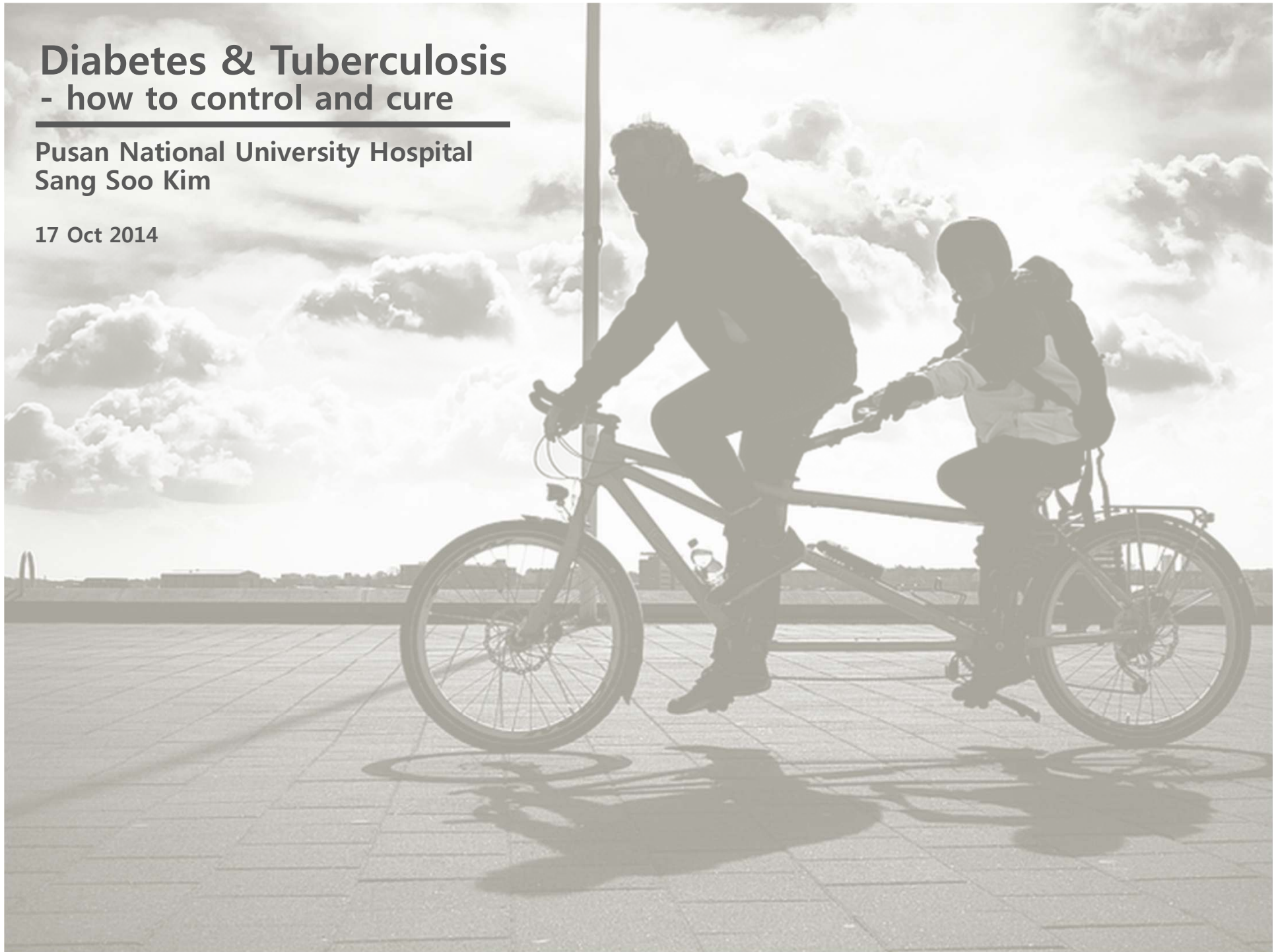


Diabetes & Tuberculosis

- how to control and cure

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17 Oct 2014



Contents

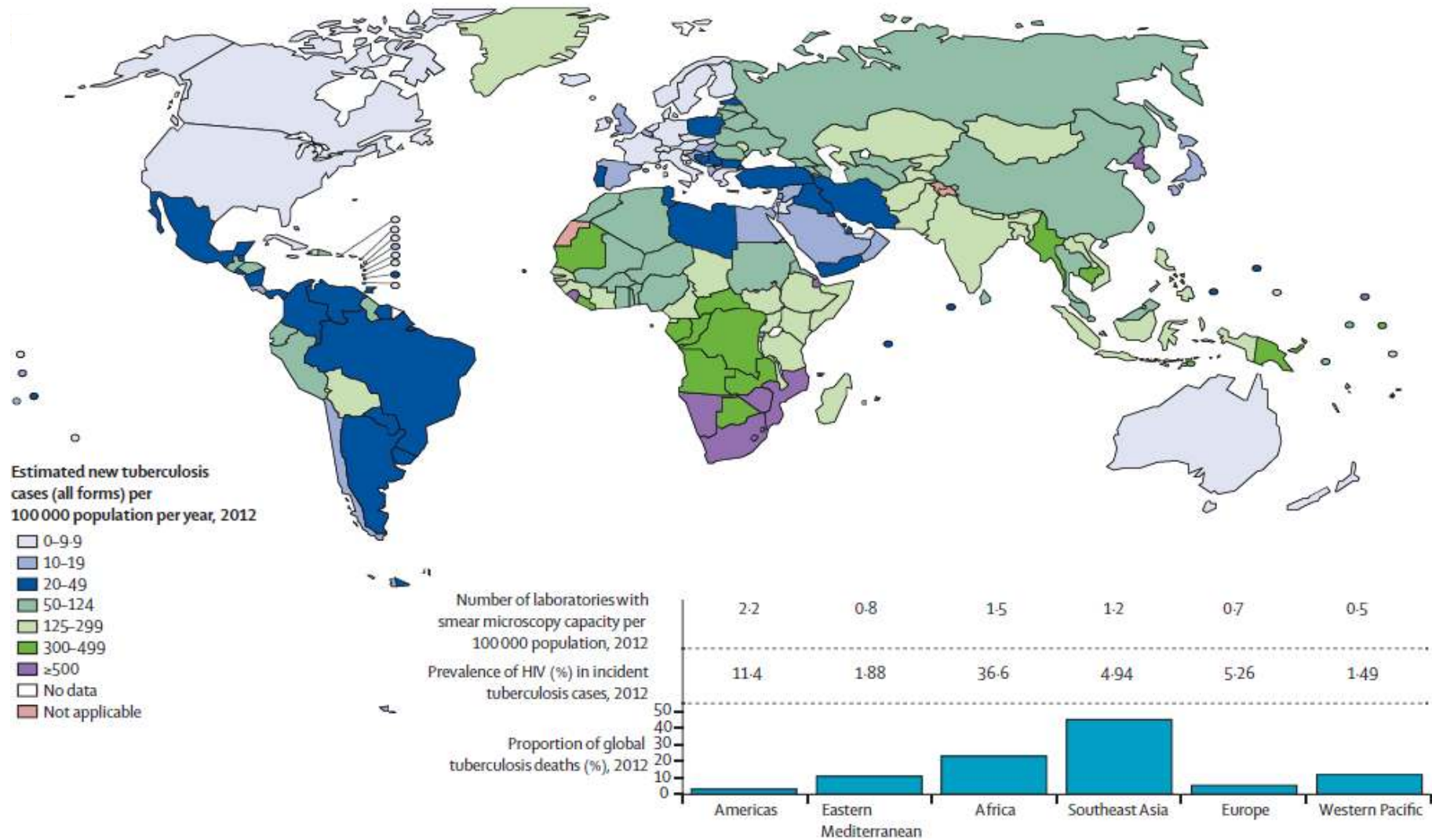


- **Epidemiology of DM & TB**
- **Bi-directional screening for TB & DM**
 - Screening for TB in DM
 - Screening for DM in TB
- **Management for concurrent TB & DM**
 - Treatment of TB in DM
 - Treatment of DM in TB
- **Implications for health service delivery and health economics**

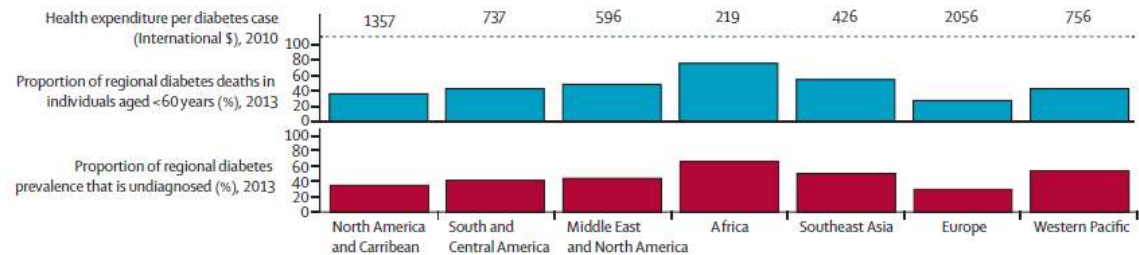
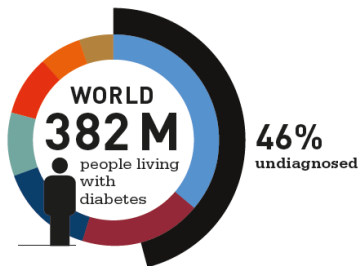
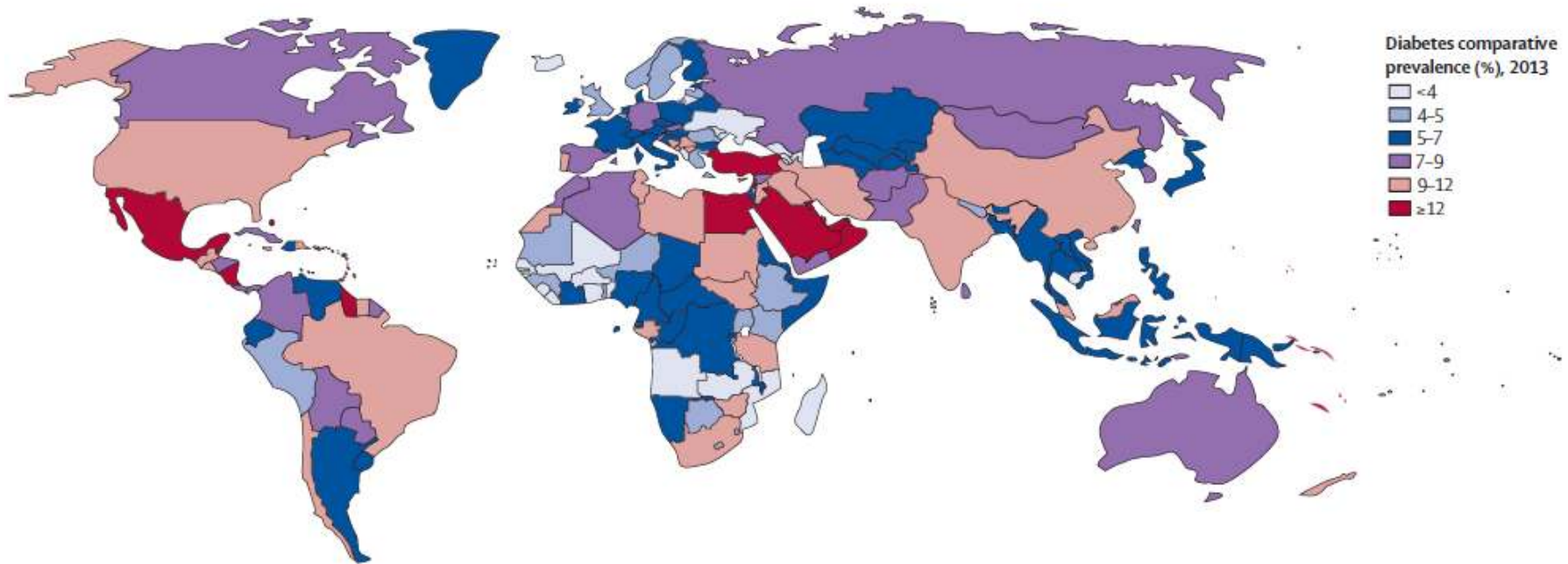


