

Syndemic Burden: Bridging the gap between Tuberculosis and Mental Health Care for Integrated Patient-Centered Solutions – a comprehensive review

Sofia Sousa, Ana Aguiar

University of Porto, Porto, Portugal

Abstract

Introduction: Mental health issues are prevalent, yet their treatment remains inadequate. Tuberculosis presents substantial mental health challenges. Their co-occurrence is a frequent phenomenon. However, the integration of mental health professionals or services is not a common practice.

Purpose: To review the evidence about the relation between tuberculosis and mental health, and its consequences concerning the implementation of policies and services.

Methodology: We conducted a comprehensive review using the MeSH terms "Tuberculosis" and "Mental Health" on PubMed. We identified and assessed systematic reviews, regular reviews, scoping review and meta-analyses for their appropriateness and relevance.

Results: A total of 341 studies were accessed for eligibility and 17 studies were included. Mental disorders and tuberculosis are frequent comorbidities. Their relation is commonly described as "syndemic". Shared risk factors, social vulnerabilities, and upstream social determinants are prevalent in both conditions. There is a potential for the integration of both conditions into policy and service organization.

Conclusions: Mental disorders treatment gap could be shortened by addressing mental health problems among TB patients. The WHO Global End TB Strategy prioritizes integrated patient-centered care, and fostering collaborative partnerships between tuberculosis and mental health services could enhance its implementation.

Keywords

Tuberculosis; Mental Health; Syndemic

Address for correspondence:

Sofia Sousa, MD, University of Porto, Porto, Portugal
E-mail: assousa@icbas.up.pt

This work is licensed under a Creative Commons Attribution-Non-Commercial 4.0 International License (CC BY-NC 4.0).



©Copyright: Sousa, 2024

Publisher: Sciendo (De Gruyter)

DOI: <https://doi.org/10.56508/mhgci.v7i1.180>

Submitted for publication: 19
October 2023

Revised: 24 January 2024

Accepted for publication: 31
January 2024

Introduction

Mental health (MH) constitutes an integral component of human flourishing. Mental disorders not only stand as prominent contributors to disability but also pose substantial risks for premature mortality (Charlson et al., 2015; Rehm and Shield, 2019). This burden associated with mental disorders is on the rise across all levels of sociodemographic development (Patel, Saxena, Lund, Thornicroft, Baingana, Bolton, Chisholm, Pamela Y Collins, et al., 2018). Beyond the strain placed on healthcare budgets, MH disorders exert a substantial burden on societies. This impact extends to individuals, families, workplaces, and the overall economy, leading to reduced labor engagement, earlier retirements, and increased welfare dependency, as evidenced by Doran in 2017 (Doran and Kinchin, 2019).

While the high burden of disease attributable to MH is primarily due to high prevalence conditions such as depression and anxiety, in most low and middle income countries (LMIC), by far, the majority of expenditure is on treatment/care of severe conditions such as schizophrenia and bipolar mood disorder (Freeman, 2022). Budgets for prevention and promotion are usually minimal or even non-existent in most LMIC (Freeman, 2022). According to Global Burden of Disease 2017, mental disorders have consistently formed more than 14% of Disability-Adjusted Life Years for nearly three decades, and have greater than 10% prevalence in all regions (James et al., 2018). The burden of mental disorders affects individuals of all sexes and spans across age groups. It begins in childhood, with conditions like idiopathic intellectual disability and autism spectrum disorders, and persists into later life, encompassing depressive disorders, anxiety disorders, and schizophrenia (James et al., 2018). Moreover, stands as a prominent cause of disability on a global scale and plays a significant role in contributing to the overall burden of disease worldwide (World Health Organization, 2020).

The connection between Tuberculosis (TB) and mental disorders is widely acknowledged, even though it has received relatively less research attention (Janse Van Rensburg et al., 2020). Research has indicated that mental disorders are frequently observed as comorbidities among TB patients, but they are not always readily recognized by healthcare workers and physicians (Doherty et al., 2013; Koyanagi et al., 2017; Plana-Ripoll et al., 2019; Janse Van Rensburg et al., 2020).

Depression affected more than 264 million people of all ages in 2019 (Sweetland et al., 2014). Depression and TB often coexist in individuals and share common risk factors (Duko, Bedaso and Ayano, 2020). TB patients who are depressed are less likely to seek medical advice and adhere to prescribed treatment regime, which results in: prolong infectiousness, emergence of drug resistance, increased morbidity and mortality. Thus, depression may be a silent driver of global TB epidemic (Ruiz-Grosso et al., 2020) and the emergence of Multidrug resistant TB (MDR-TB) (Sweetland et al., 2014). Undiagnosed depression can threaten the robustness of directly observed treatment (DOT) model despite large public health investment (Chandra et al., 2019). There is compelling evidence indicating that depressive symptoms are linked to reduced adherence to treatment regimens for chronic conditions, particularly those with therapeutic requirements similar to TB, such as HIV (Wagner et al., 2011; Blashill, Gordon and Safren, 2014).

Purpose

A clear understanding of the specific types of MH disorders and social stressors that may be common to TB patients is needed to design, evaluate and monitor effective interventions (Alene et al., 2018). In this sense, we aim to comprehensively review the relation between tuberculosis and mental health, in order to answer to the following specific objectives:

1. To review the evidence about the relation between tuberculosis and mental health, considering social determinants of health;
2. To assess the effects of mental health disease in the treatment and clinical outcomes of patients with TB;
3. To analyze the effects of TB on patients' mental health outcomes;
4. To analyze potential consequences to the implementation of policies and services

Methodology

Search of studies

A comprehensive review of systematic reviews was conducted in PubMed, Cochrane library and PsycINFO, according to PRISMA guidelines. A search using the MeSH terms "Tuberculosis" and "Mental Health" was conducted on referred databases in December 2023, being our final search expression (for Pubmed and PsycINFO) as follow: ("tuberculosis"[All Fields] OR "tuberculosis"[MeSH Terms] OR "tuberculosis"[All Fields] OR "tuberculoses"[All Fields] OR

"tuberculosis"[All Fields] AND ("mental health"[MeSH Terms] OR ("mental"[All Fields] AND "health"[All Fields]) OR "mental health"[All Fields]). In order to address the objectives mentioned, in an exploratory way, we filtered the article type to include only systematic reviews, reviews and meta-analysis. In the case of Cochrane library, we only use the term "Tuberculosis" in the search expression, since the joint of "Tuberculosis" and "mental health" only delivered 4 reviews, not related with any of the terms.

