Co-morbilidad TB-DM: ¿tormenta perfecta?

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¿Una tormenta perfecta?

SUPPLEMENT ARTICLE

HIV Infection and Multidrug-Resistant Tuberculosis—The Perfect Storm

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Background. Multidrug-resistant (MDR) tuberculosis (TB) has emerged as a global epidemic, with ~425,000 new cases estimated to occur annually. The global human immunodeficiency virus (HIV) infection epidemic has caused explosive increases in TB incidence and may be contributing to increases in MDR-TB prevalence.

Methods. We reviewed published studies and available surveillance data evaluating links between HIV infection and MDR-TB to quantify convergence of these 2 epidemics, evaluate the consequences, and determine essential steps to address these epidemics.

Results. Institutional outbreaks of MDR-TB have primarily affected HIV-infected persons. Delayed diagnosis, inadequate initial treatment, and prolonged infectiousness led to extraordinary attack rates and case-fatality rates among HIV-infected persons. Whether this sequence occurs in communities is less clear. MDR-TB appears not to cause infection or disease more readily than drug-susceptible TB in HIV-infected persons. HIV infection may lead to malabsorption of anti-TB drugs and acquired rifamycin resistance. HIV-infected patients with MDR-TB have unacceptably high mortality; both antiretroviral and antimycobacterial treatment are necessary. Simultaneous treatment requires 6–10 different drugs. In HIV-prevalent countries, TB programs struggle with increased caseloads, which increase the risk of acquired MDR-TB. Surveillance data suggest that HIV infection and MDR-TB may converge in several countries.

Conclusions. Institutional outbreaks, overwhelmed public health programs, and complex clinical management issues may contribute to the convergence of the MDR-TB and HIV infection epidemics. To forestall disastrous consequences, infection control, rapid case detection, effective treatment, and expanded program capacity are needed urgently.

Am. J. Trop. Med. Hyg., 75(6), 2006, pp. 1025–1026
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EDITORIAL
MDR-TB AND HIV: THE PERFECT STORM?

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Tuberculosis has afflicted humans as far back as we have records, predating written history. *Mycobacterium tuberculosis* is exclusively a human pathogen, so it has had to adapt to its only host, and we in turn have adapted to it. It is estimated that one third of the world's population is currently infected, of diagnosis, despite receiving directly observed therapy (DOT) with INH, rifampin, pyrazinamide, and ethambutol. Thus, in the absence of effective antibiotics and an effective immune system, bacterial growth was unchecked and quickly led to death. The mortality of this group of patients was much

Editorial

Diabetes and tuberculosis: a gathering storm?

John Moore-Gillon

The number of cases of active tuberculosis (TB) continues to rise in the UK and in many other parts of the world.[1 2] In analysing the reasons behind this rise, it needs to be kept in mind that only a small proportion of those who become infected with TB will progress to become ill with active TB disease in the weeks and months after infection. They do, however, remain at risk of reactivation of their latent TB infection in the years (and indeed decades) to come. Clearly, a co-existing medical condition which impairs the immune response to the TB bacterium might increase the likelihood of direct progression to active disease shortly after infection, or increase the likelihood of latent TB infection in later life. Co-infection with HIV is a striking example; the relative risk of developing TB in HIV-positive individuals compared

risks for TB in those with diabetes are derived from a Korean study. The authors point out, however, that these appear to be the best tools available for the job they wished to do, and it is indeed arguable that a line of scientific enquiry should not be ignored simply because the available techniques for its investigation are as yet imperfect.

With the frank admission that 'given the nature of the data available, considerable uncertainty surrounds these estimates', the authors go on to suggest that the population attributable fraction (PAF) of diabetes for pulmonary TB in England is 19.6% for Asian men (95% CI 10.9% to 33.1%) and 14.2% for Asian women (95% CI 7.1% to 26.5%). The figures for white and black men are similar to each other at around 7%, and about 8.5% for white and black women. Expressed differently, the

What can be done? TB services in most countries—even wealthy ones—are hard pressed, and tackling the rising tide of obesity (the principal cause of the rise in diabetes) may be a task too far. This means dealing with the consequences while others struggle, probably unsuccessfully, with the underlying cause. Walker and Unwin suggest that, based on their figures, around one-third of Asians with newly diagnosed TB in England will have diabetes. There seems no reason to suspect that the figure would be markedly lower in other parts of the UK nor, probably, in other socioeconomically similar countries. In the UK there are probably around half a million undiagnosed diabetics[11] and, although their rates of TB may well be less than among diagnosed diabetics, we can at least ensure that newly diagnosed TB patients have a documented assessment of the presence or absence of diabetes. Active screening for evidence of latent TB in diabetics is part of US guidelines,[12] but not those from the National Institute for Health and Clinical Excellence (NICE).[15] Indeed, the NICE guidelines suggest that, although the relative risk of TB is increased in diabetics, the absolute

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Special Report: Combating Diabetes

Link between diabetes and tuberculosis comes under fresh scrutiny

Diabetics are at a far higher risk of contracting tuberculosis

Save

NOVEMBER 13, 2014 by: Andrew Jack

When "Manuel", a 62-year old-New Yorker who had rarely sought medical help, went into hospital after complaining of coughing and chest pains this spring, he received a double shock. Not only was he diagnosed with tuberculosis, requiring isolation and six months of treatment, but diabetes as well.

His experience reflects the growing realisation of the links between the two diseases. Those with diabetes are at far

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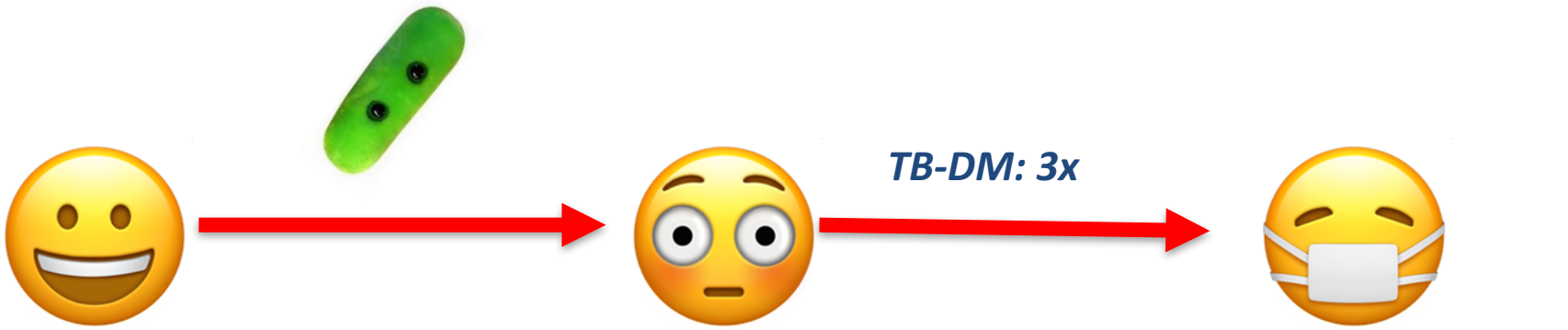
Interacción TB-DM

Susceptible **TB Latente** **TB Activa**



TB-DM: 3x

Inflamasoma desregulado
Inflamación Crónica

Respuesta innata retardada

Fagocitosis ↓

Hiperglicemia Crónica
↓
Respuesta adaptativa retardada
↓
Peor presentación clínica

