

2025

# Assessing the acceptability, feasibility, and cost-effectiveness of in-home point-of-care tuberculosis testing during household contact investigations in South Africa

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BOSTON UNIVERSITY  
SCHOOL OF PUBLIC HEALTH

Dissertation

**ASSESSING THE ACCEPTABILITY, FEASIBILITY, AND COST-  
EFFECTIVENESS OF IN-HOME POINT-OF-CARE TUBERCULOSIS TESTING  
DURING HOUSEHOLD CONTACT INVESTIGATIONS IN SOUTH AFRICA**

by

**CHARL BEZUIDENHOUT**

B.COM., University of Stellenbosch, 2009  
M.COM., University of Stellenbosch, 2013

Submitted in partial fulfillment of the  
requirements for the degree of  
Doctor of Public Health

2025



Approved by

First Reader

---

Lawrence C. Long, Ph.D.  
Research Associate Professor of Global Health

Second Reader

---

Brooke Nichols Ph.D.  
Associate Professor of Global Health

Third Reader

---

Gesine Meyer-Rath, M.D., Ph.D.  
Research Associate Professor of Global Health

Fourth Reader

---

Matthew Fox, D.Sc.  
Professor of Epidemiology  
Professor of Global Health

Fifth Reader

---

Andrew Medina-Marino, Ph.D.  
Principal Investigator  
Desmond Tutu Health Foundation, South Africa  
Adjunct Associate Professor of Psychiatry  
University of Pennsylvania

## **DEDICATION**

I dedicate this work to those who continue to be missed.

## ACKNOWLEDGMENTS

This dissertation represents the culmination of years of observing, listening, learning and continued dedication to contribute, in some modicum way to advancing equitable healthcare. My continued personal and academic growth would not have been possible without the support and encouragement of many individuals and organizations.

First and foremost, I would like to express my deepest gratitude to my advisor, Dr Lawrence Long who graciously agreed to join me on this journey. His patience, dedication, and shared commitment to advancing public health created an environment of continuous learning and idea sharing. Thank you for believing in my ideas and for always challenging me to think critically and creatively. Your mentorship has been instrumental in shaping my academic and professional growth.

I would also like to extend my thanks to the members of my dissertation committee, for their insightful feedback and support. Their constructive critiques and encouragement helped refine my research and enriched my understanding of the key role that health economics and value assessment plays in public health.

I thank the Desmond Tutu Health Foundation for their willingness to collaborate on this project and the staff for their continued support. I specifically want to thank Dr Andrew Medina-Marino who has shepherded me since I started my exploration in the field of public health. I thank him for affording me the freedom to explore uncharted territories and for continuing to place his faith in me.

To the Bezuidenhout and Bresenham families, thank you for your unwavering support and love. The sacrifices you have made and the obstacles that you removed in my

way, made this achievement possible. To my wife Dana, who continues to teach me to empathize, reserve judgement, and to believe in what I do. You have been an inspiration, friend, and mentor during this journey together and I'm so proud of you.

Most importantly, I want to acknowledge all the participants and contributors to my research. Your willingness to share your experiences and insights is the foundation of this work, and I am deeply grateful.

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**CHARL BEZUIDENHOUT**

Boston University School of Public Health, 2025

Major Professor: Lawrence C. Long, Ph.D., Research Associate Professor of Global  
Health

**ABSTRACT**

**Background:** Early detection and treatment of tuberculosis (TB) are critical for reducing TB-related mortality and disease transmission. Delayed and missed diagnosis are a persistent barrier to TB control, partly driven by limitations associated with sputum collection and an unmet need for decentralized testing. The TB Home Study aimed to optimize the delivery of in-home point-of-care (POC) TB testing of household contacts of people with TB using a portable molecular testing platform, as part of household contact investigations. The acceptability, feasibility, and cost-effectiveness of in-home POC TB testing strategies are hitherto undescribed and may offer a plausible solution to persistent barriers hampering the effectiveness of community-based active case finding.

**Methods:** Cost and intermediate outcome data collected during phase 1 of the TB Home Study were used to conduct a cost- and cost-effectiveness analysis of different testing strategies implementable during household contact investigations. The cost from the provider's perspective of program implementation over a 2-year period was estimated and compared across different strategies. Decision analytic modeling was used to estimate and

compare the incremental cost-effectiveness ratio, measured as the incremental cost per additional household contact with TB disease detected and linked to a clinic for treatment, between competing testing strategies. As part of a subsequent analysis, data collected during phase 2 of the TB Home Study were used to assess the acceptability of targeted universal TB testing (TUTT) from the client's perspective. In parallel, a feasibility assessment was conducted to assess and compare different sampling and testing methods employed in the delivery of in-home TUTT.

**Results:** The total combined cost of conducting household contact investigations and TB testing to 300 households over a 2-year period ranged from \$84,962 (standard of care, *SOC*) to \$93,969 (*POC Combined Sputum and Individual Tongue Swab Testing*). The average cost-per-test was highest for testing strategies employing sputum-based testing (\$20.08). Individual tongue swab- (\$19.29) and pooled tongue swab tests (\$15.73) showed a 4% and 22% lower cost-per-test, respectively. The cost per household contact with TB detected and linked to a clinic for treatment was the least expensive (\$131.38) but also the least effective under the *SOC*. Household contact investigations employing any of the in-home POC testing strategies consistently showed higher effectiveness compared to *SOC* albeit at a higher cost per household contact. Analysis from the decision analytic modeling showed *POC Sputum Testing* and *POC Combined Sputum and Individual Tongue Swab Testing* to be the most cost-effective strategies with incremental cost-effectiveness ratios of \$543.74 and \$547.29, respectively, both below the \$2,760 willingness to pay threshold. Of 313 eligible household contacts in phase 2, 267/313 (85.3%) consented to in-home POC

TUTT. The mean in-home POC TUTT acceptability score (5=highly acceptable) was 4.5/5 (SD= 0.2). In-home POC TUTT using either sputum or tongue swab specimens was highly feasible and acceptable. Tongue swab specimens greatly increase the proportion of household contacts tested compared to sputum.

**Conclusion:** An in-home POC molecular testing strategy utilizing combined testing of tongue swabs and sputum specimens would increase program cost by 10.6%, compared to SOC, over a 2-year period. The increased sample yield from tongue swabs combined with immediate result notification following in-home POC testing would increase the number of new TB cases detected and linked to care by more than 800%. In-home POC TUTT using a combination of sputum and tongue swab specimens is acceptable and feasible and could mitigate shortcomings to existing active case finding strategies.

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## ABBREVIATIONS

|             |                                      |
|-------------|--------------------------------------|
| DALY .....  | Disability Adjusted Life Years       |
| HIV .....   | Human Immunodeficiency Virus         |
| ICER .....  | Incremental Cost Effectiveness Ratio |
| ILTFU ..... | Initial Loss to Follow Up            |
| PCR.....    | Polymerase Chain Reaction            |
| POC.....    | Point-of-Care                        |
| STI.....    | Sexually Transmitted Infections      |
| TB .....    | Tuberculosis                         |
| TUTT .....  | Targeted Universal TB Testing        |
| USD .....   | United States Dollar                 |
| WHO.....    | World Health Organization            |

## CHAPTER ONE: INTRODUCTION

### A. Problem Statement

Tuberculosis (TB) is the most common opportunistic infection and the world's leading cause of death from a single infectious agent after COVID-19.<sup>1</sup> Despite decades of concerted efforts to reduce the burden of TB, there has been a minimal decrease in global TB incidence. In 2021, an estimated 10.6 million people fell ill with TB globally, an increase of 4.5% from the 10.1 million in 2020.<sup>2</sup> The World Health Organization (WHO) developed the End TB strategy in 2014, which aims to reduce TB incidence by 90% by 2035.<sup>3</sup> Progress towards this goal has been stifled. South Africa, a member of the United Nations, is dedicated to achieving the Sustainable Development Goals aimed at ending TB as an epidemic by 2030. Through efforts driven by the Department of Health, it has committed to reducing TB cases and deaths by 80% and 90%, respectively by 2030. In alignment with the 2023–28 National Strategic Plan for Human Immunodeficiency Virus (HIV), TB, and sexually transmitted infections (STI), the National TB program emphasizes investment in new evidence-based interventions to address gaps along the TB care cascade, especially among populations at highest risk.<sup>4</sup>

Early detection and treatment of TB are critical for reducing TB-related mortality and disease transmission. Delayed and missed TB diagnosis remain pervasive in high-burden settings.<sup>5</sup> Undiagnosed (missed) TB cases lead to missed treatment initiation, prolonging the infectious period and contributing to higher rates of transmission.<sup>6</sup> The burden placed on individuals to present at local clinics for molecular TB testing remains a major barrier

and contributes to delayed presentation and diagnosis.<sup>7</sup> To bridge this gap, existing TB programs need to consider alternative diagnostic strategies including the integration of rapid molecular diagnostic platforms that can be delivered at the point-of-care (POC).<sup>8</sup> There is an urgent need to identify and assess strategies focused on integrating novel POC diagnostic platforms into routine care.

### **B. Specific Aims**

To achieve the aims of this dissertation, primary data were collected during the implementation of the TB Home Study. The primary aims of this dissertation are:

1. To estimate the cost and to compare the cost-effectiveness of different in-home POC testing strategies measured as the incremental cost per additional household contact with TB detected and linked to a clinic for treatment.
2. To assess the acceptability and feasibility of delivering in-home targeted universal POC TB testing during household contact investigation strategies.

### **C. Study Setting**

The Eastern Cape is one of nine provinces in South Africa, with a population of 7.2 million people.<sup>9</sup> It has the highest TB incidence among all nine provinces, with an estimated 692 cases per 100,000 people, far higher than the national average (520).<sup>10</sup> The TB Home Study was implemented in the Buffalo City Metropolitan Health District, Eastern Cape Province. The metro has a population size of approximately 893,000 of which the majority (86.7%) are Black, an estimated 58.2% of people live in poverty, and 31.1% remain unemployed.<sup>11</sup>

Buffalo City Metropolitan has 113 health care facilities which include 82 clinics, 7 community health centers, 6 hospitals, and 18 mobile clinics.<sup>11</sup> The majority of clinics are concentrated in urban areas, due to rural-urban migration driven by employment opportunities. This influx has led to overburdened facilities, which negatively affects the accessibility of healthcare services. In Buffalo City Metropolitan, TB is the leading cause of death (18.4%) amongst the 25–64 age group.<sup>11</sup>

#### **D. This Research and its Contribution to the Field**

The goal of this dissertation is to assess novel POC TB testing strategies aimed at improving early TB case detection that improve effective linkage to treatment in high-burden, low-resourced settings like Buffalo City Metropolitan. To achieve this, data collected during the TB Home Study are used to assess and compare the cost-effectiveness of five novel in-home POC TB testing strategies against the standard-of-care, when implemented as part of household contact investigations. Further analyses are executed to assess the acceptability and feasibility of delivering such strategies. Acceptability is measured from the perspective of the client while feasibility is measured as the relative success to which such strategies can be implemented by a provider during household contact investigations.

WHO's End TB Strategy report of 2022 highlighted the importance of increased research and innovation, increasing access to services, and the delivery of rapid diagnostic testing to improve service delivery. This research aims to assess and compare novel strategies aimed at delivering in-home POC TB testing to promote early case detection and

improve linkage to treatment in line with South African National TB Program goals.

A basket of new testing strategies, accompanied by an economic evaluation of the cost and effectiveness of combination testing strategies, equips South African policy- and decision makers with the necessary resources to make informed healthcare policy decisions. Findings from this research can be used to guide the development of TB program initiatives that align with South African national strategic priorities while fitting within stringent resource plans and budgets.

The dissertation provides several products intended for use by a range of stakeholders in both academic and practice settings, summarized as the following deliverables:

1. An adapted measure of acceptability that can be used to assess the acceptability of novel healthcare diagnostics and healthcare programs from the perspective of the person seeking care.
2. A manuscript to submit to a peer review journal that summarizes the findings of the comparative cost-effectiveness analysis of different in-home POC TB testing strategies.
3. A manuscript to submit to a peer review journal that summarizes the findings of the acceptability and feasibility assessment of conducting in-home universal POC TB testing as part of household contact investigations.

### **E. Overview of Dissertation Chapters**

Chapter 2 provides an overview of the current state of TB, focusing on the global burden of the disease as well as the burden in South Africa. It offers a detailed comparison of the two primary TB case detection strategies—passive and active case finding—highlighting challenges related to delayed diagnosis and treatment initiation, particularly in resource-limited settings. The chapter further explores advances in POC molecular testing, which aim to enhance early case detection and reduce initial loss to follow-up.

Chapter 3 contains a description of the dissertation research aims and the methodology used to investigate them.

Chapter 4 presents the results of dissertation aim one: Estimating the cost and comparing the cost-effectiveness of different in-home POC testing strategies measured as the cost of detecting a new TB case and linking them to treatment.

Chapter 5 presents the results of dissertation aim two: Assessing the acceptability and feasibility of delivering in-home POC universal TB testing during household contact investigations.

Chapter 6 provides a summary of the findings and provides recommendations for public health practice based on the findings from this research.

## **CHAPTER TWO: LITERATURE REVIEW**

### **A. Chapter Overview**

This chapter offers a comprehensive overview of the TB burden, global targets for reducing TB incidence and related mortality, and the ongoing barriers impeding progress. It details and compares passive and active case-finding strategies for TB detection and linkage to treatment. The chapter concludes by highlighting the need for innovative strategies that incorporate molecular POC TB testing platforms into active case-finding approaches to enhance access to testing and improve treatment uptake.

### **B. Tuberculosis Globally**

TB is the most common opportunistic infection and the leading cause of death from a single infectious agent after COVID-19.<sup>1</sup> In 2021, an estimated 10.6 million people fell ill with TB globally, an increase of 4.5% from the 10.1 million in 2020. The TB incidence rate rose by 3.6% between 2020 to 2021, reversing declines of about 2% per year for most of the previous two decades.<sup>2</sup> Similar trends are observed in the burden of drug-resistant TB which increased by 3%, with 450,000 incident cases of rifampicin resistant TB over the same period.<sup>12</sup> These figures point to the devastating impact the COVID-19 pandemic had on key TB program indicators including a 15% reduction in people treated for drug-resistant TB, 21% decrease in preventive treatment delivery, and a 5% decrease in allocated TB programmatic funding.<sup>13</sup>

### **C. Tuberculosis in South Africa**

South Africa is among WHO's list of 30 high-burden TB countries who in 2020 collectively contributed to 86% of the estimated incident cases worldwide.<sup>14,15</sup> The South African National Tuberculosis Program has long been active in responding to the country's TB burden. The National TB Program sits within the National Strategic Plan for HIV, TB, and STIs, 2023–2028 and has been developed to align with broader international and national strategies (i.e., WHO's End TB Strategy, United Nations Sustainable Development Goals, and Stop TB Partnership's Global Plan to End TB).<sup>16</sup> The National strategic Plan provides a broad agenda for government, parastatal, non-governmental, funding, and implementation agencies with the aim of eliminating HIV, TB, and STIs as public health threats by 2030, by adopting innovative strategies to provide equitable access to care. As an example, South Africa was among the first countries to adopt and implement rapid molecular diagnosis with Xpert MTB/RIF assay technology.<sup>17</sup> Despite this, South Africa still has the world's highest TB incidence and HIV-TB co-epidemic (~60% HIV co-infected).<sup>18</sup>

The South African 2018 National TB Prevalence Survey, one of the first to use TB prevalence surveys and parallel testing with Xpert MTB/RIF Ultra and mycobacterial culture (the current gold standard), yielded some alarming findings.<sup>15</sup> The survey confirmed that TB remains rampant with an estimated prevalence of 852 (95% CI: 679–1,026) cases per 100,000 population, substantially higher than the WHO 2018 estimate (567 per 100,000).<sup>19</sup> The estimated prevalence among those with HIV is 1,743 (95% CI 1,219–2,249) per 100,000 population, almost double the prevalence amongst HIV-negative

cases.<sup>12</sup> A key takeaway from the prevalence survey findings was the need for targeted case detection strategies aimed at reducing the prevalence-to-notification gap.<sup>20</sup>

#### **D. Tuberculosis Case Detection**

##### **Passive case finding**

Currently two main TB case detection approaches are adopted in South Africa: passive and active. Passive case finding approaches place emphasis on strengthening the delivery of primary health care level TB screening and molecular testing of sputum specimens. TB screening protocols used at a primary health care level comply with the South African National Tuberculosis Management Guidelines which is derived from WHO's TB guidelines.<sup>21</sup> Individuals self-presenting at a primary health care clinic are screened for TB symptoms with sputum samples collected for testing following a positive screening result.<sup>22</sup> The Xpert MTB/RIF polymerase chain reaction assay (Cepheid, California, United States) is used routinely for TB diagnosis using client sputum. Test results, which determine the therapeutic intervention and management in line with the diagnostic algorithm, are returned within two days.<sup>23</sup>

Despite improved time to diagnosis and treatment, the introduction of Xpert MTB/RIF in primary health care does not reduce TB-related mortality at 6 months, when compared with routine diagnostic smear microscopy.<sup>24,25</sup> This could be due to several factors. Despite being less resource intensive, passive case finding heavily relies on individuals recognizing their symptoms and seeking care, resulting in significant delays in diagnosis and treatment initiation.<sup>26</sup> Additionally, due to the long turnaround time for

sputum results, clients are required to return to the clinic for result notification 48 hours later. The inability to provide same-day diagnosis results in high levels of pre-treatment, initial loss to follow-up which has been shown to contribute to TB deaths.<sup>27,28</sup> In low-and middle-income countries with a high TB burden an estimated 4–38% of people with a confirmed TB diagnosis never initiate treatment.<sup>29</sup> In South Africa, 66% of people don't return to a primary health care clinic within 48 hours of sputum collection and 32% never return.<sup>30</sup> Reducing the number of people lost along the cascade of care, requires strategies that expand access to services and delivers rapid POC testing and result notification in a single client encounter.

Passive case finding strategies still remain the dominant approach in South Africa. The South African National Tuberculosis Program has been criticized for placing too much emphasis on treatment success rates to the detriment of upstream indicators including, screening and referral, case detection, linkage-to-care, and treatment initiation, none of which are reflected in the current treatment success indicators.<sup>31</sup> The adverse repercussions of this approach were powerfully evident following an analysis of the South African TB Cascade which estimated that a mere 53% of suspected cases successfully completed treatment. Cases were being lost at each step in the care cascade: 5% at test access, 13% at diagnosis, 12% at treatment initiation, and 17% prior to successful treatment completion.<sup>32</sup> Finding the '**missing cases**' is crucial for effective TB control, as these individuals may act as reservoirs for the transmission of both drug-sensitive and drug-resistant strains of *Mycobacterium tuberculosis*.<sup>33</sup>

### **Active case finding**

Active case finding is a proactive approach to controlling TB whereby community health workers systematically search for undiagnosed TB cases within specific populations or communities, thereby reducing the time of infectiousness and potential for disease transmission.<sup>34</sup> Three traditional approaches to active case finding are adopted in South Africa and include: 1) targeted case-finding aimed at high-risk populations or settings, 2) untargeted community-wide case-finding, and 3) spatially targeted case-finding. Untargeted community-wide active case finding strategies have yielded mixed results. The DETECTTB study screened over 100,000 people using mobile vans and door-to-door visits and reduced disease prevalence from 6.5 to 3.7 per 1,000 individuals.<sup>35</sup> In contrast, the ZAMSTAR study, conducted active case finding among approximately 45,000 people but did not demonstrate any population-wide benefit on TB prevalence.<sup>36</sup> There is insufficient evidence supporting the effectiveness of untargeted community-wide active case finding approaches, which are resource-intensive and inefficient for routine use.

Targeted case-finding aimed at high-risk populations including household contacts of known TB cases has proven to be an effective strategy for detecting undiagnosed cases.<sup>37</sup> Household contact investigation of confirmed TB index cases has become one of the most prominent and effective active case finding strategies in high-burden settings and has been endorsed by WHO since 2014.<sup>38</sup> Household contact investigation entails in-home TB screening of all known household contacts of people with confirmed TB by community health workers. Screening is done using the WHO-recommended four-symptom screener.<sup>39</sup> Household contacts who screen positive are referred to a primary health care clinic where

sputum is collected for testing. Household contacts are subsequently requested to return to the clinic for result notification and if needed, treatment initiation. The relative success of this approach is due to the high prevalence of TB among contacts, reported to be as high as 7.8% (95% CI, 5.6%–10.0%).<sup>40</sup> Despite the potential for increased case detection, low uptake of community-to-clinic referrals, delayed test turnaround time, and overburdened healthcare facilities remain significant shortcomings limiting the effectiveness of household contact investigations.<sup>41,42</sup>

### **E. Integrating POC Molecular Platforms into Active Case Finding**

Active case finding strategies using mobile vans equipped with POC molecular platforms like GeneXpert (Cepheid, Sunnyvale, CA, USA) have demonstrated feasibility, improved access to diagnostics, and may improve case detection and same-day linkage to treatment.<sup>43–45</sup> The GeneXpert® System is a molecular platform that can run cartridge-based, automated PCR tests for multiple diseases, including TB, and is WHO-endorsed.<sup>46</sup> Notably, these approaches are personnel intensive and use high-cost, non-scalable equipment that could result in costs that are three times more expensive than conventional laboratory testing.<sup>23,47</sup> Noting these shortcomings, WHO has highlighted the importance of increased research and innovation geared towards increasing access to TB services, in particular, increasing the delivery of rapid diagnostic testing that reduces turnaround times and improves service delivery.<sup>2</sup>

Heeding the call for innovation, Cepheid announced the development of a new portable diagnostic device, GeneXpert-Edge (Xpert-Edge; Cepheid, Sunnyvale, CA,

USA). The Xpert-Edge is a portable, smartphone-controlled molecular diagnostic system that performs POC, sample-to-answer PCR testing using Cepheid's existing cartridges. With 12-hours battery life, the device holds promise for integration into active case finding for both HIV and TB.<sup>48</sup> For the first time TB diagnosis could be delivered closer to a client's home, reducing the complexity of tedious service delivery pathways and long diagnostic delays.<sup>49</sup>

Preliminary findings from the AmazonEdge project, a 2-year prospective study delivering POC testing on a boat in Brazil using the Xpert-Edge platform, found it to be highly acceptable and feasible for use during active case finding and accessing hard-to-reach populations.<sup>48</sup> Similarly, a study done in South Africa explored the acceptability and feasibility of implementing in-home POC sputum testing using the Xpert-Edge as part of household contact investigation. In-home POC testing was found to be acceptable and feasible.<sup>50</sup> Furthermore, the delivery of rapid in-home POC testing followed by immediate result notification improved the proportion of household contacts tested and reduced the time to clinic presentation compared to those referred for clinic-based testing.<sup>51</sup> Despite this relative success, the reliance on sputum expectoration for testing in addition to the high cost of test cartridges were highlighted as major barriers to scale up.

The collection of sputum has consistently been reported as a barrier to testing, especially for children, people living with HIV, and individuals with early stage TB disease, all of which constitute factors hindering bacteriological confirmation of TB.<sup>49,52</sup> Similar to concerns related to asymptomatic or pre-asymptomatic cases being missed with symptomatic screening, is the concern of individuals who screen positive but are unable to

expectorate sputum, resulting in missed cases.<sup>53</sup> Early diagnosis of individuals presenting with limited symptoms could prevent disease progression, subsequent morbidity, and mortality as well as reduce up to 50% of transmission.<sup>54</sup> In reaction to this, WHO highlighted the importance of developing rapid, accurate, non-invasive, and sputum-free tests for triaging and confirmatory diagnosis.<sup>55</sup>

#### **F. Reimagining Point-of-Care Molecular Testing for Tuberculosis**

In the search for an easier, less invasive, and more effective sampling method for TB testing a variety of alternatives have been assessed, including saliva, urine, blood, and exhaled breath concentrate.<sup>56,57</sup> However efforts have been futile with alternative sample types showing lower sensitivity and/or specificity compared to sputum.<sup>58</sup> Oral swabs have been proposed as an alternative sample type offering a potential non-invasive, easy to collect solution.<sup>59,60</sup> Tongue swabbing has been shown to yield significantly stronger signals compared to cheek or gum swabbing. Furthermore, the use of two tongue swabs per client exhibited a combined sensitivity of 92.8%, relative to sputum GeneXpert while the diagnostic yield was identical to laboratory-diagnosed TB. Specificity of tongue swabs were 91.5%.<sup>58</sup> Findings among children however have been less promising. Using Xpert MTB/RIF Ultra, oral swabs showed 22% sensitivity and 100% specificity when compared to sputum samples among children.<sup>61</sup> Further limitations include the accuracy of tongue swab testing in people with smear-negative TB (low bacterial concentration in sputum) and its capability to detect drug resistance, as is possible with sputum samples.<sup>62</sup>

Continued innovation and refinement of optimal sample collection and processing

protocols could establish tongue swab-based TB testing as a viable alternative to sputum-based methods, potentially enhancing sample yield and testing.<sup>60</sup> The cost of test cartridges however remains a barrier. Despite a 40% reduction in GeneXpert cartridge cost in 2012, it still exceeds costs associated with smear microscopy.<sup>63</sup> A study done in Uganda found the cost associated with GeneXpert cartridges to account for up to 70% of the total cost of active case finding (compared to 26% for human resources).<sup>64</sup>

With many low-resource settings heavily dependent on donor funding for TB programs, cost remains an important consideration. Pooled sputum testing has been introduced to decrease test costs. Pooled testing of 3–4 sputum samples using Xpert-Ultra has previously been shown to detect 100% of individual positive results and save up to 35% of cost.<sup>65</sup> Similar cost-saving methods could be considered for tongue swab-based testing. Combined, the collection of tongue swabs to increase sample collection yield and the pooling of samples to decrease cost, could improve scalability of in-home POC testing during household contact investigations.

To stop the global epidemic of TB and decrease the number of missed TB cases, The Global Plan to Stop TB stresses key strategies, including: 1) the development of rapid and affordable non-sputum-based tests for diagnosis or triage; 2) operational and implementation science research into strengthening and scaling up active TB case finding, especially among contacts and high risk groups; and 3) rapid uptake of new interventions and strategies.<sup>66</sup> Towards these goals, this dissertation uses data collected as part of the TB Home Study to conduct a cost analysis of household contact investigations from the provider perspective. In addition, study findings are used to formulate five novel in-home

POC testing strategies. Using decision analytic modeling of different diagnostic pathways, we analyze and compare the cost-effectiveness of different testing strategies implementable as part of household contact investigation. In addition, we assess the acceptability of in-home POC universal TB testing while evaluating the feasibility of using different sample types for testing.

### **G. Use of the Medical Research Council Framework to Optimize In-Home POC TB Testing**

The TB Home Study is part of an ongoing partnership between FIND and the Desmond Tutu Health Foundation to optimize in-home, POC TB testing during household contact investigations. In the initial proof-of-concept study, conducted in 2018, a GeneXpert 1 (Cepheid, Sunnyvale, CA, USA) platform was used for piloting in-home TB testing.<sup>50</sup> Because the GeneXpert 1 was not a true “portable” platform it required additional machine re-engineering to enable the delivery of in-home TB testing, limiting its scalability as an evidence-based intervention. Additional barriers to scalability included the collection of sputum, and the high cost of Xpert-Ultra cartridges. To this end, the TB Home Study aimed to use less invasive tongue swabs to increase sample collection yield combined with pooled testing of multiple swabs to reduce testing cost. The ultimate aim of these preliminary studies is to develop and refine different in-home POC testing strategies to be tested in a formal randomized control trial.

The gold standard method for assessing the effectiveness of healthcare interventions is a randomized control trial.<sup>67</sup> A trial’s ability to standardize conditions, exert control over extraneous factors, and reduce bias is seen as the embodiment of sound

research.<sup>68</sup> It is however the rigorous standardization of interventions that has received criticism for limiting the generalizability of findings across different contexts.<sup>69</sup> These limitations become particularly acute when evaluating complex interventions like in-home TB testing during household contact investigations. Intervention complexity is largely determined by the properties of the intervention itself, including the number of components involved, range of behaviors targeted, level of expertise required to deliver the intervention, and the complexity of the setting in which implementation takes place.<sup>70</sup>

The Medical Research Council Framework has been developed in response to the complexity of developing and evaluating complex interventions in a randomized control trial.<sup>70,71</sup> The framework divides complex intervention design into four, not necessarily sequential, phases: Phase 1) development or identification of the intervention, Phase 2) assessment of feasibility, Phase 3) evaluation, and Phase 4) implementation (Figure 2.1).<sup>70,72</sup> A researcher might begin at any phase, depending on the nature and level of uncertainty about the intended intervention. A set of core elements are considered during each phase of intervention refinement.

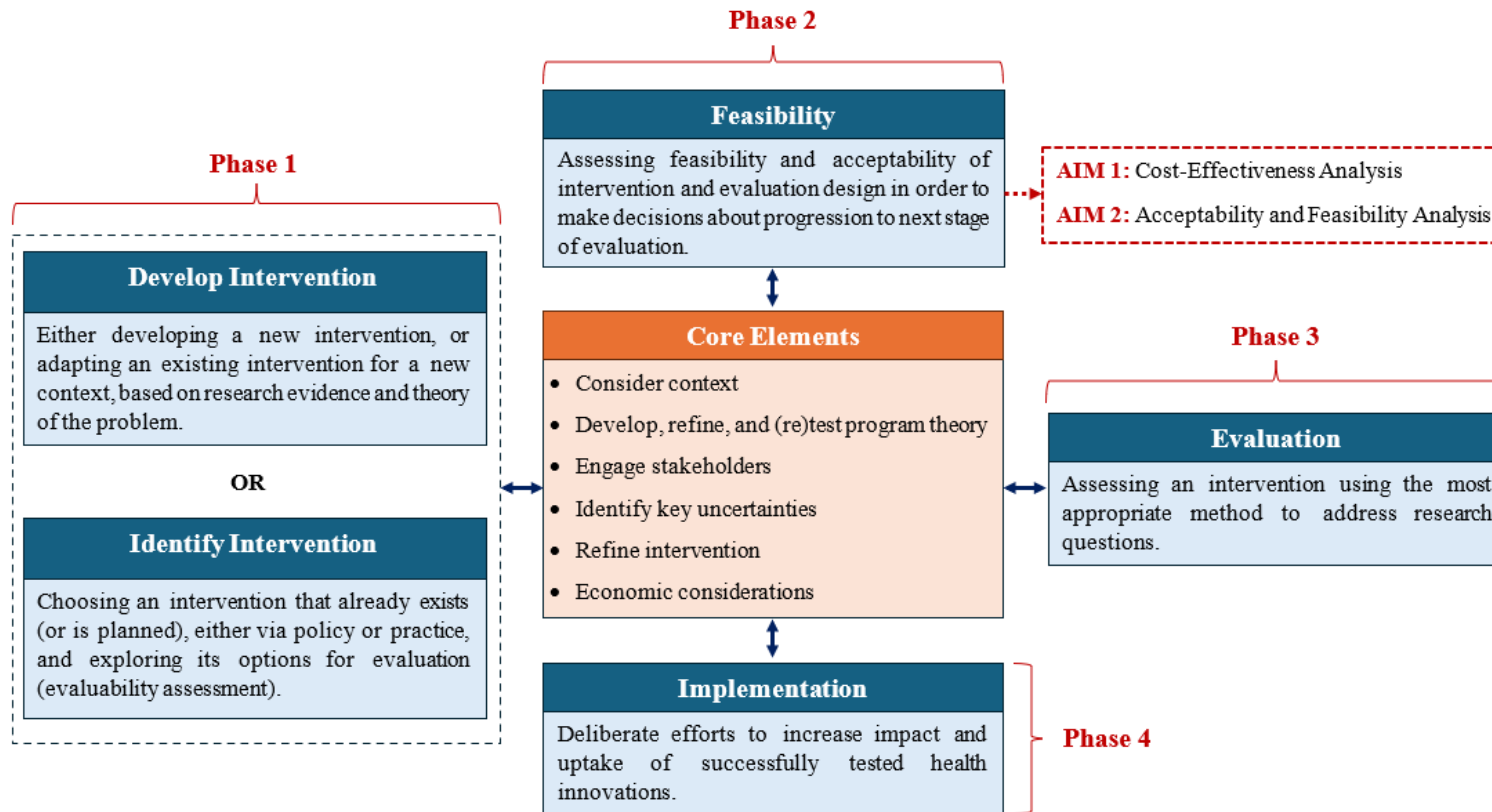
Phase 1 spans the whole process of designing and planning an intervention, from initial conception through to a feasibility, pilot, or evaluation study. In phase 2, aspects related to the design i.e. optimal delivery, acceptability, adherence, and likelihood of cost effectiveness of an intervention are assessed. Evaluation (phase 3) involves going beyond asking whether an intervention works (in the sense of achieving its intended outcome), to a broader range of questions including: a) identifying what other impact it has, b) theorizing how it works, c) taking account of how it interacts with the context in which it is

implemented, or d) how the evidence can be used to support decision-making in the real world.<sup>70,73,74</sup>

Several study designs could be considered during the evaluation phase. Alternatives to standard randomized control trials include, adaptive designs, SMART trials (sequential multiple assignment randomized trials), or hybrid effectiveness-implementation designs to improve the efficiency of complex intervention research.<sup>75</sup> Considerations for implementation (phase 4) across each of the aforementioned phases increases the likelihood of developing an intervention that can be widely adopted and maintained in real world settings.

