the index case				
One person	19 (26)	16 (26)	3 (30)	0.717
Two persons or more	53 (74)	46 (74)	7 (70)	
Parents/caregivers had knowledge of prevention of transmission of TB[a]	66 (92)	58 (94)	8 (80)	0.192
Parents/caregivers have knowledge on the role of IPT[b]	23 (32)	22 (35)	1 (10)	0.153

IPT= Isoniazid preventive therapy; TB = Tuberculosis; [a] aware about using a mask when breastfeeding, avoiding sleeping in the same room or bed with child contacts, opening windows and doors for improved ventilation, practicing hygiene while coughing. [b]Knowledgeable about the administration of INH for 6 months to protect child contacts against TB.

Table 4. 3: Characteristics of Child contacts eligible for IPT by IPT uptake

Characteristics	Under five years old child contacts (N=94) (%)	Child contacts who started IPT (N=84) (%)	Child contacts who did not start IPT (N=10) (%)	P-value
Age group				
=< 3 Years	66 (70)	63 (75)	3 (30)	**0.007**
>3 Years	28 (30)	21 (25)	7 (70)	
Sex child contact				0.504
Female	43 (46)	37 (44)	6 (60)	
BCG_scar				
Yes	90 (96)	80 (95)	10 (100)	1.000
Children tested for HIV	47 (50)	39 (46)	8 (80)	0.091
HIV test Result Positive	2 (4)	2 (5)	0 (0.0)	0.051
Relationship to the Index case				
Child	70 (75)	65 (77)	5 (50)	0.060
Others	24 (25)	19 (23)	5 (50)	
Had TB-related symptom during the screening	23 (24)	19 (23)	4 (40)/	0.252
Share the same bedroom with index cases	48 (51)	42 (50)	6 (49)	1.000
Time spend with index cases				
>= 8 hours	75 (80)	66 (79)	9 (90)	0.681

BCG = Bacille Calmette-Guerin; IPT= Isoniazid Preventive Therapy, TB = Tuberculosis; HIV = Human Immunodeficiency Virus; [a] TB-related symptom = to have one of those symptoms (a cough, fever and weight loss)

All the 94 eligible child contacts were screened for TB by PHC providers whence 84 (89%, 95% CI 81- 94) were initiated on IPT for 6 months as per the national and WHO guidelines [69,184]. The reasons given by parents/caregivers for not initiating child contacts on IPT were lack of awareness of the need to do so; (5/10 or 50%); failure to initiate IPT (4 or 40%); and poor health care service experienced at the PHC (10%).

In univariate analysis, the age of child contacts, sex of the household head and relationship between health care providers and parents/caregivers were associated with the uptake of IPT (Table 4.4). Child contacts over 3 years old were more likely not to be initiated on IPT than those who were below 3 years old (OR=7, 95%CI: 1.65-29; p<0.008). Children living in the

households headed by a female were more likely not to be initiated on IPT than those living in the households headed by a male (OR=4.6, 95%CI: 1.18-17.9; p<0.028). Child contact whose parents/caregivers did not find friendly health care providers at the PHC were also more likely not to be initiated on IPT than those whose parents/caregivers did (OR=10, 95%CI: 1.26-83; p<0.029).

In multivariate analysis, the sex of household head had no significance. The final explanatory variables of no uptake of IPT were age group of child contacts (=< 3years vs. >3 years), HIV status of child contacts (HIV positive vs. HIV negative), relationship between child contacts and index cases (child vs. others), HIV status of index case (HIV-positive vs. HIV-negative), household income (Income <50.000 Rwandan Franc vs. >= 50.000 Rwandan Franc), and relationship between health care providers and parents/caregivers (Friendly vs. Unfriendly). After adjusting the variables, the age of child contacts and relationship between health care providers and parents/caregivers remained associated with the uptake of IPT. Child contacts above 3 years older were more likely not to be initiated on IPT than those less than 3 years old (aOR=29, 95%CI: 2.17-400; p<0.011). Moreover, the child contacts whose parents/caregivers found health care providers unfriendly were also more likely not to be initiated on IPT than those whose parents/caregivers found them friendly (aOR=19, 95%CI: 2.51-140; p<0.017). The HIV status of index cases and the relationship between child contacts and index cases were also associated with no uptake of IPT in multivariate analysis. Child contacts living with HIV-positive index cases were more likely not to be initiated on IPT than those living with HIV-negative ones (aOR=8.1, 95% CI 2.53-537; p<0.038). Furthermore, the child contacts who were not children of index cases were more likely not to be initiated on IPT than those who were index cases' children (aOR=59, 95%CI 2.74-127; p<0.009).

Table 4. 4: Risk factors for non uptake of IPT

Factors	OR (95%CI)	P-value	aOR (95% CI)	P-value
Child contacts				
>3 Years	7.0 (1.65-29)	0.008	29 (2.17-400)	0.011
HIV positive	5.0 (1.0-25)	0.050	10 (0.61-174)	0.105
Not child of the index case	3.4 (0.89-13)	0.072	59 (2.74-127)	0.009
Index cases				
HIV-positive	4.0 (0.97-16.77)	0.054	8.1 (2.53-537)	0.038
Household factors				
Sex of the head of the household	4.6 (1.18-17.9)	0.028	-	
Income <50.000 Rwandan Franc	0.1 (0.22-1.57)	0.123	0.1 (0.01-1.01)	0.050
Heath facility factors				
Provider not friendly	10 (1.26-83)	0.029	19 (2.514-140)	0.017

IPT= Isoniazid Preventive Therapy; HIV = Human Immunodeficiency Virus; CI= confidence interval; OR= odds ratio; aOR= adjusted OR

Discussion

The primary aim of this study was to assess the uptake of IPT by child contacts and associated factors in order to inform the NTP on its implementation. Despite the diversity methodology designs, the IPT uptake established in this study (89%) was found to be higher than 6% [139], 18.7% [140], 26.8% [141] and 33% [35] and 64.3% [200] reported in Malawi, Timor-Leste, South Africa, South India, and Ethiopia, respectively. In contrast, recent studies conducted in the Gambia [201] and Benin [202] have reported an 89% and 99% of IPT uptake, which is similar to and higher than this study's findings, respectively. The integration of IPT into the programmatic delivery of health care might explain the high uptake reported in this study as well as in study findings reported in the Gambia and Benin. This is in contrast with earlier studies that were conducted in a health care facility environment [140,141]. Rwanda's NTP strategy adopts the visits of the index cases' households by health care providers at the beginning of sputum-smear PTB treatment. These visits help screen child contacts and initiate them on IPT. Our high IPT

uptake finding corroborates the results published in the 2013-2014 and 2015-2016 annual reports of Rwanda's NTP revealing an uptake of 85% and 78%, respectively. However, these reports do not provide information on the actual number of eligible contacts who had access to IPT in the community.

The WHO provided the first estimates of preventive therapy coverage for eligible children under the age of 5 years in 2016 [97]. The estimates showed that only 5.6% of an estimated 440,000 child contacts received preventive therapy in 2015 in the African region. However, Rwanda was among a few countries in Africa that provided data to the WHO from routine surveillance of preventive therapy for young child contacts [97]. Therefore, the high uptake in our study may reflect the particular attention being given by Rwanda NTP to TB in children in accordance with the Rwanda government's priority intervention aimed at preventing and addressing the most important causes of child mortality [99,100]. Additionally, the goal of Rwanda NTP strategies is to strengthen more than 30 indicators outlined in the PBF since 2009. The outlined indicators include "number of children eligible for IPT who received it" and "number of children aged below 5 who completed IPT". The funding of health care services according to the PBF is based on the performance of medical facilities in enhancing the quantity and quality of preventive and curative treatment to the people [88]. Hence, the PBF has improved the quantity and quality of health care in many countries [87,203,204]. Our study showed that most parents/caregivers of child contacts had some general knowledge on how to prevent TB in children. That level of knowledge was higher than the one reported in studies conducted elsewhere [205,206]. Information, Education, and Communication sessions are organized twice a week at health care facilities by service providers, at the community level by the CHW and at local politico-administrative authorities level as well as through media, to inform the population about TB. Other studies have shown that low-level knowledge on TB could negatively affect the health-seekingbehaviour of the people [206,207]. Contrasting findings have been reported in a study conducted in Malawi, where only 8% of parents with sputum smear-positive TB took their children to a medical clinic for screening despite having clear information on the need to do so [146].

The geographical accessibility can also explain the high uptake of IPT in Rwanda. Across the country, there has been an improvement in access to health care centres. Countrywide, the average time to access the nearest health care centre is less than 1 hour [208]. Transport cost was not mentioned as a limiting factor by any parent/caregiver whose child was not initiated on IPT in our study as it was the case in the study conducted in Malawi [46]. Furthermore, a study carried out in Bangkok, Thailand by Tornee et al [147] shows that the short distance from home to the nearest medical clinic was associated with adherence of the households' contact to screening.

In the univariate analysis, the significance of the sex of household heads was lost when it was adjusted for other variables. This finding suggests that the sex of index cases was a confounder variable in this study. Therefore, additional studies are needed to investigate the role of gender in the decision to initiate IPT.

In multivariate analysis, our study established that the child contacts who were not children of index cases were more likely not to be initiated on IPT than those who were their children. This finding corroborates a study conducted in Timor-Leste [140] and a qualitative study in Bangkok, Thailand [147]. Both studies reported lack of screening of child contacts who were not children of index cases. The approach is slightly different in Rwanda, whereby the visits of the household of the index cases with sputum smear-positive PTB by health care providers helps in screening child contacts and initiating them on IPT. Thus, child contacts who are not children of the index cases have a high possibility of being screened even though the initiation of IPT amongst these children may be low. When an index case is not the biological parent of a child contact, the latter may choose to be visited by a health care provider in the absence of the former. Often, health care providers inform the index cases about the intended home visit so that children can be screened but not necessarily initiate on IPT. This is because the index cases may not inform the parents or caregivers of the children the need for initiating their children on IPT. This could explain the 100% screening of eligible child contacts in this study whence only 89% were initiated on IPT. The parents/caregivers of 50% of child contacts who were not initiated on IPT reported their lack of information about its usefulness.

Our study also established that child contacts above 3 years old were more likely not to be initiated on IPT than those aged below 3. These findings can be explained by the fact that parents/caregivers protect their younger children from contracting TB more than their older children. Similar findings were reported in a qualitative study conducted in Bangkok, Thailand, by Tornee et al [147], which showed that parents/caregivers worry that their younger children might get TB infection and so take them to health care facilities for screening.

The parents/caregivers who found unfriendly health care providers at the PHC were also more likely not to initiate their children on IPT than those who found them friendly. Child contacts living with HIV-positive index cases were less likely to be initiated on IPT than those living with HIV-negative index cases. Those two factors may be correlated. A study demonstrated that interactions and negative experience of people seeking treatment in government health care facilities contribute to a reduction in subsequent medical visits or follow-ups [209], which is mostly observed among the HIV-positive population.

Besides the negative experience from unfriendly health care providers, the HIV-positive people have to cope with social stigma [210]. A study revealed that women, who often take children to health care facilities, experience stigma-related problems more than men [211]. In our study, 71% index cases were treated at public PHC and 56% of them whose children did not start the IPT were HIV infected. This suggests that negative experience in government health care facilities and social stigma among TB-HIV co-infected persons have a negative impact on the uptake of IPT among child contacts. This finding is a cause of concern in Rwanda since the health care-seeking behaviour of HIV-positive parents/caregivers influences TB screening and management in children.

The study has some limitations. First, the research was conducted in Kigali; thus, the findings cannot be generalized to the whole country, especially remote rural areas where health care-seeking behaviour may be different. Second, the sample size was small to enable comparative analyses that may have limited our statistical detection of small differences in the IPT uptake.

Conclusion

Findings from our study reveal that the NTP policy on the provision of IPT has been effectively implemented in Rwanda under the set programmatic conditions. Despite differences in methods of study, the percent of IPT uptake revealed in this study is higher than that reported in Malawi, Timor-Leste, South Africa, South India and Ethiopia, and similar to and lower than the one reported in the Gambia and Benin, respectively. Special attention should be given to child contacts who are more than 3 years old, child contacts who are not children of index cases, and child contacts who are children of HIV infected persons in order to identify the challenges experienced in initiating the IPT. Future interventions should find strategies to (1) fight against social stigma, especially in TB co-infected patients and (2) eradicate the unfriendly attitude of the health care providers towards all patients in general and TB co-infected patients in particular.

Chapter 5

Paper III

Adherence to isoniazid preventive therapy among child contacts in Rwanda: A mixed methods study.

Francine Mwayuma Birungi, Stephen Michael Graham, Jeannine Uwimana, Angèle Musabimana , Brian van Wyk. Published by Plos one. DOI: 10.6084/m9.figshare. 6395984.

Abstract

Background: The World Health Organization recommends isoniazid preventive therapy (IPT) for six months for child contacts without tuberculosis (TB), who are exposed to an adult with active TB. The effectiveness of IPT depends on 80% or greater adherence to medication. In the current study, we assessed IPT adherence and explored barriers to and facilitators of adherence among eligible child contacts in Kigali, Rwanda.

Methods: A mixed method study design was used to prospectively assess adherence to IPT among eligible child contacts and its associated factors through a quantitative, observational cohort study, and to explore barriers to and facilitators of adherence to IPT through a descriptive qualitative study.

Results: Of the 84 child contacts who started IPT, 74 (88%) had complete adherence and ten (12%) had incomplete adherence. There were no factors (individual characteristics of index cases, households and or health facility characteristics) found to be significantly associated with IPT adherence in the bivariate and multivariate analysis. In the qualitative analysis, we identified factors relating to parents/caregivers, disease, household and health care providers as major themes determining IPT adherence.

Conclusion: There was a high rate of IPT completion in this cohort of eligible child contacts living in Kigali. However, structural factors (poverty and relocation) were found to be the main barriers to IPT adherence that could be addressed by health care providers.

Introduction

Young children exposed to an adult or older child with tuberculosis (TB), referred to as an index case [1], are at high risk of infection with *Mycobacterium tuberculosis* [2,3]. Without any intervention, 5-10% of infected children will develop active TB within one year, and the risk is the highest among the youngest (<2 years old) or HIV-infected children [2,4]. Also, infants and young children are at high risk of developing severe disseminated forms of TB such as TB meningitis and miliary TB, and of TB-related mortality [5,6].

The World Health Organization (WHO) has for many years recommended isoniazid preventive therapy (IPT) for at least six months for young (<5 years) children who are exposed to a TB index case and who do not have active TB disease [12,13]. More recently, TB preventive treatment has received greater attention as a key element of the WHO's End TB strategy, which aims to reduce TB incidence by 90% by 2035 [30]. The most recent WHO guidelines for treatment of latent TB infection now include the consideration of older (≥5 years) child contacts without active TB for preventive therapy [128]. IPT has been proven effective in reducing TB incidence [8,9] and is included in the national TB programme (NTP) guidelines of many resource-limited countries [10]. However, IPT is not consistently offered to at-risk children, and when offered, is often unsupervised and characterised by poor uptake and adherence [72,79,130,215]. The effectiveness of IPT is dependent on 80% or greater adherence to medication [8]. Several studies from Indonesia, Ethiopia, Brazil and South Africa show inadequate adherence to IPT among child contacts [79,142–145]. Among these, the two studies conducted in Indonesia [143,144] revealed that access, social support and regime, caregivers and health care related factors were barriers and facilitators to IPT adherence. Studies from Indonesia and Brazil also reported that transport and medication costs were associated with incomplete adherence [143,145].

Rwanda established the IPT policy in 2005, and recently the NTP has focussed on TB in children because case detection and TB treatment are recognised as an opportunity to reduce child mortality [98,99]. Since 2009, the NTP strategy has been promoting the uptake and adherence to IPT as one of the 30 performance indicators. However, to date, no study has been conducted in

Rwanda to assess the IPT adherence among child contacts, and little is known about the factors associated with inadequate adherence.

In Rwanda community health workers (CHWs) are involved in the management of child contacts. Other local interventions include free TB care, increased number of primary health care centres (PHCs) and a community-based health insurance scheme to increase geographic and financial access to health care. In addition, performance-based financing has been implemented to motivate health care providers to improve service output and quality of care. The current study reports on IPT adherence and explores the facilitators and barriers to IPT adherence in Kigali, Rwanda.

Methods

Settings and participants

This study is part of a cross-sectional research project that was conducted in Kigali, the capital of Rwanda by a consortium of researchers from South Africa, Australia and Rwanda between 1 August 2015 and 29 February 2016 [165]. The study aimed to evaluate the diagnostic performance of the Xpert MTB/RIF assay in sputum collected by the gastric Lavage (GL) technique from symptomatic child contacts. Kigali has 35 primary health care centres (PHCs) that offer tuberculosis (TB) diagnosis and treatment services, which are also regarded as entry points for TB care. Thirteen of these PHCs were included in the main study based on them meeting the criterion of recording at least ten sputum smear-positive pulmonary TB (PTB) between January and June 2015.

Overall, 346 index cases of sputum smear-positive PTB were diagnosed and treated for the main project. Of these, 136 (39%) had at least one child contact who was younger than 15 years old at the time of the study. The 136 index cases had 270 child contacts. From the 136 index cases, 105 (77%) met the inclusion criteria of index cases and had 216 child contacts who met the inclusion criteria for the main project.

Of the 105 index cases, only those whose child contacts started IPT were recruited for the present prospective study that was conducted between August 2015 and August 2016. Eligible child contacts for the current study were younger than 5years old, who started IPT according to

the WHO recommendations [69]. They also shared the same households with the selected index cases in the three months before diagnosis of the latter. Only children who had their parental or primary caregivers' written consent were enrolled in the present study. Child contacts born after the index cases were diagnosed and had initiated TB treatment, child contacts on TB treatment, and those who were not living in the same households as the index cases before diagnosis were excluded from this study.

This study presents specific data elements that were derived from the main project. Those elements can influence IPT adherence which is under study in the current research. They include the characteristics of index cases, child contacts, households, health facility, TB screening results together with physical and chest X-ray (CXR) results [165].

Study design

In this study, we used a mixed research method design to prospectively assess IPT adherence and outcomes among child contacts through a quantitative, observational cohort study. Furthermore, we explored barriers to and facilitators of adherence to IPT through a descriptive qualitative study [173].

Data collection for the quantitative component

In August 2015, each TB focal person based at the selected PHC used a specific form, provided by researchers, to record each time the child came to collect a month's supply of IPT. A TB focal person, usually an experienced nurse working at the PHC, is responsible for coordinating and managing all activities such as providing TB treatment or IPT, contact screening, reporting, follow-up and supervision of TB patients and contacts.

Before data collection, TB focal persons from the selected PHC were trained on data collection procedures for two days. The training aimed at equipping them with skills to provide follow-up care (for example, monthly screening and transfer to the next level when a child has symptoms suggestive of TB) of children on IPT [S1 Appendix].

The researchers requested the parents/caregivers of child contacts who had been initiated on IPT to visit the PHC for clinical evaluation and receive the next month's supply of IPT each month until the end of the treatment. In this study, researchers measured "adherence" through a monthly

collection of isoniazid [16]. “Complete adherence” refers to the collection of six of the child’s monthly prescriptions, whereas “incomplete adherence" means that the child had received/collected less than six of his/her monthly prescriptions. IPT failure in this study is defined as a proportion of child contacts on IPT who developed TB during the monitoring period. To achieve this, the researchers monitored all eligible child contacts for symptoms suggestive of TB such as persistent one-week fever (>1 week), cough (>2 weeks), weight loss, night sweats for 12 months following the initial evaluation.

During the six months of monitoring, while receiving IPT, the TB focal person screened the child contacts for TB at each visit for the presence of symptoms suggestive of TB, using the IPT form [S1 Appendix]. For the second six months’ follow-up (post-IPT), the TB focal person evaluated the child contacts at 3 months and 6 months after finishing IPT. The researchers provided transport fees to all parents/caregivers who brought child contacts for screening during those two visits, which were not part of the routine clinical follow-up and monitoring. The post-IPT (at six months) visits were done to evaluate the impact of the IPT.

During the follow-up, the TB focal person referred any child contact showing symptoms suggestive of TB to the district hospital for further TB evaluation including smear microscopy, Xpert MTB/RIF assay and solid culture using sputum collected through gastric lavage. If a child contact was diagnosed TB positive, he/she was treated according to the national guidelines.

Data collection for the qualitative component

The researchers carried out in-depth interviews with 23 parents/caregivers of child contacts and ten health-care providers working in the TB service. Three focus group discussions (FGDs) were held with 24 CHWs who provided TB support in the community.

The researchers used purposive sampling to select parents/caregivers from the different catchment areas around the participating PHC to represent child contacts with complete adherence. They also used purposive sampling to select TB focal persons to represent different districts and types of PHCs (faith-based and public PHCs). The study included all available parents/caregivers with incomplete adherence.

Telephone numbers of parents/caregivers of child contacts available from the previous study database [165] and those of CHWs provided by TB focal persons, were used to inform and invite

participants about their selection in this study. If in agreement, they were requested to go to the nearest PHC at a time and date indicated by the researchers.

Fieldworkers conducted interviews with parents/caregivers whose children had complete adherence and the health facilities staff until the data saturation was achieved (i.e. until no new data emerged). However, existing themes could accommodate new findings [193]. Each FGD involved eight CHWs who were purposefully selected to represent the different districts and PHCs in line with Krueger methodology [216].

Three fieldworkers (female senior nurses) experienced in qualitative methodology were recruited to conduct interviews in the local language using interview guides designed for this specific study. Two days of debriefing sessions were held with the qualitative fieldworkers before the fieldwork started. In the debriefing sessions, the principal investigator discussed each question with them explaining the nature of the response that each one was meant to elicit. Discussions on how to probe for further explanations were also held.

Different interview guides were used for parents/caregivers and health-care providers (TB focal persons and CHWs). Parents/caregivers whose child contacts had incomplete adherence were interviewed to explore possible barriers related to IPT access. The questions were framed to avoid apportioning blame for non-collection of IPT for their children as recommended by the Ethics Review Board of the University of Rwanda, College of Medicine and Health Sciences.

Interview guides were pretested, and no further modification was needed. The pre-test was done using four parents/caregivers as participants (two whose child contacts had IPT complete adherence and two others whose child contacts had incomplete IPT adherence) and one TB focal person from a non-selected PHC based in Kigali. Parents/caregivers involved in the pre-test were identified by the TB focal person where the pre-test was done.

Participants signed a written informed consent form after reading it and after the researchers had read an introduction explaining the purpose and benefit of the study. The interview with health facility staff took place at their workplace (in the absence of their superior or any other staff), and the one with parents/caregivers took place at the PHC nearby their homes. These interviews

lasted between 45 minutes to one hour. None of the participants declined to participate in the interview.

Depending on the participants (parents/caregivers, TB focal persons or CHWs) answering the questions, the researchers investigated their experiences about providing or receiving IPT. They also investigated barriers to and facilitators of IPT adherence, and expectations and suggestions. Two experienced qualitative researchers conducted the FGD in the local language at the PHC proposed by the selected CHWs. These fieldworkers used a discussion guide during the FGD; which lasted between 1½ to 2 hours.

After obtaining their agreement, the fieldworkers, under the supervision of the principal investigator, audio-recorded all interviews and FGD. For quality control, at the end of each interview session, the fieldworkers summarised the salient points of the interviews with confirmation or adjustments from the participants when necessary. Hereafter, the fieldworkers fully transcribed interviews and FGDs in Kinyarwanda. Afterwards, the principal investigator checked the transcriptions and carried out necessary alterations before analysis. The transcripts were then translated into English by a qualified translator. The English transcripts were verified by a bilingual member of the research team to ensure that these were clear, and participants' views adequately reported.

Data analysis and management of the quantitative component

The researchers double-entered the quantitative data into a Microsoft Excel worksheet and exported these to STATA13 Software [187] for statistical analysis after checking their consistency. Continuous variables, such as the age of the child contacts or monthly household income, were categorised following epidemiological or economic constructs. Age of child contacts was dichotomised into two values (≤2 years and >2 years) as the literature suggests that infants who are ≤2 years old are more likely than those >2 years old to acquire TB [15,213]. The variable monthly household income was categorised in two values (Incomes ≤50.000 and 50.000 Rwandan Franc) following the poverty headcount ratio of Rwanda in 2018, which is $1.90 a day [217], equivalent to 50, 000 Rwandan Francs.