We opted to utilize the term "mental health" because its definition encompasses all psychological disorders. This choice allows us to include a greater number of articles related to tuberculosis. Additionally, prior evidence emphasized the role of depression more prominently than other mental health illnesses. As a result, we chose to adopt a broader term for the current review.

For the definition of the construct of "mental health" we considered the definition proposed by the WHO as "a state of well-being in which an individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and is able to make a contribution to his or her community" (World Health Organization, 2022).

Selection of studies

We considered all the studies found from inception until December 2023 to this comprehensive review.

Title and abstracts were screened for appropriateness and relevance in the first step of the review. Articles were excluded if: did not include the terms "Tuberculosis" or "Mental health" in the title and abstract; studies that only focused on "tuberculosis" or only on "mental health"; studies that were not systematic reviews, reviews or meta-analysis; studies related with drug secondary effects, alcohol or drug addiction or latent TB infection.

Data extraction and analysis

Following the conclusion of the search process, the two authors independently carried out the selection of articles for inclusion and the extraction of key findings from the studies. The research team evaluated the ultimate collection of manuscripts, and subsequently, they extracted thematic information regarding the study's objectives, the employed methodology the study's setting, and noteworthy findings.

Moreover, since we included systematic reviews, reviews, scoping reviews and meta-analysis, we summarized the information of the studies using a narrative approach. We extracted qualitative evidences using the 'thematic

synthesis' method and methodically organized them into broader descriptive themes (Barnett-Page and Thomas, 2009), which were then compared for interrelationships and categorized into four final themes. Furthermore, considering the type of articles included for revision and the full nature of the present comprehensive review, we did not assess the quality of the included studies since, by default, among epidemiological studies, the systematic reviews and meta-analysis articles are on the top of the pyramid considering higher quality of reported evidence and lower risk of bias.

Ethical considerations

Our data was already published in peer-review journals that demand ethically approved research, so ethical approval or personal consent have not been necessary.

Results

A total of 341 results were found (Figure 1). Of these, 320 were excluded because they did not include "tuberculosis" or "mental health" in the title or abstract or were not systematic reviews, reviews, scoping reviews or meta-analysis (Figure 1). A total of 17 studies were included in our final revision (Table 1). The time-frame between the included studies ranged from 2013 and 2023. Concerning the number of articles referred in each included review, the smallest review was from Chandra et al., 2019 (Chandra et al., 2019), with 3 articles included and, the largest, was published by Doherty et al., (2013), had a total of 189 articles revised.

Epidemiology of Mental Health and Tuberculosis

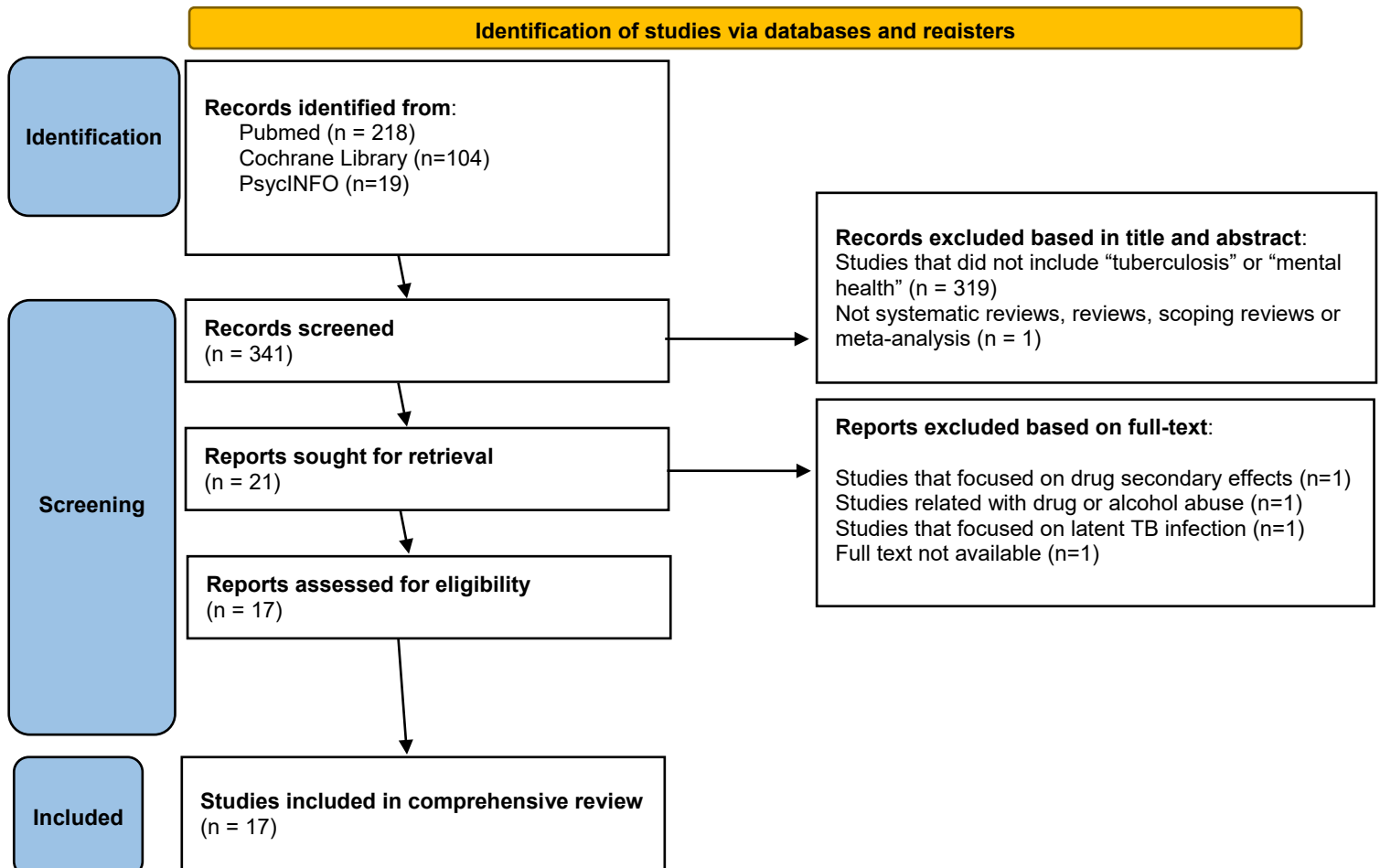
The epidemiology of mental health in tuberculosis (TB) patients reveals a significant burden of mental health (MH) disorders, social stressors, and diminished health-related quality of life, particularly among multidrug-resistant TB (MDR-TB) patients. Compared to the general population, TB patients exhibit a higher prevalence of MH disorders (Doherty et al., 2013). Depression, for instance, is three to six times more common among TB patients than in healthy controls, while anxiety rates are almost twice as high. Alarmingly, one in ten MDR-TB patients experiences psychosis (Alene et al., 2018). Respiratory diseases such as TB are significantly more prevalent in people with schizophrenia compared with the general population (Suetani et al., 2021). Suicide was reported in 0.92% of TB patients at the end of 2 years, whereas 2.2% to 8.4% of all TB deaths were reported due to suicide (Patwal et al., 2023).

