

## Addressing diabetes mellitus as part of the strategy for ending TB

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As we enter the new era of Sustainable Development Goals, the international community has committed to ending the TB epidemic by 2030 through implementation of an ambitious strategy to reduce TB-incidence and TB-related mortality and avoiding catastrophic costs for TB-affected families. Diabetes mellitus (DM) triples the risk of TB and increases the probability of adverse TB treatment outcomes such as failure, death and recurrent TB. The rapidly escalating global epidemic of DM means that DM needs to be addressed if TB-related milestones and targets are to be achieved. WHO and the International Union Against Tuberculosis and Lung Disease's *Collaborative Framework for Care and Control of Tuberculosis and Diabetes*, launched in 2011, provides a template to guide policy makers and implementers to combat the epidemics of both diseases. However, more evidence is required to answer important questions about bi-directional screening, optimal ways of delivering treatment, integration of DM and TB services, and infection control. This should in turn contribute to better and earlier TB case detection, and improved TB treatment outcomes and prevention. DM and TB collaborative care can also help guide the development of a more effective and integrated public health approach for managing non-communicable diseases.

**Keywords:** Bi-directional screening, Diabetes mellitus, End TB Strategy, Prevention of latent TB, Treatment outcomes, Tuberculosis

### Introduction

The Sustainable Development Goals (SDGs) will now drive the international development agenda for the next 15 years.<sup>1</sup> The SDGs, which were first formally discussed at the United Nations Conference on Sustainable Development held in Rio de Janeiro, Brazil, in 2012 (Rio+20), have replaced the eight Millennium Development Goals (MDGs) when these expired at the end of 2015. The MDGs had three health-related goals: MDG 4 (to reduce child mortality), MDG 5 (to improve maternal health) and MDG 6 (to combat AIDS, malaria and other diseases, including TB). The SDGs in contrast have 17 goals and 169 targets, but there is just one overarching health goal (SDG 3: ensure healthy lives and promote well-being for all at all ages) that has 13 health-related targets. The third target (SDG 3.3) is focused on ending epidemics of the major communicable diseases such as AIDS, TB and malaria, and neglected tropical diseases by 2030, while the fourth target

(SDG 3.4) is focused on reducing by one-third premature mortality from non-communicable diseases through prevention and treatment. While this paper is focused predominately on addressing diabetes mellitus (DM) as part of the strategy for ending TB, its content must also be viewed within the wider context of the SDGs, which explicitly aim for the first time to reduce morbidity and mortality from both communicable and non-communicable diseases.

### TB

One of the targets of MDG 6 was to halt and begin to reverse the incidence of TB by 2015 compared with 1990, and this has been achieved. In 1995, WHO launched the 'DOTS' (directly observed treatment, short-course) strategy and this evolved into the Stop TB Strategy a decade later. The WHO strategy has been embraced

by nearly all countries in the world. TB incidence worldwide has fallen by an average of 1.5% per year from 2000, TB-related mortality (deaths per 100 000 population per year) has decreased by 47% overall between 1990 and 2014, and an estimated 43 million lives were saved between 2000 and 2014 through TB treatment (supported by antiretroviral therapy [ART] in people living with HIV).<sup>2</sup>

Despite this laudable progress, the disease continues to be a major public health threat. One-third of the world's population is thought to be infected with *Mycobacterium tuberculosis*, and between 5 and 10% of infected persons are at risk of developing active TB during their lifetime. In 2014, an estimated 9.6 million people developed new active TB and 1.5 million people died from the disease, 390 000 of whom had associated HIV-infection.<sup>2</sup> The burden of TB is highest in Asia and Africa, with India and China together accounting for almost 40% of the world's TB cases.

