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Review

The global dynamics of diabetes and tuberculosis: the impact of migration and policy implications

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SUMMARY

The convergence between tuberculosis (TB) and diabetes mellitus (DM) will represent a major public health challenge in the near future. DM increases the risk of developing TB by two to three times and also increases the risk of TB treatment failure, relapse, and death. The global prevalence of DM is predicted to rise significantly in the next two decades, particularly in some of the low- and middle-income countries with the highest TB burden. Migration may add further complexity to the effort to control the impact on TB of the growing DM pandemic. Migration may increase the risk of DM, although the magnitude of this association varies according to country of origin and ethnic group, due to genetic factors and lifestyle differences. Migrants with TB may have an increased prevalence of DM compared to the native population, and the risk of TB among persons with DM may be higher in migrants than in autochthonous populations. Screening for DM among migrants, screening migrants with DM for active and latent TB, and improving access to DM care, could contribute to mitigate the effects of DM on TB.

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Introduction

Tuberculosis (TB) is now the most common infectious disease cause of death worldwide, and developing countries carry a large burden of the 1.6 million deaths caused by TB every year.[1] The disease burden in developing countries due to non-communicable diseases is also increasing and is no longer limited to communicable diseases. Diabetes mellitus (DM) is a global epidemic disease affecting both the developed and developing countries. Approximately 15% of TB patients have comorbidity with diabetes. The convergence between the ongoing TB epidemic and some non-communicable diseases such as diabetes will present a major public health challenge in the near future.[2] It has been estimated that the global prevalence of diabetes will grow significantly in the coming decades, and this increase may be particularly marked in some of the low-income and middle-income countries with the highest burden of TB.[3] Migration flow from these countries has had a major impact on the global dynamics of both diseases,[4,5] and the complex interaction among migration, TB, and diabetes needs to be addressed in the context of the efforts to make progress towards the ambitious goals of the post-2015 End TB Strategy.[6]

This review summarizes current knowledge on the biological and epidemiological aspects of the association between TB and diabetes and focuses on the interaction of international migration with these two conditions. The available evidence on the impact of migration on the DM–TB co-epidemics is also presented, and the need for specific interventions to tackle this public health problem is discussed.

The diabetes–tuberculosis co-epidemic

Although the link between type 2 diabetes and TB is well recognized, it is only in the last decade that appreciation of its relevance as a widespread public health problem has become the focus of global attention. Four systematic reviews quantifying the increased risk of developing TB among people with type 2 DM have been published recently, and they show that DM increases the risk of active TB by two to three times.[7–10] Moreover, the severity of DM seems to be related to the magnitude of this risk: insulin-dependence – as a marker of disease severity – predicts increased TB risk,[11,12] and poor glycaemic control has been identified as a risk factor for TB.[13]

Epidemiological considerations

At the population level, a study by Goldhaber-Fiebert et al., performed between the 1990s and the early 2000s, showed that TB prevalence and incidence were more likely to increase in countries in which diabetes increased.[14] An ecological longitudinal study exploring the relationship between TB and diabetes globally in the period 2000–2012 also found an increase in the prevalence of diabetes with the incidence of TB, although this was limited to countries with high diabetes prevalence rates (> 7.6%), which were primarily on the Asian Continent.[15]

The convergence of the diabetes and TB pandemics represents a new phenomenon in the classic epidemiological transition predicted by Omran in 1971,[16] since the original theory did not predict that elements of globalization and economic development could so quickly generate an 'age of degenerative diseases' before the 'age of receding pandemics' was over. Due to the abundance of calorie-dense/low-fibre foods and the adoption of sedentary lifestyles, the diabetes epidemic is rapidly growing, while the spread of TB remains a global public health threat. The comorbidity of TB and diabetes exemplifies an epidemiological transition where chronic diseases occur simultaneously with infectious diseases, "not simply in the same population, but in the same individual".[17]

