

# The Natural History of Untreated Pulmonary Tuberculosis in Adults: A Systematic Review and Meta-Analysis

## Authors

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## **SUMMARY (170 of 150 words)**

Key stages in TB disease can be delineated by radiology, microbiology and symptoms, but transition between relevant stages remains unclear. We sought to quantify progression and regression across the TB disease spectrum by systematically reviewing studies of individuals with untreated TB undergoing follow up. Summary estimates were extracted to align with TB disease transitions in a conceptual model and meta-analysis was performed thereon. Progression from microbiologically negative to positive disease (based on smear or culture) in those with radiographic TB evidence occurred at an annualized rate of 10% (95% CI:6.2-13.3) with “active” TB imaging, and 1% (95% CI:0.3-1.8) with “inactive” TB imaging. Reversion from microbiologically-positive to -undetectable in prospective cohorts occurred at an annualized rate of 12% (95% CI: 6.8-18.0). Studies reported symptoms poorly disallowing direct estimation of transitions for subclinical (asymptomatic, culture positive) disease. Our findings can inform the parameterization of models to more accurately determine global disease burden estimates, and impact clinical guidelines and policy decisions through informing on the risk of progression in relation to CXR findings.

## **KEY MESSAGES**

1. This systematic review has used historical literature to better capture progression and regression during the early stages of TB , delineated by radiology, microbiology and symptoms, using 34 cohorts with a combined sample of 139,212 participants within our analysis.
2. We show that adults and adolescents with CXRs suggestive of active TB who are microbiologically negative progress to microbiologically-positive disease at a rate of 10% per year
3. We show adults and adolescents with CXRs suggestive of inactive TB who are microbiologically-negative progress to microbiologically-positive disease at a rate of 1% per year
4. We quantify reversion (self-cure) from being microbiologically -positive to microbiologically-negative occurs at a rate of 12% per year
5. Our results highlight that those with CXR changes suggestive of active TB are at high risk of progression. Clinical trials are needed to better determine the optimal interventions for this group.
6. This data will help to more precisely parameterise TB models enabling more accurate assessment of global TB burden and potential impacts of innovative control models and new diagnostic tools.

## **INTRODUCTION (484 words)**

Despite a clinical awareness of tuberculosis (TB) for centuries, its natural history is incompletely understood. We have oscillated between characterizing TB with binary states of latent infection and active disease, to a condition existing on a dynamic continuum(1–4). In the early 20th century, TB control relied on early identification of those with evidence of disease, particularly through chest X-ray (CXR) screening. Researchers were able to highlight the heterogeneity and dynamics of disease evolution between individuals, through longitudinal assessment(5–8). With the discovery of effective treatment in the mid-20<sup>th</sup> century and driven by the need for scalable, programmatic treatment algorithms, a binary description of disease states reflecting two extremes (‘latent infection’ and ‘active disease’) became established(9). Although this provided a useful paradigm, the more nuanced understanding of disease natural history was arguably forgotten.

An accurate understanding of the kinetics of TB natural history is now increasingly critical at both population and individual level, with implications for disease management, population-level prevention and control, and disease burden estimations. Treatment of patients that fall between active and latent TB - for instance having abnormalities suggestive of active disease on X-ray but microbiologically negative - is not adequately covered by management algorithms, but progress could be driven by adequate understanding of the risk of disease progression. A better understanding of this natural history is also a key priority for vaccine development(10). In addition, estimates of TB incidence currently rely strongly on assumptions around the progression, regression and mortality from untreated TB, of which only mortality estimates are informed by systematic review of available literature(11–13). Furthermore, estimation methods do not cater to different stages of TB which are detected in disease prevalence surveys, including individuals who have culture positive disease but a negative symptom screen (referred to as subclinical), or those with TB suggestive X-rays(14). Given the implications for health care seeking and potential for interrupting or preventing transmission, a better understanding of this natural history is key to inform TB burden estimation and policies for care and prevention.

