

# **TUBERCULOSIS AND DIABETES**

## **The 21<sup>st</sup> Century Pandemic**



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# Catastrophic collision of two ancient diseases

Egyptian papyrus describing a 'rare disease causing rapid loss of weight and frequent urination'

c 1550 BC



## TB MAY BE MORE ANCIENT STILL

Egyptian mummy 1550-1080 BC

- Extensive pleural adhesions,
- Left lung collapsed.
- Severe anterior destruction of lumbar vertebral bodies

113 bp sequence of *Mycobacterium tuberculosis* detected



Nerlich et al. Lancet 1997;350:1404

**TB DNA detected in a 900 year old pre-Columbian mummy.**

97 bp sequence of IS6110 specific for *Mycobacterium tuberculosis* detected

V. Morell. Science:1994;263:1686

**So TB was in the Americas before Europeans arrived**

**Did it cross the Bering straits thousands of years ago???**



**New World microbes.** This 900-year-old mummy had TB DNA.

Is this a recent convergence????

THE  
AMERICAN JOURNAL  
OF THE MEDICAL SCIENCES  
FEBRUARY, 1935

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ORIGINAL ARTICLES.

THE CHANGING CAUSE OF DEATH IN DIABETES MELLITUS.

By JOHN M. FLYNN, M.D.,  
JUNIOR ASSOCIATE IN MEDICINE, PETER BENT BRIGHAM HOSPITAL,  
BOSTON, MASS.

3. There were four common causes of death. These were: (a) Coma with or without a terminal infection; (b) sepsis; (c) cardiovascular renal disease, including gangrene; (d) pulmonary tuberculosis.

Coma and pulmonary tuberculosis tended to occur more frequently in the younger patients; cardiovascular renal disease,

# **DIABETES IS A CHRONIC METABOLIC DISEASE**

- **Named in the 2<sup>nd</sup> Century AD by Araetus of Cappadocia after the Greek word for syphon.**
- **Diabetes is better understood as a continuum of impaired glucose metabolism rather than a discrete disease.**
- **This impairment ranges from pre-diabetes to diabetes.**
- **The severity of diabetes is usually measured by the level of fasting blood glucose and of glycated hemoglobin (HbA1c)**
- **The more severe the diabetes the more common the many complications—one of which is tuberculosis.**

# American Diabetes Association: 2010 Criteria for diagnosis of diabetes

- 1. Glycated hemoglobin (HbA1c)  $\geq$  6.5%**  
**OR**
- 2. Fasting blood glucose  $\geq$  126 mg/dl**  
**OR**
- 3. Oral Glucose Tolerance Test (OGTT) 2 hour post  
glucose load of  $\geq$  200 mg/dl**  
**OR**
- 4. In a patient with classical symptoms, random blood  
glucose of  $\geq$  200 mg/dl**

*HbA1c = glycated hemoglobin or A1C*

*Percent of hemoglobin molecules in red blood cells with glucose molecules attached. Since the life of red blood cells is about 120 days, this is a measure of glucose control over the preceding three months.*

## **THERE ARE THREE MAJOR TYPES OF DIABETES**

- **Type 1 diabetes (also known as juvenile onset involving pancreatic  $\beta$ -cell destruction usually leading to absolute insulin deficiency). Usually immune mediated.**
- **Type 2 diabetes (also known as adult onset). Often associated with obesity.**
- **Other types of diabetes: a very long list!**

**TODAY MORE THAN 95% OF DIABETES IS TYPE 2.  
DIABETES IS PART OF THE CURRENT MASSIVE  
PANDEMIC OF NON-COMMUNICABLE DISEASES (NCDS).**