It was recently estimated that in 22 countries that carry 80% of the global burden of TB, the proportion of cases attributable to diabetes increased from 10% in 2010 to 15% in 2015%,[6] and it was stated that this fraction could grow further in the near future. In fact, current predictions are that the prevalence of diabetes, primarily type 2 diabetes, is set to rise beyond 592 million by 2035,[2] and approximately 80% of these cases will be in low- and middle-income countries, where the disease strikes at younger ages and even lower body mass indexes,[18] and where the prevalence of TB is also high. By 2030, India, China, Indonesia, Pakistan, and Brazil together are projected to have half of the world's people living with diabetes, and these countries are likely to see the most significant impacts of this co-epidemic in the near future.[14,19]

Clinical considerations of diabetes–tuberculosis comorbidity

Patients with TB–diabetes appear to have poor TB treatment outcomes. Those TB patients with poor blood sugar control have increased rates of treatment failure, relapse, and death than those with good glycaemic control. Diabetic patients with TB are also more likely to develop multidrug-resistant TB (MDR-TB). Diabetes modifies the clinical presentation of pulmonary TB, is associated with atypical radiological presentation,[20] and increases the risk of failure,[20,21] death,[22,23] reactivation, and relapse.[13,20] Diabetes has been found to be an independent risk factor for higher prevalence or a greater severity of some symptoms, such as cough, haemoptysis,[14] and fever, and delayed sputum conversion.[20,21] Data indicating higher bacillary burden in sputa of diabetic patients are conflicting.[24–26]

Diabetes, immunosuppression, and increased susceptibility to tuberculosis

It is well known that HIV infection increases the risk of developing TB, and persons living with HIV have an increased risk of metabolic syndromes, which in turn predispose them to diabetes, possibly linked to the use of antiretroviral drugs.[27–30] The relationship between HIV infection and the TB–diabetes comorbidity, however, is still poorly explored, and more studies are needed on this issue.

It is unclear whether diabetes increases susceptibility to initial *Mycobacterium tuberculosis* infection or the risk of progression from TB infection to active disease, but evidence for defects in innate and adaptive immunity of patients with diabetes suggests that this chronic disease can have an impact on both TB stages.[31] Current findings on the underlying biology that promotes the TB–diabetes association support an inefficient innate immunity, followed by a hyper-reactive cellular response to *M. tuberculosis*; however, the contribution of these altered responses to TB susceptibility or to the more adverse clinical outcomes of TB patients with diabetes remains unclear.

Regarding innate immunity, hyperglycaemia per se, apart from that found in diabetes, has been shown to have a negative impact on immune function through the accumulation of advanced glycation end-products that alter phagocyte function.[32,33] In particular, a reduction in *M. tuberculosis* phagocytosis, change in the expression of genes that contribute to *M. tuberculosis* containment[34] or antigen presentation,[35] and secretion of anti-mycobacterial peptides[36] have been described. Peripheral blood-monocytes may also have defects in cell trafficking due to higher levels of CCR2 expression.[37] This chemokine receptor plays an important role in the migration of mononuclear cells to the lung, and since the ligand of CCR2 (MCP1) is increased in the circulation of patients with type 2 diabetes, these monocytes may be actively retained in the circulation rather than traffic to the site of disease.[38]

Regarding the adaptive immunity, higher levels of Th1 (interferon gamma (IFN-γ), interleukin (IL)-2) and Th17 (IL-17A, but not IL-22) cytokines and a lower frequency of natural T-regulatory cells (CD4+,CD25+,CD127−) at baseline have been reported. However, this is associated with higher IL-10 as well, suggesting that both anti- and pro-inflammatory cytokines are up-regulated in TB patients with diabetes compared to those with TB without diabetes.[38] In contrast, at the site of TB disease, in bronchoalveolar lavage specimens from TB patients with diabetes, higher baseline IL-10 but lower IFN-γ has been found, suggesting that the lung compartment may have a biased Th2 response in diabetes.[39] Results from studies on induced IFN-γ secretion have yielded conflicting results.[38–44] Some have shown that higher inducible cytokine levels are correlated with poor glucose control (high HbA1c).[38,41]

