## REVIEW ARTICLE

# Epidemiology and interaction of diabetes mellitus and tuberculosis and challenges for care: a review

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The global burden of diabetes mellitus (DM) is immense, with numbers expected to rise to over 550 million by 2030. Countries in Asia, such as India and China, will bear the brunt of this unfolding epidemic. Persons with DM have a significantly increased risk of developing active tuberculosis (TB) that is two to three times higher than in persons without DM. This article reviews the epidemiology and interactions of these two diseases, discusses how the World Health Organization and International Union Against Tuberculosis and Lung Disease developed and launched the Collaborative Framework for the care and control of TB and DM, and examines three important challenges for care. These relate to 1) bi-directional screening of the two diseases, 2) treatment of patients with dual disease, and 3) prevention of TB in persons with DM. For each area, the gaps in knowledge and the priority research areas are highlighted. Undiagnosed, inadequately treated and poorly controlled DM appears to be a much greater threat to TB prevention and control than previously realised, and the problem needs to be addressed. Prevention of DM through attention to unhealthy diets, sedentary lifestyles and childhood and adult obesity must be included in broad non-communicable disease prevention strategies. This collaborative framework provides a template for action, and the recommendations now need to be implemented and evaluated in the field to lay down a firm foundation for the scaling up of interventions that work and are effective in tackling this dual burden of disease.

Chronic, non-communicable diseases such as cardiovascular disease, diabetes mellitus (DM), cancer and chronic obstructive pulmonary diseases have emerged as the next twenty-first century global epidemic, and have already become the leading causes of death and disability worldwide.[1] Among these diseases, the global burden of DM is immense. In 2012, there were an estimated 371 million people living globally with DM, with numbers expected to rise to 552 million by 2030.[2] Over half of these patients are undiagnosed, and complications due to diabetes are a major cause of disability and reduced quality of life.

Tuberculosis (TB) is a major communicable disease which, along with the human immunodeficiency virus and acquired immune-deficiency syndrome (HIV/AIDS) and malaria, is responsible for considerable morbidity and mortality worldwide. Although TB control has come a long way in the last 20 years, the disease still exacts a huge toll, especially among the poorest people on the globe.[3] Several key obstacles continue to thwart control efforts: many people are infected with *Mycobacterium tuberculosis* and are at risk of developing active TB during their lifetime; many vulnerable people with presumptive TB do not have access to affordable, high-quality TB diagnostic and treatment services; multidrug-resistant TB (MDR-TB, defined as *M. tuberculosis* resistant to at least isoniazid and rifampicin) is a serious threat in some settings; and in Africa, especially in the southern part of the continent, HIV/AIDS fuels an already burgeoning epidemic. Other risk factors have also emerged in recent years as important determinants of the TB epidemic, one of which is DM.

In this review, we discuss 1) the global epidemiology of and evidence for interaction of the two diseases, DM and TB; 2) the new collaborative framework for the care and control of TB and DM; and 3) challenges for care.

## GLOBAL EPIDEMIOLOGY OF DIABETES MELLITUS AND TUBERCULOSIS

### Diabetes mellitus

DM is a chronic condition that occurs when the body cannot produce enough insulin or cannot use it effectively. As a result, a person with DM does not utilise glucose properly, and glucose circulates in the blood at high levels (hyperglycaemia), causing tissue damage over time. DM was first recognised in 1500 BC by the ancient Egyptians, and the term diabetes mellitus was used by Greek physicians to describe persons with urinary frequency and in whom the urine also tasted sweet.[4] According to the World Health Organization (WHO), three common forms of DM account for the majority of cases: type 1, type 2 and gestational diabetes mellitus (GDM); their definitions are given in Table 1.[5] People with high blood glucose levels that are below the thresholds required for a diagnosis of DM are said to have pre-diabetes. This may occur either as impaired fasting glucose or as impaired glucose tolerance (IGT), and these people have an increased risk of type 2 DM.

