Commentary: Co-occurrence of tuberculosis and diabetes: new paradigm of epidemiological transition

Matthew J Magee,1* Henry M Blumberg1,2,4 and KM Venkat Narayan1,3,4

1Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA 30322, 2Division of Infectious Diseases, Department of Medicine, Emory University School of Medicine, Atlanta, GA 30303, 3Department of Medicine, Emory University School of Medicine, Atlanta, GA 30303 and 4Hubert Department of Global Health, School of Medicine, Emory University, Atlanta, GA 30322, USA

*Corresponding author. Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Rd, NE, Atlanta, GA 30322, USA. E-mail: mjmagee@emory.edu

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In his classic 1971 paper, Abdel Omran put forward the theory of The Epidemiologic Transition, positing that societies experience three principal stages of disease status: beginning with an Age of Pestilence and Famine, followed by an Age of Receding Pandemics and finally an Age of Degenerative Disease.1 Although exceptions to Omran’s theory exist,2–4 the concept remains relevant to contextualize major shifts in epidemic dynamics. The recently observed co-occurrence of tuberculosis (TB) and diabetes mellitus (DM) pandemics, however, represents a new phenomenon in the classic epidemiological transition, a consequence of rapidly growing non-communicable diseases (i.e. DM)—a result of transitioning lifestyles towards greater intake of calories and lower physical activity—coupled with an inability to reduce the global burden of TB. The shifting epidemiology, sociology and clinical care of the concurrent DM–TB disease state, like the combination of other infectious and chronic diseases, will influence public health agendas and challenge the classical silos of communicable vs non-communicable diseases. This situation, however, may also offer major opportunities for research and for rethinking health systems’ orientation and structure.

Omran accurately predicted that societal improvements in economic, social, cultural and political capacities would affect epidemic transitions, but he did not foresee that elements of globalization and economic development could so quickly bring about an Age of Degenerative Diseases before the Age of Receding Pandemics was curtailed. The increasing co-occurrence of TB and DM is a clear case in point, especially in countries with rapidly emerging economies such as India and China, resulting in a confluence of two pandemics—one communicable and another non-communicable. In this issue of the IJE, Goldhaber-Fiebert et al.5 report an association between DM and TB from a population-based survey of low- and middle-income countries (LMIC) that is consistent with findings from previous research.6–8 DM has been recognized as a risk factor for TB for decades, but although the link between DM and TB is not new, only with the recent explosive DM pandemic has the importance of understanding the relationships between DM and TB emerged as a global health priority.7,9 TB causes enormous morbidity and mortality globally; annually, >9 million people develop active TB and nearly 2 million die due to TB—now the second leading cause of death from an
infectious disease. The overwhelming number of TB cases and deaths occur in LMIC. At the same time, more than 285 million adults globally have DM and this number is projected to increase to 440 million by 2030, with three-fourths of affected people living in LMICs, where the disease strikes at younger ages and even lower body mass indices (BMIs). 11,12

The evolving epidemiology of concomitant DM and TB is of particular importance in middle-income countries with emerging economies, which still have large TB burdens coupled with dramatic increases in DM due to rapid changes in lifestyles. DM may contribute to a significant proportion of the TB cases in many such countries. Goldhaber-Fiebert et al. demonstrate the strength of the association (adjusted prevalence odds ratio of 1.81) between DM and TB in a large population-based survey, and use ecological data to highlight the impact of an expanding DM epidemic on TB incidence in high-burden countries. Table 1 shows the TB and DM burden in five countries (Brazil, China, India, Indonesia and Pakistan) identified as most concerning by Goldhaber-Fiebert because of their population size, TB burden and projected DM increases. These five countries were estimated to consist of 50% (43% according to International Diabetes Federation 13) of the world’s prevalent DM cases by 2030 and also contributed 45% of global incident TB cases in 2008. Even if these middle-income countries currently have relatively lower prevalence of DM than high-income countries, the population impact of DM on TB is greater in regions of high-TB incidence, many of which also have large populations. A recent review of TB and DM estimated that among the 10 highest-burden TB countries in 2010, 11.4% of incident cases were attributable to DM; by 2030 this figure is estimated to be 14.1%. Furthermore, the largest increases in DM during the next two decades are anticipated among the high-burden TB countries, and by 2030 an estimated 70% of patients with DM will live in an erstwhile high-burden TB country. 14

