



Diabetes and tuberculosis 1

Improving tuberculosis prevention and care through addressing the global diabetes epidemic: from evidence to policy and practice

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This is the first in a **Series** of three papers about diabetes and tuberculosis

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Diabetes triples the risk of tuberculosis and is also a risk factor for adverse tuberculosis treatment outcomes, including death. Prevalence of diabetes is increasing globally, but most rapidly in low-income and middle-income countries where tuberculosis is a grave public health problem. Growth in this double disease burden creates additional obstacles for tuberculosis care and prevention. We review how the evolution of evidence on the link between tuberculosis and diabetes has informed global policy on collaborative activities, and how practice is starting to change as a consequence. We conclude that coordinated planning and service delivery across communicable and non-communicable disease programmes is necessary, feasible, and creates synergies that will help to reduce the burden of both tuberculosis and diabetes.

Introduction

Increased access to high quality tuberculosis care has improved the chances of patients with tuberculosis to be cured, and has substantially decreased the number of fatalities in the past two decades. Tuberculosis mortality decreased by 45% between 1990 and 2012,¹ but the effect on tuberculosis transmission was only slight. The Millennium Development Goal for tuberculosis—to have halted and begun to reverse incidence by 2015²—has been reached ahead of 2015. However, that target was unambitious and the decrease in cases globally is very slow, about 2% per year¹; this rate is much lower than the decrease of 5–10% per year forecasted by the Global Plan to Stop TB 2006–15.³ As a result, despite substantial progress, tuberculosis still remains a grave global public health concern, particularly for the poorest people in low-income and middle-income countries, where tuberculosis is one of the diseases that contributes most to the loss of disability-adjusted life years.⁴ In 2012, 8.6 million people developed tuberculosis and 1.3 million died from the disease.¹ Tuberculosis rates vary considerably across different regions of the world. These rates are particularly high in countries in sub-Saharan Africa that have a very high HIV prevalence, especially as HIV infection is the strongest risk factor for tuberculosis.⁵ Multidrug-resistant (MDR) tuberculosis is an important challenge, and in parts of eastern Europe and central Asia prevalence of MDR-tuberculosis has risen alarmingly.^{6,7}

Tuberculosis is preventable and curable. Elimination of tuberculosis as a public health concern is therefore an appropriate long-term worldwide vision. However, to move towards the elimination of tuberculosis worldwide, prevention and care efforts need to be further intensified. To that effect, WHO's Global Tuberculosis Programme has developed a post-2015 global tuberculosis strategy that defines ambitious

targets and the actions needed to achieve them. The strategy, endorsed by the World Health Assembly in May 2014,⁸ aims to decrease global tuberculosis incidence by 90% from 2015 to 2035, which would equate to fewer than ten cases per 100 000 population in 2035. This 2035 figure is equivalent to the present average incidence in Organisation for Economic Cooperation and Development (OECD) countries. A second target is to reduce tuberculosis deaths by 95% by 2035. Finally, WHO's strategy has a specific target to provide financial risk protection, to ensure that no affected household face catastrophic costs. These targets could be achieved through a range of actions to improve prevention, diagnosis, treatment, and care (table 1). The post-2015 strategy not only builds on the core elements of previous global tuberculosis strategies—the DOTS strategy^{9,10} and the Stop TB Strategy 2006–15¹¹—but also adds to and elaborates on elements that allow the strategy to be adapted to new challenges and opportunities.

One of the key challenges addressed in the new strategy is the changing landscape of tuberculosis care and prevention caused by the global epidemiological and demographic transitions. Increases in the burden of non-communicable diseases and ageing populations are changing the importance of different risk factors for tuberculosis, and the profile of comorbidities and clinical challenges for people with tuberculosis.^{12,13} Although classic risk factors and comorbidities such as overcrowding, undernutrition, silicosis, and HIV infection are crucial to address, chronic conditions that impair host defences against tuberculosis, such as diabetes, are important factors in many settings.^{5,12,13}

The link between tuberculosis and diabetes has been described throughout history.¹⁴ Solid epidemiological evidence of a causal link has accumulated and several systematic reviews have concluded that diabetes

