Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Commentary

Sorry for the delay

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Until the coronavirus disease 2019 pandemic, tuberculosis had been the leading cause of death by an infectious disease worldwide. According to the WHO, there were 1.41 million deaths attributed to tuberculosis in 2019. Globally, the burden of tuberculosis is asymmetrically distributed with two-thirds of all individuals affected by tuberculosis coming from only eight countries. Further, it is estimated that more than one-third of all patients who developed tuberculosis in 2019 were living in India and China [1].

Of all patients who initiate treatment with anti-tuberculosis medicines, approximately 85% achieve a successful treatment outcome [1]. Early diagnosis of tuberculosis and access to adequate anti-tuberculosis therapies, especially in high-burden countries like India and China, are key elements to decrease the burden of tuberculosis worldwide [2].

In this edition of *CMI*, Zhang et al. [3] report the results of a retrospective cohort study on 400 patients with bacteriologically confirmed tuberculosis; they ascertained reasons for delay in the diagnosis of tuberculosis in 20 hospitals across 17 provinces in China. The main findings from this study are that more than half of the patients had a diagnostic delay with a median time of 20 days and diagnostic delay was more common in low-level care facilities than in higher-level care facilities where more diagnostic equipment was present. High-level care facilities underutilized the diagnostic equipment, resulting in unnecessary delays.

Importantly, only 2.5% (10/400) of patients had a diagnosis of tuberculosis confirmed by culture, and 31% (124/400) had a diagnosis of tuberculosis confirmed by a rapid molecular assay. In the remaining two-thirds of patients (266/400), the 'bacteriologically confirmed' diagnosis of tuberculosis was either based on the detection of acid-fast bacilli on sputum smear microscopy (261/400) or on histopathological findings (5/500), methods that do not distinguish *Mycobacterium tuberculosis* from species of non-tuberculous mycobacteria. The WHO defines tuberculosis as 'bacteriologically confirmed' if a biological specimen is positive by smear microscopy, culture or WHO-recommended rapid diagnostic test, such as the Xpert MTB/RIF® assay [1]. Most patients with 'bacteriologically confirmed' tuberculosis are not confirmed by *M. tuberculosis* culture.

As some of the risk factors for tuberculosis and non-tuberculous mycobacterial pulmonary diseases overlap, it has to be assumed that an unknown proportion of patients reported here as patients with bacteriologically confirmed tuberculosis actually have a different cause of their disease. In a recent systematic review from China, non-tuberculous mycobacteria were isolated from approximately 5% of patients with a suspected diagnosis of tuberculosis [4]. This limitation adds to the dilemma of diagnostic delay, which is in fact a problem of diagnostic availability, utility and awareness.

A number of individual level factors have been shown to result in delays in the patient pathway to care. Diagnostic delays are more likely among children, people living with human immunodeficiency virus and those with extrapulmonary manifestations of

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tuberculosis, reflecting the inadequacy of currently available diagnostic tests to detect paucibacillary and extrapulmonary disease. In addition to diagnostic delay, the diagnosis of tuberculosis can be delayed by patient delay, which is defined as time from onset of tuberculosis symptoms to seeking care. Unemployment, low income, low education level, pulmonary abnormalities, living with human immunodeficiency virus and seeking initial care from an informal provider have been associated with patient delay [5]. Female sex has consistently been associated with a longer overall time to tuberculosis diagnosis; this has most recently been demonstrated among patients referred to a large tuberculosis referral hospital in China [6].

Reasons for diagnostic delay in patients affected by tuberculosis can vary in different regions around the world. In high-incidence countries, where health-care systems usually face significant financial shortcomings, a crucial determinant of diagnostic delay is the reduced access to rapid and accurate diagnostics [7]. This affects especially citizens who live on the periphery, where diagnostic delays may be most severe and often adequate diagnostic equipment is not available. In contrast, in countries with low incidence of tuberculosis, with adequate financing of health care and availability of modern laboratory infrastructure, diagnostic delay is a common phenomenon because of low awareness about tuberculosis among physicians and other health-care providers [8].