People with DM may suffer from a number of serious health problems, such as cardiovascular disease, renal disease (nephropathy), eye disease (retinopathy), nerve damage (neuropathy), diabetic foot and infections that include TB. DM may be diagnosed on the

**TABLE 1** Classification of diabetes mellitus*

| Classification | Definition |
| --- | --- |
| Type 1 DM | Type 1 diabetes mellitus encompasses the majority of cases that are primarily due to pancreatic islet beta-cell destruction, attributable either to an autoimmune process or to an unknown cause (idiopathic). These patients are prone to ketoacidosis and require insulin injections for survival. It does not include cases with beta-cell destruction or failure to which specific causes can be assigned (e.g., cystic fibrosis, mitochondrial defects, etc.) |
| Type 2 DM | Type 2 is the most common form of diabetes mellitus. It is characterised by disorders of insulin action and insulin secretion, either of which may be the predominant feature. Both are usually present at the time that this form of diabetes manifests clinically. By definition, the specific reasons for the development of these abnormalities are not yet known. |
| Gestational DM | Gestational diabetes is carbohydrate intolerance resulting in hyperglycaemia of variable severity, with onset or first recognition during pregnancy. It does not exclude the possibility that the glucose intolerance may antedate pregnancy but had been previously unrecognised. The definition applies irrespective of whether or not insulin is used for treatment or whether the condition persists after pregnancy. Gestational DM usually resolves after pregnancy, but mothers and babies both have a higher risk of developing type 2 DM later in life. |

*Adapted from World Health Organization.[5]
DM = diabetes mellitus.

**TABLE 2** World Health Organization diagnostic criteria for DM or pre-diabetes*

|  | DM | Pre-diabetes |
| --- | --- | --- |
| Fasting plasma glucose | ≥7.0 mmol/l ≥126 mg/dl | 6.1–6.9 mmol/l 110–125 mg/dl |
| 2 h plasma glucose after OGTT | ≥11.1 mmol/l ≥200 mg/dl | 7.8–11.0 mmol/l 140–199 mg/dl |
| Random plasma glucose | ≥11.1 mmol/l ≥200 mg/dl | |
| Glycosylated haemoglobin | ≥6.5% | |

*Adapted from World Health Organization and International Diabetes Federation.[6]
DM = diabetes mellitus; OGTT = oral glucose tolerance test.

basis of fasting plasma glucose, 2-hour plasma glucose following a 75 g oral glucose tolerance test (OGTT), random plasma glucose in a patient with classic hyperglycaemic symptoms or glycosylated haemoglobin (HbA1c). The different cut-off values used by the WHO, which are generally those used in most low- and middle-income countries (LMICs), are shown in Table 2.[6] In recognition of the widespread use of capillary sampling in these countries, fasting values for venous and capillary plasma glucose are regarded as identical,[6] although not all front-line clinicians are prepared to accept this stance.

Recent, up-to-date estimates of the worldwide DM burden are provided by the International Diabetes Federation in their Diabetes Atlas.[2] Data for this are supplemented through epidemiological studies, health examination surveys, population-based prevalence studies and WHO STEPwise surveillance studies.[7,8] In the 2012 update to the Atlas, it was estimated that 371 million people worldwide had DM. About 80% live in LMICs, and, if the trends of the past 10–15 years continue, over 550 million people will have DM by 2030. This equates to one in ten globally, although there will be marked differences from country to country, depending on factors such as urbanisation and lifestyle. In 2012, a further 280 million people worldwide had IGT, with the number expected to rise to 398 million by 2030.

The majority of people with DM are in the age group 40–59 years, with little difference in terms of sex. The mean age at onset of type 2 DM in LMICs is at least a decade earlier than in industrialised countries. Given the association between DM and lifestyles such as unhealthy diet and physical inactivity, there are more people with DM in urban areas than in rural areas, with the divide in 2030 estimated at 314 million to 143 million, respectively. It is estimated that about 50% of people who have DM, mostly those with type 2 disease, are undiagnosed. In 2012, an estimated 4.8 million people aged 20–79 years died from DM, with little difference between males and females. LMICs account for 88% of all premature mortality due to DM.[2]

Asia is the global region most affected by DM.[2,9] The disease develops at a younger age than in white populations of European descent, and associated cardiovascular disease is common in young Asian people. China and India are the two countries with the highest prevalence of DM, with respectively 92.3 million and 63 million people aged 20–79 years estimated to have the disease in each country. In India, DM prevalence peaks at 60–69 years, while in China it peaks later, at 70–89 years. 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, with most Asian patients having a first-degree relative with the disease. It is unclear at present whether this strong family history is genetic and/or whether it is a result of shared risk behaviour and early life programming.

