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

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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-20th 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 (PRIMSA) 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 31st 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 (≥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 ≥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.

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

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

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

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.

Regression to negative microbiology in those with positive microbiology at baseline

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

DISCUSSION (1913 words)

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

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

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

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

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

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

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

Future direction for treatment

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

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

Contemporary approaches to understanding disease natural history in humans

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

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

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

CONTRIBUTORS

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. 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 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 had final responsibility for the decision to submit for publication.

DECLARATION OF INTERESTS

We declare no competing interests.

DATA SHARING

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

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Figures Legends

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

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

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

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

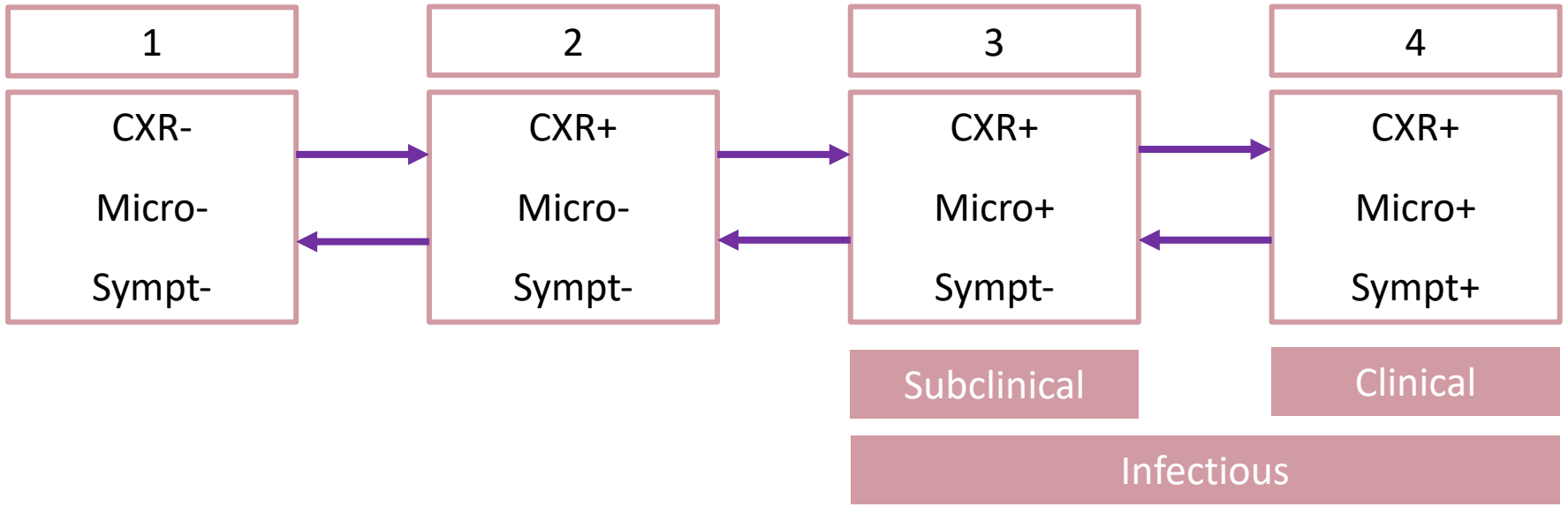
Figure 3 – Table of study characteristics

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 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 cumulative follow-up refers to studies that cumulatively captured events over time. †Starting points and endpoints have three characteristics or states, including radiology (ie, CXR negative, positive, or unknown), microbiology (ie, negative, positive, unknown, or mixed), and symptom status (ie, negative, positive, unknown, or mixed). ‡Study dates not reported.

