

Addressing the double burden of diabetes and tuberculosis: is programme integration at the primary care level possible?

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Diabetes and Infection

It is known for long time that diabetes mellitus is one of the most frequent metabolic disease predisposing for infectious diseases.

Allergies and Diabetes as Risk Factors for Dengue Hemorrhagic Fever: Results of a Case Control Study

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Abstract

Background: The physiopathology of dengue hemorrhagic fever (DHF), a severe form of Dengue Fever, is poorly understood. We are unable to identify patients likely to progress to DHF for closer monitoring and early intervention during epidemics, so most cases are sent home. This study explored whether patients with selected co-morbidities are at higher risk of developing DHF.

Methods: A matched case-control study was conducted in a dengue sero-positive population in two Brazilian cities. For each case of DHF, 7 sero-positive controls were selected. Cases and controls were interviewed and information collected on demographic and socio-economic status, reported co-morbidities (diabetes, hypertension, allergy) and use of medication. Conditional logistic regression was used to calculate the strength of the association between the co-morbidities and occurrence of DHF.

Results: 170 cases of DHF and 1,175 controls were included. Significant associations were found between DHF and white ethnicity (OR=4.70; 2.17–10.20), high income (OR=6.84; 4.09–11.43), high education (OR=4.67; 2.35–9.27), reported diabetes (OR=2.75; 1.12–6.73) and reported allergy treated with steroids (OR=2.94; 1.01–8.54). Black individuals who reported being treated for hypertension had 13 times higher risk of DHF than black individuals reporting no hypertension.

Conclusions: This is the first study to find an association between DHF and diabetes, allergy and hypertension. Given the high case fatality rate of DHF (1–5%), we believe that the evidence produced in this study, when confirmed in other studies, suggests that screening criteria might be used to identify adult patients at a greater risk of developing DHF with a recommendation that they remain under observation and monitoring in hospital.

Table 3. Crude and adjusted* Odds Ratio of the association of Dengue Hemorrhagic Fever with chronic co-morbidities.

<i>Exposure</i>	<i>Cases</i>	<i>Controls</i>	<i>Matched OR crude**</i>	<i>95% CI</i>	<i>OR Adjust</i>	<i>95% CI</i>
Hypertension						
No	150	1,027	1		1	
Yes	20	148	0.90	0.50–1.62	0.93	0.51–1.70
Diabetes						
No	161	1,144	1		1	
Yes	9	31	2.46	1.03–5.87	2.75	1.12–6.73
Allergy						
No	112	896	1		1	
Yes	58	279	1.59	1.11–2.28	1.29	0.87–1.89
Asthma						
No	160	1,113	1		1	
Yes	10	62	0.93	0.46–1.89	0.87	0.41–1.84

*Adjusted Odds Ratio were obtained from a multivariate conditional logistic regression with hypertension, diabetes, allergy, and asthma being adjusted by selected self-reported skin color, income and education.

**Matched OR and 95 CI calculated using McNemar's test.

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Figueiredo MA et al. [Allergies and diabetes as risk factors for dengue hemorrhagic fever: results of a case control study](#). PLoS Negl Trop Dis. 2010;4(6):e699.

