Post-tuberculosis lung disease: towards prevention, diagnosis, and care

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Lancet Respir Med 2025; 13: 460–72

Published Online March 21, 2025 https://doi.org/10.1016/S2213-2600(24)00429-6

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There is a growing body of data describing the high burden of respiratory sequelae seen among tuberculosis survivors, including children, adolescents, and adults. This group of sequelae are known as post-tuberculosis lung disease and include parenchymal damage, airway disease, and pulmonary vascular disease. It is thought that approximately half of pulmonary tuberculosis survivors have ongoing structural pathology, lung function impairment, or respiratory symptoms after the resolution of active disease. Post-tuberculosis lung disease has been associated with adverse patient outcomes, including persistent symptoms and functional impairment, ongoing health seeking, and impacts on income and employment. There is still much to understand about the epidemiology and nature of post-tuberculosis lung disease, but in this Review we focus on strategies for prevention, diagnosis, and care to inform the ongoing work of tuberculosis-affected communities, health-care providers, researchers, and policy makers. We summarise recent data, highlight evidence gaps, and suggest key research priorities for those working in the field.

Introduction

Tuberculosis disease remains a critical cause of morbidity and mortality worldwide, with an estimated 10·8 million incident cases in 2023.[1] The treatment success rate for tuberculosis disease continues to improve,[1] but emerging data suggest a high burden of residual physical, psychological, and socioeconomic morbidity among tuberculosis survivors, even after treatment completion.[2,3]

Factors contributing to this morbidity include localised organ damage caused by tuberculosis-associated inflammation and fibrosis; the effects of systemic inflammation;[4] the side-effects of anti-tuberculous medication;[2] and the broader socioeconomic effects of tuberculosis disease, including stigma, social isolation, and loss of income and employment.[5,6] Modelling studies suggest that almost half of the global morbidity regarding to tuberculosis disease could fall in the post-tuberculosis period.[7]

Although the importance of mitigating tuberculosis-associated catastrophic costs was captured in The Global Plan to End TB strategy targets,[8] the need for tuberculosis programmes to measure and prevent broader tuberculosis-associated sequelae has not yet been recognised. This Review focuses on post-tuberculosis lung disease as an important consequence of tuberculosis, which is relevant to the long-term wellbeing of pulmonary tuberculosis survivors.[3]

Key messages

- People affected by tuberculosis disease face a high burden of physical, psychosocial, and economic sequelae after treatment completion
- Post-tuberculosis lung disease is a heterogenous condition that includes residual damage to the airways and parenchyma and can be associated with ongoing respiratory symptoms, functional impairment, and health-seeking after treatment completion
- The burden of post-tuberculosis lung disease is increasingly well described in resource-constrained, high tuberculosis incidence settings, but data on strategies for prevention, diagnosis, and care remain scarce
- Approaches to prevention could include measures to address the upstream social determinants of tuberculosis disease, support early tuberculosis diagnosis and treatment, novel treatment regimens, and host-directed therapies
- Efforts to improve accurate diagnosis of post-tuberculosis lung disease must address its heterogeneity and challenges around the decentralised implementation of respiratory diagnostics in resource-constrained settings
- Post-tuberculosis clinical care should include the active management of post-tuberculosis lung disease and the diagnosis and prevention of secondary complications (eg, superimposed respiratory infections) and recurrent tuberculosis disease
- Across all interventions for prevention, diagnosis, and management, it is important to address the needs of children and adolescents and to develop feasible, equitable, and sustainable health systems for implementation

The burden of post-tuberculosis lung disease

The body of literature on post-tuberculosis lung disease has grown substantially since 2010, with the condition defined as "evidence of chronic respiratory abnormality with or without symptoms attributable at least in part to previous tuberculosis".[9] This pragmatic definition recognises the broad range of respiratory damage caused by tuberculosis disease and the heterogeneity of resulting symptoms, impairment, and disability. This definition also recognises the challenge of differentiating lung damage caused by tuberculosis disease from that caused by other harmful respiratory exposures (eg, smoking, occupational exposures, and air pollution), which might be common in tuberculosis-affected communities.[10] However, there are no specific case definitions for post-tuberculosis lung disease for use in research, and studies have used diverse approaches to describe the prevalence of disease, behaviour over time, and secondary complications, making evidence synthesis challenging.

The majority of data on post-tuberculosis lung disease are from low-income and middle-income countries, with little data from high-income countries. The heterogenous patterns and severity of post-tuberculosis

