VII Jornadas de Tuberculosis en Sevilla.

21 marzo 2024

Infección latente TB

¿Qué es?

¿Cuándo tratar?

Luis Anibarro García
Unidad de TB
Complexo hospitalario universitario de Pontevedra
luis.anibarro.garcia@sergas.es

SERVIZO GALEGO de SAÚDE | Complexo Hospitalario de Pontevedra Pontevedra

The term "latency" has two meanings:

- in biology, it means a dormant state of an organism when environmental conditions are not suitable for growth and proliferation

- in medicine, it is a stage of a disease when the symptoms are not yet clinically manifested

  Latent TB Infection is characterized by a permanent immune response to Mtb antigens in the absence of any clinical manifestation of the disease

Khabibullina NF. Trop Med Inf Dis 2022

Infección de tuberculosis latente

Las bacterias de la tuberculosis pueden vivir en su cuerpo sin que usted enferme.

Su cuerpo puede combatir las bacterias para impedir que se multipliquen.

No tiene ningún síntoma.

No puede transmitir las bacterias de la tuberculosis a los demás.

Por lo general, tiene una reacción positiva en la prueba cutánea de la tuberculina o un resultado positivo en el examen de sangre para detectar la tuberculosis.

Pueden presentar enfermedad de tuberculosis si no reciben tratamiento para la infección de tuberculosis latente.

DE

L'AUSCULTATION MÉDIATE,

OU

TRAITÉ DU DIAGNOSTIC DES MALADIES DES POUMONS ET DU CŒUR,

FONDÉ PRINCIPALEMENT SUR CE NOUVEAU MOYEN D'EXPLORATION.

PAR R. T. H. LAENNEC,

D. M. P., Médecin de l'Hôpital Necker, Médecin honoraire des Dispensaires, Membre de la Société de la Faculté de Médecine de Paris et de plusieurs autres sociétés nationales et étrangères.

Μέγα δὲ μέρος ἡγεῦμαι τῆς τέχνης εἶναι τὸ δύνασθαι σκοπεῖν.

Pouvoir explorer est, à mon avis, une grande partie de l'art. HIPP., *Epid.* III.

TOME SECOND.

A PARIS,

CHEZ J.-A. BROSSON et J.-S. CHAUDÉ, Libraires, rue Pierre-Sarrazin, n° 9.

1819.

que dans les cas où la maladie était ancienne et arrivée à un très-haut degré : encore même beaucoup de cas qui présentent ces conditions échappent-ils à l'observation des plus habiles médecins ou chirurgiens, à plus forte raison les cas moins graves et qui donneraient le plus d'espérance de sauver le malade. Je pense que cette vérité paraîtra démontrée si l'on rapproche les faits que nous avons exposés en parlant de la pleurésie latente et du pneumo-thorax, de ceux que nous venons de rapporter. Je ne crois

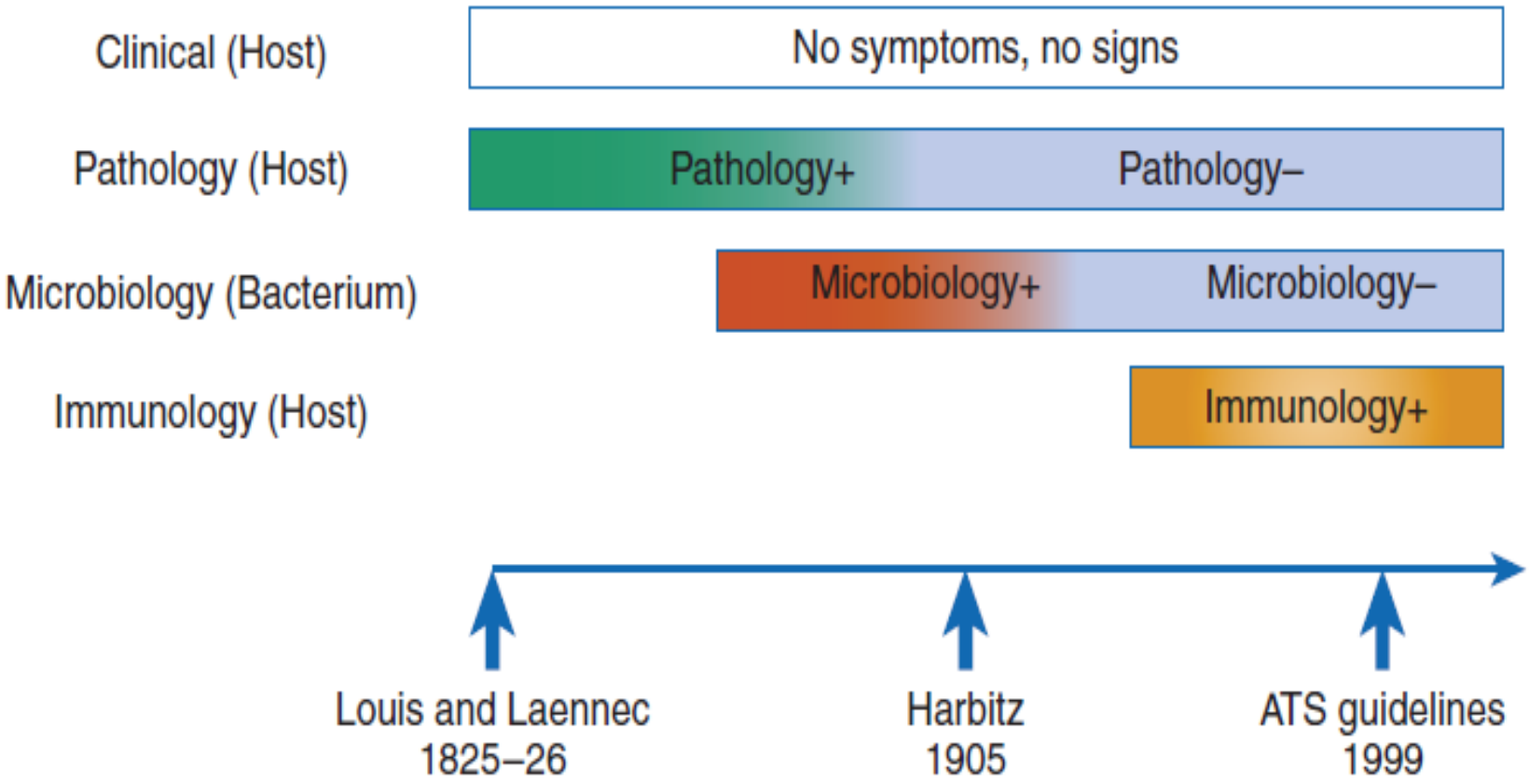
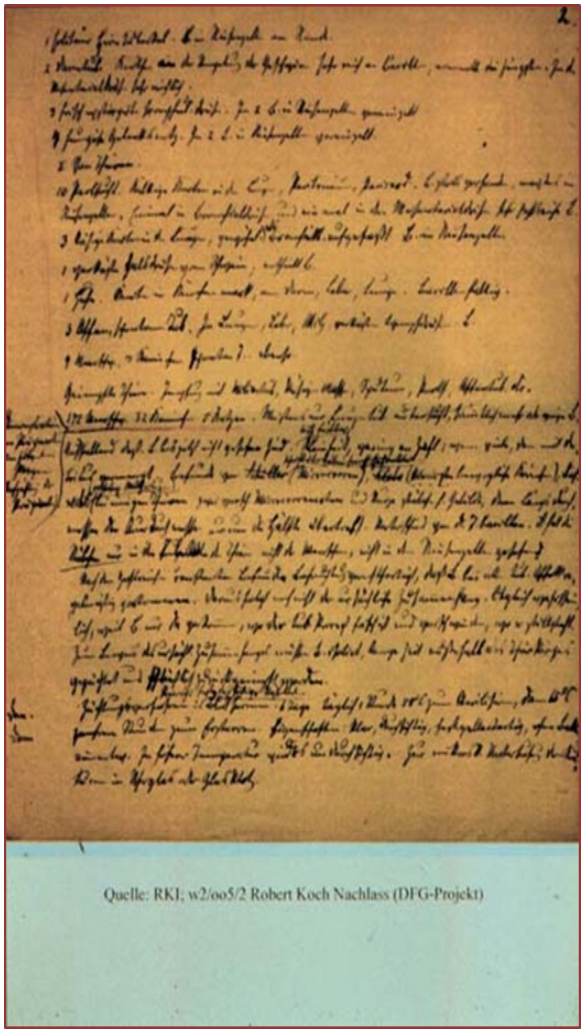


Figure 2. Shifting definitions of latent tuberculosis over time. Both pathology and microbiology positivity were ascertained postmortem. Immunologic testing is done antemortem.

Behr M. Am J Resp Crit Care Med 2021



Quelle: RKI, w2/oo5/2 Robert Koch Nachlass (DFG-Projekt)

Premio Nobel, 1905

Robert Koch injects one of his patients with tuberculin. He hoped that it would be a cure to tuberculosis.

Extra-Ausgabe

Donnerstag № 46a. 13. November 1890.

DEUTSCHE

MEDICINISCHE WOCHENSCHRIFT.

Mit Berücksichtigung des deutschen Medicinalwesens nach amtlichen Mittheilungen, der öffentlichen Gesundheitspflege und der Interessen des ärztlichen Standes.

Begründet von Dr. Paul Börner.

Sechszehnter Jahrgang.

Redacteur Sanitäts-Rath Dr. S. Guttmann in Berlin W. Verlag von Georg Thieme, Leipzig-Berlin.

Nachdruck nur unter Quellenangabe gestattet.

I. Weitere Mittheilungen über ein Heilmittel gegen Tuberculose.

Von Professor R. Koch, Berlin.

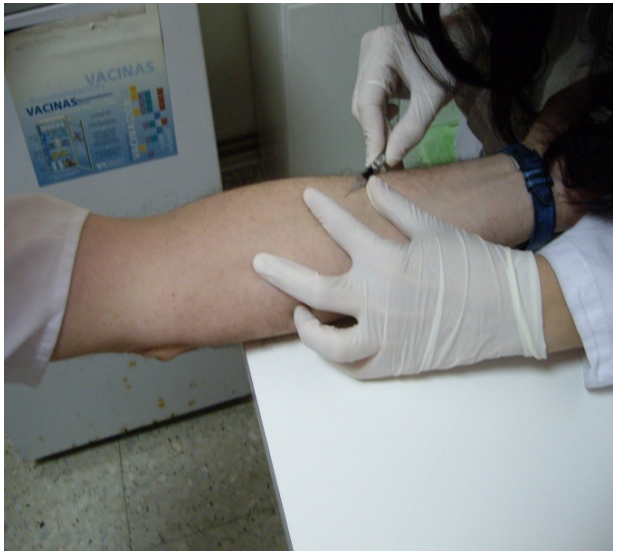
In einem Vortrage, welchen ich vor einigen Monaten auf dem internationalen medicinischen Congresse hielt, habe ich ein Mittel erwähnt, welches im Stande ist, Versuchsthiere unempfänglich gegen Impfung mit Tuberkelbacillen zu machen und bei schon erkrankten Thieren den tuberculösen Krankheitsprocess zum Stillstand zu bringen. Mit diesem Mittel sind inzwischen Versuche am Menschen gemacht, über welche im Nachstehenden berichtet werden soll.