Tuberculosis and diabetes application	
Pillar 1: Integrated patient-centred care and prevention	
Early diagnosis of tuberculosis including universal drug susceptibility testing, and systematic screening of contacts and high-risk groups	In settings with a high tuberculosis burden: systematic screening for active tuberculosis in people with diabetes
Treatment of all people with tuberculosis including MDR tuberculosis, and patient support	Health information, patient support, and close treatment supervision during the first 2 months, and continuously during at least 4 more months (longer for MDR-tuberculosis); for people with diabetes, especially those who are newly diagnosed, the close patient support and supervision of tuberculosis treatment is an opportunity for integrated management, including health information about diet and physical activity, fine-tuning of medical treatment, and monitoring of diabetes complications
Collaborative tuberculosis and HIV activities and management of comorbidities	In all settings: systematic screening for diabetes in all people diagnosed with tuberculosis, and referral or management of diabetes
Preventive treatment of people at high-risk, and vaccination against tuberculosis	Screening for and treatment of latent tuberculosis infection in people with diabetes, who are close contacts of a patient with active tuberculosis, and others with a high likelihood of recent infection; trials are needed to establish the indications for treatment of latent tuberculosis infection in people with diabetes
Pillar 2: Bold policies and supportive systems	
Political commitment with adequate resources for tuberculosis care and prevention	Resources for training on the screening and management and referral of comorbidities, including diabetes, for health staff who diagnose and treat patients with tuberculosis
Engagement of communities, civil society organisations, and public and private providers	Includes all clinical aspects related to tuberculosis-comorbidities and risk factors, including diabetes, listed in pillar 1
Universal health coverage policy; regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control	Universal health coverage, including for non-communicable diseases, is needed to ensure good access for people with tuberculosis; universal health coverage for people with conditions that constitute tuberculosis risk factors, such as diabetes, is particularly important to ensure early diagnosis and treatment for tuberculosis; infection control involves infectious disease departments and other facilities attended by people with tuberculosis, including general outpatient department and endocrinology wards
Social protection, poverty alleviation, and actions on other determinants of tuberculosis	Social protection provides financial risk protection related to all direct and indirect costs of tuberculosis and comorbidities, including diabetes; to address other determinants involves actions to address direct tuberculosis risk factors (including prevention and care for diabetes) and shared upstream social determinants (eg, living and working conditions, education, environment, and nutrition)
Pillar 3: Intensified research and innovation	
Discovery, development, and rapid uptake of new techniques, interventions, and strategies	Basic research on tuberculosis immunity and biomarkers, including mechanisms of impaired immune response related to diabetes and other risk factors; new diagnostics, medicines, and vaccines of potential relevance to prevent and manage tuberculosis in people with diabetes
Research to optimise implementation and effectiveness and promote innovations	Operational research to optimise all aspects of coordinated tuberculosis and diabetes action
MDR=multidrug-resistant.	
Table 1: Pillars and components of the post-2015 global tuberculosis strategy and the relevance of the tuberculosis-diabetes link	

increases the risk of active tuberculosis by about three times, principally by impairing the host-defences and thereby increasing the risk of progression from tuberculosis infection to active disease.^{14–20} Moreover, people with tuberculosis who have diabetes have a poorer response to treatment than do those without diabetes and are therefore at a higher risk of tuberculosis treatment failure, death, and relapse after cure.²¹ Diabetes thus needs to be addressed both for tuberculosis prevention and to optimise tuberculosis treatment responses. Conversely, tuberculosis, similar to other infections, can worsen glycaemic control and complicate clinical management of diabetes.¹⁵ Bidirectional screening and integrated management can help to improve early diagnosis and health outcomes for both conditions.

The prevalence of diabetes worldwide has increased by about 20% in the past three decades, with particularly large rates of increase in low-income and middle-income

countries and in emerging economies that are undergoing a rapid epidemiological and demographic transition (figure).²⁵ These countries are where tuberculosis is among the primary causes of death, and this double burden leads to substantial strain on individuals, families, health systems, and society. Further increases in the prevalence of diabetes are predicted if current risk factors prevail.²⁴

In this Series paper, we briefly summarise the epidemiological evidence between tuberculosis and diabetes and the latest epidemiological estimates of the dual burden (which has been reviewed in depth elsewhere^{14–21}), and discuss these data in relation to intervention options. We describe how the emerging evidence on the link between tuberculosis and diabetes has informed global policy on collaborative activities, how practices are starting to change as a result (by the use of examples of country implementation), and how future actions should be promoted and planned.

Entry points for interventions

The ambitious epidemiological targets in WHO's new global tuberculosis strategy are based on an accelerated decrease of the global tuberculosis incidence, from the present 2% per year to 10% per year by 2025. At the same time, the tuberculosis cases fatality rate needs to be more than halved from 15% to 6.5% by 2025.²⁶ The target to eliminate the risk of catastrophic costs for families affected by tuberculosis will need further improvements to the health-care delivery system and social protection interventions to minimise or compensate for the often high direct and indirect costs of care.²⁷⁻²⁹ Intensified actions, including collaborative activities on tuberculosis and diabetes, will therefore be needed on several fronts to improve tuberculosis prevention, treatment, and care.