## PRACTICAL TIP

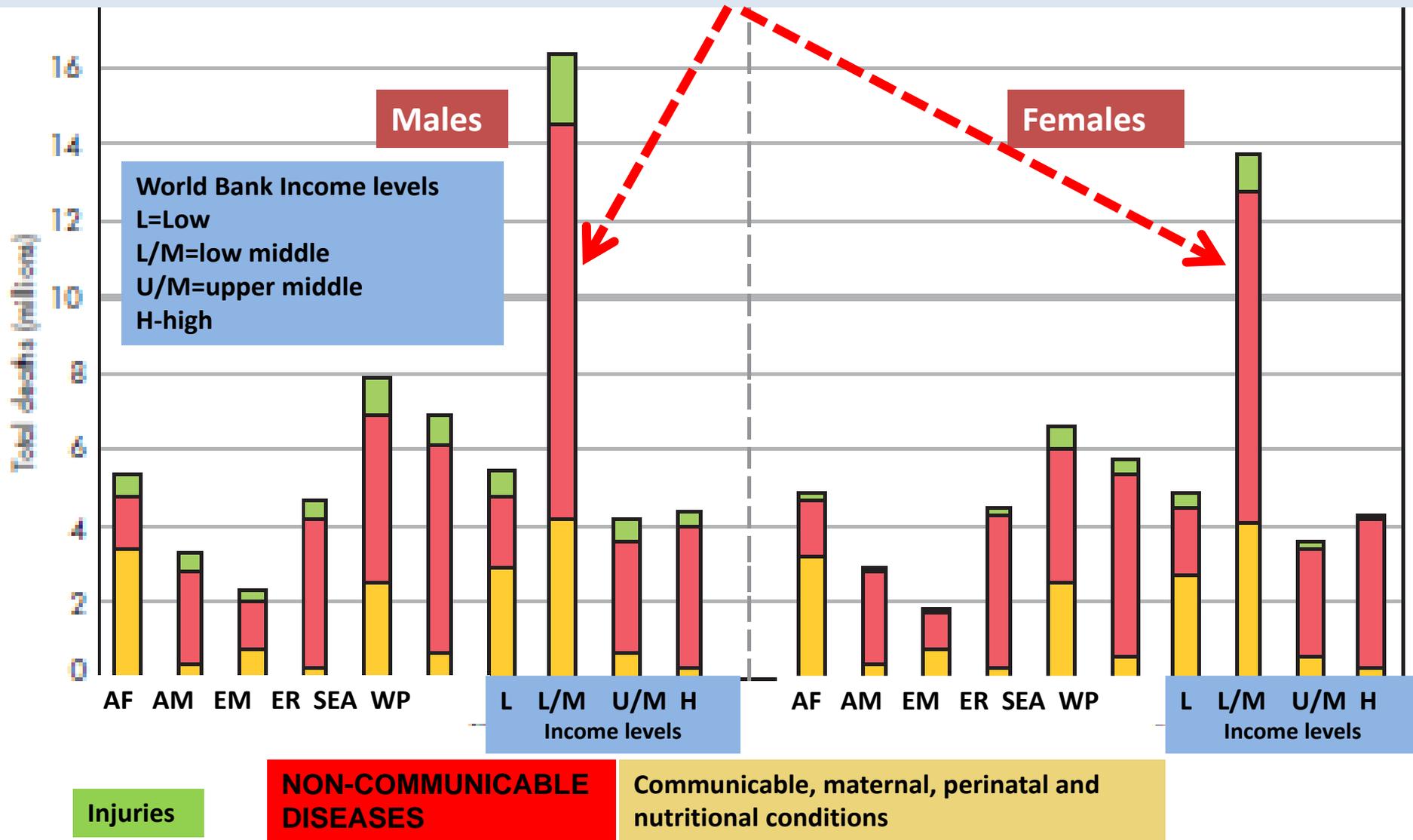
- In a TB clinic it is reasonable to screen by using the random blood glucose (RBG).
- If the RBG is  $\geq 200$  mg/dl you can assume diabetes, or at least impaired glucose metabolism
- This tells you the patient may have problems with TB medication and is at increased risk of poor outcome.
- Confirmation of diabetes can be done later and the patient referred for diabetes management.

## PROBLEM

**Diabetes and TB health care systems do not talk to each other.**

# TOTAL DEATHS BY BROAD CAUSE BY WHO REGION/WORLD BANK INCOME 2008.

**80% of diabetes is in the LMICs where there is most TB.**



AF=Africa, AM=Americas, EM=Eastern Mediterranean, ER=European Region, SEA=South East Asia, WP=Western Pacific

**Data from the seven high burden tuberculosis countries with the highest numbers of people with diabetes showing rates of tuberculosis and prevalence and numbers with diabetes in 2013. (Data from WHO and IDF)**

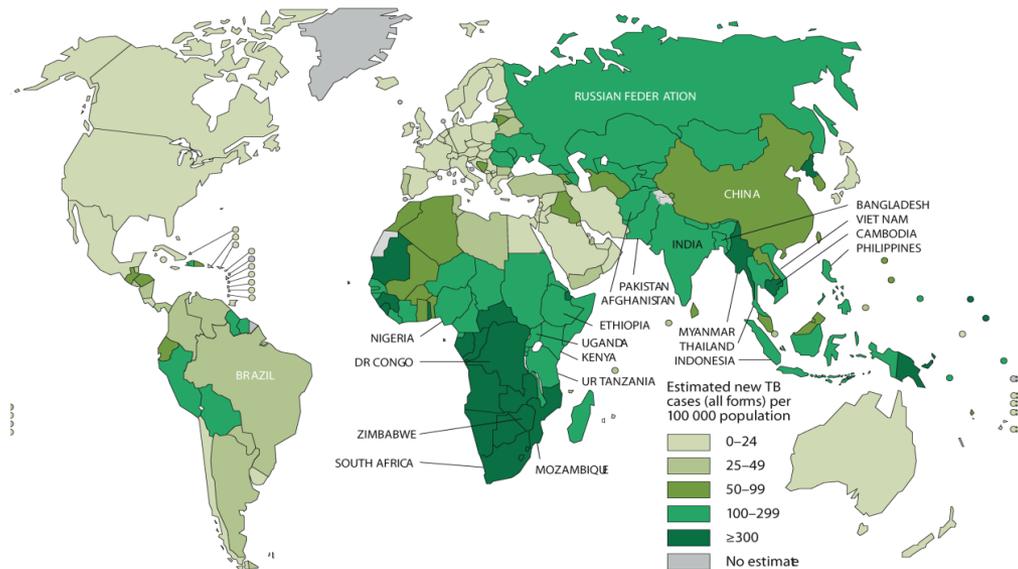
Country	Tuberculosis	Diabetes Estimates		
	Reported cases	Reported Prevalence	Diabetes	Undiagnosed diabetes
	Rate/100,000	%	million	million
China	99	9.6	98.4	53.2
India	230	8.6	65.1	31.9
Brazil	59	9.0	11.9	2.9
Russian Federation	121	10.0	10.1	3.8
Indonesia	185	5.6	8.6	4.6
Pakistan	376	6.8	6.7	3.4
Bangladesh	434	5.5	5.1	2.2

