WORLD DIABETES FOUNDATION

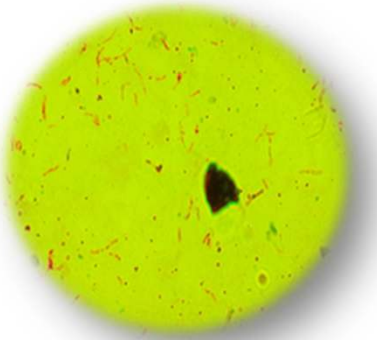
DM and TB Double Burden

Anil Kapur

Association Between TB and DM

WORLD DIABETES FOUNDATION

Tubercle Bacilli



2.0 billion people carry these in their bodies

Tuberculosis

Life-time risk of active TB = 5-15%

Risk of active TB increased in…

- Silicosis
- Other causes of immune suppression (steroids)
- **HIV/AIDS**
- **Diabetes mellitus**
- **Malnutrition**
- **Smoke from domestic stoves and cigarettes**

The association between DM and TB was known to ancient Roman and Indian physicians.

In 1883, Bouchardat stated 'at autopsy every case of diabetes had tubercles in the lungs'.

"In the latter half of the 19th century the diabetic patient appeared doomed to die of pulmonary TB if he succeeded in escaping coma". Root HF, N Engl J Med, 1934;1:210.

Global Burden of DM and TB

WORLD DIABETES FOUNDATION

Diabetes Mellitus: 2011

[IDF Atlas 5th Edition 2011]

- 366 M People Affected
- 7 M New Cases
- 4.6 M Deaths

Tuberculosis: 2011

[WHO- Global TB Control 2012]

- 12.0 M Cases
- 8.7 M New Cases
- 1.4 M Deaths

Global Distribution of DM and TB

WORLD DIABETES FOUNDATION

Diabetes Mellitus: 2011

[IDF Atlas 5th Edition 2011]

- South East Asia 19.5%
- Western Pacific 36%
- Africa 5%
- 79% in LIC and MIC

Tuberculosis: 2011

[WHO- Global TB Control 2012]

- South East Asia 41.6%
- Western Pacific 20.8%
- Africa 20.8%
- 95% in LIC and MIC

Studies on DM and TB Association

WORLD DIABETES FOUNDATION

Jeon CY, Murray MB.

PLoS Medicine 2008; 5: e152

Systematic review of 13 observational studies with 1,786,212 participants and 17,698 TB cases

- DM associated with increased risk of TB
  - Cohort studies = RR 3.1, 95% CI (2.3 – 4.3)
  - Case control studies = OR 1.2 – 7.8
- Higher risks in young people and Communities with high background TB incidence

Stevenson et al

(Chronic Illn, 2007):

Medline search for studies after 1995

- Diabetes Mellitus increases risk of active tuberculosis
  - Increased RR or OR of 1.5 – 7.8
  - Risk higher in younger people

Stevenson et al

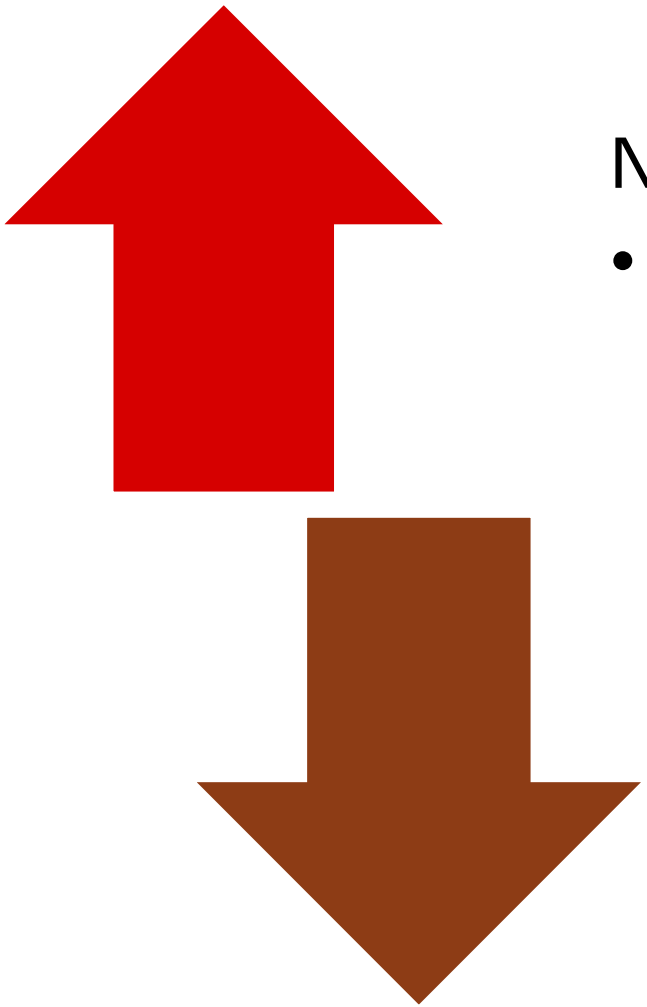
BMC Public Health 2007

Epidemiological model based on 21M adults with DM and 900,000 new TB cases in 2000 in India

- DM accounted for
  - 15% PTB (CI 7% - 23%)
  - 20% smear +ve PTB (CI 8% - 42%)
- Diabetes mellitus contributes substantially to new TB burden in India
- Urban areas more affected than rural areas

Association between TB and DM

WORLD DIABETES FOUNDATION



Not in doubt

- Biologically plausible

Limitations:-

- Most studies from industrialised countries; almost none from Africa
- Many are health facility-based and are secondary analyses of routine data sources
- Many critical unanswered questions

TB/Diabetes Framework development process

WORLD DIABETES FOUNDATION

WHO, The Union, and WDF met in Geneva early 2009 to identify scope of work, funds mobilized from WDF

→

Outsourcing of a systematic review to Harvard School of Public Health

→

Expert meeting in Paris, November 2009 (Researchers, TB and DM technical experts and agencies, practitioners, programme managers)

↓

Symposium in The Union conference, Cancun, December 2009

→

Series of papers published

→

Framework developed by writing committee, endorsed by the WHO TB Departments external Strategic and Technical Advisory Group, and the WHO Guideline Review Committee.

