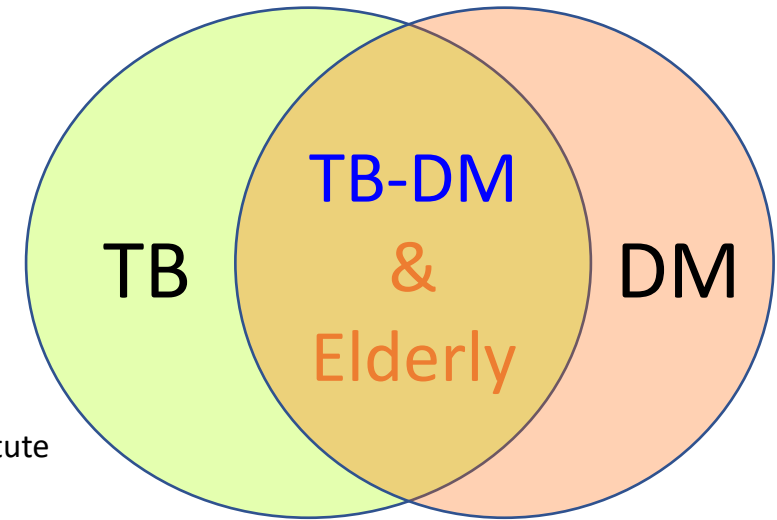# Tuberculosis, diabetes y la tercera edad

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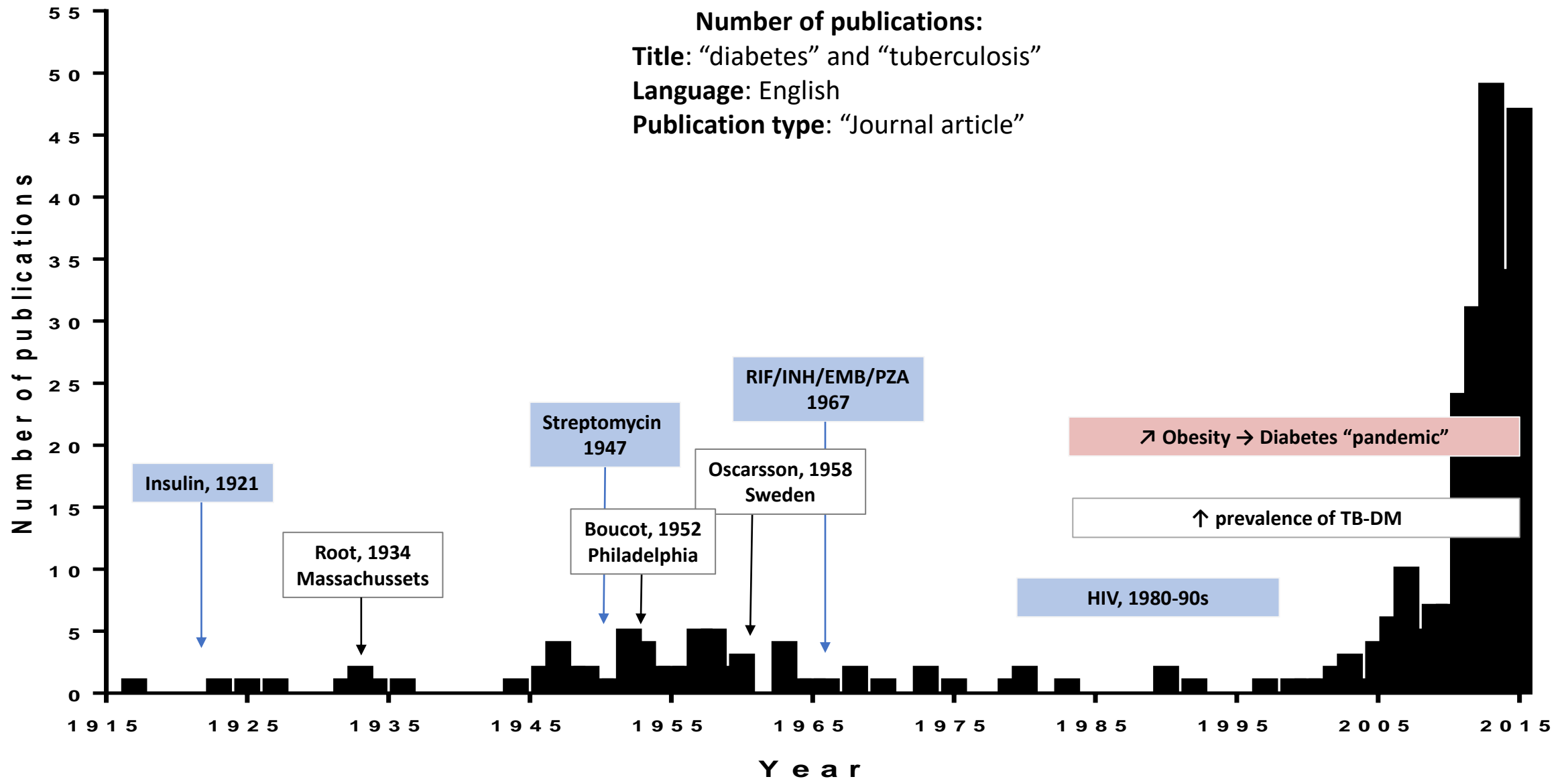
Marzo 25, 2021

Seminar structure

- **Tuberculosis (TB) and diabetes mellitus (DM)**
  - Introduction: DM as a re-emerging risk factor for TB
  - TB-DM epidemiology: Our findings
  - Public health implications

- **TB in the elderly**
  - Why study the elderly?
  - Preliminary observations
  - Clinical implications

WEBINAR
Tuberculosis y comorbilidades
¿problema de salud pública?

