Challenges to tuberculosis control in the border region

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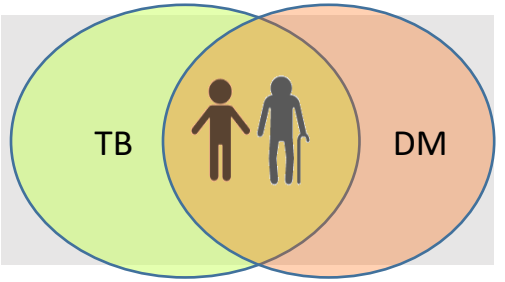

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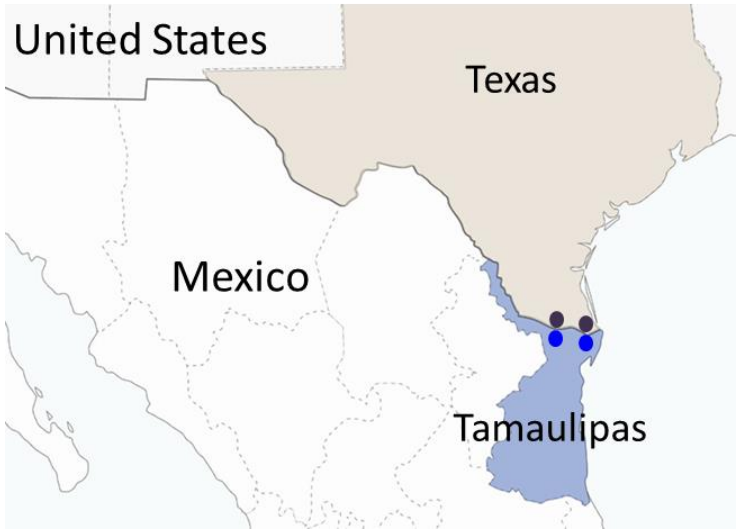
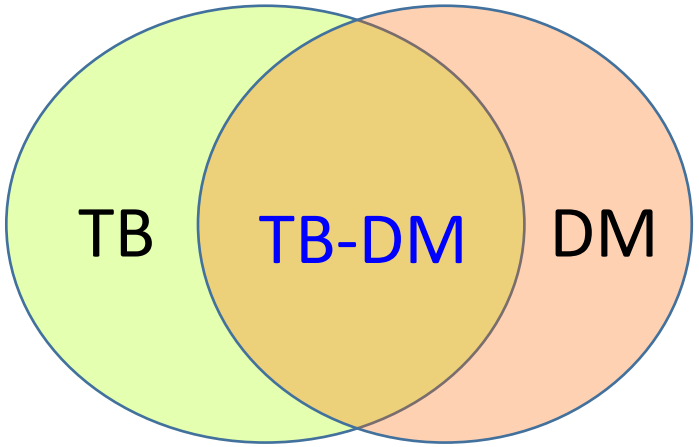


Task Force of Border Health Officials
Office of Border Health Public,
Department of State Health Services
Austin, TX (remote presentation)
April 9, 2025

Seminar structure

- **Tuberculosis (TB) and Type 2 diabetes mellitus (T2D; DM)**
  - Epidemiology
  - Underlying biology
  - Public health impact



- **TB and T2DM in older adults**
  - Unexpected observations
  - Public health impact

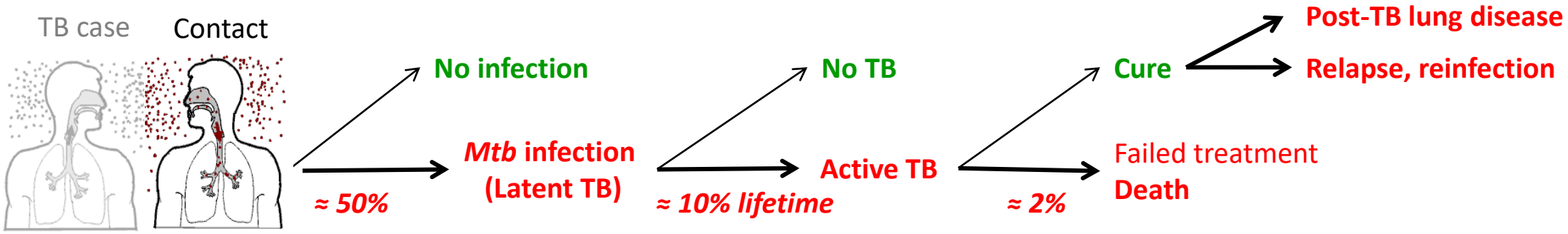
- **Drug-resistant (DR) TB diagnostics**

Backwoods/Biorender icons

Mycobacterium tuberculosis (Mtb) → tuberculosis disease (TB)

10.6 million new cases and 1.3 million deaths in 2022

(Leading microbial killer)



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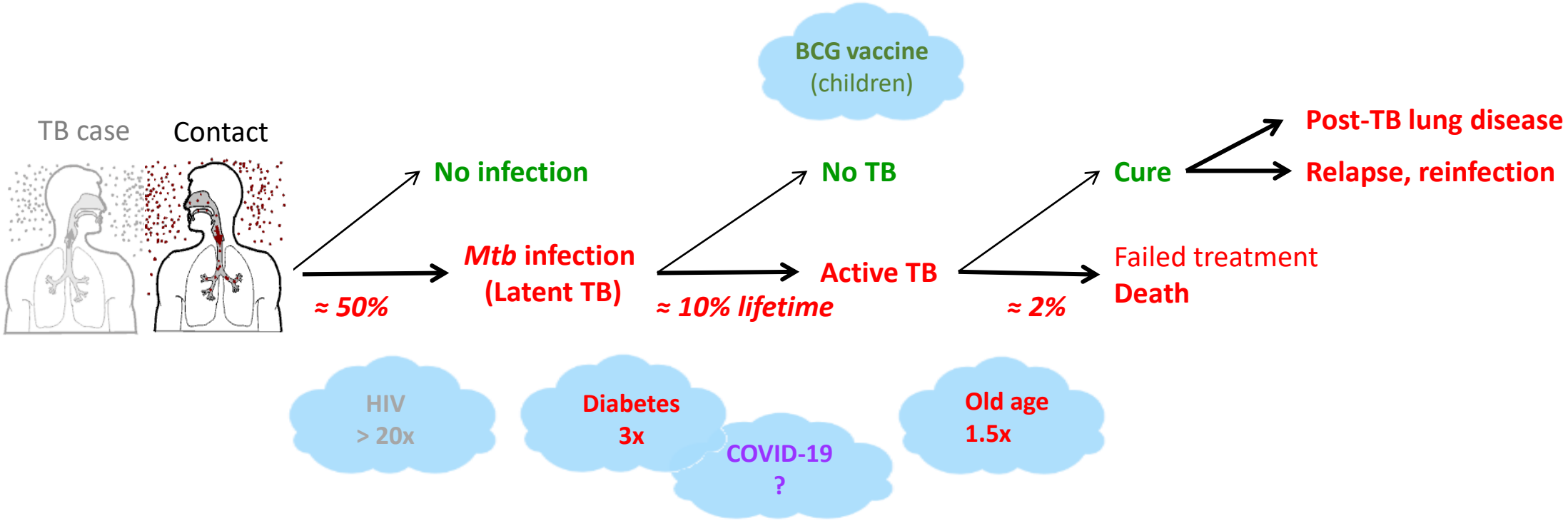