WHO THE STOP TB DEPARTMENT

List of Publications based on Systematic Review

WORLD DIABETES FOUNDATION

Ottmani SE, Murray MB, Jeon CY, Baker MA, Kapur A, Lönnroth K Harries AD. Consultation Meeting on Tuberculosis and Diabetes Mellitus: Meeting summary and recommendations. Int J Tuberc Lung Dis 2010; 14(12):1513–1517

Harries AD, Murray MB, Jeon CY, Ottmani SE, Lönnroth, K, 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

Jeon CY, Harries AD, Baker MA, Hart JE, Kapur A, Lönnroth K, Ottmani SE, Goonesekera S, Murray M. Bi-directional screening for tuberculosis and diabetes: a systematic review. TMIH 2010 doi:10.1111/j.1365-3156.2010.02632

Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, Ottmani SE, Goonesekera SD, Murray MB. Systematic Review: The impact of diabetes on tuberculosis treatment outcomes. BMC Medicine 2011 doi:10.1186/1741-7015-9-81

Harries AD, Lin Y, Satyanarayana S, Lönnroth K, Li L, Wilson N, et al. The looming epidemic of diabetes-associated tuberculosis: learning lessons from HIV-associated tuberculosis. Int J Tuberc Lung Dis 2011; doi.org/10.5588/ijtld.11.0503

Key finding in the Systematic Review

WORLD DIABETES FOUNDATION

Diabetes increases the risk of active TB about 3-fold, risk seems to increase with poor glucose control

Diabetes increases the risk of adverse TB treatment outcomes

- Delayed sputum conversion
- Higher relapse rate
- Higher death rate

No trials on the efficacy of alternative TB treatment regimens in people with diabetes

Key finding in the Systematic Review

WORLD DIABETES FOUNDATION

Number of TB cases needed to screen to find one diabetes case is generally low (<10)

- In some setting the DM prevalence among TB patients is 40-50% (e.g. Mexico, Pacific Islands, and growing number of middle income countries)

Appropriateness of TB screening in people with diabetes depends on local TB burden.

- If TB prevalence is less than 25 per 100,000 persons, at least 1000 people with DM would need to be screened to diagnose one case of TB, whereas in high TB burden countries the number needed to screen is about 100-300.

Some drug-drug interactions may complicate treatment

Very little evidence on the effectiveness of preventive TB treatment (e.g. isoniazid) in people with diabetes suspected

Screening people with TB for DM

WORLD DIABETES FOUNDATION

Diabetes prevalence was higher in patients with TB than in the comparisons where available.

Jeon CY, Harries AD, Baker MA, Hart JE, Kapur A, Lönnroth K, Ottmani SE, Goonesekera S, Murray MB: Bi-directional screening for tuberculosis and diabetes: a systematic review. Trop Med Int Health 2010, 15:1300-1314.

DM Prevalence in cases of Pulmonary TB Compared to General Population in recent studies (2012-2014)

WORLD DIABETES FOUNDATION

Country	Region	DM Prevalence Gen Pop	DM Prevalence TB Cases	Preval Ratio	OR	% Newly detected	Method Used	Author
India	Chennai	10.4%	25.3%	2.4	3.1	37%	OGTT	Vishwanathan V et al
	Kerala	18.0%	44.0%	2.4		48%	HbA1c	Balakrishnan S et al
	Various		13.0%			38%	FPG	India TB DM Group
China	Various	9.7%	12.4%	1.3		22%	FPG	Liang L et al
	Linyi (rural)	4.7%	6.3%	1.3	3.2	43%	FPG	Wang Q et al
Pakistan		7.0%	16.0%	2.3	3.6		HbA1c	Coldin A et al
Nigeria	Lagos	5.6%	12.0%	2.1		67%	FPG/RPG	Ogbera A et al
USA	South Texas	19.5%	39.0%	2.0		10%	FPG/RPG	Resterpro BI et al
Mexico	North East	15.0%	36.0%	2.4		53%	FPG/RPG	Resterpro BI et al
	South Mexico	15.0%	30.0%	2.0				Jimnez-Carona et al
Tanzania		9.4%	16.7%	1.8	2.2		OGTT	Faurholt - Jepsen et al
Uganda		6.4%	8.5%	1.3			RBS	Kibirige D et al

Screening People with DM for active TB

WORLD DIABETES FOUNDATION

In 12 studies prevalence of active TB among people with DM varied widely based on the country and time of study; the annual incidence ranged from 280 / 100 000 people with DM in Korea to 488 / 100 000 people with DM in Ethiopia. Five of the 12 studies provided an estimate of the TB prevalence in the population that gave rise to the study group. Prevalence ratios ranged from 2.0 in Hungary and United States to 5.1 in Korea.

Jeon CY, Harries AD, Baker MA, Hart JE, Kapur A, Lönnroth K, Ottmani SE, Goonesekera S, Murray M. Bi-directional screening for tuberculosis and diabetes: a systematic review. TMIH 2010 doi:10.1111/j.1365-3156.2010.02632

Prevalence of Active TB in people with DM – Recent Studies

WORLD DIABETES FOUNDATION

In China screening 11331 DM cases over three quarters identified 55 cases of TB, the average case notification rates of TB among DM patients was 423/100,000 compared to 77/100,000 in general population. The prevalence ratio was about 5.5.