Preliminary work done by Dr Medina-Marino and his team between 2018 and 2020 satisfies the first two phases of the Medical Research Council Framework. During phase 1 key opinion leaders, local clinical staff, and researchers were consulted to inform the initial intervention components underpinning in-home POC TB testing during household contact investigations. These components formed the basis of the initial proof-of-concept study.<sup>51</sup> Both qualitative and quantitative methods were then used to evaluate and refine intervention components to be used in the TB Home Study.<sup>50</sup> Continuing with this schema, this dissertational work includes additional analyses under phase 2 (Figure 2.1), using data collected during the implementation of the TB Home Study as it seeks to assess the acceptability, feasibility, and potential cost-effectiveness of different in-home POC testing strategies. Findings from this additional phase 2 work will be used to select and compare different in-home POC TB testing strategies, to be compared in a formal randomized control trial (phase 3).

**Figure 2.1 Adapted Medical Research Council Framework**



Framework for developing and evaluating complex interventions. **Context:** any feature of the circumstances in which an intervention is conceived, developed, evaluated, and implemented; **Program theory:** describes how an intervention is expected to lead to its effects and under what conditions—the program theory should be tested and refined at all stages and used to guide the identification of uncertainties and research questions; **Stakeholders:** those who are targeted by the intervention or policy, involved in its development or delivery, or more broadly those whose personal or professional interests are affected (that is, who have a stake in the topic)—this includes patients and members of the public as well as those linked in a professional capacity; **Uncertainties:** identifying the key uncertainties that exist, given what is already known and what the program theory, research team, and stakeholders identify as being most important to discover—these judgments inform the framing of research questions, which in turn govern the choice of research perspective; **Refinement:** the process of fine tuning or making changes to the intervention. once a preliminary version (prototype) has been developed; **Economic considerations:** determining the comparative resource and outcome consequences of the interventions for those people and organizations affected.

## **CHAPTER THREE: RESEARCH DESIGN AND METHODOLOGY**

### **A. Chapter Overview**

As described in Chapter 2, the Medical Research Council Framework (Figure 2.1) is used to guide the evaluation of the TB Home Study to identify and evaluate intervention components that can be included in a randomized control trial aimed at testing strategies to optimize in-home POC TB testing during household contact investigations. This chapter presents a comprehensive overview of the TB Home Study, describing the eligibility of study participants, study procedures, and sample collection and testing protocols. It outlines the research questions of this dissertation, provides a thorough discussion of the rationale for each of the dissertation aims, its corresponding data collection methods, and analysis plan. The chapter concludes with a summary of limitations to the current research.

### **B. The TB Home Study**

#### **Overview**

The TB Home Study was part of an ongoing collaboration between FIND and The Desmond Tutu Health Foundation to identify and adopt optimal evidence-based strategies focused on the integration of the Xpert-Edge platform into existing active case finding TB strategies. Sputum collection is a major barrier to the delivery of in-home TB testing of contacts of people with TB.<sup>51</sup> In addition to the difficulty collecting sputum, the health risk posed to health care workers collecting sputum inside the household is also a major concern.<sup>22,76</sup>

To address these concerns, the TB Home Study aimed to use the Xpert-Edge platform to conduct post-laboratory field validation of pooled tongue swab specimens (vs. sputum) as a triage test to detect TB among household contacts of people with TB during household contact investigation. Using primary data collected during the TB Home Study, this dissertational work aimed to achieve the following objectives and activities:

**Objective 1:** To estimate the costs and compare the cost-effectiveness of different in-home POC testing strategies, measured as the incremental cost per additional household contact with TB disease detected and linked to a clinic for treatment.

- *Activity 1:* Conduct a cost analysis to estimate the cost of different in-home POC testing strategies for TB, from the provider's perspective.
- *Activity 2:* Build a decision analytic model to compare the cost-effectiveness of different in-home POC testing strategies. Strategies are compared using incremental cost effectiveness ratios measured as the incremental cost of one new person with TB detected and presenting at a clinic for TB treatment initiation.

**Objective 2:** Assess the acceptability and feasibility of delivering in-home POC universal TB testing during household contact investigations.

- *Activity 1:* Evaluate the acceptability of delivering in-home POC universal TB testing during household contact investigations, measured from the perspective of the client.
- *Activity 2:* Use a feasibility framework to assess and compare the feasibility of different sample testing methods when delivering in-home POC universal TB testing during household contact investigations.

### **Study setting**

The study was conducted in the Buffalo City Metropolitan, Eastern Cape Province, South Africa. In 2014 (the last year for which data are assessable), Buffalo City Metropolitan had a rifampicin resistance rate of 8.6%. Based on national, provincial, and district-level estimates for the number of “missing” TB cases, in 2018 the South African National Department of Health identified Buffalo City Metropolitan as one of 20 national priority districts for intensified TB case finding in its “Strategy for Finding the Missing TB Cases.”<sup>77</sup> In 2019, TB incidence there based on bacterially confirmed TB cases was 831/100,000, one of the highest in South Africa.<sup>78</sup>

### **Eligibility criteria**

The TB Home Study employed a prospective observational cohort design. The two main cadres of study participants and their corresponding eligibility criteria are summarized below:

#### **Individuals with active TB:**

*Eligibility:* 1) receiving care and treatment from a collaborating health facility; 2) diagnosed with pulmonary TB; 3) live in Buffalo City Metropolitan; 4) live in a home with other household members; 5) willing to provide written informed consent; 6) agreeing to the collection and storage of tongue swab and sputum specimens.

#### **Household contacts:**

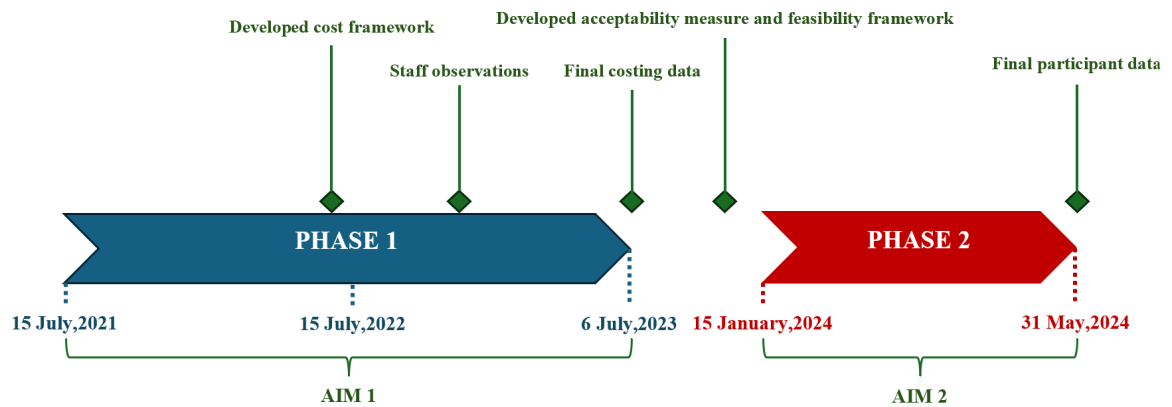
*Eligibility:* 1) household member of a person with confirmed TB; 2) 18 years old or older; 3) not currently on TB treatment; 4) live in Buffalo City Metropolitan; 5) provided written

informed consent; 6) agreed to the collection and storage of tongue swab and sputum specimens.

### **Study duration**

The TB Home Study was conducted in two phases of data collection (Figure 3.1). Phase 1 data collection stretched from 15 July 2021 to 6 July 2023. Data collected during phase 1 of the TB Home Study were used to achieve Aim 1 of this dissertation. Phase 2 of the TB Home Study was conducted between 15 January 2024 and 31 May 2024. Data collected during phase 2 of the TB Home Study were used to achieve the outcomes of Aim 2 of this dissertation.

**Figure 3.1. TB Home Study and Dissertation Activity Timeline**



**Study procedures**

A household contact investigation was conducted for each participating person with confirmed existing TB. Contact tracing teams consisting of three lay community health workers made up to three attempts to reach all the household members. During each investigation, household contacts were screened for study eligibility and invited to participate in the research. Once consented, a community health worker collected two tongue swab samples and one sputum sample from each participant. For participants unable to expectorate sputum, sputum induction using a nebulizer was offered. Household contacts unable to provide a sputum sample for in-home testing were referred to a clinic for further clinical evaluation.

One tongue swab from each household contact present at the time of the investigation was pooled for immediate in-home testing using the Xpert-Edge platform. The second tongue swab was prepared, packaged, and sent for centralized laboratory testing. The sputum sample from each participant was also tested immediately at the home using the Xpert-Edge platform. Both the pooled tongue swabs and individual sputum samples were all tested using Xpert-Ultra. Participants with a positive sputum test result were referred to the nearest clinic for treatment while those with a negative result were referred for further clinical evaluation. Study staff at clinics extracted participant record data related to clinic presentation and clinical evaluation outcome.

The average runtime of a sample on the Xpert-Edge platform is 90 minutes. Contact tracing teams were equipped with up to three machines to enable simultaneously testing of multiple samples. While samples were tested, community health workers administered a

series of questionnaires that were preloaded onto REDCap. Figure 3.2 provides a graphical summary of the study flow while Figure 4.3 provides a summary of the data collection activities.

**Figure 3.2. TB Home Study Flow**

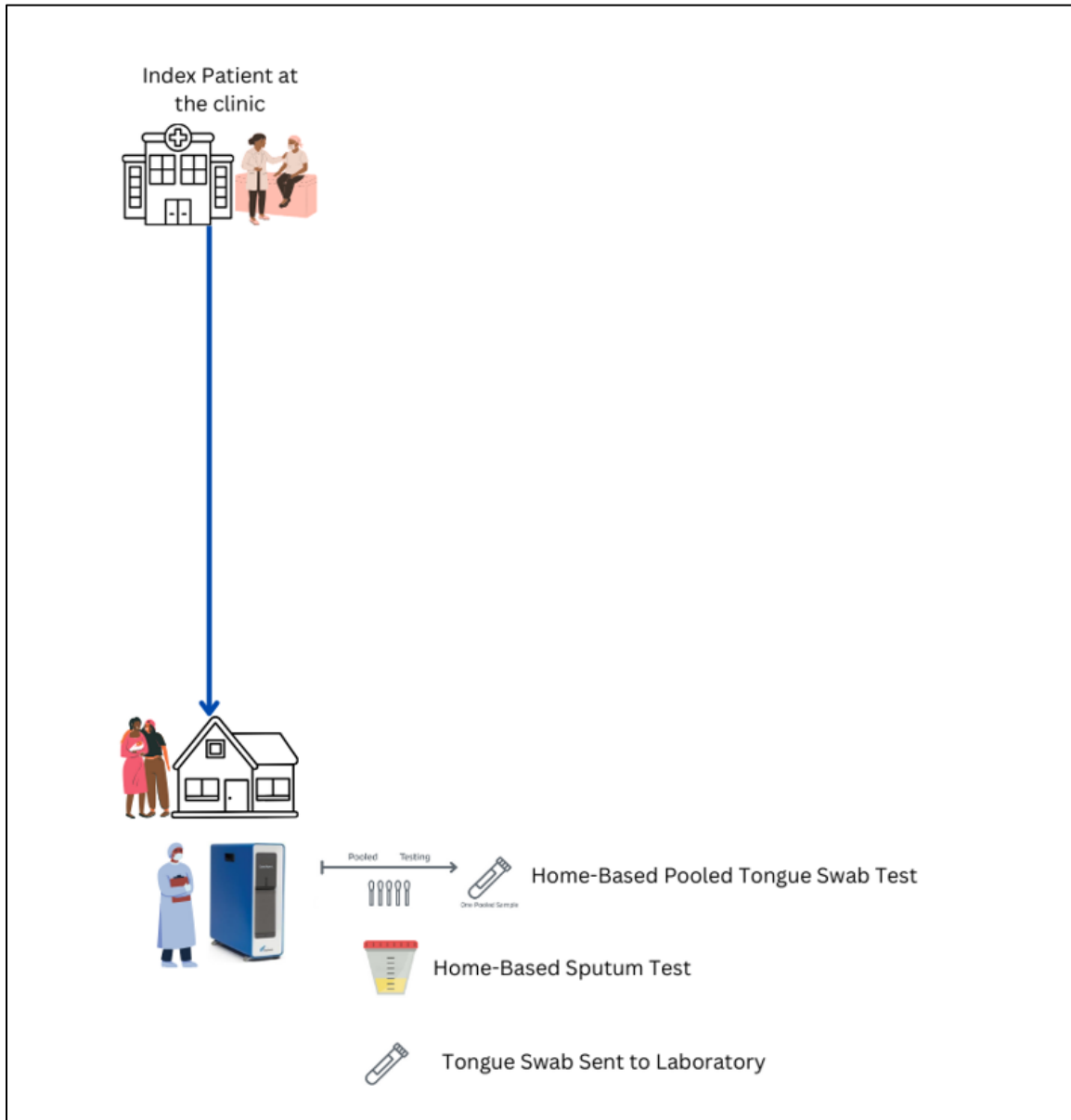
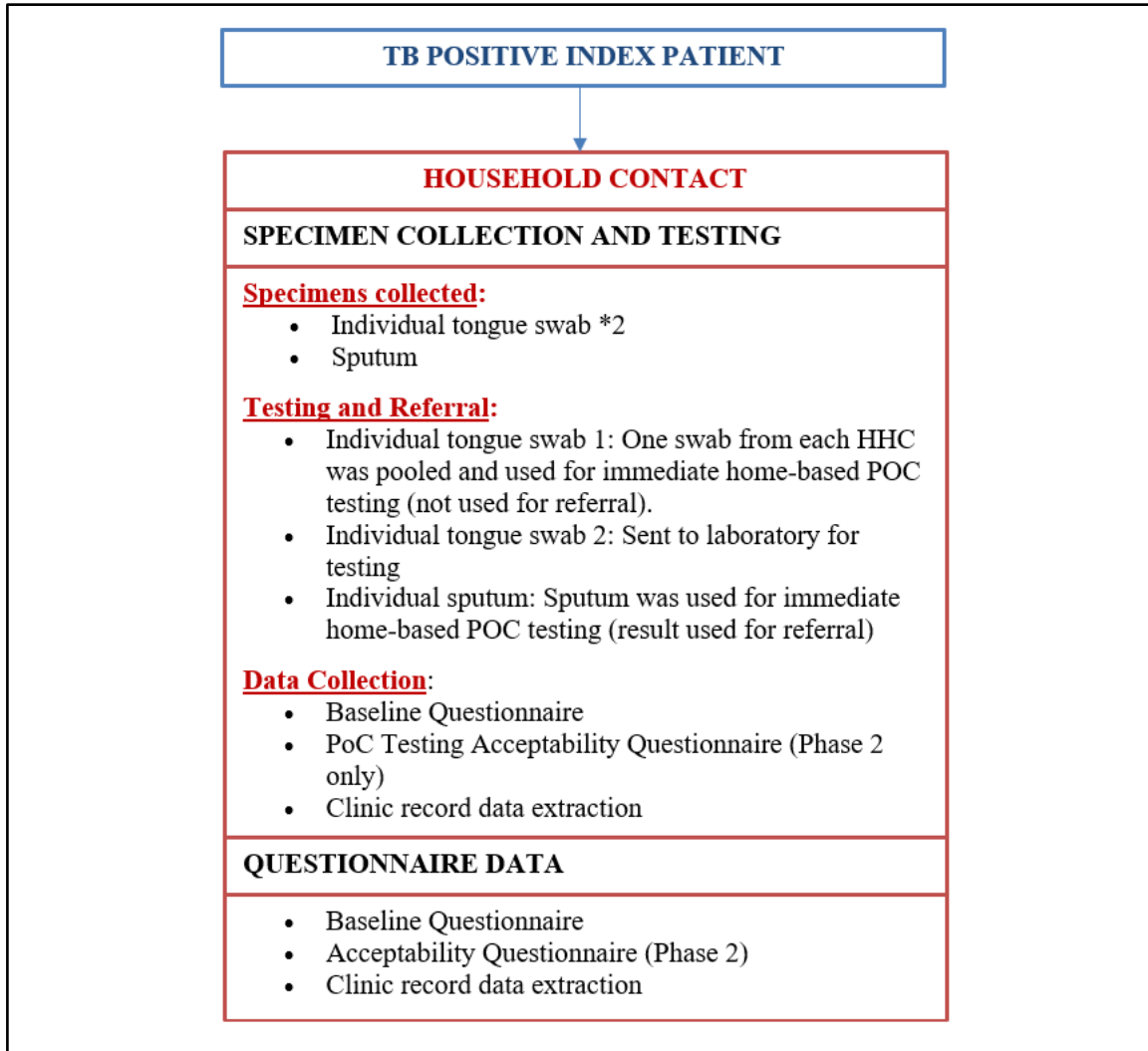


Figure 3.3. TB Home Study Data Collection Activities



### **C. DrPH Research Aim 1: Cost and Cost-Effectiveness**

#### **Research aim**

Using data collected during phase 1 of the TB Home Study in dissertation aim 1 we set out to:

**Aim 1:** Estimate the costs and compare the cost-effectiveness of different in-home POC testing strategies, measured as the incremental cost per additional household contact with TB detected and linked to a clinic for treatment.

- **Activity 1:** Conduct a cost analysis to estimate the cost of different in-home POC testing strategies for TB, from the provider's perspective.
- **Activity 2:** Build a decision analytic model to compare the cost-effectiveness of different in-home POC testing strategies. Strategies are compared using incremental cost effectiveness ratios (ICERs), measured as the incremental cost per additional household contact with TB detected and linked to a clinic for treatment.

#### **Rationale**

Free markets rarely exist in healthcare, therefore decisions have to be made about which health services or programs receive funding.<sup>79</sup> Most health systems, especially those in low- and middle-income countries, face a high demand for public health services but operate within constrained budgets, making it essential to determine how best to allocate limited resources to deliver equitable care.<sup>80</sup> A key goal for policy makers is to evaluate healthcare interventions to select those that show the greatest value for money, while adhering to the budgetary constraints of the health system. Economic evaluation, defined

as the comparison of two alternatives options in terms of their cost and consequences, is often used in healthcare to guide decision making.<sup>81</sup>

Cost-effectiveness analysis is the most commonly used form of economic evaluation and has become a central policy tool used in decision making. Under this method, both the health- and cost impact of an intervention is compared to that of a competing alternative. Differences in the costs of competing interventions are divided by the differences in expected health gains, measured in a pre-defined natural unit, and expressed as an ICER. An ICER represents the ratio of incremental costs to incremental health benefits.<sup>82</sup> Ultimately, it provides evidence on how much additional spending is required per unit of health gain when introducing a new healthcare intervention or treatment compared to the alternative.

Randomized trials are often used to generate the evidence on costs and consequences of a healthcare intervention. Often however, decision models are used when data from a randomized trial is insufficient or unavailable. Decision models like decision trees allow for the comparison of multiple interventions and comparators. In addition, they provide the opportunity to make use of evidence generated from multiple sources, rather than a single randomized trial.<sup>83</sup> A decision model used for cost-effectiveness analysis represents a biologically plausible set of health outcomes resulting from different decisions made, and their associated outcomes, during the delivery of a healthcare intervention. The model not only considers the relationship between actions and outcomes but also quantifies the probability of their occurrence. When parameterizing the model mathematically, researchers can utilize real-world effectiveness data instead of relying solely on

randomized trials, allowing for a more pragmatic approach to estimating outcomes.<sup>84</sup> Ultimately, a decision analytic model provides a framework for compiling clinical and economic evidence in a systematic fashion, determining the value of a healthcare intervention or product, and communicating that value to decision makers.

A key criticism of active case finding is its resource-intensive nature. Analyses using model-based economic evaluations support the cost-effectiveness of active case finding under a variety of conditions.<sup>85,86</sup> However, the additional cost and potential corresponding epidemiological and economic benefits resulting from the integration of active case finding into existing programs, remain largely unknown.<sup>87</sup> With the introduction of new POC technologies, an increased focus on finding the missing cases, and increased funding and coordinated global initiatives, economic evidence is needed to support decisions regarding strategic adoption and scale-up of new active case finding interventions.

### **Research questions**

The primary research questions for this aim were:

1. What are the different costs from the provider's perspective to deliver a household contact investigation intervention with integrated in-home POC TB testing using the Xpert-Edge platform?
2. What is the total cost, over a 2-year period of delivering a household contact investigation intervention with integrated in-home POC TB testing using the Xpert-Edge platform?

- a. How would the total cost of the intervention vary across different in-home POC testing strategies (described below)?
  - b. What is the cost-per-test for different in-home POC testing strategies?
3. What is the incremental cost-effectiveness, expressed as the incremental cost per additional household contact with TB detected and linked to a clinic for treatment, of different in-home POC testing strategies?
    - a. Which in-home POC testing strategy is most cost-effective?
    - b. Which in-home POC testing strategies would fall within a willingness to pay threshold of \$2,760?

### **Testing strategies**

A conceptual model was developed detailing the client diagnostic pathways for five novel in-home POC TB testing strategies and a standard-of-care approach:

1. *Standard-of-Care*: In line with South African National TB Guidelines, a household contact investigation is conducted, and all household contacts are screened using the WHO standard four-symptom screener. Those with TB-related symptoms are referred for clinic-based sputum collection and asked to return for result notification. Upon return to the clinic for result notification, those with a positive result are immediately initiated on TB treatment.<sup>88</sup>
2. *POC Sputum Testing*: As part of a household contact investigation, all household contacts present are asked to expectorate sputum. Sputum samples are immediately tested using Xpert-Ultra and Xpert-Edge. Household contacts with a positive test result

are immediately referred for clinic-based treatment initiation. Household contacts unable to expectorate sputum are referred to a clinic for further TB evaluation and services (i.e., TB testing; TB preventive therapy).

3. *POC Pooled Tongue Swabs with Confirmatory Sputum Testing:* As part of a household contact investigation, all household contacts present are asked to provide a tongue swab specimen. A maximum of three swab specimens are pooled at a time for immediate testing in a single Xpert-Ultra cartridge. Immediate, in-home confirmatory testing is done following a positive pooled test while clinic referrals are provided to those with a negative result for further TB evaluation and services. Confirmatory testing is done individually for each household contact able to expectorate sputum. Household contacts with a positive confirmatory sputum result are immediately referred for clinic-based treatment initiation while those with a negative result are referred to a clinic for further TB evaluation and services.
4. *POC Pooled Tongue Swabs with Confirmatory Tongue Swab Testing:* As part of a household contact investigation, all household contacts present are asked to provide a tongue swab specimen. A maximum of three swab specimens are pooled at a time for immediate testing in a single Xpert-Ultra cartridge. Immediate, in-home confirmatory testing is done following a positive pooled test while clinic referrals are provided to those with a negative result to attend a clinic for further TB evaluation and services. Confirmatory testing is done individually for each household contact able to provide a tongue swab. Household contacts with a positive confirmatory result are immediately referred for clinic-based treatment initiation while those with a negative result are

referred to a clinic for further TB evaluation and services.

5. *POC Individual Tongue Swab Testing*: As part of a household contact investigation, all household contacts present are asked to provide a tongue swab specimen for immediate, individual testing using Xpert-Ultra and Xpert-Edge. Household contacts with a positive test result are immediately referred for clinic-based treatment initiation while those with a negative result are referred to a clinic for further TB evaluation and services.
6. *POC Combined Sputum and Individual Tongue Swab Testing*: As part of a household contact investigation, all household contacts present are asked to expectorate sputum for immediate, individual testing using Xpert-Ultra and Xpert-Edge. Those unable to expectorate sputum are asked to provide a tongue swab specimen for immediate, individual testing. All household contacts with a positive sputum or tongue swab result are immediately referred for clinic-based treatment initiation. Those with a negative test result are referred for further TB services i.e. TB preventative therapy.

Common elements across diagnostic pathways were identified and retained to promote consistency across activity descriptions at each decision node. All household contacts follow a similar diagnostic pathway starting with a household contact investigation, household contact verification, Xpert-Ultra testing (either in-home POC or clinic-based depending on the strategy), and treatment initiation following a positive test. The model follows household contacts through each step of the diagnostic pathway, estimating costs, transition probabilities, and outcomes. The conceptual model (Figure 3.4) was used to guide the collection of costing data, implementation outcomes, and to develop the final decision tree (Figure 4.1).

### **Cost estimation**

We calculated the total implementation cost (programmatic costs + testing costs), and the cost-per-test associated with each testing strategy. A provider's perspective under routine conditions was adopted considering both fixed and variable costs. Fixed costs included building, infrastructure, and fully dedicated staff. Variable costs were based on expenditure established posteriori from quantities used, including testing supplies, consumables, Xpert-Edge operating costs, and salaries for staff conducting testing. Costs were categorized and estimated separately to distinguish programmatic costs from testing costs. Programmatic costs included all expenses related to the planning and execution of household contact investigations. Testing costs included costs associated with household contact verification and collection, preparation, and testing of samples. Purely research-related expenses were excluded (i.e., time and resources spent on additional sample transportation and testing and/or collection of data used for research purposes).

To estimate the total programmatic cost, we conducted top-down costing. Costs were categorized into equipment, personnel, laboratory costs, stationery, consumables, travel, overheads, and other miscellaneous expenses. These costs were sourced from the TB Home Study's electronic general ledger and supplemented by interviews with key finance representatives. The total programmatic cost was estimated by summing the cost of each of the categories. The cost of a household contact investigation for a single household contact was estimated by dividing the total programmatic cost by the number of household contacts reached.

Bottom-up, micro-costing was deployed to calculate the testing costs for each

testing strategy. Specific inputs and their quantities needed for each test strategy were estimated. Direct observations in combination with an electronic tracking tool built in REDCap were used to capture resources required and time needed for test activities. Estimates were used to calculate the average cost-per-test for each strategy. The total cost for each test strategy was calculated by multiplying the cost-per-test with the expected number of tests conducted, informed by study findings.

Capital assets including furniture costs were annuitized and depreciated based on expected life-years at a 3% annual discount rate. The average cost for running a test on Xpert-Edge was calculated by dividing the cost of the platform by the total number of tests it would be able to perform across its useful lifetime. The platform can run an average of four tests per day, 892 over a year, and 4,460 over its estimated 5-year lifetime. With the total cost of the machine being \$8,416, the unit cost per test would be  $8,416/4,460$ , or US\$1.89. The Global Fund-negotiated price of \$7.97 was used for Xpert-Ultra cartridges.<sup>89</sup> All cost-estimation data were obtained from the TB Home Study. All costs were inflated to 2023 prices based on annual inflation data provided by Statistics South Africa.<sup>90</sup> Costs were then converted from South African Rand to US\$ at the average 2023 World Bank conversion rate (1 US\$ = 18.45 Rand).<sup>91</sup>

### **Outcomes and measurement of effectiveness**

We derived measures of effectiveness from operational and intermediate outcomes captured in the TB Home Study. Our primary cost-effectiveness outcome was the incremental cost per additional household contact with TB disease detected and linked to a clinic for treatment initiation, comparing each testing strategy.

## **Analysis**

### ***Decision analytic model for cost-effectiveness***

For a testing strategy to be considered by policy makers it needs to be either as effective but less costly than standard-of-care; or if more costly, the increase in effectiveness needs to be clinically/diagnostically relevant enough to warrant such an increase. To this aim, ICERs were used as a metric to compare competing test strategies. The efficacy results from the TB Home Study were used to construct a simplified decision analytic model using TreeAge Pro 2024 (TreeAge Pro, Williamston, Massachusetts, USA) to determine the cost-effectiveness of each testing strategy. The full list of parameters used in the model is provided (Appendix 1 and 2).

### ***Willingness-to-pay***

If the ICER for a proposed testing strategies is lower than the amount policy makers are willing to pay for an additional unit of effectiveness, it would be deemed cost effective.<sup>92,93</sup> The WHO-CHOICE criterion, a hitherto widely used benchmark for estimating cost-effectiveness thresholds uses gross domestic product per capita of a country to estimate willingness-to-pay thresholds.<sup>94</sup> By this measure the willingness-to-pay threshold for a cost-effective intervention in South Africa would be \$20,299 or \$6,766 per disability adjusted life year (DALY) averted for a highly cost-effective intervention.<sup>95</sup> This criterion has been widely criticized for its insufficient rationale and for producing inflated thresholds that offer little value to policymakers in assessing trade-offs.<sup>94,96-100</sup> For active case finding interventions like household contact investigation, understanding incremental benefits and

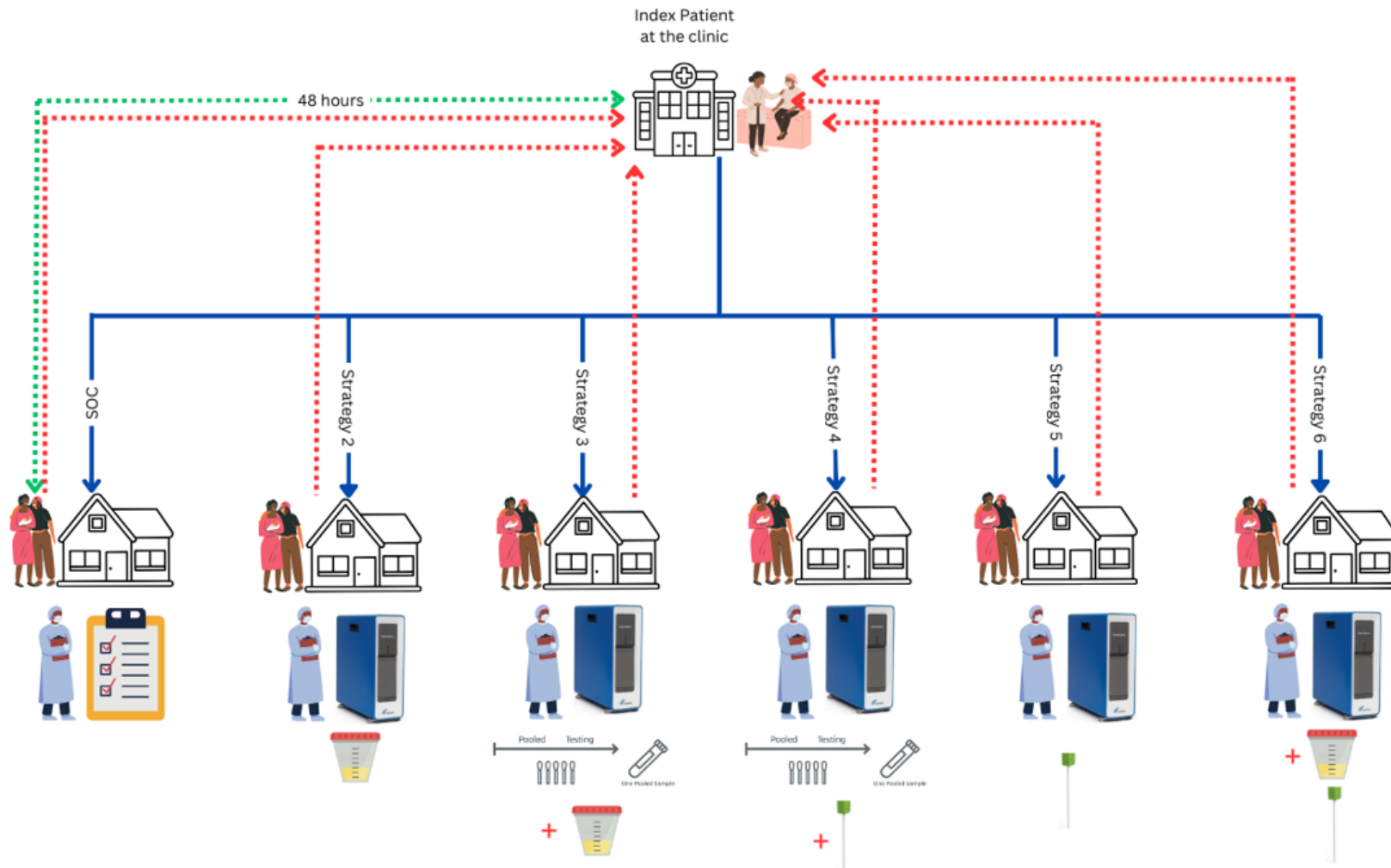
costs can be challenging.<sup>87</sup> The TB REACH initiative which has funded over 300 active case finding projects since 2010 abandoned its initial threshold of \$350 noting that active case finding costs vary significantly due to factors like setting, human resource cost, and operational costs.<sup>101</sup> In addition, metrics like “Cost per TB case detected” often used in active case finding do not accurately capture the long-term value of interventions.<sup>87</sup> To fill this gap, a prior economic analysis used a transmission model of the TB epidemic in South Africa to estimate the epidemiologic impact and cost-effectiveness of feasible active case finding strategies over a short-term time horizon. The analysis found a willingness-to-pay threshold of \$2,760 per TB positive contact detected and initiated on treatment during active case finding as cost-effective over a 2-year time horizon.<sup>86</sup> The \$2,760 threshold was used in the current analysis to evaluate the cost-effectiveness of competing in-home POC testing strategies against the standard-of-care.