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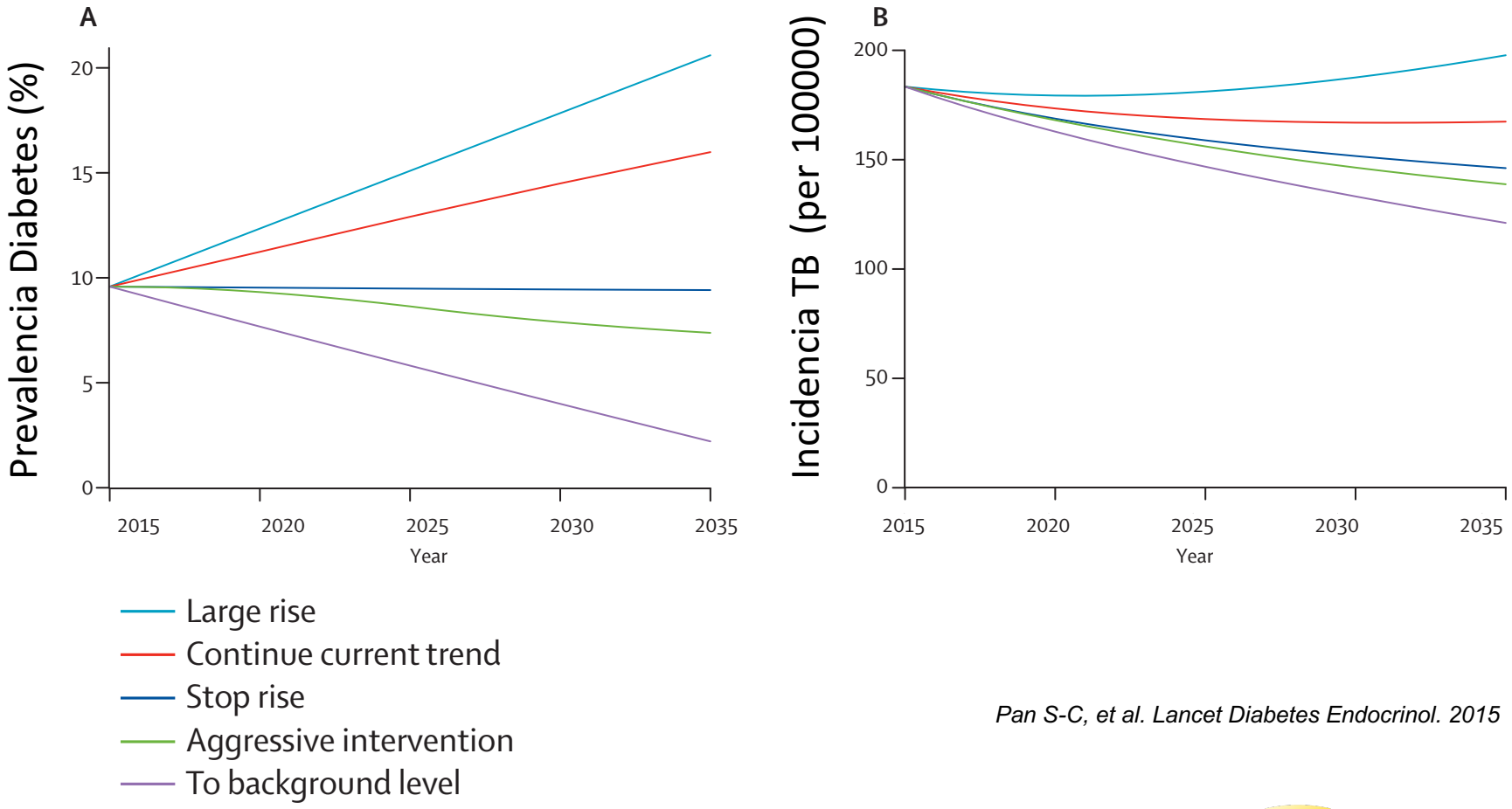
Incidencia TB proyectada (B) bajo diferentes escenarios de control de DM (A)



Pan S-C, et al. Lancet Diabetes Endocrinol. 2015

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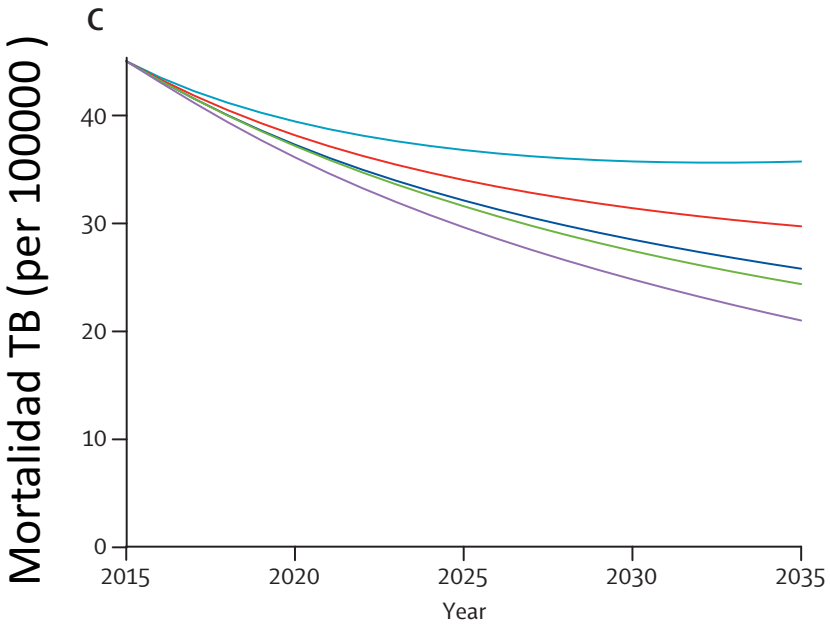
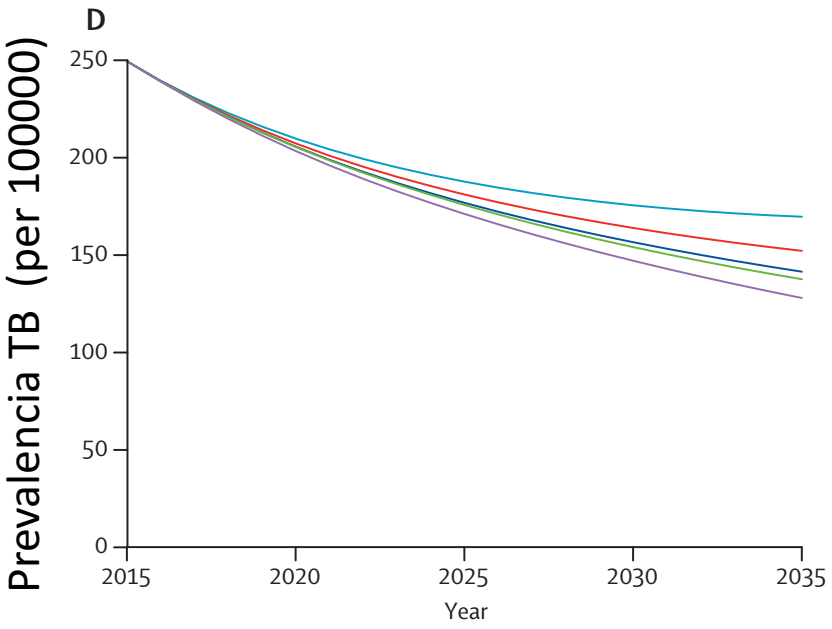
Mortalidad/Prevalencia proyectada de TB (C/D) bajo diferentes escenarios de control de DM