*Tuberculosis*

TB is an infectious disease of equally great antiquity as DM, with evidence of spinal involvement being found in Egyptian mummies dating back to several thousand years BC. Although common in various populations over the centuries, it acquired notoriety during the Industrial Revolution in Europe as 'the captain of all these men of death'.[10] The discovery of the tubercle bacillus in 1882 by Robert Koch, the documentation of the close link between TB and poverty, undernutrition and poor living conditions, the discovery and use of anti-tuberculosis drugs between the 1940s and 1970s and the introduction of combination chemotherapy to cure disease and prevent the development of drug resistance all led to modern-day control efforts.

In 1994, the WHO developed a standardised framework for TB control, branded as 'DOTS'.[11] The crucial components of DOTS are: 1) standardised case finding and registration, 2) standardised anti-tuberculosis treatment regimens for new and previously treated disease, and 3) monitoring, recording and reporting of cases and treatment outcomes using internationally agreed definitions.[12] The Stop TB Partnership, which has been in existence for nearly a decade and has over 700 partners worldwide, endorsed two epidemiological targets in 2000, linked to the Millennium Development Goals. These targets are by 2015 to reduce TB prevalence and death rates by 50% compared with 1990 levels, and by 2050 to eliminate TB as a public health problem (defined as an incidence of less than 1 TB case per million people per year). To achieve these targets, a Stop TB Strategy was agreed upon in 2006 (Table 3) and launched along with a Global Plan to Stop TB.[13,14] The Stop TB Strategy is focused on the expansion of high quality DOTS, but at the same time addresses other important issues such as HIV-associated TB, drug-resistant TB, engagement of all public and private health care providers, health systems strengthening, patient-centred approaches and programme-based operational research.

From 1995, DOTS-based programmes were initiated worldwide, and by 2011, 204 countries and territories were using DOTS and reporting data to the WHO. During this time, the global case detection rate of TB rose from 15% to 67%, and the treatment success rate in new smear-positive pulmonary TB rose from 77% to 87%.[15] It is estimated that 51 million people have been successfully treated for TB in countries that have adopted the DOTS strategy, saving 20 million lives, and as a consequence of such efforts, the incidence of and mortality from TB have been falling for several years.

Despite the progress made, TB continues to be a major public health problem in many LMICs. In 2011, there were an estimated 8.7 million cases of TB (13% co-infected with HIV) and 1.4 million TB-related deaths.[15] 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; India has an estimated 2.2 million cases per annum and China about 1.0 million. Globally, 5.8 million TB cases were notified and reported to the WHO in 2011, leaving 2.9 million patients unaccounted for. The emergence of MDR-TB has been of major global concern: of the 310000 estimated new MDR-TB cases in 2011, only 19% were notified and even fewer were treated according to international recommendations.[15]

About one third of the world's population is infected with *M. tuberculosis*, of whom about 5–10% will develop active TB at some time in their lives, the greatest risk being within the first few years of infection. Infants and young children up to the age of 5 years are at relatively high risk, while those aged 5–15 years are relatively resistant; the risk then rises again through adolescence, remains stable during adulthood and increases once again in the elderly. Other risk factors, including DM, are shown in Table 4. HIV/AIDS is the strongest risk factor, with the incidence of TB increasing as the CD4 lymphocyte count declines.[16] Although at the individual level the risk of developing TB is considerably lower in people with DM compared with those who have HIV, the much larger and rapidly growing pool of people with DM makes the global and population-attributable fraction of TB due to DM similar to that seen with HIV.[3]

## INTERACTION BETWEEN DIABETES MELLITUS AND TUBERCULOSIS

### *Evidence of interaction*

The association between DM and TB was suggested as far back as Roman times and, since then until recently, anecdotal reports and case studies have kept the link alive. As effective treatment for both DM and TB became available and successful public health measures were put in place to control TB, the association between the two diseases was perceived to be less relevant, especially as TB became relatively rare in high-income countries where DM was prevalent, while DM was believed to be a minor problem in poor countries where TB was endemic.