Diabetes and Tuberculosis

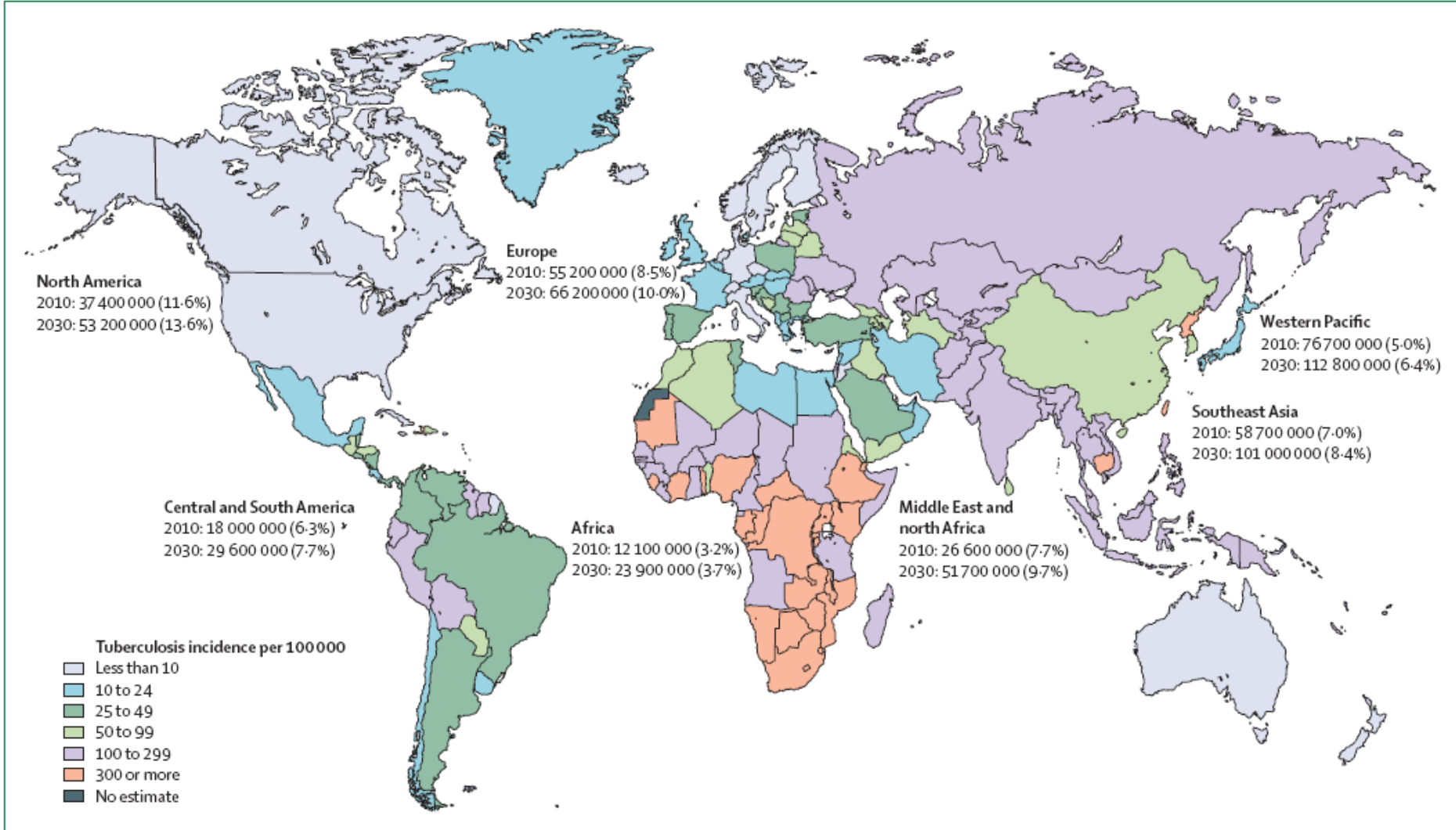


Figure: Projected prevalent diabetes cases and current worldwide tuberculosis incidence

Estimated number and percent of individuals with diabetes mellitus in 2010 compared with 2030 projections are shown. Tuberculosis incidence per 100 000 population data for 2007 are shown. Data from International Diabetes Foundation and WHO.^{10,11}

The epidemic of non-communicable diseases, especially diabetes mellitus, is steadily growing. Diabetes mellitus in particular threatens TB control efforts and the achievement of the 2015 TB targets

There are a reasonable amount of evidences
that Diabetes increases the risk for TB
occurrence

Diabetes Mellitus Increases the Risk of Active Tuberculosis: A Systematic Review of 13 Observational Studies

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Abbreviations: CI, confidence interval; DM, diabetes mellitus; RR, relative risk; TB, tuberculosis

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ABSTRACT

Background

Several studies have suggested that diabetes mellitus (DM) increases the risk of active tuberculosis (TB). The rising prevalence of DM in TB-endemic areas may adversely affect TB control. We conducted a systematic review and a meta-analysis of observational studies assessing the association of DM and TB in order to summarize the existing evidence and to assess methodological quality of the studies.

Methods and Findings

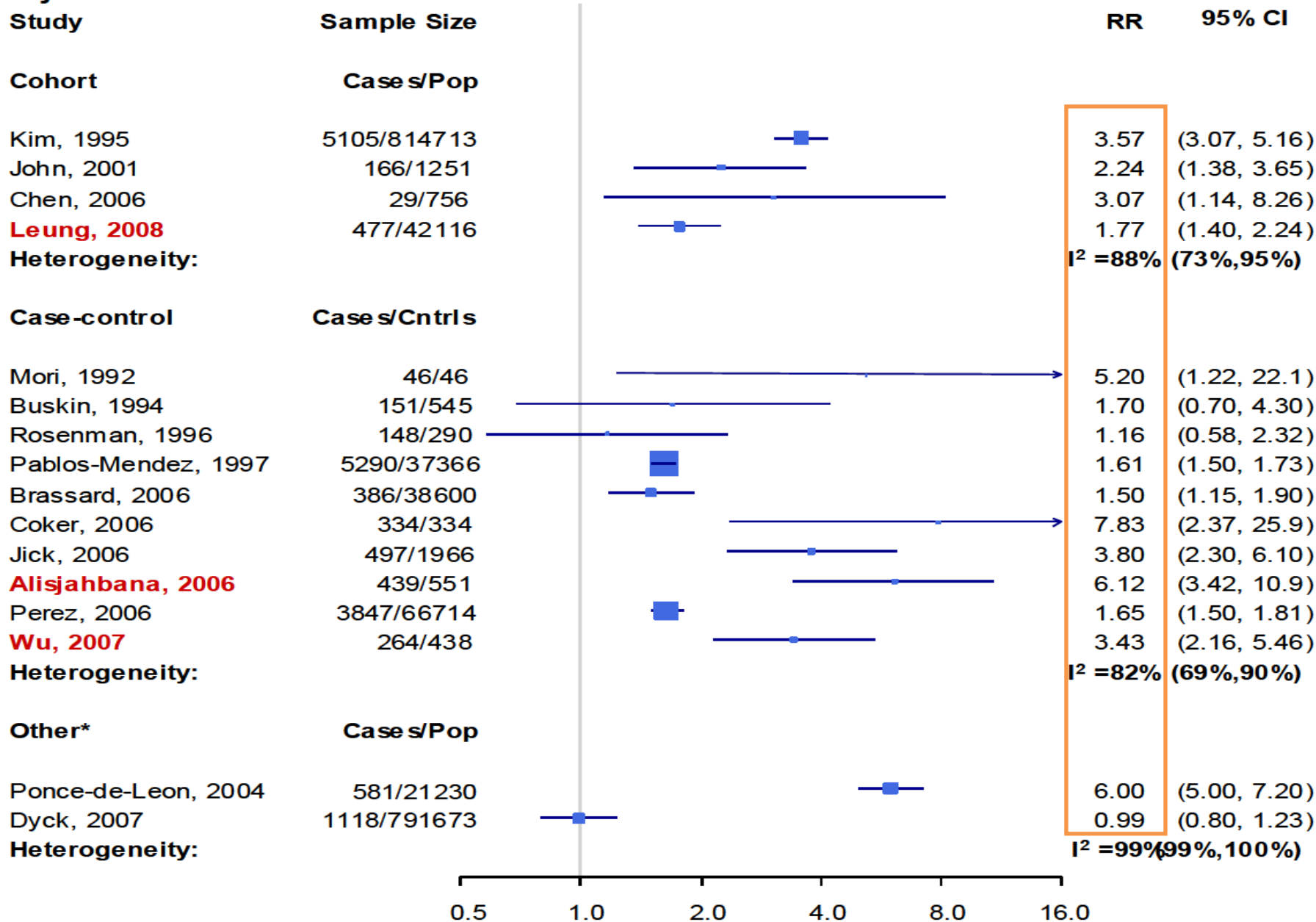
We searched the PubMed and EMBASE databases to identify observational studies that had reported an age-adjusted quantitative estimate of the association between DM and active TB disease. The search yielded 13 observational studies ($n = 1,786,212$ participants) with 17,698 TB cases. Random effects meta-analysis of cohort studies showed that DM was associated with an increased risk of TB (relative risk = 3.11, 95% CI 2.27–4.26). Case-control studies were heterogeneous and odds ratios ranged from 1.16 to 7.83. Subgroup analyses showed that effect estimates were higher in non-North American studies.