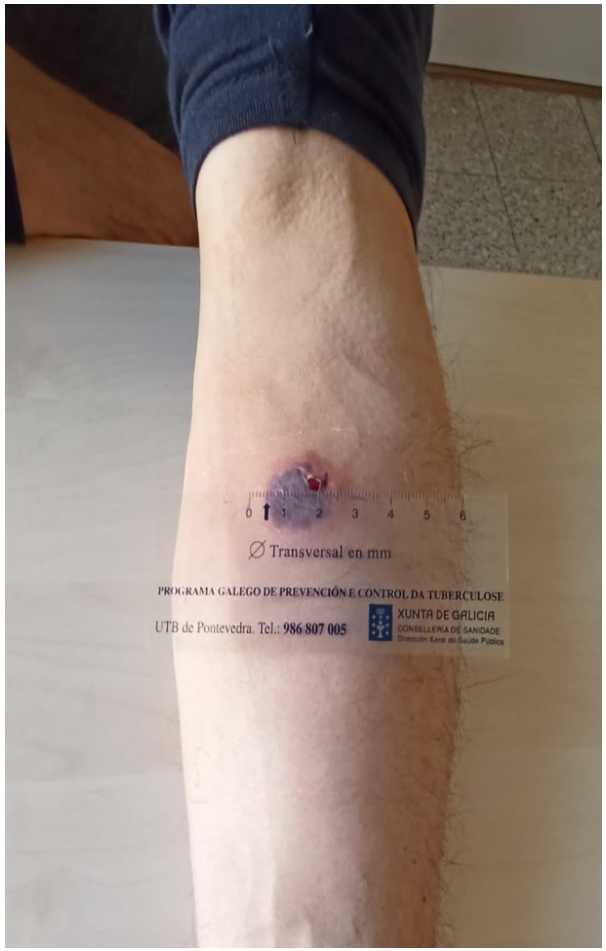
Eigentlich war es meine Absicht, die Untersuchungen vollständig

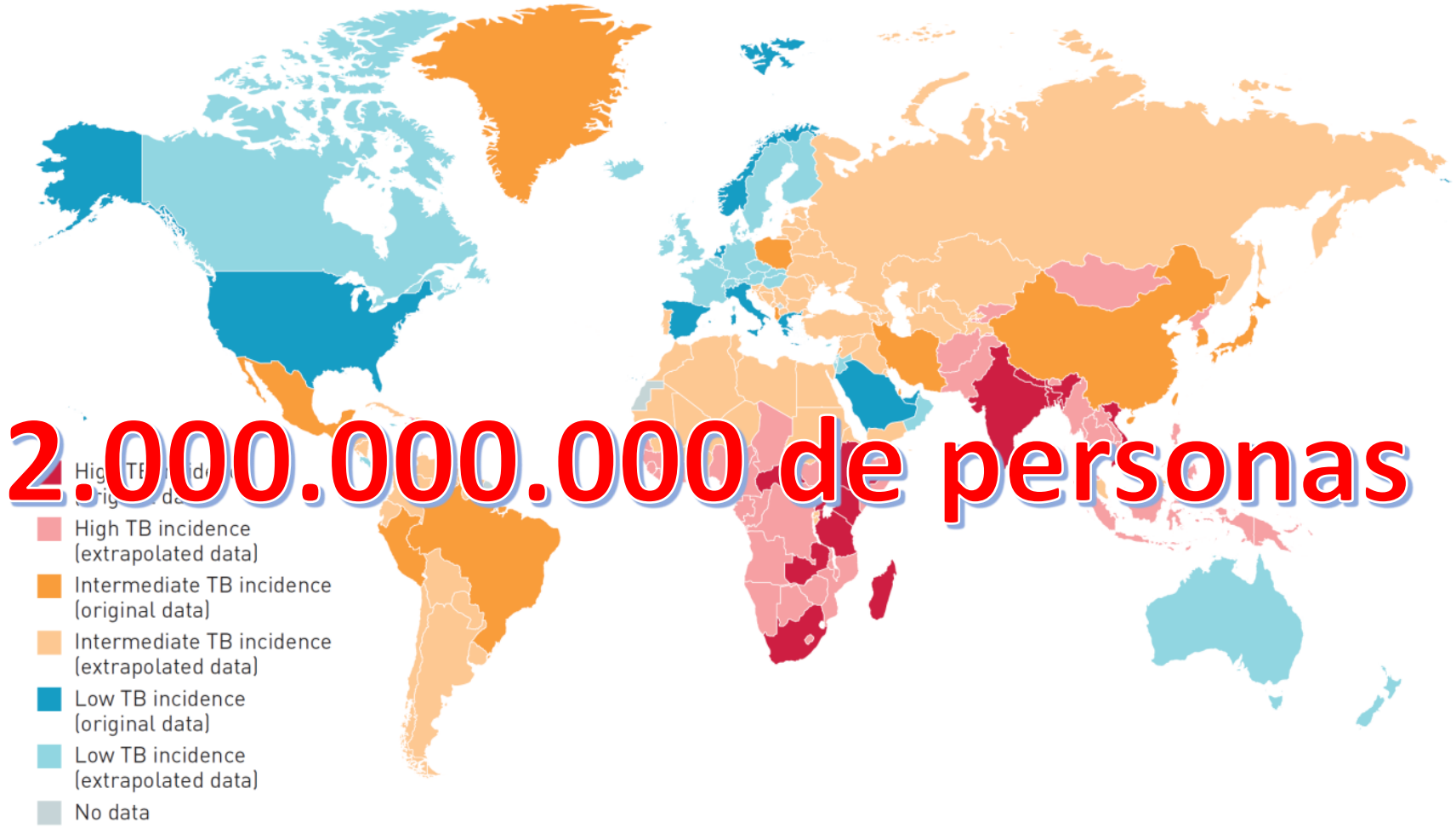
Das Mittel besteht aus einer bräunlichen klaren Flüssigkeit, welche an und für sich, also ohne besondere Vorsichtsmaßregeln, haltbar ist. Für den Gebrauch muss diese Flüssigkeit aber mehr oder weniger verdünnt werden, und die Verdünnungen sind, wenn sie mit destillirtem Wasser hergestellt werden, sterilisirt; es entwickeln sich darin sehr bald Bacterienvegetationen, sie werden trübe und sind dann nicht mehr zu gebrauchen. Um dies zu verhüten, müssen die Verdünnungen durch Hitze sterilisirt und unter

Berlín, 4 agosto 1890


685461.7
Tuberculina PPD
Evans
RT-23
2UT
Solución inyectable
Para test de Mantoux
1,5 ml
CELLTECH
685461.7
Tuberculina PPD
Evans 2UT
Tuberculina PPD
Solución inyectable
Para test de Mantoux
1,5 ml
Cantidad suficiente
para 10 dosis

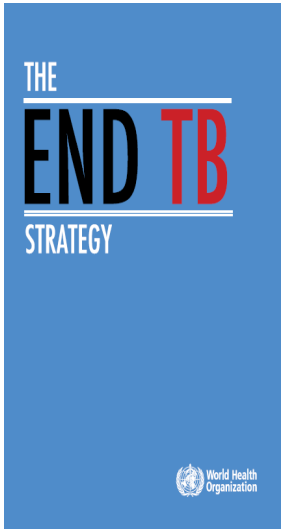

VACINAS
VACINAS

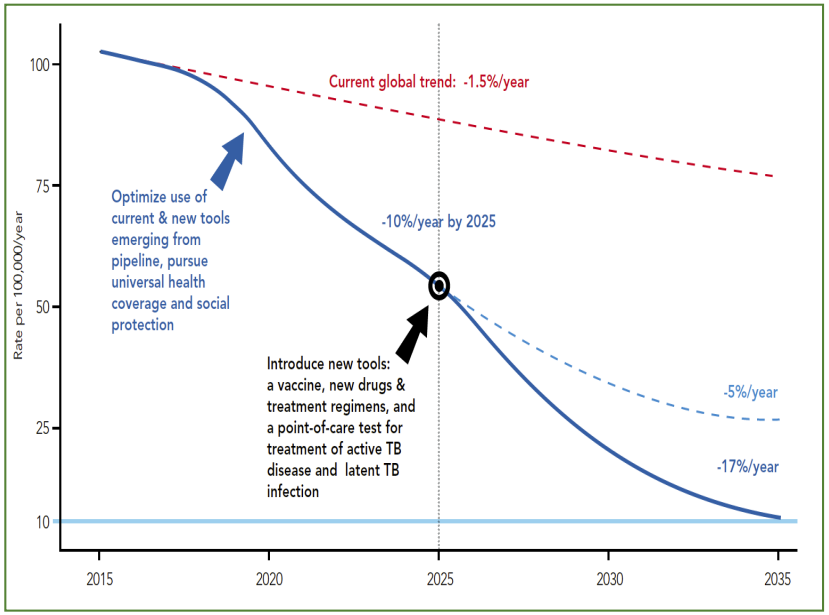

0 1 2 3 4 5 6
∅ Transversal en mm
PROGRAMA GALEGO DE PREVENCIÓN E CONTROL DA TUBERCULOSE
UTB de Pontevedra. Tel.: 986 807 005
XUNTA DE GALICIA
CONSELLERÍA DE SANIDADE
Dirección Xeral de Saúde Pública

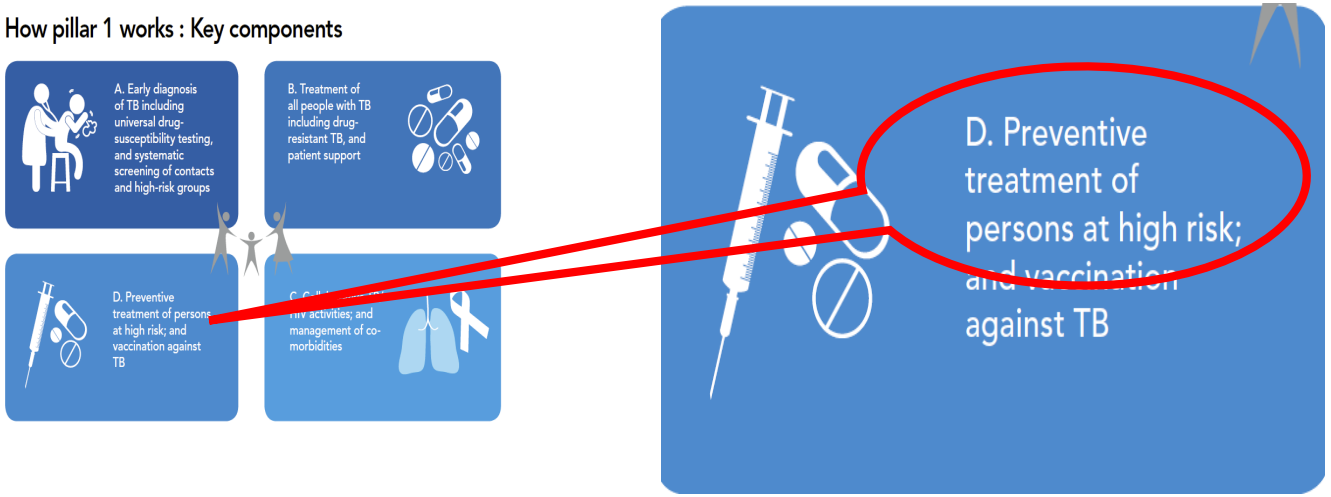


The global prevalence of LTBI was 24.8% (95% CI 19.7–30.0%)