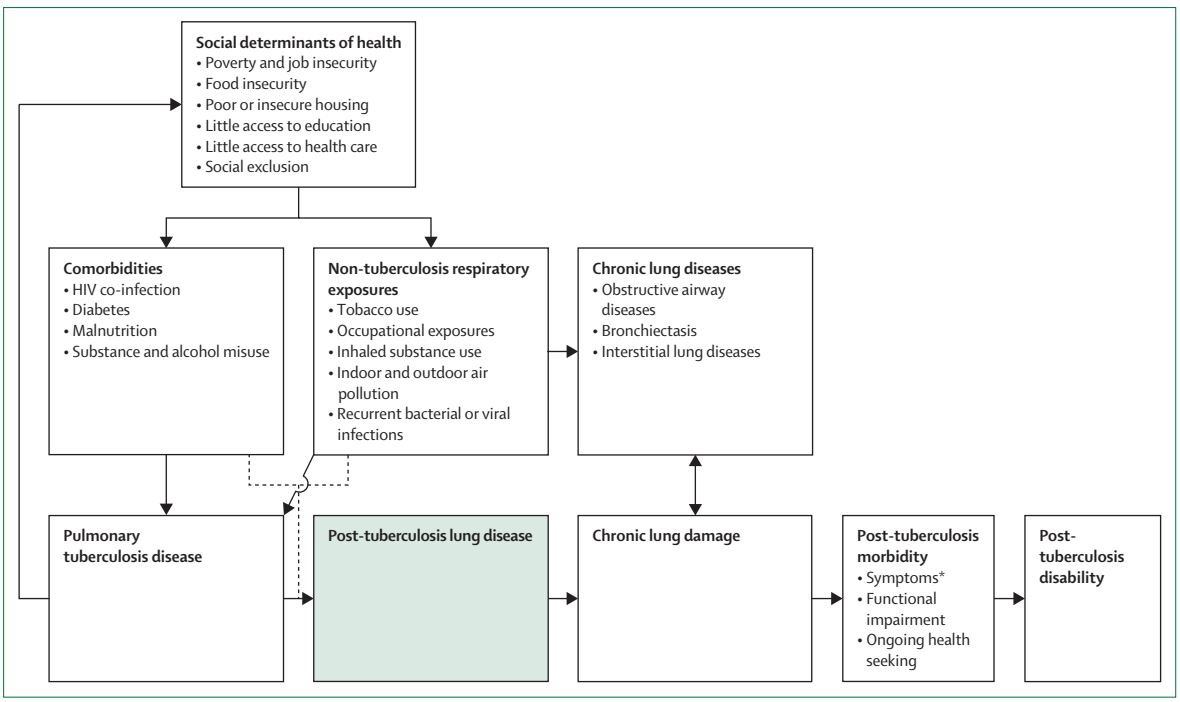

Figure 1: **Conceptual framework describing potential drivers of post-tuberculosis lung disease and associated impairments and disabilities**
Dashed lines denote potential effect modification of the relationship between tuberculosis disease, the host immune response, and residual lung damage by non-tuberculosis respiratory exposures and comorbidities. *Includes cough, dyspnoea, sputum production, wheeze, and chest pain.

lung disease have been described in several narrative reviews.[3,9,11,12] Three systematic reviews focused on lung function abnormalities after pulmonary tuberculosis disease suggest that approximately half of those treated for pulmonary tuberculosis disease have abnormal spirometry at or after treatment completion,[13,14] with severe disease in 10–15% of survivors[15] and a mixture of low forced vital capacity (FVC), obstructive, and mixed patterns of deficit observed.[14,15] Those treated for multidrug-resistant disease are more likely to have impaired spirometry and more severe disease than those treated for drug-sensitive disease.[14,15] Residual imaging abnormalities are common, with bronchiectasis observed in 35–86% of pulmonary tuberculosis survivors.[16,17] Approximately a quarter of tuberculosis survivors are symptomatic, with a Medical Research Council dyspnoea score of 3–5 at the end of treatment.[14] Few studies have described the relationship between HIV infection and residual post-tuberculosis lung disease. Some suggest that although HIV is associated with less severe post-tuberculosis lung disease,[16] antiretroviral therapy-mediated immune reconstitution in those with tuberculosis–HIV co-infection might be followed by increased inflammation within the lungs and loss of lung function.[18–20] Research to date has not identified differences in the burden or nature of post-tuberculosis lung disease by sex. However, males have a higher tuberculosis incidence than females and often present later with more advanced tuberculosis disease.[21] Exposures to harmful occupational exposures (eg, silica exposure through mining), can be heavily gendered. Investigation of the relationship between sex, occupational exposures, and post-tuberculosis lung disease could be relevant for tailored strategies for prevention and care.

Prospective cohort data describing post-tuberculosis lung disease behaviour over time suggest an improvement in FEV_1 and FVC measures during tuberculosis treatment and in the 6–12 months after treatment completion, before plateauing.[22] A study published in 2022 showed that up to a third of Malawian pulmonary tuberculosis survivors had persistent pulmonary impairment or symptoms, with a possible subset of patients having accelerated lung function decline.[22] High rates of ongoing health seeking for respiratory complaints have been described in several settings, particularly in the first year after tuberculosis treatment completion.[16,23] Tuberculosis survivors face significantly increased mortality rates compared with the general population or tuberculosis-naive control individuals, even after treatment completion, with an estimated standardised mortality ratio of 2·9 (95% CI 2·2–3·8).[24–26] When cause of death data are available, cardiovascular disease, cancer, and respiratory diseases are among the leading causes of death for tuberculosis survivors. This trend is consistent with the increased burden of cardiovascular morbidity and lung cancer observed among pulmonary tuberculosis survivors compared with those who have not been treated for tuberculosis disease.[24,27]

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Causal pathways underlying post-tuberculosis lung disease

The causal pathways underlying the heterogeneous prevalence and patterns of post-tuberculosis lung remain poorly understood. Pathogenesis has been described in detail elsewhere and likely relates to the burden and site of mycobacterial infection; the duration of infection and rate of clearance; the nature and force of the host immune response; and the healing response seen within the lung, including the potential for excessive remodelling and fibrosis.[28] The roles of broader respiratory exposures—including inhaled tobacco and drugs, occupational dusts and fumes, indoor and outdoor air pollution, and bacterial or viral co-infection—and poverty-related factors—such as malnutrition—in shaping the extent and pattern of lung damage during tuberculosis disease remain unclear. It is challenging to differentiate between the direct effect of these exposures on the lung and damage mediated by tuberculosis disease. It is important to recognise that post-tuberculosis disability is not just the result of the extent or pattern of lung damage sustained during tuberculosis disease, but is also determined by the symptoms and functional impairments that result from this damage, as well as access to health services for ongoing care and the broader physical and social contexts in which people live and work (figure 1).[5] Data on interventions to support the prevention, diagnosis, and management of post-tuberculosis lung disease at either the population level or individual patient level remain scarce.