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Association between TB and DM

TB case

Contact

~ 40% → No TB infection

~ 60% → TB infection

Diabetes

3x

No TB

90% lifetime risk

10% lifetime risk

TB

Cured

- Delayed *Mtb* clearance
- Relapse/re-infection
- Death
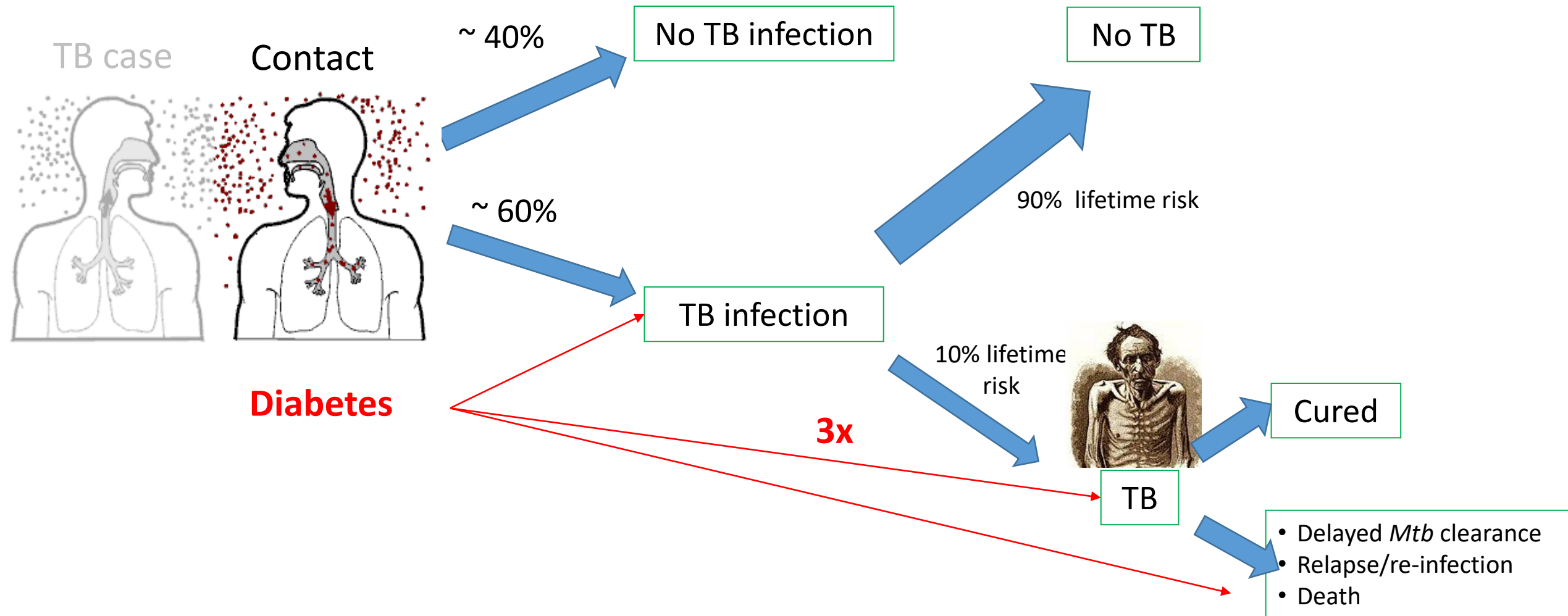
DM: a re-emerging risk for TB

Adapted from Cadena et al, Tuberculosis 2020

Overlap of TB and diabetes
80% of diabetes cases occur in low and middle income countries (LMIC)

TB
"high burden"
by WHO (n=22)
80% of TB cases

China
India
Brazil
Bangladesh
Indonesia
Pakistan
Russia
(Tx-Mexico)

Diabetes
Ten countries
with highest
number of
diabetes cases
world-wide

Modified from Restrepo 2017

Study sites and designs

United States

Mexico

N. Laredo · south Texas · Edinburg/Brownsville · Reynosa · Matamoros

Tamaulipas

Chiapas

	South Texas	Tamaulipas
TB incidence	11/100,000	32/100,000
DM prevalence	20%	15%

Texas

South Africa

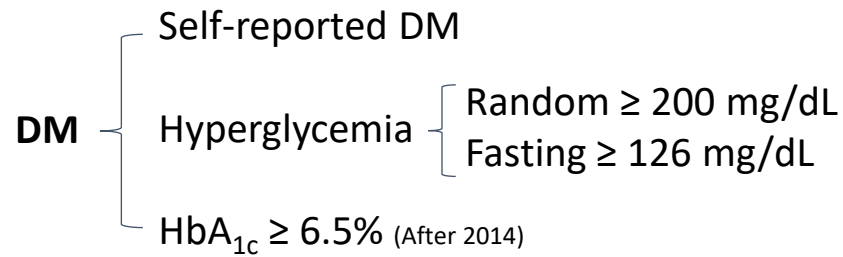| Retrospective epidemiology studies (TB surveillance datasets)						
Study site	n	Controls	Contacts	Active TB	Years	Reference
S. Texas, USA	1,441			▓	1996 - 2002	Restrepo et al, 2006; Fisher-Hoch et al, 2008; Restrepo et al, 2008
Tamaulipas, Mx	3935			▓	1998 - 2003	Restrepo et al, 2006
Tamaulipas, Mx	8,431			▓	2005 - 2013	Abdelbary et al, 2016; Abdelbary et al, 2017
Chiapas, Mx	5,508			▓	2010 - 2014	Raskak et al, 2019