Within the disease continuum, key stages in the evolution of pulmonary TB can be marked by diagnostic tests that have been available for over a century, to allow for categorization within a widely accepted conceptual framework (Figure 1)(1,2). The emergence of disease pathology is generally first visible by typical radiographic features, with differing sensitivity according to radiographic tool used. Microbiological detection in sputum signals presence of bacilli (and potential infectiousness), and the reporting of symptoms marks the development of active, clinical disease. Transitions across all of these stages can only be fully studied in the absence of treatment and hence can no longer be ethically investigated. We conducted a systematic review focusing on articles from the pre-chemotherapy era to determine which of the transitions could be adequately described by existing literature, with the aim of providing parameters for the rate of progression and regression of disease across the spectrum.



## **METHODS (1110 words)**

### **Search strategy and selection criteria**

This systematic review and meta-analysis was conducted following a protocol registered at PROSPERO (CRD42019152585). The study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines(17). We searched for articles from the pre-chemotherapy era combining electronic and manual searches. Electronic searches were conducted in Medline (via PubMed), EMBASE and Web of Science from the start of the database (1946, 1947, and 1900 respectively) until 31<sup>st</sup> December 1960, in two languages with high yield for study designs of interest in this period: English and German. Additionally, we manually searched titles from Index Medicus between 1903 and 1945; volumes from 1895-1902 were not available. The systematic search was restricted to manuscripts published prior to 1960 to include cohorts observed from the pre-chemotherapy era while allowing for a publication delay of earlier cohorts. Furthermore, supplementary searches were conducted in extensive author collections. Further references were snowballed from those articles that met the criteria for data extraction and from key review articles. Personal libraries and snowballed references were searched without date restriction.

Electronic search terms used both modern and historical terminology in English and German (full search strategies in supplementary pages 30-32). All titles were imported into Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). After de-duplication, titles and abstracts were screened for relevance by two independent reviewers, with a third reviewer resolving conflicts (English: BS, ASR, BF, FB, AO-A, TH, RMGJH, HE; German: TH, BH, KK) . Full text articles were sought online, within the library stores at the Wellcome and British libraries (English articles) and the library of the German Central Committee against Tuberculosis (DZK) and the German Tuberculosis Archive (DTA) (German articles), and on online archive websites (e.g HathiTrust.org and archive.org). If manuscripts could not be found through any of these sources, they were not included. At full-text stage, two independent reviewers reviewed eligibility. Articles were included if they presented a longitudinal cohort of at least 25 adolescents ( $\geq 10$  years) and/or adults followed up (radiologically, microbiologically and clinically) for at least 12 months from the point of either (1) positive Tuberculin Skin Test (TST) following recent TB exposure, (2) radiographic abnormalities

suggestive of TB or (3) positive microbiology for TB (smear microscopy and/or mycobacterial culture). A minimum of 12 months was selected in order to ensure an adequate number of events. Articles were excluded if they made no attempt at microbiological confirmation of disease, presented no new data (i.e. review article), all participants received a therapeutic (medical or surgical) intervention or those who did not receive a therapeutic intervention could not have data extracted separately, or where  $\geq 5\%$  of the cohort were paediatric (<10 years) and these children could not be separated from the adolescent/adult data.

Eligible articles were assessed for risk of bias with an adapted Newcastle-Ottawa Scale (NOS) to a maximum of seven stars (NOS - General Quality Assessment) by two reviewers per language (supplementary page 3) with conflicts resolved by consensus (English: BS, ASR, BF, FB, AO-A, TH, RMGJH, HE; German: TH, BH, KK). To pass the quality assessment, studies could only lose two stars in the “Study Selection” and “Outcome” domains of the NOS. The “comparability” domain was not assessed as this systematic review did not use control groups. An additional quality assessment tool was designed to assess the quality of specific diagnostic compartments in study cohorts i.e. radiological, microbiological and symptoms (supplementary pages 4-5). While this Specific Quality Assessment was captured to get a sense of quality of the study designs, it did not inform study eligibility. Those that passed the NOS were extracted in a standardized electronic tool by one reviewer and then datapoints confirmed by a second reviewer with conflicts were resolved by consensus, involving input from additional reviewers if needed.