### **Sensitivity analysis**

To explore key drivers of cost and effectiveness, we performed one-way deterministic sensitivity analysis. Parameter values were changed, with the corresponding upper and lower bound values (Appendix 1 and 2). The upper and lower bounds were estimated based on available literature or, in the absence of literature, as a 25% increase and decrease of the point estimate. Each parameter was varied to observe its effect on the overall ICER, presented in a tornado diagram. Probabilistic sensitivity analyses using Monte Carlo simulations with 10,000 iterations was conducted to explore the effects of combined uncertainties across all model parameters. Beta distributions were used for probabilities of

effectiveness, and gamma distributions for cost data. Probabilistic sensitivity analyses results are graphically demonstrated in the Cost-Effectiveness Acceptability Curve (Appendix 3).

Figure 3.4. Conceptual Model of Different In-home POC TB Testing Strategies



\*The red dotted lines represent client's movement to treatment initiation at clinic. The green dotted line represents client's movement to clinic for sputum production.

## **D. DrPH Research Aim 2: Acceptability and Feasibility**

### **Research aim**

Using data collected during phase 2 of the TB Home Study in dissertation aim 2 we set out to:

**Aim 2:** Assess the acceptability and feasibility of delivering in-home POC universal TB testing during household contact investigations.

- **Activity 1:** Evaluate the acceptability of delivering in-home POC universal TB testing during household contact investigations, measured from the perspective of the client.
- **Activity 2:** Use a feasibility framework to assess and compare the feasibility of different sample testing methods when delivering in-home POC universal TB testing during household contact investigations.

### **Rationale**

Household contact investigations, which involves the in-home screening and referral of household contacts of people with TB has become one of the most prominent and effective active case finding strategies aimed at increasing testing access.<sup>38,102</sup> Current standard of care household contact investigation only includes verbal screening of household contacts. The use of a portable molecular diagnostic platform like the Xpert-Edge to conduct immediate in-home testing is novel. Assessing the acceptability from the client's perspective is imperative when designing patient-centered healthcare interventions. The in-home collection, preparation, and testing of tongue swab samples for TB testing has not

been done before. In proof-of-concept studies it is crucial to assess the feasibility of new technologies and methods to assess potential for real-world adoption and scaleup.

### **Research questions**

The primary research questions of aim 2 were:

1. How acceptable is the delivery of in-home POC universal TB testing among household contacts when delivered as part of a household contact investigation?
2. Is it feasible to collect, prepare, and test different sample types like sputum and tongue swabs for in-home molecular POC TB testing using a portable molecular platform like the Xpert-Edge?

### **Data collection and analysis**

While Xpert-Ultra testing of consenting household contacts was being conducted, a contact investigation team member collected basic socio-demographic and clinical history data from each participant. Descriptive statistics (median [IQR] for continuous variables and counts [%] for categorical variables) were used to characterize distributions of study variables in the sociodemographic questionnaire. Data collected pre- and post-testing were analyzed to assess the acceptability of in-home POC universal TB testing. Pre-test acceptability was assessed as the proportion of household contacts consenting to participate out of the eligible population to whom study participation was offered. Post-test acceptability was assessed using survey data collected following the conclusion of a household investigation. The development of the post-test acceptability survey was

informed by the Theoretical Framework of Acceptability, and adapted specifically for this study.<sup>103,104</sup> This survey evaluated a respondent's level of acceptability of a healthcare intervention across eight different constructs using a 5-point Likert scale.

Implementation outcomes associated with sample collection and testing of sputum and tongue swab samples were captured and used to assess the feasibility of different testing methods and included: 1) type of sample collected; 2) success of sample collection; 3) processing and preparation of sample for testing; 4) outcome of test; and 5) referral outcome. The final feasibility assessment was guided by elements of the, Metrics to Assess the Feasibility of Rapid Point-of-Care Technologies Framework, which was designed to assess the feasibility of rapid POC technologies during proof of concept studies.<sup>105</sup> This framework was used to select and define four metrics to be included in the current assessment, including: 1) sample collection rate; 2) test processing rate; 3) test success rate; and 4) client notification rate. The performance of both sputum and tongue swab testing methods against each metric was calculated and reported.

## CHAPTER FOUR: COST AND COST-EFFECTIVENESS ANALYSIS

At the time of this dissertation submission, Manuscript 1 was in pre-print (medRxiv) and under review at Clinical Infectious Diseases. For the purposes of this dissertation the final manuscript submitted for publication is presented here using the sections and layout prescribed by the journal. The article has been reformatted to match the dissertation style as prescribed by Boston University. See Appendix 4 for a PDF version of the most recent version of the manuscript following journal review.

**Reference:** Bezuidenhout C, Long L, Nichols B, Meyer-Rath G, Fox MP, Theron G, Fourie B, Olifant S, Penn-Nicholson A, Ruhwald M, Medina-Marino A. Sputum and tongue swab molecular testing for the in-home diagnosis of tuberculosis in unselected household contacts: a cost and cost-effectiveness analysis. *medRxiv [Preprint]*. 2024 Oct 18:2024.10.18.24315746. doi: 10.1101/2024.10.18.24315746. PMID: 39484233; PMCID: PMC11527052.

## **Abstract**

### **Background**

Delayed and missed diagnosis are a persistent barrier to tuberculosis control, partly driven by difficulties collecting sputum and an unmet need for decentralized testing. Household contact investigation with point-of-care testing of non-invasive specimens are hitherto undescribed and may offer a cost-effective solution to strengthen active case finding.

### **Methods**

In-home molecular point-of-care testing was conducted using sputum and tongue specimens collected from household contacts of people with confirmed tuberculosis residing in South Africa. A health economic assessment was executed to estimate and compare the cost and cost-effectiveness of different in-home point-of-care testing strategies, against centralized sputum testing (standard of care) from a provider's perspective. The incremental cost effectiveness ratio of detecting a new case and linking them to treatment was compared across strategies.

### **Results**

The total implementation cost of delivering the standard of care for a 2-year period was \$84,962. Strategies integrating in-home point-of-care testing ranged between \$87,844 – \$93,969. The cost-per-test for in-home point-of-care sputum testing was the highest at \$20.08 per test. Two strategies, Point-of-Care Sputum Testing and Point-of-Care Combined Sputum and Individual Tongue Swab Testing were the most cost-effective with

incremental cost effectiveness ratios of \$543.74 and \$547.29 respectively, both below a \$2,760 willingness-to-pay threshold.

### **Conclusion**

In-home point-of-care molecular TB testing strategies utilizing combination testing of tongue swabs and sputum specimens can meaningfully improve the number of people tested, diagnosed, and notified during active case finding, while being cost-effective.

## A. Introduction

An estimated 25,000 people still die from TB every week, despite the disease being curable.<sup>106</sup> Globally in 2022, 10.6 million people developed TB of which 3.1 million were never diagnosed or treated.<sup>12</sup> People with missed or delayed diagnoses have elevated morbidity and mortality, drive on-going transmission, and experience increased individual and health systems costs.<sup>107</sup> Therefore, implementation of effective, evidence-based strategies that can increase access to testing, deliver real-time POC diagnosis, and reduce time to treatment initiation, are urgently required.<sup>108</sup>

Early screening and diagnosis is a key to TB control and underpins the post-2015 END TB strategy.<sup>109</sup> Active case finding strategies like household contact investigation of known cases is widely recognized as an important component of any strategy to end TB.<sup>110</sup> WHO target product profile for new TB diagnostics place standalone, non-sputum-based POC tests as one of its highest priorities.<sup>51</sup> For an optimal POC diagnostic test, its cost-effectiveness is mainly a trade-off between the invasiveness of sample collection, sensitivity and specificity of the test, and the cost of resources required to conduct the test.<sup>111</sup> Progress has been made towards this end. Recent studies have shown that it is feasible to integrate real-time POC molecular platforms like the GeneXpert-Edge (Xpert-Edge; Cepheid, Sunnyvale, CA, USA) into active case finding approaches, thus decentralizing testing services and increasing access to testing for those at-risk for TB.<sup>50,51</sup> However, these studies have continued to rely on sputum-based testing alone.

Non-invasive tongue swab specimens tested with rapid molecular diagnostic platforms are emerging as an alternative to sputum.<sup>112</sup> Recent work reported tongue swab

quantitative polymerase chain reaction (qPCR) sensitivity and specificity to be 93% and 99%, respectively, against a microbiological reference standard, rivaling that of sputum-based molecular testing.<sup>113</sup> However, most tongue swab studies have recruited individuals already in primary care or with TB-related symptoms, limiting our understanding of the potential benefit of integrating tongue swab testing into existing active case finding strategies. Towards this, the TB Home Study recently found that testing of household contacts of people with confirmed TB using tongue swabs resulted in >95% of all household contacts being tested for TB, irrespective of symptoms or ability to provide sputum, and increased the diagnostic yield of cases detected when integrated into household contact investigations.<sup>114</sup>

Successful implementation of household contact investigation depends on costs and affordability, while consideration for adoption is influenced by the anticipated improvement in population reach and case detection. As part of the TB Home Study, we collected resource use and cost to conduct an economic evaluation of household contact investigation from the provider perspective, comparing the total cost of delivering five novel testing strategies against the current standard-of-care (SOC), over a 2-year period. Additionally, we employed decision analytic modeling to map the diagnostic pathways for each strategy, enabling the analysis and comparison of their cost-effectiveness when integrated into household contact investigation. Together our analysis combines empirical cost estimates from financial data and intermediate participant outcome data with decision analytic modeling of care pathways to estimate resource use and implementation outcomes of different testing strategies deployed as part of household contact investigation.

## **B. Methods**

### **Study design and participants**

We used data from the TB Home Study conducted between July, 2021 and June, 2023 in the Buffalo City Metropolitan Health District, Eastern Cape Province, South Africa. The study sought to evaluate the predictive value of pooled individual tongue swab specimens vs. sputum as a household-level triage test for TB during household contact investigations using the MTB/RIF Ultra cartridge (Xpert-Ultra; Cepheid, Sunnyvale, CA, USA) with the Xpert-Edge as POC diagnostic platform. Household contact investigations of people with confirmed TB were performed as described.<sup>114</sup> Household contact investigations of 300 people with confirmed TB were performed. A total of 630 consenting household contacts were asked to first provide two tongue swabs and one sputum specimen. One swab from each household contact was then pooled for immediate Xpert-Ultra testing in the household. The second swab was placed in Prime Store Molecular Transport Media and tested at a centralized lab. For all household contacts able to produce a spot-sputum, immediate in-home POC testing was performed. Household contacts with a positive sputum test result were immediately referred for clinic-based treatment initiation while those with a negative result are referred to a clinic for further TB evaluation and services. Referral outcomes (i.e., proportion of household contacts presenting to the clinic; time-to-clinic presentation; treatment initiation outcomes) have been described elsewhere.<sup>114</sup>

### **Economic evaluation overview**

We used intermediate outcome and cost data empirically collected from the TB Home Study to formulate, analyze, and compare the total cost and cost-effectiveness of different testing strategies, deployed as part of household contact investigation. Emphasis was placed on assessing the economic impact of strategies that incorporate in-home POC testing of non-invasive specimens like tongue swabs. We complied with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022) reporting guidelines.<sup>115</sup> A completed checklist is provided in Appendix 5.

### **Decision analytic model design and approach**

A conceptual model was developed detailing the participant diagnostic pathways for five novel household contact investigation POC TB testing strategies and a standard-of-care approach:

1. *Standard of Care:* In line with South African National TB Guidelines, a household contact investigation is conducted, and all household contacts are screened using the WHO standard four-symptom screener. Those with TB-related symptoms are referred for clinic-based sputum collection and asked to return for result notification. Upon return to the clinic for result notification, those with a positive result are immediately initiated on TB treatment.<sup>88</sup>
2. *POC Sputum Testing:* As part of a household contact investigation, all household contacts present are asked to expectorate sputum. Sputum samples are immediately tested using Xpert-Ultra and Xpert-Edge. Household contacts with a positive test

result are immediately referred for clinic-based treatment initiation. Household contacts unable to expectorate sputum are referred to a clinic for further TB evaluation and services (i.e., TB testing; TB preventive therapy).

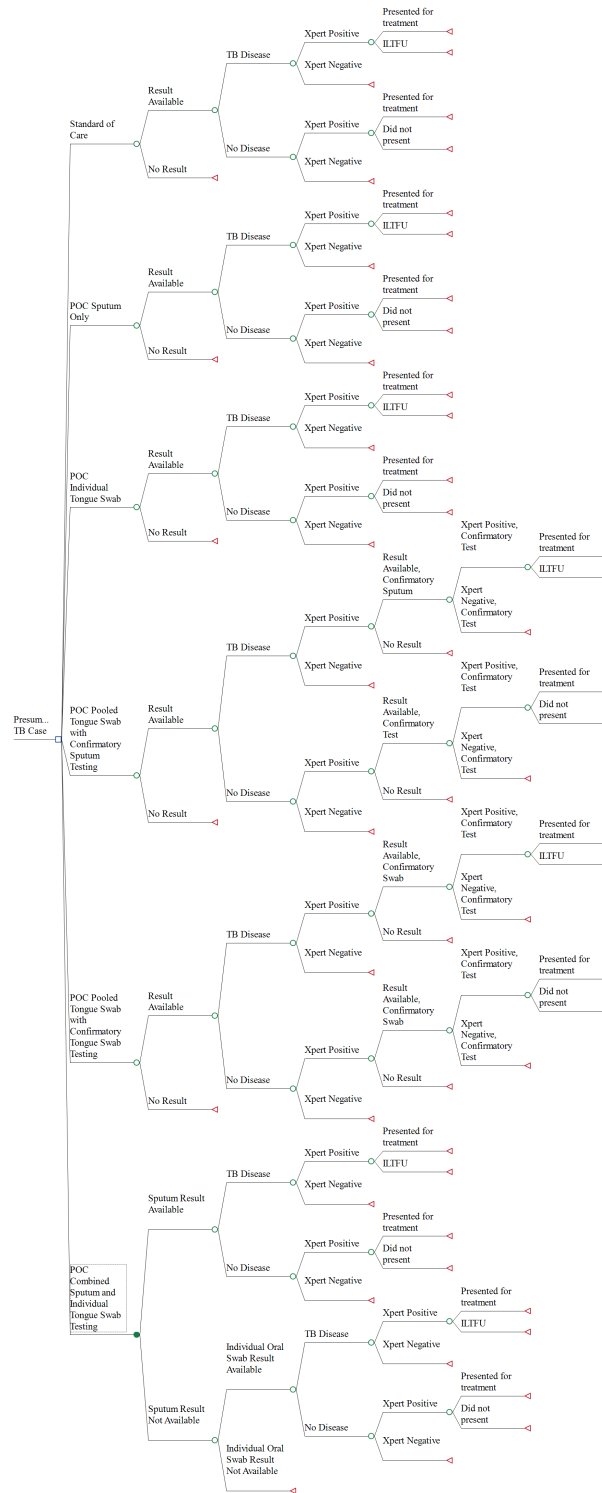
3. *POC Individual Tongue Swab Testing:* As part of a household contact investigation, all household contacts present are asked to provide a tongue swab specimen for immediate, individual testing using Xpert-Ultra and Xpert-Edge. Household contacts with a positive test result are immediately referred for clinic-based treatment initiation while those with a negative result are referred to a clinic for further TB evaluation and services.
4. *POC Pooled Tongue Swabs with Confirmatory Sputum Testing:* As part of a household contact investigation, all household contacts present are asked to provide a tongue swab specimen. A maximum of three swab specimens are pooled at a time for immediate pooled testing in a single Xpert-Ultra cartridge. Immediate, in-home confirmatory testing is done following a positive pooled test while clinic referrals are provided to those with a negative result. Confirmatory testing is done individually for each household contact able to expectorate sputum. Household contacts with a positive confirmatory sputum result are immediately referred for clinic-based treatment initiation while those with a negative result are referred to a clinic for further TB evaluation and services.
5. *POC Pooled Tongue Swabs with Confirmatory Tongue Swab Testing:* As part of a household contact investigation, all household contacts present are asked to provide a tongue swab specimen. A maximum of three swab specimens are pooled at a time for

immediate testing in a single Xpert-Ultra cartridge. Immediate, in-home confirmatory testing is done following a positive pooled test while clinic referrals are provided to those with a negative result. Confirmatory testing is done individually for each household contact able to provide a tongue swab. Household contacts with a positive confirmatory result are immediately referred for clinic-based treatment initiation while those with a negative result are referred to a clinic for further TB evaluation and services.

6. *POC Combined Sputum and Individual Tongue Swab Testing:* As part of a household contact investigation, all household contacts present are asked to expectorate sputum for immediate, individual testing using Xpert-Ultra and Xpert-Edge. Those unable to expectorate sputum are asked to provide a tongue swab specimen for immediate, individual testing. All household contacts with a positive sputum or tongue swab result are immediately referred for clinic-based treatment initiation while those with a negative result are referred to a clinic for further TB evaluation and services.

These diagnostic pathways guided the development of the final decision analytic model (Figure 4.1). Common elements across diagnostic pathways were identified and retained to promote consistency across activity descriptions at each decision node. All household contacts follow a similar diagnostic pathway starting with a household contact investigation, household contact verification, Xpert-Ultra testing (either in-home POC or clinic-based depending on the strategy), and treatment initiation following a positive test. The model follows household contacts through each step of the diagnostic pathway, estimating costs, transition probabilities, and outcomes.

Figure 4.1. Simplified Decision Analytic Model



\*The diagram shows the diagnostic pathway from testing to treatment initiation. ILTFU: Initial loss to follow up refers to HHCs who tested positive but never present for treatment initiation.

**Cost estimation**

We calculated the total implementation cost (Programmatic cost + Testing cost), and the cost-per-test associated with each testing strategy. A provider's perspective under routine conditions was adopted considering both fixed and variable costs. Fixed costs included building, infrastructure, and fully dedicated staff. Variable costs were based on expenditure established posteriori from quantities used, including testing supplies, consumables, Xpert-Edge operating costs, and salaries for staff conducting testing. Costs were categorized and estimated separately to distinguish programmatic costs from testing costs. Programmatic costs included all expenses related to the planning and execution of household contact investigations. Testing costs included costs associated with household contact verification and collection, preparation, and testing of samples. Research-related expenses were excluded.

To estimate the total programmatic cost, we conducted top-down costing. Costs were categorized into equipment, personnel, laboratory costs, stationery, consumables, travel, overheads, and other miscellaneous expenses. These costs were sourced from the TB Home Study's electronic general ledger and supplemented by interviews with key finance representatives. The total programmatic cost was estimated by summing the categories. The cost of a household contact investigation for a single household contact was estimated by dividing the total programmatic cost by the number of household contacts reached.

Bottom-up, micro-costing was deployed to calculate the testing costs for each testing strategy. Specific inputs and their quantities needed for each test strategy were

estimated. Direct observations in combination with an electronic tracking tool built in REDCap were used to capture resources required and time needed for test activities. Estimates were used to calculate the average cost-per-test for each strategy. The total cost for each test strategy was calculated by multiplying the cost-per-test with the expected number of tests conducted, informed by study findings.

Capital assets, including furniture were annuitized and depreciated based on expected life-years at a 3% annual discount rate. The unit cost for running a test on Xpert-Edge was calculated by dividing the cost of the platform by the total number of tests it would be able to perform across its useful lifetime. The platform can run an average of four tests per day, 892 over a year, and 4,460 over its estimated 5-year lifetime. With the total cost of the machine being \$8,416, the unit cost per test would be  $8,415/4,460$ , or US\$1.89. The Global Fund-negotiated cost of \$7.97 was used for Xpert-Ultra cartridges.<sup>89</sup> All cost-estimation data were obtained from the TB Home Study. All costs were inflated to 2023 prices based on annual inflation estimates provided by Statistics South Africa.<sup>90</sup> Costs were then converted from South African Rand to US\$ at the average 2023 World Bank conversion rate (1 US\$ = 18.45 Rand).<sup>91</sup>

### **Outcomes and measurement of effectiveness**

We derived measures of effectiveness from operational and clinical outcomes captured in the TB Home Study. Our primary cost-effectiveness outcome was the incremental cost per additional household contact with TB disease detected and linked to a clinic for treatment initiation, comparing each testing strategy.

### **Decision analytic model for cost-effectiveness**

For a test strategy to be considered by policy makers it needs to be either as effective but less costly than SOC; or if more costly, the increase in effectiveness needs to be clinically/ diagnostically relevant enough to warrant such an increase. To this aim, incremental cost-effectiveness ratios (ICERs) were used as a metric to compare competing test strategies. The efficacy results from the TB Home Study were used to construct a simplified decision analytic model using TreeAge Pro 2024 (TreeAge Pro, Williamston, Massachusetts, USA) to determine the cost-effectiveness of each testing strategy. The full list of parameters used in the model is provided (Appendix 1 and 2).

If the ICER for a given strategy is lower than the amount policy makers are willing to pay for an additional unit of effectiveness, we assume it to be cost-effective. A previous economic evaluation concluded that 2-year active case finding campaigns done in South Africa that cost \$2,760 per case detected (and started on treatment) are considered highly cost-effective.<sup>86</sup> A willingness-to-pay threshold of \$2,760 per household contact newly diagnosed and linked to treatment was used for the current economic evaluation.

### **Sensitivity analysis**

To explore key drivers of cost and effectiveness, we performed one-way deterministic sensitivity analysis. Parameter values were changed, with the corresponding upper and lower bound values (Appendix 1 and 2). The upper and lower bounds were estimated based on available literature or, in the absence of literature, as a 25% increase and decrease of the point estimate. Each parameter was varied to observe its effect on the overall ICER,

presented in the tornado diagram (Figure 4.3). Probabilistic sensitivity analyses using Monte Carlo simulations with 10,000 iterations was conducted to explore the effects of combined uncertainties across all model parameters. Beta distributions were used for probabilities of effectiveness, and gamma distributions for cost data. Probabilistic sensitivity analyses results are graphically demonstrated in the Cost-Effectiveness Acceptability Curve (Appendix 3).

### **Ethics approval**

This study was conducted according to the ethical principles set forth in the Declaration of Helsinki, ICH-GCP, European Directive 2001/20/EC, US Code of Federal Regulations Title 21, South African Good Clinical Practice Guidelines, and other local regulatory requirements. The study protocol was approved by the University of Pretoria Human Research Ethics Committee (HREC 391/2021). Work related to the cost-effectiveness analysis was approved by Boston University Institutional Review Board (H-44118).

## **C. Results**

### **Cost analysis**

Appendix 6 provides a summary of the total estimated implementation cost (Programmatic cost + Testing cost) of delivering each household contact investigation testing strategy to 300 households over a 2-year period. The total cost of conducting household contact investigations (programmatic cost) was \$81,327. The majority of programmatic cost (60%) was for salaries of two fully dedicated staff members followed by travel costs (24%) to

transport staff to households. The total testing cost ranged from \$3,635 for SOC to \$12,642 for *POC Combined Sputum and Individual Tongue Swab Testing*. The total implementation cost ranged from \$84,962 (SOC) to \$93,969 for *POC Combined Sputum and Individual Tongue Swab Testing*. The integration of the Xpert-Edge platform with Xpert-Ultra to conduct in-home POC testing would result in a 3%–10% increase in total implementation cost, compared to SOC. The average cost-per-test (Appendix 7) was highest for sputum-based testing (\$20.08). Individual tongue swab- (\$19.29) and pooled tongue swab tests (\$15.73) showed a 4% and 22% lower cost-per-test, respectively. The cost of Xpert-Ultra was a major driver (42%) of cost-per-test.

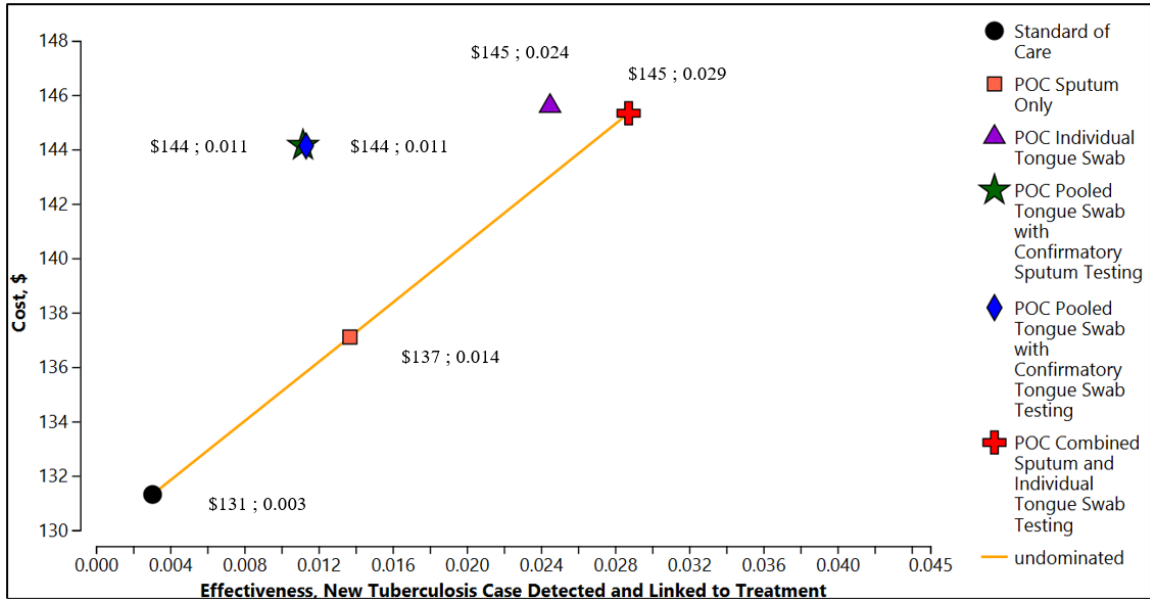
### **Probabilities**

Probability data (Appendix 1 and 2) for the cost-effectiveness analysis were informed by the TB Home Study and supplemented by available literature. The prevalence of TB among household contacts was estimated at 4.5% and ranged between 3.3% and 7.8%. The probability of obtaining a test result when adopting SOC was estimated to be 10.7% compared to 38.3% when in-home POC Sputum Testing was conducted. The probability of obtaining a test result from all other strategies ranged between 82.7% and 89.8%, highlighting the increased collection yield of less invasive samples. The sensitivity of different testing strategies ranged from 51.4% for POC pooled tongue swab tests to 93.2% for sputum-based tests. Intermediate outcome data from the TB Home Study suggests that the likelihood of treatment initiation following a positive in-home POC sputum test was 84.6%, compared to a published 68% likelihood when adopting SOC.

### **Cost-effectiveness analysis**

Figure 4.2 summarizes the results of the cost-effectiveness analysis. The cost-effectiveness plane (gold line) connects undominated strategies, i.e., those not outperformed by other strategies and deemed most cost-effective. Although being the least expensive (\$131.38), SOC was also the least effective. All five in-home POC testing strategies showed higher effectiveness compared to SOC albeit at a higher cost per household contact tested. *POC Pooled Tongue Swab Testing with Confirmatory Individual Tongue Swab Testing* and *POC Individual Tongue Swab Testing*, despite showing promise, were both extendedly dominated. This suggests that higher effectiveness at a lower cost could be obtained by a combination strategy located somewhere on the cost-effectiveness plane between the two undominated strategies. Table 4.1 summarizes the cost, effectiveness, and corresponding ICER values of the two undominated testing strategies, *POC Sputum Testing* and *POC Combined Sputum and Individual Tongue Swab Testing*. The corresponding ICERs, \$543.74 and \$547.29, respectively, fell below the \$2,760 willingness-to-pay threshold.

