Aus der

Medizinischen Klinik und Poliklinik IV

Klinikum der Ludwig-Maximilians-Universität München

Predictors and dynamics of household Mtb transmission in high tuberculosis incidence settings

Dissertation

zum Erwerb des Doctor of Philosophy (Ph.D.)

an der Medizinischen Fakultät

der Ludwig-Maximilians-Universität München

vorgelegt von

Edson Tawanda Marambire

aus

Gokwe / Simbabwe

Jahr

2025

Mit Genehmigung der Medizinischen Fakultät der
Ludwig-Maximilians-Universität München

Erstes Gutachten:	Priv. Doz. Dr. Norbert Heinrich
Zweites Gutachten:	Prof. Dr. Katharina Kranzer
Drittes Gutachten:	Priv. Doz. Dr. Camilla Rothe
Viertes Gutachten:	Prof. Dr. Sören Schubert

Dekan: Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung: 05.11.2025

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dean's Office
Medical Faculty

MMRS MUNICH MEDICAL RESEARCH SCHOOL

Affidavit

Marambire Edson Tawanda

Surname, first name

Biomedical Research and Training Institute

Street

Harare

Zip code, town

Zimbabwe

Country

I hereby declare, that the submitted thesis entitled

Predictors and dynamics of household Mtb transmission in high tuberculosis incidence settings

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the submitted thesis or parts thereof have not been presented as part of an examination degree to any other university.

Munich, 07 November 2025

Place, date

Edson Tawanda Marambire

Signature doctoral candidate

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dean's Office
Medical Faculty

MMRS MUNICH MEDICAL RESEARCH SCHOOL

Confirmation of congruency between printed and electronic version of the doctoral thesis

Marambire Edson Tawanda

Surname, first name

Biomedical Research and Training Institute

Street

Harare

Zip code, town

Zimbabwe

Country

I hereby declare that the electronic version of the submitted thesis, entitled

Predictors and dynamics of household Mtb transmission in high tuberculosis incidence settings

is congruent with the printed version both in content and format.

Munich, 07 November 2025

Place, date

Edson Tawanda Marambire

Signature doctoral candidate

Abstract

Introduction: Tuberculosis (TB) remains a critical global health challenge, disproportionately affecting high-burden regions in Southern Africa. Household contacts of people with TB (PWTB) face elevated risks of *Mycobacterium tuberculosis (Mtb)* infection, yet gaps persist in understanding predictors of transmission and the role of multimorbidity (e.g., HIV, malnutrition, non-communicable diseases). This PhD research investigated predictors and transmission dynamics of household *Mtb* in high TB incidence settings.

Methods: The research was nested within the multinational ERASE-TB cohort study in which household contacts (≥10 years) of adult microbiologically confirmed (medium-high) PWTB were recruited from Zimbabwe, Mozambique and Tanzania. Three interrelated studies were conducted. The first characterised multimorbidity and socioeconomic disparities in TB-affected households. The second developed and evaluated predictive models for *Mtb* infection (IGRA positivity) among household contacts using multivariable regression with cross-validation and decision curve analysis. The third employed mixed-effects logistic regression to assess influence of HIV/ART status of PWTB on household transmission dynamics.

Results: Findings from the first study reveal a substantial burden of chronic conditions and socioeconomic disparities that amplify TB risk. Multimorbidity affected 61% of adults, with high prevalence of HIV (15%), malnutrition (18%), and diabetes (9.4%). Predictive models demonstrated limited utility (AUROC: 0.59–0.60), reflecting challenges in using individual- and household-level factors for *Mtb* infection risk stratification in settings with high community transmission. The third study demonstrated that HIV-positive PWTB not on ART exhibited 55% lower odds of household *Mtb* transmission (aOR: 0.45, 95% CI: 0.29–0.69) compared to HIV-negative PWTB and those on ART, even after controlling for bacterial burden and symptom duration.

Conclusion: Household *Mtb* transmission in high-burden settings is shaped by intersecting biological, socioeconomic, and structural factors. Findings emphasize the importance of integrated health screening as a means to improve household health and potentially reduce risk of progression to TB among household members. While predictive models showed limited clinical utility, this underscores the dominance of community transmission. The reduction in transmission among untreated HIV-positive PWTB challenges conventional assumptions, suggesting unmeasured behavioural or healthcare access mediators. Policies must prioritize integrated health screening among TB-affected households, context-adapted *Mtb* diagnostics, and innovative TB/HIV program integration. Future research should explore feasibility of integrated health screening, develop effective and affordable diagnostic tools and explore mechanisms underlying HIV/ART-related transmission dynamics to optimize prevention strategies.

Keywords: Mycobacterium tuberculosis; Household transmission; Predictive modelling; High TB incidence settings; Multimorbidity

Table of contents

List of figures

List of abbreviations

ART	Antiretroviral Therapy
AUDIT-C	Alcohol Use Disorders Identification Test-Concise
AUROC	Area Under the Receiver Operating characteristic Curve
COPD	Chronic Obstructive Pulmonary Disease
ERASE-TB	Early Risk Assessment in TB Contacts by New Diagnostic Tests
HIV	Human Immunodeficiency Virus
IGRA	Interferon Gamma Release Assay
IQR	Interquartile Range
Mtb	Mycobacterium tuberculosis
MTB/Rif	GeneXpert MTB/Rif Ultra, a molecular diagnostic test for TB and rifampicin resistance
NCDs	Non-Communicable Diseases
OR	Odds Ratio
aOR	Adjusted Odds Ratio
PLHIV	People Living with HIV
PWTB	People with Tuberculosis
TB	Tuberculosis
TPT	TB Preventive Therapy
TST	Tuberculin Skin Test
TTP	Time to Culture Positivity
UN	United Nations
WHO	World Health Organization

List of publications

Paper A

HIV, malnutrition, and non-communicable disease epidemics among tuberculosis affected households in East and Southern Africa: A cross-sectional analysis of the ERASETB cohort

Paper B

Prediction models for *Mycobacterium tuberculosis infection* among adolescent and adult household contacts in high tuberculosis incidence settings

Additional Contributions:

Paper C (Appendix A)

Impact of HIV and ART status of persons with tuberculosis on household *Mycobacterium tuberculosis* transmission in tuberculosis incidence settings

Paper D (Appendix B)

Protocol paper:

Early risk assessment in paediatric and adult household contacts of confirmed tuberculosis cases by novel diagnostic tests (ERASE-TB): protocol for a prospective, non-interventional, longitudinal, multi-country cohort study.

1. My contribution to the publications

1.1 Contribution to paper A

In paper A, “HIV, malnutrition, and non-communicable disease epidemics among tuberculosis affected households in East and Southern Africa: A cross-sectional analysis of the ERASE-TB cohort”, I oversaw data collection, contributed to data analysis and interpretation, including providing contextual insights. I wrote the first draft of methods section of the paper and reviewed and refined the manuscript, ensuring the relevance of the discussion to local public health policy and practice in the southern and east African region. I am second author on the paper.

1.2 Contribution to paper B

In the second paper, “Prediction models for *Mycobacterium tuberculosis* infection among adolescent and adult household contacts in high tuberculosis incidence settings”, I was the first and corresponding author. I led the conceptualization, design, analysis and execution of this study. I developed the research objectives and analysis plan, conducted statistical analyses, and interpreted the results. I drafted the manuscript, integrating feedback from co-authors, and ensured the overall scientific rigour and coherence of the paper.

1.3 Contribution to paper C (Appendix A)

In the third paper, “Impact of HIV and ART status of persons with tuberculosis on household *Mtb* transmission in high tuberculosis incidence settings”, I was the first and corresponding author. I led the study design, analysis, and manuscript development. I performed statistical analyses to examine the impact of HIV and ART status on household *Mtb* transmission, ensuring robust and accurately results presentation. I wrote the manuscript and integrated feedback from co-authors.

1.4 Contribution to paper D (Appendix B)

I am the first and corresponding author of this manuscript. It is a protocol paper for the Early Risk Assessment in TB contactS by new diagnostic tEsts (ERASE-TB) study in which my PhD research was embedded. I was the Zimbabwean site research coordinator for the study. In that role, I oversaw the successful implementation of the research project. This included leading site set-up, monitoring recruitment, overseeing data collection, ensuring adherence to study protocols, and maintaining data quality. I drafted the manuscript and integrated feedback from co-authors.

2. Introductory summary

2.1 Global tuberculosis background

Tuberculosis (TB) remains a major public health problem, with more than 10 million new cases and 1.2 million deaths globally in 2023[1]. Southern Africa bears a disproportionate burden, accounting for nearly 30% of global TB cases, driven by high HIV prevalence and socioeconomic inequities.[2] Despite being preventable and typically curable, a persistent gap in prevention, diagnosis, and treatment continues. TB, caused by *Mycobacterium tuberculosis (Mtb)* complex, is primarily spread through aerosols, putting household members of people with TB (PWTB) at high risk of infection.[3] An estimated quarter of the global population is infected with *Mtb*[4]; of which 10% will progress to active TB in their lifetime. Chronic and non-communicable conditions including malnutrition, diabetes, chronic obstructive pulmonary disease (COPD), and HIV/AIDS can weaken the immune system, making individuals more susceptible to infections, including *Mtb*. TB preventive therapy (TPT) can reduce the risk of TB by up to 90% and therefore it is a cornerstone of the World Health Organisation's (WHO) 'End-TB strategy'.

In 2014, WHO 'End-TB' Strategy set out to achieve a 90% reduction in TB incidence and 95% reduction in TB deaths by 2035, with 2020 and 2025 milestones already missed.[5] Achieving the End-TB targets requires innovative strategies to screen, diagnose and treat TB at earlier stages to prevent onward transmission and better-targeted, shorter and more effective TPT.[2,6,7]

The first United Nations (UN) High-Level Meeting on TB in 2017 set ambitious five-year commitments and targets that included specific goals for TPT coverage. These targets were not achieved and were subsequently revised in 2023, with a new goal of reaching 90% TPT coverage among household contacts by 2027, while emphasising integrating TPT into primary healthcare.

Household contacts of PWTB are recognized as a high-risk group for TB and hence they are an important group for targeted interventions e.g. early diagnosis through case finding and TPT. Although the majority of *Mtb* transmission may occur outside the household,[8] household contacts are readily identifiable and contribute an important proportion of *Mtb* transmission events. Hence, interventions targeted towards TB household contacts may be an effective approach to reducing population-level TB burden.[9,10] These may include TB screening and TPT for contacts at the highest risk of getting infected with and progressing to TB disease. Also, integration of other services such as testing and treatment for HIV or diabetes as well as malnutrition into household contacts tracing may provide an opportunity to improve people' immune system ultimately preventing progression to TB.

TPT is currently recommended by the WHO for children aged <5 years who are household or close contacts of people with bacteriologically confirmed pulmonary TB as well as adults living with HIV.[11] TPT is conditionally recommended older children, adolescents and adults who are TB household contacts, TPT is conditionally recommended , following exclusion of TB by clinical evaluation, and ideally after a test for *Mtb* infection such as tuberculin skin tests (TST) or interferon-gamma release assays (IGRA).[11] Despite the availability of preventive therapy, its implementation particularly in Southern Africa, remains limited due to challenges that include suboptimal predictive value of the tests,[12] resources unavailability, and weak integration of TB preventive strategies into routine healthcare services.[13–15]

To address these challenges, strategies proposed include the development and application of innovative techniques capable of more accurately predicting household *Mtb* infections while accessible, especially in limited resource settings, as well as research into household transmission dynamics. Integrated screening for chronic conditions such as undernutrition, HIV and diabetes among TB-affected households may also provide valuable insights into the risk factors and mechanisms of *Mtb* transmission and TB disease and provide an avenue by which people with chronic conditions can be offered TPT, or the underlying condition addressed, reducing the risk of progression to TB disease.[16] Such efforts aim to better direct TPT to individuals at the highest risk of developing TB in settings with limited resources such as laboratory equipment, sophisticated infrastructure and trained personnel.

2.2 Rationale and Objectives

The persistent global TB epidemic is driven by complex interactions between biological, social, and structural determinants. While TPT is a cornerstone of the WHO End-TB Strategy, its global roll-out has been stymied by a lack of accurate diagnostic tests to identify individuals recently infected with *Mtb* infection. This is most pronounced in high TB-burden settings where access to diagnostics such as TST and IGRA is limited, leading to either widespread overtreatment or restricted access to TPT for those who could benefit most,[1] with the latter being the most common.

Household contacts of PWTB are a readily identifiable high-risk group, presenting an opportunity for targeted interventions. However, the high prevalence of two or more coexisting conditions (multimorbidity) in TB-affected households, including HIV, malnutrition, and non-communicable diseases (NCDs), adds complexity to designing and implementing effective strategies. Addressing these intertwined health challenges requires innovative diagnostic and predictive tools, as well as the integration of TB services with broader primary healthcare systems.

Given the high susceptibility of household contacts to *Mtb* infection, it is crucial to identify and manage chronic diseases associated with immunosuppression that may exacerbate the risk of

progression to disease once infected. Screening for conditions such as HIV, malnutrition, diabetes, and chronic lung disease can help in early detection and timely intervention, thereby mitigating the spread of *Mtb* within households. Understanding individual and household level characteristics as well as the burden of multimorbidity within TB-affected households could be critical to informing factors that can predict the susceptibility of individual members to TB.

In the pre-ART era, rising HIV prevalence was a strong driver of increased TB incidence across Southern Africa.[17,18] More recently, the wide availability of antiretroviral therapy (ART) has led to a change in TB epidemiology and hence the need to explore the impact of the HIV and ART status of the PWTB on transmitting *Mtb* to their household contacts.

This PhD research, nested within the Early Risk Assessment in TB contactS by new diagnostic tEsts (ERASE-TB) cohort study,[19] aims to address these gaps by developing and evaluating predictive models, and exploring household *Mtb* transmission dynamics. Such knowledge is critical to informing policy and improving the implementation of targeted TB preventive interventions.

2.2.1 PhD Objectives

1. To assess the characteristics of TB-affected households, burden of multimorbidity and role of integrated health screening in high TB-burden settings.
2. To identify household and individual level factors that predict household *Mtb* infection among household contacts of PWTB, including multimorbidity and the impact of HIV and ART status.
3. To develop and validate predictive models that incorporate integrated health screening data to identify individuals at highest risk of *Mtb* infection.
4. To understand how HIV and ART status of PWTB impacts household *Mtb* transmission in high TB incidence settings

2.3 Methods

2.3.1 Study design and setting

This PhD research was embedded in a large multi-national, observational, prospective cohort study ERASE-TB that was conducted in three East and Southern African countries; Maputo (Mozambique), Mbeya (Tanzania), and Harare (Zimbabwe).

The research paper D (appendix B) details all ERASE-TB study procedures. At each study visit (every 6 months for up to 24 months), enrolled household contacts underwent TB screening

(WHO symptom screen and chest X-ray, followed by Xpert MTB/Rif Ultra if either was suggestive of TB) and collection of samples for novel diagnostic tests and biobanking. All household contacts who were offered HIV testing if they were not known to be living with HIV. IGRAs (STANDARDTM F TB-Feron FIA [IFN-gamma; SD Biosensor, Republic of Korea]) were conducted at baseline and at subsequent visits dependent on reagent availability. Individual and household-level questionnaires collected data on socioeconomic characteristics, living conditions, past medical history, and risk factors associated with *Mtb* infection.

2.3.2 Study Population

Household contacts aged ≥10 years living with recently diagnosed PWTB (index cases) were eligible for inclusion. Index cases were defined as adults (≥18 years) with a positive smear (at least +1) and/or a medium or high-level positive Xpert MTB/Rif sputum result. Household contacts were screened for TB using WHO-recommended symptom screening, chest X-rays, and IGRA testing, with pathogen sequencing data collected for index cases at the Zimbabwe site.

2.3.3 Statistical analysis

Epidemiological research methods were implemented, resulting in three manuscripts. Two manuscripts have been published whilst one has been submitted and is under review. The methodologies of the three papers were designed to build on one another, creating a cohesive progression from risk identification to predictive modelling and mechanistic exploration.

2.3.3.1 Paper A: HIV, malnutrition, and non-communicable disease epidemics among tuberculosis affected households in East and Southern Africa: A cross-sectional analysis of the ERASE-TB cohort

The analysis for this paper focused on describing the prevalence and distribution of multimorbidity among household contacts. Descriptive statistics, including means, medians, and proportions, were used to summarise demographic and clinical characteristics. Logistic regression models were employed to explore associations between multimorbidity and various demographic, clinical, and household-level factors, such as age, sex, HIV status, and household crowding. These models allowed for the identification of key predictors of multimorbidity.

2.3.3.2 Paper B: Prediction models for *Mtb* infection among adolescent and adult household contacts in high tuberculosis incidence settings

In this study, the dataset was split into a training (70%) and evaluation (30%) dataset. A 10-fold cross-validation technique with stepwise-backward elimination was used to develop predictive

models for *Mtb* infection, as measured by IGRA results using the training dataset. Two models were developed, one model with basic individual- and household-level predictors, ascertainable from the person with TB by a nurse or community health worker using just a questionnaire (basic model) and another with all eligible individual and household predictors (comprehensive model). Paper A and a systematic review of the literature (currently drafted for publication) informed the predictors selected for the models. Candidate predictor variables included both individual- and household-level factors, and index case characteristics. Models' predictive performance was assessed using the area under the receiver operating characteristic curve (AUROC) to evaluate discrimination, alongside sensitivity and specificity measures on an evaluation dataset. Decision curve analysis was applied to determine the net clinical benefit of using these models compared to universal treatment approaches, offering a practical evaluation of their utility in resource-limited settings. A sensitivity analysis was done using endline IGRA test results

2.3.3.3 Paper C (Appendix A): Impact of HIV and ART status of persons with tuberculosis on household *Mtb* transmission in high tuberculosis incident settings

The impact of HIV and ART status of the PWTB on *Mtb* transmission was analysed after HIV appeared as a prevalent risk factor in paper A, and with the highest predicting score in paper B. Mixed-effects logistic regression models were used, accounting for clustering of contacts within the same household. The models were adjusted for confounding factors (including age and sex of household contacts and PWTB) and mediators (bacterial burden, symptom duration) ensuring a comprehensive evaluation of the relationship between HIV/ART status and transmission dynamics. Sensitivity analyses using adolescent household contacts (≤ 19 years) were conducted to assess the robustness of the findings, particularly concerning potential misclassification of extra-household transmission.

2.4 Results

2.4.1 Paper A: HIV, malnutrition, and non-communicable disease epidemics among tuberculosis affected households in East and Southern Africa: A cross-sectional analysis of the ERASE-TB cohort

The study revealed high prevalence of behavioural factors and chronic disease associated with increased risk of *Mtb* infection and TB disease among both PWTB and household contacts. Whilst smoking was significantly higher in men (16% compared to 1.4% in women), smoking was uncommon, with 7.1% of participants reporting ever smoking. Alcohol consumption was more

prevalent, with 33% of participants reporting ever having drank alcohol. AUDIT-C screening revealed hazardous alcohol consumption levels of 21% in men, 9% amongst women and 1.5% in adolescents. Socioeconomic deprivation was widespread, with 20% of households experiencing overcrowding (at least three people per room) and 90% living below the international poverty line (USD $ 1.90 per person per day). On average each household hosted five individuals. Food insecurity was significantly higher in urban-based sites (Mozambique; 35% and Zimbabwe; 41%) compared to Tanzania (5.8%) which was predominantly a rural site, reflecting differences in urban versus rural contexts. These factors underscore the interplay of behavioural and socioeconomic determinants in shaping TB risk within households.

The analysis of multimorbidity among TB-affected households revealed a significant burden of chronic conditions, with 61% of adults found to have at least one chronic disease. There was high prevalence of conditions associated with increased risk of TB (HIV 15%, malnutrition 18% and diabetes 9.4%). Except HIV, most people with chronic and non-communicable diseases were undiagnosed and hence untreated, prior to recruitment. Logistic regression identified significant predictors of multimorbidity, including age, HIV status, and household socioeconomic conditions.

2.4.2 Paper B: Prediction models for *Mtb* infection among adolescent and adult household contacts in high tuberculosis incidence settings

Prediction models were developed using data from household contacts to identify factors associated with baseline IGRA positivity. A comprehensive model was developed incorporating all ‘good-to-have’ variables related to *Mtb* infection, including factors identified in paper A; HIV status of PWTB and household contact, household crowding, nutritional status and food insecurity. This enhanced model showed modest performance, achieving an AUROC of 0.60. Applying this model necessitated evaluation of each individual household contact. Thus, a basic model was created including six key predictors ascertainable through lay healthworker interviewing of a household contact: contact’s age, caregiver role, index case’s symptom duration, HIV status, Xpert MTB/Rif positivity category and household crowding. This model also demonstrated moderate discriminatory performance (AUROC 0.59). A sensitivity analysis using IGRA positivity at the last visit did not change the performance of the models. A risk score applicable to clinical settings was developed from the basic model. Index case’s symptom duration above 3 months demonstrated the highest predicting score while HIV-positive index cases who were not on ART had the lowest predicting score. Calibration plots revealed that the model lacked stability, as the predicted probabilities did not maintain a consistent relationship with the observed outcomes. Decision curve analysis indicated that the prediction models demonstrated lower net clinical benefit compared to the ‘treat all’ strategy across all threshold

probabilities. This study suggests that the developed prediction models do not add value in guiding TPT use in high-tuberculosis burden settings.

2.4.3 Paper C (Appendix A): Impact of HIV and ART status of persons with tuberculosis on household *Mtb* transmission in high tuberculosis incident settings

Paper A revealed that HIV is common among PWTB (32% prevalence, of which 11% were not on ART). Paper B indicated that HIV and ART status of PWTB was an important predictor of *Mtb* transmission within a household. Paper C explored this further: household contacts exposed to PLWH who were not on ART had significantly lower odds of IGRA positivity (aOR 0.45, 95% CI 0.29-0.69) compared to contacts exposed to those who were on ART and HIV-negative PWTB, after adjustment for important confounders. This association persisted even after accounting for bacterial burden and symptom duration (potential mediators of the association), suggesting that PWTB who are living with HIV but not on ART transmitted *Mtb* at lower rates compared to HIV-negative or people with HIV and on ART, independent of traditional markers of infectiousness. Household contacts of PWTB who were living with HIV and on ART faced higher transmission risks, similar to those of HIV-negative PWTB.

This study also revealed that 30% of HIV-positive PWTB were diagnosed with HIV at the time of TB diagnosis, underscoring missed opportunities for earlier HIV diagnosis and care. Time to culture positivity was shortest among HIV-negative TB patients and longer among PLHIV not on ART, further highlighting the interplay between bacterial load, immune suppression, and transmission dynamics.

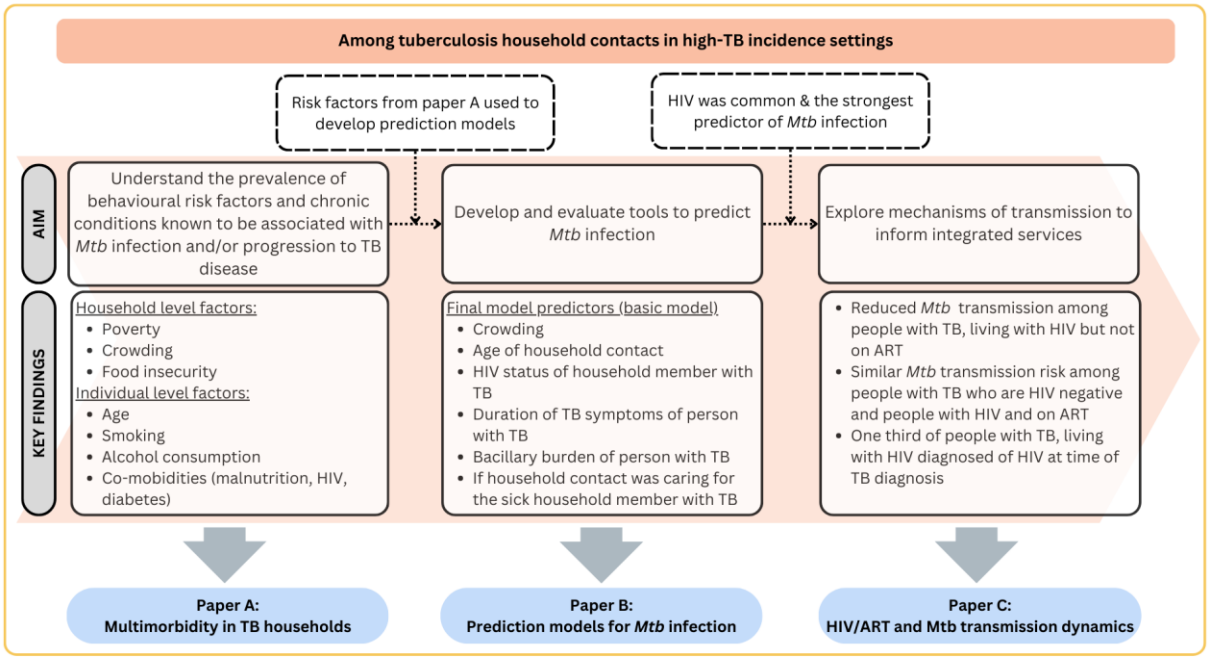
2.5 Discussion

This PhD research aimed to investigate predictors of *Mtb* transmission in high TB-incidence settings, using data from the ERASE-TB cohort. The synthesis of findings provides a nuanced understanding of household-level and individual-level factors contributing to transmission dynamics. Each paper addresses a distinct aspect of this complex issue, providing a comprehensive view of the challenges and opportunities for targeted interventions.

By first identifying behavioral risk factors and multimorbidity patterns in TB-affected households (Paper A), I developed predictive tools to prioritize high-risk contacts (Paper B). Paper C refined these insights by contextualizing HIV/ART's role in transmission dynamics. Collectively, these studies advance a unified framework for understanding household *Mtb* transmission in high-TB burden settings, in an era of high population-level awareness of HIV status and coverage of ART.

Figure 2.1 shows the progression of the three papers and their contribution to the PhD aim.

Figure 2.1: Conceptual framework for the PhD research



Paper A underscores the high prevalence of multimorbidity in TB-affected households, with a significant burden of HIV, malnutrition, and NCDs including diabetes – all factors associated with immunosuppression, high risk of progression to TB and hence individuals that would benefit from TPT. This paper provides further evidence of the overlapping epidemics (social and biological) that compound vulnerability to *Mtb* transmission and thus TB. The findings emphasize the importance of integrated health screening as a means to improve household health and potentially reduce risk of progression to TB among household members. By identifying clusters of modifiable risk factors, this work demonstrates the importance of multimorbidity in the context of TB vulnerability, emphasizing the need for holistic integrated health strategies. Further, this research informed papers two and three by highlighting the complex interplay of biological, social, and structural determinants TB-affected households face which may impact on risk of *Mtb* transmission and TB disease.

Paper B focuses on developing predictive models for *Mtb* infection among household contacts. Although the models showed modest predictive performance, they provided valuable insights into risk factors associated with IGRA positivity. These include age, caregiver role, and index case characteristics. These findings underscore the inadequacy of the prediction models in accurately predicting *Mtb* infection within high-TB-incidence settings, probably due to the high levels of community transmission. This paper advances the methodological framework for identifying high-

risk individuals, laying the groundwork for targeted preventive strategies. The modest performance of the models also highlights the limitations of relying solely on individual- or household-related predictors in high TB-burdened settings, where community transmission plays a significant role. Paper B also highlights the need for innovative diagnostic approaches tailored to resource-limited contexts where there is a high prevalence of community transmission.

Paper C explores the impact of HIV and ART status on household *Mtb* transmission. In a population of PWTB who have high bacterial loads, HIV-positive PWTB not on ART had lower transmission likelihood compared to those on ART or HIV-negative individuals, even after adjusting for confounders and variables on the causal pathway. This counters conventional understanding that lower *Mtb* transmission among people with TB and HIV but not on ART was mostly attributable to the pauci-bacillary nature of the disease resulting from compromised immunity. Our intriguing finding underscores the complexity of transmission dynamics, hypothesizing that behavioral, biological and other factors such as better access to health care (including proactive screening for TB) affect duration of infectiousness (which is not necessarily synonymous with symptom duration). Additionally, despite the widespread availability of free HIV testing and ART [20–22], 30% of PLHIV with TB were previously undiagnosed with HIV. This suggests loopholes to current community-based HIV interventions on equitable access to HIV testing particularly to people at high risk of TB. These findings emphasise the importance of targeted and integrated TB and HIV programs to optimise prevention strategies and reduce household transmission. This paper adds critical evidence to our understanding of how HIV-related factors influence *Mtb* transmission dynamics. It also highlights the need for further research into the mechanisms underlying reduced transmission among HIV-positive individuals not on ART.

Collectively, the three manuscripts contribute significantly to the overarching aim of investigating predictors of *Mtb* transmission in high TB-incidence settings. Beginning with a foundational understanding of characteristics and health challenges within TB-affected households, emphasizing the need for integrated health approaches. The research advanced the methodological framework for identifying high-risk individuals, laying the groundwork for targeted preventive strategies. The study concluded by adding depth to our understanding of how HIV-related factors influence transmission dynamics, providing critical insights for tailoring interventions in diverse epidemiological contexts.

2.5.1 Policy Implications

This research highlights the necessity of addressing TB prevention through a multifaceted lens. Key recommendations for policymakers include:

1. Integrated Health Services:
    i. Integrate TB screening with broader health assessments for social risk factors such as smoking, alcohol intake, malnutrition, and NCDs to optimize household-level interventions.
    ii. Targeted strengthening and integrating of HIV and TB programs to address missed opportunities for early HIV diagnosis and ART initiation, as highlighted by the high proportion of undiagnosed HIV among TB patients.
2. Scalable Diagnostic Tools: Prioritize the development and deployment of context-appropriate, affordable diagnostic tools to improve diagnostic accuracy for identifying those most in need of preventive strategies in high-burden settings.

These recommendations align with the WHO's End-TB Strategy and emphasise the need for holistic, equity-focused approaches to TB control.

2.5.2 Future Research

This research highlights the need for future studies focusing on:

1. Diagnostic Innovations: Developing affordable, effective and context-appropriate diagnostic tools to improve risk stratification while at the same time catering for people across different age ranges, risk factor patterns and with or without chronic single or multiple diseases.
2. Implementation Research: Evaluating the feasibility and impact of integrated health approaches within primary healthcare systems, particularly in resource-limited settings.
3. Longitudinal Studies: Exploring the long-term effects of ART on *Mtb* transmission dynamics to optimize HIV-TB co-management strategies as well as investigating the paradoxical finding of reduced transmission among HIV-positive individuals not on ART to disentangle behavioural, biological, and healthcare access factors.

Such research will bridge gaps in knowledge and practice, paving the way for sustainable TB prevention in high-burden regions.

This PhD research underscores the complex nature of household *Mtb* transmission, highlighting the critical need for integrated and targeted approaches in addressing transmission and thus reducing TB incidence. By bridging gaps in knowledge and practice, these findings pave the way for more effective and sustainable TB prevention efforts in high TB-burden settings.