Towards prevention

Interventions that minimise the lung damage sustained during pulmonary tuberculosis disease and treatment will be crucial to prevent post-tuberculosis respiratory morbidity. Strategies might include public health interventions to ensure early diagnosis and treatment, and the clinical use of novel treatment approaches or host-directed therapies. However, evidence in this space is inadequate, and sustained investment in clinical trials and intervention studies is needed to generate robust data.

Addressing the social determinants of tuberculosis disease

Upstream interventions that address the social determinants of tuberculosis[1] (eg, overcrowding and malnutrition) could be essential to mitigate post-tuberculosis lung disease, either by directly reducing the incidence of tuberculosis disease or by modifying the extent or pattern of tuberculosis-related lung damage. The harmful effects of poverty-related risk factors on lung development are well described[29] and those affected will likely have less respiratory reserve to manage further disease. However, data on the effects of non-pharmacological interventions to minimise post-tuberculosis lung disease remain scarce. For example, although the RATIONS trial showed the efficacy of macronutrient (food rations) and micronutrient support in reducing tuberculosis incidence and mortality among household contacts of individuals with microbiologically confirmed pulmonary tuberculosis, it did not report on respiratory outcomes.[30]

Early diagnosis and treatment

Longer time to tuberculosis diagnosis is associated with more extensive lung damage or pathology on chest x-ray at diagnosis,[31,32] which in turn is associated with more extensive lung pathology at treatment completion.[33] It is therefore likely that measures to promote early diagnosis and treatment will reduce the burden of post-tuberculosis lung disease at or after treatment completion.[34] The cost-effectiveness of interventions to promote early diagnosis would be further strengthened if they could be shown to minimise post-tuberculosis sequelae, as well as improving case detection rates.

Active case finding, in which people who are not seeking health care for symptoms are invited to be screened for tuberculosis disease, holds promise. A trial of South African gold miners randomly assigned to receive radiological screening every 6 months or 12 months showed no difference in tuberculosis detection rates, but those screened more frequently had less extensive disease on chest radiographs.[35] Although this study describes a specific subpopulation with concurrent silica exposure, these findings suggest some benefit of active screening to enable early diagnosis and mitigate lung damage. However, broader active case-finding interventions have largely been evaluated from a population health perspective by measuring changes in community tuberculosis prevalence over time.[36] Most trials of community-based active case-finding programmes have not compared the extent of chest x-ray pathology or other respiratory measures at or after tuberculosis treatment completion between active and passive case-finding groups.[37,38]

There is now a growing recognition of subclinical tuberculosis disease—in which individuals are asymptomatic but have bacteriologically confirmed tuberculosis—as a substantial contributor to transmission.[39] It remains unclear how many individuals with subclinical disease will go on to develop symptomatic, clinical disease.[40] However, several studies indicate that those with subclinical disease have minimal radiographical involvement: a 2024 individual participant data meta-analysis reported that only 970 (2·8%) of 35 241 participants without cough had positive findings on chest radiographs.[41] A population-based cohort study from Canada found absent or minimal radiographical findings in 247 (86·4%) of 286 patients with subclinical disease.[42] Diagnosis and treatment of

patients at this early stage of disease could prevent progression of damage and the development of lasting post-tuberculosis lung disease.

Novel tuberculosis treatment regimens

The pursuit of novel antimicrobial drug regimens that are shorter, safer, and simpler than existing regimens is ongoing, with a move towards individualised tuberculosis regimens tailored to patients' comorbidities and the site and extent of disease.[43] However, we are not aware of any modern randomised clinical trials of antitubercular therapies that have prioritised the reporting of pulmonary impairment after treatment as a primary outcome.

Trials of new tuberculosis treatment strategies often use sputum culture conversion (eg, at 2 months and 6 months after treatment initiation) and time-to-culture conversion as markers of disease activity or predictors of relapse-free cure.[44–46] However, because pulmonary damage is likely primarily driven by host-mediated inflammation, rather than directly by mycobacterial factors,[28] it is unknown whether improved microbiological metrics—such as early bactericidal activity and faster culture conversion—will be associated with the pattern or severity of post-tuberculosis lung disease. The TRUNCATE-TB trial, an adaptive platform trial of shortened courses of treatment for drug-susceptible tuberculosis published in 2023, included chest radiographs, spirometry, and assessment of respiratory symptoms at 96 weeks as secondary outcomes and did not find substantial differences between treatment groups.[47]

Another area of interest for reducing long-term pulmonary morbidity is inhaled antimicrobials, which could have better activity in areas with extensive tissue destruction and cavities where drug penetration from the blood compartment can be poor. A small clinical trial (N=91) from Thailand found that participants randomly assigned to receive an inhaled dry powder formulation of isoniazid, rifampicin, pyrazinamide, and levofloxacin in addition to standard treatment had no significant difference in sputum culture conversion at 8 weeks.[48] However, these participants did have more rapid resolution of cough and a trend towards more rapid improvement in the extent of disease on chest radiographs than those receiving standard oral antituberculosis treatment only.[48] Additional trials are needed to confirm these preliminary findings and their implications.

Modifying the host immune response

Host-directed therapies are adjuvant treatments given alongside antimicrobials to modify the host immune response. These therapies aim to reduce pathology or improve bacillary killing. Agents of interest include those that modify eicosanoid pathways (eg, non-steroidal anti-inflammatory drugs and lipoxygenase inhibitors); reduce inflammation (eg, corticosteroids, ibuprofen, and N-acetylcysteine); improve autophagy and intracellular bacillary processing (eg, metformin, statins, and tyrosine kinase inhibitors); and antifibrotics and agents that modulate the extracellular matrix and associated proteases, including matrix metalloproteinases.[28] Host-directed therapies for tuberculosis have been reviewed elsewhere,[49,50] but are discussed below in the context of respiratory health outcomes.