Reducing tuberculosis risk by targeting diabetes as an underlying risk factor

Increases in diabetes prevalence in populations with high ongoing tuberculosis transmission rates, or high transmission rates in the past (which results in high prevalence of latent tuberculosis infection in the growing elderly population), counteracts the positive effects of tuberculosis control efforts. In 2013, an estimated 15% of adult cases of tuberculosis worldwide were attributed to diabetes, which corresponds to around 1 million cases of diabetes-associated tuberculosis per year (table 2). The estimated global cases of incident tuberculosis attributable to diabetes have increased substantially in the 22 countries that together have 80% of the global tuberculosis burden, from 10% in 2010,⁵ to 15% in 2013, because of a 52% increase in the estimated diabetes prevalence in these countries, from 5.4% in 2010, to 8.2% in 2013.²⁴ More than 40% of diabetes-associated tuberculosis cases are in India and China (table 2). The prevalence of diabetes has increased in both countries in the past decade.

Increases in diabetes prevalence could have contributed to the surprisingly slight decrease in tuberculosis rates in many areas by offsetting the expected effect of intensified tuberculosis control efforts. An ecological analysis³⁰ of the association between changes in diabetes prevalence and changes in tuberculosis burden in 163 countries from 1990 to 2004 showed that an increase in tuberculosis incidence was nine times more likely to occur in countries with increases in diabetes prevalence, controlling for changes in gross domestic product. An analysis of the effect of nutritional and demographical changes on tuberculosis trends in India suggested that the reported increase in diabetes prevalence in India from 3.0% in 1998, to 3.7% in 2008, caused an additional 900 000 tuberculosis cases.²¹ These diabetes-associated cases might have contributed to the absence of a decrease in tuberculosis incidence during 1998–2008, despite substantial improvements in tuberculosis diagnosis and treatment. In India, the differential changes in nutrition patterns, increases in the prevalence of obesity and

diabetes in urban areas, and increases in the prevalence of undernutrition in men who live in rural areas led to a compounded negative affect of the nutritional transition on tuberculosis incidence.³¹

The impact of diabetes on tuberculosis rates could worsen in future decades. The International Diabetes Federation (IDF) has forecasted that the global diabetes prevalence will continue to increase from 8% in 2013, to about 10% in 2035.²⁴ Mathematical modelling suggests that such an increase would offset the present downward tuberculosis incidence trajectory by about 3% during this time period. In a more pessimistic scenario, with an increase in diabetes prevalence to 13%, the global tuberculosis trend would be offset by 8%.³² These estimates do not take into account the secondary negative effect on onward transmission from people with diabetes who develop tuberculosis as a result (people who are latently infected can progress to active

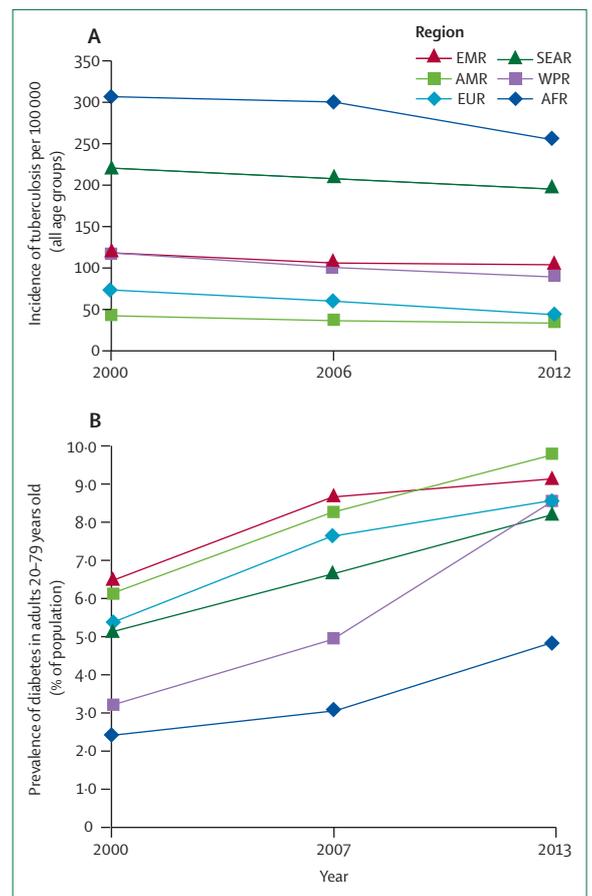


Figure: Incidence of tuberculosis and prevalence of diabetes in adults in different WHO regions

(A) Incidence of tuberculosis, 2000–12. Data source: WHO Global tuberculosis report 2013.¹ (B) Prevalence of diabetes, 2000–13. Adapted from: International Diabetes Federation Diabetes Atlas from 2000,²² 2006 (estimates 2007 prevalence),²³ and 2013.²⁴ AFR=African region. AMR=Americas region. EMR=eastern Mediterranean region. EUR=European region. SEAR=southeast Asian region. WPR=western Pacific region.

tuberculosis because of a weakened immune system, which can be due to diabetes, and the onward transmission to others that can occur from people with active tuberculosis is not accounted for in the model; people with latent tuberculosis have no symptoms, do not transmit the disease, and only around 5–10% will develop the active form) so they underestimate the potential negative effect of an increased diabetes burden on tuberculosis incidence.