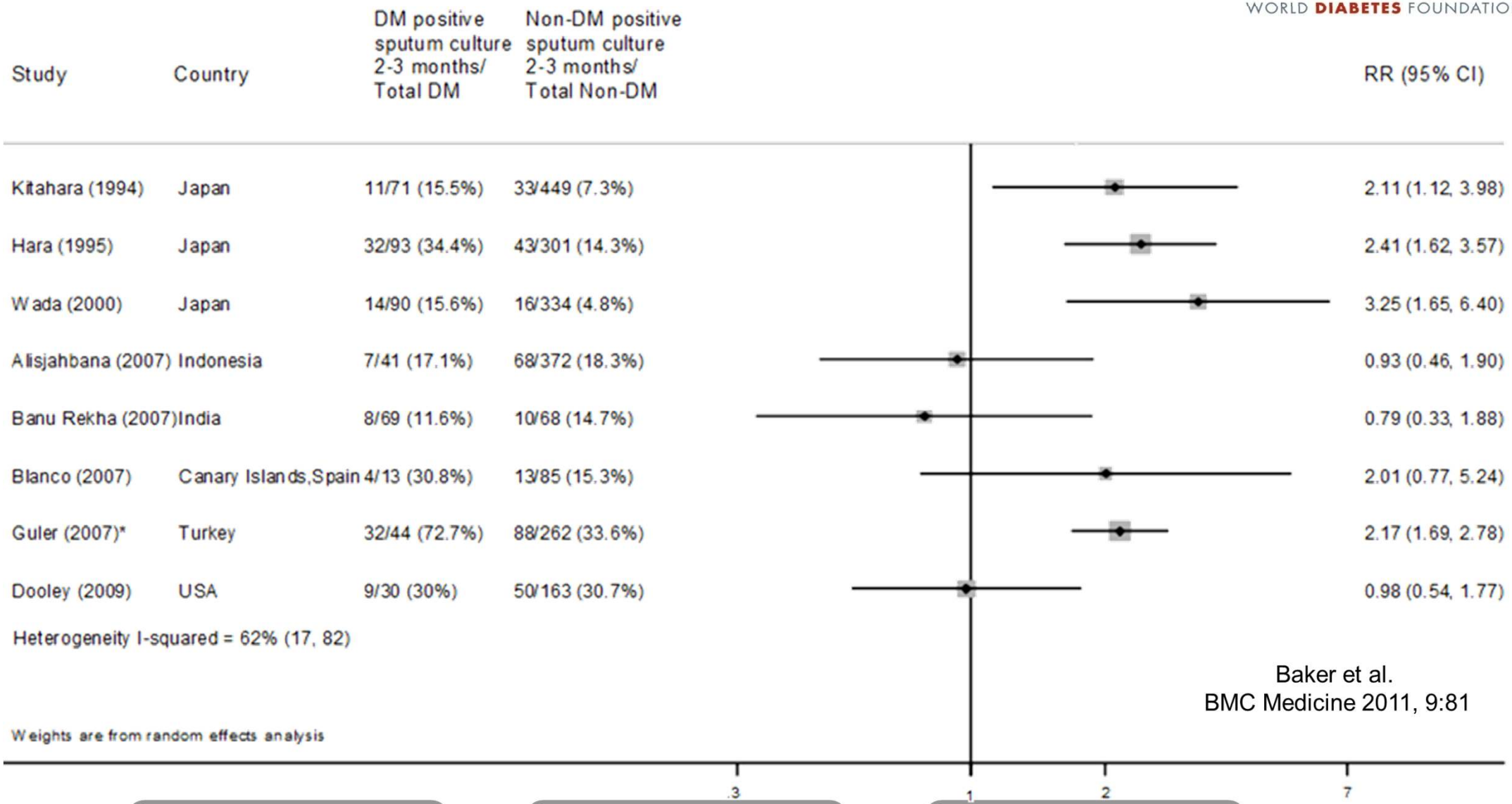
Lin Y, Li L, Mi F, Du J, et al. Screening patients with diabetes mellitus for tuberculosis in China. Trop Med Int Health. 2012;17:1302-8.

In India screening 13068 DM cases over three quarters identified 254 cases of TB, the average TB case notification rate was 810/100,000 DM cases compared to about 110 /100,000 in the general population. Prevalence ratio was about 7.4

India Diabetes Mellitus--Tuberculosis Study Group. Screening of patients with diabetes mellitus for tuberculosis in India. Trop Med Int Health. 2013;18:646-54