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

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

584
585
586 **Figure 4: participants entering cohorts with abnormal chest X-rays and negative microbiology,**
587 **transitioning to positive microbiology:** forest plot of the random effects meta-analysis of annualized rates
588 (as described fully in methods section) with annual proportion and 95% confidence intervals for subgroups.
589 Subgroups are as per the historical authors' provided data on radiographic classification being either
590 "active", "inactive" or where the group was "mixed".
591
592 **Figure 4b: participants entering cohorts with positive microbiology, transitioning to negative**
593 **microbiology:** forest plot of the random effects meta-analysis of annualized rates (as described fully in
594 methods section) with proportion and 95% confidence intervals for subgroups, according to study design
595
596 **Figure 5:**
597 Shows two CXR representing each of Inactive TB (with no previous TB history), Active TB with negative
598 culture and Active TB with positive culture. CXR are digital and from a recent active case finding setting.
599 For these examples findings were confirmed by CT scan. Abnormalities are marked with arrow to assist
600 identification given the small size of the panels. The table to the left show description of lesions associated
601 with active and inactive TB based on that in those in the 2008 US Department of Health Technical
602 instructions for the Tuberculosis component for the medical examinations (Ref 18). We also describe in
603 supplementary table 3 the description of abnormalities used in the included trials to distinguish as active or
604 inactive TB.
605


1
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CXR-
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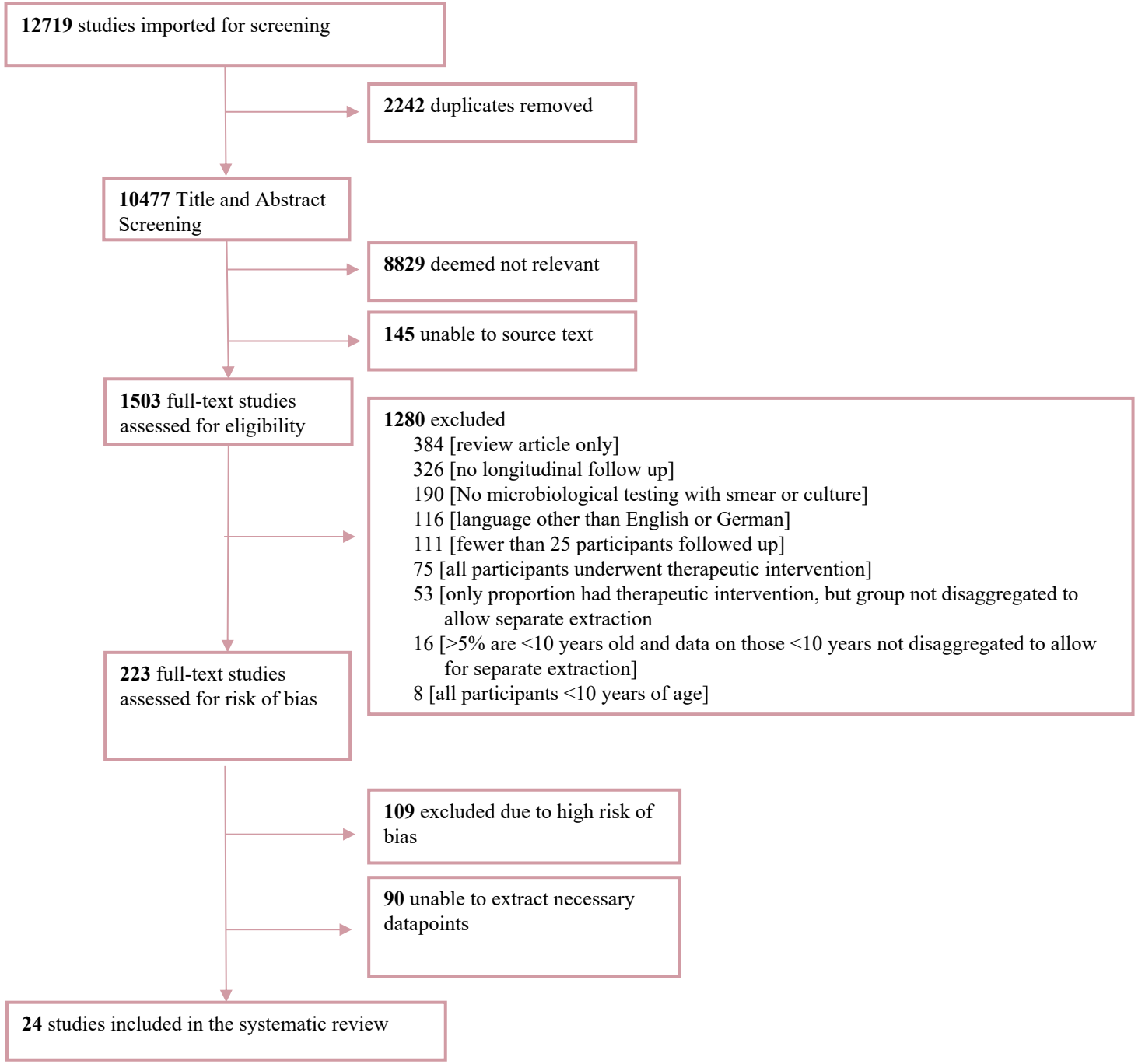
Clinical
Infectious