**Total estimate with diabetes in just 7 high burden countries: 206.7 million**

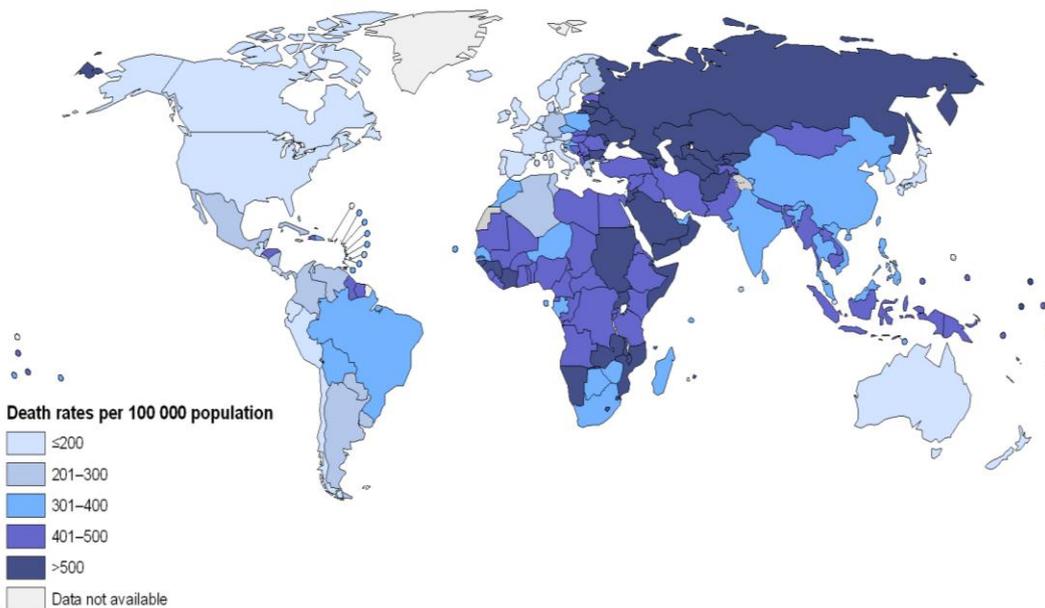
**In India diabetes estimated to have increased TB cases 46%.**