Corticosteroids have been widely evaluated, with many studies completed before the use of rifamycin-based therapies. A systematic review and meta-analysis of randomised trials from 1959 to 1999 found more rapid radiographical resolution of pulmonary infiltrates and higher rates of cavity closure in those treated with steroids compared to those without steroids, particularly during the initial months of treatment.[51] However an updated analysis including studies from 1966 to 2014 identified a positive effect of steroids in only two of five trials reporting lung function outcomes over the tuberculosis treatment period.[52] The Pred-ART trial randomly assigned antiretroviral therapy-naive adults with HIV, $CD4^+$ cell counts less than or equal to 100 cells per µL, and diagnosed pulmonary tuberculosis to 4 weeks of prednisone or placebo alongside antimicrobials. A subanalysis of the trial showed faster improvements in spirometry, the 6-min walk test, and symptom-related quality of life between baseline and week 4 in the intervention group compared with the placebo group, but these differences were not observed after steroid treatment ceased.[53] Taken together, steroids might improve clinical manifestations of pulmonary inflammation early in treatment or during administration, but consistent evidence of sustained benefits is absent.

Several trials of broader host-directed therapy agents are ongoing. A randomised clinical trial of the anti-inflammatory agent and type 4 phosphodiesterase inhibitor CC-11050 in adults without HIV with moderate to severe radiographical involvement at pulmonary tuberculosis diagnosis showed greater recovery of FEV_1 at day 180 compared with control individuals.[54] A similar effect was seen in the same trial with everolimus, an inhibitor of mTOR that might reduce inflammation and fibrosis.[54] Effects attributed to CC-11050 and everolimus (approximately 6%, or 200 mL by 180 days) were approximately twice the magnitude considered clinically meaningful in chronic obstructive pulmonary disease trials and, in contrast to the effect observed in trials of corticosteroids, appeared only later during follow-up.[53] Statins have been associated with accelerated bacterial clearance in preclinical models,[55,56] and reduced rates of incident tuberculosis disease in clinical studies,[57] but their effects on post-tuberculosis lung disease remain unclear. A phase 2b, randomised trial of rosuvastatin given for 8 weeks during tuberculosis treatment showed no difference in the change in FEV_1 to FVC ratio, chest

Panel 1: **Observed patterns of tuberculosis-related lung damage**

Parenchyma
- Cavitation
- Parenchymal destruction
- Emphysematous change
- Atelectasis
- Fibrosis with volume loss and anatomical distortion

Airways
- Bronchiectasis
- Small airways disease
- Obstructive airway disease

Pleura
- Pleural thickening and calcification

Pulmonary vasculature
- Venous thromboembolism[62]
- Pulmonary hypertension[63]

radiographs, or quality of life scores from baseline to week 24 between intervention and control groups.[58] By contrast, a randomised trial of atorvastatin showed a greater reduction in chest x-ray severity score in the statin group versus the standard of care group.[59] Faster resolution of imaging and cavity closure has also been observed in a small trial (N=30) of the matrix metalloproteinase inhibitor doxycycline,[60] and adjunctive N-acetyl cysteine has been associated with improved lung function recovery.[61] A trial evaluating ibuprofen and aspirin as anti-inflammatory host-directed therapies for tuberculosis is ongoing (NCT04575519).

Towards diagnosis

There is little consensus about when and how patients and survivors should be evaluated for residual respiratory morbidity. Routine surveillance of post-tuberculosis lung disease within tuberculosis programmes would provide data on the local burden of disease for research purposes and would inform health service planning for post-tuberculosis care. At the individual level, diagnosis would support linkage to care. However, it has been challenging to agree on standardised approaches to post-tuberculosis lung disease measurement, given its heterogeneity, the scarcity of prospective data on the patterns of disease associated with adverse clinical outcomes, and few data on the implementation of screening and diagnostic approaches in real-world settings.

Heterogeneity of post-tuberculosis lung disease

Tuberculosis disease can affect multiple pulmonary compartments, including the lung parenchyma, large and small airways, vasculature, and pleura (panel 1). Severe disease can also cause deconditioning and respiratory muscle weakness. Diverse patterns of pathology can be observed between people, but also within the lung tissue of a single individual,[16] making measurement of post-tuberculosis lung disease as a single clinical entity challenging. Symptoms also vary widely; some individuals with abnormal imaging or lung function might be asymptomatic, but others might have shortness of breath, cough, chest discomfort, or sputum production. The variable relationship between lung function, imaging, and respiratory symptoms observed in individuals with post-tuberculosis lung disease makes its accurate identification with a single diagnostic tool challenging.[64] Finally, patterns and severity of post-tuberculosis lung disease evolve over time—even after treatment completion—with diverse trajectories observed between individuals, thus raising questions about the timing of diagnosis.[22,65,66] Most individuals have some recovery in lung function and imaging in the year after tuberculosis treatment completion, which is probably driven by resolving inflammation and tissue remodelling.[22] However, [^{18}F]fluorodeoxyglucose PET-CT studies show persistent or new metabolic activity within the lung during this year, suggesting a possible role for ongoing tissue inflammation, and some tuberculosis survivors might also have accelerated lung function decline over this period.[22,67] These three issues—heterogeneous patterns, absence of a single approach to measuring disease, and diverse and ongoing evolution over time—have made it challenging for clinicians and researchers to reach consensus on the timing and approach to the diagnosis of post-tuberculosis lung disease.

