

GOOD to GREAT: Strategies to improve the detection of TB amongst household contacts in South Africa

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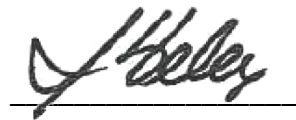
A thesis submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy

Johannesburg, 6th September 2018

Supervisors: Prof. Salome Charalambous and Prof. James Lewis

Declaration

I, Kavindhran Velen, declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university

A handwritten signature in black ink, appearing to read 'K Velen', is written over a horizontal line.

Kavindhran Velen

Date: 6th September 2018

Executive Summary

Background

Tuberculosis (TB) remains one of the leading public health problems globally, owing to high annual rates of morbidity and mortality. In addition, HIV has exacerbated the epidemic, accounting for 11% of all new TB cases in 2015. The global situation necessitated and subsequently ushered in a bolder strategy from the World Health Organization, the End TB Strategy which proposes global targets for TB prevention, care and control after 2015. The strategy introduces people-centered targets, the 90-(90)-90 targets: reach 90% of all people who need TB treatment; including 90% of people in key populations; and achieve at least 90% TB treatment success. South Africa, a high TB burden country, recently cemented its commitment to TB eradication through its National TB Programme (NTP) Strategy; a roadmap to the End TB strategy emphasising evidence-based interventions likely to realize significant population-level impact. Household Contact Tracing (HHCT), an intervention considered to effectively prevent TB has been debated in recent years despite guideline evidence supporting its use; largely because of reported heterogeneity in the yield of undiagnosed TB from its use coupled with high costs inherent with its implementation. HHCT provides an ideal platform for integration of TB/HIV activities however more research is required to optimize its implementation.

Two studies, investigating TB Contact tracing, formed the basis of studies for this PhD:

- a) The *CDC-Aurum Contact Tracing* study, a household contact tracing study investigating the difference in yield of TB amongst contacts of patients with multi-drug resistant TB compared to drug susceptible TB index patients within the Bojanala District.
- b) The *Inhibit-TB* study, investigating the addition of two HIV interventions, namely point-of-care CD4 count (PoC CD4) and household INH to a routine TB contact tracing intervention, conducted in Ekurhuleni and Sekhukhune districts.

Objectives

This PhD aimed to identify the optimal approach to HHCT thereby contributing to realizing the End TB Strategy. This was achieved through four objectives;

- 1) To identify factors which may account for heterogeneity in the yield of undiagnosed TB,
- 2) To determine which screening tool or combination of screening tools are most effective at identifying TB among adults and children household contacts;
- 3) To determine uptake and factors associated with uptake of HIV counselling and testing among TB household contacts, and
- 4) To determine the effect of PoC CD4 testing on HIV entry into care and to determine the effect of household IPT provision on uptake and retention of IPT among household TB contacts

Methods

A systematic review was conducted to determine factors associated with heterogeneity in the yield of TB from HHCT. Literature was searched on PubMed, Google Scholar and Global Index Medicus for studies published up to 31st March 2017. Univariable random effects meta-regression models were developed to regress the proportion of TB identified among household contacts by specific study characteristics.

The performance evaluation of Xpert MTB/RIF was nested within the *CDC-Aurum Contact Tracing* study. Household contacts were screened for TB and anyone presenting with ≥ 1 TB symptom on the four-symptom screen, provided one spot sputum for smear microscopy, Xpert MTB/RIF testing and MGIT culture. Diagnostic yield, sensitivities and specificities of Xpert MTB/RIF were evaluated using MGIT culture as a referent standard.

The uptake of HIV testing was evaluated within the *Inhibit-TB* study. Household contacts ≥ 14 years old were offered HIV counselling and testing (HCT) during scheduled visits. Factors associated with HCT uptake among contacts with an unknown or negative status were investigated using a random effects logistic regression model.

The effect of PoC CD4 testing on linkage into HIV care and provision of household IPT was pragmatically evaluated within the *Inhibit-TB* study households. Households were randomised to receive one of 3 types of care: 1) Standard of Care (SoC) TB and HIV testing (referred to as Arm 1); 2) SoC with PoC CD4 for those testing HIV positive (referred to as Arm 2); and 3) SoC with PoC CD4 and IPT for eligible household members (referred to as Arm 3). Linkage into HIV care within 3 months was assessed through either patient visits (at 10 weeks and 6 months) or via telephonic contact.

Results

For the systematic review, 3,631 citations were identified of which 37 were evaluated with a median of 802 household contacts (interquartile range [IQR], 461-1,918) from a median 307 index TB patients (IQR, 137-648). The pooled yield was 2.3% (95% CI, 2.0%-2.7%, $I^2=96.5\%$) among household contacts. Factors contributing to differences (although not statistically significant) were 1) background TB incidence (unadjusted odds ratio (uOR) 1.10 [95% CI, 0.97-1.27] with every 100 cases per 100,000 population increase in the background TB incidence); 2) HIV burden (uOR 1.9 [95% CI, 0.9-3.7] comparing high burden settings with those in low burden); and 3) proportion of contacts <5 years old (uOR 2.0 [95% CI 0.98-4.0] with every 10% increase in the proportion of contacts screened who were <5 years old; 15 studies).

In evaluating the performance of Xpert MTB/RIF, 619 contacts were enrolled from 216 index TB patients; 54.3% (336/619) had ≥ 1 TB symptom, of which 297/336 (88.4%), provided a sputum specimen and 289 had complete microbiological testing. MGIT culture identified 33/289 (11.4%) as positive for *Mycobacterial tuberculosis* (MTB), 16/289 (5.5%) was identified as positive for MTB by Xpert MTB/RIF and 6/289 (2.1%) were positive for acid fast bacilli on smear microscopy. Xpert MTB/RIF sensitivity was 21.2% (95% confidence interval [CI]: 9.0, 38.9), specificity 98.3% (95% CI: 95.6, 99.5), positive predictive value (PPV) 63.6% (95% CI: 30.8, 89.1), negative predictive value (NPV) 90.0 (95% CI: 85.7, 93.4).

The *Inhibit-TB* study enrolled 2,243 index TB patients and 3,012 household contacts across 3 study arms; 26 (1.2%) self-reported currently being on TB treatment. When evaluating the uptake of HIV testing among household contacts ≥ 14 years old in Arm 1, 52% (984/1,887) were available during a household visit and offered HCT; 108 (11%) self-reported being HIV-

positive. Of the remaining 876, a total of 304 agreed to HCT (35%); 26 (8.6%) were newly diagnosed as HIV positive in Arm 1. Factors associated with HCT uptake were 1) prior testing (adjusted odds ratio [aOR] 1.6; 95% confidence interval [CI]: 1.1–2.3) and 2) another member in the household testing (aOR 2.4; 95% CI: 1.7–3.4).

Across all 3 arms, 98 newly diagnosed HIV patients were identified; linkage to care within three months was recorded for 8/26 (30.8%) in Arm 1, and 16/38 (42.1%) in Arm 2 (Relative Risk [RR] 1.37; CI: 0.68–2.76, $p = 0.382$). 20/21 contacts (95.2%) initiated IPT in Arm 3, compared to 3/20 (15.0%) in Arm 2 ($p = 0.004$; p -value from Fisher's exact test < 0.001).

Conclusions

The programmatic success of HHCT will require consideration to three key components; *resources*, *yield* and *fidelity*. South Africa, like many other countries grappling with high TB and HIV rates, will need to consider evidence-based interventions to maximize available *resources* and impact on these dual epidemics.

As evidenced by the systematic review, TB household contact tracing, despite variations in its implementation, will be a key intervention in pursuing the End TB strategy as it achieves a high yield of TB among household contacts (relative to the general population and other key populations) particularly in settings with high background rates of TB and HIV.

However, more consideration should be given to the types of tests and the screening when conducting TB contact tracing. The utility of culture testing in HHCT diagnostic algorithms needs to be considered, as the poor sensitivity of Xpert MTB/RIF in this population jeopardizes the very principle of finding “missing” TB cases. Fundamentally, HHCT provides a platform for integrating TB/HIV activities, illustrated in the reported improvement in uptake between household-initiated versus clinic-initiated IPT, however results suggest that increasing complexity of services offered in the household, although pecuniarily sensible, may dilute the quality of these respective offerings. The use of PoC CD4 testing and provision of household IPT has potential, but may require additional consideration within HHCT particularly in South Africa where guidelines have shifted to a universal test and treat for HIV positive patients and IPT eligibility has expanded.

This thesis has highlighted important considerations to enable evidence-based approaches to TB/HIV integration, specifically to optimize HHCT, thereby improving its *yield* as an intervention and subsequent *fidelity*.

List of original papers

1. Systematic review of factors associated with the yield of TB among household contacts.

Kavindhran Velen, Piotr Hippner, James J. Lewis, Sarita Shah, Laura J. Podewils, Salome Charalambous

Paper has been submitted to International Journal of Lung Disease and Tuberculosis (IJTLD) on 16th March 2018 and awaiting feedback

2. Performance of Xpert MTB/RIF for diagnosing tuberculosis among household contacts of index TB patients in South Africa.

Kavindhran Velen, Laura J. Podewils, Sarita Shah, James J. Lewis, Tiro Dinake, Gavin J. Churchyard, Mary Reichler, Salome Charalambous

Paper is in preparation for imminent journal submission

3. Household HIV testing uptake among contacts of TB patients in South Africa.

Kavindhran Velen, Lewis JJ, Charalambous S, Page-Shipp L, Popane F, Churchyard GJ, Hoffmann CJ

Household HIV Testing Uptake among Contacts of TB Patients in South Africa. PloS one. 2016;11(5):e0155688. PubMed PMID: 27195957. Pubmed Central PMCID: PMC4873208. Epub 2016/05/20. eng.

4. Household point of care CD4 testing and IPT initiation in a household TB contact tracing programme in two districts in South Africa. Liesl Page-Shipp[¥], James J. Lewis[¥],

Kavindhran Velen, Sedikanelo Senoge, Elizabeth Zishiri, Flora Popane, Violet N. Chihota, Dave Clark, Gavin J. Churchyard, Salome Charalambous

Household point of care CD4 testing and isoniazid preventive therapy initiation in a household TB contact tracing programme in two districts of South Africa. PloS one.

2018;13(3):e0192089. PubMed PMID: 29499060. Pubmed Central PMCID: PMC5834159. Epub 2018/03/03. eng.

[¥] Co-first authors of publication

The publishers have given permission for reprinting of published papers. My roles in each of the publications are outlined in Appendix A

Dedication

For my Father, Kasaval (Kenny) Velen

12 March 1946 – 10 August 2005

Rest In Peace

Acknowledgements

I would like to acknowledge the relentless support and mentorship that I have received over many years from my supervisors Prof. Salome Charalambous and Dr. James Lewis. My journey with Salome extends beyond this PhD but from the time I joined my current organization. She has been instrumental in developing me as a researcher on innumerable levels; my perspective to public health research, my scientific capabilities and knowledge of TB, my exposure to local and international researchers, and my development on a personal level. She has been more than a formal PhD supervisor to me, she has been a close friend and navigator on my life's journey. As her first supervised PhD student, I hope that I have satisfied all of her expectations, hopefully encouraging her to consider more students in the future. Dr. James Lewis played a vital role in my analytical development; I will remember him for his patience with explaining statistical concepts throughout this PhD, his emphasis on having a "clean" dataset to work from, and lastly, the importance of GOOD coffee as the creative juice for any researcher.

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I would like to acknowledge my amazing parents, Kenny and Nadira Velen who I credit for all that I am by instilling strong values of integrity and purpose on me. In particular my father, who always embellished the power of education especially having grown up in an era when knowledge was the key to emancipation. He was never afforded the opportunity to pursue his own dreams but everything that he did for me allowed me to pursue mine.

Lastly, I would like to acknowledge my amazing wife, Joshna and my son, Kayur. Joshna has been my pillar of strength and support through my PhD journey. It is, as most who complete

a PhD will attest to, a constant rollercoaster ride of emotions that are easier to traverse when you have an unbelievable person by your side; Joshna has always been there for me. In addition, she accommodated the demands of my PhD while we were pregnant for my son and particularly since he was born. Therefore, I also acknowledge my son in this PhD as he too sacrificed time spent with me in order for this degree to be completed. I hope too sincerely make up for all the time that I sacrificed over the past years and reciprocate the support you have given to me in return.

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Abbreviations

3HP	High dose Rifapentine INH for 3 months
ART	Antiretroviral Therapy
CFU	Colony Forming Unit
CI	Confidence Interval
CPT	Cotrimoxazole Preventive Therapy
CXR	Chest X-Ray
DS-TB	Drug-sensitive Tuberculosis
ELISA	Enzyme-linked immunosorbent assay
HCT	HIV Counselling and Testing
HHCT	Household Contact Tracing
HIV	Human Immunodeficiency Virus
ICD-10	International Statistical Classification of Diseases
IPT	Isoniazid Preventive Therapy
IQR	Interquartile Range
MDR-TB	Multi-drug Resistant Tuberculosis
MGIT	Mycobacteria Growth Indicator Tube
MTB	<i>Mycobacterium tuberculosis</i>
NDoH	National Department of Health
NOS	Newcastle-Ottawa Scale
NPV	Negative Predictive Value
NTP	National Tuberculosis Programme
PhD	Doctorate of Philosophy
PoC	Point-of-Care
PPV	Positive Predictive Value
RR	Risk Ratio
SoC	Standard of Care
STIs	Sexually Transmitted Infections
TB	Tuberculosis
TST	Tuberculin Skin Test
TTCP	Time-to-culture Positivity
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UTT	Universal Test and Treat
WHA	World Health Assembly
WHO	World Health Organization

1. Introduction

Tuberculosis and its importance in public health

Tuberculosis (TB) is a respiratory disease caused by the *Mycobacterium tuberculosis* bacillus and is transmitted via an airborne mechanism. Transmission of TB starts when a person with active TB disease coughs or sneezes into the air resulting in the aerosolization of viable bacilli; once inhaled by a human host, the droplet nuclei, if small enough, deposit into alveoli, where a single organism may initiate infection [1 2]. The first stage in TB pathogenesis is more commonly referred to as latent TB infection and it is estimated that one-quarter of the world population is latently infected with TB [3]. Progression to active TB disease is determined by bacterial, host and environmental factors [4]. In addition, the suppression of the cellular immunity by human immunodeficiency virus (HIV) infection [5] contributes to an increased risk of active TB disease progression. Approximately 5-15% of the 2-3 billion people infected with *M. tuberculosis* will develop active TB disease during their lifetime [6].

TB control remains an important global priority due to its high rates of morbidity and mortality annually. A recent Global TB report estimated that in 2016 there were 10.4 million new TB cases worldwide of which 10% were among children [7]. In 2016, there were an estimated 1.3 million TB deaths, and although the mortality rates have fallen by 22% in the last fifteen years, TB has remained one of the top ten causes of death globally. The epidemiological burden of these new TB cases are more often attributed to low- and middle-income countries [8]; recent estimates acknowledge India, Indonesia, China, the Philippines and Pakistan with a 56% contribution of all new cases [7]. Thus it seems important that developing countries with their resource constraints identify effective strategies that are evidence-based to enable them to make progress towards controlling TB.

Since the infancy of the HIV epidemic, it became evident that there were real associations between TB and HIV [9], further highlighted over time in the struggle to curb the TB epidemic [10]. In 2016, people living with HIV accounted for approximately 10% of all new TB cases [7]. HIV has fuelled a three to five times increase in tuberculosis incidence rates in many high HIV prevalence countries in sub-Saharan Africa, especially in the south and east of the continent [8 11]. TB mortality among HIV-positive patients has been difficult to

determine owing to the use of the International Classification of Diseases system (ICD-10) which usually classifies death in such patients as “HIV-related”. Despite this, it is estimated that in 2016 alone, 374,000 deaths were resulted from TB disease among people living with HIV [7]. The HIV epidemic poses a serious threat to the success of TB control efforts and therefore more consideration should be given to synergize interventions to ensure that they address both epidemics.

TB in South Africa

The past two decades have seen an unprecedented rise in the burden of TB in Southern Africa [12]. The TB notification rate in South Africa, which is defined as new and recurrent episodes of TB notified to the World Health Organization (WHO) for a given year, currently stands at 423 per 100,000 population [7]. Equally concerning is that South Africa has an estimated incidence of 781 cases per 100,000 people per year [7], and combined with India and Bangladesh account for 77% of the estimated 4.3 million missed TB cases [6]. The large difference between notification rates and the reported incidence of TB suggests that we are certainly missing a lot of cases, and in the process allowing these infectious cases to go undiagnosed in our communities. The late and lack of diagnosis among these patients has important implications on continued transmission, but also explains why South Africa continues to have a high annual death rate attributed to tuberculosis [13]. Some have also argued that present strategies in South Africa have failed to control TB effectively [14]. The premise of this argument rests on the fact that if South Africa were effectively controlling TB, we would have seen a significant reduction in TB incidence, prevalence or mortality; instead these rates although declining slowly, remain unacceptably high. One possible contributor in Sub-Saharan Africa has been the HIV epidemic, which has fuelled the TB transmission and resulted in the largest TB/HIV co-infected population worldwide as 80% of TB cases in this region occur in people living with HIV [15-17]. The HIV prevalence in South Africa among the general population is approximately 12.8%; a recent report estimates that in South Africa among TB patients with a known HIV status, 59% were HIV-positive [7]. Such staggering numbers justify a bolder strategy for controlling TB and HIV collectively; a definite departure from “business as usual” thinking.

