Diabetes related TB and a primer on Therapeutic Drug Monitoring

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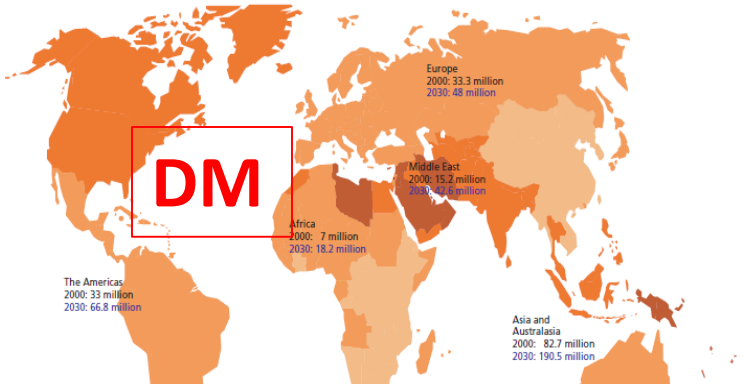
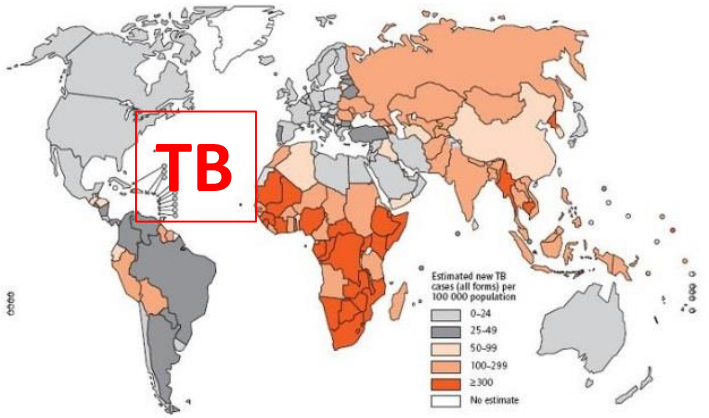


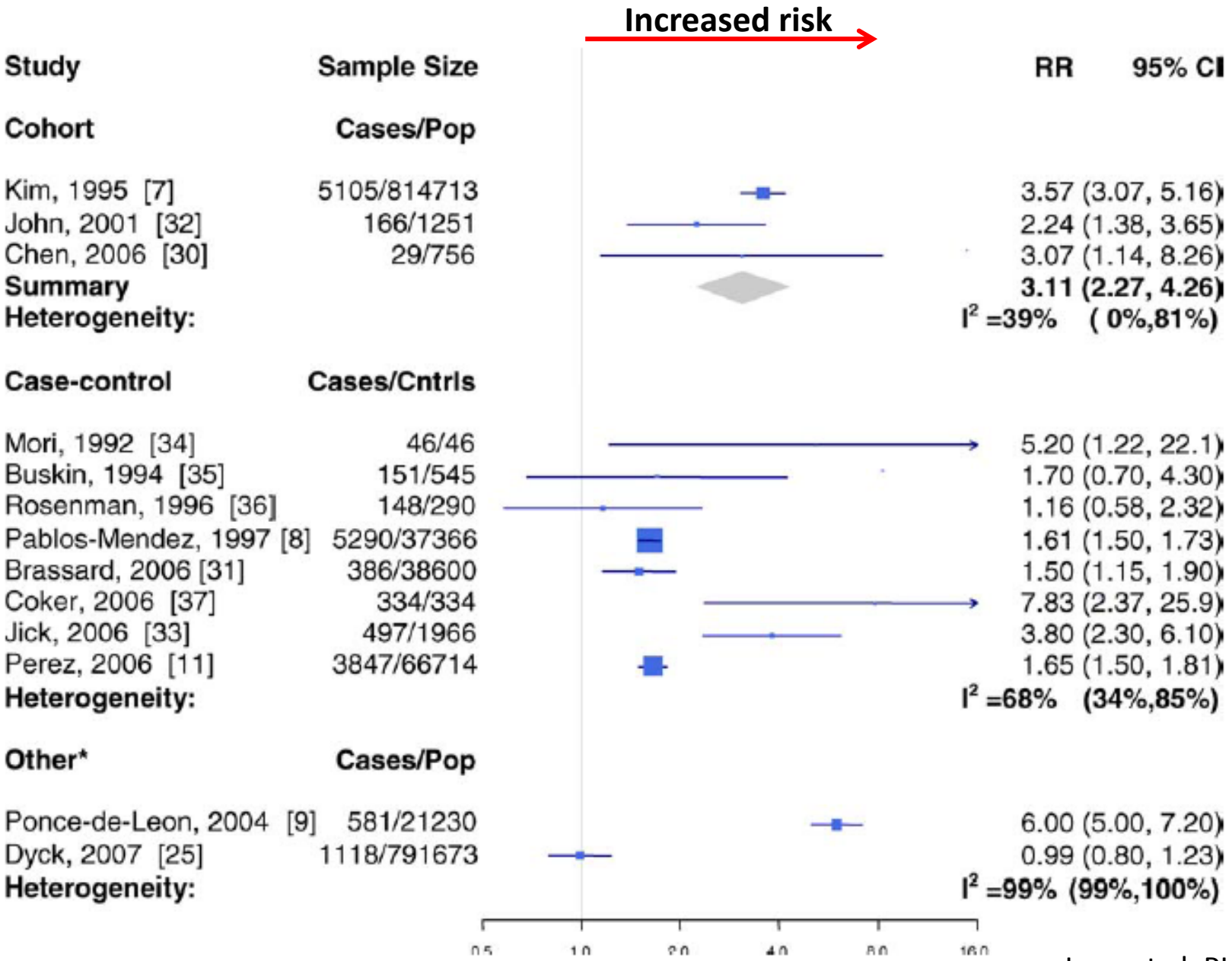
Outline



- **Overview** of diabetes (DM) and tuberculosis (TB) interaction
- **Local case study**
- **Pathophysiology**
- **Global case study**: Dhaka, Bangladesh
- The case for **metformin**
- What we are doing in **Virginia**→

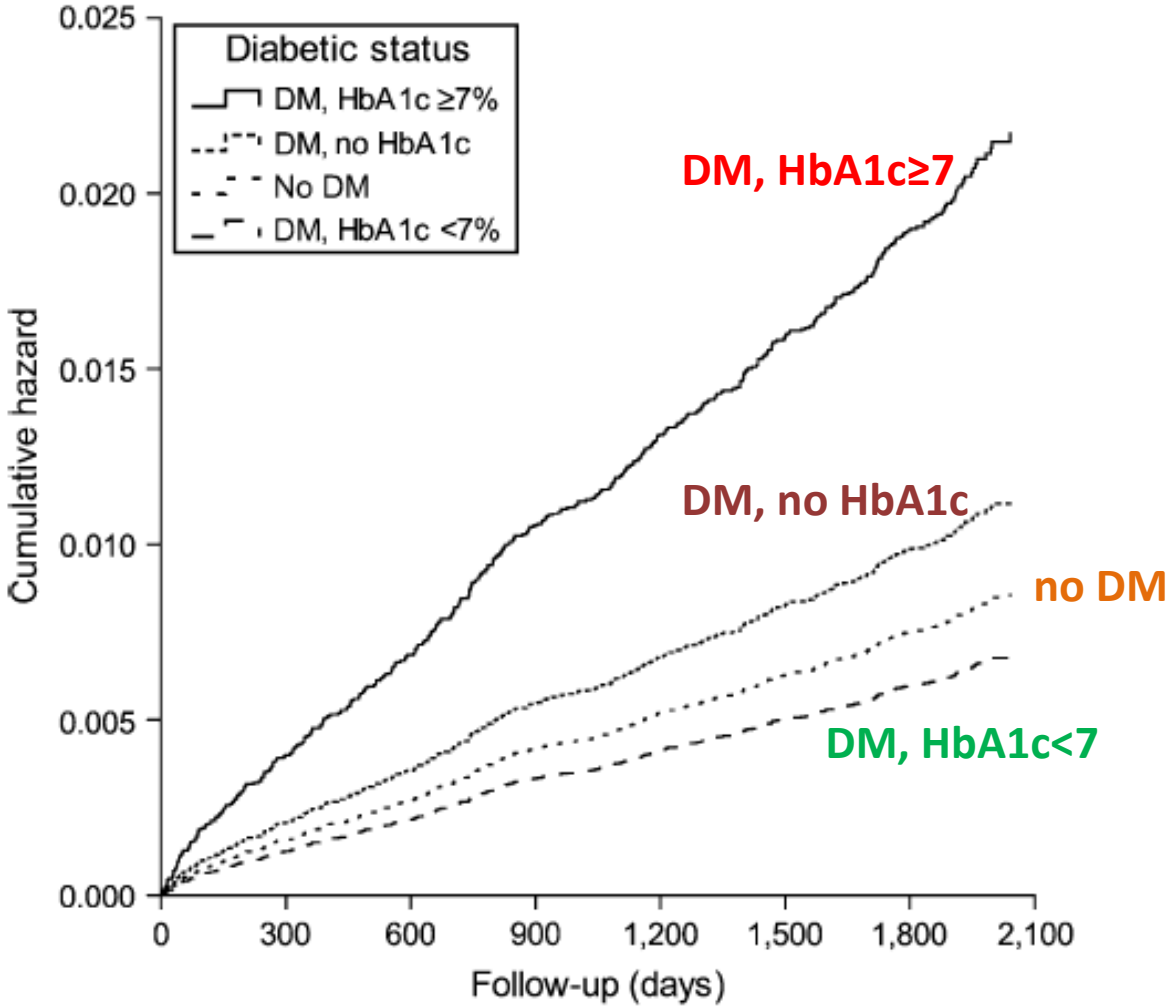
-screening for DM in TB patients (hemoglobin A1c)
-linkage to DM care (metformin)
-early **therapeutic drug monitoring**
-patient/provider education (DM-TB flipchart)
-future study of therapeutic drug monitoring from urine

