

TB multimorbidity: a global health challenge demanding urgent attention

DEFINED BY THE WHO as the existence of two or more chronic health conditions in the same individual, multimorbidity is associated with adverse health outcomes and increased healthcare costs.¹ TB commonly coexists with a range of other serious chronic conditions such as HIV, diabetes mellitus (DM) and depression.² However, within health systems with limited capacity and access to care, services (including TB services) typically focus on single conditions and neglect to identify and manage multimorbidity, thereby missing opportunities to prevent, screen and treat coexisting chronic conditions.

Although there has been some progress in our understanding of how TB coexists with other single conditions (e.g., TB in people living with HIV),³ little is known about the burden, characteristics and clusters of multimorbidity in people with TB (referred to hereafter as TB multimorbidity). We wish to highlight the challenge posed by TB multimorbidity and its current neglect in healthcare. We invite policy makers and healthcare providers to rethink more joined-up, patient-centred care that capitalises on opportunities and synergies in the approach to recognise and manage TB multimorbidity.

The magnitude of the mortality and morbidity burden associated with TB is well recognised and is reflected in the global advocacy efforts, financial investments and technical advances in the prevention and control of TB. However, despite its undoubted importance, evidence on the determinants, disease patterns, burden and consequences of TB multimorbidity has only recently emerged. TB multimorbidity is associated with complex mental and physical symptoms, worsening of disabilities, poor quality of life, excess healthcare use, premature deaths and high healthcare costs.⁴

Among mental health conditions, depression affects one in every four individuals with TB, adversely affecting adherence to treatment and recovery.⁵ TB and depression share several common determinants and risk factors; depression also affects the immune system and increases the risk of acquiring TB.⁶ If it remains untreated, depression in people with TB may lead to treatment default, greater disability, poorer quality of life and increased risk of death.⁷ Conversely, TB may increase the severity of depression by adversely affecting quality of life, and because of the additional stigma associated with TB.⁸

Among chronic infections, evidence on the co-occurrence and the bidirectional adverse interactions between TB and HIV is most well established. HIV increases the risk of acquiring TB 20- to 40-fold; hence the HIV/AIDS epidemic between 1990 and 2005 led to a five-fold increase in TB incidence in sub-Saharan Africa.⁴ Currently, an estimated one in six people with TB has HIV co-infection; the presence of TB also worsens HIV outcomes.⁹ For example, the TB mortality rate in those with HIV co-infection may be twice that of those without HIV.³

Most adults with TB have one or more co-existing non-communicable diseases (NCDs), the likelihood of which increases with age.¹⁰ In a secondary data analysis of the World Health Survey (WHS) conducted in 48 low- and middle-income countries, we found that around two thirds of people with TB had at least one NCD.¹⁰ Prevalence of NCD in people with TB was twice that of those without TB.¹⁰ This clustering of TB with NCDs is attributable to several common risk factors, including social factors (stigma), economics (poverty), health risk behaviours (smoking, alcohol and drug abuse), impaired immunity and drug interactions.¹¹

TB and NCDs interact adversely, resulting in a multiplier effect on their respective disease burdens and health outcomes.¹² The WHS analysis estimated that at least one third of all morbidity (measured in years lived with disability [YLD]) in individuals with TB is attributable to coexisting NCDs.¹⁰ At a population level, TB and NCDs act as a syndemic or synergistic epidemic, which sustains and magnifies both epidemics. NCDs and their risk factors have a substantial influence on maintaining the TB epidemic in high-burden countries.¹²

DM and chronic respiratory disorders are considered to be the two most common NCDs coexisting with TB.^{13,14} DM increases the risk of developing active TB three-fold; in high TB and high DM burden countries (such as India), almost every other person with TB may have DM or pre-DM.¹⁵ People with both TB and DM are likely to have poor outcomes: they are less likely to recover from TB and more likely to die, suffer TB recurrence, have a poor quality of life and develop multidrug-resistant TB.¹⁶ Moreover, TB adversely affects glycaemic control and its progression towards complications.¹⁷ The global DM epidemic impedes achievement of Global End TB