The End TB Strategy

In 2014, the World Health Assembly (WHA) adopted the WHO “Global strategy and targets for tuberculosis prevention, care and control after 2015”, also referred to as the End TB Strategy (2016-2035) [18 19]. This strategy frames the global fight against TB as a development, social justice and human rights issue, while re-emphasizing the public health and clinical fundamentals of TB care and prevention [20]. The cornerstone of its ambition to realize a world free of TB by 2035, are three specific indicator targets: 1) 95% reduction in the number of TB deaths compared with 2015; 2) 90% reduction in TB incidence rate compared with 2015; and 3) 0% TB-affected families facing catastrophic costs due to TB [19]. In addition, there exists the Global Plan to End TB (2016-2020) which is a costed plan for implementing the first five years of the End TB Strategy [19]. The Global Plan takes the End TB Strategy as its foundation and provides countries and policy makers with a path towards achieving the Strategy’s milestones path towards achieving the Strategy’s milestones [19]. The Global Plan also introduces three people-centered targets, commonly referred to as the 90-(90)-90 targets; reach 90% of all people who need TB treatment, including 90% of people in key populations, and achieve at least 90% treatment success [19]. In 2016, South Africa was estimated to have missed 162,000 TB cases [21] and if we are to realize such ambitious targets, particularly the “first 90”, we will need to consider more effective strategies that are able to identify persons with TB earlier on in their development of disease, along with timely initiation and successful treatment completion.

South Africa and Multidrug-resistant TB (MDR-TB)

In South Africa the TB epidemic is further complicated by the advent of MDR-TB. The proportion of new TB cases diagnosed with MDR-TB is approximately 3.5% according to recent estimates [6], which in terms of MDR-TB incidence within the general population, places South Africa as a high-burden country [22]. More importantly, the management of MDR-TB despite only accounting for less than 5% of all tuberculosis cases, is estimated to consume over one-third of the total tuberculosis programme resources [22 23]. There are two accepted pathways for the increased incidence of MDR-TB; 1) poor treatment management of TB patients which has led to development of drug resistance, and 2) primary transmission within communities directly from MDR-TB patients [24]. HIV has

added further complications to MDR-TB, as although patients with or without HIV co-infection, can be infected with drug-resistant TB strains, those co-infected with HIV are much more likely than are their counterparts to progress to active tuberculosis disease after initial infection [25]. With such high levels of HIV in the general population, the environment seems perfectly primed for proliferation of MDR-TB unless effective TB strategies are employed that identify persons with TB so that they are started on treatment, thus minimizing their possibility of transmission. In our efforts to curb the TB epidemic, we cannot lose sight of the importance of HIV co-infection; we need a consolidated approach to these epidemics.

South Africa's National Tuberculosis Programme (NTP) Strategy

The South African government has made a substantial commitment to the fight against TB; evident in the \$425 million budget allocated to the NTP, one of the highest among the 30 high TB burden countries [6]. Despite such financing, these funds are insufficient to provide comprehensive resources for TB control and care. This implies that in the absence of adequate resources, more evidence-based approaches and synergies across programmes are needed to maximize the current resources if we are to make progress toward the End TB strategy. The National Strategic Plan for HIV, TB and STIs 2017–2022 (NSP) provides the strategy and framework of a multi-sector partnership for South Africa to overcome HIV, TB and STIs as public health and social challenges [26]. The NSP specifies eight broad goals to realize a South Africa free from HIV, TB and STIs; three are specifically relevant to addressing the TB and HIV epidemic: 1) accelerate prevention to reduce new HIV and TB infections and STIs, 2) reduce morbidity and mortality by providing HIV, TB and STI treatment, care and adherence support for all, and 3) reach all key and vulnerable populations with customised and targeted interventions. These high-level goals are needed to guide a synergized effort for South Africa to overcome TB and HIV although more detailed strategies that are evidence-based are required for us to meet the End TB targets.

The South Africa National Department of Health (NDoH) recently developed a specific NTP strategy as a roadmap to the End TB strategy targets focusing on the next five years (2017-2021), with an emphasis on implementation of interventions with evidence-based potential for population-level impact on TB infection and mortality [27]. These specific interventions

are intended to complement the current ongoing programme of activities. South Africa is using a “Find→Treat→Prevent” approach to address the TB epidemic and it is anticipated that these additional interventions will be implemented with appropriate targeted strategies specific to their setting [27]. The five specific interventions that have been identified include: 1) targeted facility-based screening, 2) active TB case-finding among select key populations, 3) scale-up of short-course MDR-TB treatment, 4) reduce initial loss to follow up for TB and MDR-TB patients, and 5) scale-up high dose rifapentine and INH for three months (3HP) for all household contacts and HIV-positive patients. 3HP is a new preventive treatment regimen that consists of Isoniazid and Rifapentine. TB household contact tracing was identified as a main activity within the active TB case-finding intervention and an important conduit to scaling up 3HP.

Undiagnosed TB

Community-based prevalence surveys have shown that much undiagnosed tuberculosis exists in communities [28 29]. One study conducted within 24 communities from South Africa and Zambia supported this when they found 894 undiagnosed cases of active TB amongst 64,463 randomly selected individuals [12]. A few studies have tried to explore the risk factors for this high burden of undiagnosed TB within the communities. A study in Cape Town identified two such risk factors for transmission; 1) persistently large numbers of smear positive cases within the community and 2) high numbers of defaulting patients which result in retreatment cases [16]. It is subsequent contact with these smear-positive or retreatment patients, sometimes in the household, which has resulted in an increase in the incidence of TB [30]. Other risk factors which may explain the current levels of undiagnosed TB in the communities relate to environmental conditions, such as living and work conditions or contacts made during public transit. The average person spends considerable exposure time commuting between home and work, and this it is not surprising that social contact within transit is a risk factor for contracting TB [31]. What is evidenced from all these studies is that if we are to reduce the incidence of TB in South Africa and meet the End TB targets, we need to direct interventions aimed at finding and treating these “missing cases” of TB in our communities.

Household TB Contact Tracing (HHCT)

In 2012, the WHO released guidelines which recommended investigating the contacts of persons with infectious TB in low- and middle-income countries [32]; the specific emphasis being the clinical investigation for all contacts of known index TB patients, who were symptomatic, HIV-positive or <5 years old. The rationale for such a guideline was to promote a strategy for resource-limited countries to identify missed cases of TB, one which has enabled high-income countries to make progress towards TB elimination. There are a number of different phrases which have been used to define the “investigating” or screening of patients for active TB. The terms intensive case finding, active case finding, and enhanced case finding are often used interchangeably and all refer to strategies to identify and treat people with tuberculosis who have not sought diagnostic services on their own initiative [33]. When it involves tracing the contacts of known index TB patients and screening them for TB, it is referred to as household contact tracing (HHCT). HHCT is considered an effective strategy for preventing TB cases [34]. The support for its value as a strategy has been seen in several areas; TB and HIV yield, reaching paediatric populations (<5 years old), and MDR-TB.

Recent years have seen a number of pilot studies demonstrating feasibility of HHCT in South Africa; one study conducted in the North West Province of South Africa, reported a yield of 3.1% among household contacts ≥5 years, and more striking, a yield of 9.4% among those <5 years, the latter being a combination of clinical and bacteriologically diagnosed TB cases [35]. Shapiro *et al*, who conducted HHCT in the same province, also reported a high TB yield with 7.8% of all household contacts diagnosed with TB; interestingly, only 11% of these reported symptoms suggestive of TB [36]. The high yield identified among the <5 year group, a population with high mortality rates particularly as a contact to index TB patients [37], highlights the intrinsic value of HHCT; these include potentially identifying asymptomatic patients particularly as we embark on finding the “missing” TB cases and eradicating TB.

Childhood TB represents 5–15% of cases occurring each year and this proportion could be as high as 25% in some high-incidence countries [38 39]. In South Africa, approximately 7.3% of all incident TB cases for 2015 occurred in children <14 years old; this represents a very high

proportion and warrants serious consideration. In most cases, the burden of TB in this population is underestimated, largely due to the difficulties in mycobacterium isolation in children [38-40]. It is the observed rates of TB among children, particularly in the <5 year old age group that warranted the WHO's recommendation for their investigation as contacts of index TB patients and the use of IPT in this group [32]. HHCT has been shown to be very effective in identifying children with TB [41-43] and might be a viable mechanism to not only identify undiagnosed TB, but improve the uptake of IPT in this high risk group [44]. The identification and treatment of active and latent TB in children will ultimately provide a litmus test for the NTP on progress made towards meeting the End TB strategy i.e. it would be an indicator of population-level impact on TB transmission as a result of various interventions that are being proposed, initially increasing through case finding, but eventually decreasing as transmission decreases.

HIV services within HHCT

The impact of HIV on the TB epidemic has placed a greater importance on synergizing strategies that address both of these diseases; HIV/TB integration as it has become known. Proponents of TB/HIV service integration argue that it may improve TB and HIV programme efficiencies through better use of human resources, reduce delays in accessing care by patients, patient visits and costs, and may result in better continuity of care and retention in care [45-47]. HHCT provides the perfect platform for such HIV/TB service integration; the opportunity cost for including HIV testing as part of HHCT is merited by the high rates of HIV co-infection among TB patients and the population reach that is inherent in such a strategy. HHCT studies that included HIV testing for household contacts, have reported a yield of undiagnosed HIV up to 26.2% [35], while researchers also found that HIV disease in household contacts was less advanced than in index patients, suggesting that morbidity and mortality may be reduced if one is able to link these people in care [48]. Such findings lend credibility to testing for HIV in a population that is considered high risk [49-50]. The evidence makes a case that HIV testing should be incorporated into TB contact tracing activities, however implementation may not be as easy; Shapiro *et al* found that when HIV testing was offered in households, only 53% agreed to test [36]. The Ribolola study found a similar trend with the uptake of HIV testing at household level, with only 37% of eligible contacts testing for HIV [35]. HIV testing to inform people of their status is a key activity for controlling the

HIV epidemic and more importantly, realizing the HIV 90-90-90 strategy. The 90-90-90 targets are a bold direction adopted by the Joint United Nations Programme on HIV/AIDS (UNAIDS) to establish a new narrative on HIV treatment targets; diagnosing 90% of all HIV cases, putting 90% of these HIV-positive patients on treatment, and finally ensuring that 90% of those on treatment are virally suppressed [51]. South Africa has adopted these targets and prioritized the need for HIV counselling and testing (HCT) in the general population, evident in the mass HCT campaigns which have been ongoing since 2010 [52].

Various HCT platforms exist with differing levels of success; facility-based, mobile, stand-alone and household [53 54]. If we are to meet the 1st 90 HIV target, we need to employ mixed approaches of these platforms, bringing into focus a greater importance of understanding barriers to testing for HIV at household level given the demonstrated impact that HIV has had on the transmission of TB. The 2nd 90 HIV target is equally important and ultimately, a test result is of no value if the patient has not been linked into HIV care. Estimates indicate that approximately 20-60% of patients who test positive link into HIV care within 90 - 180 days [55 56]. A recent systematic review suggested that streamlining services to minimize patient facility visits, providing adequate counselling, medical and peer support, and providing incentives may decrease attrition between HIV testing and antiretroviral treatment (ART) initiation [55]. HHCT has potential to mitigate some of these barriers to HIV care linkage [57], although more evidence is needed to optimize TB/HIV integration at household-level.

Isoniazid preventive therapy (IPT) has been shown to be effective in reducing TB incidence amongst HIV positive [58] and high-risk HIV-negative individuals [59], and is recommended as part of the WHO's "Three I's" policy to reduce the burden of TB amongst people living with HIV [60]. Evidenced-based interventions will among other things, allow us to identify the "missing cases" of TB, but also provide a platform for preventive treatment of latent TB infection among high risk groups as currently recommended [32]. South Africa has guidelineed the use of IPT among child contacts <5 years old and among HIV-positives with no indication of active TB disease [61 62], however IPT uptake in these risk groups have been suboptimal despite high quality evidence to support its benefit [63 64]. In 2018, the WHO revised their initial guidelines to recommend IPT for all household contacts of index TB patients [65], which has raised the importance of household contact tracing for reaching

these high-risk populations and providing IPT. Despite the renewed importance of IPT, various reasons have been cited to its suboptimal uptake, ranging from insufficient TB screening of high risk groups [64], availability of IPT at facility-level [63], limited coverage of HIV testing [66], protective benefit of IPT wanes when treatment course is completed [67], and potential diverting of attention from more effective treatment priorities [14].

Modelling data suggests that for South Africa, although active case finding will provide the most population level impact on the TB epidemic, there is also evidence to suggest that IPT might have a significant impact but would be largely dependent on population coverage among the target groups [68]. If we are to aim to meet the End TB strategy we need to think more innovatively around how we might improve IPT uptake among high risk groups, particularly as modelled data suggests treatment of active and latent TB will make the biggest difference to realizing those targets [69]

Challenges with HHCT

Despite the growing evidence suggesting the benefit of HHCT and its potential contribution to realizing the End TB strategy, it has been strongly opposed in certain settings, owing to a number of interwoven reasons. At the centre of this argument has been high costs of implementation [70], coupled with heterogeneity in the yield of TB diagnosed through HHCT [71]. The median cost per additional case of TB identified through activities which included active case finding ranged from \$58 – \$1390 [72]. A recent summary of 28 different ACF programs (20 programs screened contacts of TB index patients) across 12 high-burden countries estimated that 17,236 additional smear-positive cases (relative to control populations) were detected at a cost of \$14.9 million, or an average cost per smear-positive case detected of \$865 [73 74]. Limited evidence has shown HHCT to be cost effective; one study reported an additional cost of \$35 per TB case detected when including combination of chest x-rays and Xpert MTB/RIF testing [75], while another study reported its cost effectivity particularly for identifying TB in children and delivery of IPT [76]. In addition to high costs inherent with HHCT, other issues discouraging its value include logistical problems such as limited transport available for health staff travelling to households, difficulties with finding index TB households that necessitates multiple attempts, and perceived safety of staff conducting HHCT in high-risk communities such as informal settlements. Although more evidence is needed to determine the cost effectiveness of

HHCT, an important contributor to its cost effectiveness will be the yield of TB diagnosed through such an intervention; ensuring that we maximize this yield will allow for the strongest case to be made for its use. More interrogation of what could be contributing factors to the heterogeneity of this yield is therefore required.

Previous studies have shown varying levels of success in terms of the yield of undiagnosed TB through household contact tracing [35 36 77-82]. The yield of undiagnosed TB in these studies has varied from 0.4% to 11.4% among contacts ≥ 5 years old and who could provide sputum for testing. A systematic review by Shah *et al* also found significant heterogeneity between studies involving household contact tracing [34]. Success it would seem may have differed based on the type of HHCT strategy implemented i.e. the approach to HHCT with regards to timing of contact tracing, TB screening algorithm used, methods for sputum collection, and diagnostic tests used. All these variations in yield would suggest that it is still unclear which approach works best to improve HHCT despite a few options being tried in the recent past [83]. The relevance of this information will be more critical in resource-constraint settings, usually high-burden TB countries, where funds will be apportioned to differing TB strategies based on their merits to find the “missing cases”. If we are to implement an optimal HHCT strategy then we need to explore what are the factors which may account for this heterogeneity in the yield.

The number and type of TB symptoms used for TB screening have a significant effect on the yield of undiagnosed TB [84]. However, the type of diagnostic test used for screening along with other factors such as age or stage of HIV, also effect sensitivity and specificity of symptom screening [85-87]. Although sputum-smear microscopy has been the mainstay of TB diagnosis [88], TB diagnostics in recent times has shifted to tests that have demonstrated increased sensitivity and faster turnaround times such as the Xpert MTB/RIF; an automated molecular test for *Mycobacterium tuberculosis* and resistance to rifampicin [89]. In South Africa, HHCT has traditionally used a mixture of smear microscopy and culture, with some programs utilizing chest x-rays (CXR) for patients who are suspected of TB [29 78 90-92]. To date, few studies have evaluated the use of Xpert MTB/RIF for identifying undiagnosed TB among household contacts through HHCT [41 81 82 93 94]. South Africa adopted the use of Xpert MTB/RIF for TB testing since 2011 and thus seems particularly important that we evaluate its diagnostic performance as ideally, HHCT requires a test that will provide the

highest yield of undiagnosed TB amongst adults and children. Ultimately, the effort and cost associated with HHCT should be maximized by utilizing a diagnostic test that is sensitive while negating the need for additional testing or work-up.

HHCT provides an ideal platform for the integration of TB and HIV activities, but also a range of other potential services, particularly with the shift towards decentralized healthcare [95]. More evidence is required to understand what services can be taken to the household during HHCT, in some cases as a conduit to improving how they are delivered at facility-level; this will enable better synergies between TB and HIV programmes and contribute to realizing the End TB strategy and 90-90-90 HIV targets respectively. Integration of TB and HIV services may also influence cost-effectiveness of HHCT as new HIV cases identified and linked to care can contribute to the outcomes of the intervention. Loss to follow-up of HIV positive patients after counselling and testing but before initiation of ART can exceed 50% in low-income settings and is a challenge to scale-up of treatment [96 97]. Point-of-Care (PoC) CD4 technology has provided an innovative way to deliver CD4 testing and when used at facility-level, limit the attrition from HIV testing to treatment initiation [98]. HHCT provides an opportunity to offer not only HIV testing, but to provide PoC CD4 testing. Jani *et al* showed that by introducing a rapid PoC CD4, the median time from enrolment to ART initiation reduced from 48 days to 20 days, primarily because of a reduction in the median time taken to complete CD4 staging, which decreased from 32 days to 3 days [96]. The extent of this benefit however, has been observed mainly in mobile settings [99]; a systematic review from 2014 on the use of PoC CD4 and linkage into HIV care suggested that there is potential for its use at a household level [100].

HHCT may provide the impetus required to overcome the scourge of TB and HIV that continues to ravage communities in South Africa and across the globe. However, the current body of evidence for its support is mixed, possibly owing to the absence of an optimal approach for household contact tracing. In addition, greater synergies are necessary for TB and HIV approaches to maximize limited resources but also provide a more holistic, patient-centered approach, thus enabling the realization of ending TB within our generation.

2. Justification and Objectives

The global impact of tuberculosis cannot be understated especially in countries with limited resources, this despite the fact that it is a curable disease. Efforts to reduce incidence rates has seen some progress being made particularly in high TB burden countries, however this rate of decline is not adequate if we are to materialize the End TB Strategy. Fundamentally, we need an intervention to adequately identify missed TB cases if this ideal of a “world free of TB by 2035” is to be realized. Household contact tracing is one such intervention with the potential to identify these missed TB cases, however variations in the yield of undiagnosed TB have restrained its value on the agenda of many national TB programmes.