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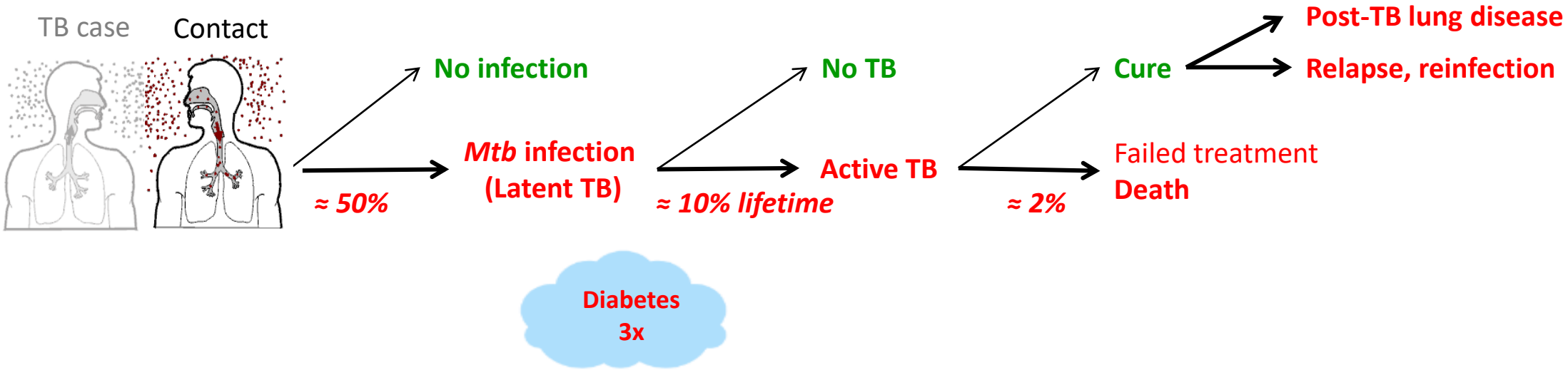
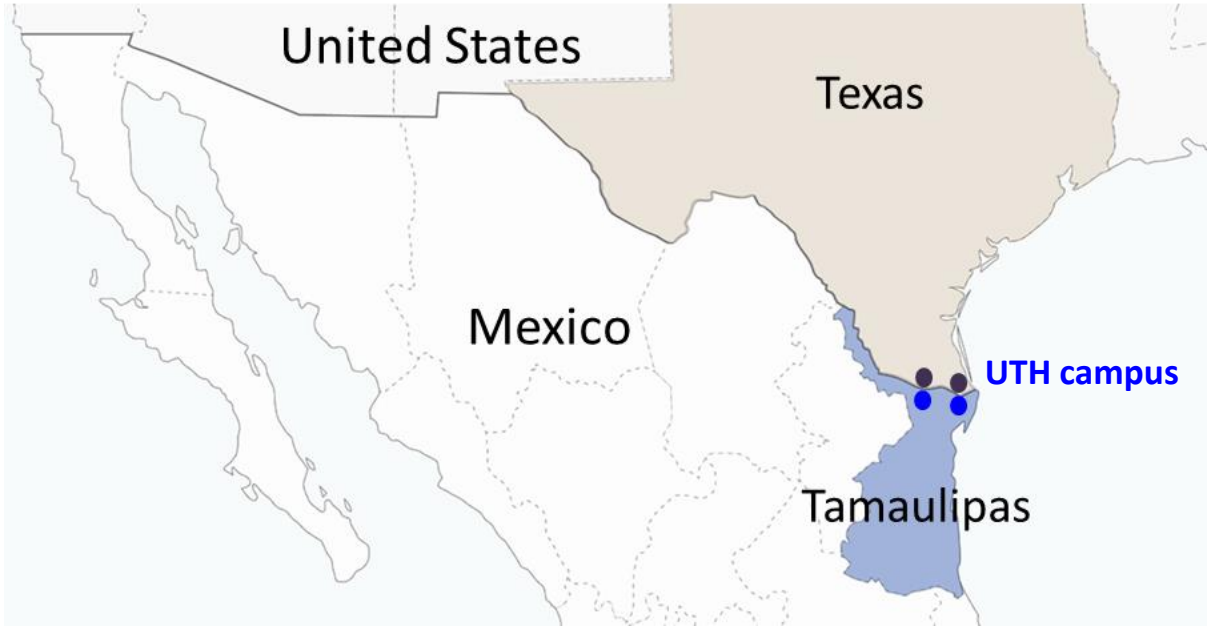


Study site: US-Mexico border



Border communities burdened by:

- Stress from migration, drug cartels
- Poverty
- Severe health disparities:
  - ↑TB, ↑Obesity → Type 2 diabetes mellitus