The situation has changed dramatically in the last decade, with recognition of the enormous and unfolding epidemic of DM in LMICs, a slower decline in global TB incidence rates than would be expected from epidemiological modelling, and a rekindling of interest in the association between DM and TB. The interaction between the two diseases was brought to global attention by three important publications in 2007 and 2008. Catherine Stevenson

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**TABLE 3**   The 2006 Stop TB Strategy*

1 Pursue high quality DOTS expansion and enhancement
   • Secure political commitment with adequate and sustained funding
   • Ensure case detection through quality-assured bacteriology
   • Provide standardised treatment, with supervision and patient support
   • Ensure an effective drug supply and management system
   • Monitor and evaluate performance and impact

2 Address TB-HIV, MDR-TB and needs of poor, vulnerable populations
   • Implement and scale up collaborative TB-HIV activities
   • Scale up the prevention and control of MDR-TB
   • Address the needs of prisoners, refugees and other high-risk groups and situations

3 Contribute to health systems strengthening based on primary health care
   • Actively participate in efforts to improve health policies, human resources, financing, management, service delivery and information systems
   • Strengthen infection control in health services and congregate settings
   • Upgrade laboratory networks and implement the Practical Approach to Lung Health
   • Adapt successful approaches and innovations from other fields

4 Engage all care providers
   • Involve public-public and public-private mix (PPM) approaches
   • Promote the use of International Standards for Tuberculosis Care (ISTC)

5 Empower people with TB and communities through partnership
   • Pursue advocacy, communication and social mobilisation
   • Foster community participation in TB care and prevention
   • Promote use of the Patient's Charter for Tuberculosis Care

6 Enable and promote research
   • Conduct programme-based operational research
   • Advocate research to develop new diagnostics, drugs and vaccines

*Adapted from World Health Organization.[13]
TB = tuberculosis; HIV = human immunodeficiency virus; MDR-TB = multidrug-resistant tuberculosis (*Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin).

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**TABLE 4**   Risk factors for the development of active TB

• HIV/AIDS
• Other causes of immune suppression (e.g., treatment with corticosteroids)
• Silicosis
• Malnutrition
• Indoor air pollution
• Cigarette smoking
• Harmful alcohol use and other drug abuse
• Diabetes mellitus

TB = tuberculosis; HIV = human immunodeficiency virus; AIDS = acquired immune-deficiency syndrome.

and colleagues undertook a Medline literature search of studies published after 1995 that quantified the association between DM and TB.[17] They identified nine studies that all showed significant and clinically important associations, with the increase in the risk (odds) of TB varying from 1.5 to 7.8 for those with DM. Limitations were that most studies had not measured or controlled adequately for potential confounders. The same group further assessed through an epidemiological model the potential impact of DM as a risk factor for incident pulmonary TB in India.[18] In 2000, it was estimated that DM accounted for 14.8% of pulmonary TB cases (uncertainty range 7.1–23.8%) and 20.2% of smear-positive pulmonary TB cases (uncertainty range 8.3–41.9%). A systematic review and meta-analysis by Jeon and Murray used various databases to identify observational studies dating back to 1965 that had reported an age-adjusted quantitative estimate of the association between DM and active TB.[19] Thirteen observational studies met the selection criteria, with 1 786 212 participants and 17 698 TB cases. Across the three cohort studies, the relative risk of TB in DM patients was 3.1 (95% confidence interval [CI] 2.3–4.3), and in the case control studies the odds ratios (ORs) ranged from 1.16 to 7.83. Further reviews have confirmed these findings and have suggested that overall the risk of TB in persons with DM is two to three times higher.[20,21]