DM delays sputum culture conversion at 2-3 months

WORLD DIABETES FOUNDATION



Baker et al.
BMC Medicine 2011, 9:81

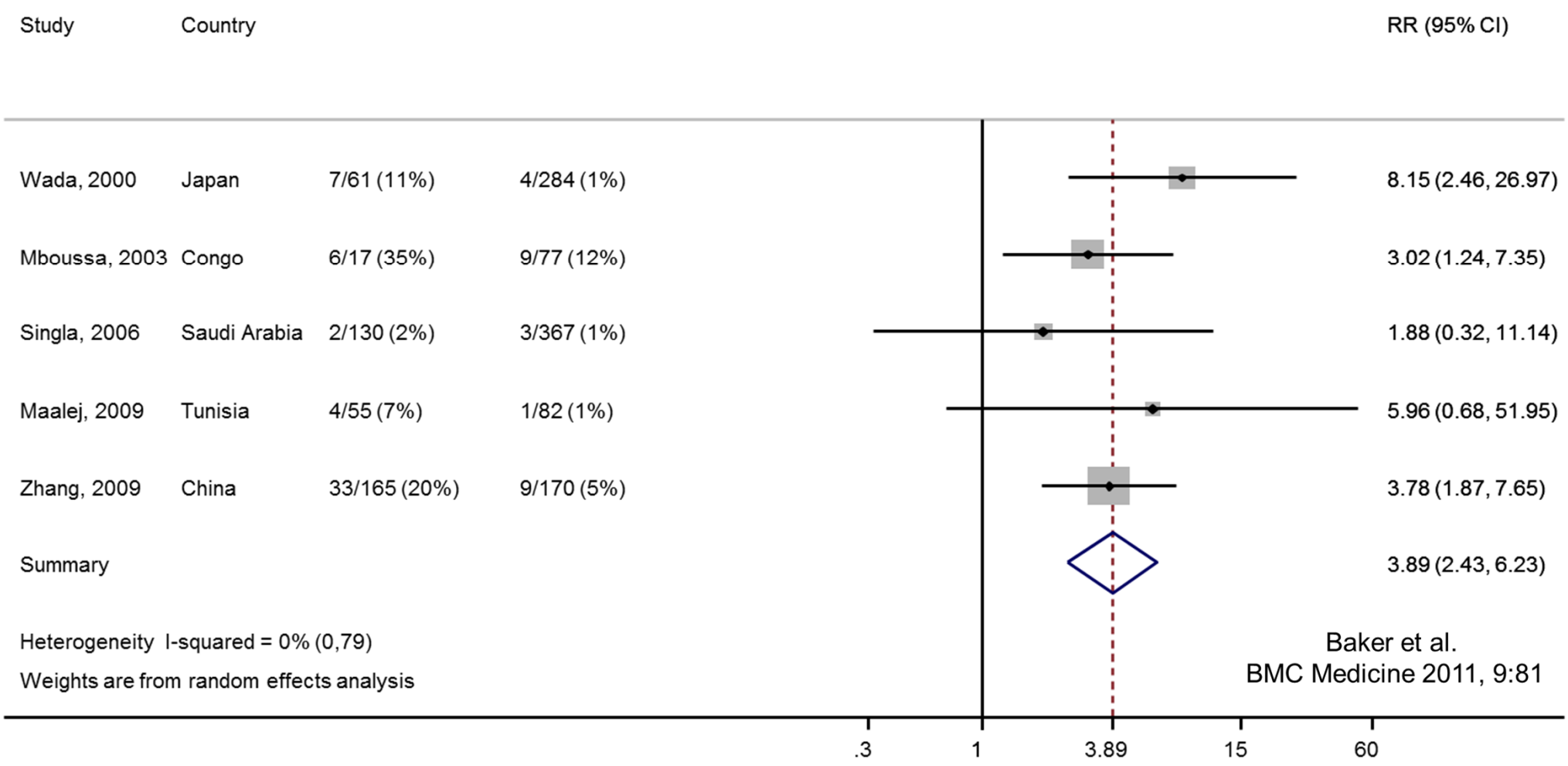
8 studies comparing DM with non-DM

Relative risks from 0.8 – 3.2

Five of eight studies had RR > 2

Increased risk of TB relapse

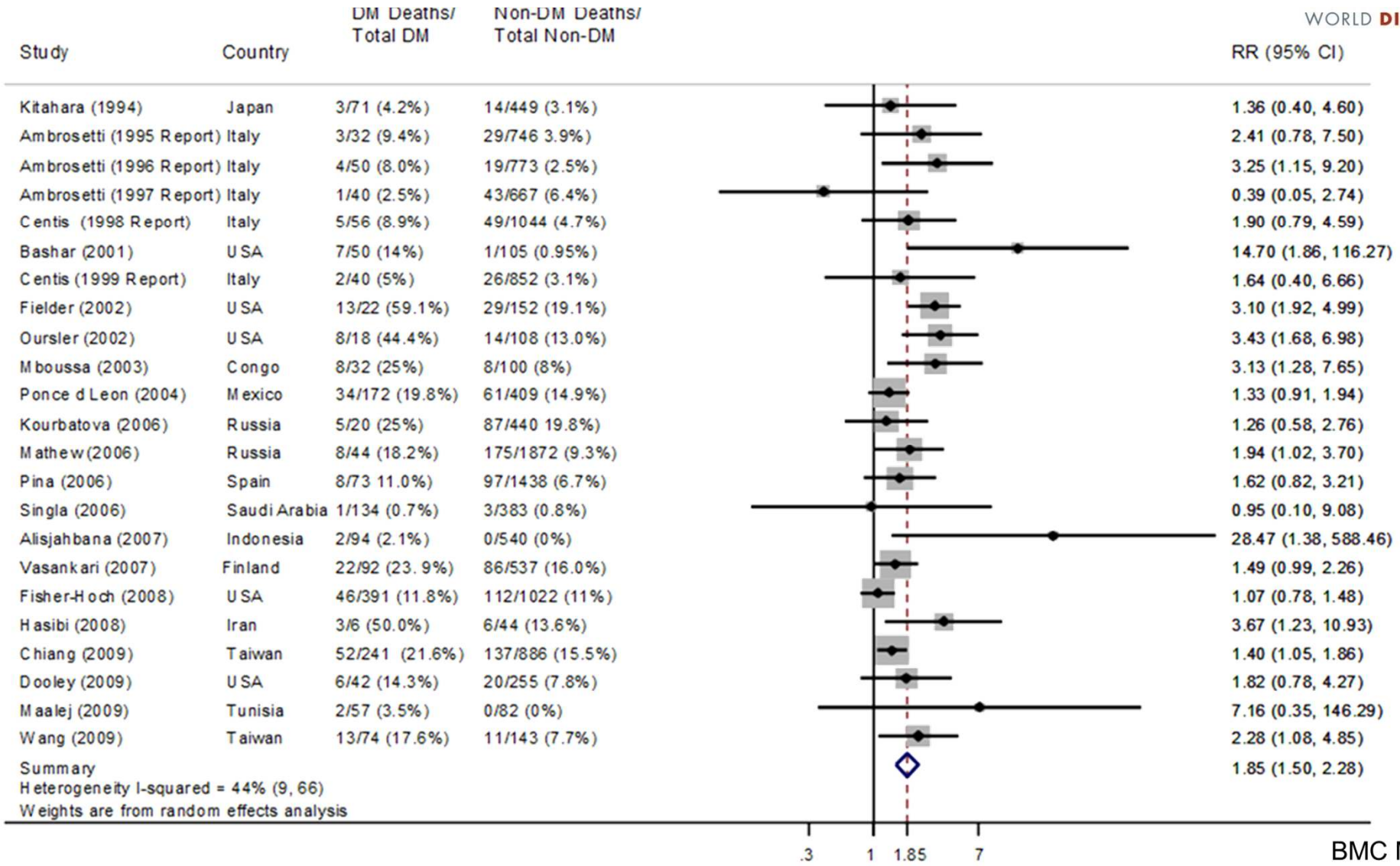
WORLD DIABETES FOUNDATION



For Relapse, pooled RR = 3.89 (95% CI, 2.1 – 7.5)

DM increases risk of death in TB

WORLD DIABETES FOUNDATION



Baker et al.
BMC Medicine 2011, 9:81

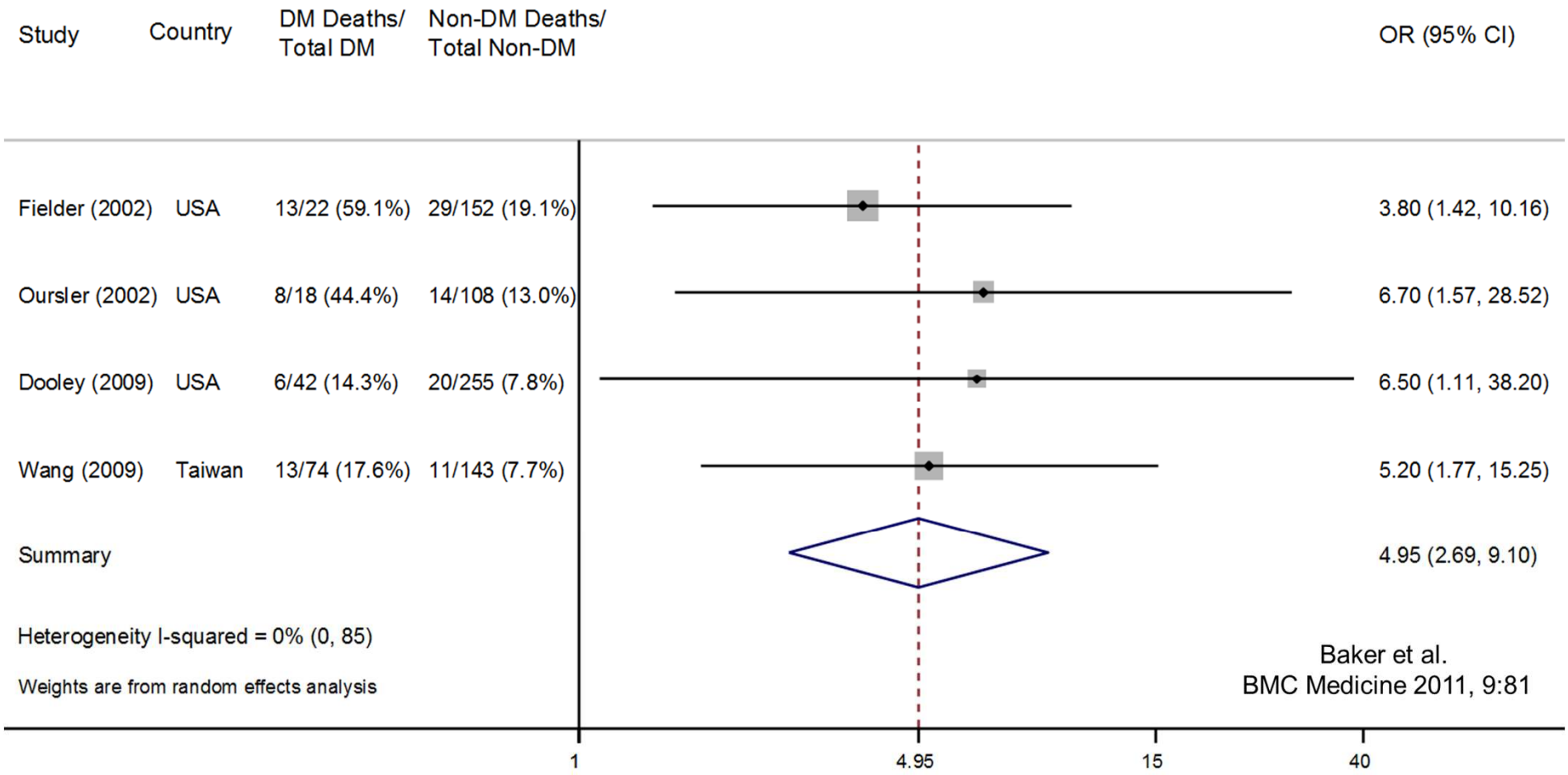
23 studies comparing risk of death in DM and non-DM patients