Table 1: included studies, year of publication, title, number of articles, and main objective.

Author	Year	Country/countries	Title	N articles	Main objective(s)
Doherty et al	2013	-	A review of the interplay between tuberculosis and mental health.	189	Examine the interplay between tuberculosis and mental health; Identify the key issues which are likely to be of clinical importance in treating patients with psychiatric comorbidity in tuberculosis.
Thomas et al	2016	-	Psycho-Socio-Economic Issues Challenging Multidrug Resistant Tuberculosis Patients: A Systematic Review.	15	Review the psychosocial challenges faced by Multidrug Resistant Tuberculosis (MDR-TB) patients which complicates the MDR-TB treatment.
Magee et al	2017	-	Integrated Public Health and Health Service Delivery for Noncommunicable Diseases and Comorbid Infectious Diseases and Mental Health.	-	Explore the epidemiology of joint burdens, risk factors, and prognoses of these co-occurring conditions.
Alene et al	2018	-	Mental health disorders, social stressors, and health-related quality of life in patients with multidrug-resistant tuberculosis: A systematic review and meta-analysis	40	Quantify mental health disorders, social stressors, and health-related quality of life in patients with multidrug-resistant tuberculosis.
Zhang et al	2019	-	The interplay between depression and tuberculosis.	-	Discuss the hypotheses on the association between depression and TB, highlighting the immuno-inflammatory response and lipid metabolism as potential mechanisms.
Chandra et al	2019	-	Tuberculosis - Depression syndemic: A public health challenge.	3	To study the evidence base for Depression-Tuberculosis Syndemic.
Kane et al	2019	low- and middle-income countries	A scoping review of health-related stigma outcomes for high-burden diseases in low- and middle-income countries.	186	Provide a critical overview of the breadth of research on stigma for each of five conditions (HIV, tuberculosis, mental health problems, epilepsy and substance use disorders) in low- and middle-income countries.
Rensburg et al	2020	Low-to-middle income countries	Comorbidities between tuberculosis and common mental disorders: a scoping review of epidemiological patterns and person-centred care interventions from low-to-middle income and BRICS countries	100	Review the nature and extent of tuberculosis and common mental disorder comorbidity and person-centred tuberculosis care in low-to-middle income countries and emerging economies.
Lee et al	2020	-	Impact of mental disorders on active TB treatment outcomes: a systematic review and meta-analysis.	10	Determine whether TB patients with concurrent mental disorders have poorer treatment outcomes than patients without mental disorders.
Duko et al	2020	-	The prevalence of depression among patients with tuberculosis: a systematic review and meta-analysis.	25	Quantitatively summarize epidemiologic evidence on the prevalence of depression among patients with TB and formulate a recommendation for future clinical practice as well as research.
Farooq et al	2021	-	Pharmacological or non-pharmacological interventions for treatment of common mental disorders associated with Tuberculosis: A systematic review.	26	Review the literature on interventions for treating Common Mental Disorders (CMD) in people with TB.
Suetani et al	2021	-	Increased rates of respiratory disease in	21	Establish the prevalence and association of respiratory diseases in people with schizophrenia

			schizophrenia: A systematic review and meta-analysis including 619,214 individuals with schizophrenia and 52,159,551 controls		
Janusz Rybakowski	2022	-	Infections and mental diseases: from tuberculosis to COVID-19	-	Conduct a narrative review on the relationship between mental diseases and infectious factors such as tuberculosis
Hayward et al	2022	-	The relationship between mental health and risk of active tuberculosis: a systematic review	10	Examine the association between mental health and TB disease risk to inform clinical and public health measures.
Njie et al	2022	United States	Prevalence of Tuberculosis and Mental Disorders Comorbidity: A Systematic Review and Meta-analysis	9	Examine Tuberculosis and mental disorder comorbidity prevalence and its impact on TB treatment outcomes.
Patwal et al	2023	-	Prevalence of suicidal ideations and suicide attempts in patients with tuberculosis: A systematic review and meta-analysis.	9	Assess the prevalence of suicidality and identify the factors associated with suicidality in patients with TB.
Alemu et al	2023	East Africa	Prevalence of depression in people with tuberculosis in East Africa: a systematic review and meta-analysis	9	Examine evidence concerning the prevalence of depression among tuberculosis patients in East Africa.

Figure 1. Flowchart with the included studies



Research consistently demonstrates that individuals undergoing TB treatment are at an elevated risk of mental illness (Alene et al., 2018; Plana-Ripoll et al., 2019). A 2020 review involving 25 studies reported a prevalence of depression among TB patients, using the Hamilton Depression Rating Scale, at 45.19% (Duko, Bedaso and Ayano, 2020; Njie and Khan, 2022). Furthermore, the prevalence is even higher among MDR-TB patients at 52.34% (Duko, Bedaso and Ayano, 2020). In another review in East Africa countries, the pooled prevalence estimate of depression amongst tuberculosis patients was 43.03% (Alemu and Zeleke, 2023).

MDR-TB patients, who undergo prolonged treatment with anti-TB drugs and face severe side effects, are particularly vulnerable to MH issues (Thomas et al., 2016). Reviews have indicated varying prevalence rates of anxiety among TB patients, ranging from 2% to 27% (Janse Van Rensburg et al., 2020). Depression, in particular, independently contributes to higher morbidity, mortality, drug resistance, TB reactivation, and community TB transmission (Chandra et al., 2019). Depressed individuals with TB often delay seeking care and exhibit inconsistent medication adherence, increasing the risks of drug resistance, morbidity, and mortality (Sweetland et al., 2014).