Researchers then analysed the data using descriptive and multivariate statistics, described categorical variables using frequency tables and proportionate methods. The researchers further

performed the univariate and multivariate logistic regressions to determine characteristics associated with IPT adherence. Where appropriate, the researchers performed the Chi-square test or Fisher's exact test to assess the association between two variables and included those variables with a p-value <0.2 in univariate analysis in the logistic regression model using backwards stepwise method.

The final model included the following variables: sex of the child, child contact' s HIV status, sleeping in the same room as index case, the index case's sex and HIV status, the income of the household, if the head of the household had knowledge of IPT protection and attitude of health providers towards patients. This further included calculating the odds ratios (OR) and adjusted OR along with its 95% confidence interval using STATA13 software [187]. In this case, the researchers declared the associations as significant if the p-value was <0.05.

Data analysis and management of the qualitative component

Two researchers analysed the qualitative data using thematic analysis as described by Braun et al. [174]. They repeatedly read the transcripts for full immersion and carried out an inductive thematic analysis using Atlas.ti-7 software [218]. Two researchers coded portions of the transcripts together. Discrepancies were discussed and resolved by consensus. Then they grouped codes into sub-themes and organised them under themes.

Ethical approval

The Biomedical Research Ethics Committee of the University of the Western Cape and the Ethics Review Board of the University of Rwanda, College of Medicine and Health Sciences approved the study protocol. Permission was obtained from Rwanda NTP to collect data from the eligible PHC. The researchers assured the participants' anonymity and confidentiality: for the focus group discussions. Numbers were allocated to each participant at the start of the discussions, and they were asked to refer to one another according to these. Regarding the in-depth interviews, during transcription, pseudonyms were used to ensure the identity of the participants remains anonymous. All records were stored in a password-protected folder in the computer, and the hard copies of the data (printed transcripts) were locked at the School of Public Health of the University of Rwanda, College of Medicine and Health Sciences (SPH-

CMHS-UR in a cupboard accessible only to the principal investigator who is the employee of the university of Rwanda. .

Results

Quantitative results

Among 270 below 15year-old child contacts recruited from 136 eligible sputum smear-positive PTB index cases (n=346) diagnosed and treated at 13 PHCs in Kigali, 94 (35%) child contacts from 72 index cases were below five years old and eligible for IPT. To evaluate adherence in this study, 84 (89%) who started the IPT were enrolled from 61 index cases. As shown in Fig 5.1, 74 (88%) completed six months of IPT, with only ten (12%) who did not complete the treatment. Fig 5.2 shows the number of months for which child contacts who were initiated into IPT failed to complete the 6 months treatment.

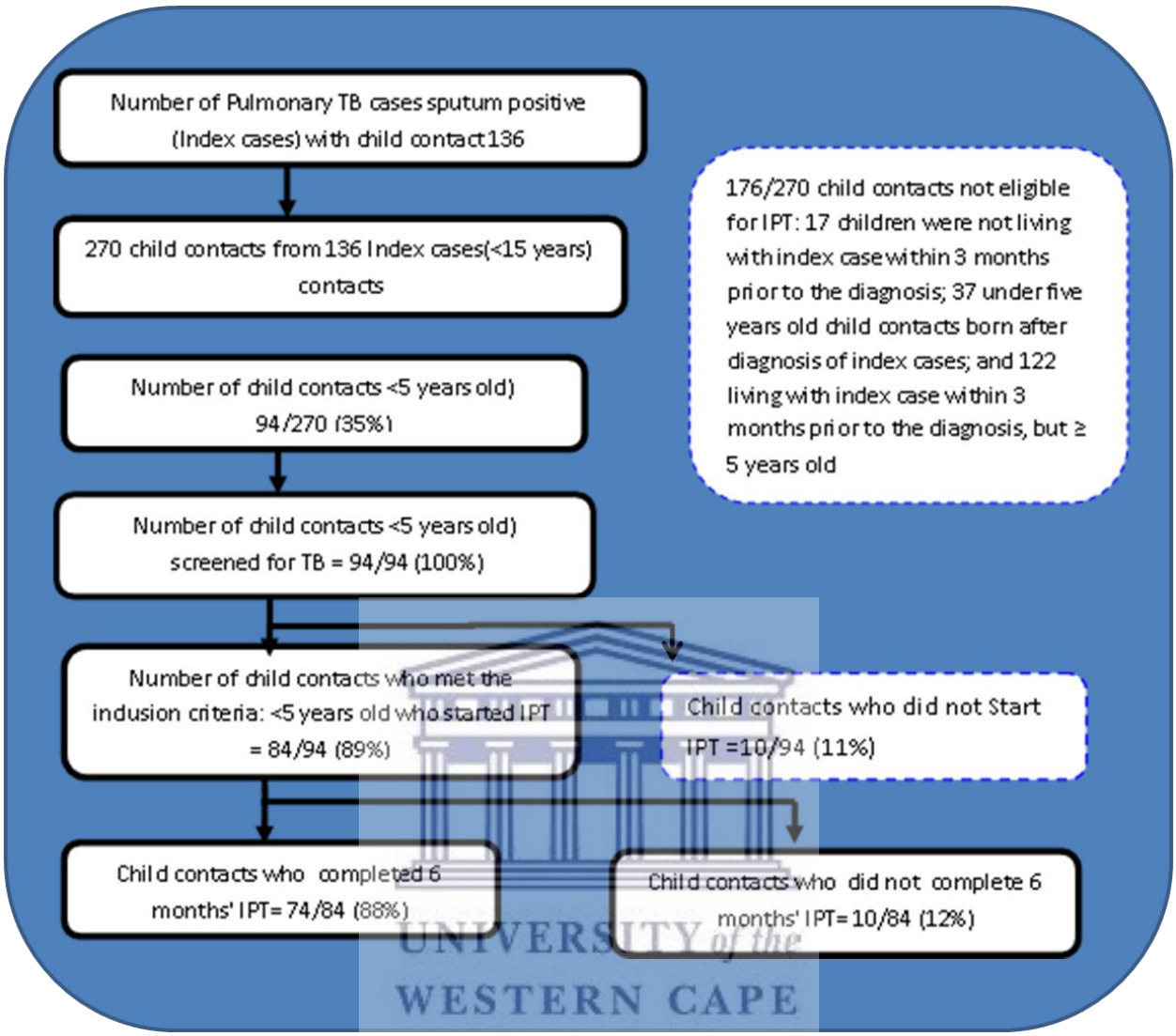


Figure 5. 1: Flow diagram of child contacts from recruitment to IPT completion

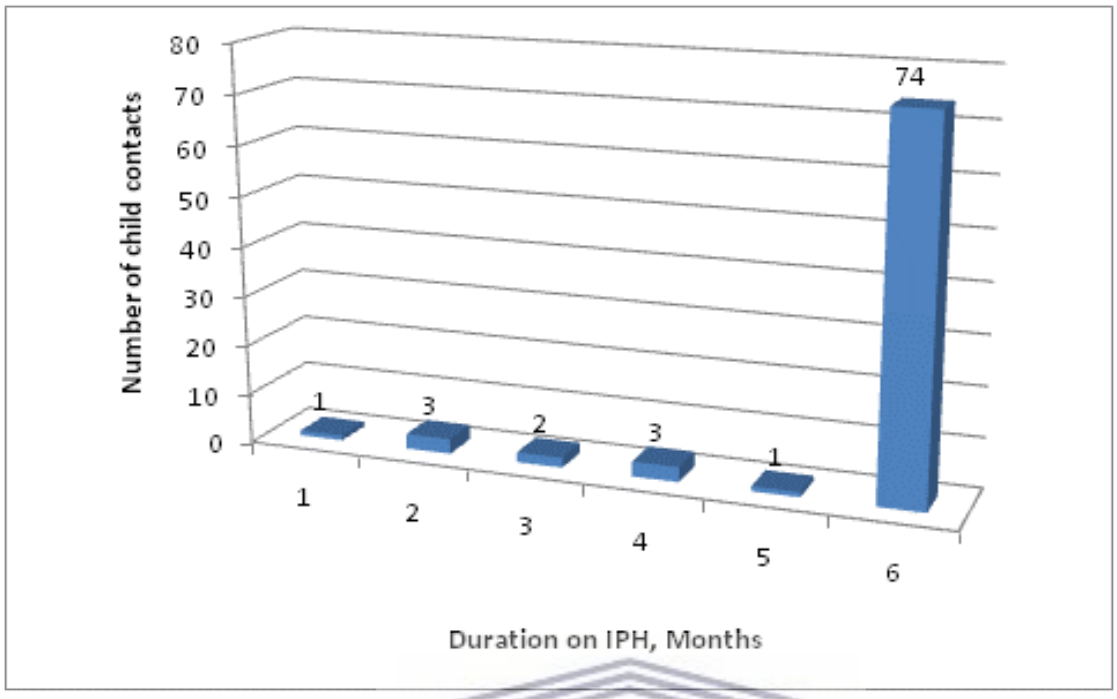


Figure 5. 2: Distribution of number of months IPT prescription was collected

The characteristics of child contacts who started IPT are shown in Table 5.1 There was no statistically significant difference in the characteristics of children who completed six months of IPT compared to those who did not.

Table 5. 1: Characteristics of child contacts who started isoniazid preventive therapy by adherence group (N=84)

Characteristics	Total (%)	Complete Adherence (n=74)	Incomplete Adherence (n=10)	*P-value*
Age group				
≤ 2 Years	37/84 (44)	32/74 (43)	5/10 (50)	0.69
Sex				0.07
Female	37/84 (44)	30/74(41)	7/10 (70)	
BCG scar present				
Yes	80/84(95)	70/74(95)	10/10(100)	0.59
Tested for HIV				
Yes	39/84 (46)	32/74 (43)	7/10 (70)	0.17
HIV test Result				0.10
Positive	2/39 (5)	1/32 (3)	1/7 (14)	
Relationship to Index case				0.10
Child	65/84 (77)	55/74 (74)	10/10 (100)	
Others	19/84(23)	19/74 (26)	0	
Had symptoms suggestive of TB during the initial screening	19/84 (23)	17/74 (23)	2/10 (20)	0.83
Share the same bedroom with index cases				
Yes	42/84 (50)	36/74 (49)	6/10 (60)	0.73

BCG = bacille calmette-guerin; IPT = isoniazid preventive therapy, TB = tuberculosis; HIV = human immunodeficiency virus

Table 5.2 contains the characteristics of child contacts, index cases, households and health facilities. None of the characteristics we evaluated was significantly associated with the incomplete adherence to IPT in the bivariate and multivariate analysis.

Table 5. 2: Risk factors for non-adherence to isoniazid preventive therapy

Factors	TOTAL (%)	OR (95%; CI)
Child contacts (n=84)		
Female	37 (44)	3.4 (0.14-3.7)
HIV positive	2/39 (5)	5.1 (0.28-94)
Not sleeping in the same room as the index case	35 (42)	0.3 (0.06-1.5)
Index cases (n=61)		
Female	28 (46)	3.4 (0.81-14.3)
HIV-positive	13/51 (25)	0.3 (0.05-1.36)
Household factors (n=61)		
Income >50.000 Rwandan Franc	23 (38)	0.3 (0.08-1.95)
No knowledge of IPT protection[a]	38 (62)	5.5 (0.65-45)
Heath facility factors (n=61)		
Provider not friendly	1/61 (1.6)	8.1 (0.46-141)

IPT = isoniazid preventive therapy; HIV = human immunodeficiency virus; CI = confidence interval; OR = odds ratio;

[a]Not knowledgeable about the administration of INH for six months to protect child contacts against TB.

Only one (1.2%) of the 84 child contacts who started IPT developed TB six months after completing the full 6-month IPT, i.e. at 12 months following initial screening and uptake. He was a 3-year-old male, HIV uninfected, who had a clinical diagnosis of TB based on history, physical examination, and CXR. He had TB-related symptoms at the time of initial screening, but further clinical evaluation and CXR were negative for a diagnosis of TB. He remained asymptomatic while on IPT.

Qualitative findings

Interviews were conducted with ten TB focal persons from selected PHCs and 15 parents/caregivers whose children had complete adherence, and eight whose children had incomplete adherence. The characteristics of parents/caregivers are presented in Table 5.3.

The FGDs were attended by 24 CHWs, which included eight participants from each district.

Table 5. 3: Demographic characteristics of parents/caregivers

Characteristics	Complete adherence (n=15)	Incomplete adherence (n=10)
Age in years, median (IQR)	36 (22-63)	33 (28-43)
Relationship to child		
Mother	11	7
Father	2	0
Grandmother	2	1
Education level		
Never attended school	5	0
Primary school	5	6
Secondary school	4	2
Socio-economic status		
Low	8	6
Middle	7	2
District of residence		
Nyarugenge	5	1
Kicukiro	2	2
Gasabo	8	5
Relation to Index case		
Herself	6	2
Wife	6	6
Others	3	0

IQR = interquartile range

The barriers to and facilitators of the IPT adherence, with themes and sub-themes, are presented in Fig 5.3. The figure has four boxes and each box represents a theme. Also, each bullet in a box represents a sub-theme which can be a facilitator or barrier to IPT adherence.

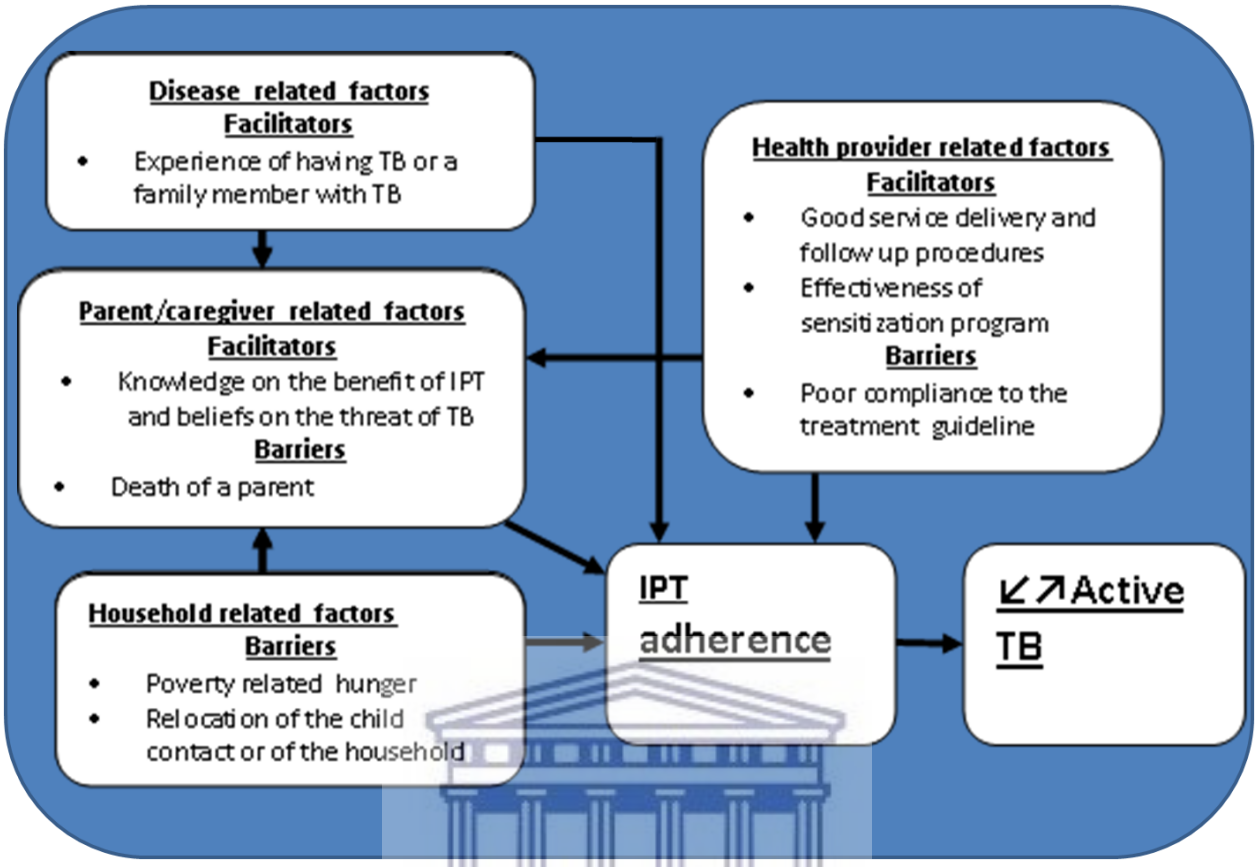


Figure 5. 3: A framework mapping factors influencing isoniazid preventive therapy adherence in Kigali, Rwanda

The reported facilitators of IPT adherence included themes around parents/caregivers, disease, and health-care provider-related factors which are described in detail below.

Parent-/caregiver-related factors

Parents/caregivers' knowledge about the benefit of IPT and beliefs about the threat of TB disease were reported as a facilitator of IPT adherence.

I knew that this medicine protects my child from getting TB. I know that TB is a bad disease, so I put that programme (to give him IPT) among my obligations. (Mother, 29 years, complete adherence)

Disease-related factors

Overall parents/caregivers whose children had complete adherence mentioned their own TB disease experience or experience taking care of a relative with TB as the core factor motivating them to provide IPT to their children as recommended by health-care providers.

I'm telling you, from my experience when you have experienced TB disease, you cannot really wish to see your child contaminated and feel what you have experienced, and hence that fear helps you to give the medicine as prescribed by the doctor to protect the child from contamination. (Mother, 33 years, complete adherence)

I saw how seriously sick my mother-in-law was when she was struggling with the TB, which had evolved into multi-drug resistant TB; and I was the one who took care of her. Recalling that situation pushed me to act quickly and get medicine for my children. I always made sure they took it as prescribed. (Mother, 40 years, complete adherence)

Health-care providers' factors

Most of the participants reported on the positive support by health-care providers and CHWs as facilitators of IPT adherence. They commended health-care providers for the way they taught, provided them with information and education on the IPT adherence and for their successful follow up.

It is the nurses in charge of the follow-up of the TB patients who often go on the fields, and we (CHWs) make them visit people to whom we give IPT and TB treatment. They also inquire about their [TB patients, child contacts] health status, ask them questions about how they take their treatment or give children treatment. This [follow up] could have increased the number of child contacts who finished IPT. (CHW6, Nyarugenge district)

It's CHWs who help those (child contacts) to take their medicine and also us (TB focal person). We supervise CHWs many times because if we gave them medicine, they (CHWs) are supposed to make sure that children take it well and on time. When we visit them (CHWs), we check if they gave the medicine to children as we prescribed.(TB focal points 1, Public PHC)

Through sensitisation programmes conducted by nurses, we are well informed that immunisation protects our children from contracting a disease.(Mother, 31 years, complete adherence)

We also explored the barriers to IPT adherence. The reported barriers included themes around caregivers, household and health care factors which are described in detail below.

Factors related to parents/caregivers

Parents/caregivers whose child contacts had complete adherence and some health-care providers reported that the death of a parent/caregiver led to the child being placed in another family, whose members did not share the importance of continuing the adherence to IPT or were living too far from the PHC.

...sometimes a mother who was following her child's treatment well can die before the treatment is complete, and those who take care of the child may neglect to continue the child's treatment. (Health-care provider, 35 years, public PHC)

There are children who can have the tragedy of losing their parents when on IPT. For example, in my village, there was a woman whom I was giving TB treatment, and she had a child who was on IPT. That woman died, and we buried her in her province. This means the child was taken by his mother's relatives and we did not know who took him to allow us to continue with the follow-up. Such kind of child contacts is included among those who did not finish the IPT.(CHW4, Nyarugenge district)

Parents/caregivers' belief that medications taken without food are harmful was reported as a barrier to IPT adherence by some CHWs who supplied IPT at the community level. Parents/caregivers believe that a hungry child could not be given medicine because it is difficult and harmful.

It is quite a challenge when you come to give a child his/her medicine you are told by a parent/caregiver: please stop... stop! The child has not eaten anything since the previous day and looks concerned. The child has gone hungry and yet has to take medicines and, as you know, it is not easy to swallow pills/tablets even for an adult and it is more difficult for a child and also harmful to take medicine on empty stomach!(CHW4, Nyarugenge district)

Household-related factors

Many of the parents/caregivers whose child contacts had incomplete adherence reported poverty and relocation as the foremost barriers to IPT adherence. Parents/caregivers reported that poverty

led to a lack of food, therefore by necessity, they gave priority to getting a job and being able to provide food for their children rather than going to the PHC to collect medication.

Sometimes you ask yourself where the meal for the child will come from if I take the child to the PHC. Because of this, you may decide to look for a job today and plan to take the child to the PHC tomorrow. But still, you may also fail to get the job that day, and that will compel you to try again the following day. Finally, you will not find any time and stop the treatment altogether. (Mother, 34 years, incomplete adherence)

The relocation, either of a child contact or the household, was reported as a barrier to IPT adherence. Some participants reported that parents/caregivers are often compelled to place their children with relatives.

It may happen that you start taking medicine; before its completion, you move to another place and find yourself in a situation where you are not able to pay for transport to go to the place where you used to get the medicine from. That is what happened to me!(Mother, 30 years, incomplete adherence)

For example, a mother may start giving her child the medicine, but only halfway to completing the treatment, she may come and tell you that she does no longer live with the child, that she has sent him/her to his/her grandmother's. In that case, you understand that the child stops taking the medicine. (Health-care provider, 30 years, Public PHC)

Health-care providers' factors

The lack of compliance with the treatment guideline by health-care providers was reported as a barrier to complete adherence by a parent/caregiver whose child had incomplete adherence.

This is something that I myself experienced. My child didn't complete the six months of treatment, because when I finished my dose, I was told to stop his treatment too, although he started it one month later than I did. You do understand that the decision to stop the medicine was not mine; it was rather the decision of the nurses, who convinced me that my child was no longer running any risk since they followed me up to my full recovery. (Mother, 28 years, incomplete adherence)

Discussion

The rate of complete IPT adherence of 88% in this study is higher than the range of adherence rates 26%-76% reported elsewhere [42,79,143–145,180,219]. To be more precise it is comparable to the 86% and 94.5% rates reported for Benin [202] and the Gambia [201], respectively. IPT adherence is often poor, and a recent systematic review did not identify a particular intervention to improve implementation [23]. However, the successful delivery of IPT may be setting-specific relying on system factors that may be completely different from other similar studies but in different settings such as urban Indonesia [18]. In Rwanda, the government's commitment through NTP to implement local interventions, especially those targeting to improve IPT adherence, such as performance-based financing, free TB services and treatment, increasing the number of PHCs, and involving CHWs in the management of child contacts. The findings from the qualitative study support this assumption. Factors such as financial challenges regarding medication collection including the cost of medication and transport, and long waiting times that were reported as barriers to IPT adherence in other countries where such interventions are not implemented [143–145], were not reported by participants in this study.

Parents/caregivers' own experience concerning TB disease or their experience of taking care of a relative with TB has been identified as one of the main factors facilitating IPT adherence. The fear to see their offspring suffering from TB, a disabling and killer disease, has been a primary factor motivating them to make sure that their children had complete IPT adherence. This is consistent with a study conducted in Indonesia [144] where the experience of having a family member with TB was found to be a factor in facilitating IPT adherence.

The effective sensitisation programme, service delivery (for example, friendly health providers, supportive and providing all the needed information, especially information on the benefits of IPT or length of treatment) and follow-up procedures have been identified as facilitators of IPT adherence in this study. This finding reinforces the quantitative result that revealed that only one parent/caregiver experienced the health care providers to be unfriendly. Furthermore, only one parent/caregiver whose child had incomplete adherence reported a lack of compliance with the

treatment guidelines by health care providers as a barrier to IPT adherence. Also, none of parents/caregivers whose child contacts did not have complete adherence reported the unawareness of the benefits or length of treatment as barrier to IPT adherence in our study. The results of this study are corroborated by other studies, which indicated that provision of follow-up and service delivery were facilitators of preventive and TB treatment [220,221]. Poor follow-up and service delivery such as poor interpersonal communication between patients/caregivers and health care providers, lack of attention and support at the health facilities, difficulty for patients continue with his/her treatment if s/he missed treatment, were also found to be barriers to preventive and TB treatment adherence [222–224]. For example, studies found that when a patient missed treatment for a period and for any reason want to re-joint the TB service, s/he is jugged, insulted and sometimes requested to provide a guarantor from the community who could vouch for his/her ability and willingness to complete their course of treatment [222,225]. Therefore, to avoid those bad experiences, patients prefer to no re-join TB service. Parents/caregivers' knowledge on the benefit of IPT and beliefs that TB is a severe and killer disease were reported as facilitators of IPT adherence. This is consistent with other studies that found that IPT completion was related to parents/caregivers' belief about the severity of TB disease and knowledge about the benefit of IPT [143,144,226]. However, most parents/caregivers with incomplete IPT adherence in this study were knowledgeable about its benefits. The incomplete adherence observed among their child contacts could be explained by the underlying reasons for incomplete adherence. In a systematic review [220], reasons such as poverty and relocation were identified as structural factors. The latter overrides the willingness of parents/caregivers to complete IPT, despite their knowledge of the importance of adherence. Structural factors are those present in the society that influence treatment-taking behaviour, but on which the patient has little personal control.