Diabetes is consistently a risk factor for developing active TB



Jeon et al. PLoS Med 2008

Severity of diabetes increases the risk for TB

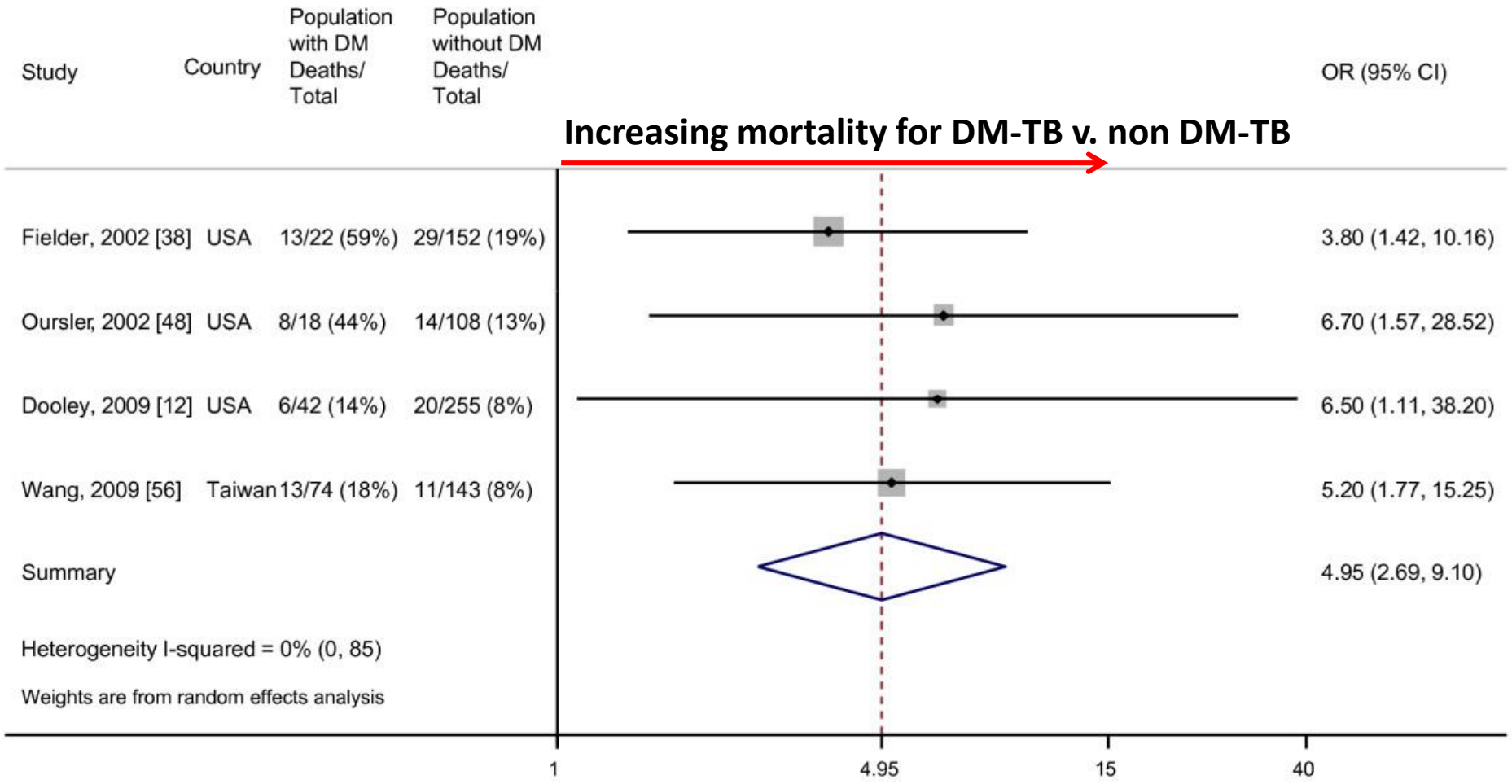


42,000 adults >65 years old from Hong Kong*

Diabetes with HbA1C≥7 compared to <7; odds for developing active PTB were **3.63 (1.79-7.33)***

1. Pablos-Mendez et al. *Am J Pub Health* 1997
*2. Leung et al. *Am J Epi* 2008

All cause mortality increased in diabetics during TB treatment (compared to non-diabetics)



Baker et al. *BMC Med* 2011

A local case

70 year-old man was admitted to UVA this month with 2 weeks of **fever**

ROS also elicits a **chronic cough** (which was not the patient's primary complaint) and he notices a foreign body sensation in his **throat** for months

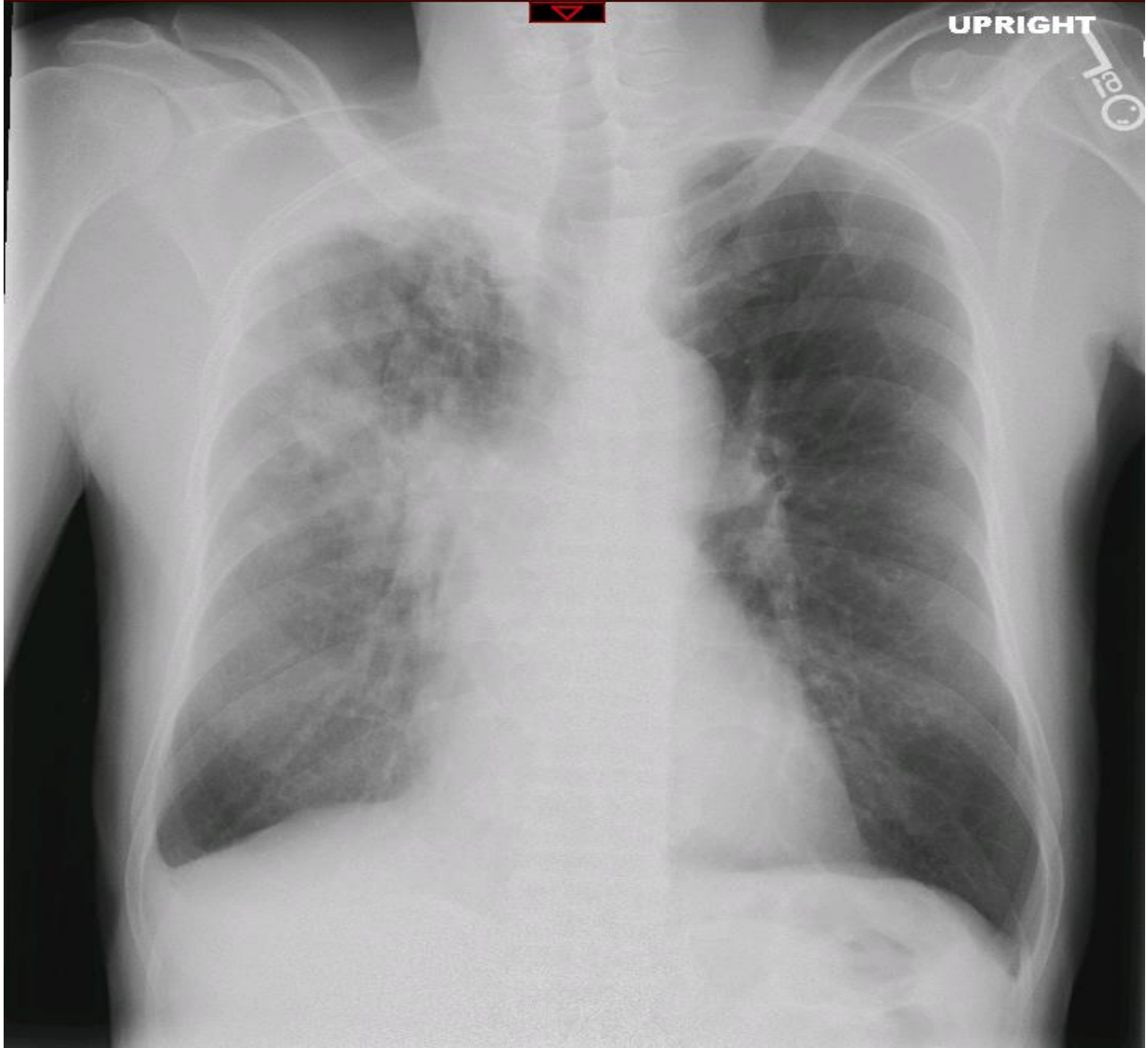
Fever wakes him at night, though does not soak the bed sheets, and accompanied by significant malaise. He notes 6-7 kg **weight loss** over the past 3 months.

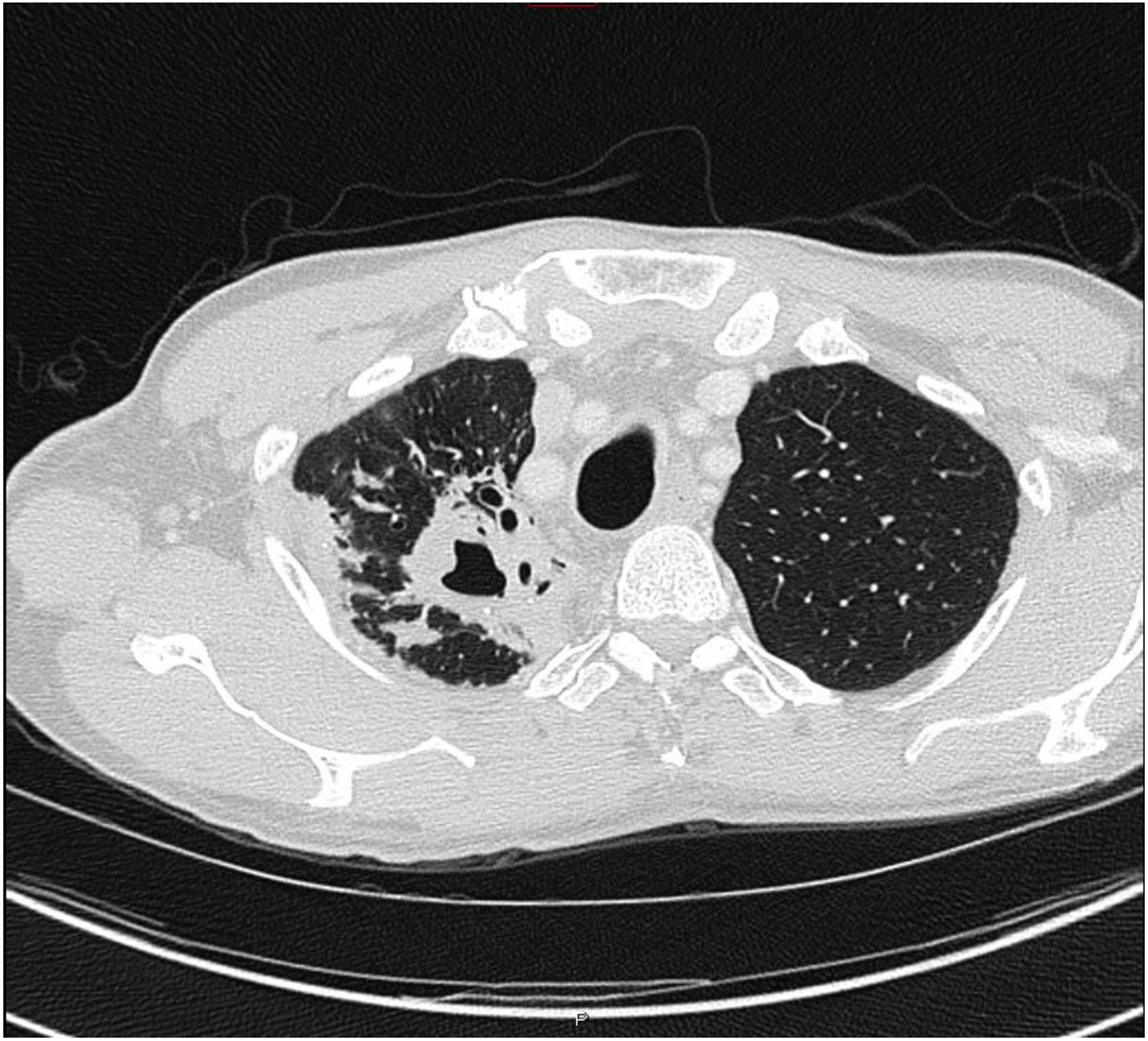
Now it gets even more interesting…

Patient is originally from Ghana and returned last week following a 6 month visit. In Ghana he was treated with an anti-malarial that did not help his cough or his fever. He denies known TB contacts.