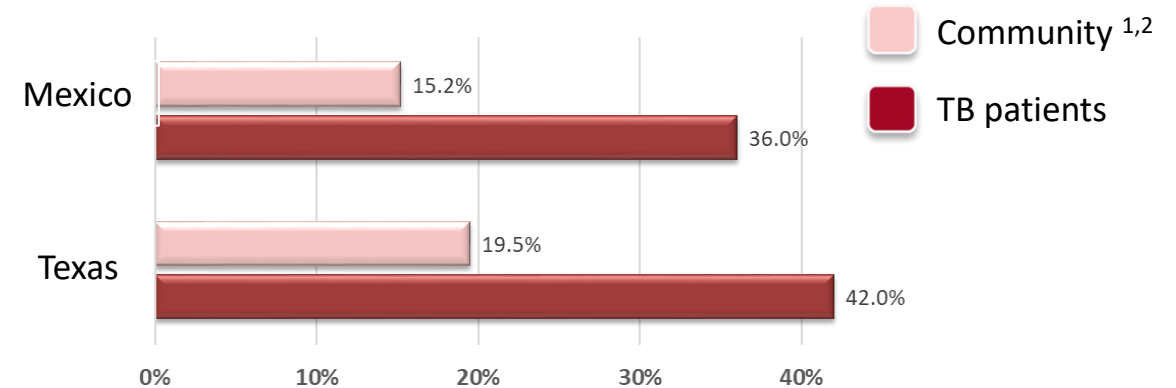| Prospective epidemiology studies						
		Controls	Contacts	Active TB		
Texas - Tamaulipas border	233	▓		▓	2006-2010	Restrepo et al, 2008; Fisher-Hoch et al, 2010; Restrepo et al, 2011; Walsh et al, 2011
Texas - Tamaulipas border vs South Africa	106, 95		▓		2016 - 2018	Restrepo et al, 2018
Texas - Tamaulipas border	657	▓	▓	▓	2016-2021	*in preparation*

Results: Diabetes prevalence in the Texas-Mexico border

DM definition in our studies:

- American Diabetes Association (2010 – 2018)
- 98% Type 2 DM

DM
- Self-reported DM
- Hyperglycemia
  - Random ≥ 200 mg/dL
  - Fasting ≥ 126 mg/dL
- HbA_{1c} ≥ 6.5% (After 2014)

Confirmed DM (2006-2010)

Community [1,2]

TB patients

Mexico — 15.2% / 36.0%
Texas — 19.5% / 42.0%

[1] US-Mexico border diabetes prevention and control program, PAHO report;
[2] Cameron County Hispanic Cohort for south Texas (Fisher-Hoch et al, 2010)
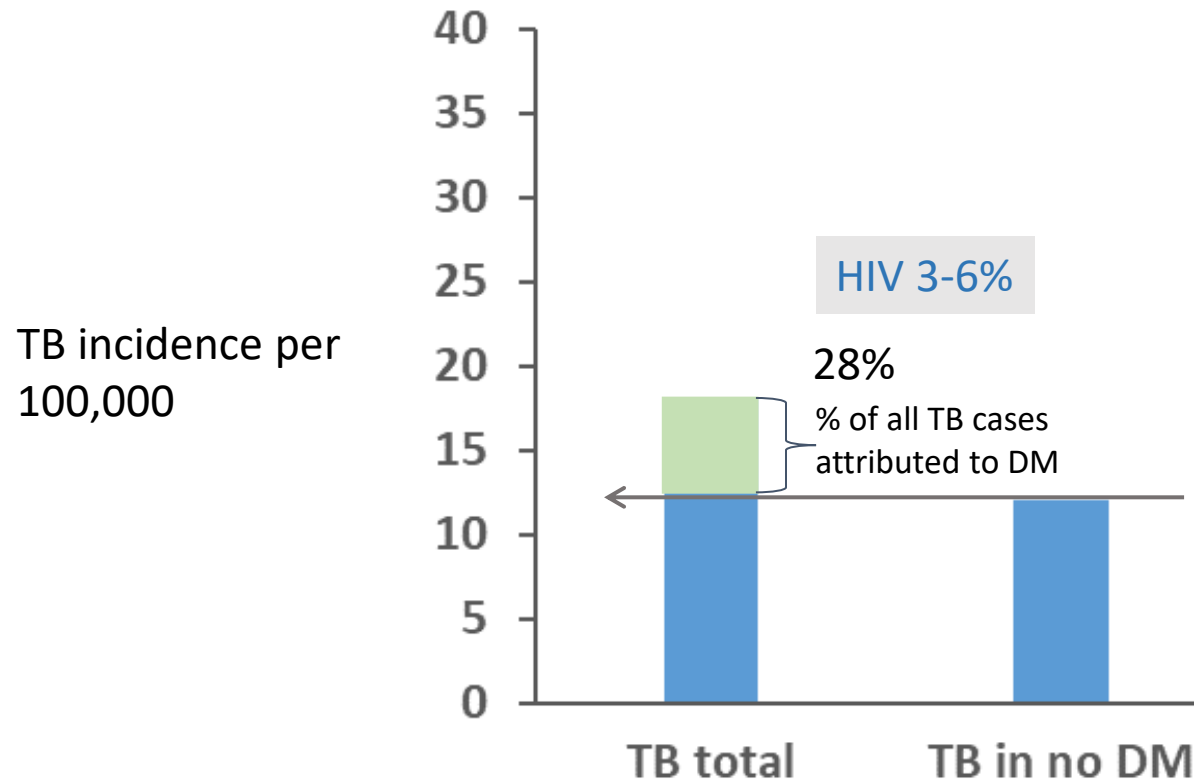
Conclusions:

Prevalence: Significantly higher among TB patients when compared to community controls ($p ≤ 0.05$)