Pooled RR = 1.85 (95% CI, 1.5 – 2.3)

4 studies adjusted for age /other confounders: pooled OR = 4.95 (95% CI, 2.7 – 9.1)

Odds of death for DM TB compared to non-DM TB *[adjusted for age and other confounders]*

WORLD DIABETES FOUNDATION



In Mwanza, Tanzania within 100 days of TB treatment DM was associated with a five fold increased risk of death among HiV uninfected and a two fold increased risk among HiV co infected patients

Faurholt-Jepsen D,. Diabetes is a strong predictor of mortality during TB treatment: a prospective cohort study among TB patients from Mwanza, Tanzania. PhD thesis Faculty of Science university of Copenhagen 2012

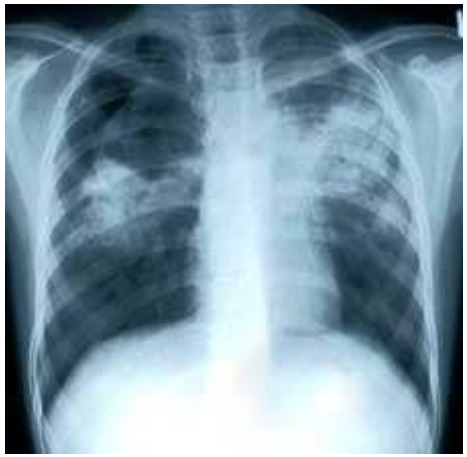
Does TB present differently in patients with DM?

WORLD DIABETES FOUNDATION

Pulmonary TB more common than Extra Pulmonary TB

"infiltrates more common in lower lung fields"

- Turkey *[Bacakoglu et al, 2001]*
- Saudi Arabia *[Shaikh et al, 2003]*
- Pakistan *[Jabbar et al 2006]*
- Taiwan *[Wang et al, 2008]*



Why an increased risk of adverse outcomes?

WORLD DIABETES FOUNDATION

Drug-drug interactions between oral hypoglycaemic drugs and rifampicin *(decreased RF concentrations and poor glycaemic control)*

DM is a risk factor for hepatic toxicity with TB drugs

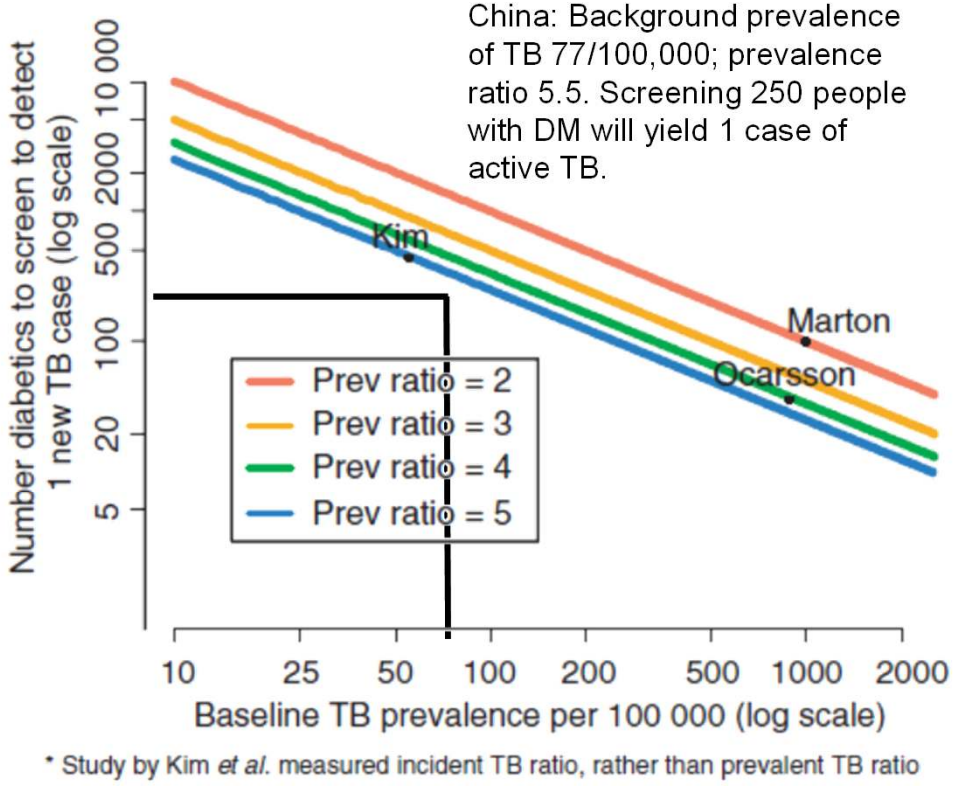
DM is associated with co morbid conditions (renal insufficiency)