He is HIV negative, but has a known history of HTN, BPH and **Type II Diabetes** (on oral medications– not regular fingerstick monitoring while in Ghana)

While sick, he boards an international flight for Charlottesville


UPRIGHT



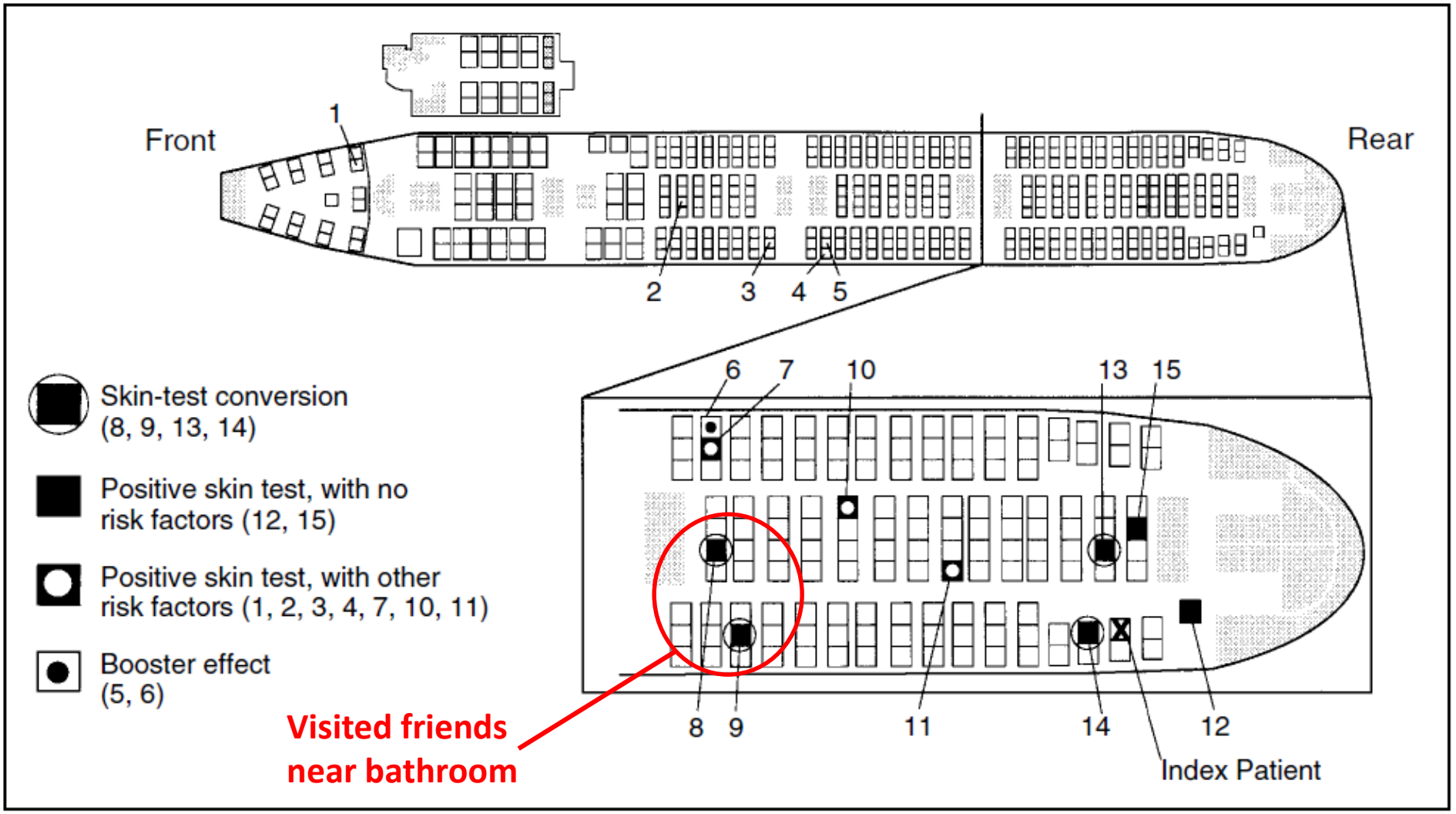
Multiple sputum specimens 2-3+ AFB smear pos

***M. tuberculosis* complex (Xpert)**

Remainder of susceptibilities pending

Defervesced on INH, RIF, EMB, PZA

1994: MDR-TB patient flew 747 from Honolulu→Chicago→Baltimore



925 contacts, 802 responded to survey: 11 skin test conversions→ more likely on the longer flight and proximity to index patient

Kenyon et al. NEJM 1996

The New England
Journal of Medicine

VOLUME 210 JANUARY 4, 1934 NUMBER 1

THE ASSOCIATION OF DIABETES AND TUBERCULOSIS*

Epidemiology, Pathology, Treatment and Prognosis

BY HOWARD F. ROOT, M.D.†

(a) The development of pulmonary tuberculosis in juvenile diabetics occurred more than ten times as frequently as among non-diabetic Massachusetts grade and high school children.

TB more frequent in those with poor diabetes control

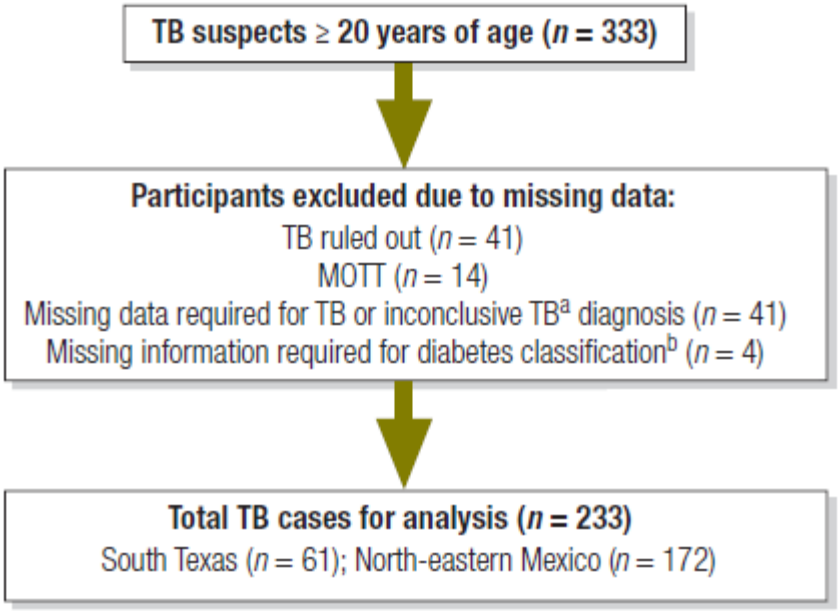
(b) Pulmonary tuberculosis developed in 8 per cent of diabetic patients within three years of recovery from coma.

No "special insidiousness" of signs and symptoms in the "tuberculous diabetic"

(c) The incidence of pulmonary tuberculosis in adult diabetics is increasing despite the general decrease of tuberculosis mortality with consequent reduction of contacts in the community.

Not explained by familial contact, occupation, race, poverty or alcoholism

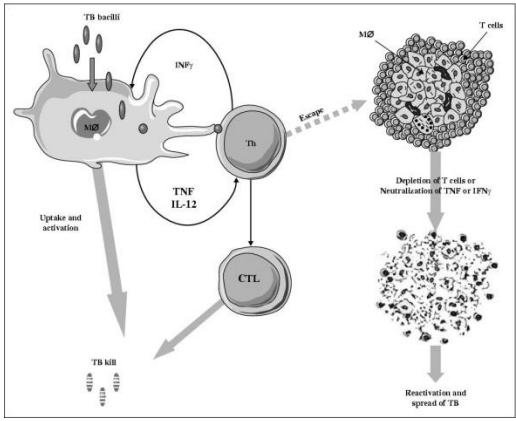
Attributable risk of TB from Diabetes > HIV in Texas/Mexico border



Age (years)	Diabetes			HIV infection		
	RR (95% CI)	$AR_{exposed}$ (%)[a]	$AR_{population}$ (%)[b]	RR (95% CI)	$AR_{exposed}$ (%)[a]	$AR_{population}$ (%)[b]
South Texas						
20+ (*n*=61)	2.7 (1.6–4.4)	63	26	17.8 (6.5–9.0)	94	5
20–34 (*n*=20)	0.9 (0.1–6.8)	–9	1	34.4 (8.0–147.7)	97	6
35–64 (*n*=32)	5.1 (2.6–10.2)	80	48	12.2 (2.9–50.9)	92	5
65+ (*n*=9)	1.7 (0.5–5.8)	41	22	0[c]	NA	NA
NE Mexico						
20+ (*n*=172)	3.1 (2.3–4.2)	68	24	16.0 (7.5–34.0)	94	3

Restrepo et al. *Bull WHO* 2011

Diabetes alters phagocyte chemotaxis, activation and antigen presentation in presence of *M. tuberculosis*



Monocytes from diabetic patients have impaired chemotaxis that does not improve with insulin[1]

Mice with streptozotocin induced diabetes, macrophages had 1/10 of phagocytic activation, despite similar in vitro killing→ 90% died after *M. tuberculosis* challenge, compared to only 10% of non-diabetic mice[2]

In TB patients, alveolar macrophages are less activated and produce less hydrogen peroxide in diabetics compared to non-diabetics[3]

Insulin deficiency causes impaired Fc receptor internalization and rats that have been pancreatectomised have deficient Fc-mediated phagocytosis[4,5]

1. Moutschen et al. *Diab Metab* 1992
2. Saiki et al. *Infect Immun* 1980
3. Wang et al. *Tuberc Lung Dis* 1999
4. Abbras. *Clin Immunol Immunopath* 1991
5. Chang et al. *Diab Res Clin Pract* 1995

Global case study: The city of Dhaka, Bangladesh

- ~18.8 million people in Dhaka

- 1/3 of all diabetics living in 48 lowest income countries in the world, are from **Bangladesh**