Conversely, changes in dietary patterns that are associated with increases in diabetes could have a compensatory positive effect on tuberculosis prevention through decreases in undernutrition. If these projections for diabetes are coupled with the elimination of undernourishment, a net effect of a further 18% reduction in tuberculosis incidence could occur by 2035 (more than present downward trajectory). For tuberculosis prevention, the balance between the positive effect of reducing food insecurity in the world and the negative effects of obesity and increased diabetes prevalence is important. Ideally, both extremes of malnutrition would be addressed so the elimination of world hunger would be coupled with a decrease in obesity and thus in diabetes. A worst case scenario for tuberculosis would be an increase in disparities that results in simultaneous increases in undernutrition, obesity, and diabetes.

A decrease in worldwide diabetes prevalence is desirable, but not probable in the near future on the basis of present trends of diet and lifestyle changes. However, the negative effects of diabetes on tuberculosis could be diminished, in theory, through improved diabetes diagnosis and management. No trials have been reported that assess the effects of a improved diagnosis and management of diabetes for tuberculosis prevention. Nevertheless, indirect evidence of such an effect might be deduced from observational studies that show an increased risk of tuberculosis in people with poorly regulated diabetes than people with well-regulated diabetes, which could be attributable to severe tuberculosis leading to worse glycaemic control.^{18,33}

46% of people with diabetes are estimated to be undiagnosed worldwide, and 84% of those undiagnosed live in low-income and middle-income countries, where tuberculosis rates are high.³⁴ Undiagnosed and poorly regulated diabetes might be the dominant contributor to diabetes-related tuberculosis, and intensified efforts for early diabetes diagnosis and optimised management might diminish the risk of tuberculosis in people with diabetes. Mathematical modelling suggests that an optimistic scenario, with elimination of diabetes-associated tuberculosis (or chemoprophylaxis; see below), would lead to a 15% decrease in global tuberculosis incidence by 2035.³² Again, this potential positive effect is underestimated because further disease prevention would occur as a result of the reduced secondary transmission from prevented tuberculosis cases.

	Tuberculosis incidence per 100 000 (all age groups)*	Number of adults with diabetes† (millions)	Diabetes prevalence in adults†	Population-attributable fraction of diabetes for adult tuberculosis cases‡	Number of adult tuberculosis cases associated with diabetes§
World	122	379	8.3%	15%	1 042 000
Regions					
Africa	255	22	5.0%	9%	194 000
The Americas	29	60	9.6%	17%	41 000
Eastern Mediterranean	109	33	9.4%	17%	94 000
Europe	40	56	8.5%	15%	51 000
Southeast Asia	187	87	7.6%	14%	423 000
Western Pacific	87	121	9.1%	16%	238 000
22 high tuberculosis burden countries¶	159	233	8.2%	15%	957 000
Top 10 countries with the highest incidence of tuberculosis associated with diabetes					
India	176	65	8.6%	15%	302 000
China	73	98	9.6%	17%	156 000
South Africa	1000	3	8.3%	15%	70 000
Indonesia	185	9	5.6%	10%	48 000
Pakistan	231	7	6.8%	12%	43 000
Bangladesh	225	5	5.5%	10%	36 000
Philippines	265	3	6.0%	11%	29 000
Russia	91	11	10.0%	17%	23 000
Burma	377	2	5.7%	11%	21 000
Democratic Republic of Congo	327	2	5.4%	10%	19 000

*WHO estimates for 2012, for member states and WHO-defined regions.¹ †20 years and older, as estimated for 2013 by the International Diabetes Federation.³⁴ ‡Population-attributable fraction was calculated for each country based on country prevalence of diabetes as reported by the International Diabetes Federation³⁴ and relative risk of diabetes from a systematic review by Jeon and Murray,³⁵ as: $[\text{country diabetes prevalence} \times (\text{relative risk of tuberculosis in people with diabetes} - 1)] / [\text{country prevalence of diabetes} \times (\text{relative risk} - 1) + 1]$. §Absolute number estimated from the population-attributable fraction and from WHO-estimated number of incident adult tuberculosis cases; adult tuberculosis cases were estimated using age-disaggregated tuberculosis notification data for each region assuming that case detection gaps were similar across age groups.¹ ¶ Afghanistan, Bangladesh, Brazil, Burma, Cambodia, China, Democratic Republic of Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Nigeria, Pakistan, Philippines, Russia, South Africa, Thailand, Uganda, Tanzania, Vietnam, Zimbabwe.

