

## Consultation meeting on tuberculosis and diabetes mellitus: meeting summary and recommendations

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### SUMMARY

The steadily growing epidemic of diabetes mellitus (DM) poses a threat for global tuberculosis (TB) control. Previous studies have identified an important association between DM and TB. However, these studies have limitations: very few were carried out in low-income countries, and none in Africa, raising uncertainty about the strength of the DM-TB association in these settings, and many critical questions remain unanswered. As a result of these questions and uncertainties, the International Union Against Tuberculosis and Lung Disease (The Union), the World Diabetes Foundation and the World Health Organization Stop TB Department undertook a

series of consultations as of January 2009. A systematic review and meta-analysis was undertaken by the Department of Epidemiology, Harvard School of Public Health between May and August 2009, and a consultation meeting involving the experts who reviewed the report took place at The Union Headquarters in Paris on 6 and 7 November 2009. This paper constitutes a summary report of the findings, the research gaps and prioritised areas of research, and the recommendations from that meeting.

**KEY WORDS:** diabetes mellitus; tuberculosis; meeting report; screening; treatment outcomes

IT IS ESTIMATED that, worldwide in 2010, there were 285 million people living with diabetes mellitus (DM), accounting for 3.5 million deaths, with the numbers predicted to rise to 438 million by 2030.<sup>1</sup> In 2008, there were an estimated 9.4 million cases of tuberculosis (TB), accounting for 1.8 million deaths.<sup>2,3</sup> Since 1994, the DOTS and Stop TB strategies have been successfully implemented in more than 180 of the 212 World Health Organization (WHO) member states. The treatment success rate has recently gone above the 85% WHO global target, but the TB case detection rate is only 63%, still below the 70% global target set for 2005 by the WHO and the Stop TB Partnership.<sup>2,3</sup> WHO estimates indicate that the annual TB incidence is stabilising or slightly declining in most of the WHO regions. Worldwide, the estimated absolute number of TB-affected people is increasing on a yearly basis, while the annual incidence is decreasing very slightly, at a rate of <1% per year. It is expected that, at this rate of decline, the impact of TB control efforts on the global TB burden will not be significant and the elimination of TB (defined as <1 TB case per 1 million people) is unlikely to be achieved by 2050.

Recent literature reviews have shown that people with DM have a significantly higher risk of develop-

ing active TB compared to those without DM.<sup>4–6</sup> This association is supported by animal models in mice, and the physiopathological characteristics inherent to DM that increase the risk for TB in DM patients (low levels of interferon-gamma, pulmonary microangiopathy, renal failure, micronutrient deficiency). While the association between DM and TB seems not to be in doubt, the available evidence has limitations: 1) many of the studies were health facility-based, with a case-control design; 2) most of the studies were carried out in industrialised countries; and 3) none of the studies used the oral glucose tolerance test (OGTT) to diagnose DM.

The strength of the association between DM and TB in low-income countries, and particularly in sub-Saharan Africa, remains uncertain. Moreover, additional issues need to be clarified, such as: 1) the risk of DM in TB patients; 2) whether the clinical picture of TB is different in DM patients; 3) the effect of DM on treatment outcomes of TB; and 4) whether recurrent TB and anti-tuberculosis drug resistance have any relation to DM.

In order to establish the current knowledge base, identify gaps and recommend future courses of action, including establishing an agenda for future research and development of policy for action on TB

and DM co morbidity, the International Union Against Tuberculosis and Lung Disease (The Union), the World Diabetes Foundation (WDF) and the WHO Stop TB Department undertook, as of January 2009, a series of consultations. Based on these consultations, it was established that an additional literature review was needed to:

- 1 update any new evidence regarding the association of DM with active TB as well as with latent TB infection;
- 2 establish the need, if any, for screening DM and TB patients for the other condition to facilitate early detection of the co-morbidity as well as to assess any impact of chemoprophylaxis in preventing active TB in DM patients;
- 3 assess the impact of DM on the clinical and programmatic management of TB, with a focus on sputum smear/culture conversion, TB treatment outcome, recurrent TB, pharmacokinetic interactions between DM and TB medications and anti-tuberculosis drug resistance; and
- 4 identify existing evidence, if any, of the effect of DM prevention on TB burden.