Epidemiology of DM & TB

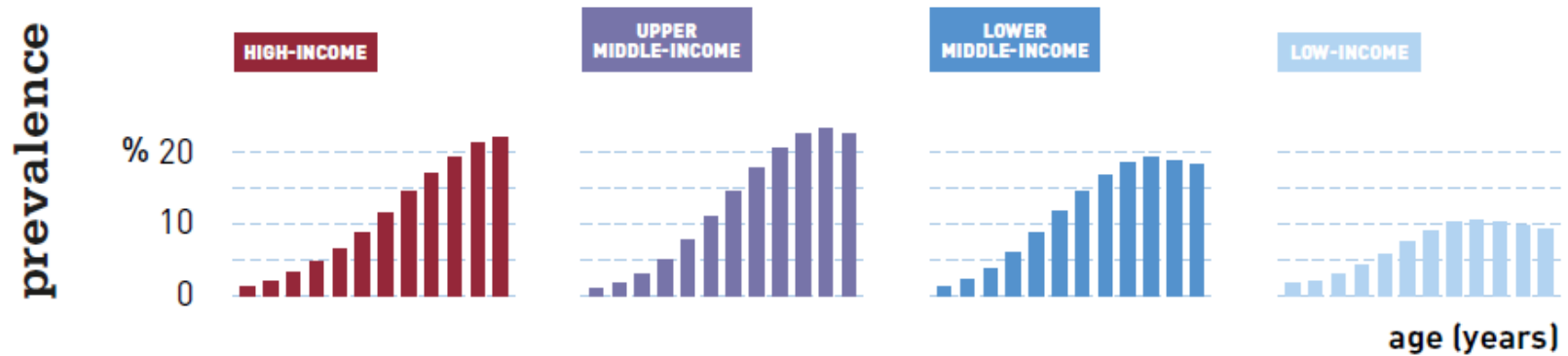
TB incidence in 2012 for each WHO region



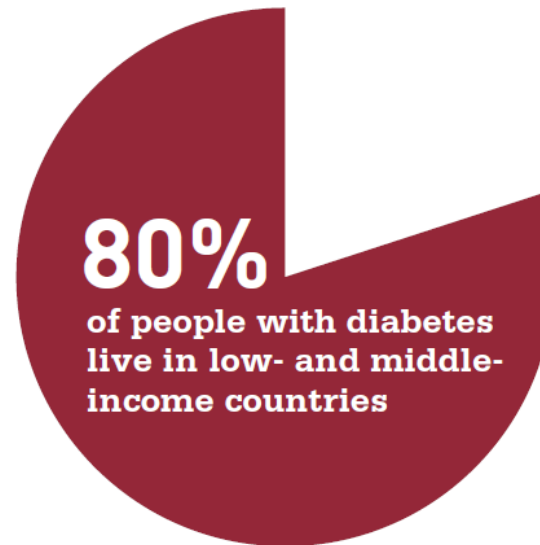
Diabetes, 2013



Prevalence of DM by income & age

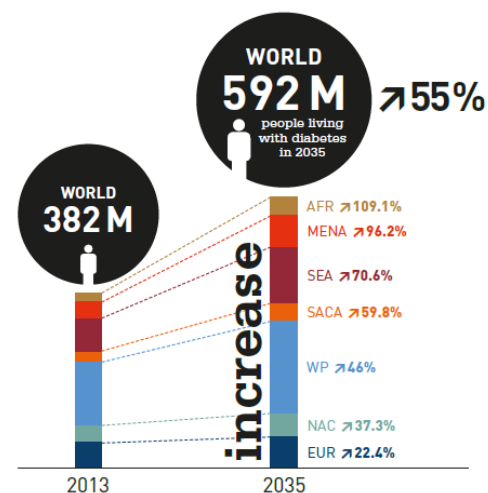


All nations – **rich and poor** – are suffering the impact of the diabetes epidemic.



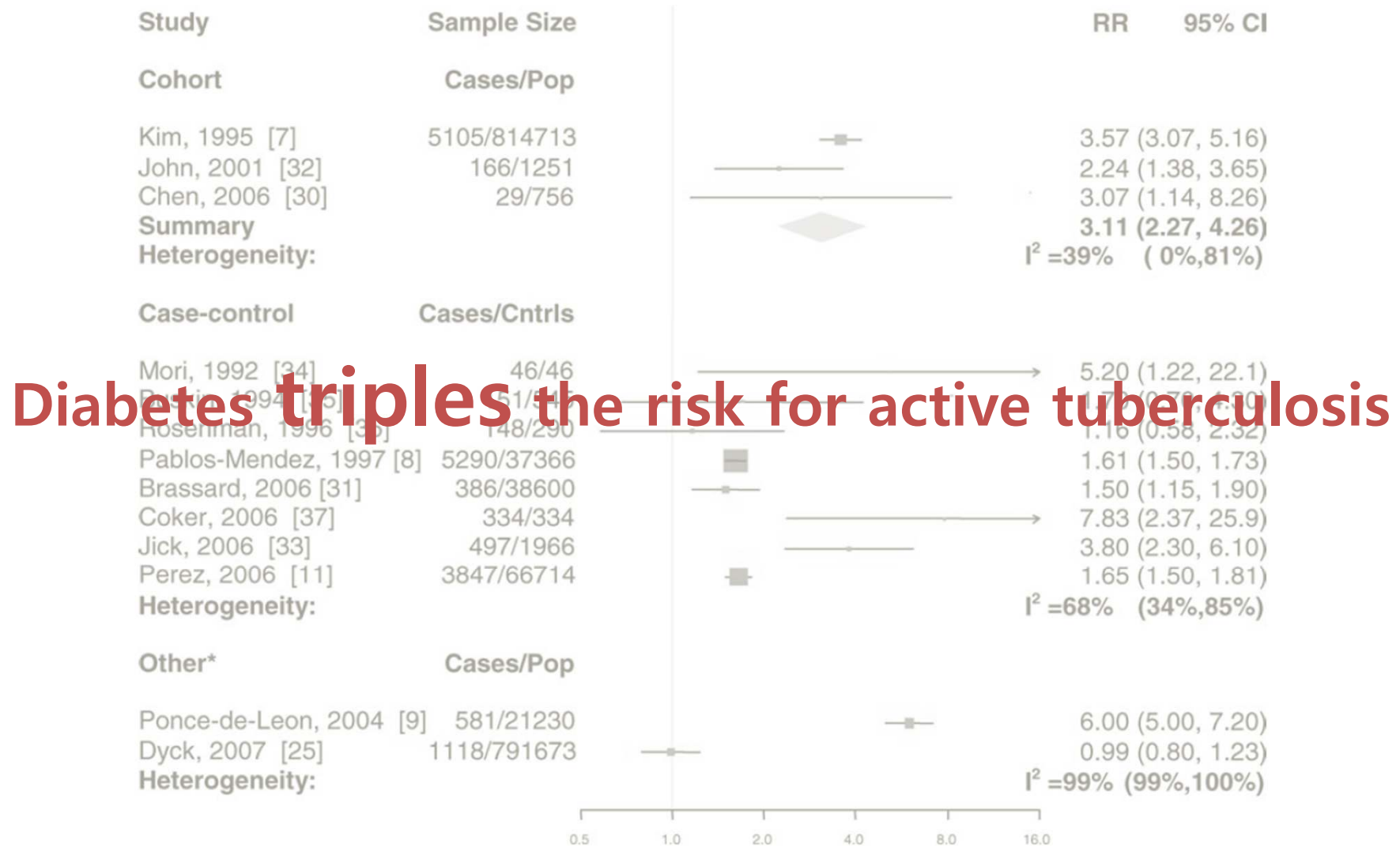
DM prevalence is increasing substantially

Diabetes is a **huge and growing problem**, and the costs to society are high and escalating.

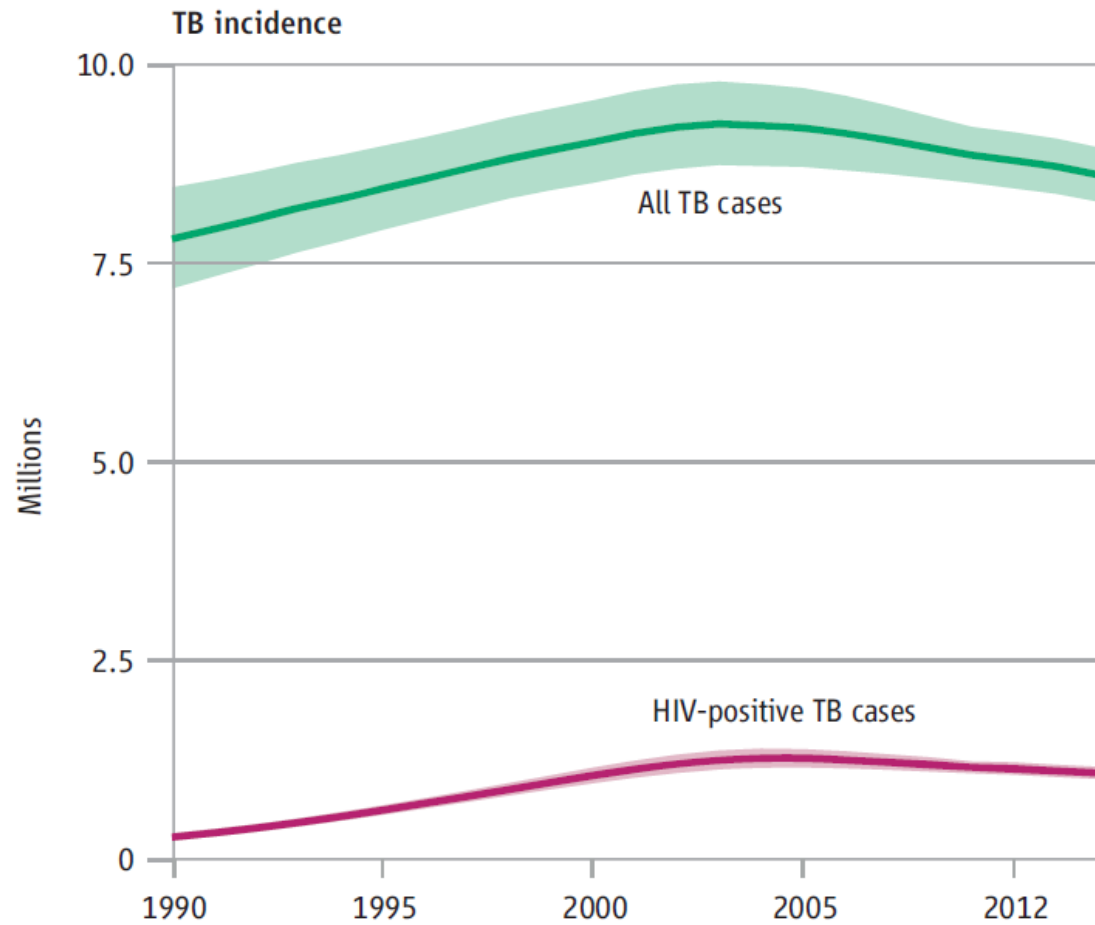


IDF REGION	2013 MILLIONS	2035 MILLIONS	INCREASE %
Africa	19.8	41.4	109%
Middle East and North Africa	34.6	67.9	96%
South-East Asia	72.1	123	71%
South and Central America	24.1	38.5	60%
Western Pacific	138.2	201.8	46%
North America and Caribbean	36.7	50.4	37%
Europe	56.3	68.9	22%
World	381.8	591.9	55%

More prevalent of active TB in DM



Tuberculosis, 2012



The estimated proportion of TB attributable to DM

12.6% (in 2030, 25.5% compared to 2010)