The confluence of the DM and TB epidemics in India is particularly alarming. The Revised National TB Control Program (RNTCP) in India is the largest TB control agency in the world; in 2008, the RNTCP treated 1.51 million patients with TB, including 616,000 (24% of the global total) new smear-positive pulmonary TB cases. 15 Currently, 51 million Indians have DM and by 2030, this number is projected to grow to 87 million, lending India to be dubbed as the infamous ‘diabetes capital of the world’. 16 An estimated additional 34 million Indians currently have impaired glucose tolerance, and are at high risk of developing DM within the next 5–10 years. Rapid economic growth, urbanization, inter-generational poor nutrition and gene–environment interactions predispose populations in LMIC to increased DM risk and higher rates of DM lead to an ever-increasing proportion of TB cases attributable to DM.

The proportion of TB cases in India attributable to DM has been estimated using RNTCP data and a population-based survey of DM prevalence in 77 centres throughout the country. 17 In 2000, an estimated 14.8% (uncertainty range 7.1–23.8%) and 20.2% (uncertainty range 8.3–41.9%) of incident TB and incident smear-positive TB cases were attributable to DM, respectively. The increasing prevalence of DM among TB patients poses new challenges for TB programmes globally—TB symptoms, treatment outcomes, development of drug resistance and mortality rates are all potentially affected by DM. It also provides opportunities to target high-risk patients such as those with DM for TB screening and active case finding. Conversely, TB may also pose challenges for control of DM, and patients with TB may be viewed as potential targets for DM screening. The impact of concurrent TB and DM pandemics on the global burden of disease is evident, but whereas the association between TB and DM is well known,6,8 the mechanisms by which DM causes an increased risk of initial TB infection, or increases the rate of

<table>
<thead>
<tr>
<th>Country</th>
<th>Population size</th>
<th>GDP</th>
<th>2008 TB incident cases</th>
<th>Global TB incidence (%)</th>
<th>2010 DM prevalent cases</th>
<th>Proportion of 2010 global DM (%)</th>
<th>2030 DM prevalent cases</th>
<th>Proportion of 2030 global DM (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td>201</td>
<td>2182</td>
<td>89.2</td>
<td>1.0</td>
<td>763.2</td>
<td>2.7</td>
<td>12,707.6</td>
<td>2.9</td>
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<tr>
<td>China</td>
<td>1330</td>
<td>10,084</td>
<td>1301.3</td>
<td>13.9</td>
<td>43,157.2</td>
<td>15.2</td>
<td>62,553.0</td>
<td>14.3</td>
</tr>
<tr>
<td>India</td>
<td>1173</td>
<td>4001</td>
<td>1982.6</td>
<td>21.2</td>
<td>50,768.3</td>
<td>17.8</td>
<td>87,036.1</td>
<td>19.8</td>
</tr>
<tr>
<td>Indonesia</td>
<td>242</td>
<td>1027</td>
<td>429.7</td>
<td>4.6</td>
<td>6963.5</td>
<td>2.4</td>
<td>11,980.0</td>
<td>2.7</td>
</tr>
<tr>
<td>Pakistan</td>
<td>184</td>
<td>465</td>
<td>409.4</td>
<td>4.4</td>
<td>7146.4</td>
<td>2.5</td>
<td>13,833.0</td>
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</tr>
<tr>
<td>Global</td>
<td>6,880</td>
<td>74,004</td>
<td>9,369</td>
<td>4,425,650</td>
<td>284,814</td>
<td>438,667</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
progression from inactive TB infection to disease, are poorly understood. Whether patients with DM who develop TB have similar disease manifestations at diagnosis, or whether patients with DM have a greater burden or severity of disease (such as cavitary pulmonary disease) compared with patients with TB who do not have DM is unclear. There are limited data on the response to therapy and the pharmacokinetics of anti-TB drugs among patients with DM. The role that DM plays on TB-related clinical manifestations has important consequences for individual and programmatic TB treatment strategies, but to date we are limited to estimating these effects from the few observational studies that use non-standardized measures of DM, TB and TB therapeutic outcomes. Some have suggested that those with DM respond less well to standard anti-TB therapy, but there remains a need for data from prospective studies to assess the impact of DM on treatment outcomes in persons with TB.