Globally, about 6 million TB cases were notified and reported to WHO, leaving 3.6 million (37%) who were either not diagnosed or were diagnosed but not reported to national TB control programmes.<sup>2</sup> Multidrug-resistant TB (MDR-TB; resistant to at least rifampicin and isoniazid) is a growing threat. Globally, 3.3% of new TB cases and 20% of previously treated TB cases were estimated to have MDR-TB, translating into 480 000 cases in 2014. Of these, only 111 000 (23%) started specific treatment with a documented treatment success rate that was about 50%.<sup>2</sup> HIV is the strongest known risk factor for the development of TB and globally 1.2 million people were estimated to develop HIV-associated TB in 2014. However, only 51% of TB patients had a documented HIV test result and only 77% of those known to be HIV-infected were started on ART. There are several other important determinants of the TB epidemic, one of which is DM.<sup>3</sup>

## Diabetes mellitus

DM is a chronic condition that occurs when the body cannot produce enough insulin or cannot effectively utilise insulin, which results in high levels of glucose in the blood stream (hyperglycaemia) causing tissue damage over time. There are three common forms of DM that account for the majority of cases: type 1, type 2 and gestational diabetes mellitus (GDM). Recent and up to date estimates of the DM burden worldwide are provided by the International Diabetes Federation (IDF) in their Diabetes Atlas.<sup>4</sup> In 2013, it was estimated that 382 million people worldwide had DM, with 90% or more having Type 2 disease. About 80% of these people live in low- and middle-income countries (LMIC), and if the trends of the past 10–15 years continue with 10 million new cases occurring every year, an estimated 592 million people will have DM by 2035.

The greatest number of people with DM is in the age group 40–59 years, with little gender difference, although with the evolving epidemic, DM is increasingly being seen in younger persons especially in LMIC. Given the association between DM and lifestyles such as unhealthy diets and physical inactivity, there are more people with DM in urban areas compared with rural areas. It is estimated that about 50% of those who have DM, mostly those with type 2 disease, are undiagnosed. In 2013, an estimated 5.1 million people aged 20–79 years died from DM, with again little difference between males and

females. LMIC account for 88% of all premature mortality due to DM.<sup>4</sup>

Asia is the global region most affected by DM. The disease develops at a younger age than in white European populations and is associated with a high prevalence of cardiovascular disease. China and India are the two countries with the highest prevalence of DM, with 98.4 million and 65.1 million people aged 20–79 years estimated to have the disease, respectively, in each country in 2013.<sup>4</sup> Other high burden Asian countries include Indonesia, Japan, Pakistan, Bangladesh, Malaysia and the Philippines. Type 2 DM in Asia is often associated with a strong family history of diabetes but it is unclear whether this is genetic or is a result of shared risk behaviour and early life programming.

## Interaction between diabetes mellitus and TB

For 30 years or more there have been anecdotal reports and case studies about the interaction between DM and TB, but until recently this aroused little global interest because TB was relatively rare in rich countries where DM was prevalent and DM was believed to be a minor problem in LMIC countries where TB is endemic. However, the last decade has seen a radical change in thinking with recognition of the rapidly growing epidemic of DM in LMIC and a slower decline in global TB incidence rates than would be expected from epidemiological modelling.

The years 2007 and 2008 marked a turning point in global interest about the association and interaction between the two diseases. Two systematic reviews highlighted the important risk that DM poses for the development of active TB, with cohort studies indicating a relative risk of 3.1 (95% CI 2.3 to 4.3) and case-control studies indicating odds ratios of 1.2 to 7.8.<sup>5,6</sup> These findings have been confirmed and it is now generally accepted that the overall risk of TB in persons with DM is three times higher than in the general population.<sup>7</sup> Both type 1 and type 2 DM can increase the risk of TB, but as type 2 disease accounts for 90% or more of the global cases of DM, the public health burden of co-morbid disease from type 2 DM dominates the interaction. In 2012, the population attributable fraction of DM for adult TB cases globally was estimated at 15% with the number of adult TB cases associated with DM being 1 042 000, almost the same as that observed for HIV-associated TB.<sup>7</sup> The top ten countries with the highest incidence of TB associated with DM are shown in Table 1. These estimates were made using the conventional method to calculate population attributable fraction. However, considerably higher estimates have been reported using dynamic modelling accounting for dynamic effects of onward transmission.<sup>8</sup>