Autophagy is required for the effective control of intracellular pathogens including *M. tuberculosis*,[44–49] and is regulated by mammalian target of rapamycin (mTOR) complex [1,50] a serine/threonine kinase, and adenosine monophosphate-activated protein kinase (AMPK).[51,52] Alterations of the autophagy network and AMPK signalling have previously been associated with *M. tuberculosis* virulence.[53] It has been shown recently that the AMPK-activating anti-diabetic drug metformin inhibits the intracellular growth of *M. tuberculosis*, restricts disease immunopathology, and enhances the efficacy of conventional anti-TB drugs.[54] In relation to metabolic disorders, it has been shown that *M. tuberculosis* can also reside and persist in adipose tissues in a non-replicating state, evading recognition by the host immune system and forming a reservoir for possible reactivation.[55]

Malnutrition per se or due to diabetes may also alter the function of the immune system. Malnutrition may lead to vitamin deficiency. In particular, if vitamin D is decreased, several problems related to the host defence against *M. tuberculosis* may arise, as this is a potent modulator of innate immunity[56,57] and an up-regulator of autophagy in macrophages.[57,58]

Migration and diabetes

The number of international migrants or displaced people worldwide continues to increase; it reached 244 million in 2015, an increase from the 173 million reported in 2000. In 2015, India had the largest 'diaspora' in the world (16 million), followed by Mexico, the Russian Federation, China, Bangladesh, Pakistan, and Ukraine.[59] In addition, the unprecedented number of detections of illegal border crossings occurring around and across the Mediterranean in 2015 should be added to the official figures: an estimated one million asylum seekers and migrants arrived at European Union (EU) country borders declaring that they hailed from Syria and Afghanistan.[60]

Several factors influence the link between migration status and disease, including genetic factors and pre-migration history (socio-economic level, lifestyle habits, exposure to infections), as well as the quality of health care in the countries of destination and level of integration of the migrant population.[61] According to the Organisation for Economic Co-operation and Development (OECD)/EU,[62] in 2012, most migrants perceived themselves to be in overall good health, with no chronic illnesses, and no health-related limitations; only those living in the Baltic countries or Poland, where the immigrant populations are the oldest, complained about their health status. Regarding unmet health care needs, after adjusting for age, foreign-born people living in Estonia, Sweden, Italy, Belgium, and Switzerland reported a higher proportion of unmet medical needs than native-born people.

Two synergistic hypotheses have been formulated to explain the reported lower levels of all-cause mortality and incidence of some diseases such as stroke and cancer[63] in many migrant populations as compared to local-born populations:[63–67] (1) the 'salmon bias effect', which assumes that out-migration is selective for the sickest migrants, and (2) the 'healthy migrant effect', which implies that in-migration is selective for the healthiest individuals.[68,69] Both are difficult to examine due to the scarcity of data on the health of populations in the countries of origin. As an alternative, a few studies have evaluated the 'healthy migrant effect' hypothesis by comparing health outcomes for migrant groups and those born locally in immigration countries[70,71] in the USA, Netherlands,[69] and Denmark,[72] and have arrived at more complex than expected explanatory models for selective migration and for disease occurrence dynamics over time (including the role of past exposures to infectious agents and the effects of trauma and of the migration process itself).

