Characterising progression and regression patterns across the spectrum of tuberculosis: a multistate modelling approach

Leyla Larsson, Claire J Calderwood, Edson T Marambire, Rishi K Gupta, Denise Banze, Alfred Mfinanga, Mishelle Mugava, Etienne Leroy-Terquem, Joseph Jacob, Daisuke Yamada, Francisco Trinchan Fernandez, Patrick Lungu, Anita Mesic, Celso Khosa, Tina Minja, Junior Mutsvangwa, Michael Lauseker, Kathrin Held, Norbert Heinrich, Katharina Kranzer* on behalf of the ERASE-TB consortium†*

Summary

Background The conceptualisation of tuberculosis has undergone a paradigm shift from binary states to a spectrum, resulting in the International Consensus for Early TB (ICE-TB) framework. This study aimed to use data from a prospective, observational cohort study and multistate modelling to address the lack of contemporary data to quantify movement between ICE-TB states.

Methods ERASE-TB was a prospective, observational cohort study evaluating novel diagnostic tests for earlier detection of tuberculosis. Household contacts aged at least 10 years in Zimbabwe, Tanzania, and Mozambique were followed up 6-monthly for 12–24 months with comprehensive tuberculosis investigations at each visit. Those not diagnosed with prevalent tuberculosis, with state classification from at least two timepoints were included. ICE-TB states were defined by use of symptomatology, interferon gamma release assays, chest radiographs, and sputum microbiology. A Markov multistate model based on ICE-TB was applied with one initial state (*Mycobacterium tuberculosis* non-infection), two intermediate states (*M tuberculosis* infection and non-infectious disease [asymptomatic–symptomatic]), and one absorbing state (infectious disease [asymptomatic–symptomatic]). Transition probabilities were predicted.

Findings 1789 (84·8%) of 2109 recruited household contacts were included. At enrolment, most (1000 [55·9%]) did not have *M tuberculosis* infection; 674 (37·7%) had *M tuberculosis* infection, and 115 (6·5%) had non-infectious disease. 34 people developed infectious disease (23 asymptomatic, 11 symptomatic). In the multistate model, the transition probabilities of progressing from *M tuberculosis* non-infection to *M tuberculosis* infection and *M tuberculosis* infection to non-infectious disease were 13% and 3% by month 12. For those in non-infectious disease, the probabilities of regression and progression by month 12 were 85% and 13%, respectively.

Interpretation This study applied the ICE-TB framework to describe movement between states by use of contemporary, granular, longitudinal data. Although most people remained static over time, the non-infectious state was more dynamic, with most people regressing over time.

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*Joint last authors

†Members are listed in the appendix

Institute of Infectious Diseases and Tropical Medicine, Ludwig Maximilian University Hospital, Munich, Germany (L Larsson MSc, E T Marambire PhD, K Held PhD, N Heinrich MD, Prof K Kranzer PhD); **The Health Research Unit Zimbabwe, Biomedical Research and Training Institute, Harare, Zimbabwe** (C J Calderwood PhD, E T Marambire, M Mugava BSc, Prof K Kranzer); **UCL Respiratory, Division of Medicine, University College London, London, UK** (R K Gupta PhD, Prof J Jacob PhD); **Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK** (C J Calderwood); **Instituto Nacional de Saúde, Marracuene, Mozambique** (D Banze MD, C Khosa PhD); **National Institute for Medical Research-Mbeya Medical Research Centre, Mbeya, Tanzania** (A Mfinanga MD, T Minja MD); **Soutien Pneumologique International, Paris, France** (E Leroy-Terquem MD); **Satsuma Lab, UCL Hawkes Institute, University College London, London, UK** (Prof J Jacob, D Yamada PhD); **Bulawayo City Health, Bulawayo, Zimbabwe** (F T Fernandez MD); **East, Central, and Southern Africa-Health Community, Arusha, Tanzania** (P Lungu PhD); **Médecins Sans Frontières, Amsterdam, Netherlands** (A Mesic PhD); **Unit of HIV & TB, Clinical Science Department, Institute of Tropical Medicine Antwerp, Antwerp, Belgium** (A Mesic); **Department of Clinical Science and**

Introduction

The global burden of tuberculosis remains substantial despite advances in diagnostic development and drug discovery, with over 10·9 million incident cases and 1·3 million deaths in 2023, primarily due to missed diagnosis.[1] Our understanding of individual disease trajectories following exposure to *Mycobacterium tuberculosis* is largely informed by studies done during the prechemotherapy era.[2–4] These data have recently been synthesised and used in mathematical modelling studies to estimate disease progression and regression.[4,5]

Historically, tuberculosis was categorised into two discrete states—latent and active tuberculosis—with the former referring to *M tuberculosis* infection and the latter describing disease with actively replicating *M tuberculosis* bacilli. This simplistic categorisation has now been replaced by a disease framework with more clearly defined states, published by the International Symposium on New Concepts in Early TB Disease (International Consensus for Early TB [ICE-TB]) after a consensus exercise, which assumes a spectrum of disease.[6–9] The ICE-TB framework includes one non-disease state (*M tuberculosis* infection) and four disease states (asymptomatic tuberculosis non-infectious, asymptomatic tuberculosis infectious, symptomatic tuberculosis non-infectious, and symptomatic tuberculosis infectious disease); defined by varying degrees of symptomatology, macroscopic pathology, and microbiology. Thus far, quantification of the movement along the spectrum of tuberculosis has been estimated with mathematical modelling.[10]

Multistate models are frameworks that describe complex longitudinal processes, often involving multiple states of disease. They therefore offer a promising avenue