The reasons for the increased risk of TB in DM are not clear and revolve around dysfunctional and exaggerated T-cell and cytokine responses. The biological and immunological mechanisms contributing to the double burden of DM and intracellular bacterial infections are the subject of intensive basic science research.<sup>9</sup> Whatever the molecular mechanisms, there is also growing evidence that patients with uncontrolled hyperglycaemia are at higher risk for TB than those with controlled blood glucose levels suggesting that hyperglycaemia is an important determinant in this interaction.<sup>10,11</sup> DM not only increases the risk of developing active TB but also adversely affects TB treatment outcomes. A systematic review of studies from 1980 up to 2010 focused on patients being treated with dual disease and assessed results of

**Table 1.** Countries with the highest number of estimated cases of TB associated with diabetes mellitus (DM)

Country	TB incidence per 100 000 (all forms and all age groups)	Number of adults with DM (millions)	Population attributable fraction of DM for adult TB cases	Number of adult TB cases associated with DM
India	176	65	15%	302 000
China	73	98	17%	156 000
South Africa	1000	3	15%	70 000
Indonesia	185	9	10%	48 000
Pakistan	231	7	12%	43 000
Bangladesh	225	5	10%	36 000
Philippines	265	3	11%	29 000
Russia	91	11	17%	23 000
Myanmar	377	2	11%	21 000
Democratic Republic of Congo	327	2	10%	19 000

Data are for 2012. The table is adapted from Lonroth et al.<sup>7</sup>

**Box 1.** Reducing the dual burden of diabetes mellitus and TB: recommended activities in the *Collaborative Framework for Care and Control of Tuberculosis and Diabetes*

A. Establish mechanisms for collaboration

- A.1. Set up means of coordinating diabetes and TB activities
- A.2. Conduct surveillance of TB disease prevalence among people with diabetes in medium and high-TB burden settings
- A.3. Conduct surveillance of diabetes prevalence in TB patients in all countries
- A.4. Conduct monitoring and evaluation of collaborative diabetes and TB activities

B. Detect and manage TB in patients with diabetes

- B.1. Intensify detection of TB among people with diabetes
- B.2. Ensure TB infection control in health care settings where diabetes is managed
- B.3. Ensure high-quality TB treatment and management in people with diabetes

C. Detect and manage diabetes in patients with TB

- C.1. Screen TB patients for diabetes
- C.2. Ensure high-quality diabetes management among TB patients

Adapted from WHO & International Union Against Tuberculosis and Lung Disease.<sup>15</sup>

sputum culture conversion at 2–3 months of anti-TB treatment, death during treatment and relapse of TB after successful completion of treatment.<sup>12</sup> There is some evidence, although not consistent, that DM prolongs culture positivity at 2–3 months of treatment. DM increases the risk of death during TB treatment, with 23 studies finding a pooled relative risk of 1.89 (95% CI 1.52 to 2.36).<sup>12</sup> DM increases the risk of TB relapse with five studies finding a pooled relative risk of 3.89 (95% CI 2.43 to 6.23).<sup>12</sup> It is still unclear whether relapse is due to a recurrence of the former infection (true relapse) or re-infection with a new strain of *M. tuberculosis*. No consistent associations have been found between DM and drug-resistant TB, although this area requires more detailed and prospective research. Finally, there is growing evidence that in persons with DM poor glycaemic control

adversely affects TB treatment outcomes,<sup>13</sup> and that smoking more than one pack of cigarettes per day significantly increases the risk of death in patients with dual disease.<sup>14</sup>

In August 2011, 18 months after the convening of an expert group meeting on the two diseases, WHO and the International Union Against Tuberculosis and Lung Disease (the Union) launched the *Collaborative Framework for Care and Control of Tuberculosis and Diabetes* to assist policy makers and implementers to move forward to combat the looming epidemic of DM and TB. The key recommendations are highlighted in Box 1.<sup>15</sup> The Framework provides guidance on bidirectional screening and treatment of the two diseases while at the same time encouraging operational and other research to build the evidence base so that more specific and definitive recommendations can be made in the future.