### **Data extraction and analysis**

We extracted data corresponding to the proportion of individuals in the cohort transitioning between diagnostic states (figure 1) over a specified period of time. Recognizing that description of symptom status in particular may not always be explicit by current standards this could be recorded as unknown as long as microbiological status was clear. Where authors differentiated abnormal chest imaging that was suggestive of TB versus not suggestive then we only extracted the TB-suggestive group as abnormal. In addition, where authors provided a subgroup of abnormal chest X-rays that were limited to only calcified nodules then we did not deem these to be an abnormal X-ray for the purpose of this review, based on guidance for this group being

that they require no intervention or follow up(18). The clinical classification method of the National Tuberculosis Association Diagnostic Standards and Classification of Tuberculosis facilitated extraction of the data(19).

Certain studies presented the proportion of individuals who progressed within a window of time rather than at a specific time point; in these cases, we have presented datapoints as at the midpoint of the time window provided. All summary estimates are presented with 95% confidence intervals, calculated from the point data provided. To allow for exploration of the data and any heterogeneity, we attempted to collect data on variables of interest, namely: age distribution, sex, frequency of follow up visits, microbiological test used (i.e. culture versus smear), CXR characteristics described by the historical study's authors, TST data, local disease burden as per today's WHO classification(20), features of the study design (i.e. passive versus active versus mixed case finding and whether the data was generated from two cross-sectional assessments of participants ("single follow-up") or through a cumulative count of events over time ("cumulative count")), the enrollment setting, and symptom status.

To allow comparison of the varying follow-up times, the last data point of each study was annualised and the expected number transitioning in the first year calculated. The variance of the annualised rate was then calculated using the `escalc` function from the `metafor` package(21), specifying the raw proportion measure. Meta-analysis was then conducted using the `rma` function with the study outcome and variance as inputs. By default each study was weighted proportional to the inverse of the variance calculated in the previous step. The forest plots were created using the `forest` function from the `meta` package. Confidence interval proportions were limited to between 0 and 1 by the `observation limit` argument within the `forest` function. Sub analyses were also conducted using the `rma` function and added to the forest plot using the `addpoly` function from `metafor`. Heterogeneity was assessed with the  $I^2$  and  $\tau^2$  statistics. This analysis with abovementioned packages was done with R (version 4.0.3).

## **Role of the funding source**

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

## **RESULTS (1218 words)**

After de-duplication a total of 10477 titles and abstracts were screened of which 8829 were deemed not relevant (figure 2). 145/1648 (8.8%) full texts could not be sourced. A further 1280 studies were deemed to meet exclusion criteria, leaving 223 for bias assessment. A high risk of bias was found in 109 studies and an additional 90 could not reliably have data extracted and therefore did not contribute to our results (supplementary pages 21-25). In total, 22 English and two German articles, with a combined sample of 139,212 participants contributed 34 cohorts for analysis. Eight of the 24 studies scored maximal scores on the General Quality Assessment. The quality of data on symptom status was generally poor, with 10 studies scoring zero stars in the Specific Quality Assessment (supplementary page 6).

The setting for the 34 longitudinal cohorts were as follows: workplace or university screening (n=5), general community screening (n=7), from household contact studies (n=4), clinical cohorts at clinics or sanatoria (n=9) and control arms of therapeutic interventions (n=9) (table 2 and supplementary page 20). Cohorts were conducted in Europe (n=10), Asia (n=11), North America (n=11), Africa (n=1) and South America (n=1). Eleven of the 34 cohorts provided an estimate of the local burden of TB disease in the study setting and related time period. The majority (n=9/11) of these settings would be classified as endemic or high burden TB settings, and the remainder (n=2/11) as medium burden, based on today's WHO classification(20). Cohorts were conducted between 1923 and 2004 with 20/34 (58.8%) prior to 1960.