Table Interventions for screening, prevention and management of TB multimorbidity

	Screening	Prevention and treatment
HIV and AIDS	HIV testing and counselling for patients with presumptive and diagnosed TB	Initiating antiretroviral therapy in people living with HIV, regardless of WHO clinical stage and at any CD4 cell count
Diabetes	Plasma fasting glucose or HbA1c (where available) measurements	Oral hypoglycaemic agents, monitoring glycaemic control, dietary advice, promoting physical activity, physical health checks and appropriate referrals, optimal hypertension control, smoking cessation support, aspirin, statins, and other health risk modifications. Referral to diabetes care after intensive phase of anti-TB treatment
Depression	Administering the Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7)	Brief psychotherapy and where appropriate, antidepressant medications
COPD	Spirometry: forced expiratory volume in 1 sec as a proportion of the estimated forced vital capacity	Inhaled short-acting β_2 agonists, inhaled steroids and/or long-acting bronchodilators, smoking cessation support, support to manage symptoms of shortness of breath

AIDS = acquired immune-deficiency syndrome; HbA1c = glycated haemoglobin; COPD = chronic obstructive pulmonary disease.

targets, and poor TB outcomes increase the global disease burden attributable to DM through poor glycaemic control and rapid progression to complications.¹¹

TB also increases the risk of developing and worsening outcomes of chronic respiratory disorders;¹⁸ those with both conditions have a two-fold increased risk of death within 12 months of being diagnosed with TB.¹⁹ TB also increases the risk of developing chronic respiratory infections during and after anti-TB treatment.²⁰

Complex TB multimorbidity

In addition to the increased prevalence of comorbid individual chronic conditions in TB, there is also the significant problem of “complex” TB multimorbidity, which poses significant additional challenges for people with TB and TB services. We define complex TB multimorbidity as the co-occurrence of two or more chronic conditions with TB. There is an urgent need to better understand and identify the most common ‘clusters’ of mental disorders, chronic communicable and NCDs that co-occur with TB, which clusters are associated with the greatest burden, and how to address these.²¹

The needs of people with multimorbidity, including TB multimorbidity, are largely neglected in traditional, single-disease focused health programmes, despite the fact that the common patient experience is of multiple chronic conditions.²¹ The care for people with TB multimorbidity typically remains vertical, fragmented and non-personalised, with numerous missed opportunities to prevent, screen and manage coexisting serious chronic conditions. On the other hand, the synergies between TB and other chronic conditions (and between these other conditions) demand effective joined-up approaches to prevention, screening and treatment of co-occurring conditions. The significant disease burden attributable to multimorbidity and the potential health gains through exploiting synergies in managing multiple

chronic conditions, makes TB multimorbidity a priority in high-burden countries.²¹

The need to address multimorbidity through effective, integrated and scalable interventions in healthcare is gaining international attention.²² The WHO is advocating for an integrated person-centred approach through coordination and alignment within and across healthcare settings.²³ Moreover, there is a growing recognition of the need for strong global and national policy support to address TB multimorbidity (e.g., the WHO’s ‘End TB Strategy,’ Stop TB Partnership’s ‘The Paradigm Shift: Global Plan to End TB 2018–2022’ and the ‘Global Fund Support for Co-infections and Co-morbidities’).²⁴ An increasing global focus on NCDs and the establishment of NCD services in several high TB burden countries is also an opportunity to coordinate care across NCDs and TB services to address multimorbidity.

