COSTING ANALYSIS OF LEVOFLOXACIN AS ANTIBIOTIC PROPHYLAXIS FOR PEDIATRIC HOUSEHOLD CONTACTS OF MULTI-DRUG RESISTANT TUBERCULOSIS PATIENTS IN A SOUTH AFRICAN SETTING

Suereta Fortuin
(FRTSUE001)

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Supervisor: Mr. Thomas Wilkinson

Health Economics Unit

School of Public Health and Family Medicine

Faculty of Health Sciences

University of Cape Town

DECLARATION

I, Suereta Fortuin, , hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole 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 authorise the University to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

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DEDICATION

This Master's thesis is dedicated to:

My beloved mother, Rose, my best friend and biggest fan.

ABSTRACT

Background

The incidence of TB in children under 15 years, accounts for 8% of the global TB burden. In 2018, the World Health Organisation (WHO) estimated that there were approximately 11 000 multi-drug resistant (MDR) TB cases in South Africa. Despite having very clear guidelines on TB treatment programs and management, availability of inexpensive diagnostic tests, curative and preventive therapies, and the widespread use of the BCG vaccines, South Africa continues to have the highest the number of MDR-TB cases per capita. Levofloxacin is used as part of the group of fluoroquinolones in the drug regimen recommended in the treatment of MDR-TB patients. In addition to investigating the clinical impact of levofloxacin as preventative antibiotic therapy, the expected costs of the intervention will be a critical input to determining feasibility and costs effectiveness, which will inform policy and implementation considerations.

Methods

We performed a cost analysis on using existing data from the Tuberculosis Child Multi-drug-resistant Preventative Therapy (TB-CHAMP) trial, conducted from a TB control program perspective. We used data from 510 childhood household contacts of MDR-TB patients in South Africa that were treated with levofloxacin for 6 months as a preventative therapy for MDR-TB. In our analysis we evaluated the estimated health system cost associated with provision of levofloxacin to childhood contacts of MDR-TB patients in South Africa.

Results

The mean total cost of treating a child household contact, irrespective of their weight band is ZAR 5,289.79. When the cost were analysed by weight categories we found that the cost increased by weight category; ZAR 2,146.78 (under 5 kg), ZAR 4,714.58 (between 5-15.9 kg) and ZAR 6,606.67 (over 16 kg). We performed a comprehensive sensitivity analysis and found that the scheduled clinic visits were the major cost driver. Aside from the scheduled visits we observed that there was an increase in additional health service utilization for children with a weight more than 5kg.

Conclusion

We envisage that based on our analysis we will be able to inform policy decisions about the management and prevention of childhood household contacts of MDR-TB patients in developing TB themselves.

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Psalm 121: *"My help comes from the LORD, the Maker of heaven and earth."*

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LIST OF ABREVIATIONS

TB-CHAMP	Tuberculosis Child Multi-drug-resistant Preventative Therapy
MDR	Multi-drug resistant
RR	Rifampicin resistant
XDR	Extensively drug-resistant
TB	Tuberculosis
WHO	World Health Organisation
ZAR	South African Rand
INH	Isonaizid

PZA	Pyrazinamide
EMB	Ethambutol
ETH	Ethionamide
DTTC	Desmond Tutu TB Centre, Stellenbosch University (SU), Cape Town
PHRU	Motlosana Perinatal HIV Research Unit, Klerksdorp, Wits Health Consortium
WRHI	Wits Reproductive Health and HIV Institute Shandukani Research Centre
UCT	University of Cape Town
HREC	Human Research Ethics Committee
GDG	Guideline Development Group
HIV	Human Immunodeficiency Virus
STI	Sexually transmitted infection
CEA	Cost effectiveness analysis
CUA	Cost-utility analysis
CBA	Cost-benefit analysis
CMA	Cost minimisation analysis
ICER	Incremental cost-effectiveness ratio
QALY	Quality Adjusted Life Years
GDP	Gross Domestic Product
HTA	Health Technology assessment
IPT	Isoniazid preventative treatment
IGRA	Interferon Gamma release assay
TST	Tuberculin Skin Test
NHLS	National Health Laboratory Service
VCT	voluntary counselling
ICF	intensified case finding

PART A: THESIS PROTOCOL

1. Introduction

It is estimated that 25% of the world's population is infected with *Mycobacterium tuberculosis* (*M.tb*) the causative agent of tuberculosis (TB) and amongst the top 10 leading causes of death in the developing world [1]. The incidence of TB in children under 15 years accounts for 8% of the global TB burden [2]. In 2018, the World Health Organization (WHO) estimated that there were approximately 11 000 multi-drug resistant (MDR) TB cases in South Africa [3]. Despite having very clear guidelines for adults on TB treatment programs and management, availability of inexpensive diagnostic tests, curative and preventive therapies, and the widespread use of the bacille Calmette-Guerin (BCG) vaccines, South Africa continues to have the highest the number of MDR-TB cases per capita [4], [5]. However, it is of great concern that there are no clear guidance on treatment and preventive therapies for pediatric TB in the South African setting [6]–[8]. The WHO estimates that in areas with a high incidence of TB, at least two children are in direct household contact with an adult with active TB leaving them at high risk of developing TB disease themselves [9]. TB disease amongst children is commonly underappreciated as a major contributor to childhood morbidity and mortality, despite successful treatment outcomes [10]. In the majority of childhood TB cases, diagnosis with standard sputum-based assays are complicated due to the difficulty of expectorating sputum as well as pediatric tuberculosis that are usually pauci-bacillary and often extra-pulmonary [10]. Although new treatments are becoming available, the treatment of MDR-TB in children are complex, expensive, extensive, involves long hospitalization and is associated with side effects due to drug toxicity [11].

Previous studies indicate that pediatric TB is a result of recent and within household transmission [12]–[14]. Therefore, the prevention and management of MDR-TB in children is very important. The need for the assessment of preventive therapy for children in contact with MDR-TB cases had been identified over two decades ago. However, previous studies had not been able to provide the WHO with recommendations for this vulnerable group. Currently underway are 3 clinical studies invested in prophylactic therapies of household contacts of adult MDR-TB patients in order to prevent paediatric MDR-TB disease [15].

An observational prospective study was done on 105 children (< under 5 years) who were direct household contacts of infectious MDR-TB cases in South Africa [16]. Forty one of the 105 children received effective treatment combinations of isoniazid (INH)/ pyrazinamide (PZA)/ ethambutol (EMB) / ethionamide (ETH) for 6 months and were followed for 30 months. Two (4.9%) of the children in the treatment arm developed TB compared to 13 (20.3%) in the group that did not receive treatment. This observational study was the first of its kind to demonstrate the effectiveness of using anti-TB treatment in the prevention of developing active TB in children in South Africa [16]. However, household contact investigations are severely underutilised in most high-burden settings, including in South Africa [2]. Studies have demonstrated that Isonaizid Preventive Therapy (IPT) efficacy can be greater than 90% in the prevention of susceptible pediatric TB when patients demonstrate good adherence, [17], [18]. In a model study, preventive treatment of MDR-TB adults with fluoroquinolone showed it could lead to a substantial health system saving, a reduction in mortality, a reduction in incidence of MDR-TB and incidence of acquired fluoroquinolone resistant disease as well as improved outcomes notwithstanding effectiveness of therapy in preventing MDR-TB of only 10% [19].

Levofloxacin is used as part of the group of fluoroquinolones in the drug regimen recommended in the treatment of MDR-TB patients. It functions by inhibiting enzymes that are necessary to separate bacterial DNA, thereby inhibiting cell replication. Occasional side effects of Levofloxacin are generally well tolerated and may include nausea, vomiting, diarrhoea, trouble sleeping, dizziness and sensitivity to light. Some of the rare side effects include peripheral neuropathy and tendon rapture [20], [21].

In addition to investigating the clinical impact of preventive antibiotic therapy in this patient group, the expected costs of the intervention will be a critical input to determining feasibility and costs effectiveness, which will inform policy and implementation considerations. We propose to do a cost analysis on data collected for the TB-CHAMP clinical trial where child household contacts of MDR-TB patients in South Africa are treated with Levofloxacin for 6 months as a preventive therapy for MDR-TB. In our analysis we will evaluate the estimated health system cost associated with provision of Levofloxacin to child contacts of MDR-TB patients in South Africa. We will consider a wide range of

variables which will inform an analysis of the cost-effectiveness of Levofloxacin preventive treatment amongst children under the age of 5 years. We envisage that based on our analysis we will be able to inform policy decisions about the management and prevention of child household contacts of MDR-TB patients in developing TB themselves.

2. Problem statement

What is the cost of providing preventive antibiotic therapy in the management of pediatric household contacts of MDR-TB patients in South Africa?

3. Purpose of study

3.1. *Primary aim*

The aim is to measure and cost the activity from a health system perspective associated with providing preventive antibiotic therapy for pediatric household contacts of MDR-TB adult patients.

4. Methodology

4.1. *Study design*

The study design will be a cost analysis using data from the Tuberculosis Child Multi-drug-resistant Preventive Therapy (TB-CHAMP) trial, conducted from a TB control program perspective. The TB-CHAMP trial is a two arm, phase III cluster randomised, double blinded placebo-controlled TB prevention trial to assess the efficacy of Levofloxacin as preventive antibiotic therapy in child (under 5 years) household contacts of people with MDR-TB over 72 weeks. This includes, 24 weeks of treatment, i.e. placebo or Levofloxacin, followed by 48 weeks of post-treatment follow-up.

Costs will be related to utilisation of Levofloxacin as preventive treatment for a child household contact of an MDR-TB adult to prevent them from developing MDR-TB disease themselves. The cost of resources will be values and presented in 2020 South African Rand (ZAR).

4.2. *Setting and population*

Within this ongoing TB-CHAMP trial, we analysed data from 510 participants that were randomly allocated to an intervention of control arm followed by a 48 post-treatment follow-up. All children living in the same household were allocated to the same treatment arm.

Three primary health care facilities in South Africa participated in the TB-CHAMP trial:

1. Desmond Tutu TB Centre, Stellenbosch University (SU), Cape Town (DTTC)
2. Motlosana Perinatal HIV Research Unit, Klerksdorp, Wits Health Consortium (PHRU)
3. Wits Reproductive Health and HIV Institute Shandukani Research Centre (WRHI)

Children in the treatment arm are given Levofloxacin every day for 24 weeks. While, children in the control arm are given a placebo every day for 24 weeks. In this "double blind" study neither the children (or their family) or the researchers know whether the tablets each child is taking are Levofloxacin or placebo. All participants remained in the trial for the purpose of follow-up and data analysis; unless the parent/guardian withdraws their consent at any stage during the trial.

4.3. *Cost analysis*

The data fields with cost implications have been identified and will be extracted from the TB-CHAMP trial data set for patients within the treatment and control arms. Direct cost will be attached to data that will be extracted from routine data collection forms from the TB-CHAMP therapy trial, estimating direct primary health care costs for pediatric household contacts of MDR-TB patients. This will be done by retrospectively reviewing routine data collection from the TB-CHAMP therapy trial. In particular, data from form 3 (Micro-specimens), form 6 (Child screening and eligibility), form 7 (Child investigations), form 10 (Child enrolment), form 12 (Child follow-up) and form 16 (Final visit) will be extracted from routinely data collected and reviewed to provide insight into child screening cost, facility expenditure, utilisation costs of Levofloxacin prophylaxis treatment regimen for child household contacts of MDR-TB patients (the data field extraction form is attached in Appendix 1). The extracted data will describe characteristics (variables) of the child at entry and at subsequent visits during the study will include: age of child, gender, date of recruitment, child's health, height, weight, diagnostic tests done, blood tests, blood and urine for later test, TB tests, routine clinical care in children exposed to MDR-TB, how well do they take their medicines, problems taking their medicine, side effects with regards to Levofloxacin. The data that will be extracted from MDR-TB case records

and will include: age of MDR-TB case, gender of MDR-TB case, treatment regimen (combination), date of diagnosis, visits and tests.

4.4. *Sensitivity analysis*

The most relevant uncertainties in the study include the resource utilisation cost of administering of Levofloxacin in order to prevent child household contacts from developing MDR-TB disease themselves. A one-way sensitivity analysis will be performed on key parameters including the cost of scheduled clinic visits, diagnostics, Levofloxacin, additional clinic visits and hospitalisations to deal with uncertainty.

4.5. *Data analysis and management*

The collected data will be recorded in Microsoft Excel in order to perform cost analysis from a health care provider's perspective. Cost distributions and functions will be developed on key parameters including Levofloxacin drug cost, associated monitoring costs, and in-patient accommodation costs. The key input prices for Levofloxacin unit costs, hospital and clinic visits will be obtained from publicly available sources including the National Department of Health Master Procurement Catalogue and District Health Barometer (DHB) survey . This cost analysis is expected to provide an estimated cost of a pediatric case treated as well as identify major cost drivers and costing structures which will be a critical input to any policy consideration of this intervention. Further this analysis will provide the costs to scale up and implement the program on a provincial and national level in South Africa.

5. Ethical approval

This ancillary cost analysis is a component of the TB-CHAMP trial and will utilise primary data on costs from the trial. A secondary analysis will be conducted of participants case report forms to obtain types and quantities of resources consumed in providing preventive treatment, Levofloxacin, to child household contacts of MDR-TB adults. The TB-CHAMP trial previously obtained ethical approval from Human Research Ethics Committee (HREC) Stellenbosch University (HREC reference number M16/02/009). Furthermore, this study is undertaken within UCT for a Master in Public Health

dissertation ethical approval was obtained from the HREC University of Cape Town (UCT) prior to the beginning of the study (HREC REF:709/2019).

6. Potential benefits and risk

Benefits: This study will make a significant contribution to the body of knowledge about the cost-effectiveness of a potential therapy to prevent MDR-TB in pediatric patients. To inform current policies and achieve impact, it is insufficient to only understand clinical effect alone. Thus collecting the costs of treating child household contacts of MDR-TB patients with Levofloxacin will help to determine the relative cost-effectiveness and thereby directly inform treatment protocols in South Africa and abroad.

Risks: This study has minimal risks to patients as it is use of anonymised data that has already been collected as part of the TB-CHAMP trial. A critical analytical risk is that the results observed in the sample are not reflective of normal MDR-TB care in the South African setting. This will be mitigated by comprehensively detailing the costing structures and environment to allow consideration of transferability to other contexts.

7. **Informed consent**

Informed consent was obtained as part of the TB-CHAMP trial protocol.

8. Confidentiality and privacy

Confidentiality and privacy will be assured. Information will not be linked to individuals. No names will appear in the case report forms, reports or publications.

9. Publication and dissemination policy

This study will be submitted for the Masters in Public Health: Health Economics Degree. The study will also be submitted to TB-CHAMP trial and an article will be drafted for publication in a peer review journal (Journal Pharmacoeconomics).

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PART B: LITERATURE REVIEW

1. Introduction to pediatric multi-drug resistant tuberculosis

1.1. Global burden of pediatric tuberculosis

In 2020, more than 130 years after *Mycobacterium tuberculosis* (*M.tb*) was discovered to cause tuberculosis (TB), it remains one of the major causes of disease worldwide and the leading cause of death due to infectious diseases for children of all ages in the developing world. TB is caused by the infectious agent *M.tb* and approximately 25% of the world population is infected with this airborne pathogenic bacteria and around 10 million people developed TB disease during 2018 [1]. Over the last few decades the TB epidemic is further exacerbated by the emergence of Human Immune Deficiency Virus (HIV). In 2019, the World Health Organization (WHO) reported 1.2 million deaths due to TB amongst the HIV negative people and an additional 251 000 deaths amongst the HIV- positive people [1]. Despite these devastating statistics TB is preventable and curable with timely diagnosis and treatment and transmission can be prevented.

Geographically, eight countries accounted for two third of the global TB burden. These include India (27%), China (9%), Indonesia (8%), the Philippines (6%), Pakistan (6%), Nigeria (4%), Bangladesh (4%) and South Africa (3%). Thirty high burden countries have been identified by the WHO which accounts for 87% of the total TB burden worldwide [1]. The global incidence for children under 15 years diagnosed with TB accounts for 8% of the total TB burden and the mortality rates for those co-infected with HIV or not were 13 and 14%, respectively [1]. In 2018, the WHO reports that 1,3 million children under the age of 5 years were household contacts of bacteriologically confirmed pulmonary TB cases and only 349 487 (27%) of these went on preventive treatment during that year [1].

1.2. Pediatric multi-drug resistant TB epidemic in South Africa

1.2.1. Tuberculosis transmission and infection in young children

TB is an airborne disease caused by *M.tb* and responsible for mainly causing chronic infection the lungs but other organs like the kidney, spine, brain and lymph nodes can also be infected [2]. *M.tb* is transmitted through the respiratory route when small (1-5 μm) infected droplet are aerosolized from people with pulmonary or laryngeal TB and inhaled into the alveoli by close contacts [3]. In order for

M.tb to infect the host it has to survive after it was ingested by the alveolar macrophages. For most immune-competent individuals the innate immune response provides protection to the extent that they remain uninfected. While in others the innate immune does not induce a sufficient response and the adaptive immune response is initiated [4]. In the case of immune-compromised individuals when the innate immune system fails to clear the infection, the adaptive immune response is triggered and the macrophages and dendritic cells present *M.tb* antigens to T-cells in order to control the infection. Next, adaptive immune responses are triggered when macrophages and dendritic cells present *M.tb* antigens to T-cells, including Th-1 type CD4+ T- cells, CD8+ cytotoxic T-cells, and gamma- delta (γδ) T-cells which further potentiate key cytokine secretion to control the infection [5].

In high burden countries, such as South Africa, diagnosis of childhood TB is neglected and treatment thereof is less of a priority [6]. Similar to adults, a susceptible child would inhale a droplet containing *M.tb* through the respiratory route from an infectious TB diseased close contact. Extended exposure and close proximity of the child to the infectious close contact increases the risk of transmission of *M.tb* [7]. Even though South Africa has a successful bacille Calmette-Guerin (BGC) immunisation program for children, childhood TB remains a major concern. Immune-competent children at 3 years of age are at lower risk of developing TB disease after primary infection [6]. However, in high burden settings most of these low risk children develop TB disease after 2-3 years [6]. Evidence from a study done in a high endemic TB area South Africa, the Western Cape, reported that an annual risk of child TB infection (ARTI) of 4% in child household contacts of adults with TB disease [8], [9].