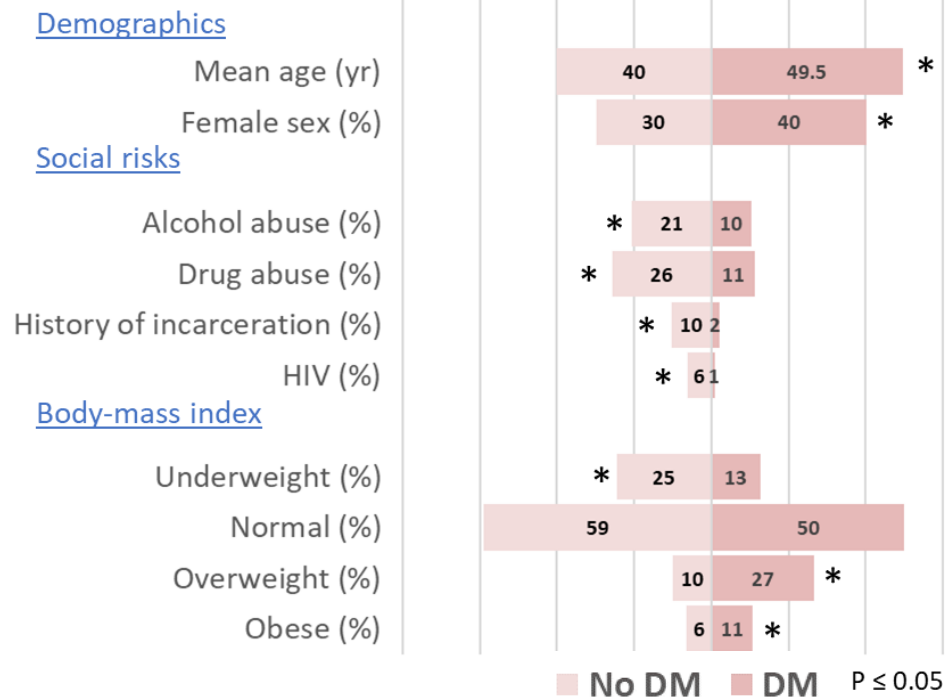**Odds ratio ~ Relative risk of TB in DM patients**
Texas: 3.0 (2.3 – 4.2)
Mexico: 2.7 (1.6 – 4.4)

Restrepo et al, 2006; Restrepo *et al., Bull WHO* (2011)

Population attributable risk of TB due to diabetes (PAR%)

TB incidence per 100,000

HIV 3-6%

28%

% of all TB cases attributed to DM

- Restrepo *et al., Bull WHO* (2011)

Profile of the TB-DM patient …..vs TB-no DM

Socio-demographic characteristics:

DM ⟶ TB

History of DM:

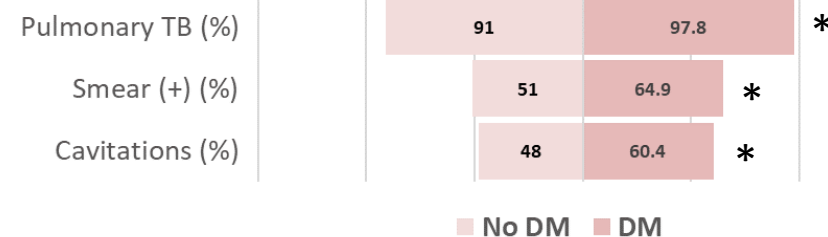### Diabetes awareness and history (TB patients, 2006-2010)

	Texas (n=27)	Mexico (n=79)	Total (n=106)
n with DM	11	27	38
Self-reported, n (%)	11 (**100%**)	22 (**81%**)	33 (**87%**)
Years with DM (in self-reported)	**12.3** (8.8)	**7.6** (7.6)	**8.9** (8.2)

* DM using 2004 American Diabetes Association definition (no HbA$_{1c}$)

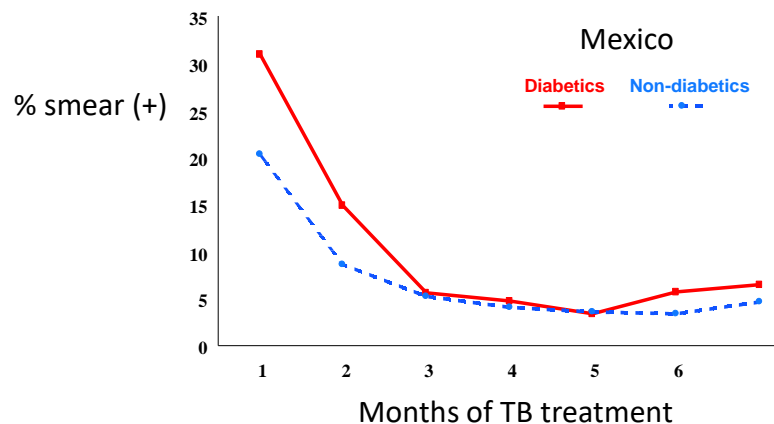## TB characteristics at the time of TB diagnosis:

Conclusions:

- Female patient > 40 years old
- No "classical" profile for TB
- Chronic history of DM

THINK TB!! ….. and a more <u>contagious</u> TB?

Restrepo *et al., Bull WHO* (2011); Restrepo et al, Epidemiol Infect (2007)

TB treatment outcomes

1. Mycobacterial clearance:

Restrepo et al, AJTMH, 2008

2. Drug resistance:

	Diabetes	No diabetes	p value	OR
Texas (1996-2002)	**n=401**	**n=1,041**		
DR-TB	41 (10.2%)	98 (9.4%)	NS	
MDR-TB	18 (4.5%)	31 (3.0%)	**0.018**	**1.1 (1.1, 4.4)***
Tamaulipas (1998-2003)	**n=343**	**n=1,384**		
DR-TB	83 (24.2%)	255 (18.4%)	**0.024**	**1.4 (1.1, 1.9)***
MDR-TB	59 (17.2%)	173 (12.5%)	**0.040**	**1.5 (1.0, 2.1)***
Tamaulipas (2006-2013)	**n=2132**	**n=6357**		
DR-TB	81 (3.8%)	178 (2.8%)	**0.021**	**1.4 (1.1, 1.8)**
MDR-TB	20 (0.9%)	35 (0.6%)	**0.055**	**1.7 (0.98, 3.0)**