International Public Health, Liverpool School of Tropical Medicine, Liverpool, UK (C Khosa); **Biomedical Research and Training Institute, Harare, Zimbabwe** (J Mutsvangwa PhD); **Institute for Medical Information Processing, Biometry, and Epidemiology, Ludwig Maximilian University, Munich, Germany** (M Lauseker PhD); **German Center for Infection Research, Partner site Munich, Munich, Germany** (K Held, N Heinrich); **Fraunhofer Institute for Translational Medicine and Pharmacology, Immunology, Infection and Pandemic Research, Munich, Germany** (K Held); **Department of Clinical Research, London School of Hygiene & Tropical Medicine, London, UK** (Prof K Kranzer)

Correspondence to: Claire Calderwood, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK
claire.calderwood2@lshtm.ac.uk

See Online for appendix

Research in context

Evidence before this study

The current understanding of tuberculosis recognises it as a spectrum of disease rather than the outdated binary classification of latent and active tuberculosis. Most of the understanding has however remained conceptual (eg, the International Consensus for Early TB [ICE-TB] framework) and it is important to apply these conceptual models to understand whether they fit the reality of tuberculosis progression and regression. We searched PubMed for articles published before April 23, 2025 in any language using the terms ("tuberculosis" OR "TB") AND ("spectrum" OR "undul*") AND ("model"). Most current estimates of tuberculosis progression and regression are derived from mathematical models based on historical data from the prechemotherapy era. Horton and colleagues developed a deterministic model that incorporates various stages of tuberculosis, including minimal, subclinical, and clinical tuberculosis. Their findings suggest that 92·0% of individuals self-clear the infection within 10 years, whereas 7·9% progress to tuberculosis, with a proportion developing infectious disease. Richards and colleagues and Ryckman and colleagues quantified the progression and regression across the tuberculosis spectrum using a Bayesian framework. No studies have used individual-level data or multistate modelling to quantify transitions in a contemporary and prospective cohort.

Added value of this study

This is, we believe, the first study to use individual-level data and apply a multistate modelling approach to a large, prospective, longitudinal cohort of household contacts to quantify tuberculosis state transitions by use of the ICE-TB classification. Unlike many previous studies of tuberculosis disease dynamics, which have concentrated on microbiologically confirmed disease, our analysis devotes particular attention to the earlier states of the spectrum, *Mycobacterium tuberculosis* infection, and non-infectious disease, by use of the ICE-TB framework. This focus allows us to characterise undulating pathways in the premicrobiologically confirmed phase, a period that might be amenable to preventive therapy and other early interventions. By integrating high-fidelity and operational reference standards, as proposed in the consensus manuscript by ICE-TB, we provide empirical estimates of progression and regression across the spectrum of tuberculosis. Our findings show that most participants with early tuberculosis states (ie, non-infectious disease; microbiologically negative disease) regressed to non-disease states (*M tuberculosis* infection or non-infection) without treatment. We also highlight the importance of reference standard choice on state allocation and movement, with implications for study design and data interpretation.

Implications of all the available evidence

These findings support a shift from viewing tuberculosis progression as linear and highlight the heterogeneity of disease trajectories and complexity of diagnosis. We also further underscore the regression patterns that are seen particularly among those in non-infectious disease states, which has implications for diagnostic and therapeutic development. Future research and interventions, including biomarker development and vaccine trials, should consider the dynamic nature of early tuberculosis. Importantly, our findings provide a proof-of-concept for the utility of multistate models to track disease transitions, offering a foundation for pooled analyses across longitudinal tuberculosis cohorts to better understand predictors of progression or regression.

by which to understand the movement across the spectrum of tuberculosis states.[11] In this study, we described the movement between ICE-TB states and aimed to establish whether multistate modelling was a suitable approach to quantify tuberculosis progression and regression dynamics within a longitudinal cohort of tuberculosis household contacts. We also modelled the effect of varying definitions of states using symptomatology, pathology, and infectiousness based on an operational reference standard and a higher fidelity reference standard proposed by the ICE-TB group.

Methods

Study design

ERASE-TB was a prospective, observational cohort study evaluating novel diagnostic tests for earlier detection of tuberculosis among household contacts aged at least 10 years.[12] The study enrolled 2109 household contacts of people with highly infectious microbiologically confirmed tuberculosis in three countries in east and southern Africa (Zimbabwe, Mozambique, and Tanzania). Recruitment started in March, August, and September, 2021, in Zimbabwe, Mozambique, and Tanzania, respectively, and continued until 700 household contacts were recruited per site. The household contacts were subsequently followed up every 6 months for 18–24 months.[12]

At enrolment, individual-level and household-level information such as sociodemographics, previous medical history, risk factors, and tuberculosis history was recorded. Tuberculosis screening was done at every visit by use of a combination of the WHO four-symptom screen (W4SS; presence of any of cough, fever, night sweats, or weight loss) and a chest x-ray, evaluated by a local clinical officer. Anyone with a positive symptom screen or abnormal chest x-ray underwent microbiological testing on spontaneous sputum (0·5% underwent sputum induction) by use of Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, CA, USA); hereafter termed Xpert Ultra. Participants with a positive Xpert Ultra result were asked for repeat samples for Xpert Ultra testing and liquid (BACTEC Mycobacterial Growth Indicator Tube system, Becton Dickinson Microbiology Systems, Franklin Lakes, NJ, USA) and solid culture

(Löwenstein–Jensen).[12] Tuberculosis preventive therapy was available to household contacts in all three sites during the recruitment period, but uptake within the cohort was low (<1%). Participants were additionally tested with Xpert Ultra at least once during follow-up, regardless of symptoms and chest x-ray. This approach aimed to maximise microbiological detection among those with negative symptom screens or normal chest x-rays, while recognising that collecting sputum at every visit was not operationally feasible. Chest x-rays were externally reviewed by an expert respiratory physician and a radiologist who classified them into normal or abnormal (unlikely or probable tuberculosis). Certainty of tuberculosis diagnosis and time of diagnosis was established by an endpoint review committee using all available clinical information collected throughout the study. The endpoint review committee classified participants into unlikely, possible, likely, or confirmed tuberculosis (appendix p 2). Participants underwent review by the endpoint review committee if there was discordance between two ERASE-TB study clinicians on study outcome, after the participant had been flagged as having possible tuberculosis.