12719 studies imported for screening
2242 duplicates removed
10477 Title and Abstract Screening
8829 deemed not relevant
145 unable to source text
1503 full-text studies assessed for eligibility
1280 excluded
384 [review article only]
326 [no longitudinal follow up]
190 [No microbiological testing with smear or culture]
116 [language other than English or German]
111 [fewer than 25 participants followed up]
75 [all participants underwent therapeutic intervention]
53 [only proportion had therapeutic intervention, but group not disaggregated to allow separate extraction
16 [>5% are <10 years old and data on those <10 years not disaggregated to allow for separate extraction]
8 [all participants <10 years of age]
223 full-text studies assessed for risk of bias
109 excluded due to high risk of bias
90 unable to extract necessary datapoints
24 studies included in the systematic review

Author (Location of study)	Study Type	Years of study/ year of publication‡	Age	Cohort Size (n)	X-ray Description	Follow up*	Starting point†	Endpoint§
Alling[22] (USA)	Retrospective cohort (Clinic/Hospital/ Sanatorium)	1938 - 1948	Mean: 52 years	58	Inactive	Cumulative	cxr.pos | micro.neg | sympt.unk [arrested¶]	cxr.pos | micro.pos | sympt.unk
Anastasatu[23] (Romania)	Control/Placebo arm of prospective clinical trial	Pub 1985	Not reported	143	Inactive	Cumulative	cxr.pos | micro.neg | sympt.neg	cxr.pos | micro.pos | sympt.unk
Aneja[24] (India)	Control/Placebo arm of prospective clinical trial	1975 - 1977	Minimum: 12 years	110	Not specified	Single	cxr.pos | micro.neg | sympt.pos	cxr.pos | micro.pos | sympt.unk
Beeuwkes[25] (USA)	Prospective cohort (Household Contact Study) 4 subgroups based on CXR lesion type and sputum microbiology	1933 - 1938	Not reported	784	Neg	Single	cxr.neg | micro.neg | sympt.neg	cxr.unk | micro.pos | sympt.pos
				79	Inactive	Single	cxr.pos | micro.neg | sympt.neg	cxr.unk | micro.pos | sympt.pos
				43	Active	Single	cxr.pos | micro.neg | sympt.pos	cxr.unk | micro.pos | sympt.pos
				28	Active	Single	cxr.pos | micro.pos | sympt.pos	cxr.unk | micro.neg | sympt.unk
Bobrowitz[26,27] (USA)	Prospective cohort (Clinic/Hospital/ Sanatorium)	1938 - 1945	Not reported	191	Mixed	Single	cxr.pos | micro.neg | sympt.unk	cxr.pos | micro.pos | sympt.unk
Borgen[28,29] (Norway)	Prospective cohort (Occupational /Student Screening) 2 subgroups based on symptoms	1947 - 1949	Minimum: 15 years	24	Active	Single	cxr.pos | micro.neg | sympt.pos	cxr.pos | micro.pos | sympt.pos
				120	Active	Single	cxr.pos | micro.neg | sympt.neg	cxr.pos | micro.pos | sympt.pos
Breu[30] (Germany)	Prospective cohort (General Community Survey)	1949 - 1952	Minimum: 15 years	904	Mixed	Single	cxr.pos | micro.neg | sympt.unk	cxr.pos | micro.pos | sympt.unk
Cowie[31] (South Africa)	Prospective cohort (Occupational /Student Screening)	1979-1984	Not reported	152	Active	Cumulative	cxr.pos | micro.neg | sympt.unk	cxr.pos | micro.pos | sympt.unk
Downes[32] (USA)	Retrospective cohort (Clinic/Hospital/ Sanatorium)	1923 - 1935	Range: 15-69 years	342	Active	Cumulative	cxr.pos | micro.pos | sympt.pos	cxr.pos | micro.neg | sympt.neg