Table 2: Estimated tuberculosis and diabetes burden, and tuberculosis burden attributable to diabetes

The projected difference between a worst-case scenario of an 8% increase and the best-case scenario of a 15% decrease in diabetes-related tuberculosis does not translate into a make-or-break situation for tuberculosis control, but improvements to diabetes prevention and care, would provide important overall health benefits and also make an important contribution to diminish the tuberculosis burden.³² Places where diabetes prevalence is high or increasing quickly have the most to lose or gain from failures and successes in diabetes strategies. However, a combination of such strategies with other tuberculosis-preventive efforts will be crucial in all settings.

Chemoprophylaxis for people with diabetes and latent tuberculosis infection

About 2 billion people (a third of the world's population) have latent infection with *Mycobacterium tuberculosis*,

with most living in low-income and middle-income countries.¹ Chemoprophylaxis decreases the risk of progression to active tuberculosis disease by about 60% for people at high risk of progression.³⁵ The effectiveness of chemoprophylaxis has been well established for close contacts of people with active tuberculosis such as household members (tuberculosis contacts). Tuberculosis contacts with additional risk factors such as diabetes probably benefit more from treatment than those without additional risk factors. However, no randomised controlled trials have been done to specifically assess the effectiveness of chemoprophylaxis to prevent tuberculosis disease for people with diabetes, contacts, or others. Two observational studies from the 1950s and 1960s have reported a lower risk of tuberculosis in people with diabetes who were taking chemoprophylaxis than in those who were not. A study³⁶ reported a reduced risk of tuberculosis relapse for a small number of patients given isoniazid for 6–24 months after a course of treatment for active tuberculosis was completed, compared with a cohort not given isoniazid. The second study³⁷ reported a lower incidence of tuberculosis in a period of 5 years in people with diabetes who received chemoprophylaxis than non-treated controls. The quality of both studies was poor; neither study specified the indication for chemoprophylaxis or controlled for confounders.

Chemoprophylaxis with 6 months of isoniazid treatment is associated with a small risk (0.4%) of severe toxic effects on the liver.³⁵ This risk of harm is larger than the potential benefit for people with a low risk of progression to active tuberculosis disease. A new regimen of 3 months of treatment with rifapentine and isoniazid had similar efficacy as 6 months of isoniazid treatment, and might have less toxic effects,³⁸ but further postmarketing surveillance is needed for confirmation. A risk–benefit trade-off is important for all risk groups, and generally only patients with the greatest risk of progression should be given prophylactic treatment. No test can accurately predict the risk of progression in patients with tuberculosis.

WHO recommends chemoprophylaxis for people living with HIV³⁹ and tuberculosis contacts who are younger than 5 years.⁴⁰ WHO is developing new recommendations on latent tuberculosis infection diagnosis and management, which are expected to be finalised around December, 2014.

The development of improved diagnostic techniques for latent tuberculosis infection with a high predictive value for disease progression, and effective and safe chemoprophylaxis, could substantially enhance the prospects of tuberculosis prevention in people with diabetes. Mathematical modelling has suggested that a reduction in tuberculosis risk associated with diabetes could help to greatly reduce tuberculosis incidence.³² Basic, epidemiological, and clinical research on latent tuberculosis infection diagnosis and management are needed to fully exploit this potential.

Screening for active tuberculosis in people with diabetes

One of the key actions highlighted in the global tuberculosis strategy is intensified and early detection of tuberculosis.²⁶ One approach for tuberculosis detection would be to systematically screen for active tuberculosis in selected risk groups, including people with diabetes.^{16,41} Every year worldwide, about a third (almost 3 million) of all people who develop active tuberculosis are not accounted for in national tuberculosis surveillance systems, either because they are not diagnosed or the cases are not notified.¹ Even patients who are diagnosed and properly treated are often diagnosed late in the course of the disease,⁴² which impairs treatment outcomes and the chance to effectively reduce tuberculosis transmission.⁴¹

Systematic screening for tuberculosis in people with diabetes could improve early detection in settings with a high tuberculosis burden. The number needed to be screened to detect one previously undetected case of tuberculosis in countries with a high tuberculosis-burden range from 17 to 776, dependent on background tuberculosis epidemiology and the sensitivity of the screening algorithm. In areas with a low tuberculosis prevalence, the number needed to be screened is often several thousands, making such screening cost-ineffective.^{43–45} Although empirical evidence, at the population level, of the epidemiological effect is inadequate,⁴⁶ it might contribute to improved health outcomes for individuals screened and for infection control in health facilities.