Large rise
Continue current trend
Stop rise
Aggressive intervention
To background level

Pan S-C, et al. Lancet Diabetes Endocrinol. 2015

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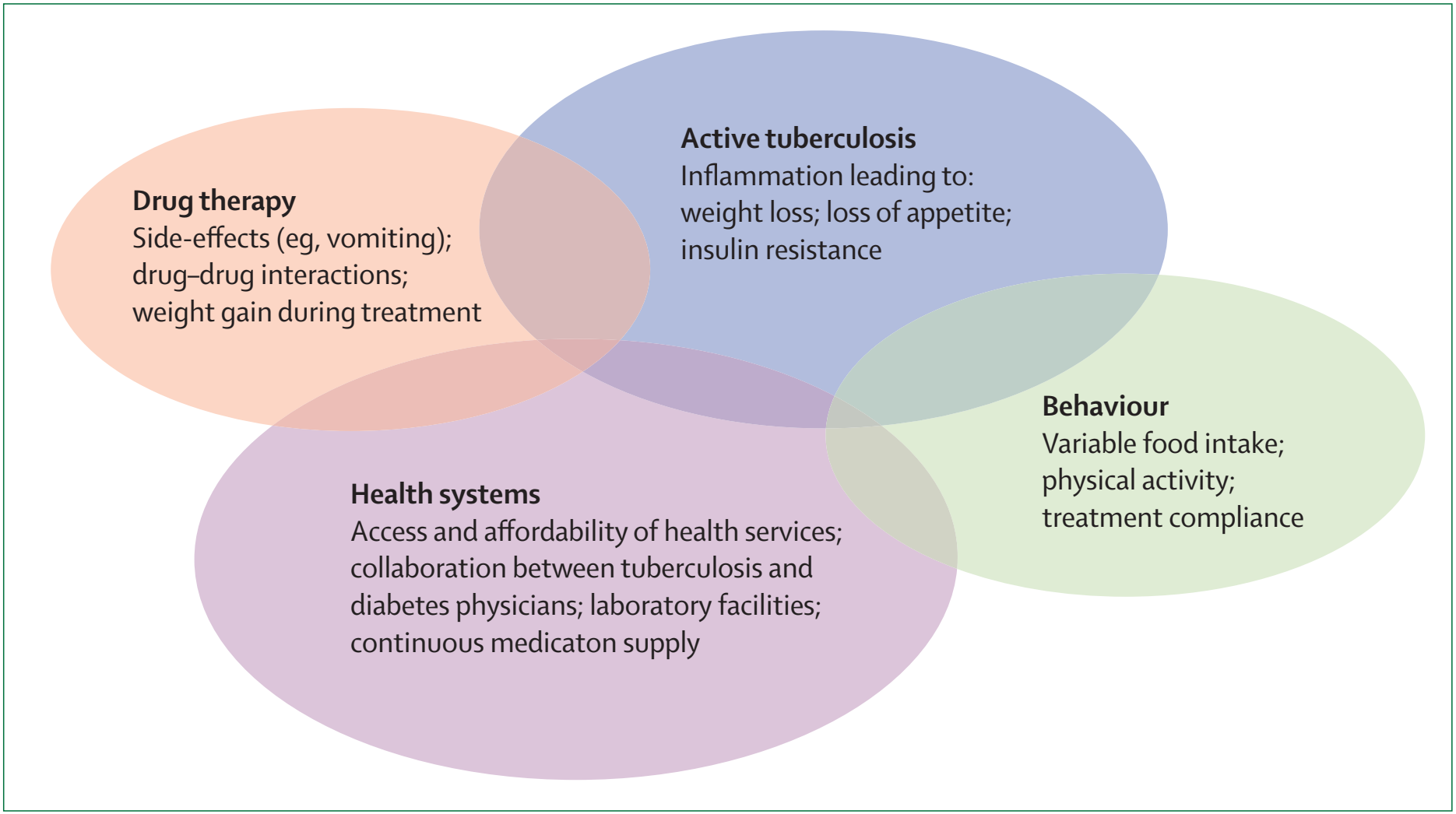
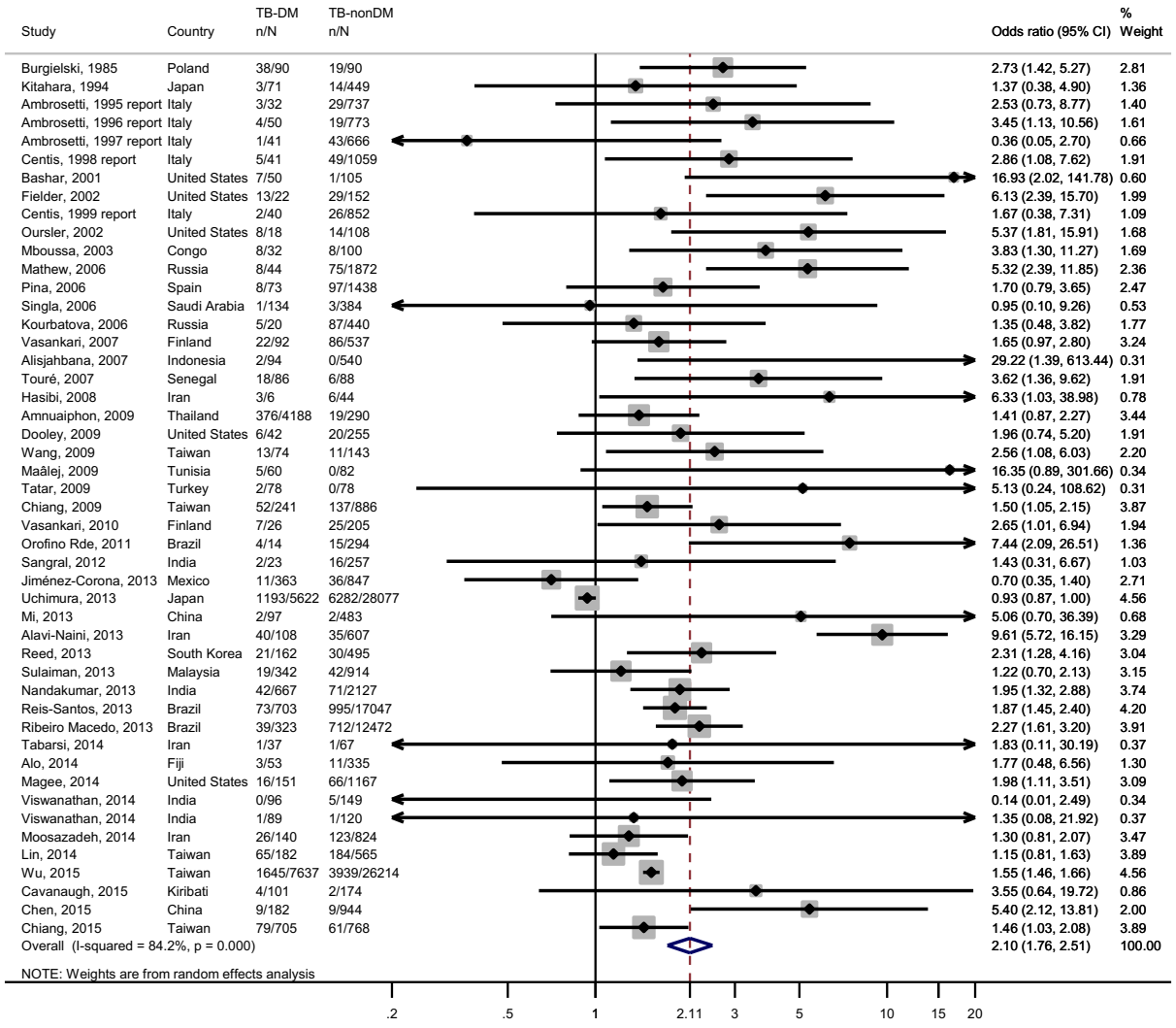