Simply diagnosing tuberculosis is not enough at times of emerging *M. tuberculosis* drug resistance. In some high-burden countries, such as Namibia or Papua New Guinea, results of second-line phenotypic drug susceptibility testing are not available for decision-makers for months because bacterial cultures have to be shipped out of the country to distant reference laboratories for comprehensive drug susceptibility testing. Rapid molecular testing for the prediction of drug susceptibility or resistance is currently only readily available for one out of five WHO Group A and Group B priority drugs for the treatment of patients with multidrug-resistant tuberculosis. Lack of proper drug susceptibility testing in patients with multidrug-resistant tuberculosis results in inadequate initiation of anti-tuberculosis treatment and has been associated with poor treatment outcomes in some settings [9,10], while the delay did not influence treatment outcomes in other settings [11,12]. More information is needed on whether and how a diagnostic delay affects tuberculosis treatment outcomes.

We live in turbulent times: natural disasters, wars and pandemics can all critically disrupt the diagnosis and treatment of tuberculosis. At times of crisis, tuberculosis programmes are often hardest hit by disruptions. During war and natural disasters, patients find it difficult to access health-care facilities for diagnostic investigations or to receive their medicines, resulting in delayed diagnosis and interrupted treatment of tuberculosis. Migration and population displacement have played a historic role in the spread of tuberculosis over the centuries with migrants and refugees being among the most vulnerable groups for tuberculosis infection and disease because of their precarious living conditions [13]. Recent evidence from England specifically demonstrates that language barriers were associated with a 40% longer presentation delay [14]. Following England's introduction of the Migrant Cost Recovery Programme, which increased the cost for migrants to receive health care, the median time to tuberculosis treatment increased by 20 days among migrants [15].

Finally, mention must be made of the huge toll that the severe acute respiratory syndrome coronavirus 2 pandemic has currently taken on tuberculosis diagnosis and control. The WHO estimates that this pandemic is likely to have a lasting and profound impact on tuberculosis diagnosis and control leading to an estimated, additional 6.3 million cases of tuberculosis and 1.4 million additional deaths from 2020 to 2025 [1]. It is apparent that the lockdowns adopted by many countries disrupted health services, changed health-seeking behaviour, and delayed the diagnosis and notification of tuberculosis [16]. Medical supply and drug shortages resulted in treatment interruptions and will possibly contribute to the amplification of drug-resistant tuberculosis.

When a person suffers from fever, night sweats, weight loss and cough; when there is recent or remote tuberculosis contact in an individual who falls ill; when there is unexplained abnormality on (thoracic) imaging studies the diagnosis of tuberculosis must be considered. While diagnostic methods need constant improvements, currently available methods for the diagnosis of tuberculosis already have a high degree of accuracy and a rapid diagnosis of pulmonary tuberculosis can be achieved in the majority of affected adult patients within less than 2 hours by automated *M. tuberculosis* nucleic acid amplification from sputum specimens. However, technologies like the Xpert MTB/RIF® assay are not universally available in less affluent regions at the locations where the diagnosis of tuberculosis should be made. A substantial reduction in the delay from symptom onset to the initiation of appropriate treatment can be achieved by raising patient awareness through public health education, providing continuing medical education to health-care providers to ensure that tuberculosis is considered in the differential diagnosis, and ensuring better access to modern rapid diagnostics.

It still needs to be shown if and how decreases in these delays translate to improved prognosis for those affected by tuberculosis and whether they contribute to the decrease of the global burden of this disease.

CRediT statement

The corresponding author developed the concept of the manuscript. Writing of the original draft, reviewing and editing was shared among all authors.

Transparency declaration

German Center for Infection Research (DZIF). Dr. Lange reports personal fees from Chiesi, Gilead, Janssen, Novartis, Oxford Immunotec and Insmed outside the submitted work.

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