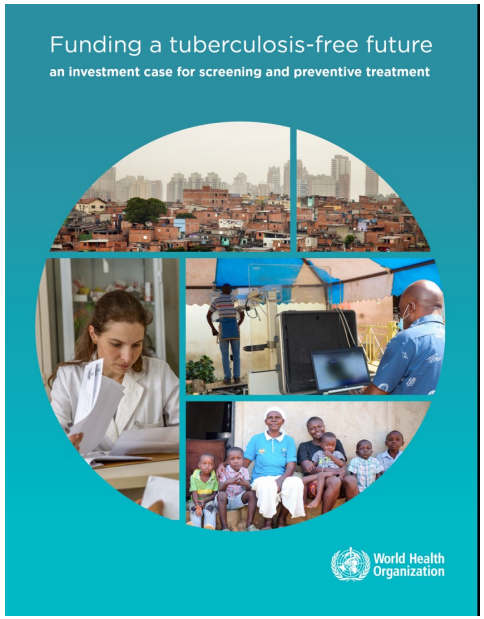
Cohen A. Eur Respir J 2019

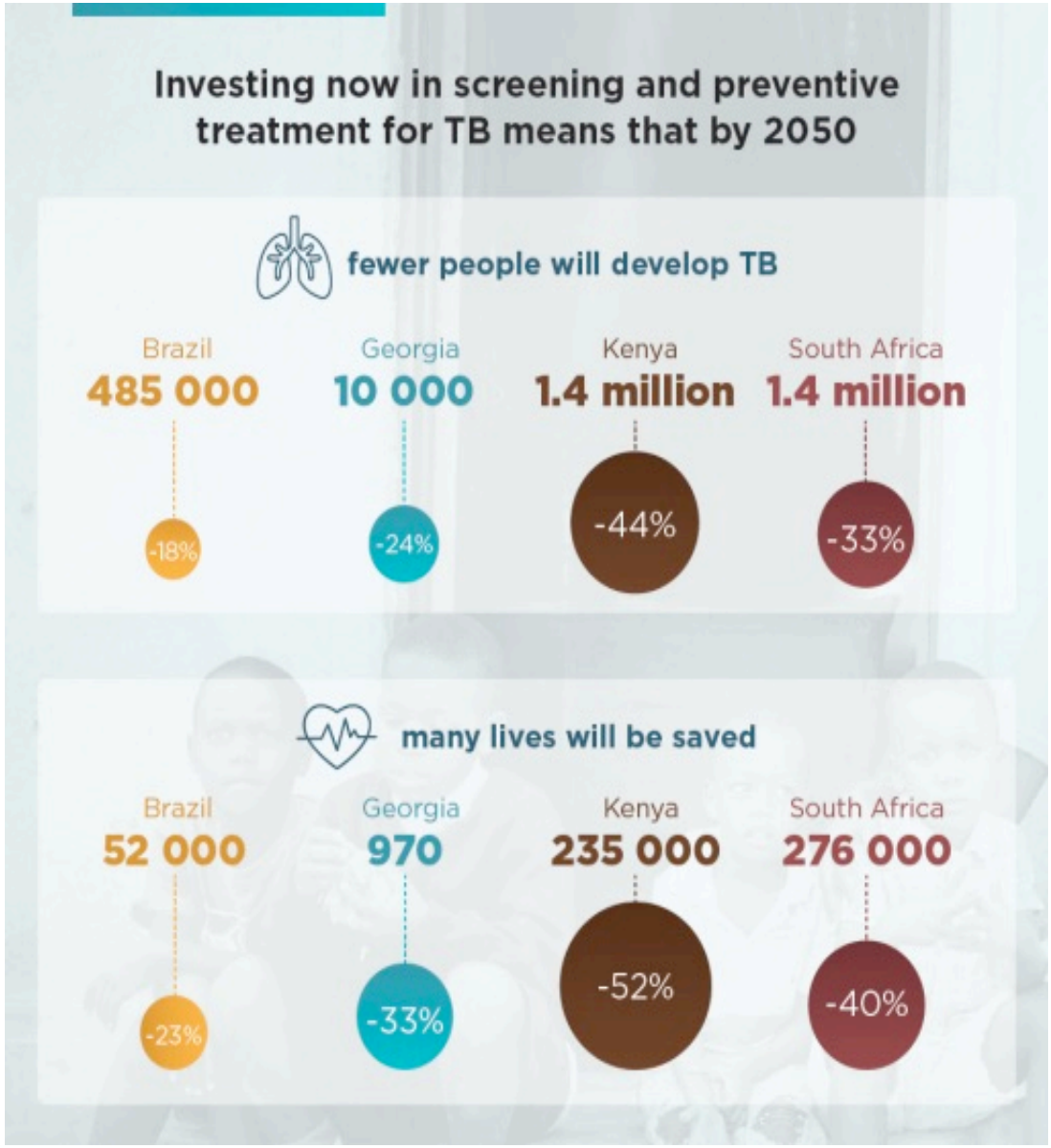






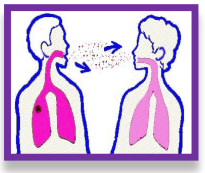
2015. World Health Organization


Funding a tuberculosis-free future
an investment case for screening and preventive treatment
World Health Organization


Investing now in screening and preventive treatment for TB means that by 2050
fewer people will develop TB
Brazil
485 000
-18%
Georgia
10 000
-24%
Kenya
1.4 million
-44%
South Africa
1.4 million
-33%
many lives will be saved
Brazil
52 000
-23%
Georgia
970
-33%
Kenya
235 000
-52%
South Africa
276 000
-40%

WHO 2024

CADENA EPIDEMIOLÓGICA DE LA TB



TUBERCULOSIS
CONTAGIOSA

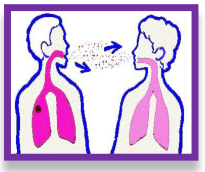
EXPOSICIÓN

INFECCCIÓN
LATENTE

TUBERCULOSIS
NO CONTAGIOSA

PT/IGRA - → **PT/IGRA -** → **PT/IGRA +** → **PT/IGRA +**

CADENA EPIDEMIOLÓGICA DE LA TB



TUBERCULOSIS
CONTAGIOSA

EXPOSICIÓN

INFECCCIÓN
LATENTE

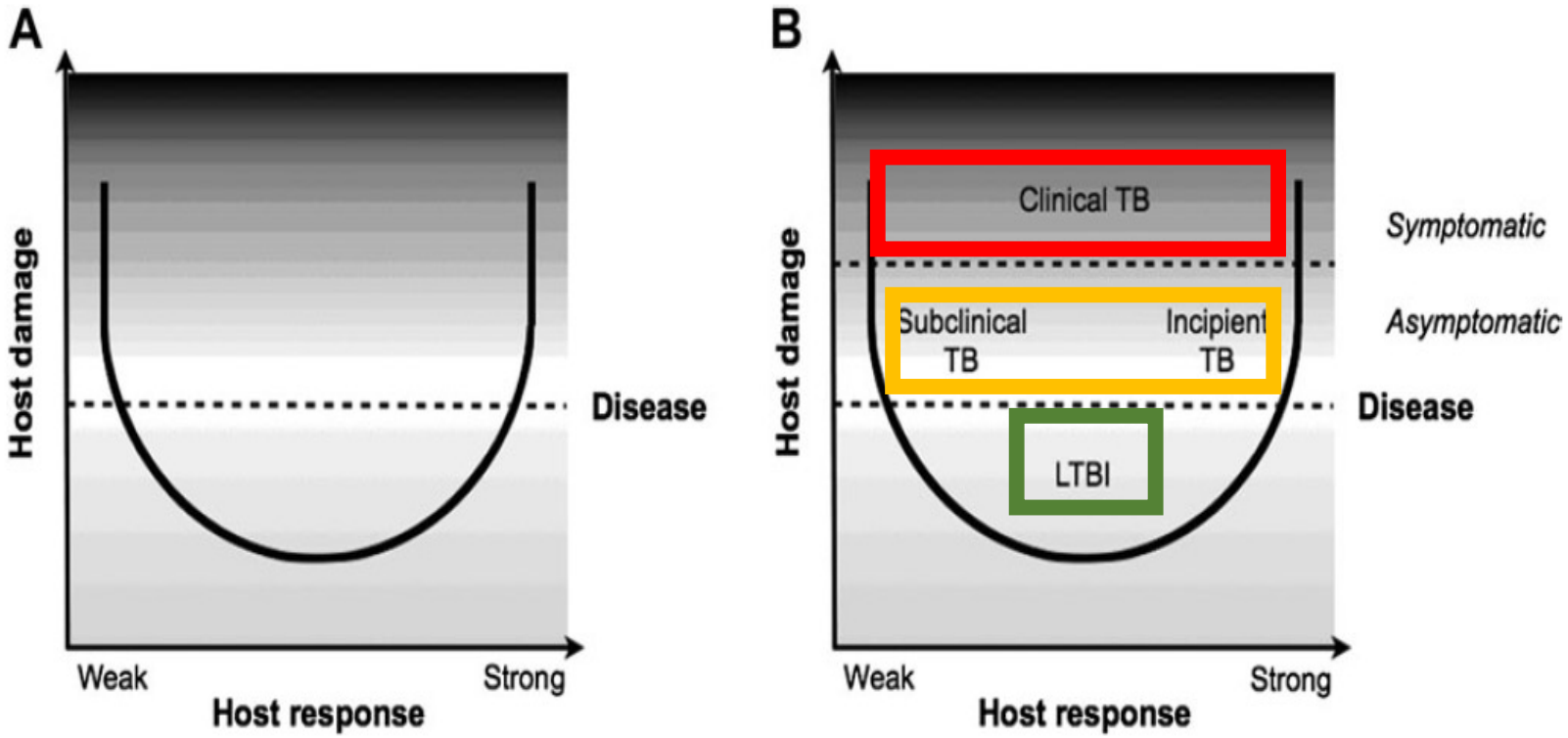
TUBERCULOSIS
NO CONTAGIOSA

Quién desarrollará TUBERCULOSIS??????

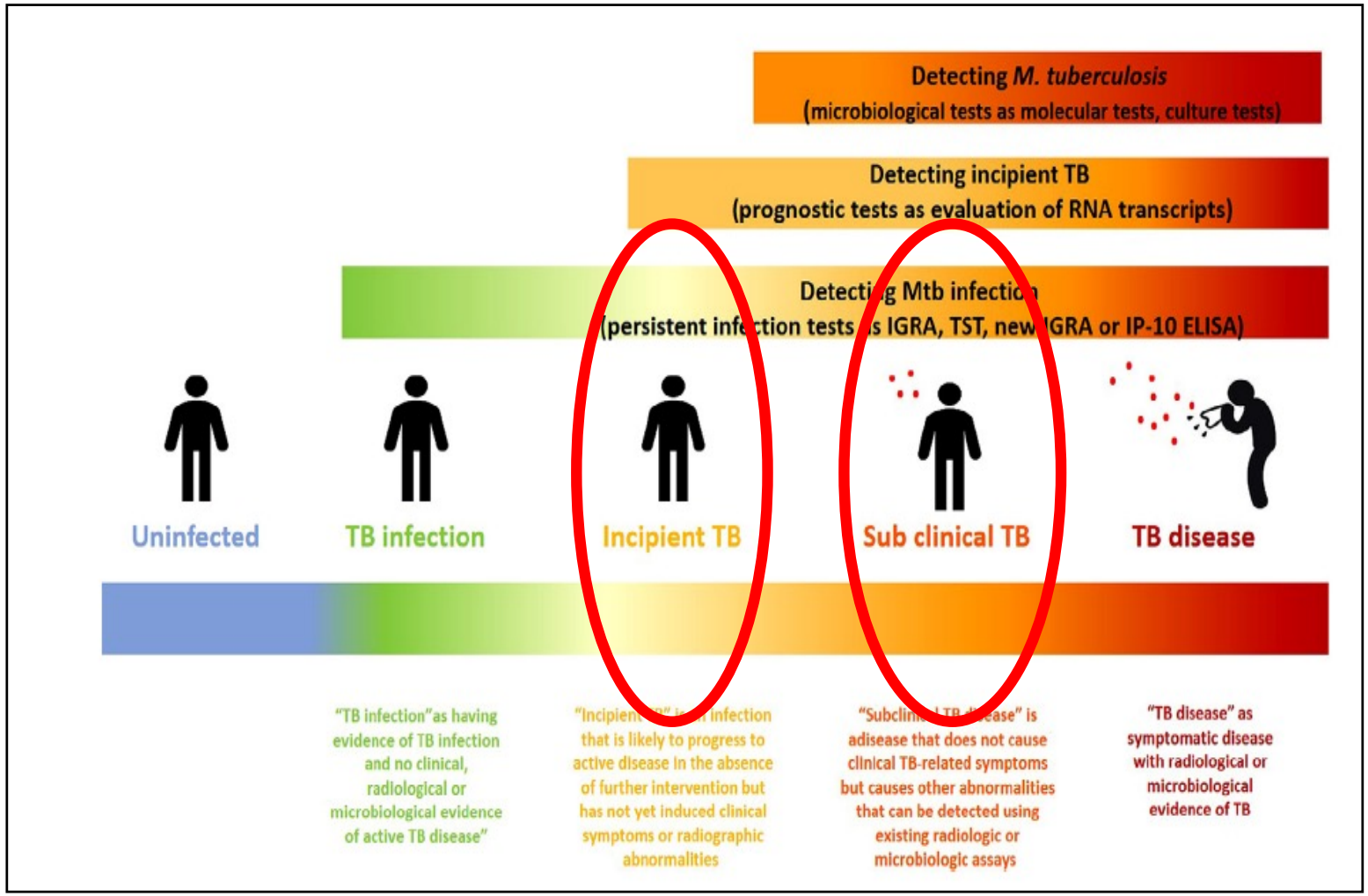
Incipient and Subclinical Tuberculosis: Defining Early Disease States in the Context of Host Immune Response