* OR adjusted for age and sex; Fisher-Hoch et al, 2008; Abdelbary et al, 2016

3. Death during TB treatment:

Host factors associated with death during TB treatment, Tamaulipas 2006-2013, AdjOR (sex, age*)
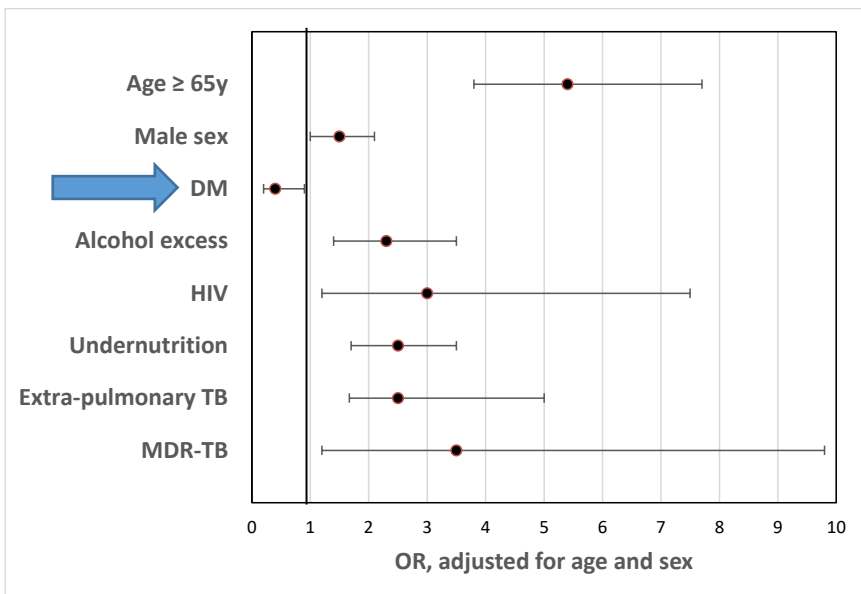
* Similar findings in TB patients from Chiapas, 2010-2014

Adapted from Abdelbary et al, Epidemiol Infect, 2017

4. Relapse and re-infections:

- Relapse OR 3.89 (2.43, 6.23) Baker et al, BMC Medicine, 2011 (Systematic review)
- Relapse aOR 1.96 (1.22, 3.15) Lee et al, PLoS One, 2014

Conclusion:

DM is associated with more adverse TB treatment outcomes

Public health implications.....

▶ **TB clinics:**

   ▶ **Strategic site to <u>screen</u> for <u>new</u> DM**

     ● **Among TB <u>patients</u>: Yes.** (even in developed countries!)

     ● **Among TB <u>contacts</u>? Maybe**

   ▶ **Strategic site for <u>joint management</u> of TB and DM?**

     ● **Maybe. At least during first phase of TB treatment?**
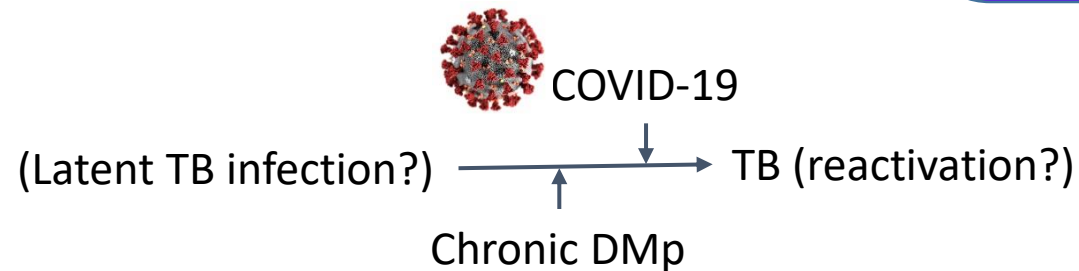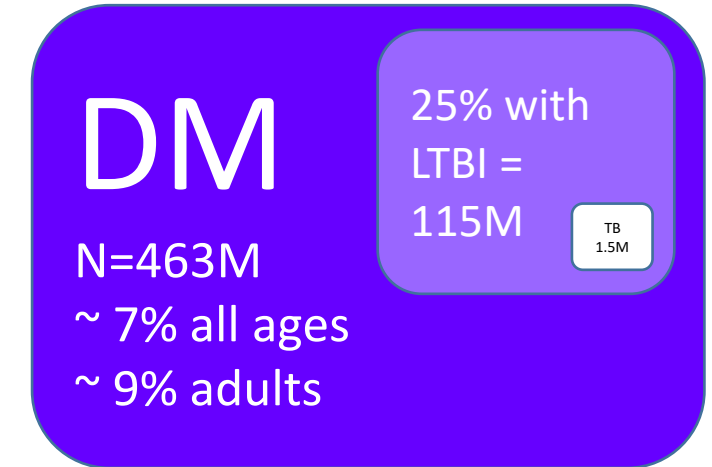
▶ **DM clinics:**

   ▶ **Screen for Active TB. Per WHO guidelines**

   ▶ **Screen for LTBI?? Not per WHO guidelines.... If screen → LTBI+ → LTBI treatment**

   ▶ Need more Information to stratify TB risk among diabetes patients....

▶ **General clinics:**

   ▶ **Impact of COVID-19 and DM on TB?**

Among....	Location	% new DM/DM [3]
TB (20+ yrs) [1]	Texas	18%
	Mexico	36%

DM

N=463M
~ 7% all ages
~ 9% adults

25% with LTBI = 115M

TB 1.5M

COVID-19

(Latent TB infection?) ———→ TB (reactivation?)