Unique TB program in mainland US

Crossing the Rio Grande River

TB clinic DOTS supervisors

Specimen collection

US Customs & Border Protection Agriculture Specialists

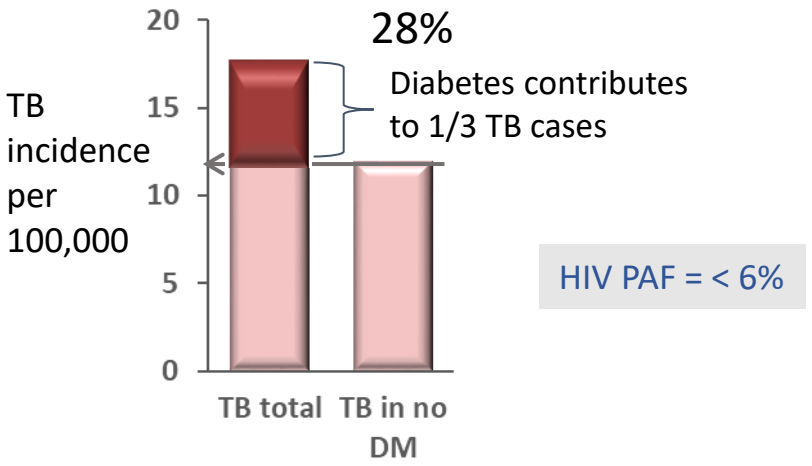
Curry *et al*. J Imm Min Health, 2021

Study site: US-Mexico border: T2DM → TB

Diabetes increases the risk of active TB

- **Mexico**: **2.7** (95% CI 1.6 – 4.4)
- **Texas**: **3.0** (95% CI 2.3 – 4.2)

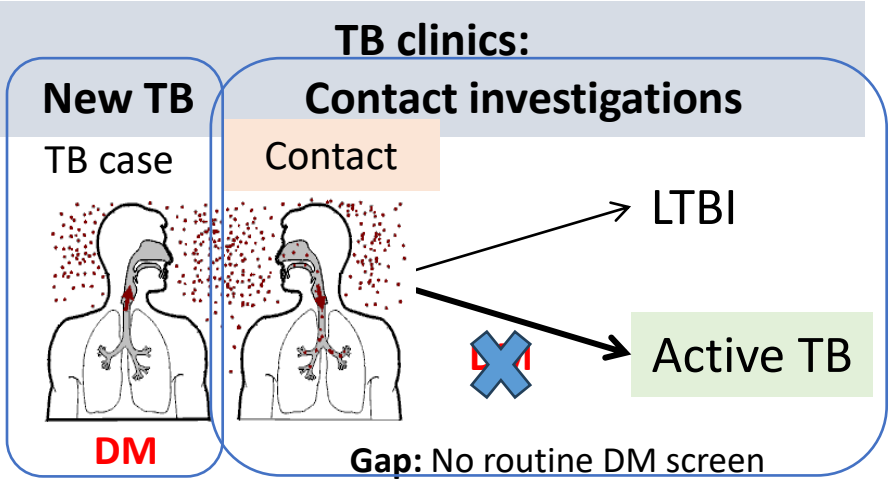
Population attributable fraction (PAF)



HIV PAF = < 6%

Restrepo *et al*, Epidemiol Infect 2006; Restrepo *et al.*, Bull WHO (2011); Rashak *et al*, Epidemiol Infect, 2019; Cadena et al., 2020

TB clinics: Hub for new diabetes diagnosis



TB contacts: Proportion of DM cases with "new" DM

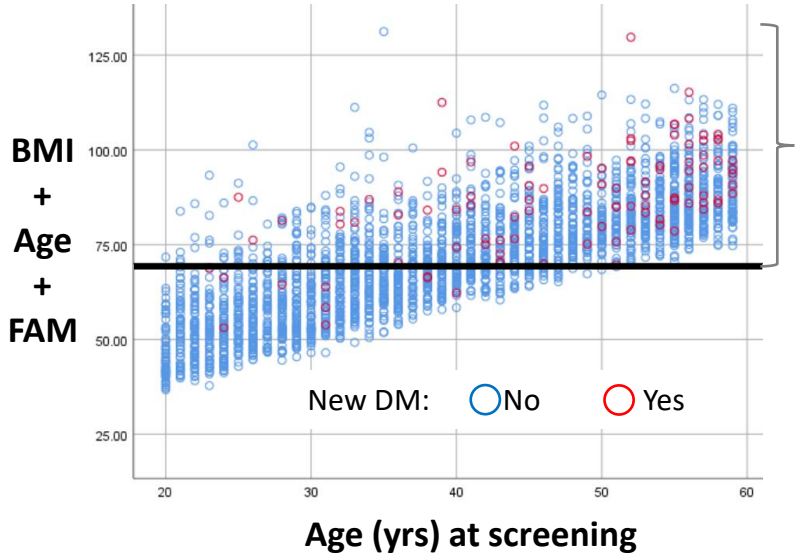
Location	% New DM / Total DM	New DM *vs* known DM
Texas	40%	↑ males ↓ complications
México	29%	
S. Africa	45%	

≥ 1/3 of TB contacts with DM are not aware

Need for DM screening at TB clinics.

1. Simple model to predict high risk of DM in TB contacts

2. Is DM screening of TB contacts cost-effective?
   - **Results**: Cost-effective, ↑ Lifespan, ↑ Healthspan



Screen 70% of contacts
Identify 95% of DM

Summary:
- TB clinics: Strategic sites for "*Extended contact investigations*" with 2º screening for DM
  ** NEXT: TRANSLATION RESEARCH GOAL

Lopez-Alvarenga *et al, to be submitted;* McGowan *et al, BMJ Public Health, 2024*