Conclusion

DM was associated with an increased risk of TB regardless of study design and population. People with DM may be important targets for interventions such as active case finding and treatment of latent TB and efforts to diagnose, detect, and treat DM may have a beneficial impact on TB control.

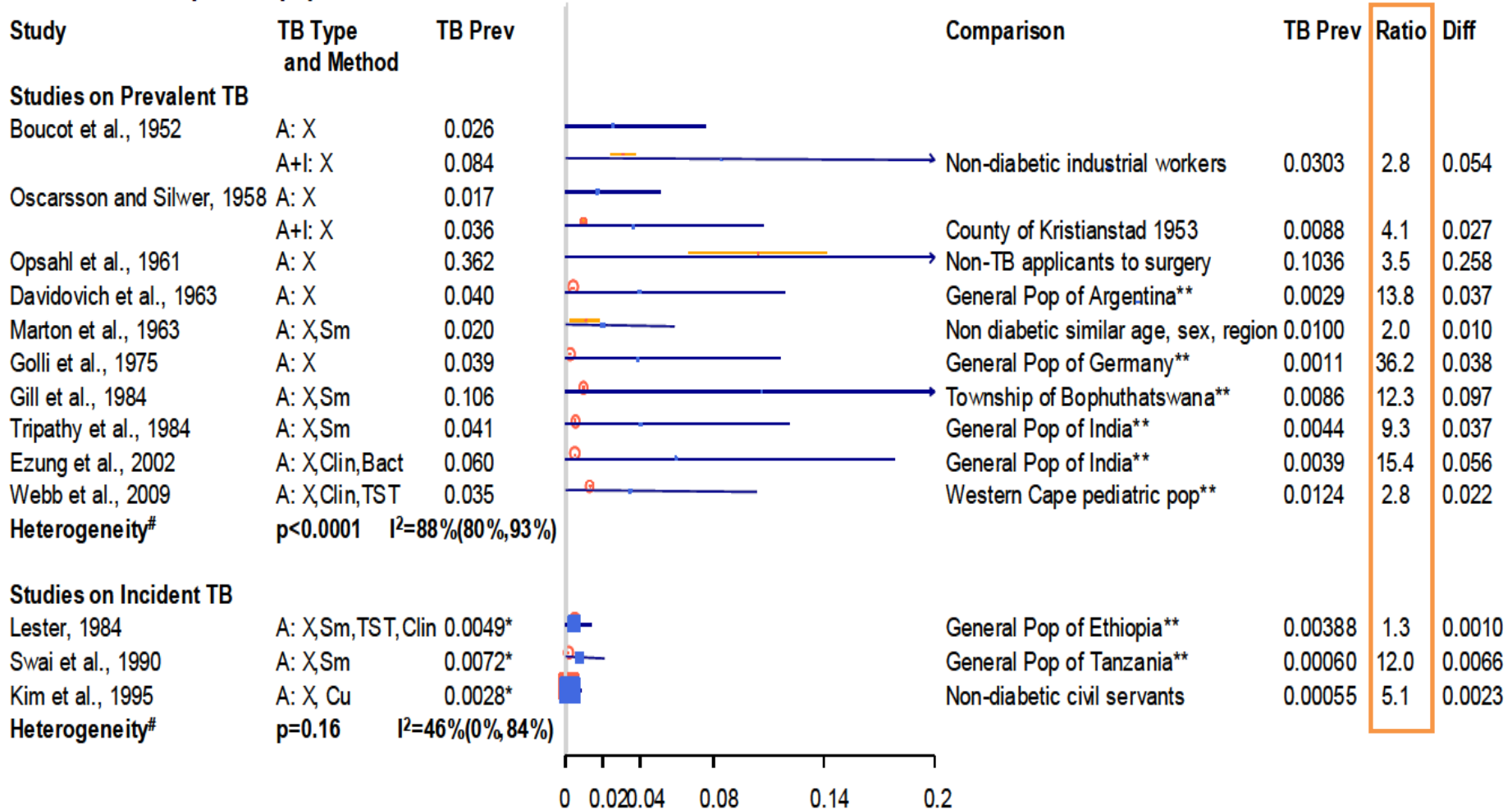
The Editors' Summary of this article follows the references.