ERASE-TB was approved by regulatory and ethics committees of the participating institutions and national ethics committees: 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), the ethics committees of the London School of Hygiene & Tropical Medicine, UK (22 522–2), and the medical faculty of the Ludwig Maximilian University, Germany (20–0771). Informed consent was obtained from all eligible adult household contacts. For minors (aged <18 years), informed consent was provided by the parent or guardian and assent was sought from the minor, depending on the local guidelines.

Reference standards and classification

This analysis adopted the ICE-TB framework for the four disease states (asymptomatic–symptomatic and non-infectious–infectious disease) for pulmonary tuberculosis. The ICE-TB consensus group designed the framework with the assumption that a person had to have *M tuberculosis* infection to enter; hence, absence of *M tuberculosis* infection in their model is termed *M tuberculosis* elimination. Herein, we defined the absence of *M tuberculosis* infection (and disease) as *M tuberculosis* non-infection, since initial infection is not a prerequisite for inclusion in the current analysis. Classification into either *M tuberculosis* infection or non-infection was based on the interferon gamma release assay (IGRA), whereby a participant with a positive IGRA was classified into *M tuberculosis* infection and a participant with a negative IGRA was considered to be *M tuberculosis* non-infection.

The disease dimensions required to classify participants into the ICE-TB disease states are symptomatology (measured by presence of symptoms), pathology (measured by presence of radiological abnormalities), and infectiousness (measured by detection of *M tuberculosis* from respiratory samples). For the ICE-TB classification in this study, we used a high-fidelity reference standard, whereby symptomatology was defined as a positive W4SS, pathology as abnormal chest x-ray attributable to tuberculosis on the basis of expert radiology review, and infectiousness as likely or confirmed tuberculosis on the basis of the endpoint review committee (table 1). We also evaluated an operational reference standard, which included symptomatology defined as presence of cough, pathology defined as abnormal chest x-ray attributable to tuberculosis on the basis of local clinical officer reading, and infectiousness defined as Xpert Ultra positivity. To handle potential discordance between dimensions of the ICE-TB framework, state allocation followed a prespecified hierarchy. Microbiological confirmation of tuberculosis (Xpert Ultra or culture positivity) was sufficient to classify participants as infectious disease, irrespective of IGRA status, symptoms, or radiographic findings. In the absence of microbiological confirmation, non-infectious disease was assigned on the basis of radiological evidence. For participants without evidence of disease by these criteria, IGRA status determined classification as *M tuberculosis* infection (IGRA positive) or *M tuberculosis* non-infection (IGRA negative). This hierarchy was applied at every visit and ensured that participants with discordant results (eg, microbiology positive but IGRA negative) were classified by use of the most definitive evidence available rather than excluded or assigned on a single dimension alone.

To illustrate the effect of varying assessment methods on state allocation, we also investigated overlap between different definitions for each disease dimension (table 1). Definitions of symptomatology included any symptom, W4SS, presence of cough, and persistent cough of at least 2 weeks. Pathology was defined as abnormality on chest x-ray attributable to tuberculosis defined by clinical officer, abnormality on chest x-ray attributable to tuberculosis by radiology expert review, or a Computer-Aided Detection

	Macroscopic pathology	Infectiousness	Symptomatology
High-fidelity reference standard	Chest x-ray attributable to tuberculosis (expert review)	ERC (likely or confirmed tuberculosis)	W4SS
Operational reference standard	Chest x-ray attributable to tuberculosis (clinical officer)	GeneXpert MTB/RIF Ultra	Cough
Alternative options	Chest x-ray attributable to tuberculosis (clinical officer), chest x-ray attributable to tuberculosis (expert review), CAD4TBv8 ≥50	ERC (likely or confirmed tuberculosis), Xpert Ultra, culture	Any symptom, W4SS, cough, cough ≥2 weeks

CAD4TBv8=Computer-Aided Detection for Tuberculosis, version 8. ERC=endpoint review committee. GeneXpert MTB/RIF Ultra=WHO-recommended rapid tuberculosis test. W4SS=WHO four-symptom screen.

Table 1: **Disease dimensions and evaluated diagnostic criteria to define the dimensions**

software for tuberculosis [CAD4TB version 8, Delft, 's-Hertogenbosch, Netherlands] score higher than the manufacturer-recommended threshold of 50 (range 0–100 with higher scores increasing probability of tuberculosis).[13] Lastly, infectiousness definitions included tuberculosis classification from the endpoint review committee, Xpert Ultra positivity, or at least one positive culture.

Statistical analysis

This analysis included ERASE-TB participants who were not diagnosed with tuberculosis at baseline, had at least two study visits, and had chest x-rays externally reviewed. Participants were classified into the ICE-TB states both at baseline and over time according to both the high-fidelity and the operational reference standards. Overlap between our definitions of symptomatology, pathology, and infectiousness was described by use of Euler diagrams. Any missing data needed to define disease dimension classifications (chest x-ray, symptoms, and microbiology) was considered to be a negative result (eg, absence of chest x-ray pathology among those with missing chest x-rays). IGRA testing was not systematically done at the three study sites and was hence not available at all scheduled visits (appendix p 1). For participants without evidence of disease, missing IGRA results were replaced with the most recent available result. Distribution of missing results by visit is found in the appendix (p 1).