Rank	Country	Population in 2007 (×1000)*	TB		Diabetes		TB attributable to diabetes		
			Incidence in 2007 (all cases/10 ⁵ /year)*	New cases in 2007*	Estimated prevalence (%) in 2010†	Estimated prevalence (%) in 2030†	Excess TB cases because of DM (2010)	% of all TB cases (2010)	% of all TB cases (2030)
1	India	1 169 016	168	1 963 947	7.0	9.0	252 745	12.9	16.0
2	China	1 328 630	98	1 302 057	4.0	6.0	101 341	7.8	11.2
3	Indonesia	231 627	228	528 110	5.0	6.0	50 399	9.5	14.4
4	Nigeria	148 093	311	460 569	3.9	4.0	35 019	7.6	7.8
5	South Africa	48 577	948	460 510	6.0	7.0	39 934	8.7	9.5
6	Bangladesh	158 665	223	353 823	8.0	9.0	39 760	11.2	12.9
7	Ethiopia	83 099	378	314 114	4.5	5.0	12 719	4.0	6.0
8	Pakistan	163 902	181	296 663	2.0	3.0	42 844	14.4	16.0
9	Philippines	87 960	29	255 084	7.0	8.0	32 827	12.9	14.4
10	DR Congo	62 636	392	245 533	2.6	3.0	12 769	5.2	6.0
		N	Q	N*Q	P ₁₀		TBaDM	TBaDM/N*Q	

NETO BANCA

 VENETO BANCA

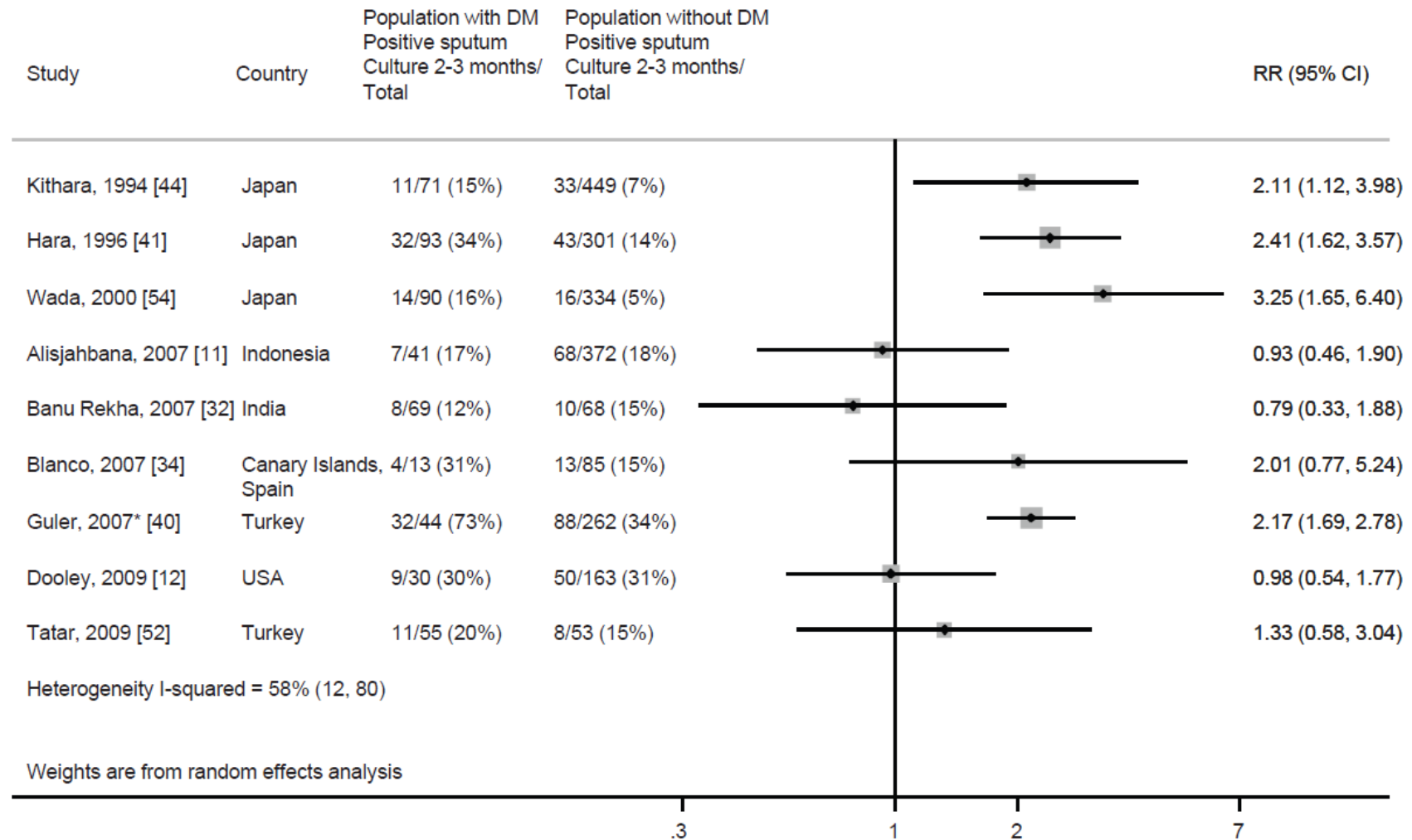
 VENETO BANCA

 VENETO

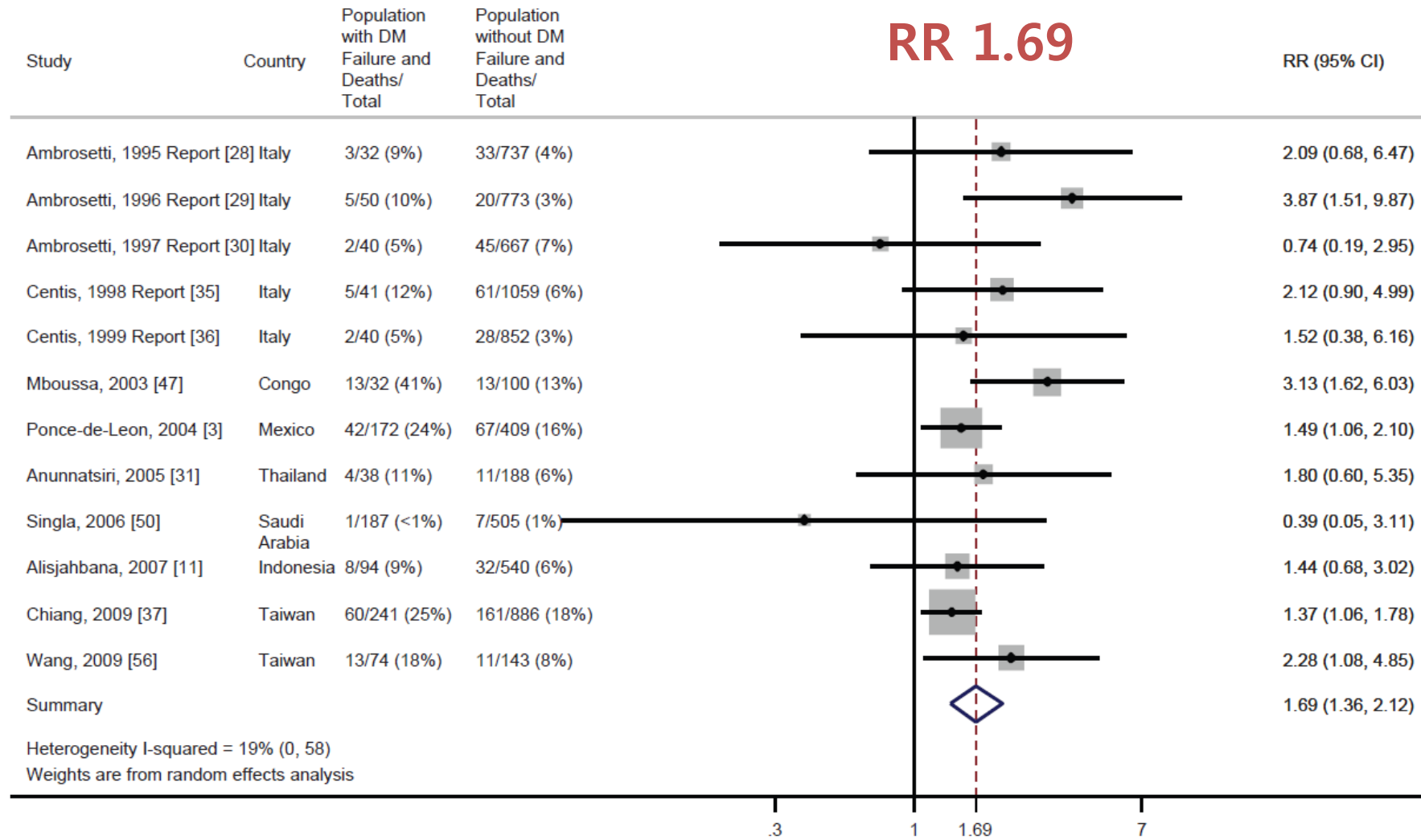
Co-infections increased risk for poor outcome