TB services may be particularly well-placed to develop innovative approaches to address multimorbidity. Services endeavour to engage with those diagnosed with TB for at least 6 months, offering multiple opportunities to prevent, screen and manage other chronic conditions. Their (relatively) strong and well-resourced infrastructure may provide a platform for interventions to address multimorbidity, without sacrificing recent gains in TB outcomes. The concordance between treatments for TB and for some NCDs is also an opportunity to link care across healthcare teams to address TB multimorbidity.⁴

Evidence-based frameworks for integration and person-centred care, screening approaches and effective interventions, which can be used to tackle TB multimorbidity do exist.^{25,26} In people with HIV-associated TB, antiretroviral therapy has been hugely beneficial in reducing mortality and recurrence of TB.²⁷ Cost-effective interventions to address common risk factors for TB and NCDs are rarely offered routinely within TB healthcare,²⁸ but could prevent the onset and/or progression of multimorbidity. For example, there is emerging evidence that smoking cessation support is effective²⁸ and improves TB

outcomes.²⁹ Similarly, better DM control in TB patients through screening, treatment and monitoring could improve TB treatment success, reduce TB transmission and potentially avert more than a million deaths in high-burden countries over the next 15 years.³⁰ Likewise, screening for and treating depression would not only reduce its severity, but also improve motivation and adherence to TB treatments.⁶ The Table outlines the interventions for screening, prevention and management of TB multimorbidity that could be implemented in a resource-limited, high TB burden country. Patients will need continued care for their chronic conditions even after completing their anti-TB treatment. The proposed interventions to address TB multimorbidity will also require additional financial support from domestic and international sources (e.g., Global Fund).

The key obstacles to better management of TB multimorbidity include fragmented care delivery, limited access to other specialists and financial obstacles to complex health care. A joined-up approach, specifically between TB and NCD services, to detect and manage TB multimorbidity, could better serve the needs of people with TB. This step-change may offer a better, more patient-centred healthcare, where individuals do not have to negotiate multiple, disparate care pathways for their needs. Instead, people could have access to timely, coordinated care, which meets their complex needs and supports them to adopt healthy behaviours and improves outcomes.

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Acknowledgements

This work was supported by the Medical Research Council, London, UK (grant number MC_PC_MR/T037806/1 TB Multimorbidity); and by the National Institute for Health Research, London (grant 17/63/130 NIHR Global Health Research Group: Improving Outcomes in Mental and Physical Multimorbidity and Developing Research Capacity [IMPACT]) in South Asia at the University of York, York, UK) using aid from the UK Government to support global health research.

The views expressed in this publication are those of the author(s)

and not necessarily those of the funding bodies or the UK government.

Conflicts of interest: none declared.