A time-homogeneous continuous-time Markov multistate model was generated on the basis of a condensed ICE-TB framework with one initial state (*M tuberculosis* non-infection; state 1), two intermediate states (*M tuberculosis* infection; state 2, non-infectious disease [asymptomatic and symptomatic]; state 3), and one absorbing state (infectious disease [asymptomatic and symptomatic]; state 4). The ICE-TB framework was condensed from six to four states owing to the small proportion of participants who ultimately progressed to disease. We specified a time-homogeneous continuous-time Markov model, which assumes constant transition intensities between states over the follow-up period. This approach allows estimation of the probability of occupying each state at any timepoint but does not allow for hazards that change with time since exposure or study entry. Although study visits were scheduled every 6 months, the multistate model used exact time in days between observations (converted to months for reporting) to account for variation in follow-up timing. Participants were right censored at the date of last observation if they were diagnosed with tuberculosis, completed follow-up without tuberculosis, were lost to follow-up, withdrew, or died.

A transition probability matrix was defined whereby only transitions between the following states were possible: *M tuberculosis* non-infection to *M tuberculosis* infection, *M tuberculosis* infection to *M tuberculosis* non-infection, *M tuberculosis* infection to non-infectious disease, non-infectious disease to *M tuberculosis* non-infection, non-infectious disease to *M tuberculosis* infection, and finally non-infectious disease to infectious disease (appendix p 4). As infectious disease was considered to be an absorbing state, exiting transitions were not possible, reflecting the fact that participants were initiated on treatment and exited the study on microbiological confirmation of disease. We considered the transitions between two states to occur between the (fixed) visits.

On the basis of the multistate model, the state occupation probabilities in a 12-month interval were estimated by use of the msm package (version 0.0.3) in R (version 4.4.1). Considering that there is household-level clustering of states, we randomly selected one person per household for the analysis and repeated the process 1000 times. Analogous to multiple imputation, models were combined by use of Rubin's rules. State occupation probabilities were estimated from the transition intensities of this combined model. We did the analysis using the high-fidelity reference standard in the primary analysis. In sensitivity analyses, we first used the operational reference standard, and second ignored clustering by household.

Role of the funding source

The funders had no role in the study design, data collection, data analysis, and data interpretation; in the writing of the manuscript; or in the decision to submit the paper for publication.

Results

1789 people were included in this study, reflecting the population from the ERASE-TB cohort who were not diagnosed with microbiologically confirmed tuberculosis at baseline (21 household contacts had prevalent tuberculosis) and thus excluded from the analysis, had at least two study visits, and who had their chest x-rays externally reviewed (appendix p 5). 608 (34·0%) people were from 237 households in Zimbabwe, 564 (31·5%) from 229 households in Mozambique, and 617 (34·5%) from 256 households in Tanzania (table 2). Most participants (1242 [69·4%]) were adults (aged ≥18 years) and a higher proportion of the cohort was female (1123 [62·8%]). Median time in the study was 23·7 months (IQR 21·7–26·2). At enrolment, 324 (18·1%) people were W4SS positive (307 [94·8%] of 324 had presence of cough) and 77 (4·3%) had likely tuberculosis pathology on chest x-ray according to clinical officer reading (115 [6·4%] on the basis of expert review). 34 (1·9%) of 1789 participants were diagnosed with tuberculosis during follow-up, 289 (16·2%) were lost to follow-up, 11 (0·6%) died, and 1455 (81·3%) completed follow-up.

Baseline ICE-TB classification resulted in most people being classified as *M tuberculosis* non-infection (1000 [55·9%]), followed by *M tuberculosis* infection

(674 [37·7%]), asymptomatic non-infectious disease (90 [5·0%]) and, finally, symptomatic non-infectious disease (25 [1·4%]; table 2, operational reference standard in the appendix p 6).

The overlap of criteria for the disease dimensions was explored by use of Euler diagrams (figure 1). Most variability occurred within the definitions of radiological pathology, with little overlap between CAD4TB, clinical officer reading, and expert review. Of all chest x-rays that were identified as positive by at least one of the modalities, expert review identified 46% as likely tuberculosis, with 31% identified as likely tuberculosis by expert review only (figure 1).

If the participants started the study in a non-disease state (ie, *M tuberculosis* non-infection or *M tuberculosis* infection), then they usually remained in that state throughout the study (figure 2, appendix p 7). Of those who started in *M tuberculosis* non-infection (n=1000), 842 (84·2%) of 1000 were still in *M tuberculosis* non-infection at their last visit, of whom 811 (96·3%) of 842 had remained in the state throughout the study. Of those who started in *M tuberculosis* infection (n=674), 559 (82·9%) of 674 were still in *M tuberculosis* infection at their last visit, of whom 547 (97·9%) of 559 had remained in the state throughout the entire study. On the other hand, participants who started in the non-infectious disease state (n=90) more frequently moved across the spectrum: six (6·7%) of 90 were still in a non-infectious disease state at their last visit, all of whom had remained in that state throughout the entire study. Most of the movement from non-infectious disease was regressive; 74 (82·2%) of 90 moved to a non-diseased state whereas ten (11·1%) of those who started as non-infectious disease progressed to infectious disease. Overall, 34 participants reached an infectious disease state (23 asymptomatic and 11 symptomatic; table 2). Of the 34 participants who reached an infectious disease state, nine started as *M tuberculosis* non-infection, 11 as *M tuberculosis* infection, ten as asymptomatic non-infectious, and four as clinical non-infectious.

Overall, among the 174 people (174 [9·7%] of 1789) who were in a disease state at any point, 20 (11·5%) had started and ended in a disease state, 26 (14·9%) started and ended in a non-disease state but had intermittent disease between these timepoints, 95 (54·6%) started in a disease state but completed follow-up in a non-disease state, and 33 (19·0%) started in a non-disease state but completed follow-up in a state of disease.

We investigated longitudinal clinical measurements (BMI and CAD4TB) among those who reached a non-infectious disease state stratified by whether they then progressed, remained stable, or regressed (appendix p 8). Those with non-infectious disease who progressed to infectious disease had a lower median BMI (median 18·3, IQR 17·2–20·5) compared with those who did not (median 21·7, 18·9–25·8). When looking at CAD4TB results over time, those who progressed to disease had higher median scores (median 52·0, 11·5–72·3) compared with those who did not (median 4·2, 2·3–10·2).