Frimodt-Moller[33] (India)	Control/Placebo arm of prospective clinical trial	1960 - 1961	Minimum: 15 years	86	Active	Cumulative	cxr.pos | micro.neg | sympt.unk	cxr.pos | micro.pos | sympt.unk
Hong Kong Chest Service[34-37] (Hong Kong)	Control/Placebo arm of prospective clinical trial	Pub: 1979-1981	Range: 15-75	176	Active	Cumulative	cxr.pos | micro.neg | sympt.mix	cxr.pos | micro.pos | sympt.unk
IUAT Committee on Prophylaxis[38] (Europe)	Control/Placebo arm of prospective clinical trial	Pub: 1982	Mean: 50 years	6990	Inactive	Cumulative	cxr.pos | micro.neg | sympt.unk	cxr.pos | micro.pos | sympt.unk
Lincoln[39] (USA)	Retrospective cohort (Clinic/Hospital/ Sanatorium)	1937 - 1947	Minimum: 14 years Mean: 24 years	314	Inactive	Cumulative	cxr.pos | micro.neg | sympt.unk [arrested[¶]]	cxr.pos | micro.pos | sympt.unk
Manser[40] (Switzerland)	Retrospective cohort (Clinic/Hospital/ Sanatorium)	1941 - 1951	Range: 60-83 years	40	Active	Single	cxr.pos | micro.pos | sympt.unk	cxr.pos | micro.neg | sympt.unk
Marshall[41] (United Kingdom)	Control/Placebo arm of prospective clinical trial	1947-1948	Range: 15-30 years	52	Active	Cumulative	cxr.pos | micro.pos | sympt.pos	cxr.pos | micro.neg | sympt.unk
National Tuberculosis Institute[43-50] (India)	Prospective cohort (General Community Survey) 3 subgroups based on CXR and sputum microbiology	1961 - 1968	Minimum: 5 years	31490	Neg	Single	cxr.neg | micro.neg | sympt.unk	cxr.pos | micro.pos | sympt.unk
				329	Active	Single	cxr.pos | micro.neg | sympt.unk	cxr.pos | micro.pos | sympt.unk
				269	Active	Single	cxr.pos | micro.pos | sympt.unk	cxr.pos | micro.neg | sympt.unk
Norregaard[51] (Denmark)	Control/Placebo arm of prospective clinical trial	1978 - 1985	Minimum: 20 years	28	Active	Cumulative	cxr.pos | micro.neg | sympt.mix	cxr.pos | micro.pos | sympt.neg
								cxr.pos | micro.pos | sympt.pos
Okada[52] (Cambodia)	Retrospective cohort (General Community Survey) 2 subgroups based on CXR and sputum microbiology	2002 - 2004	Minimum: 10 years Median: 30.6 years	309	Active	Single	cxr.pos | micro.neg | sympt.neg	cxr.pos | micro.pos | sympt.unk
								cxr.pos | micro.pos | sympt.pos
								cxr.neg | micro.neg | sympt.unk