1.2.2. Epidemiology of paediatric multi drug resistant-TB in South Africa

In 2018 the incidence of TB in South Africa were 301 600 of which 11 000 were multi-drug resistant/rifampicin resistant (MDR/RR)-TB. MDR-TB is TB disease caused my strains of *M.tb* that is resistant to at least to isoniazid and rifampicin [10]. Alarming mortality rates soared with 21 000 HIV-negative TB deaths and 42 000 HIV-positive deaths. A total of 235 652 new cases were diagnosed in South Africa in 2018 alone. Of these new cases 3.4% were diagnosed with MDR/RR-TB and 7.1% of previously TB treated cases were diagnosed with MDR/RR-TB [1]. The 2030 WHO International

Sustainability Goals for childhood related indicators aim to reduce the mortality rate of children under the age of 5 years to as low as 25 per 1000 live births. The South African probability of dying under the age of 5 years per 1000 live births in 2018 was 34. In 2018, the global incidence of pediatric TB was 1.1 million children under the age of 5 years [11] of which 205 000 children died due to TB disease. Approximately 16 496 new cases of children under 14 years were diagnosed in South Africa alone making it the fourth leading cause of child mortality [12]. The pediatric TB disease represents with a diverse spectrum of pathology and remains challenging to diagnose. The spectrum of childhood TB disease range from limited TB disease with low *M.tb* bacillary load to more severe disease with high bacillary load and pathological representations include intra-thoracic TB, extra-thoracic TB, miliary TB and TB meningitis [6], [13].

1.2.3. Management of pediatric MDR-TB

According to global reports the major challenges in managing pediatric MDR-TB are three-fold. i.e. (1) underdiagnosed pediatric MDR-TB, (2) treatment and (3) prevention of household contacts to develop active TB disease [14]. Briefly, the difficulty of diagnosing pediatric TB is due to young children struggling to producing sputum and less likely to have a culture confirmation of TB. The drug sensitivity tests are often not possible which in turn leads to a delay in the decision to initiate treatment and/or second line therapy with clinical and radiological evidence of TB disease. Children diagnosed and treated MDR-TB have successful health outcomes. However, children with poor health outcomes are due a delayed decision to initiate treatment due to a delay in TB diagnosis and the adult TB contact history. In 2019 the WHO released the WHO Consolidated Guidelines on drug resistant TB treatment, where the Guideline Development Group (GDG) recommend drug resistant treatment with Delamanid for children older than 3 years and Bedaquiline for children older than the age of 6 [1]. Children that are eligible for treatment have to be closely monitored by experienced doctors since these 2nd-line drugs cause adverse side effects including hearing loss, nephrotoxicity, electrolyte abnormalities, injection pain and local site complications. Therefore and urgent need exists for thorough investigation into efficacy of the long term treatment of children with 2nd-line MDR drugs [15].

Children are most commonly infected with *M.tb* through contact with an adult or adolescent within their own home or community [16]–[19]. Currently, 1.3 million child household contacts under the age of 5 years that are bacteriologically confirmed pulmonary TB cases do not have access to preventive therapy. However, only 27% of child household contacts went on to receive preventive isoniazid treatment in 2018 for susceptible TB [11]. In 2019, the WHO report that only 59% of children under the age of 5 years that are household contacts of bacteriologically confirmed TB cases in South Africa are on preventive treatment [1].

In an effort to increase preventive therapy the WHO and United Nations International Children's Emergency Fund (UNICEF) identified the Prevention Gap which refers to the failure to prevent TB disease through preventive therapy for at risk children. Pediatric prophylactic treatment is one of the key targets to prevent transmission and development of TB disease. South Africa's National Strategic Plan for HIV, TB and STIs 2017-2022 introduced the 90-90-90 approach with the aim to increase TB case detection by 90% and reduce TB incidence by at least 30%, from 843/100 000 population (2015) to less than by 584/100 000 population (2022). Strategies include that each patient tested for HIV as well as their household contacts will be screened for TB. The strategic plan makes serious consideration for improving immediate contact tracing, screening, improve diagnosis and treatment capacity for child household contacts under the age of 5 years to reduce pediatric TB [20].

1.3. Levofloxacin as prophylaxis for pediatric MDR-TB prevention

1.3.1. Guidelines for preventing pediatric MDR-TB in South Africa

Guidance for choosing prophylactic treatment of contacts of MDR/Extensively drug-resistant (XDR)-TB is limited. This is exacerbated by limited evidence for optimal pediatric prophylaxis to prevent MDR/XDR-TB in child household contacts [21]. It is well established globally that there is a 59% reduction in the overall risk of progression from latent TB infection to active disease when Isoniazid Preventive Therapy (IPT) is used as a prophylaxis. According to the National childhood TB guidelines (2013) all child household contacts, under the age of 5 years, should be treated with IPT for 6 months to prevent susceptible and low-level isoniazid resistant TB [22]. It is estimated that children are likely

to be infected with MDR-TB due to exposure of the MDR-TB household adult and should be treated according to the drug susceptibility patterns of the source case [23]. The cost of treating MDR-TB in both adults and children are significantly higher and duration of treatment is up to four times longer than drug sensitive TB [24]. Despite the very expensive MDR-TB treatment, the cure rates for MDR-TB in adults is considerably lower (62%) than that of susceptible TB (85-90%) [25]. These observations highlights the urgent need for new preventive and treatment options for managing MDR-TB compared to what is currently available [24], [26]. Globally, MDR-TB transmission and the accompanying treatment challenges emphasises the urgent need for effective preventive treatments. According to the WHO consolidated guidelines on treatment of drug-resistant TB recommend that those patients with isoniazid-resistant and rifampicin-susceptible TB should be treated with Ethabutol, Pyrazinamide and Levofloxacin for a duration of 6 months. Furthermore, Levofloxacin should be included in treatment of those patients with MDR/RR-TB on long-term regimens [1]. MDR-TB treatment for children are complex since those with less severe disease would not require an intensive treatment as children with more severe disease would [13]. Drug toxicity and lack of child-friendly formulations of second-line MDR-TB medication makes long-term (18-20 months) hard to tolerate in children [27].

1.3.2. Pharmacokinetics of Levofloxacin

Levofloxacin is a third generation and one of the most favored fluoroquinolones with potent antimicrobial activity most commonly used in children with TB [28], [29]. This antibiotic inhibits DNA gyrase, an enzyme that is essential for bacterial replication and how both bactericidal and sterilising action against *M.tb* [30]. Levofloxacin is increasingly being used to replace Isoniazid in the treatment of Isoniazid resistant MDR-TB [31], [32]. The potential role of Levofloxacin in preventive therapy for MDR-TB in children was highlighted in an animal model study of latent TB infection and several observational studies done in children [18], [28], [29]. They found that Levofloxacin is well-tolerated over short treatment periods and caused reduced QT- prolonging effect compared to the other fluoroquinolones which cause QT interval prolongation in young children [33], [34]. The advantage of administering smaller child-friendly formulations to children allows for the rapid absorption after oral

administration with a bioavailability of >90% and is mainly cleared form the body through renal excretion. The assessment of musculoskeletal toxicity in children after long-term Levofloxacin treatment showed no clinical detectable difference when compared to the control group [35]. Prior to 2008 all treatment for MDR-TB was based on clinical observations, clinical opinions and patients' health history. The current recommendations by the WHO for treating children with Levofloxacin for susceptible and MDR-TB is not clearly defined [36]. This highlights the need for more and extensive investigations with regards to the pharmacokinetics and prophylactic therapy is required.

Currently two phase III clinical trials (TB-CHAMP in South Africa and V-QUIN in Vietnam) are underway to investigate the effectiveness of using Levofloxacin as preventive therapy in children under the age of 5 years [18], [29].

2. Economic Evaluation in healthcare

Economic evaluations is essentially the comparative analysis of two or more interventions in terms of their cost and effect [37]. Economic evaluations can be divided into two levels, i.e. full and partial economic evaluations. Even though the this review will focus on costing analysis, a fundamental aspect of economic evaluation, it will also represent the wider spectrum of economic evaluations and the use thereof in policy making.

The purpose of using economic evaluations in health care is to inform health care providers and the patients' decision making process using the best available research evidence about the efficacy and allocation of resources to improve their health care and outcomes [38].

2.1. Types of Economic Evaluations

There are 4 different kinds of full economic evaluations by which costs and consequences of two or more health care intervention and its outcomes can be compared. These full economic evaluation include cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA) and cost minimisation analysis (CMA) [37], [39].

Cost effectiveness analysis is a full economic evaluation which measures the health outcomes in naturally occurring health related units. i.e. lives saved, life year gained [37]. These health outcomes are combined with costs and ratio (cost-effectiveness ratio) of the net change in cost between two interventions. The net change in cost reflect the extra cost required to achieve the difference in outcome. Incremental Cost-effectiveness Ratio (ICER) is a statistic used in cost-effectiveness analysis to summarize the cost-effectiveness of a health care intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect [37].

Cost utility analysis is a variant of cost-effectiveness analysis which compares similar health -related interventions as well as the advantages it produces. CUA utilises a generic measure of health gain such as quality adjusted life years (QALYs) and disability-adjusted life years (DALYs) measured directly form patients [37]. A QALY is a generic measure of disease burden which includes both the quality and the quantity of life lived. One QALY is equivalent to one year in perfect health and combines mortality and morbidity into single summary effectiveness measure through the number of years gained by a utility [37]. Utility refers to the preference individuals/society have for a particular set of health outcomes. Cost utility analysis are used in economic evaluation to assess the value of medical interventions.

Cost benefit analysis expresses the consequence of an intervention in monetary terms when comparing interventions and it values health outcomes depending on subjective judgements with techniques such as willingness to pay [37]. This is calculated as the incremental cost, including both cost and outcomes are measured in monetary terms, between two intervention divided by the difference in the expected QALYs produced by the two interventions [37].

Cost analysis is a partial economic evaluation which only measures the program or disease cost that includes the cost-of-illness analysis and program cost analysis [37], [40]. Even though cost-analysis does not measure or valuate the consequence, it does provide the valuable information and important input for a full economic evaluation.

2.2. Role and relevance of Economic Evaluations

An economic evaluation is the process of systematic analysis through identification, measurements and valuation of relevant inputs and outcomes of two or more relative health care alternatives with the intention of informing decision based on the available evidence [37]. Therefore the comparative analysis of alternative courses of action in terms of both their cost and consequences determines which choice have to be made in allocation of the resources. Economic evaluations are important to healthcare and government agencies who are involved in provision and purchasing of healthcare. In 2017 South Africa, a middle income country with a population of 57 million, with a $USD 70 613 Gross Domestic Product (GDP) per capita had a health expenditure of 8.113% (GDP per capita) [41], [42]. In a resource poor country like South Africa, economic evaluations have the potential to inform good decision making about limited health care resources such as health care staff, health care facilities, medical equipment, medication and specialised care services [43]. Here, the systematic and organised evaluation of relevant alternative healthcare options to informing decision making to commit one health care resource to one instead of another are extremely important.

As South Africa strives to expand and strengthen their current health care systems with the aim to roll out the National Health Insurance, economic evaluations become vitally important in the decision making process of providing efficient and equal health care access. A 2012 study reviewed the quality of 108 economic evaluation studies (Economic Evaluations n=45 and Cost Analysis n=63) conducted in South Africa [44]. This study found that despite only having economic evaluations for a limited number of diseases the quality is comparable to other middle-income countries like Thailand.

Using economic evaluations in decision making is highly dependent on the target audience and the decision-makers' perspective. The perspective of the cost-analysis should be determined in advance before commencing data collection and remain consistent through-out the analysis process. Most economic evaluations are conducted from a providers perspective since they are usually funders and decision-makers of health care interventions. However, the patients and societal perspective are also major drivers in the successful implementation of certain interventions. Issues that prevent the patient from accessing the specific intervention is as important providing a service [45].

2.3. Costing method in healthcare

The key components for performing and costing analysis includes, (1) the perspective, (2) Identification of resource use, (3) measurement of the resource use and valuation of resource use [46]. The perspective of the costing analysis should depend on the intended decision maker. The various kinds of decision-makers include the health care provider, the individual patient and the clinician, or policy makers acting in the interests of broader society. In a costing analysis it is crucial to identify all the resources of a specific health care intervention as comprehensively as possible which will allow decision makers can make decisions about the frame of the study. Lastly, once the identified resources including labour inputs and outputs are measured and reflected in costs it can be valued by multiplying the units of resource used to yield the total cost.

Two strategies can be can be useful in valuation of resources micro-costing (bottom-up) and gross costing (top-down) [36], [47], [48]. A detailed bottom-up approach to costing also known as micro-costing involves the detailed measurement of individual identified items used in the provision of a specific health intervention or service consumed by a patient [36]. This ingredients-based approach costs all the resources utilised or consumed in the health care service provision separately. The data for costing can be collected through interviews, time-in-motion data collections and observation of work sampling techniques of the health care provider. Important measurements to include in micro-costing are measurement of building facilities, equipment, staff time [49]. The valuation of these individual items used in the provision of a health care service is important since it makes unit costs comparable across comparison with other health care intervention. For valuation the current prices should be obtained from the records kept by the health facility. Annuitizing takes into account opportunity cost, depreciation and the life-years of the capital item. Recommended discounting rates for annuitizing is 3%. Life-years of a capital item or equipment reflect the number of usable years of the item [37], [50]. Buildings are usually allocated usable life-years of 30 to 50 years, equipment five to ten years, and furniture one to five years [37], [51], [52].

On the contrary, the top-down costing approach also known as gross-costing involves the estimation of costing by using national averages or expenditure accounts from a facility. Gross-costing identify, count, and price out health care encounters or other health care units that represent some aggregate of a bundle of health care service items. The health care units could include for example, average cost per hospital day is a bundled resource, hospital stay, physician visits, emergency room. In practice, micro-costing and gross-costing approaches can be complementary and the validity of costing methods exists on a continuum [53] and micro-costing could be performed on the listed items within each of the health care unit. Gross costing weights are often easier to find and are more reliable, but important resources differences between treatment groups may be lost in bundling of resources. Price weights can be determined naturally or centre- specific and are depended on perspective, convenience, completeness.

The most common method for costing resources involves measuring medical services used in the study case report forms and translating the utilization into cost by multiplying the number of units of each medical services by price weights for those services [54]. Health Technology assessment (HTA) involves the systematic evaluation of properties, effects and/or impacts of health technologies and interventions with the intention to inform policy makers. HTA covers both the direct, intended consequences of technologies and interventions and their indirect, unintended consequences using the best scientific evidence on medical social economic and ethical implications of investments in health care [55]. HTAs are informed by economic evaluations, a tool for comparing costs and consequences of different health care interventions, and thereby providing the decision maker efficient use of available resources for maximising health benefits. Costing information aids the funder's decision on the adoption and use of a health care technology or for price negotiations with pharmaceutical companies or industry [37], [56].

Until recently the different countries used methods recommended by national and local levels to perform costing and funding of TB services. Towards the end of 2019 the WHO released the Costing Guidelines for TB Intervention with the aim to provide guidance on estimating the cost of TB

interventions [36]. Estimating the costs of TB interventions is essential for planning, prioritising and managing the funding of TB health care services. These guidelines explain how to cost TB interventions from the providers perspective. The providers perspective takes the point of view of the provision of service, the cost are those incurred by hospital, clinic or TB facility that is providing the service.

2.4. Cost analysis of tuberculosis preventive therapies in South Africa

To date only two research publications investigated the cost of TB preventive therapy in South Africa. In the first study, Mandalakas et al. investigated the use of Isonaizid Preventive Therapy (IPT) for young household contacts, under the age of 5 years, of infectious TB cases [57]. They used a decision model to determine the health and economic outcomes of 5 TB infectious screening strategies in young household contacts. The 5 strategies were (1) no testing with IPT, (2) TST testing, (3) IGRA testing, (4) TST positive followed by IGRA, (5) TST negative followed by IGRA and used a bottom- up (ingredients-based) costing approach. In the no-testing strategy (strategy 1) all young household contacts were eligible IPT. However, testing strategies (strategies2-5), IPT is initiated after the young household contact have tested positive. The presence of true *M.tb* infection is equal to a positive test result (positive predictive values) and the absence of *M.tb* infection is equal to a negative test result (negative predictive value) [57]. These positive and negative predictive values were derived from sensitivity and specificity estimates from a number of countries with varying levels of income [58].

By using an ingredients-based costing method they multiplied the quantities of resources by the respective unit cost to obtain the total cost. From a National TB control program (provider) perspective, cost associated with screening to exclude active TB (including tests for infection, chest radiography and culture), routine chest radiography screening for all TB contacts, HIV diagnostic tests, out-patient, in-patient visit, laboratory diagnostic tests and labour (National Health Laboratory Service, NHLS), clinical procedures in children with pulmonary and disseminated TB, IPT and TB drugs (Cape Town City Health). Since the diagnostic tests were not available in the South African public health sector, their cost were based on the realistic manufacturer's pricing (Serum Statens Institute, Copenhagen, Denmark for TST; Oxford Immunotec for T-SPOT.TB) and pricing from the Foundation

for Innovative New Diagnostics (Geneva, Switzerland for QTF). Unit costs for inpatient and outpatient visits and patient costs were derived from previously published data.

In this analysis the adverse effect of IPT were excluded since it was found to be rare in children. They found, in age categories of 0 to 2 years, the no testing strategy saved the most lives and cost much less than the testing strategies. While IGRA after TST negative testing saved more lives than the no testing strategy. Based on these results, using a decision model to determine the implementation of IPT for young household contacts, screening for TB without testing (strategy 1) and IPT should be used in high burden TB settings for young household contacts of infectious TB adults. This can only be achieved through good and correct adherence to IPT usage.