By month 12, the transition probability of going from *M tuberculosis* non-infection to *M tuberculosis* infection

	Total (n=1789)	Zimbabwe (n=608)	Mozambique (n=564)	Tanzania (n=617)
Number of households	722	237	229	256
Tuberculosis outcome (endpoint review committee)				
Incident tuberculosis	34 (1·9%)	10 (1·6%)	15 (2·7%)	9 (1·5%)
No tuberculosis	1755 (98·1%)	598 (98·4%)	549 (97·3%)	608 (98·5%)
Age, years				
10–17	547 (30·6%)	171 (28·1%)	191 (33·9%)	185 (30·0%)
18–35	590 (33·0%)	219 (36·0%)	192 (34·0%)	179 (29·0%)
>35	652 (36·4%)	218 (35·9%)	181 (32·1%)	253 (41·0%)
Sex				
Female	1123 (62·8%)	383 (63·0%)	345 (61·2%)	395 (64·0%)
Male	666 (37·2%)	225 (37·0%)	219 (38·8%)	222 (36·0%)
HIV status*				
Positive	286 (16·0%)	104 (17·1%)	93 (16·5%)	89 (14·4%)
Negative	1503 (84·0%)	504 (82·9%)	471 (83·5%)	528 (85·6%)
ICE-TB classification at baseline†‡				
M tuberculosis non-infection	1000 (55·9%)	299 (49·2%)	377 (66·8%)	324 (52·5%)
M tuberculosis infection	674 (37·7%)	273 (44·9%)	154 (27·3%)	247 (40·0%)
Asymptomatic (non-infectious)	90 (5·0%)	30 (4·9%)	28 (5·0%)	32 (5·2%)
Symptomatic (non-infectious)	25 (1·4%)	6 (1·0%)	5 (0·9%)	14 (2·3%)
ICE-TB classification at endline†‡				
M tuberculosis non-infection	971 (54·3%)	306 (50·3%)	357 (63·3%)	308 (49·9%)
M tuberculosis infection	765 (42·8%)	282 (46·4%)	186 (33·0%)	297 (48·1%)
Asymptomatic (non-infectious)	18 (1·0%)	9 (1·5%)	6 (1·1%)	3 (0·5%)
Symptomatic (non-infectious)	1 (0·1%)	1 (0·2%)	0	0
Asymptomatic (infectious)	23 (1·3%)	6 (1·0%)	9 (1·6%)	8 (1·3%)
Symptomatic (infectious)	11 (0·6%)	4 (0·7%)	6 (1·1%)	1 (0·2%)
Presence of symptoms at baseline§				
No	1465 (81·9%)	490 (80·6%)	510 (90·4%)	465 (75·4%)
Yes	324 (18·1%)	118 (19·4%)	54 (9·6%)	152 (24·6%)
Chest x-ray results at baseline (clinical officer)				
Findings attributable to tuberculosis	77 (4·3%)	38 (6·2%)	17 (3·0%)	22 (3·6%)
Findings unlikely tuberculosis	146 (8·2%)	18 (3·0%)	18 (3·2%)	110 (17·8%)
Normal	1324 (74·0%)	506 (83·4%)	369 (65·3%)	449 (72·8%)
Not done¶	243 (13·6%)	46 (7·6%)	161 (28·5%)	36 (5·8%)
Chest x-ray results at baseline (expert review)				
Findings attributable to tuberculosis	115 (6·4%)	36 (5·9%)	33 (5·9%)	46 (7·5%)
Findings unlikely tuberculosis	62 (3·5%)	22 (3·6%)	12 (2·1%)	28 (4·5%)
Normal	1368 (76·5%)	502 (82·7%)	360 (63·7%)	506 (82·0%)
Not done¶	245 (13·7%)	48 (7·9%)	160 (28·3%)	37 (6·0%)

Data are n (%). ICE-TB=International Consensus for Early TB. *Includes both known positive and newly diagnosed during ERASE-TB study procedures. †ICE-TB classification is based on the main diagnostic criteria used in the study: *M tuberculosis* infection or elimination based on interferon-gamma release assay positivity and disease states based on pathology defined as clinician chest x-ray interpretation attributable or unlikely tuberculosis, infectiousness defined by the endpoint review committee, and signs and symptoms based on any presence of symptoms. ‡First classification is based on first available classification—ie, if no baseline classification is available, second visit is used. Last classification is based on the last available classification—ie, if no classification is available at the last visit, classification at the penultimate visit is used. §Indicates missing values in variable. ¶A larger proportion of chest x-rays were not conducted in Mozambique in the beginning of the study due to issues with machines being broken.

Table 2: **Cohort characteristics by study site among participants included in this study**