Risk of remaining sputum culture positive

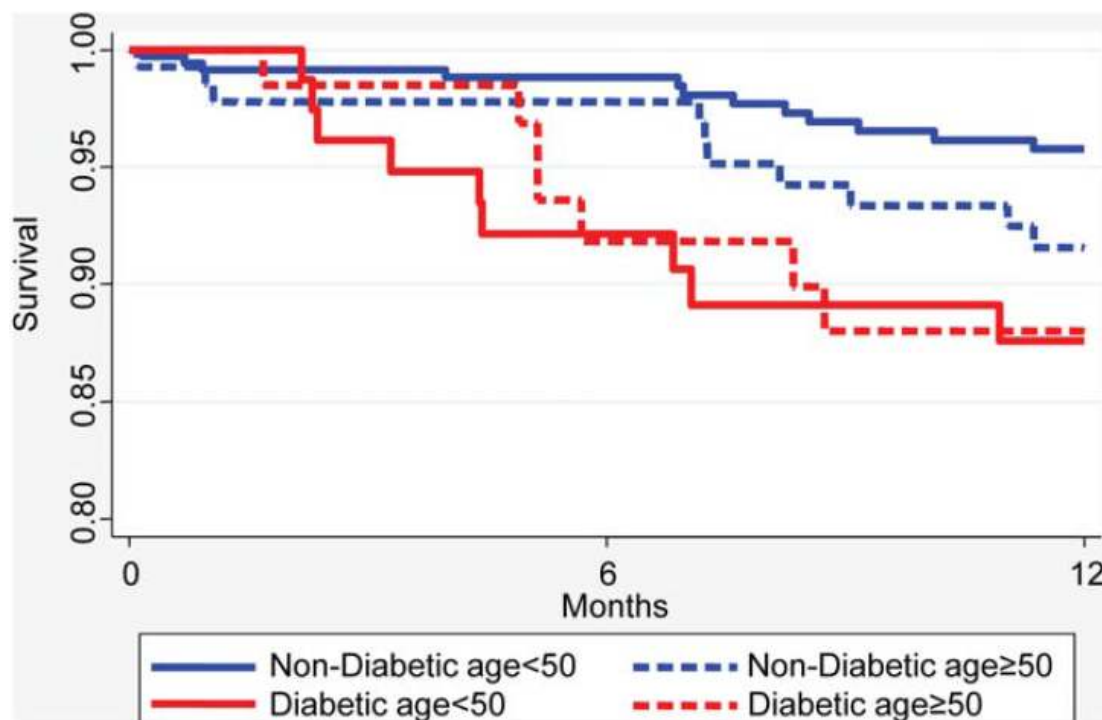


Risk of failure/death for TB



Impact of DM and Smoking on Mortality in TB

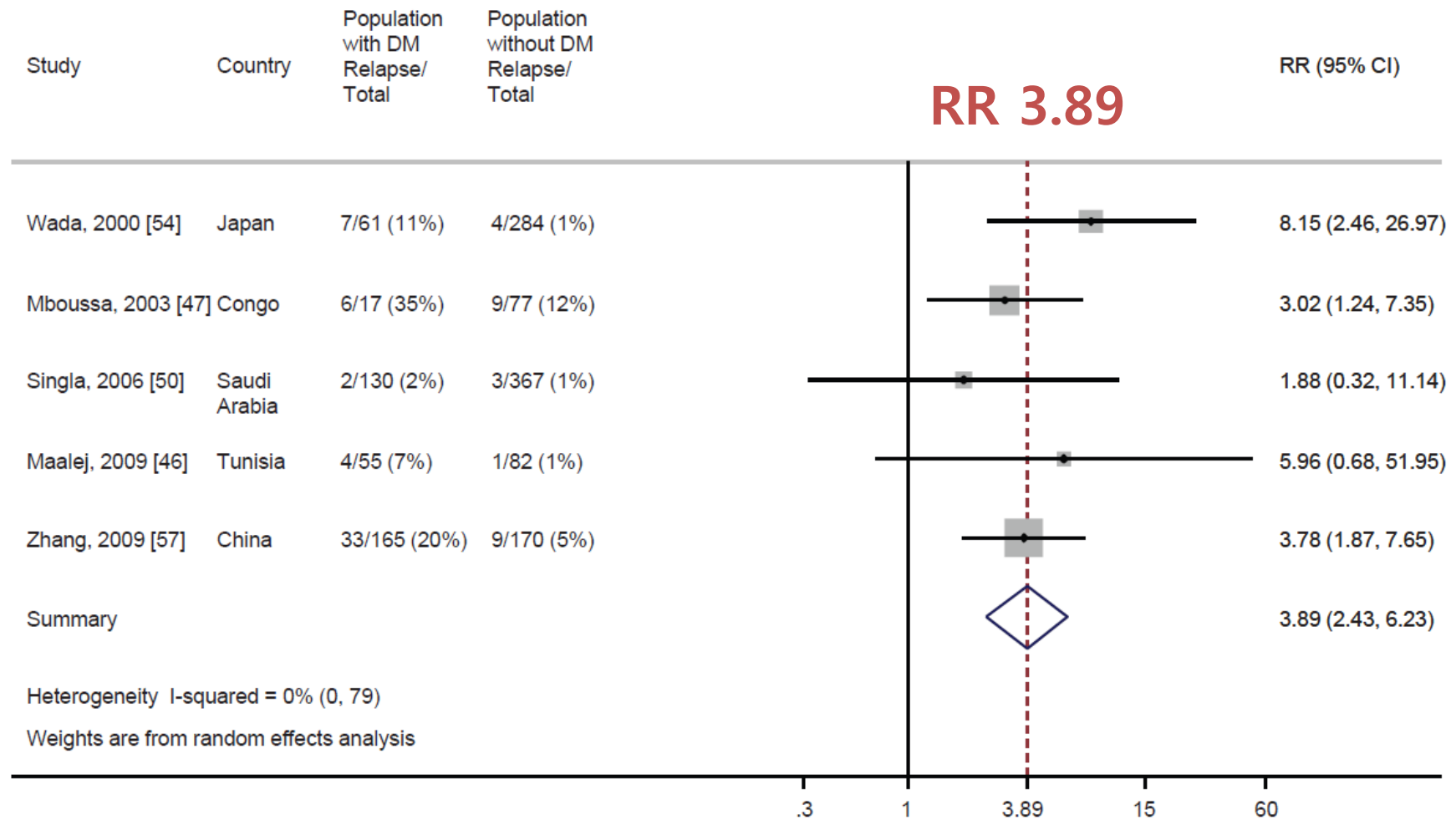
A longitudinal cohort study in Korea (National Masan Tuberculosis Hospital)
657 Subjects (DM 25%)



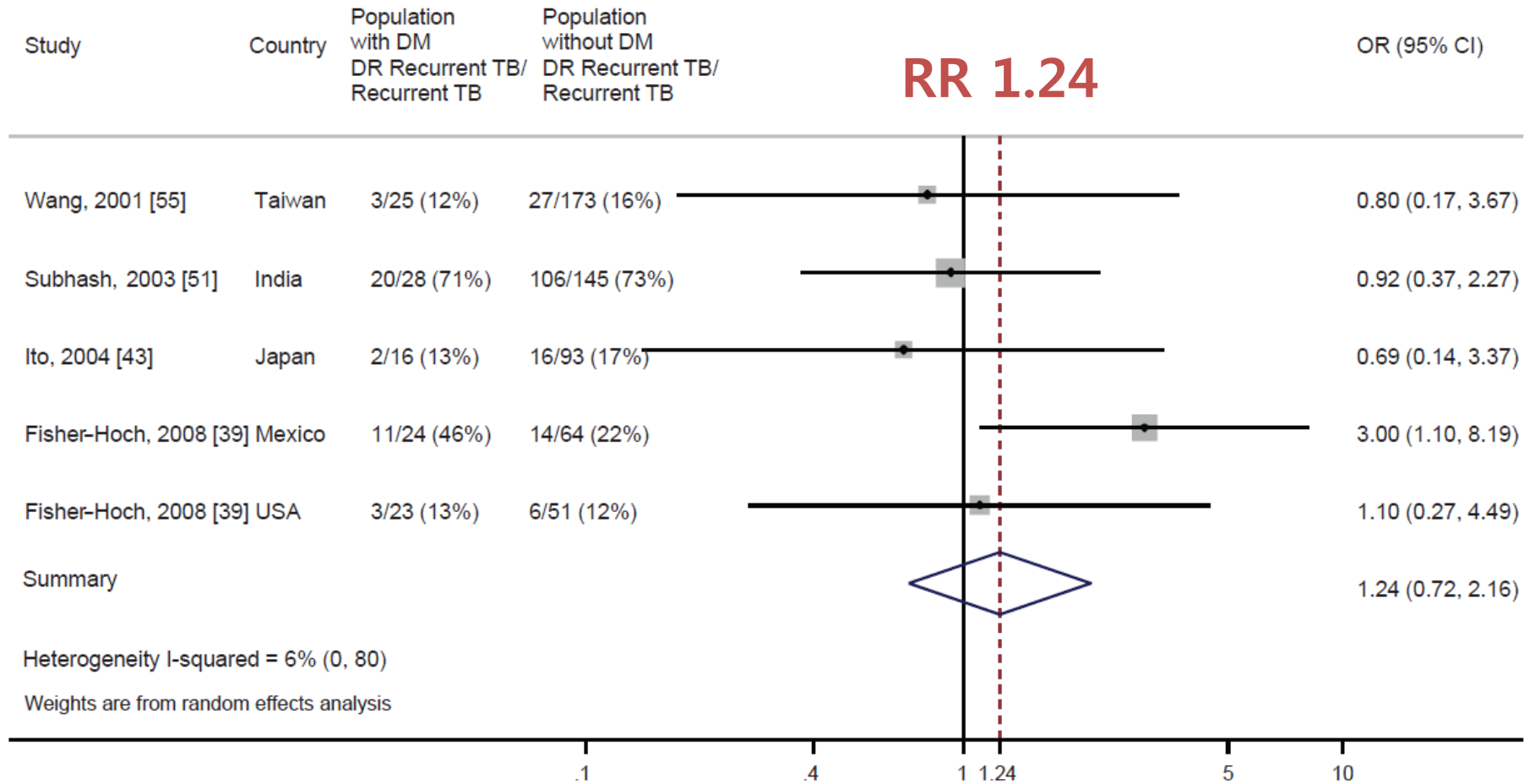
The combined effect of DM and smoking

→ **↑ 6 times** of TB mortality

Risk of TB relapse for TB with DM



Risk for recurrent TB that is DR





Bi-directional screening for TB & DM

Directly Observed Therapy Short-Course (DOTS)

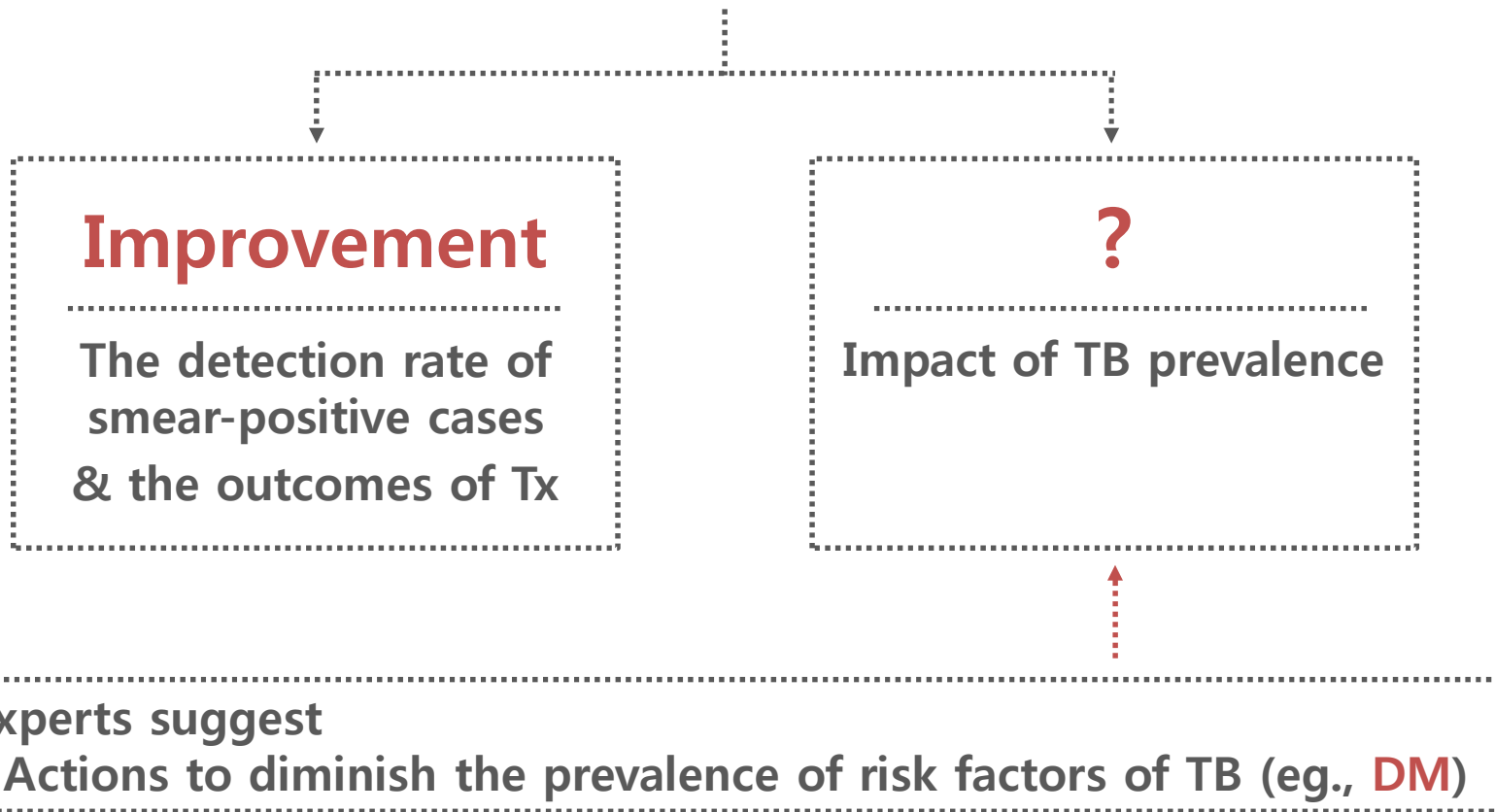
Government commitment

Case detection by **sputum smear microscopy**.