3. References

1. World Health Organisation (WHO). *2024 Global Tuberculosis Report*.; 2024.
2. World Health Organization (WHO). *Global Tuberculosis Report 2023*.; 2023. https://iris.who.int/.
3. Centres for Disease Control and Prevention (CDC). How TB Spreads | TB | CDC. Accessed March 23, 2023. https://www.cdc.gov/tb/topic/basics/howtbspreads.htm
4. Houben RMGJ, Dodd PJ. The Global Burden of Latent Tuberculosis Infection: A Re-estimation Using Mathematical Modelling. *PLoS Med*. 2016;13(10):e1002152. doi:10.1371/JOURNAL.PMED.1002152
5. World Health Organization. *The End TB Strategy for Tuberculosis Prevention, Care and Control after 2015a*.; 2014.
6. Ending the Global Tuberculosis Epidemic | Global HIV and TB | CDC. Accessed February 6, 2025. https://www.cdc.gov/global-hiv-tb/php/our-approach/combatingglobaltb.html?utm_source=chatgpt.com
7. Stop TB Partnership. Stop TB Partnership | The Global Plan to End TB | The Global Plan to Stop TB 2016 - 2020. Accessed July 27, 2021. http://www.stoptb.org/global/plan/plan2/
8. McCreesh N, White RG. An explanation for the low proportion of tuberculosis that results from transmission between household and known social contacts. *Scientific Reports 2018 8:1*. 2018;8(1):1-9. doi:10.1038/s41598-018-23797-2
9. World Health Organization (WHO). WHO Policy on TB Infection Control in Health-Care Facilities, Congregate Settings and Households. Published online 2009.
10. World Health Organization (WHO). Systematic screening for TB disease. *World Health Organization (WHO)*. Published online 2022.
11. World Health Organization. WHO consolidated guidelines on tuberculosis. Accessed December 23, 2021. https://apps.who.int/iris/bitstream/handle/10665/340255/9789240022676-eng.pdf
12. Zhou G, Luo Q, Luo S, et al. Interferon-γ release assays or tuberculin skin test for detection and management of latent tuberculosis infection: a systematic review and meta-analysis. *Lancet Infect Dis*. 2020;20(12):1457-1469. doi:10.1016/S1473-3099(20)30276-0
13. Van Ginderdeuren E, Bassett J, Hanrahan C, Mutunga L, Van Rie A. Health system barriers to implementation of TB preventive strategies in South African primary care facilities. *PLoS One*. 2019;14(2):e0212035. doi:10.1371/JOURNAL.PONE.0212035
14. van de Water BJ, Wilson M, le Roux K, Gaunt B, Gimbel S, Ware NC. Healthcare worker perceived barriers and facilitators to implementing a tuberculosis preventive therapy program in rural South Africa: a content analysis using the consolidated framework for implementation research. *Implement Sci Commun*. 2023;4(1):107. doi:10.1186/S43058-023-00490-8
15. Chandra DK, Moll AP, Altice FL, Didomizio E, Andrews L, Shenoi S V. Structural barriers to implementing recommended tuberculosis preventive treatment in primary care clinics in rural South Africa. *Glob Public Health*. 2022;17(4):555-568. doi:10.1080/17441692.2021.1892793
16. Bhargava A, Bhargava M, Meher A, et al. Nutritional support for adult patients with microbiologically confirmed pulmonary tuberculosis: outcomes in a programmatic cohort nested within the RATIONS

trial in Jharkhand, India. *Lancet Glob Health*. 2023;11(9):e1402-e1411. doi:10.1016/S2214-109X(23)00324-8

17. World Health Organization Regional Office for Africa. *Tuberculosis in the WHO African Region: 2023 Progress Update*.; 2023. Accessed October 8, 2024. https://www.afro.who.int/sites/default/files/2023-09/Tuberculosis%20in%20the%20African%20Region_2023%20report.pdf

18. Olivier C, Luies L. WHO Goals and Beyond: Managing HIV/TB Co-infection in South Africa. *SN Compr Clin Med*. 2023;5:251. doi:10.1007/s42399-023-01568-z

19. Marambire ET, Banze D, Mfinanga A, et al. Early risk assessment in paediatric and adult household contacts of confirmed tuberculosis cases by novel diagnostic tests (ERASE-TB): protocol for a prospective, non-interventional, longitudinal, multicountry cohort study. Shepherd A Bruchfeld J, Sundling C, Sandy C, Mugava M, Bandason T, Chipinduro M, Mutasa K, Rukobo S, Sudi L, Haule A, Sichone E, Qwaray P, Mtafya B, Mwambola H, Minja L, Sabi I, Edwin P, Ngalison D, Luswema S, Olomi W, Pamba D, Mwanyonga S, Nhamuave C, M DHM, Consortium ET, eds. *BMJ Open*. 2022;12(7):e060985. doi:https://dx.doi.org/10.1136/bmjopen-2022-060985

20. Population-based HIV Impact Assessment (PHIA). Mozambique Final Report 2021 (En, Port) - PHIA Project. 2021. Accessed December 2, 2024. https://phia.icap.columbia.edu/mozambique-final-report-2021-en-port/

21. Population-based HIV Impact Assessment (PHIA). Release of Tanzania Population-based HIV Impact Assessment Data Shows Notable Progress, and Identifies Gaps that Stand in the Way of Epidemic Control - PHIA Project. 2022. Accessed December 2, 2024. https://phia.icap.columbia.edu/release-of-tanzania-population-based-hiv-impact-assessment-data-shows-notable-progress-and-identifies-gaps-that-stand-in-the-way-of-epidemic-control/

22. ZIMBABWE Ministry of Health and Child Care. ZIMBABWE POPULATION-BASED HIV IMPACT ASSESSMENT ZIMPHIA 2020 KEY FINDINGS. Published online 2020. Accessed September 3, 2021. https://phia.icap.columbia.edu/wp-content/uploads/2020/11/ZIMPHIA-2020-Summary-Sheet_Web.pdf

4. Publications

4.1 Paper A

Calderwood CJ, **Marambire ET**, Larsson L, Banze D, Mfinanga A, Nhamuave C, Appalarowthu T, Mugava M, Ribeiro J, Towo PE, Madziva K, Dixon J, Held K, Minja LT, Mutsvangwa J, Khosa C, Heinrich N, Fielding K, Kranzer K. HIV, malnutrition, and noncommunicable disease epidemics among tuberculosis-affected households in east and southern Africa: A cross-sectional analysis of the ERASE-TB cohort. PLoS Med. 2024 Sep;21(9):e1004452. doi: 10.1371/journal.pmed.1004452. eCollection 2024 Sep. PubMed PMID: 39283906; PubMed Central PMCID: PMC11441706.

PLOS MEDICINE

RESEARCH ARTICLE

HIV, malnutrition, and noncommunicable disease epidemics among tuberculosis-affected households in east and southern Africa: A cross-sectional analysis of the ERASE-TB cohort

Claire Jacqueline Calderwood[1,2]*, Edson Tawanda Marambire[2,3], Leyla Larsson[2,4], Denise Banze[3,5], Alfred Mfinanga[3,6], Celina Nhamuave[5], Tejawsi Appalarowthu[4], Mishelle Mugava[2], Jorge Ribeiro[5], Peter Edwin Towo[6], Karlos Madziva[2], Justin Dixon[7], Kathrin Held[4,8,9], Lilian Tina Minja[6], Junior Mutsvangwa[10], Celso Khosa[5], Norbert Heinrich[4,8,9], Katherine Fielding[11], Katharina Kranzer[1,2,4,8], ERASE-TB consortium[¶]

1 Clinical Research Department, London School of Hygiene & Tropical Medicine, London, United Kingdom, **2** The Health Research Unit Zimbabwe, Biomedical Research and Training Institute, Harare, Zimbabwe, **3** CIH[LMU] Center for International Health, University Hospital, LMU Munich, Munich, Germany, **4** Division of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich, Munich, Germany, **5** Instituto Nacional de Saúde (INS), Marracuene, Mozambique, **6** National Institute for Medical Research–Mbeya Medical Research Centre, Mbeya, Tanzania, **7** Department of Global Health and Development, London School of Hygiene & Tropical Medicine, London, United Kingdom, **8** German Centre for Infection Research (DZIF), partner site Munich, Germany, **9** Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology, Infection and Pandemic Research, Munich, Germany, **10** Biomedical Research and Training Institute, Harare, Zimbabwe, **11** TB Centre, London School of Hygiene & Tropical Medicine, London, United Kingdom

¶ Membership of the ERASE-TB consortium is provided in Supporting information file S1 Acknowledgments.
* claire.calderwood2@lshtm.ac.uk

Citation: Calderwood CJ, Marambire ET, Larsson L, Banze D, Mfinanga A, Nhamuave C, et al. (2024) HIV, malnutrition, and noncommunicable disease epidemics among tuberculosis-affected households in east and southern Africa: A cross-sectional analysis of the ERASE-TB cohort. PLoS Med 21(9): e1004452. https://doi.org/10.1371/journal.pmed.1004452

Received: April 7, 2024

Accepted: July 29, 2024

Published: September 16, 2024

Data Availability Statement: The data to recreate these analyses are archived in LSHTM data compass (https://doi.org/10.17037/DATA.00004267). Researchers can request access by completing the form at the stated DOI.

Funding: Supported by a grant (RIA2018D-2508 ERASE-TB) to NH through the European and Developing Countries Clinical Trials Partnership (EDCTP), with assistance from the Department of Health and Social Care UK under the EDCTP2 programme supported by the European Union. Further funding is contributed by the German

Abstract

Background

As a result of shared social and structural risk factors, people in households affected by tuberculosis may have an increased risk of chronic conditions; at the same time, tuberculosis screening may be an opportunity for interventions. We sought to describe the prevalence of HIV, nutritional disorders, and noncommunicable diseases (NCDs) among members of tuberculosis-affected households in 3 African countries.

Methods and findings

A part of a multicountry cohort study, we screened for tuberculosis, HIV, nutritional disorders (underweight, anaemia, overweight/obesity), and NCDs (diabetes, hypertension, and chronic lung disease) among members of tuberculosis-affected households aged ≥10 years in Mozambique, Tanzania, and Zimbabwe. We describe the prevalence of these conditions, their co-occurence within individuals (multimorbidity) and household-level clustering. Of 2,109 household contacts recruited, 93% (n = 1,958, from 786 households) had

Center for Infection Research (DZIF; TTU 02.912_00) to KH. CJC is funded by the Wellcome Trust (225466/Z/22/Z). The funders had no role in study design, data collection and analysis, preparation of the manuscript or decision to publish.

Competing interests: EDCTP Grant funding for this research to NH's institution. DZIF Grant funding for this research to NH's institution. Funding by Beckman Coulter to NH's institution.

Abbreviations: 95%CI, 95% confidence interval; BMI, body mass index; HbA1c, glycated haemoglobin; IQR, interquartile range; NCD, noncommunicable disease; VPC, variation partition coefficient; WHO, World Health Organization.

complete data and were included in the analysis. Sixty-two percent were female, median age was 27 years, and 0.7% ($n = 14$) were diagnosed with co-prevalent tuberculosis. Six percent of household members ($n = 120$) had previous tuberculosis, 15% ($n = 294$) were living with HIV, 10% ($n = 194$) had chronic lung disease, and 18% ($n = 347$) were anaemic. Nine percent of adults ($n = 127$) had diabetes by HbA1c criteria, 32% ($n = 439$) had hypertension. By body mass index criteria, 18% household members ($n = 341$) were underweight while 29% ($n = 549$) were overweight or obese. Almost half the household members ($n = 658$) had at least 1 modifiable tuberculosis risk factor. Sixty-one percent of adults ($n = 822$) had at least 1 chronic condition, 1 in 4 had multimorbidity. While most people with HIV knew their status and were on treatment, people with NCDs were usually undiagnosed and untreated. Limitations of this study include use of point-of-care HbA1c for definition of diabetes and definition of hypertension based on single-day measurements.

Conclusions

Households affected by tuberculosis also face multiple other health challenges. Integrated approaches to tuberculosis screening may represent an opportunity for identification and treatment, including prioritisation of individuals at highest risk for tuberculosis to receive preventive therapy.

Author summary

Why was this study done?

- Tuberculosis-affected households are a particular priority group for interventions to address infectious, nutritional, and noncommunicable causes of illness and death. These household members may be at particular risk of these conditions due to underlying structural determinants of health, while the opportunity to intervene presented by tuberculosis screening may enable chronic conditions to be addressed, reducing tuberculosis incidence and improving overall health.
- Few studies have reported on the prevalence of conditions other than HIV among members of TB-affected households, therefore the burden of infectious, nutritional, and noncommunicable diseases within TB-affected households is unknown.

What did the researchers do and find?

- As part of a cohort study of people living in tuberculosis-affected households in 3 east/southern African countries, we screened 1,958 adolescents and adults for tuberculosis, HIV, nutritional disorders (including underweight, anaemia, overweight/obesity), and noncommunicable diseases (NCDs; diabetes, hypertension, and chronic lung disease).
- We found a high prevalence of these conditions and identified a very large gap in access to care for NCDs. While some conditions clustered within households (HIV, undernutrition), others (NCDs) did not.

- One in 2 tuberculosis household contacts had a modifiable tuberculosis risk factor (HIV, diabetes, chronic lung disease, underweight, current smoker, or potential alcohol misuse) while one in 5 had 2 or more chronic conditions (i.e., multimorbidity), most commonly due to the coexistence of HIV and an NCD.

What do these findings mean?

- In Africa, households affected by tuberculosis are impacted not only by tuberculosis but by multiple colliding epidemics including HIV, malnutrition, and NCDs.
- Screening for tuberculosis among household contacts represents an opportunity to intervene, improving the health of a vulnerable community while preventing tuberculosis. There is now clear evidence, including that from this study, to justify such an approach.
- Implementation research including health economic evaluations are now needed to support guideline development and scale up.

Introduction

The epidemiological transition model describes a shift in population-level burden of disease from infections and undernutrition to noncommunicable diseases (NCDs) due to social, economic, and demographic change. However, the reality is often a "double" or "triple" burden of disease; resulting from an increased prevalence of NCDs, and associated risk factors, and a slow decline or persistence of infectious diseases and malnutrition [1]. This collision of epidemics is reinforced by shared underlying structural and social determinants of health including poverty, low health literacy, and lack of universal health coverage [2]. Consequently, the impact is greatest among socioeconomically vulnerable communities who can least afford the consequences of ill health [3,4].

Chronic conditions, including HIV, diabetes, undernutrition, and behavioural risk factors such as alcohol use disorder and smoking are the major attributable causes of tuberculosis globally [5]. While transmission of diseases such as tuberculosis and HIV commonly occurs within households, households also share behavioural (e.g., diet, smoking, physical activity) and genetic characteristics. As a result, members of tuberculosis-affected households may be at increased risk of both infectious and noncommunicable chronic conditions; however, the existing evidence is limited. In Africa, previous studies have described the prevalence of HIV (systematic revew of 13 studies; pooled prevalence 7.3% [6]) or diabetes ($n = 3$ studies, prevalence range 5.2% to 17.4% [7–9]). No previous studies from Africa have explicitly evaluated prevalence of undernutrition, obesity, or chronic lung disease among members of tuberculosis-affected households and none have considered more than one of these conditions or described their overlap in individuals and households.

Systematic screening for tuberculosis among household contacts may present an opportunity to identify and treat chronic conditions and risk factor clusters, reducing progression to tuberculosis and improving overall health [9–11].

As part of a multinational, observational, prospective cohort study (Early Risk Assessment in tuberculosis contactS by new diagnostic tEsts [ERASE-TB]), we sought to describe the prevalence of HIV, nutritional disorders, and NCDs among members of tuberculosis-affected

households in 3 African countries. We hypothesised that the prevalence of these conditions would be high, that most NCDs would be undiagnosed or untreated, and that there would be evidence for clustering of chronic conditions at household level.

Methods

ERASE-TB study overview

The ERASE-TB study protocol has been published [12]. In brief, the study consists of 3 primary and 3 secondary objectives. The primary ERASE-TB objectives relate to determination of diagnostic accuracy of novel tuberculosis tests to diagnose TB earlier, using prospective cohort data. The secondary objectives are (1) to determine *Mycobacterium tuberculosis* infection prevalence among household contacts at baseline and during follow-up; (2) to establish a biorepository of cryopreserved specimens for future development and validation of diagnostic tests; and (3) to assess the prevalence of selected chronic diseases among household contacts and their association with tuberculosis. Secondary objective 3 is addressed in the present manuscript.

The study population is people aged at least 10 years old and living with someone with recently diagnosed, highly infectious, microbiologically confirmed (Xpert MTB/RIF "medium" or higher) pulmonary tuberculosis, enrolled at 3 sites (Maputo, Mozambique; Mbeya, Tanzania; and Harare, Zimbabwe; recruitment: March 2021 to March 2023) and followed up every 6 months for up to 24 months (projected end date: December 2024). We use "household contacts" to differentiate these individuals from the person with tuberculosis whose diagnosis resulted in recruitment of the household. This analysis followed a prespecified analysis plan (February 2022; S1 Appendix) and uses data collected at baseline or within the first 12 months of follow up, if missing at baseline (S1 Appendix). Thus data contributing to this analysis were collected between March 2021 and March 2024. The sample size was determined by the primary objective of determining sensitivity and specificity of novel tuberculosis diagnostics.

Definition of chronic conditions

Baseline data were used for analysis. If NCD testing was not done at baseline, it was performed at a subsequent timepoint (Table A in S1 Appendix). Tuberculosis screening comprised a World Health Organization (WHO) symptom screen and chest X-ray, followed by Xpert MTB/Rif Ultra (Cepheid, USA) if either suggested tuberculosis. Point-of-care HIV testing followed national guidelines and height and weight were measured for calculation of body mass index (BMI). Handheld spirometry (EasyOne Air or Easy on-PC) was performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) standards [13]. Among adults aged 18 years and older, glycated haemoglobin (HbA1c) (A1c Care, SD Biosensor) testing was offered and blood pressure assessed according to the WHO STEPwise approach to surveillance protocol [13]. An interviewer-administered questionnaire included demographics, medical history, smoking history, and the alcohol use disorders identification test short-form (AUDIT-C) [14]. Conditions were categorised using internationally agreed definitions (Tables B–D in S1 Appendix). While we use the terms diabetes and hypertension, these are based on screening on a single day; we acknowledge that this does not fulfil diagnostic criteria [15,16]. Chronic lung disease was defined as previously diagnosed lung disease or an obstructive or mixed defect on pre-bronchodilator spirometry, interpreted using ATS/ERS standards with Global Lung Initiative "other" reference (S1 Appendix). Absolute BMI (adults) and BMI-for-age Z-scores (adolescents) were used to create combined categories; notably BMI-for-age Z-score $<$-2 among adolescents (termed "thinness" per WHO) was categorised as moderate/severe underweight (Table C in S1 Appendix). Multimorbidity was defined as 2 or more

chronic conditions in one individual [17]. Participants screening positive for any condition were referred according to local standards of care.

Statistical analysis

Statistical analyses were performed in R (version 4.2.2); packages are detailed in S1 Appendix. Analyses are reported in accordance with Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (S1 STROBE Checklist). Following description of missing data (Table F in S1 Appendix), a complete case records analysis was conducted. All analyses, aside from analyses characterising household-level clustering (below) were adjusted for household-level clustering using design-based standard errors.

The number of household contacts with symptoms or chest X-ray suggestive of tuberculosis, and the number diagnosed with co-prevalent tuberculosis was described. Subsequent analyses focused on other chronic conditions (HIV, diabetes, hypertension, anaemia, chronic lung disease), BMI category, and stunting. For each of these, overall prevalence and prevalence stratified by age category (adolescent [10, 17 years], younger adult [18,39], and older adult [40 and older]), sex and study site were calculated. Prevalence and associated 95% confidence intervals (95% CI) were additionally stratified by sex and age-standardised to the WHO reference population using direct standardization to aid comparisons. HIV prevalence was additionally calculated stratified by HIV status of the person with tuberculosis as an exploratory analysis. Following peer review, we additionally considered prevalence of chronic conditions, stratified by area of residence (rural, per-urban, and urban) within the Tanzanian site where participants across these areas were included.

Among adults, a cascade of care was constructed for HIV, diabetes, and hypertension. This described the proportion of people with the condition who knew their status, the proportion of those with known status who were on treatment, and the proportion of people of those who had "disease control." Disease control was defined as CD4 >350 cells/μl for HIV, HbA1c <6.5% for diabetes, and systolic BP <140 and diastolic BP <90 for hypertension. HIV viral loads were not available.

We explored the coexistence of conditions within individuals through intersection plots, and the trajectory of nutritional indices across years of age through calculation of age-specific Z-scores among both adolescents and adults (S1 Appendix).

The clustering of conditions within households was described by constructing a multilevel model including each condition, in turn, as the outcome, no individual-level explanatory variables, and a random-effect for household. The variation partition coefficient (VPC) and *p*-value for a random-effect at household level was considered as a measure of the residual variation that is attributable to unobserved household characteristics, with the VPC being equivalent to the intra-cluster correlation coefficient.

Sensitivity analyses

Recognising the insufficiency of single-day blood pressure measurements to confirm hypertension [16,18] and in view of the very high prevalence of hypertension (based on a single-day reading) in our dataset, we calculated the proportion of people categorised as "screening detected" hypertension who were confirmed through a second elevated blood pressure measurement at the subsequent follow-up visit.

Ethical considerations

Informed written consent was obtained from all participants aged 18 years and older; individual assent and guardian consent was obtained from participants aged 10 to 17 years. Ethical

approval was granted by all relevant institutions: the Medical Research Council in Zimbabwe (MRCZ/A/2618), the Mbeya Medical Research and Ethics Review Committee (SZEC-2439/R.A/V.1/101), the National Health Research Ethics Committee in Tanzania (NIMR/HQ/R.8a/Vol.IX/3608), and Tanzanian Medicines and Medical Devices Authority (TMDA-WEB0021/CTR/0004/03), the National Bioethics Committee for Health in Mozambique (541/CNBS/21), and the ethical committees of London School of Hygiene & Tropical Medicine, United Kingdom (22522–2) and the medical faculty of the Ludwig Maximilian-Universität München, Germany (20–0771).

Results

Participant characteristics

Between March 2021 and March 2023, 2,649 household contacts were identified from 905 people with TB (median 3 [interquartile range (IQR) 2, 5]; 2 [IQR 2, 3] and 2 [IQR 1, 4] per household in Mozambique, Tanzania, and Zimbabwe, respectively). Of these, 2,109 (80%) from 822 households were recruited, with a median of 2 contacts recruited per household in each country (Mozambique, IQR 1, 4; Tanzania and Zimbabwe, IQR 1, 3). The maximum household size recruited was 18 people. No participants were missing an HIV result, 2 participants were missing BMI, fewer than 1.8% of people were missing results for each of CD4 and BP; 3.6% people were missing HbA1c and 2.7% people were missing haemoglobin (Table F in S1 Appendix). A total of 1,958 people (93%; 680 (96%) in Mozambique, 650 (93%) in Tanzania, and 628 (90%) in Zimbabwe) from 786 households were included in the analysis (Fig 1). Demographic details for included and excluded participants are shown in Table G in S1 Appendix.

Among included participants, 62% (n = 1,217) were female and the median age was 27 years (IQR 16, 42), with 31% of household contacts (n = 602) being adolescents aged 10 to 17

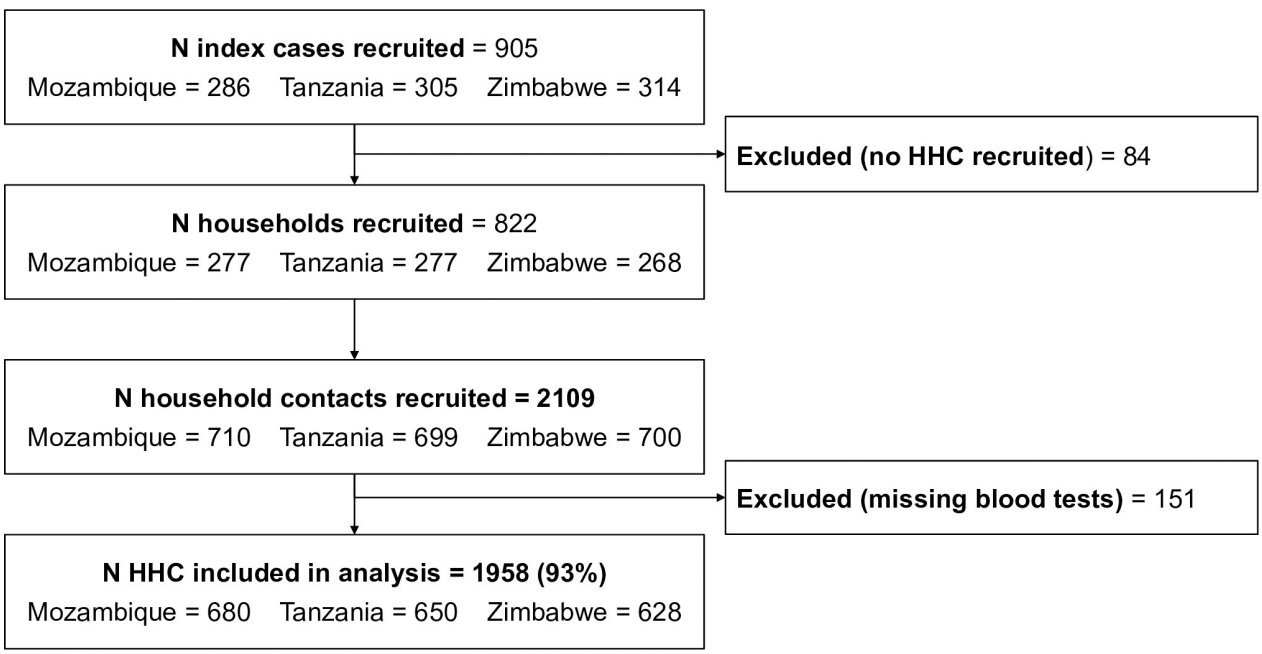


Fig 1. Flow diagram illustrating recruitment of participants and inclusion in analysis data set. HHC, household contacts; N, number.

https://doi.org/10.1371/journal.pmed.1004452.g001

Table 1. Characteristics of study population (*N* = 1,958).

Characteristic	Overall *N* = 1,958	Mozambique *N* = 680	Tanzania *N* = 650	Zimbabwe *N* = 628
Sex				
Women	1,217 (62%)	411 (60%)	416 (64%)	390 (62%)
Men	741 (38%)	269 (40%)	234 (36%)	238 (38%)
Age, years	27 (16, 42)	23 (16, 39)	29 (16, 44)	28 (17, 42)
Age category				
10–17 years	602 (31%)	221 (33%)	203 (31%)	178 (28%)
18–39 years	807 (41%)	298 (44%)	235 (36%)	274 (44%)
40+ years	549 (28%)	161 (24%)	212 (33%)	176 (28%)
Highest educational level*				
None or primary school	897 (48%)	253 (39%)	472 (75%)	172 (29%)
At least secondary school	973 (52%)	390 (61%)	156 (25%)	427 (71%)
Pregnant†	38 (3.1%)	8 (1.9%)	14 (3.4%)	16 (4.1%)
Smoking status				
Non smoker	1,819 (93%)	654 (96%)	612 (94%)	553 (88%)
Smoker (current and/or former)	138 (7.1%)	26 (3.8%)	38 (5.8%)	74 (12%)
Pack years smoking	1.8 (0.6, 4.6)	1.8 (1.2, 3.6)	1.5 (0.5, 4.2)	2.1 (0.8, 5.8)
Alcohol consumption				
Never drunk alcohol	1,308 (67%)	437 (64%)	425 (65%)	446 (71%)
Alcohol, AUDIT-C negative	384 (20%)	162 (24%)	124 (19%)	98 (16%)
Alcohol, AUDIT-C positive	265 (14%)	80 (12%)	101 (16%)	84 (13%)
Insufficient food‡	535 (27%)	241 (35%)	38 (5.8%)	256 (41%)
Relationship to index case				
Spouse	330 (17%)	109 (16%)	123 (19%)	98 (16%)
Parent	499 (25%)	193 (28%)	165 (25%)	141 (22%)
Sibling	368 (19%)	134 (20%)	118 (18%)	116 (18%)
Child	267 (14%)	90 (13%)	91 (14%)	86 (14%)
Other	494 (25%)	154 (23%)	153 (24%)	187 (30%)

Presented as number (percentage) or median (interquartile range).

*Educational level not known for 88 participants.

†The denominator for pregnancy is the number of women.

‡Insufficient food was defined as participants as answering yes to "was there any day in the past 6 months where you did not have enough food."

AUDIT-C, alcohol use identification test, short form; TB, tuberculosis.

https://doi.org/10.1371/journal.pmed.1004452.t001

years (Table 1). Men were, on average, younger than women (median 21 [IQR 14, 37] years versus 30 [18, 45] years): 22% of women (*n* = 267) were spouses of people with tuberculosis, compared to 8.5% men (*n* = 63), resulting in more adult women than men (Table H and Fig A in S1 Appendix). Smoking was relatively infrequent, with 7.1% participants (16% of men and 1.4% women) ever having smoked, the median pack-year smoking exposure was 1.8 (IQR 0.6, 4.6) years. Overall, 33% people (5.3% [*n* = 32] adolescents) reported drinking alcohol; 14% people (*n* = 265; 21% of men [*n* = 155], 9.0% of women [*n* = 11] and 1.5% of adolescents [*n* = 9]) screened positive for hazardous use of alcohol using AUDIT-C.

Socioeconomic deprivation was common: 20% of households were crowded (*n* = 157; defined as at least 3 people per room) and 90% (*n* = 583) were under the international poverty line (income less than United States Dollar 1.90 per person per day; Table 2). In 41% (*n* = 321) of households, the primary income earner was the person who had tuberculosis. Food

Table 2. Characteristics of study households (*N* = 786).

Characteristic	Overall *N* = 786	Mozambique *N* = 269	Tanzania *N* = 264	Zimbabwe *N* = 253
N* people in household	5 (3, 6)	6 (4, 7)	4 (3, 6)	5 (3, 6)
Crowding*	157 (20%)	64 (24%)	18 (6.8%)	75 (30%)
Household income per person per day, USD†	0.64 (0.34, 1.09)	0.66 (0.41, 1.03)	0.42 (0.23, 0.85)	0.74 (0.41, 1.56)
Primary earner is the person with TB	321 (41%)	68 (26%)	137 (52%)	116 (46%)
Household income <1.90 USD per person per day	583 (90%)	209 (90%)	171 (95%)	203 (86%)
Area of residence				
Rural	103 (13%)	5 (1.9%)	97 (37%)	1 (0.4%)
Peri-urban	262 (33%)	196 (73%)	56 (21%)	10 (4.0%)
Urban	420 (54%)	68 (25%)	110 (42%)	242 (96%)
HIV status of person with TB‡				
Negative	499 (68%)	173 (68%)	172 (71%)	154 (65%)
Positive, on ART	154 (21%)	57 (22%)	46 (19%)	51 (21%)
Positive, not on ART	82 (11%)	24 (9.4%)	25 (10%)	33 (14%)

Presented as number (percentage) or median (interquartile range).

*The total number (*N*) of people in a household includes both people eligible for the study and children under the age of 10, who were not eligible. Crowding using UN definition (≥3 people per room).

†Income not known for 137 households. A threshold of 1.90 USD was used as this was the international poverty line threshold in 2021 when data collection began. In September 2022, the threshold was increased to 2.15 USD.

‡HIV status not known for 51 people with TB.

ART, anti-retroviral therapy; *N*, number; TB, tuberculosis; USD, United States Dollars.

https://doi.org/10.1371/journal.pmed.1004452.t002

insecurity varied by site: in Mozambique and Zimbabwe (majority urban/peri-urban) 35% and 41% people, respectively, reported food insecurity, compared to 5.8% in Tanzania (where the proportion of peri-urban and rural participants was higher).

Chronic conditions among tuberculosis household contacts

Overall, 6% (*n* = 120) people had a previous history of tuberculosis. Three hundred and seventy-five people (20%) were screened as possible tuberculosis (322 had symptoms suggestive of tuberculosis and 87 had a CXR suggestive of tuberculosis on review by a clinical officer; 34 had both criteria met). Fourteen people were diagnosed with co-prevalent tuberculosis: 13 had a positive Xpert and 1 was diagnosed through chest X-ray.