To screen people with diabetes for tuberculosis, diabetes has to have first been diagnosed and therefore, screening is conditioned on improved access to diabetes diagnostic services. Increases in access to health services is key to improve the early diagnosis of both diseases, and needs to be integrated across health conditions and health sectors.²⁸

Optimisation of tuberculosis treatment responses through improved diagnosis and management of diabetes

Globally, 87% of new patients with tuberculosis in quality-assured tuberculosis programmes are successfully treated.¹ However, the treatment success rate is much lower in some regions, such as Europe and the Americas, partly because of the high proportion of elderly people with comorbidities that increase the risk of death. Treatment success rates are lower in susceptible individuals such as people with diabetes, who have a higher risk of tuberculosis treatment failure, relapse, and death, than they are in patients with tuberculosis but not diabetes.²¹

People with MDR-tuberculosis present a particular challenge, with a treatment success rate worldwide of less than 50%.¹ This rate is attributable to drug-resistance and the difficulties for patients to fully adhere to a cumbersome and often toxic treatment course that can

exceed 18 months. However, comorbidities complicate management of the two diseases and hamper treatment response. Although not yet studied in detail, diabetes might contribute to poor treatment responses in people with MDR-tuberculosis, perhaps even more so than in people with drug-susceptible tuberculosis.

Many opportunities exist for coordinated screening and comanagement of tuberculosis and diabetes. Both diseases need health education, frequent clinical care, and supportive consultations, particularly in the early post-diagnostic phase. The intensive tuberculosis treatment period (minimum 2 months) is conventionally delivered under strict supervision and support, and includes many encounters with health-care staff. Integrated health education and clinical management of tuberculosis and diabetes would benefit patients. Standardised patient records are a mainstay in tuberculosis care, and the mechanisms for detailed records, and reports of treatments, and treatment responses can be extended to the care of diabetes and other chronic conditions.¹⁵

Access barriers and social protection

Improvements to joint prevention schemes and care for tuberculosis and diabetes will require a combined effort to strengthen health-systems and social protection. High care costs create barriers to access care and adherence to treatments for both diseases, especially for the poorest patients.^{28,29} Direct costs of seeking and accessing care, and income loss due to disability, time spent in health care, and, in the case of tuberculosis, infection control measures, often accumulate to catastrophic economic results for patients and their families, which aggravates underlying vulnerabilities.²⁷

Universal health coverage, which should provide free-of-charge diagnosis and treatment, and social protection schemes to minimise or compensate for other illness and high care costs are essential to enable diagnosis and successful treatment, and to ensure financial protection.²⁸ Interventions, such as these, have improved the uptake and adherence to tuberculosis treatments.⁴⁷⁻⁴⁹

From evidence to policy

The post-2015 global tuberculosis strategy specifies essential future actions and is organised as ten intervention areas within three fundamental pillars: (1) integrated, patient-centred care and prevention; (2) bold policies and supportive systems; and (3) intensified research and innovations. Tuberculosis and diabetes collaborative aspects are incorporated into each intervention area (table 1).

The inclusion of diabetes in the new strategy is the result of a policy development process that has evolved in the past 5 years. In December 2009, an expert meeting was convened to review the evidence of association between diabetes and tuberculosis,⁵⁰ define the research agenda,⁵¹ and commission systematic reviews. In August

2011, a framework was launched⁵² that included provisional recommendations within three main themes: first, establishment of mechanisms for collaboration; second, detection and management of tuberculosis in patients with diabetes; and third, detection and management of diabetes in patients with tuberculosis. The 2011 framework acknowledged that the evidence base on the effectiveness and cost-effectiveness of interventions of tuberculosis and diabetes collaborative activities was weak. The framework encouraged operational and other research to address outstanding questions about the most appropriate methods for bidirectional screening and the co-management of tuberculosis and diabetes. The evidence base has since been expanded, particularly with operational research (discussed later), although randomised controlled trials are scarce and have not provided evidence for several key research questions.

The framework recommends screening for diabetes in all patients diagnosed with tuberculosis, and screening for tuberculosis in people with diabetes in settings that have a high prevalence of tuberculosis (provisionally defined as 100 cases per 100 000 people). The threshold of more than 100 cases per 100 000 people was later reiterated in general WHO guidelines on systematic screening for active tuberculosis, based on an assessment of benefit, risk, cost, and feasibility of screening.⁵³ WHO's 2011 framework further recommends that people with diabetes are treated with the same tuberculosis regimens as people without diabetes, because no published randomised controlled trials have assessed different treatments in people with diabetes. Additional research is needed to identify the most effective and cost-effective approaches for screening and management of diabetes and tuberculosis. Paper 2 in this Series discusses in more detail the evidence for screening, diagnosis, and clinical co-management of tuberculosis and diabetes.⁵⁴ Research priorities to reduce the burden of tuberculosis and diabetes comorbidities⁵¹ are promoted as part of the pillar of the post-2015 strategy that focuses on intensified research.