Immune-suppressive effects of DM

Determining number of patients to be screened to detect one new case

WORLD DIABETES FOUNDATION

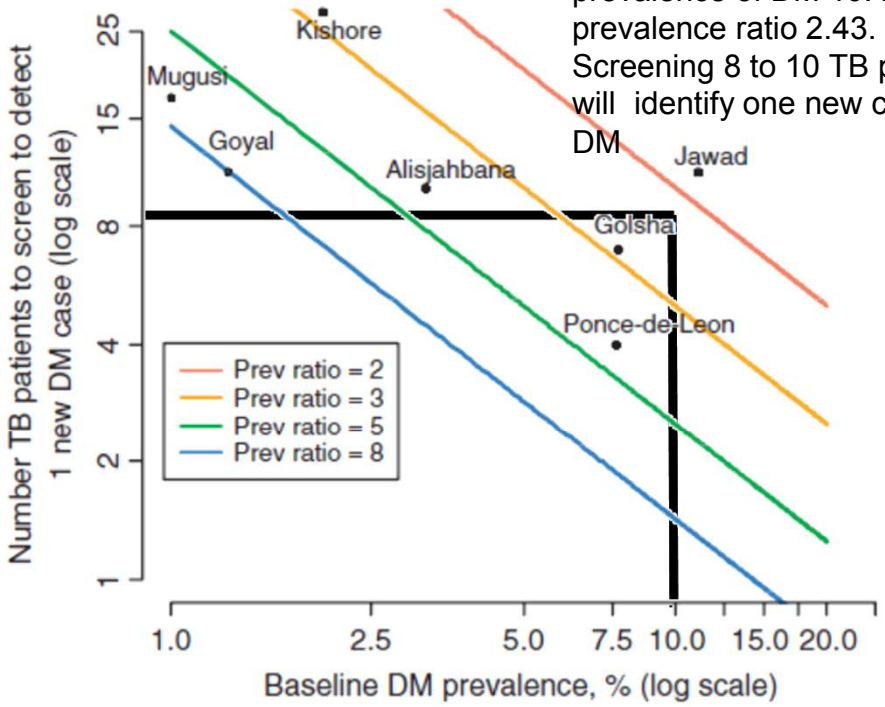
China: Background prevalence of TB 77/100,000; prevalence ratio 5.5. Screening 250 people with DM will yield 1 case of active TB.



* Study by Kim *et al.* measured incident TB ratio, rather than prevalent TB ratio

Number of people with diabetes to screen to detect one additional case of tuberculosis by varying baseline tuberculosis prevalence, given prevalence ratios found in screening studies.

India – Chennai. Background prevalence of DM 10.4%; prevalence ratio 2.43. Screening 8 to 10 TB patients will identify one new case of DM



Number of patients with tuberculosis to screen to detect one additional case of diabetes by varying baseline diabetes prevalence, given prevalence ratios found in screening studies.

Jeon CY, Harries AD, Baker MA, Hart JE, Kapur A, Lönnroth K, Ottmani SE, Goonesekera S, Murray MB: Bi-directional screening for tuberculosis and diabetes: a systematic review. Trop Med Int Health 2010, 15:1300-1314.

Circulated to the WHO and The Union networks, and other partners in TB control

Presented at the UN Summit on NCDs

- NCD Alliance 17th September 2011
- PAHO Partners Forum 20th September 2011

Presentations in The Union conference in Lille

Field testing in countries:

- Sri Lanka
- Mexico
- China
- India etc…

Research, including operational research linked to field testing

Document available at: http://www.who.int/tb/publications/2011/en/index.html

The recommendations

- A-	ESTABLISH MECHANISMS FOR COLLABORATION
1	Set up a means of coordinating diabetes and TB activities
2	Conduct surveillance of TB disease prevalence among people with diabetes in medium and high-TB burden settings
3	Conduct surveillance of diabetes prevalence in TB patients in all countries
4	Conduct monitoring and evaluation of collaborate diabetes and TB activities
- B-	**DETECT AND MANAGE TB IN PATIENTS WITH DIABETES**
1	Intensify detection of TB among people with diabetes
2	Ensure TB infection control in health-care settings where diabetes is managed
3	Ensure high-quality TB treatment and management in people with diabetes
- C-	**DETECT AND MANAGE DIABETES IN PATIENTS WITH TB**
1	Screen TB patients for diabetes
2	Ensure high-quality diabetes management among TB patients

Document available at: http://www.who.int/tb/publications/2011/en/index.html

The TB/DM Framework, building on the TB/HIV policy

WORLD DIABETES FOUNDATION

TB control need	TB/HIV Approach	DM/TB Approach
TB screening in risk groups, for early and comprehensive TB diagnosis	Screening people living with HIV for TB	Screen people with DM for TB, in high TB burden settings
Quality care for TB comorbidities to improved health outcomes among people with TB	HIV screening among people with TB, quality treatment and care, including ARV	Screen TB patients for DM, provide high quality DM treatment, adapt "DOTS" model
Better prevention of TB by reducing population prevalence of TB risk factors	Scale up quality HIV treatment and care, and reduce HIV prevalence	Broad DM prevention and care efforts, TB programmes can help advocate
Health Systems Strengthening through synergistic collaboration	Collaborative structure, sensible integration	Collaborative structure, sensible integration

Implementing the DM-TB Collaborative Framework – public health implications

WORLD DIABETES FOUNDATION

In two recent large studies in China using FBG to screen for DM amongst cases of PTB (Liang Li et al TMIH 2012 and Wang Q et al PLoS ONE 2013) 2.9% and 2.8% patients had previously undetected diabetes and 7.8% and 7.4% had IFG.

If DM screening was scaled up nationwide and implemented at the level of performance achieved in these pilot projects, a prevalence of approx. 3% undetected DM among 1 million patients with TB will translate to 30,000 new DM cases diagnosed each year - an important contribution to case finding of DM and identification of approx. 75000 cases of people at risk of DM.

Only a third of all cases with diabetes in China are diagnosed and 50% of adult population has pre diabetes. (Xu Y et al JAMA 2013)

Implementing the DM-TB Collaborative Framework – public health implications

WORLD DIABETES FOUNDATION

In three recent studies in India using various methods to screen for DM amongst cases of PTB 5% (FPG); 9.4% (OGTT) and 21% (HbA1c) patients had previously undetected diabetes. These constituted 38%, 37% and 48% cases of TB and DM

If DM screening was scaled up nationwide and implemented at the level of performance achieved in these pilot projects, a prevalence of approx. 6-9% undetected DM among 2.2 million patients with TB will translate to 132,000 to 198,000 new DM cases diagnosed each year - an important contribution to case finding of DM.

Only a half of all cases with diabetes in India are diagnosed

Implementing the DM-TB Collaborative Framework – public health implications

WORLD DIABETES FOUNDATION

New TB case notification rate amongst people with DM in China have been reported to vary between 335 to 595 per 100,000 known DM cases screened for TB. (Lin Y et al TMIH 2012)

There are 40 million (3.5% of 114 million) people with known DM in China (Xu Y et al JAMA 2013)

If the TB screening protocol used in the pilot project was implemented nationally this would translate to between 134,000 to 238,000 new cases of TB detected amongst people with known DM.