Figure I.4 The association of diabetes and active TB in 16 observation studies with age-adjustment



Jeon et al. 2009. Systematic review to provide the evidence to guide policies and research needs on the interaction of diabetes mellitus and tuberculosis

Figure II.2 Prevalence of TB found by screening among diabetics in 13 observational studies and corresponding TB prevalence values from comparison populations



TB Prevalence of screened DM population in blue, TB Prevalence of comparison population in orange. Estimates of TB prevalence for comparison population obtained from external source is marked with orange circles. Arrow indicates the truncation of confidence intervals due to limited graph size.

Heterogeneity assessed among only active TB prevalences.

* Prevalence estimated by dividing the proportion provided in the study by the number of years of follow-up

** Prevalence and Incidence estimates for the region from external reference

Prev=Prevalent TB, Inc=Incident TB, A=Active, I=Inactive, X=X-ray, Sm=Smear, Cu=Culture, TST=Tuberculin Skin Testing, Clin=clinical symptoms, Bact=Bacteriology, Ratio = Prevalence or Incidence Ratio, Diff = Prevalence or Incidence Difference

Tuberculosis and diabetes mellitus: convergence of two epidemics

Kelly E Dooley, Richard E Chaisson

The link between diabetes mellitus and tuberculosis has been recognised for centuries. In recent decades, tuberculosis incidence has declined in high-income countries, but incidence remains high in countries that have high rates of infection with HIV, high prevalence of malnutrition and crowded living conditions, or poor tuberculosis control infrastructure. At the same time, diabetes mellitus prevalence is soaring globally, fuelled by obesity. There is growing evidence that diabetes mellitus is an important risk factor for tuberculosis and might affect disease presentation and treatment response. Furthermore, tuberculosis might induce glucose intolerance and worsen glycaemic control in people with diabetes. We review the epidemiology of the tuberculosis and diabetes epidemics, and provide a synopsis of the evidence for the role of diabetes mellitus in susceptibility to, clinical presentation of, and response to treatment for tuberculosis. In addition, we review potential mechanisms by which diabetes mellitus can cause tuberculosis, the effects of tuberculosis on diabetic control, and pharmacokinetic issues related to the co-management of diabetes and tuberculosis.

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Diabetes and tuberculosis: the impact of the diabetes epidemic on tuberculosis incidence

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Abstract

Background: Tuberculosis (TB) remains a major cause of mortality in developing countries, and in these countries diabetes prevalence is increasing rapidly. Diabetes increases the risk of TB. Our aim was to assess the potential impact of diabetes as a risk factor for incident pulmonary tuberculosis, using India as an example.

Methods: We constructed an epidemiological model using data on tuberculosis incidence, diabetes prevalence, population structure, and relative risk of tuberculosis associated with diabetes. We evaluated the contribution made by diabetes to both tuberculosis incidence, and to the difference between tuberculosis incidence in urban and rural areas.

Results: In India in 2000 there were an estimated 20.7 million adults with diabetes, and 900,000 incident adult cases of pulmonary tuberculosis. Our calculations suggest that diabetes accounts for 14.8% (uncertainty range 7.1% to 23.8%) of pulmonary tuberculosis and 20.2% (8.3% to 41.9%) of smear-positive (i.e. infectious) tuberculosis.

We estimate that the increased diabetes prevalence in urban areas is associated with a 15.2% greater smear-positive tuberculosis incidence in urban than rural areas – over a fifth of the estimated total difference.

Conclusion: Diabetes makes a substantial contribution to the burden of incident tuberculosis in India, and the association is particularly strong for the infectious form of tuberculosis. The current diabetes epidemic may lead to a resurgence of tuberculosis in endemic regions, especially in urban areas. This potentially carries a risk of global spread with serious implications for tuberculosis control and the achievement of the United Nations Millennium Development Goals.

Table 2: Fraction of tuberculosis attributable to diabetes in India in 2000 in the adult population aged 25 years and over

	Total pulmonary tuberculosis			Smear-positive tuberculosis		
	Attributable Fraction (Population) % (upper and lower bounds)	Excess cases	Percentage of excess cases	Attributable Fraction (Population) % (upper and lower bounds)	Excess cases	Percentage of excess cases
Overall (crude)	15.1 (2.8 – 38.9)	141,548	-	20.8 (7.7 – 41.0)	119,622	-
Overall (age-adjusted)	14.8 (7.1 – 23.8)	138,767	100.0	20.2 (8.3 – 41.9)	116,389	100.0
Women age in years:						
25–29	12.5 (0.4 – 51.4)	7,455	5.4	10.6 (1.3 – 35.0)	3,683	3.2
30–39	23.9 (17.0 – 32.2)	21,926	15.8	16.5 (2.2 – 47.3)	8,993	7.7
40–49	14.9 (10.9 – 19.7)	7,316	5.3	35.4 (23.2 – 49.2)	11,016	9.5
50–59	6.2 (4.1 – 8.8)	1,755	1.3	17.6 (9.5 – 28.3)	3,112	2.7
60+	5.0 (0.5 – 11.6)	982	0.7	17.0 (2.6 – 41.7)	2,128	1.8
Men age in years:						
25–29	12.5 (0.4 – 51.4)	13,544	9.8	10.6 (1.3 – 35.0)	6,691	5.7
30–39	23.9 (17.0 – 32.2)	49,034	35.3	16.5 (2.2 – 47.3)	20,261	17.4
40–49	14.9 (10.9 – 19.7)	24,809	17.9	35.4 (23.2 – 49.2)	37,511	32.2
50–59	6.2 (4.1 – 8.8)	7,398	5.3	17.6 (9.5 – 28.3)	13,091	11.2
60+	5.0 (0.5 – 11.6)	4,548	3.3	17.0 (2.6 – 41.7)	9,903	8.5