Compounding these challenges, mental illness often emerges during the TB disease trajectory, with detrimental consequences, particularly in low and middle income countries grappling with complex issues like poverty, gender disparities, limited education, and inadequate healthcare systems (Janse Van Rensburg et al., 2020). Furthermore, TB, especially MDR-TB, is associated with long-term physical complications, sparking interest in how these sequelae affect mental health and social functioning (Chakaya, Kirenga and Getahun, 2016; Alene et al., 2018).

The interconnection between mental illness and TB is claimed to be bidirectional and influenced by biological, psychological, social, and healthcare system factors (Zhang et al., 2019; Janse Van Rensburg et al., 2020). TB and MH are both influenced by common social determinants, such as poverty, inadequate access to healthcare, and housing conditions (Whiting, Unwin and Roglic, 2010). These factors can increase the risk of both TB and mental illness.

MH disorders may develop following TB infection, but patients with such disorders also appear to have an increased risk of TB. In fact, most mental disorders are associated with an elevated risk of subsequent medical conditions

(Oh et al., 2017; Momen et al., 2020). TB is relatively common among patients with psychiatric disorders, with rates of major depression being even higher than in the general population, particularly in individuals diagnosed with TB (Doherty et al., 2013).

Recognizing and addressing the MH needs of TB patients is crucial for improving overall outcomes and reducing the burden of both conditions.

TB is a chronic illness that can cause significant psychological distress (Pachi et al., 2013). The physical symptoms, social isolation, and fear of transmission can lead to anxiety and depression among TB patients.

Stigma detrimentally affects the support networks and the quality of services provided to individuals with stigmatized conditions. Mistreatment TB patients can lead to adverse MH outcomes, maladaptive coping behaviors, and the emergence of other comorbid conditions. Furthermore, TB-related stigma has the potential to erode the resilience of affected patients (Kane et al., 2019; Alfaiate et al., 2023).

The stigma associated with TB can exacerbate psychological distress. People with TB may be ostracized, discriminated against, or excluded from their communities, leading to feelings of shame and social isolation.

Psychological factors and patient perception about illness are important factors for adherence to a long term therapy required in chronic illness like TB (Pachi et al., 2013). In order to maximize the rate of adherence, health workers involved in the management of these patients should develop a higher index of suspicion for possible psychopathology and utilize the available consultation/liaison psychiatric services (Pachi et al., 2013).

Moreover, depression alone serves as a risk factor for TB. Cohort studies have demonstrated that patients with depression are more likely to develop TB, with a dose-response relationship observed between the severity of depression and the subsequent risk of TB (Oh et al., 2017). There is robust evidence from cohort studies in Asia demonstrating that depression and schizophrenia can increase risk of active TB, with effect estimates ranging from Hazard Rate (HR)=1.15 (95% CI 1.03 to 1.28) to 2.63 (95% CI 1.74 to 3.96) for depression and HR=1.52 (95% CI 1.29 to 1.79) to Relative Risk (RR)=3.04 for schizophrenia (Hayward et al., 2022).

TB and mental illness frequently co-occur due to shared risk factors such as homelessness, HIV positivity, substance abuse, and migrant status (Doherty et al., 2013). Patients with mental illness face an increased risk of TB infection due to factors like higher rates of homelessness, shelter

or group home residence, and potential contributors to disease progression such as smoking, poor nutrition, diabetes, and HIV infection (Doherty et al., 2013). Social stressors like discrimination, reduced income, divorce, and stigma are prevalent among individuals with TB, significantly affecting their quality of life and treatment outcomes (Alene et al., 2018).

The relationship between TB and socioeconomic conditions is intricate, with social vulnerability and mental disorders acting as intertwined factors. Both conditions are influenced by upstream health determinants, often coexisting in a substantial portion of the population. Poverty emerges as a formidable determinant of TB, shaping its various stages, from exposure risk to susceptibility, diagnosis, treatment compliance, and successful treatment (Knut Lönnroth, Ernesto Jaramillo, Brian Williams, 2010; Hargreaves et al., 2011; World Health Organisation, 2013; Duarte et al., 2018; Janse Van Rensburg et al., 2020). Overcrowded and poorly ventilated living and working environments directly increase TB transmission risk, while undernutrition contributes significantly to the development of active disease (World Health Organisation, 2013). Poverty is also associated with limited health knowledge and a lack of empowerment to address health-related risks (World Health Organisation, 2013).

Moreover, research consistently underscores the robust connection between social disadvantage and poor MH (Patel, Saxena, Lund, Thornicroft, Baingana, Bolton, Chisholm, Pamela Y. Collins, et al., 2018). Factors such as poverty, childhood adversity, and violence emerge as critical risk factors for the onset and persistence of mental disorders. These MH challenges, in turn, often result in income loss due to limited educational attainment and reduced employment opportunities and productivity. This intricate interplay between social determinants, mental disorders, and economic disadvantage creates a vicious cycle that perpetuates poverty across generations (Patel, Saxena, Lund, Thornicroft, Baingana, Bolton, Chisholm, Pamela Y. Collins, et al., 2018).

Possible causal mechanisms

Psychiatric disorders may be connected with an infection in various periods of life (Rybakowski, 2022). Depression appears to be the predominant mental illness associated with TB patients in existing studies. However, the exact nature of the relationship between depression and TB remains unclear, and it seems to have bidirectional association. Understanding this mechanism is crucial for directing research efforts to enhance TB therapy effectiveness and reduce

comorbidity with depression (Zhang et al., 2019). The causal pathways connecting TB and depression are complex and multidirectional, encompassing biological, social, behavioral, pharmaceutical, and psychosocial factors (Ugarte-Gil et al., 2013; Janse Van Rensburg et al., 2020).

Biological factors likely contribute to this bidirectional relationship. TB infection or reactivation may trigger depression, possibly due to the host's inflammatory response and alterations in the hypothalamic-pituitary-adrenal axis. TB infection can induce chronic inflammation, releasing pro-inflammatory cytokines that affect central nervous system enzymes. Additionally, certain anti-TB medications might contribute to mental health issues like depression (Duko, Bedaso and Ayano, 2020). Conversely, depression may raise the risk of TB through immuno-inflammatory responses and lipid metabolism. Increased pro-inflammatory cytokines seen in depression can dampen cellular and humoral immune system activation, potentially aiding TB progression (Zhang et al., 2019).