Relocation has been identified as a barrier to IPT adherence in this study. Similar results were displayed by other studies [221,223]. Some parents/caregivers are often compelled to place their children in the care of their relatives who are wealthier than what they are. Additionally, TB patients are often displaced from their area of residence because they are either unable to pay the rents where they are staying or asked to move because they can potentially infect their neighbours. Appropriate counselling for parents/caregivers to inform health-care providers when

they need to relocate and the establishment of a formal system at the health facility is needed. The communication is needed between the referral and recipient health-care providers of the child contacts to ensure they reach their destination and pursue the IPT.

In this study, poverty has been identified as a barrier to IPT. Poverty correlates with a lack of food, in fact, parents/caregivers believe that medication taken without food is harmful. Similar results have been found in other studies [150,227]. Health-care providers have to identify child contacts of poor parents/caregivers and provider them with nutritional support. Additionally, we recommend the NTP to conduct a quantitative study at the national level to access the impact of poverty on IPT adherence. Although the long duration of treatment has not been reported as a barrier to IPT, NTP has to consider the availability of shorter regimens equally effective to IPT and safer known to be associated with better adherence [128].

Incomplete adherence to IPT in this study was not associated with any individual characteristics of index cases, households or health facility characteristics as in other studies [143,144]. However, the small sample size is a limitation of this study that may have limited the ability of researchers to detect differences in the IPT uptake, with the low numbers of incomplete adherence for comparison. Nevertheless, the addition of qualitative methodology strengthened the findings by soliciting for more information, which provided an overview of barriers and facilitating factors of IPT adherence according to the views of all participants involved in IPT adherence.

Another limitation is that the data were collected by nurses. That might have compromised the qualitative data in the sense that participants might have preferred to say what the nurses wanted to hear. However, the use of nurses not involved in the treatment of child contacts or index cases, climate of trust and confidence that researchers created before starting each interview might have reduced such probability. Still, another limitation is that the research was conducted in Kigali and findings might not be generalised to elsewhere in Rwanda, especially to remote rural areas where barriers and facilitating factors to IPT adherence may be different.

Finally, the measures used to assess the IPT adherence in this study were less objective than the measures used in other studies [201,226]. These measures include pill counts or detection of INH

metabolites in the urine among other things. We assumed that when a parent/caregiver attended the PHC to collect INH for his/her child, he/she also administered the medication to the child.

Conclusions

There was a high rate of completion of IPT in this cohort of eligible child contacts living in Kigali. The success is likely attributed in part to the government's commitment through NTP to implement local interventions, especially those targeting to improve IPT adherence such as performance-based financing, free TB services and treatment, increasing numbers of PHCs and involving CHWs in the management of child contacts.

However, structural factors (poverty and relocation) were found to be the main barriers to IPT adherence. These structural factors have to be used by health-care providers to identify parents/caregivers whose child contacts are at risk of incomplete adherence, therefore, provide specific follow up adapted to their need.

Chapter 6

Conclusions and Recommendations

In this thesis, we aimed to determine the diagnostic yield of Xpert MTB/RIF in sputum collected by GL in symptomatic children who are contacts of index cases with sputum smear-positive TB and to perform a mixed-methods evaluation of the implementation of IPT.

6.1 Summary of main findings and discussion

What is the diagnostic yield for case detection of Xpert MTB/RIF in symptomatic child contacts?

The use of Xpert MTB/RIF in two sputum samples collected by GL did not contribute to the bacteriological confirmation of active TB in child contacts in this study. Although the number of symptomatic children included for evaluation was small (n=37),our findings are similar to a study conducted in Indonesia among 269 child contacts using Xpert MTB/RIF in two separate samples obtained by induced sputum, where none of the diagnosed cases was bacteriologically confirmed [105]. A possible explanation for a low yield from Xpert MTB/RIF assay is that active contact screening might select children with early, paucibacillary disease compared to hospital-based studies of children with presumptive TB that reported higher yields [55,58–61]. The use of Xpert MTB/RIF Ultra cartilage could overcome this Xpert MTB/RIF assay's limitationof being inadequate to detect TB when few bacilli are present in a clinical specimen. Recently, a novel cartilage using the same Xpert MTB/RIF platform was developed by Cepheid as the next-generation assay to overcome the limitations of Xpert MTB/RIF assay such as low sensitivity in smear negative, HIV-associated TB and children are known to be patients with paucibacillary disease [228]. The Xpert MTB/RIF Ultra has a limit of detection of 16 bacterial colony forming unit (cfu) per ml compared to131 cfu per ml for Xpert MTB/RIF [56,188,189,229].

Results from studies suggested that Xpert MTB/RIF Ultra will improve TB case detection rates in subjects with paucibacillary TB such as those with HIV co infection, but also in pediatric patients with TB and those with extra pulmonary forms of tuberculosis [229,230]. However, this increase in sensitivity came at the expense of a decrease in specificity. Studies have found that

the specificity of Xpert MTB/RIF Ultra was low compared to Xpert MTB/RIF. This has to be considered when using the Xpert MTB/RIF Ultra, mostly in patients with a history of TB [229,231].

The overall prevalence of TB in child contacts in this study was low **(Paper 1)** which also may reflect the high coverage of preventive therapy in the under-five child contacts because of successful programmatic implementation by the Rwanda NTP. This may explain why all child contacts clinically diagnosed with TB in this study were older children (≥5 years old), that is, not eligible to IPT [69]. Similar results in studies in Uganda and Indonesia found that none of the eligible child contacts who started IPT developed active TB during follow-up [180].

What are the perceptions and perspectives of various stakeholders (laboratory staff, health care workers and programme managers) on the strength, weakness and challenges of Xpert MTB/RIF, especially using GL as a sample, in diagnosing TB among child contacts in Rwanda? (Paper 4)

Participants also reported that the use of GL in Xpert MTB/RIF contributes to TB diagnosis in children than microscopy, especially in inpatients children. However participants highlighted that the contribution was minimal, especially among outpatients children. The contribution of Xpert MTB/RIF in GL to diagnose TB among children was mainly reported by participants from the referral hospital. It's know that children at referral hospitals are inpatients at the advanced stage of the TB disease. It's known that the sensitivity of Xpert MTB/RIF increases in inpatients compared to outpatients [55,61,105]. This may explain the contrast of the findings of this study **(Paper 4)** with the findings of the quantitative study conducted in the same setting **(Paper 1),** which showed that Xpert MTB/RIF assay did not improve the diagnosis of PTB among child contacts. None of the diagnosed cases was bacteriologically confirmed [165].

Feedback from stakeholders suggested that Xpert MTB/RIF facilitated early detection of PTB and DR-TB among older children (5-14 years old), which is explained by their ability to provide quality sputum, as is the case with adults. However, stakeholders highlighted that the detection rate was minimal. The findings of this study (**Paper 4**) corroborated those of a study conducted

in Kenya, where the proportion of bacteriologically confirmed cases were higher among older children [195].

Feedback from stakeholders suggested that the overall yield of Xpert MTB/RIF in diagnosing TB among child contacts was minimal. That the yield from Xpert for child TB diagnosis under programmatic conditions is low (<10%) [183] and that the yield is lowest in children who are not inpatients, such as household contacts is well recognised [164].

Several weaknesses in the utilisation of Xpert MTB/RIF were reported in this study. The identified weaknesses included the inability of primary health care providers to assume TB in a child contact, the inability of some district or referral hospitals' health care providers to collect quality GL samples, inability to perform laboratory tests on samples other than sputum, and the health care providers' lack of awareness of the availability and indication of the Xpert MTB/RIF test. For instance, the inability to perform laboratory tests on samples other than sputum in most of the district hospitals reported by participants may represent a missed opportunity of using Xpert MTB/RIF test in GL in those hospitals. To avail the standard operation procedure (SOP) and train laboratory technicians in the use of Xpert MTB/RIF test in GL could increase its use and increase the opportunity of detecting positive cases.

All reported weaknesses could potentially reduce the diagnostic yield and case detection from the Xpert MTB/RIF test by contributing to its underutilisation or lowering its sensitivity through the use of inferior quality samples [63,197]. These weaknesses have also been reported by studies from Mongolia and India [62,63].

Moreover, other implementation challenges in the utilisation of Xpert MTB/RIF were reported such as the restriction of performing the GL at PHCs, lack of utilising Xpert MTB/RIF, and no formal system of sample transportation from the PHC to the district hospital. Most of these challenges are health system related [198], which might limit the practice of staff. For instance, it is not permitted to perform GL at the PHC level, where most child contacts with symptoms suggestive of TB will present for health care and evaluation. Even if GL could be performed at the PHC level, the availability of Xpert MTB/RIF machines is limited to district hospitals which increases the need for multiple visits to the hospital by parents/caregivers to complete their

child's screening to detect TB or exclude active TB before IPT [46,148]. Consequently, most child contacts with symptoms suggestive of TB and who are unable to expectorate, need to be referred and transferred to the district hospital for further evaluation causing significant delays or missed opportunities for TB diagnosis or IPT initiation [15,19–23].

Overall, along with the low yield, the use of Xpert MTB/RIF is currently limited by a few implementation challenges as shown in a study conducted in five Sub-Saharan African countries which presented the challenges observed during the Xpert MTB/RIF implementation. In this study, it was found that Xpert MTB/RIF utilisation was at 15% of its full capacity, proving a missed opportunity to diagnose potential TB and DR-TB cases because of inadequate transport and referral systems [232].

What is the uptake of isoniazid preventive therapy by eligible child contacts in Kigali, Rwanda, and its associated factors?

The policy of the NTP regarding IPT delivery was effectively implemented in Kigali, Rwanda **(Paper 2)**. IPT uptake was found to be higher than the experience in many resource-limited countries [35,139–141,200]. The high IPT uptake finding corroborates the results published in the 2013-2014 and 2015-2016 annual reports of Rwanda's NTP [95,162]. This high uptake may reflect the particular attention being given to TB in children by Rwanda's NTP according to the government's priority intervention aimed at preventing and addressing the most important causes of child mortality [99,100].

To inform the population about TB, the integration of IPT into the programmatic delivery of health care and performance-based financing, the high-level knowledge of parents/caregivers on how to prevent TB in children might explain the high uptake reported in this study. Other explanations could be sessions on information, education, and communication organised twice a week by service providers at health care facilities, at the community level by CHW, at the local politico-administration level and in the media. Additionally, geographical accessibility can also explain the high uptake of IPT in Rwanda. Countrywide, the average time to access the nearest health care centre is less than one hour [208]. A study carried out in Bangkok, Thailand by

Tornee et al. [147] showed that the short distance from home to the nearest medical clinic was associated with adherence of the households' contact to screening.

The reasons for not initiating IPT in the child contacts who did not start IPT were parents/caregivers' lack of information on the need for IPT, refusal to give IPT to their children, and poor quality services offered at health centres. Factors associated with no uptake of IPT included children being more than three years old, unfriendly health care providers and HIV infected index cases. These findings can be explained by the fact that parents/caregivers protect their younger children from contracting TB more than their older children. Similar findings were reported in a qualitative study conducted in Bangkok, Thailand by Tornee et al. [147], which showed that parents/caregivers worry that their younger children might get TB infection and take them to health care facilities for screening. The index case not being the child's parent was also associated with no uptake of IPT. This finding corroborates the findings in a study conducted in Timor-Leste [140] as well as a qualitative study in Bangkok, Thailand [147]. Both studies reported a lack of screening of child contacts who were not children of index cases. The parents/caregivers who found unfriendly health care providers at the PHCs were also more likely not to initiate their children on IPT than those who found them friendly. Child contacts living with HIV-positive index cases were less likely to be initiated on IPT than those living with HIV-negative index cases. These two factors may be correlated. Besides the negative experience from unfriendly health care providers, the HIV-positive people have to cope with social stigma [210]. This negative experience in government health care facilities and social stigma among TB-HIV co-infected persons suggest a negative impact on the uptake of IPT among child contacts. This finding is a cause of concern in Rwanda since the health care-seeking behaviour of HIV-positive parents/caregivers influences TB screening and management in children.

What is the isoniazid preventive therapy adherence and exploratory facilitators and barriers in Kigali, Rwanda?

The rate of complete IPT adherence was higher in this study than the range of adherence rates reported in most other TB endemic settings [42,79,143–145,180,233,234]. These rates are comparable to those recently reported for Benin [202] which is known to have a well-functioning NTP over many years and from The Gambia [201] where there is a large amount of research on

child health. In Rwanda, the government's commitment through NTP to implement local interventions, especially those targeting the improvement of the IPT adherence – such as performance-based financing, free TB services and treatment, increasing PHC numbers, and involving CHW in the management of child contacts – might explain the high adherence reported in this study. Parents/caregivers' own experience concerning TB disease or their experience of taking care of a relative with TB has been identified as one of the main factors facilitating IPT adherence. This finding is consistent with a study conducted in Indonesia [144], where the experience of having a family member with TB was found to be a factor in facilitating IPT adherence.

The effective sensitisation programme, service delivery (friendly health providers, providing all the needed information, supportive) and follow-up procedures have been identified as facilitators of IPT adherence in this study. Thus the results are corroborated by other studies, which indicated that the provision of follow-up and service delivery were facilitators of preventive and TB treatment [220,221]. On the other hand, inadequate follow-up and service delivery were found to be barriers to preventive and TB treatment adherence [223,235]. Parents/caregivers' knowledge and beliefs about the threat of TB disease were reported as facilitators of IPT adherence, which is consistent with the results of other studies [143,144,235].

The relocation has been identified as a barrier to IPT adherence in this study,with similar results displayed by other studies [221,223]. In this study, poverty has been identified as a barrier to IPT, which correlates with a lack of food. In fact, parents/caregivers believe that medication taken without food is harmful. Similar results have been found in other studies [150,227].

6.2 Methodological considerations

The strengths of this thesis included the use of multiple research methods, viz. quantitative, qualitative and mixed methods. The use of these different research methods had two main objectives, first, to ensure that the limitations of one type of data are balanced by the strengths of another; and second, to investigate whether the findings are complementary despite the use of different methodologies.

Data enumerators were rigorously selected among people familiar with collecting health-related data in the country and were trained on how to use the questionnaire. Furthermore, during data collection, researchers made sure that the enumerators conducted interviews consistently.

The same participants and research team were involved in the study throughout. Participants were thus able to develop a sense of ownership and involvement in the outcome of the research and strengthen the quality of their commitment to this study.

The questionnaire, interview and focus discussion guides were initially tested using participants and an environment similar to what we used during the study. Furthermore, the questionnaire was adapted from different studies including the International Expert Panel in childhood TB [13,176]. Finally, all these data collection tools were revised before accepting finals versions.

Overall, this thesis has approached the question of IPT and the role of Xpert MTB/RIF test in improving the diagnosis and prevention of TB in children exposed to index cases with PTB from several angles. All stakeholders involved in the management of child contacts were used such as parents/caregivers, health care providers, laboratory microbiologists and technicians, and NTP managers. Therefore, our results are sufficiently comprehensive to inform the potential practice and policy.

The results of this thesis are not without limitations. The study was only conducted in Kigali, Rwanda. Thus, the findings might not represent the situation in the whole country. However, considering that the management of childhood TB in the country is under the NTP and the policies leading its management are the same countrywide, we believe that our findings may be relevant to the rest of the country.

Another limitation is that the sample size was too small to enable comparative analyses that limited detection of small significant differences among comparators for diagnosis, IPT uptake and adherence (**Paper 1**). However, the addition of qualitative methodology (**Paper 4**) strengthened the findings by soliciting for more information from all stakeholders involved in the use of Xpert MTB/RIF in Kigali, which provided their perspective of the utility of Xpert MTB/RIF as a diagnostic tool in child contacts. Also, it provided an overview of the barriers and facilitating factors of IPT adherence according to the views of all participants involved in IPT adherence.

Many other limitations were specific to each study and are mentioned in the relevant chapters of this thesis.

6.3 Implications for practice

The evaluation of IPT and the role of the Xpert MTB/RIF test in improving the diagnosis and prevention of TB in children exposed to PTB index cases in Kigali, Rwanda comes at a time when all stakeholders involved in TB worldwide are concerned about this issue in children [27]. At this time these stakeholders have noticed that the end TB strategy cannot be realized if special attention is not paid to the early diagnosis of TB in children and early initiation of treatment or prophylaxis [30]. Additionally, the evaluation of IPT comes at a time when the WHO recommends prophylaxis of TB to any exposed child regardless of his/her age [128]. Therefore, it is evident that infected children constitute a reservoir of imminent TB in the community, and treating them prevents forthcoming TB transmission [13,29].

The results of this study will inform the country on the current status of the implementation of the IPT and the adherence, IPT facilitators and barriers. This information is valuable and will allow the country to implement the new WHO recommendations with confidence [128]. Moreover, the results of this study are of public health significance, as they will provide research-based information for future studies and public health programmes aimed at assessing or improving the detection and prevention of TB in child contacts. For instance, the results of this study revealed that the contribution of Xpert MTB/RIF in diagnosing TB in child contacts was minimal. This important information could be used by the NTP to strengthen clinical diagnosis and management of child contacts at the primary health care level through the training of health care providers and CHW. The potential for improving the diagnosis and management of child TB can thus be improved. The decentralisation and strengthening of TB services at the peripheral level of care have shown to be effective in increasing TB diagnosis and uptake of preventive therapy in a study conducted in Uganda [236].

Currently, most of the NTP in resource-limited countries have failed to implement the IPT among the under 5-year-old child contacts [35,39,80,106,139,141]; and even when IPT was initiated, its uptake and adherence are often poor [16,79,142–145]. However, in this study, we

found that the NTP policy on the provision of IPT was successfully implemented in Kigali, Rwanda, under the set programmatic conditions. A lot of facilitating factors contributed to such successful implementation of IPT. We assume that the involvement of the government through local interventions targeting improvement of IPT adherence, such as performance-based financing, free TB services and treatment, increasing PHC numbers, and involving CHW in the management of child contacts, may have played an essential role to that success. These are local interventions sensitive to social context required for ending the child TB epidemic [27].

6.4 Conclusions

In conclusion, the effectiveness of Xpert MTB/RIF in GL was inadequate, and its yield remains minimal because of its technical shortcomings in child contacts in general and multiple implementation challenges, which reduce its impact. However, it could detect a few cases of TB and DR-TB in old child contacts, especially at an advanced stage of the disease. Therefore, the early diagnosis of TB among child contacts should rely not only on Xpert MTB/RIF but mostly on clinical diagnosis [47–49]. Although addressing the implementation challenges could relatively improve the impact of Xpert MTB/RIF, but its technical shortcomings will still limit its capacity in diagnosing TB in child contacts. Xpert MTB/RIF Ultra which has high sensitivity than Xpert MTB/RIF and could be a solution to the technical shortcomings of the later [228]. But the problem of its low specificity comparing to the Xpert MTB/RIF specificity could constitute a barrier to its performance as it can lead to the over treatment of the cases. Another major limitation of Xpert Ultra is that is can only be implemented in referral hospitals and districts in opposite to Xpert which can be implemented at the peripheral level. The implementation challenges such as no formal system of sample transportation from the PHC to the district hospital could constitute a challenge for Xpert Ultra.

In this study we found that the IPT was successfully implemented in Kigali, Rwanda, where the government's commitment to implement local interventions through the NTP has contributed to that success.

Factors such as the age of child contacts, the unfriendliness of health care providers, child contacts living with HIV-positive index cases, poverty and relocation of child contacts

contributed to non-initiation of IPT and incomplete adherence. Health-care providers should use these barriers to identify parents/caregivers whose child contacts are at risk of not initiating IPT and having incomplete adherence to providing specific counselling and conduct follow-up adapted to their need.

6. 5 Future perspectives

6.5.1 Policy and practice implication

Findings from this thesis highlighted the operational challenges in the utilisation of Xpert MTB/RIF in detecting TB in child contacts and the role played by relocation as barriers to the IPT adherence. In conclusion, this study lends itself to the following recommendations, which should be contextualised to effectively improve the diagnostic and management of child contacts at the PHC:

At the national level

- Considering that the yield of Xpert MTB/RIF was inadequate in child contacts, we recommend strengthening clinical diagnosis at PHC and community levels. Therefore, conducting regular and continual training focusing on building the capacity of health care providers at the PHC and CHW to recognise symptoms suggestive of TB in child contacts or any other children including management of childhood TB is needed. The training should also focus on the importance of good service delivery by health care providers (friendly health providers, supportive and providing all the needed information). That training will address the inability of health care providers and CHW to assume TB in a child contact and eradicate their unfriendly attitude which was found to be a source of inadequate IPT uptake. In doing this will increase the detection of children with TB and improve their management at the PHC and community levels.

  The NTP in collaboration with the PHC without Xpert MTB/RIF machines should establish a formal system of sample transportation from PHCs to the district hospital. A formal system of sample transportation supposes that frequencies of sample transfer are predetermined, and

transport means is known in advance. The annual budget to cover the sample transport must also be prepared and made available. All this is needed to ensure the sample transportation system which should be regular and continuous.

- The NTP should conduct a national awareness-raising campaign on the availability and indication of the Xpert MTB/RIF test for enhancing its utilisation by health care providers and compliance to the policy or guideline related to its use in the country.

- The NTP should conduct the training of laboratory staff on the use of Xpert MTB/RIF in samples other than sputum. Also, it should make available the standard procedure for the use of Xpert MTB/RIF in samples other than sputum by reducing technical error sources of false negative results, thus increasing the probability of positive results.

- The NTP should advocate at national policy level the inclusion of GL practice at PHC to reduce the transfer of child contacts from PHCs to the district or referral hospital, source of delays in TB diagnosis or treatment and IPT initiation, and child contacts lost because of a lack of communication feedback between the PHC and a higher level of care. Additionally, a regular and continual training of health care providers at all levels on the performance of GL technique for improving the quality of samples source of negative results is required.

- We recommend that the NTP introduce an indicator called "*effective reference of child contacts*, "which is an indicator that determines the number of child contacts on TB prophylaxis who are transferred, reach the referral PHC and continue with their treatment.

A similar indicator is used in all public and faith-based health facilities in Rwanda when a patient is transferred, for any reason, from a PHC to a district hospital. The aim is to reinforce the communication between the two health facilities and build the capacity of health care providers of the PHC by returning the information from the district hospital. This information includes the diagnosis and treatment that the referred patients received, which may help health care providers at the PHC to treat similar cases in the future. However, in the context of IPT, it aims to inform the PHC that referred the child contact that s/he reached the destination and is continuing the preventive treatment.

The indicator should be paid by PBF to give it substantial weight. PBF counts the numbers of stamps on the transfer letter for paying this indicator. Only referral letters with three stamps are paid (two of the PHC that referred the child and one of that one receiving the referral):

- The first stamp: is the one put on the transfer letter which is given to the parent/caregiver.

- The second stamp: is the one put on the transfer letter by the PHC that receives the child contact, attesting that the child reached the PHC where s/he was sent and is continuing her/his treatment. That information should be written by the health care provider who receives the child, stamps and returns the transfer letter to the PHC that transferred the child.

- The third stamp: Once the health care provider of the PHC that originally referred the child receives the feedback from his/her correspondent, s/he has to acknowledge that by signing and putting a second stamp on the letter. Then the transfer letter (with three stamps) has to be photocopied and the copy and original transfer letters have to be shared between the two PHCs. This indicator is used in Rwanda by HIV services for any transfer of an HIV-positive patient from one health facility to another. We assume that this indicator could stimulate health care providers to regularly sensitise parents/caregivers of child contacts, who are on TB prophylaxis to request a transfer letter when they are about to relocate.

- Finally, we recommend that the NTP creates a Childhood TB case-sharing Panel.

The idea behind creating this panel is inspired by the "case-sharing meeting", a monthly meeting that was set up by ICAP International in Rwanda to improve the management of people living with HIV in the areas where it was operating. A group of HIV specialists from ICAP, the National HIV division, doctors and nurses in charge of HIV in the various health facilities supervised by ICAP International met to discuss and manage difficult cases that they were not able to manage solely at their respective health facilities. These cases were presented in those meetings, and the decision on their management was taken based on an agreement between all members of the group. At the next meetings, before introducing new cases, group members inquired about the evolution of cases presented at the previous meetings.