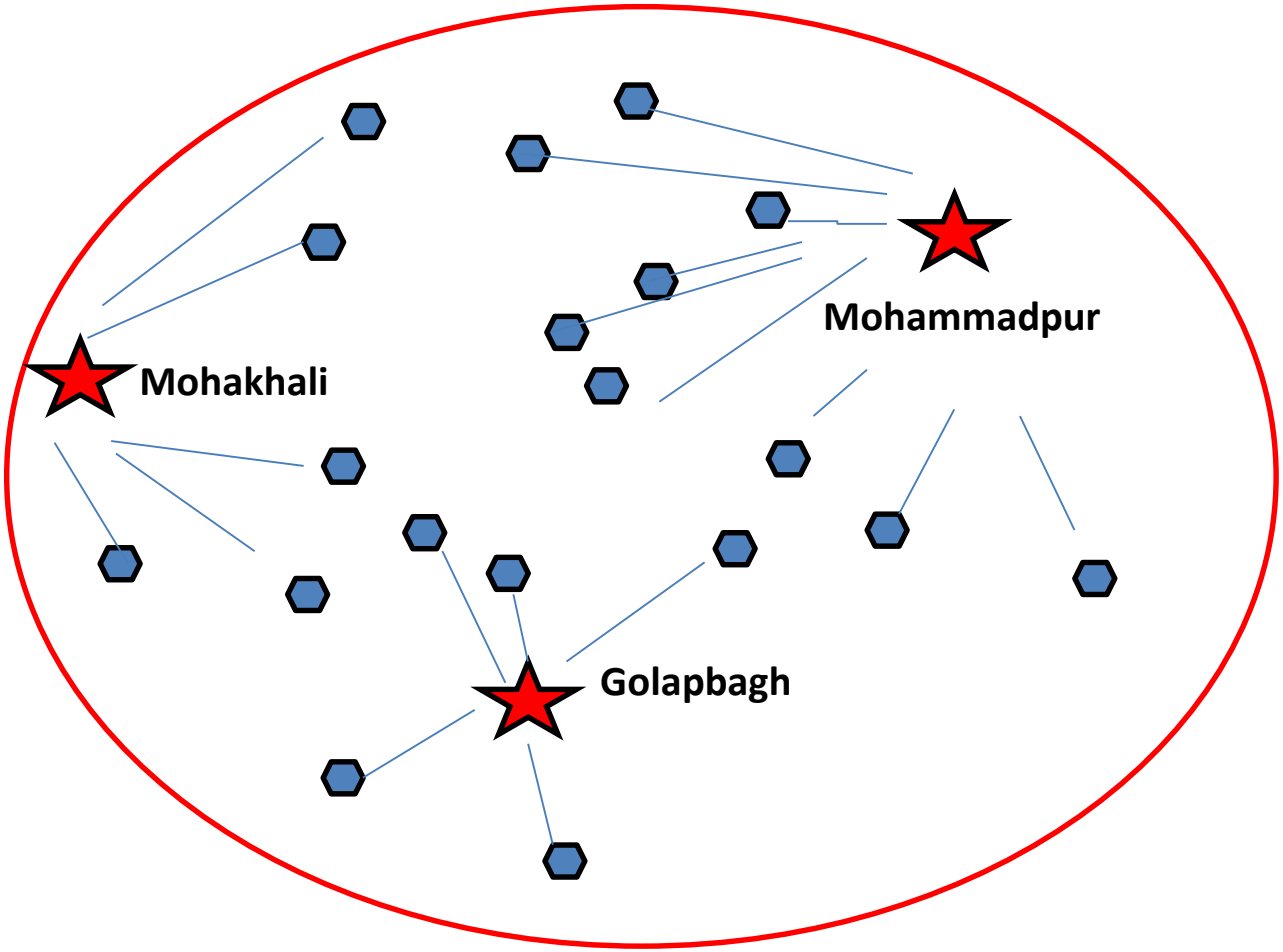
A typical morning commute

Dhaka Tribune, 2014

Screening Centre network of private clinics/ providers in Dhaka

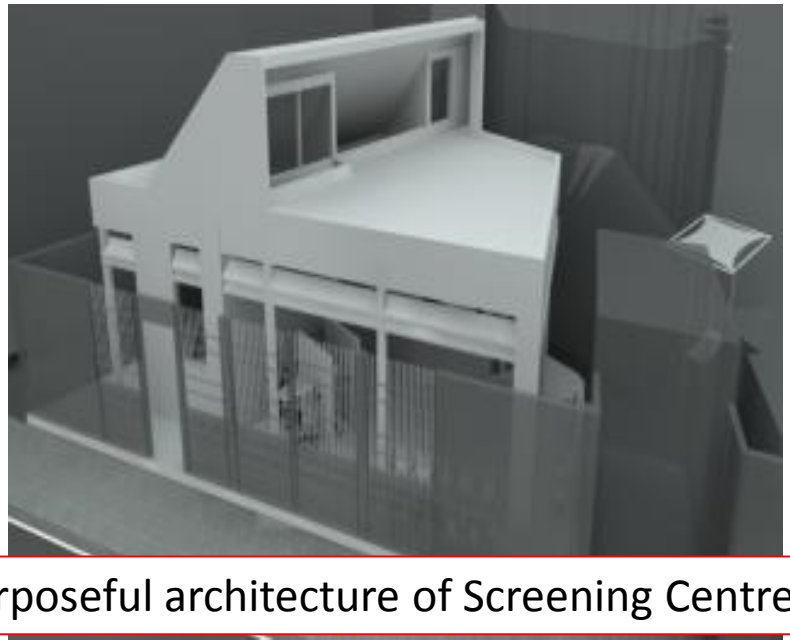
Private clinic in icddr,b network
N= 1,300 physicians or clinics!
- 1 Community Screener at clinic

icddr,b Screening Centre
N= 3
- ~2,200 new TB patients identified annually



Target population:
~8 million working poor accessing low-cost private clinics

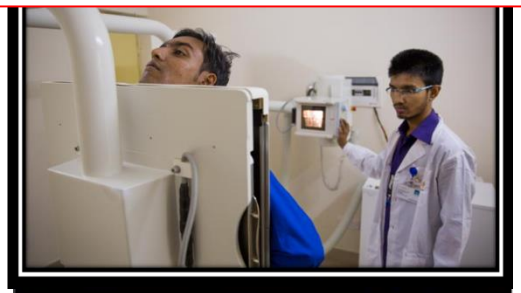
icddr,b

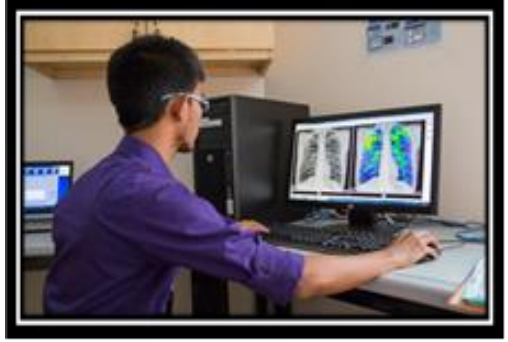


Purposeful architecture of Screening Centre

Waiting area with high air exchange

CAD4 chest x-ray: automatic TB score





Xpert MTB/RIF

In 12 months, **glucometry** in patients: 7,647 underwent testing

832/ 6443 (12.8%) with diabetes among those with **negative Xpert** MTB/RIF

252/ 1204 (20.9%) with diabetes among those with **positive Xpert** MTB/RIF

courtesy Sayera Banu

Diabetics in Indonesia more likely culture positive at 6 months of treatment (22%)

Table 3. Treatment response and outcome of patients with tuberculosis (TB) with and without diabetes mellitus (DM).

Period, variable	No. (%) of patients with TB		Crude OR (95% CI)	Adjusted OR (95% CI)
	With DM (n = 94)	Without DM (n = 540)		
Intensive phase				
AFB negative[a]	67 (71.3)	455 (84.3)	…	…
AFB positive	17 (18.1)	54 (10.0)	2.14 (1.17–3.9)	1.90 (0.82–4.42)
No sputum sample available, hospital transfer, and/or study default	8 (8.5)	31 (5.7)	…	…
Death	2 (2.1)	0 (0)	…	…
Culture result positive for *Mycobacterium tuberculosis*	7/41 (17.1)	68/372 (18.3)	0.92 (0.39–2.16)	0.90 (0.30–2.68)
End of treatment				
AFB negative[a]	70 (74.5)	435 (80.6)	…	…
AFB positive	4 (4.3)	17 (3.1)	1.46 (0.48–4.47)	1.06 (0.17–6.60)
No sputum sample available, hospital transfer, and or study default	18 (19.1)	88 (16.3)	…	…
Death	2 (2.1)	0 (0)	…	…
Culture result positive for *M. tuberculosis*[b]	6/27 (22.2)	32/333 (9.6)	2.69 (1.01–7.14)	7.65 (1.89–30.95)

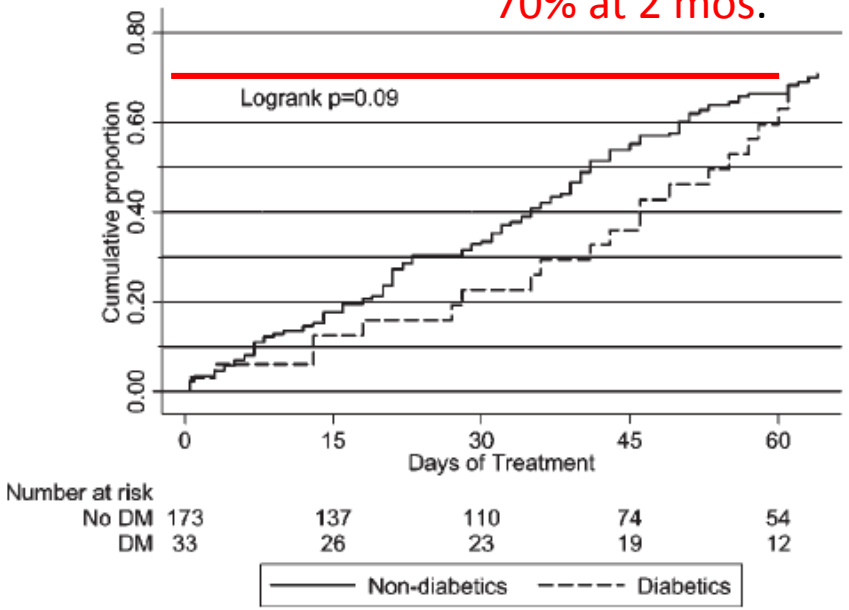
NOTE. The intensive phase was the first 2 months of treatment, and end of treatment was at 6 months. AFB, acid-fast bacilli.

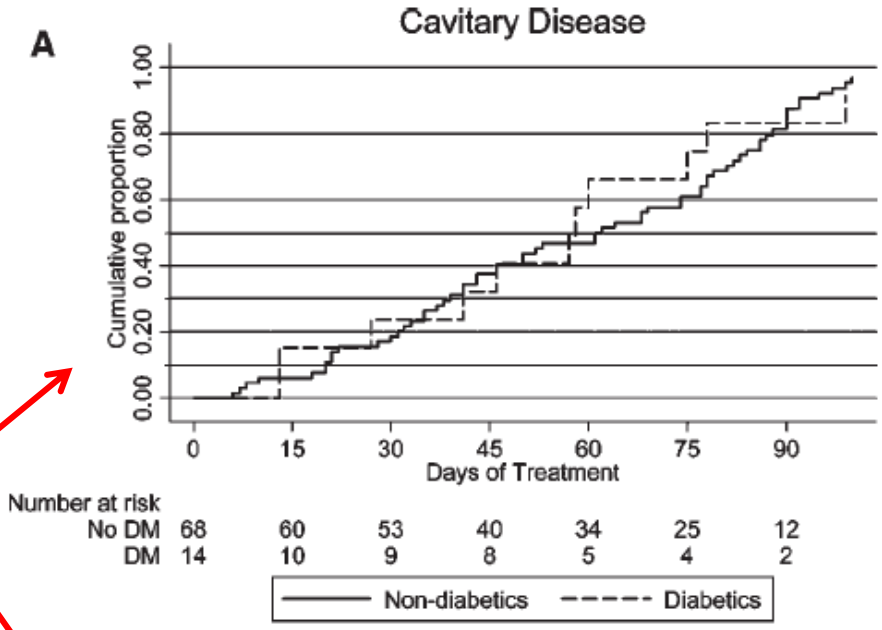
- **14.8% prevalence of undiagnosed DM in new TB patients**
- **TB-DM had greater symptoms at time of diagnosis**

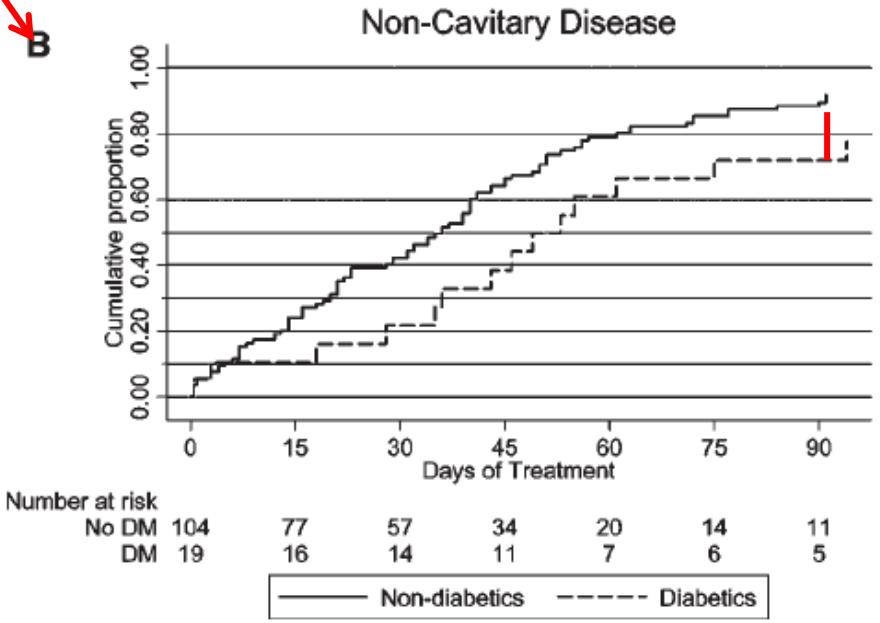
Alisjahbana et al. Clin Infect Dis 2007

Slower culture conversion in diabetics (without cavitary disease)

70% at 2 mos.