Lastly, there is growing interest in tuberculosis endotypes, which are distinct patterns of immunological and molecular mechanisms that vary between people and drive tuberculosis disease heterogeneity. As our understanding of the links between pathogenesis, treatment response, and lung recovery grow, this concept could be extended to the clinical manifestations of post-tuberculosis lung disease. This extension could help develop more nuanced diagnostic biomarkers or categories of disease, which will facilitate a more precision medicine-based approach to diagnosis and care.

Implementation challenges

Several countries are considering including post-tuberculosis lung disease surveillance or individual-level screening within national tuberculosis guidelines.[68,69] These screening approaches must be low cost, acceptable, reliable, and feasible to implement if they are to be used by decentralised tuberculosis services in resource-constrained settings, and it might be effective to use existing tuberculosis diagnostic tools (eg, chest radiographs) to support this. There could be benefits from implementing screening for lung damage during tuberculosis treatment, to support interventions to mitigate respiratory damage and improve recovery.

	Advantages	Disadvantages	Priority data needed
Symptom screening	Low cost; quick; does not require specialist training; potentially strong predictor of patient outcomes; could be used alongside questions for broader morbidity (eg, anxiety and depression); identifies symptoms, which is a patient-focused outcome	Misses asymptomatic PTLD; captures non-respiratory causes of dyspnoea; does not differentiate between PTLD phenotypes; subject to recall bias	Relationship between end-of-treatment symptoms and long-term morbidity; validity, interobserver, and intra-observer variability of different symptom questions or tools; sensitivity and specificity of a PTLD-specific symptom screening tool compared with existing tests for specific phenotypes
Exercise testing	Low cost; does not require specalist training; identifies functional impairment, which is a patient-focused outcome	Time consuming; requires space and a standardised testing environment; interpretation dependant on reference ranges; misses mild PTLD; captures non-respiratory causes of functional limitation; does not differentiate between PTLD phenotypes; restricted to patients that can walk and stand	Relationship between end-of-treatment functional capacity and long-term morbidity; validity of different exercise tests in different PTLD phenotypes; reference values for populations in high tuberculosis burden settings
Spirometry	Sensitive; non-invasive; specific to respiratory pathology; differentiates between PTLD phenotypes; associated with adverse health outcomes in broader respiratory conditions (eg, COPD)	Time consuming; requires specialist training; requires specialist equipment; highly operator dependant and requires quality control and oversight; interpretation dependant on reference ranges	Relationship between end-of-treatment spirometry and long-term morbidity; real-world feasibility data describing the use of spirometry in decentralised services outside of the research setting; reference values for populations in high tuberculosis burden settings
Chest x-ray imaging	Sensitive; non-invasive; specific to lung pathology; equipment already in use for tuberculosis disease diagnostics; potential for interpretation by AI; end-of-treatment imaging could be used as a baseline for investigations of recurrent disease; differentiates between PTLD phenotypes	High cost; not yet available in all settings; requires specialist equipment; restricted sensitivity might not detect airways disease; requires trained staff or AI for interpretation	Relationship between patterns of pathology on end-of-treatment chest x-ray and long-term morbidity; development of AI algorithms for the interpretation of end-of-treatment (instead of diagnostic) chest x-ray imaging
Oxygen saturation	Low cost; quick; equipment required is more broadly relevant for clinical care; specific to respiratory pathology; focused on those with severe disease	Misses mild–moderate disease; does not differentiate between PTLD phenotypes	Relationship between hypoxia at end of treatment and long-term morbidity

AI=artificial intelligence. COPD=chronic obstructive pulmonary disease. PTLD=post-tuberculosis lung disease.

Table: **Potential tools for post-tuberculosis lung disease surveillance and screening**

Screening at existing tuberculosis clinic visits could also be more efficient from a patient and provider perspective. Ideally, post-tuberculosis lung disease screening should identify individuals at greatest risk of adverse outcomes. However, longitudinal data on outcomes remain scarce and it is challenging to identify the predictors of adverse post-tuberculosis outcomes with existing datasets. The advantages, disadvantages, and data gaps for various tools that could be used for surveillance and screening are shown in the table.

More advanced respiratory diagnostics, such as chest CT, body plethysmography, or gas transfer might better differentiate between post-tuberculosis lung disease-specific pathological patterns or phenotypes.[16,65] However, although the inclusion of these tests in clinical research studies will advance our understanding of pulmonary pathology and long-term cardiorespiratory sequelae, they are unlikely to be widely available in most high tuberculosis burden settings in the near future.

Towards care

As evidence on the burden and effects of post-tuberculosis lung disease emerge, there are growing calls for interventions to improve post-tuberculosis care. Clinical standards and expert statements have been produced to guide this process,[9,70,71] but primary data on the clinical effects of interventions to manage established post-tuberculosis lung disease, prevent and manage secondary complications, and address the high burden of recurrent tuberculosis disease among survivors remain scarce. Given the heterogeneity of post-tuberculosis lung disease, an approach that addresses treatable traits (including lifestyle or clinical factors) for individual patients might be of benefit. The potential benefit of routine follow-up of tuberculosis survivors after treatment completion in the absence of robust interventions remains unclear and could incur health system and patient costs. Data on the preferences of tuberculosis survivors regarding follow-up timing, duration, and approach are urgently needed.

Managing established post-tuberculosis lung disease

There are no evidence-based guidelines for the management of those with established post-tuberculosis lung disease, whether they are diagnosed at tuberculosis treatment completion or return with symptoms or complications months or years later.