Table 3: Proportion of tuberculosis attributable to diabetes in the subpopulation of people with diabetes

	Attributable Fraction (Exposed)	
	Total pulmonary tuberculosis %(upper and lower bounds)	Smear-positive tuberculosis % (upper and lower bounds)
Overall	80.5 (39.9 – 93.7)	85.9 (65.9 – 94.2)
Age in years		
25–29	87.2 (15.3 – 98.1)	84.9* (39.4 – 96.2)
30–39	90.0 (85.4 – 93.1)	84.9* (39.4 – 96.2)
40–49	78.8 (72.1 – 83.9)	92.1 (86.6 – 95.4)
50–59	56.5 (45.4 – 65.5)	80.7 (67.4 – 88.5)
60+	43.2 (6.5 – 65.6)	74.7 (27.5 – 91.2)

*As no relative risk (RR) was available for smear-positive tuberculosis incidence for the age band 25–29, the RR for the age band 30–39 was used.

Tuberculosis and Diabetes in Southern Mexico

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OBJECTIVE — To determine the impact of diabetes on the rates of tuberculosis in a region where both diseases are prevalent.

RESEARCH DESIGN AND METHODS — Data from a population-based cohort of patients with pulmonary tuberculosis undergoing clinical and mycobacteriologic evaluation (isolation, identification, drug-susceptibility testing, and IS6110-based genotyping and spoligotyping) were linked to the 2000 National Health Survey (ENSA2000), a national probabilistic, polystage, stratified, cluster household survey of the civilian, noninstitutionalized population of Mexico.

RESULTS — From March 1995 to March 2003, 581 patients with *Mycobacterium tuberculosis* culture and fingerprint were diagnosed, 29.6% of whom had been diagnosed previously with diabetes by a physician. According to the ENSA2000, the estimated prevalence of diabetes in the study area was 5.3% (95% CI 4.1–6.5). The estimated rates of tuberculosis for the study area were greater for patients with diabetes than for nondiabetic individuals (209.5 vs. 30.7 per 100,000 person-years, $P < 0.0001$).

CONCLUSIONS — In this setting, the rate of tuberculosis was increased 6.8-fold (95% CI 5.7–8.2, $P < 0.0001$) in patients with diabetes due to increases in both reactivated and recently transmitted infection. Comorbidity with diabetes may increase tuberculosis rates as much as coinfection with human immunodeficiency virus (HIV), with important implications for the allocation of health care resources.

association between tuberculosis and diabetes but did not determine whether this is due to an increase in recently transmitted or reactivated infection of tuberculosis. We now report the results of a population-based molecular epidemiologic study of tuberculosis among persons with and without diabetes in a developing country. We linked the results of this population-based study with those obtained from the 2000 National Health Survey (ENSA2000) to estimate the relative risk of on going transmission and reactivation of tuberculosis among diabetic and nondiabetic population resident of the study area. Because this community typifies communities that are undergoing health care transition, these results have general applicability.

RESEARCH DESIGN AND METHODS

ENSA2000

ENSA2000 was a probabilistic, multi-stage, stratified, cluster household survey conducted by the Mexican Secretariat of Health from November 1999 to June 2000. Research design and methods have been described previously (2). As part of this survey, 1,334 individuals were randomly selected from the population of Mexico

Table 2—Incidence rates (per 100,000 person-years) among diabetic and nondiabetic populations (clustering within 1 year of diagnosis)

Age-group (years)	TB patients with diabetes (n)	Incidence rate of TB among diabetic population	TB patients without diabetes (n)	Incidence rate of TB among nondiabetic population	Ratio of rates (95% CI)	P	Population attributable risk (%)
Clustered cases							
20–44	18	127.3	62	6.9	18.6 (10.3–31.8)	<0.0001	21
45–64	15	39.3	25	8.0	4.9 (2.4–9.6)	<0.0001	29
65–89	9	30.2	12	10.1	3.0 (1.1–7.8)	0.01	28
Total	42	51.2	99	7.4	6.9 (4.7–9.9)	<0.0001	25
Reactivated cases							
20–44	25	176.8	192	21.2	8.3 (5.3–12.7)	<0.0001	10
45–64	78	204.1	75	24.1	8.5 (6.0–11.8)	<0.0001	44
65–89	27	90.7	43	36.1	2.5 (1.5–4.2)	0.0004	23
Total	130	158.3	310	23.2	6.8 (5.5–8.4)	<0.0001	25
Total cases							
20–44	43	304.2	254	28.1	10.8 (7.6–14.9)	<0.0001	13
45–64	93	243.4	100	32.2	7.6 (5.6–10.1)	<0.0001	41
65–89	36	121.0	55	46.2	2.6 (1.7–4.0)	<0.0001	24
Total	172	209.5	409	30.7	6.8 (5.7–8.2)	<0.0001	25

TB, tuberculosis.