Factores que afectan el control glicemico de pacientes con DM durante el tratamiento de TB

Riza AL, Pearson F, Ugarte-Gil C, et al. Lancet Diabetes 2014

Asociación entre DM y muerte en paciente en tratamiento TB



48 estudios

OR combinado: 2.1 (1.8-2.5)

Huangfu P, Ugarte-Gil C, Golub J, Pearson F, Critchley J. 2017

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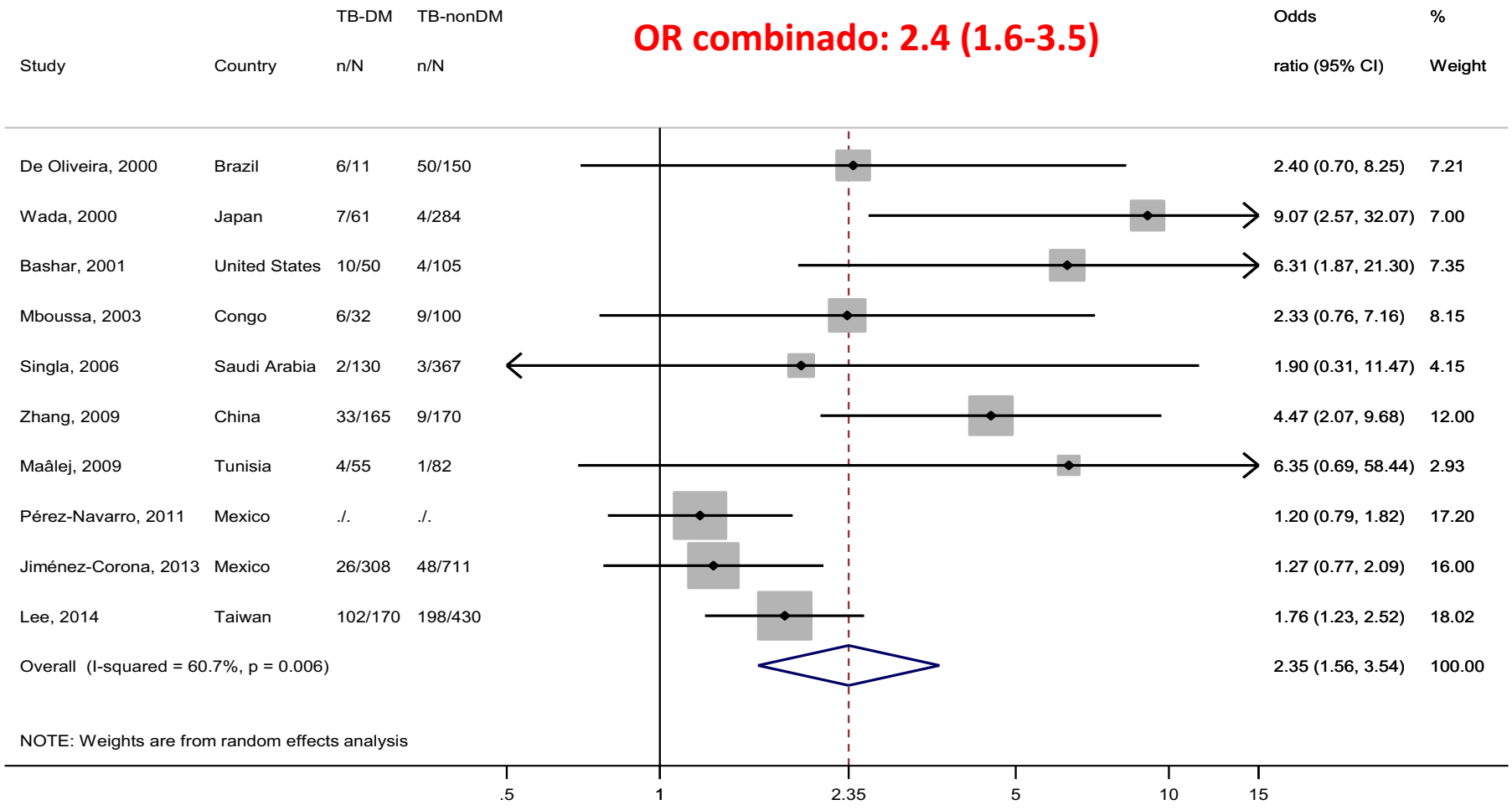
Asociación entre DM y recaídas en paciente con tratamiento TB



Huangfu P, Ugarte-Gil C, Golub J, Pearson F, Critchley J. 2017

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Estudio TANDEM – Lima

- 600 pacientes con TB enrolados, 47 had DM
- → ***prevalencia 7.8% (95%CI: 5.9%-10.3%)***

- ***31/47*** con diagnóstico previo de DM y ***16/47*** eran Nuevos diagnósticos

… próxima publicación 2017 (2337 pacientes en 4 países)

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Características TB-DM: TANDEM Lima

- Mediana edad (RIQ): 52.0 (47.0-58.5) años
- Mediana IMC (RIQ): 24.7 (21.8-28.4)
- Mediana HbA1c% (RIQ): 10.6 (9.0-13.3)
- Más del 55% de los pacientes tenían menos de 5 años de diagnóstico de DM
- Historia familiar de DM: 40.4%

RIQ: Rango interquartil
HbA1c: Hemoglobina glicosilada

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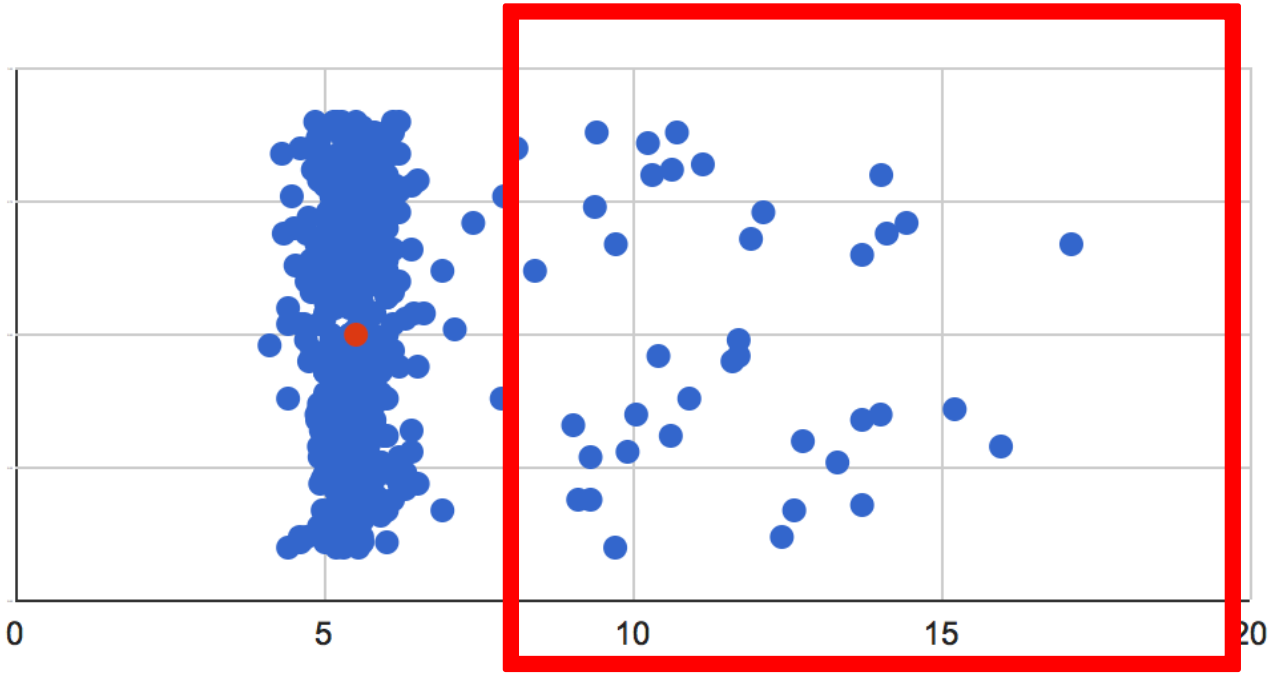
HbA1c en cohorte TANDEM - Perú