In the second study, Hausler et al. evaluated the cost-effectiveness of the WHO supported TB/HIV interventions package, PROTEST, in adults which included (1) voluntary counselling (VCT) and testing with rapid HIV-testing, (2) screening of TB through intensified case finding (ICF), (3) Isoniazid preventive treatment (IPT), (3) Cotrimoxazole preventive treatment (CPT) and (4) improved management of opportunistic infections [59]. The PROTEST package is aimed at reducing HIV transmission through VCT, reducing TB transmission through ICF and preventing TB reactivation through IPT. Here a bottom-up (ingredients-based) costing were used where each component of a activity, including capital and recurrent cost for one financial year. Capital costs included start-up costs and initial training of counsellors based since the effect of these activities last for more than one year. Recurrent costs included the financial records and interviews with project staff. Parameters to measure the total cost included health education, pre-test counselling, HIV testing, post-test counselling, screening for IPT/CPT, follow-up IPT/CPT and supervision/training/mentorship. The cost for screening or a follow-up is determined by the time multiplied by the cost per minute multiplied by the number of patients. Even though the management of opportunistic infections were measured the research cost and the cost of drugs for opportunistic infections were not included since it could not be separated from the drugs dispensed for other infections. The data were obtained by interviewing clinical staff to estimate the time spend on either screening or follow-up of patients on prophylaxis.

The cost-effectiveness analysis revealed that the cost of clinical preventive interventions such as completing the 6 month IPT incremental to ICF was lower than the combination of IPT and ICF. Furthermore, based on these findings they recommend by using lay counsellors for VCT and rapid HIV testing can reduce HIV and TB in South Africa. In addition, cost-saving interventions such as ICF, IPT and CPT should be offered at primary health care facilities for HIV-positive patients [59].

Table 1. Summary of cost/cost-effectiveness studies for TB interventions including TB treatment and intensive/passive/active case finding from South Africa

Reference	Author/Year	Intervention	Intervention details	Study Population	TB Type	Costing method	Perspective	Costing Approach	Location
[59]	Hausler/2006	Active Case Finding	Diagnostic : Mycobacterium Growth Indicator Tube (MGIT) with Löwenstein-Jensen (LJ) medium	Adult patients	TB	Cost-effectiveness	Provider	Incremental cost	South Africa
[57]	Mandalakas/2013	Intensive Case Finding	Diagnostic care: Sputum sampling strategy	Adult patients	TB	Cost analysis	Provider and Societal	Bottom up	Cape Town
[60]	Floyd/1997	Intensive Case Finding	Diagnostic : Coinfection HIV and TB	Adult patients	TB	Cost analysis	Societal	Bottom up	Cape Town, SA
[61]	Van Rie/1997	Passive Case Finding	Diagnostic : Point of care Xpert MTB/RIF	Adult patients	TB	Cost analysis	Provider	Bottom up	Primary care clinic, Johannesburg, SOUth Africa
[62]	Schnippel/2012	Passive Case Finding	Diagnostic: Xpert MTB/RIF	Adult patients	TB/RR-TB	Cost analysis	Provider	Top-down and Bottom up	South Africa
[47]	Cunnama/2016	Passive Case Finding	Diagnostic: Thibela TB study	Adult patients	TB	Cost analysis	Provider	Bottom up	South Africa
[63]	Pooran/2013	Passive Case Finding	Diagnostic: Light-emitting diode microscopy in HIV–tuberculosis-co-infected patients	Adult patients	TB	Cost analysis	Provider	Bottom up	Two primary care clinics in Cape Town, South Africa
[64]	Sinanovic/2015	Passive Case Finding	Diagnostic : Practical Approach to Lung Health in South Africa (PALSA)	Adult patients	TB	Cost effectiveness analysis	Provider	Top-down	South Africa
[65]	Sinanovic and Kumaranaya/2006 a	Passive Case Finding	Diagnostic: Local Tuberculosis(TB) control programme	Adult patients	TB	Cost-effectiveness	Provider	Bottom up	Boland health district, Cape Town, South Africa
[66]	Janson/2012	Treatment	Community based diretly observed treatment (DOT)	Adult patients	TB	Cost-effectiveness	Societal	Top-down	Hlabisa Health District, South Africa
[67]	Dorman/2012	Treatment	Xpert MTB/RIF: laboratory versus clinic-based roll-out	Adult patients	MDR-TB/ XDR-TB	Cost analysis	Provider	Top-down	South Africa
[68]	Whitelaw/2011	Treatment	National TB program	Adult patients	DS/ MDR-TB/ XDR	Cost analysis	Provider	Bottom up	South Africa
[69]	Fairall/2010	Treatment	Different treatment models of Rifampicin-resistant TB	Adult patients	MDR-TB	Cost: Patient	Patient	Top-down	South Africa
[70]	Peter/2013	Treatment	TB treatment provider partnership	Adult patients	TB	Cost analysis	Provider	Bottom up	South Africa
[71]	Hudson/2000	Treatment	TB treatment provider partnership	Adult patients	TB	Cost analysis	Societal	Bottom up	South Africa
[72]	Zishiri/2015	treatment	XTEND study	Adult patients	TB/MDR-TB	Cost analysis	Provider	Bottom up	South Africa

Table 1. Summary of cost/cost-effectiveness studies for TB interventions including TB treatment and intensive/passive/active case finding from South Africa (continue)

Reference	Author/Year	Intervention	Intervention details	Study Population	TB Type	Costing method	Perspective	Costing Approach	Location
[73]	Meyer-Rath/2012	Treatment	SAPiT	Adult patients	TB/MDR-TB	Cost analysis	Provider	Bottom up	South Africa
[74]	Cox/2015	Treatment	Hospitalisation of MDR-TB patients	Adult patients	MDR/RR-TB	Cost analysis	Provider	Bottom up	South Africa
[75]	Dick and Henchie/1998	Treatment	Diagnosing TB patients	Adult patients	TB/MDR-TB	Cost analysis	Provider	Bottom up	Cape Town, SA
[76]	Wilkinson/1997	Treatment	Clinic-based care versus community-based observation and treatment	Adult patients	TB treatment	Cost analysis	Societal	Top-down	Gugulethu and Nyanga, Cape Town, South Africa
[77]	Clarke/2006	Treatment	TB treatment supervision methods: clinic, self and community-based	Adult patients	TB	Cost analysis	Provider	Top-down	Elsies rivier, Cape Town, South Africa
[78]	Chihota/2010	Treatment	TB management strategy	Adult patients	TB	Cost analysis	Provider	Top- down	Hlabisa health district, Kwazulu-Natal, South Africa.
[79]	Schnippel/2013	Treatment	Inpatient treatment of MDR-TB	Adult patients	MDR-TB	Cost analysis	Provider	Top-down	Klerksdorp/Tshepong Hospital Complex in North West Province, South Africa
[80]	Kranzer/2012	Treatment/Active Case Finding	Diagnostic: TB screening	Adult patients	TB	Cost analysis	Provider	Bottom up	South Africa
[81]	Sinanovic and Kumaranayake/ 2006b	Treatment/Passive Case Finding	Diagnostic: Scaling up GeneXpert MTB/RIF	Adult patients	TB/MDR-TB	Cost analysis	Provider	Bottom-up	South Africa

Table 1 summarises 25 publications of cost/cost-effectiveness studies for TB interventions including TB treatment and intensive/passive/active case finding from South Africa. Even though South Africa has the highest number of reported TB studies and unit cost estimates for countries on WHO's 30 high burden country list, only two studies investigated preventive TB treatment indicating that costing for preventive therapies remains an unmet research need. In summary, those studies focused on the cost effectiveness of improved treatment initiatives and revealed that the cost of treating MDR/XDR-TB is extremely expensive compared to drug susceptible TB due to long term hospitalisation [14], [63], [64], [79]. Several studies show that community-based direct observed treatment (DOT) (decentralised model) is a more cost-effective and feasible alternative compared to treating multi—drug resistant patients in hospital (centralised model) [64], [66], [74], [82]. Further, those studies that focused on intensive/passive/active case finding found that cost-effectiveness of interventions was dependent on the context of the clinical setting. For example, the Xpert diagnostic tool is cost-effective for diagnosing smear negative TB patients in settings lacking facilities for liquid culture or smear microscopy laboratories and reduces the time to detection and initiation of treatment in cases of TB/HIV coinfection [61], [62], [67], [73].

3. Conclusion

Global MDR-TB transmission and the incidence of pediatric MDR-TB disease remains a major global concern despite the implementation of numerous interventions to improve child health outcomes. Limited evidence for optimal prophylactic treatment to prevent MDR-TB in childhood household contacts further exacerbates urgent need for effective preventive treatments.

This literature review highlights the complexity of prevention and managing the spectrum of pediatric TB, including MDR-TB disease. These challenges include screening child household contacts of MDR-TB adults, diagnostic delays, drug toxicity and unfriendly child formulations. Observational studies have shown that Levofloxacin, a potential preventive therapy for MDR-TB in children, is well-tolerated

when administered in smaller child-friendly formulations periods over short treatment periods and has reduced side effects compared to the other fluoroquinolones currently in use.

To date only a single economic evaluation have investigated the use of IPT in young children under the age of 5 years to prevent susceptible TB in South Africa [57]. Based on their decision modelling in combination with a bottom-up costing analysis it was recommended that child household contact tracing combined with IPT (good and correct adherence) without testing in high endemic areas to children under the age of 5 years were cost effective and saved more lives [57].

This literature review also highlights the key methods of economic evaluations and its contribution towards decision making process on the adoption and use of health technologies. This review will contribute to the literature on the cost of providing Levofloxacin preventive treatment to child household contacts of MDR-TB adults as part of the ongoing TB-CHAMP phase III clinical trial in South Africa.

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PART C. JOURNAL ARTICLE

Proposed journal: Pharmacoeconomics

Abstract

Background

The incidence of TB in children under 15 years, accounts for 8% of the global TB burden (Global tuberculosis report, WHO, 2018). In 2018, the World Health Organization (WHO) estimated that there were approximately 11 000 multi-drug resistant (MDR) TB cases in South Africa. Despite having very clear guidelines on TB treatment programs and management, availability of inexpensive diagnostic tests, curative and preventive therapies, and the widespread use of the BCG vaccines, South Africa continues to have the highest the number of MDR-TB cases per capita. Levofloxacin is used as part of the group of fluoroquinolones in the drug regimen recommended in the treatment of MDR-TB patients. In addition to investigating the clinical impact of Levofloxacin as preventive antibiotic therapy, the expected costs of the intervention will be a critical input to determining feasibility and costs effectiveness, which will inform policy and implementation considerations.

Methods

We performed a cost analysis on using data from the Tuberculosis Child Multi-drug-resistant Preventive Therapy (TB-CHAMP) trial, conducted from a TB control program perspective. We used data from 510 childhood household contacts of MDR-TB patients in South Africa that were treated with Levofloxacin for 6 months as a preventive therapy for MDR-TB. In our analysis we evaluated the estimated health system cost associated with provision of Levofloxacin to childhood contacts of MDR-TB patients in South Africa.

Results

The mean total cost of treating a child household contact, irrespective of their weight band is ZAR 5,289.79. When the cost were analysed by weight categories we found that the cost increased by weight category; ZAR 2,146.78 (under 5 kg), ZAR 4,714.58 (between 5-15.9 kg) and ZAR 6,606.67 (over 16 kg). We performed a comprehensive sensitivity analysis and found that the scheduled clinic visits were the major cost driver. Aside from the scheduled visits we observed that there was an increase in additional health service utilisation for children with a weight more than 5kg.

Conclusion

We envisage that based on our analysis we will be able to inform policy decisions about the management and prevention of childhood household contacts of MDR-TB patients in developing TB themselves.

Keywords: Cost analysis, Pediatric MDR-TB, Preventive therapy, Levofloxacin

1. Introduction

In 2018, the global incidence of pediatric tuberculosis (TB) caused by the causative agent *Mycobacterium tuberculosis* (*M.tb*), was 1.1 million for children under the age of 5 years [1] of which 205 000 children died due to TB disease. Approximately 16 500 new cases of TB were diagnosed in children under 14 years in South Africa alone in 2018, making it the fourth leading cause of child mortality [2]. Pediatric TB disease presents with a diverse spectrum of pathology and remains challenging to diagnose. The spectrum of childhood TB disease range from limited TB disease with low *M.tb* bacillary load to more severe disease with high bacillary load and pathological representations including intra-thoracic TB, extra-thoracic TB, miliary TB and TB meningitis [3], [4].

Despite having very clear guidelines on TB treatment programs and management, availability of inexpensive diagnostic tests, curative and preventive therapies, and the widespread use of the bacille Calmette-Guerin (BCG) vaccine, South Africa continues to have the highest the number of MDR-TB cases per capita [5], [6]. However, pediatric TB diagnosis and treatment in the South African setting has shown some improvements [2], [7], [8]. The WHO estimates that in areas with high TB incidence at least two children are in direct household contact with an adult with active TB leaving them at high risk of developing TB disease themselves [9]. TB disease amongst children is commonly underappreciated as a major contributor to childhood morbidity and mortality, despite successful treatment outcomes [10]. In the majority of childhood TB cases, diagnosis with standard sputum-based assays are complicated due to the difficulty of expectorating sputum as well as pediatric tuberculosis that are usually pauci-bacillary and often extra-pulmonary [10]. Furthermore, the treatment of MDR-TB in children is complex, expensive, extensive, involves long hospitalization and is associated with side effects due to drug toxicity [11].

Levofloxacin is used as part of the group of fluoroquinolones in the drug regimen recommended in the treatment of MDR-TB patients. It functions by inhibiting enzymes that are necessary to separate bacterial DNA, thereby inhibiting cell replication. Occasional side effects of Levofloxacin are generally well tolerated

and may include nausea, vomiting, diarrhoea, trouble sleeping, dizziness and sensitivity to light. Some of the rare side effects include peripheral neuropathy and tendon rapture [12], [13].

The Tuberculosis Child Multi-drug-resistant Preventive Therapy (TB-CHAMP) clinical trial involved 510 child household contacts of MDR-TB patients in South Africa and investigated the use of Levofloxacin preventive therapy compared to placebo. The participants were followed for 72 weeks; 24 weeks of treatment and 48 weeks post-treatment.

In addition to investigating the clinical impact of preventive antibiotic therapy in this patient group, the expected costs of the intervention will be a critical input to determining feasibility and costs effectiveness, which will inform policy and implementation considerations. Here, we performed a cost analysis on Levofloxacin preventive therapy in the TB-CHAMP trial from a health systems perspective.

We envisage that this analysis will inform policy decisions about the management and prevention of child household contacts of MDR-TB patients in developing TB themselves.

2. Methodology

2.1. Study design

We performed a cost analysis to determine the economic impact of providing Levofloxacin as preventive treatment to child household contacts under the age of 5 years of MDR-TB adults in South Africa. The analysis was performed from the perspective of the South African National TB Control Program using secondary data from the TB-CHAMP trial. Costs are related to utilisation of Levofloxacin as preventive treatment for a child household contact of an MDR-TB adult to prevent them from developing MDR-TB disease themselves; cost (incurring direct and additional health services utilisation) related to Levofloxacin, clinic visits, diagnostic/monitoring tests and hospitalisations. The cost of resources will be values and presented in 2020 South African Rand.

2.2. Setting and population

Within this ongoing TB CHAMP trial, we analysed data from 510 participants that were randomly allocated to an intervention of control arm followed by a 48 post-treatment follow-up. All children living in the same household were allocated to the same treatment arm.

Three primary health care facilities in South Africa participated in the TB-CHAMP trial:

1. Desmond Tutu TB Centre, Stellenbosch University (SU), Cape Town (DTTC), 219 children
2. Motlosana Perinatal HIV Research Unit, Klerksdorp, Wits Health Consortium (PHRU), 205 children
3. Wits Reproductive Health and HIV Institute Shandukani Research Centre (WRHI), 86 children

Children in treatment arm are given Levofloxacin every day for 24 weeks. While, children in control arm are given a placebo every day for 24 weeks. In this double-blind RCT, our cost analysis we remained blinded with regards to which child household contact were randomised to the treatment or control arm of the study. The direct costs involved in providing Levofloxacin as preventive treatment to child household contacts of MDR-TB adults included; (i) cost of scheduled clinic visits during TB-CHAMP trial (screening visit, treatment initiation visit, treatment visits and follow-up visits summarised in table 4); (ii) costs diagnostic and monitoring tests; and (ii) cost of Levofloxacin.

Additional healthcare services cost were determined by additional clinic visits and hospitalisations if the child developed potential drug toxicity or other clinical event outside of the scheduled TB CHAMP clinic visits.

2.3. Data collection

The data fields from specific Case Report Forms (CRF) in the TB- CHAMP trial data set with cost implications on the direct cost and additional healthcare service utilisation costs have been identified and extracted to estimate direct costs for treating child household contacts of MDR-TB patients with Levofloxacin prophylaxis. The list of CRF are attached in the appendixes containing recorded data about (i) child eligibility to be enrolled in the TB CHAPM trial, (ii) diagnostic testing an screening, (iii) dispensing of

Levofloxacin, (iv) child clinical investigations during the treatment and follow-up visits. The retrospective cost analysis were performed from a health care provider's perspective on the extracted data, using a combination of STATA 15 and Microsoft Excel.

2.4. Costing approach

In the top down (gross costing) cost approach, we estimated the costs of direct treatment incurred by the children enrolled in the TB-CHAMP clinical trial as well as additional health care service utilisation from a providers perspective using national averages and expenditures [14]. The mean unit costs is determined by the number of scheduled clinic visits, Levofloxacin and diagnostics calculated for the total number of children that were initiated on preventive Levofloxacin treatment irrespective of their weight category. Subsequent to this, sub analysis for each weight categories (below 5 kg, between 5 and 16 kg, and above 16 kg). Calculation of medicine use by weight categories is based on the assumption that tablets cannot be split and, depending on the prescribed dosage regiment (Table 2), whole tablets (30 tablets or 90 tablets times 0.25 mg dose of Levofloxacin) are dispensed at each treatment visit, with remainder wasted. The cost of Levofloxacin was based on the current per unit price of Levofloxacin tablets on national state tender (ZAR 1.78) The additional health healthcare service utilisation costs include additional clinic visits and hospitalisations due to drug toxicity and other clinical events during the trial period. In clinical trials there is usually as small number of study participants that require substantial more medical services, referred to a outliers, that leads to a cost that is several standard deviations above the mean [14]. In our analysis excluded the 6 hospitalised patients that had extended beyond 10 days the hospitalisation cost. Cost were estimated using a price multiplied by utilisation approach [14]. We determined both the normative as well as the empirical cost of treatment therapy. The normative cost of treatment therapy assume 100% compliance by participants and is in-line with the treatment algorithm providing an estimated cost of treatment therapy. While the empirical cost is determined by the observed clinical data from the participant during the trial and provides a more accurate cost of what is happening in reality.