### *Is the interaction between diabetes mellitus and tuberculosis biologically plausible?*

The answer is 'yes'. DM increases the general risk of infection, but the precise mechanisms by which DM predisposes to TB are still not clear and require further research. Unlike the situation with HIV infection, in which cell-mediated immunity is gradually compromised by progressive depletion and dysfunction of CD4 T-lymphocytes, DM impairs cell-mediated immunity by impairing the function and activation of macrophages, monocytes and lymphocytes, with additional potential roles played by pulmonary microangiopathy, renal dysfunction and vitamin deficiencies.[17] In addition, patients with uncontrolled hyperglycaemia appear to be at higher risk for TB than those with controlled blood glucose levels, suggesting that uncontrolled hyperglycaemia is an important determinant in this interaction.[22,23]

### *Collaborative Framework for Care and Control of Diabetes and Tuberculosis*

In December 2009, an expert meeting was held in Paris to review the evidence of the association between DM and TB,[24] to define the research agenda needed to reduce the dual burden of disease,[25] and to assess whether the evidence was strong enough to formulate international guidelines for the care and control of dual disease. After much reflection, it was decided that the currently available evidence to support specific recommendations, although incomplete, was sufficient to develop a provisional framework for action, and that this should be used to stimulate further research to strengthen the evidence base for appropriate interventions. This framework was launched in August 2011, and it now serves as a guide to help policy makers and implementers move forward to combat the looming epidemic of DM and TB.[26] The framework includes provisional recommendations (pending better evidence) packaged under three main themes: 1) the establishment of mechanisms for collaboration, 2) the detection and management of TB in patients with DM, and 3) the detection and management of DM in patients with TB (Table 5).[26] Operational and other research is encouraged to build the evidence base, which will be reviewed in 2015 to determine whether recommendations at that time can be made more definitive.

**TABLE 5**   Collaborative activities to reduce the dual burden of diabetes and TB*

1 Establish mechanisms for collaboration
  • Set up means of coordinating diabetes and TB activities
  • Conduct surveillance of TB disease prevalence among people with diabetes in medium and high TB burden settings
  • Conduct surveillance of diabetes prevalence in TB patients in all countries
  • Conduct monitoring and evaluation of collaborative diabetes and TB activities
2 Detect and manage TB in patients with diabetes
  • Intensify detection of TB among people with diabetes
  • Ensure TB infection control in health care settings where diabetes is managed
  • Ensure high-quality TB treatment and management in people with diabetes
3 Detect and manage diabetes in patients with TB
  • Screen TB patients for diabetes
  • Ensure high-quality diabetes management among TB patients

*Adapted from World Health Organization and International Union Against Tuberculosis and Lung Disease.[26]
TB = tuberculosis.

## CHALLENGES FOR CARE FOR DUAL DISEASE

Within the Framework for Care and Control of DM and TB,[26] there are three main challenges, which are discussed below.

### *Bi-directional screening of diabetes and tuberculosis in routine settings*

The framework provisionally recommends screening for DM in all people diagnosed with TB, and screening for TB in people with DM in countries with a high prevalence of TB (>100 per 100 000 population). The latter recommendation has recently been repeated in the WHO's 2013 guidelines on systematic screening for active TB in risk groups.[27]

A systematic review of bi-directional screening for DM and TB in 2009 using strict inclusion criteria identified 12 studies on screening people with DM for TB and 18 studies on screening TB patients for DM.[28] In persons with DM, screening for TB showed high rates of TB, ranging from 1.7% to 36%, with the screening yield being highly dependent on the underlying TB prevalence and on the severity of DM. Because DM is much more common than TB, in patients with TB the screening for DM yielded a high prevalence of DM, ranging from 1.9% to 35%.