# FATAL OVERLAP

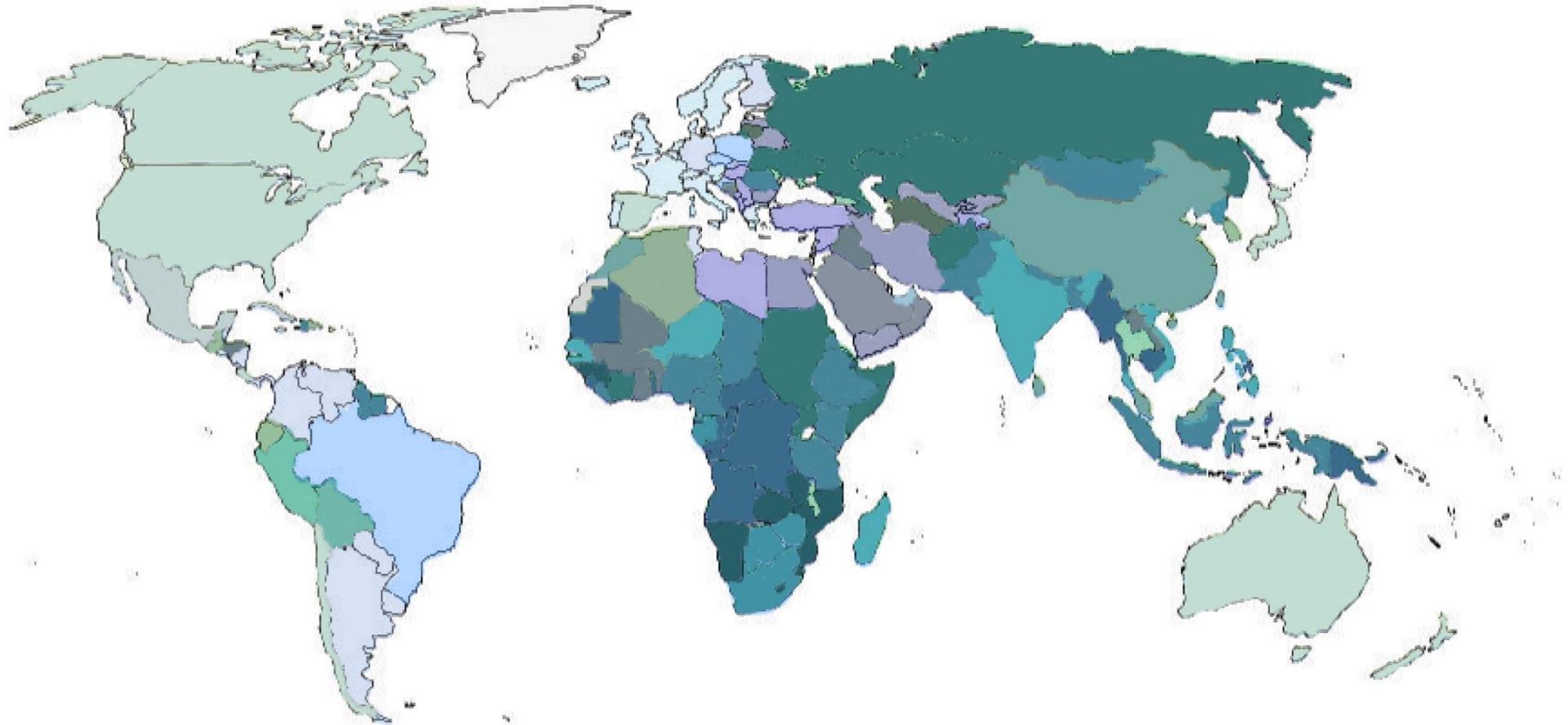
## New TB cases



## Deaths/100,000 from Diabetes and CVD



# THIS IS THE PROBLEM



Overlap of new TB cases and deaths from Diabetes and CVD

**From the US perspective, immigrants may come from places where diabetes is common and is a major driver of TB and also of MDR-TB. Tourists also visit these places in increasing numbers, and like to shop in the bazaar!**

# THE LOOMING CO-EPIDEMIC OF TB-DIABETES: A CALL TO ACTION

**Report issued on November 20<sup>th</sup> 2014 at the Barcelona  
45th Union World Conference on Lung Health by the  
World Diabetes Federation**

<http://www.theunion.org/what-we-do/publications/technical/the-looming-co-epidemic-of-tb-diabetes>

**Knut Lönnroth, WHO**

**Diabetes is rampant in low- and middle-income countries, affecting the poor and rich alike, and increasing the risk of TB across all population segments.**

**If we fail to act, the consequences could prove catastrophic for healthcare systems in areas that are impacted.**

# Prevalence of Diabetes in TB Patients: Recent Studies

Region	TB Patients w/Diabetes	Year Published
Karnataka State, India	32%	2011
Kerala State, India	44%	2012
Tamil Nadu State, India	25%	2012
Texas, USA	39%	2011
Mexico	36%	2011
Tanzania	17%	2011
Pakistan	16%	2012
South Pacific	40-45%	2013

# TODAY DIABETES THREATENS TUBERCULOSIS CONTROL GLOBALLY

- Diabetes increases risk of tuberculosis three fold
- Diabetes increases and can spread MDR-TB
- Diabetes is a greater threat at the population level than AIDS
  - **382 million people globally have diabetes**
    - **25.5 million in the US**
  - **An estimated 34 million globally have AIDS.**
    - **1.5 million in the US**

## Ratio of **diabetes** to **AIDS**

**Globally**                    **14:1**

**In US**                        **22:1**

### **THE ISSUE IS NUMBERS AND EXPOSURE**

- **The threat of diabetes to tuberculosis control is much higher than that of AIDS**
- **This is because of the sheer number of people with diabetes far outstrips those with AIDS**

**The Population Attributable Fractions (PAF)\* globally are:**

**Diabetes**                    **14.4%**

**AIDS**                        **6.4%**

*\* PAF = percent of cases directly attributable to this underlying disease*

We were among the first, but not the first

MPH student



*Nuevo Santander Tuberculosis Trackers*  
Third annual meeting  
November 2004  
Reynosa, Mexico