**Figure 4.2. Cost-effectiveness plane of different household contact investigation testing strategies**



**Table 4.1. Results of cost-effectiveness analyses of different household contact investigation testing strategies.**

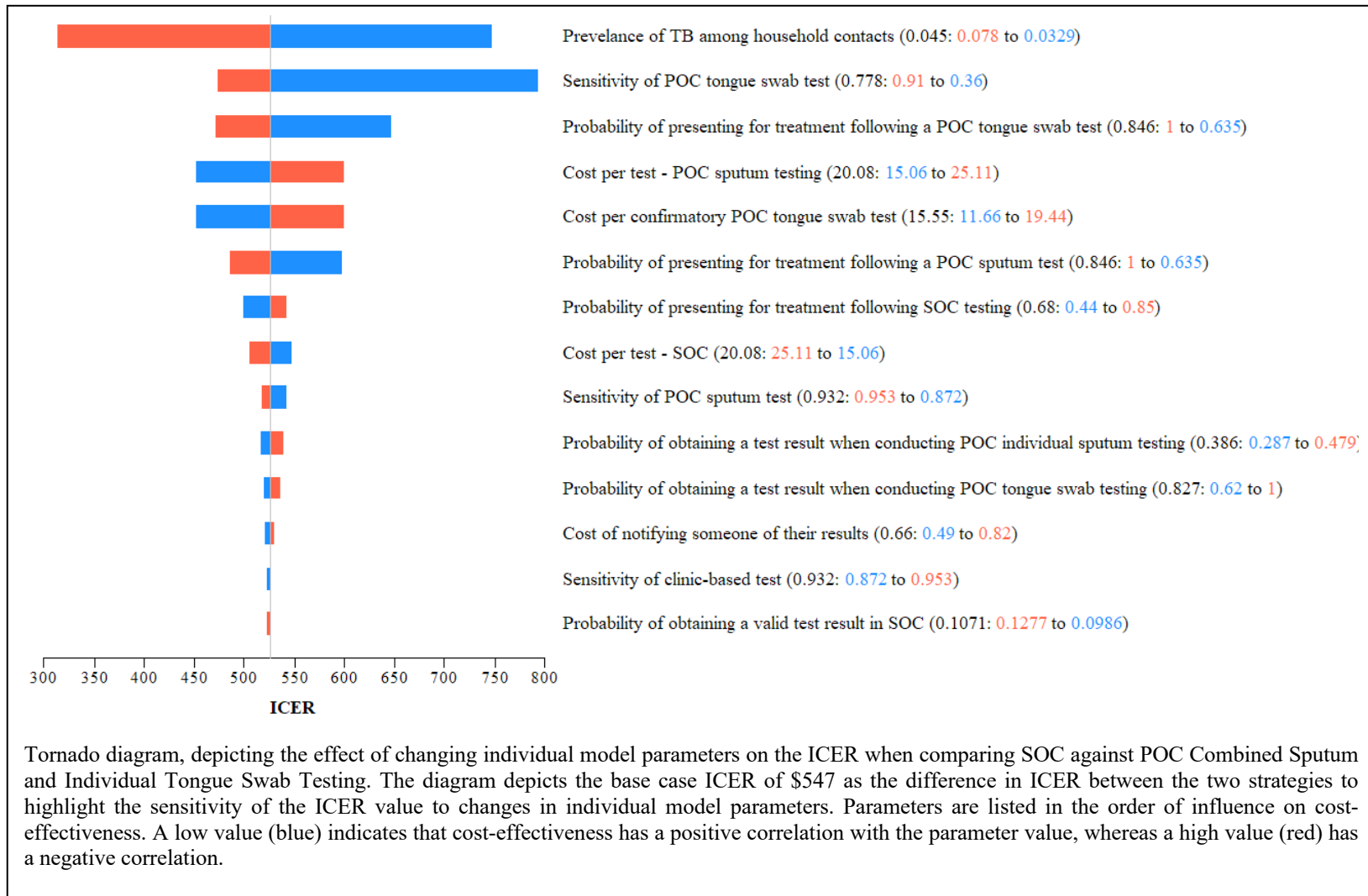
| Test Strategy  | Cost (\$) | Incremental Cost (\$) | Effectiveness | Incremental Effectiveness | ICER   |
|--|-----------|-----------------------|---------------|---------------------------|--------|
| Standard of Care                                       | 131.31    |                       | 0.003         |                           |        |
| POC Sputum Testing                                     | 137.10    | 5.79                  | 0.014         | 0.011                     | 543.74 |
| POC Combined Sputum and Individual Tongue Swab Testing | 145.33    | 8.23                  | 0.029         | 0.015                     | 547.29 |

### Sensitivity analysis

The deterministic sensitivity analysis (Figure 4.3) showed prevalence of TB among household contacts, followed by the sensitivity of a tongue swab test to be the most influential parameters impacting the ICER. An increase in either estimate would result in a decrease in the ICER with clear indication that a reduction in the sensitivity of individual

tongue swabs would result in a drastic increase in the ICER, albeit not exceeding the willingness-to-pay threshold. None of the included parameters showed variability to the extent it would shift the ICER beyond the \$2,760 willingness-to-pay threshold. Results from the probabilistic sensitivity analysis (Appendix 3) confirmed that *POC Combined Sputum and Individual Tongue Swab Testing* was the most optimal strategy in 100% of model iterations at the given willingness-to-pay threshold of \$2,760.

**Figure 4.3. Deterministic Sensitivity Analysis**



#### **D. Discussion**

We conducted a costing analysis to estimate the resources required to implement a household contact investigation program in line with the South African National TB Guidelines (SOC) or when adopting one of five alternative in-home POC test strategies. The empirical estimates derived from the TB Home Study revealed a 3%–10% increase in total implementation cost to roll out household contact investigation with integrated in-home POC molecular testing compared to SOC. The increased cost is due to the increase in materials and resources required to conduct additional testing, resulting in increased number of people appropriately tested for, diagnosed with, and promptly treated for TB. This finding aligns with global health priorities emphasizing the need for rapid and accurate POC diagnostics and the adoption of active case findings strategies to increase access to testing, improve client outcomes, and reduce the number of missing TB cases.<sup>116</sup>

Results from the micro-costing suggest that despite being more sensitive, test strategies that rely on sputum samples have the highest cost-per-test (\$20.08). Despite lower levels of sensitivity, the 4% and 22% reduction in cost-per-test combined with increased sample yield of individual and pooled tongue swab tests could provide strong alternative solutions to increase population test coverage.<sup>117</sup> The highest share (42%) of the cost-per-test is attributable to the cost of the Xpert-Ultra cartridge. This finding was in line with reports from work done in other low- and middle- income settings.<sup>118</sup> Despite a lower negotiated price, the cost of cartridges remain a barrier to scale-up of Xpert-Ultra as a routine test. The optimal number of tongue swabs as well as optimal collection methods that yield the maximum amount of DNA remain under investigation. As the science

evolves and the next generation of ultra-sensitive tests become available, the feasibility of using tongue swabs as well as the pooling of tongue swabs to address the aforementioned barriers, become more plausible.<sup>62</sup>

The cost of detecting a new TB case and linking them to treatment (effectiveness outcome) when adopting *POC Sputum* and *POC Combined Sputum and Individual Tongue Swab* testing was \$137 and \$145, respectively. Although being \$6 and \$14 more expensive than SOC, these strategies would increase the likelihood of detecting TB and linking a case to treatment by 0.011 and 0.026, respectively. The associated ICERs for these two strategies were \$543.47 and \$547.29. These findings suggest that both *POC Sputum* and *POC Combined Sputum and Individual Tongue Swab* testing strategies were highly cost-effective given the threshold of \$2,760. The increased sample yield of tongue swabs combined with immediate result notification and a higher likelihood of treatment initiation following an in-home POC test significantly improved the effectiveness of these two strategies. Findings from the cost-effectiveness analysis suggest that in a sample of 100,000 household contacts and a TB prevalence of 4.5%, a *POC Combined Sputum and Individual Tongue Swab* testing strategy would detect and link to treatment approximately 2,900 new TB cases compared to 300 (SOC).

An intermediate outcome, new TB case detected and linked to treatment, instead of a utility outcome like DALY was used to compare test strategies. This decision was largely due to the preference of using study-measured outcomes and limiting the use of modeling assumptions. Evidence from previous economic models propose a ratio of 1:1, i.e., 1 new case detected and linked to treatment equaling to 1 DALY averted, suggesting the ICERs

calculated in the current analysis would remain unchanged if DALYs were to be used.<sup>86</sup> The likelihood of strategies being adopted ultimately depends on the willingness-to-pay of policy makers.<sup>119</sup> The \$2,760 threshold used in this analysis was far more conservative than the prescribed WHO-CHOICE threshold. The impact of household contact investigation at the population level is only realized over the long term. Our current threshold is modeled off a 2-year time horizon which potentially only considers 15% of the epidemiological impact of household contact investigation.<sup>86</sup> Despite being conservative as well as potentially underestimating the long-term effects, both undominated test strategies fell far below \$2,760. These findings suggest that the adoption of in-home POC testing as part of household contact investigation shows great potential to yield positive economic returns in the long-term and should therefore be considered.

A key strength of this economic evaluation is the use of empirical cost and implementation data collected within a highly pragmatic study. This reduces reliance on modeling and findings from different contexts as both costs and effectiveness are measured in the same population.<sup>120</sup> Most existing literature relies heavily on modeling analysis rather than prospectively obtained data for similar assessments.<sup>121</sup> Consequently, we are confident that our results closely approximate the real-world programmatic costs of integrating POC molecular testing into household contact investigations. Very little research has been done to date to assesses the economic impact of implementing rapid diagnostics at POC, while none have examined its impact when integrated into household contact investigations.<sup>122</sup>

Our analysis has several limitations. Our model does not account for effects of secondary transmission, or the increased probability of transmission associated with delayed testing. Published literature on the downstream economic impact of delayed testing would suggest it's inclusion in the current model would further strengthen the case in favor for in-home POC testing, which has shown to reduce time-to-case-notification and treatment initiation.<sup>51,123</sup> The sputum yield parameters used in this analysis might be overestimated due to the exclusion of children, who are known to have diminished capacity to expectorate sputum.<sup>124</sup>

The ongoing development and refinement of rapid, POC diagnostics holds great potential for closing gaps in the TB care cascade. However, WHO endorsement alone will not be sufficient to ensure rapid uptake and adoption into national TB programs.<sup>125</sup> Integration of technologies into existing programs must be complemented by relevant system strengthening to adequately support implementation and scale-up. To promote adoption and integration, implementation studies should aim to generate the evidence needed for local policy makers to make informed decisions. This said, this study provides robust economic evidence supporting the integration of rapid POC TB testing into existing household contact investigation strategies. Future research should aim to compare these test strategies under more controlled conditions of a randomized control trial. Furthermore, studies should explore the scalability and sustainability of these strategies across diverse settings to inform tailored policy recommendations and optimize resource allocation in the fight against TB.

**CHAPTER FIVE: ACCEPTABILITY AND FEASIBILITY OF IN-HOME POC  
UNIVERSAL TB TESTING DURING HOUSEHOLD CONTACT  
INVESTIGATION.**

At the time of this dissertation submission, Manuscript 2 was published as a pre-print in medRxiv and is under review at BMC Global Health. For the purposes of this dissertation the final manuscript submitted for publication is presented here using the sections and layout prescribed by the journal. The article has been reformatted to match the dissertation style as prescribed by Boston University. See Appendix 8 for a PDF version of the most recent version of the manuscript following journal review.

**Reference:** Bezuidenhout C, Long L, Nichols B, Meyer-Rath G, Fox MP, Theron G, Fourie B, Olifant S, Penn-Nicholson A, Theron G, Ruhwald M, Medina-Marino A. Using Sputum and Tongue Swab Specimens for In-Home Point-Of-Care Targeted Universal Testing for TB Of Household Contacts: An Acceptability And Feasibility Analysis. *medRxiv [Preprint]*. 2024 Nov. doi: 10.1101/2024.11.01.24316570.

## **Abstract**

### **Introduction**

Effective strategies are needed to facilitate early detection and diagnosis of tuberculosis (TB). The over-reliance on passive case detection, symptom screening, and collection of sputum, results in delayed or undiagnosed TB, which directly contributes to on-going TB transmission. We assessed the acceptability and feasibility of in-home, Targeted Universal TB Testing (TUTT) of household contacts using GeneXpert MTB/RIF Ultra (Xpert-Ultra) at point-of-care (POC) during household contact investigation and compared the feasibility of using sputum vs. tongue swab specimens.

### **Methods**

Household contacts receiving in-home POC TUTT as part of the TB Home Study were asked to complete a post-test acceptability survey. The survey explored household contact's level of comfort, confidence in the test results, and the perceived appropriateness of in-home POC TUTT. We used the Metrics to Assess the Feasibility of Rapid Point-of-Care Technologies framework to assess the feasibility of using sputum and tongue swab specimens for in-home POC TUTT. Descriptive statistics were used to report participant responses and feasibility metrics.

## **Results**

Of 313 eligible household contacts, 267/313 (85.3%) consented to in-home POC TUTT. Of those, 267/267 (100%) provided a tongue swab and 46/267 (17.2%) could expectorate sputum. All specimens were successfully prepared for immediate, in-home testing with Xpert-Ultra on GeneXpert-Edge (Xpert-Edge). Of 164 tongue swab tests conducted, 160/164 (97.6%) generated a valid test result compared to 44/46 (95.7%) sputum-based tests. An immediate test result was available for 262/267 (98.1%) individuals based on in-home swab testing, and 44/46 (95.7%) based on in-home sputum testing. The mean in-home POC TUTT acceptability score (5=highly acceptable) was 4.5/5 (SD= 0.2).

## **Conclusion**

In-home, POC TUTT using either sputum or tongue swab specimens was highly acceptable and feasible. Tongue swab specimens greatly increase the proportion of household contacts tested compared to sputum. In-home POC TUTT using a combination of sputum and tongue swab specimens can mitigate shortcomings to case detection.

### A. Introduction

TB remains one of the world's leading infectious disease killers. Despite being preventable, treatable, and curable it caused an estimated 1.3 million deaths in 2022.<sup>126</sup> Persistent gaps in the cascade of care include TB diagnosis, notification, and linkage to treatment, all of which remain major contributors to TB burden, transmission, and mortality.<sup>120</sup> Early screening and diagnosis with World Health Organization (WHO)-recommended rapid molecular diagnostic tests like GeneXpert MTB/RIF Ultra (Xpert-Ultra; Cepheid, Sunnyvale, CA, USA) remains a key priority to meet the WHO End TB goal to achieve an 80% reduction in the annual TB deaths by 2030.<sup>126</sup> Rapid diagnosis followed by immediate treatment initiation is crucial to eradicating TB. However, despite the introduction of rapid molecular diagnostic tests like Xpert-Ultra, diagnosis remains the weakest link in the cascade of care.<sup>127</sup>

In 2021, South Africa's TB incidence was estimated to be 513 per 100,000 population, equating to ~304,000 people living with TB, of which ~120,000 were not tested, diagnosed, or initiated on treatment.<sup>128</sup> Persistent gaps in testing are attributable to a variety of factors including reliance on symptoms, symptom screening, passive case detection, limited access to testing, and fragmented delivery of testing services that requires clients to return for multiple clinic visits.<sup>51,129-131</sup> Closing these gaps necessitates strategies that are patient-centered, deliver testing at or near the POC, are conducted in a single client consultation, and are consistently provided to high risk groups.<sup>127,132</sup>

Active case finding strategies, including household contact investigation of people diagnosed with TB, have shown to be cost-effective compared to passive case detection and are increasingly recognized as a cornerstone of TB programs aimed at improving early case detection.<sup>133</sup> However, low uptake of clinic referrals, long clinic waiting times, and continued reliance on a hub-and-spoke model of sputum transportation and centralized testing (resulting in long test result turnaround) have all been cited as challenges hampering effective implementation of such strategies.<sup>134</sup> To address some of these limitations, we previously explored the acceptability and feasibility of using the GeneXpert-Edge (Xpert-Edge; Cepheid, Sunnyvale, CA, USA) for in-home, Xpert-Ultra POC testing of symptomatic household contacts as part of household contact investigation. This adapted household contact investigation strategy was acceptable and feasible, improved the proportion of symptomatic household contacts tested, and reduced test notification turnaround time, compared to those referred for clinic-based testing.<sup>50,51</sup> Despite the relative success, reliance on symptom-based screening and sputum production limited case detection.<sup>114,135</sup>

Non-specific clinical symptoms, the paucibacillary nature of sputum, and the challenge of collecting induced or expectorated sputum have all been reported as barriers to effective diagnostic testing.<sup>136,137</sup> Furthermore, the high cost of Xpert-Ultra testing as part of community-based active case finding strategies severely limits its scalability in resource constrained settings with a high TB burden.<sup>64</sup> However, major strides have been made to overcome both these barriers. Specifically, using tongue swab specimens as an alternative, less invasive sample, when sputum is not available has received increased

attention, especially as sensitivity approaches that of sputum-based molecular tests.<sup>113</sup> Moreover, pooled testing of multiple samples in a single cartridge on Xpert-Ultra has shown to save up to 48% of assay cost.<sup>138</sup> Combined, the collection of tongue swabs to increase sample yield and the pooling of samples to decrease cost may increase the likelihood of scalability of in-home POC testing during household contact investigation. Given the introduction of TUTT of all household contacts, irrespective of symptoms, there is urgent need for rapid, affordable, and accurate TB screening (and testing) strategies that could be applied universally.<sup>132</sup>

Exploration of the acceptability and feasibility of in-home POC TUTT using tongue swab specimens is warranted. In order to make prudent decisions about adopting new technologies, decision-makers need well-executed studies assessing their acceptability and feasibility.<sup>125</sup> Just because a rapid test is easy to perform does not mean it's easy to implement, especially at POC.<sup>139</sup> A variety of contextual factors and client preferences could ultimately determine the success of new healthcare interventions. It's imperative to explore and understand dynamics at the level of intended use.<sup>140</sup> To this end, we sought to: 1) assess the acceptability of in-home POC TUTT of household contacts using the Xpert-Edge; and 2) to compare the test feasibility of using sputum vs. tongue swab specimens.

## **B. Methods**

### **Study design**

This acceptability and feasibility assessment was nested within the larger TB Home Study. Data for this assessment were collected between March and September 2024. The TB Home Study sought to evaluate the predictive value of individual and pooled tongue swab specimens vs. sputum as a household-level triage test for TB during household contact investigations.<sup>114</sup> In brief, individuals with microbiologically confirmed TB were asked for permission to visit their homes and conduct a household contact investigation. All consenting household contacts were asked to provide both a sputum and tongue swab for immediate, in-home TB testing using the Xpert-Edge platform with Xpert-Ultra. All household contacts were asked to complete an acceptability survey following the completion of in-home testing. The Theoretical Framework of Acceptability guided the development of survey items designed to assess household contacts' experiences with in-home POC TB testing.<sup>103</sup> The Metrics to Assess the Feasibility of Rapid Point-of-Care Technologies framework was used to assess implementation outcomes associated with the feasibility of using sputum vs. tongue swab samples during in-home POC TURT.<sup>105</sup>

### **Study setting**

The TB Home Study was conducted in the Buffalo City Metropolitan Health District, Eastern Cape Province, South Africa. Buffalo City Metropolitan has a population size of approximately 893,000 of which 86.7% are Black. An estimated 45.3% of households are headed by women, and 24.9% of households reside in informal dwellings. An estimated 58.2% of people live in poverty and 31.1% remain unemployed.<sup>11</sup> In 2019, Buffalo City

Metropolitan had an estimated TB incidence of 876 per 100,000 population.<sup>11</sup> In 2018, the last year in which data are available, Buffalo City Metropolitan had a drug-susceptible TB treatment success rate of 71.2% (the lowest in South Africa), a loss-to-TB-care rate of 17.6% (second highest in South Africa), and an estimated 40% of TB cases missed by the health system.<sup>16</sup> TB is the leading cause of death (18.4%) amongst the 25–64 age group in Buffalo City Metropolitan.<sup>11</sup>

### **Household contact recruitment**

Details regarding the household contact investigation methods have been previously described.<sup>114</sup> Briefly, household and household contact information was obtained from people with microbiologically confirmed TB accessing services at collaborating public healthcare clinics. Contact investigation teams consisting of 2–3 trained lay community healthcare workers made up to three household visits to reach all household contacts listed. During each household visit, the contact investigation team would conduct a household contact verification check, screen for study eligibility, and introduce the study to all those present. Household contacts were deemed eligible if they were: 1) age  $\geq 18$  years; 2) not currently on TB treatment; and 3) willing to provide informed consent. Once recruited into the study, participating household contacts were asked to respond to a series of survey questions as well as provide specimens for immediate in-home testing.

### **Specimen collection and testing**

Details regarding the sample collection and testing have also been previously reported.<sup>50,51,114</sup> Briefly, prior to sputum collection, Copan FLOQSwabs were used to collect tongue swab specimens from all study participants present at the time of the household contact investigation. Tongue swabs were pooled from up to three individuals for immediate in-home testing using a single Xpert-Ultra cartridge. If a household had more than three household contacts, the additional swabs were pooled and tested in a separate reaction. Pooled tests could contain either two or three swabs at a time. Sputum samples were collected from all study participants while the tongue swab test was being conducted. Participants unable to expectorate sputum were offered sputum induction using a nebulizer. Those still unable to expectorate sputum were referred to a clinic for further clinical evaluation. Sputum samples were individually prepared and tested immediately in the house using Xpert-Ultra with the Xpert-Edge platform. Testing took ~90 minutes. Participants were referred for TB treatment based on positive sputum results while those with a negative result on sputum or positive result on a tongue swab test were referred to a clinic for further clinical evaluation.

### **Data collection and analysis**

While Xpert-Ultra testing was being conducted, a contact investigation team member collected basic socio-demographic and clinical history data from each participant. Descriptive statistics (median [IQR] for continuous variables and counts [%] for categorical variables) were used to characterize distributions of study variables in the sociodemographic questionnaire. Data collected pre- and post-testing were analyzed to

assess the acceptability of in-home POC TUTT. Pre-test acceptability was assessed as the proportion of household contacts consenting to participate out of the eligible population to whom study participation was offered. Post-test acceptability was assessed using survey data collected following the conclusion of a household investigation. The development of the post-test acceptability survey was informed by the Theoretical Framework of Acceptability, and adapted specifically for this study.<sup>103,104</sup> This survey evaluated a respondent's level of acceptability of a healthcare intervention across eight different constructs using a 5-point Likert scale (detailed in Table 5.2).

Implementation outcomes associated with sample collection and testing of sputum and tongue swab samples were captured and used to assess the feasibility of different testing methods and included: 1) type of sample collected; 2) success of sample collection; 3) processing and preparation of sample for testing; 4) outcome of test; and 5) referral outcome. The final feasibility assessment was guided by elements of the Metrics to Assess the Feasibility of Rapid Point-of-Care Technologies framework, which was designed to assess the feasibility of rapid POC technologies during proof of concept studies.<sup>105</sup> This framework was used to select and define four metrics (Table 5.3) to be included in the current assessment, including: 1) sample collection rate; 2) test processing rate; 3) test success rate; and 4) client notification rate. The performance of both sputum and tongue swab testing methods against each metric was calculated and reported.

### **Ethical considerations**

This study was conducted according to the ethical principles set forth in the Declaration of Helsinki, ICH-GCP, European Directive 2001/20/EC, US Code of Federal Regulations Title 21, South African Good Clinical Practice Guidelines, and other local regulatory requirements. The study protocol was approved by the University of Pretoria Human Research Ethics Committee (HREC 391/2021) and by Boston University Institutional Review Board (H-44118).

### **C. Results**

A total of 313 eligible household contacts were identified, of which 267/313 (85.3%) provided informed consent. All 267 participants completed the socio-demographics, clinical history, and post-test acceptability survey. The median age of participants was 41 years (IQR 28-55). The majority were Black (87.6%, 234/267), unemployed 76.4% (204/267) and had a monthly income of less than R5,000 (\$268) 89.1% (238/267). Almost a quarter (22.1%, 59/267) had a prior TB infection and just less than one fifth (16.9%, 45/267) were living with HIV. Almost a third of participants (30.3%, 81/267) screened positive for TB using the WHO-recommended four-symptom screener.

**Table 5.1. Characteristics of Household Contacts who Received In-Home POC TUTT and Completed the Post-Test Acceptability Survey**

|                                   | <b>TB symptomatic</b> | <b>Non-symptomatic</b> | <b>Overall</b> |
|-----------------------------------|-----------------------|------------------------|----------------|
|                                   | <b>n = 81</b>         | <b>n = 186</b>         | <b>N = 267</b> |
| <b>Age (years)</b> (median (IQR)) | 43 (28–56)            | 42 (28–56)             | 41 (28–55)     |
| <b>Race</b>                       |                       |                        |                |
| Black                             | 68 (84.0%)            | 166 (89.3%)            | 234 (87.6%)    |
| Colored (mixed race)              | 12 (14.8%)            | 18 (9.7%)              | 30 (11.2%)     |
| Indian                            | 0 (0%)                | 1 (0.5%)               | 1 (0.4%)       |
| Missing                           | 1 (1.2%)              | 1 (0.5%)               | 2 (0.8%)       |
| <b>Employment status</b>          |                       |                        |                |
| Unemployed                        | 63 (77.8%)            | 141 (75.8%)            | 204 (76.4%)    |
| Employed                          | 17 (21.0%)            | 44 (23.7%)             | 61 (22.8%)     |
| Missing                           | 1 (1.2%)              | 1 (0.5%)               | 2 (0.8%)       |
| <b>Education</b>                  |                       |                        |                |
| None                              | 5 (6.2%)              | 5 (2.7%)               | 10 (3.7%)      |
| Less than grade 12                | 53 (65.5%)            | 117 (62.9%)            | 170 (63.7%)    |
| Grade 12                          | 21 (25.9%)            | 41 (22.0%)             | 63 (23.6%)     |
| Tertiary                          | 1 (1.2%)              | 20 (10.8%)             | 21 (7.9%)      |
| Missing                           | 1 (1.2%)              | 3 (1.6%)               | 3 (1.1%)       |
| <b>Income per month</b>           |                       |                        |                |
| None                              | 20 (24.7%)            | 42 (22.6%)             | 62 (23.2%)     |
| Under R2000 (\$114)               | 23 (28.4%)            | 37 (19.9%)             | 60 (22.5%)     |
| R2000 - R5000 (\$114 – \$284)     | 33 (40.8%)            | 83 (44.6%)             | 116 (43.4%)    |
| R5 000 – R10 000 (\$284 – \$569)  | 3 (3.7%)              | 12 (6.5%)              | 15 (5.6%)      |
| More than R10 000 (\$569)         | 1 (1.2%)              | 11 (5.9%)              | 12 (4.5%)      |
| Missing                           | 1 (1.2%)              | 1 (0.5%)               | 2 (0.8%)       |
| <b>HIV status</b>                 |                       |                        |                |
| Negative                          | 60 (74.1%)            | 146 (78.5%)            | 206 (77.1%)    |
| Positive                          | 16 (19.8%)            | 29 (15.6%)             | 45 (16.9%)     |
| Did not want to disclose          | 4 (4.9%)              | 10 (5.4%)              | 14 (5.2%)      |
| Missing                           | 1 (1.2%)              | 1 (0.5%)               | 2 (0.8%)       |
| <b>TB history</b>                 |                       |                        |                |
| Never                             | 61 (75.3%)            | 145 (78.0%)            | 206 (77.1%)    |
| Yes, in the last two years        | 3 (3.7%)              | 5 (2.7%)               | 8 (3.0%)       |
| Yes, more than two years ago      | 16 (19.8%)            | 35 (18.8%)             | 51 (19.1%)     |
| Missing                           | 1 (1.2%)              | 1 (0.5%)               | 2 (0.8%)       |

### **Acceptability of in-home POC TUTT**

Table 5.2 lists each of the eight acceptability constructs measured, the associated survey question, and its mean score. Of the 313 household contacts that met the study eligibility criteria, 267 (85.3%) provided informed consent, suggesting a high level of acceptability for in-home POC TUTT, prior to being tested. The mean score for overall post-test acceptability of in-home POC TUTT across all eight acceptability constructs was 4.5 (SD=0.2), with 5 representing the highest level of acceptability. All constructs measuring a positive attitude towards in-home TB testing had mean scores above 4. The two constructs measuring negative attitudes toward in-home TB testing (i.e., burden and opportunity cost), had mean scores of 1.4 and 1.3, respectively, with 1 representing the least negative response. When given the option to choose between sputum or tongue swabs for future in-home TB testing, 226/267 (84.6%) chose tongue swabs.

**Table 5.2. Acceptability of In-home, POC TUTT Among Household Contacts During Household Contact Investigation**

| <b>Acceptability Construct</b> | <b>Survey Question</b>  | <b>Mean Score (SD)</b> |
|--------------------------------|---|------------------------|
| Affective attitude             | How comfortable did you feel with the in-home TB testing today?   | 4.4 (0.88)             |
| Burden                         | How much effort did it take in order for you to be tested today?  | 1.4 (0.76)             |
| Ethicality                     | How appropriate is it for healthcare workers to go to someone's household to provide TB testing services? | 4.4 (0.75)             |
| Perceived effectiveness        | The delivery of in-home testing motivates me to go to a clinic for additional TB services when I need it  | 4.2 (0.69)             |
| Intervention coherence         | It is clear to me how a positive test result would motivate someone to go to the clinic for TB treatment  | 4.3 (0.51)             |
| Self-efficacy                  | How confident are you in the test result you received today?  | 4.4 (0.60)             |
| Opportunity costs              | How did the in-home testing impact your other daily activities?   | 1.3 (0.68)             |
| General acceptability          | How acceptable was it to you for a healthcare worker to come to your house to offer TB testing?           | 4.5 (0.50)             |
| General acceptability          | How likely are you to recommend in-home TB testing to someone else?                                       | 4.5 (0.57)             |

### **Feasibility of sputum and tongue swab-based in-home POC testing methods**

Table 5.3 lists and defines the four metrics used to assess feasibility and the associated performance of each testing method. Tongue swab-based testing outperformed sputum testing on *Sample Collection Rate*. All 267 (100%) study participants were able to provide a tongue swab while only 17.2% (46/267) were able to successfully expectorate sputum for testing. Contact investigation teams successfully prepared all samples for immediate POC testing during a household contact investigation, irrespective of the sample type or number of samples pooled. The *Test Processing Rate* was consequently 100% for both specimen types. The *Test Success Rate* for tongue swab-based tests (97.6%, 160/164) was comparable to sputum (95.7%, 44/46). Two sputum tests failed to provide a test result due to a testing-error (44/46) resulting in a *Test Success Rate* of 95.7%. Tongue swab-based tests had a 97.6% (160/164) *Test Success Rate* due to 3 tests returning an error result. All participants with actionable test results were immediately notified at the time of the household investigation. Due to a higher *Test Success Rate*, tongue swab-based tests had a higher *Client Notification Rate* (98.1%) as 262 of the 267 participants received a valid in-home test result. Of the 46 participants able to provide a sputum, 44 (95.7%) received a valid, in-home test result. Among the various tongue swab-based testing methods, the pooling of three samples had a better outcome compared to both two-sample pooling and individual testing across all feasibility metrics.

**Table 5.3. Performance of Sputum and Tongue Swab Specimens During In-Home POC TUTT.**

| Metric                   | Definition   | Sputum            | Tongue Swab        |                  |                    |                    |
|--------------------------|--|-------------------|--------------------|------------------|--------------------|--------------------|
|                          |  | Total             | Total              | Single Swab      | Two Pooled Swabs   | Three Pooled Swabs |
| Sample Collection Rate   | The proportion of participants able to provide a sample for testing  | 46/267<br>(17.2%) | 267/267<br>(100%)  | 82/82<br>(100%)  | 122/122<br>(100%)  | 63/63<br>(100%)    |
| Test Processing Rate     | The proportion of tests for which all samples were prepared and processed successfully to conduct testing  | 46/46<br>(100%)   | 267/267<br>(100%)  | 82/82<br>(100%)  | 122/122<br>(100%)  | 63/63<br>(100%)    |
| Test Success Rate        | The proportion of tests that produced an actionable test result  | 44/46<br>(95.7%)  | 160/164<br>(97.6%) | 79/82<br>(96.3%) | 60/61*<br>(98.4%)  | 21/21*<br>(100%)   |
| Client Notification Rate | The proportion of participants completing the test procedure who received an immediate result notification | 44/46<br>(95.7%)  | 262/267<br>(98.1%) | 79/82<br>(96.3%) | 120/122<br>(98.4%) | 63/63<br>(100%)    |

\*The number of tests conducted is less than the number of samples collected, because samples were pooled into a single Xpert-Ultra cartridge.

#### **D. Discussion**

To our knowledge, The TB Home Study is the first to examine in-home collection and testing of sputum and tongue swabs for universal POC TB testing during household contact investigations. Our initial proof-of-concept study reported that among household contacts with TB-related symptoms, in-home testing using sputum was both acceptable and feasible.<sup>50,51</sup> The current findings demonstrate high acceptability for in-home POC TB testing among household contacts, irrespective of symptom presentation. In addition to sputum, the collection, pooling, and testing of tongue swab samples was highly feasible. Furthermore, the high collection yield of tongue swab specimens (100%) compared to sputum (17.2%) is a testament to the potential benefit of using less invasive, more readily collected sample types for TB testing if paired with highly sensitive backend molecular platforms. These results align with findings from previous research.<sup>58,112,141–143</sup>

The low yield of sputum specimens is consistent with previous studies highlighting a major shortcoming of sputum-based TB testing.<sup>49</sup> Similar to concerns related to asymptomatic or pre-symptomatic cases being missed with symptom screening is the concern of individuals who are missed who are symptomatic but unable to expectorate sputum, resulting in missed cases.<sup>53</sup> There is growing evidence highlighting the potential of tongue swabs as a viable additional or alternative specimen for TB testing due to the increased sample yield and potentially higher probability of case detection.<sup>144,145</sup> The acceptability of swab collection, highlighted during the COVID-19 pandemic, aligns with our findings, which showed high participant comfort and trust in the tongue swab-based testing process.<sup>146</sup> A relatively low (30.3%, 81/267) proportion of household contacts

presented with symptoms, highlighting the large proportion that would not have received further clinical evaluation under routine conditions. TUTT of high risk groups like household contacts could increase case detection by as much as 17%.<sup>135</sup>

While our findings support the acceptability and feasibility of in-home POC TUTT, other published work suggest that implementing rapid POC testing at scale could be challenging due to a myriad of logistical, operational, and resource constraints.<sup>147,148</sup> Earlier research on rapid diagnostic tests for malaria has shown that contextual factors such as community trust, healthcare worker training, and resource availability can influence the successful implementation of POC testing.<sup>139</sup> The accuracy of tongue swab testing for TB remains a concern.<sup>62</sup> The optimal number of swabs and approach necessary to optimize DNA recovery during processing remains an active area of research.<sup>62</sup> Similarly, although the pooling of sputum samples has been shown to be efficient at reducing costs and producing highly accurate results, uncertainty remains whether the same would hold true when pooling tongue swabs.<sup>149</sup> While the sensitivity of tongue swabs for TB diagnosis remains variable, the specificity seems notably high, yielding an overall favorable diagnostic effect.<sup>112</sup> These findings suggest that tongue swabs, in the absence of sputum, may serve as a suitable screening test for active TB disease, with a negative test result informing subsequent clinical decision making regarding eligibility for TB preventive treatment.