On the other hand, a series of factors may expose migrants to a higher risk of developing certain diseases after arrival in host countries.[4,61] Urbanization, mechanization, changes in nutrition and lifestyle including physical inactivity, gene–environment interactions, stress, and behaviours such as those experienced by migrants originating from a poverty-ridden rural area in early life and moving to an obesogenic urban environment in later life, could confer an increased risk of obesity and diabetes among both inter- and intra-country migrants in developed and developing countries. The availability and abundance of calorie-dense/low-fibre foods and the adoption of sedentary lifestyles is associated with increased risks of morbidity and mortality from chronic diet and lifestyle-related diseases. This phenomenon could be especially relevant for recent migrants, while in the long term some migrants may adopt healthier lifestyles.[73]

A number of studies have investigated the link between migration and diabetes.[4] For example, migrant Asian Indians living in the UK were found to be more obese, to have higher blood pressure, total cholesterol, and blood glucose levels, and to be more insulin-resistant than their non-migrant siblings living in India.[74] Migration itself seems to contribute to a further increase in truncal subcutaneous abdominal adiposity, which has already been reported among Asian Indians and South Asians.[75,76] Lower indices of obesity, insulin resistance, and type 2 diabetes have been reported in the people of African origin residing in Nigeria than in those of African origin living in the USA, while values in those living in Jamaica were intermediate.[77–79]

A recent review by Montesi et al. collected and analysed the evidence from the existing literature on diabetes and migration, with special attention to host countries:[61] in Europe, with a few exceptions, the prevalence, incidence, and mortality rates[80–82] for diabetes were found to be much higher in migrants than in the native people.[4,83] Studies conducted in the UK have reported differences in incidence and prevalence rates for migrants of both South Asian origin (Afghanistan, Bhutan, Maldives, Nepal, and Sri Lanka)[84,85] and Sub-Saharan origin.[86,87] Regarding the complications of diabetes, vascular complications and retinopathy were found to be more common amongst some ethnic groups of

migrants than in native residents in some studies[85,88,89], while according to the results reported by Choukem et al.,[90] the prevalence of diabetic nephropathy was higher in Africans living in Cameroon than among Africans who had emigrated to France. The diagnosis of diabetes was at a younger age than in natives and than in non-migrants from the same country of birth.[87, 90, 91] This latter phenomenon may be explained by the selection bias of age at migration, by late diagnosis of diabetes in the home country, or may truly reflect a population trend of earlier onset of type 2 diabetes due to the rapid changes in lifestyle experienced by migrants in the host country.[92] Once diagnosed, diabetes care seems to be of lower quality (higher likelihood of treatment with oral drugs and longer length of hospital stay for migrants).[91] Among persons migrating to the USA, the prevalence rates of both diabetes and overweight were shown to vary according to region of birth, ranging from 3.1% in Europe to 10.0% in the Indian subcontinent. The three largest Asian American, native Hawaiian, Pacific Islander subgroups – from China, South Asia, and the Philippines – are all at increased risk of developing diabetes,[93] this risk being higher than among non-Hispanic whites but lower than that of African Americans and Latinos.[94,95] In the Fremantle Diabetes Study conducted in Australia, the prevalence in Asians and the general population was similar, but the Asian patients were younger, less obese, and less likely to be hypertensive.[96]while the Melbourne Collaborative Cohort Study found more than three-fold higher baseline prevalence and cumulative incidence of type 2 diabetes in migrants born in Greece or Italy than in individuals born in Australia.[97]

In summary, the available evidence suggests that migration may contribute to the onset of diabetes, and that persons migrating from low- or middle-income countries to high-income countries may have a higher prevalence of diabetes when compared to the autochthonous population. However, significant variations by ethnic group have been recorded, and behavioural, lifestyle, and genetic factors may contribute to this variability.

Migration and tuberculosis

In most low-incidence countries, international migration dynamics trends are known to contribute largely to TB incidence.[5,98–100] From 2000 to 2013, a disparity became evident in high-income countries: while local-born cases remained static or decreased, foreign-born cases decreased slowly or increased.[5] In 2013, foreign-born cases in many high-income countries exceeded 50% of all TB cases,[101–109]with incidence rates 8.7 to 18.4 times higher than among natives.