Interventions proposed to date include nutritional support (micronutrients or calorie supplementation) to promote recovery, chest physiotherapy and pulmonary rehabilitation, smoking cessation, inhaled therapies, oxygen therapy and respiratory support, and surgical resection of destroyed lung tissue. Most of these suggestions are rooted in the morbidity and mortality benefits seen in other chronic respiratory diseases, but there remain little robust data on their clinical effects, feasibility, and cost-effectiveness in post-tuberculosis lung disease.[72,73]

Pulmonary rehabilitation is a low-cost intervention with growing interest and evidence; it can be delivered in community settings, has a mortality benefit in other chronic lung conditions, might address general deconditioning and muscle loss, and has been included in published clinical standards for post-tuberculosis lung disease care.[70] However, data on long-term effects in individuals with post-tuberculosis lung disease are scarce.[72,73] A 2023 review identified seven studies of pulmonary rehabilitation reporting on patient outcomes after tuberculosis treatment completion, including only two small trials (N=60 and N=62), with little data on sustained effects over time.[72]

Although inhaled steroids and bronchodilators are often used for post-tuberculosis lung disease, the pathophysiology of findings, such as airway obstruction, might be different in those with tuberculosis versus smoking-related disease, and it is important to obtain direct evidence of the role of these treatments among tuberculosis survivors, rather than extrapolating findings from broader chronic obstructive pulmonary disease studies. It will be particularly important to understand the benefit of inhaled therapies in settings where the diagnosis and treatment of chronic respiratory disease might be stigmatising and costly.[74] There is a need to include patient-centred outcomes (eg, quality of life measures) or qualitative data when designing and evaluating interventions for post-tuberculosis care.

Managing secondary complications

Secondary complications of post-tuberculosis lung disease can include secondary pulmonary infections, pulmonary hypertension and cor pulmonale,[63] lung cancer,[75] and respiratory failure.[76] There are few data describing the incidence and time to these complications, but they are well described in case series and well recognised by clinicians in high tuberculosis incidence settings. Post-tuberculosis cardiovascular disease is increasingly recognised and was the leading cause of death in a 2019 meta-analysis of post-tuberculosis mortality.[24]

Tuberculosis survivors with bronchiectasis or destroyed parenchyma might be at increased risk of secondary pulmonary infections, but little is known about the microbiology of bronchiectasis in many resource-constrained settings. Studies of patients with all-cause non-cystic fibrosis bronchiectasis in high tuberculosis burden settings, such as India, where more than a third of disease is probably tuberculosis-related, report a high burden of gram-negative infections,[77] but substantial geographical variation is expected. Pulmonary tuberculosis survivors with residual cavities or destroyed lung are also likely at increased risk of fungal lung disease, including aspergilloma and invasive pulmonary aspergillosis. Although existing data suggest moderate rates of *Aspergillus* IgG seropositivity among tuberculosis survivors,[78,79] data on the prevalence, patterns, and time to clinically relevant fungal lung disease remain lacking. The incidence of non-tuberculous mycobacterial pulmonary disease in high tuberculosis incidence settings is poorly described, including among tuberculosis survivors.

Further data will be needed to inform our approaches to the prevention, diagnosis, and management of secondary infections among tuberculosis survivors. Vaccination against respiratory pathogens, including influenza, SARS-CoV-2, and pneumococcus, have been suggested at tuberculosis treatment completion[3] in keeping with practice in broader chronic respiratory diseases. However, data on infection microbiology, infection risk, and vaccine immunogenicity is needed to determine the clinical efficacy and potential timing of respiratory vaccinations in this patient group.

Prevention and diagnosis of recurrent tuberculosis disease

Survivors are at risk of recurrent disease through either endogenous relapse or exogenous reinfection,[80] and surveillance data from several African sites have shown that previous tuberculosis disease remains a dominant risk factor for a new tuberculosis diagnosis.[81,82] A systematic review and meta-analysis of 175 studies found a pooled estimate of tuberculosis incidence of 2·26 per 100 person-years at risk (95% CI 1·87–2·73) among tuberculosis survivors, with a mean follow-up of 2·3 years.[83] However, rates of recurrence vary widely between settings, with higher rates in high tuberculosis incidence settings and among those treated for drug-resistant tuberculosis or those with HIV.[84] Although there is heterogeneity between settings, disease relapse remains the most common cause of recurrent tuberculosis disease, accounting for 70% (95% CI 42–74) of cases in a review of 48 studies that used DNA fingerprinting.[83]

The relationship between post-tuberculosis structural lung damage, tuberculosis relapse, and tuberculosis reinfection remains unclear. Cavitary tuberculosis disease has been associated with higher rates of treatment failure and disease relapse than non-cavitary disease.[85] However, this association could reflect a high burden of bacterial disease in those with cavitation, and issues

around drug penetrance during the initial tuberculosis treatment episode, rather than the effect of structural lung pathology on post-tuberculosis immunity. Recurrent disease might also reflect high rates of re-exposure among those returning to similar social environments or unchanged underlying social determinants of health (eg, poverty and malnutrition). Research exploring the effect of tuberculosis disease and treatment on patterns of systemic inflammation, the host immune response, the microbiome, and their effects on post-tuberculosis infection is ongoing.[86]

The diagnosis of recurrent disease can be challenging among pulmonary tuberculosis survivors, many of whom have residual or recurrent respiratory symptoms due to post-tuberculosis lung disease or secondary bacterial or fungal infections. Antibiotics for possible bacterial infection are often part of the diagnostic pathway for recurrent tuberculosis disease, but there are few microbiology data to guide the choice of antibiotic for post-tuberculosis lung disease exacerbations, and no robust data to support empirical antibiotics as part of the diagnostic pathway.[87] The challenge of diagnosis is exacerbated by the reduced specificity of nucleic acid amplification tests, such as Xpert MTB/Rif—increasingly used as a primary tuberculosis investigation instead of sputum smear—among tuberculosis survivors compared with tuberculosis-naive adults, particularly within 2 years of treatment completion.[88,89] The specificity of Xpert Ultra is lower than that of Xpert MTB/Rif in this patient group.[90] First-line use of chest x-ray to diagnose recurrent tuberculosis disease is challenging in patients with residual structural pathology after a first episode of tuberculosis disease, and artificial intelligence algorithms for tuberculosis diagnosis on chest x-ray frequently do not account for previous disease.