Studies in the last 2–3 years have shown a high frequency of TB and DM co-morbidity in many areas of the world. Unpublished reports show a very high prevalence of DM in people with TB in the South Pacific of between 40% and 45%. In South India, one study in the state of Karnataka showed a DM prevalence of 32% in TB patients;[29] in the state of Kerala, 44% of TB patients had DM,[30] and in the state of Tamil Nadu, 25% of TB patients had DM and a further 25% had IGT.[31] On the Texas-Mexico border, the prevalence of DM among TB patients was 39% in Texas and 36% in Mexico.[32] In a recent study from Tanzania, the prevalence of DM in TB patients was 16.7% compared with 9.4% amongst controls, with a stronger association among non-HIV-infected compared with HIV-infected patients.[33] A similar case-control study in Pakistan reported a DM prevalence of 16.0% and an IGT prevalence of 34% among TB patients, compared with 7% and 28%, respectively, in the general community.[34]

There is little published information on whether DM has any effect on TB case notifications or estimated case numbers at country level. An ecological association between changes in DM and TB prevalence across 46 countries has been observed,[35] and an

analysis in India has suggested that increased DM prevalence between 1998 and 2008 contributed to an increase in the total number of TB cases which exceeded the rate of population growth during the same time period.[36] It will be important to monitor these associations more closely in the future, especially in countries in Asia with escalating DM epidemics.

At the health facility level, there are various challenges with bi-directional screening. In TB patients, DM cannot be recognised clinically and some form of blood glucose measurement is therefore required to determine its presence or absence. How this is best done in a routine situation still needs to be clarified. In India and China, two large operational studies showed that TB patients could be screened for DM at the time of registration by asking first about the presence or absence of known DM, and, in those denying any known disease, using random blood glucose measurements to identify those at risk, followed by fasting blood glucose measurements in those needing further screening.[37,38] In both countries, the large majority of patients were willing to be screened, and a total of 12–13% of TB patients screened had DM, with previously unrecognised new disease being diagnosed in 3% of patients in China and 5% of patients in India based on fasting blood glucose values. The majority of these patients were referred for diabetes care. Screening of TB patients is thus useful in helping to identify the large proportion of persons with DM who have undiagnosed disease in the community and who would benefit from earlier diagnosis and treatment.

Many questions, however, need to be answered. For example, previous studies have shown that it may be more reliable to screen for DM later in the course of anti-tuberculosis treatment rather than at the start, because as a chronic infectious disease TB may elevate blood glucose levels, resulting in false-positive diagnoses.[39–42] On the other hand, in a large DM prevalence study in China,[7] it was found that screening with fasting blood glucose missed nearly half of the DM patients diagnosed with a 2 h 75 g OGTT. The latter test is suitable for research surveys but inappropriate for screening individuals within routine general health services. These issues highlight the need at the screening level for better, simpler and non-expensive point-of-care glucose measurement tests.

In India and China, pilot studies assessed the screening of DM patients for TB with a traditional symptom-screen approach every time the patient came to the clinic, and referral of those with a positive screen for TB investigations.[43,44] This approach was feasible and resulted in high detection rates of TB that varied from 300 to 800 per 100 000 people screened per quarter in China to 600–950/100 000 in India. However, several operational challenges were identified that need to be overcome if such screening is to be rolled out on a larger scale. These include 1) the reluctance of busy DM doctors to take on the additional work needed to screen for and monitor this infectious disease, 2) the low sensitivity of current TB diagnostic approaches that rely on sputum smear examination and chest radiography, and 3) the absence of structured recording or reporting systems in most DM clinics, making it difficult to have reliable denominators for calculating TB case detection rates. In particular, symptom screening has low sensitivity, especially for the detection of TB early in the course of the disease. Screening by chest radiography would give a higher yield,[45] but the cost and logistical challenges would also be greater. More research is needed to determine the most appropriate screening and diagnostic algorithm and the cost-effectiveness of different approaches.

With both bi-directional screening systems, more information is also needed about what phenotypes are especially at risk of dual

disease (age, sex, body mass index), the effects of co-morbid disease and associated exposures such as alcohol and smoking, and how dual care can best be integrated within the same health facility or clinic while at the same time paying attention to good TB infection control.