Drug-resistant TB, including multi-drug resistant (MDR)-TB (resistance to at least both isoniazid and rifampicin, the best first-line anti-TB drugs) has emerged as a major challenge to global TB control and is associated with increased morbidity and mortality. Several recent studies have suggested a higher prevalence of MDR-TB among those with DM, but whether this is a result of increased susceptibility to a primary resistant infection or acquired resistance is unclear; further investigations in this association and causal mechanisms are needed. Altered pharmacokinetics of rifampicin in TB patients with DM (e.g. reduced rifampicin absorption) may affect treatment outcomes but only two known studies have explored this area. Rifampicin is the most important antibiotic for TB treatment, and achieving suboptimal serum concentrations may be an important factor in increasing the likelihood of acquiring drug resistance and clinical failure. In order to explore whether patients with TB and DM are at greater risk for primary MDR-TB infection or have lower rifampicin levels (potentially resulting in treatment failure and/or acquired resistance) than patients with TB and no DM requires investment in TB-related research, including a better understanding of TB–DM interactions. The importance of this research will have broad clinical relevance regarding the need for therapeutic drug monitoring and regimen selection in subgroups of TB patients.

There are also limited data about the impact of TB and its treatment upon DM incidence and management. The combination of anti-TB drugs with DM medications has potentially important drug interactions. Rifampicin is a potent inducer of both the hepatic and intestinal cytochrome P-450 (CYP) enzyme system and P-glycoprotein (P-gp) transport system, which results in numerous clinically significant drug interactions; for example, oral hypoglycaemic agents may result in enhanced clearance and low serum levels of sulphonylureas. In addition, fluoroquinolones, key antibiotics used to treat MDR-TB, may cause both hyperglycaemia and hypoglycaemia. The accepted association between TB and DM is most frequently assumed to be a result of DM predisposing patients to an increased risk of developing TB disease although the exact mechanisms are not well understood. Despite challenges in capturing incident cases of DM in epidemiological studies, additional studies should consider the risk of TB infection among newly diagnosed DM patients and interventions (such as treatment of latent TB infection) which can prevent the progression from infection to active TB disease. Such interventions are limited by lack of effective and safe short-course regimens for treatment of latent TB infection and emphasize the urgent need for new tools for TB control including new drugs, new diagnostics and an effective vaccine.

The confluence of the TB and DM pandemics requires a response that includes linking often divergent infectious and non-communicable disease approaches to clinical and public health practice, research and policy development. Care, research and public health practices regarding DM and TB can no longer be approached as two separate silos with their own internally valid assumptions. Strategies are needed to efficiently explore knowledge gaps in both disciplines in an integrated fashion. Addressing the new research questions brought about by the co-occurrence of TB and DM, such as the examples we highlighted, will inform the development of policies, prevention strategies and treatment guidelines for patients with both diseases. Innovative strategies such as expanding TB directly observed therapy to include additional health services for patients that also have DM have the potential to help countries with high burden of both diseases efficiently reduce morbidity and mortality. In populations where the prevalence of both diseases is high, screening TB patients for DM and screening DM patients for TB is another strategy that may lead to improvements in prevention, diagnosis and ultimately care.

The convergence of TB and DM pandemics exemplifies an epidemiological transition where chronic diseases commonly occur simultaneously with infectious diseases, not simply in the same population, but in the same individual. This concurrent state of commonly prevalent infectious diseases (TB) with prevalent and increasingly incident non-communicable diseases (DM) points to the need for a modified conceptual framework for the epidemiological transition theory. We must recognize the impact of globalization on the quick rise of chronic non-communicable diseases, and generate innovative solutions that
integrate approaches to prevention and control of both non-communicable and infectious diseases.

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References