Jacqueline M. Achkar and Elizabeth R. Jenny-Avital

Department of Medicine, Albert Einstein College of Medicine, Bronx, New York

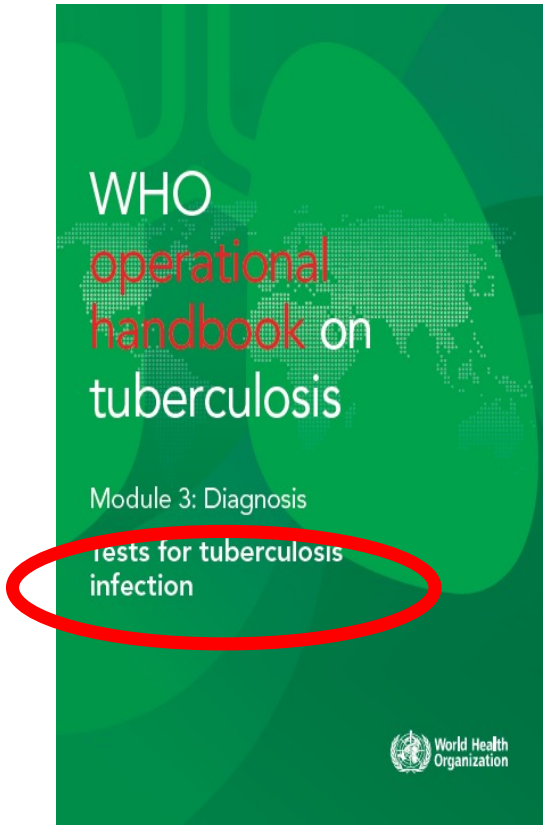


Achkar JM. JID 2011

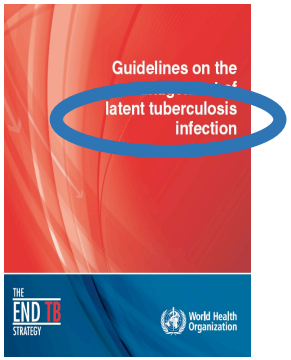


Golleti D. Int J Infect Dis 2022

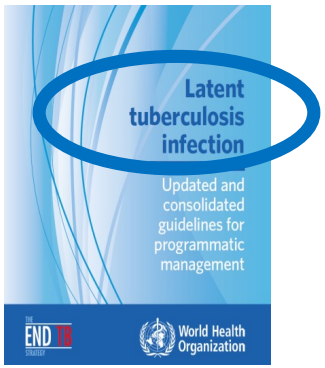
INFECCIÓN (LATENTE) TB



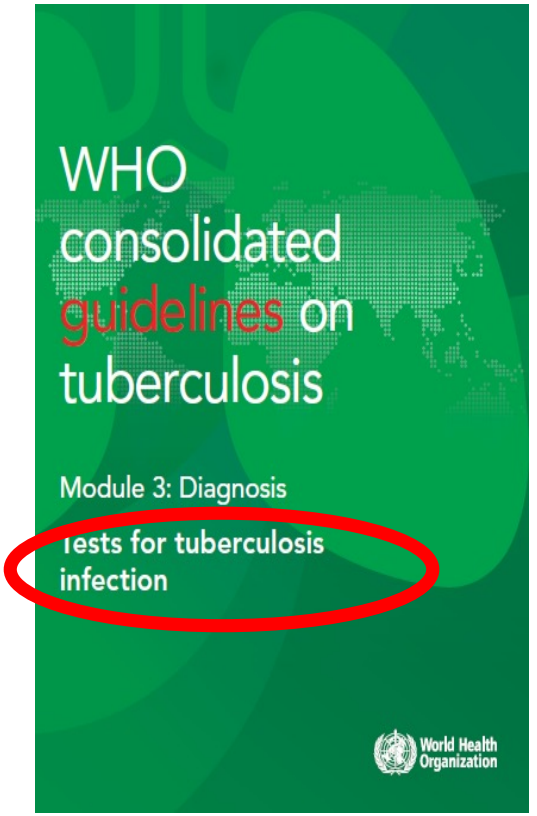
WHO 2022



WHO 2015

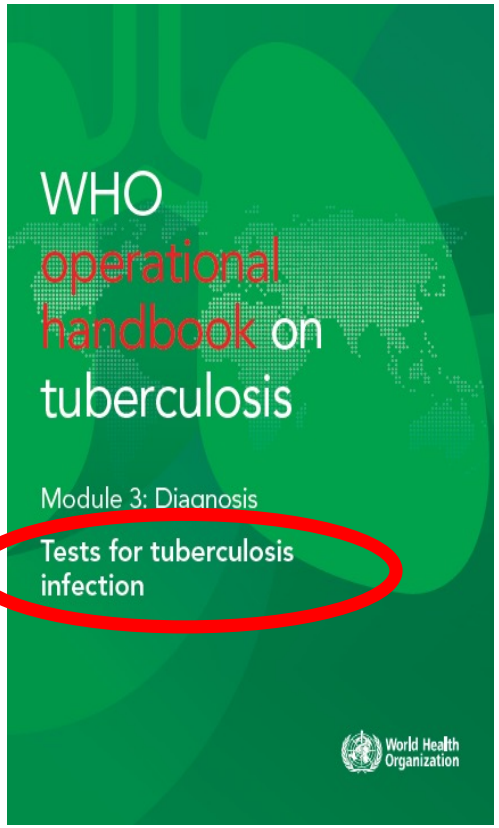


WHO 2018

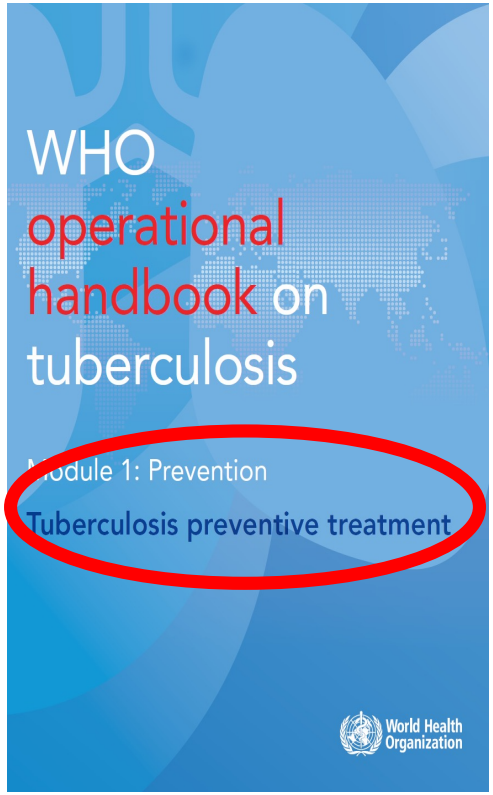


WHO 2022

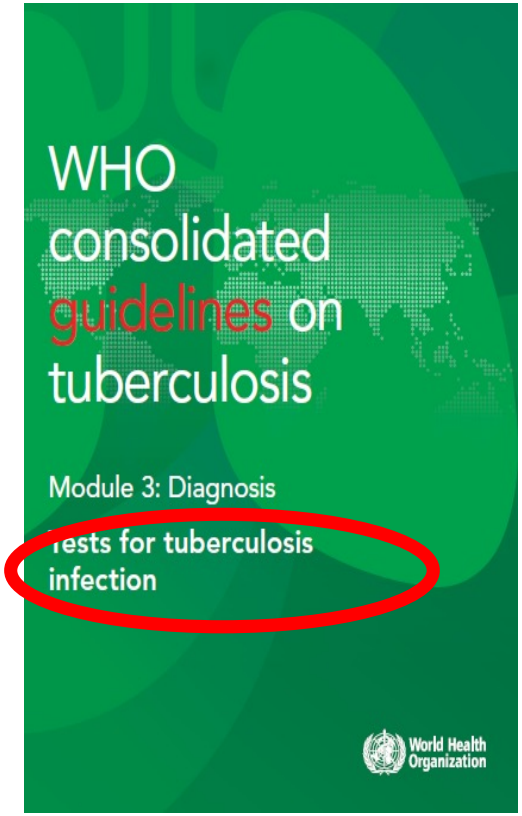
INFECCIÓN (LATENTE) TB



WHO 2022

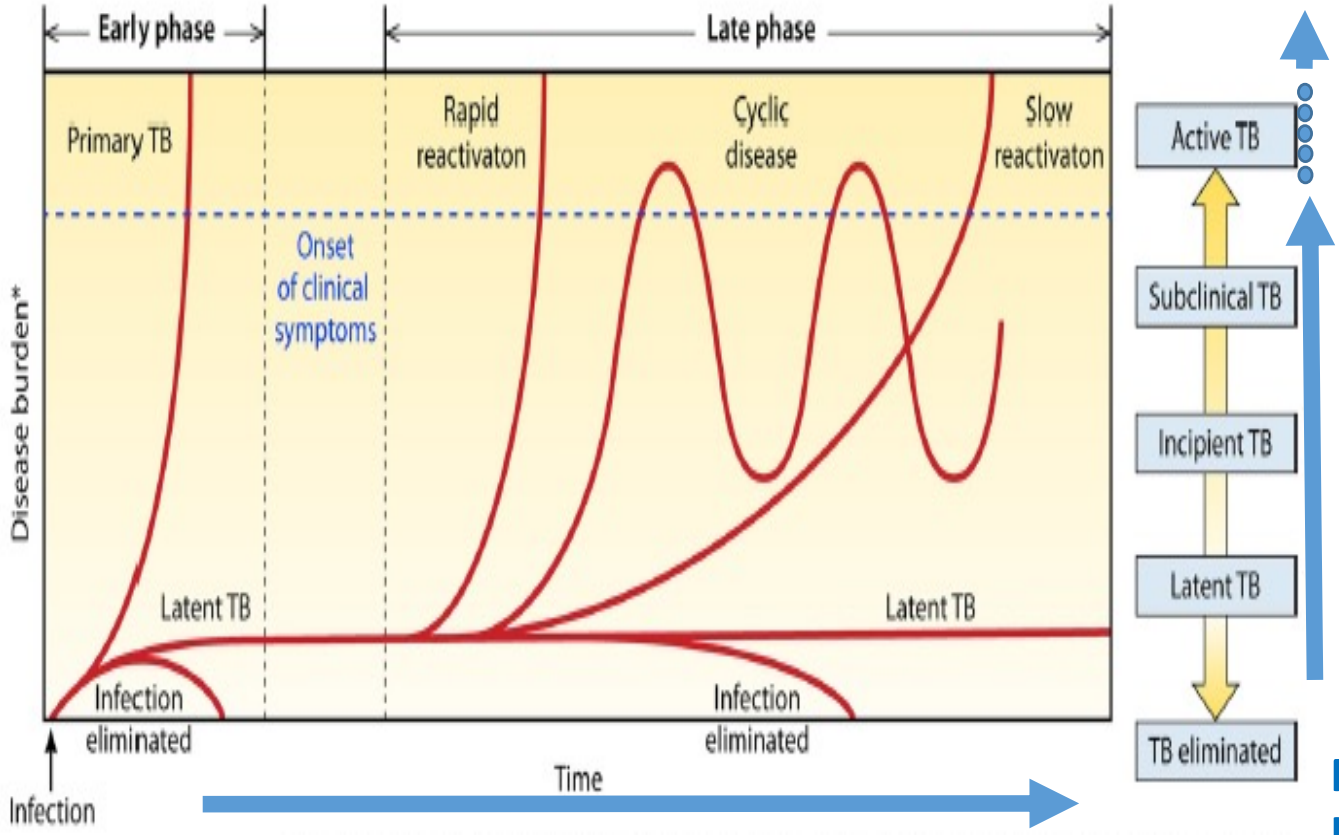


WHO 2022



WHO 2022

PT / IGRAs negativas (20-30%)