From policy to practice

Several countries have piloted tuberculosis and diabetes collaborative activities since the 2011 framework was launched. In India and China (the two countries with the highest absolute dual burden of diabetes and tuberculosis; table 2), large operational research studies were done to help provide answers to outstanding questions about the most appropriate approaches on how to create a supportive policy and clinical environment for collaboration and integration;⁵⁵⁻⁶⁴ the full results have not yet been reported. Additionally, the completed studies will provide a better understanding about the most effective clinical approaches for bidirectional screening and coordinated management of tuberculosis and diabetes. Table 3 shows methods used in India and China to ensure national level buy-in and implement pilot

	Key people	Activities
Step 1: National stakeholders meeting	Managers and authorities from the national tuberculosis programme and non-communicable disease programme, national experts in the field of tuberculosis and diabetes, WHO, Union, and World Diabetes Foundation	Review of WHO and Union framework for diabetes and tuberculosis; agree on how to screen patients in routine settings; design monitoring and evaluation records, registers, and treatment cards; agree on method of reporting every 3 months; and selection of pilot sites for broad geographical coverage
Step 2: Train health-care staff from pilot sites	Health-care implementers from the selected pilot sites, managers from national tuberculosis programme and non-communicable disease programme, Union and WHO staff	Develop standard operative guidelines for screening; develop and use monitoring methods and every 3 months report forms; agree to a timeframe; and set up, every 3 months, supervision from Union offices
Step 3: Debrief health-care staff from pilot sites	Health-care implementers from the selected pilot sites, managers from national tuberculosis programme and non-communicable disease programme, Union and WHO staff	Review challenges with screening; review site specific data; aggregate data for reports and papers; and write reports and papers on bidirectional screening
Step 4: National stakeholders meeting	Managers and authorities from the national tuberculosis programme and non-communicable disease programme, national experts in the field of tuberculosis and diabetes, WHO, Union, and World Diabetes Foundation	Review aggregate data and implementation challenges from selected pilot sites; agree on next steps; and agree on whether the evidence is robust to make a national policy

Union=International Union Against Tuberculosis and Lung Disease.

Table 3: Methods used in India and China to translate global policy to national policy and practice for diabetes and tuberculosis

studies. In both countries, these collaborative interventions became part of routine activities and costs and are thus paid for by routine budgets (ie, mainly free-of-charge tuberculosis care, but potentially high out-of-pocket expenditure for diabetes care).

Both countries used the same methodology for bidirectional screening activities for diabetes in patients with tuberculosis.^{44,45,55,56} At the time of registration, patients were asked about the presence or absence of known diabetes, and for those who denied any known disease a random blood glucose test was done to identify those at risk. Patients with high random blood glucose concentrations were then followed up with fasting blood glucose measurements. In both countries, most patients were willing to be screened. 12%–13% of patients with tuberculosis had diabetes, and 3% of patients in China and 5% of patients in India were diagnosed with previously unrecognised diabetes on the basis of fasting blood glucose values. Random glucose testing at the start of tuberculosis treatment could have resulted in false-positive diagnoses.^{57,58,65,66} However, false-negative diagnoses are also possible with this approach, because screening with fasting blood glucose misdiagnoses nearly half of patients with diabetes that can be identified with a 2 h 75 g oral glucose tolerance test (OGTT).⁶⁷ A full OGTT is inappropriate for routine screening and highlights the need for straightforward, accurate, and inexpensive point-of-care tests for routine screening.⁶⁸

People with diabetes were screened for tuberculosis with a symptom-based questionnaire on every visit to the clinic, and patients with a positive screen were referred for tuberculosis investigations. This approach was feasible and resulted in high detection rates of tuberculosis that varied from 300–800 per 100 000 people screened in China, to 600–950 per 100 000 people screened in India.^{44,45,56} These rates were several times

higher than in the general populations for both countries. Several operational challenges were encountered, including the reluctance of busy diabetes doctors to take on the additional work needed to screen for tuberculosis, the low sensitivity of tuberculosis diagnostic approaches that rely on symptom screening and sputum smear examinations for diagnosis, and the absence of structured recording or reporting systems in most diabetes clinics, which makes it difficult to have reliable denominators to calculate tuberculosis case detection rates.