Migrants from high TB incidence countries could either have active TB on arrival, or remotely-acquired latent TB infection (LTBI) that reactivates post arrival due to socio-economic vulnerability augmented by stressful migration conditions,[109] or could acquire TB through local transmission in the host country. The highest incidence and risk of active TB following migration has been reported for those migrating from Asia and Africa, for recent migrants, refugees, and individuals with comorbidities (such as HIV infection and diabetes).[101–107,109]

Addressing the special needs of migrants and cross-border issues, and undertaking screening for active and latent TB in TB contacts and selected high-risk groups, are among the priority action areas defined by the World Health Organization (WHO) in 2014 as part of the framework towards TB elimination in low-incidence countries.[109,110]

Migrants as a vulnerable group for tuberculosis–diabetes comorbidity

A review of published studies examining the impact of migration on the association between diabetes and TB was performed. The methods used to retrieve and select the articles reviewed in this section are reported in Appendix A.

Four studies conducted in high-income–low TB burden countries examined the prevalence of diabetes among patients with TB by country of origin (Table 1).

Table 1
Diabetes mellitus prevalence in foreign-born and native patients with tuberculosis.

Author, year	City, country	Study period	Type of study Source	Results
Caraffa et al. 2016[111]	Rome, Italy	2007–12	Cross-sectional Hospital-based Medical records	• DM prevalence among TB patients overall: 63/971 (6.5%) • Foreign-born proportion in the study population: 723/971 (74.5%) • DM prevalence among foreign-born patients: among 723 foreign-born TB patients, DM prevalence was 5.4%; DM prevalence was 12.7% (8/63) among those born in countries with DM prevalence ≥8%, 4.7% (31/660) among patients from countries with DM prevalence <8% • DM prevalence among native patients: 24/248 (9.7%) • DM prevalence in the general population: 5.13%
Demlow et al. 2015[112]	California, USA	2010–12	Cross-sectional Population-based Registry data	• DM prevalence among TB patients overall: 1463/6050 (24.2%) • Foreign-born proportion in the study population: 83.3% • DM prevalence among foreign-born patients: 25.7% • DM prevalence among native patients: 16.6% • DM prevalence in the general population: 8.6% (California Diabetes Program data, 2011^^
Suwanpimolkul et al. 2014[113]	San Francisco, California, USA	2005–12	Cross-sectional retrospective Hospital-based Medical records	• DM prevalence among TB patients overall: 126/791 (15.9%) • Foreign born proportion in the study population: not reported • DM prevalence among foreign-born patients: Philippines-born 31.9%, China-born 17.2%, Mexico-born 8.3% • DM prevalence among native patients: 9.2% • DM prevalence in the general population: 9.1% (California Diabetes Program data, 2009
Uchimura et al. 2013[114]	Japan	2007–10	Cross-sectional Population-based Tuberculosis registry	• DM prevalence among TB patients overall: 12 694/96 689 (13.1%) • Foreign-born proportion in the study population: 3.8% • DM prevalence among foreign-born patients: 3.4% • DM prevalence among native patients: 13.5% • DM prevalence in the general population: 5.1%

DM, diabetes mellitus; TB, tuberculosis. ^Report of Tuberculosis in California, 2011, California Department of Public Health, ^^Estimates provided by California Diabetes Program using data from Behavioural Risk Factor Surveillance System, 2001–2010, National Health and Nutrition Examination Survey 2007–2008, California S Hearth Interview Survey 2009, and California Census Data, 2010

In a hospital-based study conducted in Italy among 971 TB patients, 63 (6.5%) had diabetes.[111] Diabetes prevalence was highest among patients from countries with a diabetes prevalence ≥8% (8/63, 12.7%), followed by those born in Italy (24/248, 9.7%) and by foreign-born patients from countries with a diabetes prevalence <8%. Almost 70% of foreign-born TB–diabetes patients were from a country with a diabetes prevalence ≥8%, most frequently from Africa (Egypt, Libya, and Morocco) and Asia (India). Foreign-born patients were younger than those born in Italy. In the multivariable analysis, after adjusting for age, foreign-born patients from countries with a diabetes prevalence <8% were three times more likely to have diabetes, and patients from countries with a diabetes prevalence ≥8% were six times more likely to have diabetes, compared to those born in Italy.