The importance of our findings is supported by a growing recognition for the need for accurate tests that enable prompt linkage to care, are implementable at POC often in

the community, by healthcare workers with minimal training, and with results that are available in a single client encounter.<sup>148</sup> Consideration of the feasibility of collecting, processing, and testing specimens outside of a traditional clinical setting is essential to estimating the true potential of using alternative sample types for TB testing during community-based active case finding. Despite the introduction of several new platforms, gaps in the current TB diagnostic pipeline still remain.<sup>117</sup> Exploring the potential of new platforms, assays, and testing methods that show promise for POC deployment across different use case scenarios plays an essential role in refining target product profiles.<sup>62</sup> Findings from this research can be used to inform new use case development as well as to refine target product profiles aimed at delivering near-POC and POC TB testing.

A key strength of this study was the ability to use lay community healthcare workers to conduct household contact investigations and deliver in-home POC TUBT. South Africa continues to face a severe shortage of qualified health care workers, which has resulted in task shifting to a range of lay healthcare workers.<sup>150</sup> The delivery of TB services by community healthcare workers has been shown to enhance population coverage, increase testing, improve early diagnosis and linkage to care.<sup>151</sup> Another strength of the current analysis is the use of a theory-informed instrument to measure acceptability. No standardized or validated healthcare intervention acceptability instrument currently exists.<sup>103</sup> Similar to most other evaluations, our previous work assessing the acceptability of in-home POC TB testing relied on behavioral measures of acceptability such as study enrollment and/or dropout rate. However, several reasons other than low acceptability could explain why people decline or withdraw from a healthcare intervention, including

lack of motivation, distrust, or privacy concerns. The Theoretical Framework of Acceptability is innovative in that it provides conceptually distinct constructs that capture key dimensions of acceptability allowing the assessment of complex healthcare interventions.<sup>104</sup>

Our study had several limitations. First, the high level of acceptability of POC TB testing among household contacts might be an overestimation of broader acceptability beyond household contacts. The acceptability of TB testing might be higher among contacts of people with confirmed TB compared to the general population due to increased perceived risk and awareness of the disease. Household contacts directly exposed to TB have a heightened understanding of the importance of early detection and treatment.<sup>152</sup> Secondly, this analysis did not include a cost- or cost-effectiveness analysis to estimate and compare the difference in cost and outcomes of each testing method. Pooling tongue swabs into a single Xpert-Ultra cartridge aims to reduce the total number of cartridges required, often cited as a significant factor driving testing costs.<sup>153</sup> However, sputum remains the gold standard for TB testing due to its superior sensitivity over tongue swabs.<sup>154</sup> Future studies should explore the cost-effectiveness of these different testing methods to weigh potential cost savings with decreasing test accuracy, assessing the “financial feasibility” and scalability of the proposed testing methods.<sup>132</sup> Lastly, we only offered testing to household contacts older than 18 years of age. In 2022, over 1 million children under the age of 16 developed TB globally, with an estimated 225,000 children dying from TB and associated complications.<sup>155</sup> In the same year, 7% of South Africa’s notified TB cases occurred in children age 14 years and younger.<sup>156</sup> The majority of TB deaths in children

occur from lack of diagnosis and treatment.<sup>157</sup> Effective TB diagnosis in children is hampered by several factors, including the paucibacillary nature of TB, its shared symptoms with other common childhood diseases, and most significantly, difficulties collecting samples for testing.<sup>158</sup> The collection of non-invasive samples like tongue swabs for TB screening among children during household contact investigation combined with the delivery of TB preventative treatment could have a significant public health impact and be cost-effective in preventing TB deaths in South Africa.<sup>159</sup> Failing to prioritize children and adolescents in future studies will continue to stifle progress towards TB targets.

### **E. Conclusion**

As novel platforms and diagnostics for decentralized molecular testing become more readily available, this study provides evidence to support their integration into existing strategies, including household contact investigation. Furthermore, these findings provide support for the expansion of in-home universal TB testing by minimally trained lay healthcare workers. The ability to integrate molecular POC testing into community-based strategies can reduce the workload of already overburdened laboratory and clinical facilities, improve client satisfaction, and remove persistent barriers preventing equal access to services.<sup>160</sup> In-home POC TUTT using either sputum or tongue swabs is highly acceptable and feasible. Rapid molecular TB testing with immediate result notification at POC reduces the burden placed on those at highest risk by offering testing services in a single consultation, improves access to testing, and shows great potential for early case detection and result notification.

## **CHAPTER SIX: SUMMARY OF KEY FINDINGS, RECOMMENDATIONS FOR PRACTICE, AND FUTURE RESEARCH**

### **A. Chapter Overview**

In Chapter 4, we presented the results of a cost and cost-effectiveness analysis comparing five novel in-home, POC TB testing strategies with the current standard of care. In Chapter 5, we presented the findings of an acceptability and feasibility assessment of in-home POC universal TB testing in South Africa. This body of work offers deeper insight into the costs and potential health impact resulting from integrating rapid, POC diagnostics into active case-finding initiatives, such as household contact investigation. The results from this research will inform the development of POC testing strategies for rigorous evaluation in future randomized controlled trials.

This chapter will start with a summary of the key research findings presented in Chapters 4 and 5. This is followed by a description of the practice implications resulting from these findings and how it pertains to TB policy formulation in South Africa. The conclusion includes key suggestions for future research and a brief overview of upcoming research resulting from this work.

## B. Key Findings

### **Aim 1: Cost and cost-effectiveness analysis**

Primary data collected as part of the TB Home Study were combined with additional data collected as part of this dissertational work as well as publicly available literature to formulate and compare five novel in-home POC TB testing strategies, integrated into household contact investigation.<sup>131</sup> Cost and outcome data were used to conduct a cost analysis and build a decision analytic model to compare the cost-effectiveness of competing testing strategies. The total implementation cost of delivering household contact investigation to the study population (300 households), based on the current South African National Tuberculosis Guidelines (SOC) over a 2-year period, was estimated at \$84,962. In contrast, the cost of integrating in-home POC testing into household contact investigation ranged from \$87,844 to \$93,969, depending on the testing strategy deployed.

Sputum-based testing strategies were the most expensive, with a cost-per-test of \$20.08, driven largely by the cost of Xpert-Ultra cartridges, which accounted for 40% of the total cost. Decision analytic modeling was used to estimate and compare the ICERs of competing strategies. The two most cost-effective strategies, *POC Sputum Testing* and *POC Combined Sputum and Individual Tongue Swab Testing* had ICERs falling well below the \$2,760 willingness-to-pay threshold, previously established for active case finding strategies implemented in South Africa.<sup>86</sup>

In-home POC molecular testing for TB during household contact investigation could be a cost-effective strategy for increasing TB detection and linkage to treatment. In light of the revised 2024 target product profiles for TB diagnostics set by WHO, these

findings provide valuable insight to guide the deployment of new diagnostics for different use cases and in different settings. As new diagnostic platforms are introduced to the market, economic evaluations that assess the optimal combinations of tests and algorithms will remain a top priority. Budget impact analyses would also inform the feasibility and scale of such strategies within the financial constraints of local policy frameworks. Future active case finding programs should consider the use of portable molecular testing platforms to allow near-POC and POC TB testing, especially in high TB burden, resource constrained settings.

**Aim 2: Acceptability and feasibility of universal in-home POC TB testing during household contact investigation**

We measured the acceptability of delivering universal in-home POC TB testing during household contact investigations in the Buffalo City Metropolitan Health District, Eastern Cape Province, South Africa. Pre-test acceptability was measured as the proportion of eligible household contacts who consented to an in-home POC universal TB test while post-test acceptability was evaluated using an adapted theoretical framework of acceptability. Of the 313 eligible household contacts, 85.3% consented to TB testing at home. The mean post-test score for overall acceptability was 4.5 (SD:0.2), with 5 presenting the highest level of acceptability. Participants expressed a strong preference for tongue swab collection over sputum, with 84.6% recommending its use in future in-home POC TB testing strategies.

The feasibility of two in-home POC testing methods—sputum vs. tongue swab—was assessed using an adapted feasibility framework. Tongue swab-based testing outperformed sputum-based testing in terms of *Sample Collection Rate*. All 204 participants (100%) successfully provided a tongue swab, while only 46 (17.2%) could expectorate sputum. The *Test Processing Rate* was 100% for both methods, however the *Test Success Rate* was higher for tongue swabs (97.6%) compared to sputum (95.7%). Additionally, the *Client Notification Rate* was higher for tongue swab tests (98.1%) compared to sputum (95.7%).

These findings demonstrate high acceptability for in-home POC universal TB testing and strong feasibility for both sputum- and tongue swab-based methods. Importantly, the 100% sample yield for tongue swabs addresses a key limitation in sputum-based TB testing. This finding highlights the value of increased diagnostic yield resulting from less invasive sample collection, a factor often omitted in current diagnostic evaluations.<sup>141,161</sup> While these results support the viability of in-home POC universal TB testing, scaling in-home POC TB testing may pose logistical, operational, and resource challenges.

Several recommendations were proposed in light of these concerns, particularly regarding the variability in the sensitivity of tongue swabs for TB diagnosis. Most importantly, the diminished accuracy of tongue swabs should not be a reason for its exclusion in testing strategies. Tongue swab testing should be considered for inclusion in combination testing algorithms as well as to guide clinical decision making to inform eligibility for delivering TB preventative therapy. The central role that community health

workers play in the delivery of community-based active case finding was also highlighted. Task-shifting TB screening and testing to community health workers holds promise for expanding population coverage and reducing the burden on overcrowded public healthcare clinics.

### **C. Recommendations for Practice**

#### **1. Adapting to innovation in TB diagnostics**

The global TB diagnostic gap is estimated at 30%, which means of the estimated 10 million TB cases, about 3 million remain undiagnosed.<sup>162</sup> Equally concerning is the estimated 15% of known cases which are lost-to-follow-up prior to treatment initiation.<sup>32,163</sup> The resulting impact of these persistent shortcomings on continued TB transmission has been highlighted throughout this dissertation. Globally, these findings have highlighted the urgent need for decentralized, rapid, non-sputum-based, molecular TB testing and linkage to care.<sup>164</sup> The findings presented in the preceding chapters shows progress towards this end through the successful delivery of in-home POC TB testing using tongue swab samples. However, despite its potential, tongue swab testing requires further operational optimization to improve its performance relative to sputum.<sup>142</sup>

Despite significant advancements made in the field of diagnostic development, none have met the stringent optimal triage or confirmatory test criteria detailed in WHO's 2014 target product profiles.<sup>165</sup> In the absence of diagnosis, efforts to provide adequate and prompt treatment, and hence curb transmission, cannot be undertaken. Improved testing not only includes highly sensitive and specific assays for diagnosis but also tests that are

affordable, rapid, and can be conducted at POC by lay health care workers with minimal training using less invasive samples types.<sup>166,144</sup> Several technologies, especially those with the potential for non-invasive, non-sputum based testing, like the Xpert-Edge mentioned throughout this work, hold great promise for efficient POC triaging and confirmatory testing.<sup>51,143,165</sup> The TB field however would greatly benefit from the availability of a variety of additional TB diagnostic solutions.<sup>167</sup>

WHO releases high-priority target product profiles for novel diagnostics in order to foster innovation and link end-user demands with test targets and specifications.<sup>161</sup> In 2024 WHO released its updated target product profiles for a rapid test detecting TB at the peripheral level. The updated target product profiles included, for the first time, definitions for a POC test and near-POC test. Additionally, distinction was made between sputum- and non-sputum-based tests, suggesting that either option would be suitable if required targets are met. The specificity target (>98%) was consistent across test types while sensitivity was set at 75% and 65% for non-sputum, near-POC tests and non-sputum, POC tests, respectively. Accuracy estimates were informed by modelling which incorporated trade-offs between test accuracy and increased access to testing. Our findings presented in Chapter 3 highlighted the cost-effectiveness of using tongue swab samples because of its increased sample yield, despite lower accuracy. The revised accuracy estimates described in the updated target product profiles have provided further justification for the adoption of novel POC test strategies like those presented in this dissertation.

An assortment of other sample types and POC diagnostic tests, in addition to Xpert-Edge and tongue swabs, could be considered for future POC triage and confirmatory

testing. Antigen tests like Fujifilm SILVAMP TB LAM which uses urine and returns results in an hour has shown >65% sensitivity and 98% specificity.<sup>168</sup> Comparably, C-reactive protein testing has shown 78% sensitivity and 73% specificity while digital chest X-ray coupled with AI software has shown >90% sensitivity and 70% specificity.<sup>169</sup> This technological progress have created a myriad of diagnostic possibilities that could be embedded in tailored clinical algorithms, making them increasingly more feasible for use during active case finding in resource-limited settings.<sup>167</sup>

The implementation of novel, less invasive tests should commence despite their shortcomings, even if in combination with more accurate, well documented approaches like sputum-based testing.<sup>62</sup> Tongue, or perhaps in the near future “pooled tongue swabs”, in combination with more accurate rapid molecular tests for diagnosing TB should be considered. The overall diagnostic yield of such approaches is significantly increased and lives can be saved.<sup>170</sup> The findings presented throughout this dissertation provide evidence in support of this form of combination testing. Ultimately, the adoption of such strategies are dependent on the settings in which they are implemented, the needs of the targeted population, and the willingness to pay of decision makers.<sup>165</sup>

Actualizing the potential of these technologies ultimately lies with local policymakers and health workers who determine the extent to which they are adopted. Political will combined with continued investment is required to encourage developers’ interest in low-and middle-income countries, the primary market for TB diagnostics.<sup>167</sup> The South African National Department of Health has realized the importance of prioritizing innovation and integration of novel strategies into existing TB programs. This is evident

from the 2023–2028 National TB Strategic Plan. Key provincial activities have been outlined to ensure effective integration of new TB testing platforms into active case finding including: 1) training of community health workers to deliver community-based screening and testing, 2) scale-up of screening and testing modalities that do not rely on sputum, 3) testing all priority populations irrespective of symptoms.<sup>171</sup>

We suggest that the South African government implement a multi-pronged strategy in both policy and execution to ensure the successful integration of novel TB testing platforms into existing programs. Policymakers should focus on incorporating the latest WHO recommendations into national guidelines while ensuring that procurement processes are streamlined to facilitate the rapid adoption of new diagnostic technologies. Investment in infrastructure and healthcare workforce training is essential to scale up diagnostic services, especially in rural areas. Additionally, establishing public-private partnerships and increasing funding for TB research and development will be key to ensuring that South Africa remains at the forefront of TB diagnostics and ultimately meets its ambitious targets for TB elimination.

Essential provincial activities highlighted include:

1. Established improved community-based models for TB screening and testing.
2. Test all priority populations, including recent contacts for people with confirmed TB, regardless of symptom presentation.
3. Improving referral networks between community-based testing and treatment uptake at primary care facilities, using electronic tracking tools.<sup>172</sup>

4. Advocate to private sector to assist with strengthening network communication between health facilities and a community-based workforce.<sup>173</sup>

Essential national activities highlighted include:

1. To monitor the development of new platforms and technologies and, if appropriate, liaise with SAHPRA to streamline approval and adoption and thereby removing barriers to entry.<sup>171</sup>
2. Updating community health worker training manual to further strengthen community-based screening and testing.
3. Update TB guidelines as new technologies and evidence-based interventions become available.
4. Liaise with primary healthcare Directorate and HIV Programme to support test and treat initiatives, including provision of child-, adolescent-, and men-friendly screening and diagnostic services.

**2. Engaging community health workers**

Effective deployment of community health workers is crucial for progress towards the Sustainable Development Goals and health system transformation aimed at attaining universal health coverage.<sup>174</sup> Community health workers, in partnership with other health professionals, bridge the gap between communities and healthcare service provision within primary healthcare clinics.<sup>150</sup> This healthcare cadre has played a key role in the transition of healthcare in South Africa following the abolishment of apartheid. As the South African primary healthcare system prioritized equitable provision, prevention, and health promotion, there was a renewed focus on the role of community health workers to task-

shift HIV/AIDS and TB care in lieu of major health worker shortages. By 2010, approximately 70,000 community health workers were employed by over 3,000 community-based organizations across the country.<sup>175</sup> Initially however community health workers were narrowly focused to achieve specific directives, restricting focus to single-diseases and limiting integration into the formal primary healthcare system.<sup>150,176</sup>

To address these shortcomings, the primary healthcare re-engineering strategy was launched in 2011, formalizing the establishment of community health workers teams, referred to as Ward-based Primary Healthcare Outreach Team, forming a critical component of the updated strategy.<sup>174</sup> Ideally, teams comprise of six to ten community health workers, supervised by an outreach team leader, usually a nurse.<sup>177</sup> Community health workers are selected from the communities where they live and are accountable to the same communities.<sup>177</sup> Each team is responsible for approximately 2,000 households in a ward with each community health workers servicing nearly 250 households.<sup>174</sup> Since its inception, the need for expansion of Ward-based Primary Healthcare Outreach Team programs have received increased attention as an affordable and critical intervention in attaining universal healthcare coverage.<sup>174</sup>

The implementation of active case finding for TB is well described as part of community-based services implemented by Ward-based Primary Healthcare Outreach Teams in a number of settings.<sup>151</sup> Active case finding strategies like household contact investigation of known TB cases have shown to be cost-effective compared to passive case detection and are increasingly recognized as a cornerstone of TB programs aimed at improving early case detection and increasing access to care.<sup>133</sup> Community-based service

delivery by community health workers relieves the burden placed on clinic-based staff while simultaneously expands reach to people that are unlikely to self-present at clinics. Implementation mandates driven by individual provinces in South Africa have however resulted in implementation variability.<sup>176</sup> Currently there are only half the Ward-based Primary Healthcare Outreach Teams needed to cover all 4,277 wards across the country.<sup>150</sup> In the Eastern Cape, only two-thirds of the clinics are engaged with active case finding for TB, despite 88.7% having community health workers in their catchment area.<sup>151</sup> Increased emphasis needs to be placed on the importance of effective management of these programs to realize improvements across the entire continuum of TB care.<sup>178</sup>

A plethora of research has documented the successes across the TB care continuum resulting from effective integration of Ward-based Primary Healthcare Outreach Team programs. The DETECTB study leveraged door-to-door screening to significantly increase case detection rates from 287/100,000 to 380/100,000.<sup>35</sup> The ZAMSTAR trial in South Africa showed positive trends towards decreased TB incidence in homes receiving household-level interventions.<sup>36</sup> Further modeling done in South Africa demonstrated that community health workers can be capacitated to conduct cost-effective community-based TB case detection with a threshold of \$6,618 per life year saved.<sup>179</sup> Operation ASHA deployed in India have equipped community health workers with digital screening algorithms resulting in 100% linkage to care following a positive TB diagnosis.<sup>180</sup> Similarly, Ethiopian community health workers reduced treatment default rates from 21% to 3% within only 4.5 years.<sup>181</sup>

Despite the Ward-based Primary Healthcare Outreach Team strategy being anchored in formal policy in South Africa, several challenges need to be addressed to realize its potential in the delivery of active case finding for TB. Major constraints continue to hinder effective scale up and performance of Ward-based Primary Healthcare Outreach Teams. Lack of clear national leadership and budgetary commitments, poor governance, limited training and vocational guidance, absence of community health workers team leaders, and poor service integration have all been documented as areas in need of improvement.<sup>182-184</sup> The successful integration of in-home POC TB testing into household contact investigation will be determined by the success to which the South African National Department of Health is able to effectively mobilize the Ward-based Primary Healthcare Outreach Team workforce.

Recommendations to improve successful mobilization include:

1. Defining relationships between Ward-based Primary Healthcare Outreach Teams and governance structures at the community-, primary health care-, and provincial level.<sup>175,185</sup>
2. Conducting staffing need assessments to estimate the optimal ratio of community health workers to households.<sup>185,186</sup>
3. Developing a comprehensive, supportive supervision framework for Ward-based Primary Healthcare Outreach Teams that includes regular in-service training and development.<sup>187,188</sup>

4. Refocusing efforts to wards at most need, potentially restricting active case finding to rural areas while further resources are identified for complete quality coverage.<sup>189,190</sup>
5. A mobile health solution to streamline referral pathways between providers and improve referral uptake.<sup>191</sup>

#### **D. Future Research**

Recommendations for future research in POC TB testing during active case finding should focus on: 1) improving the diagnostic accuracy of available platforms and testing methods, 2) updating testing algorithms, 3) system strengthening, and 4) evaluating the cost-effectiveness of different testing strategies.

The current diagnostic pipeline is diverse and multiple test concepts and testing algorithms could be developed, assessed, and compared.<sup>147,166,192</sup> Continued research should focus on refining current assay performance by including other potential biological markers.<sup>193</sup> Further optimization of sample collection, processing, and testing protocols should be prioritized to maximize accuracy of novel sample testing techniques.<sup>167</sup> It is important for researchers and policymakers to move beyond the singular focus on diagnostic accuracy as the sole measure of the diagnostic value of a test.<sup>141,194</sup> More research should focus on how tests can be optimally combined to form combination testing algorithms. Test developers, international agencies (like FIND, USAID, Global Fund), and local policymakers should consider WHO's updated target product profiles in their future planning and decision making.

Realistically, the introduction of novel platforms and testing algorithms should be phased and tailored to local contexts. It is imperative that we engage in more operational research to investigate how TB screening and diagnostic tools can be better implemented to deliver improved person-centered care, including in-home testing.<sup>194</sup> This operationalization should be done on a country-by-country basis, considering existing diagnostic gaps, and prioritizing the streamlining of different deployment strategies.<sup>141</sup>

The potential increase in the number of people tested, resulting from improved POC access to TB diagnostic testing coupled with the ease of non-invasive sample collection, and rapid results, must be planned for.<sup>108,165</sup> Health system strengthening aimed at supporting the implementation of new diagnostics and strengthening linkage to treatment of new cases is essential. Active case finding with integrated delivery of at-home TB testing requires coordination of multiple steps with each potentially affected by numerous complicating factors. Operational research should aim to identify core components of such strategies to improve implementation across a variety of local contexts. The Unitaaid-funded START 4-ALL project, for example aims to advance research on TB screening and diagnostic algorithms and combinations of tools with the aim of generating evidence to support the expansion of TB screening and diagnostic testing in community and primary care settings.<sup>195</sup>

It is crucial to consider the impact of improved test access on the overall tuberculosis program, particularly with respect to human resources and budget.<sup>196</sup> To improve future implementation of household contact investigation, especially in resource constrained settings, further studies should evaluate strategies to increase efficiency.

Health economic research is needed to assess the costs associated with using different tests while comparing the effectiveness of different test algorithms. Comparative cost-effectiveness analysis questions, similar to those explored in this dissertation, should be investigated. Research towards these aims will elucidate valuable evidence to inform the optimal deployment of combinations of tools for different use cases and in different settings. As new diagnostic platforms are introduced in the market these forms of economic evaluation of optimal combinations of tools and algorithms will continue to be a high priority.

Findings from this dissertation are currently being used to inform a subsequent grant application to the National Institutes of Health. We aim to conduct a randomized controlled trial to compare the delivery of three different in-home POC TB testing strategies. To address some of the limitations in our existing work, household contacts will be assigned to receive a singular POC testing strategy allowing for more rigorous cost and effectiveness comparison across mutually exclusive strategies. In addition, we have included the delivery of TB preventive therapy during in-home POC testing to further aid in our efforts to curb TB transmission.

**APPENDIX 1. BASE VALUE, RANGE, AND DESCRIPTION OF VARIABLES USED IN COST-EFFECTIVENESS ANALYSES COMPARING DIFFERENT HOUSEHOLD CONTACT INVESTIGATION TESTING STRATEGIES**

| PARAMETER  | BASE-CASE VALUE | LOW                | HIGH               | SOURCE    |
|--|-----------------|--------------------|--------------------|-----------|
| Prevalence of Tuberculosis among Household Contacts            | 0.045           | 0.033              | 0.078              | 197–200   |
| <b>SOC</b>   |                 |                    |                    |           |
| Probability of Test Result Available                           | 0.107           | 0.099              | 0.128              | 41,*      |
| Sensitivity of Test  | 0.932           | 0.872              | 0.953              | 201–203   |
| Specificity of Test  | 0.964           | 0.963              | 0.981              | 201–203   |
| Probability of Presenting for Treatment Initiation             | 0.680           | 0.440              | 0.850              | 30,62     |
| <b>POC Sputum Testing</b>                                      |                 |                    |                    |           |
| Probability of Test Result Available                           | 0.383           | 0.287 <sup>†</sup> | 0.479 <sup>†</sup> | 204,205,* |
| Sensitivity of Test  | 0.932           | 0.872              | 0.953              | 206–208   |
| Specificity of Test  | 0.964           | 0.963              | 0.981              | 206–208   |
| Probability of Presenting for Treatment Initiation             | 0.846           | 0.635 <sup>†</sup> | 1 <sup>†</sup>     | *         |
| <b>POC Individual Tongue Swab Testing</b>                      |                 |                    |                    |           |
| Probability of Test Result Available                           | 0.827           | 0.620 <sup>†</sup> | 1 <sup>†</sup>     | *         |
| Sensitivity of Test  | 0.778           | 0.360              | 0.910              | 112,209   |
| Specificity of Test  | 0.930           | 0.660              | 1 <sup>†</sup>     | 209       |
| Probability of Presenting for Treatment Initiation             | 0.846           | 0.635 <sup>†</sup> | 1 <sup>†</sup>     | *         |
| <b>POC Pooled Tongue Swab with Confirmatory Sputum Testing</b> |                 |                    |                    |           |
| Probability of Pooled Test Result Available                    | 0.898           | 0.674 <sup>†</sup> | 1 <sup>†</sup>     | *         |
| Sensitivity of Test  | 0.514           | 0.333              | 0.910              | *         |
| Specificity of Test  | 1               | 0.660              | 1                  | *         |

|  |       |                    |                    |             |
|--|-------|--------------------|--------------------|-------------|
| Probability of Confirmatory Test Result Available  | 0.682 | 0.386              | 0.852              | *           |
| Sensitivity of Confirmatory Sputum Test  | 0.932 | 0.872              | 0.953              | 206-208     |
| Specificity of Confirmatory Sputum Test  | 0.964 | 0.963              | 0.981              | 206-208     |
| Probability of Presenting for Treatment Initiation Following Sputum Test                 | 0.846 | 0.635 <sup>†</sup> | 1 <sup>†</sup>     | *           |
| <b>POC Pooled Tongue Swab with Confirmatory Tongue Swab Testing</b>                      |       |                    |                    |             |
| Probability of Pooled Test Result Available  | 0.898 | 0.674 <sup>†</sup> | 1 <sup>†</sup>     | *           |
| Sensitivity of Pooled Test   | 0.514 | 0.333              | 0.910              | *           |
| Specificity of Pooled Test   | 1     | 0.660              | 1                  | *           |
| Probability of Confirmatory Test Result Available  | 0.829 | 0.622 <sup>†</sup> | 1 <sup>†</sup>     | *           |
| Sensitivity of Confirmatory Tongue Swab Test   | 0.778 | 0.360              | 0.910              | 112,209     |
| Specificity of Confirmatory Tongue Swab Test   | 0.930 | 0.660              | 1                  | 112,209     |
| Probability of Presenting for Treatment Initiation Following Individual Tongue Swab Test | 0.846 | 0.635 <sup>†</sup> | 1 <sup>†</sup>     | *           |
| <b>POC Combined Sputum and Individual Tongue Swab Testing</b>                            |       |                    |                    |             |
| Probability of Sputum Test Result Available  | 0.383 | 0.287 <sup>†</sup> | 0.479 <sup>†</sup> | 204,205,*   |
| Sensitivity of Sputum Test   | 0.932 | 0.872              | 0.953              | 202,206,207 |
| Specificity of Sputum Test   | 0.964 | 0.963              | 0.981              | 202,206,207 |
| Probability of Presenting for Treatment Initiation Following Sputum Test                 | 0.846 | 0.635 <sup>†</sup> | 1 <sup>†</sup>     | *           |
| Probability of Individual Tongue Swab Test Result Available                              | 0.827 | 0.620 <sup>†</sup> | 1 <sup>†</sup>     | *           |
| Sensitivity of Individual Tongue Swab Test   | 0.778 | 0.360              | 0.910              | 112,209     |
| Specificity of Individual Tongue Swab Test   | 0.930 | 0.660              | 1                  | 112,209     |
| Probability of Presenting for Treatment Initiation Following Individual Tongue Swab Test | 0.846 | 0.635 <sup>†</sup> | 1 <sup>†</sup>     | *           |

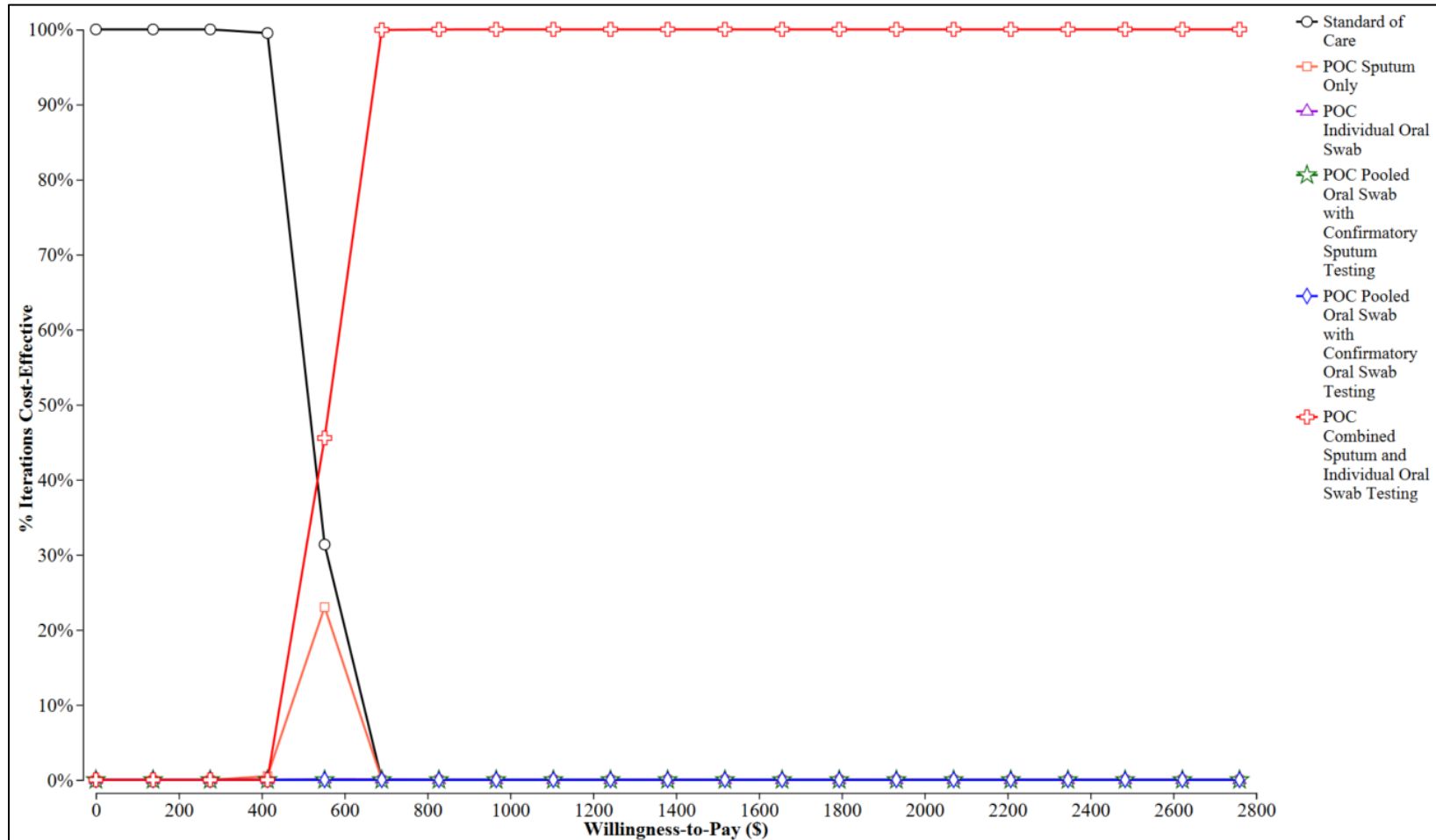
\*Obtained from primary study data <sup>†</sup> Bound defined as a 25% decrease from point estimate. TB = tuberculosis; SOC = standard of care; POC = point of care.