Prevalence of HIV was 15.0% (95% confidence interval [95% CI] 13.2, 17.0%; *n* = 294), with 13 people (4.4%; 95% CI 2.6, 7.4%) with HIV having advanced disease (CD4 count less than 200 cells/μl; Table 3; confidence intervals are shown in Table I in S1 Appendix). Table J and Fig C in S1 Appendix shows prevalences by site. Prevalence of HIV was higher among women compared to men (19.1% [16.7, 21.6%; *n* = 232] versus 8.4% [6.4, 10.8%; *n* = 62]), although this difference was partially attenuated in age-standardised prevalence estimates (19.7% [17.3%, 22.0%] versus 12.5% [8.7%, 16.4%]; Table 4). While HIV prevalence was low among adolescents (*n* = 16, 2.7% [1.6, 4.3%]), 7/16 adolescents with HIV were not aware of their status. When stratified by the HIV status of the index case, 9.8% (95% CI 8.0, 12.0%; *n* = 121) household contacts of HIV–negative index cases had HIV (0.9% [*n* = 11] were diagnosed through screening) compared to 25.2% (95% CI 21.2, 29.6%; *n* = 143) household contacts of HIV–positive index cases (2.8% [*n* = 16] were diagnosed through screening; Table L in S1 Appendix).

Table 3. Chronic conditions among tuberculosis household contacts (*N* = 1,958).

Condition	Level	Overall	Women	Men	10–17 years	18–39 years	40+ years
All participants		***N* = 1,958**	***N* = 1,217**	***N* = 741**	***N* = 602**	***N* = 807**	***N* = 549**
HIV prevalence		15.0%	19.1%	8.4%	2.7%	14.3%	29.7%
CD4 category*	≥500 cells/μl	63.5%	66.7%	51.6%	76.5%	59.6%	64.8%
	200–499 cells/μl	32.1%	29.9%	40.3%	23.5%	36.8%	29.7%
	<200 cells/μl	4.4%	3.4%	8.1%		3.5%	5.5%
Median CD4 (cells/μl)*		584	603	526	678	565	589
BMI category†	Moderate/severe underweight	3.9%	2.5%	6.1%	8.1%	2.2%	1.6%
	Mild underweight	13.5%	9.6%	20.0%	27.4%	9.2%	4.7%
	Healthy weight	54.5%	49.8%	62.3%	57.0%	59.4%	44.8%
	Overweight	17.4%	22.0%	9.7%	6.3%	18.8%	27.3%
	Obese	10.7%	16.0%	1.9%	1.2%	10.4%	21.5%
Chronic lung disease prevalence‡		10.3%	11.0%	9.2%	9.1%	9.4%	13.0%
Anaemia prevalence§		17.7%	20.7%	12.8%	16.6%	18.0%	18.6%
Anaemia category§	None	82.3%	79.3%	87.2%	83.4%	82.0%	81.4%
	Mild anaemia	11.5%	12.2%	10.3%	11.8%	10.7%	12.4%
	Moderate anaemia	5.6%	7.6%	2.4%	4.3%	6.6%	5.6%
	Severe anaemia	0.6%	0.9%	0.1%	0.5%	0.7%	0.5%
Hb (g/dL)		135	130	144		137	135
Adolescents		***N* = 602**	***N* = 305**	***N* = 297**	***N* = 602**		
Stunting‖	Normal	56.6%	62.3%	50.8%	56.6%		
	Mild stunting	26.7%	26.2%	27.3%	26.7%		
	Moderate stunting	12.8%	8.9%	16.8%	12.8%		
	Severe stunting	3.8%	2.6%	5.1%	3.8%		
Adults		***N* = 1,356**	***N* = 912**	***N* = 444**		***N* = 807**	***N* = 549**
Diabetes prevalence		9.4%	10.4%	7.2%		4.8%	16.0%
HbA1c category	<6.0%	62.8%	62.5%	63.3%		68.9%	53.7%
	6.0–6.4%	28.8%	27.9%	30.9%		27.1%	31.3%
	6.5–6.9%	5.3%	6.0%	3.8%		2.7%	9.1%
	≥7.0%	3.1%	3.6%	2.0%		1.2%	5.8%
HbA1c (%)		5.8	5.8	5.8		5.7	5.9
Hypertension prevalence		32.4%	35.3%	26.4%		16.1%	56.3%
BP category	Normal BP	54.8%	53.7%	57.0%		71.9%	29.7%
	High-normal BP	15.6%	14.6%	17.6%		14.1%	17.7%
	Grade 1 HTN	16.3%	16.9%	15.1%		9.0%	27.0%
	Grade 2 HTN	13.3%	14.8%	10.4%		5.0%	25.7%
Systolic BP (mmHg)		119.5	120	119		120	137
Diastolic BP (mmHg)		76.5	78	74		77	86.5

Values are presented as percentages (for categorical variables) or medians (for continuous variables). "Prevalent" disease is defined as either known or screening detected.

*CD4 counts are only reported among people living with HIV, excluding 5 people with missing CD4 count (*N* = 293).

†BMI categories were created using BMI for age Z-scores among adolescents (<19 years) with WHO references and absolute BMI thresholds among adults (≥19 years). Mod/severe underweight = Z-score <-2 or BMI < 17 kg/m^2; mild underweight = Z-score ≥-2 and <-1 or BMI 17–18.49 kg/m^2; normal weight = Z-score ≥-1 and ≤+1 or BMI 18.5–24.9 kg/m^2; overweight = Z-score >+1 and ≤+2 or BMI 25–29.9 kg/m^2; obese = Z-score >+2 or BMI >30.0 kg/m^2.

‡Chronic lung disease was defined as either a previous diagnosis, or an obstructive or mixed defect on pre-bronchodilator spirometry (less than lower limit of normal using Global Lung Initiative "Other" reference standard). 80.8% (*n* = 1,582) participants had an adequate quality spirometry, those missing spirometry traces were categorised as not having a chronic lung disease (unless self-reported).

§Anaemia was categorised using age and sex-specific thresholds recommended by WHO (S1 Appendix).

‖Stunting was only calculated among adolescents, using WHO reference standards. Mild stunting was defined as a height of age Z-score of <-1 and ≥-2; moderate stunting as Z-score of <-2 and ≥-3 and severe stunting as Z-score <-3.

BMI, body mass index; BP, blood pressure; Hb, haemoglobin; HbA1c, glycosylated haemoglobin; HTN, hypertension; *N*, number; WHO, World Health Organization.

https://doi.org/10.1371/journal.pmed.1004452.t003

Table 4. Prevalence of chronic conditions among tuberculosis household contacts, standardised to the World Health Organization reference population.

Condition*	Overall	Women	Men
HIV	16.9% (14.7%, 19.1%)	19.7% (17.3%, 22.0%)	12.5% (8.7%, 16.4%)
Diabetes	9.6% (8.0%, 11.3%)	10.8% (8.7%, 13.0%)	7.6% (5.1%, 10.0%)
Hypertension	36.8% (34.2%, 39.3%)	39.1% (36.2%, 41.9%)	33.0% (28.6%, 37.4%)
Anaemia	16.7% (15.0%, 18.5%)	20.0% (17.7%, 22.3%)	11.5% (9.0%, 14.0%)
Underweight	15.2% (13.4%, 16.9%)	9.6% (8.3%, 11.0%)	23.9% (20.0%, 27.8%)
Overweight/Obese	30.5% (28.5%, 32.6%)	40.1% (37.4%, 42.8%)	15.4% (12.5%, 18.3%)
Chronic lung disease	10.4% (8.6%, 12.2%)	10.2% (8.4%, 12.0%)	10.8% (7.4%, 14.2%)

*N = 1958 overall, 1217 women and 741 men; other than for diabetes and hypertension where prevalence was calculated among adults only (N = 1356, 912 women and 444 men). 95% confidence intervals (presented in brackets) were calculated using design-based standard errors within the 'survey' package in R.

https://doi.org/10.1371/journal.pmed.1004452.t004

A total of 127 adults had diabetes (9.4% [7.9, 11.1%]) and 439 had hypertension (32.4% [29.8, 35.1%]). A further 28.8% of adults (n = 391) had an HbA1c of between 6.0% and 6.5% while 15.6% (n = 211) had a blood pressure in the high-normal range. The prevalence of HIV, diabetes, and hypertension increased with age, with a linear association between each of HbA1c, systolic and diastolic blood pressure and age (Figs D and E in S1 Appendix). The prevalence of chronic lung disease was 10.3% (8.9, 11.9%; n = 194), similar across sex and slightly higher in older adults.

Overall, 17.7% people were at least mildly underweight (95% CI 15.6, 19.4%; n = 341); 3.9% were moderately or severely underweight (3.0, 4.9%; n = 76); 17.4% people were overweight (95% CI 15.7, 19.2%; n = 340) and a further 10.7% were obese (95% CI 9.4, 12.2%; n = 209). More adolescents and men were underweight, while overweight and obesity were more common among older adults and women (Fig F in S1 Appendix). BMI-for-age Z-scores increased with age, notably among women between the ages of 10 and 40 years. Prevalence of anaemia was 17.7% (95% CI 15.9, 19.7%; n = 347), higher among women than men.

Forty-nine percent of adults (n = 658) and 38% adolescents (n = 228) had at least 1 modifiable tuberculosis risk factor (HIV, diabetes, underweight, current smoker, or AUDIT score suggestive of alcohol use). Sixty-one percent of adults (n = 822) had at least 1 chronic condition (any of HIV, diabetes, hypertension, chronic lung disease, or anaemia); 24% (n = 326) had multimorbidity (2 or more of the above). The most common multimorbidity was of hypertension and HIV (10%; Fig 2A). In Mbeya (Tanzania), prevalence of NCDs appeared higher in peri-urban and rural areas, compared to urban residents, albeit with overlapping confidence intervals (Tables O and P in S1 Appendix).

Overall, 81% adults (n = 1,179) had blood pressure readings from at least 1 subsequent study visit and were included in the sensitivity analysis of "confirmed" hypertension, with 58.8% percent of people (n = 151/257) with hypertension detected through screening at baseline having this confirmed. If 2 consecutive elevated blood were required for criteria for hypertension to be met, the prevalence of hypertension among adult household contacts was 19.6% (n = 227).

Cascade of care for chronic conditions

Fig 2B and Table M in S1 Appendix illustrate the cascade of care for adults with HIV, diabetes, and hypertension. The majority of people with HIV knew their status (91.7% of those with HIV; 95% CI 87.7, 94.5%; n = 255), were on treatment (95.2% of those with known status; 95%

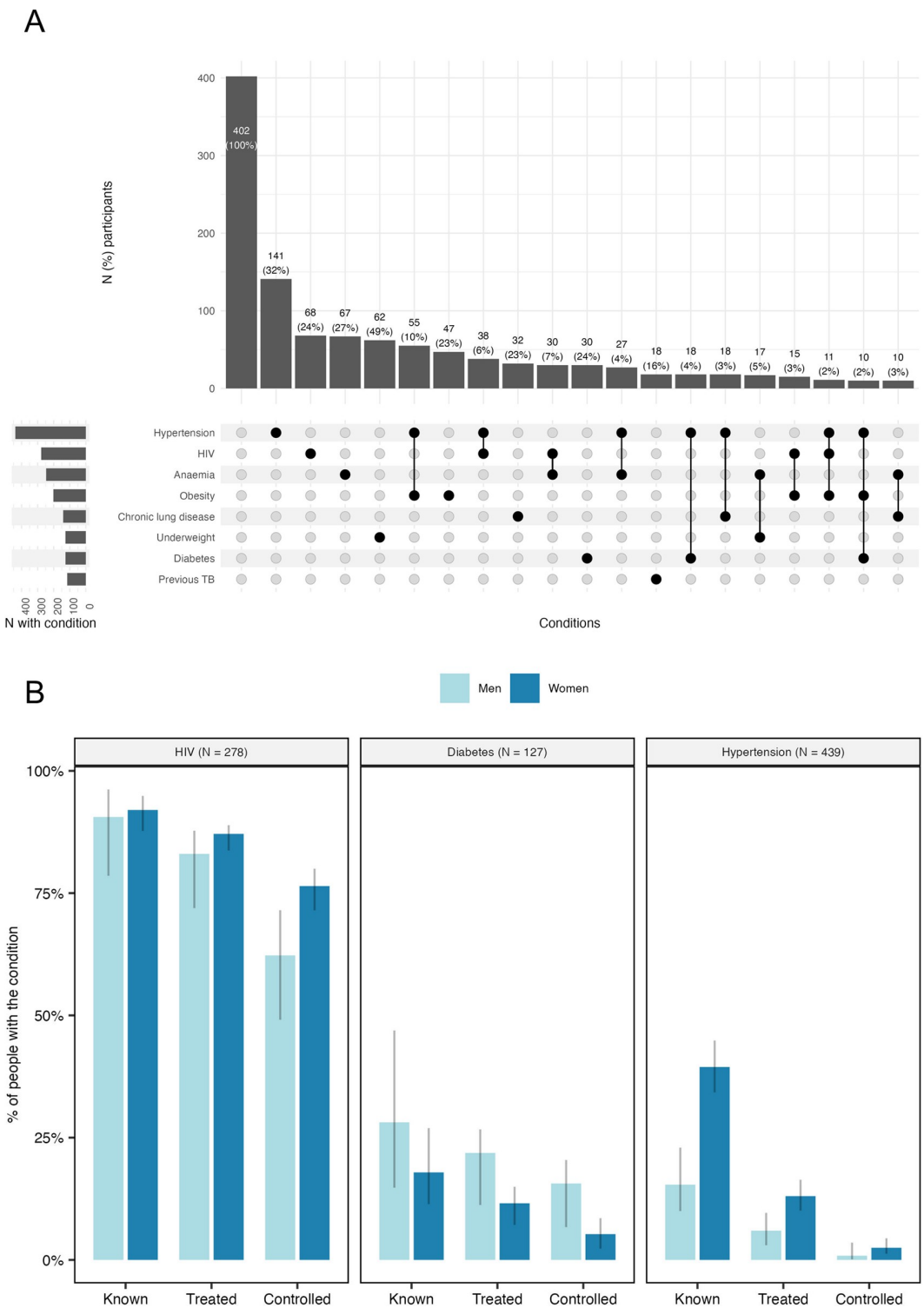


Fig 2. Intersection of chronic conditions (A) and cascade of care for HIV, diabetes, and hypertension (B) among adult tuberculosis household contacts (*N* = 1,356). For panel A, Intersections are exclusive (i.e., individuals are only represented in the graph once) and only intersections containing at least 10 individuals are shown. The bottom sub-panel shows the included chronic conditions (y axis), with the left section indicating the overall number (*N*) participants with each and the right section showing the specific disease combinations (represented by black circles). The top sub-panel shows intersection size, i.e., the

percentage and number of participants with each disease combination. For panel B, known (disease) was defined as a self-report of having, or being on medication for a condition; treated was defined as being on a relevant medication for the condition; controlled was defined as, for HIV, CD4 count >350 cells/μl, for diabetes, an HbA1c of <6.5% and for hypertension, as a blood pressure of <140 mmHg systolic and <90 mmHg diastolic. These are presented as relative proportions of the total number of people with each condition (100%, with number of people with disease [*N*] shown in sub-panel header), stratified by sex, with their 95% confidence intervals (grey lines).

https://doi.org/10.1371/journal.pmed.1004452.g002

CI 91.8, 97.3%; *n* = 240), and had a CD4 count of at least 350 cells/μl (85.4% of those on treatment; 95% CI 80.1, 89.5%; *n* = 205). Among people with diabetes, 20.5% were aware of this (95% CI 14.5, 28.2%; *n* = 26), 69.2% of those were on treatment (95% CI 49.1, 84.0%; *n* = 18), and 55.6% of those had controlled disease (32.7, 76.3%; *n* = 10). Among people with hypertension the corresponding figures were 33.0% (28.8, 37.6%; *n* = 145), 33.8% (26.7, 41.6%; *n* = 49), and 18.4% (9.8, 31.8%; *n* = 9). The gap in diagnosis for hypertension and diabetes appeared larger in Tanzania than the other 2 sites (Fig G in S1 Appendix).

Clustering within households

In keeping with the individual-level analysis, household-level prevalence of chronic conditions was high. Almost a third of households (31%, *n* = 245) had at least 1 member with HIV, half (48%, *n* = 379) had 1 member with an NCD (Table N in S1 Appendix), and a third (32%, *n* = 253) had at least 1 member who was underweight. Eleven percent of households included both someone who was underweight and someone who was overweight or obese (Fig H in S1 Appendix).

There was strong evidence for correlation within households for HIV, anaemia, and underweight status (Table 5). The highest variation particion coefficient (VPC) was for HIV (42%) suggesting that almost half the variation in HIV prevalence was due to household characteristics; the lowest VPC was for hypertension (9.2%) suggesting that the majority of variation in hypertension prevalence was due to individual-level rather than household-level variation.

Table 5. Household-level clustering of chronic conditions.

	Fixed effect model*	Mixed effects model*			
	Prevalence (95% CI)	Prevalence (95% CI)†	Variance	VPC‡	p value§
All participants (N = 1958)					
HIV‖	15.0% (13.2, 17.0%)	9.4% (7.2, 12.1%)	2.38	42.0%	<0.001
Anaemia	17.7% (15.9, 19.7%)	13.7% (11.5, 16.4%)	1.13	25.5%	<0.001
Underweight	17.4% (15.6, 19.4%)	14.0% (11.8%, 16.6%)	0.79	19.3%	<0.001
Adults (N = 1356)					
Diabetes	9.4% (7.9, 11.1%)	7.4% (5.0, 10.6%)	0.69	17.4%	0.06
Hypertension	32.4% (29.8, 35.1%)	30.9% (27.9, 34.1%)	0.33	9.2%	0.02

* The fixed effect model is a single-level model including only the outcome. The mixed effects model additionally included a random effect for household. In the fixed effect model, 95% confidence intervals (95% CI) are adjusted for household level using robust standard errors.

† Prevalence in the mixed effects model is calculated from the intercept and equivalent to a geometric mean.

‡ The variance partition coefficient (VPC) is an estimate of how much residual variation in prevalence is due to unobserved level 2 (household) characteristics.

§ p value for a random effect at level 2 (household level).

‖Restricting HIV analysis to adults only (to aid comparison with diabetes and hypertension) Fixed effect model: prevalence 20.5% (18.3, 23.1%), Mixed effects model: prevalence 12.9% (9.7, 17.0%), variance 3.07, VPC 48.2%, p < 0.001.

https://doi.org/10.1371/journal.pmed.1004452.t005

Discussion

This study demonstrated a high prevalence of HIV, diabetes, hypertension, anaemia, and chronic lung disease among household contacts of people with tuberculosis in Mozambique, Tanzania, and Zimbabwe. While awareness of and effective treatment for HIV was high, most people with diabetes and hypertension were unaware of their status, those who were diagnosed were often un- or suboptimally treated. Over a third of adolescents were at least mildly underweight. By contrast, fewer adults were underweight, while overweight and obesity was very common, particularly among women. Together, these data demonstrate that households are affected not only by tuberculosis but by multiple colliding epidemics which increase the risk of tuberculosis and poor tuberculosis-specific outcomes, and result in other poor health outcomes.

There are very limited data on the prevalence of chronic conditions among tuberculosis household contacts, with this being the first study to simultaneously consider more than one infectious and noninfectious chronic condition. Previous studies from Africa have described the prevalence of single diseases including HIV (pooled prevalence from 13 studies 7.3% [3.6, 11.1%] [6]) and diabetes (2 studies: Ethiopia [prevalence 5.2%] and South Africa [prevalence 17.4%; 44% undiagnosed] [7,8]) among tuberculosis household contacts. One study compared tuberculosis household contacts to community controls, finding an elevated risk of HIV in the former [19]. For other chronic conditions, whether there is a higher risk of chronic conditions among members of tuberculosis-affected households compared to others living in the same community is unknown. Here, to provide some insights into this, we calculated age-standardised prevalence to facilitate comparisons with published estimates (Tables E and K in S1 Appendix). While prevalence of most conditions was similar, underweight appeared more common among our population compared to country-specific national-level estimates. We also found strong evidence of correlation within households in HIV status, underweight and anaemia but not NCDs. In other words, household members appear to resemble each other in terms of HIV, anaemia, and underweight, but less so in terms of hypertension or diabetes. This may suggest that, while tuberculosis-affected households have a specific risk of HIV (due to transmission within households) and undernutrition (due to shared diet), drivers of NCDs do not act at household level. The high prevalence of NCDs in our study population, under this interpretation, reflects tuberculosis-burden communities being at high risk of other health conditions due to shared structural and social determinants of health, rather than a specific increased risk among these households compared to matched community controls [20]. Assuming that household members are genetically similar, it also suggests the most important drivers of NCDs are environmental and structural, not genetic. Tuberculosis can therefore be considered an "indicator" of a high-risk community, at the centre of biosocial syndemics, rather than reflecting a direct biological association between tuberculosis and risk of NCDs. While comparison of tuberculosis-affected household members to community controls may provide further insights, the high burden of disease demonstrated here, together with the opportunity presented by tuberculosis screening to intervene are, in our view, sufficient to justify inclusion of interventions addressing upstream determinants of tuberculosis during household contact screening.

Strengths of our study include the large, multi-centre design, with objective screening for a range of conditions, rather than relying on self-report which can severely underestimate disease prevalence. This also enabled us to quantify the gap in access to care. Most eligible household contacts identified participated, limiting selection bias. While most of our participants were women, the gender-balance of households when including the person with tuberculosis was even, suggesting this reflects the majority of people with tuberculosis being men (in

keeping with local tuberculosis epidemiology) rather than underparticipation by men. This was facilitated by flexible visits, including weekends and holidays, supporting participation by people in work.

Limitations of this study include a relatively limited assessment of nutritional status and use of point-of-care HbA1c, which may underestimate diabetes prevalence [21]. We used measurement of blood pressure on a single day as the primary definition of hypertension to align with the WHO STEPs protocol and other screening studies; our sensitivity analysis suggested this may have overestimated the absolute prevalence of confirmed hypertension by 12.8%. This is similar to results elsewhere [18]. Our definition of chronic lung disease was limited to obstructive airways or self-reported disease and therefore chronic lung diseases not included in this definition may have been missed. While participation by eligible household contacts was high overall, we cannot exclude that household contacts with health concerns were more likely to participate, resulting in overestimation of prevalence of chronic diseases. Data were missing for some assessments due to delayed implementation of chronic disease screening in the study owing to delays in shipping of consumables and ethical approvals in the context of COVID-19. There was no evidence that the people with missing data were systematically different to those who were included; this is unlikely to have resulted in bias.

Recently, the potential impact of addressing upstream determinants to prevent tuberculosis and improve outcomes was demonstrated in a large cluster-randomised trial in India, where provision of macro- and micro-nutrient support to tuberculosis household contacts reduced tuberculosis incidence by 40% [10]. In that trial, undernutrition was very common (e.g., 40% among adult women), while few people were overweight or obese. In our context, where both undernutrition and overweight/obesity coexist, it is likely that a locally developed intervention including a nuanced communication strategy will be needed [22]. This double burden of malnutrition is likely to become increasingly relevant for tuberculosis programmes as economic globalisation reaches the poorest communities worldwide, resulting in a shift in the burden of overweight/obesity from the richest to the poorest, while undernutrition persists [23].

The very high risk of tuberculosis among people with HIV is well recognised [5]. In our study yield of screening among contacts of people with tuberculosis and HIV was higher than among people without HIV. People with diabetes have up to 3 times elevated risk of tuberculosis compared to those without [24], while achieving diabetic control may reduce tuberculosis risk [25]. Screening for diabetes among tuberculosis household contacts, together with prompt treatment, could improve outcomes in people with co-prevalent tuberculosis and prevent incident tuberculosis [26,27]. In the context of slow rollout of tuberculosis preventive therapy, and low tuberculosis preventive therapy completion, identification of people with conditions that increase the risk of tuberculosis may also facilitate prioritisation of the highest risk household contacts for tuberculosis preventive therapy initiation and adherence support. However, the resource implications of chronic disease screening within tuberculosis screening interventions need to be evaluated.

The gap in access to care described in this study is not specific to tuberculosis-affected households: as east and southern African countries approach or exceed the 95-95-95 targets for HIV, it is estimated that two-thirds of people with diabetes and half of people with hypertension do not know their status, while half of those with a diagnosis are not on effective treatment [28,29]. While recognising the need for population-wide interventions to prevent, diagnose, and treat NCDs, leveraging strong, disease-specific programmes to provide a wider range of services may be one approach to expanded service provision [11]. This is gaining traction with differentiated service delivery for other chronic diseases within HIV care, and recommendations for screening for diabetes, HIV, and undernutrition among people with tuberculosis [30,31]. In the context of preexisting financial insecurity, the catastrophic

healthcare expenditure associated with tuberculosis is likely to exacerbate already extremely high barriers to accessing healthcare, particularly care for NCDs which, in Africa, are usually associated with high clinic, medication, and other costs [32]. Households affected by tuberculosis divert resources to support the person who is unwell; this is likely to include delaying health seeking and interrupting treatment for chronic conditions where that will cut costs. In order to improve outcomes, it is imperative that screening interventions among high-tuberculosis burden communities include clear pathways to onward care, and support for the financial costs of accessing care and adhering to treatment.

Overall, our study shows, for the first time, that tuberculosis household contacts in east and southern Africa are living with a range of chronic health concerns, many of which are associated with an increased risk of tuberculosis. Recognising that barriers to healthcare are often greatest for poor and vulnerable communities, the most recent WHO guidance on systematic screening for tuberculosis recommends that "where possible, community screening should be combined with screening for other diseases or risk factors and with health-promotion or social support activities" [33]. Aligned to this goal, our study supports integration of screening for other conditions among tuberculosis household contacts in Africa. Such an approach may reduce tuberculosis incidence and reduce the consequences of poor health among a community who can least afford them.

Supporting information

S1 STROBE Checklist. Completed STROBE checklist.
(PDF)

S1 Acknowledgements. Membership of the ERASE-TB consortium.
(PDF)

S1 Protocol. Study protocol.
(PDF)

S1 Appendix. Supplementary methods and results.
(PDF)

Acknowledgments

We are grateful to the study personnel from the Biomedical Research and Training Institute and the Zvitambo Research Institute, Zimbabwe, the Instituto Nacional de Saúde, Mozambique, and the National Institute for Medical Research—Mbeya Medical Research Centre, Tanzania, and all the people who participated in the study.

Cepheid provided test kits at no cost to the consortium.

Author Contributions

Conceptualization: Claire Jacqueline Calderwood, Kathrin Held, Norbert Heinrich, Katharina Kranzer.

Data curation: Claire Jacqueline Calderwood, Leyla Larsson, Tejawsi Appalarowthu, Mishelle Mugava, Jorge Ribeiro, Peter Edwin Towo.

Formal analysis: Claire Jacqueline Calderwood.

Funding acquisition: Claire Jacqueline Calderwood, Kathrin Held, Norbert Heinrich, Katharina Kranzer.

Investigation: Claire Jacqueline Calderwood, Denise Banze, Alfred Mfinanga, Celina Nhamuave, Mishelle Mugava, Jorge Ribeiro, Peter Edwin Towo, Karlos Madziva, Kathrin Held, Lilian Tina Minja, Junior Mutsvangwa, Celso Khosa, Norbert Heinrich.

Methodology: Claire Jacqueline Calderwood, Katherine Fielding, Katharina Kranzer.

Project administration: Edson Tawanda Marambire, Denise Banze, Alfred Mfinanga, Celina Nhamuave, Tejawsi Appalarowthu, Mishelle Mugava, Jorge Ribeiro, Peter Edwin Towo, Karlos Madziva, Lilian Tina Minja, Celso Khosa.

Supervision: Justin Dixon, Kathrin Held, Lilian Tina Minja, Junior Mutsvangwa, Celso Khosa, Norbert Heinrich, Katherine Fielding, Katharina Kranzer.

Validation: Edson Tawanda Marambire, Leyla Larsson.

Visualization: Claire Jacqueline Calderwood, Leyla Larsson.

Writing – original draft: Claire Jacqueline Calderwood, Katharina Kranzer.

Writing – review & editing: Claire Jacqueline Calderwood, Edson Tawanda Marambire, Leyla Larsson, Denise Banze, Alfred Mfinanga, Celina Nhamuave, Tejawsi Appalarowthu, Mishelle Mugava, Jorge Ribeiro, Peter Edwin Towo, Karlos Madziva, Justin Dixon, Kathrin Held, Lilian Tina Minja, Junior Mutsvangwa, Celso Khosa, Norbert Heinrich, Katherine Fielding, Katharina Kranzer.

References

1. Santosa A, Wall S, Fottrel E, Högberg U, Byass P. The development and experience of epidemiological transition theory over four decades: a systematic review. Glob Health Action. 2014; 7. https://doi.org/10.3402/gha.v7.23574 PMID: 24848657
2. Kaluvu L, Asogwa OA, Marzà-Florensa A, et al. Multimorbidity of communicable and non-communicable diseases in low- and middle-income countries: A systematic review. J Multimorb Comorbidity. 2022; 12:26335565221112593. https://doi.org/10.1177/26335565221112593 PMID: 36081708
3. Allen L, Williams J, Townsend N, et al. Socioeconomic status and non-communicable disease behavioural risk factors in low-income and lower-middle-income countries: a systematic review. Lancet Glob Health. 2017; 5:e277–89. https://doi.org/10.1016/S2214-109X(17)30058-X PMID: 28193397
4. Bukhman G, Mocumbi AO, Atun R, et al. The Lancet NCDI Poverty Commission: bridging a gap in universal health coverage for the poorest billion. Lancet. 2020; 396:991–1044. https://doi.org/10.1016/S0140-6736(20)31907-3 PMID: 32941823
5. World Health Organization. Global tuberculosis report 2023. Geneva: World Health Organization, 2023.
6. Seid G, Alemu A, Dagne B, Sinshaw W, Gumi B. Tuberculosis in household contacts of tuberculosis patients in sub-Saharan African countries: A systematic review and meta-analysis. J Clin Tuberc Mycobact Dis. 2022; 29:100337. https://doi.org/10.1016/j.jctube.2022.100337 PMID: 36425906
7. Smith AGC, Kempker RR, Wassie L, et al. The Impact of Diabetes and Prediabetes on Prevalence of Mycobacterium tuberculosis Infection Among Household Contacts of Active Tuberculosis Cases in Ethiopia. Open Forum Infect Dis. 2022;9:ofac323. https://doi.org/10.1093/ofid/ofac323 PMID: 36420425
8. Restrepo BI, Kleynhans L, Salinas AB, et al. Diabetes screen during tuberculosis contact investigations highlights opportunity for new diabetes diagnosis and reveals metabolic differences between ethnic groups. Tuberculosis (Edinb). 2018; 113:10–8. https://doi.org/10.1016/j.tube.2018.08.007 PMID: 30514492
9. Lebina L, Fuller N, Osoba T, et al. The Use of Xpert MTB/Rif for Active Case Finding among TB Contacts in North West Province, South Africa. Tuberc Res Treat. 2016; 2016:4282313. https://doi.org/10.1155/2016/4282313 PMID: 27493800
10. Bhargava A, Bhargava M, Meher A, et al. Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial. Lancet. 2023;0. https://doi.org/10.1016/S0140-6736(23)01231-X PMID: 37567200

11. Calderwood CJ, Timire C, Mavodza C, et al. Beyond tuberculosis: a person-centred and rights-based approach to screening for household contacts. Lancet Glob Health. 2024; 12:e509–15. https://doi.org/10.1016/S2214-109X(23)00544-2 PMID: 38365421

12. Marambire ET, Banze D, Mfinanga A, et al. Early risk assessment in paediatric and adult household contacts of confirmed tuberculosis cases by novel diagnostic tests (ERASE-TB): protocol for a prospective, non-interventional, longitudinal, multicountry cohort study. BMJ Open. 2022; 12:e060985. https://doi.org/10.1136/bmjopen-2022-060985 PMID: 36427173

13. World Health Organization. STEPwise approach to NCD risk factor surveillance (STEPS). Available from: https://www.who.int/teams/noncommunicable-diseases/surveillance/systems-tools/steps (accessed Aug 21, 2023).