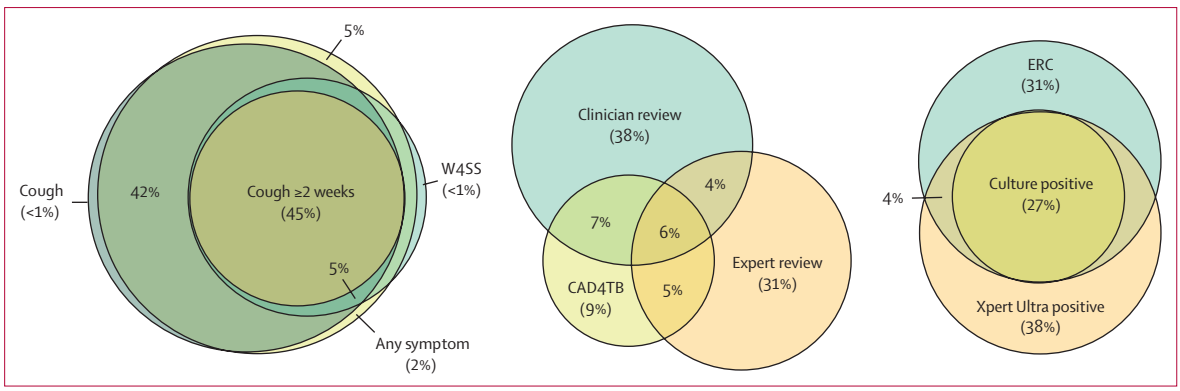

Figure 1: **Overlap between different definitions for presence of symptoms, pathology, and infectiousness as criteria for the ICE-TB states**
CAD4TB score ranged from 0 to 100 and a score higher than 50 was considered positive according to manufacturer-defined thresholds. CAD4TB=computer-aided detection software for tuberculosis. ERC=endpoint review committee. ICE-TB=International Consensus for Early TB . W4SS=WHO four-symptom screen.

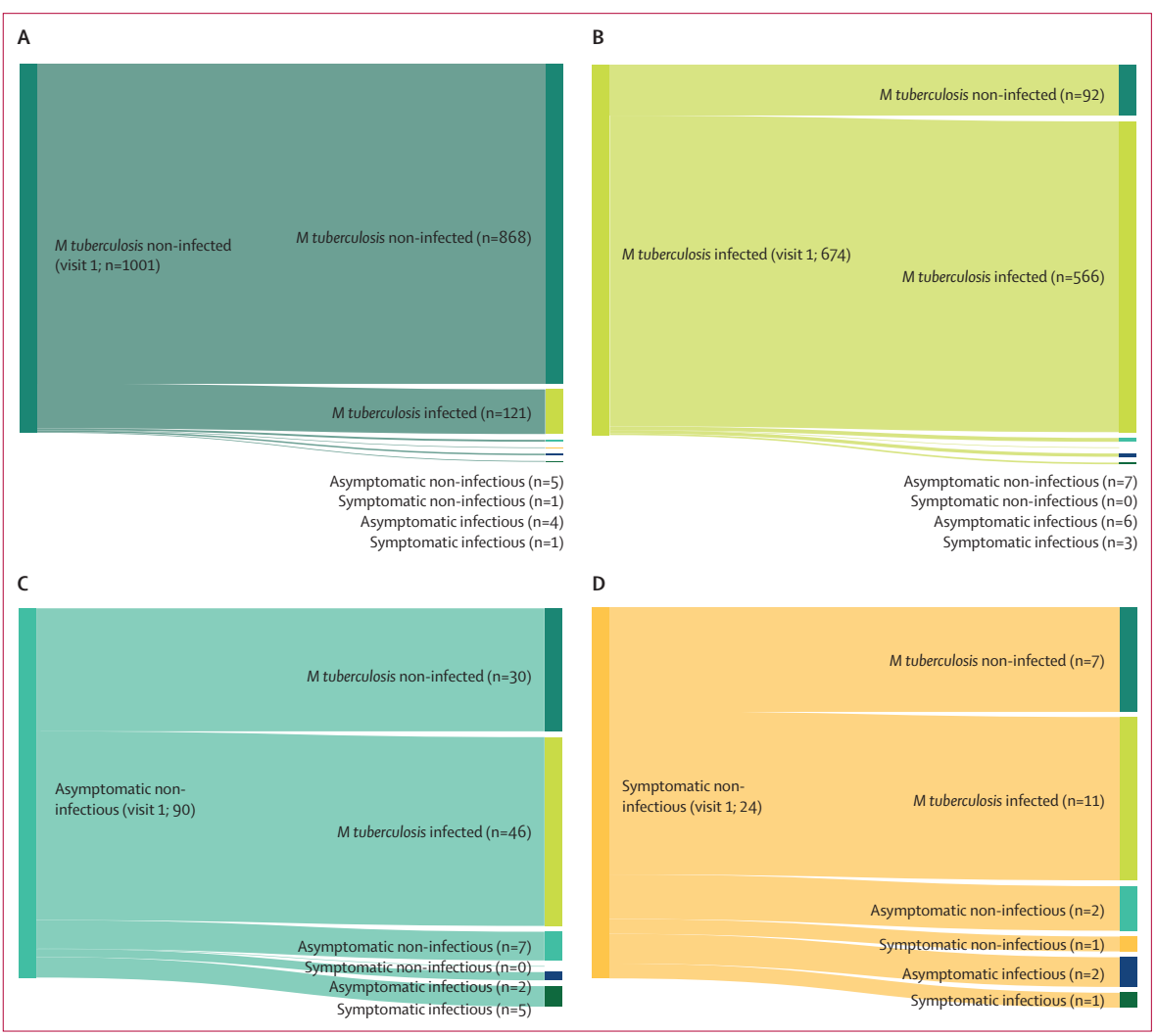

Figure 2: **Proportion of progression and regression across the ICE-TB states between first and last visit**
(A) *M tuberculosis* non-infection. (B) *M tuberculosis* infected. (C) Non-infectious disease. (D) Infectious disease. ICE-TB=International Consensus for Early TB. M *tuberculosis*=*Mycobacterium tuberculosis*.

was 13% (figure 3; transition intensities in the appendix p 9). Starting from *M tuberculosis* infection, the transition probabilities of moving to *M tuberculosis* non-infection, continuing in *M tuberculosis* infection, or progressing to non-infectious disease were 13%, 83%, and 3%. If starting in the non-infectious disease state, the probabilities of regressing to *M tuberculosis* non-infection or *M tuberculosis* infection by month 12 were 34% and 51%, respectively. The probability of non-infectious disease progressing to infectious disease was 13%, whereas only 3% were predicted to remain in non-infectious disease. In sensitivity analyses, proportions were similar when ignoring clustering by household, although use of the operational reference standard almost halved the 12-month infectious disease state occupational probability (appendix pp 10–11).