**APPENDIX 2. BASE-CASE COST-PER-TEST, RANGE, AND DESCRIPTION OF COSTS IN COST-EFFECTIVENESS ANALYSES COMPARING DIFFERENT HOUSEHOLD CONTACT INVESTIGATION TESTING STRATEGIES**

| PARAMETER  | BASE-CASE VALUE (\$) | LOW (\$)           | HIGH (\$)           | SOURCE |
|--|----------------------|--------------------|---------------------|--------|
| Household contact investigation cost per contact       | 129·09               | 96·82 <sup>†</sup> | 161·36 <sup>†</sup> | *      |
| Cost of result notification                            | 0·66                 | 0·49 <sup>†</sup>  | 0·82 <sup>†</sup>   | *      |
| <b>SOC</b>   |                      |                    |                     |        |
| Cost per test  | 20·08                | 15·06 <sup>†</sup> | 25·11 <sup>†</sup>  | *      |
| <b>POC Sputum Testing</b>                              |                      |                    |                     |        |
| Cost per test  | 20·08                | 15·06 <sup>†</sup> | 25·11 <sup>†</sup>  | *      |
| <b>POC Individual Tongue Swab Testing</b>              |                      |                    |                     |        |
| Cost per test  | 19·29                | 14·47 <sup>†</sup> | 24·12 <sup>†</sup>  | *      |
| <b>POC Pooled Tongue Swab with Sputum Testing</b>      |                      |                    |                     |        |
| Cost per pooled test                                   | 15·73                | 11·80 <sup>†</sup> | 19·67 <sup>†</sup>  | *      |
| Cost per confirmatory sputum test                      | 16·34                | 12·23 <sup>†</sup> | 20·43 <sup>†</sup>  | *      |
| <b>POC Pooled Tongue Swab with Tongue Swab Testing</b> |                      |                    |                     |        |
| Cost per pooled test                                   | 15·73                | 11·80 <sup>†</sup> | 19·67 <sup>†</sup>  | *      |
| Cost per confirmatory tongue swab test                 | 15·55                | 11·66 <sup>†</sup> | 19·44 <sup>†</sup>  | *      |
| <b>POC Combined Sputum and Tongue Swab Testing</b>     |                      |                    |                     |        |
| Cost per sputum test                                   | 20·08                | 15·06 <sup>†</sup> | 25·11 <sup>†</sup>  | *      |
| Cost per individual tongue swab test                   | 15·55                | 11·66 <sup>†</sup> | 19·44 <sup>†</sup>  | *      |

\*Obtained from primary study data. <sup>†</sup>Bound defined as a 25% increase/decrease from point estimate. SOC = standard of care; POC = point-of-care.

### APPENDIX 3. COST-EFFECTIVENESS ACCEPTABILITY CURVE



**APPENDIX 4. MANUSCRIPT 1: SPUTUM AND TONGUE SWAB MOLECULAR TESTING FOR THE IN-HOME DIAGNOSIS OF TUBERCULOSIS IN UNSELECTED HOUSEHOLD CONTACTS: A COST AND COST-EFFECTIVENESS ANALYSIS**

**Title: Sputum and tongue swab molecular testing for the in-home diagnosis of tuberculosis in unselected household contacts: a cost and cost-effectiveness analysis**

**Authors:**

Charl Bezuidenhout<sup>1\*</sup>, Lawrence Long<sup>1,2</sup>, Brooke Nichols<sup>1,3,4</sup>, Gesine Meyer-Rath<sup>1,2,5</sup>, Matthew P Fox<sup>1,2,6</sup>, Grant Theron<sup>7</sup>, Bernard Fourie<sup>8</sup>, Sharon Olifant<sup>8</sup>, Adam Penn-Nicholson<sup>9</sup>, Morten Ruhwald<sup>9</sup>, Andrew Medina-Marino<sup>10,11,12\*</sup>

**Affiliations:**

Charl Bezuidenhout: 1. Department of Global Health, Boston University School of Public Health, Boston, U.S.

Lawrence Long: 2. Health Economics and Epidemiology Research Office, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; 1. Department of Global Health, Boston University School of Public Health, Boston, U.S.

Brooke Nichols: 1. Department of Global Health, Boston University School of Public Health, Boston, USA; 2. FIND, Geneva, Switzerland; 3. Wits Diagnostic Innovation Hub, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; 4. Department of Global Health, Amsterdam Institute for Global Health and Development, Amsterdam University Medical Center, Amsterdam, the Netherlands

Gesine Meyer-Rath: 2. Health Economics and Epidemiology Research Office, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; 1. Department of Global Health, Boston University School of Public Health, Boston, US; 5. The South African Department of Science and Innovation/National Research Foundation Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch University, Stellenbosch, South Africa

Matthew P Fox: 2. Health Economics and Epidemiology Research Office, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; 6. Department of Epidemiology, Boston University School of Public Health, Boston, USA; 1. Department of Global Health, Boston University School of Public Health, Boston, USA

Grant Theron: 7. DSI-NRF Centre of Excellence for Biomedical Tuberculosis Research, South African Medical Research Council Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Bernard Fourie: 8. Department of Medical Microbiology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

Sharon Olifant: 8. Department of Medical Microbiology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

Adam Pen-Nicholson: 9. Find, Geneva, Switzerland

Morten Ruhwald: 9. Find, Geneva, Switzerland

Andrew Medina-Marino: 10. Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa; 11. Eastern Cape Research Site, Desmond Tutu Health Foundation, East London, South Africa; 12. Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania

**Co-Corresponding Authors:**

Andrew Medina-Marino, Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa. Email: [andrewmedinamarino@gmail.com](mailto:andrewmedinamarino@gmail.com)

Charl Bezuidenhout, Boston University School of Public Health, Department of Global Health. Email: [cwbips@gmail.com](mailto:cwbips@gmail.com)

**Summary:**

We evaluated the cost-effectiveness of in-home point-of-care TB testing of household contacts. The findings indicate that combined testing strategies using tongue swab and sputum specimens could significantly increase TB case detection and linkage to treatment, with modest additional program costs.

**ABSTRACT:****Background**

Delayed and missed diagnosis are a persistent barrier to tuberculosis control, partly driven by difficulties collecting sputum and an unmet need for decentralized testing. Household contact investigation with point-of-care testing of non-invasive specimens are hitherto undescribed and may offer a cost-effective solution to strengthen active case finding.

**Methods**

In-home molecular point-of-care testing was conducted using sputum and tongue specimens collected from household contacts of people with confirmed tuberculosis residing in South Africa. A health economic assessment was executed to estimate and compare the cost and cost-effectiveness of different in-home point-of-care testing strategies, against centralized sputum testing (standard of care) from a provider's perspective. The primary cost-effectiveness outcome was measured as the incremental cost per additional household contact with TB detected and linked to treatment. Decision analytic modeling was used to estimate and compare incremental cost effectiveness ratios across strategies.

**Results**

The total implementation cost of delivering the standard of care for a 2-year period was \$84 962. Strategies integrating in-home point-of-care testing ranged between \$87 844 - \$93 969. The cost-per-test for in-home point-of-care sputum testing was the highest at

\$20.08 per test. Two strategies, *Point-of-Care Sputum Testing* and *Point-of-Care Combined Sputum and Individual Tongue Swab Testing* were the most cost-effective with ICERs of \$543.74 and \$547.29 respectively, both below a \$2 760 willingness-to-pay threshold.

### **Conclusion**

In-home point-of-care molecular TB testing strategies utilizing combination testing of tongue swabs and sputum specimens can meaningfully improve the number of people tested, diagnosed, and notified during household contact investigation, while being cost-effective.

**Key Words:** Tuberculosis, Active Case Finding, Cost-Effectiveness

**INTRODUCTION:**

An estimated 25 000 people still die from tuberculosis (TB) every week, despite the disease being curable.<sup>1</sup> Globally in 2022, 10.6 million people developed TB of which 3.1 million were never diagnosed or treated.<sup>2</sup> People with missed or delayed diagnoses have elevated morbidity and mortality, and drive on-going transmission.<sup>3</sup> Therefore, implementation of effective, evidence-based strategies that can increase access to testing, deliver real-time point-of-care (POC) diagnosis, and improves treatment initiation, are urgently required.<sup>4</sup>

Early screening and diagnosis is key to TB control.<sup>5</sup> Active case finding strategies like household contact investigation (HCI) of known cases is widely recognized as a cornerstone of TB programs, but remains hampered by difficulties collecting sputum and an unmet need for decentralized testing.<sup>6</sup> To this end, the WHO target product profile for new TB diagnostics place standalone, non-sputum-based POC tests as one of its highest priorities.<sup>7</sup> For optimal POC diagnostic tests, its cost-effectiveness is mainly a trade-off between sample collection yield, sensitivity and specificity, and cost.<sup>8</sup> Recent studies have shown that it is feasible to integrate real-time POC molecular platforms like the GeneXpert Edge (Xpert-Edge; Cepheid, Sunnyvale, CA, USA) into HCI, thus decentralizing testing services and increasing access to testing for those at-risk for TB.<sup>9,10</sup> However, these studies have continued to rely on sputum-based testing alone.

Non-invasive tongue swab specimens are emerging as an alternative to sputum.<sup>11</sup> Recent work reported tongue swab qPCR sensitivity and specificity to be 93% and 99%, respectively, against a microbiological reference standard, rivaling that of sputum-based

molecular testing.<sup>12</sup> However, most tongue swab studies have recruited individuals already in care or with TB-related symptoms, limiting our understanding of the potential benefit of its integration into HCI strategies. The TB Home Study recently found that testing of household contacts (HHCs) of people with confirmed TB using tongue swabs resulted in >95% of all contacts being tested for TB and increased the diagnostic yield of cases detected when integrated into HCI.<sup>13</sup>

Consideration for the adoption of HCI is influenced by the anticipated cost and expected population reach and case detection. Similarly, diagnostic accuracy, costs, and operational characteristics, guide policy decision making around the adoption of novel tests. As part of the TB Home Study, we collected resource use and costs to conduct an economic evaluation of HCI from the provider perspective, comparing the total cost of delivering five novel in-home POC testing strategies against centralized sputum testing (SOC; standard-of-care), over a 2-year time horizon. Additionally, we employed decision analytic modeling to estimate and compare the cost-effectiveness of different strategies.

**METHODS:****Study Design and Participants**

We used data obtained from the TB Home Study, which has been described in detail elsewhere.<sup>13</sup> Participants were enrolled between July, 2021 and June, 2023 in the Buffalo City Metro Health District, Eastern Cape Province, South Africa. The study sought to evaluate the predictive value of pooled individual tongue swab specimens vs. sputum as a household-level triage testing strategy for TB during HCI using the Xpert MTB/RIF Ultra cartridge (Xpert-Ultra; Cepheid, Sunnyvale, CA, USA) with the Xpert-Edge. HCI of 300 people with confirmed TB were performed. A total of 630 consenting HHCs were asked to first provide two tongue swabs followed by a single sputum specimen.<sup>13</sup> One swab from each participant was first pooled for immediate, in-home Xpert-Ultra testing. The second swab was placed in Prime Store Molecular Transport Media (Longhorn Diagnostics, Inc, USA), transported, and tested at a centralized lab. For all participants, irrespective of symptoms, able to produce a spot-sputum, immediate in-home testing was performed using Xpert-Ultra on Xpert-Edge. Those with a positive sputum test result were immediately referred for clinic-based treatment initiation. Population characteristics and referral outcomes (i.e., proportion of HHCs presenting to the clinic for treatment; time-to-clinic presentation) have been described.<sup>13</sup>

**Decision Analytic Model Design and Approach**

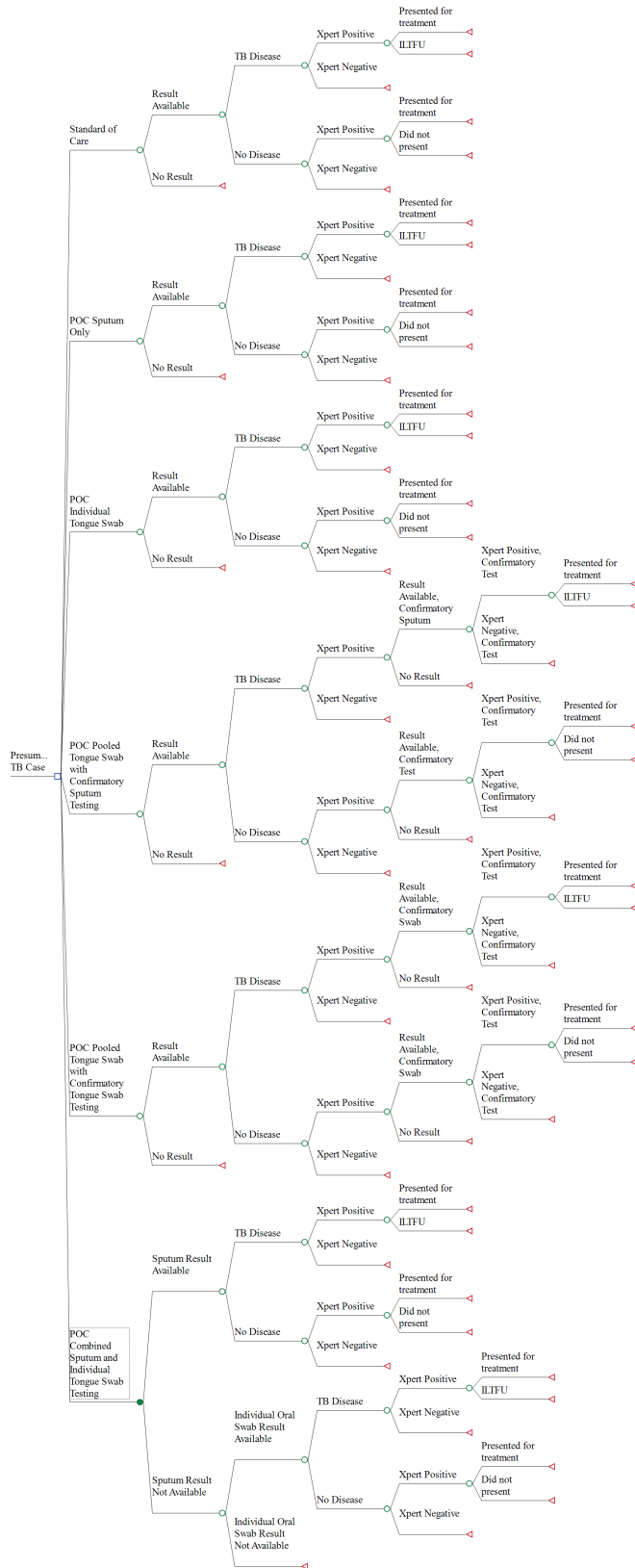
We used intermediate outcome and cost data empirically collected from the TB Home Study to formulate, analyze, and compare the total cost and cost-effectiveness of different

testing strategies, deployed as part of HCI. Emphasis was placed on estimating and comparing the economic impact of strategies that incorporate in-home POC testing, against centralized sputum testing (SOC). A conceptual model was developed detailing the patient diagnostic pathways for each strategy, ultimately informing the final decision analytic model (Figure 1). The conceptual model guided the identification of common elements across diagnostic pathways to promote consistency across activity descriptions at each decision node. Five novel in-home POC testing strategies in addition to the SOC are listed below and further detailed in Supplemental Table 1:

- 1) **Standard-of-Care:** Centralized sputum-based testing on Xpert-Ultra.
- 2) **Point-of-Care Sputum Testing:** In-home POC individual sputum-based testing on Xpert-Ultra using Xpert-Edge.
- 3) **Point-of-Care Individual Tongue Swab Testing:** In-home POC individual tongue swab-based testing on Xpert-Ultra using Xpert-Edge.
- 4) **Point-of-Care Pooled Tongue Swabs with Confirmatory Sputum Testing:** In-home POC pooled tongue swab-based testing on Xpert-Ultra using Xpert-Edge followed by confirmatory individual sputum-based testing on Xpert-Ultra using Xpert-Edge.
- 5) **Point-of-Care Pooled Tongue Swabs with Confirmatory Tongue Swab Testing:** In-home POC pooled tongue swab-based testing on Xpert-Ultra using Xpert-Edge followed by confirmatory individual tongue swab-based testing on Xpert-Ultra using Xpert-Edge.

- 6) **Point-of-Care Combined Sputum and Individual Tongue Swab Testing:** In-home POC sputum-based testing on Xpert-Ultra using Xpert-Edge with tongue swab-based testing offered to those unable to expectorate sputum.

We assumed all HHCs would follow a similar diagnostic pathway starting with a HCI, HHC verification, Xpert-Ultra testing, and treatment initiation following a positive test. We complied with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS 2022) reporting guidelines (Supplemental Table 2).<sup>14</sup>



### **Cost Estimation**

We calculated the total implementation cost (programmatic cost + testing cost) and the cost-per-test for each testing strategy. A provider's perspective under routine conditions was adopted considering both fixed and variable costs. Costs were categorized and estimated separately to distinguish programmatic costs from testing costs. Research-related expenses were excluded.

Programmatic costs included all expenses related to the planning and execution of HCIs and were estimated using top-down costing. Costs were sourced from an electronic general ledger and through discussions with finance representatives before being categorized into equipment, personnel, laboratory costs, stationery, consumables, travel, overheads, and other miscellaneous expenses. The total programmatic cost was estimated by summing the categories while the cost of a HCI per HHC was obtained by dividing the total by the number of HHCs reached (630).

Testing costs included those incurred during HHC verification and the collection, preparation, and testing of samples and were calculated using bottom-up, micro-costing. Direct observations in combination with an electronic tracking tool built in REDCap were used to record specific inputs and their quantities needed for different test activities. Estimates were used to calculate the average cost-per-test for each strategy which was then multiplied by the expected total number of people tested, to ultimately obtain the total testing cost per strategy.

Capital assets including furniture costs were annuitized and depreciated based on expected life-years at a 3% annual discount rate. The unit cost for running a test on Xpert-Edge was calculated by dividing the cost of the platform and its maintenance by the total number of tests it would be able to perform across its useful lifetime. The platform can run an average of four tests per day, 892 over a year, and 4 460 over its estimated 5-year lifetime. With the total cost of the machine being \$8 416, the unit cost per test would be  $8\,416 / 4\,460$ , or US\$1.89. The negotiated cost of \$7.97 was used for Xpert-Ultra cartridges.<sup>15</sup> All costs were inflated to 2023 prices based on annual inflation estimates provided by Statistics South Africa.<sup>16</sup> Costs were then converted from South African Rand (ZAR) to US\$ at the average 2023 World Bank conversion rate (1 US\$ = 18.45 ZAR).<sup>17</sup>

### **Outcomes and Measurement of Effectiveness**

We derived measures of effectiveness from operational and intermediate outcomes captured in the TB Home Study. Our primary cost-effectiveness outcome was the incremental cost per additional HHC with TB disease detected and linked to treatment, comparing each testing strategy.

### **Decision Analytic Model for Cost-Effectiveness**

For a testing strategy to be considered it needs to be either as effective but less costly than SOC; or if more costly, the increase in effectiveness needs to be clinically/diagnostically relevant enough to warrant such an increase. To this aim, incremental cost-effectiveness ratios (ICERs) were used as a metric to compare competing testing strategies. The efficacy results from the TB Home Study were used to construct a simplified decision analytic

model using TreeAge Pro 2024 (TreeAge Pro, Williamston, Massachusetts, USA) to determine the cost-effectiveness of each testing strategy. HHCs are followed through each step of the model, estimating costs, transition probabilities, and outcomes. The full list of cost- (Table 1) and probability parameters (Table 2) are presented.

If the ICER for a given strategy is lower than the amount policy makers are willing to pay for an additional unit of effectiveness, we assume it to be cost-effective. A previous economic evaluation concluded that active case finding programs with a 2-year time horizon done in South Africa could be deemed cost-effective if the cost of detecting one new TB case and linking them to treatment was less than \$2 760.<sup>18</sup> The current economic evaluation uses the same intermediate outcome, new TB case detected and linked to treatment, over the same 2-year time horizon. Therefore, a willingness-to-pay (WTP) threshold of \$2 760 per HHC newly diagnosed and linked to treatment was used to assess the cost-effectiveness of the different testing strategies.

### **Sensitivity Analysis**

To explore key drivers of cost and effectiveness, we performed one-way deterministic sensitivity analysis (DSA). Parameter values were changed, with the corresponding upper and lower bound values (Tables 1 and 2) which were obtained from available literature or, in the absence of literature, as a 25% increase/decrease from the point estimate. Each parameter was varied to observe its effect on the overall ICER, presented in the tornado diagram (Figure 3). Probabilistic sensitivity analysis (PSA) using Monte Carlo simulations with 10 000 iterations was conducted to explore the effects of combined uncertainties

across all model parameters. Beta distributions were used for probabilities of effectiveness, and gamma distributions for costs.

### **Ethics Approval**

The study protocol was approved by the University of Pretoria Human Research Ethics Committee (HREC 391/2021). Work related to the cost-effectiveness analysis was approved by Boston University Institutional Review Board (H-44118).

## **RESULTS**

### **Cost Analysis**

Supplemental Table 3 provides a summary of the total estimated implementation cost (programmatic cost + testing cost) of delivering each HCI testing strategy to 300 households over a 2-year time horizon. The total programmatic cost was \$81 327 of which the majority (60%) was for salaries of two fully dedicated staff members. The total testing cost ranged from \$3 635 for *SOC* to \$12 642 for *POC Combined Sputum and Individual Tongue Swab Testing*. The total implementation cost ranged from \$84 962 (*SOC*) to \$93 969 for *POC Combined Sputum and Individual Tongue Swab Testing*. The integration of in-home POC testing into HCI would result in a 3%-11% increase in total implementation cost, compared to *SOC*. The average cost-per-test (Table 1) was highest for sputum-based testing (\$20.08). Individual tongue swab (\$19.29) and pooled tongue swab tests (\$15.73) showed a 4% and 22% lower cost-per-test, respectively. The cost of Xpert-Ultra was a major driver (42%) of cost-per-test (Supplemental Table 4).

**Table 1: Base-case cost-per-test, range, and description of costs in cost-effectiveness analyses comparing different HCI testing strategies**

| PARAMETER   | BASE-CASE VALUE (\$) | LOW (\$)           | HIGH (\$)           | SOURCE |
|---|----------------------|--------------------|---------------------|--------|
| HOUSEHOLD CONTACT TRACING COST PER CONTACT                      | 129.09               | 96.82 <sup>†</sup> | 161.36 <sup>†</sup> | *      |
| COST OF RESULT NOTIFICATION                                     | 0.66                 | 0.49 <sup>†</sup>  | 0.82 <sup>†</sup>   | *      |
| <b>SOC</b>  |                      |                    |                     |        |
| COST PER TEST   | 20.08                | 15.06 <sup>†</sup> | 25.11 <sup>†</sup>  | *      |
| <b>POC SPUTUM TESTING</b>                                       |                      |                    |                     |        |
| COST PER TEST   | 20.08                | 15.06 <sup>†</sup> | 25.11 <sup>†</sup>  | *      |
| <b>POC INDIVIDUAL ORAL SWAB TESTING</b>                         |                      |                    |                     |        |
| COST PER TEST   | 19.29                | 14.47 <sup>†</sup> | 24.2 <sup>†</sup>   | *      |
| <b>POC POOLED ORAL SWAB WITH CONFIRMATORY SPUTUM TESTING</b>    |                      |                    |                     |        |
| COST PER POOLED TEST  | 15.73                | 11.80 <sup>†</sup> | 19.67 <sup>†</sup>  | *      |
| COST PER CONFIRMATORY SPUTUM TEST                               | 16.34                | 12.23 <sup>†</sup> | 20.43 <sup>†</sup>  | *      |
| <b>POC POOLED ORAL SWAB WITH CONFIRMATORY ORAL SWAB TESTING</b> |                      |                    |                     |        |
| COST PER POOLED TEST  | 15.73                | 11.80 <sup>†</sup> | 19.67 <sup>†</sup>  | *      |
| COST PER CONFIRMATORY ORAL SWAB TEST                            | 15.55                | 11.66 <sup>†</sup> | 19.44 <sup>†</sup>  | *      |
| <b>POC COMBINED SPUTUM AND INDIVIDUAL ORAL SWAB TESTING</b>     |                      |                    |                     |        |
| COST PER SPUTUM TEST  | 20.08                | 15.06 <sup>†</sup> | 25.11 <sup>†</sup>  | *      |
| COST PER INDIVIDUAL ORAL SWAB TEST                              | 15.55                | 11.66 <sup>†</sup> | 19.44 <sup>†</sup>  | *      |

\*Obtained from primary study data. <sup>†</sup>Bound defined as a 25% increase/decrease from point estimate. SOC = standard of care; POC = point-of-care.

**Probabilities**

The prevalence of TB among HHCs was estimated at 4.5% and ranged between 3.3% and 7.8%. The probability of obtaining a test result when adopting SOC was estimated to be 10.7% compared to 38.3% when in-home POC sputum testing was conducted. The probability of obtaining a test result from all other strategies ranged between 82.7% and 89.8%, highlighting the increased collection yield of tongue swab samples. The sensitivity of different testing strategies ranged from 51.4% for *POC Pooled Tongue Swab Testing* to 93.2% for sputum-based tests. Intermediate outcome data from the TB Home Study suggests that the likelihood of treatment initiation following a positive in-home POC sputum test was 84.6%, compared to a published 68% likelihood when adopting SOC.<sup>19,20</sup>

**Table 2. Base-case value, range, and description of variables used in cost-effectiveness analyses comparing different household contact tracing testing strategies.**

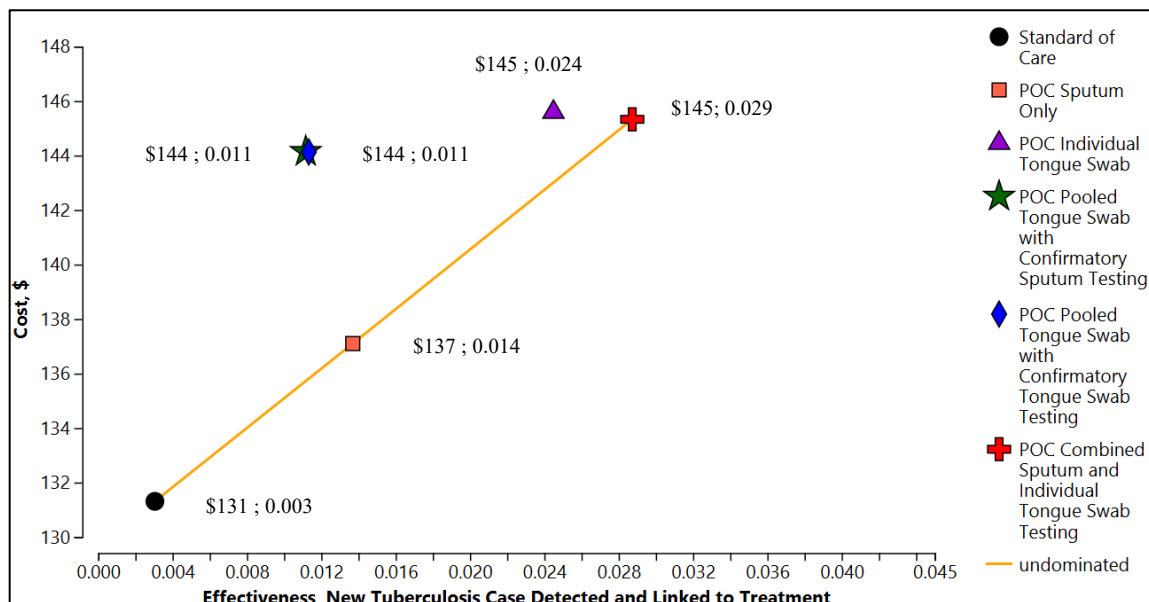
| PARAMETER  | BASE-CASE VALUE | LOW                | HIGH               | SOURCE   |
|--|-----------------|--------------------|--------------------|----------|
| <b>PREVALENCE OF TUBERCULOSIS AMONG HOUSEHOLD CONTACTS</b>               | 0.045           | 0.033              | 0.078              | 21–24    |
| <b>SOC</b>   |                 |                    |                    |          |
| PROBABILITY OF TEST RESULT AVAILABLE                                     | 0.107           | 0.099              | 0.128              | 25,*     |
| SENSITIVITY OF TEST  | 0.932           | 0.872              | 0.953              | 26–28    |
| SPECIFICITY OF TEST  | 0.964           | 0.963              | 0.981              | 26–28    |
| PROBABILITY OF PRESENTING FOR TREATMENT INITIATION                       | 0.680           | 0.440              | 0.850              | 19,20    |
| <b>POC SPUTUM TESTING</b>  |                 |                    |                    |          |
| PROBABILITY OF TEST RESULT AVAILABLE                                     | 0.383           | 0.287 <sup>†</sup> | 0.479 <sup>†</sup> | 29,30,*  |
| SENSITIVITY OF TEST  | 0.932           | 0.872              | 0.953              | 31–33    |
| SPECIFICITY OF TEST  | 0.964           | 0.963              | 0.981              | 31–33    |
| PROBABILITY OF PRESENTING FOR TREATMENT INITIATION                       | 0.846           | 0.635 <sup>†</sup> | 1 <sup>†</sup>     | *        |
| <b>POC INDIVIDUAL ORAL SWAB TESTING</b>                                  |                 |                    |                    |          |
| PROBABILITY OF TEST RESULT AVAILABLE                                     | 0.827           | 0.620 <sup>†</sup> | 1 <sup>†</sup>     | *        |
| SENSITIVITY OF TEST  | 0.778           | 0.360              | 0.910              | 11,34    |
| SPECIFICITY OF TEST  | 0.930           | 0.660              | 1 <sup>†</sup>     | 11,34    |
| PROBABILITY OF PRESENTING FOR TREATMENT INITIATION                       | 0.846           | 0.635 <sup>†</sup> | 1 <sup>†</sup>     | *        |
| <b>POC POOLED ORAL SWAB WITH CONFIRMATORY SPUTUM TESTING</b>             |                 |                    |                    |          |
| PROBABILITY OF POOLED TEST RESULT AVAILABLE                              | 0.898           | 0.674 <sup>†</sup> | 1 <sup>†</sup>     | *        |
| SENSITIVITY OF TEST  | 0.514           | 0.333              | 0.910              | *        |
| SPECIFICITY OF TEST  | 1               | 0.660              | 1                  | *        |
| PROBABILITY OF CONFIRMATORY TEST RESULT AVAILABLE                        | 0.682           | 0.386              | 0.852              | *        |
| SENSITIVITY OF CONFIRMATORY SPUTUM TEST                                  | 0.932           | 0.872              | 0.953              | 27,31,34 |
| SPECIFICITY OF CONFIRMATORY SPUTUM TEST                                  | 0.964           | 0.963              | 0.981              | 27,31,34 |
| PROBABILITY OF PRESENTING FOR TREATMENT INITIATION FOLLOWING SPUTUM TEST | 0.846           | 0.635 <sup>†</sup> | 1 <sup>†</sup>     | *        |

|  |       |                    |                    |          |
|--|-------|--------------------|--------------------|----------|
| <b>POC POOLED ORAL SWAB WITH CONFIRMATORY ORAL SWAB TESTING</b>                        |       |                    |                    |          |
| PROBABILITY OF POOLED TEST RESULT AVAILABLE  | 0.898 | 0.674 <sup>†</sup> | 1 <sup>†</sup>     | *        |
| SENSITIVITY OF POOLED TEST   | 0.514 | 0.333              | 0.910              | *        |
| SPECIFICITY OF POOLED TEST   | 1     | 0.660              | 1                  | *        |
| PROBABILITY OF CONFIRMATORY TEST RESULT AVAILABLE                                      | 0.829 | 0.622 <sup>†</sup> | 1 <sup>†</sup>     | *        |
| SENSITIVITY OF CONFIRMATORY ORAL SWAB TEST   | 0.778 | 0.360              | 0.910              | 11,34    |
| SPECIFICITY OF CONFIRMATORY ORAL SWAB TEST   | 0.930 | 0.660              | 1                  | 11,34    |
| PROBABILITY OF PRESENTING FOR TREATMENT INITIATION FOLLOWING INDIVIDUAL ORAL SWAB TEST | 0.846 | 0.635 <sup>†</sup> | 1 <sup>†</sup>     | *        |
| <b>POC COMBINED SPUTUM AND INDIVIDUAL ORAL SWAB TESTING</b>                            |       |                    |                    |          |
| PROBABILITY OF SPUTUM TEST RESULT AVAILABLE  | 0.383 | 0.287 <sup>†</sup> | 0.479 <sup>†</sup> | 29,30,*  |
| SENSITIVITY OF SPUTUM TEST   | 0.932 | 0.872              | 0.953              | 27,31,34 |
| SPECIFICITY OF SPUTUM TEST   | 0.964 | 0.963              | 0.981              | 27,31,34 |
| PROBABILITY OF PRESENTING FOR TREATMENT INITIATION FOLLOWING SPUTUM TEST               | 0.846 | 0.635 <sup>†</sup> | 1 <sup>†</sup>     | *        |
| PROBABILITY OF INDIVIDUAL ORAL SWAB TEST RESULT AVAILABLE                              | 0.827 | 0.620 <sup>†</sup> | 1 <sup>†</sup>     | *        |
| SENSITIVITY OF INDIVIDUAL ORAL SWAB TEST   | 0.778 | 0.360              | 0.910              | 11,34    |
| SPECIFICITY OF INDIVIDUAL ORAL SWAB TEST   | 0.930 | 0.660              | 1                  | 11,34    |
| PROBABILITY OF PRESENTING FOR TREATMENT INITIATION FOLLOWING INDIVIDUAL ORAL SWAB TEST | 0.846 | 0.635 <sup>†</sup> | 1 <sup>†</sup>     | *        |

\*Obtained from primary study data <sup>†</sup> Bound defined as a 25% decrease from point estimate. TB = tuberculosis; SOC = standard of care; POC = point of care.