				21580	Neg	Single	cxr.neg | micro.neg | sympt.neg	cxr.pos | micro.pos | sympt.unk
Orrego Puelma[53] (Chile)	Retrospective cohort (Clinic/Hospital/ Sanatorium cohort)	Pub[||]: 1945	Minimum: 15	67	Mixed	Single	cxr.pos | micro.neg | sympt.unk	cxr.pos | micro.pos | sympt.unk
Pamra[54] (India)	Control/Placebo arm of prospective clinical trial	1958 - 1968	Range: 15-45 years	178	Inactive	Cumulative	cxr.pos | micro.neg | sympt.neg	cxr.pos | micro.pos | sympt.pos cxr.pos | micro.pos | sympt.neg
Puffer[55] (USA)	Retrospective cohort (Clinic/Hospital /Sanatorium cohort) 3 subgroups based on CXR lesion type and sputum microbiology	1931 - 1943	Not reported	261	Mixed	Single	cxr.pos | micro.neg | sympt.neg	cxr.pos | micro.pos | sympt.pos
				267	Inactive	Single	cxr.pos | micro.neg | sympt.neg [arrested[¶]]	cxr.pos | micro.pos | sympt.pos
				384	Active	Single	cxr.pos | micro.pos | sympt.pos	cxr.pos | micro.neg | sympt.neg
Sikand[56] (India)	Prospective cohort (Occupational/ Student Screening)	1952 - 1958	Minimum: 15 years	167	Inactive	Cumulative	cxr.pos | micro.neg | sympt.unk	cxr.pos | micro.pos | sympt.unk
				152	Mixed	Cumulative	cxr.pos | micro.neg | sympt.unk	cxr.pos | micro.pos | sympt.unk
Styblo[57] (Czechoslovakia)	Prospective cohort (General Community Survey)	1961 - 1965	Minimum: 15 years	73000	Neg	Cumulative	cxr.neg | micro.neg | sympt.neg	cxr.unk | micro.pos | sympt.pos cxr.unk | micro.pos | sympt.unk
Tuberculosis Society of Scotland[58,59] (Scotland)	Control/Placebo arm of prospective clinical trial	1954 - 1959	Minimum: 15 years	95	Inactive	Single	cxr.pos | micro.neg | sympt.neg	cxr.pos | micro.pos | sympt.unk

Cohorts progressing to bacteriologically positive disease
Split by initial radiographical classification

Author(s) and Year	Progression	Cohort	Follow-up (months)	Proportion [95% CI]
Active				
Frimodt-Moller2, 1965	25	86	36	0.10 [0.04, 0.17]
Okada, 2012	51	309	24	0.09 [0.06, 0.12]
Cowie, 1985	88	152	58	0.16 [0.11, 0.22]
Norregaard, 1990	8	28	48	0.07 [0.00, 0.17]
Borgen, 1952.1	2	24	30	0.04 [0.00, 0.12]
Aneja, 1979	21	110	12	0.19 [0.12, 0.26]
National Tuberculosis Insitute, 1982	36	271	60	0.03 [0.01, 0.05]
Beeuwkes, 1942.2	13	43	33	0.12 [0.02, 0.21]
Hong Kong Chest Service, 1980	71	176	60	0.10 [0.05, 0.14]
RE Model for Subgroup (Q = 40.79, df = 8, p < .01; I^2 = 77.4%, τ^2 = 0.00)				0.10 [0.06, 0.13]
Inactive				
Alling, 1955	10	58	156	0.02 [0.00, 0.05]
Lincoln, 1954	36	314	72	0.02 [0.00, 0.03]
Sikand, 1959.1	5	167	12	0.03 [0.00, 0.06]
IUATCP, 1982	97	6990	60	0.00 [0.00, 0.00]
Anastasatu, 1985	6	143	24	0.02 [0.00, 0.04]
Puffer, 1945.2	10	267	62	0.01 [0.00, 0.02]
Borgen, 1952.2	2	120	30	0.01 [0.00, 0.02]
RE Model for Subgroup (Q = 12.55, df = 6, p = 0.05; I^2 = 53.2%, τ^2 = 0.00)				0.01 [0.00, 0.02]
Mixed				
Breu, 1954	48	904	25.5	0.03 [0.02, 0.04]
Sikand, 1959.2	33	152	12	0.22 [0.15, 0.28]
Pamra, 1971	57	178	72	0.06 [0.03, 0.10]
Puffer, 1945.1	9	261	62	0.01 [0.00, 0.02]
Bobrowitz, 1949	26	191	60	0.03 [0.01, 0.06]
Beeuwkes, 1942.1	3	79	33	0.01 [0.00, 0.04]
Orrego Puelma, 1945	18	67	24	0.15 [0.06, 0.23]
Tuberculosis Society of Scotland, 1963	9	95	24	0.05 [0.01, 0.10]
RE Model for Subgroup (Q = 57.80, df = 7, p < .01; I^2 = 97.3%, τ^2 = 0.00)				0.06 [0.02, 0.11]
RE Model for All Studies (Q = 223.91, df = 23, p < .01; I^2 = 97.8%, τ^2 = 0.00)				0.06 [0.03, 0.08]