Analyses to measure the difference in bidirectional screening yields for different subgroups showed that the yield of diabetes was highest in patients with tuberculosis aged older than 35 years, patients with smear-positive pulmonary tuberculosis, current cigarette smokers, and those with recurrent tuberculosis.^{59–63} The proportion with newly diagnosed diabetes was higher in patients with tuberculosis who visited peripheral health facilities than patients at tertiary care centres, emphasising the need to prioritise active screening efforts at the peripheral level. The yield of tuberculosis was increased in men, elderly people, individuals with a long duration of diabetes, those who needed combined oral hypoglycaemic drugs and insulin, and those who had poorly controlled diabetes.⁶⁴ Such operational research is needed in other countries that have a high burden of both diseases, and the growing evidence base will begin to pave the way towards optimal diagnosis and care, and ultimately better health outcomes for patients.

In China, the authorities reviewed the evidence of the pilot studies positively and advocated for a cautious approach to scale up. India agreed on a bold government policy directive that meant all patients registered with tuberculosis would be screened for diabetes. A policy directive in India now links the national tuberculosis

programme to the national programme for non-communicable diseases, which is new but evolving rapidly, and this model of convergence that adapts and incorporates the tuberculosis surveillance framework with its so-called cohort reviews is important for the evolution of the national programme.

Plans for the future

Evidence shows the importance of the link between tuberculosis and diabetes, and evidence on effective collaborative interventions is gradually accumulating. Basic collaborative activities are feasible and affordable. Further pilot and scale-up, coupled with operational research, and randomised controlled trials to answer specific research questions, should help to further strengthen the evidence base.

Plans for operationalisation of the post-2015 global tuberculosis strategy in relation to the broader post-2015 health and development agenda are in development, which include a new Global Plan to End TB, building on the present Global Plan to Stop TB 2006–15, which included operational indicators with targets, a budget, and an investment case. The new Global Plan to End TB should engage with the non-communicable disease partnership, the International Diabetes Federation, and other partners that investigate diabetes prevention and care. The 2013–20 WHO Action Plan for the Prevention and Control of Non-communicable Diseases sets an ambitious target of no increase in diabetes prevalence, which engages all stakeholders.⁶⁹

WHO promotes the development of national strategic plans for tuberculosis that are integrated with broader health plans, including for non-communicable diseases.⁷⁰ Integration should help with coherent planning and budgeting within the universal health coverage framework, and help to improve coordinated resource mobilisation through international funding mechanisms, such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria, which has developed a new funding model that promotes needs assessments based on national health plans.⁷¹ Interventions that address tuberculosis risk factors and comorbidities, such as diabetes and other non-communicable diseases, should be considered in the planning process.

With increases in the global burden of diabetes, inclusion of this disease in plans to control tuberculosis will become increasingly important. In this context, it is useful to reflect on the history of tuberculosis and HIV collaborative activities that have evolved over the past 20 years. Such collaboration was already deemed essential 20 years ago. Nevertheless, despite rapid increases in the double burden of tuberculosis and HIV in the beginning of that era, the progress was sometimes slow, and experiences have shown that barriers exist from the clinical level to the highest policy level to institute necessary changes and ensure seamless integrated care.¹⁴ Many countries now have

Search strategy and selection criteria

We searched PubMed with the terms “tuberculosis” in combination with “diabetes” and “non-communicable diseases”, with a selection preference for published systematic reviews in English. Additionally, we reviewed the reference lists of systematic reviews on tuberculosis and diabetes published between Jan 1, 2009, and Jan 31, 2014, and hand searched the issues of 2011 to 2013 of the *International Journal of Tuberculosis and Lung Disease*, to complement the search done in the systematic reviews.^{14–21}

We did an updated analysis of the proportion of tuberculosis cases attributable to diabetes by applying a conventional approach to calculate the population attributable fraction based on estimates of relative risk of tuberculosis in people with diabetes¹⁸ and the prevalence of diabetes in countries,²⁴ as has been done previously.⁵ This analysis was combined with the estimated tuberculosis incidence to generate absolute number of tuberculosis cases attributable to diabetes globally and in different regions of the world.

well-functioning tuberculosis and HIV collaborations, but the links are still suboptimal in some places. The process of establishing links between tuberculosis and diabetes strategies will probably encounter similar obstacles, and support for policy changes will need to come from the highest political levels within countries and from international providers of financial and technical support to disease programmes. Surveillance, monitoring, and assessment of progress towards effective integrated care will also be essential.

Contributors

KL did the initial literature search, the analysis of double burden and attributable fractions, wrote the first draft, and had final responsibility for the decision to submit the paper for publication. GR and ADH did complementary literature searches and contributed text for selected sections. All authors reviewed the final draft of the paper.

Declaration of interests

KL and GR are staff members of WHO. KL and GR are responsible for the views expressed in this paper and they do not necessarily represent the decisions or policies of WHO. ADH declares no competing interests.

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