14. AUDIT: the Alcohol Use Disorders Identification Test: guidelines for use in primary health care. Available from: https://www.who.int/publications-detail-redirect/WHO-MSD-MSB-01.6a (accessed Dec 20, 2023).

15. WHO. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: report of a WHO/IDF consultation. 2006.

16. World Health Organization. Guideline for the pharmacological treatment of hypertension in adults. Geneva: World Health Organization, 2021. Available from: https://iris.who.int/bitstream/handle/10665/344424/9789240033986-eng.pdf (accessed Mar 17, 2024).

17. The Academy of Medical Sciences. Multimorbidity: a priority for global health research. 2018. Available from: https://acmedsci.ac.uk/file-download/82222577.

18. Olivier S, Murray T, Matthews P, et al. Pitfalls of Single Measurement Screening for Diabetes and Hypertension in Community-Based Settings. Glob Heart. 2021; 16:79. https://doi.org/10.5334/gh.1083 PMID: 34900570

19. Mutsvangwa J, Millington KA, Chaka K, et al. Identifying recent Mycobacterium tuberculosis transmission in the setting of high HIV and TB burden. https://doi.org/10.1136/thx.2009.124891 PMID: 20388756

20. Stanifer JW, Egger JR, Turner EL, Thielman N, Patel UD. Neighborhood clustering of non-communicable diseases: Results from a community-based study in Northern Tanzania. BMC Public Health. 2016; 16:1–10.

21. Chivese T, Hirst J, Matizanadzo JT, et al. The diagnostic accuracy of HbA1c, compared to the oral glucose tolerance test, for screening for type 2 diabetes mellitus in Africa-A systematic review and meta-analysis. Diabet Med J Br Diabet Assoc. 2022; 39:e14754.

22. Escher NA, Andrade GC, Ghosh-Jerath S, Millett C, Seferidi P. The effect of nutrition-specific and nutrition-sensitive interventions on the double burden of malnutrition in low-income and middle-income countries: a systematic review. Lancet Glob Health. 2024; 12:e419–32. https://doi.org/10.1016/S2214-109X(23)00562-4 PMID: 38301666

23. Seferidi P, Hone T, Duran AC, Bernabe-Ortiz A, Millett C. Global inequalities in the double burden of malnutrition and associations with globalisation: a multilevel analysis of Demographic and Health Surveys from 55 low-income and middle-income countries, 1992–2018. Lancet Glob Health. 2022; 10: e482–90. https://doi.org/10.1016/S2214-109X(21)00594-5 PMID: 35148831

24. Obels I, Ninsiima S, Critchley JA, Huangfu P. Tuberculosis risk among people with diabetes mellitus in Sub-Saharan Africa: A systematic review. Trop Med Int Health TM IH. 2022; 27:369–86. https://doi.org/10.1111/tmi.13733 PMID: 35146851

25. Chen Z, Liu Q, Song R, et al. The association of glycemic level and prevalence of tuberculosis: a meta-analysis. BMC Endocr Disord 2021; 21:123. https://doi.org/10.1186/s12902-021-00779-6 PMID: 34134685

26. World Health Organization. Global Tuberculosis Report 2022. Geneva: World Health Organization, 2022. Available from: https://apps.who.int/iris/handle/10665/363752.

27. Huangfu P, Ugarte-Gil C, Golub J, Pearson F, Critchley J. The effects of diabetes on tuberculosis treatment outcomes: an updated systematic review and meta-analysis. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis. 2019; 23:783–96. https://doi.org/10.5588/ijtld.18.0433 PMID: 31439109

28. Manne-Goehler J, Atun R, Stokes A, et al. Diabetes diagnosis and care in sub-Saharan Africa: pooled analysis of individual data from 12 countries. Lancet Diabetes Endocrinol. 2016; 4:903–12. https://doi.org/10.1016/S2213-8587(16)30181-4 PMID: 27727123

29. Zhou B, Carrillo-Larco RM, Danaei G, et al. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet Lond Engl. 2021; 398:957–80. https://doi.org/10.1016/S0140-6736(21)01330-1 PMID: 34450083

30. World Health Organization. International Union against Tuberculosis and Lung Disease. Collaborative framework for care and control of tuberculosis and diabetes. Geneva: World Health Organization, 2011. Available from: https://apps.who.int/iris/handle/10665/44698.

31. Bygrave H, Golob L, Wilkinson L, Roberts T, Grimsrud A. Let's talk chronic disease: can differentiated service delivery address the syndemics of HIV, hypertension and diabetes? Curr Opin HIV AIDS. 2020; 15:256–60. https://doi.org/10.1097/COH.0000000000000629 PMID: 32398467

32. Murphy A, Palafox B, Walli-Attaei M, et al. The household economic burden of non-communicable diseases in 18 countries. BMJ Glob Health. 2020; 5:e002040. https://doi.org/10.1136/bmjgh-2019-002040 PMID: 32133191

33. World Health Organization. WHO consolidated guidelines on tuberculosis. Module 2: screening–systematic screening for tuberculosis disease. Geneva: World Health Organization, 2021.

4.2 Paper B

Prediction models for *Mycobacterium tuberculosis* infection among adolescent and adult household contacts in high tuberculosis incidence settings.

PLOS GLOBAL PUBLIC HEALTH

RESEARCH ARTICLE

Prediction models for *Mtb* infection among adolescent and adult household contacts in high tuberculosis incidence settings

Edson Tawanda Marambire[1,2]*, Claire J. Calderwood[1,3], Leyla Larsson[4], Kathrin Held[4], Palwasha Khan[3], Denise Banze[2,5], Celina Nhamuave[5], Lillian T. Minja[6], Alfred Mfinanga[2,6], Rishi K. Gupta[7], Celso Khosa[5], Junior Mutsvangwa[8], Norbert Heinrich[4,9,10], Katharina Kranzer[1,3,4]

1 The Health Research Unit Zimbabwe, Biomedical Research and Training Institute, Harare, Zimbabwe, **2** CIH[LMU] Center for International Health, University Hospital, LMU Munich, Germany, **3** Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom, **4** Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Munich, Germany, **5** Instituto Nacional de Saúde, Marracuene, Mozambique, **6** National Institute for Medical Research - Mbeya Medical Research Centre, Mbeya, Tanzania, **7** University College London, London, United Kingdom, **8** Biomedical Research and Training Institute, Harare, Zimbabwe, **9** German Center for Infection Research (DZIF), Partner Site Munich, Munich, Germany, **10** Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology, Infection and Pandemic Research, Munich, Germany

* Edson.Marambire@lrz.uni-muechen.de

Citation: Marambire ET, Calderwood CJ, Larsson L, Held K, Khan P, Banze D, et al. (2025) Prediction models for *Mtb* infection among adolescent and adult household contacts in high tuberculosis incidence settings. PLOS Glob Public Health 5(3): e0004340. https://doi.org/10.1371/journal.pgph.0004340

Editor: N. Sarita Shah, Emory University Rollins School of Public Health, UNITED STATES OF AMERICA

Received: November 6, 2024

Accepted: February 7, 2025

Published: March 31, 2025

Data availability statement: We are in the process of updating the already uploaded data on Data Compas (an open data repository hosted by LSHTM). Data is accessible on the following link: https://doi.org/10.17037/DATA.00004267

Abstract

Tuberculosis household contacts are at high risk of developing tuberculosis. Tuberculosis preventive therapy (TPT) is highly effective, but implementation is hindered by limited accessibility of diagnostic tests aimed at detecting *Mycobacterium tuberculosis* (*Mtb*) infection. Development of *Mtb* infection prediction models to guide clinical decision-making aims to overcome these challenges. We used data from 1905 tuberculosis household contacts (age ≥10 years) from Zimbabwe, Mozambique and Tanzania to develop two prediction models for *Mtb* infection determined by interferon-gamma release assay (IGRA) using logistic regression with backward elimination and cross-validation and converted these into a risk score. Model performance was assessed using area under the receiver operating characteristic curve (AUROC), sensitivity, and specificity. We developed a basic model with six predictors (age, caregiver role, index case symptom duration, index HIV status, household crowding, and index GeneXpert MTB/Rif results) and a comprehensive model with eleven predictors. The basic and comprehensive risk scores showed limited predictive capability (AUROC 0.592, sensitivity 76%, specificity 35% and AUROC 0.586, sensitivity 76%, specificity 36% respectively), with considerable overlap across IGRA-positive and -negative individuals. Neither model conferred net benefit over a treat-all strategy. Overall, our results suggest that the prediction models developed in this study do not add value for guiding TPT use in high-tuberculosis burden settings. This likely reflects complex *Mtb* transmission dynamics at the household- and community-level, variation in individual-level susceptibility and immune response, as well as limited accuracy of IGRA testing. Improved diagnostics to determine *Mtb* infection status in terms of ease-of-use, accuracy, and costs are needed.

Funding: ERASE-TB is part of the EDCTP2 programme supported by the European Union (grant number RIA2018D-2508-ERASE-TB to NH), the German Center for Infection Research (DZIF) (grant number: 02.710 to KK), Swedish Research Council (220-23602 to GK) and Wellcome Trust (203905/Z/16/Z to CJC). Cepheid, Inc., and SD Biosensor provided test kits and analyzers at no cost to the Consortium. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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

Introduction

Whilst in 2020 COVID-19 briefly overtook tuberculosis (TB) as the leading cause of death due to an infectious disease, TB has since regained its lead, despite being both preventable and curable [1]. TB is caused by pathogens of the *Mycobacterium tuberculosis* (*Mtb*) complex and is transmitted primarily by aerosols, putting people living with someone who has TB at particularly high risk of *Mtb* infection [2].

It is estimated that a quarter of the world's population is infected with *Mtb*, representing a vast reservoir of people at risk of developing TB [3]. One in ten people infected with *Mtb* will progress to TB [4–6], risk of progression can be significantly reduced (≤90%) by preventive therapy (TPT) which is an important pillar in the WHO End-TB strategy [7,8]. Identifying those with *Mtb* infection is a critical step in the TB prevention cascade, especially in high-burden settings. Household contacts of individuals recently diagnosed with TB represent a key population for screening and preventive interventions because of their high likelihood of exposure to *Mtb* [9,10].

The most recent WHO guidelines recommend expanding TPT to all household contacts in high-TB incidence countries [11], if possible focused on those with demonstrated *Mtb* infection, but few countries have operationalised this. Diagnostic tests to detect *Mtb* infection include tuberculin skin tests (TST) and interferon-gamma release assays (IGRA). These tests require nursing skills for intradermal injections, established cold chain, and repeat patient visits or trained laboratory staff and infrastructure. A lack of cheap, rapid and easy to use diagnostic tests to screen for *Mtb* infection partly explains the suboptimal implementation of TPT for TB household contacts [12,13].

Given costs and logistics of these tests, most high-TB burden countries either i) recommend TPT for all household contacts without prior testing for *Mtb* infection, resulting in considerable overtreatment and health-system costs [14], or ii) restrict TPT to high risk groups (such as household contacts less than 5 years old and people living with HIV).

Considering these challenges, recent efforts have focused on improving strategies to identify *Mtb* infection among household contacts, including use of prediction models based on easily ascertainable risk factors [15]. These models aim to incorporate individual- and household-level, environmental, host- and pathogen-related predictors such as proximity to the person with TB, time spent with the index case, and the infectiousness of the person with TB [16–19]. Ideally, the predictors would be easy to ascertain from the person diagnosed and being treated for TB by a nurse or community health worker, thus reducing the burden on health systems by prioritizing individuals or households for individual assessment, diagnostic testing and subsequent preventive therapy where indicated. Previous models have shown inconsistent performance, with some achieving moderate predictive accuracy in low-TB burden settings but often underperforming in high-TB burden settings [16–19], highlighting the challenges of generalizability across diverse populations and epidemiological contexts.

Here, we sought to develop and systematically evaluate whether prediction models can accurately predict IGRA positivity as a marker of *Mtb* infection among adolescent and adult TB household contacts in East and Southern Africa, to support targeted provision of TPT without IGRA or TST.

Methods

In a dataset of adult and adolescent TB household contacts from Tanzania, Mozambique, and Zimbabwe, we developed *de novo* prediction models for positive IGRA result using a large and diverse cohort with information related to household member with TB (index case), household, and household contact factors, measured at the time of diagnosis of the index case in the

Early Risk Assessment in TB contactS by new diagnostic tEsts (ERASE-TB) study. Transparent Reporting of a Multivariable Prediction Model or Individual Prognosis Or Diagnosis (TRIPOD) guidelines are used for reporting of results [20].

Study population

The study population for the development of prediction models was a large multi-national, observational, prospective cohort study (ERASE-TB). Inclusion and exclusion criteria are shown in S1 Table. We enrolled household contacts (age ≥10 years) of adults with microbiologically confirmed pulmonary TB (age ≥18 years) with a positive smear (at least +1) and/or a medium or high-level positive Xpert MTB/Rif sputum result across three sites: Maputo (Mozambique), Mbeya (Tanzania), and Harare (Zimbabwe). The enrolment periods were as follows: Maputo from 05 August 2021 to 23 March 2023, Mbeya from 31 August 2021 to 08 February 2023, and Harare from 08 March 2021 to 17 January 2023. A total of 2109 household contacts were recruited (Fig 1).

Study procedures

The study protocol for ERASE-TB, including details of all study procedures, has been published [21]. In brief, at each study visit (every 6 months for a period of up to 24 months), enrolled household contacts underwent TB screening (WHO symptom screen and chest X-ray, followed by Xpert MTB/Rif Ultra if either was suggestive of TB) and collection of

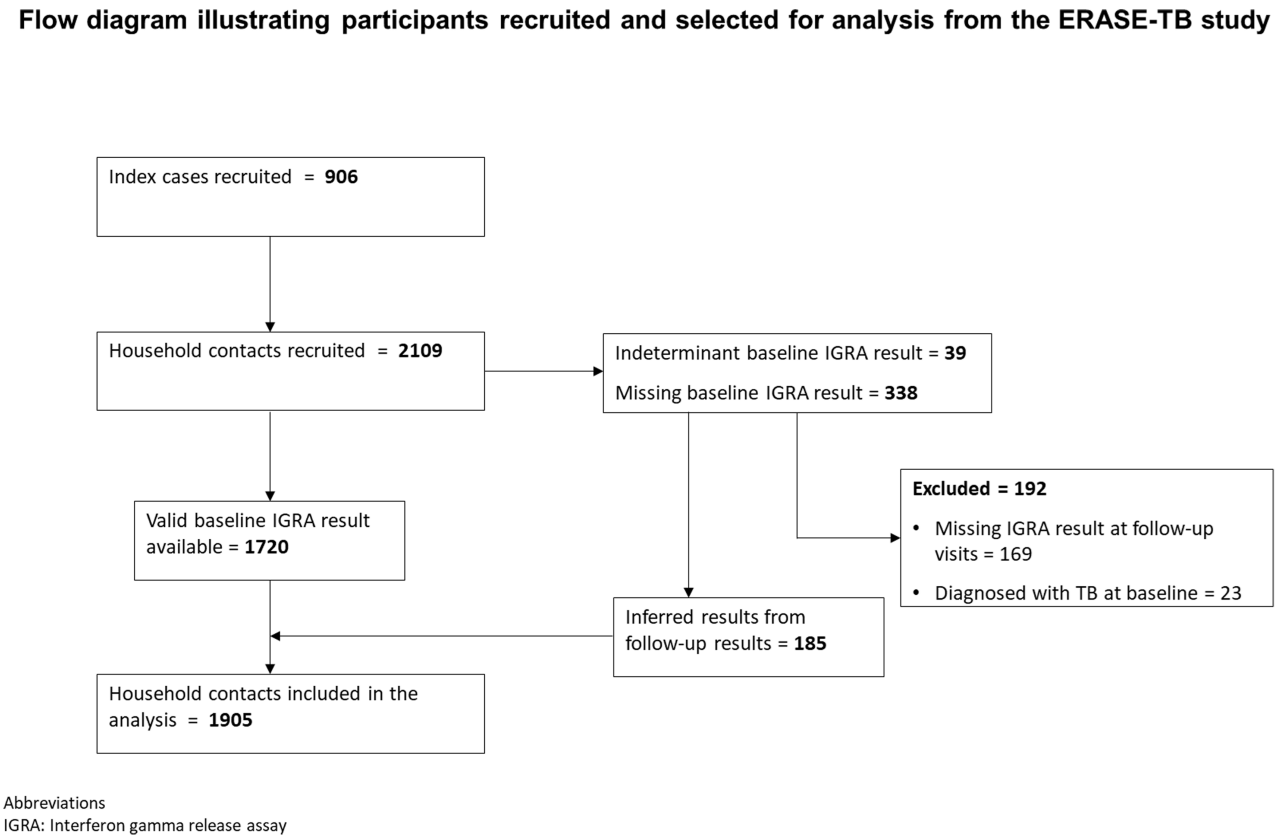


Fig 1. Flow diagram illustrating participants recruited and selected for analysis from the ERASE-TB study.

https://doi.org/10.1371/journal.pgph.0004340.g001

samples for novel diagnostic tests and biobanking. All household contacts who were not known to be living with HIV were offered HIV testing. IGRAs (STANDARD™ F TB-Feron FIA [IFN-gamma; SD Biosensor, Republic of Korea]) were conducted at baseline and at subsequent visits dependent on reagent availability. Individual- and household-level questionnaires collected socioeconomic characteristics, information about living conditions, past medical history, and factors known to be associated with *Mtb* infection.

Outcome

The primary outcome of interest was IGRA binary result (negative or positive) as a marker of *Mtb* infection, interpreted according to the manufacturer's instructions. For household contacts with indeterminant or missing IGRA results at baseline, the next available follow-up IGRA result was used to infer baseline results: a negative IGRA result at follow-up was categorised as negative, and a positive IGRA result at follow-up was categorised as positive. Household contacts diagnosed with TB within 30 days of the baseline visit and those with missing or indeterminate IGRA result after taking into account follow-up results were excluded from the analysis.

Development of prediction models

Analysis was done using R version 4.3.2. Inclusion of candidate predictor variables for the newly developed model was based on existing evidence of association with *Mtb* infection, according to reviewed literature [19,22–31] and availability in the ERASE-TB dataset. Variables related to the person diagnosed and treated for TB were regarded as household-level variables. Prior to model development, descriptive analyses were conducted. Continuous data were summarized by the mean and standard deviation or median and interquartile ranges, while categorical data was summarized as frequencies with percentages. For model development, the ERASE-TB dataset was randomly split into model development (70%) and evaluation (30%) datasets. Missing values in predictor variables were classified as "unknown".

We utilized 10-fold cross-validation technique exclusively on the training data. This technique involved dividing the training set into 10 equal subsets, iteratively training the model on 9 of these subsets, and validating it on the remaining subset. This process was repeated 10 times, ensuring that each subset served as the validation set exactly once. Performance metrics obtained from each fold were averaged to provide a robust estimate of the model's performance.

Two models were developed. We first developed a model with basic individual- and household-level predictors, ascertainable from the person with TB by a nurse or community health worker using just a questionnaire (basic model). Our goal was to be able to predict which household contacts had *Mtb* infection without having to physically review and assess every individual member of the household. We secondly developed a model with all eligible individual and household predictors (comprehensive model), to determine whether predictive performance could be enhanced using a more comprehensive approach. S2 Table shows candidate predictor variables and how data was collected.

For each model, using the training dataset, we conducted a multiple logistic regression, with backward elimination of candidate predictors contributing little predictive value to the overall multivariable model, assessed using the "varImp" function in R and examining regression coefficients and p-values (i.e., sequential removal of variables with the largest p-value and least important until variables with p-value < 0.2 remained). To derive a prediction risk score to be used by clinicians in resource-limited settings, regression coefficients were normalized into scores using the formula:

$$Score = \frac{Coefficient - Lowest\ coefficient}{\text{Highest coefficient} - Lowest\ coefficient} \times 10$$

Scores ranged from 0 to 10 (for category with the lowest and category with the highest predictive impact respectively) and were added up to compute a summative risk score for *Mtb* infection.

Risk score assessment

We assessed the predictive performance of our de novo basic and comprehensive risk scores by evaluating the agreement between observed and predicted risks using the held-back evaluation dataset. A confusion matrix was then used to assess the model's sensitivity and specificity, with a decision threshold of 0.5 and the corresponding maximum Youden Index, which indicates the optimal balance between sensitivity and specificity, was calculated. We examined area under the receiver operating characteristic (ROC) curves to compare the performance of the two risk scores and determine the added value of including detailed clinical information in the model. We stratified individuals into low-, medium-, and high-risk groups for *Mtb* infection based on score categories.

We also visually displayed the relationship between the scores and the outcome using density plots, to understand how well the scores correlated with the outcome measurement. Decision curve analysis was used to compare the net benefit of interventions to treat *Mtb* infection based on risk scores against treat-all or treat-none approaches across different threshold probabilities.

To evaluate the robustness of the model, a sensitivity analysis was conducted using the basic model. This analysis included only participants with baseline IGRA results, excluding inferred results. Additionally, the results from the last available IGRA test during follow-ups were utilized.

Ethical considerations

Informed written consent, or guardian consent and individual assent for people under the age of 18, was obtained from all participants. Ethical approval was granted by all relevant institutions: the Medical Research Council in Zimbabwe (MRCZ/A/2618), the National Health Research Ethics Committee in Tanzania (TMDA-WEB0021/CTR/0004/03), the National Bioethics Committee for Health in Mozambique (541/CNBS/21), and the ethical committees of London School of Hygiene & Tropical Medicine, United Kingdom (22522–2) and the medical faculty of the Ludwig-Maximilians-Universität München, Germany (20–0771)).

Results

Study population

In ERASE-TB, 2109 household contacts of people diagnosed with pulmonary TB were recruited from 822 households between March 2021, and March 2023. A total of 1905 (90%) were included in the analysis. Of these, 1720 (90%) had a valid baseline IGRA result and an additional185 (10%) had results inferred from follow-up results (Fig 1). 169 (8%) participants could not be classified into the outcome of interest even after inferring follow-up results and 23 (1.1%) were diagnosed with TB at baseline, and thus were excluded from the analysis. Therefore, 1905 (90% recruited) household contacts were included in the analysis. Table 1 describes the baseline individual- and household-level characteristics of included participants: 62% were female and median age was 27 (interquartile range: 17-42) years with 29% of participants being adolescents (10-17 years). A total of 292 (15%) household contacts were

Table 1. Baseline characteristics of participants.

		IGRA-Positive	IGRA-Negative
		N=811 (43%)	N=1094 (57%)
		N (%)	N (%)
INDIVIDUAL LEVEL CHARACTERISTICS (HOUSEHOLD CONTACT)			
Country	Zimbabwe	332 (49%)	342 (51%)
	Mozambique	197 (32%)	411 (68%)
	Tanzania	282 (45%)	341 (55%)
Age (years)	10-17	197 (35%)	358 (65%)
	18-25	149 (40%)	226 (60%)
	26-35	124 (42%)	172 (58%)
	36+	341 (50%)	338 (50%)
Sex	Female	511 (43%)	677 (57%)
	Male	300 (42%)	417 (58%)
HIV status of household contact	HIV negative	693 (44%)	895 (56%)
	HIV positive	112 (38%)	180 (62%)
	HIV status unknown	6 (24%)	19 (76%)
BMI category*	Underweight	72 (43%)	96 (57%)
	Normal weight	490 (41%)	697 (59%)
	Overweight	155 (44%)	197 (56%)
	Obesity	94 (48%)	104 (52%)
Frequency of contact with index person with TB	<1 day per week	9 (53%)	8 (47%)
	1-3 days per week	26 (43%)	34 (57%)
	4-6 days per week	38 (44%)	49 (56%)
	Daily	737 (42%)	1002 (58%)
Directly involved in caring for the index person with TB	No	437 (39%)	675 (61%)
	Yes	374 (47%)	419 (53%)
HOUSEHOLD LEVEL CHARACTERISTICS			
Household income per person per day (USD)	Median (IQR)	0.55 (0.30–1.06)	0.55 (0.31–0.98)
Impoverishment (< 1.90 USD/day)	Yes	751 (42%)	1030 (58%)
	No	60 (48%)	64 (52%)
Xpert semi-quantitative grade of TB index case	High	499 (44%)	632 (56%)
	Medium	312 (40%)	462 (60%)
HIV status of index	Unknown	68 (46%)	80 (54%)
	Negative	533 (45%)	665 (55%)
	Positive	210 (38%)	349 (62%)
Index ART status**	Not on ART	48 (29%)	118 (71%)
	On ART	162 (41%)	231 (59%)
Index TB presenting symptoms	Cough	808 (43%)	1089 (57%)
	Haemoptysis	163 (43%)	217 (57%)
Duration of index case symptoms before start of treatment (days)	<30 days	91 (31%)	200 (69%)
	30-89 days	348 (41%)	502 (59%)
	≥90 days	372 (49%)	387 (51%)
Crowding***	No	619 (41%)	876 (59%)
	Yes	192 (47%)	218 (53%)

Footnotes:

BMI = body mass index.

IGRA = interferon-gamma release assay.

(Continued)

Table 1. (Continued)

TB = tuberculosis.

IQR = inter-quartile range.

ART = anti-retroviral therapy.

UN = United Nations.

USD = United States Dollars

*BMI Categories were created using the WHO categories [32]

**ART status among index cases with HIV only

***Crowding categorised as per UN Habitat definitions (≥3 people per room) [33].

https://doi.org/10.1371/journal.pgph.0004340.t001

living with HIV. Overall, 811/1905 (43%) of the included participants were IGRA positive. The highest prevalence of IGRA positivity was in Zimbabwe (49%) and among older adults (50%, compared to 33% among adolescents aged 10-14 years).

Development and validation of risk prediction model

The training subset consisted of 1334 (70%) household contacts, and evaluation subset 571 (30%). Eleven individual- and household-level *Mtb* candidate predictor variables were included in the initial multivariable logistic regression (S1 Code), constituting the comprehensive model (S3 Table). The final basic model included six individual- and household-level predictors. Individual-level predictors were age, and whether the household contact cared for the index, while household-level predictors included duration of illness of the index case, index HIV status, Xpert/smear positivity level, and household crowing according to United Nations definition (≥3 people per room) (Table 2). TB index cases, not on ART contributed the lowest score while index symptom duration of more than 3 months had the highest score.

Neither the basic nor the comprehensive model achieved adequate prediction for positive IGRA result among TB household contacts. The basic model yielded low AUROC (0.592; Fig 2). At a threshold of 0.5, the model had a sensitivity of 76% (95% CI: 70 – 79), specificity of 35% (95% CI: 27 – 39), and Youden Index of 0.08 (95% CI: 0.01 – 0.15). The comprehensive model had an equally low AUROC of 0.586, while at a threshold of 0.5 the model had a sensitivity of 76% (95%CI: 72 – 82), specificity of 36% (95% CI: 30 – 42) and Youden Index of 0.13 (95% CI: 0.05 – 0.19). Sensitivity analysis of the basic model using only participants who had baseline IGRA results available (without inferring missing or indeterminate baseline result) as well as using results of last available IGRA test result during follow-up did not change the model performance, yielding AUROCs of 0.61 and 0.60 respectively (S1 Fig**).**

We developed a risk score to assess the risk of positive IGRA result in a clinical setting, based on the basic prediction model (Table 2**).** Each response to a variable in the final model contributed to the score independently. The maximum possible risk score for the model was 42, while the minimum score was 20. Risk score categories were developed as low positive IGRA risk (<30), medium positive IGRA risk (30≤score>35), high positive IGRA risk score (≥35). These categories were determined based on the distribution of the scores, where approximately 25% of the scores are less than 30, and the upper 25% are above 35. This approach was taken to ensure a balanced representation across the risk categories. Risk score categories among IGRA positive and IGRA negative participants showed a small difference in proportions of people categorized as medium- and low-risk in both groups (Fig 3A). Using this risk stratification, the basic model classified 53% and 8.3% of IGRA negative participants as medium and high risk respectively, while 24% of IGRA positive participants were classified as low risk. The density plot revealed substantial overlap between the scores assigned to IGRA

Table 2. Basic model predictors of *Mtb* infection.

	Coefficient	P-Value	Score
Mtb risk factors			
Age (years)			
10-14			4
15-17	0.2813	0.217	6
18-25	0.1880	0.331	5
26-35	0.3227	0.104	6
36 +	0.6677	<0.001	9
Cared for the index			
No			4
Yes	0.2785	0.021	6
Index HIV status			
Negative			4
Positive, not on ART	-0.4768	0.027	0
Positive, on ART	-0.0623	0.668	3
Unknown	0.3231	0.126	6
Index Symptom duration			
<1 month			4
1≤ months<3	0.5828	0.001	8
3 months and above	0.8447	<0.001	10
Household crowding (≥3 people per room)			
No			4
Yes	0.2629	0.058	6
GeneXpert MTB/Rif Ultra index positivity			
Medium			4
High	0.1801	0.498	5
Lowest/Highest possible score			***20/42***

https://doi.org/10.1371/journal.pgph.0004340.t002

negative and positive participants, with the IGRA positive group showing a distribution with slightly higher scores compared to the IGRA negative group (Fig 3B). This overlap implies that the model does not distinguish between these two groups effectively, overestimating risk for IGRA negative contacts, and underestimating risk for IGRA positive contacts. This is further evidenced by the calibration plot (Fig 3C), (**S2 Code)** which demonstrates that the model's predicted probabilities do not align well with the observed outcomes.

Decision Curve Analysis (DCA) of our basic model predicting IGRA positivity compares the net benefit of interventions to treat *Mtb* infection based on risk scores against treat-all or treat-none approaches across different threshold probabilities (i.e., the probability of disease at which the health system/provider would provide treatment). When considering our model in the context of TB preventive interventions for TB household contacts, the net benefit of treat-all decision surpasses that of using risk scores across the range of threshold probabilities considered (Fig 4**).**

Discussion

TB remains a significant global health challenge, particularly in resource-limited settings where the burden of disease is highest [34]. Using risk prediction tools to guide use of TPT among household contacts has been proposed as one pragmatic approach to improve delivery of TPT in settings where current diagnostic tests are not feasible.