South Africa is a key stakeholder to realizing a world free of TB by 2035, as along with India, Indonesia, China, Pakistan and Nigeria, account for 60% of all new cases. The high HIV co-infected rates among TB patients in South Africa coupled with a high MDR-TB prevalence has further exacerbated TB control efforts and demanded interventions that will synergize the response to these two raging epidemics. In addition, high costs associated with treating MDR-TB patients and the increased transmission risk such patients pose in the community have necessitated the identification of evidence-based interventions for a population-level impacts on TB transmission and control. Focusing on a “Find→Treat→Prevent” approach will allows us to identify missing TB cases currently hindering progress to TB control and elimination efforts; finding and treating active and latent TB early ultimately reduces transmission and morbidity [101].

Persons who live with a tuberculosis patient are at high risk for tuberculosis infection and disease due to prolonged, intense exposure to index patients [102 103]. In this regard, the WHO has recommended intensified case finding approaches such as HHCT as an important strategy for the control of TB; a strong backbone of South Africa’s NTP strategy. The strong focus of preventive therapy for all contacts within the NTP makes HHCT an ideal mechanism to address the identification of missing TB cases and treatment of latent TB infection. However, although finding and screening contacts of index TB patients may be a very effective method of increasing case detection rates [104], heterogeneity in the yield of TB from HHCT has started a debate around what is the best approach to conducting such an intervention [105] and its potential to provide TB/HIV integrated services. For us to effectively respond to the TB and HIV epidemic and specifically eliminate TB in our lifetime,

we need to understand what the most optimal approach to HHCT is in order to maximize its effectiveness; a key intervention determined to make a population-level impact. To inform this approach more evidence is required by interrogating a number of differing elements: 1) current factors that may be contributing to heterogeneity in the yield of TB from HHCT, 2) evaluating the value of new generation diagnostic tests such as Xpert MTB/RIF assay for HHCT, and 3) evaluating the uptake of HIV services at household-level among TB contacts.

HHCT activities are usually resource intensive [106] and as such we need to balance the argument for such an intervention by identifying and synergizing the most effective constructs to an optimal approach to address the TB and HIV epidemic, hopefully also bringing us closer to a world free of TB and HIV.

This thesis aimed to identify an optimal approach to HHCT that would elevate its effectiveness and importance as an intervention thereby contributing to realizing the End TB Strategy. It is anticipated that the relevance of these findings will not only specifically benefit the South African landscape by informing important policy implications, but also provide a body of evidence that could assist planning and prioritization in other high TB and HIV burden countries.

The objectives of this thesis were:

1. To identify factors which may account for heterogeneity in the yield of undiagnosed TB (*Paper 1*)
2. To determine which screening tool or combination of screening tools are most effective in identifying TB among adult and children household contacts (*Paper 2*)
3. To determine uptake and factors associated with uptake of HIV testing among TB household contacts (*Paper 3*)
4. To determine the effect of PoC CD4 on HIV entry into care and to determine the effect of household IPT provision on uptake and retention of IPT among TB household contacts (*Paper 4*)

3. Conceptual Framework

The programmatic success of HHCT will require consideration to three key components; *resources*, *yield* and *fidelity*. South Africa, like many other countries grappling with high TB and HIV rates, will need to consider evidence-based interventions to maximize available *resources* and impact on these dual epidemics.

Figure 1 illustrates the conceptual framework for this PhD thesis and represents key programmatic considerations for identifying an optimal approach to TB household contact tracing: *resources*, *TB yield* and *fidelity*.

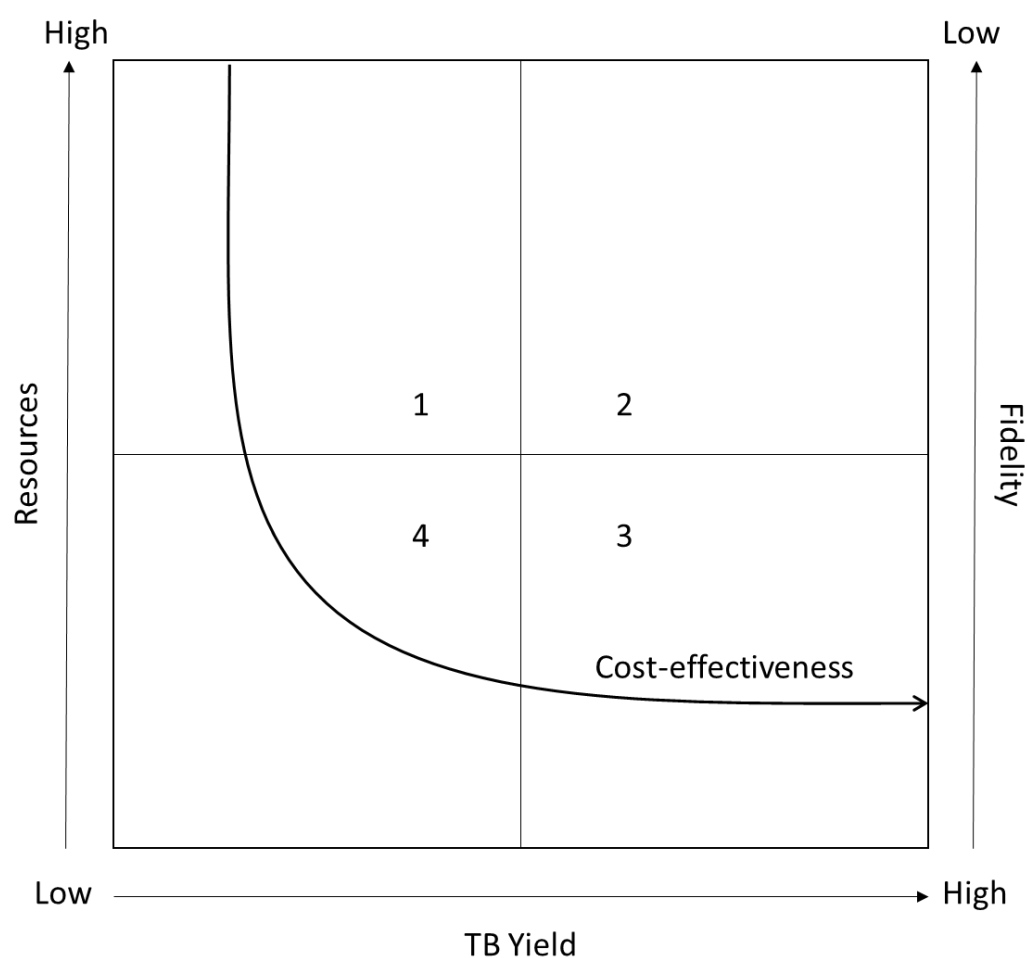


Figure 1: Conceptual framework for TB household contact tracing

The y-axis on the diagram is labelled “Resources” which refer to all the elements required for TB programmatic activities to be performed: these include human resources, diagnostic resources, logistical costs (transport of personnel or specimens), and infrastructure costs. The extent of resources required are among the key factors that drive considerations for a

given intervention i.e. the national TB programmes in resource-limited settings consider adopting a given intervention based on its demand on resources and effectiveness, essentially the best value proposition. In addition, the complexity of the intervention would also drive up the resources required for its implementation e.g. passive TB case-finding that relies on patients seeking healthcare services at a public clinic where staff and equipment are cross-subsidized by other activities in the clinic, versus household contact tracing where a specific team may visit households which is far more complex and costly. For HHCT, one would want to use the least resources to identify the highest number of patients i.e. quadrant 3 would be most desirable.

The x-axis on the diagram is labelled “TB Yield” which refers to the proportion of TB cases that are diagnosed by a given intervention, calculated as the number of undiagnosed TB cases identified among the total number of persons screened for TB. The higher the TB yield (reported as a percentage) the more efficient an intervention is considered at finding missing cases of TB. The TB yield may be influenced by a number of factors that include the population being screened, background prevalence of TB and HIV, the screening approach for identifying persons suspected of TB requiring additional testing, and the type of diagnostic test used.

Fidelity is defined as the degree to which an intervention was implemented as it was designed in an original protocol, plan, or policy [107]; this is represented on the secondary y-axis (right side). The higher the level of fidelity the more likely an intervention will be implemented as planned and therefore more likely one will be able to measure its true effectiveness. Fidelity can be affected by the complexity and perceived value of the intervention for implementers i.e. the easier an intervention, combined with a high perceived value enables an intervention to be more amenable to implementers.

The relationship of these three components drive cost per TB case of the intervention (or “cost effectiveness”) and ideally, the most optimal approach lies within the area which represents low to medium resource utilization, high TB yield and high levels of fidelity. This cost-effectiveness could be improved/worsened by the number of other interventions, such as those for HIV, that are included in the intervention, as they would lead to a sharing of resources, and ultimately reduce the cost of finding a TB case by also achieving some other

outputs such as “number of HIV cases identified” or “number of HIV cases placed on antiretroviral treatment.

Variability of these components have contributed to an ongoing debate over the utility of HHCT, however, refinements to current practices will shift its impact and cost effectiveness, moving its value from *good* to *great*; the four papers collectively provide evidence to shift HHCT from quadrant 1 to 3 (Figure 1). This PhD thesis focuses on identifying these refinements to enable such a shift, focusing on key elements such as: 1) factors associated with high yield of TB, 2) sensitivity of TB diagnostic tests, and 3) focused TB/HIV integration.

4. Methods

The data used for this thesis were derived predominantly from a combination of two parent studies, *Inhibit-TB* study and *CDC-Aurum Contact Tracing* study; paper one, a systematic review, utilized data abstracted from the literature. An overview of the PhD objectives and the source of the data is illustrated in Table 1. The detailed methodological descriptions for individual papers are contained in the method sections for each respective paper, however a brief overview of considerations for each method is highlighted below.

Table 1: Overview of PhD objectives and sources of data used

Paper	PhD objective	Parent study	Study Setting
1	To identify factors which may account for heterogeneity in the yield of undiagnosed TB	Systematic Review	PubMed Embase Google Scholar
2	To determine which screening tool or combination of screening tools are most effective in identifying TB among adult and children household contacts	CDC-Aurum Contact Tracing	Bojanala
3	To determine uptake and factors associated with uptake of HIV testing among household contacts	Inhibit-TB	Ekurhuleni and Sekhukhune
4	To determine the effect of PoC CD4 on HIV entry into care and to determine the effect of household IPT provision on uptake and retention of IPT in eligible patients	Inhibit-TB	Ekurhuleni and Sekhukhune

The *Inhibit-TB* study was a cluster randomized control trial designed to determine the effectiveness of adding Isoniazid Preventative Therapy and point-of-care CD4 testing in a household contact tracing program based in the Sekhukhune District in Limpopo Province and the Ekurhuleni District in Gauteng Province (Figure 2). The study was conceived as part of routine programme implementation, employing a randomization to assess programmatic

outcomes. The study was funded through grants provided by the Sanofi Espoir Foundation and Sanofi South Africa.

The *CDC-Aurum Contact Tracing* study is a multi-country prospective cohort study (South Africa, Kenya and China) with the primary aim of comparing the yield of active TB disease among household contacts of patients with multi-drug resistant TB (MDR-TB) with the yield of active TB among household contacts of patients with drug-susceptible TB (DS-TB). For the South African site, index patients diagnosed with MDR-TB or DS-TB are identified through routine testing within the Bojanala District in the Northwest Province (Figure 2). This study was implemented as a pure research study and did not include any programmatic aspects. The study was funded by the US Centers for Disease Control and Prevention.

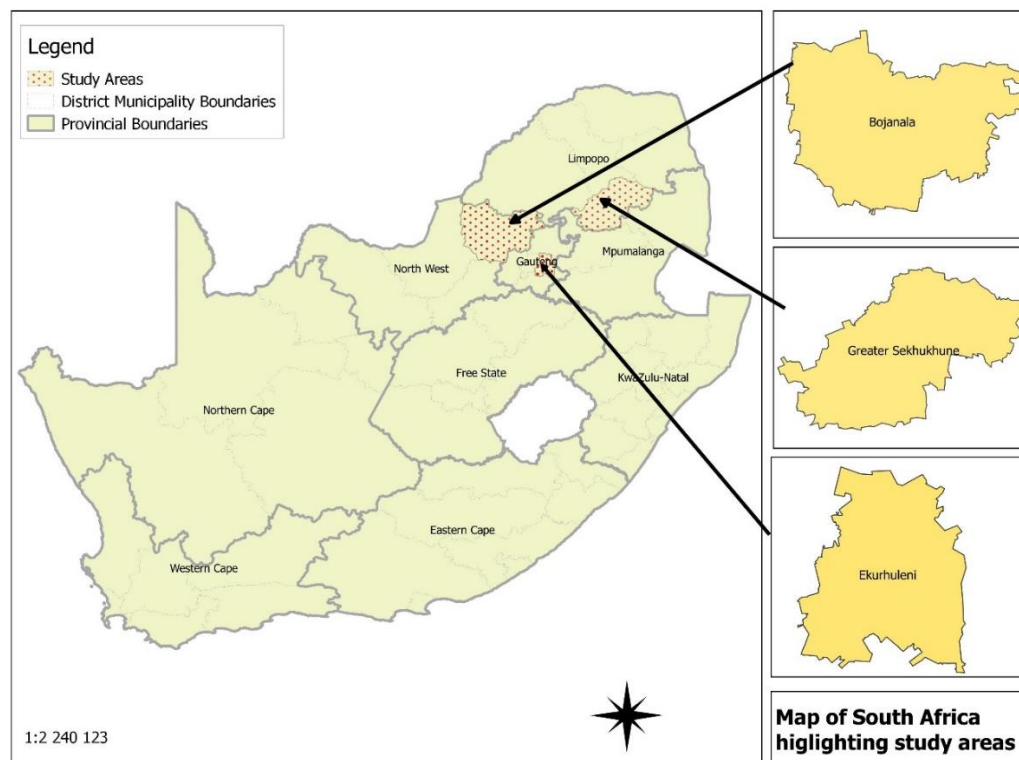


Figure 2: Maps illustrating the location of the parent studies within South Africa; Ekurhuleni and Sekhukhune districts (*Inhibit-TB study*); and Bojanala districts (*CDC-Aurum Contact Tracing*)

4.1 Study setting

According to the 2015/16 District Health Barometer, the incidence of TB in Ekurhuleni and Sekhukhune is estimated at 298 and 263 per 100,000 population respectively [108]. The TB

mortality rate is more than two times higher in Sekhukhune than Ekurhuleni (14.5% versus 6.2%); the national average is 6.6% [109] (Figure 3).

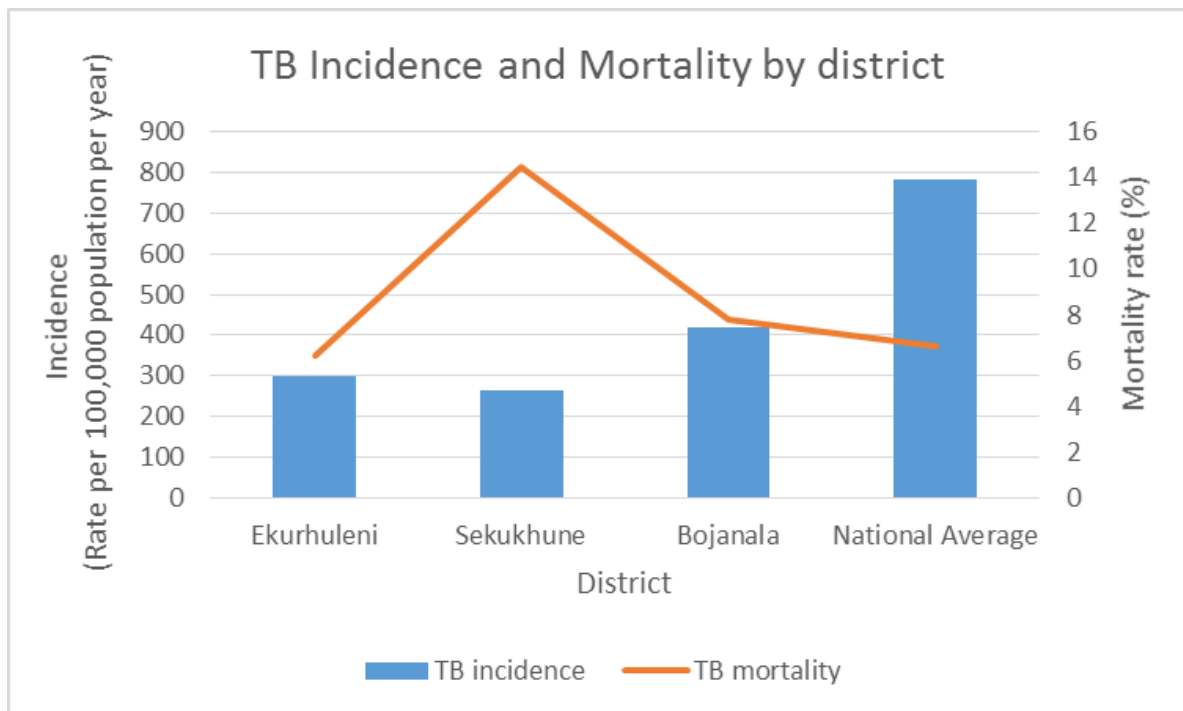


Figure 3: TB incidence and mortality rates by district against the national average

Estimated HIV testing coverage (including antenatal care) is lower in Ekurhuleni compared to Sekhukhune at 33.2% and 43.8% respectively [109] (Figure 4). The HIV co-infection rates among TB patients from Sekhukhune is estimated at 58.2% in comparison to Ekurhuleni at 67.8%, both higher than the national average of 56.7% [108] (Figure 4). Among those TB patients who are HIV co-infected, 87.3% initiated antiretroviral treatment in Ekurhuleni and 92.9% in Sekhukhune; both higher than the national average of 84.5% [108].