### *Treatment of patients with dual disease*

A systematic review of studies from 1980 to 2010 focused on the treatment of patients with dual disease and assessed the results of sputum culture conversion at 2–3 months of anti-tuberculosis treatment, death during treatment, and relapse of TB after successful completion of treatment.[46] There were nine studies assessing the influence of DM on prolonging culture positivity at 2–3 months of treatment, with six studies reporting relative risks (RRs) of >2, and three reporting RRs of <1. The risk of death during TB treatment was assessed in 23 studies, with a pooled and significantly higher RR of 1.89 (95%CI 1.52–2.36) in patients with DM. Four of these studies adjusted for age and other potential confounders and found a pooled OR of 4.95 (95%CI 2.69–9.10), suggesting that patients who die during anti-tuberculosis treatment have other strong risk factors for death, such as HIV and co-morbidities, which reduce the impact of DM in the unadjusted analyses. Five studies assessed the risk of TB relapse, with a pooled and increased significant RR of 3.89 (95%CI 2.43–6.23) in patients with DM. Whether these patients experienced a recurrence of the former infection (true relapse) or re-infection with a new strain of *M. tuberculosis* is not known. No consistent associations were found between DM and drug-resistant TB, although this area requires more detailed and prospective research.

Current international guidelines disseminated by the WHO recommend that treatment for new cases of TB be standardised for 6 months with rifampicin-based TB treatment regimens, regardless of other co-morbidities such as HIV infection or DM.[12] Whether longer or different treatment in TB patients with DM has a beneficial effect on treatment outcomes and whether it reduces the risk of recurrent disease is not known, and needs prospective research. Similarly, whether more aggressive management and control of DM might improve the treatment response to TB remains unclear. There are many other unanswered questions that include the influence of poor DM control on death and recurrent TB, the best oral hypoglycaemic drugs to use with anti-tuberculosis drugs, drug-drug interactions and overlapping toxicities, the timing and aetiology of death in DM patients, the reasons for recurrent disease, and interventions that may reduce the frequency of these adverse events. Moreover, as second-line anti-tuberculosis treatment is increasingly being offered to patients in settings with a high MDR-TB burden, we need to study the challenges of co-administration of second-line anti-tuberculosis agents with oral hypoglycaemic drugs. These questions are best answered through prospective studies, such as a recently published study from southern Mexico, which found that patients with DM and TB had higher rates of delayed sputum conversion, treatment failure and recurrent TB after treatment, with one fifth of the recurrence due to new infection.[47] While there is no direct evidence that early diagnosis and optimal treatment of DM in people with TB improves TB treatment outcomes, such an effect is plausible. Moreover, considering the high prevalence of undiagnosed DM in people with TB, screening and proper management of DM in TB patients should be pursued to improve general health outcomes.

### *Preventing tuberculosis in people with diabetes*

Two studies conducted before the 1970s showed that active TB in people with DM could be prevented with TB chemoprophylaxis.[48,49]

However, both studies were methodologically flawed, and the true benefit of chemoprophylaxis remains unknown. The question can only be properly answered through a randomised controlled trial. As poor glucose control is associated with a higher risk of developing TB, it is plausible that improved DM management in itself is a means of preventing TB disease in a person with latent tuberculous infection. However, no trial has been conducted to evaluate such an effect. Finally, it will be important to ascertain whether DM clinics are areas where TB transmission occurs, and, if so, to determine the measures that need to be put in place to prevent this spread of TB.

## CONCLUSION

In LMICs, and especially in Asia, the DM epidemic is growing rapidly. There is now strong evidence that there is an important association between DM and TB and that this association results in poor TB treatment outcomes. Undiagnosed, inadequately treated and poorly controlled DM appears to be a much greater threat to TB care and prevention than previously realised,[50,51] and this needs to be tackled. Upstream prevention of DM through attention to healthier diets, more physical activity and reduction of childhood and adult obesity must be included in broad non-communicable disease prevention strategies. Simple point-of-care diagnostic tests are needed for DM, and simple, standardised and affordable interventions to treat and monitor established DM and IGT that are easy to access must be scaled up in all countries. Adapting DOTS principles may help to bring a more structured approach to DM care delivery, something that is currently lacking in most high DM burden countries.[52,53] Heightened clinical suspicion for TB is needed for people with DM, especially among those who live in TB-endemic areas, and systematic screening should be considered. However, more research is needed to establish appropriate TB screening eligibility criteria and algorithms in people with DM. A framework has now been established for reducing the dual burden of disease, and pilot studies have started to show how to implement some of the screening and monitoring initiatives. A collection of evidence is needed to bring about the scaling up of interventions that work and that clearly make a difference.