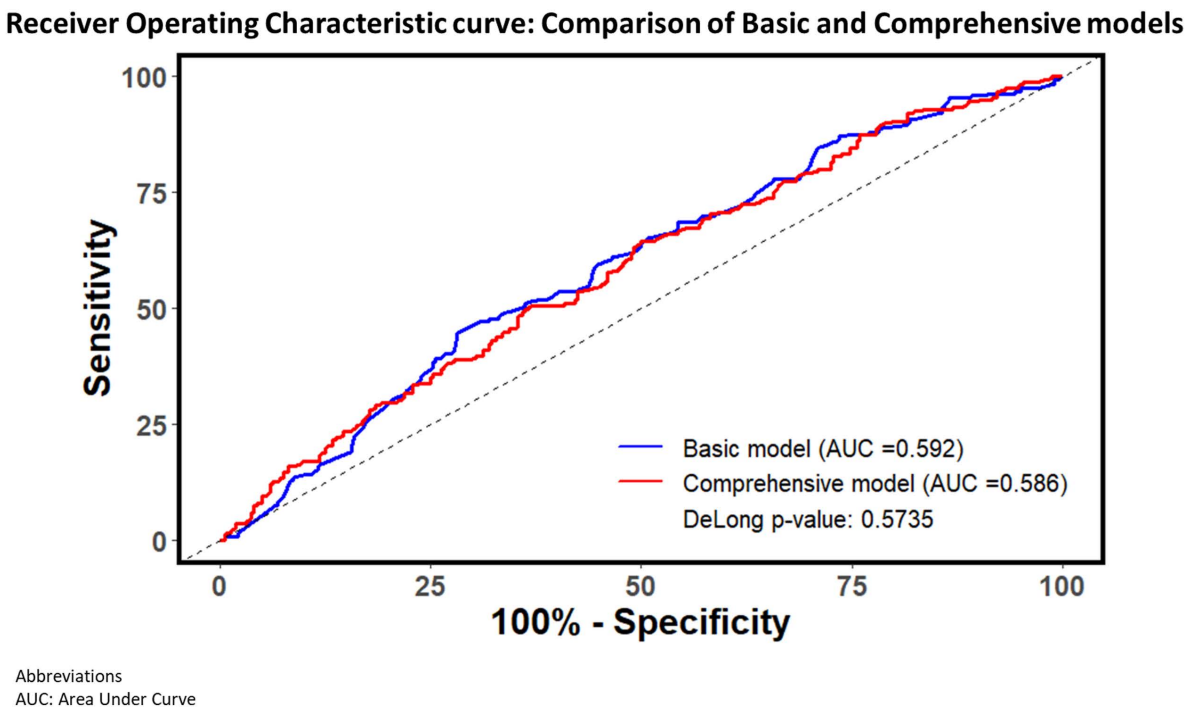


Fig 2. Performance of basic model and comprehensive models.

https://doi.org/10.1371/journal.pgph.0004340.g002

Our findings do not support use of risk prediction tools for *Mtb* infection - as defined herein by IGRA testing – among adolescents and adults in high-TB burden settings. We developed two new tools using high-quality granular data from a research cohort of adolescents and adults from TB-affected households. Both achieved poor predictive accuracy, AUC, and sensitivity and specificity estimates. In short, each model was no better than random selection. For example, our basic risk score inadvertently misclassified 61% of individuals who were not infected with *Mtb* determined by IGRA as being medium- to high-risk. Given the high proportion of household contacts misclassified by these scores, we do not recommend their use in clinical practice.

Our study highlights the challenges of developing effective prediction models for *Mtb* infection in high-TB burden settings. While previous models, such as the Mandalakas score, have shown reasonable performance in specific populations (e.g., children younger than six years), their application to adolescent and adult populations in high-TB burden environments remains problematic [18,19,31]. However, this finding is in contrast with *Mtb* infection prediction models developed in low-TB burden settings that have achieved reasonable predictive performance among adolescents and adults [16,17]. This brings to attention the complexity of *Mtb* transmission dynamics in high-TB burden settings, where community transmission is pervasive, making it difficult to rely solely on household-related predictors to identify at-risk individuals [35–37]. In high-TB incidence settings, household-related risk factors alone do not sufficiently capture the multifaceted nature of *Mtb* exposure and infection from a single exposure, as prior transmission events inside or outside the household may have occurred [35]. The high prevalence of *Mtb* infection in such environments complicates the identification of new transmission events and makes it difficult to discriminate between individuals recently infected and those with prior exposure.

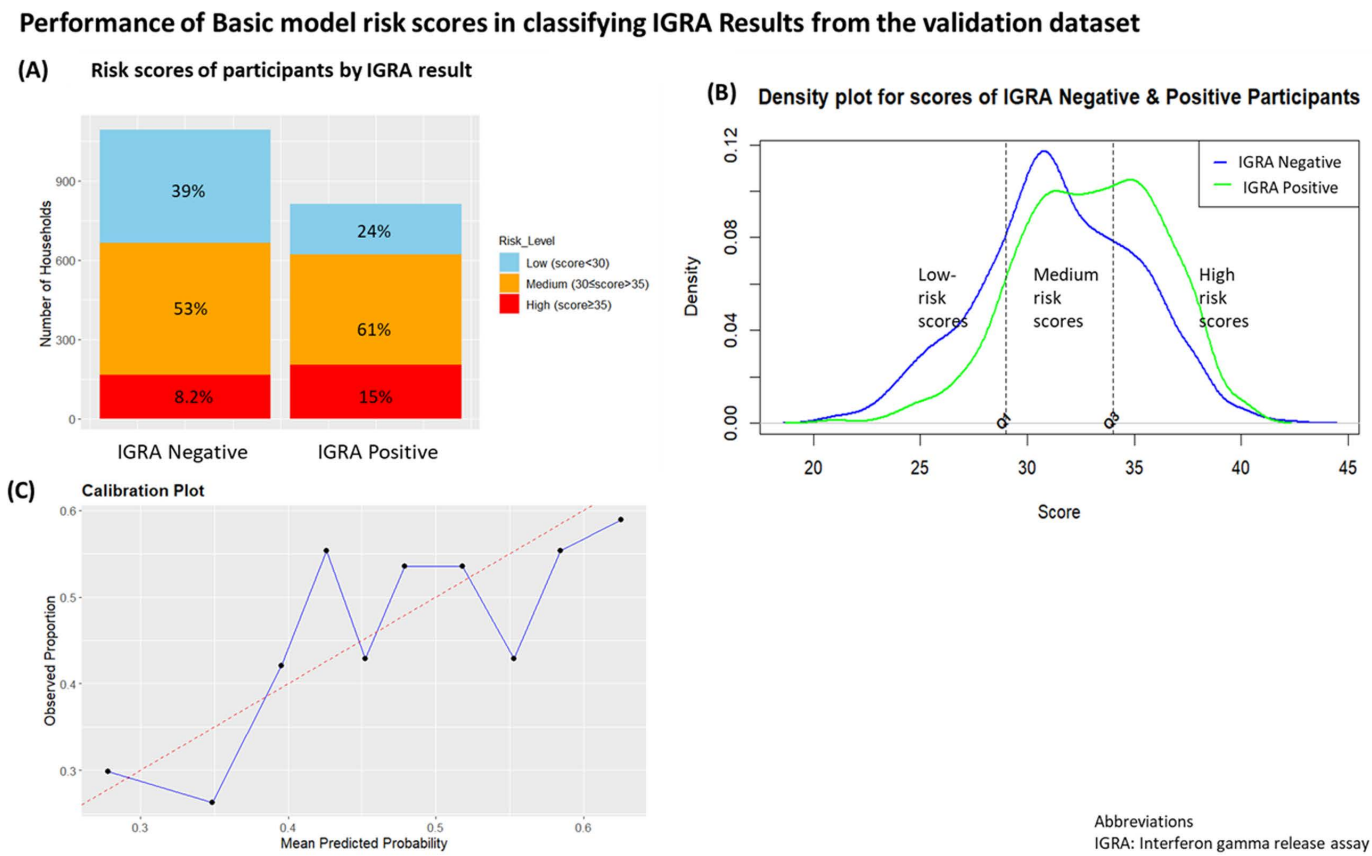


Fig 3. Performance of *de-novo* risk scores on positive and negative IGRAs.

https://doi.org/10.1371/journal.pgph.0004340.g003

Additionally, the high prevalence of HIV in these settings may partly explain the poor performance of *Mtb* prediction models. Evidence suggests that HIV-related immunosuppression in people with TB can reduce the infectiousness of the individual [38]. This was reflected in our analysis, where HIV-positive index cases on ART were assigned the lowest risk scores. These findings further underscore the intricate interplay between community-level transmission dynamics and individual-level factors, such as HIV status and ART use, in shaping *Mtb* transmission patterns.

While both our models did not achieve good enough performance, this study represents an important step forward in understanding what is needed to provide targeted treatment of *Mtb* infection for adolescents and adults in high burden settings. In this context, prediction models cannot adequately discriminate between *Mtb* infected and non-infected adolescent and adults, as measured using IGRA. Also, given that IGRA is an imperfect reference standard with limited accuracy [39], the study might be predicting the wrong outcome especially when assessed at one time-point only. Therefore, a more nuanced understanding of *Mtb* transmission dynamics, recognizing the complex interplay between household-related factors and broader community-level influences is needed. Further collaborative, interdisciplinary innovation is essential to develop more accurate, easy-to-use, affordable and accessible tests that identify people with recent *Mtb* infection, those infected in the distant past and those not infected to inform targeted interventions for TB control and prevention.

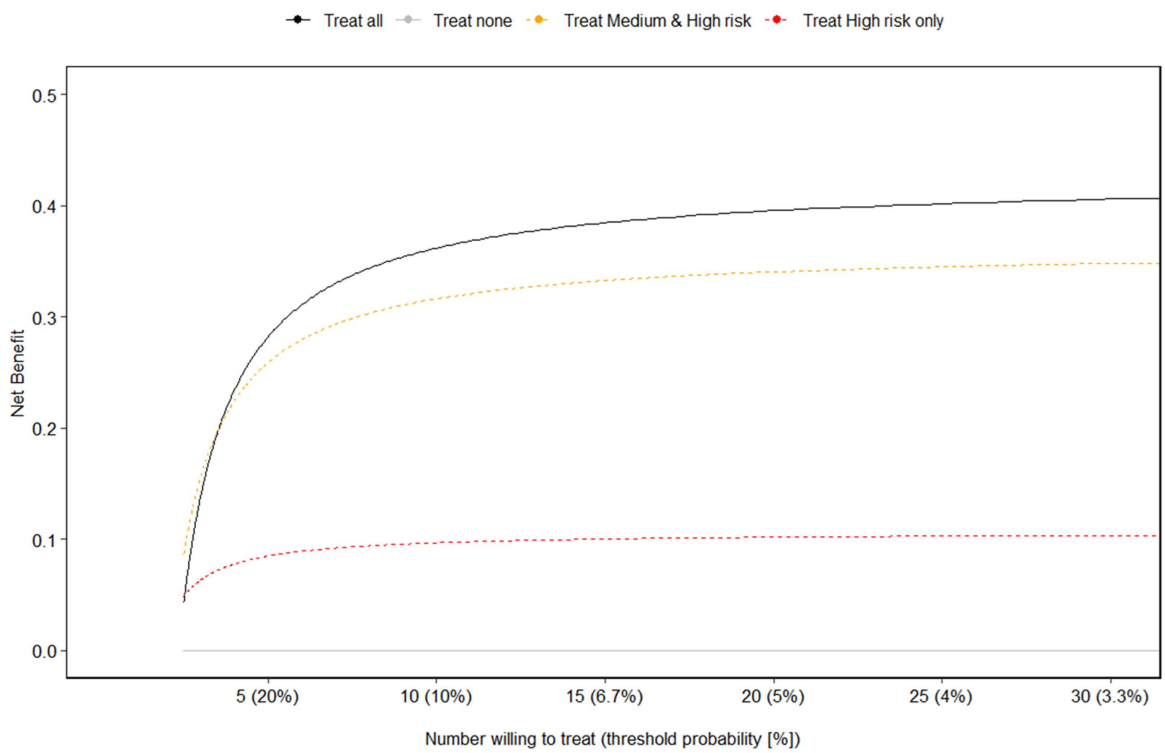


Fig 4. Decision curve analysis for basic prediction model, compared to a treat-all and a treat-none strategy.

https://doi.org/10.1371/journal.pgph.0004340.g004

Poor model performance may however also reflect the limitations of our study. For example, we only enrolled household contacts who were exposed to highly infectious TB index cases. Bacterial burden in the index case, most frequently categorized as smear positive and smear negative, is strongly associated with *Mtb* infection [40–42]. However, in this study TB index cases were only eligible if their sputum samples tested smear-positive or medium or high level Xpert MTB/Rif positive (which is equivalent to smear positive) meaning heterogeneity of bacterial burden in the index cases was limited. This limits our ability to generalize findings to lower bacterial burden categories (e.g., smear-negative or trace Xpert positive), which have also been shown to contribute to *Mtb* transmission.

In conclusion, our study provides valuable insights into the challenges of developing and or implementing predictive models for *Mtb* infection, ultimately aimed at identifying those most recently infected, in high burden settings characterized by intense community transmission. Use of individual and household predictors does not add significant benefit over the treat-all or treat-none strategies currently being the most implemented strategy in low resource settings.

Supporting infromation

S1 Table. Inclusion and Exclusion criteria for the ERASE-TB study.
(DOCX)

S2 Table. List of candidate predictors and how data was collected.
(DOCX)

S3 Table. Comprehensive model predictors.
(DOCX)

S1 Fig. Receiver Operating Characteristic curve: Complete cases of baseline IGRA and last available follow-up IGRA results.
(DOCX)

S1 Code. R code for sensitivity analysis using baseline complete cases.
(DOCX)

S2 Code. R code for calibration plot of basic prediction model.
(DOCX)

S1 Checklist. Implementation inclusivity questionnaire.
(DOCX)

Acknowledgements

We extend our heartfelt gratitude to the teams in the ERASE-TB consortium; from the Biomedical Research and Training Institute and the Zvitambo Research Institute in Zimbabwe, the Instituto Nacional de Saúde in Mozambique, the National Institute for Medical Research - Mbeya Medical Research Centre in Tanzania and the central coordination team from the University of Munich (LMU), whose exceptional efforts and contributions were instrumental in making this research possible.

Author contributions

Conceptualization: Edson Tawanda Marambire, Norbert Heinrich, Katharina Kranzer.

Data curation: Claire J. Calderwood, Leyla Larsson.

Formal analysis: Edson Tawanda Marambire.

Funding acquisition: Norbert Heinrich, Katharina Kranzer.

Investigation: Edson Tawanda Marambire, Lillian T Minja, Junior Mutsvangwa, Norbert Heinrich, Katharina Kranzer.

Methodology: Edson Tawanda Marambire, Claire J. Calderwood, Leyla Larsson, Kathrin Held, Palwasha Khan, Norbert Heinrich, Katharina Kranzer.

Project administration: Edson Tawanda Marambire, Denise Banze, Celina Nhamuave, Alfred Mfinanga, Celso Khosa.

Resources: Kathrin Held, Katharina Kranzer.

Supervision: Junior Mutsvangwa, Norbert Heinrich, Katharina Kranzer.

Validation: Rishi K Gupta, Katharina Kranzer.

Writing – original draft: Edson Tawanda Marambire.

Writing – review & editing: Claire J. Calderwood, Leyla Larsson, Kathrin Held, Palwasha Khan, Denise Banze, Celina Nhamuave, Lillian T Minja, Alfred Mfinanga, Rishi K Gupta, Celso Khosa, Junior Mutsvangwa, Norbert Heinrich, Katharina Kranzer.

References

1. World Health Organization (WHO). Global tuberculosis report 2022 [Internet]. [cited 2023 Mar 23]. Available from: https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022

2. Centres for Disease Control and Prevention (CDC). How TB Spreads | TB | CDC [Internet]. [cited 2023 Mar 23]. Available from: https://www.cdc.gov/tb/topic/basics/howtbspreads.htm
3. Houben RMGJ, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med. 2016;13(10):e1002152. https://doi.org/10.1371/journal.pmed.1002152 PMID: 27780211
4. Behr MA, Edelstein PH, Ramakrishnan L. Is Mycobacterium tuberculosis infection life long?. BMJ. 2019;367.
5. Emery JC, Richards AS, Dale KD, McQuaid CF, White RG, Denholm JT, et al. Self-clearance of Mycobacterium tuberculosis infection: implications for lifetime risk and population at-risk of tuberculosis disease. Proc. R. Soc. B. 2021;288(1954):20210345. https://doi.org/10.1098/rspb.2021.0345
6. Myers J, Bearman J, Botkins A. The natural history of tuberculosis in the human body. X. Prognosis among students with tuberculin reaction conversion before, during and after school of nursing. Dis Chest. 1968;53(6):687–98.
7. Harries AD, Kumar AMV, Satyanarayana S, Thekkur P, Lin Y, Dlodlo RA, et al. The growing importance of tuberculosis preventive therapy and how research and innovation can enhance its implementation on the ground. Trop Med Infect Dis. 2020;5(2):61. https://doi.org/10.3390/tropicalmed5020061 PMID: 32316300
8. Answers to Frequently Asked Questions on TB preventive treatment (TPT) associated with the 2020 WHO TPT guidance 1.
9. World Health Organization W. WHO policy on TB infection control in health-care facilities, congregate settings and households. 2009.
10. World Health Organization (WHO). Systematic screening for TB disease. World Health Organization (WHO); 2022.
11. World Health Organization W. Latent tuberculosis infection: Updated and consolidated guidelines for programmatic management. 2018.
12. World Health Organization. The end TB strategy for tuberculosis prevention, care and control after 2015a. 2014.
13. Swindells S, Ramchandani R, Gupta A, Benson CA, Leon-Cruz J, Mwelase N, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. N Engl J Med. 2019;380(11):1001–11. https://doi.org/10.1056/NEJMoa1806808 PMID: 30865794
14. Menzies NA, Shrestha S, Parriott A, Marks SM, Hill AN, Dowdy DW, et al. The health and economic benefits of tests that predict future progression to tuberculosis disease. Epidemiology. 2022;33(1):75–83. https://doi.org/10.1097/EDE.0000000000001418 PMID: 34669631
15. World Health Organization. New WHO recommendations to prevent tuberculosis aim to save millions of lives [Internet]. 2020 [cited 2023 Jun 2]. Available from: https://www.who.int/news/item/24-03-2020-new-who-recommendations-to-prevent-tuberculosis-aim-to-save-millions-of-lives
16. Bailey WC, Gerald LB, Kimerling ME, Redden D, Brook N, Bruce F, et al. Predictive model to identify positive tuberculosis skin test results during contact investigations. JAMA. 2002;287(8):996–1002. https://doi.org/10.1001/jama.287.8.996 PMID: 11866647
17. Aissa K, Madhi F, Ronsin N, Delarocque F, Lecuyer A, Decludt B, et al. Evaluation of a model for efficient screening of tuberculosis contact subjects. Am J Respir Crit Care Med. 2008;177(9):1041–7. https://doi.org/10.1164/rccm.200711-1756OC PMID: 18263798
18. Ma N, Zalwango S, Malone LL, Nsereko M, Wampande EM, Thiel BA, et al. Clinical and epidemiological characteristics of individuals resistant to M. tuberculosis infection in a longitudinal TB household contact study in Kampala, Uganda. BMC Infect Dis. 2014;14:352. https://doi.org/10.1186/1471-2334-14-352 PMID: 24970328
19. Acuña-Villaorduña C, Jones-López EC, Fregona G, Marques-Rodrigues P, Gaeddert M, Geadas C, et al. Intensity of exposure to pulmonary tuberculosis determines risk of tuberculosis infection and disease. Eur Respir J. 2018;51(1):1701578. https://doi.org/10.1183/13993003.01578-2017 PMID: 29348181
20. Collins G, Reitsma J, Altman D, Moons K. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD Statement. BMC Medicine. 2015;13(1):1–10. https://doi.org/10.1186/s12916-015-0468-4
21. Marambire ET, Banze D, Mfinanga A, Mutsvangwa J, Mbunda TD, Ntinginya NE, et al. Early risk assessment in paediatric and adult household contacts of confirmed tuberculosis cases by novel diagnostic tests (ERASE-TB): protocol for a prospective, non-interventional, longitudinal, multicountry cohort study. BMJ Open. 2022;12(7):e060985. https://doi.org/10.1136/bmjopen-2022-060985 PMID: 36427173

22. Lee S, Lee S, Kim Y, Cho Y, Jeong Y, Kim H, et al. Risk factors for latent tuberculosis infection in close contacts of active tuberculosis patients in South Korea: a prospective cohort study2014:1–7. https://doi.org/DOIHere

23. Faksri K, Reechaipichitkul W, Pimrin W, Bourpoern J. Transmission and risk factors for latent case-matched household contacts. 2015;46(3). https://doi.org/DOIorotheridentifier

24. Macpherson P, Lebina L, Motsomi K, Bosch Z, Milovanovic M, Ratsela A. Prevalence and risk factors for latent tuberculosis infection among household contacts of index cases in two South African provinces: Analysis of baseline data from a. 2020;725:1–14. https://doi.org/DOIHere

25. Ncayiyana JR, Bassett J, West N, Westreich D, Musenge E, Emch M, et al. Prevalence of latent tuberculosis infection and predictive factors in an urban informal settlement in Johannesburg, South Africa: a cross-sectional study. BMC Infect Dis. 2016;16(1):661. https://doi.org/10.1186/s12879-016-1989-x PMID: 27825307

26. Aman A, Zeidan Z. Latent tuberculosis infection among household contacts of pulmonary tuberculosis cases in Central State, Sudan: Prevalence and associated factors. 2017: 265–75.

27. Rathi SK, Akhtar S, Rahbar MH, Azam SI. Prevalence and risk factors associated with tuberculin skin test positivity among household contacts of smear-positive pulnionary tuberculosis cases in Umerkot, Pakistan. Int J Tuberc Lung Dis. 2002;6(10):851–7. PMID: 12365570

28. Al-Kayali R, Almekhlef A, Khouri A. Risk factors for latent tuberculosis infection in close contacts. Eur. J. Pharm. Sci. 2018;5(8):124–8.

29. Krishnamoorthy Y, Ezhumalai K, Murali S, Jose M, Sathishkumar A, Soundappan G, et al. Prevalence and risk factors associated with latent tuberculosis infection among household contacts of smear positive pulmonary tuberculosis patients in South India. 2021:1645–51.

30. Cubilla-Batista I, Ruiz N, Sambrano D, Castillo J, de Quinzada MO, Gasteluiturri B, et al. Overweight, obesity, and older age favor latent tuberculosis infection among household contacts in low tuberculosis-incidence settings within panama. Am J Trop Med Hyg. 2019;100(5):1141–4. https://doi.org/10.4269/ajtmh.18-0927 PMID: 30915957

31. Bekken G, Ritz C, Selvam S, Jesuraj N, Hesseling A, Doherty T. Identification of subclinical tuberculosis in household contacts using exposure scores and contact investigations. BMC Infect Dis. 2020;20(1):1–11. https://doi.org/10.1186/s12879-020-04856-5

32. Body mass index (BMI) [Internet]. [cited 2025 Jan 9]. Available from: https://www.who.int/data/gho/data/themes/topics/topic-details/GHO/body-mass-index?form=MG0AV3

33. UN-HABITAT. THE CHALLENGE OF SLUMS. 2003.

34. World Health Organization (WHO). Tuberculosis research [Internet]. [cited 2024 Oct 15]. Available from: https://tdr.who.int/tuberculosis-research?form=MG0AV3

35. Middelkoop K, Bekker L-G, Morrow C, Lee N, Wood R. Decreasing household contribution to TB transmission with age: a retrospective geographic analysis of young people in a South African township. BMC Infect Dis. 2014;14:221. https://doi.org/10.1186/1471-2334-14-221 PMID: 24758715

36. Pan D, Lin M, Lan R, Graviss EA, Lin D, Liang D, et al. Tuberculosis transmission in households and classrooms of adolescent cases compared to the community in China. Int J Environ Res Public Health. 2018;15(12):2803. https://doi.org/10.3390/ijerph15122803 PMID: 30544676

37. Martinez L, Lo N, Cords O, Hill P, Khan P, Hatherill M, et al. Paediatric tuberculosis transmission outside the household: challenging historical paradigms to inform future public health strategies. Lancet Respir Med. 2019;7(6):544.

38. Huang C-C, Tchetgen ET, Becerra MC, Cohen T, Hughes KC, Zhang Z, et al. The effect of HIV-related immunosuppression on the risk of tuberculosis transmission to household contacts. Clin Infect Dis. 2014;58(6):765–74. https://doi.org/10.1093/cid/cit948 PMID: 24368620

39. Diel R, Loddenkemper R, Nienhaus A. Predictive value of interferon-γ release assays and tuberculin skin testing for progression from latent TB infection to disease state: a meta-analysis. Chest. 2012;142(1):63–75. https://doi.org/10.1378/chest.11-3157 PMID: 22490872

40. Tostmann A, Kik SV, Kalisvaart NA, Sebek MM, Verver S, Boeree MJ. Tuberculosis transmission by patients with smear-negative pulmonary tuberculosis in a large cohort in the Netherlands. Clin Infect Dis. 2008;47(9):1135–42.

41. Asadi L, Croxen M, Heffernan C, Dhillon M, Paulsen C, Egedahl ML, et al. How much do smear-negative patients really contribute to tuberculosis transmissions? Re-examining an old question with new tools. EClinicalMedicine. 2022;43:101250. https://doi.org/10.1016/j.eclinm.2021.101250 PMID: 35036885

42. Médecins Sans Frontières. TB Transmission | MSF Medical Guidelines [Internet]. 2024 [cited 2024 Mar 5]. Available from: https://medicalguidelines.msf.org/en/viewport/TUB/english/1-2-transmission-20320178.html

Appendix A: Paper C

Impact of HIV and ART status of persons with tuberculosis on household *Mtb* transmission in high tuberculosis incidence settings.

Impact of HIV and ART status of persons with TB on household Mtb transmission in high TB incidence settings

Authors:

Edson Tawanda Marambire[1,2*], Claire J. Calderwood[1,3], Leyla Larsson[4], Akanksha Mimi Malhotra[1,5], Karlos Madziva[1], Fredrick Mbiba[1], Denise Banze[2,6], Celina Nhamuave[6], Lillian T Minja[7], Alfred Mfinanga[2,7], Celso Khosa[5,7], Gunilla Kallenius[8], Christopher Sundling[8], Fungai Kavenga[9], Kathrin Held[4,10,11,12], Junior Mutsvangwa[13], Norbert Heinrich[4,10,11], Palwasha Khan[3], Katharina Kranzer[1,3,4]

Affiliations

[1] The Health Research Unit Zimbabwe, Biomedical Research and Training Institute, Harare, Zimbabwe

[2] CIH[LMU] Center for International Health, University Hospital, LMU Munich, Germany

[3] Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK

[4] Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU Munich, Munich, Germany

[5] Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

[6] Instituto Nacional de Saúde, Marracuene, Mozambique

[7] National Institute for Medical Research - Mbeya Medical Research Centre, Mbeya, Tanzania

[8] Division of Infectious Diseases, Department of Medicine Solna, Center for Molecular Medicine, Karolinska Institutet, Stockholm, Sweden

[9] National TB programme, AIDs and TB unit, Ministry of Health and Child Care, Harare, Zimbabwe

[10] German Center for Infection Research (DZIF), Partner Site Munich, Munich, Germany

[11] Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Immunology, Infection and Pandemic Research, Munich, Germany

[12] Unit Global Health, Helmholtz Zentrum München, German Research Centre for Environmental Health (HMGU), Neuherberg, Germany.

[13] Biomedical Research and Training Institute, Harare, Zimbabwe

*Corresponding author:

Edson Tawanda Marambire

Address: 8 Ross Avenue, Belgravia, Harare, Zimbabwe

E-mail: Edson.Marambire@lrz.uni-muenchen.de

Phone: +263772286311

Running head

HIV/ART impact on Household *Mtb* transmission

Word count of abstract: 200

Word count of text (manuscript): 2067

Number of references: 26

Number of tables: 2

Number of figures: 2

Keywords: household contacts; bacterial burden; *Mtb*-risk; Southern Africa

ABSTRACT

Background:

Understanding the impact of HIV and antiretroviral therapy (ART) status on Mycobacterium tuberculosis (Mtb) transmission dynamics is crucial, particularly in the context of universal ART access.

Methods:

This cross-sectional analysis included adults with microbiologically confirmed pulmonary tuberculosis (medium/high Xpert MTB/Rif) and their household contacts (≥10 years) from Mozambique, Zimbabwe, and Tanzania (2021–2023). Mixed effects logistic regression assessed associations between tuberculosis patients' HIV/ART status and household IGRA positivity.

Results:

A total of 1,923 household contacts of 907 persons with TB were analysed. A third of persons with TB were diagnosed with HIV at the time of TB diagnosis. Overall, 46% of household contacts were IGRA-positive at baseline. Household contacts exposed to persons living with HIV but not on ART had significantly lower odds of IGRA positivity (adjusted odds ratio 0.46; 95% CI: 0.30–0.73) compared to those exposed to HIV-negative persons while there was no evidence of difference in transmission risk to household contacts between ART-treated and HIV-negative individuals.

Discussion:

In a selected population of people with TB with a medium to high bacillary burden measured by Xpert MTB/Rif, people living with HIV while not on ART exhibited reduced *Mtb* transmission, potentially reflecting differences in infectiousness duration and health-seeking behaviours.

Tuberculosis (TB) is a significant global health threat affecting over 10 million people each year.[1] In the early 2000s, TB incidence rapidly increased across southern Africa as a result of rising HIV prevalence.[2,3] More recently, the wide availability of antiretroviral therapy (ART) has led to a change in TB epidemiology, reducing TB incidence in the region by 36% between 2010 and 2022.[4,5] Although many Southern African countries have achieved the UNAIDS 90-90-90 targets,[6] the impact of high ART coverage on *Mtb* transmission is unknown.

Prior to the availability of ART, people living with HIV (PLHIV) who developed pulmonary TB were found to be less likely to transmit *Mycobacterium tuberculosis (Mtb)* to their household contacts. [7–9] Proposed mechanisms for reduced transmissibility included substantial immunosuppression resulting in paucibacillary disease and reduced duration of infectiousness through rapid development of symptoms, leading to seeking of healthcare and treatment or a higher risk of early demise without treatment.

This study aims to understand how HIV and ART status of a person with TB (PWTB) impacts household *Mtb* transmission in high TB incidence settings.

METHODS

Study design and population

This study used data from the Early Risk Assessment in TB contacts by new diagnostic Tests cohort study (ERASE-TB), a multi-country observational cohort study that was conducted in Maputo (Mozambique), Mbeya (Tanzania), and Harare (Zimbabwe).[10] Between March 2021 and 2023, ERASE-TB enrolled adults (≥18 years) with microbiologically confirmed pulmonary TB and high bacterial load (at least +1 positive smear and/or high/medium positive Xpert MTB/Rif) and their household contacts (aged ≥10 years) across three sites.

Enrolled household contacts were followed up every six months for a maximum of 24 months and underwent WHO four-symptom screen[11] and chest X-ray, followed by Xpert MTB/Rif Ultra if either was suggestive of TB at each visit. All household contacts were offered HIV testing if not already known to be living with HIV. Interferon-gamma release assays (IGRA; STANDARD^{TM} F TB-Feron FIA [IFN-gamma; SD Biosensor, Republic of Korea]) were also conducted at baseline and endline visit (depending on the availability of reagents) or at any follow up visit if not done at baseline. All PWTB had sputum samples collected for culture. Individual- and household-level questionnaires were administered to PWTB and household contacts to determine risk factors associated with *Mtb* transmission.

Statistical analysis

Univariable and multivariable mixed effects logistic regression models were used in R version 4.3 to investigate the effect of PWTB HIV/ART status on risk of *Mtb* transmission to household contacts. Adjustment sets were informed by existing scientific knowledge (**Figure 1**). Household contacts with missing or indeterminate baseline IGRA results were inferred using the next available IGRA results. Individuals who remained with overall missing or indeterminate IGRA results were excluded. Household contacts who tested IGRA positive at the six-month visit after a negative baseline result were considered IGRA positive, as well as those diagnosed with TB at baseline assuming they were infected with *Mtb* prior to developing TB. The explanatory variable of interest was HIV/ART status of the PWTB at the time of TB diagnosis, categorized as negative, positive and on ART, positive and not on ART, and unknown.

A sensitivity analysis was performed, restricting the analysis to household contacts aged 10-19 years to reduce misclassification due to past *Mtb* infection.

Ethical considerations

Informed written consent, or guardian consent and individual assent for people under the age of 18, was obtained from all participants. Ethical approval was granted by all relevant institutions: the Medical Research Council in Zimbabwe (MRCZ/A/2618), the National Health Research Ethics Committee in Tanzania (TMDA-WEB0021/CTR/0004/03), the National Bioethics Committee for Health in Mozambique (541/CNBS/21), and the ethical committees of London School of Hygiene & Tropical Medicine, United Kingdom (22522–2) and the medical faculty of the Ludwig-Maximilians-Universität München, Germany (20–0771).