We did not identify any cohorts, meeting our inclusion and quality criteria, closely following up confirmed recent TST converters where transition from normal chest X-ray (CXR) to CXR suggestive of TB was reported. We identified four cohorts following up participants with normal radiography, negative microbiological testing where the timepoint of initial infection was unclear, with either no evidence of symptoms (n=3 (75%)) or unrecorded symptom status (n=1 (25%)) (table 2). We identified 24 cohorts following-up participants with evidence of radiographic abnormalities and negative microbiology but with either no symptoms (n=8 (33%)), symptoms (n=3 (13%)) or mixed/unknown symptoms (n=13 (54%)) initially. Of these 24 cohorts, the radiographic abnormalities were specified by the original authors as either

active (n=9 (38%)) or inactive/fibrotic (n=7 (33%)), with the remaining being mixed or not specified (n=8 (29%)). We identified six cohorts following participants with microbiologically detectable tuberculosis either initially with symptoms (n=4 (67%)) or those with an unknown symptom status (n=2 (33%)), however there were no cohorts found in which patients were documented to be asymptomatic. There were also no studies of participants found to have microbiologically-detectable tuberculosis but with normal CXRs.

## 1 Progression to microbiologically positive disease in those with abnormal chest X-ray at baseline

2 From the 24 cohorts with abnormal chest radiography but no evidence of *M. tb* on respiratory sampling at  
3 baseline representing 11,185 participants, development of microbiologically-detectable incident disease  
4 occurred in between 1 – 58% of individuals with the studies reporting a median follow-up of three years (range  
5 12-156 months) (figure 4). Considerable statistical heterogeneity was seen across cohorts ( $I^2 = 97.3%$ ,  
6  $\tau^2=0.001$ ,  $p<0.01$ ). A funnel plot of the publications contributing to this primary analysis is available on  
7 supplementary page 29 and demonstrated asymmetry contributed to by the studies relating to inactive TB. We  
8 considered that the radiographic abnormalities categorized as active versus inactive TB (as specified by the  
9 original authors; supplementary page 17) could represent distinct pathological states contributing to clinical  
10 variability of studies. Therefore we did not pool these studies in meta-analysis, but rather conducted stratified  
11 meta-analysis to describe the progression of these two states separately. The annualized rate of transition from  
12 microbiologically negative to positive was 10% (95% CI: 6.2-13.3) for those in the nine cohorts described to  
13 have active changes on radiography compared to 1% (95% CI: 0.3-1.8) for those in the seven cohorts with  
14 inactive changes (figure 4). Over a three-year period, this would equate to an incidence of 26% (95%CI: 17-  
15 35) in those with active TB changes vs 3% (95%CI: 1-5) with inactive TB changes progressing from  
16 microbiologically negative to positive disease. Statistical heterogeneity in the active and inactive TB  
17 subgroups was lower than in all cohorts taken together,  $I^2 = 77.4%$  and  $I^2 = 53.2%$  respectively. The annual  
18 incidence in cohorts with “mixed” radiographic changes was 6% (95% CI: 1.5-11.1) - in between the values  
19 for inactive and active strata.

20  
21 Out of 24 cohorts that contributed patients to this group, 18 (75%) used culture as part of microbiological  
22 work-up and the remainder ( $n=6/24$ ) did not specify the microbiological tests undertaken. Restricting this  
23 analysis to the 18/24 cohorts explicitly using culture had little impact on these results (supplementary page  
24 26). Only 11 cohorts provided data on symptom status. Of the 9 cohorts described to have active TB changes  
25 on radiography, three were in symptomatic individuals, with  $n=117$  individuals. Progression in this subgroup  
26 was at an annualized rate of 12% (95% CI: 2.73-20.75) (supplementary page 27). There was only one cohort  
27 describing active TB changes on radiography in an asymptomatic group with the remainder unknown.

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In the four cohorts following up those with no radiographic changes suggestive of any TB (table 2), transition to microbiologically positive occurred at an annualized rate of 0.1% (95% CI: 0.1-0.17) (figure not shown). In “single follow up” and “cumulative count” studies, those with active TB changes showed similar annual progression.