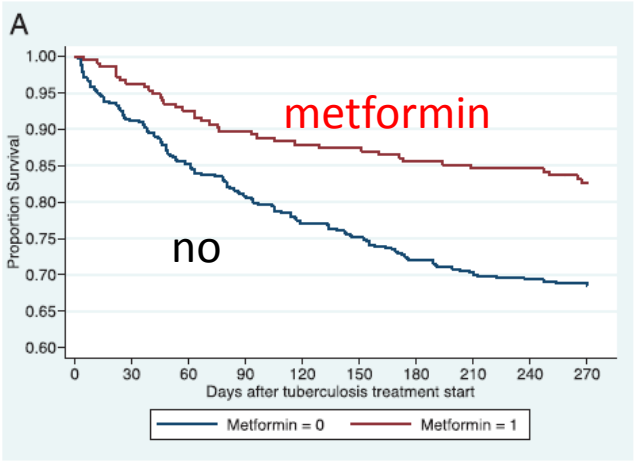


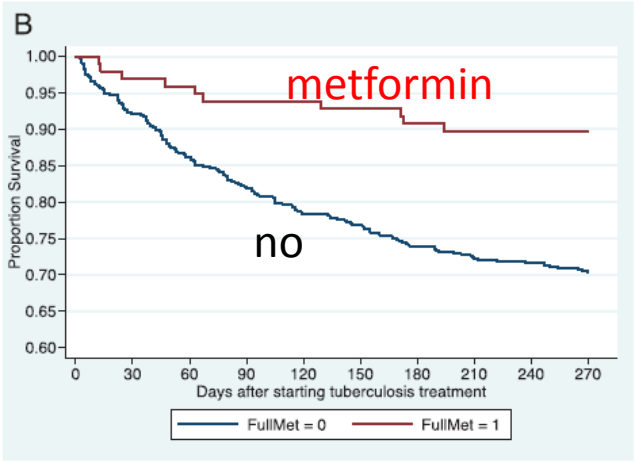
>20% of diabetics with non-cavitary pulmonary TB remain sputum positive at 3 months of treatment

Dooley et al. *Am J Trop Med Hyg* 2009

Metformin may *reverse* the trends in increased mortality among TB/diabetes

Any charted use





Used ≥80% time on TB tx

	Metformin (n=216)	Non-Metformin (n=418)	Total (n=634)	Log-Rank χ2
Death during tuberculosis treatment -%	17.6	31.3	26.7	<0.001

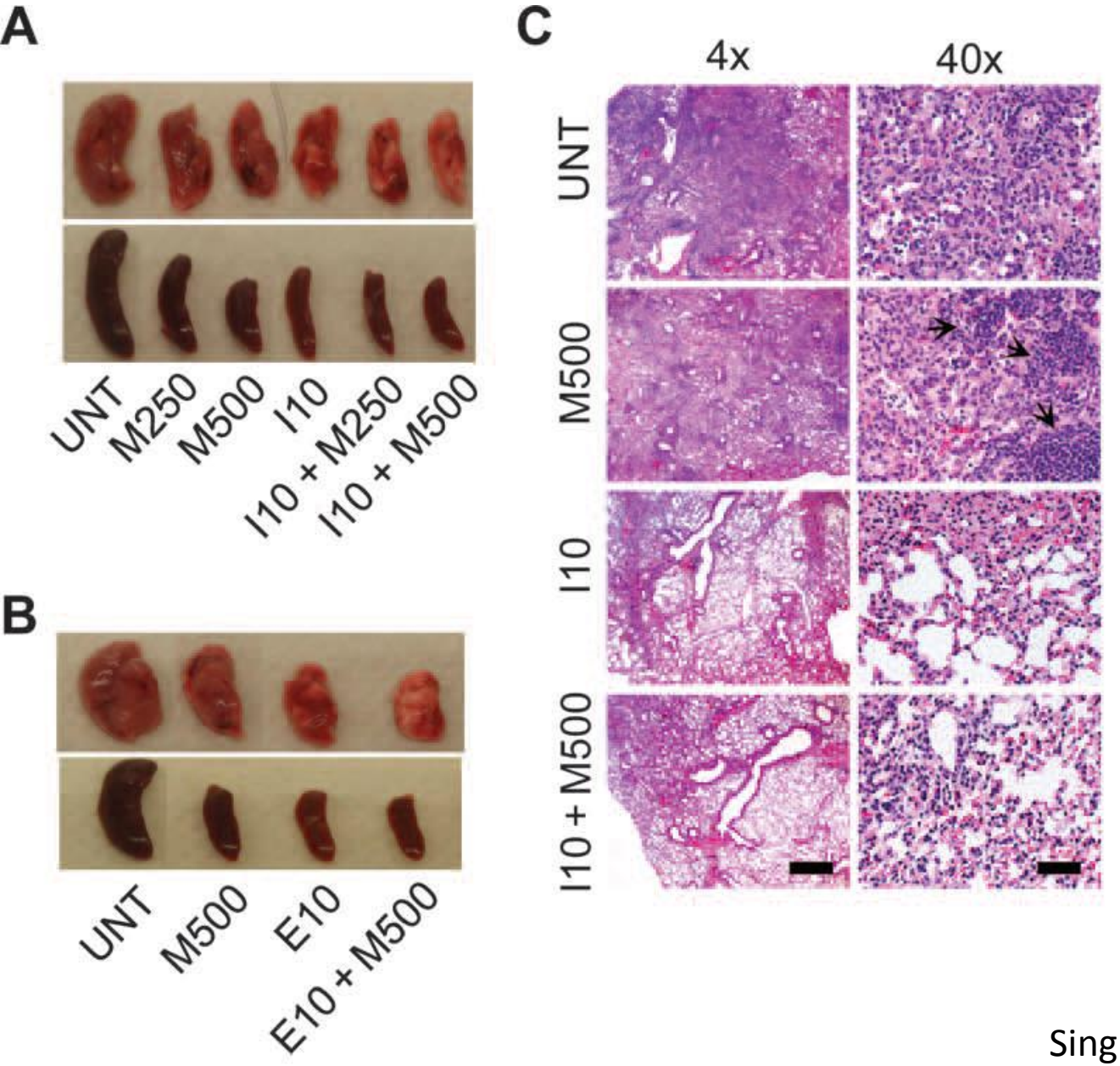
	Metformin (n=219)	Non-Metformin (n=358)	Total (n=577)	Log-Rank χ2
Death during tuberculosis treatment -%	10.2	29.7	26.7	<0.001

Table 3. Crude and Adjusted Odds Ratios, Based on a Logistic Regression Model, of 2-Month Sputum Culture Positivity for *Mycobacterium tuberculosis* (n = 1323)

Characteristic	Crude OR	(95% CI)	*P* Value	Adjusted OR[a]	(95% CI)	*P* Value
Type 2 diabetes mellitus	1.89	(1.40–2.55)	<.001	1.72	(1.25–2.38)	.001
Age	1.00	(1.00–1.01)	.510	1.00	(.99–1.01)	.693
Male	1.52	(1.10–2.10)	.012	1.43	(.98–2.08)	.062
Chronic kidney disease	1.14	(.77–1.69)	.510	1.07	(.70–1.65)	.751
Cancer	0.90	(.61–1.34)	.612	0.78	(.51–1.18)	.242
Hepatitis C virus	1.55	(.72–3.33)	.258	1.40	(.63–3.13)	.410
History of tobacco use	1.42	(1.06–1.91)	.020	1.05	(.75–1.48)	.762
Cavitary disease	4.04	(2.90–5.65)	<.001	4.03	(2.84–5.71)	<.001
Poor TB treatment adherence	1.06	(.72–1.57)	.764	1.16	(.77–1.75)	.490

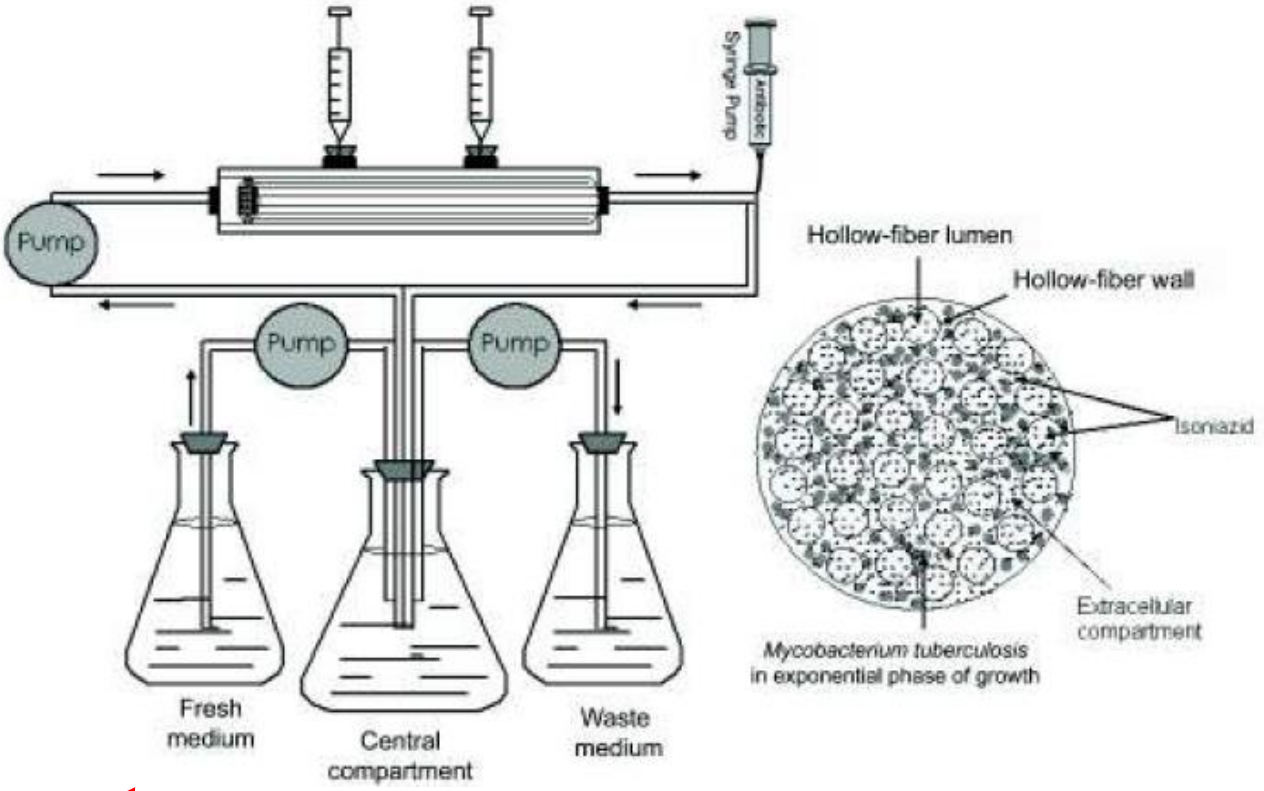
Denger et al, Clin Infect Dis 2018

Metformin reduces TB directed tissue pathology and enhances immune response



Singhal et al, Sci Transl Med 2014

Intra-patient pharmacokinetic variability (not non-adherence) predicts response and acquired resistance on anti-TB therapy