Implementing the DM-TB Collaborative Framework – public health implications

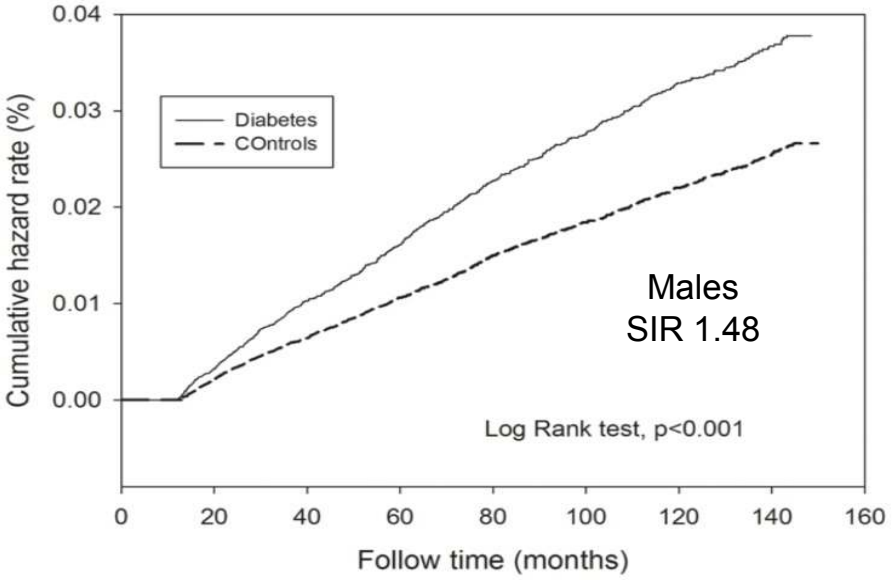
WORLD DIABETES FOUNDATION

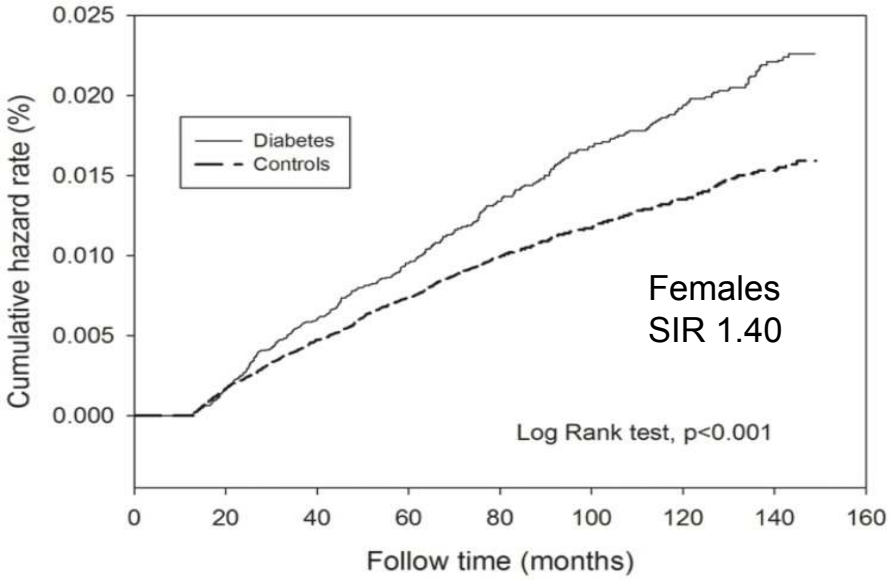
New TB case notification rate amongst people with DM in India have been reported to vary between 642 to 956 per 100,000 known DM cases screened for TB. (India DM TB Study Group TMIH 2013)

There are approx. 32 million people with known DM in India

If the TB screening protocol used in the pilot project was implemented nationally this would translate to between 205,000 to 306,000 new cases of TB detected amongst people with known DM.

Cumulative hazard rate of incident TB in diabetic patients and controls





During the study period, both female (standardized incidence ratio (SIR): 1.40, p,0.01) and male (SIR: 1.48, p,0.01) patients with type 2 diabetes were found to have a significantly higher rate of incident tuberculosis than the control group. Type 2 diabetes (HR:1.31, 1.23–1.39, p,0.001) was significantly associated with tuberculosis after adjusting sex, age, bronchiectasis, asthma and chronic obstructive lung disease.

Kuo MC, Lin SH, Lin CH, Mao IC, Chang SJ, Hsieh MC. PLoS One. 2013 Nov 13;8(11):e7892

TB likely to increase in countries with increasing DM prevalence

WORLD DIABETES FOUNDATION

Individual-level analyses using the World Health Survey on 124 607 subjects; in 46 countries done to estimate relationship between TB and DM, adjusting for gender, age, BMI, education, housing quality, crowding and health insurance.

- In lower income countries, individuals with DM are more likely than non-DM to have TB [univariable OR: 2.39; 95% CI:1.84–3.10; multivariable OR: 1.81; 95% CI: 1.37–2.39].

Longitudinal country-level analysis using data on per-capita GDP and TB prevalence and incidence; and DM prevalence for 1990–95 and 2003–04 (163 countries) was done to estimate the relationship between increasing DM prevalence and TB, identifying countries at risk for disease interactions.

- Increases in TB prevalence and incidence over time were more likely to occur when diabetes prevalence also increased (OR: 4.7; 95% CI: 1.0–22.5; OR: 8.6; 95% CI: 1.9–40.4).

Goldhaber-Fiebert JD, Jeon CY, Cohen T, Murray MB. Diabetes mellitus and tuberculosis in countries with high tuberculosis burdens: individual risks and social determinants. Int J Epidemiol. 2011 Apr;40(2):417-28

WORLD DIABETES FOUNDATION

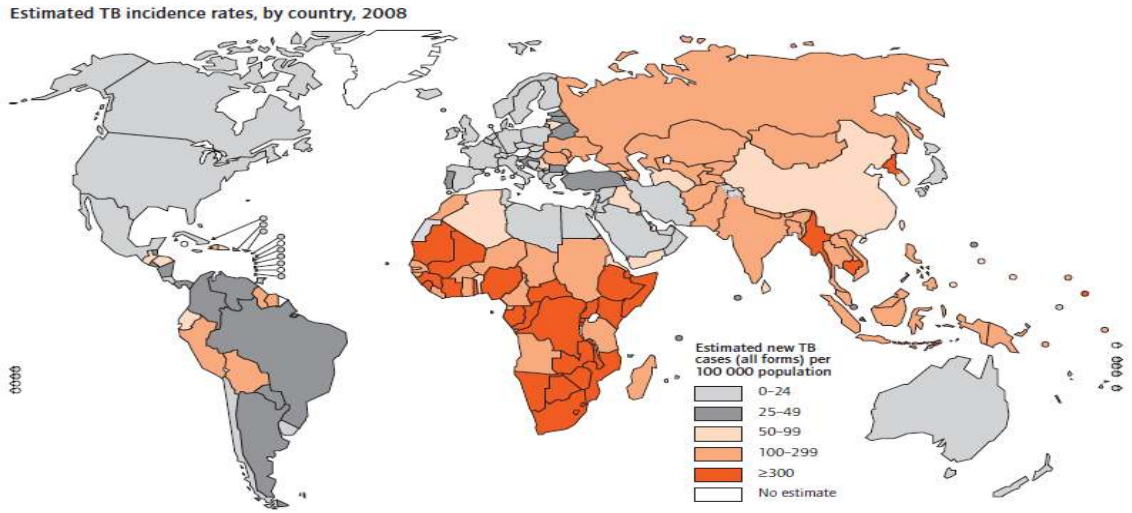
Over 10 years, TB was more likely to increase in low and middle income countries where diabetes prevalence increased.