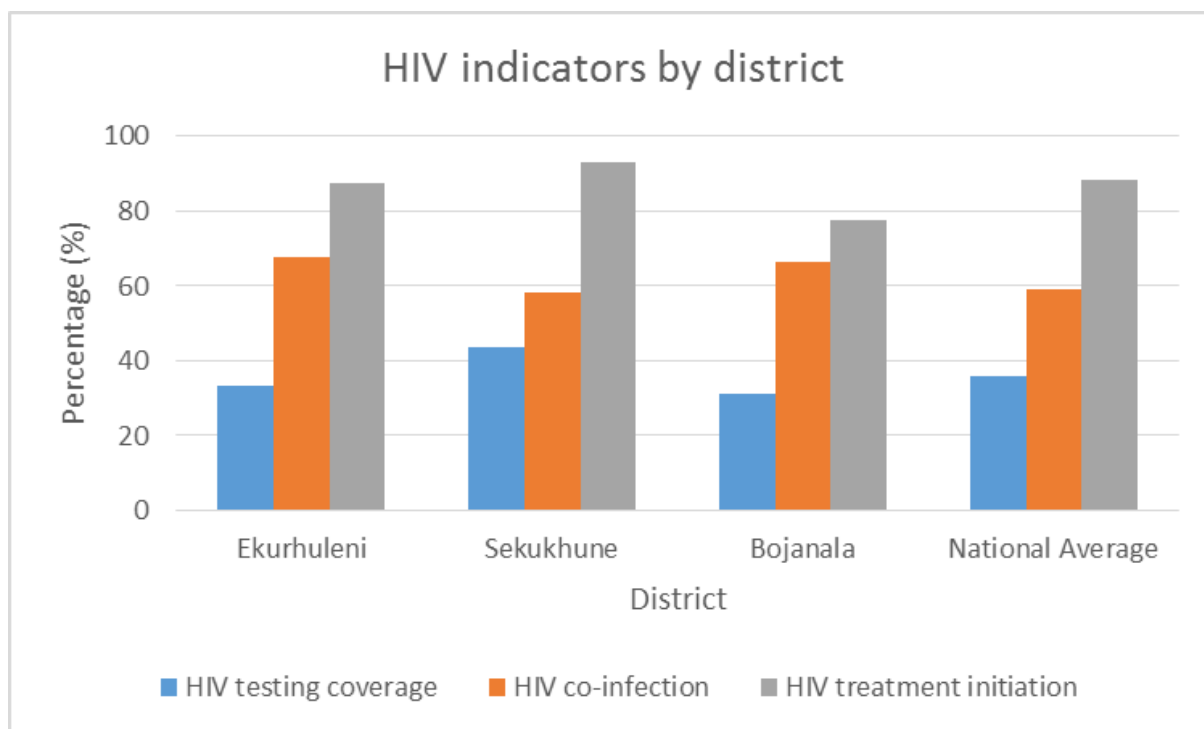


Figure 4: HIV indicators for Ekurhuleni and Sekukhune districts compared to the national average. HIV co-infection and treatment initiation rates are among TB patients.

According to the 2015/6 District Health Barometer, the incidence of TB in the Bojanala district is estimated at 419 per 100,000 population [108]; the TB mortality rate is estimated at 7.8% (Figure 3). The Bojanala district is among the poorest performing districts for HIV testing coverage with a rate of 31.1% [108] (Figure 4). The HIV co-infection rate among TB patients is estimated at 66.6%, while the proportion of these TB patients who initiate ART is 77.4% [109] (Figure 4).

4.2 Study design

Paper 1: To identify factors which may account for heterogeneity in the yield of undiagnosed TB

There has been some recently published systematic reviews on household contact tracing [34 91], however these have focused primarily on the yield of undiagnosed TB. Although these systematic reviews highlight the yield of TB and heterogeneity as an important consideration, more exploration is required to identify factors which may account for the heterogeneity in the yield of TB across studies in the literature. This systematic review

aimed to identify factors responsible for this heterogeneity and therefore provide further insight into optimizing the HHCT intervention.

This review specifically focused on published literature from HHCT studies among household contacts of drug-susceptible TB (DS-TB) index patients and not MDR-TB patients. The rationale was based on 1) DS-TB patients are more widely studied than MDR-TB patients and thus more literature is available, 2) DS-TB is the gateway for development of MDR-TB within communities versus more complex pathways to MDR-TB transmission and is thus a more appropriate starting point, 3) the value of the results would be inherently greater for DS-TB patients as most of the missing TB cases are DS-TB, and 4) if we combined both DS-TB and MDR-TB patients in this review, teasing out the factors would have been more complex as transmission dynamics are different for both types of patients.

We searched electronic databases for all publications published up to 31st March 2017; these included PubMed, Embase and Google Scholar. We chose to focus on these databases as they offered the widest coverage of articles published in English and represented the more common search engines. We also reviewed websites of conference proceedings up to 2016 from the major scientific meetings such as The Union World Conference on Lung Health, Conference on Retroviruses and Opportunistic Infections, IAS Conference on HIV Pathogenesis, Treatment and Prevention and the South African TB Conference. Search terms included *mycobacterium tuberculosis*, *contact tracing* and *case finding*. The detailed search strategy can be found in appendices for paper one.

Publications were considered on the basis of 1) an index TB patient being used as a starting point for identification of household contacts, 2) TB screening was conducted with household contacts after identification of index TB household as opposed to retrospectively linking contacts of index TB patients who may have been evaluated at a health facility through review of TB registers, 3) there needed to be ≥ 50 household contacts included in the study sample, and 4) the diagnosis of TB had to be microbiologically confirmed among household contacts. The reasons for using such criteria was to allow among other things, more specific emphasis on a classical household contact tracing approach of starting with a known index TB patient and screening their household contacts as opposed to “linking” contacts from a TB register to an index TB patient, ensuring that there would be some measure of robustness to study outcomes if there was sufficient household contacts

enrolled, and to provide credibility to yield of TB identified by focusing on microbiologically confirmed TB diagnoses to ensure that there was true TB identified rather than other pulmonary diseases.

Quality of the selected studies were evaluated using a standardized tool which was modified from the Newcastle-Ottawa Scale (NOS) specifically for cohort and cross-sectional studies [110]. The specific characteristics assessed included 1) selection bias, 2) detection bias, 3) reporting bias, and 4) confounding. These characteristics were assigned a score; the highest overall score possible was 6.5. Although an overall score of ≥ 4.5 was considered good quality, the score itself was not used as a means to include/exclude studies in the analysis. On reflection, the score mostly represented how well the necessary information characteristics were reported in the paper and thus served only as a *proxy* for identifying biases to the design of the respective studies.

Study characteristics that could provide factors for differences in the yield of TB were examined; these encompassed aspects of the contact tracing method including: 1) background TB and HIV burdens; 2) timing of contact tracing from time of index TB patient diagnosis; 3) selection of index TB patient for contact tracing i.e. smear status, etc.; 4) screening procedures; 5) diagnostic tests used; 6) sputum collection procedures; and 7) proportion of pediatric household contacts and TB diagnosed in this group. A random-effects meta-regression model was developed using STATA® 14 (Stata Corporation, College Station, Texas, USA) to regress the yield of TB from all the studies against these study characteristics. Fixed-effects meta-analysis assumes that the true yield is the same in each study i.e. only variation is random variation. The random-effects meta-analysis assumes that the true yield can differ between studies due to inherent differences i.e. not just random error; the latter was much more likely, thus a random-effects meta-regression model was chosen.

Pooled yield accounts for differing precision of estimates, so based on different sample sizes between studies. Overall yield ignores that and so weighted much more towards large studies. A measure for heterogeneity was included using the I^2 statistic and tested by the Q-statistic [111]. Findings were reported based on methodology outlined in the PRISMA statement for reporting of systematic reviews and meta-analyses [112].

Paper 2: To determine which screening tool or combination of screening tools are most effective in identifying TB among adult and children household contacts

Secondary data collected from the parent study, *CDC-Aurum Contact Tracing*, was used for this analysis. Index TB patients were identified at primary health clinics in the Bojanala district of the North West Province. An index TB patient was enrolled if diagnosed with TB in the last 2 weeks with either Xpert MTB/RIF positive or *Mycobacterial* culture positive and was also smear microscopy positive. A household contact was defined as any person who generally ate and slept in the same household as the index patient for more than one day. The justification for focusing on this specific criteria was 1) 2 weeks is considered a reasonable timeframe for contact tracing as literature suggests that 75-95% of household TB infections have already occurred at the time of index TB patient diagnosis [113], 2) 2 weeks was considered to be able to link co-prevalent TB identified among the contacts to the index TB patient as part of the main aim of the parent study, 2) it was important to include index TB patients classified as “confirmed TB”; this is considered in the local context only if the diagnosis is made on a positive Xpert MTB/RIF test or *Mycobacterial* culture, and 3) it was important to trace household contacts which were exposed to an infectious TB patient; smear positivity is considered a biomarker for infectiousness i.e. a TB patient who is smear-positive is more likely to transmit TB than a smear-negative TB patient [114].

Household contacts were screened for TB using a symptom screening questionnaire focusing on cough, fever, unintentional weight loss and night sweats; these symptoms have been universally adopted and recommended by the WHO [49]. Persons suspected of TB, defined as any person with at least one of the TB symptoms, were requested to provide a sputum sample for laboratory testing; all testing was conducted from a single sample. The use of a single sample for laboratory testing was considered because it aligns with the South African NTP guidelines, and also seemed quite feasible for other countries to adopt as they begin their roll out of Xpert MTB/RIF should this study report promising results. However, there are mixed opinions on the use of a single sputum, one study reported that it did not affect diagnostic sensitivities [115], while others suggest that it may negatively influence testing results particularly if the sample was not homogenized before splitting for the various tests; this might subsequently affect the test result due to varied quantities (low to high) of the bacilli in the sputum. Sputum collected from all persons suspected of TB were

sent to one laboratory for testing; these included smear microscopy, Xpert MTB/RIF and Mycobacteria Growth Indicator Tube (MGIT) culture. The study utilized a private quality-assured laboratory for TB testing instead of the National Health Laboratory Services (NHLS), principally because of the known rigor of testing at research standards coupled with the reliability of retrieving the data for the analysis. The laboratory was ISO 15189 and Good Clinical Laboratory Practice (GCLP) accredited. In addition, the lab has been conducting Xpert MTB/RIF testing since 2011, and to date, completed 7,626 tests. Although using a private lab was suitable for the study, not using the NHLS does sacrifice the “real-world” nature of TB testing in the public sector where sometimes inefficient systems compromise testing results and in turn TB patient care. The standard of care for TB testing in South Africa for symptomatic patients, is Xpert MTB/RIF, however as part of the study, the additional MGIT culture and smear microscopy was added; this enabled the performance comparison analysis. The parent study did also initially include a Tuberculin Skin Test (TST) and a chest x-ray for identifying persons suspected of TB, however this was discontinued shortly after the study due to unavailability of the tuberculin antigen and logistical reasons for performing the x-rays respectively. The use of TST in such a highly TB endemic area was probably not valuable given the high probability of a positive result for infection and therefore may not have affected the study. The omission of chest x-rays for screening may have resulted in missing cases in this population as reports suggest that it is a better tool than symptom screening especially among HIV-positive individuals; one study found that symptom screening missed 42% of bacteriologically confirmed TB when compared to chest x-ray [116].

For the sensitivity analysis, MGIT culture was used as the reference standard to compare the performance of Xpert MTB/RIF and smear microscopy against. A positive culture was defined as the presence of *M. tuberculosis* bacilli after testing to species level, whereas a negative culture was defined as the absence of *M. tuberculosis* bacilli after 42 days of incubation. Only household contacts with a valid MGIT culture result were used in the analysis i.e. contaminated MGIT culture results were excluded from the performance comparison.

Paper 3: To determine uptake and factors associated with uptake of HIV testing among household contacts

Secondary data collected from the parent study, *Inhibit-TB*, was used for this analysis. Index TB patients were identified and recruited from local public health clinics in Sekhukhune and Ekurhuleni districts respectively. An index TB patient was eligible for study participation if he/she was >18 years old AND tested positive on either smear, culture or Xpert MTB/RIF at time of enrolment. Consenting index TB patients were randomized to receive one of three different packages of TB/HIV care as part of the larger parent study. All of the households irrespective of randomization, were offered HCT.

HCT was offered to household contacts ≥ 14 years in accordance with national guidelines [117] and consisted of pre- and post-test counselling, with the addition of an informed consent. Household contacts <18 years old required an assent form in addition to the informed consent for participation in the study. Consenting contacts were counselled and tested in a private space to ensure confidentiality. HIV testing was conducted using a PoC rapid diagnostic test; if a person tested positive, an additional PoC confirmatory test was subsequently done to establish a positive result. An initial negative test result was reported as negative to the patient and no further testing was conducted. Where a person tested positive on the initial test, but negative on the confirmatory test, a blood sample was taken and sent to an off-site laboratory for ELISA analysis.

A questionnaire was administered to household contacts regardless of whether they agreed to HCT or not. The questionnaire contained demographic, socio-economic, previous HIV testing history, knowledge of HIV and other risk factor elements which was used to determine factors that might influence a person's willingness to test for HIV. Participant confidentiality was considered and prioritized during the HCT process; patients were counselled and tested in a private space, away from the household in a study vehicle. This was an important element to the study as willingness to test would ultimately be influenced by how comfortable an individual felt in their space at home. The use of the study vehicle as the "private space", may or may not have influenced a person's decision to test; in some respects it made HCT more noticeable to someone from the home who didn't want to test by virtue of the visit to the study vehicle. In addition, only a finger-prick rapid HIV test was offered for HCT which may have influenced HCT uptake. Recent evidence post the

implementation of this study suggested that when multiple HIV testing modalities are offered for HCT at household level, there is an increased willingness to test [118].

The group eligible for HCT included household contacts line-listed by the index TB patient who self-reported a negative or unknown HIV status at the time of study enrolment; HCT uptake was determined as the proportion of household contacts ≥ 14 years old who tested for HIV among this group. The use of self-reported HIV status may have introduced a misclassification bias into the study which could have influenced the conclusions around household HCT. A random effects logistic regression model was used to regress factors associated with HCT uptake; household and district were used as random effects in the model.

Paper 4: To determine the effect of PoC CD4 on HIV entry into care and to determine the effect of household IPT provision on uptake and retention of IPT in eligible patients

The *Inhibit-TB* study was conceptualized during a time when certain considerations were important and unknown; these included 1) ART initiation was determined by a CD4 threshold of < 350 cell/mm³, 2) CD4 testing among HIV patients was relevant due to threshold for ART initiation but PoC CD4 testing was additionally valuable due to attrition along the HIV care cascade, 3) initiation of IPT at household level was not well characterized especially within the context of HHCT. Within the context of this, the aim of *Inhibit-TB* was to understand how these interventions (PoC CD4 and household IPT) could address challenges with uptake of HCT and subsequent entry into HIV care while also evaluating if making IPT available within a TB household would address the shortcomings of poor IPT uptake at facility level. The study design chosen to evaluate the effect of these interventions was a cluster-randomized trial, a method which is considered strong design for evaluating efficacy of treatments [119]. However, although the randomizations are aimed at increasing the power of the study and its validity, there are some limitations to this design which can include but are not limited to population availability, contamination, time for follow-up, and external validity [120].

Index TB patients who consented to participate in the study had their households randomized to receive one of three variations of care; Arm 1) standard of care (SoC) for contact tracing, Arm 2) SoC plus a PoC CD4 offering, and Arm 3) SoC plus PoC CD4 plus

provision of IPT and Cotrimoxazole Preventive Therapy (CPT) depending on specific criteria. Arm 1 consisted of TB screening for household contacts using a symptom screening questionnaire and HCT for contacts ≥ 14 years old. Symptomatic household contacts provided a spot sputum for TB testing at the NHLS. This study was nested within a routine contact tracing programme and therefore TB testing and referrals for patients who tested TB or HIV positive were managed according to the guidelines within the public health sector framework. Nesting the study within a routine programme was in itself challenging, specifically around the TB testing as during the time of the study, there was a transition from using smear microscopy and mycobacterial culture to the introduction of the Xpert MTB/RIF assay. The transition of TB testing coupled with the programmatic implementation of contact tracing possibly introduced variations in procedures and outcomes among patients.

Households that received Arm 2 were afforded a rapid CD4 test if they tested HIV positive, which determined if they were immediately eligible for ART; at the time of the study, eligibility for ART was based on a CD4 count threshold of <350 cells per cubic millimetre (cell/mm^3) [121]. A referral letter was also given to anyone with a CD4 count of <350 cell/mm^3 for initiation of ART at their local health facility. The premise for including a PoC CD4 test was as a mechanism to encourage eligible patients to go to their local clinic and initiate ART, in contrast to local guideline practice that delayed this on the basis of requiring a repeat visit for CD4 staging.

Households that were randomized to receive Arm 3 services were provided all provisions included in Arm 2 plus the addition of IPT for household contacts with no symptoms for TB *and* $\text{CD4} \geq 350$ cell/mm^3 . CPT was provided to household contacts with a $\text{CD4} < 350$ cell/mm^3 and a referral letter for ART initiation. The rationale for providing IPT in households was based on the prophylactic benefit of IPT for individuals exposed to TB, a specific need in the household context given prolonged exposure to an index TB patient, and its poor uptake at facility level [122]; offering IPT in the household would potentially address both of these. In addition, provision of IPT within the households removed the need for contacts to present at health facilities, mitigating their risk of exposure to TB infection from other source cases. All household contacts enrolled in the study were followed-up at ten weeks and six months to establish if, where applicable, initiation of ART and/or completion of IPT.

The rationale for CPT inclusion was based on its value in reducing morbidity and mortality among HIV-infected individuals [123 124], particularly those with a $CD4 < 350$ cell/mm³ [125], and the inherent opportunity provided by HHCT for TB/HIV integration.

For the analysis, successful linkage into HIV care was determined if a patient self-reported visiting a private or government facility for a repeat HIV test or CD4 staging and/or ART initiation regardless of the outcome within 90 days of the baseline visit. The limitations of using self-report was that it provided “a status” to the linkage of HIV care, however the accuracy of this source can be biased and introduces misclassification as patients may sometimes provide “a status” merely to satisfy the interest of the study staff. Thus the value of the linkage outcome must be interpreted with caution taking into account variations in follow-up of this information between the different study arms. The proportion newly diagnosed with HIV that successfully linked into HIV care was compared between Arm 1 and Arm 2 to determine the effect of PoC CD4 and linkage into HIV care. The proportion of those newly diagnosed with HIV having a $CD4 \geq 350$ cell/mm³ that initiated IPT during the follow-up period was compared between Arm 2 and Arm 3. Those who received IPT in arm 3 were given a month’s supply of INH following which the study team visited the household monthly and evaluated development of TB symptoms or any possible drug-induced side effects in order to issue another one month supply of INH. Patients who received IPT in arm 2 were provided INH and monitored by the primary health clinic as per guideline practices. Detailed descriptions of the statistical analysis is contained in the specific paper.