W Tuberculosis 1

Tuberculosis control and elimination 2010–50: cure, care, and social development

Knut Lönnroth, Kenneth G Castro, Jeremiah Muhwa Chakaya, Lakhbir Singh Chauhan, Katherine Floyd, Philippe Glaziou, Mario C Raviglione

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This is the first in a [Series](#) of eight papers about tuberculosis

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(K Lönnroth PhD, K Floyd PhD, P Glaziou MD,

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Rapid expansion of the standardised approach to tuberculosis diagnosis and treatment that is recommended by WHO allowed more than 36 million people to be cured between 1995 and 2008, averting up to 6 million deaths. Yet tuberculosis remains a severe global public health threat. There are more than 9 million new cases every year worldwide, and the incidence rate is falling at less than 1% per year. Although the overall target related to the Millennium Development Goals of halting and beginning to reverse the epidemic might have already been reached in 2004, the more important long-term elimination target set for 2050 will not be met with present strategies and instruments. Several key challenges persist. Many vulnerable people do not have access to affordable services of sufficient quality. Technologies for diagnosis, treatment, and prevention are old and inadequate. Multidrug-resistant tuberculosis is a serious threat in many settings. HIV/AIDS continues to fuel the tuberculosis epidemic, especially in Africa. Furthermore, other risk factors and underlying social determinants help to maintain tuberculosis in the community. Acceleration of the decline towards elimination of this disease will need invigorated actions in four broad areas: continued scale-up of early diagnosis and proper treatment for all forms of tuberculosis in line with the Stop TB Strategy; development and enforcement of bold health-system policies; establishment of links with the broader development agenda; and promotion and intensification of research towards innovations.

	HIV*			Undernutrition†		Diabetes‡			Alcohol misuse§			Smoking¶			Indoor air pollution	
	P >15 y (%)	PAF >15 y (%)	PAF total pop (%)	P total pop (%)	PAF total pop (%)	P >15 y (%)	PAF >15 y (%)	PAF total pop (%)	P >15 y (%)	PAF >15 y (%)	PAF total pop (%)	P >15 y (%)	PAF >15 y (%)	PAF total pop (%)	P total pop (%)	PAF total pop (%)
Afghanistan	0.1%	2.5%	1.5%	23.0%	33.6%	6.6%	12.2%	6.8%	0.1%	0.2%	0.1%	21.0%	17.4%	10.0%	95.0%	27.5%
Bangladesh	0.1%	2.5%	0.2%	27.0%	37.3%	3.5%	6.8%	4.6%	0.9%	1.7%	1.1%	26.0%	20.6%	14.5%	88.0%	26.0%
Brazil	0.6%	13.4%	8.9%	6.0%	11.7%	6.0%	11.2%	8.3%	11.1%	17.4%	13.2%	16.0%	13.8%	10.3%	12.0%	4.6%
Burma	0.7%	15.2%	11.2%	19.0%	29.5%	2.8%	5.6%	4.1%	1.2%	2.2%	1.6%	29.0%	22.5%	17.5%	95.0%	27.5%
Cambodia	0.8%	17.0%	11.8%	26.0%	36.4%	3.5%	6.8%	4.4%	4.1%	7.2%	4.7%	28.0%	21.9%	15.0%	95.0%	27.5%
China	0.1%	2.5%	1.3%	9.0%	16.5%	4.5%	8.6%	6.9%	8.3%	13.6%	11.1%	34.5%	25.7%	21.4%	80.0%	24.2%
DR Congo	1.4%	20.9%	12.3%	76.0%	62.6%	2.6%	5.2%	2.8%	5.3%	9.1%	5.1%	8.0%	7.4%	4.1%	95.0%	27.5%
Ethiopia	2.1%	29.2%	18.8%	46.0%	50.3%	2.0%	4.0%	2.3%	5.3%	9.1%	5.3%	5.0%	4.8%	2.7%	95.0%	27.5%
India	0.3%	7.2%	5.0%	21.0%	31.6%	7.1%	13.0%	9.1%	5.8%	9.9%	6.9%	19.0%	16.0%	11.3%	74.0%	22.8%
Indonesia	0.2%	4.9%	2.9%	17.0%	27.2%	4.6%	8.8%	6.5%	1.2%	2.2%	1.6%	34.0%	25.4%	19.7%	72.0%	22.4%
Kenya	8.6%	62.8%	47.7%	32.0%	41.3%	2.8%	5.6%	3.2%	5.3%	9.1%	5.4%	14.0%	12.3%	7.4%	81.0%	24.5%
Mozambique	12.5%	71.0%	57.9%	38.0%	45.5%	3.3%	6.5%	3.7%	5.3%	9.1%	5.3%	12.0%	10.7%	6.3%	80.0%	24.2%
Nigeria	3.9%	43.3%	25.6%	9.0%	16.5%	3.5%	6.8%	4.0%	26.1%	33.2%	21.7%	7.0%	6.5%	3.8%	67.0%	21.1%
Pakistan	0.1%	2.5%	1.5%	23.0%	33.6%	7.6%	13.8%	9.3%	0.1%	0.2%	0.2%	21.0%	17.4%	11.8%	72.0%	22.4%
Philippines	0.1%	2.5%	0.2%	16.0%	26.0%	6.7%	12.3%	8.3%	4.1%	7.2%	4.7%	33.0%	24.8%	17.4%	47.0%	15.8%
Russia	1.1%	17.7%	11.4%	3.0%	6.2%	9.0%	15.9%	13.8%	33.3%	38.8%	35.0%	49.0%	32.9%	29.4%	7.0%	2.7%
South Africa	18.1%	78.0%	69.7%	2.5%	5.2%	4.5%	8.6%	6.0%	15.2%	22.4%	16.4%	19.0%	16.0%	11.4%	18.0%	6.7%
Thailand	1.4%	21.5%	15.8%	17.0%	27.2%	7.7%	13.9%	11.3%	18.6%	26.1%	21.8%	23.0%	18.7%	15.4%	72.0%	22.4%
Uganda	5.4%	51.4%	37.4%	15.0%	24.8%	1.7%	3.4%	1.8%	5.3%	9.1%	4.9%	12.0%	10.7%	5.8%	95.0%	27.5%
Tanzania	6.2%	54.9%	40.4%	35.0%	43.5%	2.6%	5.2%	3.0%	5.3%	9.1%	5.3%	14.0%	12.3%	7.3%	95.0%	27.5%
Vietnam	0.5%	11.4%	7.9%	14.0%	23.5%	2.9%	5.7%	4.1%	4.1%	7.2%	5.2%	23.0%	18.7%	14.0%	70.0%	21.9%
Zimbabwe	15.3%	75.0%	65.6%	40.0%	46.8%	4.1%	7.0%	5.0%	5.3%	9.1%	5.8%	19.0%	16.0%	10.4%	73.0%	22.6%
Weighted average	0.8%	16.0%	11.0%	16.7%	26.9%	5.4%	10.2%	7.5%	8.1%	13.4%	9.8%	26.5%	20.9%	15.8%	71.2%	22.2%