Standardized treatment regimen

A regular, uninterrupted drug supply

A standardized recording and reporting system



Bidirectional screening of TB in DM & DM in TB

Screening for active TB in DM

- hasten case detection
 - earlier therapy & prevention of transmission
- the administration of preventive TB therapy in TB-infected people with DM could avert progression to TB

Screening for DM in TB

- improve case detection
 - early treatment & tertiary prevention of DM
- indirectly lead to better TB-specific treatment outcomes

Screening for active TB in DM

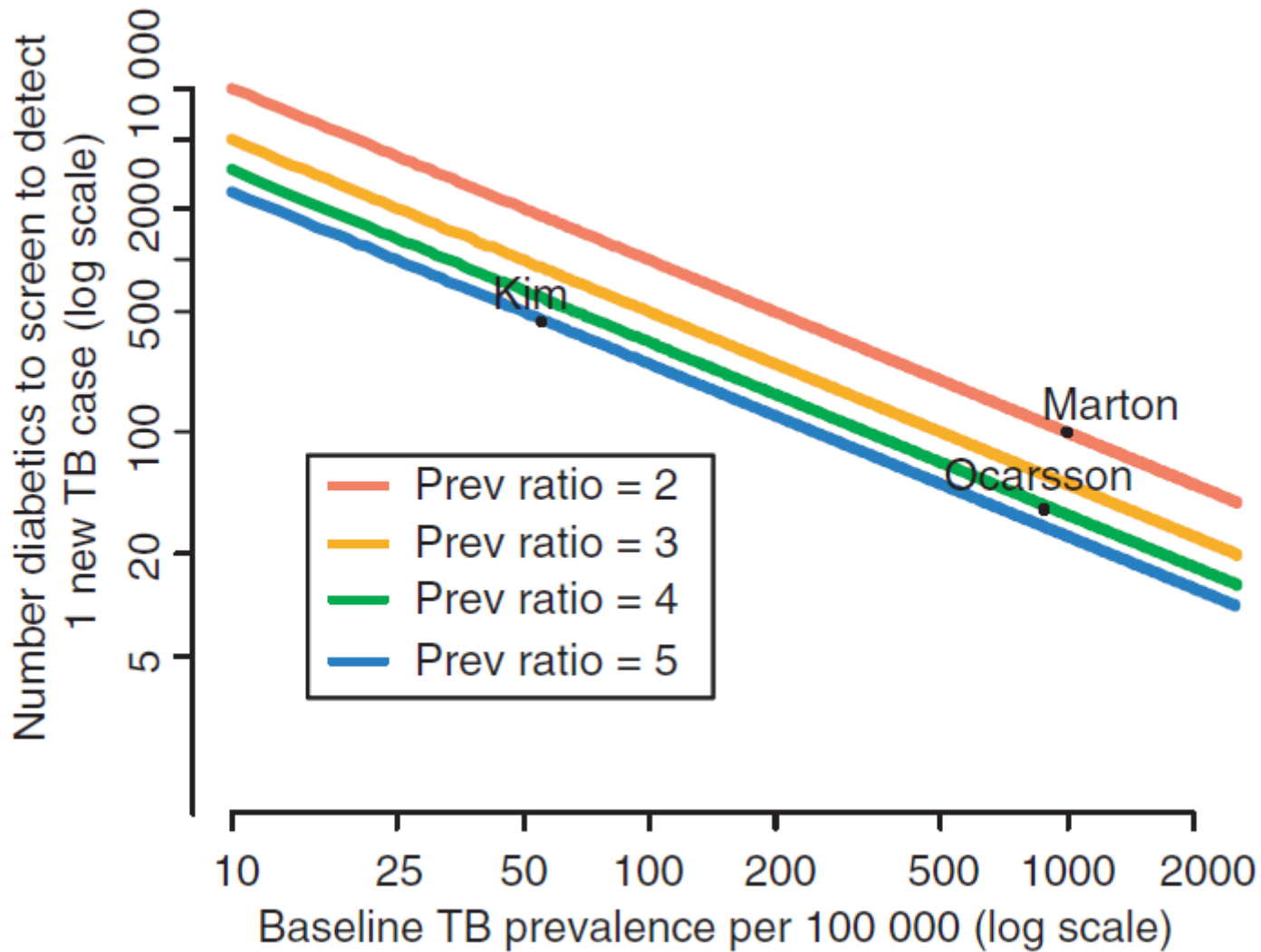
12 studies (Up to 2011)

6 studies – used radiography

6 studies – used radiography plus microbiological testing

Country	Year	Prevalence (P) or Incidence (I) of TB	No. needed to screen to detect 1 TB
Korea	1961	36% (P)	4
.	.	.	.
.	.	.	.
.	.	.	.
Sweden	1958	3.6% (P)	36
Korea	1995	0.3% (I)	442

No. of DM to screen to detect one additional TB



Tests for screening & diagnosis of active TB in DM

	Mode of action	Comparative direct cost	Time	Sensitivity and specificity	Restrictions	Issues of use in patients with diabetes
Screening tests						
Clinical assessment	Symptomatic screen and clinical exam	Low	Hours	Sensitivity: 77%; specificity: 67% (pooled data from eight screening studies for any tuberculosis symptoms* †) ³⁴	Low sensitivity and specificity	Presentation of clinical characteristics might differ in patients with diabetes; evidence base is weak
Chest radiography	Enables detection of tuberculosis-suggestive lesions, which can be present in asymptomatic individuals	Medium	Hours	Sensitivity: 98%; specificity: 75% (pooled data from three screening studies for any abnormalities on chest radiography* †) ³⁴	High rates of non-tuberculosis abnormalities in some settings	Radiographs might differ in patients with diabetes; weak evidence
Diagnostic tests						
Sputum microscopy	Smear to identify acid fast bacilli	Medium	Days	Sensitivity: 84%; specificity: 98% (LED microscopy vs culture; dependent on optimisation of microscopy, sensitivity can vary by around 20%) ³⁵	Less sensitive than culture	No standard laboratory capacity for most diabetes clinics; high numbers of patients with diabetes unwilling to provide sputum sample ³⁶
Sputum culture	<i>Mycobacterium tuberculosis</i> culture (allows subsequent resistance test)	High	Up to 8 weeks	Gold standard	Time and skill required; throughput (difficult to do as many sputum cultures as there are patients with diabetes)	No standard laboratory capacity for most diabetes clinics; high number of patients with diabetes unwilling to provide sputum sample ³⁶
Xpert MTB/RIF	<i>M tuberculosis</i> PCR; also detects rifampicin resistance	Very high	Hours	Sensitivity: 88%; specificity: 98% (pooled data from 15 screening studies with Xpert MTB/RIF as an initial test replacing smear microscopy) ³⁷	High cost, low throughput	No specific issues; automated, closed system; no laboratory or skills needed ³⁷

PCR=polymerase chain reaction. LED=light-emitting diode. *Screening completed in a general population. †Gold standard for any positive microbiological screen.

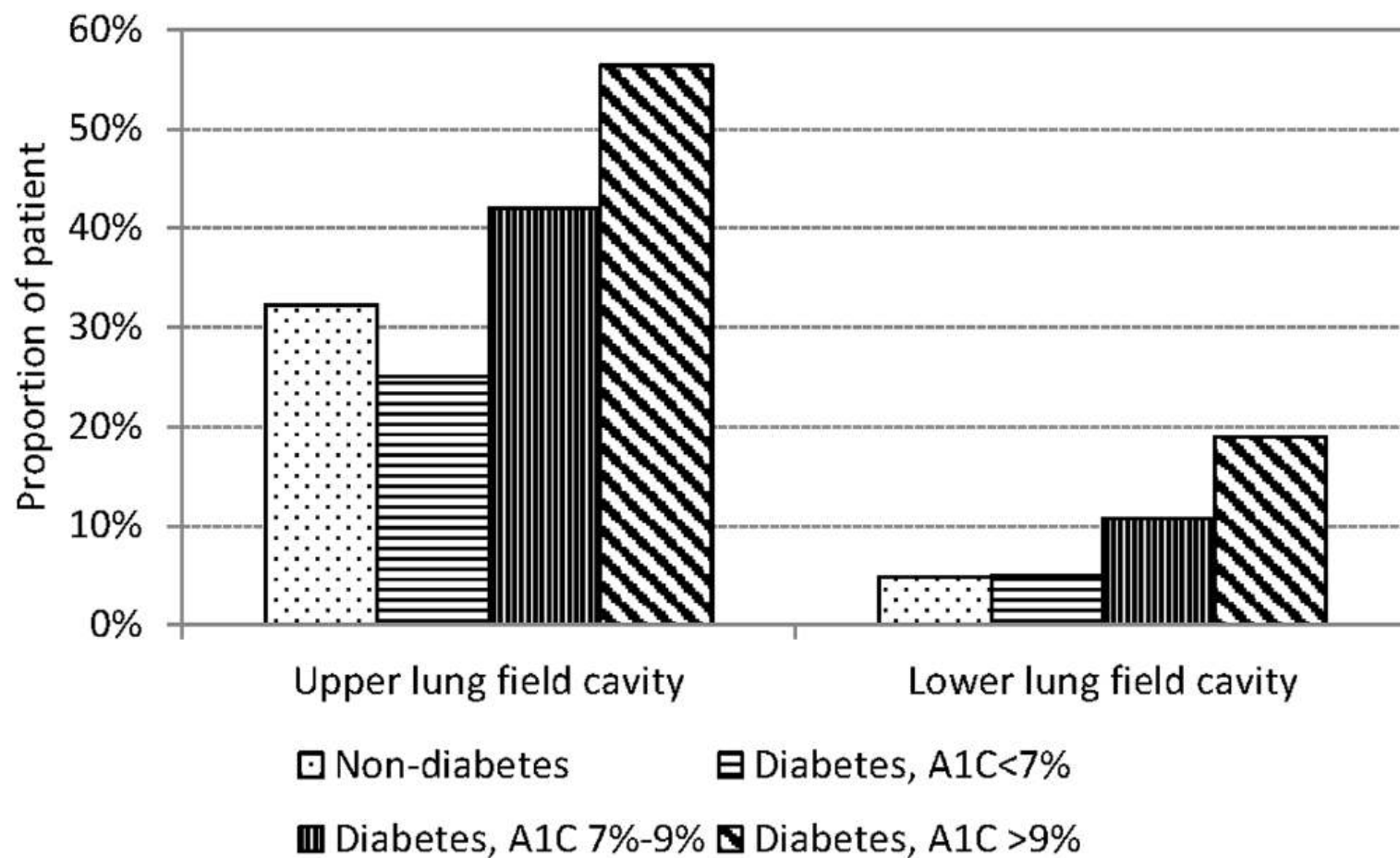
Effect of DM on radiological appearance of TB

Country, year	No. of patients with TB		Radiological findings		Reference
	DM	No DM	More lower lobe involvement in DM	More cavitations/other lesions in DM	
USA, 1974	20	182	Yes	n.a	Weaver 1974
South Africa, 1980	9	427	Yes (29 vs. 5%)	n.a	Marraiss 1980
United Kingdom, 1983	43	31	No difference	Yes (22 vs. 6%)	Hendy & Stableforth 1983
Japan, 1991	38	71	No (3 vs. 17%)	Yes (44 vs. 20%)	Frezon <i>et al.</i> 1992
USA, 1992	20	20	No difference	No difference	Morris <i>et al.</i> 1992
Turkey, 1994	37	37	More multilobar involvement in DM	Yes	Umut <i>et al.</i> 1994
Saudi Arabia, 1997	28	38	No difference	No difference	al-Wabel <i>et al.</i> 1997
Turkey, 2001	92	92	No difference	No difference in cavities Fewer reticulonodular lesions (13 vs. 30%)	Bacakoglu <i>et al.</i> 2001
Mexico, 2000–2001	192	130	Yes (19 vs. 7%)	Yes (82 vs. 59%), More lower lung cavities (29 vs. 3%)	Perez-Guzman <i>et al.</i> 2000, 2001
Saudi Arabia, 2003	187	505	Yes (23 vs. 2.4%)	Yes (51 vs. 39%)	Shaikh <i>et al.</i> 2003
Malaysia, 2005	230	1226	Yes (11 vs. 9%), NS	No (63 vs. 73%; NS)	Nissapatorn <i>et al.</i> 2005
Taiwan, 2005	99	362	No (NS)	Yes (19 vs. 10%)	Wang <i>et al.</i> 2005
Texas, 2007	401	1040	–	Yes (60 vs. 48%)	Restrepo <i>et al.</i> 2007
Taiwan, 2009	74	143	Yes (27 vs. 15.4%)	Yes (45.9 vs. 30.8%)	Wang <i>et al.</i> 2009