The idea of creating this panel was also inspired by the remarks of a clinical officer who said that "It's really difficult sometimes for one person to make a decision where the case is not straightforward. So, you always consult each other, you share. You can go to the next room, present the case, show the person the X-ray. Then you can have a small discussion in relation to the X-ray and the previous history. Then you can take a collective decision, it's not just one person who decides who is to start in difficult cases. So I think that has really assisted us, sharing information and consulting each other when we get stuck" [237]. Taking the decision alone to put a child on a long-duration treatment while not being sure of the diagnosis may explain the non-compliance of health care providers. In most of the PHCs, TB symptom-based diagnostic algorithms, which propose to initiate a child on TB treatment based on the symptoms and history of contact, are available. Therefore, the childhood TB case-sharing Panel will strengthen clinical diagnostic at the PHCs. The childhood TB case-sharing Panel will be composed of individuals/expertise as described below.

1. Proposed members of the Childhood TB case-sharing Panel

We propose that this panel be constituted by:

- TB focal persons from PHCs who will present difficult cases for which they were unable to take a decision of initiating TB treatment alone.
- Paediatricians from district or referrals hospitals.
- Childhood specialists from NTP (if available).
- TB focal persons at the district hospitals.

2. Number of Childhood TB case-sharing Panels in the country

We propose that the Panel starts in Kigali because it has the simplest logistics among all the provinces. The maximum expense for a panel member to attend a meeting cannot exceed 10 USD. This amount can be covered by the PHCs or NTP. After evaluation, if the creation of this panel improved the management of TB in children, the NTP can decide on its feasibility and scale-up.

From the findings of this thesis and recommendations that emerged, we propose three models of diagnostic algorithm for the management of TB among child contacts in the PHCs.

These models aim to avoid the physical transfer of child contacts to the district and referrals hospitals as far as possible. The latter is found to be challenging because of structural and communication disconnect between PHC level (where active screening is conducted) and the higher level of care. This causes significant delays in TB diagnosis or IPT initiation or loss of symptomatic child contacts when transferred from PHC to the higher level of care because of this lack of communication between health facilities. Additionally, in these models, we recommend that TB focal persons enter in contact with district hospitals where samples are sent or other persons who may intervene in the management of the child contacts.

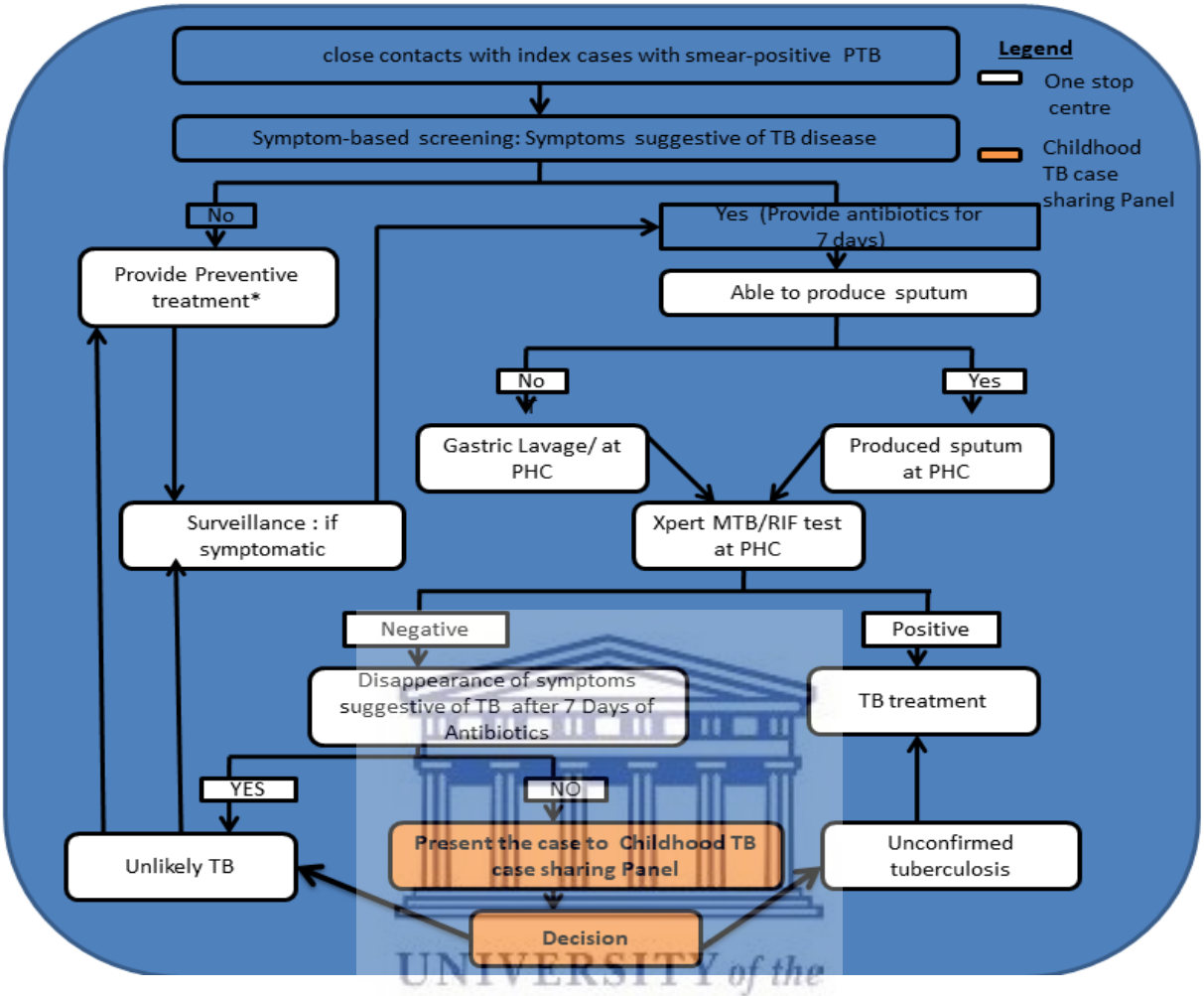
Model 1: One-stop Centre for the management of child contacts

This model is inspired by TB/HIV integrated services where an HIV-positive patient with TB receives all services at one point. This service has improved the management of TB/HIV co-infected patients [238].

In this model, the PHC has an Xpert MTB/RIF machine, is performing GL and active contact screening. Trained laboratory technicians perform Xpert MTB/RIF on any sample type. All decisions about the management of the child contact are taken at this PHC, except when the case of the child contact needs to be presented at the Childhood TB case-sharing Panel. Even in that case, the TB focal person is informed of the panel decision and s/he is the one informing parent/caregivers and put in practice the decision.

<u>Advantages of this model</u>

- It reduces delays in TB diagnosis or IPT initiation usually observed when symptomatic child contacts are transferred from the PHC to a higher level of care.
- It avoids the loss of symptomatic child contacts when transferred from PHC to a higher level of care because of a lack of feedback communication between health facilities.
  The diagnostic algorithm related to this model is presented below.
- It spares parents/caregivers from multiple visits to the hospital for completing screening of their children.



*** Following new WHO guideline**[128]

Figure 6.1: TB diagnostic algorithm for child contact at PHC with childhood TB One-stop Centre

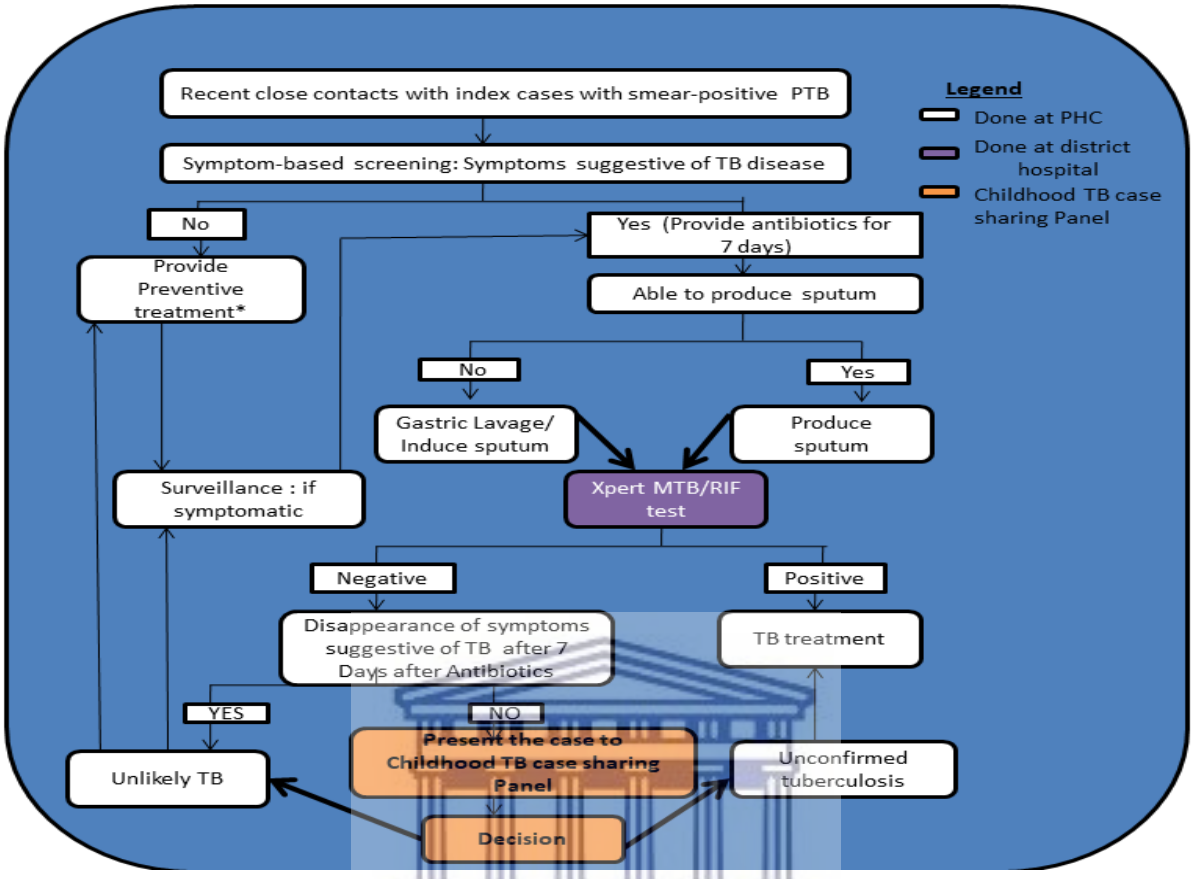
Model 2: The management of child contacts in a PHC without Xpert MTB/RIF, but where GL is performed

In this model, the PHC does not have an Xpert MTB/RIF machine but performs GL and does active contact screening. Samples are rather sent to the district hospitals. The TB focal person is responsible for collecting the results from the district hospital, informing parents/caregivers on the results and implementing the decisions according to these results (start IPT or TB treatment). When a TB focal person is not able to take the decision, s/he presents the case at the Childhood TB case-sharing Panel and informs parents/caregivers on the panel decision and implements it.

Advantages of this model

- It avoids the loss of symptomatic child contacts when transferred from the PHC to the higher level of care for sample collection because of a lack of feedback communication between health facilities.

In figure 6.2, the TB diagnostic algorithm for child contact at a PHC without Xpert MTB/RIF is presented.



*** Following new WHO guideline** [128]

Figure 6.2: TB diagnostic algorithm for child contact at a PHC without Xpert MTB/RIF

Model 3: Making use of the current childhood TB diagnostic algorithm in the country but with two changes. First, to avoid transferring children to the district hospital and to transfer only the sample for examination (if done). Second, when a health care provider is unable to take a decision alone, to put the child contact on treatment, s/he could present the case at the Childhood TB case-sharing Panel, then manage the case as by the panel recommendation. In figure 6.3, the current childhood TB diagnostic algorithm used in Rwanda is presented.

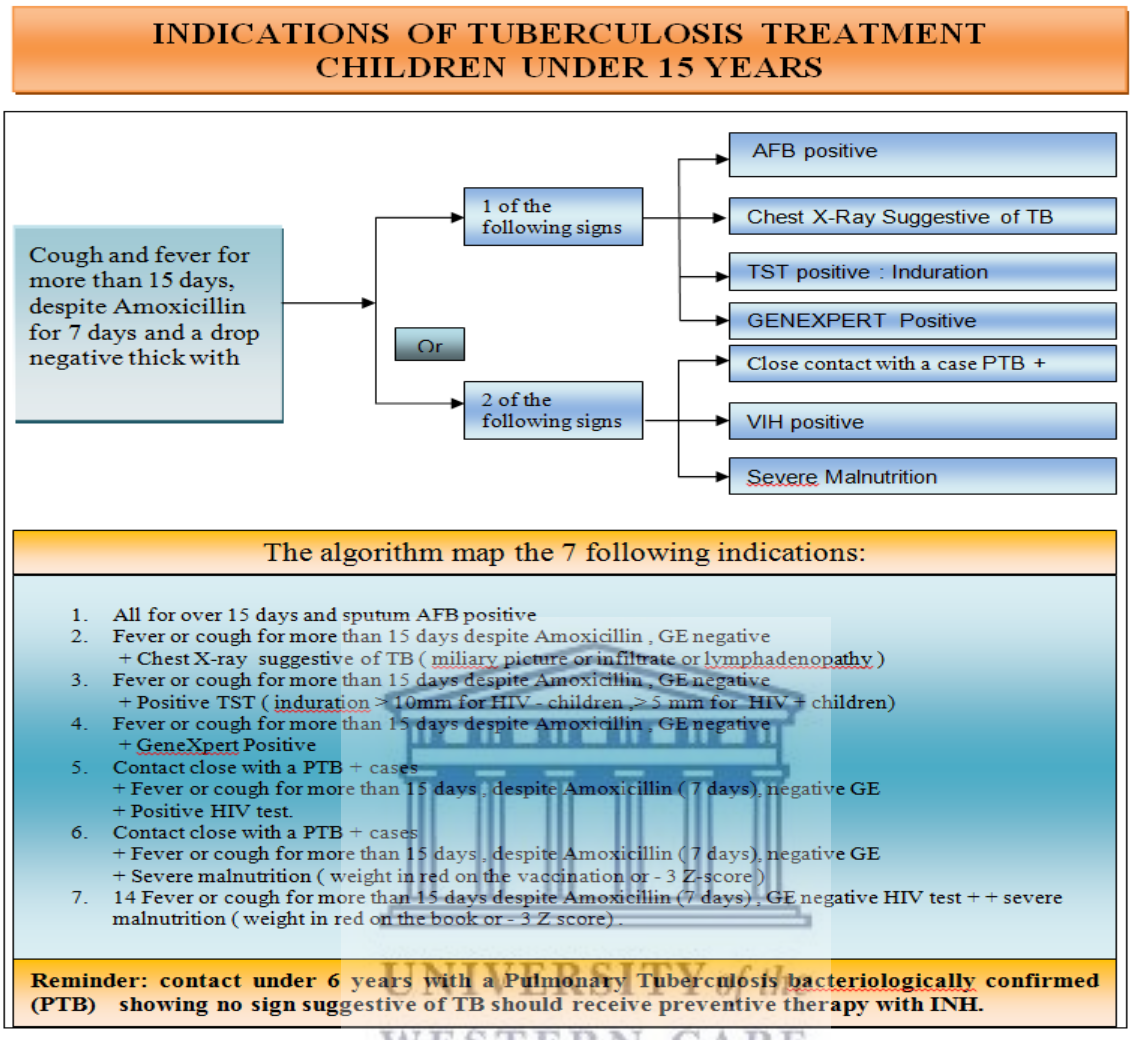


Figure 6.3: Childhood TB diagnostic algorithm currently used in Rwanda

6.4.2 Research implication

Poverty was identified among one of the main barriers to IPT adherence. In this study setting, the poverty correlated with a lack of food which implies the inability of the parents/caregivers to provide for the most basic needs of the family. There is a need for the NTP to conduct research on income generating projects with the objective to identify the impact of income generation projects on improving the IPT adherence among child contracts from poor families. The research will respond to the following questions: what are the ways in which income generation projects improves IPT adherence among child contacts of poor families? What is the impact of income

generation projects? The lack of aptitude of poor families in creating income generation projects could be at the base of their poverty. To support them in creating income generation projects could improve their lives and therefore IPT adherence.

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Appendices

Appendix 1: Consent Form for parents (English version)

UNIVERSITY OF THE WESTERN CAPE

Private Bag X 17, Bellville 7535, South Africa
Tel: +27 21-959 2809, Fax: 27 21-959 2872
E-mail: soph-comm@uwc.ac.za

CONSENT FORM

Title of Research Project: An Evaluation of Isoniazid prophylaxis treatment and the role of Xpert MTB/RIF test in improving the diagnosis and prevention of tuberculosis in children exposed to index cases with pulmonary tuberculosis in Kigali Rwanda

The study has been described to me in a language that I understand. Questions about the study have been answered. I understand what my participation will involve and I agree to participate of my own choice and free will. I understand that my identity will not be disclosed to anyone. I understand that I may withdraw from the study at any time without giving a reason and without fear of negative consequences or loss of benefits.

Participants Name :……..

Participants Signature…….

Date……

Appendix 2: Information Sheet (English version)

UNIVERSITY OF THE WESTERN CAPE

Private Bag X 17, Bellville 7535, South Africa
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INFORMATION SHEET

Project Title: An Evaluation of Isoniazid prophylaxis treatment and the role of Xpert MTB/RIF test in improving the diagnosis and prevention of tuberculosis in children exposed to index cases with pulmonary tuberculosis in Kigali Rwanda.

What is this study about?

This is a research project being conducted by **DrBirungi M. Francine** at the University of the Western Cape together with the University of Rwanda, college of Medicine and health sciences, School of Public health. We are inviting you to participate in this research project because you parents/caregivers of children who are living in the households with index cases (the persons who had or still have TB in your household) that were diagnosed with TB in Kigali Rwanda between December 2014 and May 2015. This research project aims to find out (1) the diagnostic performance of the Xpert MTB/RIF test in gastric lavage (GL) in contact children with symptoms suggestive of TB and (2) the care that contact children receive from the health centres (HC), especially Isoniazid (INH) prophylaxis treatment (IPT). IPT consists of giving INH, one of TB treatment medicines, to the contact children for six months.

The research project is being conducted by **DrBirungi M. Francine** at the University of the Western Cape together with the University of Rwanda, college of Medicine and health sciences, School of Public health. The study will be conducted in Kigali, Rwanda.

What will I be asked to do if I agree to participate?

If you agree to participate in this study, we will first of all ask you questions about the (1) index case such as identification, activities shared with the children, duration of the symptoms; (2) the selected children (age, having active TB or not, received IPT or not) and (3) household

characteristics (number of people, number of smokers, cooking environment).This will take you about 30 minutes. We will also take some information from the TB folder of the index case at the health Centre where he/she has been diagnosed. Note that during the interview using a questionnaire, you are free to stop it at any time and if there are any questions you do not want to answer, we can skip them. The interview will be conducted by trained data enumerators at the HC where the index case has been diagnosed and will last for around 45 minutes. On the same day, we will conduct the clinical screening of your child, which can take 15 to 30 minutes. It will consist of asking you specific questions on the health status of your child such as presence of cough, fever, loss of weight, absence of appetite, fatigue and their duration. If your child has one of these symptoms, we will conclude that he/she has "symptoms suggestive of TB". After we have asked you those questions, you will requested to bring the child to the HC for chest X-ray (CXR) exam the following day, if you agree, whether he/she has "symptoms suggestive of TB" or not. We will use mobile CXR. This exam will help us tell you whether your child is suspected to have TB or not. If yes, that means CXR is "consistent with active tuberculosis".

If your child falls into the category of children with symptoms suggestive of TB and /or Chest radiography "consistent with active tuberculosis, he / she will be given generic antibiotics for seven days. Then after, we will re-assess him/her. If the symptoms persist despite the antibiotics, we will invite him/her to the TB centre of Excellence based at Kigali teaching hospital (CHK) for biological tests. we will collect two samples of GL early in the morning after at least four hours of fasting; the two GL samples will be collected on two consecutive mornings, one per morning. Thus you are likely going to spend the night at the hospital. We will support all expenses. For having GL, trained nurses will collect some stomach liquid from the child's stomach through a tube. The GL will be examined using microscopy smear, Xpert MTB/RIF test and culture. The Xpert MTB/RIF is a new approach in TB diagnosis which can detect both TB and resistance to rifampicin (one of the principal medicine treating TB) in less than two hours.

The clinical screening, CXR and biological exams will provide us with two groups of children: those with TB will be given TB treatment while those without TB will (1) continue IPT if they were on it or (2) will be given IPT if they are eligible for it and were not on it and (3) will just be observed if not eligible. Children eligible for IPT are children under five years old or HIV positive ones regardless of their age. If your child is asymptomatic, which means his/her clinical

screening and CXR are negative, he/she will continue taking IPT if he/she was on it or be put on it if eligible. If he/she is five years old and above, he/she will be sent back home and allowed to come to the HC if he/she has any problem, but he will not continue to be part of this study. All children on IPT will be followed for 12 months. During the first six months of IPT treatment, a TB screening will be applied every month and the IPT adherence will be assessed. During the 6th to 12th months, due to limited budget, follow-up will take place every three months; a TB screening will be applied during the follow up. Microscopy, Xpert MTB/RIF test and culture will be performed during the period of follow-up for any child with suspected TB.

Some parents or caregivers of children who will receive IPT will be asked question at the end of the treatment about IPT adherence and factors which have influenced good and bad adherence.

Transport means will be provided any time you are requested to come to the HC for the purpose of this study.

If you do not want to take part in this study, the index case and child who are still on TB treatment or prophylaxis will continue receiving the same care in the clinic where they would if the study was not there.

Would my participation in this study be kept confidential?

The researchers commit themselves to protect your identity and the nature of your contribution. To ensure your anonymity, your answers to the questions will be marked on a form. Your name will not be on the answer sheet. Only a code will be linked to your answers. This code is called a study identification (ID), so all your answers will be kept confidential. This means that no one else, except the researcher and Investigators of this study, will have access to your answers; furthermore, they will be kept in a safe locked cabinet at the CMHS-SPH. For children eligible to GL, we need to fill in a form baring the child's ID to send to the lab.

If we write a report or article about this research project, your identity will remain unrevealed.

In this study we will need to know the factors associated with adherence to IPT. Hence we will use focus groups; therefore the extent to which your identity will remain confidential is also dependent to participants in the Focus Group maintaining confidentiality.

What are the risks of this research?

Participating in this research, especially children who will be required to provide the GL samples maybe exposed to undue risks. They may experience some discomfort, pain, epistaxis, vomiting, vocal cord trauma, esophageal perforation, anxiety, inconsolable crying. However, trained and experienced nurses with will collect samples at minimal risks.

All human interactions and talking about self or others carry some amount of risks. We will nevertheless minimize such risks and will act promptly to assist you if you experience any of them during the process of your participation in this study. Where necessary, appropriate referral to seek advice, assistance or intervention from suitable professionals will be recommended.

What are the benefits of this research?

The benefits to you include the fact that you will know whether your child has TB disease or not**.** If he/she has TB disease he / she can get the right care bringing about better outcome and stop of TB transmission by sick child in your household and the community. Also if your child is under five years old and /or HIV positive, he/she will get IPT for preventing him/her to get TB disease.

In addition, we inform you that the research will be conducted for the purpose of the PhD studies and subsequent publications. Moreover, the answers that we will get from the study will be submitted to the Government of Rwanda, which will be used to improve the management of TB among children.

Your participation in this research is voluntary. You may choose not to take part at all. If you decide to participate in this research, you may stop participating at any time. If you decide not to participate in this study or if you stop participating at any time, you will not be penalized or lose any benefits to which you otherwise qualify as receiving TB treatment if you are the person who has TB in your household.

What if I have questions?

This research study is conducted by Dr. Birungi M. Francine, a PhD student at the University of the Western Cape and Lecturer at the UR/CMHS/SPH. If you have any questions about the research study itself, please contact Dr Birungi Francine at: UR/CMHS/SPH based at Kicukiro District on this telephone: +250 (788) 462574.