Point estimate of relative risk was used. When prevalence was available only for adults, the prevalence in adults was adjusted for proportion of population younger than 15 years to estimate the total population PAF. PAF estimates presented here do not account for interaction between risk factors, nor for prevention of secondary cases. Uncertainty limits for PAF (not shown) are large, since they are determined by the confidence limits for the relative risk estimate, as well as the confidence limits for prevalence estimates. P=prevalence. y=years. PAF=population attributable fraction, which is equal to $[\text{prevalence} \times (\text{relative risk} - 1)] / [\text{prevalence} \times (\text{relative risk} - 1) + 1]$. pop=population. DR=Democratic Republic. *HIV: relative risk=26.7, 95% CI 20–35. Point estimate is for low HIV prevalence settings (0.1–1%), lower bound is for high HIV prevalence setting (>1%), and upper bound is for very low HIV prevalence settings (<0.1%). Relative risk estimates are from WHO, 2009.⁴² Different estimates have been applied according to HIV prevalence in respective country. Prevalence data are from UNAIDS, 2008.⁷⁸ †Undernutrition: relative risk=3.2, 95% CI 3.1–3.3 for body-mass index 16 kg/m² versus 25 kg/m², based on average reduction in tuberculosis incidence of 13.8% (95% CI 13.4–14.2) per unit increase in body-mass index, as reported in a meta-analysis by Lönnroth and colleagues.⁸⁸ Prevalence data are from prevalence of undernourishment as reported in: The State of Food Insecurity in the World 2008.⁷⁷ ‡Diabetes: relative risk=3.1, 95% CI 2.3–4.3. Point estimate and 95% CI are from pooled estimate in meta-analysis by Jeon and Murray (2008).⁷² Prevalence data are from IDF, 2010.⁷⁴ §Alcohol misuse: relative risk=2.9, 95% CI 1.9–4.6. Point estimate and 95% CI are from pooled estimate in meta-analysis by Lönnroth and colleagues (2008).⁷⁴ ¶Smoking: relative risk=2.0, 95% CI 1.6–2.5. Point estimate and 95% CI are from pooled estimate comparing risk of pulmonary tuberculosis in current versus never smokers, in meta-analysis by Lin and colleagues (2007).⁷⁹ Prevalence data are from WHO, 2008.⁸⁰ ||Indoor air pollution: relative risk=1.4, 95% CI 0.6–3.4. Point estimate and 95% CI from pooled estimate comparing risk of pulmonary tuberculosis in studies controlling for smoking, in meta-analysis by Lin and colleagues (2007).⁷⁹ Prevalence data are from WHO, 2006.⁸¹

Table 3: Prevalence and population attributable fractions of selected tuberculosis risk factors, in 22 high-burden countries

To build up and implement joint control strategies several questions must be answered

- How to address the double burden of diabetes and tuberculosis?
- How to integrate TB and diabetes control activities?
- How to interchange experiences from control programs of both diseases?
- How to screening TB patients to looking for and treating diabetes?
- How to screening diabetes patients looking for and treating TB?

What research gaps exist in this complex relationship between TB and diabetes?

It is clear the need for research to guide policy and practice in this area

Viewpoint

Defining the research agenda to reduce the joint burden of disease from Diabetes mellitus and Tuberculosis

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Summary The steadily growing epidemic of diabetes mellitus poses a threat for global tuberculosis (TB) control. Previous studies have identified an important association between diabetes mellitus and TB. However, these studies have limitations: very few were carried out in low-income countries, with none in Africa, raising uncertainty about the strength of the diabetes mellitus–TB association in these settings, and many critical questions remain unanswered. An expert meeting was held in November 2009 to discuss where there was sufficient evidence to make firm recommendations about joint management of both diseases, to address research gaps and to develop a research agenda. Ten key research questions were identified, of which 4 were selected as high priority: (i) whether, when and how to screen for TB in patients with diabetes mellitus and *vice versa*; (ii) the impact of diabetes mellitus and non-diabetes mellitus hyperglycaemia on TB treatment outcomes and deaths, and the development of strategies to improve outcomes; (iii) implementation and evaluation of the tuberculosis ‘DOTS’ model for diabetes mellitus management; and (iv) the development and evaluation of better point-of-care diagnostic and monitoring tests, including measurements of blood glucose and glycated haemoglobin A_{1c} (HbA_{1c}) for patients with diabetes mellitus. Implementation of this research agenda will benefit the control of both diseases.