Social determinants also play a significant role. Poverty, as mentioned earlier, is a shared risk factor for both TB and depression. Overcrowded and poorly ventilated conditions facilitate TB transmission, while exposure to violence, social exclusion, drug abuse, and malnutrition may contribute to both diseases (Janse Van Rensburg et al., 2020). Moreover, depression can mimic TB symptoms and exacerbate them. When combined with negative coping behaviors, depression can lead to non-adherence to TB treatment, posing a considerable challenge (Sweetland et al., 2018).

Psychosocial factors, including perceived stigma and treatment nonadherence, are vital in this relationship. Stigma associated with TB diagnosis can heighten the risk of depression due to the fear it engenders (Chandra et al., 2019). Multidrug-resistant TB patients often experience stigma, discrimination, isolation, and a lack of social support, which can lead to negative emotions, social rejection, low self-esteem, and impaired psychosocial well-being (C. et al., 2014; Alene et al., 2018).

The discussion surrounding the link between stigma and health outcomes is often compartmentalized within specific disease categories, hindering the identification of common moderators or mechanisms. This separation limits our understanding of stigma's overall impact on individual well-being and global disease burden (Kane et al., 2019). Additionally, pharmacological issues must be considered. Psychiatric side effects of anti-TB

agents and potential interactions between TB treatment medications and drugs used to manage psychiatric or addiction disorders are important factors to be mindful of. Managing TB in the presence of depression can be particularly challenging due to these interactions (Doherty et al., 2013).

Policy and Services

In an 2023 Operational handbook on tuberculosis and comorbidities dedicated to mental health conditions, World Health Organization (WHO) refers that mental health care is one of the health services to be integrated with TB services as outlined in the End TB Strategy and the WHO Framework for collaborative action on tuberculosis and comorbidities (World Health Organization, 2023).

WHO's strategy for achieving the elimination of TB underscores the importance of addressing the social-economic determinants of TB. To achieve this, countries must strengthen their health and social sectors by implementing universal health coverage and social protection measures (World Health Organisation, 2013; WHO, 2015; Santos, Duarte and Nunes, 2020). Moreover, actions to reduce the risk of mental disorders across the lifespan, both at the community and country levels, are imperative. Recognizing that addressing social determinants of health is a shared responsibility across health programs and sectors is vital for comprehensive care (Carod-Artal, 2017).

Integrating MH care into all levels of the general health system is essential to improve the quality of care and reduce the stigma associated with mental disorders (Levav and Rutz, 2002). Health system barriers, such as fragmented health information systems, limited patient management, and communication gaps between levels of care, exacerbate challenges during the TB disease episode (Janse Van Rensburg et al., 2020).

During anti-TB treatment, nonadherence and adverse treatment effects are common, potentially leading to delayed recovery or exacerbation of comorbid depression-like symptoms. Combining antidepressant drugs with effective nursing measures that promote good mental health may help alleviate depressive symptoms in TB patients (Oh et al., 2017). Screening and managing depression among TB patients have been identified as crucial strategies to alleviate their suffering, and integrating TB programs with regular psychiatric services can substantially reduce this burden (Duko, Bedaso and Ayano, 2020).

A pilot experience in Pakistan studied integrating units for TB and mental health within

existing TB treatment facilities. Screening and offering mental health interventions to symptomatic patients resulted in higher rates of TB treatment completion (Pasha et al., 2021). Given the high prevalence of depression among TB patients, routine social support and counseling should be integral components of TB care and management programs, with the integration of psychiatric services further reducing the burden of depression (Duko, Bedaso and Ayano, 2020).

WHO's Global End TB Strategy emphasizes integrated, patient-centered care linked to social protection and innovative research. Achieving these goals necessitates more person-centered TB care models and collaborative partnerships between TB and mental health professionals (Chandra et al., 2019; Janse Van Rensburg et al., 2020). Improving the environment, society, and family support for TB patients can enhance their mental health outcomes (Liu et al., 2021).

Addressing the co-occurrence of noncommunicable and communicable diseases presents challenges that require integrated public health and care delivery efforts (Magee et al., 2017). Integrating TB and mental health services, particularly when dealing with multidrug-resistant TB patients, is essential to screen for and manage comorbid psychopathology and promote therapy adherence (Magee et al., 2017; Sweetland et al., 2019).

Surveys indicate receptivity to integrating TB and mental health care services into TB care and prevention, despite challenges such as low awareness, limited resources, and training gaps (Sweetland et al., 2019). A 2021 review suggests the feasibility of interventions to improve mental health outcomes and treatment adherence in TB patients, including psychosocial interventions, stigma reduction, socioeconomic support, and various psychological therapies, education, or pharmacological interventions (Farooq, Tunmore and Comber, 2021). These interventions can address common mental disorders and barriers to TB control worldwide, focusing on factors like stigma, socioeconomic disadvantages, health belief models, and support for family members (Farooq, Tunmore and Comber, 2021).

Discussion

The co-occurrence of tuberculosis (TB) and mental health (MH) disorders is a complicated and diverse issue with significant public health implications (Janse Van Rensburg et al., 2020). The findings from this study highlight the importance of a comprehensive strategy to addressing this dual burden since we found a positive and independent association between common mental disorders and TB.

The epidemiological data clearly show a considerable link between TB and MH disorders, with depression being the most commonly implicated mental illness among TB patients (Chandra et al., 2019). Individuals with TB have a significantly greater frequency of MH issues, particularly depression and anxiety, than the overall population. Notably, patients with multidrug-resistant tuberculosis (MDR-TB) endure an even larger burden of mental health concerns. This epidemiological link underscores the importance of a more comprehensive strategy to TB care, one that includes comprehensive MH support (World Health Organisation, 2013; WHO, 2015; Magee et al., 2017). In light of the observed comorbidity between TB and mental illness, regardless of the direction of causality, this work carries significant implications for the delivery of care for both mental disorders and TB. There is an urgent need for the development of practical and innovative psychosocial and economic interventions tailored to assist TB patients in managing their illness, enhancing treatment adherence, improving treatment outcomes, and ultimately enhancing their overall quality of life.