Demlow et al. reported that during 2010–2012, 1463 (24%) of the 6050 active TB cases diagnosed in California had diabetes.[112] Among foreign-born patients, who constituted more than 80% of this patient population, 31% had diabetes compared to 15% among those born in the USA or Canada. In the multivariable analysis among both TB cases and the general adult population in California, persons with diabetes were more likely to be male, older than 44 years, and foreign-born.

The impact of diabetes on TB in the USA and foreign-born populations in San Francisco, California was also studied between 2005 and 2012 by Suwanpimolkul et al.[113] The prevalence of diabetes among 791 patients with TB was 15.9% (9.2% among those born in the USA and 17.8% among those foreign born) and was higher for individuals born in the Philippines (31.9%) than for those born in China (17.2%) or Mexico (8.3%). In the multivariable analysis, being born in the Philippines was significantly associated with diabetes.

In contrast to the previously mentioned studies, an analysis of Japanese TB surveillance data of all cases registered between 2007 and 2010 found a prevalence of diabetes among foreign TB patients of 3.4% compared to 13.4% among Japanese patients. However, foreigners represented less than 5% in that study, and they were younger than the Japanese patients.[115] Taken together, these studies suggest that the prevalence of diabetes among patients with TB reflects the prevalence of diabetes in the ethnic groups of origin, while these studies do not allow a direct assessment of the effect of migration on the association between diabetes and TB.

Three studies examined the risk of TB in patients with diabetes by country of origin (Table 2). In a case–control study conducted in Denmark, in which the prevalence of diabetes was assessed in patients with TB and in matched population controls, a low risk increase for TB associated with diabetes was recorded overall (odds ratio 1.18, 95% confidence interval 0.96–1.45), with a similar risk for migrants (odds ratio 1.23, 95% confidence interval 0.78–1.93). The authors noted, however, that the probability of having diabetes detected may have been lower in migrants with TB than in Danes because of a short stay in the host country or different health care-seeking behaviour.[115]

The incidence of TB among patients with diabetes by birth location was assessed in the retrospective population-based study conducted in California already mentioned above.[112] The overall incidence of TB among persons without diabetes was 6.0 per 100 000 per year compared to 21.0 per 100 000 per year among persons with diabetes; among these persons, foreign-born persons had an overall TB rate of 142/100 000, almost 12 times greater than among USA or Canadian-born persons (12/100 000). The highest TB incidence rates were recorded among persons born in Southeast Asia and the Pacific Islands, with rates in the different age strata ranging from 117 to 239 per 100 000. The overall relative risk of TB for persons with diabetes was 3.5, and was relatively consistent for different locations of birth.

The heterogeneity of risk by ethnic group recorded in California is consistent with the results of the epidemiological model constructed using data on the incidence of TB, the prevalence of diabetes, the population structure for 2005, and the age-specific relative risk of TB associated with diabetes from a large cohort study in England.[116] In this model, the estimated population attributable factor of diabetes for pulmonary TB was highest for Asian men (16.6%) and women (14.2%). Lower figures were recorded for white persons (6.9% in men and 8.2% in women) and black persons (7.4% in men and 8.9% in women) despite a higher prevalence of diabetes in the black population, reflecting a much younger mean age of pulmonary TB in the black population.