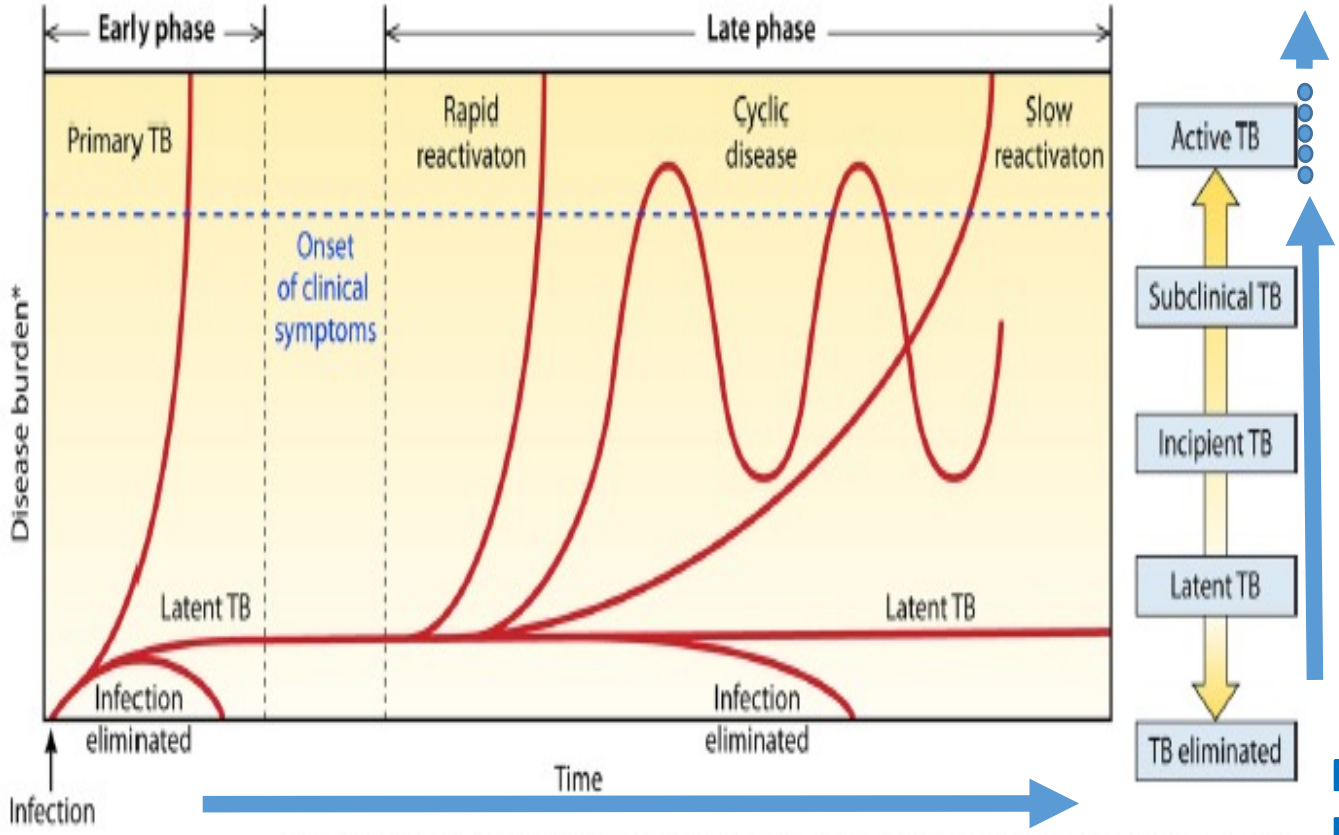


PT / IGRAs positivas

PT / IGRAs positivas

Drain PK. Clin Microb Rev 2018

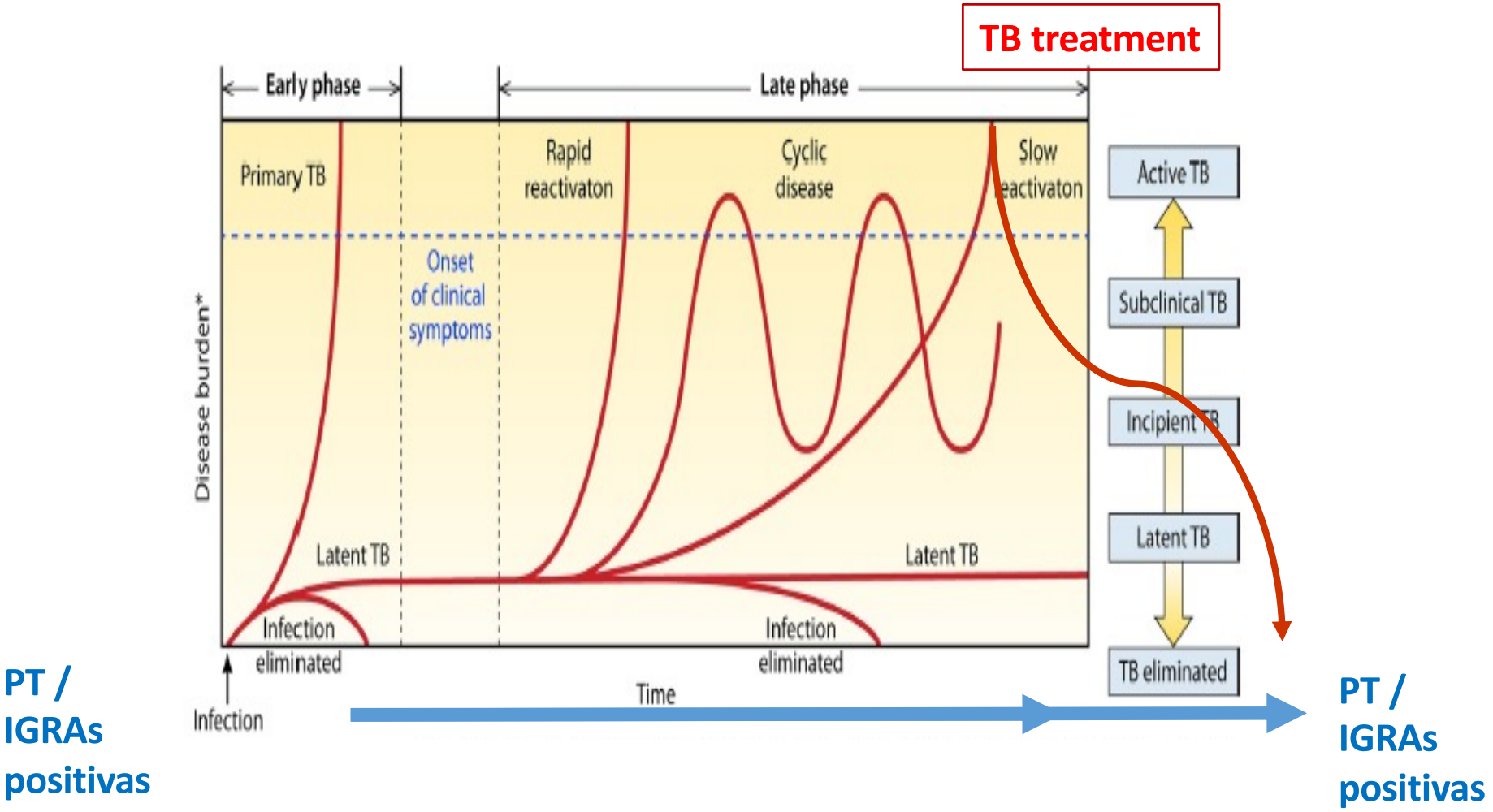
PT / IGRAs negativas (20-30%)



PT / IGRAs positivas

PT / IGRAs positivas

Drain PK. Clin Microb Rev 2018



Drain PK. Clin Microb Rev 2018

PT y/o IGRAs positivos sólo indican INMUNOREACCIÓN a antígenos de MTB

-**PT / IGRA positivos y sin embargo no hay infección**:

- Eliminación de MTB por la respuesta inmunitaria adquirida

- Eliminación de MTB tras tratamiento

- Infección por otras micobacterias (PT, tuberculina)

- Malos predictores de progresión a TB activa
  no distinguen " infección TB latente" de "infección TB incipiente"

- No distinguen TB inactiva de TB activa

- Informan indirectamente de infección TB.

PULMONARY PERSPECTIVE

Latent Tuberculosis: Two Centuries of Confusion

Marcel A. Behr[1,2], Eva Kaufmann[1,3], Jacalyn Duffin[4], Paul H. Edelstein[5,6], and Lalita Ramakrishnan[6]

Table 2. Tuberculous Infection versus Immunoreactivity

	Live *M. tuberculosis* Present = Tuberculous Infection		No Live *M. tuberculosis* Present
TB immunoreactive	TB	Tuberculous infection, no disease*†	Cleared*‡
TB nonimmunoreactive	TB	Tuberculous infection, no disease†	Never infected§

Box 1. Proposed Nomenclature for Tuberculous Infection

Uninfected: no infection, no disease, may or may not be TB immunoreactive.

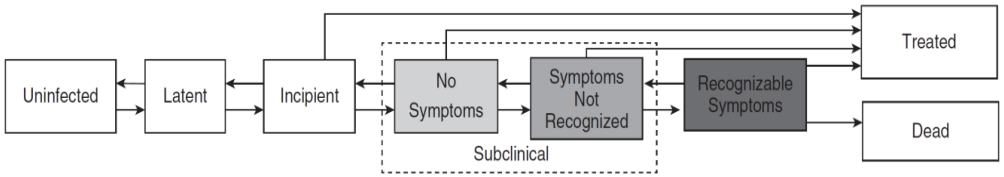
Tuberculous infection (TBI): infected with live *Mycobacterium tuberculosis.*

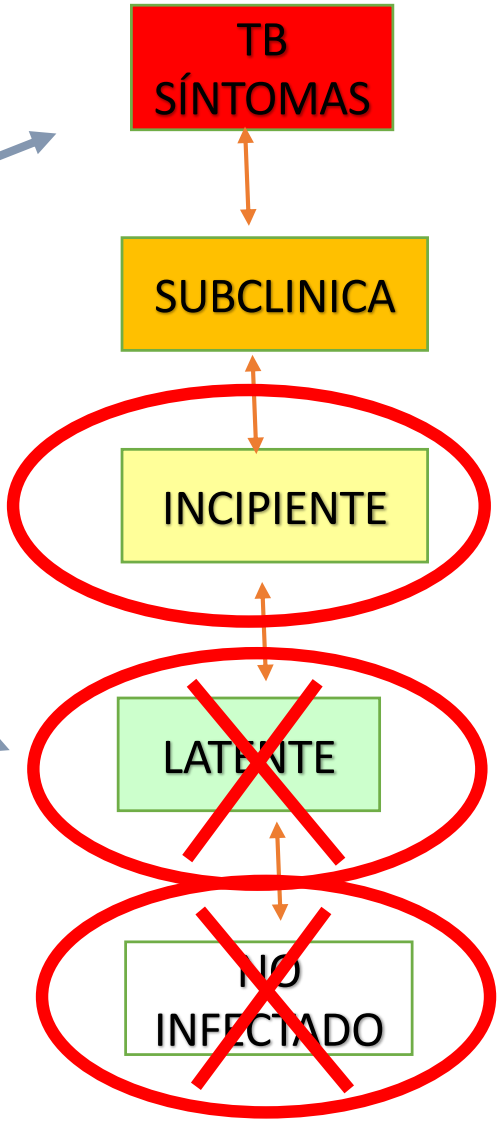
Tuberculous infection no disease (TBInd): tuberculous infection, asymptomatic and culture negative, may or may not be TB immunoreactive.

Tuberculosis (TB): symptomatic and/or culture positive, may or may not be TB immunoreactive.