# WE WERE SLOW TO SEE THE WARNING SIGNS

- Oscarsson N, Silwer H. Incidence of pulmonary tuberculosis among diabetics. *Acta Med Scand* **1958**;160 (suppl 335):23-48.
- Olmos P, Donoso J, Rojas N et al. [Tuberculosis and diabetes mellitus: a longitudinal-retrospective study in a teaching hospital]. *Rev Med Chil* **1989**;117:979-983.
- Mugusi F, Swai AB, Alberti KG, McLarty DG. Increased prevalence of diabetes mellitus in patients with pulmonary tuberculosis in Tanzania. *Tubercle* **1990**;71:271-276.
- Pablos-Mendez A, Blustein J, Knirsch CA. The role of diabetes mellitus in the higher prevalence of tuberculosis among Hispanics. *Am J Public Health* **1997**;87:574-579.
- Ponce-De-Leon A, Garcia-Garcia Md ML, Garcia-Sancho MC et al. Tuberculosis and diabetes in southern Mexico. *Diabetes Care* **2004**;27:1584-1590.
- Perez A, Brown HS, III, Restrepo BI. Association between tuberculosis and diabetes in the Mexican border and non-border regions of Texas. *Am J Trop Med Hyg* **2006**;74:604-611.
- Restrepo BI, Fisher-Hoch SP, Crespo JG et al. Type 2 diabetes and tuberculosis in a dynamic bi-national border population. *Epidemiol Infect* **2007**;135:483-491.

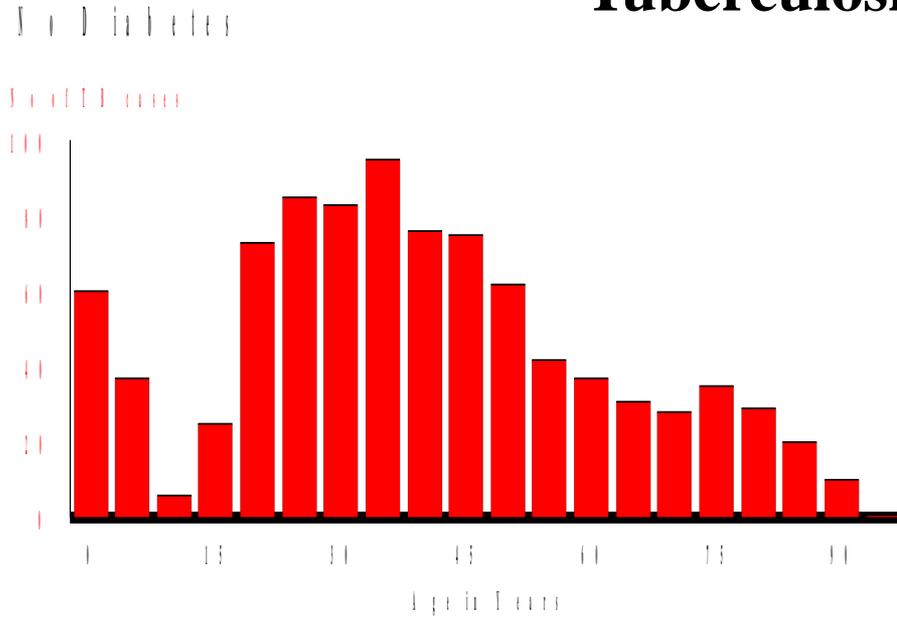
# Characteristics of TB patients in the Texas-Mexico border

	<b>Mexico (1998-2003)</b>	<b>Texas (1996-2002)</b>
<b>Total number patients</b>	<b>3,506</b>	<b>1,543</b>
<b>Average number patients/year</b>	<b>584</b>	<b>220</b>
<b>Total male</b>	<b>2,439 (69.6%)</b>	<b>1,055 (68.4%)</b>
<b>Median age (IQR) (years)</b>	<b>39(26)</b>	<b>47(29)</b>
<b>Alcohol use<sup>1</sup></b>	<b>63 (1.9%)</b>	<b>292 (20.3%)</b>
<b>Use of illegal drugs<sup>1</sup></b>	<b>84 (2.5%)</b>	<b>152 (10.6%)</b>
<b>HIV-positive<sup>1</sup></b>	<b>69 (2%)</b>	<b>85 (5.9%)</b>
<b>Diabetes mellitus<sup>1</sup></b>	<b>607 (17.8%)</b>	<b>401 (27.8%)</b>

*Restrepo, B.I., Fisher-Hoch, S.P., McCormick et al. Type 2 diabetes and tuberculosis in a dynamic bi-national border population. Epidemiol. Infect. 135, 483-491.*