#### 40 **Regression to negative microbiology in those with positive microbiology at baseline**

41 Six cohorts followed a total of 1115 participants with evidence of *M. tb* in respiratory samples at baseline and  
42 assessed the proportion transitioning to a microbiologically undetectable state without treatment or  
43 intervention. The median follow-up for the cohorts was 34.5 months (range 6-62 months). The majority of  
44 these cohorts included participants with limited or minimal disease on CXR - either due to this being entry  
45 criteria into the original study or due to the eligibility criteria of this systematic review. No studies were able  
46 to adequately describe symptom status of the participants and all were conducted prior to the discovery of  
47 HIV. Three out of six were retrospective cohorts from TB hospitals or sanatoria and three were prospective  
48 cohorts from general community/household surveys or a placebo arm of a trial. In four of the six cohorts,  
49 culture was used to assess microbiological status of participants while in two cohorts, both retrospective, either  
50 microscopy was used or nature of microbiological investigations was not specified. With meta-analysis, this  
51 transition occurred at an annualized rate of 18% (95% CI: 3.0-33.7) (figure 4b), but there was considerable  
52 heterogeneity across these studies ( $I^2 = 98.1\%$ ,  $\tau^2=0.03$ ,  $p<0.01$ ). We then restricted the meta-analysis to  
53 prospective studies, hence removing the three retrospective hospital/sanatoria cohorts, where culture had also  
54 not be used in two instances, and showed an annualized rate of 12% (95% CI: 6.8-18.0) with reduced statistical  
55 heterogeneity  $I^2 = 35.1\%$ . Over three years this would equate to 33% (95% CI: 19-45) of those initially with  
56 culture positive TB becoming culture negative.

60

61 **DISCUSSION (1913 words)**

62 This review is the first to systematically summarize key aspects of the kinetics of the natural history of  
63 untreated tuberculosis in adults, outside of the rate of mortality, making full use of historical literature in  
64 English and German. Through meta-analysis we provide estimates of the risk of progression to  
65 microbiologically positive disease in those with initially negative microbiology at an annualized rate of  
66 approximately 10% in those with “active” radiographic TB changes and 1% in those with “inactive” or fibrotic  
67 changes. For comparison, progression was approximately 0.1% for those with normal CXRs, while  
68 recognizing that this rate would be affected factors such as local burden of disease. In addition to this we  
69 provided an estimate for the reversion from culture-positive disease to culture negative without treatment (also  
70 referred to as ‘self-cure) as 12% per year.

71

72 These results highlight that individuals with CXR changes suggestive of active TB but who are found to be  
73 initially microbiologically negative are at considerable risk of disease progression. Our study is the first to  
74 determine an estimate for this transition which will be of use to modellers wanting to understand the  
75 implications of intervening in this population. We also have shown that approximately a third of those with  
76 culture positive disease could revert to culture negative without treatment over a 3-year period. While this  
77 may not inform clinical management, our results may refine parameters in models used to estimate disease  
78 incidence from prevalence survey data where the probability of so-called “self-cure” needs to be factored in.  
79 Our annual rate of approximately 12% provides empirical foundation to the slightly higher rates of 15% and  
80 20% used by Dye to parameterize “self-cure” – which was informed by a review of literature although not  
81 systematic(60,61). Although, importantly, those patients included in this systematic review may not be  
82 representative of all culture positive patients, with our focus on more minimal disease.

83

84 We used a widely accepted conceptual framework to guide our data collection which required determination  
85 of the microbiological, radiological and symptom status of participants over follow-up. We found that no  
86 single study systematically recorded these three features over the entire course of disease from exposure to  
87 final outcome. In addition we found that the recording of symptoms in these studies was not explicit,

88 particularly during follow up - meaning there was insufficient empirical data to directly determine the  
89 trajectory around subclinical (asymptomatic, microbiologically positive) TB. Subclinical TB is a commonly  
90 identified state through CXR-based active case finding but conducting contemporary natural history studies  
91 to determine the rates of progression and regression would present ethical challenges with the availability of  
92 treatment. However, the substantial additional data uncovered in this review should allow inference of the  
93 kinetics around subclinical TB, which Richards *et al* have explored in a model using a Bayesian framework  
94 to utilize the information from all data simultaneously also incorporating subsequent mortality using  
95 additional available evidence(62).The modelling work suggests that for individuals with prevalent subclinical  
96 disease, classic clinical disease is neither an inevitable nor an irreversible outcome. Over five years, 40% (95%  
97 uncertainty interval (UI) 31.3%-48.0%) recover but 18% (95% UI, 13.3%-24.0%) died from TB, with 14%  
98 (95%UI, 9.9%-19.2%) still infectious. Furthermore, 50% (95%UI, 40.0%-59.1%) of the subclinical cohort  
99 never developed symptoms over the model span. Overall, this suggests that a reliance on symptom-based  
100 screening means a large proportion of people with infectious disease may never be detected.