Utilisation was calculated from trial data where prices were prices were obtained from secondary sources including District Health Barometer (DHB) survey [15], National Health Laboratory Service (NHLS) and department of health [16]. The cost of clinic visits was calculated by the mean number of scheduled clinic visits observed by the 510 children (i.e. screening -, treatment initiation -, scheduled treatment and follow-up visits, multiplied by the mean cost of clinic visits in the Western Cape district). The Sarah Baartman DM: DC10 clinic were the lowest priced while Sedibeng DM:DC42 were the highest priced clinic for clinic visits in South Africa. The Cape Winelands DM: DC2 were the lowest priced and while Amajuba DM: DC25 were the highest priced for hospital inpatient per day in South Africa.

The number of diagnostic tests done during the treatment program was calculated by observed number of tests per child multiplied by the cost of each diagnostic test. The cost of diagnostics and monitoring tests is calculated by the mean cost per patient observed across the 510 children that was enrolled in the study. The cost of Levofloxacin is calculated by the mean cost of Levofloxacin per patient for total duration of the program with costs from the National Department of Health Master Procurement Catalogue [17].

Table 2. Levofloxacin dosages and cost per weight band prescribed by TB-CHAMP trial

Weight categories	Weight bands (kg)	Dosage	Cost
Under 5 kg	3 to 4.9	0.25	ZAR 1.78
	5 to 6.9	0.5	
5-16 kg	7 to 9.9	0.5	ZAR 1.78
	10 to 11.9	1	
	12 to 15.9	1	
	16 to 19.9	1.5	
Over 16 kg	20 to 24.9	1.5	ZAR 3.56
	>25	2	

2.5. Sensitivity analysis

The most relevant uncertainties in the study include the resource utilisation cost of administering of Levofloxacin in order to prevent child household contacts from developing MDR-TB disease themselves. In order to examine how changes in the unit cost of the TB-CHAMP trial resources affected to total cost

outcome of treating a child with preventive Levofloxacin, we carried out a comprehensive one-way sensitivity analysis on the relevant price and utilisation parameters.

2.6. Ethical approval

The TB-CHAMP trial previously obtained ethical approval from Human Research Ethics Committee (HREC) Stellenbosch University (HREC reference number M16/02/009) and the HREC University of Cape Town (UCT) (HREC REF:709/2019).

3. Results:

Table 3 describes the total costs of the presentative therapy regimen broken down by Levofloxacin (preventive drug), scheduled clinic visits, diagnostics, additional clinic visit and hospitalisations costs. The costs are divided by the direct costs associated with provision of the preventive therapy, including the preventive drug, scheduled clinic visits and diagnostics. The additional health service utilisation costs were those observed in the trial population but were not directly part of the treatment protocol.

The mean total cost of treating a child household contact, irrespective of their weight band is ZAR 5,289.79. The participant weight bands were categorised into 3 weight categories; under 5kg, between 5 and 16 kg and over 16 kg and is based on the prescribed dosage of differences of weight bands and associated cost difference between the dosages. When the cost were analysed by weight categories we found that the cost increased by weight category; ZAR 2,146.78 (under 5 kg), ZAR 4,714.58 (between 5-15.9 kg) and ZAR 6,606.67 (over 16 kg) (figure 1).

Table 3. Summary of unit costs of treatment with Levofloxacin for 24 weeks and follow-up for 48 weeks

Cost component	Description	Combined weight bands (n=510)	< 5kg (n=8)	5-16 kg (n=430)	> 16 kg (n-=72)
Direct cost		**Base**	**Base**	**Base**	**Base**
Cost of Levofloxacin	Mean Cost per patient (total treatment duration)	ZAR 372.43	ZAR 85.84	ZAR 260.75	ZAR 616.86
Cost of Scheduled Clinic visits	Mean cost for clinical visits per patient	ZAR 3,836.69	ZAR 1,509.26	ZAR 3,506.81	ZAR 5,060.46
Cost of diagnostics	Expected cost for diagnostic tests	ZAR 551.68	ZAR 551.68	ZAR 551.68	ZAR 551.68
Sub-total	*direct cost of preventive therapy*	**ZAR 4,760.79**	**ZAR 2,146.78**	**ZAR 4,319.24**	**ZAR 6,229.00**
Cost of Additional clinic visit	Baseline unit cost	ZAR 297.69	ZAR -	ZAR 302.14	ZAR 308.26
Cost of hospitalisation	Baseline cost	ZAR 230.73	ZAR -	ZAR 93.20	ZAR 69.41
Sub-total	*cost of additional observed health service utilisation in trial participants*	ZAR 528.42	ZAR -	ZAR 395.34	ZAR 377.67
Total cost		**ZAR 5,289.20**	**ZAR 2,146.78**	**ZAR 4,714.58**	**ZAR 6,606.67**

The direct cost of treating a child contact with preventive therapy consists of the cost of the Levofloxacin drug (ZAR 1.78 unit cost per tablet), total cost diagnostic testing and monitoring (ZAR 551.68 combined laboratory investigations); and costs per clinic visits (ZAR 443.90).

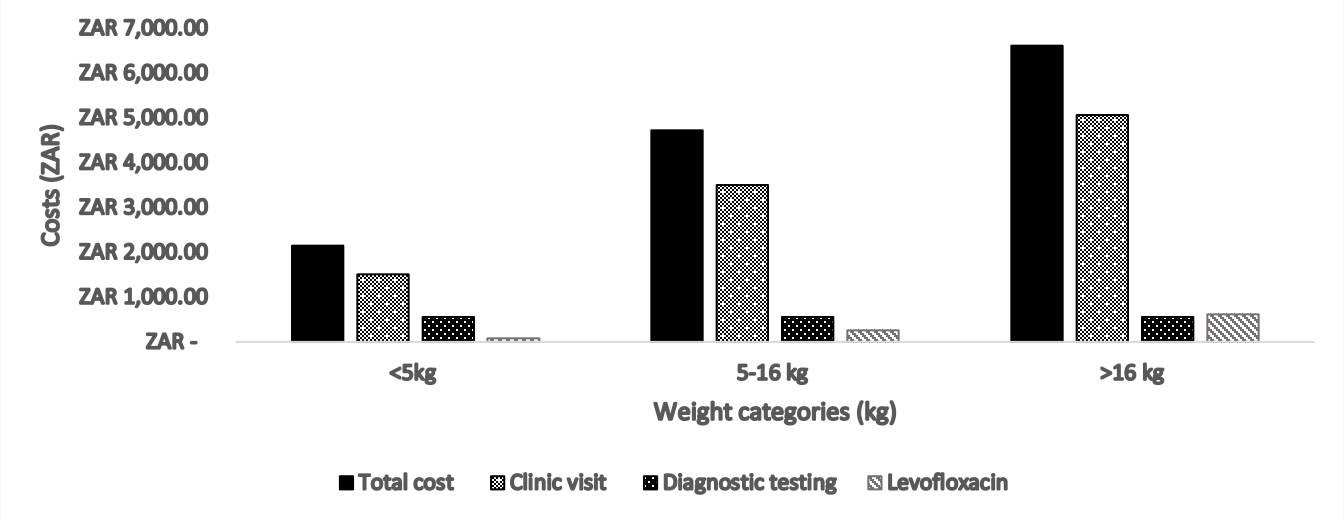

Figure 1. Summary of the cost per patient per weight category. A bar graph demonstrating the mean total cost of preventive therapy, breakdown of direct costs i.e. scheduled clinic visits, diagnostic testing and Levofloxacin per patient across the different weight categories.

3.1. Breakdown of direct costs

Scheduled clinic visits

Table 4 presents a breakdown of the scheduled clinic visits as determined by the TB-CHAMP trial. The normative mean number of scheduled visits are 11 if all participants had strictly complied to the TB-CHAMP treatment schedule the cost were ZAR 4,882.90. Despite all efforts the mean number of observed scheduled visits were 8.64 and the total cost of clinic visits were ZAR 3,836.69, irrespective of the participants' weight band. The mean cost of observed scheduled visits calculated by weight category were ZAR 1,509.26 (less than 5 kg), ZAR 3,506.81 (between 5 and 16 kg) and ZAR 5,060.46 (more than 16 kg).

Table 4. Cost of clinic visits breakdown

	Mean observed number of visits per patient					Mean cost of clinic visits				
Scheduled clinic visits	**Normative**	**Combined weight categories**	**Under 5kg**	**5-15.9 kg**	**Over 16 kg**	**Normative**	**Combined weight categories**	**Under 5kg**	**5-15.9 kg**	**Over 16kg**
Screening	1	1	1	1	1	ZAR 443.90	ZAR 443.90	ZAR 443.90	ZAR 443.90	ZAR 443.90
Treatment initiation	1	1	1	1	1	ZAR 443.90	ZAR 443.90	ZAR 443.90	ZAR 443.90	ZAR 443.90
Treatment	5	4.5	1.3	4.3	5.5.	ZAR 2,219.50	ZAR 1,983.62	ZAR 577.07	ZAR 1,908.77	ZAR 2,441.45
Follow-up	4	2.2	0.1	1.6	3.9	ZAR 1,775.60	ZAR 965.26	ZAR 44.39	ZAR 710.24	ZAR 1,731.21
Mean number of total visits	**11**	**8.64**	3.4	7.9	11.4					
Total cost for clinical trial visits						ZAR 4,882.90	ZAR 3,836.69	ZAR 1,509.26	ZAR 3,506.81	ZAR 5,060.46

Cost of Levofloxacin

At each scheduled clinic visits Levofloxacin tablets are dispensed to the participant depending on the dosage regimen determined by weight bands. The observed mean number of tablets dispensed irrespective of the weight band dosage was 209 and the mean observed cost per patient for total treatment duration, assuming tablet cannot be split, is ZAR 372.43 (summarised in table 2 and S1). The mean cost of observed Levofloxacin by weight category was ZAR 85.84 (less than 5 kg), ZAR 260.75 (between 5 and 16 kg) and ZAR 616.86 (more than 16 kg).

Cost of diagnostics

A list of diagnostic tests were performed during scheduled clinic visits during the clinical trial. The bacteriological tests included Acid- Fast Bacilli smear, GeneXpert MTB/RIF assay (or Ultra), HAIN Genotype MTBDRplus/MTBDRsI assay, *Mycobacteria Growth Indicator Tube* (*MGIT*), Solid culture, Interferon Gamma release assay (IGRA). Routine X-ray (radiology Imaging-Cat B, level 2) were also performed during screening and during the trial (Table S2). The mean cost of observed diagnostic and monitoring per patient were R551,68 per patient. This remain unchanged for weight categories.

3.2. Breakdown of additional health service utilisation

Other than the scheduled clinic visits, additional clinic visits (342) and hospitalisations (18) for the 510 trial participants were observed.

Additional clinic visits

Of the 342 additional clinic visits, 292 participants between 5 and 16 kg, and 50 participants were over 16kg. The mean cost for additional clinic visits and were ZAR 297.67; ZAR 301.44 and ZAR 308.26 respective of the weight categories.

Hospitalizations

A total of 18 out of the 510 participants were hospitalised. Five patients had lengths of stay beyond 10 days were excluded from the analysis. The mean length of stay for patients with a length of stay of 10 days and lower is 3.91 days at a cost of ZAR 9786.97. The cost of hospitalisations for four patients

hospitalized for one day was ZAR 9995.20 and increased to ZAR 24 988 for a single patient hospitalised for 10 days (figure 2).

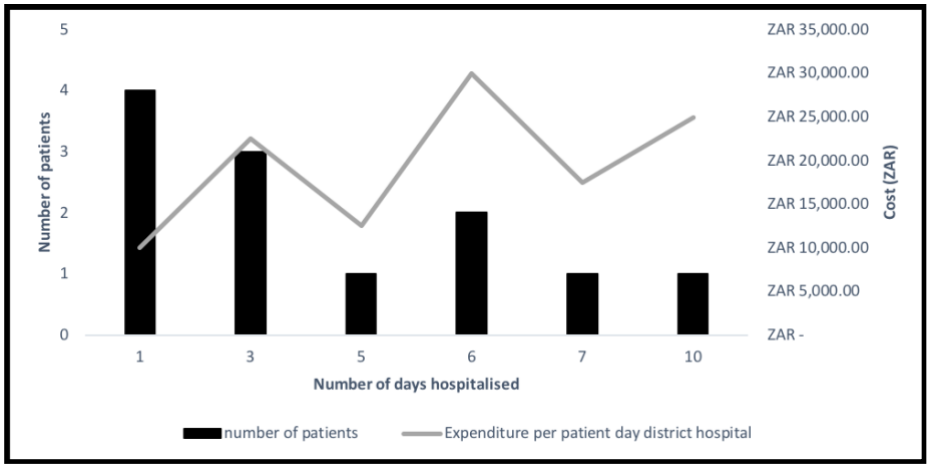

Figure 2. Cost of hospitalizations. Bar chart illustrates of the increase in the cost of hospitalisation as the number of days hospitalised per patient increase.

3.3. Sensitivity analysis

Unit cost sensitivity analysis

Figure 3 (a) illustrates our findings from our overall and sub-weight category (b-d) sensitivity analysis of unit cost. The key parameters that were included in our analysis were the cost of scheduled clinic visits, diagnostics, Levofloxacin, additional clinic visits and hospitalisations.

In our overall unit cost sensitivity analysis we used the estimated mean cost of preventive therapy of ZAR 5 289.20. There was a decrease of 14.01% in the estimated cost of preventive therapy when the cost of scheduled were determined by the lowest price of clinic visit increased by 47.92%. when the same cost was determined by the highest price of clinic visit.

In the case of additional health service utilisation costs; there was a decrease of 1.09% in the mean cost of preventive therapy when the cost of additional clinic were determined by the lowest price of clinic visit and increased by 3.72%. when the same cost was determined by the highest price of clinic visit. There was a decrease of 0.75% in the mean cost of preventive therapy when the cost of hospitalisation were determined by the lowest priced hospital inpatient per day and increased by 4.23%. when the same cost was determined by the highest priced hospital in patient per day.

Subgroup unit cost sensitivity analysis under 5kg

In the under 5kg weight category unit cost sensitivity analysis we used the estimated mean cost of preventive therapy of ZAR 2 146.87. There was a decrease of 14% in the mean cost of preventive therapy when the cost of scheduled were determined by the lowest priced clinic visit while it increased by 46%. when the same cost was determined by the highest priced clinic visit.

Subgroup Unit cost sensitivity analysis between 5 and 16 kg

In the between 5 and 16 kg weight category unit cost sensitivity analysis we used the estimated mean cost of preventive therapy of ZAR 4 714.58. There was a decrease of 14.4% in the mean cost of preventive therapy when the cost of scheduled were determined by the lowest priced clinic visit and increased by 49.1%. when the same cost was determined by the highest priced clinic visit.

In the case of additional health service utilisation costs; there was a decrease of 1.2% in the mean cost of preventive therapy when the cost of additional clinic were determined by the lowest priced clinic visit increased by 4.2%. when the same cost was determined by the highest priced clinic visit. There was a decrease of 0.3% in the mean cost of preventive therapy when the cost of hospitalisation were determined by the lowest priced hospital inpatient per day and increased by 1.9%. when the same cost was determined by the highest priced hospital in patient per day.

Subgroup Unit cost sensitivity analysis over 16 kg

In the over 16 kg weight category unit cost sensitivity analysis we used the estimated mean cost of preventive therapy of ZAR 6 606.67. There was a decrease of 0.9% in the mean cost of preventive therapy when the cost of additional clinic were determined by the lowest priced clinic visit and increased by 3.1%. when the same cost was determined by the highest priced clinic visit. There was a decrease of 0.2% in the mean cost of preventive therapy when the cost of hospitalisation were determined by the lowest priced hospital inpatient per day and increased by 1%. when the same cost was determined by the highest priced of hospital in patient per day (Table S3).

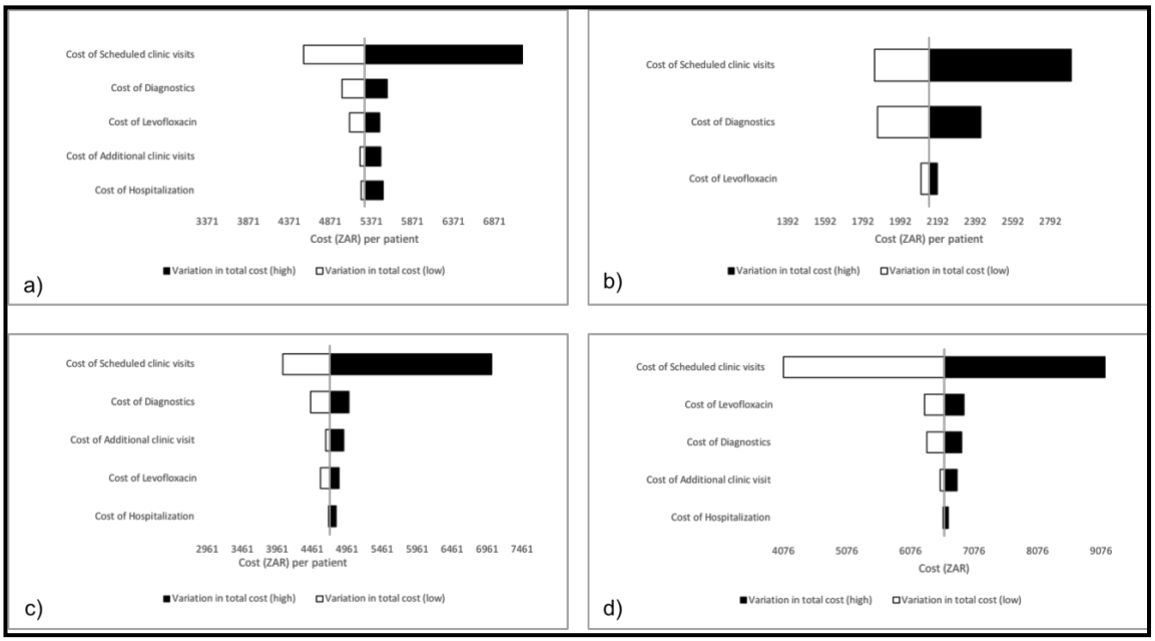

Figure 3. One way sensitivity analysis (unit costs).

a) Unit cost sensitivity analysis: Tornado diagram demonstrating variation the total cost of treatment with Levofloxacin per patient, irrespective of their weight category with an increase/decrease in cost parameters. b) Sub-Unit cost sensitivity analysis: Tornado diagram demonstrating variation the total cost of treatment with Levofloxacin per patient, in the under 5 kg weight category, with an increase/decrease in cost parameters. c) Sub-Unit cost sensitivity analysis: Tornado diagram demonstrating variation the total cost of treatment with Levofloxacin per patient, in the between 5 and 16 kg weight category, with an increase/decrease in cost parameters. d) Sub-Unit cost sensitivity analysis: Tornado diagram demonstrating variation the total cost of treatment with Levofloxacin per patient, in the over 16 kg weight category, with an increase/decrease in cost parameters.