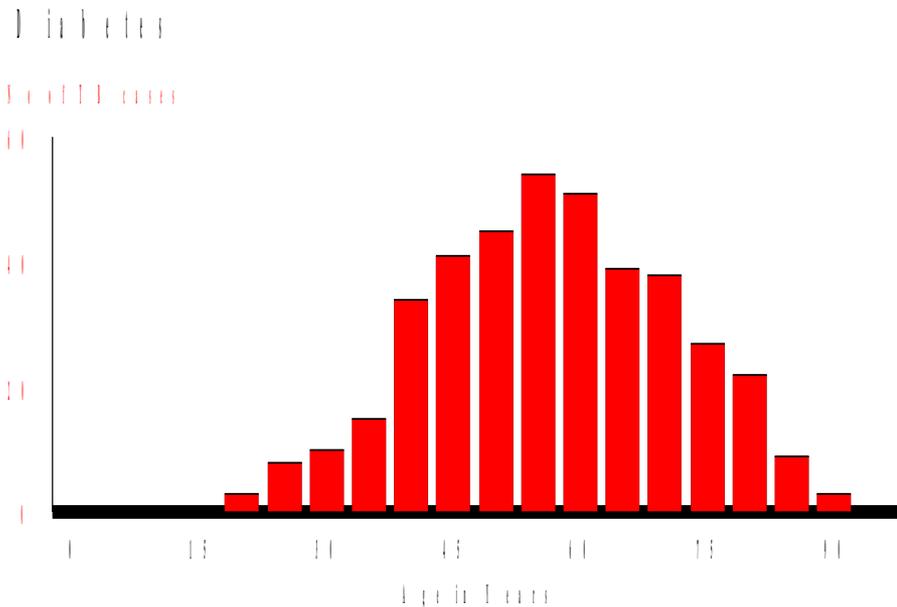
# TEXAS- Public Health Region 11

## Tuberculosis patients 1998-2002



### Risk profile without diabetes:

- Infants
- Young adults with:
  - homelessness
  - incarceration
  - Drug and alcohol use
  - HIV-positive
- Elderly homeless

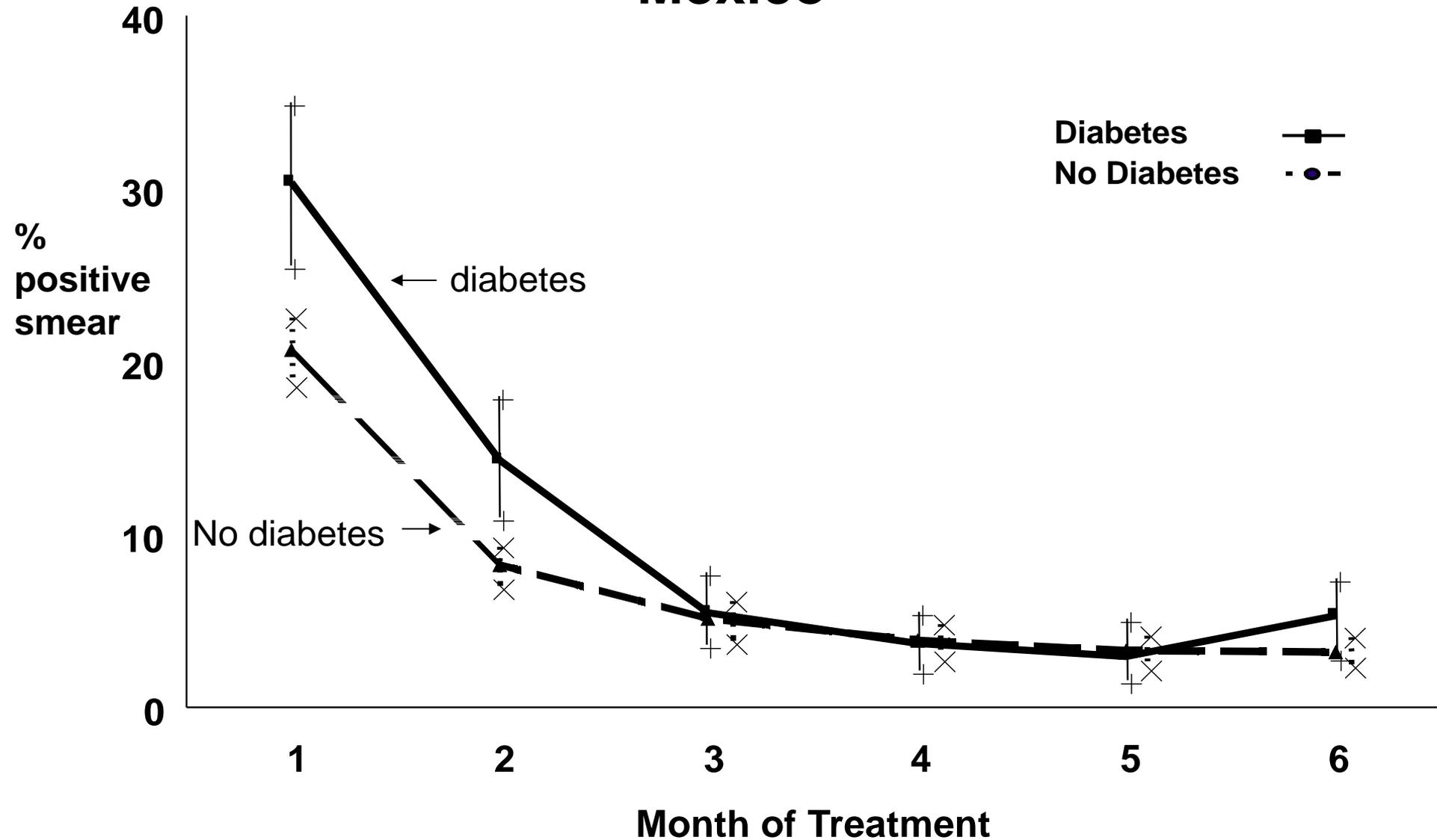


### Risk profile in diabetes:

- 40 years or older
- Type 2 diabetes
- No other social or demographic risk factor