HbA1c: pre-dx DM vs DM nuevo

	Pre-dx DM	DM nuevo	valor P
Mediana HbA1c (RIQ)	10.9 (9.7-13.5)	8.5 (6.8-11.3)	0.02

RIQ: Rango interquartil
HbA1c: Hemoglobina glicosilada

*Mann-Whitney (median) and Chi^2 (#participants)

Ugarte-Gil C, et al. 2017

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Hiperglicemia no DM: TANDEM - Lima

- Prevalencia general
  - ***39.7% (95%CI: 35.8% -43.6%)***

- Prevalencia en mayores de 35 años
  - ***27.3% (95%CI: 21.8%-33.7%)***

The Journal of Infectious Diseases

MAJOR ARTICLE

Transient Hyperglycemia in Patients With Tuberculosis in Tanzania: Implications for Diabetes Screening Algorithms

Noémie Boillat-Blanco,[1,5,6,7] Kaushik L. Ramaiya,[2,3] Maliwasa Mganga,[4] Lilian T. Minja,[1] Pascal Bovet,[8] Christian Schindler,[5,6] Arnold Von Eckardstein,[9] Sebastien Gagneux,[5,6] Claudia Daubenberger,[5,6] Klaus Reither,[1,5,6] and Nicole Probst-Hensch[5,6]

[1]Ifakara Health Institute, [2]Shree Hindu Mandal Hospital, [3]Muhimbili University of Health Sciences, and [4]Kinondoni Municipal Council, National Tuberculosis Program, Dar es Salaam, United Republic of Tanzania; [5]Swiss Tropical and Public Health Institute, and [6]Department of Sciences, University of Basel, [7]Infectious Diseases Service, and [8]Institute of Social and Preventive Medicine, Lausanne University Hospital, and [9]Institute of Clinical Chemistry, University of Zurich, University Hospital of Zurich, Switzerland

Background. Diabetes mellitus (DM) increases tuberculosis risk while tuberculosis, as an infectious disease, leads to hyperglycemia. We compared hyperglycemia screening strategies in controls and patients with tuberculosis in Dar es Salaam, Tanzania.

Methods. Consecutive adults with tuberculosis and sex- and age-matched volunteers were included in a case-control study between July 2012 and June 2014. All underwent DM screening tests (fasting capillary glucose [FCG] level, 2-hour CG [2-hCG] level, and glycated hemoglobin A1c [HbA1c] level) at enrollment, and cases were tested again after receipt of tuberculosis treatment. Association of tuberculosis and its outcome with hyperglycemia was assessed using logistic regression analysis adjusted for sex, age, body mass index, human immunodeficiency virus infection status, and socioeconomic status. Patients with tuberculosis and newly diagnosed DM were not treated for hyperglycemia.

Results. At enrollment, DM prevalence was significantly higher among patients with tuberculosis (n = 539; FCG level > 7 mmol/L, 4.5% of patients, 2-hCG level > 11 mmol/L, 6.8%; and HbA1c level > 6.5%, 9.3%), compared with controls (n = 496; 1.2%, 3.1%, and 2.2%, respectively). The association between hyperglycemia and tuberculosis disappeared after tuberculosis treatment (adjusted odds ratio [aOR] for the FCG level: 9.6 [95% confidence interval {CI}, 3.7–24.7] at enrollment vs 2.4 [95% CI, .7–8.7] at follow-up; aOR for the 2-hCG level: 6.6 [95% CI, 4.0–11.1] vs 1.6 [95% CI, .8–2.9]; and aOR for the HbA1c level, 4.2 [95% CI, 2.9–6.0] vs 1.4 [95% CI, .9–2.0]). Hyperglycemia, based on the FCG level, at enrollment was associated with tuberculosis treatment failure or death (aOR, 3.3; 95% CI, 1.2–9.3).

Conclusions. Transient hyperglycemia is frequent during tuberculosis, and DM needs confirmation after tuberculosis treatment. Performance of DM screening at tuberculosis diagnosis gives the opportunity to detect patients at risk of adverse outcome.

Keywords. tuberculosis; diabetes mellitus; stress-induced hyperglycemia; transient hyperglycemia; sub-Saharan Africa.

La hiperglicemia transitoria
parece frecuente en pacientes con TB

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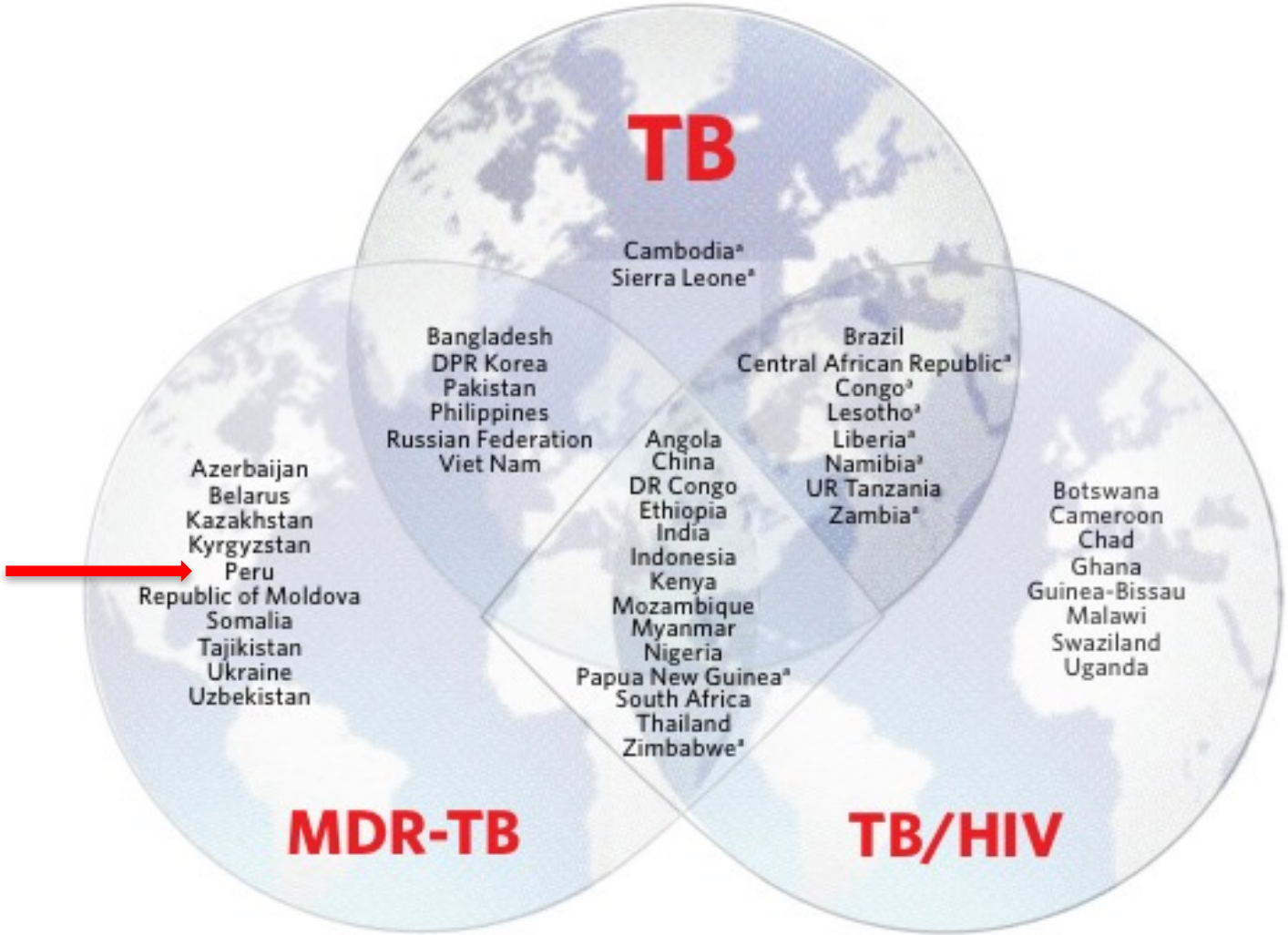
TB-MDR y DM