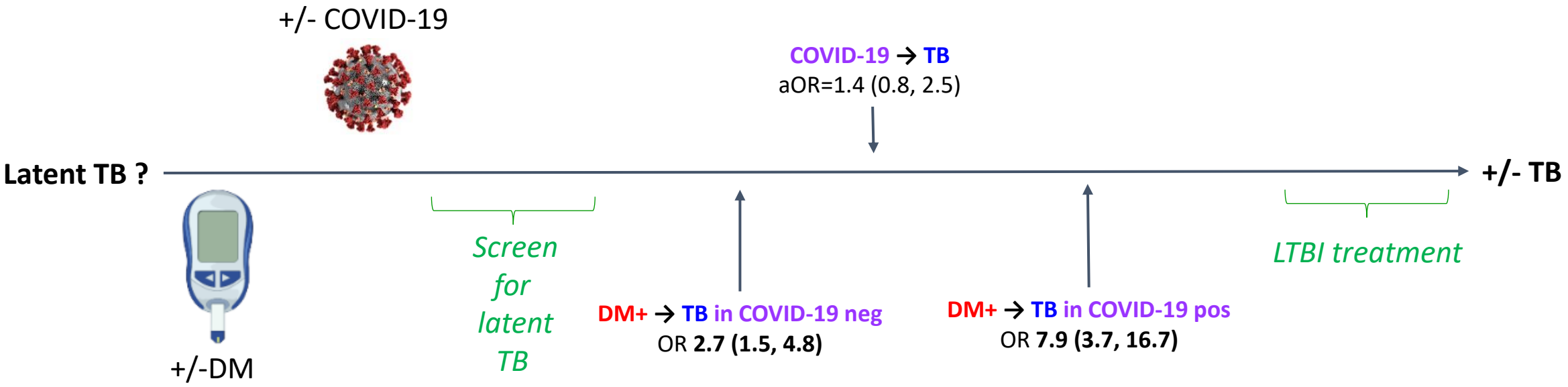
Impact of my team's findings on TB and diabetes

- Pioneered the discovery of DM as a re-emerging risk factor for TB
  - Diabetes accounts for:
    - 30% of all adult TB cases in Texas-Mexico border
    - 15-35% of all TB cases worldwide
- Clinical impact:
  - TB: Joint management of TB & DM
  - Latent TB Infection: Performance of QuantiFERON, T.Spot-TB in DM and by age
    - Our publications cited by US Task Force for management of latent TB in the US
- TB clinics: Beyond TB care → Hubs for diagnosis of new diabetes:
  - TB patients → New DM diagnosis → ↓ DM complications & improve TB outcomes
  - TB contacts: WIP→ implementation

➢Gaps:

- Studies testing of new technologies (e.g. vaccine, biomarkers) frequently exclude DM patients
- Lack of understanding of the **underlying biology** → Host directed therapy

Ho: COVID-19 → Active TB



Clinical implications?

Calles-Cabanillas et al, under review

Why study TB in older adults?

- **The global population is aging**
  - **2015**: 8.5% ≥ 65y
  - **2050**: 17% ≥ 65y

2x

- **Old age is a risk factor for**:
  - **Active TB disease**
  - **Death from TB** (6 to 8-fold)

- **Knowledge gaps**
  - Older adults are neglected and understudied
  - Most studies in Asian populations

- **Hypothesis**
  - DM major driver → active TB → Death

- **Discovery studies**:
  - Risk factors for active TB disease in the elderly
  - Risk factors for Latent TB infection in the elderly

>50% DM

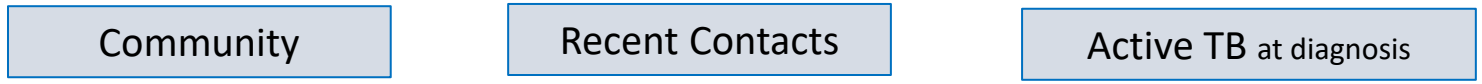
Hochberg et al, 2013; Teale et al, 1993; Yen et al, 2017; Abdelbary et al, 2017; Wang et al, 2008; Garcia-Goez et al, 2020;

Study older adults from the Texas-Mexico border

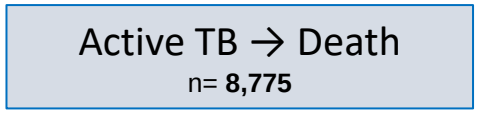
- **Design:** Cross-sectional
- **Age groups**:
  - **Young Adults** **YA**: 18-44 yrs
  - **Middle age adults** **MAA:** 45-64 yrs
  - **Older adults** **OLD: ≥ 65 yr**

- **Study populations:**

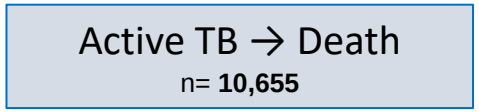
  - **Research cohort**
    - Tx-Mexico border



  - **2º analysis of TB surveillance data from health departments'**
    - Tamaulipas, Mx



    - Texas DSHS



Risk factors for active TB, by age group

Unique to OLD

All ages

Hyperglycemia *vs*. Normoglycemia

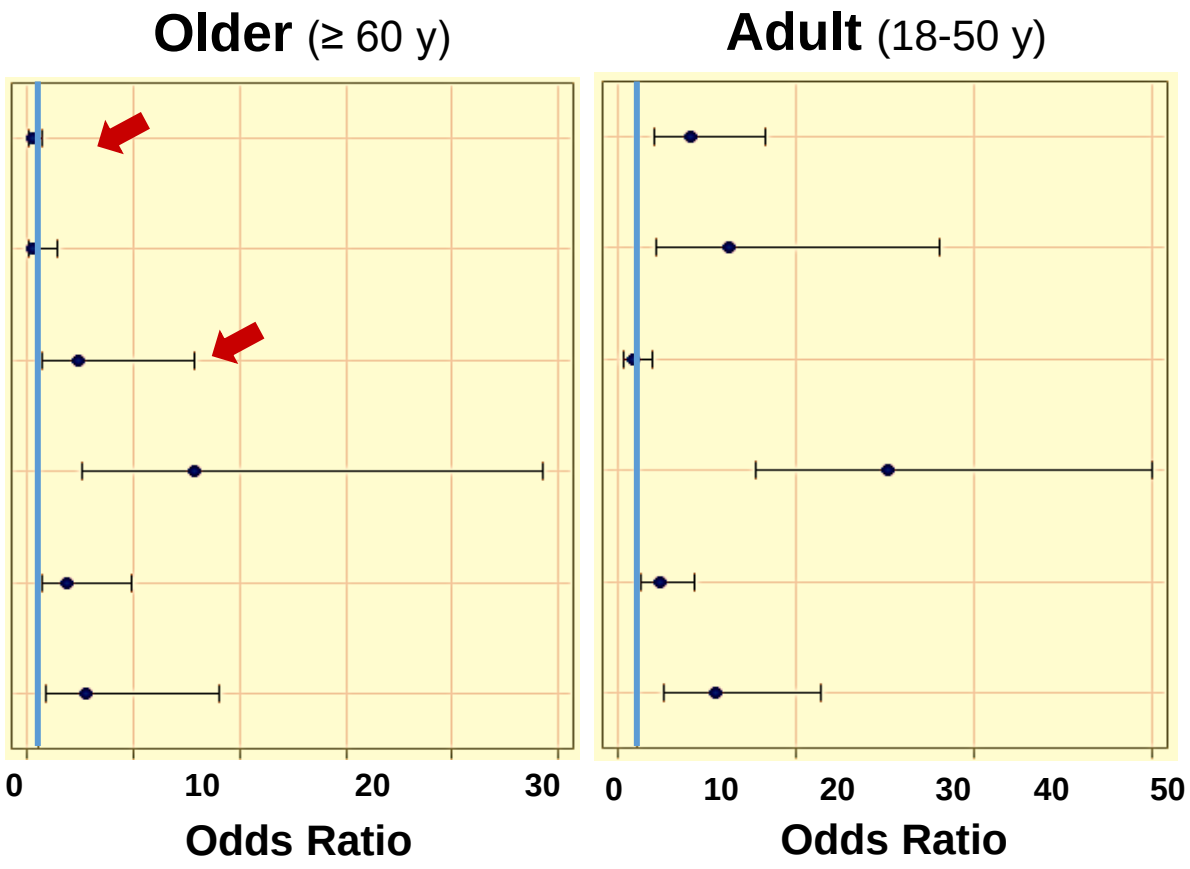
Impaired Fasting Glucose *vs*. Normoglycemia