Discussion

A major limitation to our understanding of tuberculosis progression and regression has been the lack of contemporary longitudinal observational cohort data.[14] Studies evaluating the natural history of tuberculosis by use of modern tools to investigate progression and regression such as digital chest x-rays, liquid automated mycobacterial culture systems, and molecular tests have been lacking. Here, by tracking state allocation over 2 years in a large cohort, using a newly reached consensus classification,[9] we characterised the dynamics of tuberculosis across the spectrum. We have highlighted the implications of varying reference standards and applied multistate modelling as a proof-of-concept, urging its wider use in large longitudinal cohorts.

We have shown that the ICE-TB framework was able to capture movement across the spectrum of tuberculosis. This movement was highly dynamic from the non-infectious disease state, highlighting the undulating nature of tuberculosis disease. The term incipient tuberculosis is variably defined in the literature and is often used to describe people with early or minimal disease thought to be at high risk of progression, although its strict definition implies a known trajectory of imminent progression. In contrast, the ICE-TB framework is cross-sectional and classifies individuals according to their current evidence of disease, without inferring future risk. People classified here as asymptomatic non-infectious disease could be labelled as incipient tuberculosis in some studies, but this should not be interpreted as a prediction of inevitable progression. Here, those initially classified as having non-infectious disease typically regressed, with very few progressions to infectious disease. It is important to note, however, that regression from disease (particularly infectious disease) is difficult to measure in studies such as ERASE-TB, owing to the ethical imperative to treat tuberculosis. Although the ICE-TB framework offered a springboard to conceptually delineate the spectrum of disease, it was restrictive because the point of entry is

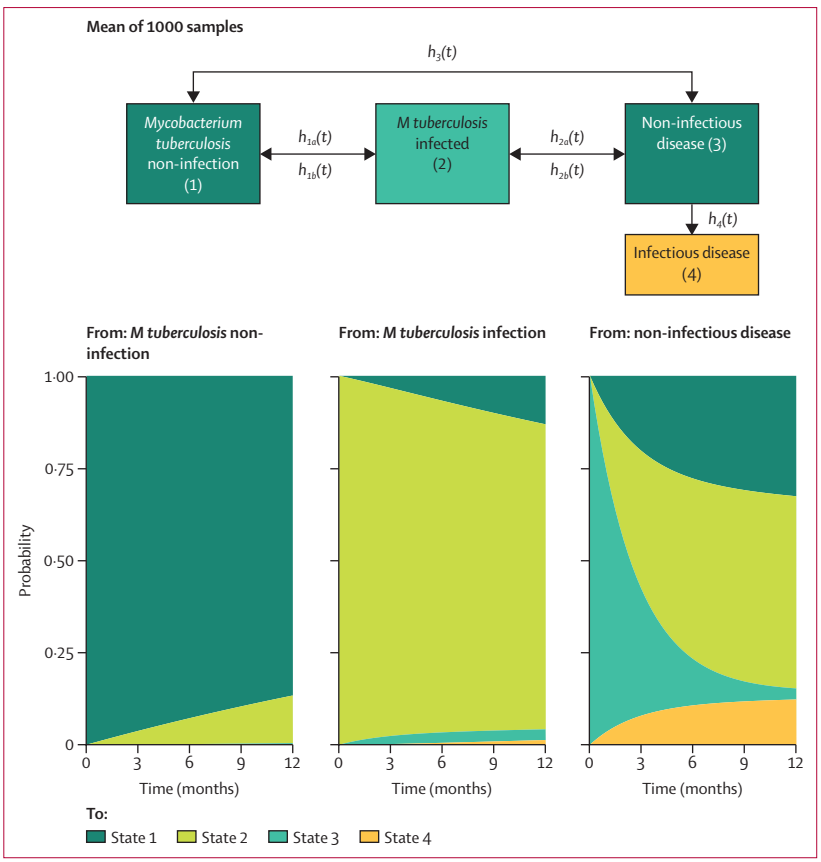

Figure 3: **State occupation probabilities between the ICE-TB states in a simulated 12-month period**
State occupation probabilities are estimated from the mean of 1000 simulated transition intensities whereby one person per household is sampled to account for household-level clustering. The analysis shown above was done on the basis of a high-fidelity reference standard. ICE-TB=International Consensus for Early TB. *h*(*t*)=transition intensity; the instantaneous rate of moving from one state to another. State 1=M tuberculosis non-infection. State 2=M tuberculosis infection. State 3=non-infectious disease. State 4=infectious disease.

M tuberculosis infection (which could be missed in observational cohort studies with infrequent follow-up) and required radiological pathology to enter a disease state (ie, the framework does not cater for positive microbiology in the absence of radiological pathology; although this restriction was not considered in this analysis).

Since the advent of anti-tubercular chemotherapy, imaging technology, mycobacterial detection, and understanding of inflammation and host response have greatly advanced, allowing the detection of more subtle changes.[15] Importantly, microbiological tests for detection of *M tuberculosis* have significantly improved in terms of quality assurance, standardisation, and limits of detection.[15] Historically, microbiological confirmation was primarily done by use of Ziehl–Neelsen sputum smear microscopy, which has a higher limit of detection and lower sensitivity than the now commonly used Xpert Ultra tests: the limit of detection of these tests has crucial implications for someone being classified as infectious or non-infectious.[16] The same holds true for classification

based on radiological macroscopic pathology (ie, chest x-ray), with improved resolution and technical quality from modern, digital chest x-ray machines compared with historical films. Inter-reader and intra-reader variability is known to occur with chest x-rays; as shown in this analysis by the disagreement between clinical officer, expert, and artificial intelligence-supported review. Variability in chest x-ray interpretation is likely to have been greater in prechemotherapy era studies with lower-resolution imaging. This lack of visibility–resolution increases the likelihood of false-negative classification of tuberculosis pathology. If such individuals later developed microbiologically confirmed tuberculosis, whether from new infection or progression of previously undetected disease, this would appear as rapid progression from an earlier disease state, thereby inflating estimated progression rates. Mathematical modelling studies largely based on these older studies might hence report higher rates of disease progression than those estimated here.[5,17] Our estimates are broadly consistent with rates observed in recent adolescent cohorts enrolled in BCG revaccination trials. In the 2025 BCG REVAX trial done in South African adolescents[18], after a median 20 months of follow-up, an initial approximately 15% QuantiFERON test conversion was observed, which is similar to our findings. Their rates of sustained conversions are smaller (7% over 30 months) but the setting is not completely comparable as South Africa has much higher tuberculosis incidence and hence community transmission rates are higher. Furthermore, the BCG trial was not done among household contacts.