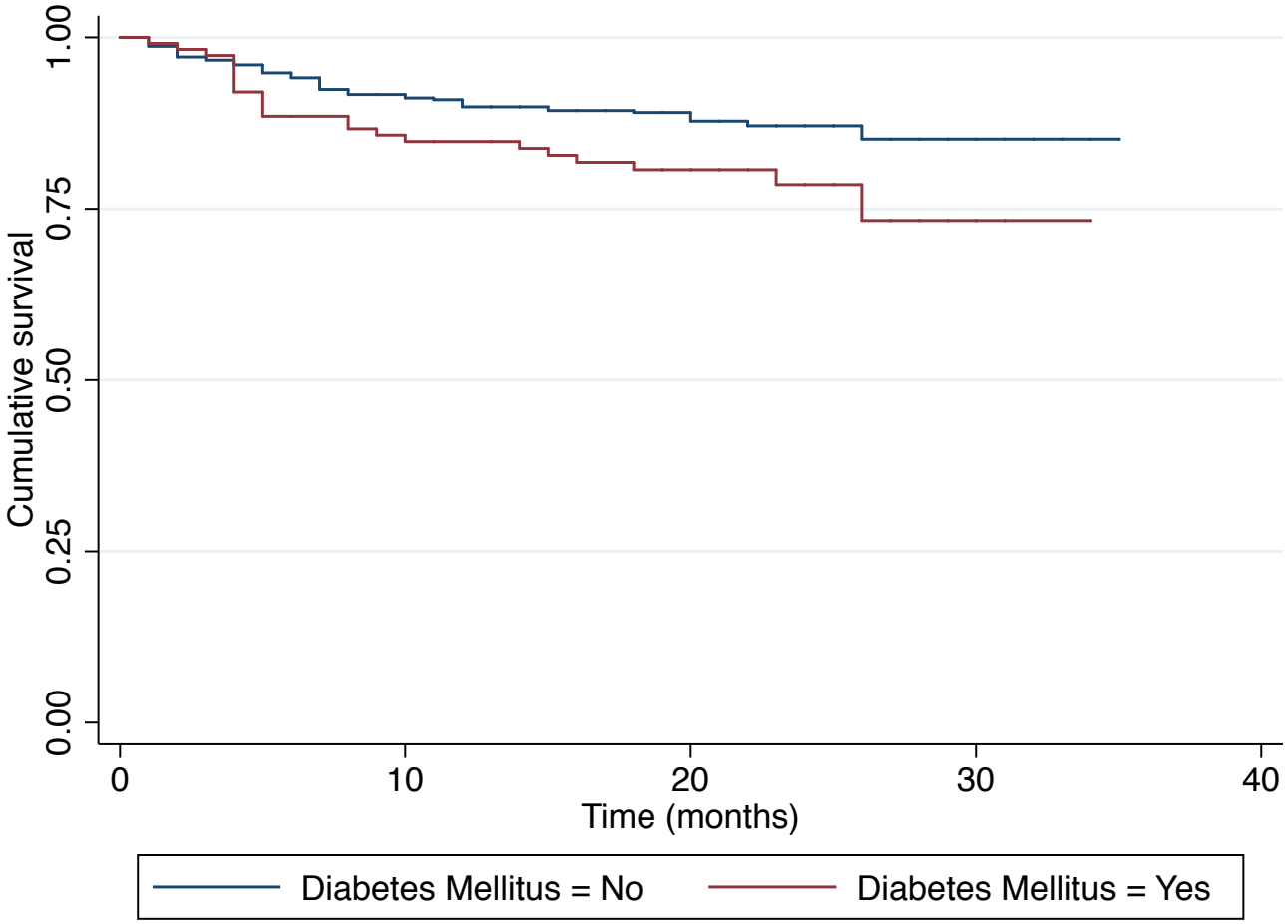
Global Tuberculosis Report. WHO 2016

Pacientes TB-MDR y DM

Características	TB-MDR no DM (n=1871)	TB-MDR DM (n=128)	p-value
Mediana Edad (RIQ)	26 (22-34)	52 (44-59)	< 0.05
Edad > 35 años (%)	460 (24.6%)	114 (89.1%)	<0.05
Mediana IMC (RIQ) (n=1652)	21.6 (19.5-23.9)	23.0 (10.7-27.1)	<0.05
IMC ≥ 25kg/m² (%) (n=1652)	283 (18.3%)	35 (34.7%)	<0.05
Mediana glucosa mg/dl (RIQ) (n=1934)	85 (76-94)	155.9 (115.4-236)	<0.05
Glucosa ≥ 200 mg/dl (%) (n=1934)	13 (0.7%)	41 (33.1%)	<0.05

Ugarte-Gil C, et al. 2017

Sobrevida al mes 36 de iniciado tratamiento MDR: mayores de 35 años



Log-rank test p-value <0.01

Ugarte-Gil C, et al. 2017

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Factores asociados a mortalidad en pacientes TB-MDR (n=1564)

Factores	HR crudo (95% CI)	HR* ajustado (95%CI)	valor p
DM	2.6 (1.7-4.0)	2.6 (1.4-4.7)	<0.05
Edad >35 (%)	2.3 (1.7-3.1)	2.5 (1.7-3.6)	<0.05
IMC ≥ 25kg/m² (%)	0.2 (0.1-0.5)	0.2 (0.1-0.4)	<0.05
VIH	4.4 (2.7-7.2)	4.7 (2.8-7.9)	<0.05

*Ajustado por género, estar en prisión, tratameinto previo de TB, BK positivo al inicio, glucosa encima de200mg/dl
HR: Hazard Ratio

Ugarte-Gil C, et al. 2017

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Situación TB-DM: Lima 2015-2016