No BCG vaccine at birth, *vs*. Yes

Lower BMI *vs*. Overweight/Obese

Male *vs*. Female

Smoking history *vs*. never



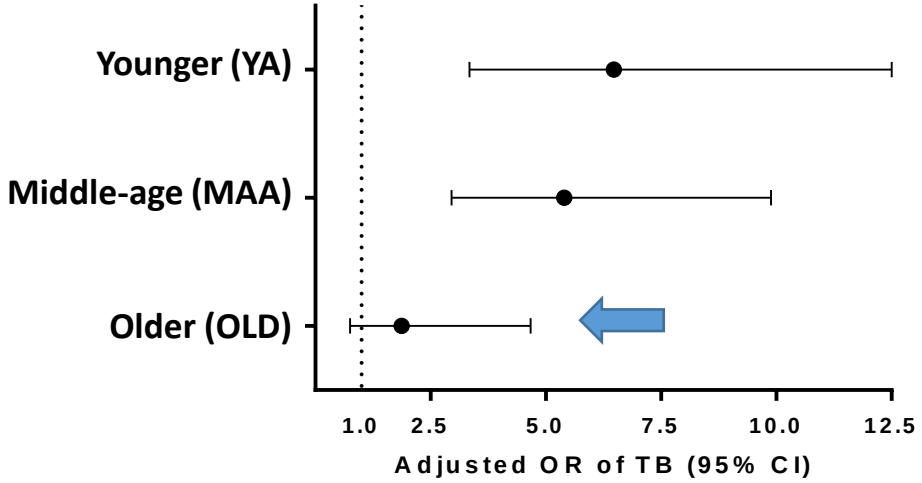
If Odds Ratio ≥ 1.0 = Risk for TB

Scordo *et al*. PLoS ONE, 2021

Confirmation: DM x Age → TB

Research cohort

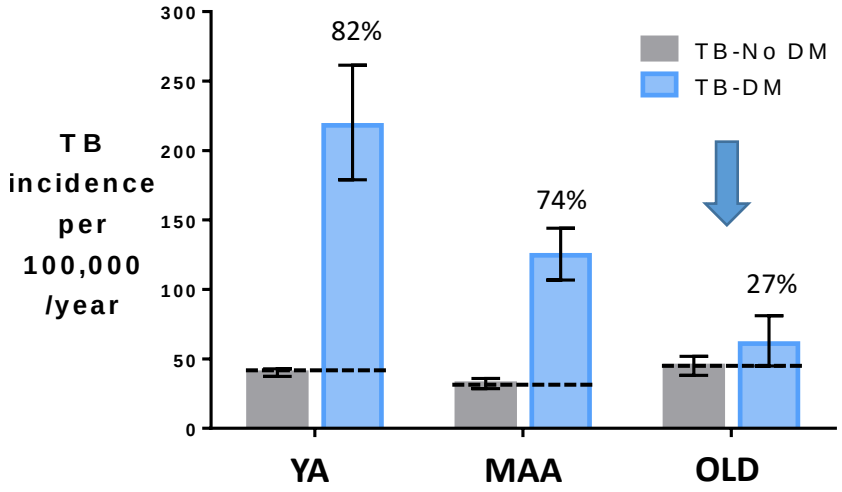
Multivariable model:
DM → Active TB
Odds ratio ~ Relative risk



(Control for BMI, smoking & sex)