Results adapted to population models

Simulated drug exposure based on PK studies

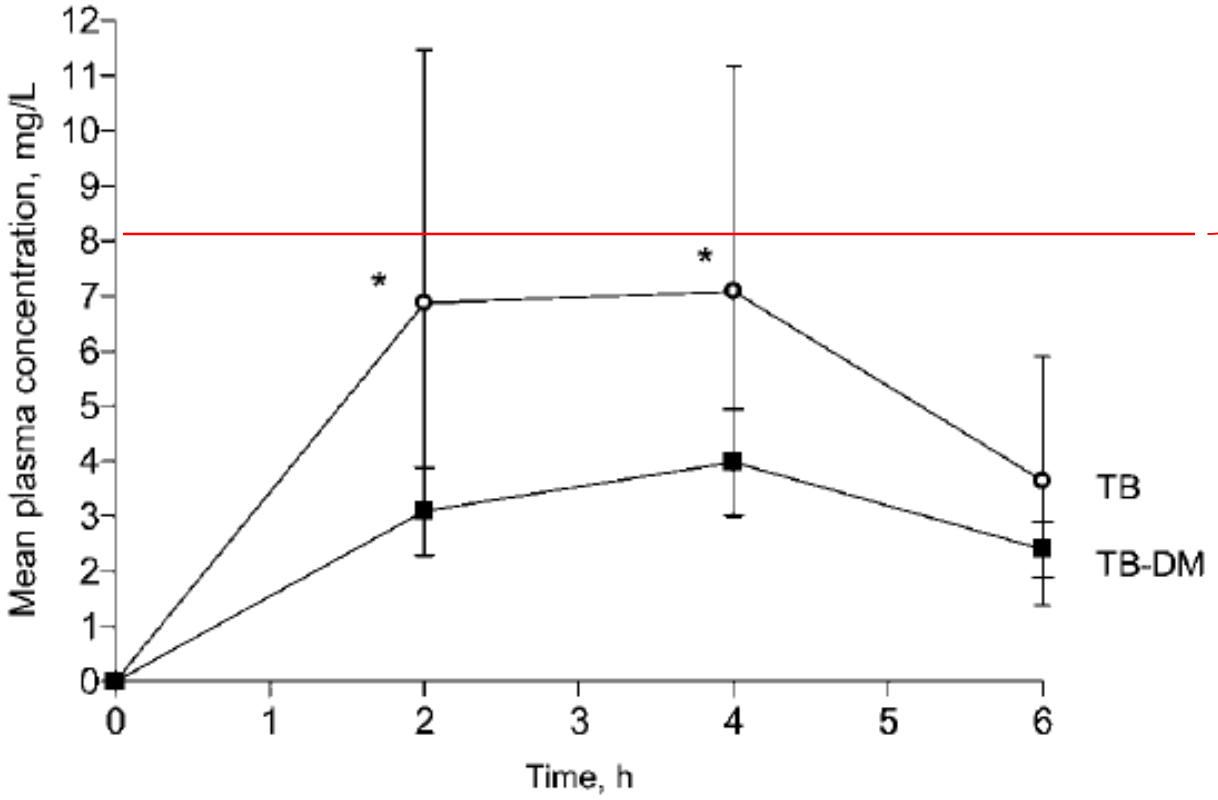
Pasipanyoda et al. *J infect Dis* 2013
Srivastava et al. *J Infect Dis* 2011
Gumbo et al. *J Infect Dis* 2007

Determinants of anti-TB drug pharmacokinetics:

1. mg/kg dosing (weight categories)
2. poor availability of drug in fixed-dose combinations in some settings or inaccurate quantity of active drug in pill
3. Adherence
4. Age
5. Gender
6. Genetic polymorphism of gut xenobiotic transport
7. Drug interactions
8. Malabsorption
   - HIV
   - Diabetes ?
   - Cystic Fibrosis
9. Poor solubility

1. Ashokraj et al. *Clin Res Reg Affairs* 2008

Rifampin exposure significantly reduced in diabetics from Indonesia



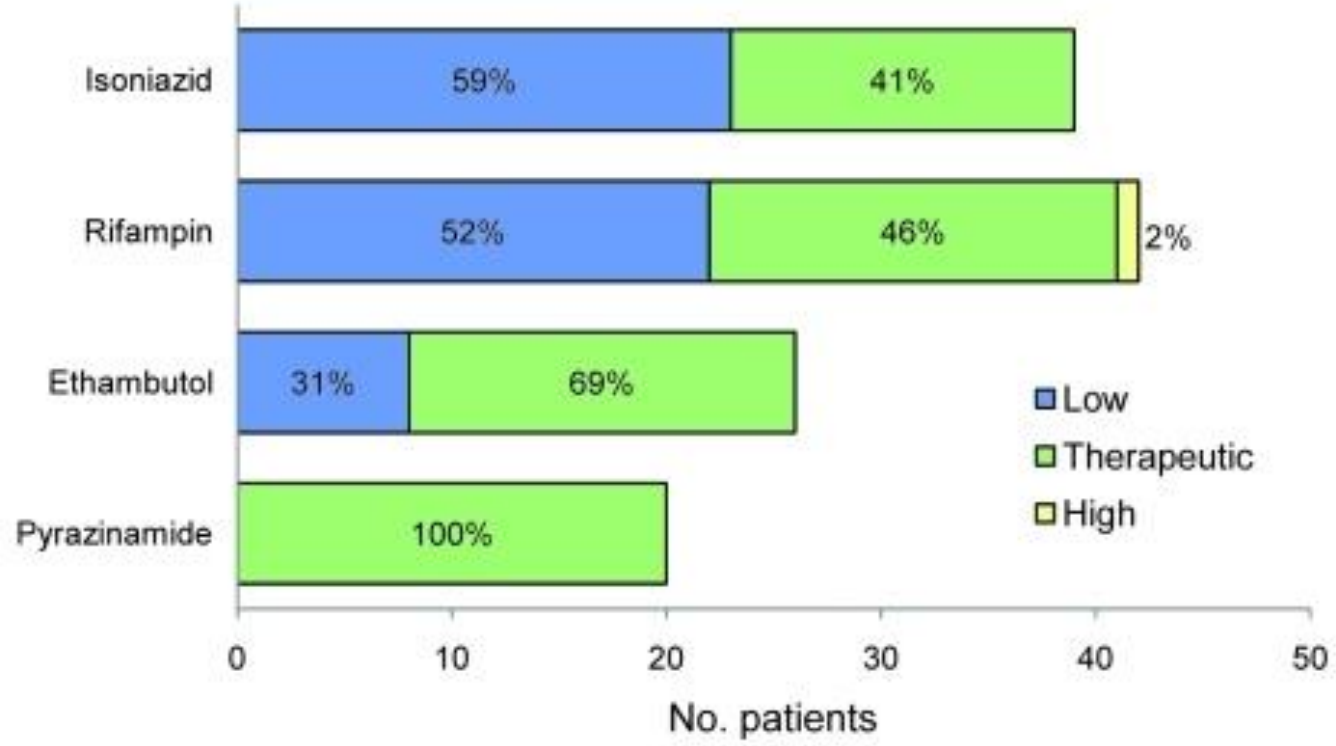
8-24 mg/L expected C_{max} range

Java, Indonesia

($AUC_{0–6\ h}$), C_{max} and overall **rifampin exposure was 53% lower in diabetics** with TB compared to non-diabetics

Nijland et al. *Clin Infect Dis* 2006

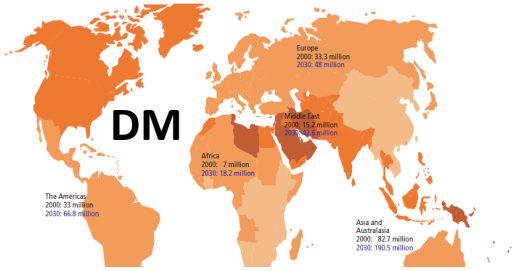
Diabetes/TB→ delayed treatment response + altered pharmacokinetics



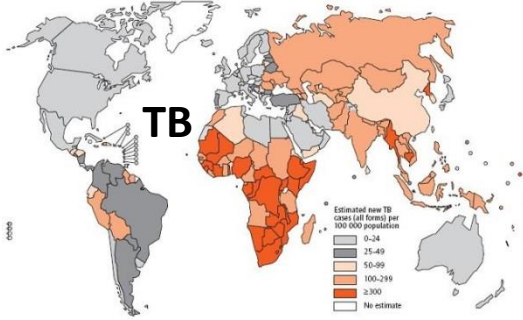
● Diabetics in Virginia were **6.3 times more likely to have slow response** ($p<0.001$) adjusted for age, gender, prior TB episodes, cavitary disease, HIV, alcohol and tobacco use

● Among slow responders, **diabetics had significantly lower rifampin levels**, measured at the time of estimated peak plasma concentration (C_{max})

Heysell et al. *Emerg Infect Dis* 2010



So to summarize thus far…



Diabetes prevalence will increase in TB endemic countries

Diabetes increases the risk of progression to active TB disease
(odds **2.4-8.3** compared to non-diabetics)
and likely higher for poorly controlled diabetics

Treatment outcomes are worse for diabetic TB patients compared to those without diabetes, but may be restored with metformin

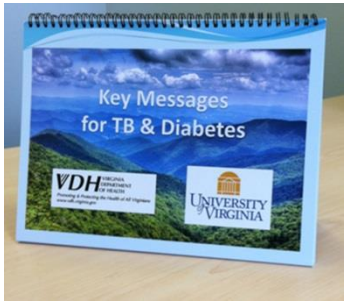
Impaired anti-TB pharmacokinetics results in worse in vitro killing of *M. tuberculosis*

Drug concentrations are suboptimal for some diabetic TB patients and may predict in whom dose increase will improve outcome

algorithmic approach in Virginia

HbA1C checked on all clients

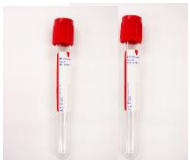
HbA1C ≥ 6.5



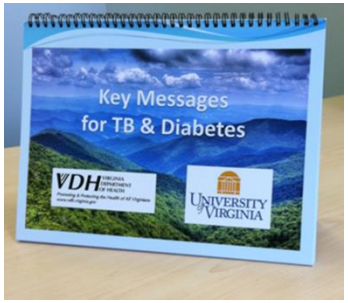
Early TDM (at 2 weeks)

and

Linkage to DM care



HbA1C <6.5, on diabetes treatment



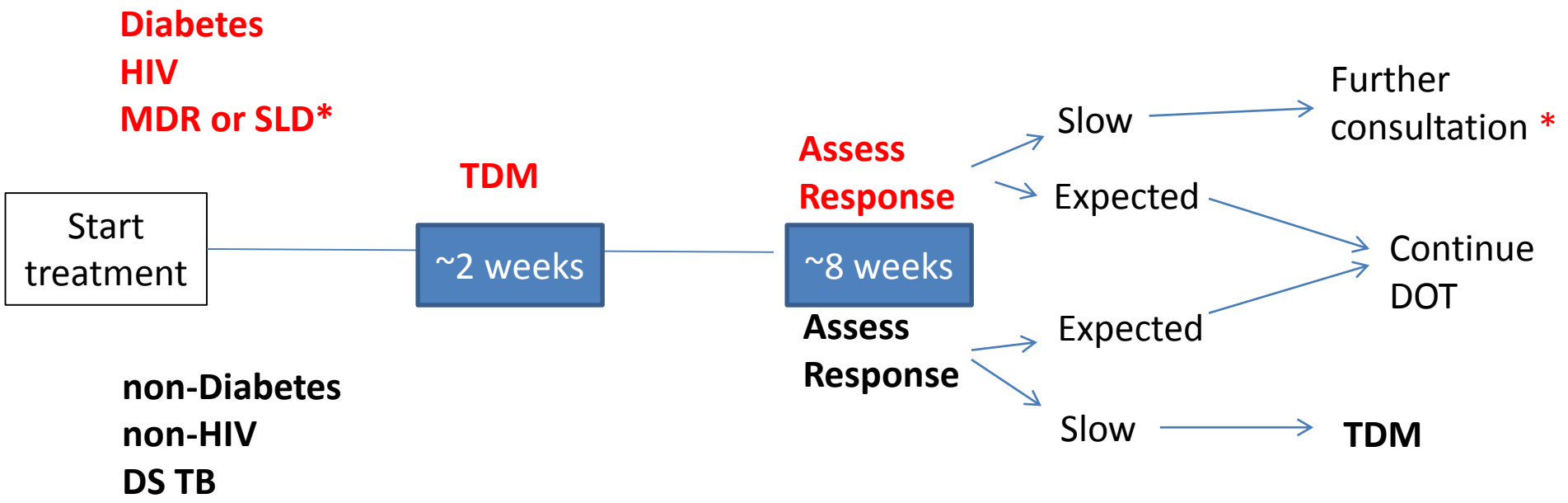
Early TDM (at 2 weeks)