Utilisation sensitivity analysis

Figure 4 illustrates the findings for the utilisation sensitivity analysis and is based on the empirical data from the TB-CHAMP trial. The key parameters that were included in our analysis were the Levofloxacin volume, total clinic visits rate and hospitalisations rates. The utilisation sensitivity analysis for Levofloxacin volume were conducted using 150 and 300 tables corresponding to the lowest and the highest number of Levofloxacin tablets utilised in the trial. We observed a decrease of 1.98% in the mean cost of preventive therapy when the Levofloxacin volume was decreased to 150 tablets per patient and an increase of 3.08%. when it was increased to 300 tablets per patient.

In the case of hospitalisation rate, the mean cost of preventive therapy decreased by 4.35% and increased by 7.98% when the number of hospital admissions were 0% (least number of hospital admissions observed) and 10% (highest number of hospital admissions observed), respectively.

In the case of total clinic visit rate, the mean cost of preventive therapy decreased by 53% and increased by 30% when the number of clinical visits were 3 (least number of clinic visits observed) and 13 (highest number of clinic visits), respectively.

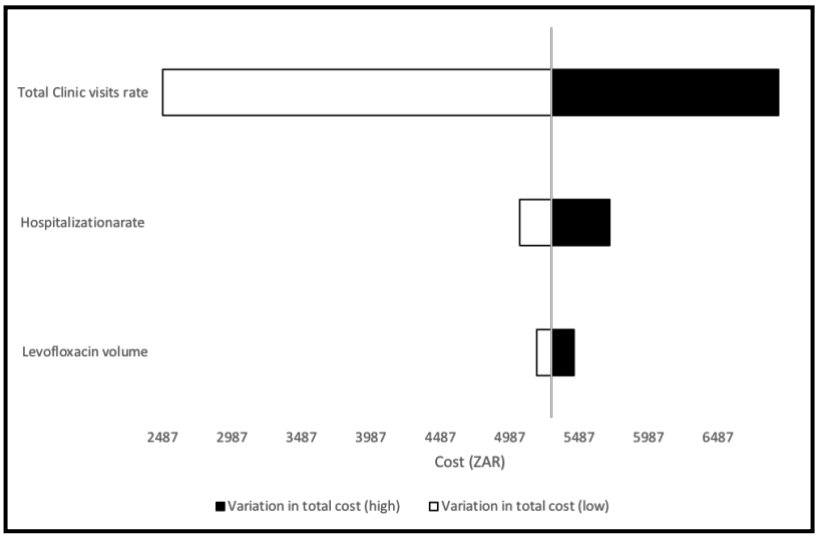

Figure 4. Utilisation sensitivity analysis. Tornado diagram demonstrating variation the total cost of preventive therapy per patient, an increase/decrease in utilisation rates.

4. Discussion

This is the first cost analysis of its kind to assess the impact of direct drivers of resource utilisation costs of preventive therapy in child household contacts of MDR-TB adults in South Africa. The key finding of this study revealed that the main cost driver of treating children with preventive therapy is the cost of scheduled clinic visits and not the drug itself.

Our analysis show that the empirical costs observed during the trial provide a much more accurate result of what is happening in reality and were lower, compared to the normative cost. The normative costing analysis would have provided an estimated utilisation based on recommended clinical practice would not have identified the reduced utilisation in terms of clinic visits etc. and would have missed the additional costs of hospitalisation and clinic visits.

The scheduled clinic visit alone contributed 72% towards the mean total cost preventive therapy. When analysed across the different 3 weight categories the scheduled clinic visits contributed between 70-77% as the weight of the child increased, while the cost of Levofloxacin only contributed

between 4-10% toward the total direct costs. This low contribution of a preventive drug towards the total cost of treatment programs are in line with findings of a decision analysis model that examined the cost effectiveness of IPT in child contacts of TB adults in a high burden setting [18]. They found that implementing IPT for young household contacts, screening for TB without testing and IPT should be used in high burden TB settings for young household contacts of infectious TB adults [18].

Due to the strict clinical evaluation of children during the TB-CHAMP trial, other clinical events have also been reported during the treatment and follow-up clinic visit. Since the TB-CHAMP trial is still ongoing it is unclear what could be leading to the trial participants seeking additional health services We hypothesis that it could be a clinical event (i) as a direct result of the preventive therapy due to any drug toxicities; (ii) as a completely independent of the preventive therapy where the patient would have accessed the health service even if they were not participating in the trial or (iii) as an indirect result of the preventive therapy in that the increased contact with the health system enabled access to health care services that would not have otherwise occurred.

Thus, we also evaluated the impact of cost of additional clinic visits and hospitalisation on the total cost of preventive therapy per patient. The child participants under 5 kg did not incur any additional health service utilisations during the trial, although this is likely due to the small number of children in this cohort (n=8). Ten children of the 16 children in the 5 to 16 kg weight category and 2 children in the over 16 kg weight category were admitted to the hospital due to drug toxicity or other clinical events. The cost of additional health service utilisations were 8.38% and 5.72% of the mean cost of preventive therapy between 5-16kg and over 16kg, respectively. The additional health service utilisation did not have a significant impact on the cost of preventive therapy.

This study revealed that the total cost of preventive therapy per patient increase as the weight category of the participant increased. The cost of scheduled clinic visits from the providers perspective is the largest cost driver of the cost of preventive therapy. The contributing cost of Levofloxacin drug in this is negligible and highlights the irregularities in the cost of health care facilities across South Africa. If the preventive treatment were provided at the cheapest clinic, in terms of cost per clinic visit

in South Africa, the mean cost of providing preventive therapy per participant would reduce by 14% and increase by 48% at the most expensive clinic. Despite the fact that some health care facilities are able to provide the preventive therapy at a lower cost the participants it might not be able to regularly attend scheduled clinic visits. Even though we did not include indirect costs in our analysis it is important to consider the location and access to the health care facility where the prevention program will be rolled out.

5. Study limitations

The study calculated direct health costs only as it represented the provider's perspective. In our analysis were did not include the indirect additional costs, i.e. transport and time off work that are borne by households were beyond the scope of this study. These costs are likely to be a significant consideration for any policy implementation of preventive therapy for these patients as many of these health care clinics are located in rural locations and it might be difficult to access due to high travel costs and limited staff and resources. This gross costing analysis only represented major cost drivers such as preventive drug, health care facility visits and diagnostics even though it is possible that additional costs may have been incurred by the participant's household. The advantage of conducting a costing analysis in conjunction with a clinical trial is that careful records of health service utilisation are recorded.

We used national schedules of prices and mean facility expenditure to estimate the costs of preventive therapy. An alternative micro-costing approach would have yielded a more granular cost structure, but it is not clear that it would be more representative of the expected costs nationally. As this costing is intended to inform national -level policy it was considered that this use of national pricing is appropriate.

If preventive therapy became routine clinical practice in South Africa, it is possible that less routine visits would be required per patient. However, because of the large number of additional clinic visits observed in the data, it is possible that preventive therapy would still incur a substantial number of

clinic visits. This indirect result of routine visits increased contact with the health system and in turn lead to increased utilisation of health care services that would otherwise not have occurred.

6. Conclusion

This study is the first of its kind to access the cost of providing Levofloxacin preventive therapy to child household contacts of MDR-TB adults in South Africa. Our results demonstrate the complexities involved in managing childhood disease and as the child grow in weight the demand for health care services increases. Despite the relatively low cost of preventive therapy, it is important to recognise that should this preventive therapy become routine in South Africa children, besides the routine treatment clinic visits, might require additional health care services. This could lead to the inflation of the total cost of preventive therapy. We envisage that based on our analysis we will be able to facilitate planning and resource allocation, inform policy decisions about the management and preventive therapy, and future cost analysis studies.

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PART D. POLICY BRIEF

POLICY BRIEF

HEALTH ECONOMICS UNIT

COST ANALYSIS OF PREVENTATIVE TREATMENT WITH LEVOFLOXACIN OF CHILD HOUSHOLD CONTACTS OF MDR-TB ADULTS IN AFRICA

Author: SUERETA FORTUIN

KEY MESSAGES

- ◊ Preventative Levofloxacin therapy decrease development of pediatric MDR-TB
- ◊ The estimated cost of preventative therapy observed in the TB-CHAMP trial is ZAR 3,836.69.
- ◊ Scheduled clinic visits major contributor towards the cost of preventative therapy
- ◊ Demand for additional health services increases as children grow and lead to increase in cost of preventative therapy.
- ◊ This cost analysis aim to facilitate planning and resource allocation, inform policy decisions about the management and preventative therapy, and future cost analysis studies.

INTRODUCTION

Despite having very clear guidelines on TB treatment programs and management, availability of inexpensive diagnostic tests, curative and preventive therapies, and the widespread use of the BCG vaccine, the number of patients with MDR-TB in South Africa continues to increase annually [1]. However, peadiatric TB diagnosis and treatment in the South African setting has shown some improvements [2]–[4]. TB disease amongst children is commonly underappreciated as a major contributor to childhood morbidity and mortality, despite successful treatment outcomes [5]. This policy brief summarizes the key findings of a cost analysis done on secondary data from the Tuberculosis Child Multi-drug-resistant Preventative Therapy (TB-CHAMP) trial that involved the provision of Levofloxacin preventative treatment to child household contacts of MDR-TB patients in South Africa.

METHODS

We performed a cost analysis using a providers perspective was conducted to determine the economic impact of providing levofloxacin as preventative treatment to 510 child household contacts under the age of 5 years of MDR-TB adults in South Africa. Costs were collected retrospectively based on a gross costing approach and are related to utilization of levofloxacin, i.e. direct -and additional health services utilization cost related to Levofloxacin, clinic visits, diagnostic/monitoring tests and hospitalizations to derive the total cost of treatment per patient. A comprehensive sensitivity analysis were used to determine the uncertainty of cost parameters on the total cost of preventative treatment per patient.

RESULTS

The average cost of preventative therapy, irrespective of their weight band is ZAR 5,289.79. When the cost were analyzed by weight categories we found that the cost increased by weight category; ZAR 2,146.78 (under 5 kg), ZAR 4,714.58 (between 5-15.9 kg) and ZAR 6,606.67 (over 16 kg) (figure 1). Overall scheduled clinic visits were the major contributor (approximately 70%), while the Levofloxacin drug only contributed (approximately 10%) toward the total cost of the preventative therapy.

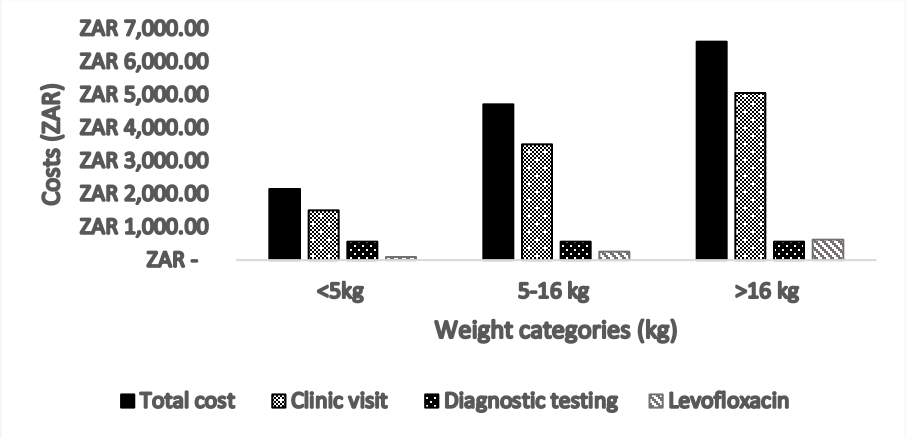

Figure 1. Summary of the cost per patient per weight category. A bar graph demonstrating the average cost of preventative therapy, breakdown of direct costs i.e. scheduled clinic visits, diagnostic testing and levofloxacin per patient across the different weight categories.

We also observed that as children increased in weight their need for additional health services increased. Even though we are unclear about what could be leading to these additional clinic visits and hospitalizations we found that it added at least 10% to the total cost of preventative therapy.

CONCLUSION

We envisage that based on our analysis we will be able to inform policy decisions about the management and prevention of childhood household contacts of MDR-TB patients in developing TB themselves.

POLICY IMPLICATIONS

In order to reduce the incidence of peadiatric MDR-TB in South Africa the following policy interventions could be considered:

- ◊ Introduce Levofloxacin as preventative therapy for children under the age of 5 years as routine clinical practice in South Africa
- ◊ Clinic visits were the major cost driver in the provision of preventative therapy. Improve child health monitoring and assessments during routine treatment visits to reduce the need for additional health care services.
- ◊ The indirect additional costs, not determined in this study, incurred by the households are likely to impact the access to preventative therapy as many of these health care clinics are located in rural locations and it might be difficult to access due to high travel costs and limited staff and resources.

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PART E. APPENDIXES

Table S1. Cost of Levofloxacin distribution per weight band

		Mean cost of total treatment per patient.		
Weight band	**Dosage**	**Assuming tablets can be split and no wastage. (Normative)**	**Assuming tablets cannot be split. (Normative)**	**Observed (Empirical)**
3 to 4.9	0.25	ZAR 62.46	ZAR 249.85	ZAR 85.84
5 to 6.9	0.5	ZAR 124.93	ZAR 249.85	ZAR 230.22
7 to 9.9	0.5	ZAR 124.93	ZAR 249.85	ZAR 238.60
10 to 11.9	1	ZAR 249.85	ZAR 249.85	ZAR 240.33
12 to 15.9	1	ZAR 249.85	ZAR 249.85	ZAR 333.86
16 to 19.9	1.5	ZAR 374.78	ZAR 499.70	ZAR 552.53
20 to 24.9	1.5	ZAR 374.78	ZAR 499.70	ZAR 610.97
>25	2	ZAR 499.70	ZAR 499.70	ZAR 687.09

Table S2. Observed diagnostics tests and cost

			Expected
***n* (510)**	**Total observed units**	**Units per patient**	**Cost for diagnostic tests**
Bacteriology test			
Acid- Fast Bacilli smear	128	0.251	ZAR 4.57
GeneXpert MTB/RIF assay (or Ultra)	100	0.196	ZAR 39.52
HAIN Genotype MTBDRplus/MTBDRsI assay (specimen)	7	0.014	ZAR 2.81
Liquid culture (MGIT)	125	0.245	ZAR 25.30
Solid culture (no growth)	107	0.210	ZAR 14.89
IGRA	515	1.010	ZAR 35.49
Diagnostics			
X-ray (radiology Imaging-Cat B, level 2)	539	1.057	ZAR 429.09

Table S3. Percentage impact of increase and decrease in parameter costs on the total cost of preventative therapy

Cost component	% change all weight bands		% change under 5kg		% change 5-16 kg		% change over 16 kg	
Direct cost	**Decrease**	**Increase**	**Decrease**	**Increase**	**Decrease**	**Increase**	**Decrease**	**Increase**
Cost of Levofloxacin	3.52	3.52	2	2	2.8	2.8	4.7	4.7
Cost of Scheduled Clinic visits	14.01	47.92	14	46	14.4	49.1	**38.3**	38.3
Cost of diagnostics	5.22	5.22	13	13	5.9	5.9	4.2	4.2
Additional Health service cost								
Cost of Additional clinic visit	1.09	3.72			1.2	4.2	0.9	3.1
Cost of hospitalization	0.75	4.23			0.3	1.9	0.2	1.0

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13 May 2016

MAILED

Prof AC Hesseling

Paediatrics & Child Health
Desmond Tutu TB Centre

Tygerberg
7500

Sender:
MR CFS WEBER
Tel: +27 (0)21 938-9657 / E-mail: fweb@sun.ac.za
Fax: +27 (0)21 931-3352

Fax: 021 938 9719

Dear Prof Hesseling

PROTOCOL: TB CHAMP PROTOCOL
A phase III cluster randomised placebo-controlled trial to assess the efficacy of preventive therapy in child contacts of multidrug-resistant (MDR) tuberculosis (TB)

ETHICS REFERENCE NO: M16/02/009

At a meeting of the Health Research Ethics Committee (HREC) held on 02 March 2016, the above project was reviewed and modifications to this project were requested. This information has now been provided and the study is now finally approved, as of the above date.

Kindly note that the Letter of Approval from the Medicine's Control Council of SA's, which includes the Investigator's participation in the study, is imperative before the commencement of the study. Please forward a copy of the Letter of Approval to the undersigned if it has not already been submitted with the documentation.