5. Results and Discussion

The detailed presentation of results and discussion thereof are contained in the relevant sections of each of the appended papers. The proceeding sections will highlight some of the key findings and considerations emanating from the papers.

Paper 1: Systematic review of factors associated with the yield of TB among household contacts

Summary of results and main discussion points

The study identified 3,631 citations during the search process and included 37 papers in the final analysis (Figure 5). These 37 papers evaluated 186,765 household contacts with a median of 802 (interquartile range [IQR], 461-1,918) from 39,036 index TB patients with a median of 307 (IQR, 137-648).

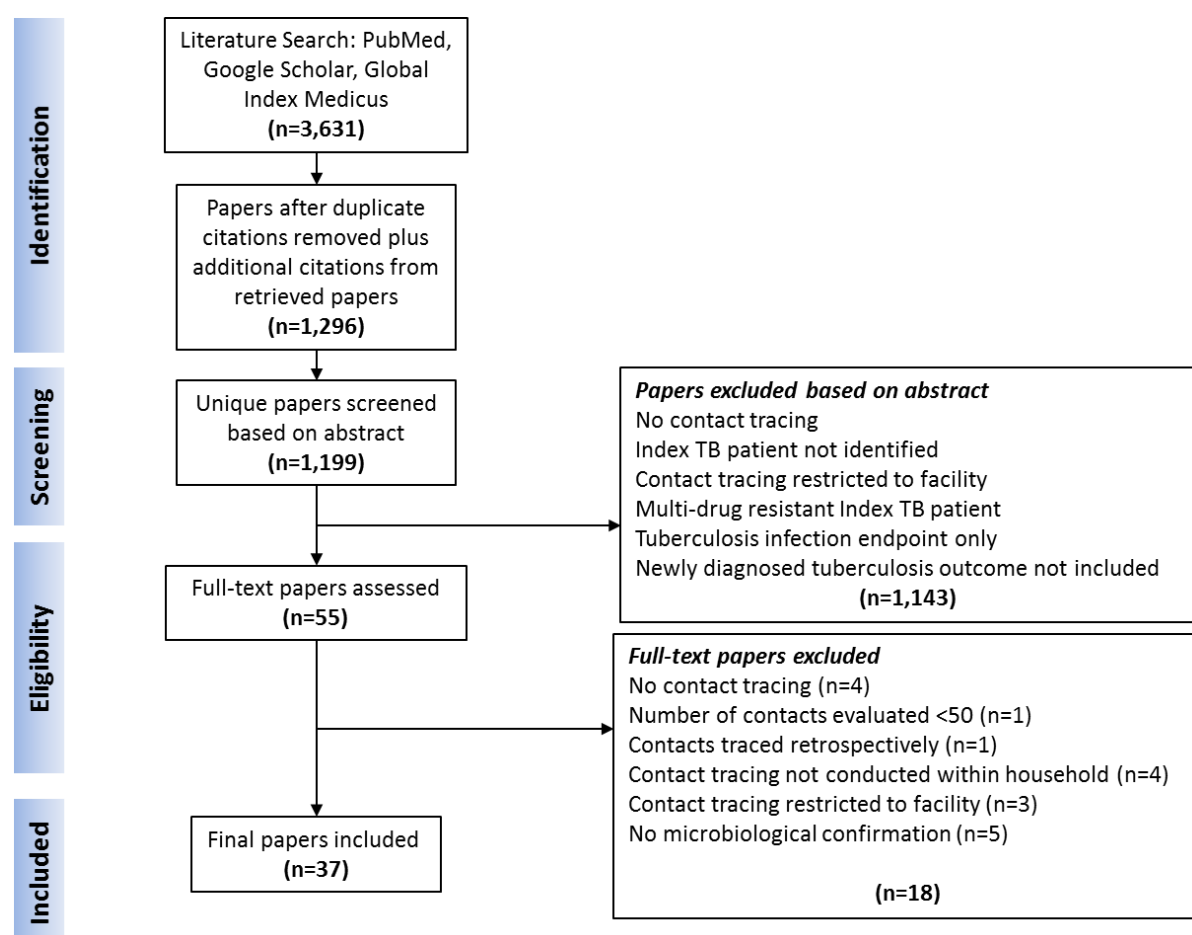


Figure 5: Flow diagram for study selection

We found significant variation in household contact tracing procedures among evaluated studies; this presumably could explain differences in the yield of TB identified through HHCT. Smear status of the index TB patient was reported in 27/37 (73.0%) studies; 27/27 (100%) reported tracing the household of a smear-positive index TB patient. The high proportion of studies focusing on smear-positive index TB patients is anticipated and considered an important starting point for HHCT; literature suggests that smear-positive patients are more infectious, thus possess a higher likelihood for transmitting TB, and therefore should be prioritized for contact investigation. Symptom screening formed the basis for 94.6% of studies to identify persons suspected of TB, however 20/37 (54.1%) also reported the use of TST. The lower proportion of studies that included TST suggests that TB programmes may be dismissing its value particularly in high TB burden settings where many individuals have by the time they reach adulthood, been infected with TB.

Once an individual was suspected of having TB, there were differences in the timing of sputum sample collection; among the 23 studies reporting this, 69.6% requested a spot sputum while 26.1% requested both spot and morning sputum. This is contrary to the accepted paradigm that sputum collected in the morning results in higher yields compared to those taken on the spot [126 127]. Smear microscopy remained the mainstay of TB microbiological testing for investigating persons suspected of TB, with 91.9% reporting including it as part of the testing algorithm. Although considered the gold standard for TB testing, mycobacterial culturing was reported in only 59.5% of evaluated studies and the relative newcomer, Xpert MTB/RIF, was used in 5/37 (13.5%) studies. The small proportion of studies that included Xpert MTB/RIF is potential indication of the slow global adoption of such testing, despite endorsements by the WHO in 2010 [128].

The importance of TB/HIV integration cannot be understated in the quest for controlling the TB and HIV epidemics, particularly in the context of HHCT; all efforts should be made to offer HIV services within the household. Despite this conventional thinking, only 32.4% of studies reporting offering HIV testing to household contacts, with no significant variation in offering by country burden of HIV. Among these 12 studies, 82.2% of household contacts were tested, of whom 9.8% were newly diagnosed with HIV. The high proportion of individuals who were newly diagnosed makes an important case for TB/HIV integration

within households as these individuals would have otherwise remained unaware of their positive status and contributed to further transmission.

HHCT identified 2,458 cases among 186,765 contacts representing a yield of 1.3% if study weighting is ignored. The overall pooled yield of TB cases diagnosed was 2.3% (95% CI, 2.0%-2.7%, $I^2=96.5\%$) and a median yield of 2.2% (IQR, 0.9%-3.5%). The pooled yield estimate is similar to a previous systematic review [71], but lower than a recent systematic review which reported an estimate of 3.1% (95% CI, 2.1%–4.5%, $I^2=98.8\%$) [91]. The difference in yield to the latter review however can be attributed to three of the 37 included studies accounting for 78.8% of evaluated contacts (only one of these three were included in the Fox *et al* systematic review), however only diagnosing a yield of 0.9% and thus skewed the overall pooled result; in the absence of these studies, the pooled yield is 2.8% (95% CI: 2.3%-3.4%).

The pooled yield of TB differed when stratified by various factors; was highest in high HIV burden settings, when a combination of spot and morning sputum sample collection was employed, when culture was included as part of the TB testing algorithm, and among paediatric (≤ 5 years old) household contacts,. When stratified by HIV burden, the pooled TB yield was 3.3% (95% CI, 2.6%-4.1%, $I^2=97.4\%$) for high HIV settings ($n=22$) compared to 1.4% (95% CI, 1.0%-1.8%, $I^2=90.3\%$) for low HIV settings ($n=15$) (Figure 6). The odds ratio for diagnosing TB among the household contacts was 1.9 (95% CI, 0.9-3.7) in settings with a high HIV burden compared with low HIV burden settings. This two-fold higher risk is consistent with the literature emphasising an increased risk of developing TB among people living with HIV as a consequence of a compromised immune system [50 129 130]. The importance for integrating TB and HIV services cannot be understated and these results suggest that the scourge of HIV will continue to inhibit efforts to curb the TB epidemic; platforms such as HHCT should be maximized and is an ideal place to offer HIV services however the low reported uptake of testing (43.8%) among household contacts in this review suggests that more exploration is required to understand possible barriers to implementation. Despite the low uptake of HIV testing, the additional 9.8% of household contacts that were diagnosed with HIV, highlights the benefit of integrating TB/HIV activities within HHCT; early diagnose of both these diseases will contribute to realizing the End TB strategy.

The pooled yield of TB in the 16 studies with spot sputum collection only was 2.4% (95% CI: 1.7%, 3.0%, $I^2=97.5\%$); 2.7% (95% CI: 1.3%, 4.2%) in the six studies with both spot and morning sputum collection; 0.7% (95% CI: 0.4%, 1.4%) in the one study with early morning sputum collection; and 3.4% (95% CI: 2.4%, 4.4%) in the 14 studies with unknown timing. It is difficult to make an inference for timing of sputum sample collection as the data were insufficient however, according to the available data, there was no statistical difference in the yield of TB diagnosed regardless of whether the sputum was collected on the spot or with both spot and morning collection. The value of sputum timing has important implications to national TB programmes as ultimately the optimal time to collect sputum may be the difference between diagnosing or not diagnosing TB especially for HHCT, but also having to make a return visit to a household for sputum collection (morning versus spot) has additional cost implications. The latter might be more costly to implement but if it results in a higher yield of TB than a spot sputum, then it makes the intervention more cost-effective, sometimes the difference between an intervention like HHCT being supported or not considered by any TB programme.

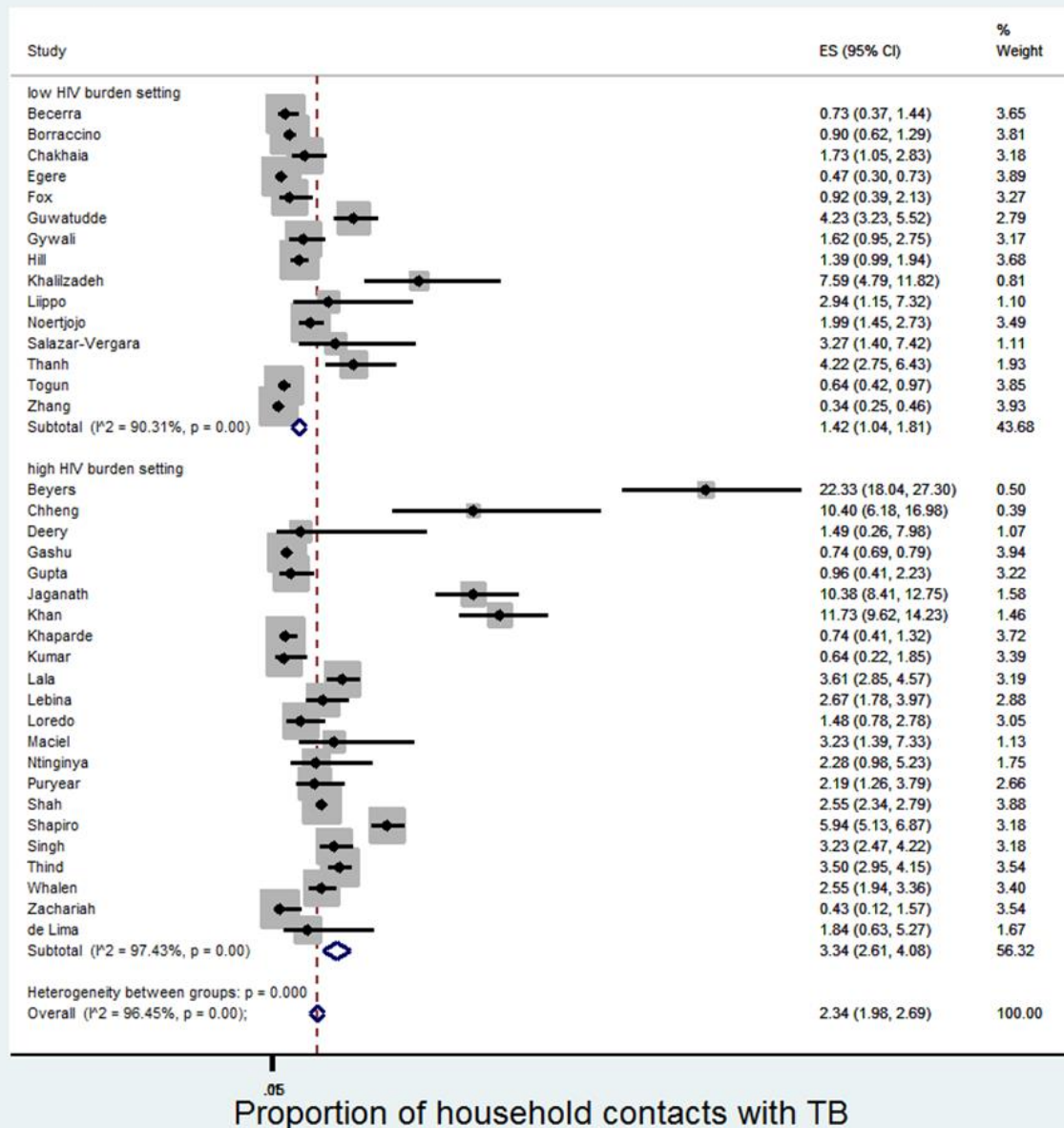


Figure 6: Forest plot for active TB diagnosed among household contacts of known index TB patients stratified by background country HIV burden (ES = estimated proportion of contacts with TB). % Weight describes the influence or “weight” of the study study’s sample size and the precision of the study results provided as a CI.

The pooled yield of TB in the studies which used smear microscopy only ($n=13$) was 1.7% (95% CI: 1.2%, 2.2%, $I^2=97.2\%$), and in the 21 studies that used both culture and smear the yield was 2.8% (95% CI: 2.1%, 3.5%, $I^2=94.5\%$). Smear microscopy although inexpensive and simple to implement in low-income settings, has low sensitivity [131] and therefore is recommended in combination with liquid culture in such settings [132]. The odds of

diagnosing TB was two times more likely in studies which included culture as part of the testing algorithm (n=22, pooled yield= 3.1% [95% CI: 2.4%-3.9, $I^2=95.2\%$]) compared to the 15 studies (pooled yield=1.5% [95% CI: 1.1-2.0, $I^2=96.8\%$]) that used smear and/or Xpert MTB/RIF without culture (OR=1.8 [95% CI, 0.9-3.7], p-value=0.09), although not statistically significant. A TB prevalence survey among gold miners in 2011 reported a similar finding of a higher TB yield among culture tests compared to smear microscopy or Xpert MTB/RIF [133]. The advent of Xpert MTB/RIF has provided an alternative to TB culture testing, primarily due to its faster turnaround in diagnosing TB, however there is still an insufficient evidence base to determine the utility of Xpert MTB/RIF in the context of household contacts. The global roll-out of Xpert MTB/RIF has gained momentum with many of the 22 high-burden countries updating their algorithms to include its use [134], however a greater evidence base is required to improve its penetration and shift a reliance away from smear microscopy. Smear microscopy is well known to be inferior in diagnostic sensitivity to mycobacterial culture, however it has remained the mainstay of testing in many high TB burden countries. This is largely due the limited infrastructure (thereby cost) and expertise required to perform, but also its faster turnaround compared to mycobacterial culture which requires 42 days to conclusively rule-out TB. The introduction of Xpert MTB/RIF provided a solution to the poor sensitivity of smear microscopy and the challenge of a long turnaround for mycobacterial culture testing with a result available in around 2 hours, a significant improvement that ultimately may impact TB transmission. Evidence from a laboratory-based study suggests that the sensitivity of Xpert MTB/RIF is comparable to mycobacterial culture at least in smear-positive TB patients [89]. The inherent lower detection threshold of culture compared to Xpert MTB/RIF [135] suggests that its sensitivity might be influenced by the bacillary burden of the sample tested, a distinct possibility in household contacts where the aim is to diagnose TB earlier in disease progression. Thus, additional evidence is required to evaluate the sensitivity of Xpert MTB/RIF among household contacts.

The numbers of paediatric contacts and the number of TB cases among children ≤ 5 years old was reported in 29.7% of included studies (four studies did not report paediatric TB cases and two additional studies reported not including paediatric contacts); eleven studies collectively screened 2,218 paediatric contacts, among whom 109 TB cases were diagnosed, giving a pooled yield in paediatric contacts across the eleven studies of 7.4% (95% CI: 4.0%-

10.9%, $I^2=96.1\%$) in comparison to the pooled yield amongst contacts >5years old within the same eleven studies of 2.4% (95% CI: 1.5%-3.2%, $I^2=91.3\%$). The odds ratio for diagnosing TB among household contacts of all ages in 15 studies reporting paediatric contacts was 2.0 (95% CI 0.98%-4.0%) with every 10% increase in the proportion of contacts that were paediatric. The increased odds for diagnosing TB and high yield demonstrated among paediatric contacts is consistent with a previous systematic review which identified them as the subgroup with the highest yield [71], and provides further support to the 2012 WHO recommendation for the investigation of contacts of known index patients with TB who are symptomatic, HIV positive, or <5 years old [49].

Ultimately, a higher yield of TB among household contacts was associated with countries with high TB incidence rates on the general population; the odds of diagnosing a household contact with TB disease was 10% higher for every 100 cases per 100,000 population increase in the background incidence of TB for that country. This finding is consistent with the consensus that TB transmission will be higher in “high TB burden” settings [136] as individuals are more prone to be latently infected. Contact with a smear-positive TB patient in the household or community results in an increase in the transmission and incidence of TB [30 137]. Specifically, Verver *et al* found that in two communities from South Africa with a high incidence of TB, only 19% of TB cases in the community resulted from transmission in the household [137]. In addition, the importance of active case finding in high TB burden areas should be further emphasized in countries with an equally high HIV burden; Shapiro *et al* reported a TB prevalence among household contacts of 6,075 per 100,000 population in a setting with high HIV prevalence [36]. The study findings provide further evidence to support the inclusion of HHCT as an important intervention within “high TB burden” countries [34], particularly within the ambit of the End TB strategy.