Chronic DMp

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TB in the elderly

TB in the elderly

- Increasing age is a risk factor for TB disease (Hochberg, 2013)

TB by age groups and sex, US, 1998-2008
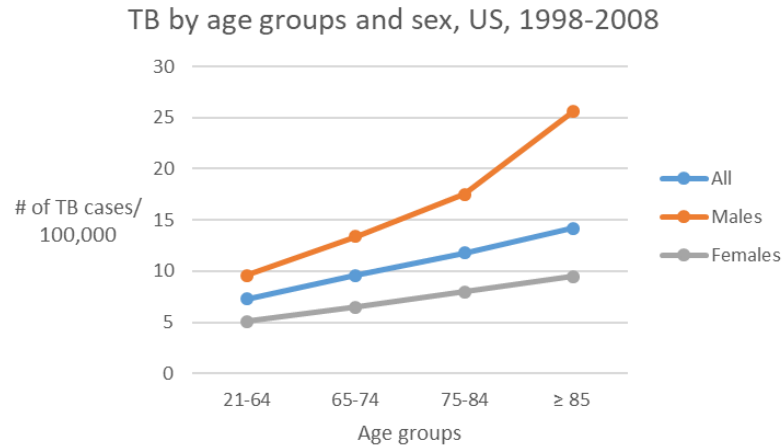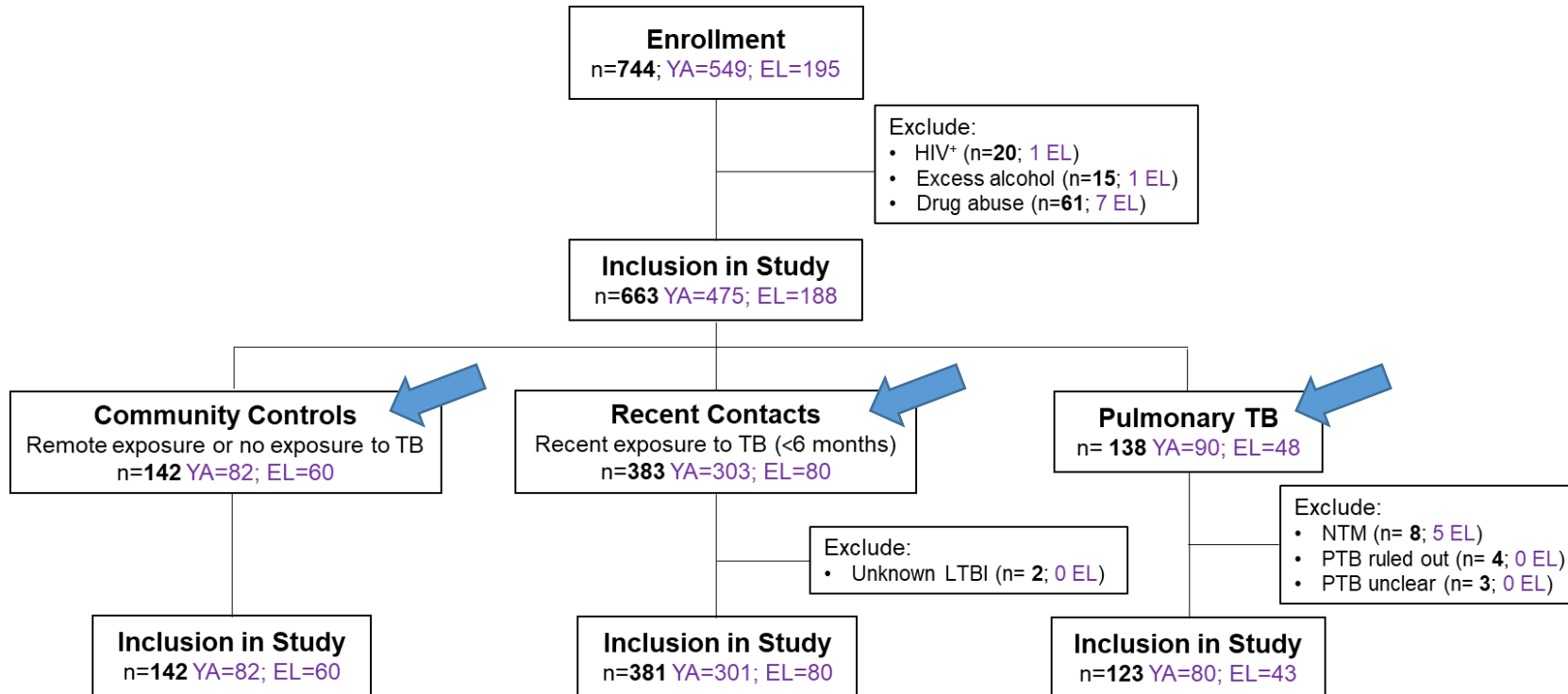

- Increasing age is a risk factor for death from TB (Hochberg, 2013)
  - 20-33%; 6-8 fold higher risk vs adults (Teale et al, 1993; Wang et al, 2008; Yen et al, 2017)
  - 50% from TB (Garcia-Goez et al, 2020)

- The global population is aging. It is estimated that the % of the global population ≥ 65y will be (US Census Bureau, 2016).
  - 2015: 8.5%
  - 2050: 17%   2x

Why are the elderly at higher risk of TB?