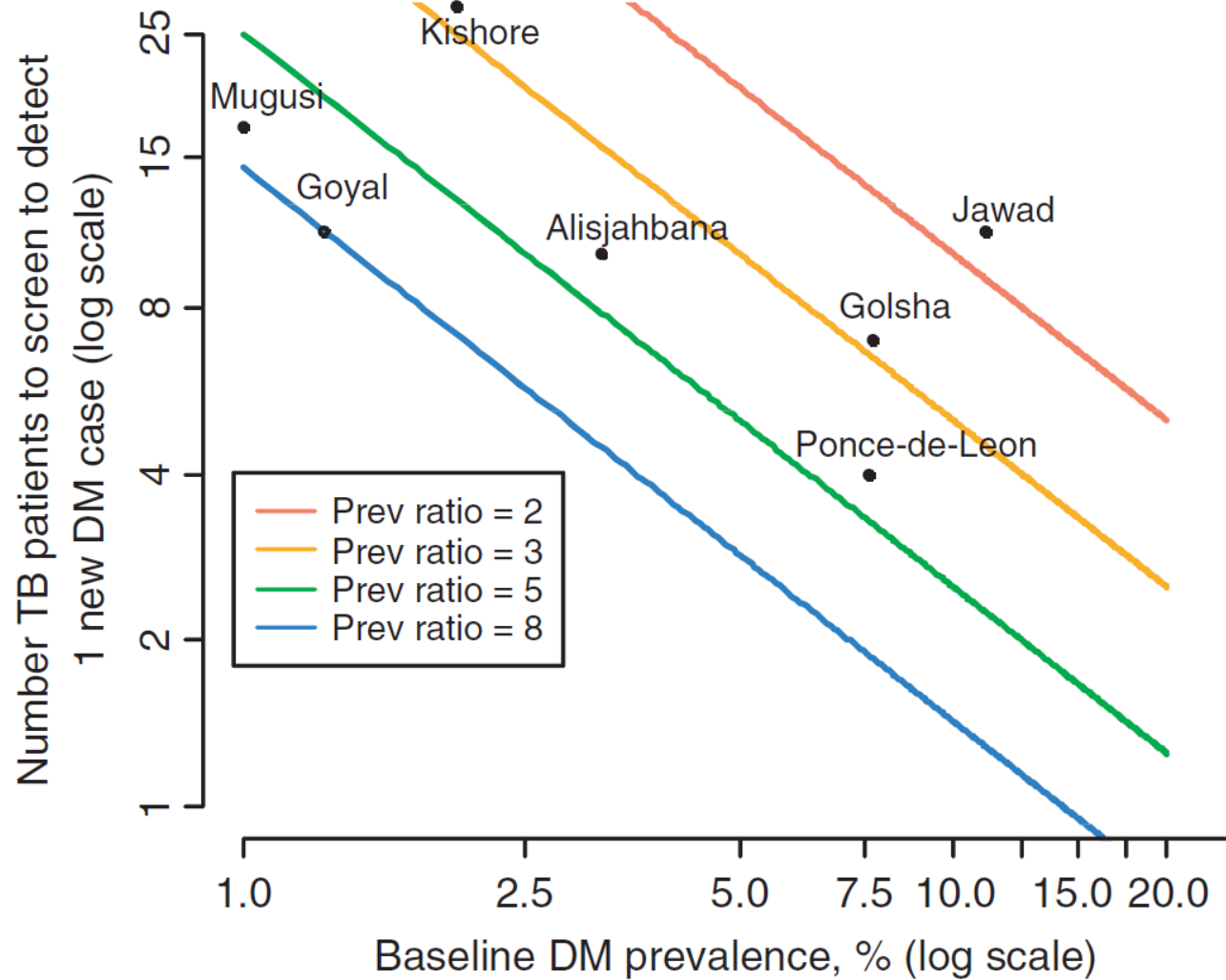
No strong evidence of differences in radiographic presentation

Glycemic control & Radiographic Manifestations

1209 culture positive pulmonary TB patients (581 with DM and 628 without DM)
3 tertiary-care hospitals in Taiwan



No. of TB to screen to detect one additional DM



Two TB control programs in India and the Pacific Islands region

- The Pacific Islands region
 - high prevalence of DM (1/3 of adults)
 - Diabetes screening is recommended for all adults (>18 year-old) with TB
- Both programs recommend repeat testing
 - DM after 2–4 weeks of TB treatment
 - Patients who develop Sx. of hyperglycemia during treatment

Best time and methods to diagnose DM in TB

- **Single measurement of blood glucose concentrations**
 - false diagnosis of DM
- **Repeat testing of blood glucose concentrations**
 - could identify transient hyperglycaemia
- **A1c**
 - is the only diabetes test that shows average glycaemia over time and in a single study
- **If screening at treatment initiation is done, a second test during tuberculosis treatment, or after treatment completion, seems logical.**

Tests for screening & diagnosis of DM in TB

	Mode of action	Comparative direct costs, and perceived benefits	Sensitivity and specificity*	Restrictions	Issues of use in patients with tuberculosis
Screening tests					
Clinical assessment	Classic signs and symptoms of diabetes	Low; fast; easy to obtain	Comparatively very low sensitivity and specificity	Very low sensitivity	Overlap with tuberculosis symptoms, diagnostic for diabetes when plasma glucose concentrations raised
Risk scores	Questionnaire to compute a score for diabetes based on clinical or socio-demographic characteristics	Low; non-invasive; easy to implement	Sensitivity 35–72%; specificity 77–83%; many alternate risk scores exist, broad ranges of sensitivity and specificity show the heterogeneity between scores available; Finnish best validated and most commonly used ⁶¹	Fewer risk scores validated in low-income and middle-income countries	Diabetes risk markers might differ in patients with tuberculosis (weak evidence)
Urinary dipstick	Point-of-care test with urine sample	Low; fast; less invasive than blood tests	Sensitivity 16–64%; specificity >98%; figures are ranges across studies; broad ranges show the heterogeneity in test reading and interpretation ^{61,62}	Low sensitivity, particularly after eating	None noted
Capillary glucose (fasting or non-fasting)	Finger-prick blood test	Low; straightforward; widely available, no need for laboratory capacity	Sensitivity 40–75%; specificity 66–96% ^{61,62}	Point-of-care meters affected by calibration, heat, humidity, and other factors	All single timepoint tests might give false positive results because of intermittent hyperglycaemia caused by tuberculosis associated inflammation

Tests for screening & diagnosis of DM in TB

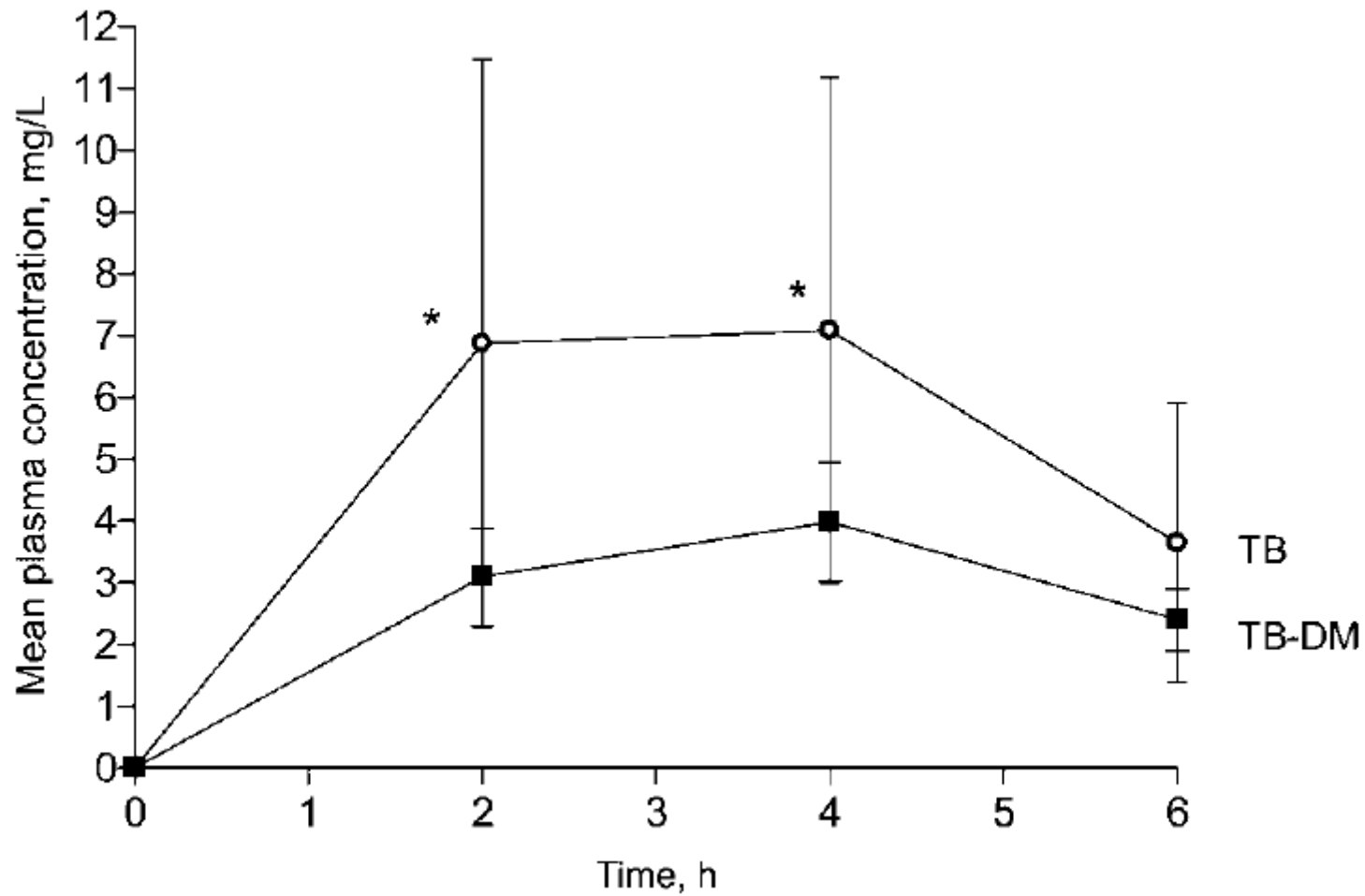
	Mode of action	Comparative direct costs, and perceived benefits	Sensitivity and specificity*	Restrictions	Issues of use in patients with tuberculosis
Diagnostic tests					
Random (non-fasting) plasma glucose	Blood sample, taken at any time	Medium; widely available through laboratory or point-of-care tests	Sensitivity 40–65%; specificity 90–93% ^{61,62†}	Must process in <2 h; difficult to interpret; affected by short-term lifestyle changes and diet	All single timepoint tests might give false positive results because of intermittent hyperglycaemia caused by tuberculosis associated inflammation
Fasting plasma glucose	Blood test taken in morning after 8 h fast	Medium; most laboratories can do this point-of-care test	Sensitivity 66–85%; specificity 98% ^{61,62†}	Must process in <30 min; affected by short-term lifestyle changes; not all patients fast fully before test; needs return appointment	Not practical in tuberculosis clinics; fasting might be contraindicated in active tuberculosis; all single timepoint tests might give false positive results because of intermittent hyperglycaemia caused by tuberculosis associated inflammation
HbA _{1c}	Blood test; requires NGSP- or IFCC-certified laboratory, or point-of-care meter	High; can provide rapid result at point of care; no fasting required	Sensitivity 44–66%; specificity 79–98% ^{62†}	High stability but less sensitive as a diagnostic test than fasting plasma glucose or oral glucose tolerance test; assays can be affected by haemoglobinopathies and anaemias	A measure of average blood glucose concentration during previous 8–12 weeks might miss new onset cases of diabetes
Oral glucose tolerance test	Blood sample after 8 h fast plus repeat testing (2 h) after oral glucose challenge	High; most sensitive test for diabetes	Gold standard†	Needs to be processed within 30 min; time consuming and complex	Not practical in tuberculosis clinics; all single timepoint tests might give false positive results because of intermittent hyperglycaemia cause by tuberculosis associated inflammation