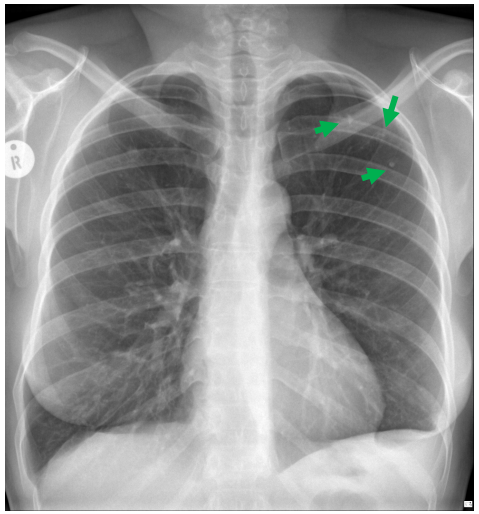
Test for Subgroup Differences: Q_M = 12.58, df = 2, p = 0.00

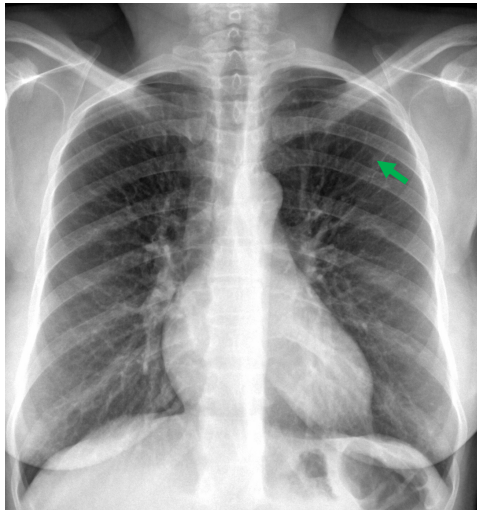
Cohorts regressing to bacteriologically negative disease
Split by study design

Author(s) and Year	Regression	Cohort	Follow–up (months)	Proportion [95% CI]
Prospective				
Marshall, 1948	2	52	6	0.08 [0.00, 0.15]
National Tuberculosis Insitute, 1982	70	178	36	0.15 [0.10, 0.20]
Beeuwkes, 1942	10	28	33	0.14 [0.01, 0.27]
RE Model for Subgroup (Q = 2.74, df = 2, p = 0.25; I^2 = 35.1%, τ^2 = 0.00)				0.12 [0.07, 0.18]
Retrospective				
Manser, 1953	15	40	6	0.60 [0.45, 0.75]
Downes, 1938	171	342	60	0.13 [0.09, 0.16]
Puffer, 1945	92	384	62	0.05 [0.03, 0.07]
RE Model for Subgroup (Q = 58.32, df = 2, p < .01; I^2 = 99.5%, τ^2 = 0.08)				0.25 [–0.08, 0.58]
RE Model for All Studies (Q = 65.12, df = 5, p < .01; I^2 = 98.1%, τ^2 = 0.03)				0.18 [0.03, 0.33]

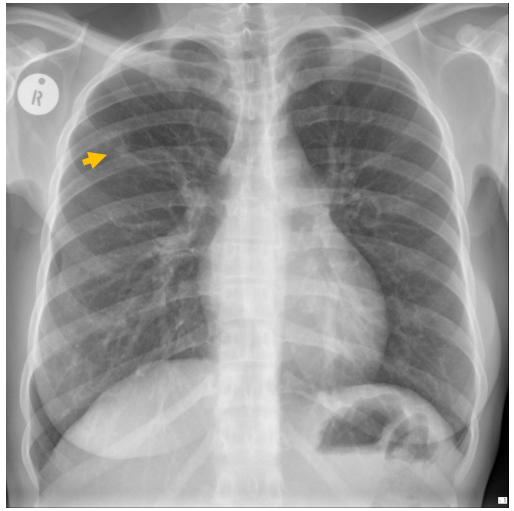
Test for Subgroup Differences: Q_M = 0.54, df = 1, p = 0.46