References

- 1 World Health Organization. Multimorbidity. Geneva, Switzerland: WHO, 2016.
- 2 Reis-Santos B, et al. Prevalence and patterns of multimorbidity among tuberculosis patients in Brazil: a cross-sectional study. *Int J Equity Health* 2013; 12: 61.
- 3 Kwan C K, Ernst J D. HIV and tuberculosis: a deadly human syndemic. *Clin Microbiol Rev* 2011; 24(2): 351–376.
- 4 Marais B J, et al. Tuberculosis comorbidity with communicable and non-communicable diseases: integrating health services and control efforts. *Lancet Infect Dis* 2013; 13(5): 436–448.
- 5 Koyanagi A, et al. 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 Med* 2017; 15(1): 209.
- 6 Oh K H, et al. Depression and risk of tuberculosis: a nationwide population-based cohort study. *Int J Tuberc Lung Dis* 2017; 21(7): 804–809.
- 7 Ambaw F, et al. Untreated depression and tuberculosis treatment outcomes, quality of life and disability, Ethiopia. *Bull World Health Organ* 2018; 96(4): 243–255.
- 8 Courtwright A, Turner A N. Tuberculosis and stigmatization: pathways and interventions. *Public Health Rep* 2010; 125 (Suppl 4): 34–42.
- 9 Ansa G A, et al. Delivering TB/HIV services in Ghana: a comparative study of service delivery models. *Trans R Soc Trop Med Hyg* 2014; 108: 560–567.
- 10 Stubbs B, et al. Tuberculosis and non-communicable disease multimorbidity: an analysis of the World Health Survey in 48 low- and middle-income countries. Preprint available at SSRN: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3667847.
- 11 Bates M, Marais B J, Zumla A. Tuberculosis comorbidity with communicable and noncommunicable diseases. *Cold Spring Harb Perspect Med* 2015; 5(11): a017889.
- 12 Duarte R, et al. Tuberculosis, social determinants and comorbidities (including HIV). *Pulmonology* 2018; 24(2): 115–119.
- 13 Noubiap J J, et al. Global prevalence of diabetes in active tuberculosis: a systematic review and meta-analysis of data from 2.3 million patients with tuberculosis. *Lancet Global Health* 2019; 7(4): e448–e460.
- 14 van Kampen S C, et al. International research and guidelines on post-tuberculosis chronic lung disorders: a systematic scoping review. *BMJ Global Health* 2018; 3(4): e000745.
- 15 Viswanathan V, et al. Prevalence of diabetes and pre-diabetes and associated risk factors among tuberculosis patients in India. *PLoS One* 2012; 7(7): e41367.
- 16 Baker M A, et al. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Med* 2011; 9: 81.
- 17 Jeon C Y, et al. Bi-directional screening for tuberculosis and diabetes: a systematic review. *Trop Med Int Health* 2010; 15(11): 1300–1314.
- 18 Byrne A L, et al. Tuberculosis and chronic respiratory disease: a systematic review. *Int J Infect Dis* 2015; 32: 138–146.
- 19 Inghammar M, et al. COPD and the risk of tuberculosis—a population-based cohort study. *PLoS One* 2010; 5(4): e10138.
- 20 Marais B J, et al. Tackling long-term morbidity and mortality after successful tuberculosis treatment. *Lancet Infect Dis* 2020; 20(6): 641–642.
- 21 Academy of Medical Sciences. Multimorbidity: a priority for global health research. London, UK: Academy of Medical Sciences, 2018.
- 22 Hurst J R, et al. Global Alliance for Chronic Disease researchers' statement on multimorbidity. *Lancet Global Health* 2018; 6(12): e1270–e1271.

- 23 Toro N. WHO global strategy on integrated people-centred health services (IPCHS)/Estrategia mundial en servicios de salud integrada centrado en las personas (IPCHS). *Int J Integr Care* 2015; 15(8).
- 24 United Nations Development Programme. Integrating tobacco control into tuberculosis and HIV responses. Washington DC, USA: UNDP, 2018. <https://www.undp.org/content/undp/en/home/librarypage/hiv-aids/integrating-tobacco-control-into-tuberculosis-and-hiv-responses.html> Accessed November 2020.
- 25 Byrne A L, et al. Feasibility and yield of screening for non-communicable diseases among treated tuberculosis patients in Peru. *Int J Tuberc Lung Dis* 2018; 22(1): 86–92.
- 26 World Health Organization. Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings. Geneva, Switzerland: WHO, 2010.
- 27 Akksilp S, et al. Antiretroviral therapy during tuberculosis treatment and marked reduction in death rate of HIV-infected patients, Thailand. *Emerg Infect Dis* 2007; 13(7): 1001–1007.
- 28 Siddiqi K, et al. Action to Stop Smoking In Suspected Tuberculosis (ASSIST) in Pakistan: a cluster randomized, controlled trial. *Ann Intern Med* 2013; 158: 667–675.
- 29 Zellweger J-P, Cattamanchi A, Sotgiu G. Tobacco and tuberculosis: could we improve tuberculosis outcomes by helping patients to stop smoking? *Eur Respir J* 2015; 45(3): 583–585.
- 30 Pan S-C, et al. Effect of diabetes on tuberculosis control in 13 countries with high tuberculosis: a modelling study. *Lancet Diabetes Endocrinol* 2015; 3(5): 323–330.