Finally, history of TB among diabetic patients was analysed using data collected in the context of the US National Health Interview Survey (NHIS) between 2000 and 2005.[117] Fourteen percent of individuals in the survey were foreign-born, and among them, the reported prevalence of diabetes rose progressively in relation to years of residence in the USA. In fact diabetics who were foreign-born and non-Hispanic had an odds ratio for TB of 2.2 (99% confidence interval 1.6–3.2) compared to those who were USA-born and non-Hispanic, and USA-born Hispanics had an odds ratio for TB of 2.1 (99% confidence interval 1.4–3.2) compared to those who were foreign-born and non-Hispanic.

Table 2
Tuberculosis incidence in foreign-born and native patients with diabetes mellitus.

Author, year	City, country	Study period	Type of study Source	Results
Demlow et al. 2015[112]	California, USA	2010–12	Cross-sectional Population-based Survey aggregated data	• TB incidence rate among DM patients overall: 21/100 000 • Foreign-born proportion in the study population: 60.5% • TB incidence rate among foreign-born patients: 142/100 000 foreign-born patients • TB incidence rate among native patients: 12/100 000 USA/Canadian-born • General population TB incidence rate: 5.9/100 000 (report on tuberculosis in California, 2011) • Relative risk for TB among persons with DM: 3.5 (95% CI 3.3–3.7) • Number of persons needed to be screened: 7930 among all adults, 2740 among adults with DM, 1526 among all foreign-born patients, and 596 among foreign-born patients with DM
Leegaard et al. 2011[115]	Northern Denmark	1980–2008	Case–control Population-based Danish National Registry of Patients and Residents Registry	• DM prevalence overall: 156/2950 (5.3%) • Foreign-born proportion in the study population: 28.6% • Adjusted OR for TB among subjects with DM: 1.18 (95% CI 0.96–1.45); the adjusted ORs for TB among DB cases were similar among native Danes (1.17, 95% CI 0.93–1.46) and immigrants (1.23, 95% CI 0.78–1.93)
Marks 2011[117]	USA	2000–05	Cross-sectional Population-based Survey individual data	• Adjusted OR for history of TB was 1.4 (99% CI 1.0–2.0), controlling for being foreign-born non-Hispanic (aOR 2.2, 99% CI 1.6–3.2), USA-born Hispanic (aOR 2.1, 99% CI 1.4–3.2)

TB, tuberculosis; DM, diabetes mellitus; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio.

These studies suggest that the relative risk of developing TB is similar for migrants and autochthonous populations in countries with a low TB burden. On the other hand, given the increased incidence of TB for those migrating from high-incidence countries, the absolute increased risk associated with diabetes is much higher for some groups of migrants. In addition, the fraction of TB cases attributable to diabetes may be considerable in some ethnic groups with a high prevalence of diabetes and TB infection.

Conclusions and policy implications

Migration may add further complexity to the efforts to control the growing diabetes pandemic. Available data suggest that in most instances persons migrating from low- and middle-income countries have a higher prevalence of diabetes compared to the native population, and also somehow higher than in persons from the same population who remain in the country of origin. However, significant heterogeneity is observed in the magnitude of association between migration and diabetes according to the country of origin and ethnic group, and this may reflect genetic factors and diet and lifestyle differences. The interaction between diabetes and migration may in turn have an impact on interventions aimed at reducing the impact of diabetes on the burden of TB.

The potential impact of interventions related to the co-epidemic on the overall trends of TB burden appears to be very high.

A model simulation assessed the impact of diabetes prevention on TB incidence in 13 countries that carry over 60% of the global TB burden and with a low-level HIV epidemic.[118] According to this model, if diabetes prevalence continues to grow in the next 20 years, this will determine a reversal in the present trend of a decrease in TB incidence. In contrast, preventing the rise in TB incidence would determine an acceleration of the declining trend in TB, and a policy that could determine a reduction in diabetes prevalence would result in 7.8 million cases of TB and 1.5 million deaths being avoided over the next two decades.