TB surveillance cohort

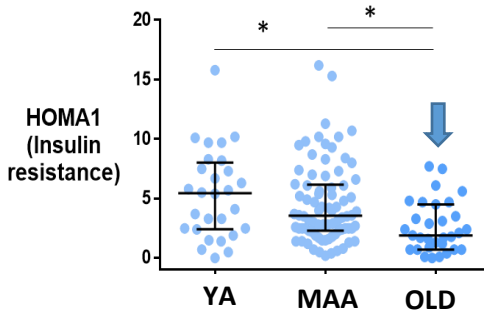
Absolute risk: Attributable fraction

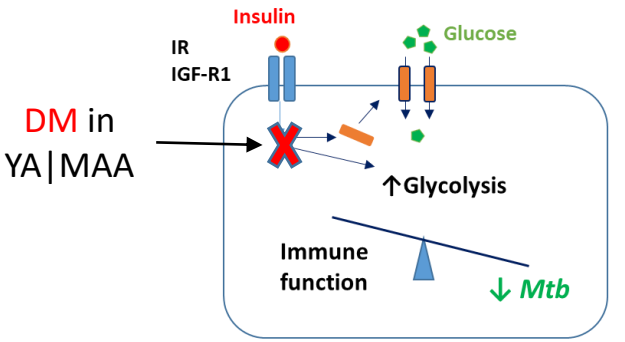


Conclusion:
Confirm TB-DM wanes with older age

Restrepo *et al*. Pathogens 2022

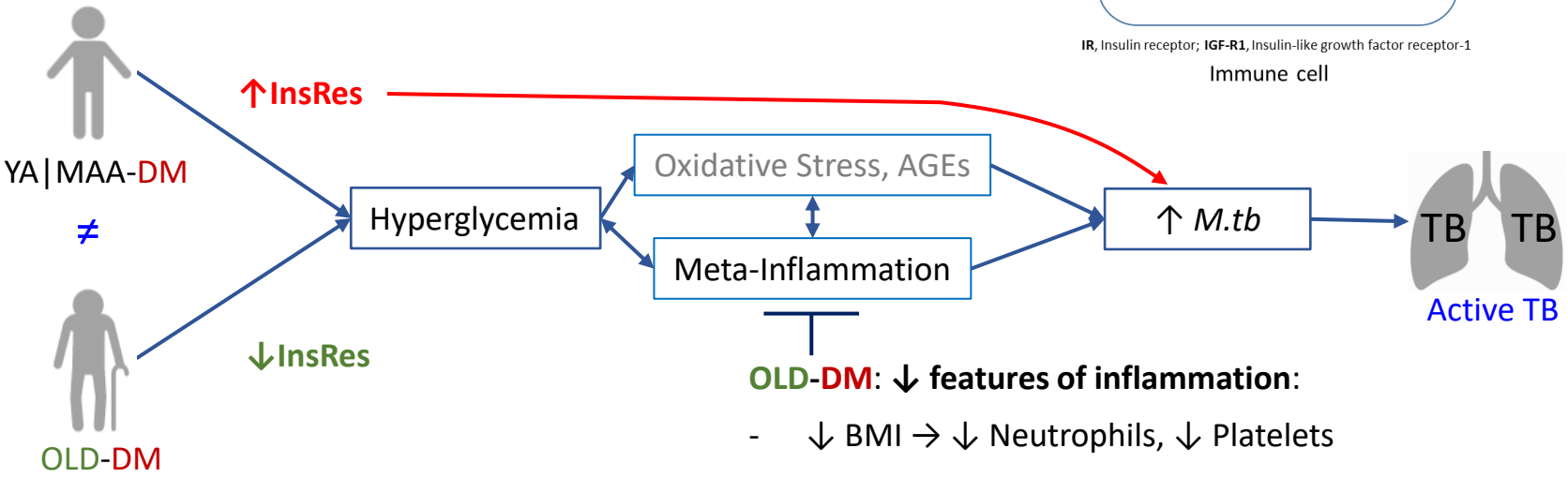
Difference between YA-DM vs OLD-DM → active TB





IR, Insulin receptor; IGF-R1, Insulin-like growth factor receptor-1

Immune cell



OLD-DM: ↓ features of inflammation:

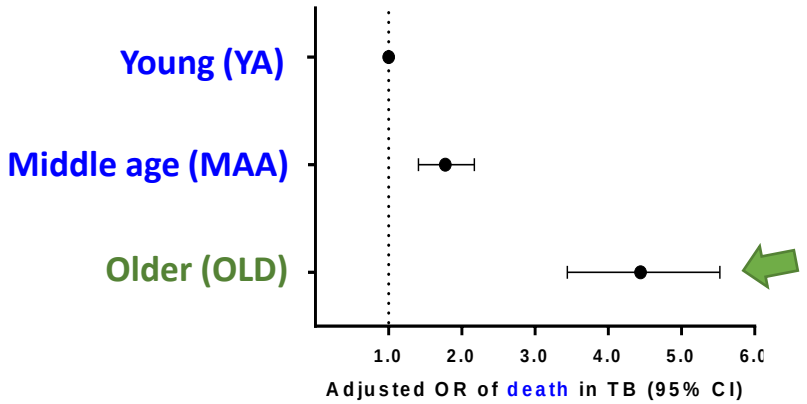
- ↓ BMI → ↓ Neutrophils, ↓ Platelets
- ↑ Pain medications, including NSAIDs
- ↑ Sulphonylureas for DM management (↑ M2-like macrophages)

Restrepo *et al*. Pathogens 2022; Quirino-Cerrillo *et al*, unpublished observations

TB x Age → Death during TB

Tamaulipas state (n=8,775)

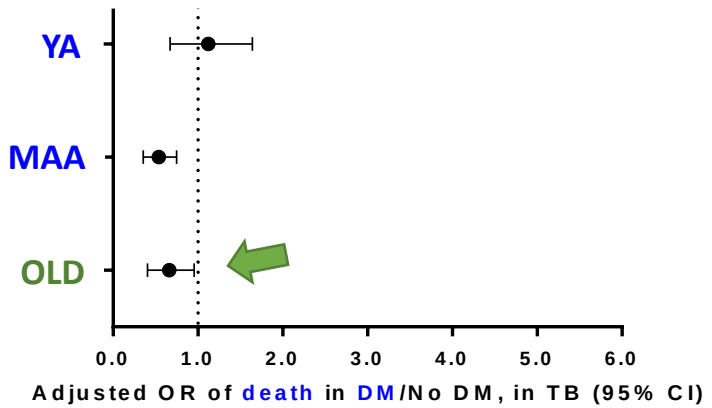
Model: Old age → Death in TB



(Control for sex, DM, HIV, IV drug use, excess alcohol, undernutrition, heart failure)

Confirm: Old age ↗ odds of death in TB

Model: DM → Death in TB, by Age



(Control for sex, DM, HIV, IV drug use, excess alcohol, undernutrition, heart failure)