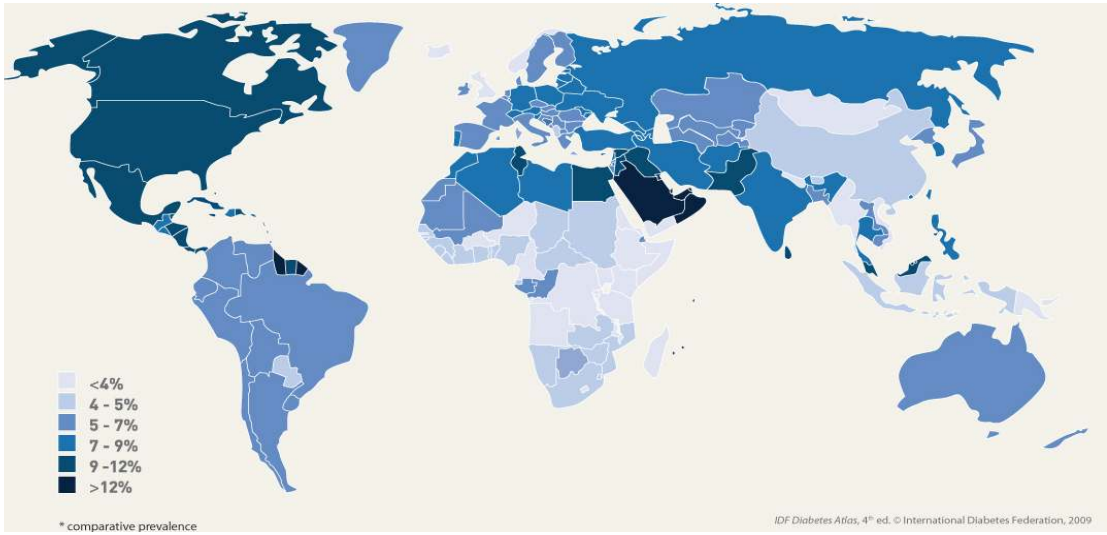
Given the association between TB and DM this requires serious reconsideration in health policies to tackle the double burden in high TB burden countries with increasing rates of DM

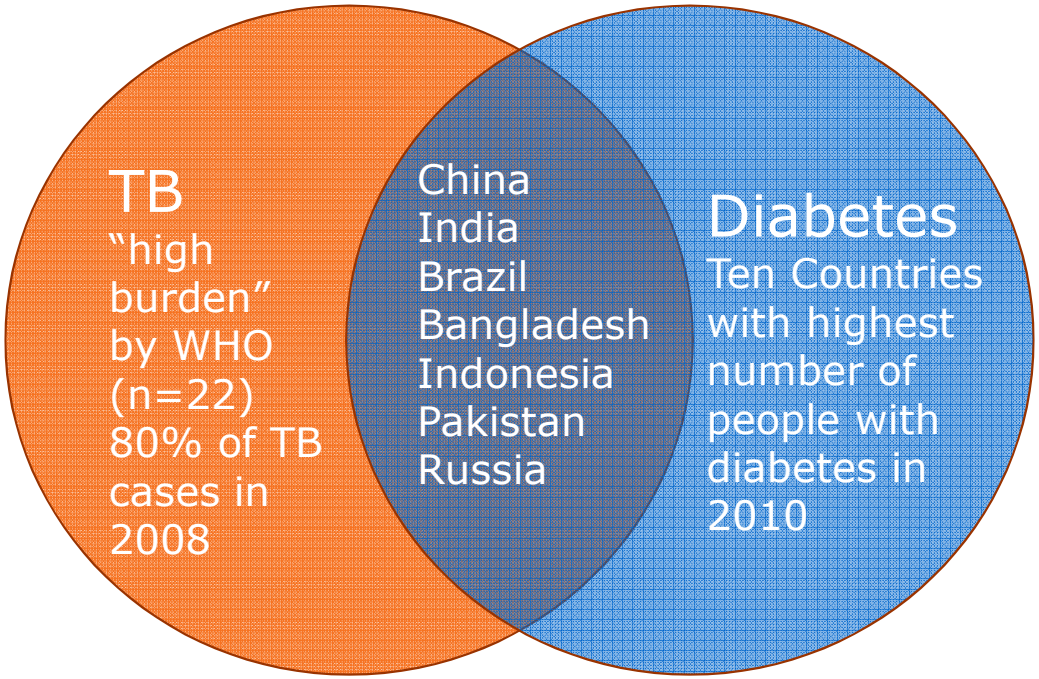
Goldhaber-Fiebert JD, Jeon CY, Cohen T, Murray MB.
Diabetes mellitus and tuberculosis in countries with high tuberculosis burdens: individual risks and social determinants. Int J Epidemiol. 2011 Apr;40(2):417-28

Diabetes And Tuberculosis – the converging pandemics

WORLD DIABETES FOUNDATION







- DM increases the risk of active TB about 3-fold
- DM increases the risk of adverse TB treatment outcomes
  - Delayed sputum conversion
  - Higher relapse rate
  - Higher death rate
- Drug-drug interactions may complicate treatment

Global Diabetes Burden

WORLD DIABETES FOUNDATION

	2011	% Population	2030	% Population
Diabetes	366,00	8,3%	552,00	9,9%
IGT	280,00	6,4%	398,00	6,7%

79% People with diabetes live in the Middle and Low Income Countries

88% Deaths attributable to diabetes occur in the same regions

WORLD DIABETES FOUNDATION

Undiagnosed, inadequately treated and poorly controlled Diabetes Mellitus is a bigger threat to TB prevention and control in high TB burden countries than previously realised.

Continuing to underplay and ignore this association will undo decades of painstaking gains in TB control and prove disastrous both in terms of health and economics