## Addressing diabetes as part of the End TB Strategy

In May 2014, WHO's post-2015 End TB Strategy with well-defined milestones and targets to assess progress along the way was adopted by the 67th World Health Assembly.<sup>16,17</sup> Relative to 2015 data, the global milestones for 2025 are a 50% reduction in TB incidence and 75% reduction in TB deaths, and for 2035 a 90% reduction in TB incidence (reaching <10 cases/100 000 globally) and 95% reduction in TB deaths. During this time no family is to face catastrophic costs due to TB. The three pillars and the associated components of the new strategy are shown in **Box 2**. The first pillar encompasses the four main technical interventions around early diagnosis, treatment and management of co-morbidities and preventive therapy for latent TB infection. The second pillar focuses on health and social policies and systems required to deliver essential health interventions, social protection and actions to address the social determinants of TB. The third pillar focuses on research and innovation.

Within the End TB Strategy, there are a number of actions that can be taken to mitigate the effect of DM on increasing the burden of TB, and these are discussed below.

### Pillar 1: Early diagnosis of TB

Ensuring early TB diagnosis requires that people who need to be investigated for TB are swiftly identified by health care providers. The most critical element is that clinicians managing patients with DM, especially in TB endemic areas, have a high index of suspicion for TB whenever TB-related symptoms and signs occur. Systematic screening for active TB among people with DM may, therefore, be considered in countries that have a prevalence of TB of >100 per 100 000.<sup>15</sup> This conditional recommendation is also endorsed in WHO's 2013 guidelines on systematic screening for active TB in high-risk groups.<sup>18</sup> In China and India, pilot implementation studies conducted within routine health services assessed the screening of DM patients for TB using a traditional

symptom-screen approach every time the patient came to the clinic. Those with a positive symptom screen were referred for TB investigations, consisting mainly of sputum smear microscopy and chest radiography.<sup>19,20</sup> This approach resulted in high detection rates of TB that varied from 300–800 per 100 000 people screened per quarter in China to 600–950 per 100 000 people screened per quarter in India. However, several operational and programmatic challenges were identified that need to be overcome if screening is to be scaled up, which include reluctance of DM doctors to take on this additional work; poor sensitivity and specificity of pulmonary TB diagnostic investigations that depend on sputum smear examination and chest radiography; challenges with diagnosing extra-pulmonary TB; and difficulties with recording and reporting. Further work is needed to determine whether screening using chest radiography and diagnosis using rapid nucleic acid amplification technology, such as Xpert MTB/RIF®, is feasible, more sensitive and cost-effective, and whether screening, when applied, should be for all persons with DM or targeted to those most at risk. This would include persons with DM who are heavily exposed to TB through occupation, lifestyle or residence in congregate settings (for example, health care workers or miners) or who have established risk factors such as longer duration of DM, poor glycaemic control, heavy smoking, higher frequency of alcohol consumption and lower body mass index.<sup>11</sup> There is currently no evidence to support the screening for latent TB in DM clinics, and this approach is not recommended in the WHO–Union Framework nor in the recent WHO Guidelines on the management of latent infection.<sup>15,21</sup>

### Pillar 1: Screening TB patients for DM and treating patients with dual disease

Among TB patients, there are several benefits of identifying undiagnosed DM (and thus contributing to reducing the large pool of un-diagnosed DM patients) and offering DM treatment to prevent or delay diabetes-related complications and improve TB treatment outcomes.<sup>12,13</sup> In China and India, implementation

#### Box 2. The WHO End TB Strategy: the three pillars and associated components

##### Pillar 1: Integrated, Patient-Centred Care and Prevention

- Early diagnosis of TB, including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
- Treatment of all people with TB, including drug-resistant TB, and patient support
- Collaborative TB/HIV activities and management of co-morbidities
- Preventive treatment of persons at high risk and vaccination against TB

##### Pillar 2: Bold Policies and Supportive Systems

- Political commitment with adequate resources for TB care and prevention
- Engagement of communities, civil society organisations, and public and private care providers
- Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
- Social protection, poverty alleviation and actions on other determinants of TB