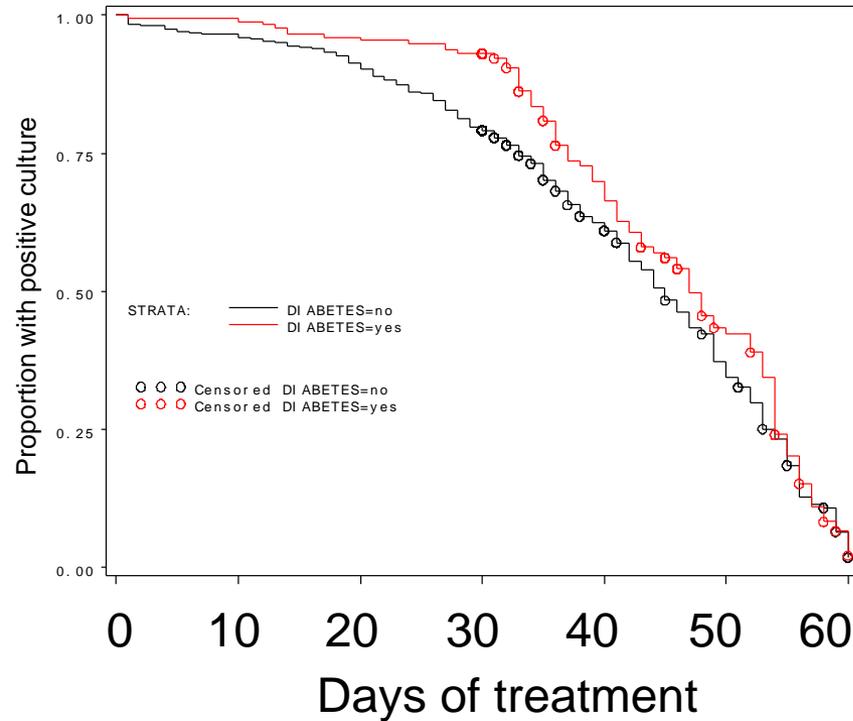
*Restrepo, B.I., Fisher-Hoch, S.P., McCormick et al. Type 2 diabetes and tuberculosis in a dynamic bi-national border population. Epidemiol. Infect. 135, 483-491.*

# Smear results during the course of treatment Mexico

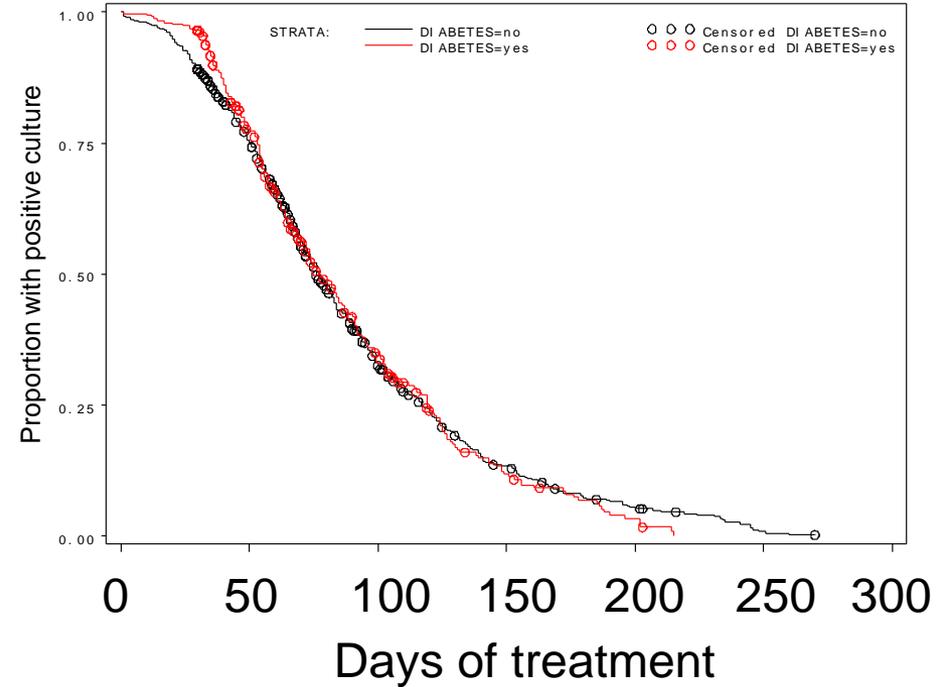


# Culture + $\longrightarrow$ Culture -

## 2 month follow-up



## 9 month follow-up



— Diabetes  
— No diabetes

*Restrepo BI, Fisher-Hoch, SP, McCormick JB et al. 2008 Mycobacterial clearance from sputum is delayed during the first phase of treatment in patients with diabetes. AJTMH;79:541-544.*