- Epidemiology
  - **Higher exposure** to TB as children (vs younger cohorts)
    - TB was more prevalent years ago
    - Larger reservoir for LTBI with risk of re-activation TB
  - **Higher risk of exposure** in long-term care facilities
- Biology
  - Higher risk of LTBI →→ TB
    - Compromised immunity
    - Co-morbidities (diabetes, renal failure, cancer)
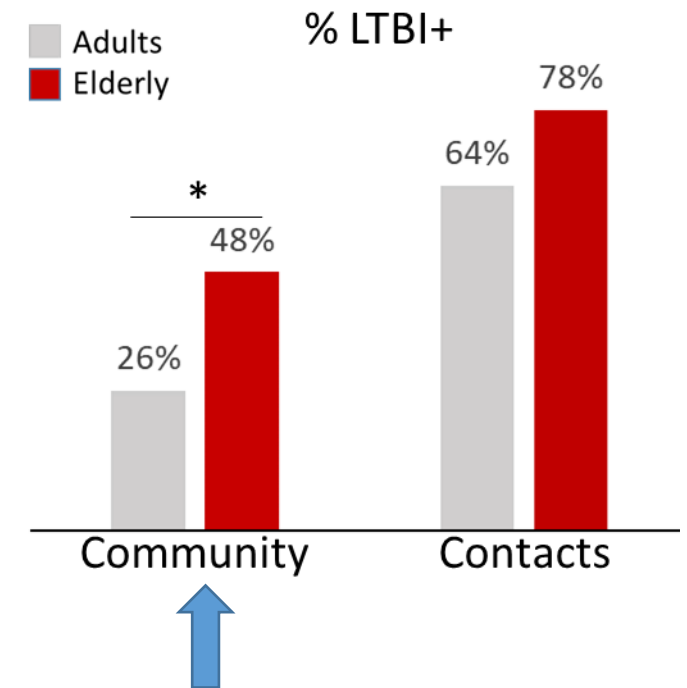   - Smoking, low BMI
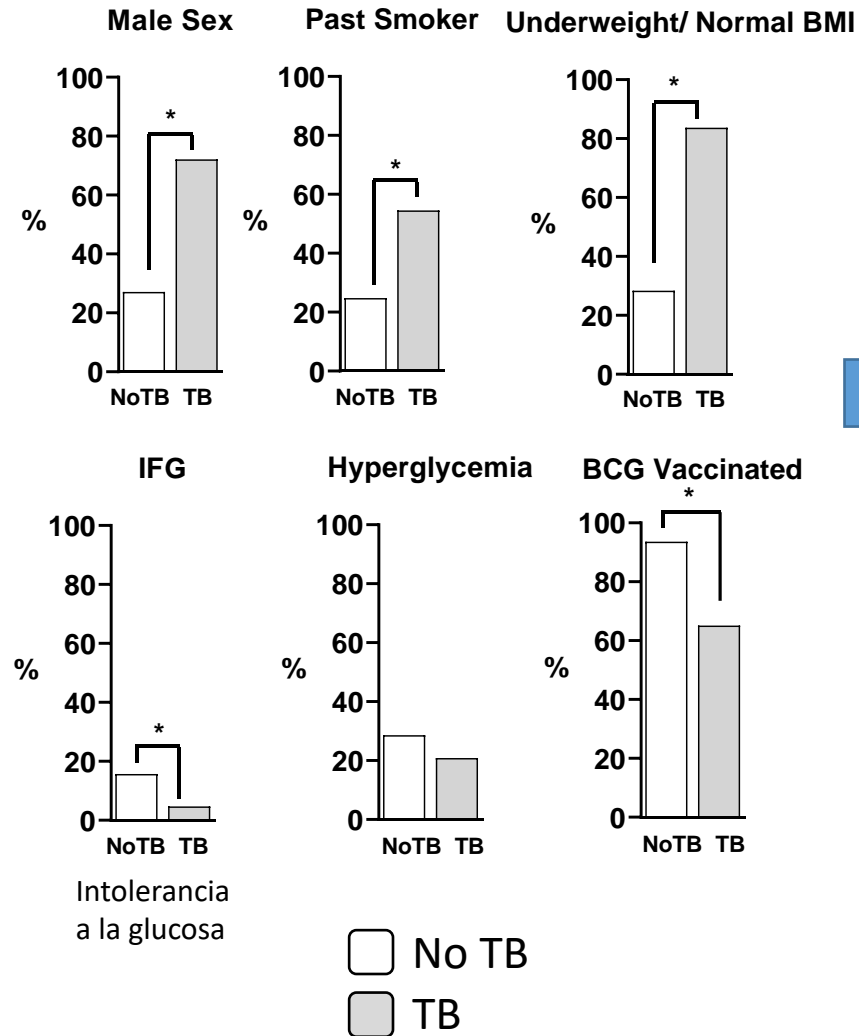
Study in the elderly: TB, contacts and controls

Enrollment
n=**744**; YA=549; EL=195

Exclude:
- HIV⁺ (n=**20**; 1 EL)
- Excess alcohol (n=**15**; 1 EL)
- Drug abuse (n=**61**; 7 EL)

Inclusion in Study
n=**663** YA=475; EL=188

Community Controls
Remote exposure or no exposure to TB
n=**142** YA=82; EL=60

Recent Contacts
Recent exposure to TB (<6 months)
n=**383** YA=303; EL=80

Pulmonary TB
n= **138** YA=90; EL=48

Exclude:
- Unknown LTBI (n= **2**; 0 EL)

Exclude:
- NTM (n= **8**; 5 EL)
- PTB ruled out (n= **4**; 0 EL)
- PTB unclear (n= **3**; 0 EL)