Generalization of findings

There was substantial heterogeneity observed among the evaluated studies, specifically around household contact tracing procedures; therefore pooled yield estimates must be interpreted with caution. The effects of such variation in procedures is possibly underpinning the heterogeneity in the yield of TB diagnosed from HHCT. Overcoming this variation was attempted through the use of random-effect models however, the magnitude of the heterogeneity meant that we could not account for all the factors which might

explain the difference in yield across studies. These differences likely introduced a level of ascertainment bias. According to various WHO recommendations, HHCT procedures are suggested for consideration by national TB programmes, however the rationale for their use is usually linked to human and financial resources, additional country-level evidence and political sentiment. Such reasons eventually contribute to large variations in HHCT practices as identified in this review; this prevented the determination of which screening and testing modalities worked best for identifying undiagnosed TB. In addition, the papers inconsistently provide information around specific indicators reviewed as part of this study and therefore diluted the meta-analysis where information was missing from the publication. This review was restricted to papers published in English and hence generalizability of findings may not account for results reported in the literature produced in other languages. The review included searching in grey literature for relevant studies; in all cases these reports, conference proceedings in particular, were subsequently found as published papers however some studies might have been missed in this process. The systematic review evaluated the quality of studies using the Newcastle-Ottawa Scale and found that 75.7% were of good quality (score of ≥ 4.5), however, it is possible that the score does not reflect the consideration of various biases in study design for the included papers, but rather an indication if the evaluated measure was proximally reported in the paper or not. Thus, the limited number and quality of papers reviewed may have biased the reported estimates. Lastly, there is a possibility of missing papers for this systematic review leading to a reporting bias i.e. studies that show a high TB yield from HHCT are more (or less) likely to have their studies published compared to those with low TB yield.

This study has provided an updated systematic review and pooled yield estimates TB from tracing the household contacts of DS-TB index patients and contributed additional information to understanding factors that are associated with differences in the yield. The study was not able to fully examine the independent contributions of each factor to the heterogeneity in the yield of TB, but illustrated the importance of conduct HHCT in settings with high TB incidence and high background HIV prevalence.

The findings from this study underscore the importance of focusing resources on the right areas to optimize TB yield i.e. the study highlights the *need* for HHCT as an intervention for identifying missed TB cases, however it also illustrates that optimal yield will only be

enabled by focusing on high TB and HIV burden areas and the paediatric population. This aligns with the PhD conceptual framework and supports the notion that ideally, HHCT can only be an effective intervention if the yield of TB is optimized. The likelihood of it being adopted by implementers of national TB programmes will be increased if it capable of identifying missed TB cases relative to the resources that are required.

These findings build on the evidence for endorsing HHCT as an effective approach for finding undiagnosed TB and HIV, as an opportunity for integrating TB/HIV services, useful intervention for targeting specific key populations such as paediatric contacts, and overall a necessary strategy if we are to meet the milestones of the End TB Strategy.

Remaining gaps for research

This study has emphasised the need for additional research that translates existing recommendations from various entities like the WHO to identify optimal approaches specific to HHCT, particularly in light of a global roll-out of new diagnostics such Xpert MTB/RIF by national TB programmes. While the penetration of Xpert MTB/RIF among high TB burden countries is progressing, the onset of an updated version, Xpert MTB/RIF Ultra is being validated in many countries. Xpert MTB/RIF Ultra was recently endorsed by the WHO as an alternative to Xpert MTB/RIF with improved analytical sensitivity [138]; early modelling data suggests that in high TB and HIV settings, it will offer a considerable mortality benefit [139].

The intrinsic benefits to conducting systematic reviews is that they provide an opportunity for synthesizing evidence, however their utility cannot be maximized unless studies adhere to a minimum spectrum of indicators that allow for meta-analysis. In this regard, a recommendation is for future published studies to include specific characteristics that could provide deeper insight into an optimized approach to HHCT; these include process for index TB identification, timing of household visits, screening and laboratory testing algorithms, stratification of laboratory results by diagnostic tests, HIV status of household contact and previous TB history.

Paper 2: Performance of Xpert MTB/RIF for diagnosing tuberculosis among household contacts of index TB patients

Summary of key results and main discussion points

This study compared different screening methods for diagnosing TB amongst 619 household contacts of 216 index TB patients (73 MDR- and 145 DS-TB) and found that Xpert MTB/RIF underperformed against a mycobacterial culture reference standard. 336 (54.3%) contacts had ≥ 1 TB symptom; 297 (88.4%) provided a sputum sample for TB testing. Complete testing results were available for 289 (97.3%) patients, MGIT culture identified 33/289 (11.4%) as positive for MTB, 16/289 (5.5%) was identified as positive for MTB by Xpert MTB/RIF and 6/289 (2.1%) were positive for acid fast bacilli on smear (Figure 7). The study reported an overall Xpert MTB/RIF sensitivity of 21.2% (95% CI: 9.0, 38.9), a specificity of 98.3% (95% CI: 95.6, 99.5), a positive predictive value (PPV) of 63.6% (95% CI: 30.8, 89.1), and a negative predictive value (NPV) of 90.0 (95% CI: 85.7, 93.4) (Table 2).

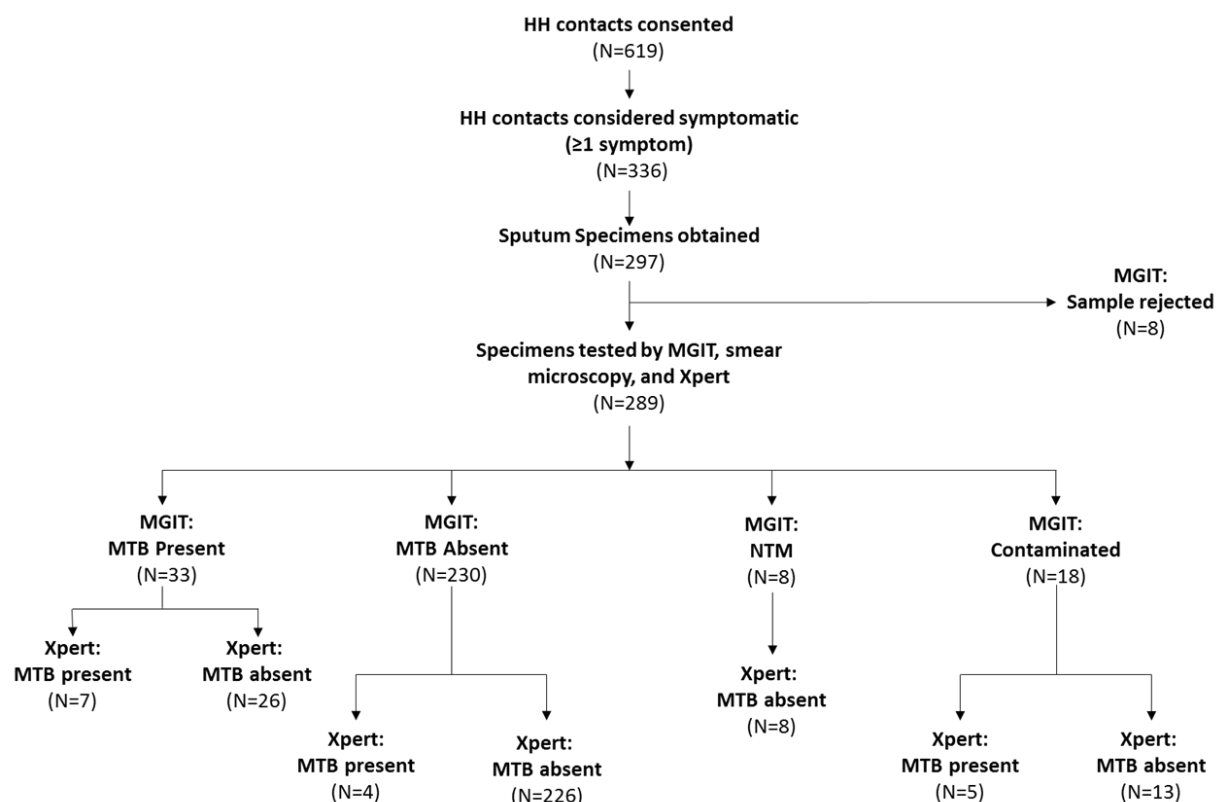


Figure 7: Flow diagram of Xpert MTB/RIF and MGIT culture testing results

The poor sensitivity of Xpert MTB/RIF is not consistent with the evidence base that has supported its recommended use, presumably because many of the initial studies evaluated

its performance in a laboratory [140] or clinical setting [141], and not among household contacts against a culture reference standard. However, the magnitude of this poor sensitivity might be skewed by virtue of nine Xpert MTB/RIF positive results occurring in among MGIT culture negative and contaminated samples, the latter not included in the sensitivity analysis. A 2014 systematic review reported that the sensitivity of Xpert MTB/RIF varied in differing settings, ranging from 58% to 100% [142], however the extent of their meta-analysis did not specifically highlight sensitivity among household contacts related to HHCT, but the reported range itself suggests that it may not perform as well as was initially reported [89]. Ntinginya *et al* reported a sensitivity of 100% for Xpert MTB/RIF compared to a culture reference standard, although this was among only 5 culture-positive contacts. Another study from the Gambia among 14 culture-positive children <15 years reported a sensitivity of 42.9% [93 143].

Previous literature indicates that in instances where the sensitivity of Xpert MTB/RIF is reduced, it is usually as a result of variations in smear or HIV status [142]. In this study, when stratifying by smear status, Xpert MTB/RIF sensitivity was higher for smear-positive specimens than for smear-negative specimens (Table 2); 100% (3/3) for smear-positive vs. 12.9% (4/30) for smear-negatives, $p=0.06$. In addition, there was no evidence to support a statistical difference in sensitivity of Xpert MTB/RIF by HIV status; 40.0% (4/10) for HIV-positive vs. 13.0% (3/23) for HIV-negatives, $p=0.21$. This finding is consistent with Rachow *et al* who reported that the performance of Xpert MTB/RIF was not affected by HIV status [141].

The overall yield of TB among household contacts, based on the proportion of TB cases diagnosed on MGIT culture, Xpert MTB/RIF or smear microscopy was 6.8% (95% CI: 4.9, 9.1). The yield of TB among household contacts is possibly driven by the background TB rates; in this study the reported TB incident rate for the study area is approximately 4.2%. This reported yield is high in comparison to many other household contact tracing studies; a recent meta-analysis of such studies reported a pooled TB yield of 3.1% (95% CI 2.1–4.5%, $I^2=98.8\%$) [91] among household contacts. The factors associated with the high observed yield might be specifically related to the HHCT procedures employed, including among other things, the TB testing algorithm. In this study, MGIT culture diagnosed a yield of 5.3% (95% CI: 3.7, 7.4), Xpert MTB/RIF with 2.6% (95% CI: 1.4 4.2) and smear microscopy with 1.0%

(95% CI: 0.4, 2.0). Dorman *et al* reported a similar finding from a TB prevalence survey among gold miners in which they also showed Xpert MTB/RIF diagnosing a higher yield of TB than smear microscopy but lower yield compared to MGIT culture [133], however more importantly, this study was *not* among household contacts and the difference in yield from MGIT culture compared to Xpert MTB/RIF was not as pronounced.

The higher Xpert MTB/RIF yield compared to smear microscopy is consistent with other studies in the literature [89 143-145]. One reason for the marked difference in the yield of TB from Xpert MTB/RIF compared with MGIT culture might be due to the inherent differences in the threshold for TB detection between the two diagnostic tests; MGIT culture has a known detection threshold of 1-10 Colony Forming Units (CFU) in comparison to Xpert MTB/RIF with 100 CFU's [135].

Patients who are diagnosed with TB at public health facilities are more often further advanced in their TB disease, by virtue of their health seeking behaviour, compared with patients diagnosed through active case finding activities such as HHCT [146]. Thus, patients with advanced TB disease generally have a high sputum bacillary burden compared to those who are diagnosed earlier in the development of TB disease such as children and household contacts [145], the latter correlating to a lower sputum bacillary burden. This lower sputum bacillary burden coupled with the inferior detection threshold in Xpert MTB/RIF compared with MGIT culture might be the reason for its poor sensitivity. One study from South Africa which looked at TB diagnosed in children <15 years within a primary health care setting, reported a 43.3% sensitivity of Xpert MTB/RIF when compared to culture [147]. Sputum bacillary burden can be estimated through certain measures such as time-to-culture-positivity (TTCP), a strong correlate of Xpert MTB/RIF positivity in pulmonary specimens. In essence, in the presence of low sputum bacillary burden, TTCP is usually longer, which correlates with poorer sensitivity of Xpert MTB/RIF [148 149]. The results of this study is consistent with such a trend as the median TTCP was shorter in Xpert MTB/RIF positive samples compared to Xpert MTB/RIF negative samples (6 days versus 18 days) and therefore lends credibility to an explanation of poor Xpert MTB/RIF sensitivity based on lower bacillary burden.

Table 2. Performance characteristics of the Xpert MTB/RIF test overall, and stratified by smear microscopy status and HIV status, using MGIT culture as the reference standard

		Overall (N=271) ^a	Smear status		HIV status	
			Positive (N=5) ^b	Negative (N=266)	Positive (N=62)	Negative (N=209)
Xpert MTB/RIF sensitivity	N/N	7/33	3/3	4/30	4/10	3/23
	% (95% CI)	21.2 (9.0, 38.9)	100.0	13.3 (3.8, 30.7)	40.0 (7.5, 70.1)	13.0 (2.8, 33.6)
Xpert MTB/RIF specificity	N/N	234/238	0/2	234/236	50/52	184/186
	% (95% CI)	98.3 (95.8, 99.5)	0.0	99.1 (97.0, 99.9)	96.1 (86.7, 99.5)	98.9 (96.2, 99.9)
Xpert MTB/RIF PPV	N/N	7/11	3/5	4/6	4/6	3/5
	% (95% CI)	63.6 (30.8, 89.1)	60.0 (14.7, 94.7)	66.7 (22.2, 95.7)	66.7 (22.3, 95.7)	60.0 (14.7, 94.7)
Xpert MTB/RIF NPV	N/N	234/260	0/0	234/260	50/56	184/204
	% (95% CI)	90.0 (85.7, 93.4)	0.0	90.0 (85.7, 93.4)	89.3 (78.1, 96.0)	90.2 (85.3, 94.0)

^a Excluded from the analysis were 18 specimens that were contaminated in MGIT culture

^b Sensitivity of smear microscopy for detection of MTB, using MGIT culture as reference standard, was 3/33 (9.0%, [95% CI: 1.9, 24.3] vs. Xpert sensitivity of 21.2% overall (p<0.001)

There are additional considerations to determining the overall performance of Xpert MTB/RIF that are not based on diagnostic endpoints such as yield, but instead relate to usability. When comparing Xpert MTB/RIF to MGIT culture, one important measure of usability is proportion of uninterpretable results after diagnostic testing. MGIT culture testing based on its method is prone to contamination, and in addition to the time it takes to result a sample, is other reason why Xpert MTB/RIF has been favoured particularly in settings with limited laboratory capacity. In this study, the contamination rate on MGIT culture was 6.2% (18/289). This rate is within the 8-10% acceptable range and slightly lower than a meta-analysis which reported a contamination rate of 8.6% when using liquid systems such as the BACTEC MGIT 960 for culturing [150]. Conversely, Xpert MTB/RIF testing is not inherently prone to contamination as the cartridges are self-contained [151], however, uninterpretable results are possible and are reported as a “failed” result. This study did not report any failed Xpert MTB/RIF tests and is consistent with a meta-analysis by Steingart *et al* that reported a very low pooled proportion of uninterpretable Xpert MTB/RIF results at 1.0% (95% CI: 0.05%, 2.0%) [142]. This is an important consideration within the context of HHCT as the high costs associated with visiting households would not favour repeat visits for more sputa as a consequence of a contaminated culture result.

Considering all the results from this study, perhaps a more favoured TB diagnostic testing approach for HHCT does not necessitate the use of a single test, but a combinational testing strategy that provides high sensitivity while being cost-effective. Each of the respective tests have their own intrinsic advantages and disadvantages. MGIT culture is considered the gold standard for TB testing however, 1) it takes up to 6 weeks to “grow *M. tuberculosis*” and result which delays diagnosing a TB case and enables further transmission, 2) requires significant laboratory capacity (human resources and equipment), and 3) is prone to high rates of contamination. Xpert MTB/RIF addresses some of the challenges with MGIT culture but potentially compromises diagnostic sensitivity, however, 1) it is able to result a sputum sample in approximately 2 hours, 2) requires minimal laboratory capacity (human resources or equipment) and doesn’t need significant preparation, and 3) is less prone to contamination. In this study, when comparing the sensitivity of each test with the “all TB cases” referent (n=42), MGIT culture sensitivity was 78.6% (95% CI: 63.2, 89.7), Xpert MTB/RIF was 38.1% (95% CI: 23.6, 54.4) and smear microscopy was 14.3% (95% CI: 5.4,

28.5). If MGIT culture and smear microscopy testing are combined, the sensitivity is 85.7% (95% CI: 71.4, 94.6) compared to 100% (95% CI: 91.6, 100.0) when MGIT culture and Xpert MTB/RIF testing are combined.

This study formed part of the *CDC-Aurum Contact Tracing* parent study which evaluated the yield of TB among household contacts of MDR- versus DS-TB index patients. Although the results from this parent study are not specifically reported here, one additional finding that is important to HHCT, is that there was no significant difference in the yield of TB among household contacts when stratified by MDR- or DS-TB index patient: 8% versus 7.4% respectively. This is an important finding and contradicts conventional thinking that MDR-TB index patient households are increased risk of TB transmission [152] and should be prioritized for HHCT. Ultimately, the study did highlight the inherent value of HHCT for identifying TB cases among household contacts of MDR-TB index patients, a key component of the NTP strategy.