In another simulation, Odone et al. analysed the potential effect of a combination of improved prevention and care of diabetes with a reduction in undernutrition as a tool to decrease the TB burden.[119] In the baseline scenario, the projected 21% global increase in diabetes prevalence by 2035 would be associated with a global TB incidence 3% higher compared with the present figures. On the other hand, implementing interventions that could decrease the effect of diabetes on the risk of TB through the treatment of LTBI and better glucose control would result in the model with a 15% lower incidence of TB in 2035 compared with the baseline scenario.

The current WHO End TB Strategy is based on three pillars: integrated patient-centred TB care and prevention, bold policies, and supportive systems. Interventions on the association between TB and diabetes are recommended for each one of these areas.[6] These interventions include screening for active TB among patients with diabetes in high TB burden settings and screening for diabetes among patients with TB; screening for and treating LTBI in diabetics at high risk of disease progression, ensuring access to health care including diabetes care; and operational research on TB–diabetes common activities.

What is the specific relevance of these interventions for migrants?

The yield of screening for active TB among diabetics varies greatly according to the tools used and the background TB prevalence, and the effectiveness of this intervention may be unacceptably low in low TB burden countries.[6,7] Nonetheless, even in these countries, screening programmes targeted at migrants with diabetes from ethnic groups disproportionately affected by diabetes and TB may eventually prove effective.

Screening for and treatment of LTBI in diabetics is not generally recommended;[120] however, similarly to screening for active TB, this intervention should be evaluated in some groups of migrants. For example, the study conducted in California mentioned previously suggested that almost 10 000 USA-born adults with diabetes would have to be screened for TB infection to prevent one case of TB, while the number that would need to be screened would be around 300 for diabetics born in Southeast Asia/Pacific Islands.[112] Screening for TB infection is recommended for persons migrating to low TB incidence countries from countries with a high TB incidence, which is usually defined as a rate above 100 per 100 000; however, this threshold should be re-evaluated, and possibly lowered, when deciding whether migrants with diabetes should be screened.

An obvious prerequisite for the above-mentioned interventions is adequate identification of diabetes in migrants. Data on the prevalence of undiagnosed diabetes among migrants are sparse; however this phenomenon is likely to be relevant. It has been estimated that globally, 45.8% or 174.8 million of all diabetes cases in adults are undiagnosed, and this proportion may be as high as 75% in some African countries.[121] An estimated 83.8% of all cases of undiagnosed diabetes are in low- and middle-income countries from which the vast majority of migrants originate. In a study conducted on the USA–Mexico border, Mexicans (43.8%) andMexican immigrants (39.0%) with diabetes were significantly more likely to be undiagnosed than were USA-born Hispanics (15.0%) or non-Hispanic whites (6.6%).[122] In another study, 58.5% of Mexican immigrants with diabetes in their first 4 years in the USA were undiagnosed, compared to 29.5% of those who had migrated a longer time ago.[123] In the UK, the risk of having undiagnosed diabetes was found to be two times higher among adults originating from Asian countries than among white Europeans.[124] In Italy, diabetes was more frequently diagnosed at the time of TB diagnosis in the foreign-born than in Italian patients (28.2% vs. 16.7%).[111] This evidence suggests that screening for diabetes should be considered an important component of health services to be provided to migrants.

There is also evidence that in Europe, migrants with diabetes have a higher incidence of complications and lower use of anti-diabetic drugs compared to the autochthonous populations,[91,125] suggesting the need to improve access to high quality diabetes care for migrants.

In conclusion, the screening of diabetics for active TB and for TB infection, screening for diabetes among migrants,[126–128] and improved access to diabetes care, could contribute to mitigate the effect of diabetes on TB among migrants. Operational research on the implementation of these interventions and the evaluation of their effectiveness in different settings and in different migrant populations are badly needed.

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Conflict of interest

The authors report no potential conflicts of interest in relation to this paper.

Author contributions

GI, EG, and AZ conceived the paper. MSS, DG, and EG retrieved and reviewed the relevant literature. All authors contributed to the interpretation of the evidence and writing of the paper.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2017.01.018.

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