This additional systematic review and meta-analysis was undertaken from May to August 2009 by Professor Megan Murray and her team (Department of Epidemiology, Harvard School of Public Health). The report on the review findings was prepared and forwarded for further input to key stakeholders from The Union, WDF, the WHO, academic institutions and diabetes organisations. Findings from the systematic review and meta-analysis will be published separately as scientific papers.

A consultation meeting involving the experts who reviewed the report took place at The Union Headquarters in Paris on 6 and 7 November 2009. The details of the meeting and the list of participants are shown in the Appendix. The decision was made to publish a short summary report and recommendations so that other stakeholders involved in TB control and interested in the intersection between communicable and non-communicable diseases would have a chance to read about the deliberations.

## OBJECTIVES OF THE CONSULTATION MEETING

The objectives of the meeting were:

- 1 To review, discuss and endorse the findings of the systematic review;
- 2 To identify knowledge gaps and identify a prioritised research agenda; and
- 3 To suggest future courses of action to address the potentially dangerous public health threat posed by the rising dual burden of DM and TB, especially in the developing countries, and to recommend actions to promote and improve collaboration

between TB and DM prevention, care and control services.

## SUMMARY OF FINDINGS OF SYSTEMATIC REVIEW

The main findings of the systematic review are to be published in two scientific papers, and will be briefly summarised below. The summary relative risk of TB in people with DM is 2.52 in cohort studies and 2.20 in case control studies. However, many issues need to be clarified, including: 1) the effect of diabetes duration and control on TB occurrence; 2) the interaction of other TB risk factors with DM; 3) the differences in the strength of the association between DM and TB in high and low TB burden country settings; 4) the effect of DM on the different forms of TB, including extra-pulmonary TB; and 5) the influence of greater exposure to health facilities amongst people with DM and the greater likelihood of exposure to TB infection.

### *Screening of TB among DM patients*

Screening of TB among DM patients, especially those with uncontrolled DM, can contribute to detecting new TB cases. Again, several issues need to be clarified, namely: 1) the profile of people with DM who need systematic screening; 2) the most appropriate TB screening method for routine use, particularly when taking into account the TB burden in a given population; and 3) the frequency of TB screening in people with DM.

### *Screening of DM among TB patients*

Screening of DM among TB patients will contribute to detecting additional DM cases, and this intervention would also facilitate early detection of uncontrolled DM, the subsequent control of which might lead to a reduction in potentially adverse outcomes for TB. TB may cause temporary hyperglycaemia that resolves during the course of TB treatment, and this can lead to a consequent risk of over-diagnosis of DM. There is a need to define the most appropriate diagnostic procedures that circumvent the issue of stress hyperglycaemia as well as the optimal timing for DM screening.

### *DM affects TB treatment outcomes*

DM affects TB treatment outcomes by increasing case fatality rates and the risk of recurrent TB. There is a lack of clarity about the relationship between DM and drug-resistant TB, but there may be an association with multidrug-resistant TB, which requires further investigation. There are also important knowledge gaps on the interaction between DM and TB medications, and on the effect of different TB treatment regimens (including length of treatment) in people with DM.

## RESEARCH GAPS AND PRIORITISED AREAS FOR RESEARCH

The research agenda, and in particular the prioritised areas for research, are the subject of a short review published in *Tropical Medicine and International Health*.<sup>7</sup> Briefly, the four main priority areas for research include: 1) when and how to screen for TB in patients with DM and vice versa; 2) the impact of DM and non-DM hyperglycaemia on TB treatment outcomes and deaths; 3) the implementation and evaluation of the TB DOTS strategy model for managing and monitoring DM; and 4) the development of better point-of-care diagnostic and monitoring tests, including measurements of glycosylated haemoglobin (HbA<sub>1C</sub>), for patients with DM.