Management for concurrent TB & DM

- Treatment of TB in DM

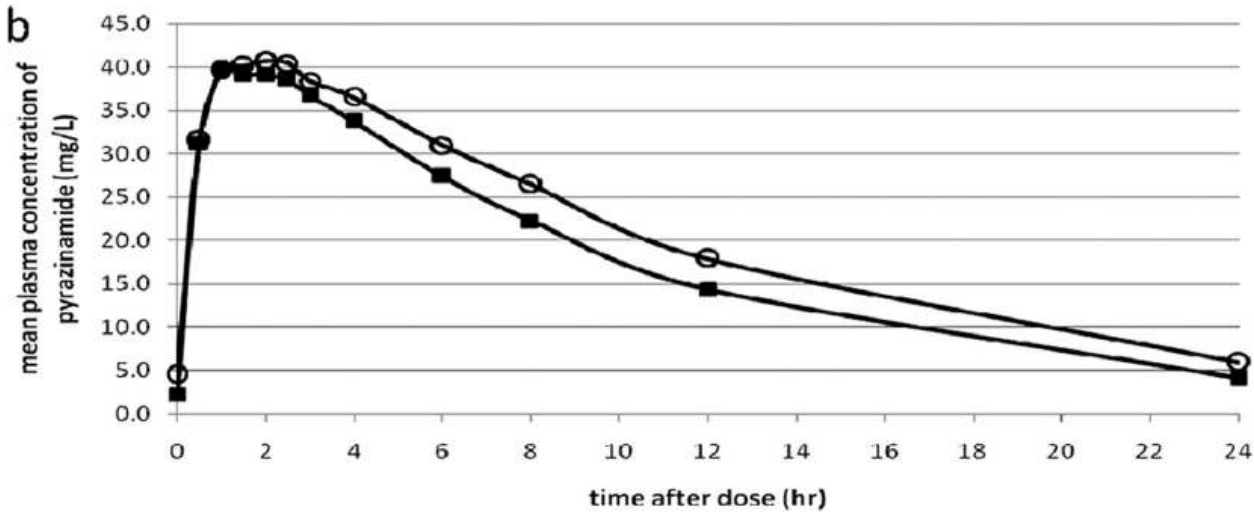


Exposure to rifampicin (RIF) is strongly reduced in TB & DM

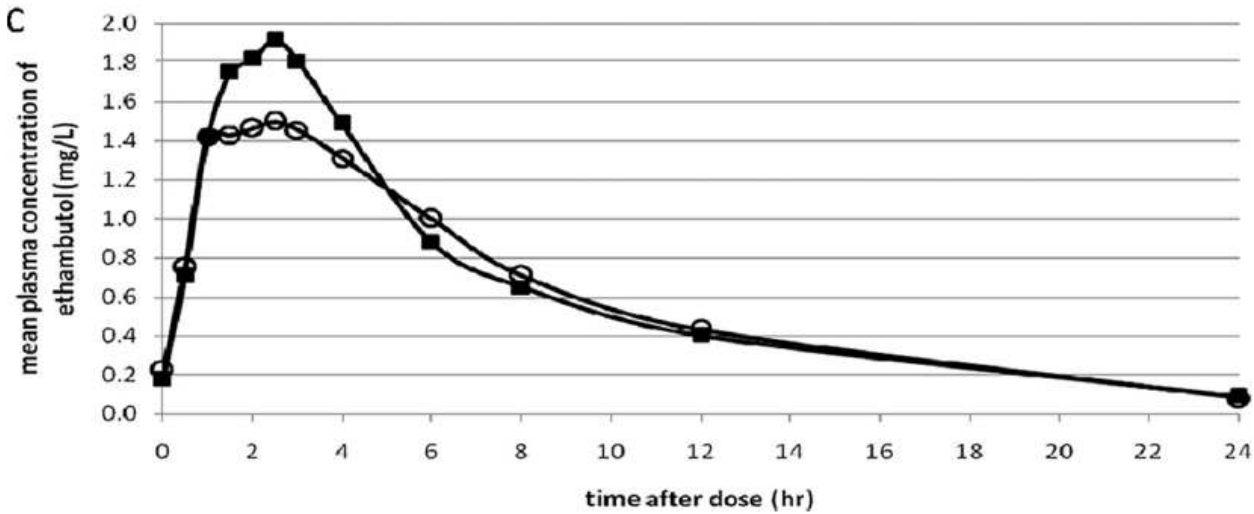


Pharmacokinetics of anti-TB drugs in TB & DM

PZA



EMB

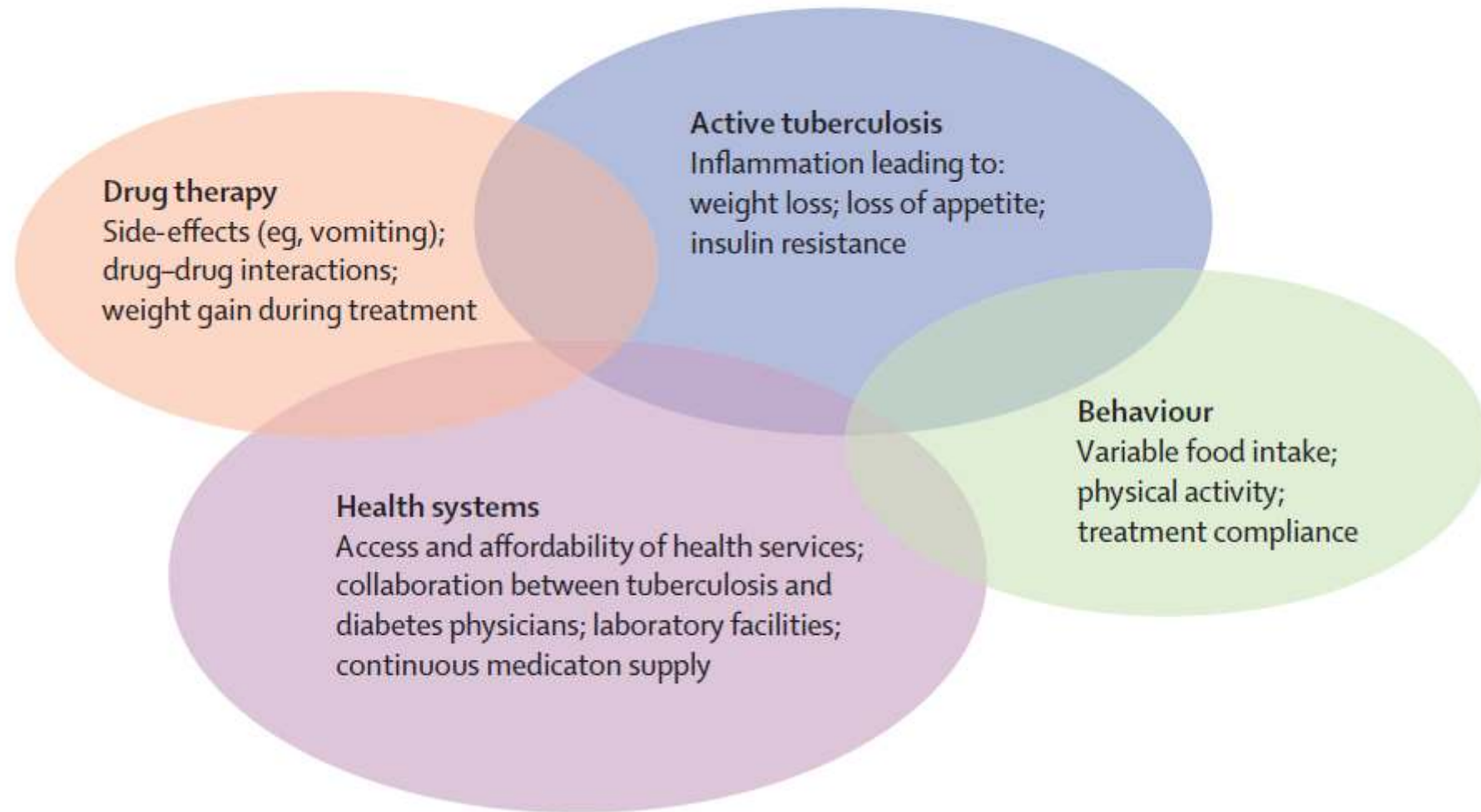


Management for concurrent TB & DM

- Treatment of DM in TB



Factors that affect glycemic control for patients with DM during treatment for TB



Effect of RIM on the exposure to antidiabetic drugs

Antidiabetic drug	Change in exposure (AUC)	Enzyme induction
Insulin	No effect anticipated	
Sulphonylureas		
Tolbutamide	Strong decrease	
Glibenclamide (Glyburide)	-39%	CYP2C9
Gliclazide	-70%	CYP2C9
Glimepiride	-34%	CYP2C9
Glipizide	-22%	CYP2C9
Biguanides		
Metformin	No effect anticipated	
Meglitinide analogues		
Repaglinide	-57%, -31%, -50%	CYP3A4, CYP2C8
Nateglinide	-24%	CYP2C9, CYP3A4
Thiazolidine-diones		
Rosiglitazone	-54%, -65%	CYP2C8
Pioglitazone	-54%	CYP2C8

Effect of **RIF** on the exposure to antidiabetic drugs



Other Anti-TB drugs

Isoniazid (INH)

- An inhibitor of some of the enzymes (CYP2C9)
- Overall effect of (INH + RIF)
: a decrease in the concentrations of other drugs
- Toxic effect, peripheral neuropathy
: one of complications of diabetes

Ethambutol (EMB)

- Unlikely whether it interacts with any antidiabetic drugs
- Ocular toxic effects
- Dosing frequency should be decreased when patients with diabetes have reduced kidney function

The choice of anti-diabetic drugs in TB

- **Insulin**

- Because insulin is not metabolised, it has no pharmacokinetic interactions with RIF or other anti-TB drugs
- At the start of TB treatment has been suggested
- Some national treatment guidelines strongly suggest the use of insulin for DM in TB

- **Metformin**

- not metabolised by P450 enzymes
- RIF increases the expression of organic cation transporter (OCT1) and hepatic uptake of metformin, leading to an enhanced glucose-lowering effect
- Possible disadvantages is gastrointestinal side effects



Implications for health service delivery and health economics

Implementation of integrated services for concurrent TB & DM: lessons learned from HIV & TB

Clinical algorithms

Evidence-based algorithms for bidirectional screening and combined treatment of tuberculosis and HIV have been developed^{40,45,46}

Tuberculosis chemoprophylaxis

Tuberculosis chemoprophylaxis (isoniazid preventive therapy) is indicated for all patients with HIV once active tuberculosis is excluded; implementation might be easier in patients with diabetes as active tuberculosis can more reliably be excluded in patients with diabetes than in those with HIV; however, the efficacy of such preventive treatment is unknown⁵⁰⁻⁵²

Health promotion

Training materials and other techniques used for HIV alone and combined HIV and tuberculosis can be adapted to create methods for lifestyle interventions for patients with concurrent tuberculosis and diabetes

Tuberculosis infection control

Evidence-based policies are available for implementation of sound tuberculosis infection control in health-care facilities, including use of available spaces, separation of infectious patients, tuberculosis surveillance and preventive therapy for health workers, and environmental controls such as ventilation systems⁹⁰

Decentralisation of health services

Mobile units have a high yield for combined screening of HIV, tuberculosis, diabetes, and hypertension in South Africa;⁹¹ linking to chronic care is challenging; successful community engagement (eg, in work sites and households) used for tuberculosis and HIV could be adapted for tuberculosis and diabetes

Human resources, task shifting

Task shifting from physician to non-physician and to lay health worker to combat growing burden of disease is safe and cost-effective⁹²⁻⁹⁴

Human resources, task shifting

Task shifting from physician to non-physician and to lay health worker to combat growing burden of disease is safe and cost-effective⁹²⁻⁹⁴

Drug delivery

Combination of treatments for several diseases leads to strengthening of health systems (eg, supply chain, laboratory services) and increases accessibility and availability of care; tuberculosis and HIV treatment is free, diabetes treatment often is not

Point-of-care diagnosis

Point-of-care diagnosis of HIV and tuberculosis has led to improved access to care and early treatment; point-of-care HbA_{1c} testing might have similar effects to increase diagnosis and care of diabetes in under-resourced settings⁹⁵