Understanding the risk factors and social determinants common to both TB and MH is essential. Poverty, homelessness, substance abuse, and social stressors emerge as shared risk factors. Overcrowded living conditions and inadequate access to healthcare further exacerbate these risks. Addressing these upstream determinants is imperative for effective prevention and management of both diseases. Poverty alleviation, improved living conditions, and social support systems are crucial components of such efforts. Efforts to alleviate poverty not only reduce the risk of TB transmission but also lower the chances of infection progressing to disease. Poverty alleviation measures improve access to healthcare services and promote adherence to recommended treatments. Addressing the determinants of ill health through holistic approaches, like "health-in-all-policies," can significantly enhance TB care and prevention.

A complex combination of biological, social, behavioral, pharmacological, and psychosocial processes underpins the bidirectional link between TB and MH issues. Both disorders are caused by biological factors such as inflammatory reactions and hypothalamic-pituitary-adrenal axis dysfunction. Poverty and violence are two social variables that further complicate this link. Furthermore, the overlap in symptoms between TB and depression, together with depression's detrimental impact on

adherence to TB therapy, produces a loop of increased disease burden.

Non-compliance as a major difficulty in the treatment of TB and mental illness. Many challenges faced by patients lie outside the formal health system sphere – transport problems, occupational issues, medication reactions and food assistance. Building a strong emotional and psychological support system for TB and mental health patients is crucial for increasing chances of their survival.

To address the co-occurrence of TB and MH issues, a comprehensive policy framework and coordinated care delivery are required. The END TB strategy of the World Health Organization highlights the importance of addressing social determinants and establishing universal health coverage. Integrating MH care into general health systems is critical for reducing stigma and improving care quality. However, bottlenecks in the health care system, fragmented information systems, and communication gaps offer substantial challenges.

Efforts to integrate psychological and TB care have showed promise in terms of enhancing treatment results and lowering depressive and anxiety symptoms. There is still a lack of thorough integration at both the policy and ground levels, particularly in diagnosing and treating depression in TB patients. The absence or scarcity of integration between TB and MH at both policy and operational levels prompts a critical question. It is prudent to explore a more holistic approach, encompassing both communicable and non-communicable diseases, to foster the integration of healthcare services within a person-centered perspective. Such an approach holds the potential to alleviate the dual burden of TB and mental health disorders, thereby improving the overall well-being of individuals affected by these intertwined conditions.

Efforts to address MH and social stressors can profoundly impact patient care. A systematic review commissioned by WHO found that TB patients who received social support during treatment were significantly more likely to adhere to their treatment regimens (Yamazaki, 2017). Integrating psychological and TB services has the potential to improve TB outcomes and progress toward TB elimination (Lee et al., 2020). However, there is a notable lack of published experiences regarding policy or ground-level integration, including the identification and appropriate management of depression in TB patients, despite repeated contact with healthcare providers in directly observed treatment (DOT) centers.

The link between TB and MH disorders is epidemiologically significant and intricately

entwined due to similar risk factors, complex pathophysiologic mechanisms, and policy implications (Doherty et al., 2013). Addressing this twofold burden requires a multifaceted approach spanning social, biological, and healthcare dimensions. Integrating MH treatments into TB care, addressing social determinants, and enacting policies that prioritize universal health coverage are all critical steps toward relieving the suffering of people suffering from both issues. Understanding this relationship is critical for improving individual health outcomes and for the worldwide endeavor to manage and eliminate TB.

To increase understanding of the possible mechanisms responsible for this association, further studies are needed. The most described relation in the literature was between TB and depression, described as 'TB-depression syndemic' (Chandra et al., 2019), which poses significant risk to the Global End TB Strategy. The bidirectional relationship between the TB and depression needs to be recognized to control the global TB epidemic (Sweetland et al., 2018). As mentioned before, depression is associated with a range of adverse outcomes in TB such as poor functional impairment, poor adherence to medication and self-care regimens, increased medical symptom burden and increased mortality. Depression may also increase risk of TB reactivation, antibiotic drug resistance, contribute to disease progression, and/or inhibit the physiological response to anti-tuberculosis treatment. Conversely, TB may precipitate depression. This results in worse prognoses for TB, treatment with drugs that have significant neuropsychiatric side effects, enhanced stigma and social isolation. These factors then lead to further depression and anxiety (Farooq, Tunmore and Comber, 2021).

Conclusions

In conclusion, the link between TB and MH disorders is both epidemiologically substantial and intricately intertwined due to shared risk factors, complex pathophysiology, and significant policy implications. To address this dual burden effectively, a multidimensional approach is necessary, involving social, biological, and healthcare aspects. Integrating MH into TB care, addressing socioeconomic factors, and prioritizing universal health coverage in policies are crucial steps to alleviate suffering in individuals with both TB and MH concerns. Understanding this complex link is critical for global TB control efforts. The scarcity or absence of integration between TB and MH at policy or ground levels prompts reasonable questioning. A

more comprehensive approach, encompassing both communicable and non-communicable diseases, could facilitate the integration of healthcare services from a person-centered perspective.

Funding

This work received financial support from the Portuguese Funds through FCT - Foundation for Science and Technology, I.P., under the projects UIDB/04750/2020 and LA/P/0064/2020. Ana Aguiar, was supported by her PhD Grant (Reference: 2020.09390.BD), co-funded by the Fundação para a Ciência e a Tecnologia (FCT) and the Fundo Social Europeu (FSE) Program. It's important to note that the funders played no role in the study's conception, data collection and analysis, decision to publish, or the preparation of the manuscript.

Conflict of interest

The authors declare that they have not conflicts of interest.

References

- Alemu, W. G. and Zeleke, T. A. (2023) 'Prevalence of depression in people with tuberculosis in East Africa: a systematic review and meta-analysis', *African Health Sciences*, 23(1), pp. 231–240. doi: 10.4314/ahs.v23i1.25.
- Alene, K. A. et al. (2018) 'Mental health disorders, social stressors, and health-related quality of life in patients with multidrug-resistant tuberculosis: A systematic review and meta-analysis', *Journal of Infection*, 77(5), pp. 357–367. doi: 10.1016/j.jinf.2018.07.007.
- Alfaiate, A. et al. (2023) 'Tuberculosis and COVID-19 Related Stigma: Portuguese Patients Experiences', *Tuberculosis and Respiratory Diseases*, 86(3), pp. 216–225. doi: 10.4046/trd.2022.0062.
- Blashill, A. J., Gordon, J. R. and Safren, S. A. (2014) 'Depression longitudinally mediates the association of appearance concerns to ART non-adherence in HIV-infected individuals with a history of injection drug use.', *Journal of behavioral medicine*, 37(1), pp. 166–172. doi: 10.1007/s10865-012-9476-3.
- C., S. et al. (2014) 'Health-related quality of life,