Generalization of findings

This study has important implications for the use of Xpert MTB/RIF in diagnosing TB among household contacts as its poor sensitivity compared with MGIT culture suggests that it would miss a substantial number of cases, and in the process, dilute the utility of HHCT as an intervention. Xpert MTB/RIF was able to diagnose nine additional TB cases in this study that were either negative or contaminated on MGIT culture, which may have likewise been “missed” if MGIT culture was used on its own. The premise for considering HHCT is to enable TB programmes to find “missing” cases of TB, and therefore although turnaround time for results is important, it should not outweigh the consideration of diagnostic sensitivity and usability. Taking into account the inherent benefits of Xpert MTB/RIF, perhaps one approach might be to combine its use with MGIT culture testing as this would complement the current reference standard for TB diagnostics and more importantly, increase the overall sensitivity when used in HHCT [141]. This study showed an increase in sensitivity to 100% from 38.1% when Xpert MTB/RIF was combined with MGIT culture. Such a suggestion will not be easily adopted as smear microscopy remains the most commonly used diagnostic owing largely to limited laboratory capacity in resource-constrained [145], however its poor sensitivity in this study highlights the need for an alternate testing method. The extensive roll-out of Xpert MTB/RIF globally means that Xpert MTB/RIF will

likely replace smear microscopy as the initial test for TB, however, as shown in this study, it's questionable performance suggests that in the context of HHCT, a more suitable testing approach which could possibly improve the yield, would be the combination of MGIT culture and Xpert MTB/RIF [143]. However, this need could be averted by the advent of Xpert MTB/RIF Ultra, introduced with a reported comparable diagnostic sensitivity to mycobacterial culture, but will still require evaluation in this population.

As with any evaluation of diagnostic performance, the rigour of testing and quality standards are crucial to results that can be generalized. In this study, the validity of the results are strengthened because all household contacts suspected with TB were tested using all three diagnostics from the same sample, making sensitivity and yield comparisons appropriate. In addition, the laboratory testing was conducted by a single established research facility to clinical trial standards.

There are however some limitations to the generalizability of the results, foremost being the sample size of the study, specifically the proportion of culture-positive cases which may inhibit the power of the results. This study was conceptualized as a result of a chance finding from the larger nested study which aimed to compare the yield of TB amongst household contacts of DR-TB and DS-TB and not to conduct a diagnostic comparison. In addition, the timing of sputum collection, which is known to contribute to higher yields of TB when done in the morning, may have impacted the overall yield as the study requested a spot sputum. Nevertheless, we did find a high yield of TB among household contacts. Lastly, the timing of household contact investigations vary within different settings, in most cases constrained by human resources. In this study households were evaluated within 2 weeks after the index TB patient was diagnosed and this could explain the disproportionate number of culture-positive cases with smear-negative results i.e. evaluating household contacts within such a short time from when the index TB patient was diagnosed, allows TB cases to be identified earlier in their disease progression but results in them having a lower bacillary burden, therefore presenting with smear-negative disease.

Lastly, the study utilized a single sputum sample from household contacts for smear microscopy, MGIT culture and Xpert MTB/RIF testing. Anecdotally, use of a single sputum sample for multiple testing may have introduced a diagnostic sensitivity bias as a consequence of inconsistently homogenizing the sample before it was split for testing. The

limited evidence from the literature however, does not suggest that performing multiple TB testing on a single sputum sample would affect diagnostic sensitivity [153].

The results from this study emphasize the components of resources and yield in the conceptual framework for this PhD. In essence, reducing the cost per TB case identified from HHCT will rely on focusing TB diagnostic testing for an increased yield, thus making HHCT more favourable as an intervention by national TB programmes. The focusing of HHCT on an optimized or evidence-based approach will consequently improve its fidelity as well.

Remaining gaps from the study

This study has highlighted important shortcomings in the performance of Xpert MTB/RIF compared with MGIT culture for case finding among household contacts of index TB patients. The inherent value of HHCT is to identify “missed” TB cases in the community which if left undiagnosed, undermine control efforts and ultimate realization of the End TB strategy. The high costs associated with HHCT necessitates the optimizing of this intervention and one important driver will be to determine the most suitable diagnostic to enable the highest TB yield. On the horizon is the arrival of an improved and updated Xpert MTB/RIF cartridge aptly called the Xpert MTB/RIF Ultra, which promises better sensitivity over its predecessor and could be considered. Initial results however suggest that the sensitivity is only marginally improved [154-156] and therefore might not provide a solution to this problem. The compromised diagnostic performance of Xpert MTB/RIF highlighted in this study will significantly impact its cost-effectiveness for diagnosing TB in this population, something which the Xpert MTB/RIF Ultra cartridge will be aiming to overcome. Additional research will likely be required to evaluate its use in the context of HHCT.

Other possible research gaps that could be explored from this study include an approach of TB testing all household contact of index TB patients regardless of whether they are symptomatic or not. The premise for this has been poor sensitivity of the WHO symptom screening tool which was initially designed for use among HIV patients being investigated for TB. A growing body of evidence suggest that relying on TB symptom screening alone for identifying persons suspected of TB, will miss a substantial number of individuals with active TB disease in the general population [157-159]. Therefore, testing all household contacts of index TB patients regardless of if they are symptomatic or not is one way of ensuring no TB

case is missed, however there are inherent cost implications to such an approach. In addition, the use of urine LAM, a novel rapid test that overcomes the need for a sputum sample, has only demonstrated high sensitivity in advanced HIV and hospitalized patients [160], thus not efficient in this population. Shapiro *et al* reported that among household contacts of index TB patients who could provide sputum for TB testing, 89% (151/169) of co-prevalent TB cases identified were asymptomatic and thus would have been missed if eligibility was based on symptom screening exclusively [36]. More evidence on the cost-effectiveness of such an approach would be required to ultimately determine its feasibility in the context of HHCT.

Paper 3: Household HIV testing uptake among contacts of TB patients in South Africa

Summary of key results and main discussion points

This study evaluated the uptake of HIV testing among 876 household contacts ≥ 14 years old present during HHCT activities without known HIV infection, and found a testing uptake of 35% ($n=304$). This is moderately consistent with other HHCT studies that included HIV testing within the household: two studies from South Africa reported an uptake of HIV testing among household contacts of 52% and 55% respectively [36 118] in contrast to other home-based HCT studies which achieved uptake ranging from 69% to 99.8% [161-163]. There are many possible reasons that could explain these differences in testing uptake, potentially at an individual-level, household-level or community-level.

At an individual level, factors associated with uptake of HIV testing in this study related to history of previous HIV testing; the odds ratio was 1.6 (95% CI: 1.1-2.3) for contacts who had previously tested for HIV compared to those who reported no previous HIV testing, increased level of education, and residing in an urban area (Table 3) which are consistent with previous studies [162 164]. The need to include HIV testing within HHCT is fundamentally important if we are to make progress towards 90-(90)-90 HIV targets or the End TB strategy, particularly in settings with high background HIV prevalence as these undiagnosed HIV cases are fuelling the ongoing TB epidemic. Programmatically however, it seems making these different HCT platforms available such as within HHCT, is only one part of the solution to improving HIV testing; consideration to these individual level factors is what will maximize the drive for HCT particularly among household contacts of index TB patients.

The household also seems to play a vital part in influencing individual uptake of HIV testing. In this study, the odds for a contact testing was almost two-and-half times more likely if someone else in the household had tested during the visit (OR 2.4 [95% CI: 1.7-3.4]). This suggests that the premise for an individual wanting to test is not based on *just* an individual-level decision but incorporates household-level dynamics [165 166]. The hierarchical nature of households makes it a complex environment to provide home-based HCT, but with deeper understanding of these dynamics, has the potential to be an important platform for

TB/HIV integration. Recent developments have suggested a family-based HCT intervention within households that can potentially overcome some of these observed barriers to uptake of HCT [167].

Table 3: Demographic characteristics of household contacts who were offered an HIV test (n=876)

Characteristic	N (column %)	Tested for HIV n (row %)	Unadjusted OR (95% CI) *	Adjusted OR (95%CI) *
Gender			p=0.504	p=0.229
Men	328 (37.4%)	109 (33.3%)	1	1
Women	548 (62.6%)	195 (35.6%)	1.13 (0.79, 1.62)	1.25 (0.87, 1.79)
Age (years)			p=0.9	p=0.2
14-24	335 (38.2%)	112 (33.4%)	1	1
25-39	201 (22.9%)	68 (33.8%)	1.05 (0.66, 1.68)	0.73 (0.44, 1.21)
≥40	340 (38.8%)	124 (36.5%)	1.06 (0.72, 1.58)	1.15 (0.70, 1.88)
District			p<0.001	p=0.009
Urban/Semi-urban	655 (74.8%)	263 (40.2%)	1	1
Rural	221 (25.2%)	41 (18.6%)	0.23 (0.13, 0.41)	0.52 (0.31, 0.86)
Level of education			p=0.02	p=0.03
≤ Grade 7	224 (25.6%)	63 (28.1%)	1	1
Grade 8-11	413 (47.1%)	153 (37.0%)	1.65 (1.04, 2.62)	1.65 (1.04, 2.61)
Grade 12	174 (19.9%)	72 (41.4%)	1.97 (1.13, 3.44)	1.77 (1.00, 3.13)
Tertiary	50 (5.7%)	13 (26.0%)	0.82 (0.34, 1.96)	0.78 (0.33, 1.84)
Missing	15 (1.7%)	3 (20.0%)		
History of previous HIV test			p<0.001	p=0.01
No	400 (45.7%)	109 (27.3%)	1	1
Yes	476 (54.3%)	195 (41.0%)	2.10 (1.43, 3.08)	1.59 (1.10, 2.32)
Another household member tested today			p<0.001	p<0.001
No	506 (57.8%)	123 (24.3%)	1	1
Yes	370 (42.2%)	181 (48.9%)	2.71 (2.02, 3.63)	2.40 (1.71, 3.37)

This study newly diagnosed 26 household contacts with HIV in the SoC arm who were unaware of their status. The positivity rate of 8.6% among household contacts tested in this study is similar to Shapiro *et al* who reported an 11% positivity among household contacts in the North West Province who accepted HCT [57] but not as high as two other studies from the same area that reported a positivity rate of 22.7% and 16.6% respectively [42 81]. Despite the differences in HIV positivity, which may have occurred as a result of geographically differences in HIV rates within the province, the identification of these cases highlights an important strength of HHCT for TB/HIV integration as these patients usually

have less advanced HIV disease, suggesting that subsequent morbidity and mortality may be reduced by their early identification provided by HHCT [57]. The premise of the 90-90-90 HIV targets is to ensure that programmatic efforts do not stop at the point of just diagnosis, but that the 2nd 90, which aims to put 90% of those diagnosed with HIV onto treatment, is the next important step.

The linkage into HIV care for this study was relatively low with 35% of newly diagnosed HIV patients reported initiating HIV care. This proportion, although low, is consistent with previous reports for household and mobile HCT that show linkage into HIV care of 10% to 35% [168 169]. In addition, a recent systematic review, which evaluated linkage into HIV care after home-based HCT, reported a range of 14.3% to 94.9% of those newly diagnosed who initiate HIV care [170]. The assumption is that poor HIV linkage might be as a result various individual- and clinic-level factors [171]. In addition, variations in linkage into HIV care following home-based HCT could be attributed to additional interventions that might facilitate referral in these other studies compared to referral-only as was done in this study [172]. Additional interventions are required to enable and improve linkage into HIV care which potentially include the use of PoC CD4 testing, home-based ART initiation, and more alignment of community HIV services with public health facilities [55].

Generalization of findings

This study provides insight into challenges associated with the integration of TB and HIV services, specifically the poor uptake of HCT within households. TB/HIV integration in principle is meant to leverage the opportunity to screen and manage patients with these diseases however in practice, this might not be as easy to implement. These results provide a real-world view of the concept of bundling health services within households. In addition, TB and HIV programmes would benefit from these findings as they also indicate the difficulties with activities downstream of HCT such as linkage into HIV from the household. The study was conducted in two distinct populations, rural and urban, which also lends credibility to their generalization in these areas. The study also reported a significant number of household contacts who were known HIV-positive (11%) and thus not eligible for HCT. Although these household contacts reduced the number eligible for HCT, this finding in itself does highlight the relative success of HCT coverage through various other programmes in these communities.

There are however some limitations to the study that will affect its generalization. Foremost, determinates of HIV testing uptake did not include a qualitative component to provide additional granular information for willingness to test or not test, however, this was moderately overcome through using HCT information derived from previous qualitative studies among similar populations to develop the questionnaire for this study. Secondly, among those household contacts with an unknown HIV status, less than half were tested for HIV and this prohibited an HIV prevalence estimate. Despite this, the HIV positivity rate was found to be similar to a number of other HHCT studies that included HCT. Thirdly, the linkage into HIV care was determined through patient self-reporting and not among all those newly diagnosed. Other studies abstract this information from clinic files so the estimates may sometimes be more accurate assuming the patient visits the referral clinic for HIV care. Lastly, the criteria for HCT among household contacts was restricted to those ≥ 14 years old and therefore a possibility exists that additional HIV cases were missed in this younger age group; HIV prevalence in this younger group is however low, estimated at 2.4% (95% CI: 1.9-2.9%) [173].

Remaining gaps from the study

Further research is required to determine how sustained and high (>80%) HCT uptake can be achieved through its integration within HHCT. Operational research would need to address factors at the individual-level (greater understanding of HIV stigma, understanding resistance to testing among younger age groups, potential use of social media and behaviour change), at the household-level (evaluating novel strategies such as family-based HCT that consider the household as a unit, value of POC CD4 testing within the household), and lastly at a community-level (determining how community mobilization could influence the success of HHCT and specifically HIV activities within the household). Linkage into HIV care is key to unlocking the potential of home-based HCT, and determining other strategies such as home-based ART initiation [174] may improve entry to this point of the HIV cascade, fundamental to achieving success of the 90-90-90 targets.

Paper 4: Household point of care CD4 testing and IPT initiation in a household TB contact tracing programme in two districts of South Africa

Summary of key results and main discussion points

This study evaluated the effect of household POC CD4 testing on entry into HIV care nested within a routine HHCT programme. The implementation of household POC CD4 only resulted in a modest increase in linkage to HIV care. In addition, in determining the effect of household IPT provision on uptake and retention of IPT among household contacts, this study provided evidence that supported its feasibility through an improved uptake of IPT among eligible patients. There were also shortcomings in the pursuit of TB/HIV integration within the HHCT programme, namely, that by bundling too many service offerings within the household, diluted the quality and focus of these specific interventions for the teams performing the activities.

There were 98 newly diagnosed HIV patients identified across all three study arms that were evaluated for linkage into HIV care and IPT uptake: 26 in Arm 1 (SoC), 38 in Arm 2 (SoC plus PoC CD4), and 34 in Arm 3 (SoC plus PoC CD4 plus household IPT). The proportion of newly diagnosed HIV patients with at least one follow-up study visit recorded was similar in across all three arms: 88.5% (23/26) in Arm 1, 89.5% (34/38) in Arm 2, and 94.1% (32/34) in Arm 3. Linkage into HIV care, defined as participant self-report of accessing a government or private clinic for repeat HIV or CD4 testing and/or ART care regardless of visit outcome, was slightly higher in Arm 2 compared to Arm 1, 42.1% versus 30.8% respectively; this resulted in a non-statistically significant risk ratio (RR) of 1.37 (95% CI: 0.68, 2.76). In addition, the Kaplan-Meier plot, although suggesting linkage into HIV care slightly better linkage in Arm 2 compared to Arm 1, was not statistically significant for an effect (p-value=0.30) (Figure 8). The results have suggested that although implementation of PoC CD4 was feasible [175], it did not significantly affect linkage into HIV care. The premise for a PoC CD4 test has been to mitigate the need for a patient to make a return visit for such results thus avoiding pre-ART losses: one-third of patients are lost between diagnosis and receipt of CD4 results [176]. A 2014 systematic review by Wynberg *et al* suggested that although the overall likelihood of initiating ART was greater when PoC CD4 was used (OR 1.8, 95% CI 1.1–2.9), however, when the analysis was limited to those studies that reported this outcome for ART eligible individuals, there was no difference between PoC and standard of care (OR 1.0, 95% CI 0.8–

1.3) [100]. In addition, their study did report improving time to eligibility assessment for ART [100], however recent recommendation for ART eligibility [177] and policy changes in South Africa [178], which advocate for ART initiation regardless of CD4 result (Universal Test and Treat [UTT]), might make the premise for PoC CD4 testing redundant. Despite this, the use of PoC CD4 will remain important for the HIV cascade continuum in resource-limited countries [175] and will play a pivotal role in their path to ultimately establishing a UTT programme thereby achieving the 90-90-90 HIV targets.