Should you have any questions regarding this study and your rights as a research participant or if you wish to report any problems you have experienced related to the study, please contact:

Prof Helen Schneider, Head of Department,
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Appendix 3: IRB approval letter

Appendix 4: IRB approval of study title change

Appendix 5: Publication (Paper 1)

Appendix 6: Publication(Paper2)

Appendix 7: Publication(Paper3)

UNIVERSITY OF RWANDA

College of Medicine and Health Sciences

CMHS Institutional Review Board

19th May, 2015

Ref: CMHS/IRB/**193**./2015

Dr BIRUNGI Mwayuma Francine
CMHS, UR

Dear Dr BIRUNGI Mwayuma Francine,

RE: ETHICAL CLEARANCE

Reference is made to your application for ethical clearance for the study entitled "**An evaluation of the role of Xpert Test and Community Health workers in improving the Diagnosis and Prevention of TB in children exposed to Index cases with PTB in Kigali Rwanda.**"

Having reviewed your protocol and been satisfied with your revised version incorporating the comments from the IRB, your study is hereby granted ethical clearance. The ethical clearance is valid for one year starting from the date it is issued and shall be renewed on request. You will be required to submit the progress report and any major changes made in the proposal during the implementation stage. In addition, at the end, the IRB shall need to be given the final report of your study.

We wish you success in this important study.

Professor Kato J. NJUNWA
Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Cc:
- Principal College of Medicine and Health Sciences
- University Director of Research and Postgraduate studies, UR

Kigali, 15/10/2015
Ref: CMHS/IRB/**314**/2015

Dr BIRUNGI Francine
School of Public Health, CMHS, UR

Dear Dr BIRUNGI Francine,

RE: Change of Title of your Study

Reference is made to your request for changing the title for your research project from **"An evaluation of the role of Xpert Test and community health workers in improving the diagnosis and prevention of TB in children exposed to Index cases with TB in Kigali Rwanda"** to "**An evaluation of Isoniazid prophylaxis treatment and the role of Xpert MTB/FIF test in improving the diagnosis and prevention of tuberculosis in children exposed to index cases with Pulmonary tuberculosis in Kigali Rwanda."**

The IRB is pleased to inform you that your request is accepted Kindly note that your original ethical clearance still holds except for the title which has changed.

We wish you success in this important study.

Professor Kato J. NJUNWA
Chairperson Institutional Review Board,
College of Medicine and Health Sciences, UR

Cc:
- Principal College of Medicine and Health Sciences, UR
- University Director of Research and Postgraduate studies, UR

PanAfrican Medical Journal

Open Access

Research

Xpert MTB/RIF assay did not improve diagnosis of pulmonary tuberculosis among child contacts in Rwanda

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Key words: Pulmonary tuberculosis, child, contact screening, Xpert MTB/RIF assay, gastric lavage

Received: 24/04/2017 - Accepted: 19/04/2018 - Published: 17/05/2018

Abstract

Introduction: To report on the diagnostic yield using the Xpert MTB/RIF assay on gastric lavage samples from children (<15 years) who were household contacts of tuberculosis (TB) cases in Kigali, Rwanda. **Methods:** A cross-sectional study was conducted among 216 child contacts of index cases with sputum smear-positive TB over a 7 month period, from 1st August 2015 to 29th February 2016. Child contacts with tuberculosis-related symptoms or abnormal chest X-ray had sputum collected by gastric lavage on two consecutive days and samples were examined by smear microscopy, Xpert MTB/RIF assay and solid culture. **Results:** Of the 216 child contacts, 94 (44%) were less than 5 years of age. Most of them 84 (89%) were receiving isoniazid preventive therapy at the time of screening. Thirty seven out of 216 children had TB-related symptoms. Only 4 (10.8%) were clinically diagnosed with TB; and none had bacteriologically confirmed tuberculosis. **Conclusion:** The use of Xpert MTB/RIF assay did not contribute to bacteriological confirmation of active TB in child contacts in this study. The low prevalence of tuberculosis in child contacts in this study may reflect the high coverage of preventive therapy in young (<5 years) child contacts. The low sensitivity of Xpert MTB/RIF assay in contacts may also suggest likely reflection of paucibacillary disease.

Pan African Medical Journal. 2018;30:39. doi:10.11604/pamj.2018.30.39.12600

This article is available online at: http://www.panafrican-med-journal.com/content/article/30/39/full/

Introduction

Tuberculosis (TB) is a major cause of morbidity and mortality among children (0-14 years) in resource-limited countries [1]. The World Health Organisation (WHO) estimated that 10% of the 9 million TB incident cases occurred in children in 2015 and that there were 210,000 TB-related deaths in children, including 170,000 in Human Immunodeficiency Virus (HIV)-uninfected children [2]. The annual report of Rwanda's 2013-2014 National Tuberculosis Program (NTP) indicated that child TB cases represented 6% of all notified TB cases, below the national target of 12% [3]. Among these cases, 68% were pulmonary TB and 22% were bacteriologically confirmed. These data suggest under-detection of TB in children in Rwanda, especially of clinically diagnosed cases. There are well recognised challenges with detection and diagnosis, particularly in young children (<5 years) with paucibacillary disease, difficulty in obtaining samples and clinical overlap of TB with other common diseases such as severe pneumonia and malnutrition [4-7]. Young children (< 5 years) who develop active TB subsequent to infection with Mycobacterium tuberculosis, usually do so within one year of infection [8]. Children who are close to a TB index case are at high risk of TB infection [9-12]. Without any intervention, 5-10% of infected children will develop active TB within one year, with the highest prevalence of TB at the time of screening being in young children (< 5 years) [8,13]. Screening of child contacts of TB cases, prioritising index cases with sputum smear-positive pulmonary TB, is almost universally recommended and plays two important roles which include identification and evaluation of symptomatic contacts of any age requiring further diagnostic assessment of TB for early treatment (i.e. active case finding), and the provision of preventive therapy to "high-risk" contacts that do not have active TB [14]. Since 2006, WHO has recommended a symptom-based screening approach that allows the initiation of contact management and the provision of preventive therapy for asymptomatic young child contacts at the household or primary care level [15,16]. However, symptomatic contacts need further evaluation for TB and this remains challenging at the primary or secondary care level given the widely recognized limitations of current diagnostic tools especially in young children.

In 2013, the WHO endorsed the Xpert MTB/RIF assay for use in children [15,17]. The Xpert MTB/RIF assay offers advantages over smear microscopy for acid-fast bacilli. Research studies reported Xpert MTB/RIF assay to be three times more sensitive than sputum smear but with sensitivity compared to culture lower in outpatient children than in inpatients (48% versus 70%) [18]. Under programmatic conditions in a large study in India, Xpert MTB/RIF assay had twice the yield of smear with similar yield from sputum collected by gastric aspirate or induced sputum [19]. The Xpert MTB/RIF assay can be implemented in a peripheral laboratory with a result in less than two hours that includes information on rifampicin resistance [17,20]. Hence, the Xpert/MTB/RIF assay can potentially improve case detection among child contacts compared to smear while overcoming other constraints to active screening that include reducing the time, cost and complexity to the individual, family and health service incurred by the need for multiple visits to a hospital to complete evaluation for TB [21,22]. Few studies have evaluated the performance of the Xpert MTB/RIF assay in the context of contact screening in children where the children with TB are outpatients and likely to have early disease that is paucibacillary compared to hospital-based studies of more advanced cases passively detected [18,23,24]. Further, no previous studies have utilised gastric lavage (GL) in the evaluation of symptomatic child contacts. The Xpert MTB/RIF assay was introduced as a diagnostic tool for all children suspected of having TB in Rwanda in 2014. However, only samples from self-expectorated sputum have been used. This study aims to evaluate the diagnostic performance of the Xpert MTB/RIF assay in sputum collected by GL in symptomatic children who are contacts of index cases with sputum smear-positive TB.

Methods

Study design and setting: This is a cross-sectional study of child contacts of sputum smear-positive index cases who were detected between 1st August 2015 and 29th February 2016 at 13 primary health centres (PHCs) based in Kigali, the capital city of Rwanda. Kigali reports the highest prevalence of TB in Rwanda and around 30% of Rwanda's total pulmonary TB (PTB) cases [**25**]. Kigali city has four referral hospitals, four District hospitals which are all TB diagnostic and treatment centres and 35 PHCs. Of the PHCs, 23 provide TB diagnostic and treatment services; thus, potential entry points for TB cases. A PHC was selected for inclusion in this study if it reported an average of at least 10 sputum smear-positive PTB cases during the first half (January to June) of 2015.

Study population: Index cases diagnosed with sputum smear-positive PTB between August 2015 and February 2016 who had at least one child less than 15 years old, but who were not a member of a household to which a previous selected index case belonged and still living in Kigali city, were eligible for inclusion in the study. Identified index cases were requested, either via telephone calls or through trained community health workers (CHWs), to bring children with whom they live with to their PHC on a specific day to coincide with visits to that PHC by data enumerators. Child contacts were defined as those contacts of less than 15 years who shared the same household with a selected index case within the 3 months prior to the diagnosis of the index case. Therefore, all child contacts born after the index cases had started treatment or were not leaving with the index cases prior to the diagnosis of the index cases were excluded. Eligible children were enrolled following written informed consent by the parent or caregiver and children of 7 years and older also signed an assent form.

Data collection and management: A structured questionnaire adapted from screening guidelines [26,27] was pre-tested and modified during a pilot study in two selected sites. Twelve data enumerators were trained to conduct interviews with parents/caregivers of selected child contacts and to collect data from TB registers and index case folders, using standardised data collection forms. We also trained 20 CHWs to explain the study to the parents/caregivers, and sensitise them to bring child contacts for screening at the PHCs. Data of the index case included: result of smear microscopy, demographic data, address of residence and telephone number. The uptake of IPT among child contacts following diagnosis of the index case was also recorded. The recorded data were validated by the index case, parents or caregivers of selected children once they were identified in order to ensure the accuracy of the data. The demographics and medical history of index cases were recorded; and all eligible children underwent clinical screening including nutritional assessment and Chest X-ray (CXR). The clinical screening focussed on symptoms suggestive of TB: cough for ≥ 2 weeks, haemoptysis, fever, failure to gain weight, absence of appetite, fatigue, and the presence of lymphadenopathy. Anteroposterior and lateral CXR were also performed on all the 216 children; and read by two independent experienced general practitioners, trained in interpreting CXR and blinded to the clinical details of participants and proofread by an experienced radiologist. Children with symptoms suggestive of TB and/or CXR "consistent with active TB", as described in Table 1, were given antibiotics for seven days as recommended by the current TB diagnostic algorithm in the country. Those children were thereafter reassessed. Children with persistence of symptoms despite appropriate treatment were referred to a district hospital as outpatients for sputum collection through GL. A trained nurse, under supervision of a senior paediatrician, collected a sputum sample (3-4ml), using GL technique, on two consecutive mornings from the children after six hours of fasting. The samples were directly transported to Kigali teaching hospital laboratory, a qualified high performance diagnostic mycobacteriology laboratory, where they were processed by trained technicians and investigated by smear microscopy, Xpert MTB/RIF assay and solid culture within two hours subsequent to their collection. Children diagnosed with TB were treated in accordance with the Rwanda NTP treatment guidelines [28]. Young child contacts of less than 5 years of age and with no evidence of active TB were offered IPT for 6 months as per national guidelines if they were not already receiving IPT at the time of screening.

Laboratory procedure: For Xpert MTB/RIF assay test, 2ml of buffer, a tampon solution of Xpert MTB/RIF assay test, was added to 1ml of fresh sample. It was then shaken and stood for 10 minutes and shaken again and stood for further 5 minutes and then, 2.5 ml of the mixed solution was transferred into the Xpert cartridge, scanned and tested. The result was read two hours later. For solid culture, 2ml of fresh sample was decontaminated with 2 ml of sodium hydroxide and then the mixed solution was neutralized with hydrochloric acid before centrifuging at 3000xg for 15 minutes by using aerosol free centrifuge cups. The sediment was thereafter re-suspended in 2ml of sterile distilled water by 0.5ml transfer pipette. At the end, 0.2 ml of sediment was inoculated onto solid media, Lowenstein Jensen media as per standard protocols [29]. The growth of Mycobacterium tuberculosis bacteria was checked every 7 days up to 8 weeks. For microscopy, a drop of sediment prepared for culture was used for fluorescent acid-fast smear microscopy following the standard procedure [29].

Data analysis: Clinical case definition categories for TB in children considered the standardised case definition recently published [30] and were based on clinical screening, X-ray and microbiological investigations. Children were categorized as follows: bacteriologically confirmed TB, unconfirmed TB and unlikely TB (Table 1). Categorical data were interpreted through frequency table with median and interquartile range (IQR) for continuous data. Chi square test or Fisher Exact test was performed to compare the proportion of the outcomes between the groups and 95%

confidence intervals (CIs) were calculated for the proportion of an outcome using the binomial exact method. The diagnostic performance of Xpert MTB/RIF assay was compared with the culture method as the primary reference standard. All analyses were conducted using Stata statistical software version 13.1 for Windows [31].

Ethical approval: The Senate Research Committee of the University of the Western Cape and the Ethic Review Board of the University of Rwanda, College of Medicine and Health Sciences approved the study protocol. Permission was obtained from Rwanda NTP to collect data from the eligible PHCs.

Results

Figure 1 outlines the study flow chart. There were 346 cases of sputum smear-positive PTB diagnosed and treated in Kigali during the study period from 1st August 2015 and 29th February 2016. Of these 346 index cases, 136 (39%) had at least one child contact and of these 136 index cases, 105 (77%) had a child contact that met the inclusion criteria. The other 31 (23%) index cases with a child contact did not meet inclusion criteria as the child was born after the diagnosis of the index case. Among the 233 child contacts of the 105 eligible index cases, 216 (93%) children met the inclusion criteria of child contacts. The other 17 (17%) were excluded, because they were not living with the index case within the 3 months prior to the diagnosis of the index case. Among these 216 child contacts, 37 (17%) children (derived from 28 index cases) had symptoms suggestive of TB and/or CXR "consistent with active tuberculosis" at the time of screening. Table 2 and Table 3 show the demographic characteristics of the eligible index cases and child contacts, respectively. The results reveal that median age of index cases was 35 years (IQR: 18-65); HIV test was done for 95 (90%) index cases and HIV prevalence was 27%. The findings show that 71 (68%) of all index cases had not yet completed TB treatment. The median age for symptomatic child contacts was 4 years (IQR: 2-13). Among those 37 children, 59% were under five years old, 54% were female, HIV test was done for 31(84%) of them, 3% were HIV positive, and 97% had the evidence of BCG vaccination recorded. IPT had previously been commenced in 84 (89%) of 94 young child contacts without active TB at the time of evaluation. Data of uptake and adherence to IPT will be presented separately once follow-up of the cohort is complete. The majority of child contacts selected in the study were asymptomatic at the time of screening: 179/216 or 83% (95% CI, 77%-87%). All symptomatic child contacts (100%) were exposed to air pollution (tobacco smoke or burning wood) and the majority (64%) had their parents as index cases with 81% in contact with index cases for more than 8 hours per day. In addition, the majorities (81%) of these children were living in the households with more than two people and 78% of those households had just one bedroom. Among the 37 symptomatic child contacts, 92% had at least one symptom suggestive of TB (Table 1) and 10.8% had a CXR "consistent with active tuberculosis". The most commonly reported symptoms were cough (65%), fever (24%), moderate malnutrition (19%) and enlarged cervical, axillary or inguinal lymph nodes (5%). The CXR was normal in 212 (98%) of all 216 children, whereas 33 (89%) of 37 symptomatic child contacts had a normal CXR. All four abnormal CXRs were reported as "air space opacification". No asymptomatic child had an abnormal CXR. Of the 37 symptomatic child contacts, 33 (89%: 95% CI 73-96) were classified as unlikely TB children and 4 (10.8%: 95% CI 3.9-26.4) had a clinical diagnosis of TB. This represented 1.8% (95% CI, 0.06-0.4) of TB cases among all 216 child contacts. All clinically diagnosed TB cases had at least one symptom suggestive of TB and a CXR consistent with active TB. All these children, who were ≥ 5 years of age, were initiated on TB treatment for six months according to the national guidelines [28] and all completed the TB treatment. None of the symptomatic contacts was bacteriologically confirmed by smear, Xpert MTB/RIF assay or culture on two GL samples.

Discussion

No child contacts were detected with bacteriologically confirmed TB, including those who were symptomatic at the time of screening. Only four (10.8%) children of all symptomatic child contacts were treated for TB based on clinical diagnosis. The very low overall yield (1.8%) of children diagnosed with TB in our study following contact screening is in sharp contrast to the high yield recently reported from Uganda where 10% of 761 contacts were diagnosed with TB of whom 71% were bacteriologically confirmed [32]. A study conducted in Indonesia among 269 child contacts using two separate samples obtained by induced sputum that also included Xpert MTB/RIF assay for M. tuberculosis diagnosed TB in 8% of 269 child contacts, but as in our study, none was bacteriologically confirmed [24]. Contrasting findings have been reported in adult

household contacts in Ethiopia [33] where the Xpert MTB/RIF assay in sputum yielded a high percentage of cases (9/14 or 64%) but numbers were small. A possible explanation for a low yield from Xpert MTB/RIF assay is that contact screening may select children with early disease as hospital based studies of children with presumptive TB have had much higher yields [18,23,34-36]. It has been demonstrated that the detection limit of Xpert MTB/RIF assay is low, showing only 131 colony forming unit (CFU) [95% CI: 106-176]/ml of specimen [20,33,37]. Our study also shows that none of the under-five years old child contacts had TB at the time of screening, despite being known to be an "at-risk" group with a high yield of active TB (around 10%) at the time of screening [8,12,13]. This is likely because a large proportion (89%) of child contacts ≤ 5 years were already on IPT at the time of screening. In the studies in Uganda and Indonesia, only 1.5% (7/490) and 0% (0/99), respectively, of eligible child contacts who started on IPT developed active TB [24,32]. Further, there was also a time delay between diagnosis of the index case and contact screening of up to 5 months. There was a low yield from Xpert MTB/RIF assay in sputum collected using GL technique in this study from two sputum samples, which suggests the need to evaluate resource implications and cost-benefit of the policy that recommends Xpert assay for children with presumptive TB who are household contacts [24]. Our study has a number of major limitations. The absence of any confirmed TB cases prevented us from making conclusive remarks about the performance of Xpert MTB/RIF assay as a diagnostic tool in child contacts in sputum using GL technique besides and there was no comparison with other collection methods. Moreover, the small number of TB cases observed could lead to the reduction of the power to detect small differences in the yield between Xpert MTB/RIF assay and clinical diagnosis, microscopy and solid culture.

Conclusion

The use of Xpert MTB/RIF assay did not contribute to bacteriological confirmation of tuberculosis in child contacts in this study in Rwanda in a setting where there was a high uptake of preventive therapy among eligible child contacts. The low sensitivity of Xpert MTB/RIF assay in contacts may also suggest likely reflection of paucibacillary disease because of early case detection.

What is known about this topic

- Performance of the Xpert MTB/RIF assay in inpatient and outpatient children (passive case detection);
- Performance of the Xpert MTB/RIF assay in Induce sputum in symptomatic contacts children.

What this study adds

- Performance of the Xpert MTB/RIF assay in the context of contact screening in contacts children already on IPT;
- Performance of the Xpert MTB/RIF assay in sputum collected by GL in symptomatic contacts children (early case detection).

Competing interests

The authors declare no competing interests.

Authors' contributions

Francine Birungi, Stephen Michael Graham, Jeannine Uwimana, Brian van Wyk, Joseph Ntaganira Conceived and designed the experiments. Francine Birungi, Stephen Michael Graham, Jeannine Uwimana, Brian van Wyk Analysed and interpreted the data. Francine Mwayuma Birungi, Stephen Michael Graham, Jeannine Uwimana, Brian van Wyk, Joseph Ntaganira, Wrote the paper. All the authors have read and agreed to the final manuscript.

Acknowledgments

We would like to express our sincere gratitude to study participants and their parents or caregivers, TB diagnostic laboratory staff, TB focal points, head of PHCs, Community health workers and data enumerators involved in this study. We thank also Jino Bahemuka and Mary Nellima Ondiaka for editing the manuscript. We also thank the Swedish International Development +Agency (Sida) that funded this study through University of Rwanda Coordination office of Research Activities (UR-CRA). We declare that the funder has no role in the study design, data collection and analysis, preparation of the manuscript and decision to publish.

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Table 1: Operational definition used in this study
Symptoms suggestive of tuberculosis
Persistent unexplained fever: a one-week unexplained fever of greater than 38°C have been reported by parent or caregiver or at least once objectively recorded
Cough for more than 2 weeks: a story of persistent, unremitting cough for more than two weeks not responding to the standard therapy
Documented weight loss or failure to thrive: unexplained weight loss for more than 5% compared with the highest weight recorded in last 3 months
Malnourished: weight for height Z score (see definition four below)
CXR "consistent with active TB" if there is a positive response to any of the radiographic features, at the same location, by at least 2 independent radiologist reviewers
Air compression and/or tracheal displacement
Soft tissue density suggestive of lymphadenopathy
Air space opacification
Nodule picture (miliary or larger widespread) and bilateral
Pleural effusion
Cavities
Calcified parenchyma and
Vertebral spondylitis
Tuberculosis disease; if the child met the following criteria
Confirmed TB: Presence of one or more symptoms suggestive of TB, a chest radiography "consistent" with active TB and microbiological confirmation (in this study Xpert MTB/RIF assay test and/or culture positive)
Unconfirmed TB: as our study is constituted by child contacts, we will consider in this category a child who will display at least one of the symptoms suggestive of TB, CXR consistent with active TB
Unlikely TB: symptomatic child contacts suspected of TB whose symptoms and/or CXR consistent with active TB spontaneously improved after seven days of antibiotics without receiving any TB treatment
Nutritional assessment using Weight-for-Height
Normal : Z score ≥ -2 of the WHO median
Moderate malnutrition: Z score -3 to < -2 of the WHO median
Severe malnutrition: Z score < -3
Abbreviation WHO: World Health Organisation; CXR: Chest X-ray

Table 2: Characteristics of the index cases of child contacts		
Characteristics	**All index cases (n=105) No (%)**	**Index cases with symptomatic Children (n=28), No (%)**
Age median (IQR)	35 (18-65)	33 (19-65)
Age group in years		
Female	51 (49)	13 (46)
Residence of children		
Nyarugenge	23 (22)	7 (25)
Kicukiro	27 (26)	8 (29)
Gasabo	55 (52)	15 (46)
Type of health facility		
Public	70 (67)	16 (57)
Faith based	35 (33)	12 (43)
Sputum smear		
Scanty	8 (7.6)	4 (14)
Positive 1	22 (20)	5 (18)
Positive 2	15 (14)	6 (21)
Positive 3	32 (30.4)	9 (32)
Positive 4	28 (27)	4 (14)
Not completed TB treatment	71 (68)	17 (61)
Index case tested for HIV	95 (90)	27 (96)
HIV positive	28 (27)**	6 (22)
Abbreviations: IQR: interquartile range; HIV: human immunodeficiency virus; **: only 95 persons were tested and this number is the denominator.		