- depression, and anxiety in patients with autoimmune hepatitis', *Journal of Hepatology*, 60(3), pp. 618–624. Available at: <http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=2014123616>.
- Carod-Artal, F. J. (2017) 'Social determinants of mental health', *Global Mental Health: Prevention and Promotion*, pp. 33–46. doi: 10.1007/978-3-319-59123-0_4.
- Chakaya, J., Kirenga, B. and Getahun, H. (2016) 'Long term complications after completion of pulmonary tuberculosis treatment: A quest for a public health approach', *Journal of Clinical Tuberculosis and Other Mycobacterial Diseases*, 3, pp. 10–12. doi: 10.1016/j.jctube.2016.03.001.
- Chandra, M. et al. (2019) 'Tuberculosis - Depression syndemic: A public health challenge', *Indian Journal of Tuberculosis*, 66(1), pp. 197–202. doi: 10.1016/j.ijtb.2019.02.007.
- Charlson, F. J. et al. (2015) 'Excess mortality from mental, neurological and substance use disorders in the Global Burden of Disease Study 2010', *Epidemiology and Psychiatric Sciences*, 24(2), pp. 121–140. doi: 10.1017/S2045796014000687.
- Doherty, A. M. et al. (2013) 'A review of the interplay between tuberculosis and mental health', *General Hospital Psychiatry*, 35(4), pp. 398–406. doi: 10.1016/j.genhosppsy.2013.03.018.
- Doran, C. M. and Kinchin, I. (2019) 'A review of the economic impact of mental illness.', *Australian health review: a publication of the Australian Hospital Association*, 43(1), pp. 43–48. doi: 10.1071/AH16115.
- Duarte, R. et al. (2018) 'Tuberculosis, social determinants and co-morbidities (including HIV)', *Pulmonology*, 24(2), pp. 115–119. doi: 10.1016/j.rppnen.2017.11.003.
- Duko, B., Bedaso, A. and Ayano, G. (2020) 'The prevalence of depression among patients with tuberculosis: A systematic review and meta-analysis', *Annals of General Psychiatry*, 19(1), pp. 1–11. doi: 10.1186/s12991-020-00281-8.
- Farooq, S., Tunmore, J. and Comber, R. (2021) 'Pharmacological or non-pharmacological interventions for treatment of common mental disorders associated with Tuberculosis: A systematic review', *Chronic Respiratory Disease*, 18. doi: 10.1177/14799731211003937.
- Freeman, M. (2022) 'Investing for population mental health in low and middle income countries—where and why?', *International Journal of Mental Health Systems*, 16(1), pp. 1–9. doi: 10.1186/s13033-022-00547-6.
- Hargreaves, J. R. et al. (2011) 'The social determinants of tuberculosis: from evidence to action.', *American journal of public health*, 101(4), pp. 654–662. doi: 10.2105/AJPH.2010.199505.
- Hayward, S. E. et al. (2022) 'The relationship between mental health and risk of active tuberculosis: A systematic review', *BMJ Open*, 12(1). doi: 10.1136/bmjopen-2021-048945.
- James, S. L. et al. (2018) 'Global, regional, and national incidence, prevalence, and years lived with disability for 354 Diseases and Injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017', *The Lancet*, 392(10159), pp. 1789–1858. doi: 10.1016/S0140-6736(18)32279-7.
- Janse Van Rensburg, A. et al. (2020) 'Comorbidities between tuberculosis and common mental disorders: A scoping review of epidemiological patterns and person-centred care interventions from low-to-middle income and BRICS countries', *Infectious Diseases of Poverty*, 9(1). doi: 10.1186/s40249-019-0619-4.
- Kane, J. C. et al. (2019) 'A scoping review of health-related stigma outcomes for high-burden diseases in low- and middle-income countries', *BMC Medicine*, 17(1). doi: 10.1186/s12916-019-1250-8.
- Knut Lönnroth, Ernesto Jaramillo, Brian Williams, C. D. and M. R. (2010) 'Tuberculosis: the role of risk factors and social determinants', in *Equity, social determinants and public health programmes*, pp. 220–237.
- Koyanagi, A. et al. (2017) 'Depression comorbid with tuberculosis and its impact on health status: Cross-sectional analysis of community-based data from 48 low- and middle-income countries', *BMC Medicine*, 15(1), pp. 1–10. doi:

10.1186/s12916-017-0975-5.

Lee, G. E. *et al.* (2020) 'Impact of mental disorders on active tuberculosis treatment outcomes: a systematic review and meta-analysis', *INT J TUBERC LUNG DIS*, 24(12), pp. 1279–1284. doi: 10.5588/ijtld.20.0458.impact.

Levav, I. and Rutz, W. (2002) 'The WHO World Health Report 2001: New understanding - New hope', *Israel Journal of Psychiatry and Related Sciences*, 39(1), pp. 50–56.

Liu, K. *et al.* (2021) 'Prevalence and Correlates of Anxiety and Depressive Symptoms in Patients With and Without Multi-Drug Resistant Pulmonary Tuberculosis in China', *Frontiers in Psychiatry*, p. 1542. Available at: <https://www.frontiersin.org/article/10.3389/fpsyt.2021.674891>.

Magee, M. *et al.* (2017) 'Integrated Public Health and Health Service Delivery for Noncommunicable Diseases and Comorbid Infectious Diseases and Mental Health.', in Prabhakaran, D. *et al.* (eds). Washington (DC). doi: 10.1596/978-1-4648-0518-9_ch16.

Momen, N. C. *et al.* (2020) 'Association between Mental Disorders and Subsequent Medical Conditions', *New England Journal of Medicine*, 382(18), pp. 1721–1731. doi: 10.1056/nejmoa1915784.

Njie, G. J. and Khan, A. (2022) 'Prevalence of Tuberculosis and Mental Disorders Comorbidity: A Systematic Review and Meta-analysis', *Journal of Immigrant and Minority Health*, 24(6), pp. 1550–1556. doi: 10.1007/s10903-021-01312-6.

Oh, K. H. *et al.* (2017) 'Depression & risk of tuberculosis: A nationwide population based cohort study', *International Journal of Tuberculosis and Lung Disease*, 21(7), pp. 804–809. doi: 10.5588/ijtld.17.0038.