- 15254 casos de Enero 2015-Diciembre 2016 mayores de 18 años:
  - 1081 (7.1%) tenia DM
  - 2769 (18.2%) no tenia prueba para descartar DM

- Comparemos con VIH
  - 769 (5.0%) tenia VIH
  - 1576 (10.3%) no tenia prueba

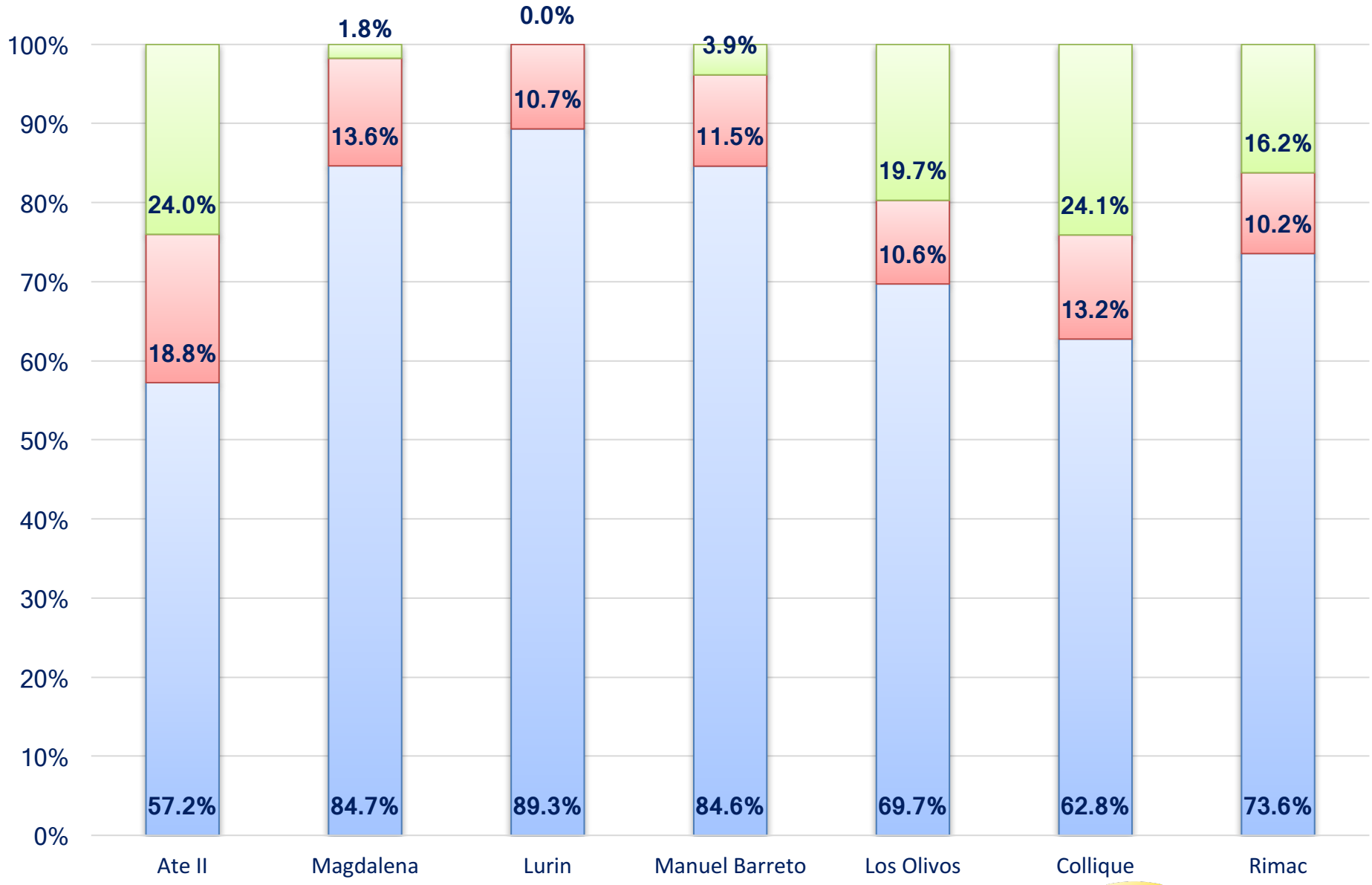
Fuente: SIGTB

Situación TB-DM: Lima 2015-2016

- Batería completa de Análisis
  - No DM: 80.1%
  - DM: 75.6%
- Batería parcial de Análisis
  - No DM: 7.1%
  - DM: 10.7%
- No realizada
  - No DM: 0.4%
  - DM: 1.2

Fuente: SIGTB

Micro redes con más de 10% de casos TB-DM



Fuente: SIGTB

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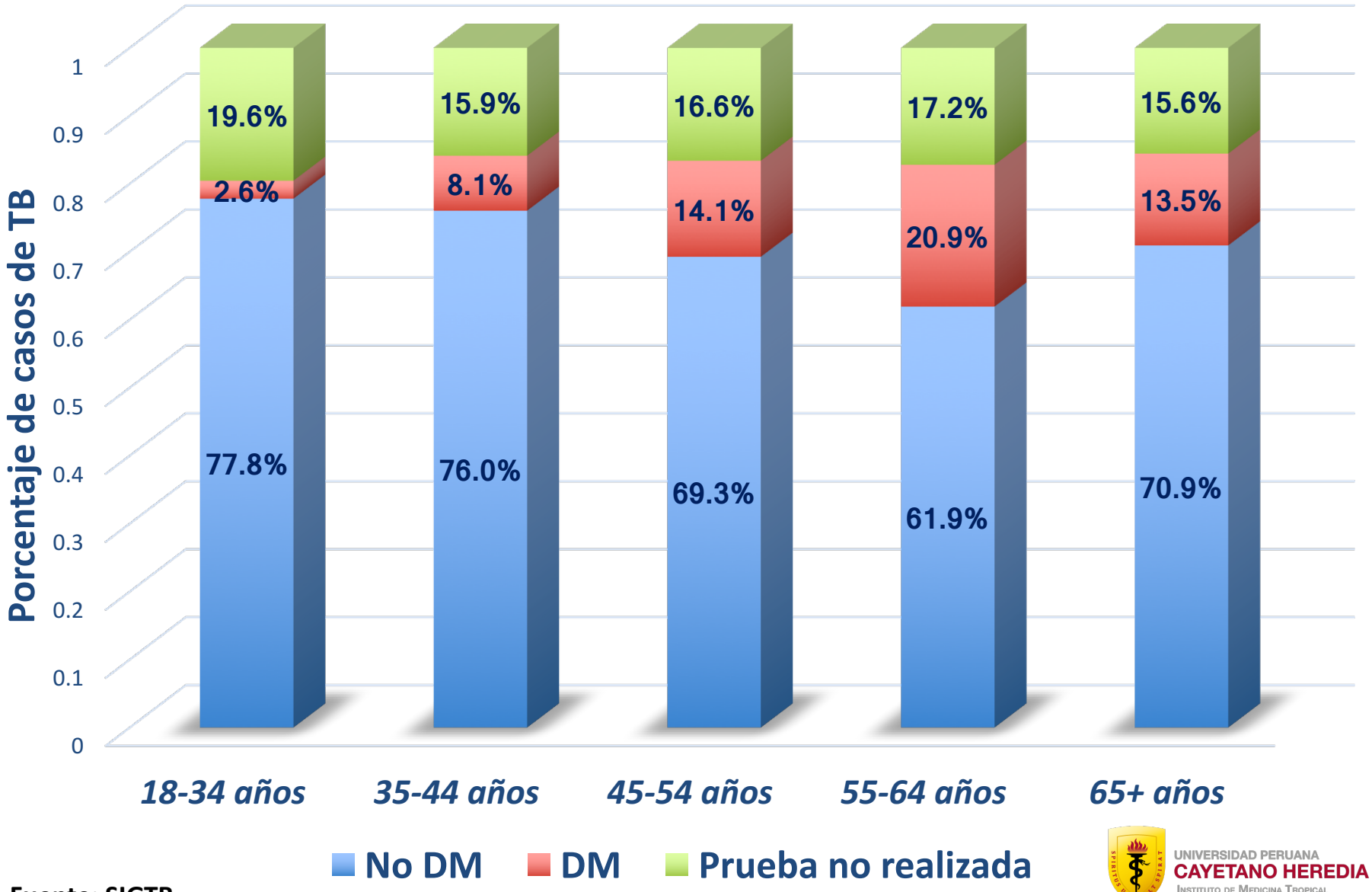
Distribución de casos TB-DM por edad – 2015/2016