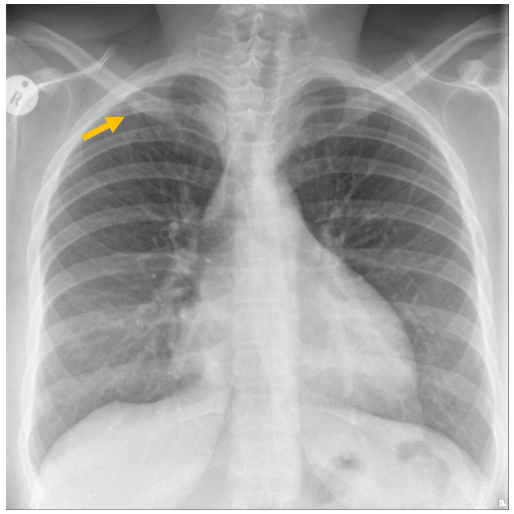
INACTIVE TB



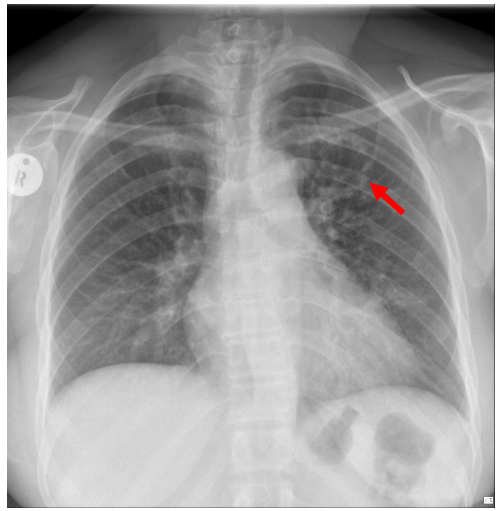


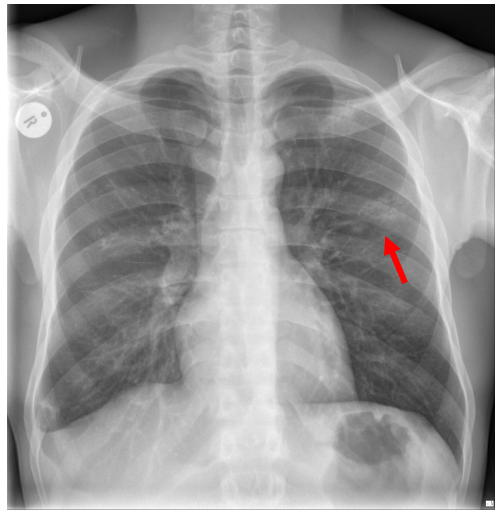
ACTIVE TB – CULT NEG





ACTIVE TB – CULT POS





Inactive TB
Discrete fibrotic scar or linear opacity Discrete linear or reticular opacity within the lung with or without volume loss
Discrete non-calcified nodules(s) One or more nodular opacities with distinct borders and no airspace consolidation
Other findings suggestive of prior TB e.g. upper lobe bronchiectasis

Active TB
Infiltrate or consolidation Opacification of airspaces within the lung parenchyma
Cavitary lesion Lucency within the lung parenchyma that may be surrounded by airspace consolidation
Nodule with poorly defined margins Round opacity withing the lung parenchyma
Pleural effusion Presence of fluid within the pleural space
Hilar or mediastinal lymphadenopathy Enlargement of lymph nodes within hila and/or mediastinum
Miliary nodules Nodules measuring 1-2mm in size distributed throughout the lung parenchyma

Table 1: Key questions for future research

- In those with normal CXR and positive sputum can pathological changes be identified within the lung using higher resolution imaging?
- Utilising modern digital CXR technologies with CAD, are the rates of disease progression similar to what is found in the historical literature?
- Are the progression/regression rates across the spectrum of disease similar by symptom status?
- In those with CXR changes suggestive of TB but with negative sputum microbiology, is the rate of progression to positive sputum microbiology constant over time?
- In those with CXR changes suggestive of TB but with negative sputum microbiology, what proportion have microbiologically positive aerosol (e.g. by face mask sampling)?
- Is there evidence for transmission of TB in those with CXR changes but negative sputum microbiology?
- What is the variation in sputum positivity over short time periods?
- Can diagnostics tests (such as CRP and host transcriptional response) help to identify those with CXR changes at risk of microbiological progression?
- What is the optimal therapeutic approach to prevent progression to microbiologically positive disease in those with CXR changes suggestive of TB?