Table 3: Characteristics of child contacts		
Characteristics	**All child contacts (n=216) No (%)**	**Symptomatic child contacts (n=37) No (%)**
Age median (IQR)	6 (2-13)	4 (2-13)
Age group in years		
< 5 years	94 (44)	23 (62)
≥ 5 years	122 (56)	15 (41)
Sex child contact		
Female	104 (49)	20 (54)
Sputum smear of index cases		
Scanty	23 (11)	8 (22)
Positive 1	36 (17)	6 (16)
Positive 2	33 (15)	7 (19)
Positive 3	58 (26)	10 (27)
BCG scar	196 (90)	36 (97)
Nutritional status (Weight for age)		
Severe malnutrition	0 (0)	0 (0)
Moderate Malnutrition	15 (7)	7 (19)
Normal	201 (93)	30 (81)
HIV positive/tested (%)	5/83 (6)	1 (3)
Receiving IPT /eligible (%)	84/94 (89)	19/23 (82)
Relationship to Index case		
Grandchild	15 (7)	5 (14)
Sibling	27 (13)	4 (11)
Child	150 (70)	23 (64)
Others	21 (10)	4 (11)
CXR "consistent with active TB"	4 (1.8)	4 (11)
Spends ≥ 8 hours per day in the same room as the index case	144 (67)	30 (81)
Shares a bed with the index case	150 (69)	15 (41)
Sleeps in the same room as the index case	77 (36)	16 (44)
Number of people living in the house at the time of the diagnosis		
One person	36 (17)	7 (19)
Two persons or more	180 (83)	30 (819)
Number of bedrooms in the house at the time of interview		
One bedroom	181 (84)	29 (78)
Two bedrooms	27 (13)	8 (22)
Three bedrooms	7 (3)	0 (0)
Indoor air pollution exposure (to tobacco or biomass cooking)	159 (74)	37 (100)
Abbreviations: IQR: interquartile range; BCG: Bacille calmette guerin; IPT: isoniazid preventive therapy		

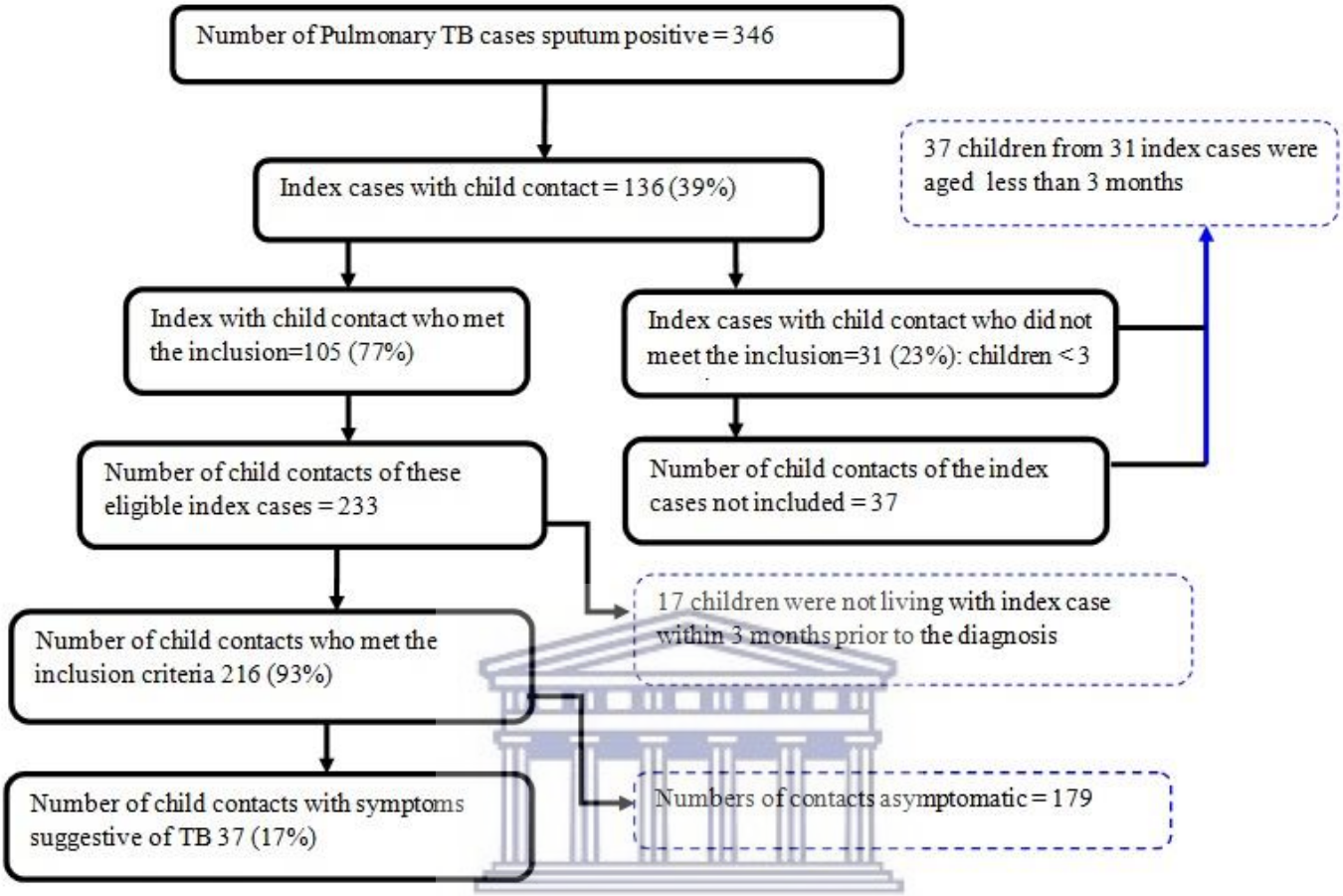

Figure 1: Flow of child contacts recruitment

Hindawi
Tuberculosis Research and Treatment
Volume 2018, Article ID 8690714, 9 pages
https://doi.org/10.1155/2018/8690714

Research Article

Assessment of the Isoniazid Preventive Therapy Uptake and Associated Characteristics: A Cross-Sectional Study

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Received 11 August 2017; Revised 2 February 2018; Accepted 25 March 2018; Published 6 May 2018

Academic Editor: Vincent Jarlier

Objective. To assess the uptake of isoniazid preventive therapy (IPT) by eligible children in Kigali, Rwanda, and associated individual, households, and healthcare systems characteristics. *Methods.* A cross-sectional study was conducted among child contacts of index cases having sputum smear-positive pulmonary tuberculosis. Data were collected from 13 selected primary health centres. Descriptive statistics were used to generate frequency tables and figures. Logistic regression models were performed to determine characteristics associated with IPT uptake. *Results.* Of 270 children (under 15 years), who were household contacts of 136 index cases, 94 (35%) children were less than 5 years old and eligible for IPT; and 84 (89%, 95% CI 81–94) were initiated on IPT. The reasons for not initiating IPT in the remaining 10 children were parents/caregivers' lack of information on the need for IPT, refusal to give IPT to their children, and poor quality services offered at health centres. Factors associated with no uptake of IPT included children older than 3 years, unfriendly healthcare providers, HIV infected index cases, and the index case not being the child's parent. *Conclusion.* The National Tuberculosis Program's policy on IPT delivery was effectively implemented. Future interventions should find strategies to manage factors associated with IPT uptake.

1. Introduction

In 2015, the World Health Organisation (WHO) estimates showed that 10% of the 9 million tuberculosis (TB) incident cases occurred in children, which resulted in 210,000 TB-related deaths including 170,000 in HIV-negative children [1]. Children exposed to index cases with TB, particularly sputum smear-positive pulmonary TB (PTB), are at risk of infection and when infected, infants and young children (<5 years old) are at high risk of developing the disease [2, 3]. WHO recommends routine screening of child contacts in resource-limited settings through a symptom-based screening approach that can be implemented in the community and provision of preventive therapy for at-risk contacts after excluding TB [4]. The most widely recommended regimen is isoniazid preventive therapy (IPT) that is provided as a daily dose for at least 6 months. Notwithstanding the potential benefits of contact screening for active case detection and initiation of IPT, these activities are rarely implemented in TB endemic settings [5, 6]. Furthermore, even when IPT is offered to eligible children, its uptake is often poor [7, 8].

Rwanda is a TB endemic resource-limited country, which had an estimated 6.6 [95% IC: 5.6–7.6] thousand new TB cases in 2015 [1]. According to the TB surveillance system, 5,763 TB cases, including 68.1% of new confirmed bacteriological pulmonary TB cases and 85.3% of sputum smear-positive PTB cases, were reported in the period between 2015 and 2016. Children under 15 years old represented 5.3% of all TB cases

reported [9]. The active contact screening and IPT are recommended by the National TB Programme (NTP) in Rwanda but TB case detection strategy is limited to passive screening. Although guidelines for IPT have been in existence since 2005, their implementation has not been assessed. For a few years, particular attention has been given to TB in children by Rwanda's NTP since TB treatment is recognized as an opportunity that prevents and addresses an important cause of child mortality [10, 11]. The NTP strategy has promoted the uptake and adherence of IPT as one of the 30 performance indicators since 2009. This paper reports about the uptake of IPT by eligible children in Kigali, the capital city of Rwanda, and evaluates the associated individual, households, and healthcare systems characteristics.

2. Methodology

2.1. Site Selection. A cross-sectional study was conducted at 13 primary health centres (PHCs) providing TB diagnostic and treatment services in Kigali. Kigali, the capital city of Rwanda, reports the highest prevalence of TB in Rwanda and around 30% of Rwanda's total pulmonary TB (PTB) cases [9]. Thus, Kigali was selected as case study site. There are 35 primary health centres (PHCs) in Kigali whence 23 PHCs provide TB diagnostic and treatment services and represent entry points for TB cases. The criterion used to select 13 PHCs from the 23 PHCs providing TB diagnostic and treatment services was a record of at least 10 sputum smear-positive PTB cases reported between January and June 2015. Among the 13 PHCs selected for this study, nine (69%) were public-funded and four were faith-based (public and private funded). Of the 13 PHCs, three had two staff members, and ten (77%) had one staff member, working in TB services. All the staff members were trained in TB management and provided counseling to parents/caregivers on IPT before their children started the regimen. In Rwanda, medication for TB is provided free of charge. Moreover, all TB index cases are offered the opportunity to choose the nearest healthcare facility or community health worker they wish to receive TB treatment or IPT.

2.2. Study Population. This study was conducted among household contacts of index cases with sputum smear-positive PTB in 13 selected PHCs from 1 August 2015 to 29 February 2016. The criteria for selecting an index case of any gender were as follows: having at least one child under the age of 5 years, not belonging to a household having a previously selected index case, and providing proof of living in Kigali during the period of study. Identified index cases were requested, through either phone conversations or trained community health workers (CHWs), to bring their children to the nearest PHC on a specific day that coincided with data enumerators' visits to the PHC. In case the index cases were not parents/caregivers of the children needed at the PHCs, they were requested to inform those children's parents/caregivers to do so.

Eligible child contacts were aged below 5 years old and shared the same household with a selected index case within 3 months prior to the diagnosis of the latter. The children were enrolled following the signing of written informed consent by parents or primary caregivers. Ineligible child contacts included those born after the index cases were diagnosed and initiated on TB treatment, child contacts on TB treatment, and those that were not living in the same household with the index cases before the diagnosis. Moreover, child contacts older than 5 years, including those infected with HIV, were also excluded in accordance with Rwanda's NTP policy.

2.3. Data Collection and Management. Data were collected in twofold, from patients' records at the PHC facilities and from parents/caregivers of eligible child contacts interviewed by trained enumerators using a structured questionnaire. The questionnaire was developed, pretested during a pilot study in two selected sites, and modified for later use in data collection. Twelve selected data enumerators were trained to conduct interviews with parents/caregivers of selected child contacts. Additionally, 20 CHWs were trained to identify and enumerate all eligible children in the households as well as explain the study to parents/caregivers and sensitize them to take child contacts to the nearest PHCs for clinical evaluation and data collection. Furthermore, by screening each child and interviewing each parent/caregiver, data enumerators ensured that the child contact was eligible or otherwise excluded even if he/she has been declared eligible by CHWs.

The uptake of IPT is defined as the proportion of children eligible to receive IPT according to the WHO recommendation [12]. Screenings conducted during this study identified all children as eligible for IPT according to the WHO recommendation [12]. To assess the uptake of IPT, every parent/caregiver of an eligible child was asked whether the child was initiated on the IPT or not. The IPT register at PHCs assisted to verify the information given by parents/caregivers. The sociodemographic characteristics and medical history of index cases, such as a result of smear microscopy, HIV status, residential address, and telephone number, were recorded. The data collected were validated by the index cases, parents, or caregivers of selected children once they were identified to ensure their accuracy. All children underwent a history, physical, and chest X-ray (CXR) examination. Anteroposterior and lateral CXR were also performed on all children; they were read by two independent experienced general practitioners, trained in interpreting CXR and blinded to the clinical details of participants; an experienced radiologist verified all CXR to rule out any discordance. The components of all reports were agreed on before a final diagnosis was determined. Symptomatic children are treated with antibiotics for seven days as recommended by the current TB diagnostic algorithm in the country. Child contacts with persistent TB-related symptoms or abnormal CXR were referred to the District Hospital for further tests including smear microscopy, Xpert MTB/RIF assay, and solid culture using sputum collected through gastric lavage following the standard procedure [13] in order to exclude TB disease.

The interview with eligible children's parents/caregivers identified the sociodemographic and economic characteristics of the index cases, their households, and knowledge on how to prevent TB in child contacts. A parent/caregiver was considered knowledgeable about, first, IPT prevention if he/she knew that administering INH for 6 months would

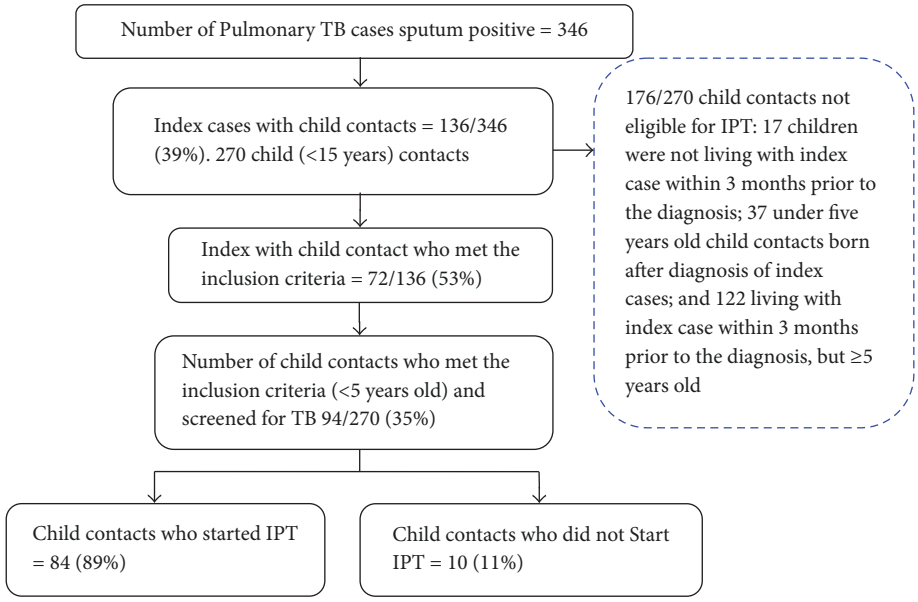

Figure 1: Flow of recruitment of child TB contacts.

protect the child contacts against TB. Second, prevention of child contacts from contracting TB if he/she knew three of the following pieces of information: using a mask when breastfeeding, avoiding to kiss him/her, avoiding to sleep in the same room or bed with him/her, opening windows and doors for good ventilation, and using arm protection when coughing. The interview with eligible children's parents/caregivers also determined characteristics of the healthcare facility such as quality of services provided and the attitude of health providers towards patients. Those characteristics were assessed by asking parents/caregivers the level of satisfaction with the quality of services offered at the PHCs and whether the healthcare service providers were friendly.

2.4. Data Analysis. The data collected were double-entered into a Microsoft Excel worksheet and exported to Stata Software for statistical analysis after checking their consistency. The data were analyzed using descriptive and multivariate statistics. Continuous variables were dichotomized using the median as the cut-off. Categorical variables were described using frequency tables and proportionate methods. Univariate and multivariate logistic regression was performed to determine characteristics associated with IPT uptake. Where appropriate, Chi-square test or Fisher's exact test was performed to assess the association between two variables. Variables with a p value < 0.2 in univariate analysis were included in the logistical regression model using backward stepwise method. The final model included those factors that retained statistical significance. The odd ratios (OR) and adjusted OR (aOR) along with its 95% confidence interval were calculated using Stata Software (version 13). The associations were declared significant if p value < 0.05.

2.5. Ethical Approval. The Biomedical Research Ethics Committee of the University of the Western Cape and the Ethics Review Board of the University of Rwanda, College of Medicine and Health Sciences, approved the study protocol. Permission was obtained from Rwanda NTP to collect data from the eligible PHCs.

3. Results

Figure 1 shows the flow of recruitment of child contacts with 136 (39%) of 346 sputum smear-positive PTB index cases diagnosed and treated at 13 PHCs in Kigali during the 7-month study period. The index cases had at least one child contact aged between 0 and 14 years. Of the 136 index cases, 72 (53%) had at least a child contact who met the inclusion criteria. Of 94 (35%) children from 72 index cases who were eligible, 84 (89%) had started IPT.

Tables 1, 2, and 3 show the characteristics of the eligible index cases, their households, and child contacts by IPT uptake, respectively. The results show no significant difference between children who started IPT and those who did not with regard to the characteristics of index cases (Table 1) and healthcare facilities (that are unfriendly versus friendly and satisfaction level of parents/caregivers on the quality of services offered). There were significant differences between children who started IPT and those who did not with regard to the sex of the head of the household (13/62 versus 5/10, p = 0.049) (Table 2) and the age of the child contact (≤3 versus >3 years, p = 0.007) (Table 3). Children living in households headed by female were more likely not to be initiated on IPT than those living in households headed by a male. Also, children aged > 3 years old were more likely not to be initiated on IPT than those ≤ 3 years old. Tuberculosis-related symptoms such as coughing, fever, and weight loss were reported by 25% (23/94) of child contacts, and those cases reported responded to generic antibiotics recommended by the current TB diagnostic algorithm in the country. Neither

Table 1: Characteristics of the index cases of the child contacts by uptake of IPT.

Characteristics	Index cases ($N = 72$) (%)	Index case whose children took IPT ($N = 62$) (%)	Index case whose children did not take IPT ($N = 10$) (%)	p value
Age group				0.716
≤35 years old	39 (54)	34 (55)	5 (50)	
>35 years old	33 (46)	28 (45)	5 (50)	
Sex, female	33 (46)	28 (45)	5 (50)	0.776
Residence of the index case				0.641
Nyarugenge	12 (17)	11 (18)	1 (10)	
Kicukiro	20 (28)	16 (26)	4 (40)	
Gasabo	40 (55)	35 (56)	5 (50)	
Type of health facility used by index cases				0.262
Public	51 (71)	42 (68)	9 (90)	
Faith-based	21 (29)	20 (32)	1 (10)	
Marital Status				0.243
Never married	11 (15.5)	8 (13)	3 (30)	
Married	50 (69)	45 (73)	5 (50)	
Separated	11 (15.5)	9 (14)	2 (20)	
Index case Head of household	29 (40)	25 (40)	4 (40)	0.985
Index case tested for HIV	61 (85)	52 (84)	9 (90)	0.617
Result of HIV test Positive	18/61 (30)	13/52 (25)	5/9 (56)	0.063

IPT = Isoniazid Preventive Therapy; HIV = human immunodeficiency virus.

of the children screened presented with an abnormal CXR nor a diagnosed TB disease [12, 14]. The majority of parents/caregivers of child contacts (66/72, 92%) had knowledge of at least one method on how to prevent transmission of TB to children and 32% (23/72) had knowledge of IPT prevention (Table 2).

All the 94 eligible child contacts were screened for TB by PHC providers whence 84 (89%, 95% CI 81–94) were initiated on IPT for 6 months as per the national and WHO guidelines [12, 14]. The reasons given by parents/caregivers for not initiating child contacts on IPT were lack of awareness of the need to do so (5/10 or 50%); failure to initiate IPT (4 or 40%); and poor healthcare service experienced at the PHC (10%).

In univariate analysis, the age of child contacts, sex of the household head, and relationship between healthcare providers and parents/caregivers were associated with the uptake of IPT (Table 4). Child contacts over 3 years old were more likely not to be initiated on IPT than those who were below 3 years old (OR 7, 95% CI 1.65–29; $p < 0.008$). Children living in households headed by a female were more likely not to be initiated on IPT than those living in households headed by a male (OR 4.6, 95% CI 1.18–17.9; $p < 0.028$). Child contact whose parents/caregivers did not find friendly healthcare providers at the PHCs were also more likely not to be initiated on IPT than those whose parents/caregivers did. (OR 10, 95% CI 1.26–83; $p < 0.029$).

In multivariate analysis, the sex of households' head had no significance. The final explanatory variables of no uptake of IPT were age group of child contacts (≤3 years versus >3 years), HIV status of child contacts (HIV-positive versus HIV-negative), relationship between child contacts and index cases (child versus others), HIV status of index case (HIV-positive versus HIV-negative), household income (income < 50.000 Rwandan Franc versus ≥ 50.000 Rwandan Franc), and relationship between healthcare providers and parents/caregivers (friendly versus unfriendly). After adjusting the variables, the age of child contacts and relationship between healthcare providers and parents/caregivers remained associated with the uptake of IPT. Child contacts older than 3 years were more likely not to be initiated on IPT than those less than 3 years old (aOR 29, 95% CI 2.17–400; $p < 0.011$). Moreover, the child contacts whose parents/caregivers found healthcare providers unfriendly were also more likely not to be initiated on IPT than those whose parents/caregivers found them friendly (aOR 19, 95% CI 2.51–140; $p < 0.017$). The HIV status of index cases and the relationship between child contacts and index cases were also associated with no uptake of IPT in multivariate analysis. Child contacts living with HIV-positive index cases were more likely not to be initiated on IPT than those living with HIV-negative ones (aOR 8.1, 95% CI 2.53–537; $p < 0.038$). Furthermore, the child contacts who were not children of index cases were more likely not to be initiated on IPT than those who were index cases' children (aOR 59, 95% CI 2.74–127; $p < 0.009$).

4. Discussion

The primary aim of this study was to assess the uptake of IPT by child contacts and associated factors in order to

Table 2: Characteristics of the household of child contacts by uptake of IPT.

Characteristics	Total (N = 72) (%)	Child contact started IPT (N = 62) (%)	Child contact did not start IPT (N = 10) (%)	p value
Head of household				
Age group				0.501
≤37 years old	38 (53)	34 (55)	4 (40)	
>37 years old	34 (47)	28 (45)	6 (60)	
Sex, female	18 (25)	13 (21)	5 (50)	**0.049**
Household monthly income				0.149
≤50.000 Rwandan Franc	47 (65)	38 (61)	9 (90)	
>50.000 Rwandan Franc	25 (35)	24 (39)	1 (10)	
Marital Status				0.967
Never married	7 (10)	6 (10)	1 (10)	
Married	56 (78)	48 (77)	8 (80)	
Separated	9 (12)	8 (13)	1 (10)	
Highest education level completed				0.625
Never attended school	9 (12)	7 (11)	2 (20)	
Primary school	43 (60)	38 (61)	5 (50)	
Secondary school and plus	20 (28)	17 (28)	3 (30)	
Household				
Number of people living in the house at the time of the diagnosis of the index case				
One person	19 (26)	16 (26)	3 (30)	0.717
Two persons or more	53 (74)	46 (74)	7 (70)	
Parents/caregivers had knowledge of prevention of transmission of TB[a]	66 (92)	58 (94)	8 (80)	0.192
Parents/caregivers have knowledge on the role of IPT[b]	23 (32)	22 (35)	1 (10)	0.153

IPT = isoniazid preventive therapy; TB = tuberculosis; [a]aware about using a mask when breastfeeding, avoiding sleeping in the same room or bed with child contacts, opening windows and doors for improved ventilation, practicing hygiene while coughing. [b]Knowledgeable about the administration of INH for 6 months to protect child contacts against TB.

inform the NTP on its implementation. Despite the diversity methodology designs, the IPT uptake established in this study (89%) was found to be higher than 6% [15], 18.7% [16], 26.8% [17], 33% [18], and 64.3% [19] reported in Malawi, Timor-Leste, South Africa, South India, and Ethiopia, respectively. In contrast, recent studies conducted in the Gambia [20] and Benin [21] have reported an 89% and 99% of IPT uptake, which is similar to and higher than this study's findings, respectively. The integration of IPT into the programmatic delivery of healthcare might explain the high uptake reported in this study as well as in study findings reported in Gambia and Benin. This is in contrast to earlier studies that were conducted in a healthcare facility environment [15, 16]. Rwanda's NTP strategy adopts the households' visit of index cases by healthcare providers at the beginning of sputum smear PTB treatment. These visits allow for screening child contacts and initiating them on IPT. Our high IPT uptake finding corroborates results published in the 2013-2014 and 2015-2016 annual reports of Rwanda's NTP revealing an uptake of 85% and 78%, respectively. However, these reports do not provide information on the actual number of eligible contacts who had access to IPT in the community.