101  
102 There are several key limitations to consider when interpreting the findings of this systematic review. HIV is  
103 a significant role-player in the epidemiology of TB in certain settings today and 22 of 24 of our studies were  
104 set prior to the discovery of the virus. It is likely that people living with HIV progress along the disease  
105 spectrum with different kinetics, also influenced by immune status (63–65). Secondly the nature of this  
106 research question and the historical focus resulted in studies being included from a period spanning almost 80  
107 years; over this time period, microbiological and radiographic methods evolved (supplementary page 36).  
108 However, from a microbiological perspective included studies predominately used culture and where they did  
109 not, we conducted sensitivity analyses. For radiology, even where studies used mass miniature radiography or  
110 fluoroscopy for screening, findings were typically confirmed with conventional chest radiography which  
111 informed data extraction. The majority of studies were conducted over fifty years ago, when socioeconomic,  
112 health access, comorbidity distribution and prevalence of TB were likely very different to what they are today  
113 these factors could affect the rate of progression and regression of disease. However, these study  
114 environments may to a certain extent remain representative of many contemporary settings with a high TB

115 burden. Furthermore, while we allowed for data capturing to occur along multiple possible pathways through  
116 the TB disease pathway, various possible trajectories do exist along this pathway and it is possible that we did  
117 not capture all options. While we found that data did not exist for certain variations (e.g. starting with a  
118 microbiologically detectable TB but radiographically normal state), this would have been impacted by the  
119 designs of the included studies but may have also been affected by the diagnostic tool in question i.e. the use  
120 of CXR rather than more modern and sensitive tools. Our findings are also possibly affected by publication  
121 bias as demonstrated by the asymmetrical funnel plot (supplementary page 29) - this appears to be mainly  
122 relevant for studies of inactive TB, suggesting small studies with no transitions may not have been published.  
123 In addition, certain studies could have a survival bias in that they required participants to meet certain entry  
124 criteria that were stable over time. Our results are drawn from studies with median follow-up of 34.5 months  
125 (approx. 3 years; IQR 24-60 months) and thereby our annualised rates are not expected to apply outside of  
126 this time period. Our transitions reflect those that were followed up and successfully provided sputum for  
127 microbiological analysis (not accounting for death and loss to follow-up) and hence it is possible that the true  
128 rates could be higher. Importantly, progression to microbiologically-positive disease from a  
129 microbiologically-undetectable state does not take into account whether this is disease progression or new,  
130 incident infection and disease – a factor which is likely affected by local burden of disease.

131  
132 There are also considerable methodological challenges in conducting a systematic review involving historical  
133 research. It is notable that 1503/1648 (91.2%) of studies were retrieved for full text review, however for 95  
134 studies that met eligibility and bias criteria, manuscript style did not allow for data extraction and authors  
135 could not be contacted for assistance. Although our work focused on the period 1903-1960, through extensive  
136 investigator collections and snowballing of references we are confident we were able to identify key literature  
137 post-1960 as evidenced by nearly half of our final 24 studies being after this date.