Inclusion in Study
n=**142** YA=82; EL=60

Inclusion in Study
n=**381** YA=301; EL=80

Inclusion in Study
n=**123** YA=80; EL=43

% LTBI+

Adults
Elderly

Community: Adults 26%, Elderly 48% *
Contacts: Adults 64%, Elderly 78%

Elderly: 60+ years old
Young adults (YA): 18-50 years old

Identifying risk factors for TB among the elderly: TB vs no TB
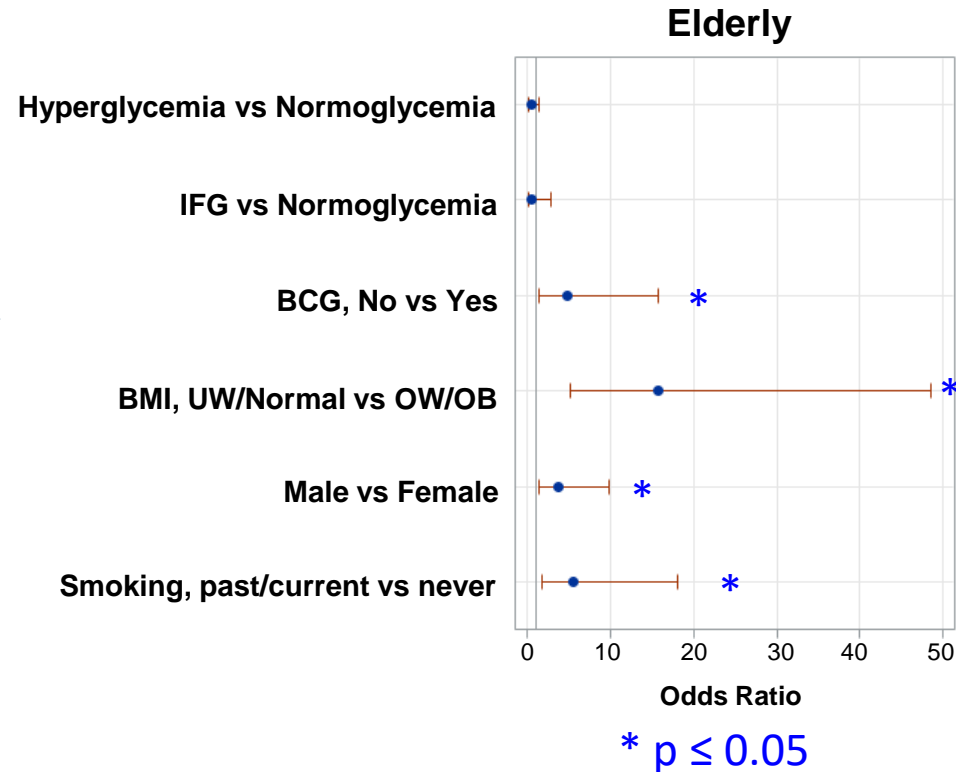
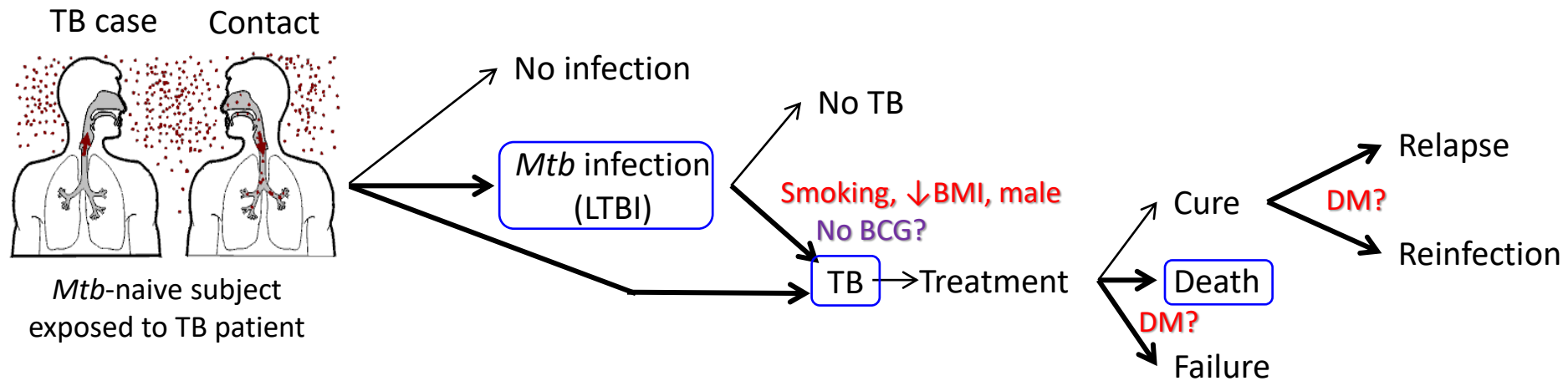# Impact of host factors on the history of TB…. in the elderly

TB case   Contact

No infection

Mtb infection (LTBI)

No TB

Smoking, ↓BMI, male
No BCG?

TB →Treatment

Cure

Relapse

DM?

Reinfection

Death

DM?

Failure

Mtb-naive subject
exposed to TB patient

Adapted from Restrepo

Acknowledgments

Restrepo team

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- <u>Reynosa</u>: **QFB Cristela Resendez,** Dr. Ericka Prieto, **MSc. Génesis Aguillón-Durán,** Mr. Jorge Pérez, TB DOTS staff
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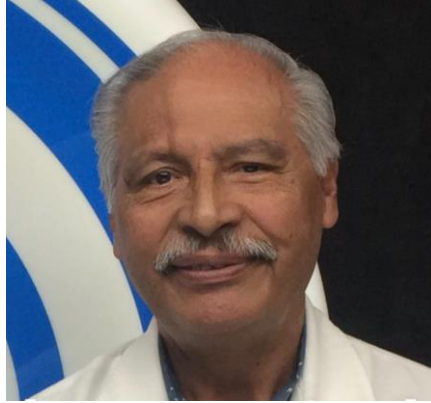
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Nuestra Clinica del Valle

- Lucy Ramirez and staff

NIH, NIAID US-South Africa Collaborative Award

In memoriam 2020…. The COVID pandemic

- ## Matamoros clinic
Dr. Francisco Mora-Guzmán

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