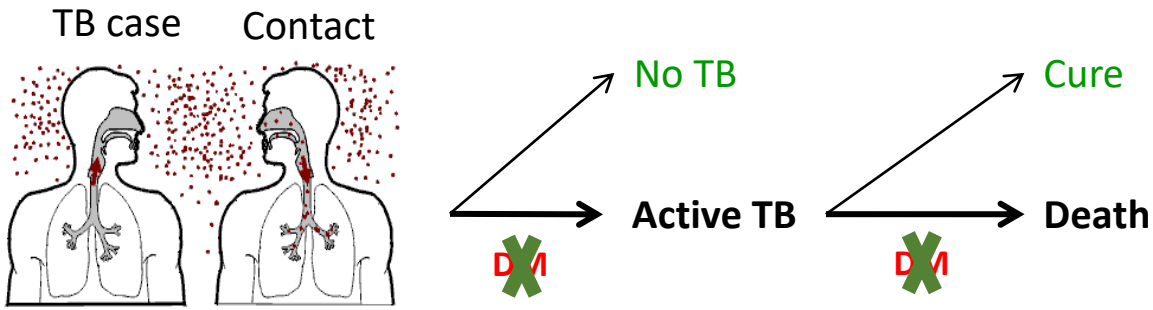
Conclude:
- DM does not increase odds of death in any age group
- …. In old age, DM is protective

Other factors:
- Protective: BCG vaccination at birth
- Exacerbate: Years of age, alcohol, COPD, low BMI

Scordo *et al*. PLoSONE, 2021; Restrepo *et al*. Pathogens, 2022; Medrano *et al,* Medicine, 2023

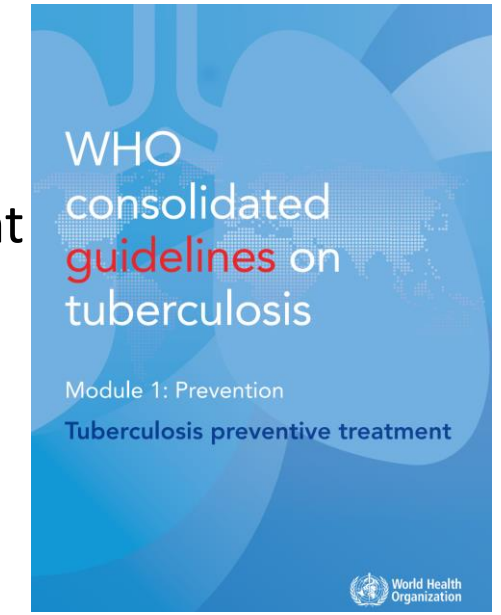
Summary: TB x OLD age

- **Impact of DM on TB is different in Older adults vs Younger adults**

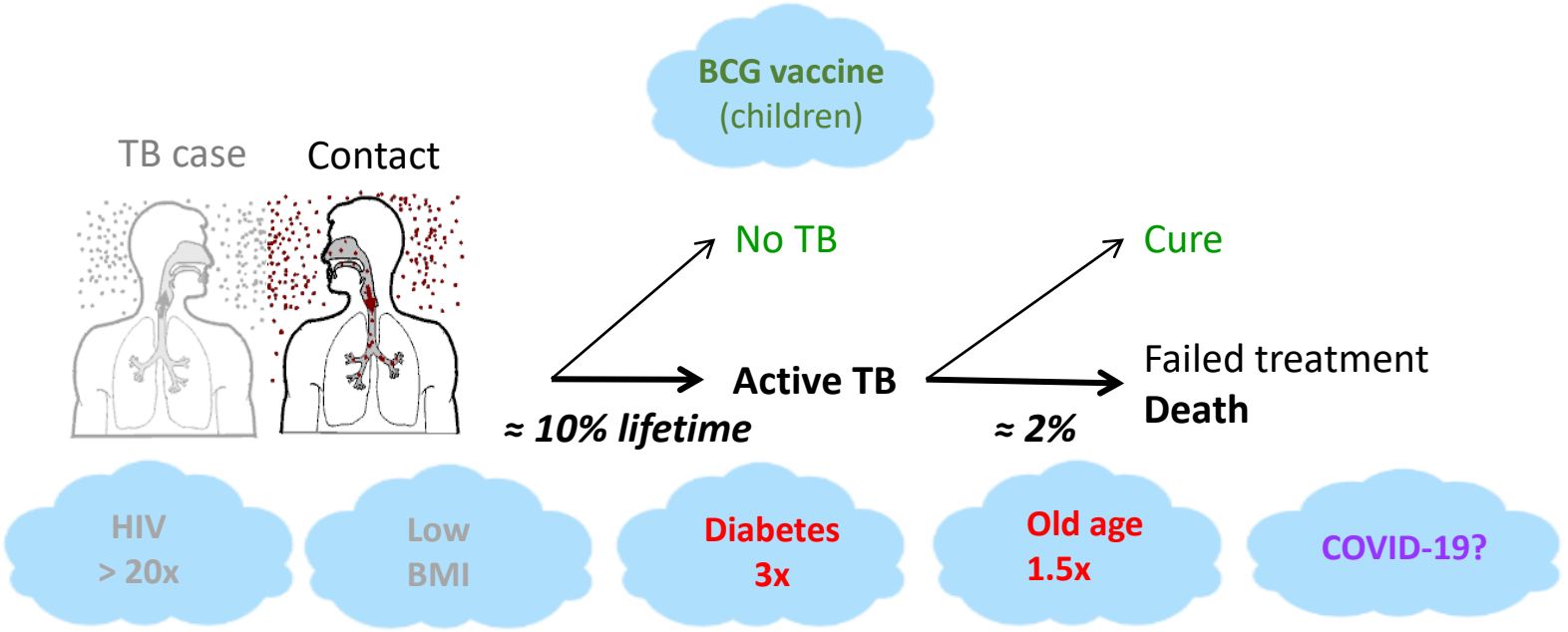


- **Older aldults:**
  - **Deserve to be studied** → improved clinical care
  - **Deserve to be added to WHO's priority list** for LTBI testing and treatment
    - Children < 5y, people with HIV/AIDS (PWHA), other vulnerable populations