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Le fardeau mondial du diabète sucré (DM) est immense et l'on s'attend à ce que le nombre de cas augmente d'ici 2030 jusqu'à plus de 550 millions. Les pays d'Asie, comme l'Inde et la Chine, devront supporter le poids principal de cette épidémie en expansion. Le risque de développer une tuberculose (TB) active est significativement accru chez les patients atteints de DM : il est de deux à trois fois supérieur à celui des personnes sans DM. Cet article fait la revue de l'épidémiologie et des interactions de ces deux maladies, discute la façon dont l'Organisation Mondiale de la Santé et l'Union Internationale Contre la Tuberculose et les Maladies Respiratoires ont élaboré et lancé le réseau de collaboration pour les soins et la lutte contre la TB et le DM et examine trois défis importants pour les soins de ces affections. Ceux-ci sont en relation avec 1) un dépistage bidirectionnel des deux maladies, 2) le traitement des patients atteints des deux maladies, et 3) la prévention de la TB chez les sujets atteints de DM. Pour chaque secteur, les déficiences en matière de connaissances et les zones prioritaires de recherche sont soulignées. Un diabète sucré non diagnostiqué, traité de manière inadéquate et médiocrement contrôlé semble une menace beaucoup plus importante pour la prévention et la lutte contre la TB qu'on ne l'avait pensé précédemment, et ce problème doit être abordé. La prévention du diabète grâce à une attention portée aux régimes inadéquats, au style de vie sédentaire et à l'obésité de l'enfant et de l'adulte doit être incluse dans de larges stratégies de prévention des maladies non transmissibles. Le réseau de collaboration fournit un modèle d'action et les recommandations doivent à présent être mises en œuvre et évaluées sur le terrain afin de donner un fondement solide à l'extension d'interventions qui fonctionnent et sont efficientes pour lutter contre le double fardeau de ces maladies.

La carga mundial de morbilidad por diabetes sacarina (DM) es considerable y se prevé que se sobrepasen los 550 millones de personas en el 2030. Países de Asia como la India y la China soportarán la mayor parte de la carga de esta epidemia en expansión. Las personas que padecen DM presentan un riesgo considerable de contraer tuberculosis (TB) activa, el cual es de dos a tres veces mayor que el riesgo de las personas que no sufren DM. En el presente artículo se consideran las características epidemiológicas de ambas enfermedades, se analizan la elaboración y la puesta en marcha del marco conjunto de atención y de lucha contra la TB y la DM de la Organización Mundial de la Salud y la Unión Internacional contra la Tuberculosis y las Enfermedades Respiratorias y se examinan además tres dificultades importantes que plantea la atención. Estos problemas hacen referencia a: 1) el cribado bidireccional de ambas enfermedades, 2) el tratamiento de pacientes aquejados de ambas enfermedades, y 3) la prevención de la TB en las personas diabéticas. Se destacaron las deficiencias en los conocimientos y los dominios prioritarios de investigación en cada aspecto. La DM no diagnosticada, tratada inadecuadamente o mal equilibrada constituye una amenaza a la prevención y la lucha contra la TB, que es más determinante de lo que se consideraba y es preciso atenderla. La prevención de la DM mediante la corrección de los regímenes poco saludables, los estilos de vida sedentarios y la obesidad infantil se debe incorporar a las estrategias globales de prevención de las enfermedades no transmisibles. El marco conjunto de atención ofrece un modelo para la acción y es preciso poner en práctica sus recomendaciones y evaluarlas en el terreno, a fin de sentar unas bases firmes a la ampliación de escala de las intervenciones que dan resultados y abordan eficazmente esta carga de morbilidad doble.