RESULTS

The analysis included 1,923 household contacts and 907 PWTB **(Figure 1:** study flowchart**)**. 275 index PWTB (30%) were PLHIV of whom 94 (34%) were not on ART. **(Table 1)**. 186 household contacts were excluded from the analysis because of missing IGRA results. Household contacts were predominantly female (61%) and adults aged >19 years (77%).

Time to culture positivity appeared shorter in PWTB who were HIV negative (median 10.7 days, interquartile range [IQR] 6-19 days) and PLHIV on ART (median 12.9 days, IQR 7-21 days respectively), versus PLHIV not yet on ART (median 14.6 days, IQR 8-25 days) (**Figure S1**). 56% of HIV negative PWTB had 'high' semiquantitative Xpert MTB/Rif results, compared to 51% of PLHIV not on ART**.** Reported symptom duration before TB treatment was similar across HIV status categories.

Overall, 46.1% (887/1923) of household contacts were IGRA positive at baseline. Of those, 7.2% (n=64) were categorized as IGRA positive based on a positive IGRA test result at six months despite a baseline negative test and 2.6% (n=23) were diagnosed with TB at baseline.

Household contacts most likely to have a positive IGRA were those exposed to PWTB who were either HIV negative (49%) or with unknown HIV status (48%). The lowest proportion of IGRA positivity was seen among household contacts of a PLHIV prior to ART initiation (32%).

The univariable odds of IGRA positivity among household contacts exposed to PWTB who were HIV positive and not on ART was 55% lower compared to those contacts exposed to PWTB who were HIV negative (odds ratio (OR) 0.45: 95% CI 0.30-0.69). Adjusting for country, household contact characteristics (age, sex, HIV status, exposure intensity, previous exposure to TB, previous TB treatment) and PWTB (age, sex) characteristics did not change the effect estimate (adjusted OR [aOR] 0.45, 95% CI 0.29-0.69). Adjusting for variables assumed to be on the causal pathway namely bacterial burden (Xpert semi-quantitative measure medium or high) and symptom duration did not change the effect estimate (aOR 0.46, 95% CI 0.30-0.73). Sensitivity analysis restricted to adolescents (aged $\leq$ 19 years) showed similar results (aOR 0.43, 95% CI 0.20-0.96) **(Table 2)**.

DISCUSSION

In this study, we used prevalence of *Mtb* immunoreactivity, defined as prevalence of IGRA positivity in household contacts as a proxy measure of household transmission from the index PWTB. IGRA positivity was higher in household contacts exposed to HIV negative PWTB compared to household contacts living with a PWTB newly diagnosed with HIV and not yet on ART, suggesting reduced transmission in the latter group. This association persisted after controlling for symptom duration and bacterial burden.

Mtb transmission is multifactorial, driven by infectiousness of the PWTB, duration of exposure, and intensity of contact. Environmental factors such as crowding and ventilation also play an important role (**Figure 2)**.[16] Most *Mtb* transmission studies use the immune response to TB antigens measured by skin tests or IGRAs, as a proxy for transmission,[12] although the tests cannot distinguish between recent and past infections and false negative test results occur especially in people with immunosuppression ((e.g. malnutrition, HIV, and diabetes).[13,14]

Prior to the wide availability of ART, HIV-associated TB was characterized by paucibacillary disease and atypical presentations, including disseminated disease and infiltrates on chest x-rays, particularly in individuals with advanced immune suppression.[7–9,15,16] These features were thought to contribute to reduced *Mtb* transmission from people co-infected with TB/HIV. However, increasing ART coverage and earlier treatment initiation have resulted in lower proportions of PLHIV presenting severely immune suppressed and as a result TB disease presentations now resemble those of HIV negatives.[17,18] Despite these shifts, our findings suggest that PWTB who are PLHIV and not on ART have lower transmission risk compared to both HIV-negative individuals and PLHIV on ART. This is noteworthy given the well-performing HIV programmes across all three countries,[19–21] and the fact that our study exclusively included individuals with microbiologically confirmed pulmonary TB and medium/high Xpert MTB/Rif positivity, comparable to smear-positive disease.[22] This association persisted after controlling for confounding. The effect estimates also did not change in the sensitivity analysis focused on adolescent household contacts only.

Possible explanations for the reduced transmission risk are differences in bacterial burden and duration of infectiousness. To further explore the effect of HIV/ART status

on risk of transmission to household contacts, we adjusted for level of Xpert MTB/Rif positivity and symptom duration as proxies for bacterial burden and duration of infectiousness. However, this adjustment did not alter the effect estimates inviting the question about other factor or mechanisms which may explain the reduced transmission risk. Importantly, duration of symptoms which is crudely approximated by self-reported symptom duration is prone to reporting bias[23,24] and further limited by increasing evidence that timing of symptoms and infectiousness do not necessarily correlate.[25] This highlights the complexity of accurately measuring and adjusting for factors contributing to *Mtb* transmission in this population.

We, therefore, hypothesise that PLHIV who are not on ART progress to symptomatic smear-positive TB disease more rapidly, potentially limiting their duration of infectiousness compared to those who are HIV negative or HIV positive and on ART. The latter may experience an undulating course of disease with periods of intermittent infectiousness with or without symptoms. A formal counterfactual causal mediation analysis approach would be needed to delineate and quantify the role of underlying mechanisms of household transmission.

Despite the wide-spread availability of free of charge HIV testing and ART services, our study also revealed that 30% of PLHIV with TB were previously undiagnosed with HIV. This proportion is higher than the average population estimates of 72%, 82% and 87% for Mozambique, Tanzania and Zimbabwe respectively,[19–21] indicating that access to HIV testing is not equitable. The proportion of undiagnosed HIV among PWTB in this study is likely underestimated as we only enrolled people with medium/high Xpert MTB/Rif TB. It is likely that the proportion of undiagnosed HIV is much higher in those presenting with paucibacillary TB who were not included in this study. Importantly HIV diagnosis and ART initiation may have prevented the TB episode in those presenting with HIV/TB co-infected not on ART. In addition, engagement in ART care would have provided an opportunity to offer TB preventive therapy.

Strengths of this study include a large and diverse sample size across three African countries and the ability to adjust for multiple confounders. Availability of household contact HIV data allowed us to account for a critical factor influencing susceptibility to *Mtb* infection, given its potential impact on IGRA positivity. This comprehensive

adjustment enhances the robustness of our findings. Limitations include potential selection bias because of the ERASE-TB eligibility criteria aimed to only include highly infectious PWTB and outcome misclassification due to inclusion of all aged > 9 years. However, sensitivity analyses restricted to adolescents corroborated the findings.

This study suggests that PLHIV who are not on ART are less likely to transmit *Mtb* despite similar bacterial loads at time of diagnosis to PLHIV on ART with TB and HIV negative PWTB, potentially reflecting shorter duration of infectiousness. These differences may stem from biological factors (immunosuppression), behavioural factors (health-seeking behaviour), or structural barriers (access to healthcare). Importantly, a large proportion of PLHIV diagnosed with TB are not on ART at the time of TB diagnosis highlighting the need for improved access to HIV diagnosis and treatment.

ACKNOWLEDGEMENTS

While this publication was produced in the framework of the ERASE-TB project, which is part of the EDCTP2 programme, views and opinions of authors expressed herein do not necessarily state or reflect those of EDCTP. We additionally thank the Biomedical Research and Training Institute and the Zvitambo Research Institute, Zimbabwe; the Instituto Nacional de Saúde, Mozambique; and the National Institute for Medical Research - Mbeya Medical Research Centre, Tanzania, for their expertise and contributions, along with all the study participants without whom this study would not have been possible.

Funding

ERASE-TB project is part of the EDCTP2 programme supported by the European Union (grant number RIA2018D-2508 ERASE-TB). Further funding is contributed by the German Center for Infection Research (DZIF) grant number: 02.710. CJC is funded by Wellcome Trust (203905/Z/16/Z).

Author contribution

The data analysis and initial manuscript drafting were led by ETM, with significant scientific guidance from KK and data analysis support from PK. KK, PK, LL, and CJC critically reviewed the manuscript, providing valuable feedback and insights. NH, JM, CK, CN, AM, LM, and KM contributed by ensuring the accuracy of site-specific data and providing contextual clarifications. Technical support was provided by KH, GK, CS, FK, and TA. All authors reviewed and approved the final version of the manuscript.

Conflicts of interest

The authors declare no conflicts of interest

Data availability

Data to replicate this analysis will be made available at the time of publication.

REFERENCES

1. World Health Organisation (WHO). *2024 Global Tuberculosis Report*.; 2024.

2. World Health Organization Regional Office for Africa. *Tuberculosis in the WHO African Region: 2023 Progress Update*.; 2023. Accessed October 8, 2024. https://www.afro.who.int/sites/default/files/2023-09/Tuberculosis%20in%20the%20African%20Region_2023%20report.pdf

3. Olivier C, Luies L. WHO Goals and Beyond: Managing HIV/TB Co-infection in South Africa. *SN Compr Clin Med*. 2023;5:251. doi:10.1007/s42399-023-01568-z

4. World Health Organization (WHO). *Global Tuberculosis Report 2023*.; 2023. https://iris.who.int/.

5. Dodd PJ, Knight GM, Lawn SD, Corbett EL, White RG. Predicting the Long-Term Impact of Antiretroviral Therapy Scale-Up on Population Incidence of Tuberculosis. *PLoS One*. 2013;8(9):e75466. doi:10.1371/JOURNAL.PONE.0075466

6. UNAIDS. New report from UNAIDS shows that AIDS can be ended by 2030 and outlines the path to get there | UNAIDS. Accessed August 6, 2024. https://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2023/july/unaids-global-aids-update

7. Hayes RJ, Halwiindi B, Luo N, et al. The impact of HIV on infectiousness of pulmonary tuberculosis a community study in Zambia Alison M. Elliott. *AIDS*. 1993;7(7). https://journals.lww.com/aidsonline/fulltext/1993/07000/the_impact_of_hiv_on_infectiousness_of_pulmonary.12.aspx

8. Huang CC, Tchetgen ET, Becerra MC, et al. The Effect of HIV-Related Immunosuppression on the Risk of Tuberculosis Transmission to Household Contacts. *Clin Infect Dis*. 2014;58(6):765. doi:10.1093/CID/CIT948

9. Carvalho ACC, Deriemer K, Nunes ZB, et al. Transmission of Mycobacterium tuberculosis to Contacts of HIV-infected Tuberculosis Patients. *https://doi.org/101164/ajrccm164122103078*. 2012;164(12):2166-2171. doi:10.1164/AJRCCM.164.12.2103078

10. Marambire ET, Banze D, Mfinanga A, et al. Early risk assessment in paediatric and adult household contacts of confirmed tuberculosis cases by novel diagnostic tests (ERASE-TB): protocol for a prospective, non-interventional, longitudinal, multicountry cohort study. Shepherd A Bruchfeld J, Sundling C, Sandy C, Mugava M, Bandason T, Chipinduro M, Mutasa K, Rukobo S, Sudi L, Haule A, Sichone E, Qwaray P, Mtafya B, Mwambola H, Minja L, Sabi I, Edwin P, Ngalison D, Luswema S, Olomi W, Pamba D, Mwanyonga S, Nhamuave C, M DHM, Consortium ET, eds. *BMJ Open*. 2022;12(7):e060985. doi:https://dx.doi.org/10.1136/bmjopen-2022-060985

11. 5.2.1 WHO-recommended four-symptom screen | TB Knowledge Sharing. Accessed December 4, 2024. https://tbksp.who.int/en/node/1421

12. de Martino M, Lodi L, Galli L, Chiappini E. Immune Response to Mycobacterium tuberculosis: A Narrative Review. *Front Pediatr*. 2019;7:464617. doi:10.3389/FPED.2019.00350/BIBTEX

13. Michelsen SW, Soborg B, Dlaz LJ, et al. The dynamics of immune responses to Mycobacterium tuberculosis during different stages of natural infection: A longitudinal study among Greenlanders. *PLoS One*. 2017;12(6):e0177906. doi:10.1371/JOURNAL.PONE.0177906

14. CDC. Clinical Testing Guidance for Tuberculosis: Tuberculin Skin Test | Tuberculosis (TB) | CDC. Accessed December 15, 2024. https://www.cdc.gov/tb/hcp/testing-diagnosis/tuberculin-skin-test.html?form=MG0AV3

15. Cruciani M, Malena M, Bosco O, Giorgio G, Serpelloni G. The impact of human immunodeficiency virus type 1 on infectiousness of tuberculosis: A meta-analysis. *Clinical Infectious Diseases*. 2001;33(11):1922-1930. doi:10.1086/324352/2/M_33-11-1922-TBL001.GIF

16. Espinal MA, Peréz EN, Baéz J, et al. Infectiousness of Mycobacterium tuberculosis in HIV-1-infected patients with tuberculosis: A prospective study. *Lancet*. 2000;355(9200):275-280. doi:10.1016/S0140-6736(99)04402-5

17. European AIDS Clinical Society. ART: TB/HIV Co-infection — EACS Guidelines. 2024. Accessed December 15, 2024. https://eacs.sanfordguide.com/eacs-part1/art/eacs-art-tb-hiv-co-infection?form=MG0AV3

18. Nachiappan AC, Rahbar K, Shi X, et al. Pulmonary tuberculosis: Role of radiology in diagnosis and management. *Radiographics*. 2017;37(1):52-72. doi:10.1148/rg.2017160032

19. Population-based HIV Impact Assessment (PHIA). Mozambique Final Report 2021 (En, Port) - PHIA Project. 2021. Accessed December 2, 2024. https://phia.icap.columbia.edu/mozambique-final-report-2021-en-port/

20. Population-based HIV Impact Assessment (PHIA). Release of Tanzania Population-based HIV Impact Assessment Data Shows Notable Progress, and Identifies Gaps that Stand in the Way of Epidemic Control - PHIA Project. 2022. Accessed December 2, 2024. https://phia.icap.columbia.edu/release-of-tanzania-population-based-hiv-impact-assessment-data-shows-notable-progress-and-identifies-gaps-that-stand-in-the-way-of-epidemic-control/

21. ZIMBABWE Ministry of Health and Child Care. ZIMBABWE POPULATION-BASED HIV IMPACT ASSESSMENT ZIMPHIA 2020 KEY FINDINGS. Published online 2020. Accessed September 3, 2021. https://phia.icap.columbia.edu/wp-content/uploads/2020/11/ZIMPHIA-2020-Summary-Sheet_Web.pdf

22. Lange B, Khan P, Kalmambetova G, et al. Diagnostic accuracy of the Xpert® MTB/RIF cycle threshold level to predict smear positivity: a meta-analysis. *Int J Tuberc Lung Dis*. 2017;21(5):493-502. doi:10.5588/IJTLD.16.0702

23. Tedla K, Medhin G, Berhe G, Mulugeta A, Berhe N. Delay in treatment initiation and its association with clinical severity and infectiousness among new adult pulmonary tuberculosis patients in Tigray, northern Ethiopia. *BMC Infect Dis*. 2020;20(1):1-10. doi:10.1186/S12879-020-05191-4/TABLES/4

24. Sathar F, Charalambous S, Velen K, et al. Health-seeking behaviour and patient-related factors associated with the time to TB treatment initiation in four African countries: a cross-sectional survey. *BMJ Public Health*. 2024;2(2):e001002. doi:10.1136/bmjph-2024-001002

25. Ku CC, MacPherson P, Khundi ME, et al. Durations of asymptomatic, symptomatic, and care-seeking phases of tuberculosis disease with a Bayesian analysis of prevalence survey and notification data. *BMC Med*. 2021;19(1):1-13. doi:10.1186/S12916-021-02128-9/TABLES/3

26. UN-HABITAT. *THE CHALLENGE OF SLUMS*.; 2003.

Figure Legends

Figure 1: Flow diagram illustrating participants recruited and selected for analysis from the ERASE-TB study

Abbreviations

TB: Tuberculosis

IGRA: Interferon Gamma Release Assay

Figure 2: Conceptual framework for household Mtb transmission

Abbreviations

HIV+: Living with HIV

TB: Tuberculosis

ART: Antiretroviral therapy

Table 1: Index and household-level demographic data of people diagnosed with TB

		Total	HIV status of the person with TB			
Person diagnosed with TB		**N=907**	**Negative N=568 (63%)**	**Positive, not on ART N=94 (10%)**	**Positive, on ART N=181 (20%)**	**Unknown N=64 (7.1%)**
Country, N (%)	Zimbabwe	314 (35%)	187 (33%)	42 (45%)	65 (36%)	20 (31%)
	Mozambique	288 (32%)	184 (32%)	26 (28%)	63 (35%)	15 (23%)
	Tanzania	305 (34%)	197 (35%)	26 (28%)	53 (29%)	29 (45%)
Men, N (%)		621 (68%)	397 (70%)	63 (67%)	116 (64%)	45 (70%)
Age, years, median (IQR)		36 (28-45)	34 (26-44)	37 (32-42)	39 (33-46)	36 (26-47)
Household crowding*		185 (20%)	113 (20%)	19 (20%)	42 (23%)	11 (17%)
Xpert MTB/Rif Ultra semiquantitative N (%)	Medium	400 (44%)	247 (44%)	46 (49%)	78 (43%)	29 (45%)
	High	507 (56%)	321 (56%)	48 (51%)	103 (57%)	35 (55%)
Days to culture positive liquid culture, medium (IQR)		11.7 (7-20)	10.7 (6-19)	14.6 (8-25)	12.9 (7-21)	11 (5-18)
Duration of symptoms, days, medium (IQR)		60 (30-90)	60 (30-120)	33 (23-90)	60 (30-90)	60 (30-90)
Household contacts		**N=1923#**	**N=1208 (63%)**	**N=169 (8.8%)**	**N=398 (21%)**	**N=148 (7.7%)**
Country, N (%)	Zimbabwe	686 (36%)	398 (33%)	71 (42%)	154 (39%)	63 (42%)
	Mozambique	611 (32%)	416 (34%)	51 (30%)	118 (30%)	26 (18%)
	Tanzania	626 (33%)	394 (33%)	47 (29%)	126 (32%)	59 (40%)
Men, N (%)		725 (38%)	477 (39%)	58 (34%)	141 (35%)	49 (33%)
Age, years, medium (IQR)		27 (17-42)	26 (17-42)	29 (17-38)	26 (16-41)	28 (17-40)
HIV status	Negative	1620 (84%)	1083 (90%)	124 (73%)	297 (74%)	116 (78%)
	Known positive	297 (15%)	121 (10%)	44 (26%)	100 (25%)	32 (22%)
	Newly positive	6 (0.3%)	4 (0.3%)	1 (0.6%)	1 (0.3%)	0 (0.0%)
Previous history of exposure to TB		84 (4.4%)	43 (3.6%)	7 (4.1%)	15 (3.8%)	19 (13%)
Past TB		118 (6.1%)	83 (6.9%)	6 (3.6%)	20 (5.0%)	9 (6.1%)
Spouse of the person with TB, N (%)		337 (19%)	219 (18%)	35 (21%)	62 (15.6%)	21 (14%)
Sleeps in the same room as the person with TB, N (%)		565 (29%)	351 (29%)	56 (33%)	117 (29%)	41 (28%)
Directly cared for the person with TB, N (%)		801 (42%)	502 (42%)	78 (46%)	158 (40%)	63 (43%)
IGRA positive, N (%)		887 (46%)	586 (49%)	54 (32%)	176 (44%)	71 (48%)

* As per United Nations definition (≥3 people per room)[26]

186 household contacts with missing IGRA result or not TB incident and were excluded from analysis

Table 2: Odds ratios of household contact being IGRA positive

	Odds ratio (95% confidence intervals)					
			Multivariable models			
			Model 1		Model 2	
Index HIV status	Crude unadjusted N = 1923	Adjusted for clustering only[1] N = 1923	Adjusted[2] N=1923	Adjusted random effect[2], Restricted to contacts aged 10-19 years N= 626	Adjusted random effect[3] N=1923	Adjusted random effect[3], Restricted to contacts aged 10-19 years N=626
Index HIV– (Reference)	1	1	1	1	1	1
Index HIV+, not on ART	0.50 (0.35-0.70)	0.45 (0.30-0.69)	0.45 (0.29-0.69)	0.40 (0.18-0.90)	0.46 (0.30-0.73)	0.43 (0.20-0.96)
Index HIV+, on ART	0.84 (0.67-1.06)	0.85 (0.64-1.14)	0.89 (0.66-1.20)	0.70 (0.42-1.17)	0.91 (0.67-1.24)	0.74 (0.45-1.23)
Index HIV status unknown	0.97 (0.70-1.38)	0.91 (0.58-1.43)	0.83 (0.52-1.31)	0.69 (0.30-1.55)	0.83 (0.52-1.33)	0.73 (0.33-1.63)

[1]Random effects model used to account for household clustering, [2]adjusted for country, household contact (age, sex, caregiver role, sleeping room sharing, other history of exposure to TB, history of TB treatment) and person with TB (age, sex) variable, [3] adjusted for country, household contact (age, sex, caregiver role, sleeping room sharing, other history of exposure to TB, history of TB treatment) and person with TB (age, sex, Gene Xpert positivity, duration of symptoms) variables

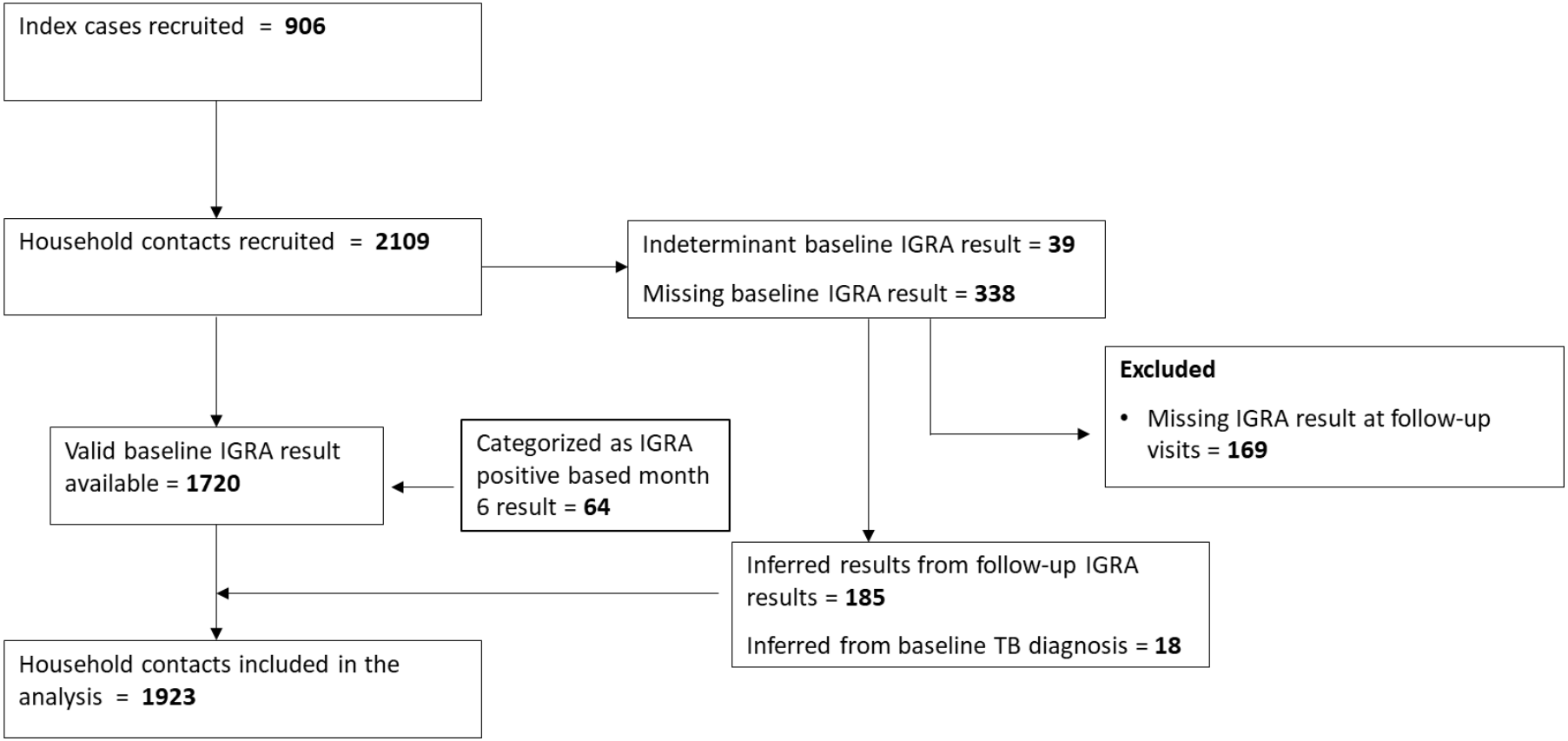
Abbreviations

HIV+ = HIV positive

ART = Antiretroviral therapy

TTP = Time to culture positive

Figure 1: Flow diagram illustrating participants recruited and selected for analysis from the ERASE-TB study

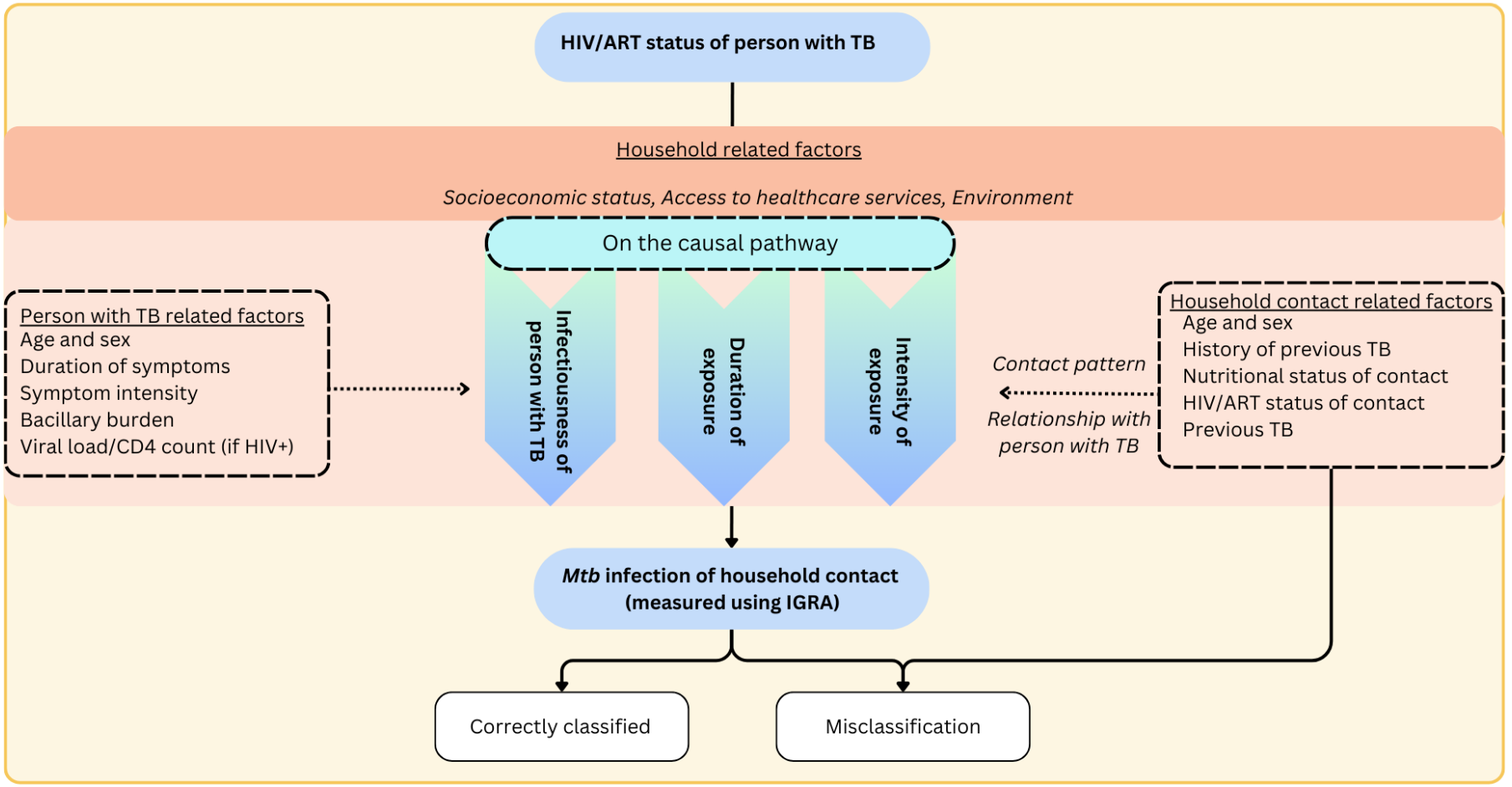


Abbreviations

TB: Tuberculosis

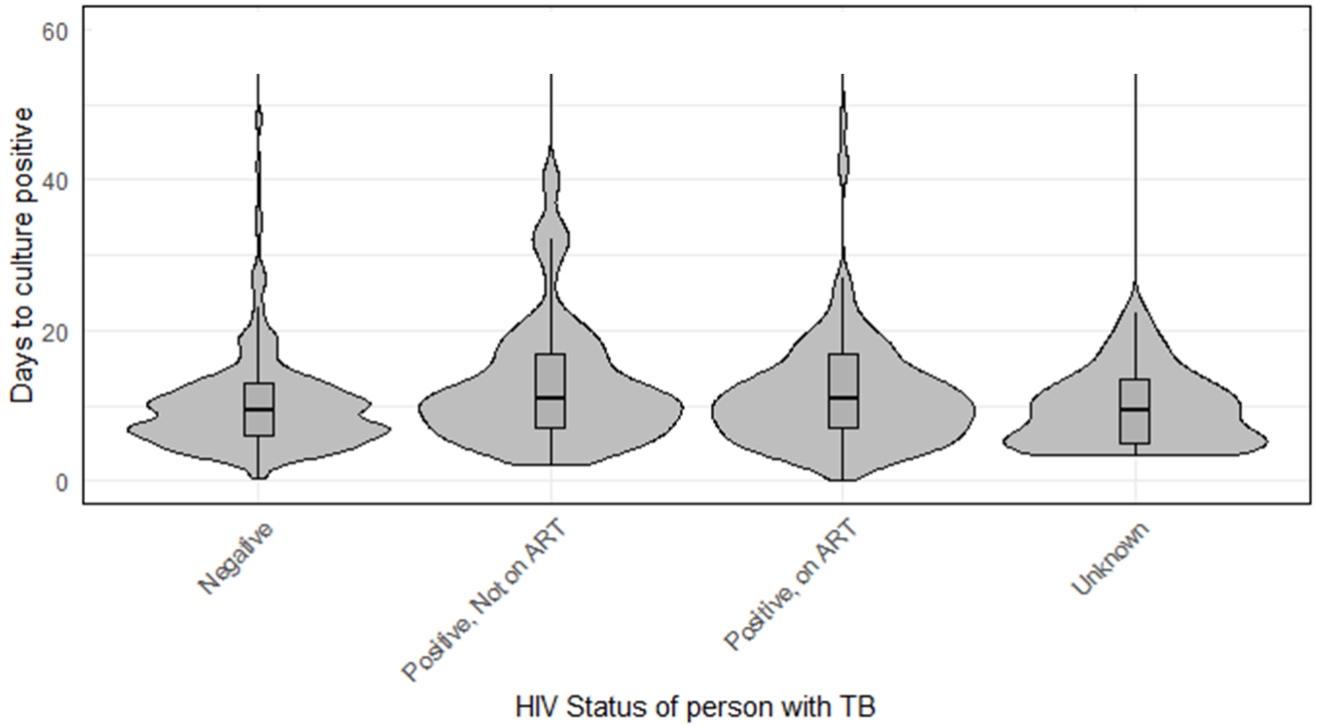
IGRA: Interferon Gamma Release Assay

Figure 2: Conceptual framework for household Mtb transmission



SUPPLEMENTS

Figure S1: Distribution of culture positivity in days by HIV status of the person with tuberculosis (TB)