Multistate modelling proved viable for estimating state occupation probabilities at different follow-up times, on the basis of time-homogeneous transition intensities between states. The strength of multistate modelling as an analytical approach particularly lies in its improved predictive accuracy owing to its allowance for time-dependent transitions and handling of competing risks. Although time-dependent (ie, not time-homogeneous) models could capture variations and changes in hazards over time, these were not implemented here owing to the small number of transitions to infectious disease and the low statistical power for estimating additional parameters. Hence, the analysis was not able to consider covariates known to affect the likelihood of progression, such as impaired cell-mediated immunity due to malnutrition or HIV. A plethora of longitudinal studies following people at high risk of tuberculosis have been done; these offer an opportunity to create a large individual-person dataset to mitigate some of these limitations.[19–21] Additionally, future studies with longitudinal follow-up, especially those evaluating vaccines to prevent progression from *M tuberculosis* infection to disease, lend themselves to detailed observational analysis of early tuberculosis states.[22] Nonetheless, this proof-of-concept analysis shows that a multistate modelling approach can be applied to describe movement across states.

Strengths of the study include comprehensive evaluation of a large cohort of household contacts over a period of 2 years. We used different methods to assess the three disease dimensions required for ICE-TB state classification, which allowed the investigation of the effect of varying reference standards. A key strength of our analysis is the explicit estimation of progression and regression rates in the premicrobiologically confirmed states of tuberculosis. By applying the ICE-TB framework, we were able to capture transitions within infection and non-infectious disease states. These findings provide valuable insights into the dynamics of early tuberculosis and highlight potential intervention points before individuals develop infectious disease.

This study, however, had limitations. Missed visits, loss-to-follow-up, interval censoring (study visits were scheduled on a 6-monthly basis), and right censoring at 24 months (the maximum follow-up time) are limitations of the analysis and of the study design. This study was also limited by a degree of missingness; although the assumption was made that missingness equated to a negative result, this might not have reflected ground truth. Particularly, IGRA testing was not systematic across all sites or visits, and missing results were imputed by use of last observation carried forward. This might have underestimated or mistimed transitions between infection and non-infection states, particularly in participants with fewer IGRA measurements. Some apparent regressions from the non-infectious state might reflect false-positive classification at the preceding visit. Even with expert chest x-ray reading, transient non-tuberculosis respiratory diseases can produce radiographic abnormalities suggestive of tuberculosis; resolution of such conditions would appear as regression in the model without representing true tuberculosis improvement. Few participants progressed to infectious disease during follow-up, limiting the precision of estimates for transitions into this state. The time-homogeneous Markov model assumed constant transition intensities throughout follow-up, which does not reflect the probable decline in progression risk after initial exposure to the index case. This simplification was necessary owing to the low number of transitions observed, but it might lead to overestimation of cumulative forward-transition probabilities when applied over a fixed time.

Our cohort reflects high-intensity, recent household exposure to an index tuberculosis case, which probably elevates IGRA conversion rates compared with community or population-based cohorts characterised by intermittent or remote exposure. Consequently, although our transition probabilities capture near-term state dynamics following close exposure, they might overestimate infection and regression rates in general population settings where exposure is lower intensity.

Compounding this, *M tuberculosis* infection was defined by use of IGRA results, which are an imperfect proxy for the presence of viable *M tuberculosis*. IGRA positivity might persist in the absence of viable bacilli or be negative in early infection before immune conversion. Some IGRA conversions during follow-up probably reflected infection acquired before enrolment, with immune conversion occurring in the weeks thereafter. Treating diagnostic results as direct state indicators, as we did here, simplifies the modelling but risks misclassification, particularly for transitions between *M tuberculosis* infection and non-infection states. Inclusion of other biomarkers could account for the imperfect sensitivity and specificity of available tests. Lastly, for the participants who progressed, it is possible that this was due to reinfection rather than true progression. This limitation highlights the broader risk that application of these frameworks to high-transmission settings is compromised by the inherent assumption that progression or regression is based on the same infection event.

In conclusion, this is, we believe, the first known longitudinal study that uses granular data and multistate modelling to describe movement between tuberculosis states. Although most people in the non-infection and infection states remained static over time, the non-infectious state was much more dynamic, with most people regressing over time. Future large-scale, high-resolution cohort studies are required to further examine predictors of progression and regression.

Contributors

NH, KK, KH, JM, CK, and TM conceptualised and acquired the funding for the ERASE-TB study. LL, CJC, ETM, DB, AMf, TM, MM, TM, EL-T, CK, JJ, DY, FTF, PL, AMe, and KK contributed to study implementation, data collection, and curation. LL, ML, and KK conceptualised the regression and progression analysis. LL did the analysis supervised by ML and KK. LL received additional analysis support from CJC, RKG, and CK. LL, CJC, EL-T, and DY had access to and reviewed the source data. LL wrote the first draft with input from KK, CJC, CK, and RKG. All authors reviewed and contributed to subsequent drafts. All authors read and approved the final manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Data to recreate this analysis will be made available on publication of the manuscript. 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.

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