### 138 139 **Future direction for treatment**

140 We have for the first time quantified the risk of disease progression in those with CXR changes suggestive of  
141 active TB with negative sputum microbiology, showing a rate of 10% per year, hence although this group is

142 at very high risk of progression, we found that this may not be inevitable. These individuals are still frequently  
143 encountered in two clinical settings. Firstly, in the context of active case finding where a target population not  
144 seeking health care is screened with CXR; this population is being increasingly recognised following recent  
145 WHO guidance on systematic screening, recommending use of CXR(66). Secondly, in those that are  
146 symptomatic and seeking healthcare, who have negative sputum investigation but are found to have CXR  
147 abnormalities. The optimal approach to management of this group is currently unclear particularly for resource  
148 limited programmatic settings where a full suite of investigations such as CT scan and bronchoscopy are not  
149 routinely available. Treatment algorithms vary widely but ultimately rely on clinician judgement factoring in  
150 symptoms, epidemiological risk, and the likelihood of resistance, with the tension between providing  
151 empirical treatment or monitoring, hence over- or under-treatment. Recent clinical trials in this patient group  
152 are limited and the current “one size fits all approach” means typically the standard 6-month, four-drug  
153 standard treatment developed for the treatment of smear positive disease is offered to this patient group with  
154 minimal disease. New approaches are needed to support management of this group. Novel diagnostics that  
155 could either provide microbiological confirmation (e.g face mask sampling) or better risk stratification (e.g  
156 CRP or host transcriptional response tests) require evaluation. In addition, clinical trials are needed that  
157 evaluate forms of preventive treatment that are better tolerated and determine the number needed to treat to  
158 improve patient choice and facilitate decision making(67).

## 160 **Contemporary approaches to understanding disease natural history in humans**

161 Our study highlights that infiltrative pathology can be evident on CXR prior to sputum positivity, that  
162 progression to sputum positivity can take months or years and that risk can be stratified by features of activity  
163 on CXR. We also show that in those with positive sputum, reversion to a sputum negative state can occur.  
164 This work reiterates to a modern day audience the chronic and dynamic natural history of TB that would have  
165 been more apparent to researchers and physicians historically. The approaches used in these historical studies  
166 have limitations compared to modern day tools. However, in contemporary studies we can only study disease  
167 natural history in humans until the point at which treatment is clinically indicated. Digital CXR technologies  
168 are now commonplace and computer aided detection software enables more consistent and highly sensitive

169 reading of CXR(66). CXR is limited in its anatomical resolution with visibility of underlying lesions impacted  
170 by their size, location and density. In studies utilising CT or PET/CT scans, earlier stages of disease can be  
171 visualised with centrilobular nodules and representing caseous material within the respiratory bronchioles  
172 which grow and coalesce to form denser consolidation that might be visible on CXR(63,68,69). Sputum  
173 investigation similarly has limitations as it requires organisms from the site of disease to enter respiratory  
174 secretions and to be effectively expectorated as sputum. In addition, assessment of sputum in studies is  
175 performed infrequently hence cannot easily capture variation in sputum positivity over short time periods.  
176 Tuberculosis transmission is through aerosols and it is becoming increasingly apparent that capture of aerosols  
177 (for example through face mask sampling) may be more sensitive than sputum microbiology and may also  
178 better reflect infectiousness(70). Furthermore as we have discussed, historical studies did not capture  
179 information about symptoms effectively especially over follow-up. Incorporating these tools into modern  
180 epidemiological studies may help to address key outstanding research questions (see table 1). The host  
181 pathogen interplay that governs the dynamic nature of the disease course and the factors that could lead to a  
182 favourable or unfavourable outcome are poorly understood. This could not so easily be studied in humans but  
183 could be addressed through animal models. Traditionally animal models of TB have aimed to replicate  
184 formation of the granuloma but not specific stages of early disease evolution. More accurate benchmarking of  
185 animal models against the early stages of TB disease will facilitate progress towards a better understanding of  
186 factors which govern disease outcome(71).

187  
188 Through our extensive review, we find that the natural history of TB is a dynamic, heterogenous process which  
189 is not adequately represented by a single ‘active disease’ state, and quantified three key transitions.  
190 Importantly, this review provides a much-needed foundation of empirical data for our ongoing re-discovery  
191 of the complexity of TB natural history, enabling a grounding for new preconceptions or dogmas, and a drive  
192 toward new clinical guidelines and policies for those suffering from TB.