Post-tuberculosis lung disease in children and adolescents

Children and adolescents (ages 0–14 years) make up approximately 12% of the global tuberculosis burden.[1] The patterns, severity, presentation, and outcomes associated with post-tuberculosis lung disease in children and adolescents depend on the timing of the lung insult, the developmental stage and maturity of the immune system, and the potential for lung recovery with lung function catch-up over time.[91] Lung damage during childhood can track over the life course[91] and post-tuberculosis lung disease in young children might substantially contribute to the overall years lived with disability and burden of tuberculosis disease.[7] Tuberculosis disease during childhood and adolescence might also have essential and lasting effects on educational, social, and psychological wellbeing.[92]

Children have different presentations to adults, with a higher burden of paucibacillary disease and primary complex tuberculosis; the nature of residual lung damage can differ accordingly. Patterns of pathology seen in children and adolescents include bronchiectasis and obstructive and restrictive lung disease, with symptoms including cough, wheeze, shortness of breath, chest pain, increased work of breathing, and stridor.[93] Birth cohort data from South Africa—although potentially confounded by socioeconomic status—suggest that young children treated for tuberculosis disease have a higher prevalence of wheezing and lung function deficits by age 5 years compared with tuberculosis-naive children, with greater impairments in those diagnosed before age 1 year.[94] Cross-sectional data from The Gambia show lower lung function indices, higher prevalence of respiratory symptoms, and lower quality of life scores among older children previously treated for tuberculosis disease compared with age-matched household control individuals.[92] A prospective study of adolescents in South Africa showed lower spirometry indices and more gas trapping in those completing tuberculosis treatment compared with household control individuals.[95] Finally, a 2024 systematic review and meta-analysis identified five studies, including data from 567 children ages 18 years or younger at varying times from tuberculosis treatment, and suggest sustained deficits in FEV_1 z-scores (–1·53 [95% CI –2·65 to –0·41]) and FVC z-scores (–1·93 [–3·35 to –0·50]), but with substantial heterogeneity.[96]

As with adults, there is a paucity of longitudinal data on change over time, little data on the burden and time to secondary complications, and little consensus about strategies for surveillance or screening for post-tuberculosis lung disease among children. Diagnosis is particularly challenging because lung function assessment can be difficult in young children and spirometry has low sensitivity for early damage.

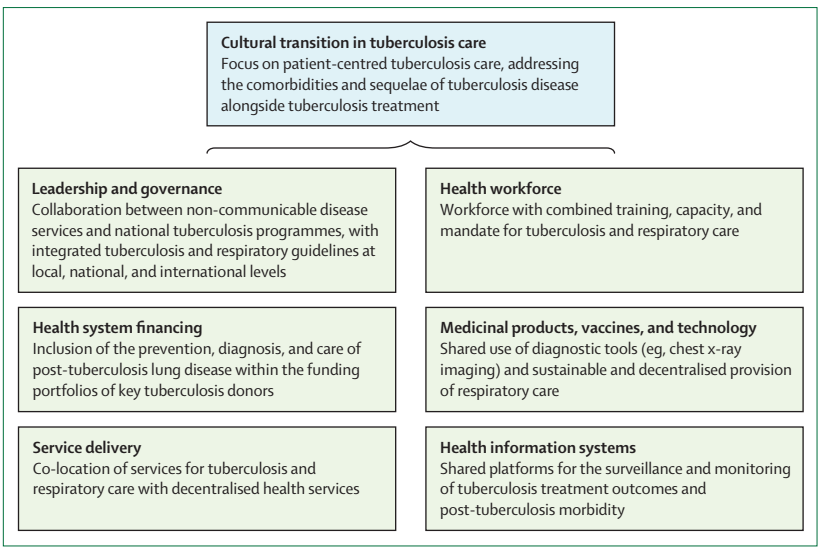

Figure 2: **Changes required to the health system pillars to deliver post-tuberculosis lung disease prevention, diagnosis, and care**

Panel 2: **Post-tuberculosis lung disease research priorities that are relevant to children, adolescents, and adults**

Towards prevention

- Studies exploring causal pathways, including effect modifiers of the relationship between tuberculosis disease and residual lung damage
- Data describing the effects of early tuberculosis diagnosis and treatment (including through active case-finding interventions) on the incidence, severity, and patterns of post-tuberculosis lung disease
- Data describing the effects of novel tuberculosis treatment regimens and time to microbiological cure on the incidence, severity, and patterns of post-tuberculosis lung disease
- Robust host-directed therapy trials that include respiratory outcomes at or after treatment completion

Towards diagnosis

- Longitudinal data on post-tuberculosis respiratory outcomes to determine trajectories over time, and to identify patient characteristics and disease patterns that can be identified early and are associated with adverse long-term outcomes
- Development of tuberculosis endotypes linking pathogenic mechanisms, the patterns and severity of lung damage, and long-term patient outcomes
- Operational research data describing the cost, feasibility, sensitivity, specificity, and predictive values of different approaches to post-tuberculosis lung disease screening
- Development and validation of dedicated symptom screening and quality of life scores
- Development of artificial intelligence algorithms for diagnosis from end-of-treatment chest radiographs