Negative/Indeterminate = 50, Culture not done = 6

Table S1 : Fixed effects model of IGRA positivity adjusted by household and country

	Variables of interest	n/N (%)	Crude Odds ratios (95% CI)	Adjusted for household clustering (random effects) aOR (95% CI)	Adjusted for household clustering (random effects) with country as fixed effect aOR (95% CI)
Contact Age	10-14 years	370 (19%)	Ref	Ref	Ref
	15-17 years	192 (10%)	1.37 (0.96-1.97)	1.37(0.91-2.05)	1.39 (0.92-2.08)
	18-25 years	376 (20%)	1.33 (0.99-1.80)	1.43 (1.02-2.02)	1.48 (1.05-2.08)
	26-35 years	303 (16%)	1.44 (1.06-1.98)	1.61 (1.12-2.31)	1.56 (1.08-2.23)
	>35 years	682 (35%)	2.06 (1.58-2.68)	2.35 (1.74-3.18)	2.32 (1.71-3.13)
Contact sex	Female	1198 (62%)	Ref	Ref	Ref
	Male	725 (38%)	0.94 (0.78-1.13)	0.92 (0.74-1.13)	0.93 (0.75-1.16)
Contact HIV status	Negative	1620 (84%)	Ref	Ref	Ref
	Known Positive	297 (15%)	0.81 (0.63-1.05)	0.81 (0.61-1.09)	0.82 (0.62-1.10)
	New positive	6 (0.3%)	0.64 (0.11-3.54)	0.61 (0.09-4.23)	0.52 (0.08-3.52)
Age of person with TB	18-25	183 (20%)	Ref		Ref
	26-35	233 (26%)	1.09 (0.83-1.43)	1.09 (0.79-1.52)	1.05 (0.76-1.45)
	35+	491 (54%)	1.15 (0.92-1.45)	1.16 (0.88-1.52)	1.13 (0.86-1.48)
Sex of person with TB	Female	286 (32%)	Ref	Ref	Ref
	Male	621 (68%)	0.90 (0.75-1.09)	0.86 (0.67-1.11)	0.83 (0.65-1.06)
HIV status of person with TB	HIV Negative	568 (62%)	Ref	Ref	Ref
	HIV+, not on ART	94 (10%)	0.52 (0.37-0.74)	0.47 (0.31-0.73)	0.45 (0.29-0.69)
	HIV+, on ART	181 (20%)	0.89 (0.71-1.12)	0.92 (0.68-1.24)	0.90 (0.67-1.21)
	Unknown	64 (7.1%)	1.06 (0.75-1.49)	0.97 (0.61-1.54)	0.88 (0.56-1.40)
Bacillary burden	Medium	400 (44%)	Ref	Ref	Ref
	High	507 (56%)	1.18 (0.98-1.42)	1.23 (0.97-1.57)	1.14 (0.89-1.46)
Symptom duration of person with TB	<30 days	145 (16%)	Ref	Ref	Ref
	30≤days<90	400 (44%)	1.51 (1.15-2.01)	1.68 (1.18-2.04)	1.80 (1.26-2.57)
	90+ days	359 (40%)	2.11 (1.58-2.80)	2.67 (1.84-3.86)	2.22 (1.54-3.22)
Proximity score			1.16 (1.09-1.24)	1.19 (1.10-1.28)	1.16 (1.08-1.25)

Appendix B: Paper D

Marambire ET, Banze D, Mfinanga A, Mutsvangwa J, Mbunda TD, Ntinginya NE, Celso K, Kallenius G, Calderwood CJ, Geldmacher C, Held K, Appalarowthu T, Rieß F, Panzner U, Heinrich N, Kranzer K. Early risk assessment in paediatric and adult household contacts of confirmed tuberculosis cases by novel diagnostic tests (ERASE-TB): protocol for a prospective, non-interventional, longitudinal, multicountry cohort study. BMJ Open. 2022 Jul 19;12(7):e060985. doi: 10.1136/bmjopen-2022-060985. PubMed PMID: 36427173; PubMed Central PMCID: PMC9301805

BMJ Open

Early risk assessment in paediatric and adult household contacts of confirmed tuberculosis cases by novel diagnostic tests (ERASE-TB): protocol for a prospective, non-interventional, longitudinal, multicountry cohort study

Edson Tawanda Marambire ,[1] Denise Banze,[2] Alfred Mfinanga,[3] Junior Mutsvangwa,[1] Theodora D Mbunda,[3] Nyanda Elias Ntinginya,[3] Khosa Celso,[2] Gunilla Kallenius,[4] Claire J Calderwood,[5] Christof Geldmacher,[6,7] Kathrin Held,[6,7] Tejaswi Appalarowthu,[6,7] Friedrich Rieß,[6,7] Ursula Panzner,[6,7] Norbert Heinrich,[6,7] Katharina Kranzer,[1,5,6] on behalf of the ERASE-TB Consortium

To cite: Marambire ET, Banze D, Mfinanga A, *et al*. Early risk assessment in paediatric and adult household contacts of confirmed tuberculosis cases by novel diagnostic tests (ERASE-TB): protocol for a prospective, non-interventional, longitudinal, multicountry cohort study. *BMJ Open* 2022;**12**:e060985. doi:10.1136/bmjopen-2022-060985

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-060985).

ETM, DB and AM contributed equally.
NH and KK contributed equally.

Received 11 January 2022
Accepted 23 June 2022

For numbered affiliations see end of article.

Correspondence to
Edson Tawanda Marambire; edsonmarambire@gmail.com

ABSTRACT

Introduction The WHO End-TB Strategy calls for the development of novel diagnostics to detect tuberculosis (TB) earlier and more accurately. Better diagnostics, together with tools to predict disease progression, are critical for achieving WHO End-TB targets. The **E**arly **R**isk **A**ssessment in TB Contacts by new diagno**S**tic t**E**sts (ERASE-TB) study aims to evaluate novel diagnostics and testing algorithms for early TB diagnosis and accurate prediction of disease progression among household contacts (HHCs) exposed to confirmed index cases in Mozambique, Tanzania and Zimbabwe.

Methods and analysis A total of 2100 HHCs (aged ≥10 years) of adults with microbiologically-confirmed pulmonary TB will be recruited and followed up at 6-month intervals for 18–24 months. At each time point, a WHO symptom screen and digital chest radiograph (dCXR) will be performed, and blood and urine samples will be collected. Individuals screening positive (WHO symptom screen or dCXR) will be requested to provide sputum for Xpert MTB/Rif Ultra. At baseline, HHCs will also be screened for HIV, diabetes (HbA1c), chronic lung disease (spirometry), hypertension and anaemia. Study outcomes will be coprevalent TB (diagnosed at enrolment), incident TB (diagnosed during follow-up) or no TB at completion of follow-up. Novel diagnostics will be validated using fresh and biobanked samples with a nested case–control design. Cases are defined as HHCs diagnosed with TB (for early diagnosis) or with incident TB (for prediction of progression) and will be matched by age, sex and country to HHCs who remain healthy (controls). Statistical analyses will include assessment of diagnostic accuracy by constructing receiver operating curves and calculation of sensitivity and specificity.

Ethics and dissemination ERASE-TB has been approved by regulatory and ethical committees in each African country and by each partner organisation. Consent, with additional assent for participants <18 years, is voluntary. Attestation by impartial witnesses is sought in case of illiteracy. Confidentiality of participants is being maintained throughout. Study findings will be presented at scientific conferences and published in peer-reviewed international journals.

Trial registration number NCT04781257.Cite Now

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Recruitment of highly infectious index cases aimed at maximising the number of tuberculosis (TB) diagnoses in the household contact (HHCs) cohort.
⇒ Sequencing of *Mycobacterium tuberculosis* isolates from both index cases and HHCs allows confirmation of household transmission and, thus, determination of timing of the transmission event; resulting in more precise estimates of new test sensitivity compared with population-based cohorts with unknown timing of infection.
⇒ Large sample size across three southern African countries with high HIV prevalence; including adolescents will ensure that study findings are generalisable to the clinically relevant population at high risk of TB compared with studies focused on adults only.
⇒ Despite the large cohort of HHCs, the number of diagnosed TB cases will be small, limiting the power of the study and subgroup analyses such as by age and HIV status.
⇒ Geographically limited to sub-Saharan Africa; therefore, results may not be generalisable to other populations, including those with lower HIV prevalence such as in South-East Asia or the Americas.

INTRODUCTION

Tuberculosis (TB) remains a leading global public health problem, with an estimated

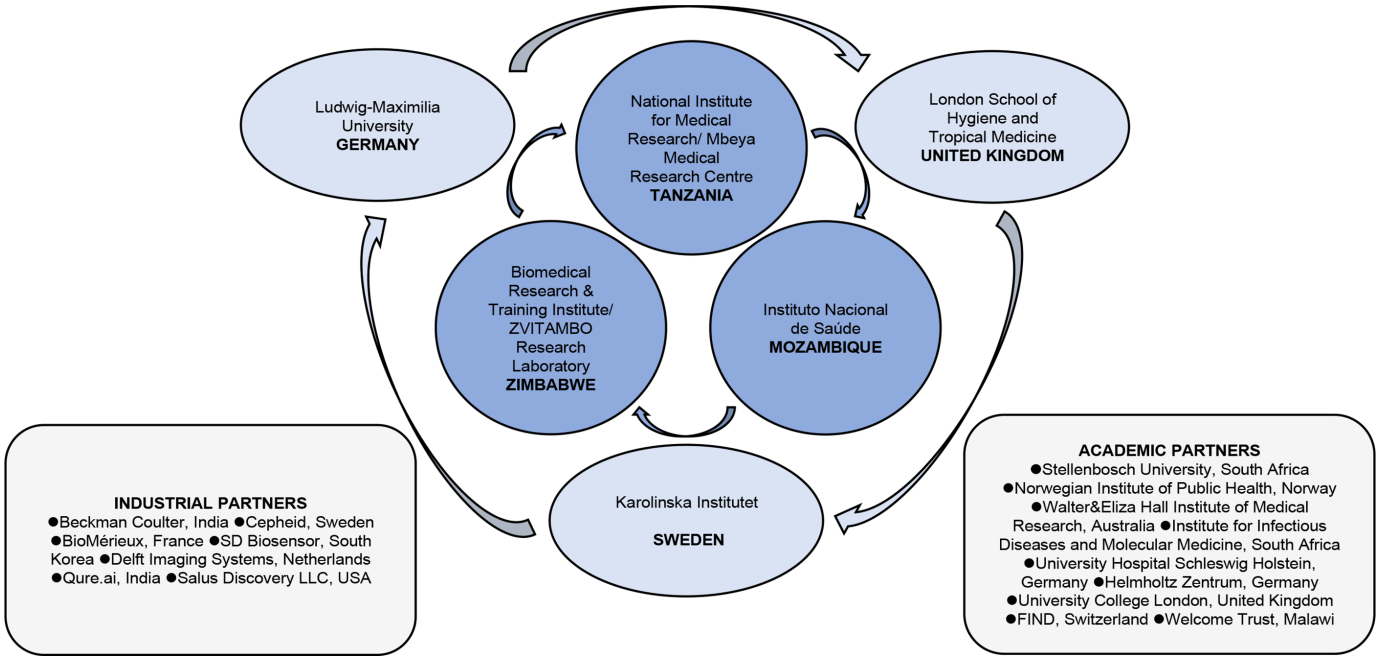


Figure 1 The ERASE-TB consortium. ERASE-TB, Early Risk Assessment in TB contactS by new diagnostic tEsts.

10 million new cases and 1.5 million deaths globally in 2020.[1] In 2014, the World Health Assembly approved the WHO End-TB Strategy, aiming for a 90% reduction in TB incidence and 95% reduction in TB deaths by 2035.[2] However, in 2019, three million TB cases ('the missing millions') remained undiagnosed and untreated globally, resulting in potentially avoidable morbidity, mortality and onward transmission. The COVID-19 pandemic has resulted in a large decrease in the number of people newly diagnosed with TB and reported. This has increased the diagnostic gap by a further 1.3 million, resulting in an estimated 4.2 million undiagnosed TB cases in 2020.[3] Also, for the first time in a decade, TB deaths have risen, from an estimated 1.4 million in 2019 to 1.5 million in 2020, as a result of reduced access to and provision of essential TB services, including diagnostics during the COVID-19 pandemic.

Without an efficacious and safe vaccine, early detection and containment are the main tools to interrupt transmission and successfully control TB. Similar to SARS-CoV2, asymptomatic spreading of *M.tuberculosis* and subclinical but infectious disease states are a major concern in the control of airborne infectious diseases.[4] Early and accurate identification of persons with TB, combined with identification of those at risk of progression to TB and provision of targeted preventive treatment, are critical to reducing TB-associated morbidity and mortality, and preventing onward transmission.

Currently available diagnostics such as sputum microscopy, mycobacterial culture and nucleic acid amplification tests are based on direct pathogen detection, thus requiring a high mycobacterial load; they, therefore, predominately target advanced TB when onward transmission and significant lung damage has occurred.[5 6] Furthermore, for many patients with minimal or no symptoms, expectoration of high-quality sputum specimens remains challenging, limiting the accuracy of sputum-based tests. The same holds true for young children and people living with HIV.

The **E**arly **R**isk **A**ssessment in TB Contacts by new diagno**S**tic t**E**sts (ERASE-TB) study aims to fill this diagnostic gap by evaluating new sputum and non-sputum-based TB diagnostics for early TB detection (before onward transmission occurs) as well as tools for more accurate prediction of TB progression to allow for targeted preventive therapy.

METHODS AND ANALYSES

Study objectives

ERASE-TB's primary objectives are (1) to determine the sensitivity and specificity of novel diagnostics to detect TB, in particular, asymptomatic or minimally symptomatic TB, (2) to evaluate novel diagnostics for detection of likely TB progression and (3) to enhance the performance of novel diagnostics by simulating testing algorithms coupled with individual risk estimates from a mathematical model. The secondary objectives are (1) to determine the TB prevalence among household contacts (HHCs) of infectious TB index cases (ICs) at baseline and during 18–24 months follow-up, (2) to establish a biorepository of cryopreserved specimens from HHCs for future development and validation of diagnostic tests and (3) to assess the association of selected chronic disease conditions and TB among HHCs.

Study endpoints

The study's primary endpoints are the presence or development of TB among HHCs with the following possible scenarios of (1) prevalent symptomatic TB at baseline,

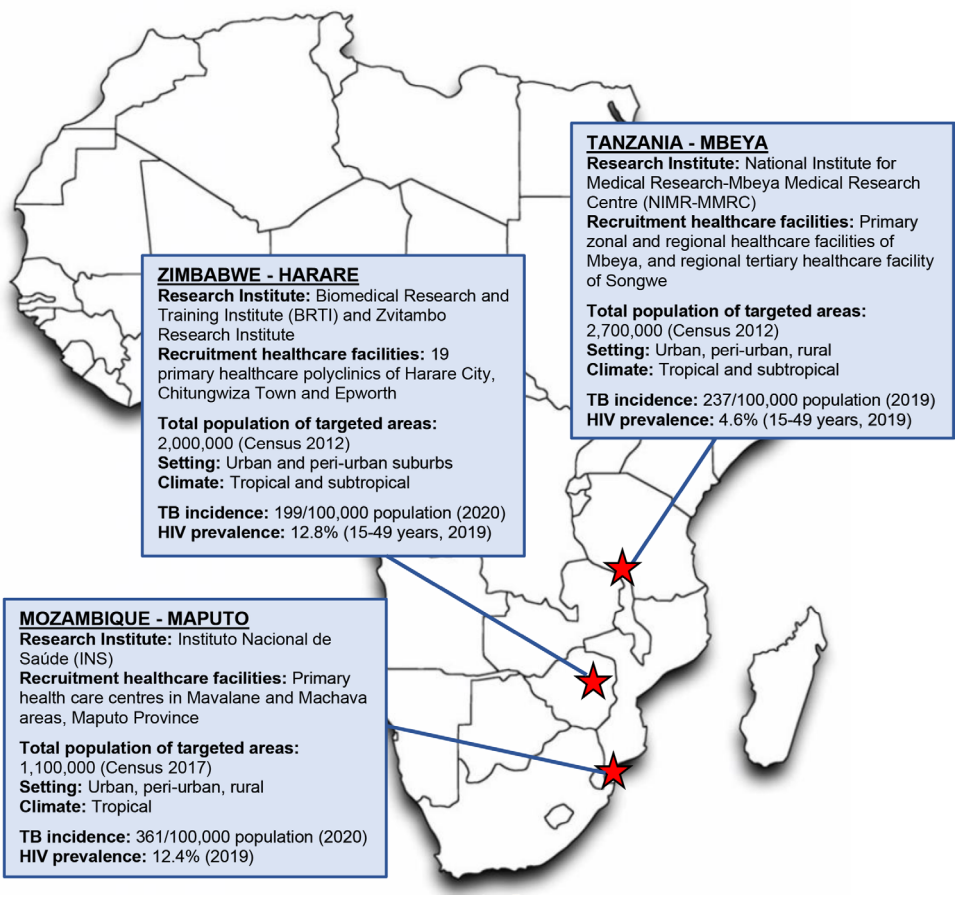


Figure 2 Location and characteristics of ERASE-TB study sites. The location of each study site is indicated by a red asterisk. Source data used within this figure are taken from the references.[7–15 40–42] ERASE, Early Risk Assessment in TB contactS by new diagnostic tEsts; TB, tuberculosis.

(2) incident TB during follow-up and (3) remained healthy until study completion. An endpoint review committee will review the data and case classification before finalisation.

Through the sequencing of *Mycobacterium tuberculosis* (*Mtb*) isolates, cases of coprevalent or incident TB will be classified either as secondary, infected by the source case—the timepoint of infection will be known; or as infected by another, unknown source of infection, with an unknown timepoint of infection.

Recruitment sites

Recruitment of ICs and HHCs at selected primary healthcare facilities and communities has commenced in Harare, Zimbabwe in March 2021, Maputo, Mozambique in August 2021, and Mbeya, Tanzania in September 2021. Partners of the ERASE-TB consortium are illustrated in figure 1. All three countries have a high TB incidence ranging from 100 to 499/100 000 population[1] and HIV prevalence among adults aged 15 years and older of 5%–20%.[7] The African research institutions have established collaborations with their respective National Tuberculosis Programs ensuring referral and appropriate follow-up of patients with TB. Figure 2 illustrates the geographic location of research institutions, healthcare facilities where recruitment is taking place, demographic characteristics of study populations and estimates on TB incidence and HIV prevalence.[8–15]

Study design

ERASE-TB is a non-interventional, longitudinal, prospective cohort study among HHCs aged ≥10 years exposed to highly infectious pulmonary TB ICs aged ≥18 years. Eligibility criteria are detailed in figure 3 and the study design is shown in figure 4. TB ICs are eligible if the bacterial load in their sputum is at least at the 'medium' level according to Xpert MTB/RIF or Xpert MTB/RIF Ultra, and they have received less than seven daily doses of anti-TB treatment before enrolment. This maximises the likelihood of culturing and storing *Mtb* isolates. The total study duration will be 36 months. This includes 12-month enrolment of ICs and HHCs, and 18-month to 24-month follow-ups of HHCs. Follow-up ends when a HHCs withdraws from the study, is lost to follow-up, dies or is diagnosed with TB and referred for treatment. Scheduled or unscheduled unwell visits can be conducted physically and/or telephonically in case of abnormal finding, for example, by abnormal digital chest radiograph (dCXR), or when a participant feels unwell in between scheduled follow-up visits.

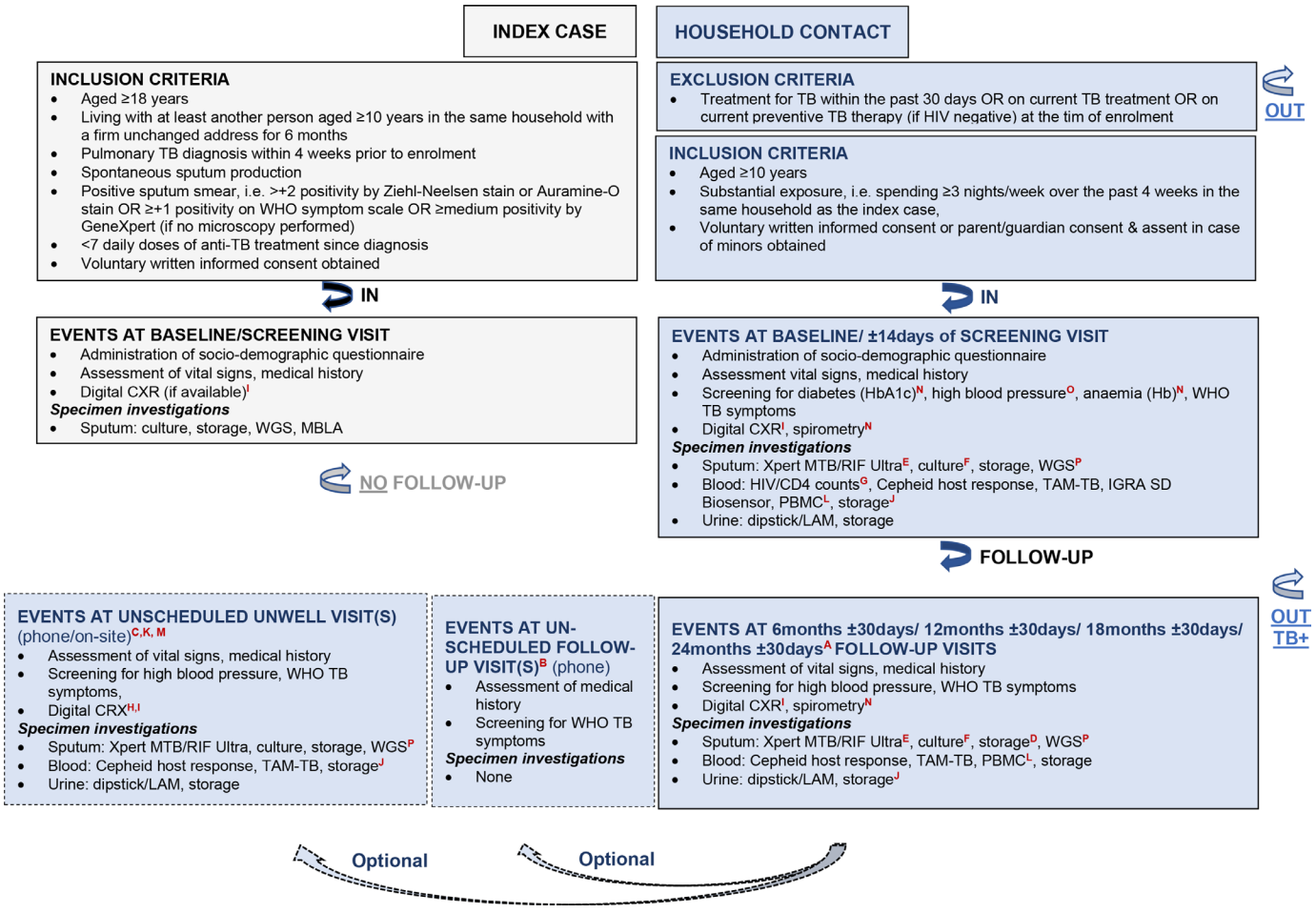


Figure 3 Eligibility criteria and schedules of events for index cases and household contacts. **A**=depending on the time point of study enrolment and consequently on the duration available for follow-up, that is, 18 or 24 months, the follow-up visit at 24 months±30 days may be conditional; **B**=the follow-up visit by phone may be conducted after the last scheduled follow-up visit at 18 months±30 days or 24 months ±30 days to assess whether symptoms suggestive of TB have occurred, TB diagnosis has been made or anti-TB treatment has been initiated; **C**=unwell visits by phone or on-site may be conducted between scheduled follow-up visits if a participant presents at a recruitment healthcare facility with signs and symptoms suggestive of TB; **D**=coached spontaneous or induced sputum collection for storage at scheduled follow-up visit at 18 months±30 days or 24 months ±30 days, and for repetition of HIV testing if tested negative at baseline; **E**=coached spontaneous or induced sputum collection on the decision of the investigating team for testing by Xpert MTB/RIF Ultra if participant presents with signs and symptoms suggestive of TB; **F**=coached spontaneous or induced sputum collection in case of Xpert MTB/RIF Ultra positivity or strong clinical suspicion of TB for repetition of the Xpert MTB/RIF Ultra; **G**=in case of HIV positivity to be followed by the assessment of CD4 counts; **H**=CXR to be conducted at an unscheduled on-site unwell visit on the decision of the investigating team depending on the nature of symptoms reported, and the time elapsed since the last CXR including its findings; **I**=not to be conducted among pregnant women; **J**=stored venous blood includes 6 mL EDTA blood for whole blood and plasma, 4 mL serum and 2.5 mL PAXgene blood, all samples will be deep frozen for retrospective testing using new diagnostics as described in text; **K**=in case the evaluation of symptoms of a participant unable to present at a recruitment healthcare facility is required an unscheduled on-site or home visit will be arranged by phone, the resolution of symptoms can alternatively be addressed by phone; **L**=collection of PBMC at baseline and follow-up visit at 6 months±30 days is optional, thus will not be performed at each participating site and for each participant; **M**=in case the evaluation of symptoms of a participant unable to present at a recruitment healthcare facility is required or doubtful if required an unscheduled unwell visit by phone will be arranged, the resolution of symptoms can alternatively be addressed by phone; **N**=spirometry and/or diabetes (HbA1c) will be performed at scheduled follow-up visits at 6 months±30 days, 12 months ±30 days and 18 or 24 months±30 days if required or not performed at baseline, anaemia (Hb) will be performed at baseline and scheduled follow-up visits at 6 months±30 days, 12 months ±30 days and 18 or 24 months±30 days if possible; **O**=blood pressure measurement will be performed at baseline and scheduled follow-up visits at 6 months±30 days, 12 months ±30 days and 18 or 24 months±30 days; **P**=WGS to be performed once *Mtb* infection is confirmed and an isolate could be recovered. CD4, cluster of differentiation 4; CXR, chest radiograph; Hb, haemoglobin; HbA1c, glycated haemoglobin; IGRA, interferon gamma release assay; LAM, lioparabinomannan; MTB, *Mycobacterium tuberculosis*; MBLA, molecular bacterial load assay; PBMC, peripheral blood mononuclear cell; RIF, rifampicin; TAM-TB, T- cell activation marker tuberculosis; TB, tuberculosis; WGS, whole genome sequencing.

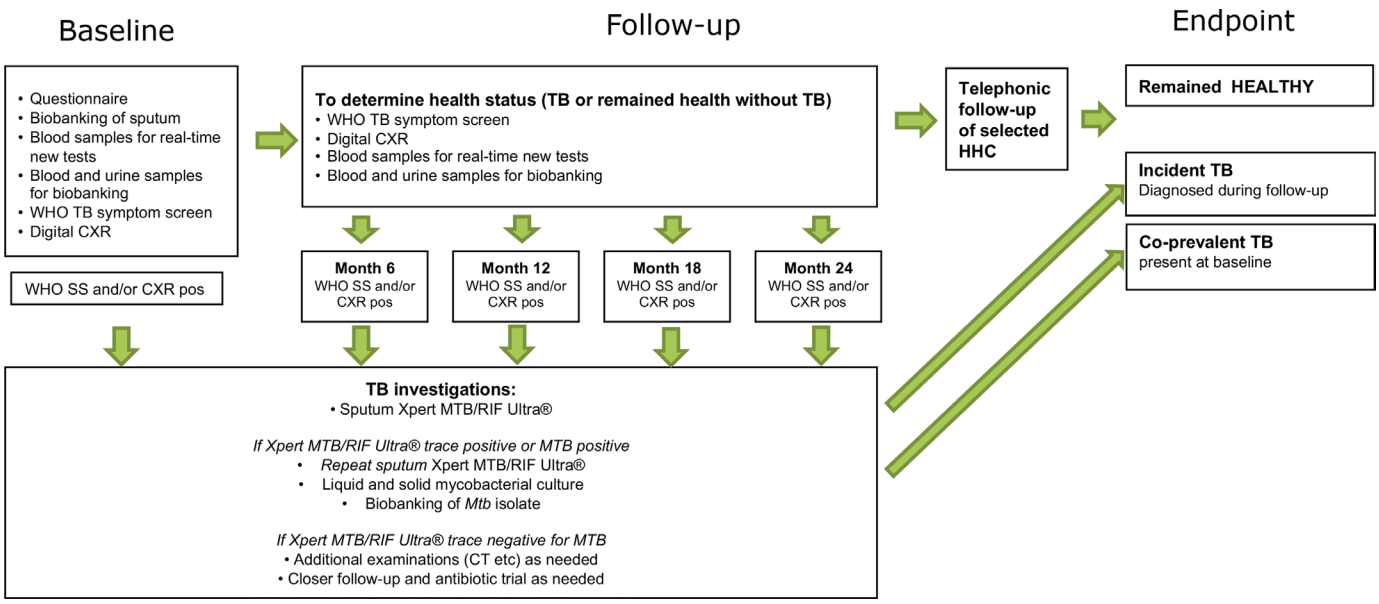


Figure 4 Study design. CXR, chest radiograph; FU, follow-up; HHC, household contact; IC, index case; MTB, *Mycobacterium tuberculosis*; pos=positive; RIF, rifampicin; SS, symptom score; TB, tuberculosis.

Procedures

TB index cases

Following informed consent obtained, a questionnaire is administered to collect sociodemographic information, TB risk factors and the medical history of TB, HIV and other diseases. Two spontaneous sputum samples are obtained, of which one is for mycobacterial culturing and one for storage for performing retrospectively Molecular Bacterial Load Assay to quantify viable *Mtb* by 16s rRNA[6]; an alternative means to quantify expectorated bacterial load for an estimate of infectiousness. Both liquid and solid mycobacterial cultures are performed on decontaminated sputum samples, with all *Mtb* isolates stored at −80° for future DNA extraction and whole genome sequencing. A questionnaire on symptom duration and TB risk factors is also administered.

Household key informant

At baseline, a household key informant (either the TB IC or one of the HHCs) is identified and asked to answer questions of a household questionnaire that collects socioeconomic elements like structure of the house or flat, income and household assets and covariates possibly associated with risk of TB infection, for example, windows/air exchange, presence of comorbid conditions and risk factors like the source of cooking energy and properties of the household kitchen.

Household contacts

Informed consent is obtained from all eligible adult HHCs. For HHC <18 years of age, the guardian is asked to provide informed consent, with assent also sought from children dependent on local guidance. At baseline, a questionnaire is administered collecting information on socioeconomic and demographic characteristics, previous medical history of TB, HIV and other diseases, exposure risk factors, smoking and alcohol history. The physical examination includes height, weight, mid-upper arm circumference and blood pressure measurement. In addition, all HHCs are offered free HIV testing according to the National Guidelines. All people with confirmed HIV infection will have CD4 counts performed and be referred for TB preventive therapy. Those not yet on antiretroviral therapy (ART) and those who interrupted ART are referred for ART at local services.

Point of care HbA1c (A1cCare, SD Biosensor, Gyeonggi-do, Republic of Korea) and haemoglobin (Hemocue 301+, Hemocue, Angelholm, Sweden) tests and spirometry (including prebronchodilation and postbronchodilation with inhaled salbutamol) are performed at baseline or the 6-month visit. HHCs who did not take up HIV testing or other screening at baseline are offered these tests at each study visit. Any HHCs with test results requiring treatment or further investigations are referred for respective services.