Behr MA. AJRCCM 2021

Transcriptómica
Proteómica
Citoquinas
Otros biomarcadores





Kendall EA. AJRCCM 2021

A blood RNA signature for tuberculosis disease risk: a prospective cohort study

Daniel E Zak*, Adam Penn-Nicholson*, Thomas J Scriba*, Ethan Thompson†, Sara Suliman†, Lynn M Amon, Hassan Mahomed,

Four-Gene Pan-African Blood Signature Predicts Progression to Tuberculosis

Sara Suliman[1,2*], Ethan G. Thompson[3*], Jayne Sutherland[4], January Weiner 3rd[5], Martin O. C. Ota[4], Smitha Shankar[3],

nature medicine

Article

https://doi.org/10.1038/s41591-022-02110-9

T cell receptor repertoires associated with control and disease progression following *Mycobacterium tuberculosis* infection

Received: 5 October 2021

Accepted: 25 October 2022

Published online: 5 January 2023

Check for updates

Munyaradzi Musvosvi[1,32], Huang Huang[2,32], Chunlin Wang[2], Qiong Xia[2], Virginie Rozot[1], Akshaya Krishnan[1], Peter Acs[1], Abhilasha Cheruku[1], Gerlinda Obermoser[1], Alasdair Leslie[1,4,5], Samuel M. Behar[6], Willem A. Hanekom[1,4,5], Nicole Bilek[1], Michelle Fisher[1], Stefan H. E. Kaufmann[7,8,9,10], Gerhard Walzl[11], Mark Hatherill[12], Mark M. Davis[2,12,13,33], Thomas J. Scriba[1,32] ✉, Adolescent Cohort Study team* & GC6-74 Consortium*

ORIGINAL ARTICLE

Four-Gene Pan-African Blood Signature Predicts Progression to Tuberculosis

Sara Suliman[1,2*], Ethan G. Thompson[3*], Jayne Sutherland[4], January Weiner 3rd[5], Martin O. C. Ota[4], Smitha Shankar[3]

RESEARCH ARTICLE

Discovery and validation of a prognostic proteomic signature for tuberculosis progression: A prospective cohort study

Adam Penn-Nicholson[1☯], Thomas Hraha[2☯], Ethan G. Thompson[3☯], David Sterling[2],

An RNA-seq Based Machine Learning Approach Identifies Latent Tuberculosis Patients With an Active Tuberculosis Profile

Olivia Estévez[1,2], Luis Anibarro[2,3,4], Elina Garet[1,2], Ángeles Pallares[5], Laura Barcia[3],

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Clinical Infectious Diseases

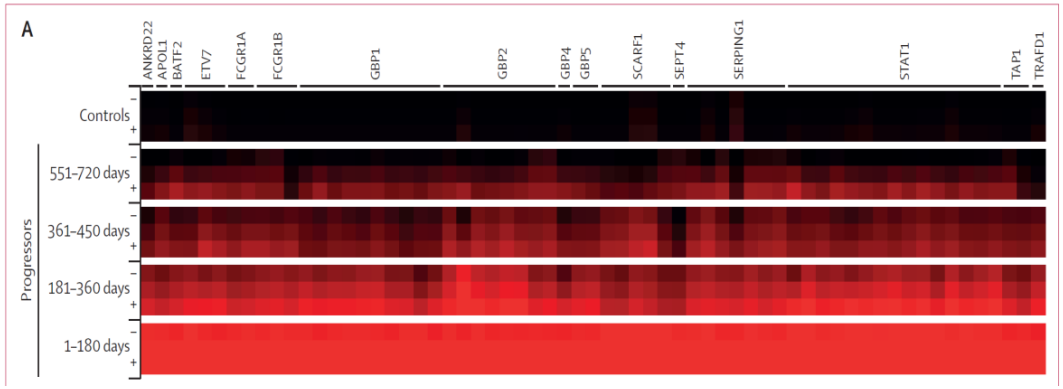
MAJOR ARTICLE

Quantiferon supernatant-based host biomarkers predicting progression to active tuberculosis disease among household contacts of tuberculosis patients

Evangeline Ann Daniel[1,2], Kannan Thiruvengadam[1], Anuradha Rajamanickam[3],

A blood RNA signature for tuberculosis disease risk: a prospective cohort study

Daniel E Zak, Adam Penn-Nicholson*, Thomas J Scriba*, Ethan Thompson†, Sara Suliman†, Lynn M Amon, Hassan Mahomed, Mzwandile Erasmus, Wendy Whatney, Gregory D Hussey, Deborah Abrahams, Fazlin Kafaar, Tony Hawkridge, Suzanne Verver, E Jane Hughes, Martin Ota, Jayne Sutherland, Rawleigh Howe, Hazel M Dockrell, W Henry Boom, Bonnie Thiel, Tom H M Ottenhoff, Harriet Mayanja-Kizza, Amelia C Crampin, Katrina Downing, Mark Hatherill, Joe Valvo, Smitha Shankar, Shreemanta K Parida, Stefan H E Kaufmann, Gerhard Walzl, Alan Aderem, Willem A Hanekom, for the ACS and GC6-74 cohort study groups‡*



A 16 gene signature of risk

Sensibilidad: 66,1%
Especificidad: 80,6%
(12 meses)

A 16 gene signature of risk was identified. The signature predicted tuberculosis progression with a sensitivity of 66·1% (95% CI 63·2–68·9) and a specificity of 80·6% (79·2–82·0) in the 12 months preceding TB diagnosis

Zak DE. Lancet 2016

Clinical Infectious Diseases
MAJOR ARTICLE

QuantiFERON Supernatant-based Host Biomarkers Predicting Progression to Active Tuberculosis Disease Among Household Contacts of Tuberculosis Patients

Evangeline Ann Daniel,[1,2,0] Kannan Thiruvengadam,[1] Anuradha Rajamanickam,[3] Padmapriyadarsini Chandrasekaran,[1] Sathyamurthi Pattabiraman,[1] Brindha Bhanu,[1] Amsaveni Sivaprakasam,[1] Mandar Paradkar,[4,5] Vandana Kulkarni,[4,5] Rajesh Karyakarte,[6] Shri Vijay Bala Yogendra Shivakumar,[1] Vidya Mave,[4,5,7] Amita Gupta,[7] Subash Babu,[3] and Luke Elizabeth Hanna[1]

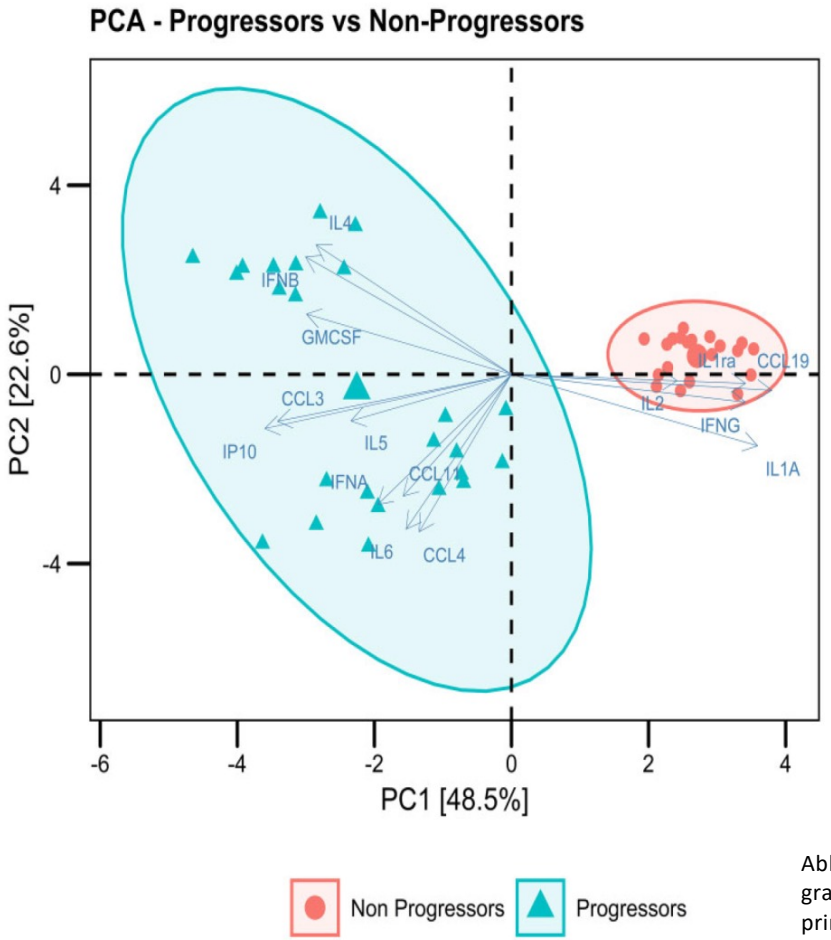


Figure 8. PCA plot of significantly different biomarkers between progressors and non-progressors: PCA shows that IP-10, CCL-19, IL-1ra, CCL3, IFN-γ, IL-2, IL-4, IL-1α, CCL4, IL-6, CCL11, IFN-α, IL-5, GM-CSF and IFN-β can clearly distinguish between progressors and non-progressors with no overlap.

a cutoff of 0.24 for IP-10/CCL19 ratio was found to be ideal for predicting short-term risk of progression to TB disease with a positive predictive value of 100 (95% confidence interval [CI] 85.8–100).

Abbreviations: CCL, chemokine ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; PCA, principal component analysis.

Daniel EA. Clin Infect Dis 2023

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

Epidemiology | Full-Length Text

Evaluation of the Cepheid 3-gene host response blood test for tuberculosis diagnosis and treatment response monitoring in a primary-level clinic in rural China

Meng Li,[1] Yong Qiu,[2] Mingcheng Guo,[2] Rong Qu,[2] Fajun Tian,[2] Gengsheng Wang,[2] Ya Wang,[2] Jian Ma,[3] Siyuan Liu,[3] Howard Takiff,[4] Yi-Wei Tang,[3] Qian Gao[1]

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

| Commentary

The elusive allure of a rapid host blood signature for tuberculosis disease

Paul K. Drain,[1] Ronit R. Dalmat[1]

Diagnostic accuracy of a three-gene *Mycobacterium tuberculosis* host response cartridge using fingerstick blood for childhood tuberculosis: a multicentre prospective study in low-income and middle-income countries

Laura Olbrich, Valsan P Verghese*, Zoe Franckling-Smith, Issa Sabi, Nyanda E Ntinginya, Alfred Mfinanga, Denise Banze, Sofia Viegas, Celso Khosa, Robina Semphere, Marriott Nliwasa, Timothy D McHugh, Leyla Larsson, Alia Razid, Rinn Song, Elizabeth L Corbett, Pamela Nabeta, Andre Trollip, Stephen M Graham, Michael Hoelscher, Christof Geldmacher, Heather J Zar, Joy Sarojini Michael*, Norbert Heinrich*, on behalf of the RaPaed-TB consortium†*

Olbrich L. Lancet Infect Dis 2024

Li M. J Clin Microb 2023

Drain PK. J Clin Microb 2024

EXPERT REVIEW OF MOLECULAR DIAGNOSTICS
https://doi.org/10.1080/14737159.2023.2240230

Taylor & Francis
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REVIEW

OPEN ACCESS Check for updates

Research tests for the diagnosis of tuberculosis infection

Tonino Alonzi*, Federica Repele* and Delia Goletti

Expert opinion:

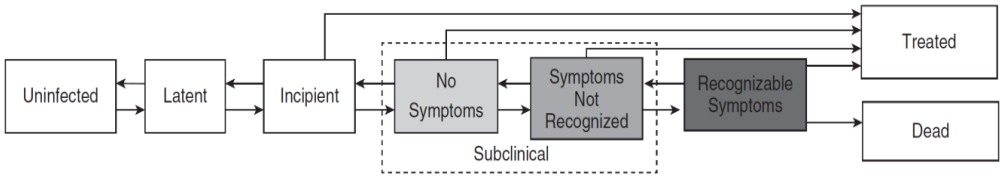
· The experimental tests described are very interesting. However, further investigation and randomized clinical trials are needed to improve sensitivity and specificity of these new research-based tests.