196 **CONTRIBUTORS**

197 HE, RH, BS, ASR, FC, and KK conceptualised the study protocol. BS, ASR, TH, BF, FB, AO, and BH carried out the literature search and data collection.  
198 ASR and BS carried out the statistical analysis and verified the final data with input and oversight from HE, RH and ER. BS wrote the first draft of the  
199 manuscript with input from ASR, RH and HE. All authors subsequently reviewed and edited the manuscript. All authors had full access to the study data and  
200 had final responsibility for the decision to submit for publication.

201  
202 **DECLARATION OF INTERESTS**

203 We declare no competing interests.

204  
205 **DATA SHARING**

206 Data is available within tables in the manuscript and supplementary materials.

207  
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337

### 338 **Figures Legends**

#### 339 **Figure 1: Conceptual framework of transitions occurring in the natural history of tuberculosis**

340 The design of this conceptual framework is based on the available literature regarding the natural history of TB, where a subclinical group is included(1,14–  
341 16)The figure demonstrates that individuals would undulate between states of having (1) normal chest x-ray, negative microbiology and being asymptomatic, to  
342 (2) chest x-ray abnormalities, but still having negative microbiology and being asymptomatic, to (3) chest x-ray abnormalities with positive microbiology but  
343 being asymptomatic, to (4) chest x-ray abnormalities with positive microbiology and being symptomatic. We recognize individuals do not always fall into these  
344 groupings while transitioning along the spectrum of disease, for example an individual may present with an abnormal chest X-ray and symptoms that may  
345 represent TB but have negative microbiology. We have made allowances to capture all combinations of CXR, microbiology and symptoms status within the  
346 review.

347

348 CXR=Chest X-ray; Micro=Microbiology; Sympt=Symptoms

349

350 **Figure 2: Study Selection:** Screened, assessed and included studies.

351

352 Figure 3 – Table of study characteristics

353

354 For details of microbiological assessments and follow-up, and description of findings on chest x-ray, see appendix pp 7–17. For details of quality assessments of  
355 these studies, see appendix p 6. CXR=chest x-ray. \*Single follow-up refers to studies with two cross-sectional assessments of the group of participants; whereas  
356 cumulative follow-up refers to studies that cumulatively captured events over time. †Starting points and endpoints have three characteristics or states, including  
357 radiology (ie, CXR negative, positive, or unknown), microbiology (ie, negative, positive, unknown, or mixed), and symptom status (ie, negative, positive,  
358 unknown, or mixed). ‡Study dates not reported.

359 Colour coding: Green = those with radiologically and microbiologically negative findings. Orange = those with radiological abnormalities but who are  
360 microbiologically negative. Red = those with confirmed microbiologically-positive disease.

361 ATT=Antituberculosis Therapy; IUAT=International Union Against Tuberculosis; Micro.=Microbiology; USA=United States of America

362

363

364 **Figure 4: participants entering cohorts with abnormal chest X-rays and negative microbiology,**  
365 **transitioning to positive microbiology:** forest plot of the random effects meta-analysis of annualized rates  
366 (as described fully in methods section) with annual proportion and 95% confidence intervals for subgroups.  
367 Subgroups are as per the historical authors' provided data on radiographic classification being either  
368 "active", "inactive" or where the group was "mixed".

369

370 **Figure 4b: participants entering cohorts with positive microbiology, transitioning to negative**  
371 **microbiology:** forest plot of the random effects meta-analysis of annualized rates (as described fully in  
372 methods section) with proportion and 95% confidence intervals for subgroups, according to study design

373

374 **Figure 5:**

375 Shows two CXR representing each of Inactive TB (with no previous TB history), Active TB with negative  
376 culture and Active TB with positive culture. CXR are digital and from a recent active case finding setting.  
377 For these examples findings were confirmed by CT scan. Abnormalities are marked with arrow to assist  
378 identification given the small size of the panels. The table to the left show description of lesions associated  
379 with active and inactive TB based on that in those in the 2008 US Department of Health Technical  
380 instructions for the Tuberculosis component for the medical examinations (Ref 18). We also describe in  
381 supplementary table 3 the description of abnormalities used in the included trials to distinguish as active or  
382 inactive TB.

383