### Cost-Effectiveness Analysis

Figure 2 summarizes the results of the cost-effectiveness analysis. The cost-effectiveness plane (gold line) connects undominated strategies, i.e., those not outperformed by other strategies and deemed most cost-effective. Although being the least expensive (\$131.38), SOC was least effective. All five in-home POC testing strategies showed higher effectiveness compared to SOC albeit at a higher cost per HHC tested. Table 3 summarizes the cost, effectiveness, and corresponding ICER values of the two undominated testing strategies, *POC Sputum Testing* and *POC Combined Sputum and Individual Tongue Swab Testing* with corresponding ICERs of \$543.74 and \$547.29, respectively, below the \$2 760 WTP threshold.



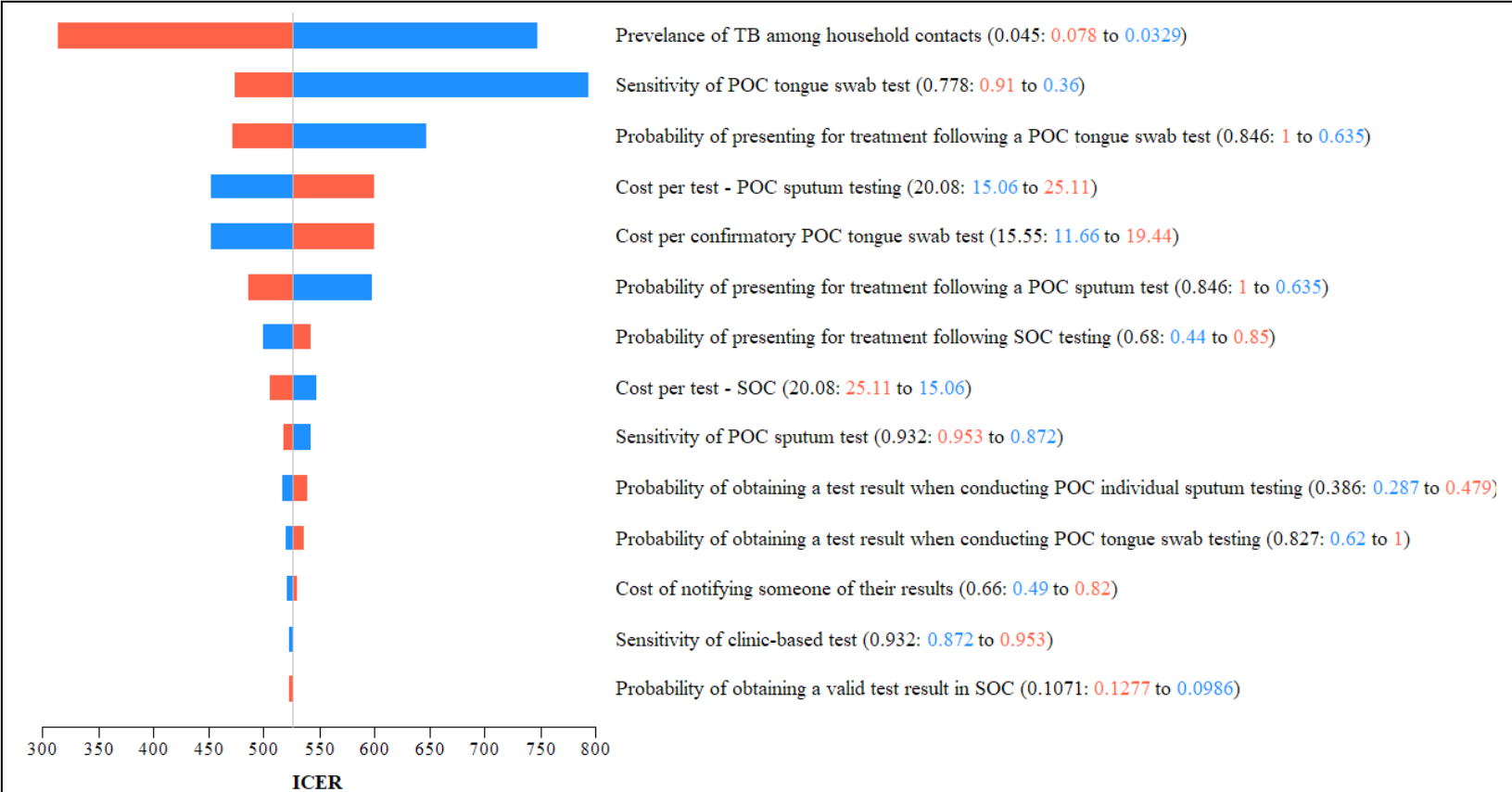
**Figure 2.** Cost-effectiveness plane of different household contact investigation testing strategies

**Table 3. Results of cost-effectiveness analyses of different household contact investigation testing strategies.**

| Testing Strategy                                       | Cost (\$) | Incremental Cost (\$) | Effectiveness | Incremental Effectiveness | ICER   |
|--|-----------|-----------------------|---------------|---------------------------|--------|
| Standard of Care                                       | 131.31    |                       | 0.003         |                           |        |
| POC Sputum Testing                                     | 137.10    | 5.79                  | 0.014         | 0.011                     | 543.74 |
| POC Combined Sputum and Individual Tongue Swab Testing | 145.33    | 8.23                  | 0.029         | 0.015                     | 547.29 |

### Sensitivity Analysis

The DSA (Figure 3) showed prevalence of TB among HHCs, followed by the sensitivity of a tongue swab test to be the most influential parameters impacting ICER values. An increase in either estimate would result in a decrease in the ICER. Lower sensitivity of individual tongue swabs would result in a drastic increase in the ICER, albeit not exceeding the WTP threshold. No parameters showed variability to the extent it would shift the ICER beyond the \$2 760 WTP threshold. The PSA findings are presented in the cost-effectiveness acceptability curve (Figure 4). *POC Combined Sputum and Individual Oral Swab Testing* was the most optimal strategy in 100% of model iterations at a \$2 760 WTP threshold.



**Figure 3. Deterministic sensitivity analysis**

Tornado diagram, depicting the effect of changing individual model parameters on the ICER when comparing SOC against POC Combined Sputum and Individual Tongue Swab Testing. The diagram depicts the base case ICER of \$547 as the difference in ICER between the two strategies to highlight the sensitivity of the ICER value to changes in individual model parameters. Parameters are listed in the order of influence on cost-effectiveness. A low value (blue) indicates that cost-effectiveness has a positive correlation with the parameter value, whereas a high value (orange) has a negative correlation.

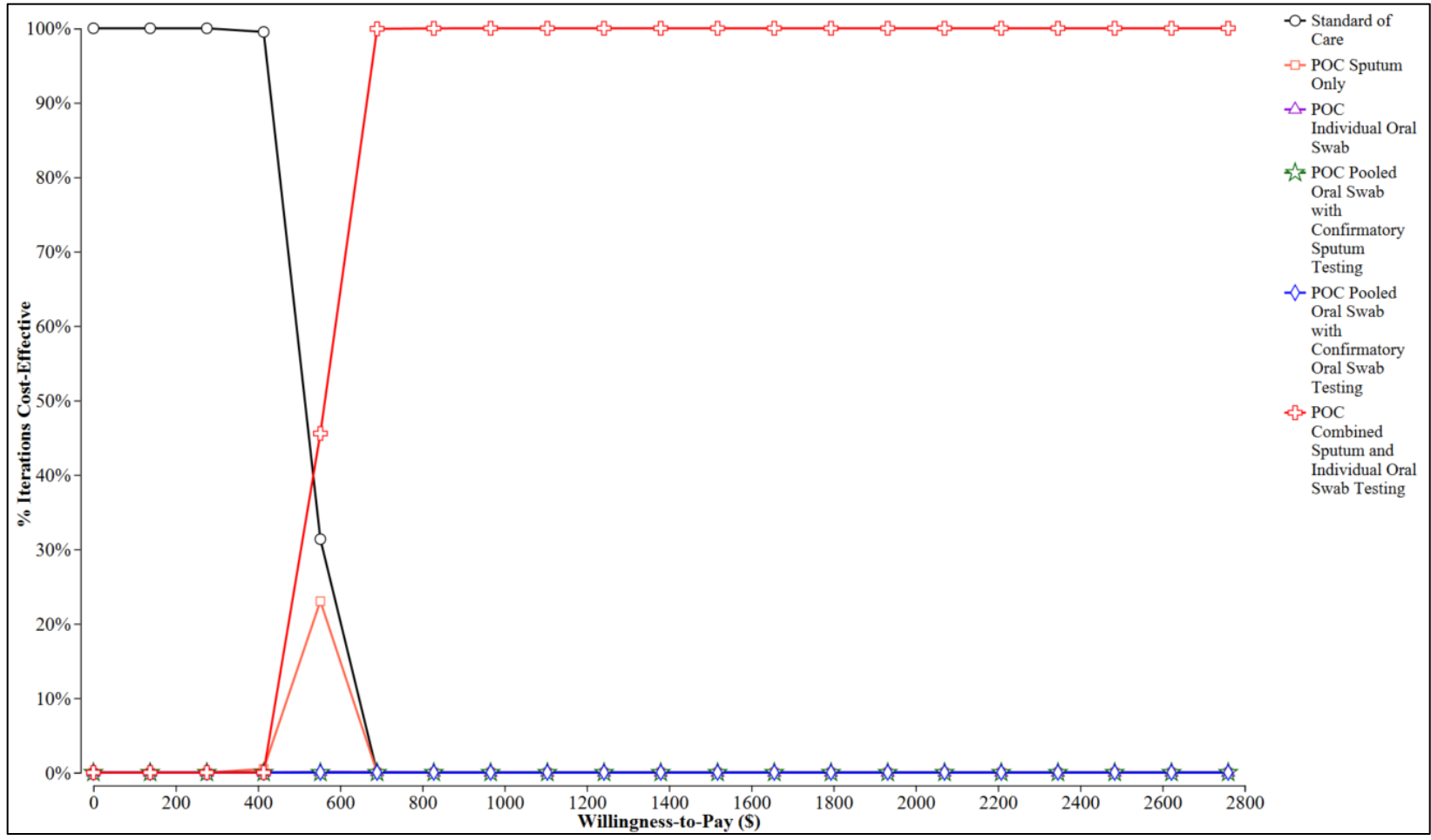


Figure 4. Cost-effectiveness acceptability curve

## Discussion

We conducted a costing analysis to estimate and compare the cost of implementing HCI with centralized sputum testing (SOC) against one of five alternative in-home POC testing strategies. The empirical estimates derived from the TB Home Study revealed a 3%-11% increase in total implementation cost (programmatic cost + testing cost) when integrating in-home POC molecular testing into HCI, over a 2-year time horizon. The increased cost is largely due to the increased testing conducted when delivered in-home, at POC. Albeit more expensive, in-home POC testing would increase the number of people tested, diagnosed, and promptly linked to treatment, echoing findings from other research which found similar improvements when testing was delivered at POC<sup>9,35-37</sup>

Although being more sensitive, in-home sputum-based testing was the costliest at a cost-per-test of \$20.08. Despite diminished sensitivity, the 4% and 22% reduction in cost-per-test combined with increased sample yield of individual and pooled tongue swab tests provide strong justification for their consideration as alternative solutions to sputum testing.<sup>38</sup> Xpert-Ultra cartridges was the biggest driver (42%) of cost-per-test, confirming findings from work done in other low- and middle- income settings.<sup>39</sup> Despite a lower negotiated price, the cost of Xpert-Ultra remains a barrier to its scale-up. The optimal number of tongue swabs and method of collection that yields the maximum amount of DNA remains under investigation. However, as the science evolves and the next generation of ultra-sensitive tests become available, the feasibility of using tongue swabs, become more plausible.<sup>19</sup>

The ICER values for *POC Sputum* and *POC Combined Sputum and Individual Tongue Swab* testing were \$543.47 and \$547.29, respectively making both testing strategies highly cost-effective given the threshold of \$2 760. The increased sample yield of tongue swabs combined with immediate result notification resulting in a higher likelihood of treatment initiation following an in-home POC test, significantly improved the effectiveness of both strategies. This suggests that in a hypothetical cohort of 100 000 HHCs with 4.5% TB prevalence, a *POC Combined Sputum and Individual Tongue Swab* testing strategy would detect and link to treatment approximately 2 900 new TB cases compared to 300 (SOC).

An intermediate outcome, HHC with TB disease detected and linked to treatment, instead of a utility outcome like DALY was used due to the preference of using a study-measured outcome thereby limiting over reliance on modeling assumptions. Evidence from previous economic models propose a ratio of 1:1, i.e., 1 new case detected and linked to treatment equaling to 1 DALY averted, suggesting the ICERs calculated in the current analysis would remain unchanged if DALYs were used.<sup>18</sup> The likelihood of strategies being adopted ultimately depends on the WTP of policy makers.<sup>40</sup> The chosen \$2 760 threshold was far more conservative than the prescribed WHO-CHOICE threshold. The impact of HCI at the population level is only realized over the long term. Our current threshold is modeled off a 2-year time horizon which potentially only considers 15% of the epidemiological impact of HCI.<sup>18</sup> Despite being conservative as well as potentially underestimating the long-term effects, both undominated testing strategies fell far below

\$2 760, suggesting great potential positive economic returns, and should therefore be considered.

A key strength of this economic evaluation is the use of empirical cost and intermediate outcome data collected within a highly pragmatic study, reducing reliance on modeling and findings from different contexts.<sup>41</sup> Most existing literature relies heavily on modeling analysis rather than prospectively obtained data for similar assessments.<sup>42</sup> Consequently, we are confident that our results closely approximate the real-world costs and outcomes when integrating in-home POC testing into HCI. Limited research on the economic impact of implementing rapid diagnostics at POC is available, while none have examined its impact when integrated into HCI.<sup>43</sup>

Our analysis has several limitations. Our model does not account for effects of secondary transmission, or the increased probability of transmission associated with delayed testing. Published literature on the downstream economic impact of delayed testing would suggest it's inclusion in the current model would further strengthen the case in favor for in-home POC testing, which has shown to reduce time-to-case-notification and treatment initiation.<sup>10,44</sup> The sputum yield parameters used in this analysis might be overestimated due to the exclusion of children, who are known to have diminished capacity to expectorate sputum.<sup>45</sup>

Further advancements in rapid, POC molecular diagnostics holds great potential for closing gaps along the TB care cascade. WHO endorsement alone will not be sufficient to ensure rapid uptake into national TB programs.<sup>46</sup> Integration must be complemented by

accompanying system strengthening to adequately support its implementation. To this end, implementation studies should aim to generate the evidence needed for local policy makers to make informed decisions. This analysis provides robust economic evidence supporting the integration of rapid POC TB testing into existing HCI strategies. Future research should aim to compare these testing strategies within a randomized control trial. Furthermore, studies should explore the scalability and sustainability of these strategies across diverse settings to inform policy recommendations and optimize resource allocation in the global fight against TB.

**Acknowledgements:**

**Funding source**

Funding was provided by the United States National Institutes of Health (Grant # R01AI150485 and R21EB023679) and FIND.

**Conflicts of Interest:**

None

**Author contributions:**

CB: data analysis, writing the manuscript

LL: writing the manuscript, supervision

BN: writing the manuscript, supervision

GMR: writing the manuscript, supervision

MPF: writing the manuscript, supervision

GT: writing the manuscript

BF: writing the manuscript

SO: writing the manuscript

APN: writing the manuscript

MR: writing the manuscript

AMM: conceptualization, funding acquisition, writing the manuscript, supervision

Data available upon request.

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**APPENDIX 5. CHEERS CHECKLIST**

|  | <b>Item</b> | <b>Guidance for Reporting</b>   | <b>Reported<br/>insection</b> |
|--|-------------|---|-------------------------------|
| <b>TITLE</b>                                     |             |   |                               |
| Title  | 1           | Identify the study as an economic evaluation and specify the interventions being compared.                                      |                               |
| <b>ABSTRACT</b>                                  |             |   |                               |
| Abstract   | 2           | Provide a structured summary that highlights context, key methods, results and alternative analyses.                            |                               |
| <b>INTRODUCTION</b>                              |             |   |                               |
| Background and objectives                        | 3           | Give the context for the study, the study question and its practical relevance for decision making in policy or practice.       |                               |
| <b>METHODS</b>                                   |             |   |                               |
| Health economic analysis plan                    | 4           | Indicate whether a health economic analysis plan was developed and where available.   | N/A                           |
| Study population                                 | 5           | Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics). | N/A                           |
| Setting and location                             | 6           | Provide relevant contextual information that may influence findings.  |                               |
| Comparators                                      | 7           | Describe the interventions or strategies being compared and why chosen.   |                               |
| Perspective                                      | 8           | State the perspective(s) adopted by the study and why chosen.   |                               |
| Time horizon                                     | 9           | State the time horizon for the study and why appropriate.   |                               |
| Discount rate                                    | 10          | Report the discount rate(s) and reason chosen.  |                               |
| Selection of outcomes                            | 11          | Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).   |                               |
| Measurement of outcomes                          | 12          | Describe how outcomes used to capture benefit(s) and harm(s) were measured.   |                               |
| Valuation of outcomes                            | 13          | Describe the population and methods used to measure and value outcomes.   |                               |
| Measurement and valuation of resources and costs | 14          | Describe how costs were valued.   |                               |
| Currency, price date, and conversion             | 15          | Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.                 |                               |
| Rationale and description of model               | 16          | If modelling is used, describe in detail and why used. Report if the model  |                               |

|   |    |   |  |
|---|----|---|--|
|   |    | is publicly available and where it can be accessed.   |  |
| Analytics and assumptions   | 17 | Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.                             |  |
| Characterizing heterogeneity  | 18 | Describe any methods used for estimating how the results of the study vary for sub-groups.  |  |
| Characterizing distributional effects                                 | 19 | Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.  |  |
| Characterizing uncertainty  | 20 | Describe methods to characterize any sources of uncertainty in the analysis.  |  |
| Approach to engagement with patients and others affected by the study | 21 | Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (e.g., clinicians or payers) in the design of the study. |  |
| <b>RESULTS</b>  |    |   |  |
| Study parameters  | 22 | Report all analytic inputs (e.g., values, ranges, references) including uncertainty or distributional assumptions.  |  |
| Summary of main results   | 23 | Report the mean values for the main categories of costs and outcomes of interest and summarise them in the most appropriate overall measure.                                |  |
| Effect of uncertainty   | 24 | Describe how uncertainty about analytic judgments, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.    |  |
| Effect of engagement with patients and others affected by the study   | 25 | Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study                     |  |
| <b>DISCUSSION</b>   |    |   |  |
| Study findings, limitations, generalizability, and current knowledge  | 26 | Report key findings, limitations, ethical or equity considerations not captured, and how these could impact patients, policy, or practice.                                  |  |
| <b>OTHER RELEVANT INFORMATION</b>                                     |    |   |  |
| Source of funding   | 27 | Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis  |  |
| Conflicts of interest   | 28 | Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.   |  |

## APPENDIX 6. COST ANALYSIS OF DIFFERENT HOUSEHOLD CONTACT INVESTIGATION STRATEGIES

| Cost Categories   | Testing Strategies |                    |                                  |   |  |  |
|---|--------------------|--------------------|----------------------------------|---|--|--|
|   | Standard of Care   | POC Sputum Testing | POC Individual Oral Swab Testing | POC Pooled Oral Swab with Confirmatory Sputum Testing | POC Pooled Oral Swab with Confirmatory Oral Swab Testing | POC Combined Sputum and Individual Oral Swab Testing |
| <b>Household Contact Tracing Programmatic Cost</b>          |                    |                    |                                  |   |  |  |
| Equipment   |                    |                    |                                  | \$2,012 (2%)  |  |  |
| Overheads   |                    |                    |                                  | \$3,889 (4%)  |  |  |
| Consumables   |                    |                    |                                  | \$3,115 (4%)  |  |  |
| Travel  |                    |                    |                                  | \$19,838 (24%)  |  |  |
| Training  |                    |                    |                                  | \$2,553 (3%)  |  |  |
| Stationery  |                    |                    |                                  | \$402 (<1%)   |  |  |
| Salaries  |                    |                    |                                  | \$48,754 (60%)  |  |  |
| Laboratory costs  |                    |                    |                                  | \$373 (<1%)   |  |  |
| Other   |                    |                    |                                  | \$391 (<1%)   |  |  |
| <b>Subtotal household contact tracing programmatic cost</b> |                    |                    |                                  | <b>\$81,327</b>                                       |  |  |
| <b>Testing Cost</b>   |                    |                    |                                  |   |  |  |
| Salaries  | \$2,846            | \$4,032            | \$6,182                          | \$4,583   | \$4,597  | \$6,382  |
| Consumables   | \$20               | \$90               | \$117                            | \$98  | \$98   | \$113  |
| Laboratory costs  | \$768              | \$2,394            | \$6,108                          | \$3,537   | \$3,576  | \$6,147  |
| <b>Subtotal testing cost</b>                                | <b>\$3,635</b>     | <b>\$6,517</b>     | <b>\$12,407</b>                  | <b>\$8,218</b>  | <b>\$8,271</b>   | <b>\$12,642</b>                                      |
| <b>Total cost</b>   | <b>\$84,962</b>    | <b>\$87,844</b>    | <b>\$93,734</b>                  | <b>\$89,545</b>                                       | <b>\$89,598</b>  | <b>\$93,969</b>                                      |

**APPENDIX 7. BREAKDOWN OF COST-PER-TEST ESTIMATE**

|  | <b>Sputum Test</b> | <b>Individual Tongue Swab Test</b> | <b>Pooled Tongue Swab Test</b> | <b>Additional Sputum Test</b> | <b>Additional Tongue Swab Test</b> |
|--|--------------------|------------------------------------|--------------------------------|-------------------------------|------------------------------------|
| Salary associated with confirming household contact at the house | \$3·74             | \$3·74                             | \$3·74                         | -                             | -                                  |
| Salary associated with testing                                   | \$6·23             | \$5·51                             | \$5·51                         | \$6·23                        | \$5·51                             |
| Surgical gloves  | 0·13               | 0·13                               | 0·13                           | 0·13                          | 0·13                               |
| Sputum jars  | 0·13               | -                                  | -                              | 0·13                          | -                                  |
| Tongue swab  | -                  | \$0·06                             | \$0·06                         | -                             | \$0·06                             |
| Ultra cartridge  | \$7·97             | \$7·97                             | \$4·41                         | \$7·97                        | \$7·97                             |
| Xpert-Edge machine   | \$1·89             | \$1·89                             | \$1·89                         | \$1·89                        | \$1·89                             |
| <b>Total</b>   | <b>\$20·08</b>     | <b>\$19·29</b>                     | <b>\$15·73</b>                 | <b>\$16·34</b>                | <b>\$15·55</b>                     |

Additional Test = Additional tests include confirmatory or alternative tests conducted.

**APPENDIX 8. MANUSCRIPT 2: USING SPUTUM AND TONGUE SWAB SPECIMENS FOR IN-HOME POINT-OF-CARE TARGETED UNIVERSAL TESTING FOR TB OF HOUSEHOLD CONTACTS: AN ACCEPTABILITY AND FEASIBILITY ANALYSIS**

**TITLE: USING SPUTUM AND TONGUE SWAB SPECIMENS FOR IN-HOME POINT-OF-CARE TARGETED UNIVERSAL TESTING FOR TB OF HOUSEHOLD CONTACTS: AN ACCEPTABILITY AND FEASIBILITY ANALYSIS**

**Authors:**

Charl Bezuidenhout<sup>1\*</sup>, Lawrence Long<sup>1,2</sup>, Brooke Nichols<sup>1,3,4</sup>, Gesine Meyer-Rath<sup>1,2,5</sup>, Matthew P Fox<sup>1,2,6</sup>, Sharon Olifant<sup>7</sup>, Grant Theron<sup>8</sup>, Kuhle Fiphaza<sup>9,10</sup>, Morten Ruhwald<sup>11</sup>, Adam Penn-Nicholson<sup>11</sup>, Bernard Fourie<sup>7</sup>, Maria Pieruccini<sup>12</sup>, Andrew Medina-Marino<sup>9,10,13\*</sup>

**Affiliations:**

Charl Bezuidenhout: 1. Department of Global Health, Boston University School of Public Health, Boston, U.S.

Lawrence Long: 2. Health Economics and Epidemiology Research Office, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; 1. Department of Global Health, Boston University School of Public Health, Boston, U.S.

Brooke Nichols: 1. Department of Global Health, Boston University School of Public Health, Boston, USA; 2. FIND, Geneva, Switzerland; 3. Wits Diagnostic Innovation Hub, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; 4. Department of Global Health, Amsterdam Institute for Global Health and Development, Amsterdam University Medical Center, Amsterdam, the Netherlands

Gesine Meyer-Rath: 2. Health Economics and Epidemiology Research Office, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; 1. Department of Global Health, Boston University School of Public Health, Boston, US; 5. South African Centre for Epidemiological Modelling and Analysis (SACEMA), Stellenbosch University, South Africa

Matthew Fox: 2. Health Economics and Epidemiology Research Office, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa; 6. Department of Epidemiology, Boston University School of Public Health, Boston, USA; 1. Department of Global Health, Boston University School of Public Health, Boston, USA

Bernard Fourie: 7. Department of Medical Microbiology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

Sharon Olifant: 7. Department of Medical Microbiology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa

Grant Theron: 8. DSI-NRF Centre of Excellence for Biomedical Tuberculosis Research, South African Medical Research Council Centre for Tuberculosis Research, Division of

Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Kuhle Fiphaza: 9. Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa; 10. Eastern Cape Research Site, Desmond Tutu Health Foundation, East London, South Africa

Adam Penn-Nicholson: 11. FIND, Geneva, Switzerland

Morten Ruhwald: 11. FIND, Geneva, Switzerland

Maria Pieruccini: 12. Department of Epidemiology, Brown University.

Andrew Medina-Marino: 9. Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa; 10. Eastern Cape Research Site, Desmond Tutu Health Foundation, East London, South Africa; 13. Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania

**Co-Corresponding Authors:**

Andrew Medina-Marino, Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa. Email: [andrewmedinamarino@gmail.com](mailto:andrewmedinamarino@gmail.com)

Charl Bezuidenhout, Boston University School of Public Health, Department of Global Health. Email: [cwbips@gmail.com](mailto:cwbips@gmail.com)

**Funding:**

Funding was provided by the United States National Institutes of Health (Grant # R01AI150485 and R21EB023679) and FIND.

**ABSTRACT:****Introduction**

Effective strategies are needed to facilitate early detection and diagnosis of tuberculosis (TB). The over-reliance on passive case detection, symptom screening, and collection of sputum, results in delayed or undiagnosed TB, which directly contributes to on-going TB transmission. We assessed the acceptability and feasibility of in-home, Targeted Universal TB Testing (TUTT) of household contacts using GeneXpert MTB/RIF Ultra at point-of-care (POC) during household contact investigations (HCIs) and assessed the feasibility of using sputum and tongue swab specimens.

**Methods**

Household contacts receiving in-home POC TUTT as part of the TB Home Study were asked to complete a post-test acceptability survey. The survey explored household contacts' level of comfort, confidence in the test results, and the perceived appropriateness of in-home POC TUTT. We used the Metrics to Assess the Feasibility of Rapid Point-of-Care Technologies framework to assess the feasibility of using sputum and tongue swab specimens for in-home POC TUTT. Descriptive statistics were used to report participant responses and feasibility metrics.

**Results**

Of 325 eligible household contacts, 281/325 (86.5%) consented to in-home POC TUTT. Of those, 278/281 (98.9%) provided a tongue swab and 50/281 (17.8%) could expectorate

sputum. All specimens were successfully prepared for immediate, in-home testing with Xpert Ultra on GeneXpert Edge. Of the 172 tongue swab-based tests performed, 169 (98.3%) produced a valid result, while 47 out of 49 (95.9%) sputum-based tests had a valid result. An immediate tongue swab-based test result was available for 274/278 (98.6%) clients while 47/49 (95.9%) sputum-based test results were immediately available. The mean in-home POC TUTT acceptability score (5=highly acceptable) was 4.2/5 (SD= 0.4).

### **Conclusion**

In-home, POC TUTT using either sputum or tongue swab specimens was highly acceptable and feasible. Tongue swab specimens greatly increase the proportion of household contacts tested due to high sample collection yield. In-home POC TUTT using a combination of sputum and tongue swabs can mitigate shortcomings to case detection.

**KEY MESSAGE:****What is already known on this topic:**

- TB transmission among household contacts of people with TB is a public health concern.
- The delivery of community-based diagnostic testing for TB is challenging and the reliance on sputum continue to hamper universal testing and result in diagnostic delay.
- A large diagnostic gap remains globally with an estimated 2.7 million of all suspected TB cases never being tested for TB.
- Molecular testing of tongue swabs has been shown to have high specificity and moderate sensitivity relative to sputum testing.

**What this study adds:**

- This is the first study to assess the acceptability of universal in-home point-of-care TB testing of household contacts during household contact investigations.
- This study assesses the feasibility of different specimen types for immediate in-home point-of-care TB testing including tongue swabs and sputum by evaluating metrics associated with sample collection yield, processing-, testing, and notification rate.