# Association between MDR-TB and Diabetes

	Diabetes		No diabetes		p value	adjOR (95%CI)
	n	%	n	%		
<b>TEXAS</b>	n=401		n=1041			
MDR	18	4.5	31	3	0.02	1.1 (1.2-4.4)
<b>MEXICO</b>	n=343		n=1384			
MDR	59	17.2	173	12.5	0.04	1.5 (1.0-2.1)

Odds Ratio adjusted for age and gender

**Conclusion: MDR-TB is more frequent in TB-DM**

# Treatment compliance

	Diabetes		Alcohol use		Drug use	
	<i>n</i> (%)	OR (95% CI)	<i>n</i> (%)	OR (95% CI)	<i>n</i> (%)	OR (95% CI)
<b>Texas</b>	<b><i>n</i>=401</b>		<b><i>n</i>=292</b>		<b><i>n</i>=152</b>	
Completed therapy	317 (81.3)	1.5 (1.1-2.0)	210 (73.4)	0.8 (0.6-1.1)	106 (74.1)	0.9 (0.6, 1.3)
Refused or incomplete therapy	1 (0.3)	0.3 (0.1, 0.6)	25 (8.7)	2.3 (1.4-3.8)	18 (12.6)	3.4 (1.9-5.9)
<b>Mexico</b>	<b><i>n</i>= 607</b>		<b><i>n</i>=63</b>		<b><i>n</i>=84</b>	
Completed therapy	445 (73.3)	1.2 (1.0-1.4)	37 (58.7)	0.6 (0.4, 1)	47 (55.9)	0.5 (0.3, 0.8)
Refused or incomplete therapy	55 (9)	0.8 (0.7, 1)	16 (25.4)	2.8 (1.6-5.0)	22 (26.2)	3.0 (1.8-4.9)

**Diabetes patients are more likely to adhere to treatment even after adjusting for age and gender**

# The Chronic Inflammatory Syndrome in Diabetes is at the root of the susceptibility to infections, particularly TB.

## Scientific Evidence shows:

- **CYTOKINES:** Cytokines (e.g. TNF alpha and Interferon gamma) that are critical for combating TB are *UPREGULATED* but ineffective in killing Mtb.
- **GENE EXPRESSION:** Patients with diabetes have *REDUCED EXPRESSION* of genes critical in controlling TB and are ineffective in killing Mtb.
- **NEUTROPHILS:** Patients with diabetes have neutrophils which *OVERREACT TO ANTIGENS* but are again ineffective in killing Mtb
- **ANTIBODY RESPONSES:** These are *ALTERED IN DIABETES* and again less effective in producing protection after vaccination.

## Viewpoint

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

**Anthony D. Harries<sup>1,2</sup>, Megan B. Murray<sup>3,4</sup>, Christie Y. Jeon<sup>3</sup>, Salah-Eddine Ottmani<sup>5</sup>, Knut Lonnroth<sup>5</sup>, Mauricio L. Barreto<sup>6</sup>, Nils Billo<sup>1</sup>, Richard Brostrom<sup>7</sup>, Ib Christian Bygbjerg<sup>8</sup>, Susan Fisher-Hoch<sup>9</sup>, Toru Mori<sup>10</sup>, Kaushik Ramaiya<sup>11,12</sup>, Gojka Roglic<sup>13</sup>, Hanne Strandgaard<sup>14</sup>, Nigel Unwin<sup>15</sup>, Vijay Viswanathan<sup>16</sup>, David Whiting<sup>17</sup> and Anil Kapur<sup>14</sup>**

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## **CONCLUSION:**

### **DIABETES THREATENS TUBERCULOSIS CONTROL GLOBALLY**

- **Diabetes increases risk of tuberculosis three fold**
- **382 million people globally have diabetes, more than tenfold more than those with AIDS.**
- **Diabetes threatens to spread MDR-TB**
- **The populations most at risk are Low and Middle Income**
- **Diabetes patients with TB are documented to have:**
  - Increased drug resistance**
  - Delayed clearance of Mtb from sputum**
  - Intolerance of TB medication and drug interactions**
  - Increased morbidity**
  - Increased relapse rates**
  - Increased deaths**

## **Needs and questions?**

- **Screen TB patients for diabetes. Should now be routine.**
- **Screen DM patients for TB. Where, how and when??**
- **Better, cheaper and safer diagnostic techniques needed for both diseases**
- **Encourage TB and DM programs to work together**
- **Model DM diagnosis and care on TB control programs**
- **Develop specific treatment regimens for DM-TB**
- **Develop registries for diabetes**
- **Educate patients, health care professionals and communities**
- **Resources for implementation and research sorely needed**
- **Political will**

# UPDATE: June 11<sup>th</sup> 2014

## [U.S. diabetes cases reached 29 million in 2012, CDC says](#)

CDC officials say diabetes cases in the U.S. reached 29 million in 2012, while another 86 million people were at an increased risk of diabetes. Researchers also found that diabetes and related complications were associated with a total of \$245 billion in health costs and lost work and wages in 2012. (Reuters)