· More reliable proofs-of-concept and simplification of technical procedures **are necessary to develop new diagnostic tools for identifying TBI patients and those that will progress from infection to TB disease.**

Alonzi T. Expert Rev Molec Diag 2023

Transcriptómica
Proteómica
Citoquinas
Otros biomarcadores

Aún no disponibles



TB SÍNTOMAS

SUBCLINICA

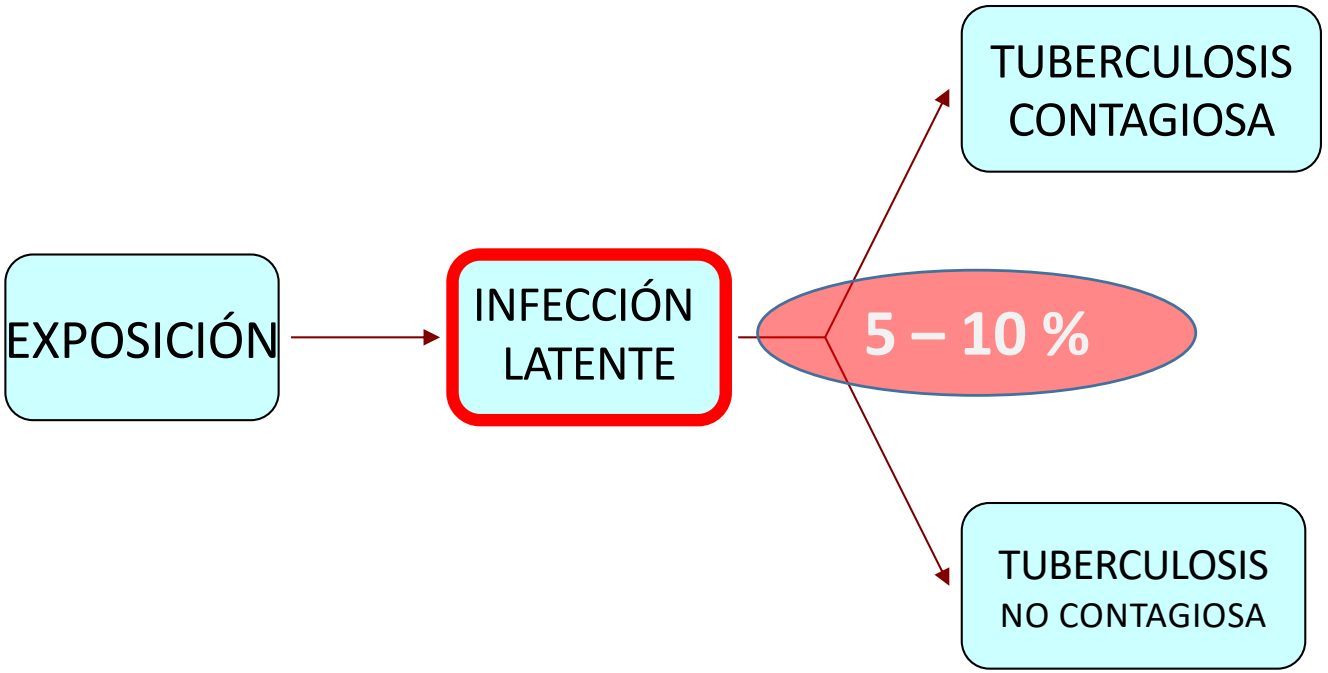
INCIPIENTE

LATENTE

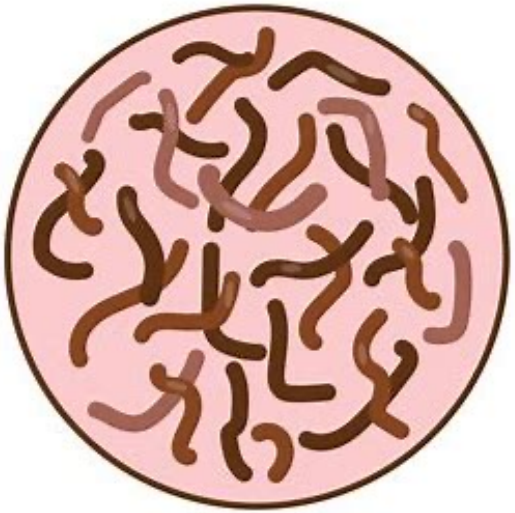
NO INFECTADO

Kendall EA. AJRCCM 2021

INFECCIÓN (LATENTE) TB



PT/IGRA - → PT/IGRA - → PT/IGRA + → PT + IGRA+



¿dónde está?

MYCOBACTERIUM TUBERCULOSIS
LATENTE

The Journal of Infectious Diseases
REVIEW ARTICLE

Anatomic and Cellular Niches for *Mycobacterium tuberculosis* in Latent Tuberculosis Infection

Jonathan Mayito,[1,2] Irene Andia,[1] Mulugeta Belay,[2] David A. Jolliffe,[2] David P. Kateete,[1] Stephen T. Reece,[3,a] and Adrian R. Martineau[2,a]

Table 1. Results of Historical Studies in Which Macroscopically Normal Tissue From Individuals Dying From Causes Other Than Tuberculosis Was Inoculated Into Laboratory Animals

Reference	Subjects	Material Inoculated	Proportion Culture-Positive
Loomis 1890, cited in [13]	30 adults	Bronchial lymph nodes	8 of 30 (26.7%)
Pizzini 1892, cited in [13]	30 adults	Bronchial and cervical lymph nodes	12 of 30 (40.0%)
Kälble 1899, cited in [13]	23 individuals	Bronchial lymph nodes	2 of 23 (8.7%)
McFadyean 1903, cited in [14]	20 individuals	Mesenteric lymph nodes	2 of 20 (10.0%)
Rosenberger 1905, cited in [14]	14 adults and children	Mesenteric lymph nodes	6 of 14 (42.9%)
Harbitz 1905, cited in [14]	91 children	Cervical, tracheal, mesenteric, and retroperitoneal lymph nodes	18 of 91 (19.8%)
Ipsen 1906, cited in [14]	74 children	Material included mesenteric lymph nodes	1 of 74 (1.4%)
Bartel 1906, cited in [14]	68 children	Cervical, bronchial, and mesenteric lymph nodes	8 of 68 (11.8%)
Weber 1907, cited in [14]	26 children aged 3 months to 12 years	Not ascertained	1 of 26 (3.8%)
Beitzke 1912, cited in [14]	27 children	Cervical, tracheobronchial, and mesenteric lymph nodes	9 of 27 (33.3%)
Eastwood 1914, cited in [14]	61 children	Bronchial, mesenteric, and cervical lymph nodes	5 of 61 (8.2%)
Griffith 1914, cited in [14]	34 children	Bronchial and mesenteric lymph nodes	2 of 34 (5.9%)
Wang [14]	18 adults and 14 children	Cervical, bronchial, mesenteric, and retroperitoneal lymph nodes	3 of 32 (9.4%)
Opie and Aronson [11]	33 adults aged 20–70 years	Tissue from lung apices, lung bases, and hilar or tracheobronchial lymph nodes of individuals with lesions elsewhere (fibrocaseous lesions/scars of apices, caseous encapsulated, or calcified nodes)	15 of 33 (45.5%)
Saenz 1938, cited in [13]	14 individuals	Normal lung	1 of 14 (7.15%)
Feldman and Baggenstoss [13]	51 adults and children aged 2 to 93 years, of whom n = 39 had at least 1 healed Ghon complex	Tissue from upper and lower lobes of the lung and hilar or tracheobronchial lymph nodes	3 of 51 (5.9%)

Mayito J. JID 2019

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Table 2. Case Reports Documenting Potential Transmission of Tuberculosis From Latently Infected Donors to Immunosuppressed Recipients

Reference	Donor	Organ(s) Donated	Recipients
Ridgeway et al [16]	Donor had normal chest radiograph and no known prior history of MTB infection or disease	Lung	Two separate recipients developed pulmonary TB with identical isolate to each other
Graham et al [17]	69-year-old female, died of intracranial hemorrhage, clear chest radiograph, no past history of TB	Kidney and liver (different recipients)	Both recipients developed active TB (renal TB at 14 months posttransplant in kidney recipient, TB osteomyelitis at 12 months posttransplant in liver recipient): matching isolates.
Lee et al [18]	51-year-old, nonsmoking, recent immigrant from China, died of intracerebral hemorrhage. No previous TB, ante-mortem chest x-ray normal, tracheal aspirate smear- and culture-negative for acid-fast bacilli.	Lung	Developed pulmonary MDR TB at 7 weeks; recipient was tuberculin negative pretransplant, with no exposure to MDR-TB.
Boedefeld et al [19]	33-year-old male, died of intracranial haemorrhage, emigrated from Peru 11 years before. Previous PPD test 24 mm, but chemoprophylaxis not given. Chest radiograph normal at time of organ donation.	Lung	Recipient developed pulmonary and pericardial TB at 3 months posttransplant; no known TB exposure.
Kumar et al [20]	42-year-old Vietnamese-born male, died of acute intracranial hemorrhage. No history of TB or positive TST. Ante-mortem CT chest scan showed no pulmonary infiltrates or granulomata.	Lung	TST-negative recipient developed pulmonary TB at 3 months posttransplant; isolate of indo-oceanic lineage, associated with Vietnam/Cambodia.
Mortensen et al [21]	Male in 20s, died in accident; previous incarceration; clear chest radiograph and normal bronchoscopy ante-mortem.	Lung	TST-negative recipient developed pulmonary TB at 2 months posttransplant. MTB isolate matched strain from previous outbreak near donor's home.
Mortensen et al [21]	Male in 20s, died in accident; previous travel to Philippines; clear chest radiograph, normal bronchoscopy and BAL culture negative for TB ante-mortem.	Lung	Recipient developed PTB at 4 months posttransplant; spoligotype "associated with Manila family," recipient had not traveled outside of the United States.
Jensen et al [22]	Donor diagnosed with latent TB 5 years before death after exposure to index case with isoniazid-resistant TB; received inappropriate treatment with single agent isoniazid.	Lung	Recipient developed pulmonary TB at 11 weeks posttransplant. MTB isolates from the index case (to whom donor was exposed) and transplant recipient matched.
Cassir et al [23]	47-year-old male, died of intracranial hemorrhage, no risk factors for TB other than chronic alcohol use and smoking. TST results unavailable. No signs of active or previous TB on ante-mortem CT chest. Pretransplantation lung biopsy culture- and PCR-negative for MTB.	Lung	41-year-old female with cystic fibrosis developed pulmonary TB at 6 weeks posttransplant. No previous TB or known TB exposure pre- or posttransplant.
Ruijter et al [24]	57-year-old woman from the Philippines, lethal brain injury. Ante-mortem abdominal ultrasound and chest radiography showed no abnormalities.	Liver	Developed hepatic TB at 6 months posttransplant; MTB isolate Manila family.

Mayito J. JID 2019

The Journal of Infectious Diseases
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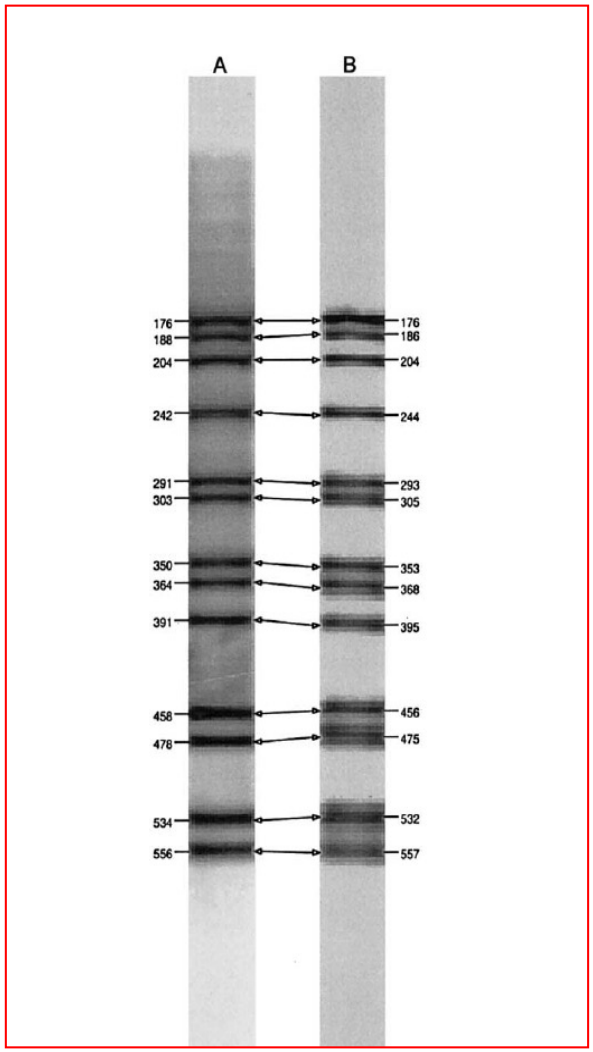
CONCLUSIONS

The presence of MTB in diverse nonphagocytic cells of latently infected individuals has been recognized for almost 20 years, but the route by which the bacillus reaches these sites has not been apparent.

Mayito J. JID 2019

¿estará siempre? ¿cuándo “atacará” de verdad?