Continue current diabetes regimen

HbA1C <6.5, no prior diabetes

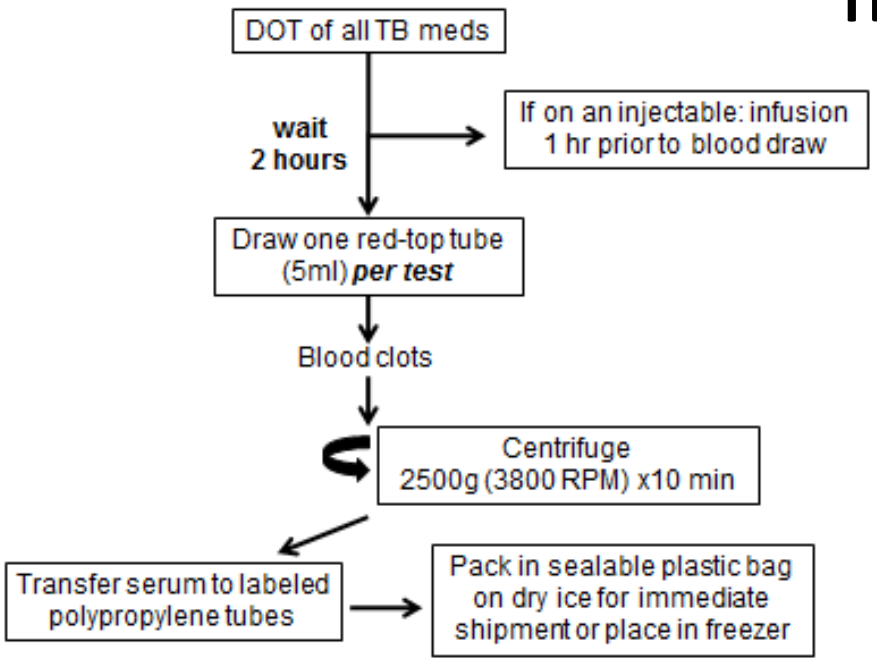
No intervention (~80% clients)

Practical use of therapeutic drug monitoring (TDM)



*All MDR cases or those needing second-line drugs in Virginia are managed by TB physician consultants

TDM is now programmatic, so timing/ procedures are consistent



http://www.vdh.virginia.gov/content/uploads/sites/112/2017/11/2017-Recommendations-and-Procedures-for-the-use-of-Therapeutic-Drug-Monitoring-TDM-112107.pdf

Table 3. Dose adjustment f

	Normal drug lev	Sub-target INH and Sub-target RIF
Initiation Phase regimen*	Continue INH 300 r and RIF 600 mg M-	Increase INH 450 mg and RIF 900 mg M-F
Continuation Phase regimen	Continue INH and R M-F or thrice week	INH 900 mg and RIF 900 mg, M-F or thrice weekly

Recommended dose adjustment for sub-target INH and RIF:
Initiation M-F→
INH 300 mg increase to 450 mg
RIF 600 mg increase to 900 mg

Continuation (M/W/F)→
INH 900 mg
RIF 900 mg

*All initiation phase regimens assume get doses of isoniazid (INH) of 5 mg/kg and rifampin (RIF) of 10 mg/kg. M-F= Monday through Friday, 5 x weekly schedule. Sub-target concentrations are any below the expected C_{2hr} range.

CDC Guidelines now provide guidance consistent with VA practice

Table 9. Conditions or Situations in Which Therapeutic Drug Monitoring May Be Helpful

Poor response to tuberculosis treatment despite adherence and fully drug-susceptible *Mycobacterium tuberculosis* strain
Severe gastrointestinal abnormalities: severe gastroparesis, short bowel syndrome, chronic diarrhea with malabsorption
Drug–drug interactions
Impaired renal clearance: renal insufficiency, peritoneal dialysis, critically ill patients on continuous renal replacement
HIV infection
Diabetes mellitus
Treatment using second-line drugs

Abbreviation: HIV, human immunodeficiency virus.

Nahid et al, *Clin Infect Dis* 2016

Table 1: Groups considered for TDM

Group	Definition	Drugs to check	Follow-up
1 - Slow responder (failure to clinically improve as expected)	Clients with smear positive pulmonary TB for a prolonged period of time without improvement (defined as a steady decrease from 4+ to 2+; 3+ to 1+; 2+/1+ to smear negative)	Isoniazid and Rifampin **ONLY**:	Dose increases in consultation with DTBNH staff and medical consultants. **Follow-up drug levels can be checked.**
2 - All diabetics (HbA1c $\geq$ 6.5)	Ideally test **2 weeks** after treatment begins. If a recent HbA1c (<3mo) result is not available, perform HbA1c to avoid delaying TDM upon intake. After 8 weeks the window of opportunity is lost so we do not perform TDM (unless slow response or another reason is identified)	Isoniazid and Rifampin **ONLY**:	Automatic dose adjustment for low level (See Table 2). **No follow-up drug levels checked.**
3 - All HIV positive (regardless of CD4 count or viral load)	Ideally test within **1- 2 weeks** after a stable regimen begins.	Isoniazid and Rifampin/Rifabutin **ONLY**:	Dose increase in consultation with DTBNH staff. **Follow-up drug levels can be checked.**
4 - Others	Other scenarios in discussion with TB consultants (e.g., new clinical deterioration, receiving second-line TB medications, sudden relapse, severe illness, other co-morbidities)	Case-by-case	Case-by-case

Concentrations increase after dose adjustment

Vancouver

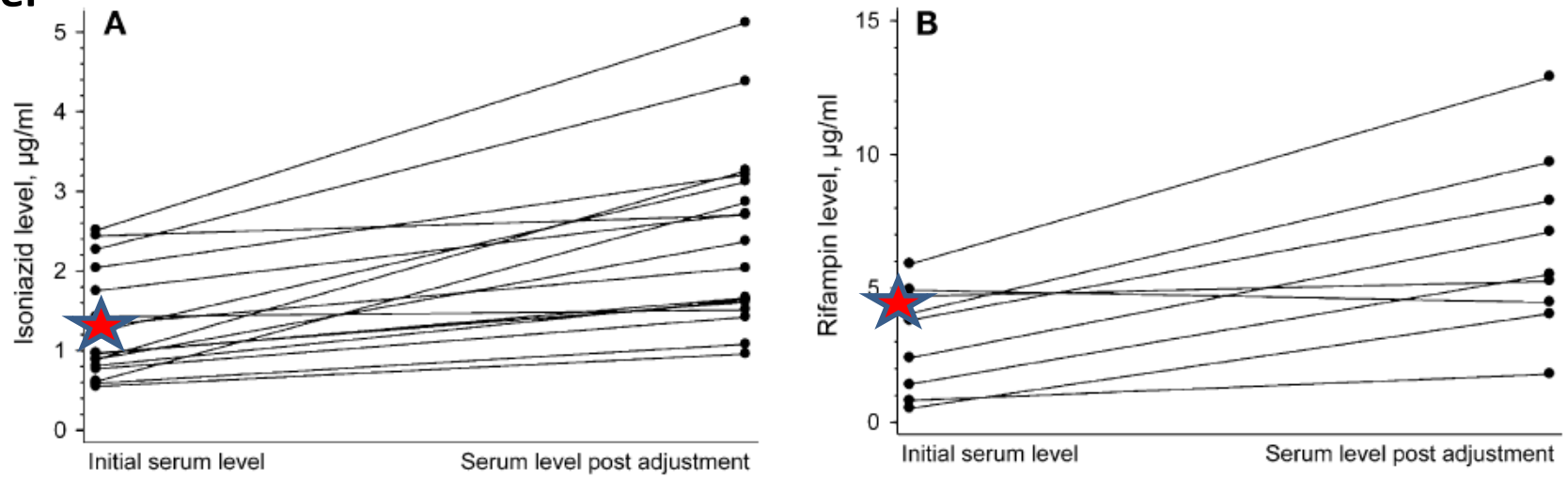
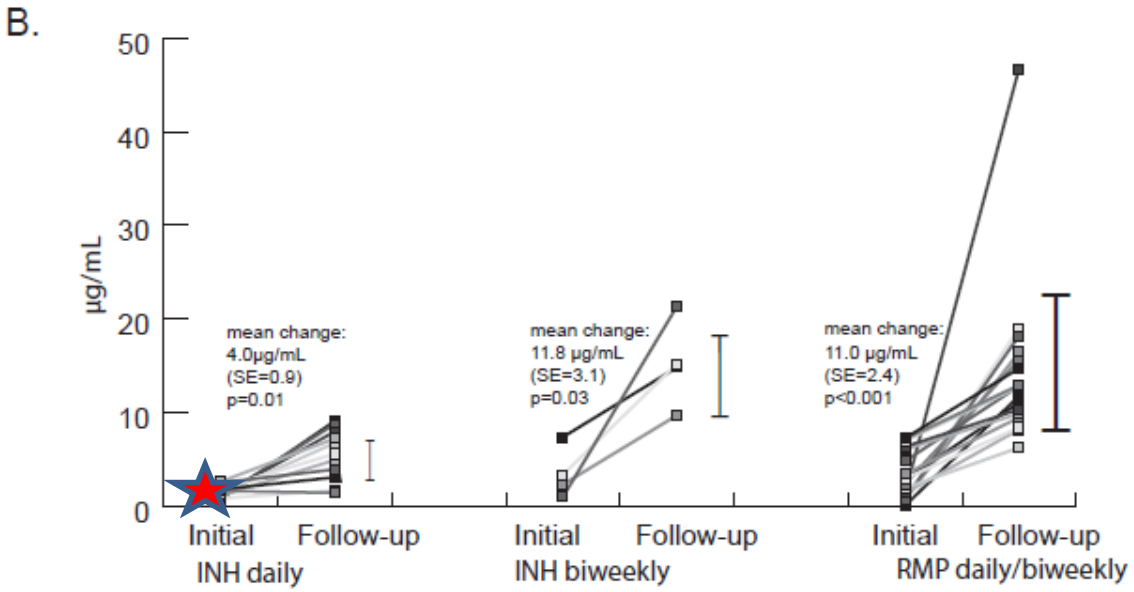


Figure Serum response per 100 mg increase in dosage. **A.** Serum isoniazid levels, $n = 17$. **B.** Serum rifampicin levels, $n = 9$.