    ** NEXT: TRANSLATION RESEARCH GOAL



Summary: Diabetes and other risk factors for TB



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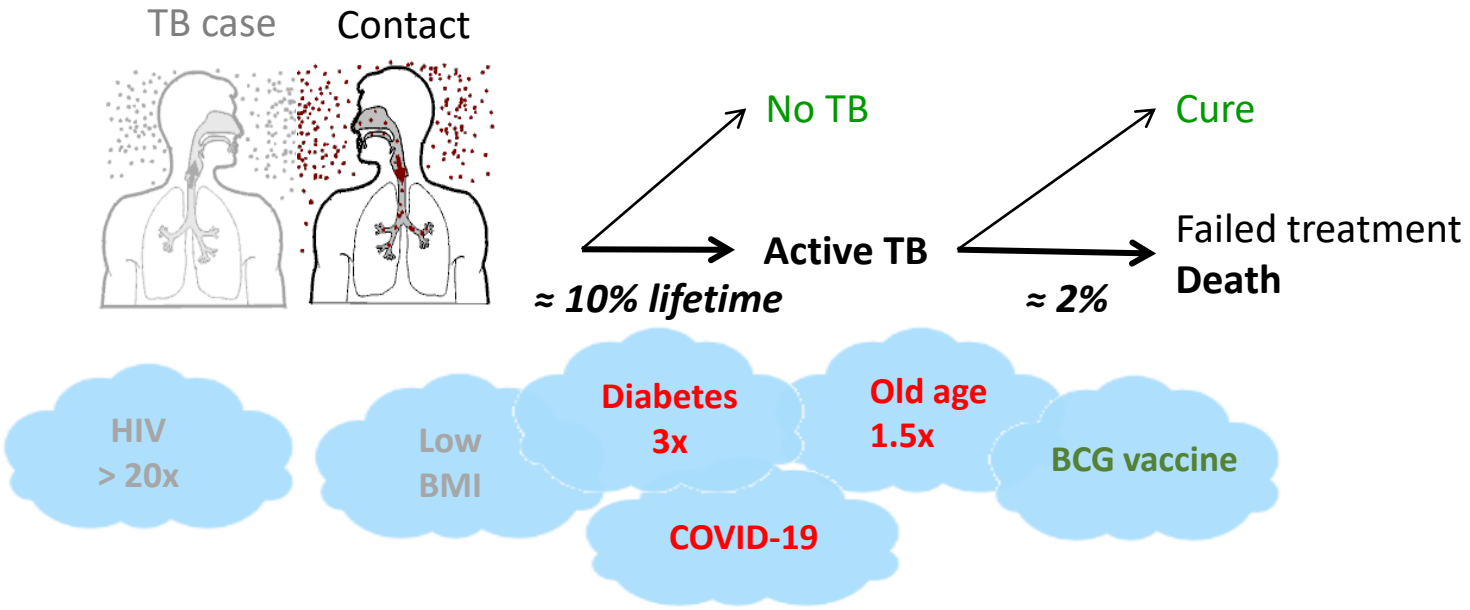


Research Focus- Restrepo team

TB - Diabetes

x old age, COVID

TB → accelerated aging

Tuberculosis

Post-TB lung disease

TB - Depression

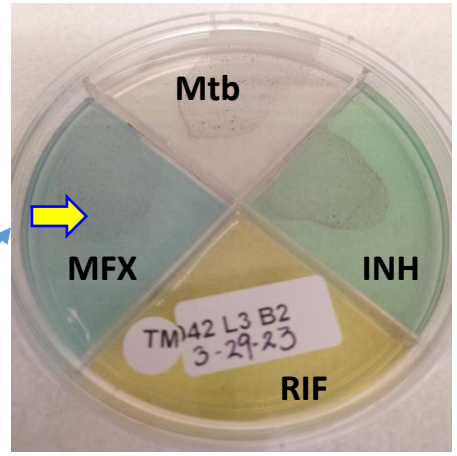
TB Diagnostics

TB diagnostics: Research → Public health impact

J. Torrelles, Juan I. Garcia, M. Yotebieng

1st generation (1G) test

Drs. Carl Nathan, Jordi Torrelles et al



MFX, Moxifloxacin

Advantages of 1G test:

- Media enhanced to promote *Mtb* growth, but not contaminants
- Colonies have red color
- ↓$
- Simple technology:
  - No need for centrifuge
  - Incubator is optional

2nd generation (2G) test

- Under development
- Field sites:
  - Mexico border: DM-TB
  - Democratic Republic of Congo: HIV-TB

Results of field testing (n=450 sputum):

- ***Mtb* detection:**
  - **99%** vs 92% for smear microsocpy
  - **100%** vs 68% vs solid culture
  - **98%** vs 94% vs liquid culture (MGIT)]
- **Drug resistance:** Concordance (kappa) **vs MGIT**
  - **INH**: 0.92 (almost perfect agreement)
  - **RIF**: 0.70 (substantial agreement)
  - **MFX**: 0.78 (substantial agreement)
- **Median (IQR) days to positive** = 17.5 (7) days
  - Smear microscopy: 1-3 days
  - Solid culture: 28 days
- **Contamination** = 1.2 – 2.9%
  - Solid culture: 14.2%
- **Public health implications: Prevalence of DR:**
  - **14%** any DR vs **6.5%** by National TB program
  - **MFX-DR**: 3.7% (??) New 4-mo regimen DS-TB

Restrepo lab: Doris Ayala, Mia Aguirre; Torrelles Lab: Juan I. Garcia, Amberlee Hicks

Acknowledgments

Restrepo field and lab team:

- Past: **Belinda Medrano**
- Current: **Texas**: Yoscelina Martinez-Lopez, Aquiles R. Ocaña, Doris Ayala, J. Felipe Joya, Mia Aguirre, Aurelio Garcia, Jaime Saveron; **Reynosa**: Génesis Aguillón-Durán, Abi Aguillón-Durán, Odalis Loredo-Loredo, Selena Zavala, Wendy de la Cruz, Jorge E. Pérez; **Matamoros**: Ilse E. Domínguez, Priscila Dominguez, Carolina Rodriguez

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- Drs. C. Jagannath

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Other collaborators

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Health Departments & Community Centers:

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- **Reynosa SSA**: Dra America Cruz and staff
- **Matamoros SSA**: Dr. Raúl Loera-Salazar, Dr. Moncerrato Garcia-Viveros, and staff
- **DIF Matamoros**: Dr. Ma. Elena Sanchez-Cantú and staff
- **DIF Reynosa**: Ing. Gabriela M. Rosas-Blanco and staff
- **ICEST**: M.Sc. Luis R. Ramirez-Garcia; Dr. Alberto Salazar

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Cameron County Health Department

- Esmeralda Guajardo, Erica Silva and team

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- Lucy Ramirez and clinic healthcare team

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