**How this study might affect research, practice or policy:**

- Household contacts perceived in-home targeted universal TB testing to be highly acceptable, prompting the need for further investigation into the cost-effectiveness of such strategies to improve early case detection.

## INTRODUCTION

Tuberculosis (TB) remains one of the world's leading infectious disease killers. Despite being preventable, treatable, and curable it caused an estimated 1.25 million deaths in 2023.<sup>1</sup> Persistent gaps in the cascade of care include TB diagnosis, notification, and linkage to treatment, all of which remain major contributors to TB burden, transmission, and mortality.<sup>2</sup> Effective delivery of World Health Organization (WHO)-recommended rapid molecular diagnostic tests like GeneXpert MTB/RIF Ultra (Cepheid, Sunnyvale, CA, USA) (Xpert Ultra) remains a key priority to meet the WHO goal of diagnosing 100% of people tested with WHO-recommended rapid tests.<sup>1</sup> Despite the introduction of rapid molecular diagnostic tests like Xpert Ultra, the global diagnostic gap is estimated to be 2.7 million of all suspected TB cases. Diagnosis remains the weakest link in the cascade of care.<sup>1,3</sup>

In 2021, South Africa's TB incidence was estimated to be 513 per 100,000 population, equating to ~304,000 people living with TB, of which ~120,000 were not tested, diagnosed, or initiated on treatment.<sup>4</sup> Persistent gaps in testing are attributable to a variety of factors including reliance on symptom presentation, limited access to testing, and fragmented delivery of testing services.<sup>5,6</sup> Closing the diagnostic gap necessitates strategies that are patient-centered, deliver testing at or near the point-of-care (POC), and are conducted in a single patient consultation.<sup>3</sup>

Active case finding strategies, including household contact investigation (HCI) of people diagnosed with TB, have been shown to be cost-effective compared to passive case

detection and form the cornerstone of TB programs aimed at improving early case detection.<sup>7</sup> However, low uptake of clinic referrals and continued reliance on a hub-and-spoke model of sputum transportation and centralized testing (resulting in long test result turnaround) continue to hamper effective implementation of such strategies.<sup>8</sup> The use of portable, rapid molecular diagnostic platforms like the GeneXpert Edge (Cepheid, Sunnyvale, CA, USA) (GX-Edge) has shown to greatly improve access to immediate testing and improve treatment uptake when integrated into HCI.<sup>9,10</sup> However, reliance on symptom-based screening and sputum-based testing continue to limit case detection.<sup>11</sup>

Non-specific clinical symptoms, the paucibacillary nature of sputum, and the challenge of collecting sputum have all been reported as barriers to effective diagnostic testing.<sup>11</sup> Furthermore, the high cost of Xpert Ultra testing severely limits its scalability in resource constrained settings.<sup>12</sup> Recently, tongue swab specimens have been proposed as an alternative, less invasive sample, when sputum is not available, especially as sensitivity approaches that of sputum-based molecular tests.<sup>13,14</sup> Moreover, pooled testing of multiple sputum samples in a single Xpert Ultra cartridge has shown to save up to 48% of assay cost.<sup>12</sup> Combined, the collection of tongue swabs to increase sample collection yield and the pooling of samples to decrease cost may increase the scalability of HCI strategies adopting portable rapid molecular testing platforms.<sup>15</sup> Given the introduction of targeted universal testing for TB (TUTT) of household contacts of people with TB, irrespective of symptoms, there is urgent need for rapid, affordable, and accurate TB testing strategies.<sup>16</sup>

Exploration of the acceptability and feasibility of in-home, POC TUTT using tongue swab specimens is warranted. In order to make prudent decisions about adopting new technologies, decision-makers need well-executed studies assessing their acceptability and feasibility. A variety of contextual factors and patient preferences could ultimately determine the success of new healthcare interventions.<sup>17</sup> To this end, we sought to: 1) assess the acceptability of in-home, POC TUTT of household contacts of people with TB using the GX-Edge; and 2) to assess the test feasibility of using sputum and tongue swab specimens.

## **METHODS**

### **Study Design**

This acceptability and feasibility assessment was nested within the larger TB Home Study. Data were collected between March and September 2024. The TB Home Study sought to evaluate the predictive value of individual and pooled tongue swab specimens vs. sputum as a household-level triage test for TB during HCIs.<sup>6</sup> In brief, individuals with microbiologically confirmed TB were asked for permission to visit their homes and conduct a HCI. All consenting household contacts were asked to provide both a sputum and tongue swab for immediate, in-home TB testing using the GX-Edge platform with Xpert Ultra. All household contacts were asked to complete an acceptability survey following the completion of in-home testing. The Theoretical Framework of Acceptability (TFA) guided the development of survey items designed to assess household contacts' experiences with in-home POC TB testing.<sup>18</sup> The Metrics to Assess the Feasibility of Rapid

Point-of-Care Technologies framework was used to assess implementation outcomes associated with the feasibility of using sputum and tongue swab samples during in-home POC TUTT.<sup>19</sup>

### **Study Setting**

The TB Home Study was conducted in the Buffalo City Metro (BCM) Health District, Eastern Cape Province, South Africa. BCM has a population size of approximately 893,000 of which 86.7% are Black. An estimated 45.3% of households are headed by women, and 24.9% of households reside in informal dwellings. An estimated 58.2% of people live in poverty and 31.1% remain unemployed.<sup>20</sup> In 2019, BCM had an estimated TB incidence of 876 per 100,000 population.<sup>21</sup> In 2018, the last year in which data are available, BCM had a drug-susceptible TB treatment success rate of 71.2% (the lowest in South Africa), a loss-to-care rate of 17.6% (second highest in South Africa), and an estimated 40% of TB cases missed by the health system.<sup>22</sup> TB is the leading cause of death (18.4%) amongst the 25-64 age group in BCM.<sup>20</sup>

### **Household Contact Recruitment**

Details regarding the HCI methods have been previously described.<sup>23</sup> Briefly, household and household contact information was obtained from people with microbiologically confirmed TB accessing services at collaborating public healthcare clinics. Contact investigation teams consisting of 2-3 trained lay community healthcare workers made up to three household visits to reach all household contacts listed. Household visits were

conducted weekdays between 8.00 – 16.00, during which the contact investigation team would conduct a household contact verification check, screen for study eligibility, and introduce the study to all those present. Healthcare workers had to attend a four-week training program during which they were trained on the study protocol, research ethics, and sample collection, preparation and testing. Household contacts were deemed eligible if they were: 1) age  $\geq 18$  years; 2) not currently on TB treatment; and 3) willing to provide informed consent. Participation in the study was voluntary, and no remuneration was provided. Once recruited into the study, participating household contacts were asked to respond to a series of survey questions as well as provide specimens for immediate in-home testing.

### **Specimen Collection and Testing**

Details regarding the sample collection and testing have been previously reported.<sup>24–26</sup> Briefly, prior to sputum collection, community healthcare workers used Copan FLOQSwabs to collect tongue swab specimens from all study participants present at the time of the HCI. Study participants were instructed not to eat, drink, rinse their mouth, or produce a sputum sample 30 minutes prior to swab- and subsequent sputum collection as part of pre-testing requirements. Tongue swabs were pooled from up to three individuals for immediate in-home testing using a single Xpert Ultra cartridge. If a household had more than three household contacts, the additional swabs were pooled and tested in a separate reaction. Pool sizes could be three, two, or in some cases a single swab. Sputum samples were collected from all study participants while the tongue swab test was being conducted.

Participants unable to expectorate sputum were referred to a clinic for further clinical evaluation. Sputum samples were individually prepared and tested immediately in the house using Xpert Ultra with the GX-Edge platform. Samples were placed into a total solution volume of 3mls – 1ml Prime Store Molecular Transport Media (PS-MTM) and 2mls Xpert sample buffer. From the ~3ml volume solution, 2mls were taken out for processing in an Xpert Ultra cartridge. Up to three GX-Edge platforms were used simultaneously allowing for testing of multiple samples concurrently, each taking ~90 minutes per test. Participants were referred for TB treatment based on positive sputum results.

### **Data Collection and Analysis**

While Xpert testing was being conducted, a contact investigation team member collected basic socio-demographic and clinical history data from each participant. Descriptive statistics (median [IQR] for continuous variables and n [%] for categorical variables) were used to characterize distributions of study variables in the sociodemographic questionnaire. Data collected pre- and post-testing were analyzed to assess the acceptability of in-home, POC TUTT. Pre-test acceptability was assessed as the proportion of household contacts consenting to participate out of the eligible population to whom study participation was offered. Post-test acceptability was assessed using survey data collected following the conclusion of a household investigation. The development of the post-test acceptability survey was informed by the TFA framework, and adapted specifically for this study.<sup>18</sup> This survey evaluated a respondent's level of acceptability of a healthcare intervention across

eight different constructs using a 5-point Likert scale (detailed in Table 2). Responses to two constructs with negatively framed questions (burden and opportunity costs), were reverse coded before calculating the mean scores to ensure interpretability and consistency with the other acceptability constructs. Standard deviation is reported to represent the dispersion of responses around the mean score for each acceptability construct.

Implementation outcomes associated with sample collection and testing of sputum and tongue swab samples were captured and used to assess the feasibility of different testing methods and included: 1) type of sample collected; 2) success of sample collection; 3) processing and preparation of sample for testing; 4) outcome of test; and 5) referral outcome. The final feasibility assessment was guided by elements of the Metrics to Assess the Feasibility of Rapid Point-of-Care Technologies framework, which was designed to assess the feasibility of rapid POC technologies during proof of concept studies.<sup>19</sup> This framework was used to select and define four metrics (Table 3) to be included in the current assessment, including: 1) Sample Collection Rate; 2) Test Processing Rate; 3) Test Success Rate; and 4) Client Notification Rate. The performance of both sputum and tongue swab testing methods against each metric was calculated and reported.

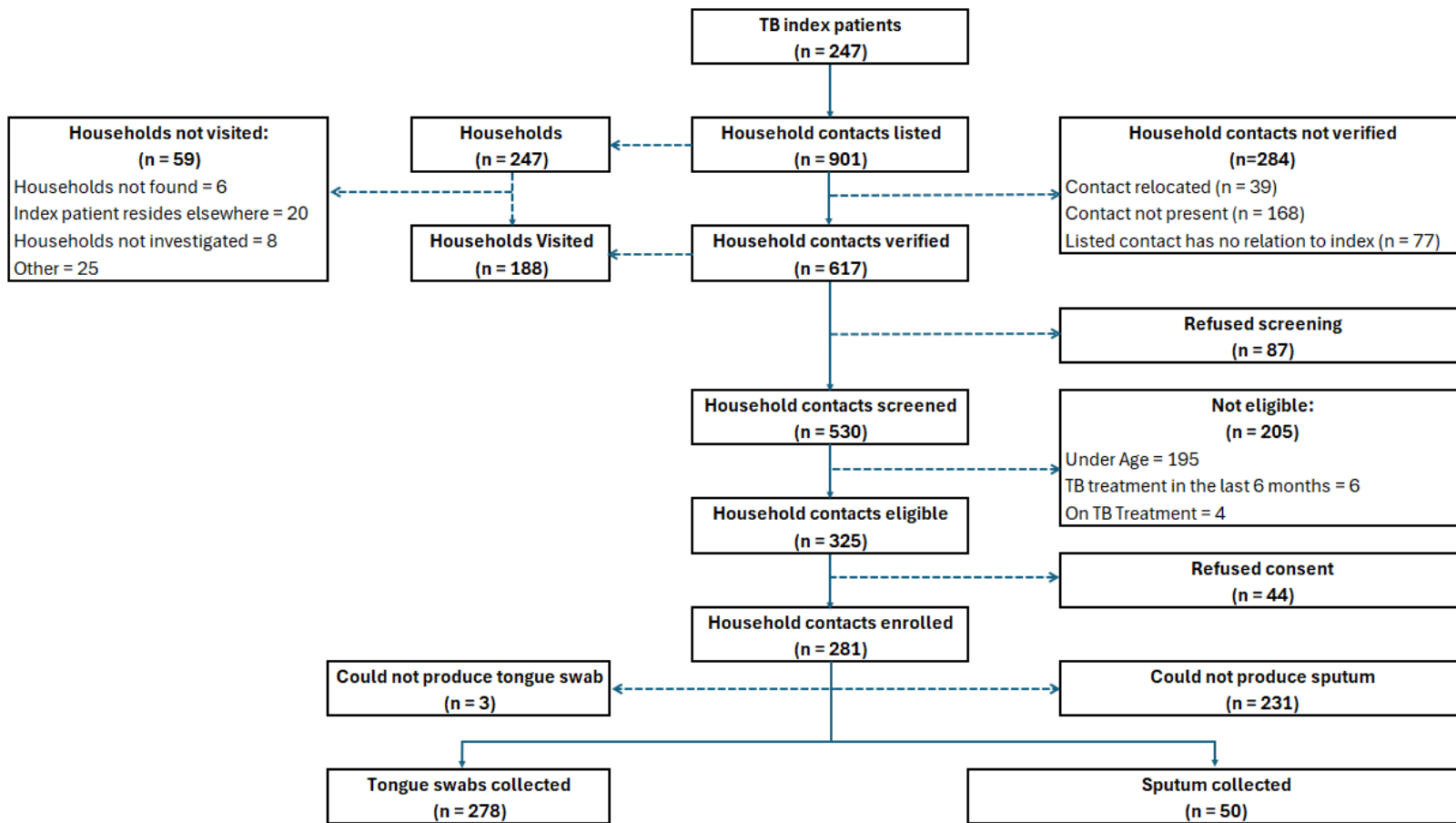
### **Ethical considerations**

This study was conducted according to the ethical principles set forth in the Declaration of Helsinki, ICH-GCP, European Directive 2001/20/EC, US Code of Federal Regulations Title 21, South African Good Clinical Practice Guidelines, and other local regulatory requirements. The study protocol was approved by the University of Pretoria Human

Research Ethics Committee (HREC 391/2021) and by Boston University Institutional Review Board (H-44118).

**RESULTS:**

Figure 1 below provides a detailed summary of the number of household contacts listed, the number of households reached, and the number of household contacts verified and screened for study eligibility. A total of 247 individuals with confirmed TB provided a household contact list with a combined total of 901 household contacts. The median household size was 3. Contact investigation teams executed a total of 468 investigations, reaching 188 (76.1%) households, and verifying the identification of a total of 68.5% (617/901) of all household contacts listed. Of 530 household contacts verified, 325 were eligible for enrolment.



**Figure 1.** Flowchart of household contact investigations, verifications, screening, and enrolment.

All 281 participants completed the socio-demographics and clinical history questionnaire. The median age of participants was 41 years (IQR 27-55). The majority were Black (87.5%, 246/281), 56.2% (158/281) were unemployed and 89.3% (251/281) had a monthly income of less than R5,000 (\$268). A quarter (21.7%, 61/281) had a previous bout of TB disease and just less than one fifth (16.0%, 45/281) were living with HIV. Almost a third of participants (31.3%, 88/281) screened positive for TB using the WHO-recommended four-symptom screener (W4SS).<sup>27</sup> Of those who screened positive for TB 25% (22/88) were able to produce sputum compared to 14% (27/193) of those who screened negative.

**Table 1:** Characteristics of Household Contacts who Received In-Home, POC TUTT and Completed the Post-Test Acceptability Survey

|                                   | <b>TB symptomatic</b> | <b>Non-symptomatic</b> | <b>Overall</b> |
|-----------------------------------|-----------------------|------------------------|----------------|
|                                   | <b>n = 88 (31%)</b>   | <b>n = 193 (69%)</b>   | <b>N = 281</b> |
| <b>Age (years)</b> (median (IQR)) | 43 (27/55)            | 40 (27/55)             | 41 (27/55)     |
| <b>Provided sputum</b>            | 23 (26%)              | 27 (14%)               | 50 (17.8%)     |
| <b>Provided tongue swab</b>       | 88 (100%)             | 192 (99.5%)            | 280 (99.6%)    |
| <b>Race</b>                       |                       |                        |                |
| Black                             | 73 (83.0%)            | 173 (89.6%)            | 246 (87.5%)    |
| Colored (mixed race)              | 14 (15.9%)            | 18 (9.3%)              | 32 (11.4%)     |
| Indian                            | 0 (0%)                | 1 (0.5%)               | 1 (0.4%)       |
| Missing                           | 1 (1.1%)              | 1 (0.5%)               | 1 (0.4%)       |
| <b>Employment status</b>          |                       |                        |                |
| Unemployed                        | 54 (61.4%)            | 104 (53.9%)            | 158 (56.2%)    |
| Employed                          | 18 (20.5%)            | 42 (21.8%)             | 60 (21.4%)     |
| Other                             | 15 (17.0%)            | 46 (23.8%)             | 61 (21.7%)     |
| Missing                           | 1 (1.1%)              | 1 (0.5%)               | 2 (0.7%)       |
| <b>Education</b>                  |                       |                        |                |
| None                              | 5 (5.7%)              | 5 (2.6%)               | 10 (3.6%)      |
| Less than grade 12                | 57 (64.8%)            | 120 (62.2%)            | 177 (63.0%)    |
| Grade 12                          | 22 (25.0%)            | 45 (23.3%)             | 67 (23.8%)     |
| Tertiary                          | 3 (3.4%)              | 20 (10.4%)             | 23 (8.2%)      |
| Missing                           | 1 (1.1%)              | 3 (1.6%)               | 4 (1.4%)       |
| <b>Income per month</b>           |                       |                        |                |
| None                              | 21 (23.9%)            | 47 (24.4%)             | 68 (24.2%)     |
| Under R2000 (\$114)               | 24 (27.3%)            | 39 (20.2%)             | 63 (22.4%)     |
| R2000 - R5000 (\$114 - \$284)     | 37 (42.0%)            | 83 (43.0%)             | 120 (42.7%)    |
| R5 000 – R10 000 (\$284 - \$569)  | 3 (3.4%)              | 12 (6.2%)              | 15 (5.3%)      |
| More than R10 000 (\$569)         | 2 (2.3%)              | 11 (5.7%)              | 13 (4.6%)      |
| Missing                           | 1 (1.1%)              | 1 (0.5%)               | 2 (0.7%)       |
| <b>HIV status</b>                 |                       |                        |                |
| Negative                          | 67 (76.1%)            | 153 (79.3%)            | 220 (78.3%)    |
| Positive                          | 16 (18.2%)            | 29 (15.0%)             | 45 (16.0%)     |
| Did not want to disclose          | 4 (4.5%)              | 10 (5.2%)              | 14 (5.0%)      |
| Missing                           | 1 (1.1%)              | 1 (0.5%)               | 2 (0.7%)       |
| <b>TB history</b>                 |                       |                        |                |
| Never                             | 67 (76.1%)            | 151 (78.2%)            | 218 (77.6%)    |
| Yes, in the last two years        | 3 (3.4%)              | 5 (2.6%)               | 8 (2.8%)       |
| Yes, more than two years ago      | 17 (19.3%)            | 36 (18.7%)             | 53 (18.9%)     |
| Missing                           | 1 (1.1%)              | 1 (0.5%)               | 2 (0.7%)       |

**Acceptability of In-Home, POC TUTT**

Table 2 lists each of the eight acceptability constructs measured, the associated survey question, and its mean score. The associated standard deviation has been included and represents the variability of responses around the mean score for each acceptability construct. Of the 325 household contacts that met all study eligibility criteria, 86.5% (281/325) provided informed consent, suggesting a high level of acceptability for in-home, POC TUTT, prior to being tested. A total of 274 (97.5%) participants completed the post-test acceptability questionnaire. The mean score for overall acceptability of in-home, POC TUTT across all eight acceptability constructs was 4.2 (SD=0.4), with 5 representing the highest level of acceptability. All constructs measuring a positive attitude towards in-home TB testing had mean scores above 4. The two constructs measuring negative attitudes toward in-home TB testing (i.e., burden and opportunity cost), had mean scores of 1.4 and 1.3, respectively, with 1 representing the least negative response. When given the option to choose between sputum or tongue swabs for future in-home TB testing, 231/274 (84.3%) chose tongue swabs.

**Table 2:** Acceptability of In-home, POC TUTT Among Household Contacts during Household Contact Investigation

| Acceptability Construct | Survey Question   | Mean Score (SD) |
|-------------------------|---|-----------------|
| Affective attitude      | How comfortable did you feel with the home-based TB testing today?  | 4.4 (0.89)      |
| Burden                  | How much effort did it take in order for you to be tested today?  | 1.4 (0.77)      |
| Ethicality              | How appropriate is it for healthcare workers to go to someone's household to provide TB testing services?   | 4.4 (0.75)      |
| Perceived effectiveness | The delivery of home-based testing motivates me to go to a clinic for additional TB services when I need it | 4.3 (0.69)      |
| Intervention coherence  | It is clear to me how a positive test result would motivate someone to go to the clinic for TB treatment    | 4.3 (0.52)      |
| Self-efficacy           | How confident are you in the test result you received today?  | 4.4 (0.60)      |
| Opportunity costs       | How did the home-based testing impact your other daily activities?  | 1.3 (0.69)      |
| General acceptability   | How acceptable was it to you for a healthcare worker to come to your house to offer TB testing?             | 4.5 (0.50)      |
| General acceptability   | How likely are you to recommend home-based TB testing to someone else?                                      | 4.5 (0.57)      |

### Feasibility of Different Sputum and Tongue Swab-based In-home, POC Testing

#### Methods

Table 3 lists and defines the four metrics used to assess the feasibility of delivering in-home POC TB testing and the associated performance of different testing methods. Tongue swab-based testing had a higher *Sample Collection Rate* compared to sputum-based testing. A total of 278 (98.9%) study participants were able to provide a tongue swab for testing. The three participants unable to provide a tongue swab for testing failed to comply with the pre-sample collection requirements. Only 17.8% (50/281) of participants were able to successfully expectorate a sputum sample for testing. Contact investigation teams successfully prepared all samples for immediate POC testing during a HCI, irrespective of

the sample type or number of tongue swab samples pooled. The *Test Processing Rate* was consequently 100% for both specimen types. The *Test Success Rate* for tongue swab-based tests (98.6%, 274/278) was comparable to sputum (95.9%, 47/49). Two sputum-based tests and two tongue swab-based tests reported errors during testing. Table 4 summarizes the test failure rate and associated error codes. Both error codes are due to complications associated with the Xpert Ultra reagent. All participants with actionable test results were immediately notified at the time of the household investigation. Due to a higher *Test Success Rate*, tongue swab-based tests had a higher *Client Notification Rate* (98.6%) as 274 of the 278 participants received a valid in-home test result. Of the 49 participants able to provide a sputum, 47 (95.9%) received a valid, in-home test result. Among the various tongue swab-based testing methods, the pooling of three samples showed slightly better test- and client notification rates compared to both two-sample pooling and individual tongue swab testing, due to no error rates occurring during any of the 63 tests run using three tongue swabs.

**Table 3:** Performance of sputum and tongue swab specimens during in-home, POC TUTT.

| Metric                   | Definition   | Sputum            | Tongue Swab        |                  |                    |                    |
|--------------------------|--|-------------------|--------------------|------------------|--------------------|--------------------|
|                          |  | Total             | Total Tongue Swabs | Single Swab      | Two Pooled Swabs   | Three Pooled Swabs |
| Sample Collection Rate   | The proportion of participants able to provide a sample for testing  | 50/281<br>(17.8%) | 278/281<br>(98.9%) | 87/88<br>(98.9%) | 128/130<br>(98.5%) | 63/63<br>(100%)    |
| Test Processing Rate     | The proportion of tests for which all samples were prepared and processed successfully to conduct testing  | 49/49<br>(100%)   | 278/278<br>(100%)  | 87/87<br>(100%)  | 128/128<br>(100%)  | 63/63<br>(100%)    |
| Test Success Rate        | The proportion of tests that produced an actionable test result  | 47/49<br>(95.9%)  | 274/278<br>(98.6%) | 85/87<br>(97.7%) | 63/64*<br>(98.4%)  | 21/21*<br>(100%)   |
| Client Notification Rate | The proportion of participants completing the test procedure who received an immediate result notification | 47/49<br>(95.9%)  | 274/278<br>(98.6%) | 85/87<br>(97.7%) | 126/128<br>(98.4%) | 63/63<br>(100%)    |

\*The number of tests conducted is less than the number of samples collected, because samples were pooled into a single Xpert Ultra cartridge.

**Table 4:** Failure rate and GeneXpert error codes associated with all in-home tests conducted, stratified by specimen type

|   | Sputum Tests (N=XX) | Tongue Swab Tests (N=XX) |             |                  |                    |
|---|---------------------|--------------------------|-------------|------------------|--------------------|
|   |                     | Total Tongue Swab Tests  | Single Swab | Two Pooled Swabs | Three Pooled Swabs |
| Successful Tests                        | 47                  | 274                      | 85          | 63               | 21                 |
| Test Failures                           | 2                   | 3                        | 2           | 1                | -                  |
| <b>Reasons for Test Failures</b>        |                     |                          |             |                  |                    |
| Probe Check Failures (error code: 5006) | 2                   | 2                        | 1           | 1                | -                  |
| Probe Check Failures (error code: 5007) | -                   | 1                        | 1           | -                | -                  |

## DISCUSSION

To our knowledge, The TB Home Study is the first to examine in-home collection and testing of sputum and tongue swabs for universal, POC TB testing during HCIs. Our initial proof-of-concept study reported that among household contacts with TB-related symptoms, in-home testing using sputum was both acceptable and feasible.<sup>9</sup> The current findings demonstrate high acceptability for in-home POC TB testing among household contacts, irrespective of symptom presentation. In addition to sputum, the collection, pooling, and testing of tongue swab samples was highly feasible. The increased sample collection yield of tongue swab specimens (98.9%) compared to sputum (17.8%) highlights the benefit of collecting less invasive sample types for TB testing, supporting findings from previous research.<sup>28</sup>

Low sputum collection yield has widely been reported as a major barrier to TB testing, especially for children and individuals living with HIV.<sup>29</sup> The 17.8% sputum collection yield was far lower than what has been reported elsewhere with ranges between 82%-93%.<sup>30</sup> Of the 50 individuals who were able to produce sputum, 46.0% (23/50) were TB symptomatic, and 17.4% (8/46) of those willing to disclose, were HIV positive. In comparison, among those unable to produce sputum, 28.6% (66/231) had TB symptoms, and 16.9% (37/219) of those willing to disclose, were HIV positive. The low sputum collection yield may be a result of several factors including the collecting spot sputum samples at different times of the day, collection being done by lay healthcare workers with limited training, or the fact that collection was done outside the traditional clinical setting

without the option to offer induction.<sup>31</sup> There is growing evidence highlighting the potential of tongue swabs as a viable alternative to sputum for TB testing due to the increased sample collection yield and potentially higher probability of case detection.<sup>28</sup> A relatively low (31.3%) proportion of household contacts presented with symptoms, highlighting the large proportion that would not have received further clinical evaluation under routine conditions. TUTT of high risk groups like household contacts could increase case detection by as much as 17%.<sup>11</sup>

While our findings support the acceptability and feasibility of in-home POC TUTT the accuracy of tongue swab testing for TB remains a concern. Variability in accuracy could increase the probability of false negatives, thereby contributing to increased risk of transmission, or alternatively, false positives resulting in misdiagnosis followed by unnecessary treatment exposure. The optimal number of swabs and approach necessary to optimize DNA recovery during processing remains under investigation.<sup>32</sup> Similarly, although the pooling of sputum samples has been shown to be efficient at reducing costs while producing highly accurate results, uncertainty remains whether the same would hold true when pooling tongue swabs.<sup>33</sup> While the sensitivity of tongue swabs for TB diagnosis remains variable, the specificity seems notably high, yielding an overall favorable diagnostic effect.<sup>34</sup> The high sensitivity of tongue swabs combined with the high sample collection yield make them highly valuable for confirmatory testing alongside other diagnostics methods. Furthermore, high specificity can assist with minimizing false positives, thereby assessing an individual's eligibility for TB preventive treatment.

The importance of our findings is supported by a growing recognition for the need for accurate tests that enable prompt linkage to care, are implementable at POC, by healthcare workers with minimal training, and with results that are available in a single patient encounter. Consideration of the feasibility of collecting, processing, and testing specimens outside of a traditional clinical setting is essential to estimating the true potential of using alternative sample types for TB testing during community-based active case finding. Despite the introduction of several new platforms, gaps in the current TB diagnostic pipeline still remain.<sup>30</sup> Exploring the potential of new platforms, assays, and testing methods that show promise for POC deployment across different use case scenarios plays an essential role in refining target product profiles.<sup>32</sup> Findings from this research can be used to inform new use case development as well as to refine target product profiles aimed at delivering near-POC and POC TB testing.

A key strength of this study was the ability to use lay community healthcare workers to conduct HCIs and deliver in-home POC TUTT. South Africa continues to face a severe shortage of qualified health care workers, which has resulted in task shifting to a range of lay healthcare workers. The delivery of TB services by community healthcare workers has been shown to enhance population coverage, increase testing, improve early diagnosis and linkage to care.<sup>35</sup> Another strength is the use of a theory-informed instrument to measure acceptability. No standardized or validated healthcare intervention acceptability instruments currently exist.<sup>18</sup> Similar to most other evaluations, our previous work assessing the acceptability of in-home, POC TB testing relied on behavioral measures of acceptability such as study enrollment and/or dropout rate. However, several reasons other

than low acceptability could explain why people decline or withdraw from a healthcare intervention, including lack of motivation, distrust, or privacy concerns, all which are assessed when using the TFA framework. The TFA framework is innovative in that it provides conceptually distinct constructs that capture key dimensions of acceptability allowing the assessment of complex healthcare interventions.<sup>18</sup>

Our study had several limitations. First, the high level of pre-test acceptability of POC TB testing among household contacts might be an overestimation. The acceptability of TB testing might be higher among contacts of TB patients compared to the general population due to increased perceived risk and awareness of the disease. Household contacts directly exposed to TB have a heightened understanding of the importance of early detection and treatment.<sup>36</sup> Furthermore, selection bias may account for the high post-test acceptability, as only household contacts who initially provided consent completed the post-test acceptability assessment. Secondly, this analysis did not include a cost- or cost-effectiveness analysis to estimate and compare the difference in cost and outcomes of each testing method. Pooling tongue swabs into a single Xpert Ultra cartridge aims to reduce the total number of cartridges required, often cited as a significant factor driving testing costs.<sup>15</sup> However, sputum remains the gold standard for TB testing due to its superior sensitivity over tongue swabs.<sup>28</sup> Future studies should explore the cost-effectiveness of these different testing methods to weigh potential cost savings with decreasing test accuracy, assessing the “financial feasibility” and scalability of the proposed testing methods.<sup>16</sup> Lastly, we only offered testing to household contacts older than 18 years of age. In 2023, an estimated 12% of all suspected TB cases were children and young adolescents.<sup>1</sup>

Effective TB diagnosis in children is hampered by several factors, including the paucibacillary nature of TB, its shared symptoms with other common childhood diseases, and most significantly, difficulties collecting samples for testing.<sup>37</sup> The collection of non-invasive samples like tongue swabs for TB screening among children combined with the delivery of TB preventative treatment could have a significant public health impact. However, the low sensitivity of tongue swabs in children remains a major concern, limiting its use. Failing to optimize testing protocols that increase accuracy and prioritize children and adolescents in future studies will continue to stifle progress towards TB targets.

## **CONCLUSION**

As novel platforms and diagnostics for decentralized molecular testing become more readily available, this study provides evidence to support their integration into existing strategies, including HCI. Furthermore, these findings provide support for the expansion of in-home TB testing by minimally trained lay healthcare workers. The ability to integrate molecular POC testing into community-based strategies can reduce the workload of already overburdened laboratory and clinical facilities, improve client satisfaction, and remove persistent barriers preventing equal access to services. In-home POC TUTT using either sputum or tongue swabs is highly acceptable and feasible. Rapid molecular TB testing with immediate result notification at POC reduces the burden placed on those at highest risk by offering testing services in a single consultation, improves access to testing, and shows great potential for early case detection and result notification.

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**CURRICULUM VITAE**