Many critical questions regarding the association between diabetes mellitus and TB remain unanswered because of either poorly conducted studies or no studies at all.

The threat of diabetes mellitus and TB requires a research agenda focussed on providing tools for national and international agencies charged with the control of both these diseases.

Table 1 Key research questions and methodology for improving the prevention, management and care of diabetes mellitus and tuberculosis (TB, tuberculosis; HIV, human immunodeficiency virus)

Key research questions	Priority	Study design and methodology
Screening for Disease: Screening patients with diabetes mellitus for active TB Screening patients with TB for diabetes mellitus	High	Prospective observational cohort studies of patients with diabetes mellitus routinely attending diabetes clinics and screened for TB, and patients with TB starting anti-TB treatment and screened for diabetes mellitus
TB treatment outcomes in patients with diabetes mellitus and with non-diabetes hyperglycaemia, including a more detailed assessment of death during anti-TB treatment, and the development and testing of strategies to improve outcomes for both diseases	High	Prospective observational cohort studies using standardized TB regimens and standardized treatment outcomes and focusing on defined primary outcomes Prospective observational cohort studies to determine when death occurs in relation to start of TB treatment, the aetiology and whether case fatality is reduced by better control of diabetes mellitus or hyperglycaemia or modification to TB drug regimens, duration of therapy and TB drug doses
Implementing and evaluating the 'DOTS' model for standardized case management of diabetes mellitus	High	Operational research that includes quarterly cohort reporting of new cases, treatment outcomes of cumulative cases including frequency of co-morbidities such as TB, and survival analysis
Development and evaluation of better point-of-care diagnostic and monitoring tests for diabetes mellitus	High	Developmental work to produce a reliable low cost finger stick test for measuring blood glucose and glycated haemoglobin A _{1c} (HbA _{1c}) in rural areas, which then needs to be tested for efficacy and feasibility in the field
Rates of hospitalization and additional medical costs associated with diagnosis and management of dual disease	Medium	Cross-sectional and case-control studies
Use of the community to improve diagnosis, management and care of patients with diabetes and TB	Medium	Operational research
Household contact tracing of adult patients with smear-positive Pulmonary TB	Medium	Prospective observational studies to determine the yield of screening household contacts of index patients with pulmonary TB for TB infection, active TB, HIV and diabetes mellitus and assess whether diabetes mellitus influences the risk of TB infection
Radiographic findings in diabetes mellitus patients with tuberculosis	Medium	Systematic review of the literature, and prospective cross-sectional studies if further evidence is required, to determine the common radiographic patterns that are associated with diabetes mellitus
Modelling the effect of the diabetes mellitus epidemic on the TB epidemic	Medium	Mathematical modelling studies, ideally informed by higher quality studies of the association between diabetes mellitus and TB, particularly from low-income settings
TB preventive therapy in patients with diabetes mellitus	Low	Randomized controlled trial assessing efficacy and safety of isoniazid preventive therapy in reducing risk of active TB in patients with diabetes mellitus

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<p>Implementing and evaluating the ‘DOTS’ model for standardized case management of diabetes mellitus</p>	High	Operational research that includes quarterly cohort reporting of new cases, treatment outcomes of cumulative cases including frequency of co-morbidities such as TB, and survival analysis
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Screening

Key questions include:

- (i) what type of screening algorithm will be most effective, i.e. should all patients with diabetes mellitus be investigated by standard TB laboratory investigations or should these investigations be targeted to those with symptoms suggesting active TB or with poor control of diabetes mellitus as defined by symptoms or measurements of blood glucose or glycated haemoglobin A1c (HbA1c);
- (ii) how often should screening be conducted;
- (iii) what are the most appropriate screening tools (sputum smear examination and chest radiography for pulmonary disease, ultrasound for extra-pulmonary abdominal lymphadenopathy) and how do these compare to the gold standard of sputum culture for *Mycobacterium tuberculosis*.

TB treatment outcomes

Primary treatment outcomes should include

- (i) liver function test;
- (ii) pharmacokinetic levels of rifampicin and oral diabetes medications;
- (iii) TB treatment outcomes;
- (iv) recurrence of TB 1 year after completion of TB treatment as determined by sputum culture;
- (v) culture and drug sensitivity testing, at the start of treatment and at the time of failure or TB recurrence to assess linkages and associations with drug-resistant TB.

The TB DOTS model for managing diabetes mellitus

The concept of using components of the Tuberculosis 'DOTS Model' for managing diabetes mellitus has already been proposed (Harries et al. 2008), and diabetes clinics in urban areas in high-burden countries need to pilot and evaluate this approach through operational research, and particularly to assess whether quarterly cohort reporting of incident cases, cumulative outcomes, complications and survival analysis can lead to better management and care, more rational drug forecasting and uninterrupted drug supplies (Harries et al. 2009).

Conclusion

- There is solid evidence that diabetes is an important factor contributing to increase the burden of TB;
- But it is necessary to intensify the search for evidences, tools and strategies to integrate the control of both these diseases.

THANKS!