The issue of whether TB chemoprophylaxis is beneficial in people with DM is of interest, but there is a dearth of knowledge in this area and a randomised controlled trial on TB chemoprophylaxis in people with DM would be needed to address this question. This would be an expensive, large and time-consuming exercise, and was judged not to be a priority research area. Potentially, however, preventive therapy could be considered for certain high-risk groups within the larger group of people with DM. For example, people with DM who have a close TB contact may have their DM assessed regularly, and the need for TB chemoprophylaxis in such circumstances would need to be evaluated.

## RECOMMENDATIONS

The consultation meeting identified four main sets of recommendations.

- 1 Collaboration between TB and DM care and control initiatives
  - Ministries of health, technical agencies, funding agencies and donors should recognise the link between DM and TB and encourage closer collaboration between National TB Programmes (NTPs) and stakeholders involved in national DM prevention and care.
  - NTPs and stakeholders involved in national DM prevention and care should develop collaborative activities in the following areas:
    - Incorporation into national guidelines on TB and DM of the relevant aspects of screening, diagnosis, management and prevention of DM and TB, respectively
    - Joint planning and training
    - Integrated care and control services
    - Coordinated supervision, monitoring and evaluation, and surveillance
    - Research
    - Development of undergraduate training curricula on TB and DM.
- 2 Screening for active TB among people with DM
  - Standardised TB suspect identification and TB diagnosis procedures should be rigorously implemented in patients with DM, especially in countries with high TB incidence.
  - In countries with high TB burden, patients with DM should be routinely screened for TB symptoms and recent exposure to TB as part of regular clinical check-ups. At a minimum, people with persistent cough (>2 weeks) should be screened for TB following the standard diagnostic algorithm used in the country.
  - The following approaches may be considered, depending on the prevalence of TB and DM, the TB case detection gap and health care resources in a given setting:
    - Initial screening for active TB with additional diagnostic tests such as X-ray, culture, abdominal ultrasound, etc.
    - Screening on wider indication based on additional TB risk markers:
      - Recent contact with people with active TB
      - Symptoms suggestive of TB (cough of any duration, weight loss, fever, etc.)
      - Poor diabetes control
      - Migrants from high TB incidence areas
      - Other TB risk factors (smoking, alcohol abuse, malnutrition, immunosuppressant treatment, congregate settings, etc.)
- 3 Screening for DM among TB patients
  - People with newly diagnosed TB should be screened for DM, at least in countries/areas with a medium to high prevalence of DM, and the results of screening should be registered, for example in the TB treatment card and/or TB treatment register.
  - While waiting for better evidence concerning the appropriate screening method and timing of screening, it is advisable to screen with either random or fasting blood glucose, urine glucose, and/or HbA<sub>1C</sub> at the time of TB diagnosis, and to repeat a positive diagnostic test after 3 months of TB treatment.
- 4 Management of TB and DM co-morbidity
  - Among patients with DM and active TB, all aspects of treatment, case management, monitoring of side effects and complications, patient support and health education for both TB and DM should be optimised, as per national guidelines and/or international best practice adapted to available resources.
  - Appropriate cross-referral of TB and DM cases should be ensured, while integrated approaches for diagnosis, management and prevention should be explored.
  - Among patients with DM and active TB, DM health education and behaviour change messages

and interventions should be part of the health education delivered as part of routine encounters with health workers for TB management.

- The applicability of the DOTS model (political commitment, quality assured diagnosis, standardised treatment with adequate patient support, ensured drug supply, and standardised monitoring and evaluation) should be explored for the management of DM.