##### Pillar 3: Intensified Research and Innovation

- Discovery, development and rapid uptake of new tools, interventions and strategies
- Research to optimize implementation and impact, and promote innovations

Adapted from WHO.<sup>16</sup>

research showed that TB patients could be routinely screened for DM at the time of registration by asking first about whether there was a known diagnosis of DM and, in those saying no, performing random blood glucose measurements to identify those at risk followed by fasting blood glucose measurements in those needing to be further screened.<sup>22,23</sup> In both countries, the large majority of patients were willing to be screened; between 12 and 13% of TB patients screened had DM and the majority were referred to diabetes care. Following this implementation research, India made a bold national policy decision to systematically screen all TB patients for DM.<sup>23</sup> Many questions still remain about how to optimally screen TB patients for DM and these include the best time to do the screening, whether to use tests more sensitive than fasting blood glucose, such as glycosylated haemoglobin (HbA<sub>1c</sub>), and whether to target specific TB patients, such as current smokers and those with a past history of TB.<sup>24</sup> Also, more information is needed on the effect of TB disease itself on blood glucose levels particularly during the early intensive phase of TB treatment when screening is conducted.

There are still uncertainties about the optimum treatment strategies in patients with dual disease,<sup>25</sup> with some of the key issues being highlighted in Table 2. Recent research has suggested that TB treatment could be extended beyond 6 months in people with DM,<sup>26</sup> but the evidence for this is weak and there are no randomised controlled trials that have assessed this issue. The WHO does not currently recommend a policy for extending treatment. Oral sulphonylurea derivatives interact with anti-TB drugs, and DM is best managed with diet, lifestyle modification, metformin and insulin. There is some evidence to suggest that metformin may also be an effective adjunct to TB treatment by augmenting protective host immune responses, endorsing the use of this

medication for treating patients with dual disease.<sup>27</sup> Peripheral neuropathy from isoniazid can usually be prevented with pyridoxine 12.5 mg daily and this should always be administered in the presence of concurrent DM. Finally, more needs to be known about facility-based TB transmission within DM clinics. For example, in Mexico, 20% of DM patients with recurrent TB had re-infection with a different strain of *M. tuberculosis*,<sup>28</sup> and it is possible that recurrent disease may result from inadvertent exposure to undiagnosed TB in DM clinics. A recent and rapid assessment of 10 DM clinics in China indeed identified inadequate infection control measures to prevent airborne transmission.<sup>29</sup>

## Pillar 2: Supportive systems

Adequate financing, government stewardship, appropriate health regulations, programmatic planning based on epidemiological surveillance, and engagement of all relevant governmental and non-governmental stakeholders are essential for ensuring universal health coverage, high-quality integrated patient-centred care, and financial risk protection for patients. Currently, most patients with DM and TB are cared for separately by their respective programmes. Joint planning and an integrated, co-management, approach would be a better option, certainly from the patients' perspective. For patients with DM and TB, the management of both diseases would best be centred at the TB clinic during the entire length of TB treatment, but this needs discussion, education, training and resources directed at staff in charge of TB clinics. Once TB treatment is completed, patients should be referred back to the DM clinic with vigilant follow-up to identify recurrent TB.

**Table 2.** Key issues related to treatment in patients with both TB and diabetes mellitus (DM)

Treatment issues	Discussion
Length of TB treatment	New drug-susceptible TB is currently treated for a total duration of 6 months with rifampicin and isoniazid for 6 months combined with pyrazinamide and ethambutol for the first 2 months. The increased rates of treatment failure and recurrent TB suggest that extended treatment might be needed. This needs to be evaluated in formal clinical trials.
Drug–drug interactions leading to reduced drug concentrations in the treatment of both TB and DM	Rifampicin increases hepatic metabolism of oral sulphonylurea derivatives; thus, reducing plasma concentrations and making dose adjustments difficult. Little is known about the interaction of rifampicin with newer anti-diabetes drugs or about the interaction of new anti-TB drugs (e.g., delamanid and bedaquiline with oral hypoglycaemic drugs).
Drug–drug toxicity and disease–drug toxicity	There are various interactions that can increase toxicity for the patient. Examples include peripheral neuropathy induced by both isoniazid and diabetes and which can be reduced by the addition of pyridoxine; ethambutol-induced ocular effects and diabetes-related retinopathy; and potentially fatal lactic acidosis as a result of interaction between metformin and isoniazid.
TB infection control	DM clinics need to be designed to minimise airborne transmission of <i>Mycobacterium tuberculosis</i> —open windows, skylights.
Lifestyle modification	Smoking and alcohol are both risk factors for development of TB and poor treatment outcomes and they also compromise healthy outcomes in patients with DM. It is, therefore, important to address these issues during treatment and assist patients with quitting smoking and reducing alcohol consumption.
Social protection	People with both TB and DM face potentially large financial and social costs related to medical care and income loss. Social protection for these patients needs special attention.