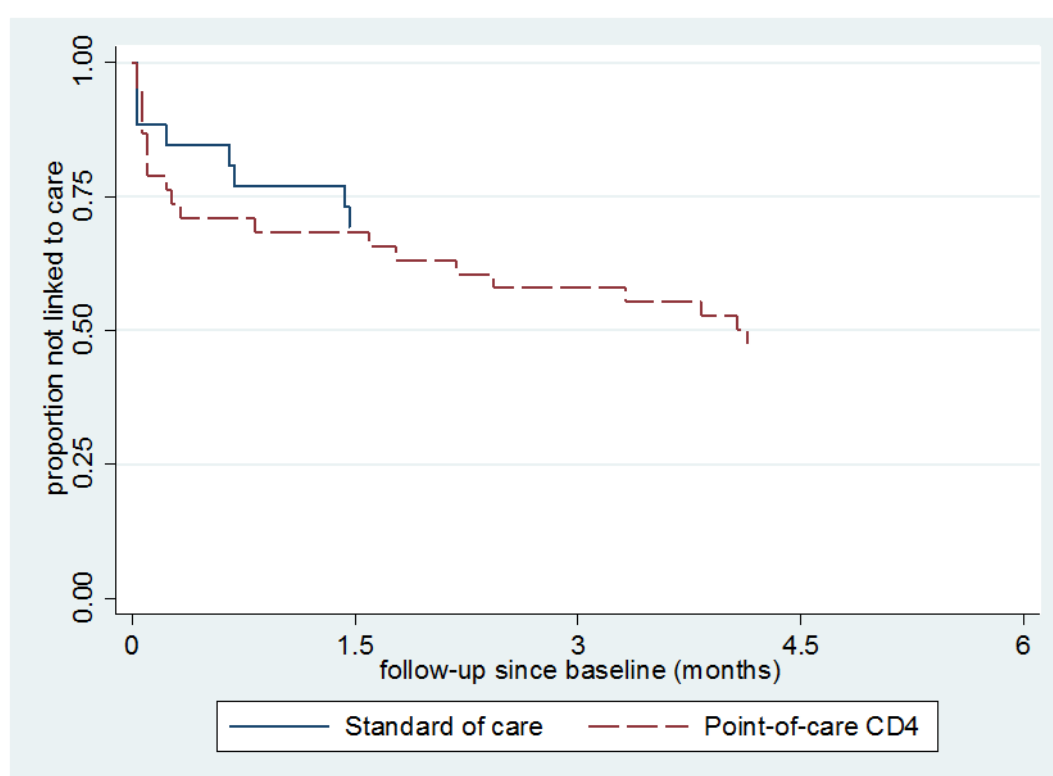


Figure 8: Kaplan-Meier plot of linkage-to-care by time since newly diagnosed HIV-positive, by study arm

Provision of household IPT was found to be feasible and resulted in increased uptake among eligible patients with no TB symptoms and $CD4 \geq 350$ cells/mm³: 15% (3/20) initiated IPT at a clinic in Arm 2 versus 95.2% (20/21) in Arm 3 who initiated IPT within the household. When compared as a risk ratio, there was strong statistical evidence for an effect on uptake through household provision of IPT with a RR of 8.20 (95% CI: 1.98, 33.95). IPT initiation at clinic level is known to be inefficiently low, varying from 18-33% [44 179-181], and this formed the rationale for such an offering to be made at a household-level. Small patient numbers reported in this study, limit a strong recommendation for household provision of

IPT, however the value of IPT should not be underestimated particularly in the context of HHCT, as its use is shown to reduce TB incidence [182]; particularly important within the framework of the End TB strategy as it forms a core entry point for TB case detection and prevention [44]. In addition, South Africa has continued its shift to UTT, and this potentially placates the value proposition for household provision of IPT, to a clinic-level offering instead.

This study utilized a routine HHCT programme to evaluate the effect of PoC CD4 on HIV linkage into care and provision of household IPT on uptake, however, its focus was also meant to identify “missed” TB cases among household contacts. The study screened 3,008 (99.9%) household contacts >14 years for TB and further investigated 439 (14.6%) who reported a symptom suggestive of TB. Among the 201 (45.8%) with a laboratory result, 15 (3.4%) had bacteriologically confirmed TB which represented an overall yield of 0.5% (95% CI: 0.3%, 0.8%) amongst those screened. This very low yield is not consistent with those reported in similar HHCT studies in South Africa, where the yield varies from 1.5% to 5.9% [35 36 81 94]. The difference in TB yield observed in this study compared to the literature might explained by the strong emphasis that was placed on “HIV service offerings” such as the PoC CD4 and household IPT, specifically because these were the primary outcomes of the study. It is conceivable that the teams conducting the HHCT de-prioritized the TB components of the programme such as TB screening, in favour of identifying contacts with HIV to be able to evaluate the primary outcomes; this resulted in sub-optimal TB screening and sputum collection. Among the 439 patients who were presented with ≥ 1 TB symptom and provided a sputum sample for TB testing, only 201 (45.8%) patient results were received; this considerable drop-off was indicative of poor fidelity. The project staff abandoned fidelity of the intervention in favour of their perceived importance for identifying HIV patients over TB activities; this undermined the value of TB/HIV integration. This has highlighted a major potential shortcoming when bundling health services in the context of HHCT i.e. increasing the expectation of TB/HIV integration within households from teams implementing HHCT, potentially dilutes the quality of services that are offered. In addition, although Arm 1 (SoC) reported a slightly higher yield of TB compared to Arms 2 and 3, there was no statistical significance to support this difference.

The findings from this study and the preceding papers underscore the importance of optimizing HHCT to be able to diagnose a significant yield of TB and impact under the auspices of one day eliminating TB. The study also illustrates how if the fidelity of the intervention is undermined, the intervention is less effective. Evidently, the complexity of HHCT as a platform for TB/HIV integration is not as simple to implement if the desired result is shifting its value from *good* to *great*. Firstly, the background TB and HIV burden contributes significantly to the likelihood of diagnosing missed TB cases among household contacts; countries with high TB and HIV burden should certainly include HHCT as part of their TB programmes as the inherent background levels of these dual epidemics places such a key population at high risk of developing TB disease but also creates competing priorities for public health programmes. The bundling of health services should consequently be evidence-based and not a “shopping-list” approach as it will likely dilute the value of the HHCT platform. Secondly, paediatric contacts remain a key population for identifying missed TB cases with their high risk of developing TB disease as contacts to index TB patients. The biggest foreseeable challenge with paediatric contacts is that the necessary diagnostic evaluations are difficult to do within a household and thus often, they are neglected or lost in the care cascade when referred for TB investigation to a local clinic; based on this PhD, this is certainly a group that should be prioritized for TB screening if we are to meet our 90-90-90 targets. Thirdly, the value of HHCT for identifying missed TB cases will only be as good as the diagnostic tool used to conduct the testing. The global adoption of the Xpert MTB/RIF assay, although addressing many of the shortcomings associated with using mycobacterial culture, might require additional evaluations as this PhD has highlighted its limited sensitivity when compared to mycobacterial culture. In addition, sufficient research and reflection should be afforded in the consideration of an improved Xpert MTB/RIF Ultra assay; specifically evaluated in populations where the possibility of lower bacillary burden might inhibit its diagnostic sensitivity, such household contacts of index TB patients.

Generalization of findings

This study is one of the largest pragmatic randomized controlled trials of HHCT and provides important insight into understanding the caveats associated with TB/HIV integration and TB contact tracing. The large numbers enrolled and high proportion followed-up (91%) allowed for robust comparison between the different study arms. Despite these strengths, there are

important considerations that may limit the generalization of these findings. Firstly, the study assumed that a higher proportion of household contacts would test for HIV and therefore identify more newly diagnosed HIV patients, who would in turn, be eligible for the PoC CD4 testing and IPT. Unfortunately many of the household contacts eligible for HIV testing already knew their status and were receiving ART. This resulted in very few household contacts subsequently evaluated in the primary outcomes and limited the power of the analysis. Secondly, the comparison of IPT uptake in Arm 2 and Arm 3 relied on different sources of information; Arm 2 was determined through self-report, while Arm 3 was documented by the study staff; this may have led to under- or over-reporting of IPT. The limitation from this potential under-reporting means that the difference in uptake of IPT between the two arms would likely have not been as strongly significant (Arm 2 could have had much more IPT initiated) and therefore diluted the possible value of household initiated IPT. Thirdly, the laboratory results were only available for less than half of those who submitted sputum for microbiological testing and this could have underestimated the yield of TB identified through HHCT. In addition, the study requested *only* a spot sputum from persons suspected of TB instead of a morning and spot sample for Xpert MTB/RIF testing, and the combination could have led to sub-optimal diagnostic sensitivity; evidence suggests that Xpert MTB/RIF has reduced sensitivity when used with pauci-bacillary sputum samples [133]. Fourthly, some of the studies included in the PhD were not conceptualized using sample size calculations and thus were not powered sufficiently for deriving statistical significant results. This implies that additional research may be needed to determine whether some of the findings hold significance or not using appropriately determined sample sizes. Finally, in South Africa, the shift to UTT, implies that the use of PoC CD4 testing and household IPT may be a moot point, as a shift is placed on ART initiation regardless of CD4 count; HHCT could however provide a platform for household-initiated ART. That being said, the value of these study findings might be important for resource-limited countries who still face challenges along the HIV continuum of care and might benefit from novel strategies like PoC CD4 testing and household IPT to potentially overcome some of these.

Remaining gaps from the study

HHCT remains an important intervention and a key contributor to realizing the End TB strategy, however, this study has evidenced some of the realities with introducing too many

offerings in the pursuit of TB/HIV integration. TB case finding should be the mainstay of HHCT and although including HIV activities is aimed at justifying the high costs associated with HHCT and its relevance to achieving TB control, the inclusion of HIV-specific activities within the household requires further research. Provision of household IPT was feasible and has the potential to be included in HHCT activities especially among HIV positive patients where it has received the strongest endorsements when used in conjunction with ART [183]; it remains an important tool in achieving TB control and household provision might ensure that it does not remain sub-optimally delivered. Other preventive therapy options on the horizon that are being evaluated include the use of weekly Rifapentine and IPT given for three months (referred to as 3HP) are already displaying better adherence and non-inferiority compared to IPT exclusively. This study has thus provided important insights into the complexity and potential for delivering TB/HIV services within the household.

6. Conclusion

This doctoral thesis sets out to determine how TB household contact tracing could be optimized in South Africa, and in the process has highlighted a number of themes for future consideration. With a specific reflection on the PhD conceptual framework the thesis has highlighted the integral nature of three components to HHCT, resources, yield and fidelity. In resource-limited settings like South Africa, the importance of evidence-based resource allocation should not be underestimated. In the context of HHCT, not identifying the correct approach to allocate resources might be the difference between an intervention making an impact or worst case, being proscribed. Effective use of resources is the over-arching paradigm that guides TB interventions in many high burden countries. Increasing the yield of TB diagnosed through HHCT by an evidence-based approach ultimately makes the use of resources more *cost-effective* and thus more likely to be adopted.

Although costing and cost effectiveness was not specifically evaluated in this PhD, the premise of these overall findings implies that through optimizing implementation of HHCT, we would be making the intervention more cost-effective. Moreover, choosing the correct diagnostic modality within HHCT is important as it will improve its cost-effectiveness i.e. using a diagnostic with optimal sensitivity will maximize identification of undiagnosed TB patients within households, ultimately improving its cost-effectiveness. South Africa is currently forging ahead with using Xpert MTB/RIF Ultra as the first-line TB diagnostic for presumptive TB patients, a performance improvement over the previous Xpert MTB/RIF cartridge, however evaluating its sensitivity in this population against MGIT culture will be important to ensure that HHCT can be cost-effective.

HHCT is inherently resource-intensive compared to passive case finding, however despite this, it is able to identify TB disease earlier in its progression thereby also mitigating transmission in the community; this is in contrast to passive case finding where patients present at health facilities usually after significant transmission has occurred. Herein lies the trade-off for various NTP's, balancing their commitment to interventions which may seem resource-intensive but may significantly impact on the TB epidemic. Impacting on the TB epidemic means identifying "missed" TB patients in the communities and importantly this cannot be done by any one intervention. HHCT will need to be included as part of a broader grouping of interventions to be able to realize the End TB strategy. Further research would

thus be required to establish the cost-effectiveness of HHCT along with other case finding interventions as a multi-pronged approach to finding the “missing” TB patients.

Household contact tracing, despite significant differences in implementation globally, is a necessary intervention for TB control programmes as it achieves high TB yields among household contacts compared to other key populations such as miners [184] or inmates [185]. Its value will be further magnified as the journey to the End TB Strategy intensifies and finding every “missed” case becomes a requisite. Specifically, countries like South Africa, with prevailing high background rates of TB and HIV will benefit from household contact tracing as within such settings, it has demonstrated high yields of undiagnosed TB and HIV. In addition, household contact tracing enables the effective reach of key populations such as paediatric contacts, an often neglected group who contribute significantly to TB burden.

The success of household contact tracing is contingent on several essential factors that will enable “missed” TB cases to be identified; 1) prioritization of all index TB patients regardless of smear status, 2) consistent execution of procedures within the household, and 3) use of a sensitive diagnostic. The high inherent costs associated with TB household contact tracing advocates for effective resource utilization, particularly in resource-limited settings like South Africa. Prioritization of index TB patients might be one approach to maximizing available resources; this thesis reported no difference in TB yield when investigating MDR-TB or DS-TB index patient households, however more research is required to categorize other factors that could enable prioritization; such an approach would improve the success of finding undiagnosed TB within the household thereby maximizing resources. An equally crucial element for optimizing household contact tracing is to ensure that regardless of the adopted procedures, the application of these should be consistently applied within the household to all contacts by well trained staff; consistent implementation translates into better TB yield. In addition, the value of household contact tracing to identify “missed” cases will only be as good as the diagnostic test used to microbiologically confirm TB cases. The introduction of the Xpert MTB/RIF assay, considered the “magic bullet” for TB control, may not be an effective test for diagnosing TB among household contacts; a lower bacillary burden found in such patients has shown to drastically reduce its sensitivity. This diagnostic limitation may systematically undermine the value household contact tracing and therefore

requires further consideration, potentially a reversion to MGIT culture testing in this population.

A fundamental benefit attributed to household contact tracing is the platform that it creates to enable integration of TB/HIV activities, a necessary step to controlling the dual epidemics. Although in principle harmonization is justified, implementation of TB/HIV activities will require more consideration and research. The findings from this thesis suggest that increasing the complexity of TB/HIV activities within the household may undermine the fidelity of the intervention; as 1) does not mean that uptake of TB and HIV services will be optimal, this was largely evident in the poor uptake of HCT within the household; and 2) often dilutes the quality of specific interventions and impedes the main premise of household contact tracing i.e. identify “missed” TB cases. HCT can and should be included as an activity within the household, however linkage into HIV care remains a significant problem that undermines its initial diagnostic value. Although use of novel approaches such as PoC CD4 testing has been shown to improve linkage into HIV care at clinic-level, when used within households has not shown to improve linkage into HIV care. However, household provision of IPT was shown to be feasible and significantly improved uptake among household contacts. Despite this, the shift in HIV care to UTT, is likely the deciding factor for what HIV services are offered within households.

The HHCT approach will require ongoing revision and re-considerations over time to adapt to prevailing resource and political climates; these considerations will ultimately drive its cost-effectiveness and subsequent fidelity. Some future considerations that need to be addressed in the South African context arise from a shift toward decentralized healthcare, commonly referred to as primary healthcare re-engineering. The emphasis on shifting health services into the communities to make them more accessible has implications for interventions such as HHCT. Specifically, it remains unclear what cadre of health staff would be responsible for delivering HHCT; more recently the idea of utilizing community health care workers has been suggested, however inherent limitations of this cadre might impede the cost-effectiveness of HHCT. In addition, there may be potential for the integration of other simpler health services at household-level such as non-communicable diseases particularly where challenges with TB/HIV integration exist; these would require further evaluating as governments shift away from vertical programmes.

The End TB strategy represents a bold direction and commitment to eradicating TB, and high burden countries like South Africa will need to adopt evidenced based interventions such as household contact tracing if they are to contribute to realizing these ambitious targets. The South African government has accepted and reflected this challenge through its NTP strategy that focuses on finding the “missing” TB cases; considerations from this thesis will ensure that household contact tracing is at the forefront of this journey.

8. References

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9. Appendices

Appendix A – Role of the student

Appendix B – Ethical clearance certificate

Appendix C – Copies of manuscripts published, submitted and in preparation as part of PhD

Appendix D – Report from “Turnitin” plagiarism software

Appendix A – Role of the student

I have been involved in various aspects of the two studies that comprise four papers in this PhD; *Inhibit-TB* and *CDC-Aurum Contact Tracing* studies; the description in my role of three papers derived from these studies are highlighted in the table below.

Study Name	Study design	Aim	Study Areas	Objectives	Student Role in studies
<i>Inhibit-TB</i>	Cluster-randomized trial	Determine the effectiveness of adding IPT and PoC CD4 testing to a TB contact tracing programme	Sekhukhune and Ekurhuleni districts	Determine uptake and factors associated with uptake of HIV testing among household contacts (Paper 3) Determine the effect of PoC CD4 on HIV entry into care and to determine the effect of household IPT provision on uptake and retention of IPT in eligible patients (Paper 4)	Research Manager for the study and was responsible for: development of main study protocol and revisions, IRB submissions, stakeholder engagement, data collection tools (eCRF's and pCRF's), management of study staff, protocol training, analysis and writing up of papers
<i>CDC-Aurum Contact Tracing</i>	Prospective cohort	Comparing the yield of active TB diagnosed among contacts of MDR- and DS-TB index patients	Multi-country; Bojanala district (SA)	Determine which screening tool or combination of tools are most effective in identify TB among adult and children household contacts (Paper 2)	Research Manager and responsible for the same activities as outlined above.

Appendix B – Ethical clearance certificate



R14/49 Mr Kavindhran Velen et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140544

NAME: Mr Kavindhran Velen et al
(Principal Investigator)

DEPARTMENT: School of Public Health
The Aurum Institute, Bojanala District, North West
Sekhukhune, Limpopo
Ekurhuleni, Gauteng Districts

PROJECT TITLE: Good to Great: Strategies to Improve the Yield of TB
of TB through Household Contact Tracing in South Africa

DATE CONSIDERED: 30/05/2014

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Dr S Charalambous

APPROVED BY:

A handwritten signature in black ink, appearing to read 'P Cleaton-Jones'.

Professor P Cleaton-Jones Chairperson, HREC (Medical)

DATE OF APPROVAL: 09/01/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and ONE COPY returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I agree to submit a yearly progress report.

A handwritten signature in black ink, appearing to read 'Kavindhran Velen'.
Principal Investigator Signature

Date 12/01/2015

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

**Appendix C – Copies of manuscripts published, submitted and in preparation
as part of PhD**

Appendix D – Report from “Turnitin” plagiarism software

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1

Liesl Page-Shipp, James J. Lewis, Kavindhran Velen, Sedikanelo Senoge et al. "Household point of care CD4 testing and isoniazid preventive therapy initiation in a household TB contact tracing programme in two districts of South Africa", PLOS ONE, 2018

Publication

2%

2

Kavindhran Velen, James J. Lewis, Salome Charalambous, Liesl Page-Shipp, Flora Popane, Gavin J. Churchyard, Christopher J. Hoffmann. "Household HIV Testing Uptake among Contacts of TB Patients in South Africa", PLOS ONE, 2016

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