The following documents were reviewed and approved by the Committee:

	Submitted Version	Date submitted	Approved Version	Date of Approval
Protocol:	TB CHAMP Protocol vers 1.0 dated 11 November 2015	12 Feb 2016	TB CHAMP Protocol vers 1.0 dated 11 November 2015	13 May 2016

	Document	Version	Description
Patient Forms:			Consent Form Index Case, version 1.0 dated 11 November 2015
			Parental/Guardian consent for Child, version 1.0 dated 11 November 2015
			Consent for PK sampling, version 1.0 dated 11 November 2015

	Document	Description
Insurance:		No fault Compensation Insurance policy number PO309814 underwritten by Lloyds
		Professional Liability Insurance policy number P01380 underwritten by Stalker Hutchison Admiral

	Document	Description
Other Documentation:		Budget breakdown and signed Declaration of sufficient funds
		Investigator Medicinal Product Dossier for Levofloxacin dispersible tablets 100 mg (Macleods Pharmaceuticals Ltd, India)
		Letter from Dr Lyn Horn, Ethics Consultant SA on the use of placebo control arm.

The following persons' participation in this study have been approved by the Committee:

Prof AC Hesseling	Principal Investigator	Desmond Tutu TB Centre
Dr J Winckler	Sub-Investigator	Desmond Tutu TB Centre
Dr E Walters	Sub-Investigator	Desmond Tutu TB Centre
Dr L Van der Laan	Sub-Investigator	Desmond Tutu TB Centre
Dr H Van Deventer	Sub-Investigator	Desmond Tutu TB Centre
Dr M van der Zalm	Sub-Investigator	Desmond Tutu TB Centre
Prof HS Schaaf	Sub-Investigator	Desmond Tutu TB Centre
Dr M Palmer	Sub-Investigator	Desmond Tutu TB Centre
Dr A Garcia-Prats	Sub-Investigator	Desmond Tutu TB Centre
Dr C De Vaal	Sub-Investigator	Desmond Tutu TB Centre
Ms R Kitshoff	Pharmacist	Desmond Tutu TB Centre
Dr S Staples	Principal Investigator	Think
Dr L Duckworth	Sub-Investigator	Think
Dr R Narasimooloo	Sub-investigator	Think
Ms E Boshoff	Pharmacist	Think

The study has been accepted as complying to the Ethics Standards for Clinical Research with a new medicine in human participants, based on FDA, ICH, SA GCP and The Declaration of Helsinki guidelines.

1. THIS APPROVAL IS SUBJECT TO THE FOLLOWING PROVISOS:

* The study is conducted according to the protocol submitted to the Health Research Ethics Committee of Stellenbosch University. Any amendments to the protocol must first be submitted to the HREC of Stellenbosch University for approval.
* During the study, the HREC of Stellenbosch University is informed immediately of :
  - Any Unexpected Serious Adverse Events or Unexpected Adverse Drug Reactions, which, in the Investigator and/or the Sponsor's opinion are suspected to be related to the study drug.
  - Any data received during the trial which, may cast doubt on the validity of the continuation of the study .
* The HREC of Stellenbosch University is notified of any decision to discontinue the study and the reason stated.
* Only the Investigators authorised by this approval participate in this study. Additional Investigators shall be submitted to the HREC of Stellenbosch University for approval prior to their participation in
* In the event of an authorised Investigator ceasing to participate in the study, the HRECof Stellenbosch University must be informed and the reason for such cessation given.

2. PRINCIPLES OF INFORMED CONSENT:
The HREC of Stellenbosch University requires that in all studies, the Principles of Informed Consent are adhered to.This applies to volunteers as well as patients.

Afdeling Navorsingsontwikkeling en -Steun • Research Development and Support Division
Posbus/PO Box 19063 • Tygerberg 7505 • Suid-Afrika/South Africa
Tel: +27 21 938 9820 • Faks/Fax: +27 21 931 3352
E-pos/E-mail: rdsdinfo@sun.ac.za

3. PROGRESS REPORTS:
The HREC of Stellenbosch University requests that the Trial / Study specific Progress Reports be submitted annually to the Ethics Office and a report of the final results, at the conclusion of trial.

4. COMMITTEE MEMBERS
The supporting list of Committee members present at the meeting is hereby attached for your records.

Yours faithfully

MR FRANKLIN WEBER
COORDINATOR HREC 1

Afdeling Navorsingsontwikkeling en -Steun • Research Development and Support Division
Posbus/PO Box 19063 • Tygerberg 7505 • Suid-Afrika/South Africa
Tel: +27 21 938 9820 • Faks/Fax: +27 21 931 3352
E-pos/E-mail: rdsdinfo@sun.ac.za

health

Department:
Health
REPUBLIC OF SOUTH AFRICA

MEDICINES CONTROL COUNCIL
The Registrar of Medicines, Private Bag X828, PRETORIA, 0001
Tel 012 395 8000 Fax 012 395 9201
Tel: *Enquiries:*
Fax: *Reference:*

FAX AND MAIL TO

MS KEDIBONE MALATJI

N2/19/8/2 ()

Dr F Verheye-Dua

Datum * Date **08 December 2016**

Desmond Tutu TB Centre,University of Stellenbosch
Francie van Zijl Avenue
Clinical Building
Tygerberg Campus
7505

Tel: 012 395 8729
Fax:

Fax: 0866899929

Dear Dr Verheye-Dua,

AUTHORISATION FOR THE IMPORTATION OF UNREGISTERED MEDICINE IN TERMS OF SECTION 21 OF THE MEDICINES AND RELATED SUBSTANCES CONTROL ACT, 1965 (ACT 101 OF 1965)

PRODUCT: LEVOFLOXACIN

Your application letter dated **11 Nov 2015** refers

1. **RESOLUTION AND APPROVAL**

It was recently resolved by the Medicines Control Council that; the clinical trial application according to the following Protocol be approved :-

TB CHAMP protocol version V 1.0 dated 11-Nov-15

A phase III cluster randomised placebo-controlled trial to assess the efficacy of preventive therapy in child contacts of multidrug-resistant (MDR) tuberculosis(TB)

1.1 **BEFORE COMMENCEMENT OF TRIAL**

Please Note: Copies of written Ethics Committee approval/(s) to be submitted to MCC before the study commences.

2. **AUTHORISATION**

Authorisation is hereby granted for the importation and administration of a sufficient quantity, for the duration of the trial, of the unregistered medicine:

LEVOFLOXACIN

solely for the purpose of a clinical trial to be conducted by:

Prof AC Hesseling	Desmond Tutu TB Centre, Stellenbosch University	Principal
Dr C de Vaal	Desmond Tutu TB Centre, Stellenbosch University	
Dr A Garcia-Prats	Desmond Tutu TB Centre, Stellenbosch University	
Dr M Palmer	Desmond Tutu TB Centre, Stellenbosch University	
Dr SE Purchase	Desmond Tutu TB Centre, Stellenbosch University	
Prof H S Schaaf	Desmond Tutu TB Centre, Stellenbosch University	
Dr L van der Laan	Desmond Tutu TB Centre, Stellenbosch University	
Dr M Van der Zalm	Desmond Tutu TB Centre, Stellenbosch University	
Dr H van Deventer	Desmond Tutu TB Centre, Stellenbosch University	
Dr E Walters	Desmond Tutu TB Centre, Stellenbosch University	

Dr J Winckler	Desmond Tutu TB Centre, Stellenbosch University	
Dr N Martinson	Perinatal HIV Research Unit (PHRU)	Principal
Dr L Lebina	Perinatal HIV Research Unit (PHRU)	
Dr S Staples	THINK Clinical Trial Unit(CTU)	Principal
Dr L Duckworth	THINK Clinical Trial Unit(CTU)	
Dr R Narasimooloo	THINK Clinical Trial Unit(CTU)	
Dr L Fairlie	Wits Reproductive Health and HIV Institute Shandukani	Principal
Dr M Masango	Wits Reproductive Health and HIV Institute Shandukani	
Dr MS Masenya	Wits Reproductive Health and HIV Institute Shandukani	

3. **PLEASE FORWARD**

It is a requirement that a copy of this letter be forwarded to all the relevant Trialist/(s), including the approving Ethics Committee(s).

4. **THIS AUTHORISATION IS SUBJECT TO THE FOLLOWING PROVISOS:**

(a) The Council shall be informed immediately of any toxic effects or death, which may occur during the Clinical Trial and of any data received which, might cast doubt on the validity of the continuation of the Clinical Trial.

(b) The Council shall be notified of any decision to discontinue the Clinical Trial. The reason for such cancellation shal be stated.

(c) The Clinical Trial shall be conducted in accordance with the Protocol submitted to the Council. Any Amendment/(s) to the Protocol shall first be submitted to the Council for approval. All Clinical Trials be conducted in accordance with ICH GCP Guidelines, and the South African Clinical Trials Guidelines.

(d) The medicine shall be administered by or under the direction of the authorised Trialist. In the case where the Trialist permits another Medical Practitioner to administer a medicine, which is exempted from the registration for the purpose of the Trial, the Trialist shall remain responsible for any eventuality arising from such usage.

(e) Where a Trialist who is not authorised in the initial Authorisation, is requested to participate in the Clinical Trial, the Council requests that the relevant MCC Curriculum Vitae Format be completed detailing their Full Names, Address and Qualifications of the proposed Trialist (Practitioner) concerned, and be submitted to the Council for Approval.

(f) In the event of the authorised Trialist ceasing to participate in the Clinical Trial, the Council shall be informed and the reason for such cessation shall be given.

5. **PROGRESS REPORTS**

The Council must be furnished with signed six-monthly Progress Report from each Trialist including a report of the Final Results.

6. **INFORMED CONSENT**

It is a Council requirement that in all Clinical Trials the 'Principles of Informed Consent' should be adhered to. This applies to Trial Volunteers, as well as Participants (Patients). (Reference: Section 4.8 of ICH GCP Guidelines and Section 3.5 of SACT Guidelines).

PLEASE NOTE: : The following Study products have been authorised for importation

1. Levofloxacin 100 mg - 453 600 tablets
2. 100 mg Levofloxacin placebo - 453 600 tablets
3. 250 mg Levofloxacin - 40 000 tablets
4. 250 mg Levofloxacin placebo - 40 000 tablets

Yours faithfully,

MS KEDIBONE MALATJI

FOR AND ON BEHALF OF REGISTRAR OF MEDICINES

MCC TRIAL REFERENCE NO: 20160128

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: Olivia.langenhoven@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

17 October 2019

HREC REF:709/2019

Mr Thomas Wilkinson
Health Economics Division
School of Public Health and Family Medicine

Dear Mr Wilkinson

PROJECT TITLE: ***COSTING ANALYSIS OF LEVOFLOXACIN AS ANTIBIOTIC PROPHYLAXIS FOR PEDIATRIC HOUSEHOLD CONTACTS OF MULTI-DRUG RESISTANT TUBERCULOSIS CASES IN SOUTH AFRICAN SETTING (MASTER'S DEGREE - DR S FORTUIN)***

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has formally **approved** the above-mentioned study.

Approval is granted for one year until the 30 October 2020.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.

(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr S. Fortuin will also be involved in this study.

Please quote the HREC reference number in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines

(DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines.

The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

TB-CHAMP FORM 3 - MICRO SPECIMENS CHILD AND INDEX CASE

Index Case ID/ Trial ID | | | | | | | | | **Month of Birth** | | | **Visit date** D D M M M Y Y Y Y

Visit week:	Primary ☐Index Case	☐ Additional Index case	☐ Child screening	☐ 0	☐ 4	☐ 8	☐ 12	☐ 16	☐ 24	☐ 36	☐ 48	☐ 72	☐ 96	☐ Unscheduled ☐ Early exit

INSTRUCTIONS

a. This form should be used to document the TB microbiology results from specimens:

- Collected by the research team for adult MDR-TB index cases **OR**
- Collected by the research team for child participants **OR**
- Collected outside of the trial at routine labs like NHLS for child participants.

b. Complete for each child participant or adult index case.

c. Use one CRF per specimen sent to the laboratory.

d. Part A is for the specimen information. Part B is for results from tests done directly on the specimen (results are available within 1 to 3 days). Part C is for culture results or tests done only if the culture is positive.

Part A: SPECIMEN INFORMATION

1. Is this form for the child or for the adult index case? Child ☐ Adult index case ☐

2. BARC/ other laboratory specimen reference number | | | | | | | | | | | | | | | |

(the number that the laboratory uses to identify the specimen: each specimen would have a unique laboratory number)

3a. What type of specimen was collected? Gastric aspirate ☐ Induced sputum ☐ Expectorated sputum ☐
Fine needle aspiration ☐ Unknown ☐ Other ☐

3b. If other, specify……

4. What was the date of specimen collection? D D M M M Y Y Y Y

5. What was the time of specimen collection: a) Unknown ☐ **b) Time** H H : M M

Part B: RESULTS FROM TESTS DONE DIRECTLY ON THE SPECIMEN

6. Was an AFB smear done on this specimen? Yes ☐ No ☐ *(If no go to Q8)*

7. Enter the result of the AFB smear using the GLI-WHO-IUATLD grading scale:

Negative ☐ **Scanty positive** ☐ **+1** ☐ **+2** ☐ **+3** ☐

8. Was a GeneXpert MTB/RIF assay done on this specimen? Yes ☐ No ☐ *(if no go to Q12)*

8a. If yes, what type of MTB/RIF assay? MTB/RIF ☐ MTB/RIF Ultra ☐

9. Enter the final result for MTB detection: Detected ☐ Not Detected ☐ Invalid ☐
(If not detected, invalid, error, no result, got to Q12) Indeterminate ☐ Error ☐ No Result ☐

10. Enter the semi-quantitative result: High ☐ Medium ☐ Low ☐ Very low ☐ Trace ☐ Not reported/ Unknown ☐

11. Enter the final result for RIF resistance Detected ☐ Not Detected ☐ Indeterminate ☐

12. Was a HAIN Genotype MTBDRplus assay done on the specimen? Yes ☐ No ☐ *(if no go to Q16)*

13. What was the final result of the HAIN MTBDRplus? M.tuberculosis complex detected ☐
(If M. tuberculosis complex not detected go to Q16, if M. tuberculosis complex detected continue) M.tuberculosis complex not detected ☐

14. What are the drug susceptibility results? (Indicate for each drug)

a. Isoniazid Susceptible ☐ Resistant ☐ Indeterminate ☐ Not done/reported ☐

b. Rifampicin Susceptible ☐ Resistant ☐ Indeterminate ☐ Not done/reported ☐

15. Are the mutations for Isoniazid reported? Yes ☐ No ☐ *(If no go to Q16)*

a. Was an inhA mutation present? Yes ☐ No ☐

b. Was a katG mutation present? Yes ☐ No ☐

16. Was a HAIN Genotype MTBDRsl assay done on the specimen: Yes ☐ No ☐ *(If no go to Q19)*

Index Case ID/ Trial ID | **Month of Birth** | **Visit date** (D D M M M Y Y Y Y)

17. What was the final result of the HAIN MTBDRsl?
M. tuberculosis complex detected ☐
M. tuberculosis complex not detected ☐

18. What are the drug susceptibility results? (Indicate for each drug)

a. Fluoroquinolones	Susceptible ☐	Resistant ☐	Indeterminate ☐	Not done/reported ☐
b. Aminoglycosides/cyclic peptides	Susceptible ☐	Resistant ☐	Indeterminate ☐	Not done/reported ☐

PART C: CULTURE RESULTS OR TESTS DONE ONLY IF THE CULTURE WAS POSITIVE

19. Was a liquid (MGIT) culture done on this specimen? Yes ☐ *(if yes, continue)* No ☐ *(if no, go to Q21)*

20. What was the liquid culture result? *(tick one only)*

- Negative for Mycobacterium tuberculosis complex (MTBC) ☐
- Positive for MTBC ☐
- Positive for MTBC and contaminated ☐
- Positive for NTM ☐
- Positive for MTBC and non-tuberculous mycobacteria (NTM) ☐
- Contaminated ☐
- Contaminated and Positive for NTM ☐

21. If positive, what was the time to detection in days and hours: **a.** ☐☐ days **b .** ☐☐ hours

22. Was a solid culture done on this specimen? Yes ☐ *(if yes, continue)* No ☐ *(if no, go to Q26)*

23. *Q23 is no longer in use.*

24. What was the solid culture result? *(tick one only)*

- Negative for Mycobacterium tuberculosis complex (MTBC) ☐
- Positive for MTBC ☐
- Positive for MTBC and contaminated ☐
- Positive for NTM ☐
- Positive for MTBC and non-tuberculous mycobacteria (NTM) ☐
- Contaminated ☐
- Contaminated and Positive for NTM ☐

25. What was the MTBC colony count?

<10 colonies ☐ *1+ (10-100 colonies)* ☐ *2+ (101-200 colonies)* ☐ *3+ (>200 colonies)* ☐ *Not done* ☐

26. Was a HAIN Genotype MTBDRplus assay done on the positive culture? Yes ☐ No ☐ *(if no, go to Q30)*

27. What was the final result of the HAIN MTBDRplus?
(If M. tuberculosis complex not detected, go to Q29, if M. tuberculosis complex detected continue)
M. tuberculosis complex detected ☐
M. tuberculosis complex not detected ☐

28. What are the drug susceptibility results? *Indicate for each drug*

a. Isoniazid	Susceptible ☐	Resistant ☐	Indeterminate ☐	Not done/reported ☐
b. Rifampicin	Susceptible ☐	Resistant ☐	Indeterminate ☐	Not done/reported ☐

29. a. Are the mutations for Isoniazid reported? Yes ☐ No ☐ *(if no, go to Q30)*

b. Was an inhA mutation present? Yes ☐ No ☐

c. Was a katG mutation present? Yes ☐ No ☐

Index Case ID/ Trial ID | | | | | | | | | **Month of Birth** | | | | **Visit date** | D | D | M | M | M | Y | Y | Y | Y |

30. Was a HAIN Genotype MTBDRsl assay done on the positive culture? Yes ☐ *(if yes, continue)* No ☐ *(if no, go to Q33)*

31. What was the final result of the HAIN MTBDRsl? *(If M. tuberculosis complex not detected, go to Q33, if M. tuberculosis complex detected continue)*

M. tuberculosis complex detected ☐

M. tuberculosis complex not detected ☐

32. What are the drug susceptibility results? *Indicate for each drug*

a. Fluoroquinolones Susceptible ☐ Resistant ☐ Indeterminate ☐ Not done/reported ☐

b. Aminoglycosides/cyclic peptides Susceptible ☐ Resistant ☐ Indeterminate ☐ Not done/reported ☐

33. Was phenotypic drug susceptibility testing (DST) done on the positive culture (using MGIT liquid culture)?

NOTE: if one drug has two results reported because it was tested at two different concentrations, use 'other, specify'.