The WHO provided the first estimates of preventive therapy coverage for eligible children under the age of 5 years in 2016 [1]. The estimates showed that only 5.6% of an estimated 440,000 child contacts received preventive therapy in 2015 in the African region. However, Rwanda was among a few countries in Africa that provided data to the WHO from routine surveillance of preventive therapy for young child contacts [1]. Therefore, the high uptake in our study may reflect the particular attention being given by Rwanda NTP to TB in children in accordance with the Rwanda government's priority intervention aimed at preventing and addressing the most important causes of child mortality [10, 11]. Additionally, the goal of Rwanda NTP strategies is to strengthen more than 30 indicators outlined in the Performance-Based Financing (PBF) since 2009. The outlined indicators include "number of children eligible for IPT who received it" and "number of children aged below 5 years old who completed IPT." The funding of healthcare services according to the PBF is based on the performance of medical facilities in enhancing the quantity and quality of preventive and curative treatment to the people [22]. Hence, the PBF has improved the quantity and quality of healthcare in many countries [23–25].

Table 3: Characteristics of child contacts eligible for IPT by IPT uptake.

Characteristics	Under five years old child contacts ($N = 94$) (%)	Child contacts who started IPT ($N = 84$) (%)	Child contacts who did not start IPT ($N = 10$) (%)	p value
Age group				
≤3 Years	66 (70)	63 (75)	3 (30)	**0.007**
>3 Years	28 (30)	21 (25)	7 (70)	
Sex child contact				0.504
Female	43 (46)	37 (44)	6 (60)	
BCG_scar				
Yes	90 (96)	80 (95)	10 (100)	1.000
Children tested for HIV	47 (50)	39 (46)	8 (80)	0.091
HIV test Result Positive	2 (4)	2 (5)	0 (0.0)	0.051
Relationship to the Index case				
Child	70 (75)	65 (77)	5 (50)	0.060
Others	24 (25)	19 (23)	5 (50)	
Had TB-related symptom during the screening[a]	23 (24)	19 (23)	4 (40)/	0.252
Share the same bedroom with index cases	48 (51)	42 (50)	6 (49)	1.000
Time spend with index cases				
≥8 hours	75 (80)	66 (79)	9 (90)	0.681

BCG = Bacilli Calmette-Guerin; IPT = isoniazid preventive therapy, TB = tuberculosis; HIV = human immunodeficiency virus; [a]TB-related symptom = to have one of those symptoms (a cough, fever, and weight loss).

Table 4: Risk factors for nonuptake of IPT.

Factors	OR (95% CI)	p value	aOR (95% CI)	p value
Child contacts				
>3 Years	7.0 (1.65–29)	0.008	29 (2.17–400)	0.011
HIV positive	5.0 (1.0–25)	0.050	10 (0.61–174)	0.105
Not child of the index case	3.4 (0.89–13)	0.072	59 (2.74–127)	0.009
Index cases				
HIV-positive	4.0 (0.97–16.77)	0.054	8.1 (2.53–537)	0.038
Household factors				
Sex of the head of the household	4.6 (1.18–17.9)	0.028	-	
Income < 50.000 Rwandan Franc	0.1 (0.22–1.57)	0.123	0.1 (0.01–1.01)	0.050
Heath facility factors				
Provider not friendly	10 (1.26–83)	0.029	19 (2.514–140)	0.017

IPT = isoniazid preventive therapy; HIV = human immunodeficiency virus; CI = confidence interval; OR = odds ratio; aOR = adjusted OR.

Our study showed that most parents/caregivers of child contacts had some general knowledge on how to prevent TB in children. That level of knowledge was higher than that reported in studies conducted elsewhere [26, 27]. Information, Education, and Communication sessions are organized twice a week at healthcare facilities by service providers, at the community level by the CHWs and at local politico-administrative authorities level as well as in media, to inform the population about TB. Other studies have shown that low-level knowledge on TB could negatively affect the health-seeking behaviour of the people [27, 28]. Contrasting findings have been reported in a study conducted in Malawi, where only 8% of parents with sputum smear-positive TB took their children to a medical clinic for screening despite having clear information on the need to do so [8].

The geographical accessibility can also explain the high uptake of IPT in Rwanda. Across the country, there has been an improvement in the ease of access to healthcare centres. Countrywide, the average time to access the nearest health-care centre is less than 1 hour [29]. Transport cost was not a limiting factor mentioned by any parent/caregiver whose children were not initiated on IPT in our study as was the case in the study conducted in Malawi [30]. Furthermore, a study carried out in Bangkok, Thailand, by Tornee et al. [31] shows

that the short distance from home to the nearest medical clinic was associated with adherence of the households' contact to screening.

In the univariate analysis, the significance of the sex of household heads was lost when it was adjusted for other variables. This finding suggests that the sex of index cases was a confounder variable in this study. Nevertheless, additional studies are needed to investigate the role of gender in the decision to initiate IPT.

In multivariate analysis, our study established that the child contacts who were not children of index cases were more likely not to be initiated on IPT than those who were their children. This finding corroborates a study conducted in Timor-Leste [16] as well as a qualitative study in Bangkok, Thailand [31]. Both studies reported lack of screening of child contacts who were not children of index cases. The approach is slightly different in Rwanda, whereby household visits of index cases with sputum smear-positive PTB by healthcare providers helps in screening child contacts and initiating them on IPT. Thus, child contacts who are not children of the index cases have a high possibility of being screened even though the initiation of IPT among these children may be low. When an index case is not the biological parent of a child contact, the latter may choose to be visited by a healthcare provider in the absence of the former. Often, healthcare providers inform the index cases about the intended home visit so that children can be screened but not necessarily start on IPT. This is because index cases may not inform the parents or caregivers of the children the need for initiating their children on IPT. This could explain the 100% screening of eligible child contacts in this study whence only 89% were initiated on IPT. The parents/caregivers of 50% of child contacts who were not initiated on IPT reported their lack of information about its usefulness.

Our study also established that child contacts older than 3 years were more likely not to be initiated on IPT than those aged below 3 years old. These findings can be explained by the fact that parents/caregivers protect their younger children from contracting TB more than their older children. Similar findings were reported in a qualitative study conducted in Bangkok, Thailand, by Tornee et al. [31], which showed that parents/caregivers worry that their younger children might get TB infection and take them to healthcare facilities for screening.

The parents/caregivers who found unfriendly healthcare providers at the PHCs were also more likely not to initiate their children on IPT than those who found them friendly. Child contacts living with HIV-positive index cases were less likely to be initiated on IPT than those living with HIV-negative index cases. Those two factors may be correlated. A study demonstrated that interactions and negative experience of people seeking treatment in government healthcare facilities contribute to a reduction in subsequent medical visits or follow-ups [32], which is mostly observed among the HIV-positive population.

Besides the negative experience from unfriendly healthcare providers, the HIV-positive people have to cope with social stigma [33, 34]. A study revealed that women, who often take children to healthcare facilities, experience stigma-related problems more than men [35]. In our study, 71% index cases were followed up in public PHCs and 56% of them whose children were not started on IPT were HIV infected. This suggests that negative experience in government healthcare facilities and social stigma among TB-HIV coinfected persons have a negative impact on the uptake of IPT among child contacts. This finding is a cause of concern in Rwanda since the healthcare-seeking behaviour of HIV-positive parents/caregivers influence TB screening and management in children.

The study has some limitations. First, the research was conducted in Kigali; thus, the findings might not be generalized to the whole country, especially remote rural areas where healthcare-seeking behaviour may be different. Second, the sample size was small to enable comparative analyses that may have limited our statistical detection of small differences in the IPT uptake.

5. Conclusion

Findings from our study reveal that the NTP policy on the provision of IPT has been effectively implemented in Rwanda under the set programmatic conditions. Despite differences in methods of study, the percent IPT uptake established in this study is higher than that reported in Malawi, Timor-Leste, South Africa, South India, and Ethiopia and similar to and lower than in Gambia and Benin, respectively. Special attention should be given to child contacts more than 3 years old, child contacts who are not children of index cases, and child contacts who are children of HIV infected persons in order to identify the challenges experienced in initiating the IPT. Future interventions should find strategies to (1) fight against social stigma, especially in TB coinfected patients, and (2) eradicate the unfriendly attitude of healthcare providers towards all patients in general and TB coinfected patients in particular.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

Francine Mwayuma Birungi conceived the idea, designed the research, and was involved in the collection, analysis, and interpretation of the data. She drafted and critically revised the paper. Brian van Wyk, Jeannine Uwimana, and Stephen Graham advised on the protocol and drafted and critically reviewed the paper for important intellectual content. All authors reviewed and approved the final manuscript for publication. All authors read and agreed on the final manuscript.

Acknowledgments

The authors would like to express their sincere gratitude to study participants and their parents or caregivers, NTP staff, TB focal points, head of PHCs, community health workers, and data enumerators involved in this study. They thank also

Mr. Gédéon Bahemuka Jino and Dr. Mary Nelima Ondiaka for editing the manuscript. This study was funded by UR-Sweden collaboration programme.

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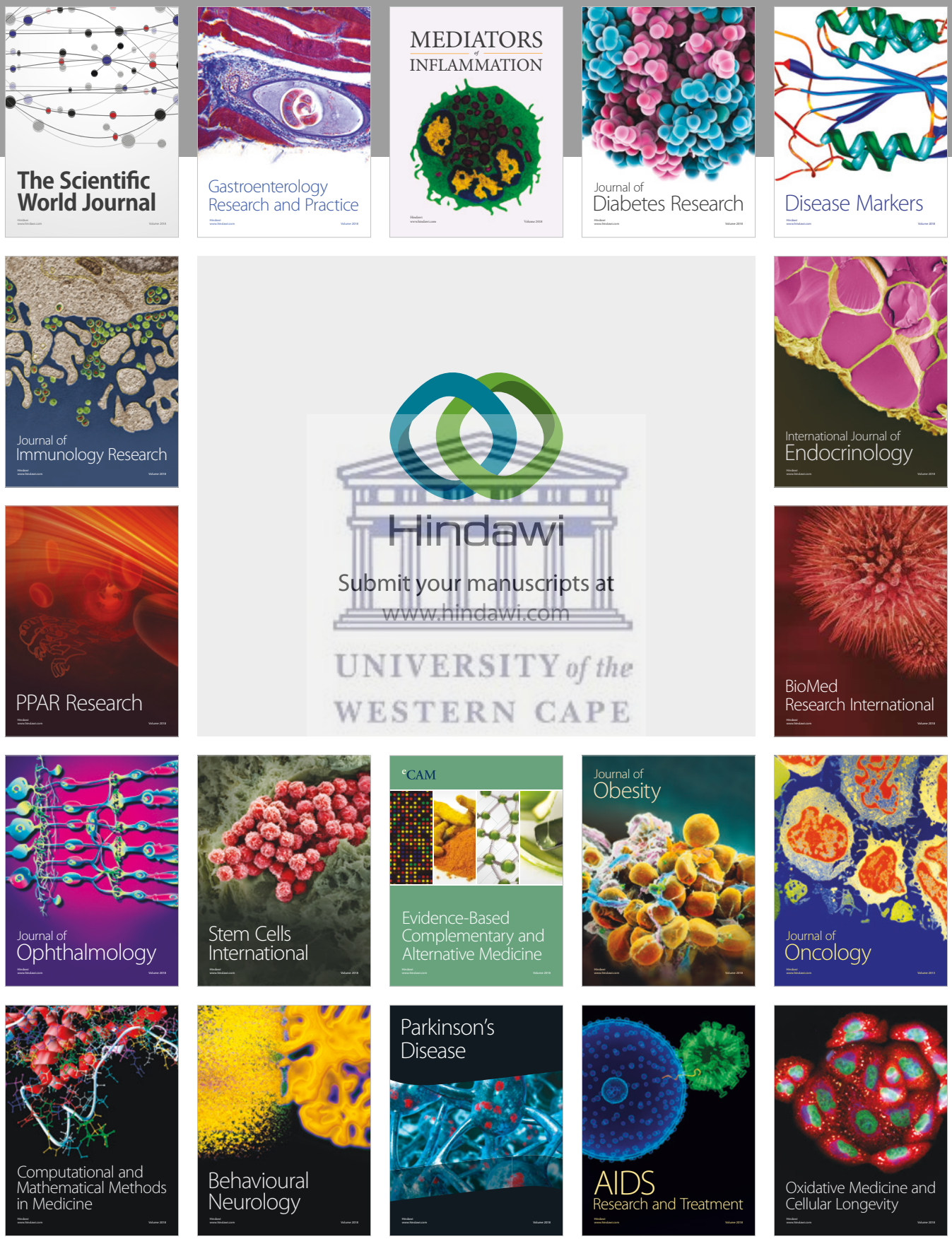

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RESEARCH ARTICLE

Adherence to isoniazid preventive therapy among child contacts in Rwanda: A mixed-methods study

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OPEN ACCESS

Citation: Birungi FM, Graham SM, Uwimana J, Musabimana A, van Wyk B (2019) Adherence to isoniazid preventive therapy among child contacts in Rwanda: A mixed-methods study. PLoS ONE 14 (2): e0211934. https://doi.org/10.1371/journal.pone.0211934

Editor: Petros Isaakidis, Médecins Sans Frontières (MSF), SOUTH AFRICA

Received: May 26, 2018

Accepted: January 24, 2019

Published: February 11, 2019

Data Availability Statement: The data set supporting the results of this article is available in figshare repository, doi: 10.6084/m9.figshare.6395984.

Funding: The project was funded by Swedish International Development Cooperation Agency through the University of Rwanda. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Background

The World Health Organization recommends isoniazid preventive therapy (IPT) for six months for child contacts without tuberculosis (TB), who are exposed to an adult with active TB. The effectiveness of IPT depends on 80% or greater adherence to medication. In the current study, we assessed IPT adherence and explored barriers to and facilitators of adherence among eligible child contacts in Kigali, Rwanda.

Methods

A mixed method study design was used to prospectively assess adherence to IPT among eligible child contacts and its associated factors through a quantitative, observational cohort study, and to explore barriers to and facilitators of adherence to IPT through a descriptive qualitative study.

Results

Of the 84 child contacts who started IPT, 74 (88%) had complete adherence and ten (12%) had incomplete adherence. There were no factors (individual characteristics of index cases, households and or health facility characteristics) found to be significantly associated with IPT adherence in the bivariate and multivariate analysis. In the qualitative analysis, we identified factors relating to parents/caregivers, disease, household and health-care providers as major themes determining IPT adherence.

Competing interests: The authors have declared that no competing interests exist.

Conclusion

There was a high rate of IPT completion in this cohort of eligible child contacts living in Kigali. However, structural factors (poverty and relocation) were found to be the main barriers to IPT adherence that could be addressed by health-care providers.

Introduction

Young children exposed to an adult or older child with tuberculosis (TB), referred to as an index case [1], are at high risk of infection with *Mycobacterium tuberculosis* [2,3]. Without any intervention, 5–10% of infected children will develop active TB within one year, and the risk is the highest among the youngest (<2 years old) or HIV-infected children [2,4]. Also, infants and young children are at high risk of developing severe disseminated forms of TB such as TB meningitis and miliary TB, and of TB-related mortality [5,6].

The World Health Organization (WHO) has for many years recommended isoniazid preventive therapy (IPT) for at least six months for young (<5 years) children who are exposed to a TB index case and who do not have active TB disease [7,8]. More recently, TB preventive treatment has received greater attention as a key element of the WHO's End TB strategy, which aims to reduce TB incidence by 90% by 2035 [9]. The most recent WHO guidelines for treatment of latent TB infection now include the consideration of older (≥5 years) child contacts without active TB for preventive therapy [10]. IPT has been proven effective in reducing TB incidence [8,9] and is included in the national TB programme (NTP) guidelines of many resource-limited countries [10]. However, IPT is not consistently offered to at-risk children, and when offered, is often unsupervised and characterised by poor uptake and adherence [11–14]. The effectiveness of IPT is dependent on 80% or greater adherence to medication [8]. Several studies from Indonesia, Ethiopia, Brazil and South Africa show inadequate adherence to IPT among child contacts [14–18]. Among these, the two studies conducted in Indonesia [16,17] revealed that access, social support and regime, caregivers and health care related factors were barriers and facilitators to IPT adherence. Studies from Indonesia and Brazil also reported that transport and medication costs were associated with incomplete adherence [16,18].

Rwanda established the IPT policy in 2005, and recently the NTP has focussed on TB in children because case detection and TB treatment are recognised as an opportunity to reduce child mortality [19,20]. Since 2009, the NTP strategy has been promoting the uptake and adherence to IPT as one of the 30 performance indicators. However, to date, no study has been conducted in Rwanda to assess the IPT adherence among child contacts, and little is known about the factors associated with inadequate adherence.

In Rwanda community health workers (CHWs) are involved in the management of child contacts. Other local interventions include free TB care, increased number of primary health-care centres (PHCs) and a community-based health insurance scheme to increase geographic and financial access to health care. In addition, performance-based financing has been implemented to motivate health-care providers to improve service output and quality of care. The current study reports on IPT adherence and explore s the facilitators and barriers to IPT adherence in Kigali, Rwanda.

Methods

Settings and participants

This study is part of a cross-sectional research project that was conducted in Kigali, the capital of Rwanda by a consortium of researchers from South Africa, Australia and Rwanda between

1 August 2015 and 29 February 2016 [21]. The study aimed to evaluate the diagnostic performance of the Xpert MTB/RIF assay in sputum collected by the gastric Lavage (GL) technique from symptomatic child contacts. Kigali has 35 primary health care centres (PHCs) that offer tuberculosis (TB) diagnosis and treatment services, which are also regarded as entry points for TB care. Thirteen of these PHCs were included in the main study based on them meeting the criterion of recording at least ten sputum smear-positive pulmonary TB (PTB) between January and June 2015.

Overall, 346 index cases of sputum smear-positive PTB were diagnosed and treated for the main project. Of these, 136 (39%) had at least one child contact who was younger than 15 years old at the time of the study. The 136 index cases had 270 child contacts. From the 136 index cases, 105 (77%) met the inclusion criteria of index cases and had 216 child contacts who met the inclusion criteria for the main project.

Of the 105 index cases, only those whose child contacts started IPT were recruited for the present prospective study that was conducted between August 2015 and August 2016. Eligible child contacts for the current study were younger than 5 years old, who started IPT according to the WHO recommendations [22]. They also shared the same households with the selected index cases in the three months before diagnosis of the latter. Only children who had their parental or primary caregivers' written consent were enrolled in the present study. Child contacts born after the index cases were diagnosed and had initiated TB treatment, child contacts on TB treatment, and those who were not living in the same households as the index cases before diagnosis were excluded from this study.

This study presents specific data elements that were derived from the main project. Those elements can influence IPT adherence which is under study in the current research. They include the characteristics of index cases, child contacts, households, health facility, TB screening results together with physical and chest X-ray (CXR) results [21].

Study design

In this study, we used a mixed research method design to prospectively assess IPT adherence and outcomes among child contacts through a quantitative, observational cohort study. Furthermore, we explored barriers to and facilitators of adherence to IPT through a descriptive qualitative study [23].

Data collection for the quantitative component

In August 2015, each TB focal person based at the selected PHC used a specific form, provided by researchers, to record each time the child came to collect a month's supply of IPT. A TB focal person, usually an experienced nurse working at the PHC, is responsible for coordinating and managing all activities such as providing TB treatment or IPT, contact screening, reporting, follow-up and supervision of TB patients and contacts.

Before data collection, TB focal persons from the selected PHC were trained on data collection procedures for two days. The training aimed at equipping them with skills to provide follow-up care (for example, monthly screening and transfer to the next level when a child has symptoms suggestive of TB) of children on IPT [S1 Appendix].

The researchers requested the parents/caregivers of child contacts who had been initiated on IPT to visit the PHC for clinical evaluation and receive the next month's supply of IPT each month until the end of the treatment. In this study, researchers measured "adherence" through a monthly collection of isoniazid [16]. "Complete adherence" refers to the collection of six of the child's monthly prescriptions, whereas "incomplete adherence" means that the child had received/collected less than six of his/her monthly prescriptions. IPT failure in this study is

defined as a proportion of child contacts on IPT who developed TB during the monitoring period. To achieve this, the researchers monitored all eligible child contacts for symptoms suggestive of TB such as persistent one-week fever (>1 week), cough (>2 weeks), weight loss, night sweats for 12 months following the initial evaluation.

During the six months of monitoring, while receiving IPT, the TB focal person screened the child contacts for TB at each visit for the presence of symptoms suggestive of TB, using the IPT form [S1 Appendix]. For the second six months' follow-up (post-IPT), the TB focal person evaluated the child contacts at 3 months and 6 months after finishing IPT. The researchers provided transport fees to all parents/caregivers who brought child contacts for screening during those two visits, which were not part of the routine clinical follow-up and monitoring. The post-IPT (at six months) visits were done to evaluate the impact of the IPT.

During the follow-up, the TB focal person referred any child contact showing symptoms suggestive of TB to the district hospital for further TB evaluation including smear microscopy, Xpert MTB/RIF assay and solid culture using sputum collected through gastric lavage. If a child contact was diagnosed TB positive, he/she was treated according to the national guidelines.

Data collection for the qualitative component

The researchers carried out in-depth interviews with 23 parents/caregivers of child contacts and ten health-care providers working in the TB service. Three focus group discussions (FGDs) were held with 24 CHWs who provided TB support in the community.

The researchers used purposive sampling to select parents/caregivers from the different catchment areas around the participating PHC to represent child contacts with complete adherence. They also used purposive sampling to select TB focal persons to represent different districts and types of PHCs (faith-based and public PHCs). The study included all available parents/caregivers with incomplete adherence.

Telephone numbers of parents/caregivers of child contacts available from the previous study database [21] and those of CHWs provided by TB focal persons, were used to inform and invite participants about their selection in this study. If in agreement, they were requested to go to the nearest PHC at a time and date indicated by the researchers.

Fieldworkers conducted interviews with parents/caregivers whose children had complete adherence and the health facilities staff until the data saturation was achieved (i.e. until no new data emerged). However, existing themes could accommodate new findings [24]. Each FGD involved eight CHWs who were purposefully selected to represent the different districts and PHCs in line with Krueger methodology [25].

Three fieldworkers (female senior nurses) experienced in qualitative methodology were recruited to conduct interviews in the local language using interview guides designed for this specific study. Two days of debriefing sessions were held with the qualitative fieldworkers before the fieldwork started. In the debriefing sessions, the principal investigator discussed each question with them explaining the nature of the response that each one was meant to elicit. Discussions on how to probe for further explanations were also held.

Different interview guides were used for parents/caregivers and health-care providers (TB focal persons and CHWs). Parents/caregivers whose child contacts had incomplete adherence were interviewed to explore possible barriers related to IPT access. The questions were framed to avoid apportioning blame for non-collection of IPT for their children as recommended by the Ethics Review Board of the University of Rwanda, College of Medicine and Health Sciences.

Interview guides were pretested, and no further modification was needed. The pre-test was done using four parents/caregivers as participants (two whose child contacts had IPT complete

adherence and two others whose child contacts had incomplete IPT adherence) and one TB focal person from a non-selected PHC based in Kigali. Parents/caregivers involved in the pre-test were identified by the TB focal person where the pre-test was done.

Participants signed a written informed consent form after reading it and after the researchers had read an introduction explaining the purpose and benefit of the study. The interview with health facility staff took place at their workplace (in the absence of their superior or any other staff), and the one with parents/caregivers took place at the PHC nearby their homes. These interviews lasted between 45 minutes to one hour. None of the participants declined to participate in the interview.

Depending on the participants (parents/caregivers, TB focal persons or CHWs) answering the questions, the researchers investigated their experiences about providing or receiving IPT. They also investigated barriers to and facilitators of IPT adherence, and expectations and suggestions. Two experienced qualitative researchers conducted the FGD in the local language at the PHC proposed by the selected CHWs. These fieldworkers used a discussion guide during the FGD; which lasted between 1½ to 2 hours.

After obtaining their agreement, the fieldworkers, under the supervision of the principal investigator, audio-recorded all interviews and FGD. For quality control, at the end of each interview session, the fieldworkers summarised the salient points of the interviews with confirmation or adjustments from the participants when necessary. Hereafter, the fieldworkers fully transcribed interviews and FGDs in Kinyarwanda. Afterwards, the principal investigator checked the transcriptions and carried out necessary alterations before analysis. The transcripts were then translated into English by a qualified translator. The English transcripts were verified by a bilingual member of the research team to ensure that these were clear, and participants' views adequately reported.

Data analysis and management of the quantitative component

The researchers double-entered the quantitative data into a Microsoft Excel worksheet and exported these to STATA13 Software [26] for statistical analysis after checking their consistency. Continuous variables, such as the age of the child contacts or monthly household income, were categorised following epidemiological or economic constructs. Age of child contacts was dichotomised into two values ($\leq$2 years and $>$2 years) as the literature suggests that infants who are $\leq$2 years old are more likely than those $>$2 years old to acquire TB [2,4]. The variable monthly household income was categorised in two values (Incomes $\leq$50.000 and 50.000 Rwandan Franc) following the poverty headcount ratio of Rwanda in 2018, which is $1.90 a day [27], equivalent to 50, 000 Rwandan Francs.