### Acknowledgement

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### References

- 1 International Diabetes Federation. IDF diabetes atlas. 4th ed. Brussels, Belgium: International Diabetes Federation, 2009. <http://www.eatlas.idf.org> Accessed August 2010.
- 2 World Health Organization. Global tuberculosis control 2009: epidemiology, strategy, financing. WHO/HTM/TB/2009.411. Geneva, Switzerland: WHO, 2009. [http://www.who.int/tb/publications/global\\_report/2009/en/index.html](http://www.who.int/tb/publications/global_report/2009/en/index.html) Accessed August 2010.
- 3 World Health Organization. Global tuberculosis control. A short update to the 2009 report. Geneva, Switzerland: WHO, 2009. <http://www.who.int/tb/country/data/download/en/> Accessed August 2010.
- 4 Jeon C Y, Murray M B. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* 2008; 5: e152.
- 5 Stevenson C R, Critchley J A, Forouhi N G, et al. Diabetes and the risk of tuberculosis: a neglected threat to public health. *Chronic Illn* 2007; 3: 228–245.
- 6 Dooley K E, Chaisson R E. Tuberculosis and diabetes mellitus: convergence of two epidemics. *Lancet Infect Dis* 2009; 9: 737–746.
- 7 Harries A D, Murray M B, Jeon C Y, et al. Defining the research agenda to reduce the joint burden of disease from diabetes mellitus and tuberculosis. *Trop Med Int Health* 2010; 15: 659–663.

## APPENDIX

### Details of the Expert Meeting and participants

*Venue:* The International Union Against Tuberculosis and Lung Disease, 68 Boulevard Saint Michel, Paris, France

*Dates:* Friday 6 and Saturday 7 November 2009

*Co-Chairs:* Professor Anthony D Harries (The Union)  
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### Apologies

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## R É S U M É

La croissance régulière de l'épidémie de diabète sucré (DM) représente une menace pour la lutte mondiale contre la tuberculose (TB). Des études antérieures ont identifié une importante association entre DM et TB. Toutefois, ces études comportent des limitations : peu d'entre elles ont été menées dans les pays à faibles revenus et aucune en Afrique, ce qui crée des incertitudes au sujet de l'importance de l'association DM-TB dans ces contextes, et de nombreuses questions critiques restent sans réponse. A la suite de ces questions et de ces incertitudes, l'Union Internationale Contre la Tuberculose et les Maladies Respiratoires (L'Union), la Fondation Mondiale du Dia-

bète et le département Stop TB de l'Organisation Mondiale de la Santé ont entrepris une série de consultations dès janvier 2009. Une revue systématique et des méta-analyses ont été entreprises par le Département d'Epidémiologie de la Harvard School of Public Health entre mai et août 2009, et une réunion de consultation impliquant les experts qui avaient revu le rapport a eu lieu au Secrétariat de l'Union à Paris les 6 et 7 novembre 2009. Cet article constitue un rapport résumé des observations, des déficiences en matière de recherche et des zones prioritaires de recherche ainsi que le résumé des recommandations issues de cette réunion.

## R E S U M E N

La intensificación continua de la epidemia de diabetes representa un obstáculo al control mundial de la tuberculosis (TB). En estudios previos se ha destacado la fuerte asociación que existe entre diabetes y TB. Sin embargo, estos estudios comportan limitaciones: muy pocos se llevaron a cabo en países de bajos ingresos y ninguno en África, por lo cual aparece la pregunta sobre la fuerza de la asociación en estos ámbitos; muchos aspectos críticos quedan por resolver. Como consecuencia de estos interrogantes y dudas, la Unión Internacional contra la Tuberculosis y las Enfermedades Respiratorias (La Unión), la Fundación Mundial contra la Diabetes y el

Departamento Alto a la Tuberculosis de la Organización Mundial de la Salud emprendieron en enero del 2009 una serie de consultas de expertos. El departamento de epidemiología de la Escuela de Salud Pública de Harvard inició un análisis sistemático y un metanálisis entre mayo y agosto del 2009, y el 6 y 7 de noviembre del mismo año se llevó a cabo una reunión de expertos donde se analizó el informe en la sede de La Unión en París. En el presente artículo se presenta una síntesis de los resultados, los vacíos de las publicaciones científicas, las prioridades en materia de investigación y las recomendaciones propuestas durante esta reunión.