## Pillar 2: Prevention through addressing underlying determinants

DM is an important population-level determinant of TB. If the prevalence of diabetes continues to increase at the present rate, this is likely to severely hamper the reduction of global TB incidence.<sup>8</sup> Conversely, better DM prevention care will help to accelerate the decline of TB, especially in countries with high DM prevalence.<sup>8,30</sup> Public health programmes focusing on communicable and non-communicable diseases, therefore, need to join forces to identify synergistic public health actions, including addressing shared social determinants. This is an agenda not only for the health care sector. It requires a whole-of-government approach and is tightly linked to the actions set out in the new SDGs.

## Pillar 3: Research and innovation

There are serious limitations around current service delivery for TB, which includes diagnostic technology, treatment of MDR-TB and preventive therapy, which make the third pillar of the End TB Strategy that focuses on innovation and research essential for success. New technology, including biomarkers to diagnose latent TB infection, new point-of-care diagnostics for active disease, new and safer drugs, and a preventive vaccine that is better than BCG will be needed if TB milestones and targets are to be achieved. Some of these, such as diagnosis of latent TB infection, new point-of-care diagnostics and better/safer drugs are relevant for DM-associated TB. In particular, as new drugs such as delamanid and bedaquiline become integrated into TB treatment regimens and used by TB control programmes, an understanding of their interactions with oral hypoglycaemic drugs will be necessary.

Operational research will also be needed to address some of the implementation issues discussed earlier. An important cornerstone of good TB control programmes is the standardised monitoring and evaluation system with quarterly reporting of cases and treatment outcomes and it has been relatively easy to build into this system a monitoring and evaluation framework for DM screening, similar to what is currently being done for HIV/AIDS and antiretroviral therapy.<sup>24</sup> However, recording the results of screening persons with DM for TB has proven to be much more difficult largely because of the absence of any globally established cohort reporting systems for patients with chronic non-communicable disease. This will need to change and non-communicable disease programmes seriously need to consider adopting the cohort analysis approach along with electronic patient databases.<sup>24</sup>

## Conclusions

Given the established links between DM and TB and the rapidly increasing global burden of DM, especially in some of the high burden TB countries, the inclusion of DM in the strategic plan to end TB will become increasingly important in the next few years. Indeed, Pillar 1 and 2 of the End TB Strategy explicitly state that co-morbidities must be identified and managed and TB determinants must be addressed for better TB prevention.<sup>16,17</sup> More research and evidence is required to answer important questions about bi-directional screening in different settings, optimal ways

of delivering treatment, integration of DM and TB services and infection control, and these answers could lead to better and earlier TB case detection, more successful TB treatment outcomes and improved TB prevention.

Within the End TB Strategy, one of the three key indicators is that no TB-affected family is to face catastrophic costs. This commitment will help in reducing the morbidity, mortality and socio-economic consequences of TB, and should also address the impact of TB comorbidities such as DM. While communicable diseases remain as major global public health threats, the emerging public health problem in both industrialised and developing nations is that of non-communicable diseases (especially DM and cardiovascular disease) for which there is largely unstructured clinic-based care. Collaborative care for patients with DM and TB offers a way to formulate a better public health approach for the prevention, diagnosis and care of non-communicable diseases and will be mutually beneficial.

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