HHCs are screened for TB using the WHO symptom screening questionnaire and a dCXR, reviewed by a clinical officer. dCXRs are not performed in pregnant HHCs. HHCs with a positive WHO symptom screening and/or abnormal dCXR are asked to provide sputum samples for TB investigations, that is, for GeneXpert and mycobacterial culture. Those with negative symptom screen and normal dCXR are asked to provide a spontaneous sputum sample for storage (with sputum induction performed if required).

At baseline, urine, serum, plasma, whole blood (native, and with RNA preservation in PAXgene tubes (BD Biosciences, New Jersey)) are stored. A finger-prick sample is taken and investigated using the Xpert TB Host Response RUO Prototype cartridge (Cepheid, Sunnyvale, California). T-cell Activation Marker Tuberculosis (TAM-TB)

assay and Interferon Gamma Release Assay (IGRA; STANDARDTM F TB-Feron FIA (IFN-gamma; SD Biosensor, Republic of Korea) are performed on fresh venous blood. In Tanzania and Mozambique, storage of peripheral blood mononuclear cells for later characterisation of the TB-specific immune response is also performed.

Procedures for follow-up and unwell visits are similar to those at baseline. Measurement of HIV status, haemoglobin (HB), HbA1c, spirometry, CD4 count and IGRA testing are not performed at follow-up visits, unless not done previously. At the last scheduled visit, all HHCs not known to have HIV are reoffered HIV testing and a spontaneous or induced sputum sample is stored for all participants.

HHCs screening positive for TB symptoms and/or with a dCXR suggestive of TB

HHCs screening positive for symptoms and/or those with dCXRs suggestive of TB are asked for a sputum sample, which is investigated using Xpert MTB/RIF Ultra (Cepheid). If this sample is positive for *Mtb* (including a trace result), a minimum of two additional sputum samples are investigated, following decontamination, with Xpert MTB/RIF Ultra, solid and liquid culture. Isolates stored from these cultures will be sequenced for matching with the IC isolates in order to verify intrahousehold transmission. Sputum induction is performed for those unable to provide a spontaneous sputum sample. HHCs with microbiologically confirmed TB are referred for TB treatment to the National TB Programme.

Patient and public involvement

The ERASE-TB study sites have established Community Advisory Boards, which are voices of communities, people affected and study participants, providing a strategic link between the communities and the study team. Community Advisory Boards meet regularly and provide feedback on design, procedures and conduct of the study. They will also be closely involved in the dissemination of study results. In addition to the Community Advisory Boards, each study site conducts community engagement activities focused on young people with the aim to foster interst in science and research, specifically in the field of respiratory diseases/illness. This includes close partnership with schools and universities. Furthermore, planned qualitative research will specifically aim to understand the perceptions of HHCs with regards to TB diagnostics and screening.

Sample size

An estimated 800 to 900 TB-confirmed ICs are required for the subsequent enrolment of an anticipated 2100 HHCs, that is, 700 HHCs per country. Loss to follow-up of HHCs is estimated to be 10%. A total of 64 HHCs (3%) are estimated to be diagnosed with TB during the study period, based on previous active case finding studies among HHCs.[16] Validation for subclinical and early TB will include incident (n=49) and coprevalent TB cases (n=15). Validation for detection of incipient *Mtb* infection will include samples of participants with incident TB (n=49) matched 1:4 to samples of participants without TB (n=196). For tests diagnosing incipient *Mtb* infection sensitivities of 73% and 82% would be detected with a precision of 59%–85% and 68%–91%, respectively. For specificities of 92% and 94%, the CIs would be 87% to 95% and 90% to 97%.

Novel test candidates

A range of novel test candidates targeted at pathogen detection or identification of host responses to *Mtb* are being applied, either in real-time (for all participants) or retrospectively (in a case–control design). While a number of novel test candidates have been prespecified, the ERASE-TB biobanking processes allow for addition of further candidate tests to be evaluated on stored samples as they become available.

DCXRs offer good sensitivity for diagnosis of pulmonary TB. However, high interinvestigator and intrainvestigator variability, and lack of trained interpreters presents a barrier to implementation in many high-TB burden settings. Computer-aided interpretation systems, such as CAD4TB (Delft Imaging, Hertogenbosch, Netherlands) and qXR (Qure.ai, India), may increase image-reading capacity, with good performance, and serve, therefore, as a systematic screening tool to identify individuals in need of confirmatory TB tests.[17 18]

Xpert MTB/RIF Ultra is a nucleic acid amplification test for *Mtb* with a lower limit of detection compared with the previous Xpert MTB/RIF generation, and, therefore, conferring higher sensitivity in paucibacillary specimens. This, however, comes at the expense of specificity, particularly in high TB incidence settings, resulting in 'false positives'.[19] WHO guidelines recommend Xpert MTB/RIF Ultra for TB diagnosis among adults and children acknowledging that further evaluation, particularly of the role of Xpert MTB/RIF Ultra for TB screening, is needed.[20 21]

FLOW-TB is an advanced ELISA for the detection of *Mtb* lipoarabinomannan (a mycobacterial cell wall component) in urinary specimens with results available within 65 min.[22]

The TAM-TB detects Mtb-specific CD4 T-cells through in vitro antigen stimulation with *Mtb*-derived peptides, that is, from ESAT-6 to CFP-10, followed by flow cytometry. TAM-TB discriminated latent *Mtb* infection from TB in freshly collected blood with 83% sensitivity and 96%–98% specificity in previous studies. Furthermore, TAM-TB may detect early TB disease progression up to 9 months prior to the identification of *Mtb* in sputum.[23–25]

Multiple transcriptomic signatures, capturing the host response to TB, have been described as promising candidate tests for earlier TB diagnosis (up to 2 years before microbiological diagnosis). An individual patient data meta-analysis suggested equivalent performance of eight signatures, with 25%–40% sensitivity and 92%–95% specificity, 0–24 months before TB diagnosis. Diagnostic

accuracy of each signature improved as the interval between testing and microbiological TB diagnosis shortened.[26] Several signatures have been developed into PCR-based assays to facilitate real-time implementation: the recent The Correlate of Risk Targeted Intervention Study (CORTIS) reported sensitivity of 48% and specificity of 75% for incipient TB for the RISK-11 transcriptomic signature of TB risk.[27] Cepheid have developed a three-transcript TB score into a fully automated in-cartridge PCR assay performed on finger-prick blood using the Xpert platform (Xpert TB Host Response RUO Prototype cartridge). This cartridge will be evaluated using freshly collected specimens in ERASE-TB; storage of RNA-stabilised blood samples also allows for retrospective evaluation of additional transcriptomic signatures in our cohort.[28 29]

An alternative approach to capture the host response to TB is through protein-based biomarker signatures. Candidate tests in this category include a serum-based or plasma-based multiplex assay assessing 13 protein biomarkers (C reactive protein, procalcitonin,[30] sTREM-1 (soluble triggering receptor expressed on myeloid cells-1),[31 32] angiopoietin-2,[33 34] IL-6,[35] TRAIL (TNF-related apoptosis-inducing ligand)[36] and IP-10[35]) that is being developed by the London School of Hygiene and Tropical Medicine; in addition, a seven biomarker signature is under development as a point-of-care test for TB diagnosis, with 94% sensitivity and 73% specificity detected in previous work.[37]

Statistical analyses

Baseline characteristics and analytical data will be summarised using descriptive statistics inclusive of mean, median, range, SD and absolute as well as relative frequencies depending on the nature of data. A logistic regression model will be used to identify characteristics of TB among ICs, households and HHCs that are predictive of incident TB. From the study database, we will simulate algorithms of different tests to obtain the testing combination with the best accuracy. We will couple tests with a mathematical model that quantifies the risk of infection and/or disease to enhance predictive performance. The reporting of the development of the prediction model will follow the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis Initiative.[38]

The validation of novel diagnostic tests for detecting TB will be analysed as a 1:4 matched nested case–control study with HHCs diagnosed with TB at baseline and during follow-up serving as cases, and HHCs who do not develop TB during follow-up as controls; controls will be matched for site, age, sex, HIV status and other risk factors for developing TB. Sensitivity and specificity of novel tests will be determined using pre-existing positive/negative cut-offs where these exist[39]; and receiver operating curves (ROC) constructed with area under the ROC curve calculated. For tests aiming to identify individuals at high risk of TB in the future, only HHCs who are diagnosed with TB during follow-up will serve as cases (ie, those diagnosed with TB at baseline will be excluded). Stored samples from all timepoints will be retrieved and diagnostic accuracy (ie, sensitivity and specificity) of the novel test determined at different timepoints before TB diagnosis. The decision of assigning the 'active TB' endpoints to participants will be blinded from the new test results to avoid inclusion bias.

Data management

All source data will be kept confidential in secured locations with restricted access by authorised personnel only inclusive of monitors, auditors and reviewers of ethical and regulatory committees in line with applicable data privacy regulations. Each participant is asked to consent to this handling of the data and is assigned a pseudonymous identification number that is used throughout the study on all source data.

Accurate documentation of paper-based and electronic source data, for example, original records and certified copies of original records, progress notes, screening logs and recorded data from automated instruments, will be maintained. The pseudonymised clinical data captured on paper-based Case Report Forms will be entered at the sites into a database using the web-based Clinical Data Management System of OpenClinica (OpenClinica LLC, Waltham, Massachusetts). The study-specific database has been built, maintained and hosted by the LMU Klinikum on a centralised secure server. Data modifications and necessary corrections performed in the database also within the context of double data entry will be documented and tracked in audit trails. Data quality and plausibility are assured by a series of preprogrammed edit and range checks in OpenClinica. Further validation checks are programmed in Stata (Statacorp, College Station, Texas) with extracts of the database and electronically received data, for example, spirometry, dCXR and laboratory, will be integrated into analyses of datasets.

Monitoring

Assigned study monitors will visit the sites at regular intervals physically and/or virtually in addition to frequent day-to-day communication. Close follow-up on all study-related aspects will be performed to ascertain compliance with standards of Good Clinical Practice, the Declaration of Helsinki and other local and national regulatory guidelines inclusive of guidelines for infection prevention and control of airborne-transmitted diseases, for example, social distancing in well-ventilated spaces, and wearing of personal protective equipment. In particular, monitors that support designated study personnel are responsible to verify (1) adequacy of the study personnels' qualifications and facilities, (2) accuracy of informed consent procedures and patient eligibility, (3) adherence to the study protocol, (4) protection of rights and well-being of participants, (5) adherence to infection prevention and control measures, (6) accuracy and completeness of study

documents and other study-related records and (7) maintenance of source documents.

Ethics and dissemination

The study protocol and informed consent/assent documents have been approved by regulatory and ethical committees of the participating institutions (Medical Research Council in Zimbabwe (MRCZ/A/2618), the National Health Research Ethics Committee in Tanzania (TMDA-WEB0021/CTR/0004/03), the National Bioethics Committee for Health in Mozambique (541/CNBS/21), and the ethical committees of London School of Hygiene & Tropical Medicine, United Kingdom (22 522–2) and the medical faculty of the Ludwig-Maximilians-Universität München, Germany (20–0771)).

Adult ICs and HHCs are asked for written informed consent prior to their participation. Underage HHCs are asked for assent in addition to obtaining the consent of their legal guardians/parents; with ages for assent depending on local guidance. In case of illiteracy, the participant is asked to give its consent by fingerprint while an adult impartial, literate witness present during the entire consent procedure signs the consent on behalf. All participants have the right to withdraw from the study at any time. Findings derived from ERASE-TB will be presented at scientific conferences and published in peer-reviewed international journals.

Current study status

The recruitment of ICs and HHCs is in progress in Zimbabwe, Mozambique and Tanzania since March, August and September 2021, respectively. The follow-up of HHCs is anticipated to be completed in March, August and September 2023 in Zimbabwe, Mozambique and Tanzania, respectively; laboratory analyses are estimated to be performed by December 2024.

Author affiliations
[1]Biomedical Research and Training Institute, Harare, Zimbabwe
[2]Instituto Nacional de Saúde, Marracuene, Mozambique
[3]National Institute for Medical Research- Mbeya Medical Research Centre, Mbeya, Tanzania
[4]Karolinska Institutet, Stockholm, Sweden
[5]Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK
[6]Division of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich, Munich, Germany
[7]German Center for Infection Research (DZIF), Partner site Munich, Munich, Germany

Twitter Edson Tawanda Marambire @EMarambire

Acknowledgements We are grateful to the study personnel from the Biomedical Research and Training Institute and the Zvitambo Research Institute, Zimbabwe, the Instituto Nacional de Saúde, Mozambique, and the National Institute for Medical Research—Mbeya Medical Research Centre, Tanzania for their exceptional efforts and contributions, which made this research possible.

Collaborators The following are members of the ERASE-TB consortium: Anna Shepherd (Faculty of Infectious and Tropical Diseases, Department of Infection Biology, London School of Hygiene & Tropical Medicine, London, UK), Hazel M Dockrell (Faculty of Infectious and Tropical Diseases, Department of Infection Biology, London School of Hygiene & Tropical Medicine, London, UK), Judith Bruchfeld (Karolinska Institute, Stockholm, Sweden), Christopher Sundling (Karolinska Institute, Stockholm, Sweden), Charles Sandy (Biomedical Research and Training Institute, Harare, Zimbabwe), Mishelle Mugava (Biomedical Research and Training Institute, Harare, Zimbabwe), Tsitsi Bandason (Biomedical Research and Training Institute, Harare, Zimbabwe), Martha Chipinduro (Biomedical Research and Training Institute, Harare, Zimbabwe), Kuda Mutasa (Zvitambo Research Institute, Harare, Zimbabwe), Sandra Rukobo (Zvitambo Research Institute, Harare, Zimbabwe), Lwitiho Sudi (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Antelmo Haule (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Emmanuel Sichone (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Paschal Qwaray (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Bariki Mtafya (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Harrieth Mwambola (National Institute for Medical Research - Mbeya Medical Research Centre, Mbeya, Tanzania), Lilian Minja (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Issa Sabi (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Peter Edwin (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Dogo Ngalison (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Stella Luswema (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Willyhelmina Olomi (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Doreen Pamba (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Simeon Mwanyonga (National Institute for Medical Research—Mbeya Medical Research Centre, Mbeya, Tanzania), Celina Nhamuave (Instituto Nacional de Saúde, Marracuene, Mozambique), António Machiana (Instituto Nacional de Saúde, Marracuene, Mozambique), Carla Madeira (Instituto Nacional de Saúde, Marracuene, Mozambique), Emelva Manhiça (Instituto Nacional de Saúde, Marracuene, Mozambique), Nádia Sitoe (Instituto Nacional de Saúde, Marracuene, Mozambique), Jorge Ribeiro (Instituto Nacional de Saúde, Marracuene, Mozambique), Christof Geldmacher (Division of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich, Munich, Germany), Andrea Rachow (Division of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich, Munich, Germany), Olena Ivanova (Division of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich, Munich, Germany), Laura Olbrich (Division of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich, Munich, Germany), Elmar Saathoff (Division of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich, Munich, Germany), Michael Hoelscher (Division of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich, Munich, Germany).

Contributors The study proposal and protocol were written by NH, KK with scientific input from CK, TM, CG, JM. ETM, UP, DB, AM wrote the initial manuscript with scientific input on the database and data management section from FR, TA. NH, KK critically reviewed the initial draft of the manuscript. KH, GK, CJC, ENN, TA, provided critical feedback on the manuscript. All authors have read and approved the final version of the manuscript.

Funding ERASE-TB is part of the EDCTP2 programme supported by the European Union (grant number RIA2018D-2508-ERASE-TB), the German Center for Infection Research (DZIF) grant number: 02.710 and the Swedish Research Council (220-23602). CJC is funded by the Wellcome Trust (203905/Z/16/Z). Cepheid, Inc., and SD Biosensor provided test kits and analysers at no cost to the Consortium.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iD
Edson Tawanda Marambire http://orcid.org/0000-0001-5944-5010

REFERENCES

1 Global tuberculosis report, 2021. Available: https://www.who.int/publications/i/item/9789240037021 [Accessed 28 Oct 2021].
2 The end TB strategy global strategy and targets for tuberculosis prevention, care and control after 2015 a, 2014. Available: https://www.who.int/tb/strategy/End_TB_Strategy.pdf [Accessed 28 Oct 2021].
3 WHO. Global tuberculosis report, 2020. Available: https://www.who.int/publications/i/item/9789240013131 [Accessed 31 Jul 2021].
4 Snider B, Patel B, McBean E. Asymptomatic cases, the hidden challenge in predicting COVID-19 caseload increases. *Infect Dis Rep* 2021;13:340–7.
5 TB Disease - Symptoms, treatment & prevention - TBFacts. Available: https://tbfacts.org/tb-disease/ [Accessed 28 Aug 2021].
6 Honeyborne I, McHugh TD, Phillips PPJ, *et al*. Molecular bacterial load assay, a culture-free biomarker for rapid and accurate quantification of sputum Mycobacterium tuberculosis bacillary load during treatment. *J Clin Microbiol* 2011;49:3905–11.
7 UNIAIDS. Unaids global AIDS update, 2021. Available: https://www.unaids.org/sites/default/files/media_asset/2021-global-aids-update_en.pdf [Accessed 28 Oct 2021].
8 ZIMBABWE POPULATION CENSUS. Women and men profile summary report, 2012. Available: https://www.zimstat.co.zw/wp-content/uploads/publications/Social/Gender/Women-and-Men-Report-2012.pdf [Accessed 15 Oct 2021].
9 Tanzania Census. Dashboard, 2012. Available: http://dataforall.org/dashboard/tanzania/ [Accessed 15 Oct 2021].
10 ZIMBABWE POPULATION-BASED HIV IMPACT ASSESSMENT ZIMPHIA. Key findings, 2020. Available: https://phia.icap.columbia.edu/wp-content/uploads/2020/11/ZIMPHIA-2020-Summary-Sheet_Web.pdf [Accessed 03 Sep 2021].
11 Xadreque H, Maunze A, Dade M. Iv RECENSEAMENTO GERAL dA POPULAÇÃO E HABITAÇÃO, 2017. Available: http://www.ine.gov.mz/iv-rgph-2017/mocambique/censo-2017-brochura-dos-resultados-definitivos-do-iv-rgph-nacional.pdf [Accessed 31 Jul 2021].
12 Population of cities in Zimbabwe, 2021. Available: https://worldpopulationreview.com/countries/cities/zimbabwe [Accessed 3 Aug 2021].
13 World atlas. Available: https://knoema.com/atlas/United-Republic-of-Tanzania [Accessed 26 Jul 2021].
14 Prevalence of HIV total (% of population ages 15-49) | data. Available: https://data.worldbank.org/indicator/SH.DYN.AIDS.ZS?locations=ZW [Accessed 03 Aug 2021].
15 Incidence of tuberculosis (per 100 000 people) - Zimbabwe. Data. Available: https://data.worldbank.org/indicator/SH.TBS.INCD?locations [Accessed 03 Aug 2021].
16 Fox GJ, Nhung NV, Sy DN, *et al*. Household-Contact investigation for detection of tuberculosis in Vietnam. *N Engl J Med* 2018;378:221–9.
17 Qin ZZ, Ahmed S, Sarker MS, *et al*. Tuberculosis detection from chest x-rays for triaging in a high tuberculosis-burden setting: an evaluation of five artificial intelligence algorithms. *Lancet Digit Health* 2021;3:e543–54.
18 MacPherson P, Webb EL, Kamchedzera W, *et al*. Computer-Aided X-ray screening for tuberculosis and HIV testing among adults with cough in Malawi (the prospect study): a randomised trial and cost-effectiveness analysis. *PLoS Med* 2021;18:e1003752–17.
19 Dorman SE, Schumacher SG, Alland D, *et al*. Xpert MTB/RIF ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicentre diagnostic accuracy study. *Lancet Infect Dis* 2018;18:76–84.
20 Who meeting report of a technical expert consultation: non-inferiority analysis of Xpert MTB/RIF ultra compared to Xpert MTB/RIF, 2017. Available: http://apps.who.int/bookorders [Accessed 19 Oct 2021].
21 World Health Organization. Who consolidated guidelines on tuberculosis: module 2: screening, 2021. Available: https://www.who.int/publications/i/item/9789240022676 [Accessed 09 Dec 2021].
22 Hamasur B, Bruchfeld J, van Helden P, *et al*. A sensitive urinary lipoarabinomannan test for tuberculosis. *PLoS One* 2015;10:e0123457.
23 Portevin D, Moukambi F, Clowes P, *et al*. Assessment of the novel T-cell activation marker–tuberculosis assay for diagnosis of active tuberculosis in children: a prospective proof-of-concept study. *Lancet Infect Dis* 2014;14:931–8.
24 Schuetz A, Haule A, Reither K, *et al*. Monitoring CD27 expression to evaluate Mycobacterium tuberculosis activity in HIV-1 infected individuals in vivo. *PLoS One* 2011;6:e27284.
25 Ahmed MIM, Ntinginya NE, Kibiki G, *et al*. Phenotypic changes on Mycobacterium tuberculosis-specific CD4 T cells as surrogate markers for tuberculosis treatment efficacy. *Front Immunol* 2018;9:2247.
26 Gupta RK, Turner CT, Venturini C, *et al*. Concise whole blood transcriptional signatures for incipient tuberculosis: a systematic review and patient-level pooled meta-analysis. *Lancet Respir Med* 2020;8:395–406.
27 Scriba TJ, Fiore-Gartland A, Penn-Nicholson A, *et al*. Biomarker-Guided tuberculosis preventive therapy (CORTIS): a randomised controlled trial. *Lancet Infect Dis* 2021;21:354–65.
28 Warsinske HC, Rao AM, Moreira FMF, *et al*. Assessment of validity of a blood-based 3-Gene signature score for progression and diagnosis of tuberculosis, disease severity, and treatment response. *JAMA Netw Open* 2018;1:e183779.
29 Sweeney TE, Braviak L, Tato CM, *et al*. Genome-Wide expression for diagnosis of pulmonary tuberculosis: a multicohort analysis. *Lancet Respir Med* 2016;4:213–24.
30 Mendelson F, Griesel R, Tiffin N, *et al*. C-Reactive protein and procalcitonin to discriminate between tuberculosis, Pneumocystis jirovecii pneumonia, and bacterial pneumonia in HIV-infected inpatients meeting who criteria for seriously ill: a prospective cohort study. *BMC Infect Dis* 2018;18.
31 Huang C-T, Lee L-N, Ho C-C, *et al*. High serum levels of procalcitonin and soluble TREM-1 correlated with poor prognosis in pulmonary tuberculosis. *J Infect* 2014;68:440–7.
32 Feng J-Y, Su W-J, Pan S-W, *et al*. Role of TREM-1 in pulmonary tuberculosis patients- analysis of serum soluble TREM-1 levels. *Sci Rep* 2018;8.
33 Kumar NP, Velayutham B, Nair D, *et al*. Angiopoietins as biomarkers of disease severity and bacterial burden in pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2017;21:93–9.
34 Kathamuthu GR, Moideen K, Baskaran D, *et al*. Tuberculous lymphadenitis is associated with altered levels of circulating angiogenic factors. *Int J Tuberc Lung Dis* 2018;22:557–66.
35 Sivro A, McKinnon LR, Yende-Zuma N, *et al*. Plasma cytokine predictors of tuberculosis recurrence in Antiretroviral-Treated human immunodeficiency virus-infected individuals from Durban, South Africa. *Clin Infect Dis* 2017;65:819–26.
36 La Manna MP, Orlando V, Li Donni P, *et al*. Identification of plasma biomarkers for discrimination between tuberculosis infection/disease and pulmonary non tuberculosis disease. *PLoS One* 2018;13:e0192664.
37 Chegou NN, Sutherland JS, Malherbe S, *et al*. Diagnostic performance of a seven-marker serum protein biosignature for the diagnosis of active TB disease in African primary healthcare clinic attendees with signs and symptoms suggestive of TB. *Thorax* 2016;71:785–94.
38 Collins GS, Reitsma JB, Altman DG, *et al*. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMC Med* 2015;13:1–10.
39 Trevethan R, Sensitivity TR. Sensitivity, specificity, and predictive values: foundations, Pliabilities, and pitfalls in research and practice. *Front Public Health* 2017;5:307.
40 Agency ZS. Quality control manual provincial report Harare central census office. Available: https://www.zimstat.co.zw/wp-content/uploads/publications/Population/population/Harare.pdf [Accessed 03 Aug 2021].
41 Population M. (demographics, maps, graphs), 2021. Available: https://worldpopulationreview.com/countries/mozambique-population [Accessed 27 Jul 2021].
42 ZIMBABWE NATIONAL HIV/AIDS AND TUBERCULOSIS CONTROL PROGRAMMES. Republic of Zimbabwe national HIV/AIDS and tuberculosis control programmes. Available: https://www.who.int/hiv/pub/guidelines/zimbabwe.pdf [Accessed 01 Sep 2021].

Acknowledgements

I would like to extend my deepest gratitude to my supervisors for their unwavering support, insightful guidance, and mentorship which have been invaluable throughout my PhD journey. Special thanks to my family and friends for their constant support, love, and patience. I also wish to acknowledge the teams in the ERASE-TB consortium; from the Biomedical Research and Training Institute and the Zvitambo Research Institute in Zimbabwe, the Instituto Nacional de Saúde in Mozambique, the National Institute for Medical Research - Mbeya Medical Research Centre in Tanzania and the central coordination team from the Institute of Infectious Diseases and Tropical Medicine, LMU University Hospital, LMU, whose exceptional efforts and contributions were instrumental in making this research possible..

Complete list of my publications

1. **Marambire ET**, Calderwood CJ, Larsson L, Held K, Khan P, Banze D, Nhamuave C, Minja LT, Mfinanga A, Gupta RK, Khosa C, Mutsvangwa J, Heinrich N, Kranzer K. Prediction models for *Mtb* infection among adolescent and adult household contacts in high tuberculosis incidence settings. PLOS Global Public Health. 2025;5(3): e0004340. doi: 10.1371/journal.pgph.0004340

2. Banze D, Calderwood C, Nhamuave C, **Marambire E**, Mfinanga A, Larsson L, Malhotra A, Minja L, Ivanova O, Zurba L, Heinrich N, Ferrand R, Fielding K, Kranzer K, Rachow A, Hurst J, Khosa C. Implications of reference equations for interpretation of spirometry in three African countries: a cross-sectional study. ERJ Open Research (2025). 00932-2024. Doi: 10.1183/23120541.00932-2024.

3. Waterous P, Chingono R, Mackworth-Young C, Nyamayaro C, Kandiye FR, **Marambire E**, Schellenberg J, Mutsvangwa J, Chonzi P, Kavenga F, Ferrand R, Kranzer K, Bernays S. Person-centered and youth-oriented interventions to improve TB Care for adolescents and young adults. PLOS Glob Public Health. 2024;4(11):e0003659. doi: 10.1371/journal.pgph.0003659. eCollection 2024. PubMed PMID: 39546535; PubMed Central PMCID: PMC11567634.

4. **Marambire ET**, Abdulahi A, Wondie A, Gize A, Mekonnen AT, Khadka K, Manhica I, Quinn N, Saiwal N, Mufune T, Valiyakath VQ, Froeschl G. Intergenerational impact of drought and famine on health systems in developing countries - symposium proceedings. BMC Proc. 2024 Nov 5;18(Suppl 23):24. doi: 10.1186/s12919-024-00310-4. PubMed PMID: 39497154; PubMed Central PMCID: PMC11536704.

5. Calderwood CJ, **Marambire ET**, Larsson L, Banze D, Mfinanga A, Nhamuave C, Appalarowthu T, Mugava M, Ribeiro J, Towo PE, Madziva K, Dixon J, Held K, Minja LT, Mutsvangwa J, Khosa C, Heinrich N, Fielding K, Kranzer K. HIV, malnutrition, and noncommunicable disease epidemics among tuberculosis-affected households in east and southern Africa: A cross-sectional analysis of the ERASE-TB cohort. PLoS Med. 2024 Sep;21(9):e1004452. doi: 10.1371/journal.pmed.1004452. eCollection 2024 Sep. PubMed PMID: 39283906; PubMed Central PMCID: PMC11441706.

6. Calderwood CJ, **Marambire E,** Nzvere FP, Larsson LS, Chingono RMS, Kavenga F, Redzo N, Bandason T, Rusakaniko S, Mujuru HA, Simms V, Khan P, Gregson CL, Ndhlovu CE, Ferrand RA, Fielding K, Kranzer K. Prevalence of chronic conditions and multimorbidity among healthcare workers in Zimbabwe: Results from a screening intervention. PLOS Glob Public Health. 2024;4(1):e0002630. doi:

10.1371/journal.pgph.0002630. eCollection 2024. PubMed PMID: 38261562; PubMed Central PMCID: PMC10805297.

7. **Marambire ET**, Chingono RMS, Calderwood CJ, Larsson L, Sibanda S, Kavenga F, Nzvere FP, Olaru ID, Simms V, McHugh G, Bandason T, Redzo N, Gregson CL, Maunganidze AJV, Pasi C, Chiwanga M, Chonzi P, Ndhlovu CE, Mujuru H, Rusakaniko S, Ferrand RA, Kranzer K. Evaluation of a comprehensive health check offered to frontline health workers in Zimbabwe. PLOS Glob Public Health. 2024;4(1):e0002328. doi: 10.1371/journal.pgph.0002328. eCollection 2024. PubMed PMID: 38190397; PubMed Central PMCID: PMC10773946.

8. Taruvinga T, Chingono RS, **Marambire E**, Larsson L, Olaru ID, Sibanda S, Nzvere F, Redzo N, Ndhlovu CE, Rusakaniko S, Mujuru H, Sibanda E, Chonzi P, Siamuchembu M, Chikodzore R, Mahomva A, Ferrand RA, Dixon J, Kranzer K. Exploring COVID-19 vaccine uptake among healthcare workers in Zimbabwe: A mixed methods study. PLOS Glob Public Health. 2023;3(12):e0002256. doi: 10.1371/journal.pgph.0002256. eCollection 2023. PubMed PMID: 38127934; PubMed Central PMCID: PMC10734954.

9. **Marambire ET**, Banze D, Mfinanga A, Mutsvangwa J, Mbunda TD, Ntinginya NE, Celso K, Kallenius G, Calderwood CJ, Geldmacher C, Held K, Appalarowthu T, Rieß F, Panzner U, Heinrich N, Kranzer K. Early risk assessment in paediatric and adult household contacts of confirmed tuberculosis cases by novel diagnostic tests (ERASE-TB): protocol for a prospective, non-interventional, longitudinal, multicountry cohort study. BMJ Open. 2022 Jul 19;12(7):e060985. doi: 10.1136/bmjopen-2022-060985. PubMed PMID: 36427173; PubMed Central PMCID: PMC9301805.

10. Chingono RMS, Nzvere FP, **Marambire ET**, Makwembere M, Mhembere N, Herbert T, Maunganidze AJV, Pasi C, Chiwanga M, Chonzi P, Ndhlovu CE, Mujuru H, Rusakaniko S, Olaru ID, Ferrand RA, Simms V, Kranzer K. Psychological distress among healthcare workers accessing occupational health services during the COVID-19 pandemic in Zimbabwe. Compr Psychiatry. 2022 Jul;116:152321. doi: 10.1016/j.comppsych.2022.152321. Epub 2022 Apr 30. PubMed PMID: 35576673; PubMed Central PMCID: PMC9055394.

11. Kavenga F, Rickman HM, Chingono R, Taruvinga T, Marembo T, Manasa J, **Marambire E**, McHugh G, Gregson CL, Bandason T, Redzo N, Maunganidze A, Magure T, Ndhlovu C, Mujuru H, Rusakaniko S, Manangazira P, Ferrand RA, Kranzer K. Comprehensive occupational health services for healthcare workers in Zimbabwe during the SARS-CoV-2 pandemic. PLoS One. 2021;16(11):e0260261. doi: 10.1371/journal.pone.0260261. eCollection 2021. PubMed PMID: 34813627; PubMed Central PMCID: PMC8610265.