Virginia



van Tongeren, *IJTLD* 2013

(similar overall mean increase)

Heysell, *Emerg Infect Dis* 2010

Diabetes (with early TDM) in 2013-14 trend toward faster sputum culture conversion compared to matched* non-diabetes, but not in 2009-10 (without early TDM)

Outcome	Matched 2009-2010			Matched 2013-14		
	non DM N=60	DM N=30	p-value	non DM N=52	DM N=26	p-value
culture conv (days ±SD)	57±35	61±32	0.62	57±37	42±22	0.08
2 months culture conv (%N)	34 (57)	15 (50)	0.55	31 (60)	21 (81)	0.12

Difference most apparent in diabetes (2009-2010) matched to diabetes (2013-2014)

Outcome	2009-10 N=26	2013-14 N=26	p-value
culture conv (days ±SD)	62±31	42±22	0.01
2 months culture conv (%N)	13(50)	21(81)	0.04

*matched for age (10 yrs), gender, smear status (pos or neg), CXR (cavity or not)

Alkabab et al, *BMC Infect Dis* 2017

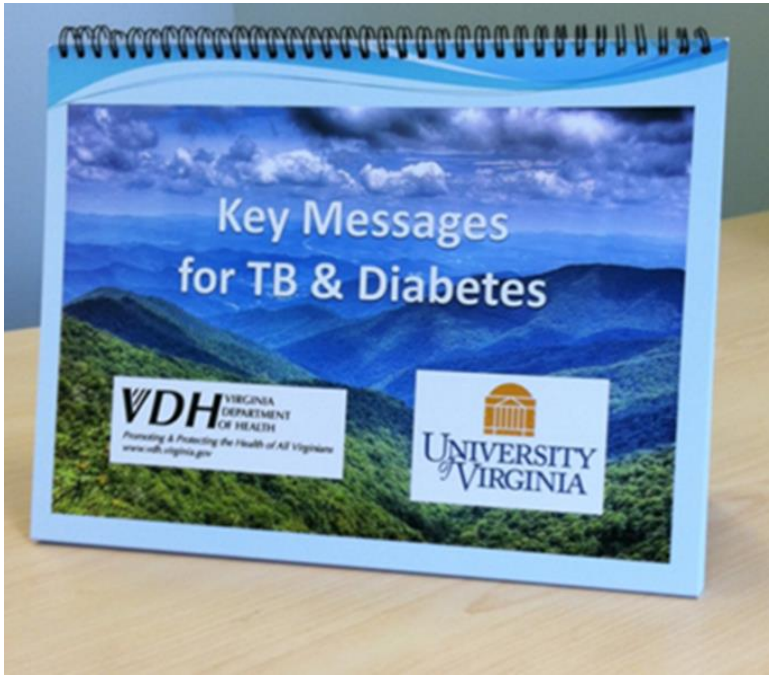
Other early interventions were taking place with therapeutic drug monitoring

- Were other interventions responsible for diabetes patients improved culture conversion?

nurse-patient

educational flipchart →

metformin (autophagy) ←



Adapted from ARC and Hawaii DOH

Patients diagnosed with TB in Virginia now receive hemoglobin A1c testing:
212 patients treated for TB in 2016
→ 2-3% are new diabetes diagnosis, primarily for triage to diabetes care

Local case: Unmasked MDR, missed opportunity for early TDM?

23 y/o man originally from the Philippines

Presented with R neck mass (lymphadenopathy), voice change

HIV + (CD4 124)

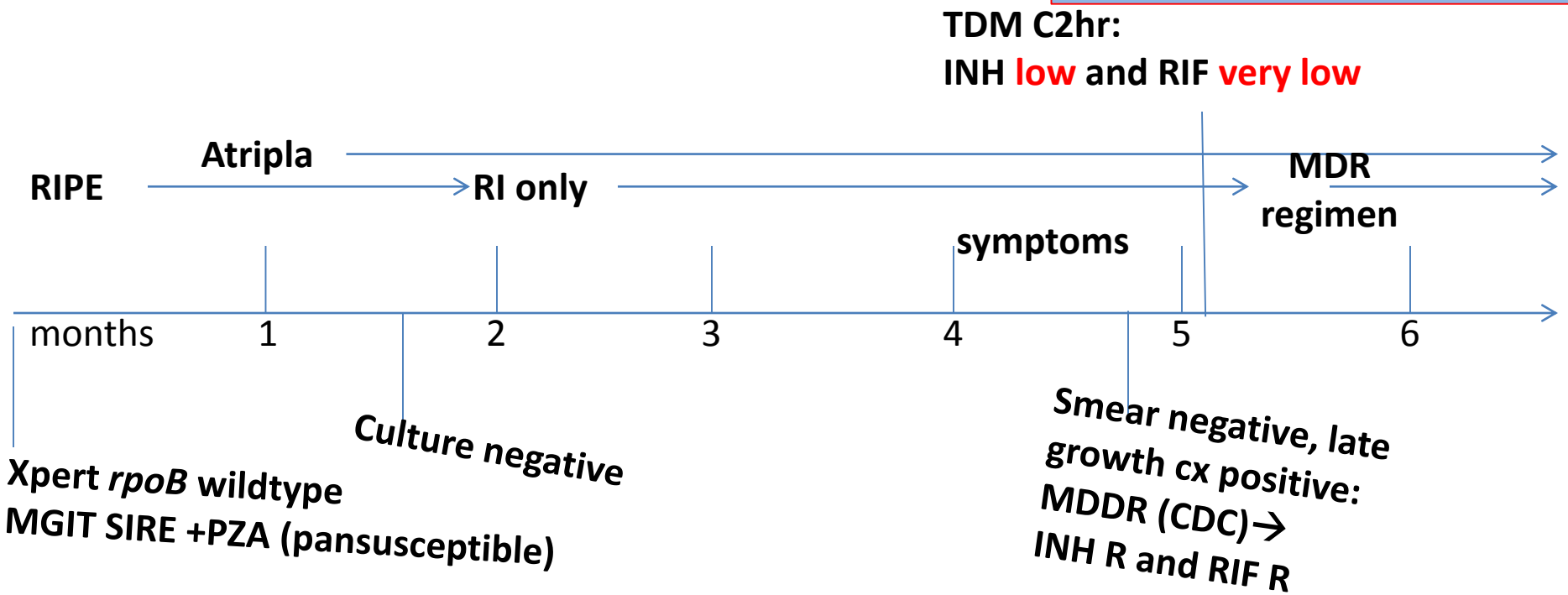
Sputum and R neck biopsy→ smear (4+ from sputum) and cult

Interestingly CXR was normal (laryngeal TB?)

Pretreatment *M tb* isolate:
embB L355L (silent)
embB G378A (neutral)

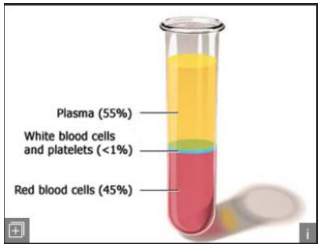
4 month treatment isolate:
embB L355L (silent)
embB G378A (neutral)

inhA C-15T→ R by MGIT
rpoB D518Q→ R by MGIT

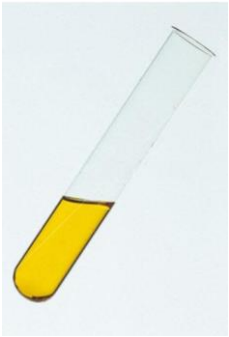


Simplifying sample collection, preparation and analysis

Current approach



HPLC/ mass spec



Spectrophotometric

Colorimetric/ mobile phone

Urine instead of blood draw

NIH R01 to Rutgers and University of Virginia

Bali Declaration: November, 2015

"That **tuberculosis and diabetes represent two of the greatest global health challenges of our time**, and their convergence globally represents a looming co-epidemic,

That this looming co-epidemic threatens progress against TB,

That, based on what we have learned from past co-epidemics, particularly TB-HIV, we must act early and decisively to avoid large numbers of avoidable deaths"

The Union

International Union Against Tuberculosis and Lung Disease

Health solutions for the poor

WORLD **DIABETES** FOUNDATION

Thank you!

All the Nurses/Case Managers
Denise Dodge
Deborah Staley
Jane Moore (retired)
Suzanne Keller (retired)

Yusra Alkabab
Tania Thomas
Eric Houpt

Sayera Banu
Shahriar Ahmed
Kishor Kumar Paul
Sara Sabrina Ferdous
S.M. Mazidur Rahman

The case of the 90 y/o man with MDR-TB

- 90 year-old man, originally from Peru
- Came to live in the U.S. in November of 2014
- He is healthy, active and asymptomatic. No prior history of TB.
- A skin test is performed because his daughter operates a child-care facility from their home→ skin test positive
- CXR→ "upper lobe infiltrate with pleural thickening, no cavity"

June 5, 2015→ smear negative, culture negative
June 6, 2015→ smear negative, culture positive (MTb complex)
June 7, 2015→ smear negative, culture positive (MTb complex)

July 1, 2015→ starts treatment with rifampin, isoniazid, pyrazinamide, ethambutol but isolate ultimately **found to be MDR** (by MGIT SIRE)…….

These DST results return

rpoB→ **mutated** (Ser531Leu)
katG→ **mutated** (Ser315Thr)
inhA→ no mutation

embB→ **mutated** (Met306Iso)
pncA→ no mutation

gyrA→ no mutation
gyrB→ no mutation

rrs→ no mutation
tlyA→ no mutation
eis→ **mutated** (G-37T)

Creatinine Clearance= 44 mL/min

Rifampin (1.0 µg/ml)→ **R** [rifabutin→ **R**]
Isoniazid (1.0 µg/ml)→ **R**
Ethionamide (10.0 µg/ml)→ **R**

Ethambutol (5.0 µg/ml)→ **R**
Pyrazinamide (100 µg/ml) MGIT 960→ S

Ofloxacin (2.0 µg/ml)→ S

Amikacin (4.0 µg/ml)→ S
Capreomycin (10.0 µg/ml)→ S
Kanamycin (5.0 µg/ml)→ **R**

Also: PAS (2.0 µg/ml)→ S
Streptomycin 2.0 µg/ml→ S
Streptomycin 10.0 µg/ml→ **R**

A range of treatment approaches→ this is *individualized* care

Levofloxacin (better tolerated?)→ 250 mg daily but ***TDM***

Pyrazinamide (continue wt based)→ 1500 mg daily but ***TDM*** given high cost of failure

PAS (given other resistance patterns, avoid cycloserine)→ 2 g po bid and ***TDM***

Linezolid (low dose given toxicities)→ 300 mg daily but ***TDM*** given reports of acquired resistance with lower dose

→ Obtain ***MIC***s including cycloserine DST and clofazimine, linezolid, bedaquiline

→Consider adding clofazimine or substitution for other oral if intolerance or toxicity

→Hold on amikacin or capreomycin for now

TDM/ MIC to optimize dose and minimize toxicity

Pyrazinamide 1500 mg daily
C2hr- **36.59** (expected C2hr: 20-60 µg/ml)
C6hr- 24.62

Levofloxacin 250 mg daily
C2hr- **4.71** (expected peak: 8-12 µg/ml)
C6hr- 2.54

↓

Levofloxacin 500 mg daily
C2hr- **5.83**

PAS 2g bid
C6hr- **4.98** (expected C4-6hr: 20-60 µg/ml)

↓

PAS 4g bid
C6hr- **46.77**

Linezolid 300 mg daily
trough –trace (expected for daily dose)
C2hr- **6.41** (expected peak: 12-26 µg/ml)

↓

Linezolid 600 mg daily
C2hr- **14.03**

Drug	Mutation	APM	MIC
INH	*katG* Ser315Thr	R	R (2)
RIF	*rpoB* Ser531Leu	R	R (>4)
EMB	*embB* Met306Ile	R	R (8)
PZA		**S** (MGIT)	
STR		R	
CAP		S	S (2)
KAN	*eis* G-37T	R	R (16)
AMK		S	S (2)
OFLOX		S	S (1)
LEVO			**S (0.5)**
MOXI			S (0.25)
PAS		**S**	
ETO		R	
CS		S	
LZD			**S (0.5)**
CFZ			S (0.06)
BDQ			S (0.06)

MIC testing: CDC and National Jewish Health