Towards care

- Qualitative data describing patient perspectives on the use, duration, and approach to post-tuberculosis follow-up and care, with a gendered perspective when appropriate
- Robust data on the risk, timing, and outcomes of secondary infections with bacteria, viruses, aspergillus, and non-tuberculous mycobacteria, particularly in low-income and middle-income countries
- Data on the immunogenicity and clinical effectiveness of respiratory vaccines in tuberculosis survivors at treatment completion
- Diagnostic accuracy studies for recurrent tuberculosis disease among survivors to inform dedicated guidelines for tuberculosis diagnosis in this group
- Development of artificial intelligence algorithms for the diagnosis of recurrent tuberculosis disease among tuberculosis survivors using chest radiographs
- Data on the long-term clinical effects, feasibility, timing, and cost-effectiveness of key interventions to mitigate post-tuberculosis morbidity (eg, nutritional support, chest physiotherapy and pulmonary rehabilitation, and inhaled therapies)

Health systems

- Stakeholder perspectives on the financing, governance, service delivery, and monitoring of approaches for the diagnosis and management of post-tuberculosis lung disease
- Pilot studies of integrated tuberculosis and respiratory care for post-tuberculosis lung disease with robust process evaluation of how these interventions work, for whom, and their effects on broader tuberculosis and non-communicable disease care

Approaches, such as tidal breathing manoeuvres, impulse oscillometry, and multiple breath washout can be more easily completed and more sensitive, but are not widely available in high tuberculosis burden settings. Access to chest x-ray imaging can also be challenging for many children. Observational work to increase our understanding of post-tuberculosis lung disease in children and adolescents is ongoing and interventional studies to develop feasible approaches to screening and management are needed.

Health systems perspectives

Little is known about the health systems that are needed to deliver prevention, diagnosis, and care for post-tuberculosis lung disease. The identification of residual morbidity at tuberculosis treatment completion will likely fall within the remit of national tuberculosis programmes, but long-term respiratory care will require collaboration with non-communicable disease services.[71] Basic post-tuberculosis lung disease services will need to be decentralised and delivered at the point of care, and gender-specific challenges around access to care must be taken into account to ensure equitable service delivery. Services are likely to be more sustainable if delivered with an integrated approach that includes both tuberculosis and respiratory care, rather than as additional, vertically implemented services.[97] However, this approach will require a shift in the culture and delivery of tuberculosis services (figure 2).

The paucity of existing models of joint tuberculosis–non-communicable disease or tuberculosis–respiratory care has previously been a key barrier to implementation of integrated services.[98] Although the approaches required to achieve this will likely be context dependent,[99] there could be opportunities to learn from the example of integrated HIV–non-communicable disease care in low-income and middle-income countries.[100] Several countries have included operational research around post-tuberculosis morbidity screening and care in funding applications to The Global Fund to Fight AIDS, Tuberculosis and Malaria as part of the 2023–25 funding cycles; others have incorporated

Search strategy and selection criteria

References for this narrative review were identified by the authors, based on data from peer-reviewed systematic reviews on post-tuberculosis lung disease, clinical statements and guidelines for post-tuberculosis care, evidence presented at the First and Second International Post-Tuberculosis Symposia, and their experience in this field. There were no restrictions on date or language of publication. No formal literature searches were completed to inform this review.

post-tuberculosis services with national guidelines for tuberculosis patient care,[68] and more robust data on implementation might be available in the future. Improved community awareness and literacy about post-tuberculosis lung disease will be essential to implementing these services, particularly given the stigma associated with tuberculosis disease,[101] respiratory symptoms (eg, cough),[102] and respiratory treatments (eg, inhalers) in many settings.[74]

Conclusion

There is a convincing body of data describing the prevalence and patterns of residual lung damage among tuberculosis survivors, and the marked effect this might have on the lives and livelihoods of tuberculosis-affected households. However, crucial gaps remain in our understanding of pathogenesis and prevention; approaches to screening and diagnosis; and data on the impact, cost, and feasibility of strategies for post-tuberculosis care. These gaps are particularly important for children and adolescents, in whom respiratory damage can persist over the life course. Further observational data are needed to describe causal pathways and disease behaviour over time, interventional work is needed to address gaps in prevention and care, and a health systems focus is needed to support feasible and sustainable implementation across all age groups (panel 2).

Although this Review has focused on post-tuberculosis lung disease, this is only one example of post-tuberculosis morbidity. Further work is needed to describe the sequelae of extra-pulmonary disease, including tuberculosis meningitis or musculoskeletal disease, and the psychosocial and economic morbidity experienced by many tuberculosis survivors, as well as to understand the broader social contexts that shape peoples' experiences of post-tuberculosis disability. Research and implementation work will be needed across these areas, if we are to truly improve the long-term wellbeing of tuberculosis-affected communities.

Contributors

JM and AR conceptualised the review. All authors contributed to the first draft of the manuscript. JM and AR reviewed and finalised the manuscript. All authors reviewed and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

JM is supported by the UK National Institute for Health and Care Research (NIHR156700) using UK international development funding from the UK Government to support global health research. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the UK government. SCA and GPB are supported by funding from the US National Institutes of Health (R01 AI166988). This report builds on the work of the post-tuberculosis lung disease working group for the Second International Post-Tuberculosis Symposium, which took place in Stellenbosch, South Africa in April, 2023, and is further informed by workshops held with delegates at the meeting. We are grateful to the symposium organisers and delegates for their input and support.

For more on the **symposium organisers and delegates** see https://www.post-tuberculosis.com/

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