Yes ☐ *(if yes, continue)* No ☐ *(if no, sign and date the form)*

	DRUG	a. TESTED		b. RESULT		
		YES	NO	SUSCEPTIBLE	RESISTANT	INDETERMINATE
34.	Isoniazid	☐	☐	☐	☐	☐
35.	Rifampicin	☐	☐	☐	☐	☐
36.	Amikacin	☐	☐	☐	☐	☐
37.	Capreomycin	☐	☐	☐	☐	☐
38.	Clofazimine	☐	☐	☐	☐	☐
39.	Cycloserine/terizidone	☐	☐	☐	☐	☐
40.	Ethambutol	☐	☐	☐	☐	☐
41.	Ethionamide	☐	☐	☐	☐	☐
42.	Kanamycin	☐	☐	☐	☐	☐
43.	Levofloxacin	☐	☐	☐	☐	☐
44.	Linezolid	☐	☐	☐	☐	☐
45.	Moxifloxacin	☐	☐	☐	☐	☐
46.	Ofloxacin	☐	☐	☐	☐	☐
47.	P-aminosalicylic acid (PAS)	☐	☐	☐	☐	☐
48.	Pyrazinamide	☐	☐	☐	☐	☐
49.	Streptomycin	☐	☐	☐	☐	☐
50.	Other (1) a. Specify drug: ……			☐	☐	☐
51.	Other (2) a. Specify drug: ……			☐	☐	☐
52.	Other (3) a. Specify drug: ……			☐	☐	☐

Completed by: RA Code	Signature	Date: D D M M M Y Y Y Y

QC by: RA Code	Signature	Date: D D M M M Y Y Y Y

Database Entry 1: RA Code	Signature	Date: D D M M M Y Y Y Y

Database Entry 2: RA Code	Signature	Date: D D M M M Y Y Y Y

TBCHAMP FORM 6 — CHILD SCREENING AND ELIGIBILITY

v1.0 18-Sep-2017

Trial ID | | | | | | | | | **Month of Birth** | | | | **Visit date** D D M M M Y Y Y Y

Visit: **Initial Child Screening** ☐ **Child Re-Screening** ☐

DO NOT PROCEED WITH SCREENING UNTIL CARER HAS SIGNED SCREENING CONSENT

CLINICAL MEASUREMENTS

1. Weight | | . | | kg **2. Height/ Length** | | | | . | | cm **3. MUAC** | | . | | cm

Please record weight and height on study specific charts and in clinic card

DEMOGRAPHICS

4. Date of birth : D D M M M Y Y Y Y **5. Sex :** Male ☐ Female ☐

6a. Race: Black/African ☐ White ☐ Asian ☐ South African coloured ☐ Mixed race ☐ Does not want to report ☐ Other ☐ 6b. *Specify*: .....

7a. Ethnicity : Sotho ☐ Zulu ☐ isiXhosa ☐ Caucasian ☐ Indian ☐ Mixed race ☐ Tswana ☐ Other ☐ 7b. *Specify* : .....

CURRENT HEALTH

8. TB Symptoms: Has the participant had any of the following symptoms in the past month?

	Yes	No
a) Cough ≥ 10 days	☐	☐
b) Fever ≥ 7 days	☐	☐
c) Poor weight gain	☐	☐
d) Weight loss	☐	☐
e) Lack of playfulness/energy	☐	☐
f) Poor feeding/appetite	☐	☐
g) Enlarged glands	☐	☐
h) Drenching night sweats	☐	☐
i) Any other worrying signs or symptoms?	☐	☐

j) If yes to Q8i, please specify other : .....

If Yes to any of above, please refer for investigation and exclusion of TB disease.

PHYSICAL EXAMINATION

9. Record clinical examination findings below:

	Normal	Abnormal*
a) General Examination	☐	☐
b) Respiratory System	☐	☐
c) Lymph Nodes	☐	☐
d) Cardiovascular	☐	☐
e) Abdominal	☐	☐
f) Nervous System	☐	☐
g) Skin	☐	☐
h) Joints	☐	☐
i) Other Not done ☐	☐	☐

j) If other, please specify.....

***If abnormal record details in progress notes**

Trial ID | | | | | | | | | **Month of Birth** | | | | **Visit date** | D | D | M | M | M | Y | Y | Y | Y |

INVESTIGATIONS REQUESTED

10. Was the child referred for a CXR? Yes ☐ No ☐

11. Was respiratory sampling or other investigation required (eg. If symptoms suggestive of TB, abnormal CXR or other clinical indication)? Yes ☐ No ☐

ELIGIBILITY CRITERIA AT SCREENING

12. Inclusion Criteria	Yes	No
a) Child < 5 years who is a household contact of an enrolled adult MDR-TB index case diagnosed during the previous 6 months	☐	☐
b) Primary residence in the household of the adult MDR-TB index case	☐	☐
c) Consent from the parent or legal guardian for the child to have an HIV test	☐	☐
d) Consent obtained from the parent or legal guardian for the child to be enrolled	☐	☐

13. Exclusion Criteria	Suggestive	Yes	No
a) Current TB disease. **Tick yes or No. If participant has new history/signs/symptoms suggestive of TB and being referred for further investigations tick 'suggestive' box.**	☐	☐	☐
b) Currently on isoniazid, or a fluoroquinolone (e.g. levofloxacin, moxifloxacin, ofloxacin or ciprofloxacin) for ≥ 14 days		☐	☐
c) Any treatment for TB disease in the previous 12 months		☐	☐
d) Known concurrent exposure to an INH-susceptible (including RIF-monoresistant) index case		☐	☐
e) Children with myasthenia gravis or Guillain-Barré syndrome		☐	☐

If no shaded boxes are ticked child is eligible. If child had not had a CXR within the last four weeks please refer for a CXR.

Completed by: RA Code	Signature	Date: D D M M M Y Y Y Y
QC by: RA Code	**Signature**	**Date:** D D M M M Y Y Y Y
Database Entry 1: RA Code	**Signature**	**Date:** D D M M M Y Y Y Y
Database Entry 2: RA Code	**Signature**	**Date:** D D M M M Y Y Y Y

TB-CHAMP FORM 7 - CHILD INVESTIGATIONS

V2.0 15-Mar-2018

Trial ID | **Month of Birth** | **Visit Date** D D M M M Y Y Y Y

Visit week: Initial Child screening ☐ | Child Re-Screening ☐ | 0 ☐ | 4 ☐ | 8 ☐ | 12 ☐ | 16 ☐ | 24 ☐ | 36 ☐ | 48 ☐ | 72 ☐ | 96 ☐ | Unscheduled ☐ | Early exit ☐

		SPECIMEN TAKEN?	DATE COLLECTED	TIME COLLECTED	RESULT
	CD4 and Viral load should be collected at Screening/ Week 0,24,48,96 in HIV-infected children only				
1.	**CD4 count**	a. Yes ☐ No ☐ N/A ☐	b. D D M M M Y Y Y Y	c. H H : M M	d. ☐☐☐☐ 10^9/l
2.	**CD4 percent**	a. Yes ☐ No ☐ N/A ☐			b. ☐☐ . ☐☐ **%**
3.	**Viral load**	a. Yes ☐ No ☐ N/A ☐	b. D D M M M Y Y Y Y	c. H H : M M	d. Less than (<) ☐ More than (>) ☐ Absolute (=) ☐ *(tick one)* e. ☐☐☐☐☐☐☐☐☐ Copies/ml
	FBC, differential and ALT, Bilirubin should be collected at Screening/ Week 0,8,16,24 in all children				
4.	**Haemoglobin**	a. Yes ☐ No ☐ N/A ☐	b. D D M M M Y Y Y Y	c. H H : M M	d. ☐☐ . ☐ g/dl
5.	**White Blood Cell Count**	a. Yes ☐ No ☐ N/A ☐	b. D D M M M Y Y Y Y	c. H H : M M	d. ☐☐ . ☐☐ 10^9/l
6.	**Platelet Count**	a. Yes ☐ No ☐ N/A ☐	b. D D M M M Y Y Y Y	c. H H : M M	d. ☐☐☐☐ 10^9/l
7.	**ALT**	a. Yes ☐ No ☐ N/A ☐	b. D D M M M Y Y Y Y	c. H H : M M	d. ☐☐☐☐ IU/l
8.	**Bilirubin**	a. Yes ☐ No ☐ N/A ☐	b. D D M M M Y Y Y Y	c. H H : M M	d. ☐☐☐☐ µmol/l
	PaxGene tube and Serum should be collected at Screening/ Week 0,8,16,24, 48, at TB event/exit				
9.	**PaxGene tube**	a. Yes ☐ No ☐ N/A ☐	b. D D M M M Y Y Y Y	c. H H : M M	
10.	**Serum**	a. Yes ☐ No ☐ N/A ☐	b. D D M M M Y Y Y Y	c. H H : M M	
	DTTC site only at Screening/ Week 0,8,16,24, 48, at TB event/exit				
11.	**Stool (biome)**	a. Yes ☐ No ☐ N/A ☐	b. D D M M M Y Y Y Y	c. H H : M M	
	Note: If not collected, please provide caregiver with container				
	IGRA should be collected at Screening/ Week 0, Week 24				
12.	**IGRA**	a. Yes ☐ No ☐ N/A ☐	b. D D M M M Y Y Y Y	c. H H : M M	d. Positive ☐ Negative ☐ Indeterminate ☐ *(tick one)*

Completed by: RA Code	**Signature**	**Date:** D D M M M Y Y Y Y
QC by: RA Code	**Signature**	**Date:** D D M M M Y Y Y Y
Database Entry 1: RA Code	**Signature**	**Date:** D D M M M Y Y Y Y
Database Entry 2: RA Code	**Signature**	**Date:** D D M M M Y Y Y Y

TBCHAMP FORM 10 — CHILD ENROLMENT

v3.0 08-Apr-2019

Trial ID | | | | | | | | | **Month of Birth** | | | | **Visit date** D D M M M Y Y Y Y

Visit Week: 0 ☑

CLINICAL MEASUREMENTS

1. Weight: ___ . ___ kg **2.Height/Length :** ___ . ___ cm **3. MUAC:** ___ . ___ cm

Please record weight and height on study specific charts and in clinic card

Completed by: RA Code …….

CURRENT HEALTH

4. TB Symptoms: Has the participant had any of the following new symptoms since screening?

	Yes	No		Yes	No
a) Cough ≥ 10 days	☐	☐	**b)** Fever ≥ 7 days	☐	☐
c) Poor weight gain	☐	☐	**d)** Weight loss	☐	☐
e) Lack of playfulness/energy	☐	☐	**f)** Poor feeding/appetite	☐	☐
g) Enlarged glands	☐	☐	**h)** Drenching night sweats	☐	☐
i) Any other worrying signs or symptoms?	☐	☐			

j) If yes to Q4i), please specify other……..

5. Other symptoms: Does the child currently have any of the following symptoms?

	Yes	No		Yes	No
a) Arthralgia (pain in the joints)	☐	☐	**b)** Pruritus (itching)	☐	☐
c) Headache	☐	☐	**d)** Fatigue/tiredness	☐	☐
e) Difficulty sleeping	☐	☐	**f)** Reporting of observed change in vision (cannot see well or clearly)	☐	☐
g) Reporting of observed change in mood or behaviour	☐	☐	**h)** Nausea	☐	☐
i) Vomiting	☐	☐	**j)** Abdominal pain	☐	☐
k) Any other worrying symptoms	☐	☐			

l) If yes to Q5k), specify other,……..

If yes to any of the above, note action taken in the progress notes

TB EXPOSURE HISTORY

6. What is the relationship of the TB index case to the child?

Mother ☐ Father ☐ Grandmother ☐ Grandfather ☐ Uncle ☐

Aunt ☐ Cousin ☐ Sibling ☐ Other family member ☐ Other non-family member ☐

7. Is the MDR-TB index case the child's primary caregiver? *(If Yes or Unknown, go to Q9)* Yes ☐ No ☐ Unknown ☐

8. If NOT the primary caregiver does the MDR index case regularly care for the child? Yes ☐ No ☐ Unknown ☐

9. Over the past 6 months, has there been daily contact between the child and the MDR-TB index case on most days? Yes ☐ No ☐ Unknown ☐

10. Over the past 6 months, has the child slept in the same room as the MDR-TB index case on most nights? Yes ☐ No ☐ Unknown ☐

11. Over the past 6 months, did the child sleep in the same bed as the MDR-TB index case on most nights? Yes ☐ No ☐ Unknown ☐

12. Over the past 6 months, on average, how many hours per day does the child spend with the MDR TB index case?

0-4 hours ☐ 5-8 hours ☐ 9-12 hours ☐ more than 12 hours ☐

ADDITIONAL TB EXPOSURE

13. In the past 6 months, has the child been exposed to any additional confirmed or suspected TB (any TB) cases other than the main MDR -TB index case? *(If No or unknown, go to Question 16)* Yes ☐ No ☐ Unknown ☐

14. If yes, how many additional TB cases: 1 ☐ 2 ☐ 3 ☐ More than three ☐

15. If yes, are any of these additional cases known or suspected to have drug sensitive TB? *(If yes child not eligible)* Yes ☐ No ☐ Unknown ☐

Trial ID | Month of Birth | Visit date (D D M M M Y Y Y Y)

PREVIOUS TB TREATMENT

16. Has the child previously been treated for TB disease? *(If No or Unknown, go to Question 21)* Yes ☐ No ☐ Unknown ☐

17. If Yes, when was TB treatment started? (D D M M M Y Y Y Y)

18. Was TB treatment completed? Yes ☐ No ☐ Unknown ☐

19. If yes, when was treatment stopped/completed? (D D M M M Y Y Y Y) *(If the child received any treatment in the last 12 months they are not eligible)*

20. Was the child treated for drug- susceptible or drug-resistant TB? DR ☐ DS ☐ Unknown ☐

Please record name of treating facility in the progress notes (not for data capture)

CURRENT TB PREVENTIVE THERAPY

21. Is the child currently on TB preventive therapy? *(If No or unknown, go to Question 24)* Yes ☐ No ☐ Unknown ☐

22. If Yes, what preventive therapy?	**a)** Isoniazid	Yes ☐	No ☐	**b)** Levofloxacin	Yes ☐	No ☐
	c) Ethambutol	Yes ☐	No ☐	**d)** Ethionamide	Yes ☐	No ☐
	e) Other	Yes ☐	No ☐			

f) If other, please specify…… ***(please update concomitant medication log if child is random-***

23. For how many weeks has child taken TB preventive therapy? < 1week ☐ 1-2 weeks ☐ More than two weeks ☐ *(Child not eligible)*

HIV HISTORY

24. Is the child's mother HIV positive? Yes ☐ No ☐ Unknown ☐

25. Is the child HIV positive? *(if no/unknown, please perform an HIV test and go to Q28)* Yes ☐ No ☐ Unknown ☐

26. If HIV positive, date of HIV diagnosis : (D D M M M Y Y Y Y)

27. Method of HIV testing: HIV DNA PCR ☐ HIV Rapid ☐ HIV Elisa ☐ Unknown/Inadequately documented ☐
(If unknown/Inadequately documented, repeat HIV testing)

28. Is the child participant currently on ART? Yes ☐ No ☐ *If no go to Q31*

29. If Yes what was the start date of ART? (D D M M M Y Y Y Y)

30. ART regimen currently used (Please tick all ARV's child is taking)	**YES**	**NO**		**YES**	**NO**
a) Abacavir	☐	☐	**b)** Lamivudine	☐	☐
c) Lopinavir/ritonavir	☐	☐	**d)** Efavirenz	☐	☐
e) Nevirapine	☐	☐	**f)** Zidovidine	☐	☐
g) Other	☐	☐	***Complete ARV log if child is randomised***		

h) If other, specify……

If child is HIV positive, answer q31-q33 If child is HIV negative, go to q34	**Unknown?**	**Date**	**Result**
31. Most recent absolute CD4 count	**a)** ☐	**b)** (D D M M M Y Y Y Y)	**c)**
32. Most recent percentage CD4	**a)** ☐	**b)** (D D M M M Y Y Y Y)	**c)** • **%**
33. Most recent viral load	**a)** ☐	**b)** (D D M M M Y Y Y Y)	**c)** **d)** Absolute result ☐ Lower limit ☐ Upper limit ☐

CHRONIC ILLNESS

34. Does the child have any significant chronic illnesses (other than HIV)? *(If No, go to Q36)* Yes ☐ No ☐

35. If yes, record event code: (please refer to TB CHAMP event code list, Multiple options may apply).

a) Illness 1: . **b) Illness 2:** . **c) Illness 3:** .

Trial ID | Month of Birth | Visit date (D D M M M Y Y Y Y)

HOSPITALISATION

36. Was the child admitted to a hospital during the last 6 months? *(If No or Unknown, go to Question 40)* Yes ☐ No ☐ Unknown ☐

37. If yes, how many times? Once ☐ Twice ☐ Three or more ☐

38. Duration of the most recent hospital admission (days)? ☐☐☐

39. Reason for most recent admission:

	YES	NO		YES	NO		YES	NO
a) Diarrhoeal diseases	☐	☐	**b)** Chest infection	☐	☐	**c)** Wheezing	☐	☐
d) Suspected TB	☐	☐	**e)** Trauma or burns	☐	☐	**f)** Not growing well	☐	☐
g) HIV treatment	☐	☐	**h)** Skin rash	☐	☐	**i)** Convulsions	☐	☐
J) Meningitis	☐	☐	**k)** Congenital abnormality	☐	☐	**l)** Fever ≥ 7 days	☐	☐
m) Poisoning	☐	☐	**n)** Other	☐	☐			

o) If other, please specify: ……..

Please indicate facility where child was admitted in progress notes.