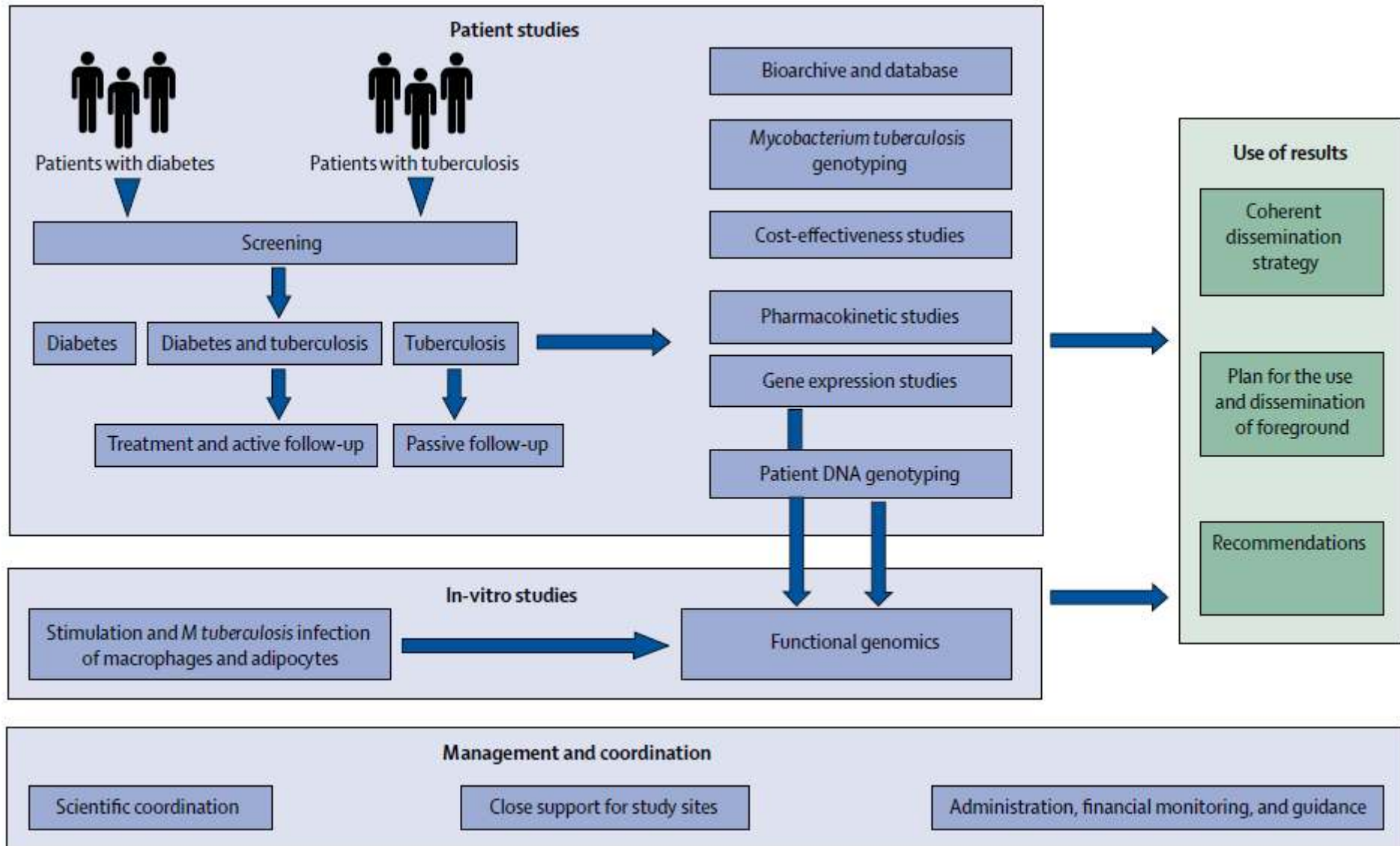
Standardised recording and reporting

Cohort records and reports from the DOTs (directly observed therapy, short course) framework were adapted and used to monitor individuals with diabetes in Malawi;⁹⁶ tuberculosis treatment cards and registers might need modifications to capture information on diabetes screening and diagnosis, just as with HIV

Adherence and retention to care

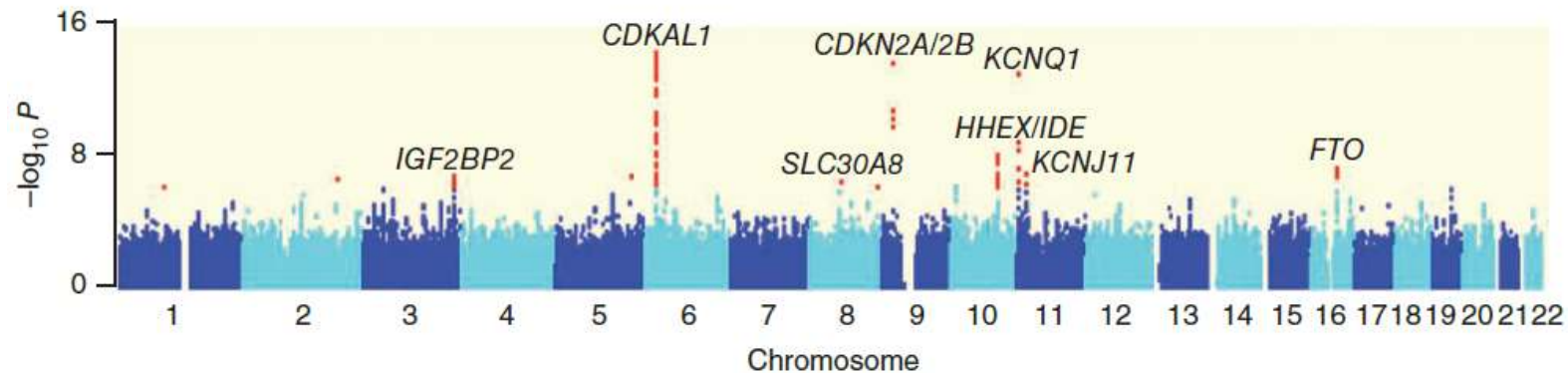
Various strategies have helped sustain long-term adherence and retention to care, including empowered patients,⁹⁷ who are actively involved in their own medical care, and mobile phone technology⁹⁸

TANDEM: DM & TB



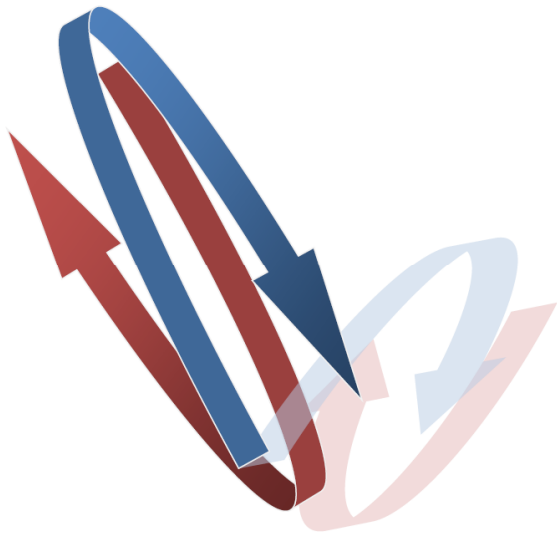
Common or rare variants affecting both susceptibility for TB and DM ?

Meta-analysis of GWAS identifies 8 new loci for T2DM in east Asians



SNP	Chr.	Position (bp)	Nearby gene	Risk allele	Other allele	Stage 1 (discovery) ^a		Stage 2 (<i>in silico</i> replication) ^b		Stage 3 (<i>de novo</i> replication) ^c		Combined (stages 1, 2 and 3) ^d	
						OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Loci showing strong evidence of association with T2D													
rs6815464	4	1,299,901	MAEA	C	G	1.09 (1.04–1.14)	8.21×10^{-4}	1.13 (1.07–1.20)	3.67×10^{-5}	1.16 (1.11–1.20)	4.15×10^{-15}	1.13 (1.10–1.16)	1.57×10^{-20}
rs7041847	9	4,277,466	GLIS3	A	G	1.09 (1.04–1.14)	1.29×10^{-4}	1.09 (1.03–1.15)	2.20×10^{-3}	1.11 (1.07–1.15)	2.89×10^{-9}	1.10 (1.07–1.13)	1.99×10^{-14}
rs6017317	20	42,380,380	FITM2-R3HDM1-HNF4A	G	T	1.10 (1.05–1.15)	2.43×10^{-5}	1.07 (0.99–1.15)	8.42×10^{-2}	1.10 (1.06–1.14)	3.96×10^{-7}	1.09 (1.07–1.12)	1.12×10^{-11}
rs6467136	7	126,952,194	GCC1-PAX4	G	A	1.12 (1.06–1.18)	6.47×10^{-5}	1.11 (1.04–1.18)	2.09×10^{-3}	1.10 (1.05–1.15)	2.31×10^{-5}	1.11 (1.07–1.14)	4.96×10^{-11}
rs831571	3	64,023,337	PSMD6	C	T	1.11 (1.06–1.17)	4.85×10^{-6}	1.06 (1.00–1.13)	4.46×10^{-2}	1.08 (1.05–1.12)	1.41×10^{-5}	1.09 (1.06–1.12)	8.41×10^{-11}
rs9470794	6	38,214,822	ZFAND3	C	T	1.11 (1.05–1.17)	1.45×10^{-4}	1.09 (1.02–1.17)	1.48×10^{-2}	1.16 (1.09–1.23)	3.20×10^{-6}	1.12 (1.08–1.16)	2.06×10^{-10}
rs3786897	19	38,584,848	PEPD	A	G	1.14 (1.08–1.20)	3.74×10^{-6}	1.05 (0.99–1.12)	1.28×10^{-1}	1.11 (1.04–1.17)	5.46×10^{-4}	1.10 (1.07–1.14)	1.30×10^{-8}
rs1535500	6	39,392,028	KCNK16	T	G	1.11 (1.06–1.16)	5.34×10^{-6}	1.07 (1.01–1.15)	3.33×10^{-2}	1.06 (1.02–1.10)	3.50×10^{-3}	1.08 (1.05–1.11)	2.30×10^{-8}
Loci showing moderate evidence of association with T2D													
rs16955379 ^e	16	80,046,874	CMIP	C	T	1.13 (1.07–1.20)	2.20×10^{-5}	1.10 (1.03–1.17)	6.59×10^{-3}	1.05 (1.01–1.10)	2.19×10^{-2}	1.08 (1.05–1.12)	2.84×10^{-7}
rs17797882	16	77,964,419	WWOX	T	C	1.12 (1.05–1.18)	1.76×10^{-4}	1.09 (1.02–1.16)	1.21×10^{-2}	1.06 (1.01–1.11)	1.61×10^{-2}	1.08 (1.05–1.12)	9.49×10^{-7}

Collaborative Framework for Care and Control of Tuberculosis and Diabetes



Key questions for future research in TB & DM

- What is the effect of glycemic control (both short term and long term) on TB infection, active TB, and TB treatment outcomes?
- What are the most feasible techniques or strategies for screening for DM in patients with TB and the converse?
- How cost effective are strategies for screening and clinical management?
- Is screening and prophylactic treatment of latent TB infection indicated for people with DM?
- What is the possible benefit and what are the operational issues related to intensified monitoring of DM and its treatment in patients with TB? And what is the respective role of insulin versus metformin or other antidiabetic drugs?
- What models of health service delivery can contribute to integration and sustainability of care for DM and TB in low-income and middle-income countries?

Summary

- The prevalence of DM with TB will continue to increase as a result of the rising global burden of T2DM.
- Although screening patients with TB for DM is recommended, many questions are unanswered with respect to the best way to implement screening in different settings.
- Screening patients with DM for active TB could be considered but the best clinical algorithm needs to be identified and cost-effectiveness remains to be established.
- Good glycemic control might improve health outcomes when TB and DM are simultaneously treated. TB treatment monitoring might need to be more intensive if patients with TB also have DM.
- Integration of health services could result in better TB prevention, an early diagnosis and start of treatment for DM, and improved care for concomitant disease.
- There is a call to clinicians and researchers to generate the necessary evidence for improvements to patient services and policies with respect to combined TB and DM.

Thank you for your attention!