Fuente: SIGTB

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Preguntas pendientes en TB-DM

- ¿Vale la pena implementar HbA1c en centros de salud?

Aparentemente: sale estudio TANDEM este año

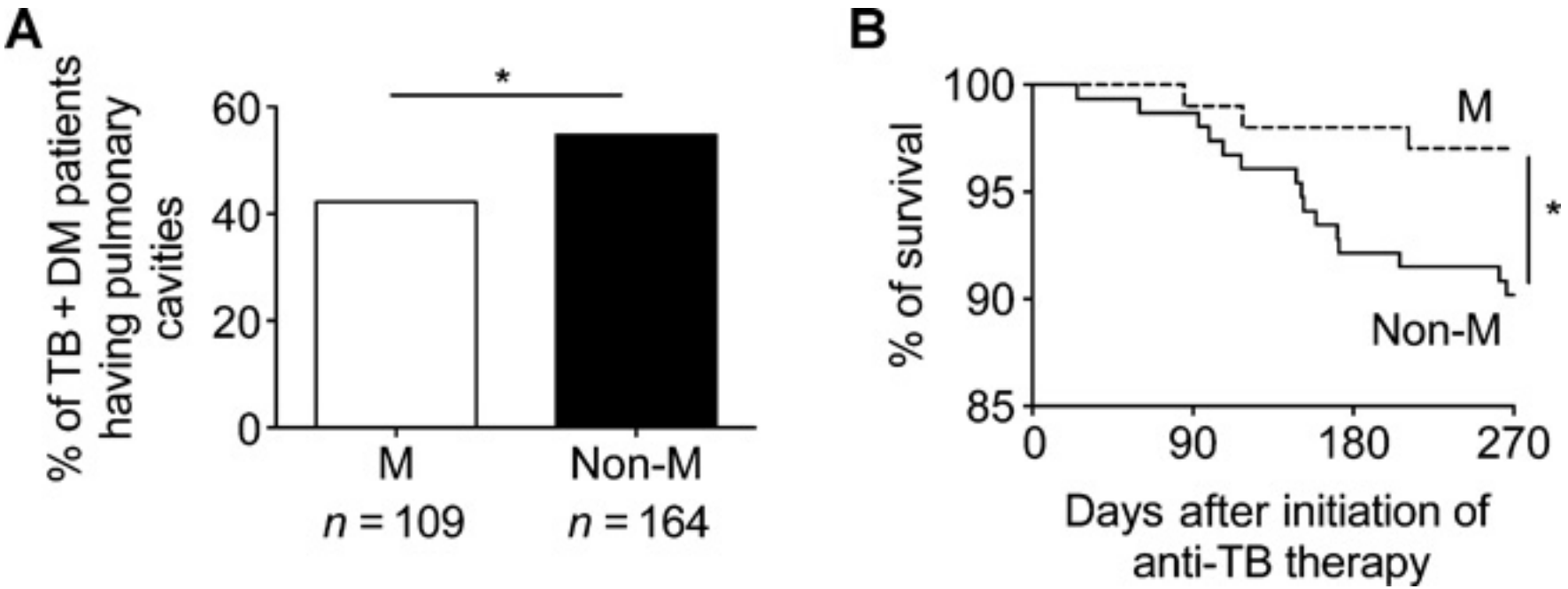
- ¿Qué barreras se presentan en el cuidado de pacientes TB-DM en Lima?

Esta corriendo el estudio de cascada de cuidado, en colaboración con la DPCTB - resultados a finales 2017

- ¿Cuál es el mejor tratamiento para DM en pacientes TB-DM?

Aun no existe evidencia cual es mejor: insulina o metformina

Efecto de la metformina en pacientes TB-DM



Amit Singhal et al., Sci Transl Med 2014;6:263ra159

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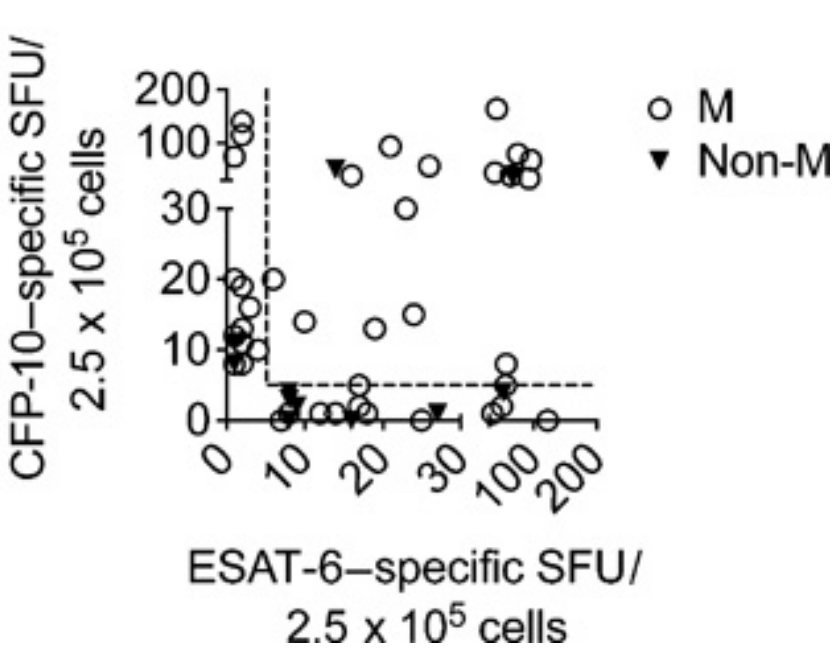
Reducción en incidencia de TB latente en pacientes TB-DM tratados con metformina

A

	T-SPOT–positive	T-SPOT–negative	
M	48 (25.6%)	139	*
Non-M	14 (42.4%)	19	

B



Amit Singhal et al., Sci Transl Med 2014;6:263ra159

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Conclusiones

- TB-DM es más común de lo que parece
- Esta fuertemente asociado a la edad, IMC y con peores resultados al tratamiento
- El manejo del paciente TB-DM es complejo y multidisciplinario ➡ para evitar recaídas

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  - World Diabetes Foundation (grant WDF15-224)

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I SIMPOSIO INTERNACIONAL SOBRE LA COMORBILIDAD TUBERCULOSIS Y DIABETES

RETOS Y OPORTUNIDADES

Dia 19 de Mayo del 2017

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