Researchers then analysed the data using descriptive and multivariate statistics, described categorical variables using frequency tables and proportionate methods. The researchers further performed the univariate and multivariate logistic regressions to determine characteristics associated with IPT adherence. Where appropriate, the researchers performed the Chi-square test or Fisher's exact test to assess the association between two variables and included those variables with a p-value $<$0.2 in univariate analysis in the logistic regression model using backwards stepwise method.

The final model included the following variables: sex of the child, child contact' s HIV status, sleeping in the same room as index case, the index case's sex and HIV status, the income of the household, if the head of the household had knowledge of IPT protection and attitude of health providers towards patients. This further included calculating the odds ratios (OR) and adjusted OR along with its 95% confidence interval using STATA13 software [26]. In this case, the researchers declared the associations as significant if the p-value was $<$0.05.

Data analysis and management of the qualitative component

Two researchers analysed the qualitative data using thematic analysis as described by Braun et al. [28]. They repeatedly read the transcripts for full immersion and carried out an inductive thematic analysis using Atlas.ti-7 software [29]. Two researchers coded portions of the transcripts together. Discrepancies were discussed and resolved by consensus. Then they grouped codes into sub-themes and organised them under themes.

Ethical approval

The Biomedical Research Ethics Committee of the University of the Western Cape and the Ethics Review Board of the University of Rwanda, College of Medicine and Health Sciences approved the study protocol. Permission was obtained from Rwanda NTP to collect data from the eligible PHC. The researchers assured the participants' anonymity and confidentiality: for the focus group discussions. Numbers were allocated to each participant at the start of the discussions, and they were asked to refer to one another according to these. Regarding the in-depth interviews, during transcription, pseudonyms were used to ensure the identity of the participants remains anonymous. All records were stored in a password-protected folder in the computer, and the hard copies of the data (printed transcripts) were locked at the School of Public Health of the University of Rwanda, College of Medicine and Health Sciences (SPH-CMHS-UR in a cupboard accessible only to the principal investigator who is the employee of the university of Rwanda.

Results

Quantitative results

Among 270 below 15 year-old child contacts recruited from 136 eligible sputum smear-positive PTB index cases (n = 346) diagnosed and treated at 13 PHCs in Kigali, 94 (35%) child contacts from 72 index cases were below five years old and eligible for IPT. To evaluate adherence in this study, 84 (89%) who started the IPT were enrolled from 61 index cases. As shown in Fig 1, 74 (88%) completed six months of IPT, with only ten (12%) who did not complete the treatment. Fig 2 shows the number of months for which child contacts who were initiated into IPT failed to complete the 6 months treatment.

The characteristics of child contacts who started IPT are shown in Table 1. There was no statistically significant difference in the characteristics of children who completed six months of IPT compared to those who did not.

In Table 2, the characteristics of child contacts, index cases, households and health facilities are listed. None of the characteristics we evaluated was significantly associated with incomplete adherence to IPT in the bivariate and multivariate analysis.

Only one (1.2%) of the 84 child contacts who started IPT developed TB six months after completing the full 6-month IPT, i.e. at 12 months following initial screening and uptake. He was a 3-year-old male, HIV uninfected, who had a clinical diagnosis of TB based on history, physical examination, and CXR. He had TB-related symptoms at the time of initial screening, but further clinical evaluation and CXR were negative for a diagnosis of TB. He remained asymptomatic while on IPT.

Qualitative findings

Interviews were conducted with ten TB focal persons from selected PHCs and 15 parents/caregivers whose children had complete adherence, and eight whose children had incomplete adherence. The characteristics of parents/caregivers are presented in Table 3.

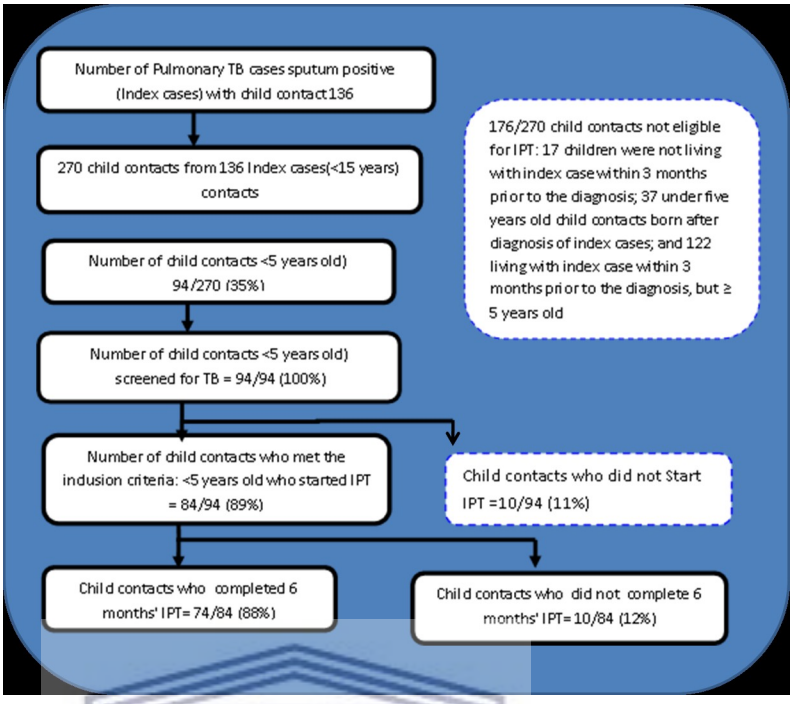

Fig 1. Flow diagram of child contacts from recruitment to IPT completion.

https://doi.org/10.1371/journal.pone.0211934.g001

The FGDs were attended by 24 CHWs, which included eight participants from each district.

The barriers to and facilitators of the IPT adherence, with themes and sub-themes, are presented in Fig 3. The figure has four boxes and each box represents a theme. Also, each bullet in a box represents a sub-theme which can be a facilitator or barrier to IPT adherence.

The reported facilitators of IPT adherence included themes around parents/caregivers, disease, and health-care provider-related factors which are described in detail below.

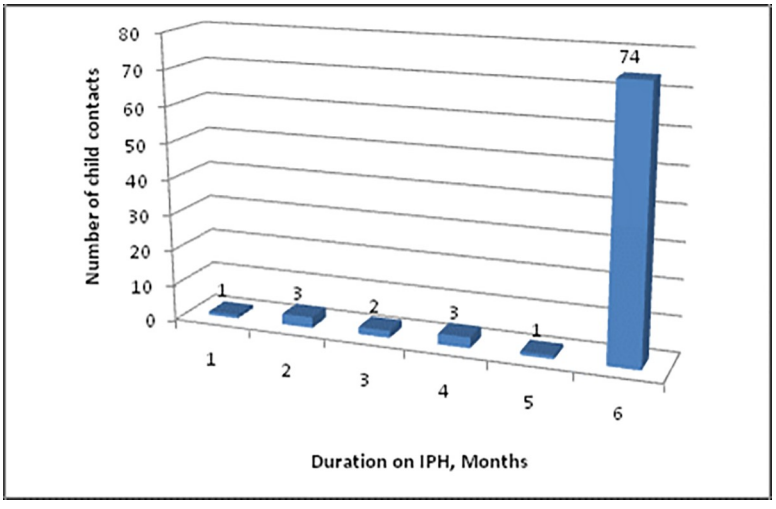

Fig 2. Distribution of number of months IPT prescription was collected.

https://doi.org/10.1371/journal.pone.0211934.g002

Table 1. Characteristics of child contacts who started isoniazid preventive therapy by adherence group (N = 84).

Characteristics	Total (%)	Complete Adherence (n = 74)	Incomplete Adherence (n = 10)	*P-value*
Age group ≤ 2 Years	37/84 (44)	32/74 (43)	5/10 (50)	0.69
Sex Female	37/84 (44)	30/74(41)	7/10 (70)	0.07
BCG scar present Yes	80/84(95)	70/74(95)	10/10(100)	0.59
Tested for HIV Yes	39/84 (46)	32/74 (43)	7/10 (70)	0.17
HIV test Result Positive	2/39 (5)	1/32 (3)	1/7 (14)	0.10
Relationship to Index case				0.10
Child	65/84 (77)	55/74 (74)	10/10 (100)	
Others	19/84(23)	19/74 (26)	0	
Had symptoms suggestive of TB during the initial screening	19/84 (23)	17/74 (23)	2/10 (20)	0.83
Share the same bedroom with index cases Yes	42/84 (50)	36/74 (49)	6/10 (60)	0.73

BCG = bacille calmette guerin; IPT = isoniazid preventive therapy, TB = tuberculosis; HIV = human immunodeficiency virus.

https://doi.org/10.1371/journal.pone.0211934.t001

Parent-/caregiver-related factors. Parents/caregivers' knowledge about the benefit of IPT and beliefs about the threat of TB disease were reported as a facilitator of IPT adherence.

I knew that this medicine protects my child from getting TB. I know that TB is a bad disease, so I put that programme (to give him IPT) among my obligations. (Mother, 29 years, complete adherence)

Disease-related factors. Overall parents/caregivers whose children had complete adherence mentioned their own TB disease experience or experience taking care of a relative with TB as the core factor motivating them to provide IPT to their children as recommended by health-care providers.

Table 2. Risk factors for non-adherence to isoniazid preventive therapy.

Factors	TOTAL (%)	OR (95%; CI)
Child contacts (n = 84)		
Female	37 (44)	3.4 (0.14–3.7)
HIV positive	2/39 (5)	5.1 (0.28–94)
Not sleeping in the same room as the index case	35 (42)	0.3 (0.06–1.5)
Index cases (n = 61)		
Female	28 (46)	3.4 (0.81–14.3)
HIV-positive	13/51 (25)	0.3 (0.05–1.36)
Household factors (n = 61)		
Income >50.000 Rwandan Franc	23 (38)	0.3 (0.08–1.95)
No knowledge of IPT protection[a]	38 (62)	5.5 (0.65–45)
Heath facility factors (n = 61)		
Provider not friendly	1/61 (1.6)	8.1 (0.46–141)

IPT = isoniazid preventive therapy; HIV = human immunodeficiency virus; CI = confidence interval; OR = odds ratio

[a] Not knowledgeable about the administration of INH for six months to protect child contacts against TB.

https://doi.org/10.1371/journal.pone.0211934.t002

Table 3. Demographic characteristics of parents/caregivers.

Characteristics	Complete adherence (n = 15)	Incomplete adherence (n = 10)
Age in years, median (IQR)	36 (22–63)	33 (28–43)
Relationship to child		
Mother	11	7
Father	2	0
Grandmother	2	1
Education level		
Never attended school	5	0
Primary school	5	6
Secondary school	4	2
Socio-economic status		
Low	8	6
Middle	7	2
District of residence		
Nyarugenge	5	1
Kicukiro	2	2
Gasabo	8	5
Relation to Index case		
Herself	6	2
Wife	6	6
Others	3	0

IQR = interquartile range

https://doi.org/10.1371/journal.pone.0211934.t003

I'm telling you, from my experience when you have experienced TB disease, you cannot really wish to see your child contaminated and feel what you have experienced, and hence that fear helps you to give the medicine as prescribed by the doctor to protect the child from contamination. (Mother, 33 years, complete adherence)

I saw how seriously sick my mother-in-law was when she was struggling with the TB, which had evolved into multi-drug resistant TB; and I was the one who took care of her. Recalling that situation pushed me to act quickly and get medicine for my children. I always made sure they took it as prescribed. (Mother, 40 years, complete adherence)

Health-care providers' factors. Most of the participants reported on the positive support by health-care providers and CHWs as facilitators of IPT adherence. They commended health-care providers for the way they taught, provided them with information and education on the IPT adherence and for their successful follow up.

It is the nurses in charge of the follow-up of the TB patients who often go on the fields, and we (CHWs) make them visit people to whom we give IPT and TB treatment. They also inquire about their [TB patients, child contacts] health status, ask them questions about how they take their treatment or give children treatment. This [follow up] could have increased the number of child contacts who finished IPT. (CHW6, Nyarugenge district)

It's CHWs who help those (child contacts) to take their medicine and also us (TB focal person). We supervise CHWs many times because if we gave them medicine, they (CHWs) are supposed to make sure that children take it well and on time. When we visit them (CHWs), we check if they gave the medicine to children as we prescribed. (TB focal points 1, Public PHC)

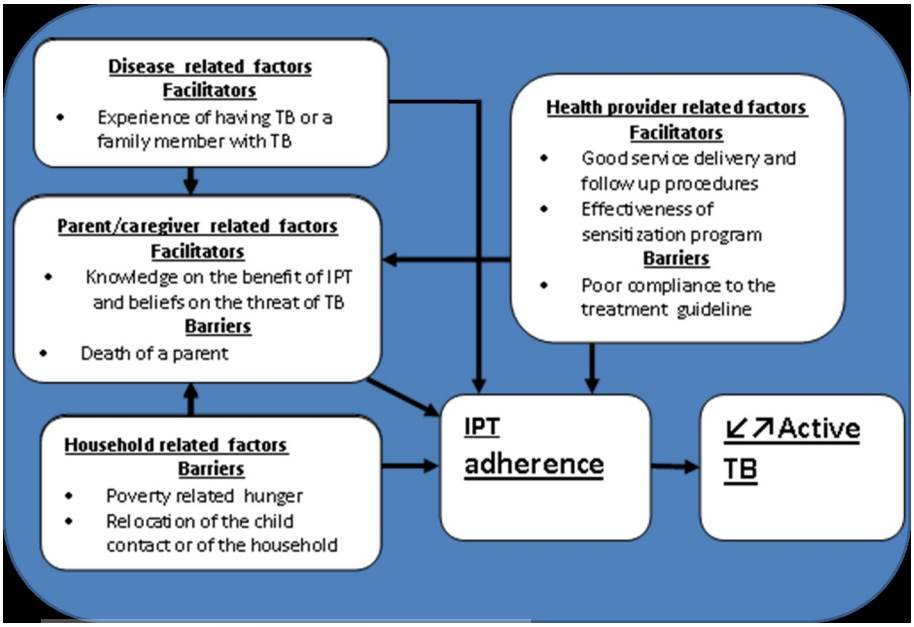

Fig 3. A framework mapping factors influencing isoniazid preventive therapy adherence in Kigali, Rwanda.

https://doi.org/10.1371/journal.pone.0211934.g003

Through sensitisation programmes conducted by nurses, we are well informed that immunisation protects our children from contracting a disease. (Mother, 31 years, complete adherence)

We also explored the barriers to IPT adherence. The reported barriers included themes around caregivers, household and healthcare factors which are described in detail below.

Factors related to parents/caregivers. Parents/caregivers whose child contacts had complete adherence and some health-care providers reported that the death of a parent/caregiver led to the child being placed in another family, whose members did not share the importance of continuing the adherence to IPT or were living too far from the PHC.

. . .sometimes a mother who was following her child's treatment well can die before the treatment is complete, and those who take care of the child may neglect to continue the child's treatment. (Health-care provider, 35 years, public PHC)

There are children who can have the tragedy of losing their parents when on IPT. For example, in my village, there was a woman whom I was giving TB treatment, and she had a child who was on IPT. That woman died, and we buried her in her province. This means the child was taken by his mother's relatives and we did not know who took him to allow us to continue with the follow-up. Such kind of child contacts is included among those who did not finish the IPT. (CHW4, Nyarugenge district)

Parents/caregivers' belief that medications taken without food are harmful was reported as a barrier to IPT adherence by some CHWs who supplied IPT at the community level. Parents/caregivers believe that a hungry child could not be given medicine because it is difficult and harmful.

It is quite a challenge when you come to give a child his/her medicine you are told by a parent/caregiver: please stop . . . stop! The child has not eaten anything since the previous day

and looks concerned. The child has gone hungry and yet has to take medicines and, as you know, it is not easy to swallow pills/tablets even for an adult and it is more difficult for a child and also harmful to take medicine on empty stomach! (CHW4, Nyarugenge district)

Household-related factors. Many of the parents/caregivers whose child contacts had incomplete adherence reported poverty and relocation as the foremost barriers to IPT adherence. Parents/caregivers reported that poverty led to a lack of food, therefore by necessity, they gave priority to getting a job and being able to provide food for their children rather than going to the PHC to collect medication.

Sometimes you ask yourself where the meal for the child will come from if I take the child to the PHC. Because of this, you may decide to look for a job today and plan to take the child to the PHC tomorrow. But still, you may also fail to get the job that day, and that will compel you to try again the following day. Finally, you will not find any time and stop the treatment altogether. (Mother, 34 years, incomplete adherence)

The relocation, either of a child contact or the household, was reported as a barrier to IPT adherence. Some participants reported that parents/caregivers are often compelled to place their children with relatives.

It may happen that you start taking medicine; before its completion, you move to another place and find yourself in a situation where you are not able to pay for transport to go to the place where you used to get the medicine from. That is what happened to me! (Mother, 30 years, incomplete adherence)

For example, a mother may start giving her child the medicine, but only halfway to completing the treatment, she may come and tell you that she does no longer live with the child, that she has sent him/her to his/her grandmother's. In that case, you understand that the child stops taking the medicine. (Health-care provider, 30 years, Public PHC)

Health-care providers' factors. The lack of compliance with the treatment guideline by health-care providers was reported as a barrier to complete adherence by a parent/caregiver whose child had incomplete adherence.

This is something that I myself experienced. My child didn't complete the six months of treatment, because when I finished my dose, I was told to stop his treatment too, although he started it one month later than I did. You do understand that the decision to stop the medicine was not mine; it was rather the decision of the nurses, who convinced me that my child was no longer running any risk since they followed me up to my full recovery. (Mother, 28 years, incomplete adherence)

Discussion

The rate of complete IPT adherence of 88% in this study is higher than the range of adherence rates 26%-76% reported elsewhere [14,16–18,30–32]. To be more precise it is comparable to the 86% and 94.5% rates reported for Benin [33] and the Gambia [34], respectively. IPT adherence is often poor, and a recent systematic review did not identify a particular intervention to improve implementation [35]. However, the successful delivery of IPT may be setting-specific

relying on system factors that may be completely different from other similar studies but in different settings such as urban Indonesia [18]. In Rwanda, the government's commitment through NTP to implement local interventions, especially those targeting to improve IPT adherence, such as performance-based financing, free TB services and treatment, increasing the number of PHCs, and involving CHWs in the management of child contacts. The findings from the qualitative study support this assumption. Factors such as financial challenges regarding medication collection including the cost of medication and transport, and long waiting times that were reported as barriers to IPT adherence in other countries where such interventions are not implemented [16–18], were not reported by participants in this study.

Parents/caregivers' own experience concerning TB disease or their experience of taking care of a relative with TB has been identified as one of the main factors facilitating IPT adherence. The fear to see their offspring suffering from TB, a disabling and killer disease, has been a primary factor motivating them to make sure that their children had complete IPT adherence. This is consistent with a study conducted in Indonesia [17] where the experience of having a family member with TB was found to be a factor in facilitating IPT adherence.

The effective sensitisation programme, service delivery (for example, friendly health providers, supportive and providing all the needed information, especially information on the benefits of IPT or length of treatment) and follow-up procedures have been identified as facilitators of IPT adherence in this study. This finding reinforces the quantitative result that revealed that only one parent/caregiver experienced the health-care providers to be unfriendly. Furthermore, only one parent/caregiver whose child had incomplete adherence reported a lack of compliance with the treatment guidelines by health-care providers as a barrier to IPT adherence. Also, none of parents/caregivers whose child contacts did not have complete adherence reported the unawareness of the benefits or length of treatment as barrier to IPT adherence in our study. The results of this study are corroborated by other studies, which indicated that provision of follow-up and service delivery were facilitators of preventive and TB treatment [36,37]. Poor follow-up and service delivery such as poor interpersonal communication between patients/caregivers and health care providers, lack of attention and support at the health facilities, difficulty for patients continue with his/her treatment if s/he missed treatment, were also found to be barriers to preventive and TB treatment adherence [38–40]. For example, studies found that when a patient missed treatment for a period and for any reason want to re-joint the TB service, s/he is jugged, insulted and sometimes requested to provide a guarantor from the community who could vouch for his/her ability and willingness to complete their course of treatment [38,41]. Therefore, to avoid those bad experiences, patients prefer to no re-join TB service. Parents/caregivers' knowledge on the benefit of IPT and beliefs that TB is a severe and killer disease were reported as facilitators of IPT adherence. This is consistent with other studies that found that IPT completion was related to parents/caregivers' belief about the severity of TB disease and knowledge about the benefit of IPT [16,17,42]. However, most parents/caregivers with incomplete IPT adherence in this study were knowledgeable about its benefits. The incomplete adherence observed among their child contacts could be explained by the underlying reasons for incomplete adherence. In a systematic review[36], reasons such as poverty and relocation were identified as structural factors. The latter overrides the willingness of parents/caregivers to complete IPT, despite their knowledge of the importance of adherence. Structural factors are those present in the society that influence treatment-taking behaviour, but on which the patient has little personal control.

Relocation has been identified as a barrier to IPT adherence in this study. Similar results were displayed by other studies [37,39]. Some parents/caregivers are often compelled to place their children in the care of their relatives who are wealthier than what they are. Additionally, TB patients are often displaced from their area of residence because they are either unable to

pay the rents where they are staying or asked to move because they can potentially infect their neighbours. Appropriate counselling for parents/caregivers to inform health-care providers when they need to relocate and the establishment of a formal system at the health facility is needed. The communication is needed between the referral and recipient health-care providers of the child contacts to ensure they reach their destination and pursue the IPT.

In this study, poverty has been identified as a barrier to IPT. Poverty correlates with a lack of food, in fact, parents/caregivers believe that medication taken without food is harmful. Similar results have been found in other studies [43,44]. Health-care providers have to identify child contacts of poor parents/caregivers and provider them with nutritional support. Additionally, we recommend the NTP to conduct a quantitative study at the national level to access the impact of poverty on IPT adherence. Although the long duration of treatment has not been reported as a barrier to IPT, NTP has to consider the availability of shorter regimens equally effective to IPT and safer known to be associated with better adherence [10].

Incomplete adherence to IPT in this study was not associated with any individual characteristics of index cases, households or health facility characteristics as in other studies [16,17]. However, the small sample size is a limitation of this study that may have limited the ability of researchers to detect differences in the IPT uptake, with the low numbers of incomplete adherence for comparison. Nevertheless, the addition of qualitative methodology strengthened the findings by soliciting for more information, which provided an overview of barriers and facilitating factors of IPT adherence according to the views of all participants involved in IPT adherence.

Another limitation is that the data were collected by nurses. That might have compromised the qualitative data in the sense that participants might have preferred to say what the nurses wanted to hear. However, the use of nurses not involved in the treatment of child contacts or index cases, climate of trust and confidence that researchers created before starting each interview might have reduced such probability. Still, another limitation is that the research was conducted in Kigali and findings might not be generalised to elsewhere in Rwanda, especially to remote rural areas where barriers and facilitating factors to IPT adherence may be different.

Finally, the measures used to assess the IPT adherence in this study were less objective than the measures used in other studies [34,42]. These measures include pill counts or detection of INH metabolites in the urine among other things. We assumed that when a parent/caregiver attended the PHC to collect INH for his/her child, he/she also administered the medication to the child.

Conclusions

There was a high rate of completion of IPT in this cohort of eligible child contacts living in Kigali. The success is likely attributed in part to the government's commitment through NTP to implement local interventions, especially those targeting to improve IPT adherence such as performance-based financing, free TB services and treatment, increasing numbers of PHCs and involving CHWs in the management of child contacts.

However, structural factors (poverty and relocation) were found to be the main barriers to IPT adherence. These structural factors have to be used by health-care providers to identify parents/caregivers whose child contacts are at risk of incomplete adherence, therefore, provide specific follow up adapted to their need.

Supporting information

S1 Appendix. Follow-up form for child contacts on isoniazid preventive therapy.
(PDF)

S2 Appendix. Interview guide English version.
(PDF)

S3 Appendix. Interview Kinyarwanda version.
(PDF)

Acknowledgments

The researchers would like to express their sincere gratitude to the study participants and their parents or caregivers, NTP staff, TB focal points, Heads of PHCs, Community health workers and data enumerators involved in this study. We also thank Mr Gédéon Bahemuka Jino and Ms Jean Fourie for editing the manuscript.

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