Pachi, A. *et al.* (2013) 'Psychiatric Morbidity and Other Factors Affecting Treatment Adherence in Pulmonary Tuberculosis Patients', *Tuberculosis Research and Treatment*, 2013, pp. 1–37. doi: 10.1155/2013/489865.

Pasha, A. *et al.* (2021) 'Impact of integrating mental health services within existing tuberculosis treatment facilities', *Medicine Access @ Point of Care*, 5, p. 239920262110113. doi: 10.1177/23992026211011314.

10.1177/23992026211011314.

Patel, V., Saxena, S., Lund, C., Thornicroft, G., Baingana, F., Bolton, P., Chisholm, D., Collins, Pamela Y. *et al.* (2018) 'The Lancet Commission on global mental health and sustainable development', *The Lancet*, 392(10157), pp. 1553–1598. doi: 10.1016/S0140-6736(18)31612-X.

Patel, V., Saxena, S., Lund, C., Thornicroft, G., Baingana, F., Bolton, P., Chisholm, D., Collins, Pamela Y. *et al.* (2018) 'The Lancet Commission on global mental health and sustainable development', *The Lancet*, 392(10157), pp. 1553–1598. doi: 10.1016/S0140-6736(18)31612-X.

Patwal, R. *et al.* (2023) 'Prevalence of suicidal ideations and suicide attempts in patients with tuberculosis: A systematic review and meta-analysis', *Journal of Psychosomatic Research*, 167, p. 111171. doi: <https://doi.org/10.1016/j.jpsychores.2023.111171>.

Plana-Ripoll, O. *et al.* (2019) 'Exploring Comorbidity Within Mental Disorders among a Danish National Population', *JAMA Psychiatry*, 76(3), pp. 259–270. doi: 10.1001/jamapsychiatry.2018.3658.

Rehm, J. and Shield, K. D. (2019) 'Global Burden of Disease and the Impact of Mental and Addictive Disorders', *Current Psychiatry Reports*, 21(2), p. 10. doi: 10.1007/s11920-019-0997-0.

Ruiz-Grosso, P. *et al.* (2020) 'Association between tuberculosis and depression on negative outcomes of tuberculosis treatment: A systematic review and meta-analysis', *PLoS ONE*, 15(1), pp. 1–13. doi: 10.1371/journal.pone.0227472.

Rybakowski, J. (2022) 'Infections and mental diseases: from tuberculosis to COVID-19', *Psychiatria Polska*, 56(5), pp. 931–944. doi: 10.12740/PP/152125.

Santos, J. A., Duarte, R. and Nunes, C. (2020) 'Host factors associated to false negative and indeterminate results in an interferon- γ release assay in patients with active tuberculosis', *Pulmonology*, 26(6), pp. 353–362. doi: 10.1016/j.pulmoe.2019.11.001.

Suetani, S. *et al.* (2021) 'Increased rates of respiratory disease in schizophrenia: A systematic review and meta-analysis

- including 619,214 individuals with schizophrenia and 52,159,551 controls', *Schizophrenia Research*, 237(October 2020), pp. 131–140. doi: 10.1016/j.schres.2021.08.022.
- Sweetland, A. *et al.* (2014) 'Depression: A silent driver of the global tuberculosis epidemic', *World Psychiatry*, 13(3), pp. 325–326. doi: 10.1002/wps.20134.
- Sweetland, A. C. *et al.* (2018) 'Addressing the tuberculosis–depression syndemic to end the tuberculosis epidemic', *INT J TUBERC LUNG DIS*, 21(8), pp. 852–861. doi: 10.5588/ijtld.16.0584.Addressing.
- Sweetland, A. C. *et al.* (2019) 'Integrating tuberculosis and mental health services: Global receptivity of national tuberculosis program directors', *International Journal of Tuberculosis and Lung Disease*, 23(5), pp. 600–605. doi: 10.5588/ijtld.18.0530.
- Thomas, B. E. *et al.* (2016) 'Psycho-socio-economic issues challenging multidrug resistant tuberculosis patients: A systematic review', *PLoS ONE*, 11(1), pp. 1–15. doi: 10.1371/journal.pone.0147397.
- Ugarte-Gil, C. *et al.* (2013) 'Association of Major Depressive Episode with Negative Outcomes of Tuberculosis Treatment', *PLoS ONE*, 8(7), pp. 1–7. doi: 10.1371/journal.pone.0069514.
- Wagner, G. J. *et al.* (2011) 'A closer look at depression and its relationship to HIV antiretroviral adherence.', *Annals of behavioral medicine: a publication of the Society of Behavioral Medicine*, 42(3), pp. 352–360. doi: 10.1007/s12160-011-9295-8.
- Whiting, D., Unwin, N. and Roglic, G. (2010) 'Equity, social determinants and public health', *Equity, social determinants and public health programmes*. Available at: http://www.who.int/social_determinants/.
- WHO (2015) 'Implementing The End TB Strategy', *Antimicrobial Agents and Chemotherapy*, 58(12), pp. 7250–7257. Available at: https://www.cambridge.org/core/product/identifier/CBO9781107415324A009/type/book_part%0Ahttp://arxiv.org/abs/1011.1669%0Ahttp://dx.doi.org/10.1088/1751-8113/44/8/085201%0Ahttp://www.ncbi.nlm.nih.gov/pubmed/25246403%0Ahttp://www.pubmedcentral.nih.gov/artic.
- World Health Organisation (2013) 'End TB Strategy', *World Health Organisation*, 53(9), pp. 1689–1699.
- World Health Organization (2020) *Depression report 2020*. Available at: <https://www.who.int/news-room/fact-sheets/detail/depression>.
- World Health Organization (2022) *Mental Health, Concepts in mental health*. Available at: <https://www.who.int/news-room/fact-sheets/detail/mental-health-strengthening-our-response>.
- World Health Organization (2023) *WHO operational handbook on tuberculosis. Module 6: tuberculosis and comorbidities - mental health conditions, Module 5: management of tuberculosis in children and adolescents*. Available at: <https://apps.who.int/iris/bitstream/handle/10665/340256/9789240022614-eng.pdf>.
- Yamazaki, M. (2017) *Guidelines for treatment of drug-susceptible tuberculosis and patient care, Kekkaku*.
- Zhang, K. *et al.* (2019) 'The interplay between depression and tuberculosis', *Journal of Leukocyte Biology*, 106(3), pp. 749–757. doi: 10.1002/JLB.MR0119-023R