ANTIBIOTIC USE HISTORY

40. Has the child received any antibiotics in the past 2 weeks? *(If No or Unknown, go to Q52)* Yes ☐ No ☐ Unknown ☐

Name of antibiotic (tick all that apply):

	YES	NO	b) If YES, duration of treatment completed (days)		YES	NO	b) If YES, duration of treatment completed (days)
41a) Amoxicillin	☐	☐	☐☐	**42a) Ampicillin**	☐	☐	☐☐
43a) Gentamycin	☐	☐	☐☐	**44a) Cefalexin**	☐	☐	☐☐
45a) Ceftriaxone	☐	☐	☐☐	**46a) Co-amoxiclav**	☐	☐	☐☐
47a) Cotrimoxazole	☐	☐	☐☐	**48a) Flucloxacin**	☐	☐	☐☐
49a) Fluoroquinolone	☐	☐	☐☐	**50a) Nalidixic acid**	☐	☐	☐☐
51a) Other	☐	☐	☐☐				

51c) If other, please specify……

52. If No or Unknown to Q40 above, has the child received any antibiotics in the past 6 months? Yes ☐ No ☐

TRADITIONAL MEDICINE

53. Has this child ever received any herbal or traditional medicine? *(If No or Unknown go to Q56)* Yes ☐ No ☐ Unknown ☐

54. If yes, when did the child receive herbal or traditional medicine?	During last month ☐	Between 1 and 3 months ago ☐	Between 3 and 6 months ago ☐	More than 6 months ago ☐

55. If yes, why? *(Tick all that apply)*

	YES	NO		YES	NO		YES	NO
a) Diarrhoeal diseases	☐	☐	**b) Chest infection**	☐	☐	**c) Wheezing**	☐	☐
d) Suspected TB	☐	☐	**e) Trauma or burns**	☐	☐	**f) Not growing well**	☐	☐
g) HIV treatment	☐	☐	**h) Skin rash**	☐	☐	**i) Convulsions**	☐	☐
J) Meningitis	☐	☐	**k) Congenital abnormality**	☐	☐	**l) Fever ≥ 7 days**	☐	☐
m) Poisoning	☐	☐	**n) Other**	☐	☐			

o) If other, please specify……

Trial ID | Month of Birth | Visit date (D D M M M Y Y Y Y)

OTHER MEDICATION USE

56. Is the child currently taking any other prescribed medication ? Yes ☐ No ☐ Unknown ☐
(If yes, complete Concomitant Medication log if child is randomised)

ROAD TO HEALTH CARD

57. Is the RTHC available? *(If No, go to Q59)* Yes ☐ No ☐

58. Does the RTHC indicate the following (Please see TB CHAMP MOP for definitions):

a) Dewormed in the previous 6 months? Yes ☐ No ☐ **b) Received vitamin A in the past 6 months?** Yes ☐ No ☐

c) Poor growth documented? Yes ☐ No ☐ **d) Immunisation up to date?** Yes ☐ No ☐

(Please complete immunization log if child is randomised)

BCG STATUS

59. Does the participant have a BCG scar? Yes ☐ No ☐ Unknown ☐

60. Is the BCG vaccination documented in the child's health card? Yes ☐ No ☐ Unknown ☐

PHYSICAL EXAMINATION

61. Record clinical examination findings below:

	Not Done	Normal	Abnormal*
a) General Examination	☐	☐	☐
b) Respiratory System	☐	☐	☐
c) Lymph Nodes	☐	☐	☐
d) Cardiovascular	☐	☐	☐
e) Abdominal	☐	☐	☐
f) Nervous System	☐	☐	☐
g) Skin	☐	☐	☐
h) Joints	☐	☐	☐
i) Other (*specify*): ……	☐	☐	☐

***If abnormal record details in progress notes**

FURTHER INVESTIGATIONS

62. Is there any clinical indication for a repeat CXR? *(If yes, participant is currently <u>not</u> eligible for enrolment)*	Yes ☐	No ☐
63. Is there any clinical indication for further TB lab investigations? *(If yes, participant is currently <u>not</u> eligible for enrolment)*	Yes ☐	No ☐

64. Is the child eligible to enter the study and can they be randomised today? Yes ☐ No ☐
If yes, please proceed with randomisation via Form 11, Child randomisation.

65. If NO, could they potentially be randomised on a later date? Yes ☐ No ☐

If YES, please indicate reason for deferral on Form 11, Child randomistion and send for data entry. Arrange for further appointments for investigations/tests/enrolment visit date as needed. Participant should be enrolled within 14 days of screening visit; if later than this, please arrange for a re-screen. If NO please indicate reason on Form 11 and send for data entry.

Completed by: RA Code	Signature	Date: (D D M M M Y Y Y Y)
QC by: RA Code	**Signature**	**Date:**
Database Entry 1: RA Code	**Signature**	**Date:**
Database Entry 2: RA Code	**Signature**	**Date:**

TB-CHAMP FORM 12 - CHILD FOLLOW-UP

Trial ID | **Month of Birth** | **Visit Date** D D M M M Y Y Y Y

Visit week: 4 ☐ 8 ☐ 12 ☐ 16 ☐ 24 ☐ 36 ☐ 48 ☐ 72 ☐ 96 ☐ Unscheduled ☐ Early exit ☐

PART A: CLINICAL MEASUREMENTS

1. Weight: ____ • ____ kg **2. Height:** ____ • ____ cm **3. MUAC:** ____ • ____ cm

Please record the weight and height on study specific growth charts and in the clinic card.

Completed by: RA Code:_____ QC by: RA Code:_____

PART B: TB EXPOSURE HISTORY

4a. Since the last visit, has the child been exposed to any additional documented confirmed or suspected TB cases (i.e. any other new TB case which is not the MDR-TB adult source case identified at enrolment)? Yes ☐ No ☐ Unknown ☐ *(If No, go to Q5)*

4b. If yes, how many additional TB cases? 1 ☐ 2 ☐ 3 or more ☐

4c. If yes, are any of these additional cases known or suspected to have drug sensitive TB? Yes ☐ No ☐ Unknown ☐

Note: If a new drug susceptible contact is confirmed, the child may need to be withdrawn from the study. Please consult with the clinical study team.

PART C: REPORTED INTERCURRENT ILLNESSES

HOSPITALISATIONS

5a. Has the child been admitted to a hospital since the last study visit? Yes ☐ No ☐ Unknown ☐ *(If no or unknown go to Q7)*

5b. If yes, how many times? 1 ☐ 2 ☐ 3 or more ☐

5c. Duration of most recent admission? ☐☐ **Days** *(if yes please indicate facility where child was admitted in progress notes)*

6. Why was the child admitted to hospital?

		YES	NO			YES	NO			YES	NO
a.	Diarrhoeal diseases	☐	☐	b.	Chest infection	☐	☐	c.	Wheezing	☐	☐
d.	Suspected TB	☐	☐	e.	Trauma or burns	☐	☐	f.	Not growing well	☐	☐
g.	HIV treatment	☐	☐	h.	Skin rash	☐	☐	i.	Convulsions	☐	☐
j.	Meningitis	☐	☐	k.	Congenital abnormality	☐	☐	l.	Fever	☐	☐
m.	Poisoning	☐	☐	n.	Other	☐	☐				

6o. If other, please specify:……

Note: If the child has been formally admitted to hospital overnight, please complete Form 13 Child Adverse Event

OTHER HEALTHCARE VISITS

7a. Since the last study visit, has the child visited a clinic or health care worker due to ill– health? Yes ☐ No ☐ Unknown ☐ *(if No or Unknown, go to Q9)*

7b. If yes, how many times? 1 ☐ 2 ☐ 3 or more ☐

8. Why did the child visit a healthcare worker or clinic?

		YES	NO			YES	NO			YES	NO
a.	Diarrhoeal diseases	☐	☐	b.	Chest infection	☐	☐	c.	Wheezing	☐	☐
d.	Suspected TB	☐	☐	e.	Trauma or burns	☐	☐	f.	Not growing well	☐	☐
g.	HIV treatment	☐	☐	h.	Skin rash	☐	☐	i.	Convulsions	☐	☐
j.	Meningitis	☐	☐	k.	Congenital abnormality	☐	☐	l.	Fever	☐	☐
m.	Poisoning	☐	☐	n.	Other	☐	☐				

8o. If other please specify:……

9a. Has the child received any herbal or traditional medicine? Yes ☐ No ☐ Unknown ☐

9b. Has the child visited a traditional healer? Yes ☐ No ☐ Unknown ☐ *(If no or unknown go to Q11)*

9c. If yes, how many times has the child visited the traditional healer? 1 ☐ 2 ☐ 3 or more times ☐

TB CHAMP **FORM 12 — CHILD FOLLOW-UP** v3.0 08-Apr-2019

Trial ID | | | | | | | | | **Month of Birth** | | | | **Visit date** D D M M M Y Y Y Y

10. Why did the child visit a traditional healer?

	Symptom	YES	NO		Symptom	YES	NO		Symptom	YES	NO
a.	Diarrhoeal diseases	☐	☐	b.	Chest infection	☐	☐	c.	Wheezing	☐	☐
d.	Suspected TB	☐	☐	e.	Trauma or burns	☐	☐	f.	Not growing well	☐	☐
g.	HIV treatment	☐	☐	h.	Skin rash	☐	☐	i.	Convulsions	☐	☐
j.	Meningitis	☐	☐	k.	Congenital abnormality	☐	☐	l.	Fever	☐	☐
m.	Poisoning	☐	☐	n.	Other	☐	☐				

10o. If other, please specify:……

PART D: NON-TB MEDICATIONS RECEIVED SINCE THE LAST STUDY VISIT

11. Since the last study visit, or at today's visit. Has the participant changed any drug in their ART regimen?
Yes ☐ No ☐ Unknown ☐ Child is not HIV positive ☐ *(If yes, update **Form 22: Cumulative ART log**)*

12. Have any new concomitant medications (excluding paracetamol, cough/cold remedies, creams and multi-vitamin supplements) been prescribed since the previous visit, at this visit or has any dose of an existing medication been changed?
Yes ☐ No ☐ Unknown ☐ *(If yes update **Form 21: Concomitant Medications Log**)*

13. Has the child received any immunisations since the last visit? Yes ☐ No ☐ Unknown ☐ *(If yes, update the **Form 19:Immunisation Log**)*

PART E: CURRENT HEALTH

14. TB Symptoms: Has the child had any of the following new symptoms since the last visit?

	Yes	No	Unknown
a. Cough	☐	☐	☐
b. Fever	☐	☐	☐
c. Poor weight gain	☐	☐	☐
d. Weight loss	☐	☐	☐
e. Lack of playfulness/energy	☐	☐	☐
f. Poor feeding/appetite	☐	☐	☐
g. Enlarged glands	☐	☐	☐
h. Drenching night sweats	☐	☐	☐
i. Any other worrying symptoms?	☐	☐	☐
j. If Yes to Q14i , please specify:……			

15. Other symptoms: Has the child had any of the following symptoms since the last visit?

	Yes	No	Unknown
a. Arthralgia (pain in the joints)	☐	☐	☐
b. Pruritus (itching)	☐	☐	☐
c. Headache	☐	☐	☐
d. Fatigue/tiredness	☐	☐	☐
e. Difficulty sleeping	☐	☐	☐
f. Reported or observed change in vision (cannot see well or clearly)	☐	☐	☐
g. Reported or observed changes in mood or behaviour	☐	☐	☐
h. Nausea	☐	☐	☐
i. Vomiting	☐	☐	☐
j. Abdominal pain	☐	☐	☐
k. Any other worrying symptoms?	☐	☐	☐
l. If Yes to Q15k, please specify:……			

If yes to any of the above, note details and the action taken in progress notes., Grade all symptoms. All grade 1 or higher AEs should be captured on Form 23-Participant Adverse Event Log

TB CHAMP **FORM 12 — CHILD FOLLOW-UP** v3.0 08-Apr-2019

Trial ID | | | | | | | | | **Month of Birth** | | | | **Visit date** D D M M M Y Y Y Y

PART F: PHYSICAL EXAMINATION

16. Record clinical examination findings below:

	Not done	Normal	**Abnormal
a. General Examination	☐	☐	☐
b. Respiratory system	☐	☐	☐
c. Lymph nodes	☐	☐	☐
d. Cardiovascular	☐	☐	☐
e. Abdominal	☐	☐	☐
f. Nervous System	☐	☐	☐
g. Skin	☐	☐	☐
h. Joints	☐	☐	☐
i. Other	☐	☐	☐

j. Other (specify):.....

If abnormal record details in progress notes

Grade all signs found on physical examination. All grade 1 or higher AEs should be captured on Form 23– Participant Adverse Event.

PART G: REPORTED ADHERENCE TO STUDY DRUG SINCE THE LAST STUDY VISIT

17a. **How many tablets were dispensed at the previous visit?** ☐☐ . ☐ **tablets** **OR**

17a(i) **If no tablets were given at the previous visit please tick here:** ☐ *If ticked go to Q19*

17b. **How many tablets of the study drug has the participant returned today?** ☐☐ . ☐ **tablets**

Since the last visit, what is the total number of days that the prescribed study treatment was not taken:

17c. **According to the above pill count?** ☐☐ **Days** **OR** **17c(i) If tablets not returned tick here:** ☐

17. **As documented in the TB treatment card?** ☐☐ **Days** **OR** **17(i) If treatment card not returned tick here:** ☐

17d. **Taking into account the above data, and any other information gathered by the study team, what is the total number of days that study treatment was not taken since the last visit, as assessed by the clinician?** **Days** ☐☐

18. Reasons if any pills were missed:

Reason doses missed	YES	NO	Reason doses missed	YES	NO
a. Caregiver forgot	☐	☐	b. Travel	☐	☐
c. Child refused the medicine	☐	☐	d. Child spat/vomited the medicine	☐	☐
e. Difficulty with or time needed to prepare the medicine	☐	☐	f. Caregiver ran out of the medicine	☐	☐
g. Caregiver decided to stop treatment	☐	☐	h. Adverse event occurred	☐	☐
i. Other	☐	☐			

TB CHAMP **FORM 12 — CHILD FOLLOW-UP** v3.0 08-Apr-2019

Trial ID | | | | | | | | | **Month of Birth** | | | | **Visit date** D D M M M Y Y Y Y

j. If other, please specify?.....

PART H: TB INVESTIGATIONS COMPLETED IN ROUTINE CARE (OUTSIDE OF THE TRIAL)

19. Were any TB investigations done since the last visit, as part of routine care (outside of the study)?
Yes ☐ No ☐ Unknown ☐ *(If No or Unknown go to Q21)*

20. If yes, what were they?

Investigations	YES	NO	Investigations	YES	NO
a. CXR (*if yes, please complete Form 8: Local Chest X-ray*)	☐	☐	**b. Bacteriology** *(If yes, please complete Form 3: Micro Specimens Child and Index Case)*	☐	☐
c. TST	☐	☐	**d. Other**	☐	☐

e. If other, please specify?.....

PART I: TRIAL INVESTIGATIONS COMPLETED AT THIS STUDY VISIT (i.e. BY THE RESEARCH TEAM)

21. Were any TB investigations (tests) completed at this visit by the study team? Yes ☐ No ☐ Unknown ☐
(If No or Unknown go to Q23)

22. If yes, what were they?:

a. CXR Yes ☐ No ☐ *(Please complete **Form 8: Local Chest X-ray**)*

b. Bacteriology Yes ☐ No ☐ *(Please complete **Form 3: Micro specimens Child and Index Case**)*

c. IGRA Yes ☐ No ☐ *(Please complete **Form 7: Child Investigations**)*

d. Blood test Yes ☐ No ☐ *(Please complete **Form 7: Child Investigations**)*

e. Other Yes ☐ No ☐

f. If other, specify:……

PART J: TB END POINTS

23. Did these TB investigations result in a potential TB disease study end point? Yes ☐ No ☐ N/A ☐

*If Yes, complete a **Form 17: TB End Point Review Information** form once the test results are available. Also complete a detailed TB case summary.*

Completed by: RA Code	Signature	Date: D D M M M Y Y Y Y
QC by: RA Code	**Signature**	**Date:** D D M M M Y Y Y Y
Database Entry 1: RA Code	**Signature**	**Date:** D D M M M Y Y Y Y
Database Entry 2: RA Code	**Signature**	**Date:** D D M M M Y Y Y Y

TB-CHAMP FORM 16 — FINAL VISIT

V2.0 15-Mar-2018

Trial ID | | | | | | | | | **Month of Birth** | | | | **Visit date** D D M M M Y Y Y Y

Visit week: 4 ☐ 8 ☐ 12 ☐ 16 ☐ 24 ☐ 36 ☐ 48 ☐ 72 ☐ 96 ☐ Unscheduled ☐

FINAL VISIT

1. **Date of final visit attended:** D D M M M Y Y Y Y

2. **Did the participant complete all the scheduled study visits?** Yes ☐ No ☐ *(if yes, go to q5)*

REASON FOR NON ATTENDANCE OF STUDY VISITS OR EARLY DISCONTINUATION

3. **Reason for non attendance of study visit or early discontinuation:**

	YES	NO		YES	NO
a. **Adverse event** *(Complete Form 13—Event)*	☐	☐	b. **Lost to follow up** *(no further surveillance)*	☐	☐
c. **Withdrew consent to any further surveillance**	☐	☐	d. **Participant not attending study visits** *(with ongoing surveillance)*	☐	☐
e. **Moved away**	☐	☐	f. **TB disease**	☐	☐
g. **Death** *(Complete Form 13—Event Form)*	☐	☐	h. **Other** *(Specify below)*	☐	☐

i. **If other, specify:**.....

.....

.....

LATE SCREENING FAILURE

4a. **Was there any late screening failure?:** Yes ☐ No ☐ *(if No, go to q5)*

4b. **If yes, please give reason:**.....

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ADDITIONAL STUDY VISITS

5. **Is an additional study visit required?** Yes ☐ No ☐ *(If No, stop and proceed to the sign off section of the form)*

6. **If yes, please specify reason:**.....

7. **If yes, scheduled date of next visit:** a. **Unknown** ☐ b. **Date** D D M M M Y Y Y Y

Completed by: RA Code	Signature	Date:
		D D M M M Y Y Y Y

QC by: RA Code	Signature	Date:
		D D M M M Y Y Y Y

Database Entry 1: RA Code	Signature	Date:
		D D M M M Y Y Y Y

Database Entry 2: RA Code	Signature	Date:
		D D M M M Y Y Y Y