Molecular Evidence of Endogenous Reactivation of *Mycobacterium tuberculosis* after 33 Years of Latent Infection

Troels Lillebaek, [illegible] Inga Bæss,[1] Benedicte Strunge,[4] Vibeke Ø. Thomsen,[1] and Åse B. Andersen[2]

[1]*International Reference Laboratory for Mycobacteriology, Statens Serum Institut (National Institute for Prevention and Control of Infectious Diseases and Congenital Disorders), and* [2]*Infectious Diseases Clinic, Rigshospitalet University Hospital, Copenhagen,* [3]*Department of Pulmonary Medicine, Gentofte University Hospital, Gentofte, and* [4]*Department of Pulmonary Medicine, Holstebro Hospital, Holstebro, Denmark*

Figure 1. Identical DNA restriction fragment–length polymorphism patterns [11] of Mycobacterium tuberculosis isolates from a father (A), in 1961, and his son (B), in 1994. Nos. indicate band positions; identical bands are marked by arrows

Lillebaek TT. J Infect Dis 2002

letter to the editor

Wien Klin Wochenschr (2008) 120: 642–643
DOI 10.1007/s00508-008-1006-5
Printed in Austria

Wiener klinische Wochenschrift
The Middle European Journal of Medicine

Reactivation of tuberculosis after total hip replacement – 58 years after primary infection

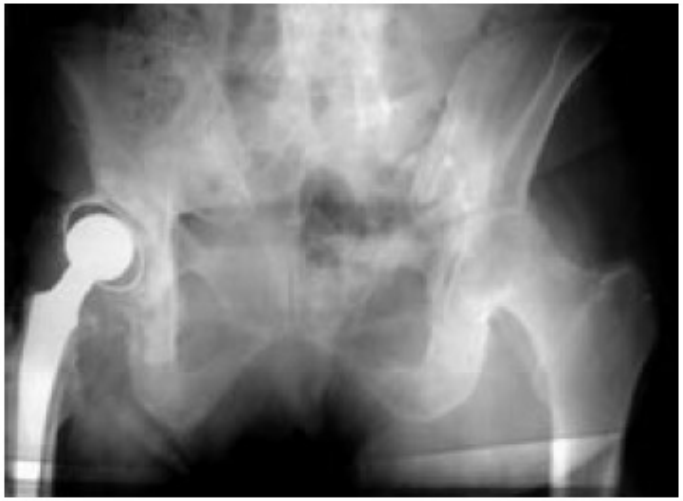


Fig. 1. Two years after primary total hip arthroplasty; loosening with migration of acetabular cup and subsidence of stem. Radiographs of a 69-year-old woman with tuberculosis of the hip

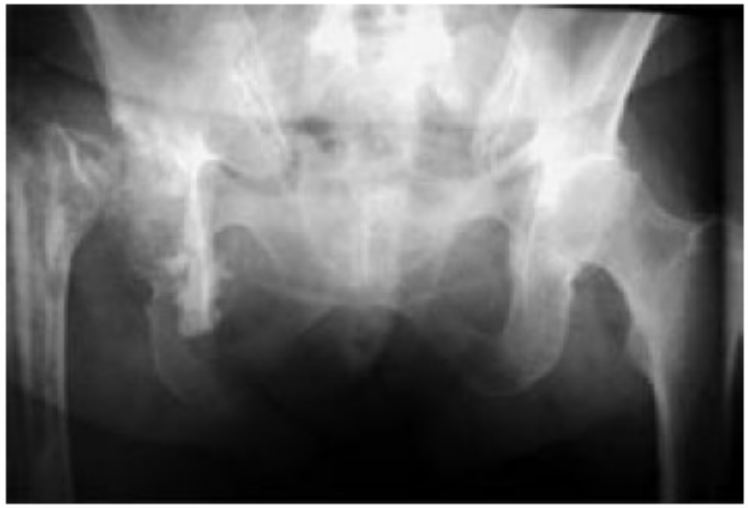


Fig. 2. Postoperatively, after Girdlestone resection arthroplasty. Small amounts of retained cement in the medullar canal. Radiographs of a 69-year-old woman with tuberculosis of the hip

Maricevic AR. Wien Klin Wochenschr 2008

PLOS ONE

Contribution of remote *M.tuberculosis* infection to tuberculosis disease: A 30-year population study

Judith R. Glynn[1], Palwasha Khan[1,2], Themba Mzembe[3,4], Lifted Sichali[3], Paul E. M. Fine[1], Amelia C. Crampin[1,3,5], Rein M. G. J. Houben[1,6]*

Table 2. Incidence rates of TB by induration size and time since TST.

	TST <5mm		
Time since TST	**TB**	**pyar**	**Rate/1000pyar (95% CI)**
< 2 years	4	82,582	0.048 (0.018–0.13)
2–9 years	40	174,592	0.23 (0.17–0.31)
10–19 years	40	68,690	0.58 (0.43–0.79)
≥ 20 years	43	40,769	1.05 (0.78–1.42)

	TST >17mm		
Time since TST	**TB**	**pyar**	**Rate/1000pyar (95% CI)**
< 2 years	22	7,826	2.81 (1.85–4.27)
2–9 years	36	20,177	1.78 (1.29–2.47)
10–19 years	18	12,402	1.45 (0.91–2.30)
≥ 20 years	7	5,921	1.18 (0.56–2.48)

Glynn JR. PLosOne 2023

PNAS RESEARCH ARTICLE | MICROBIOLOGY OPEN ACCESS

Reevaluating progression and pathways following *Mycobacterium tuberculosis* infection within the spectrum of tuberculosis

Katherine C. Horton[a,1,2], Alexandra S. Richards[a,1], Jon C. Emery[a], Hanif Esmail[b], and Rein M. G. J. Houben[a]

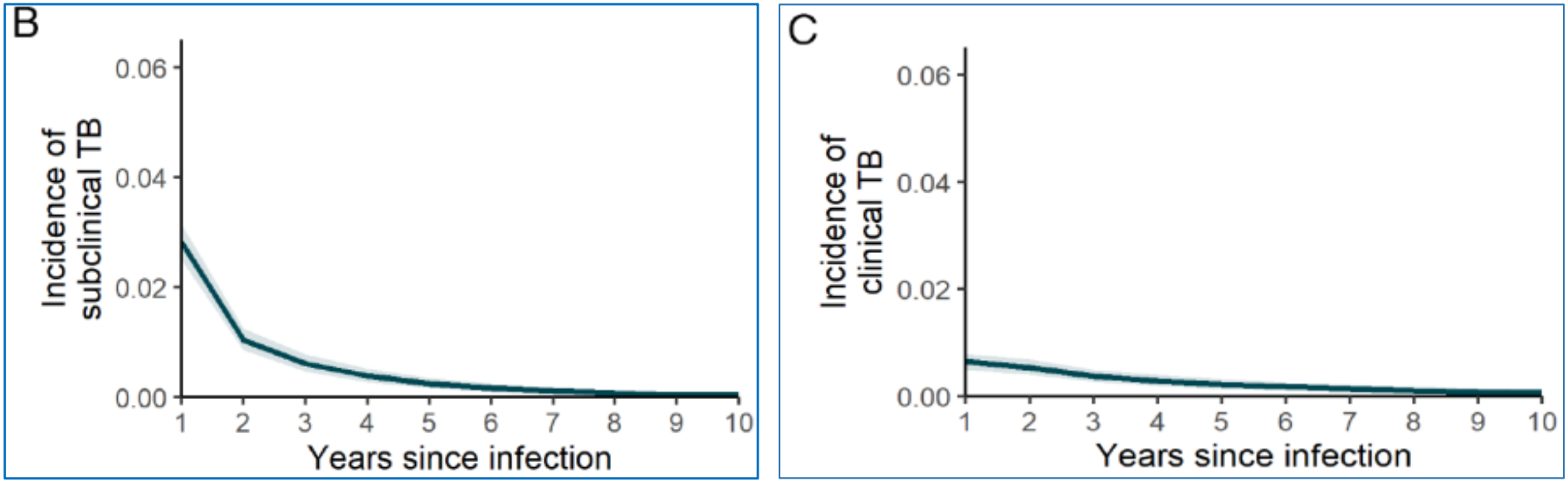


Fig. 3. Annual incidence for subclinical (*B*), and clinical (*C*) TB disease over a 10-y period following *Mtb* infection

Holron KC. Proc Natl Acad Sci USA 2023

Is *Mycobacterium tuberculosis* infection life long?

People with immunoreactivity to tuberculosis are thought to have lifelong asymptomatic infection and remain at risk for active tuberculosis. **Marcel A Behr and colleagues** argue that most of these people are no longer infected

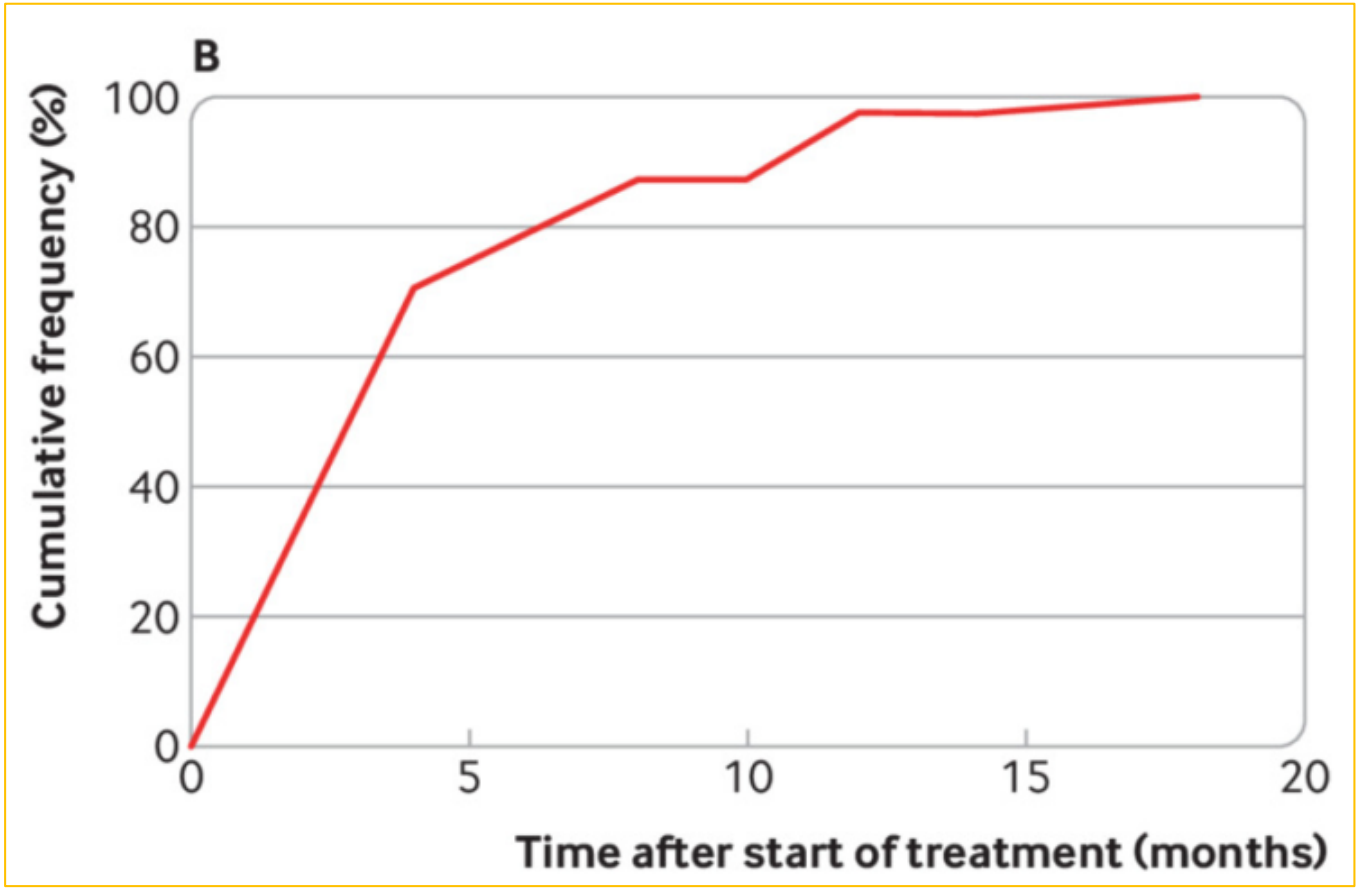


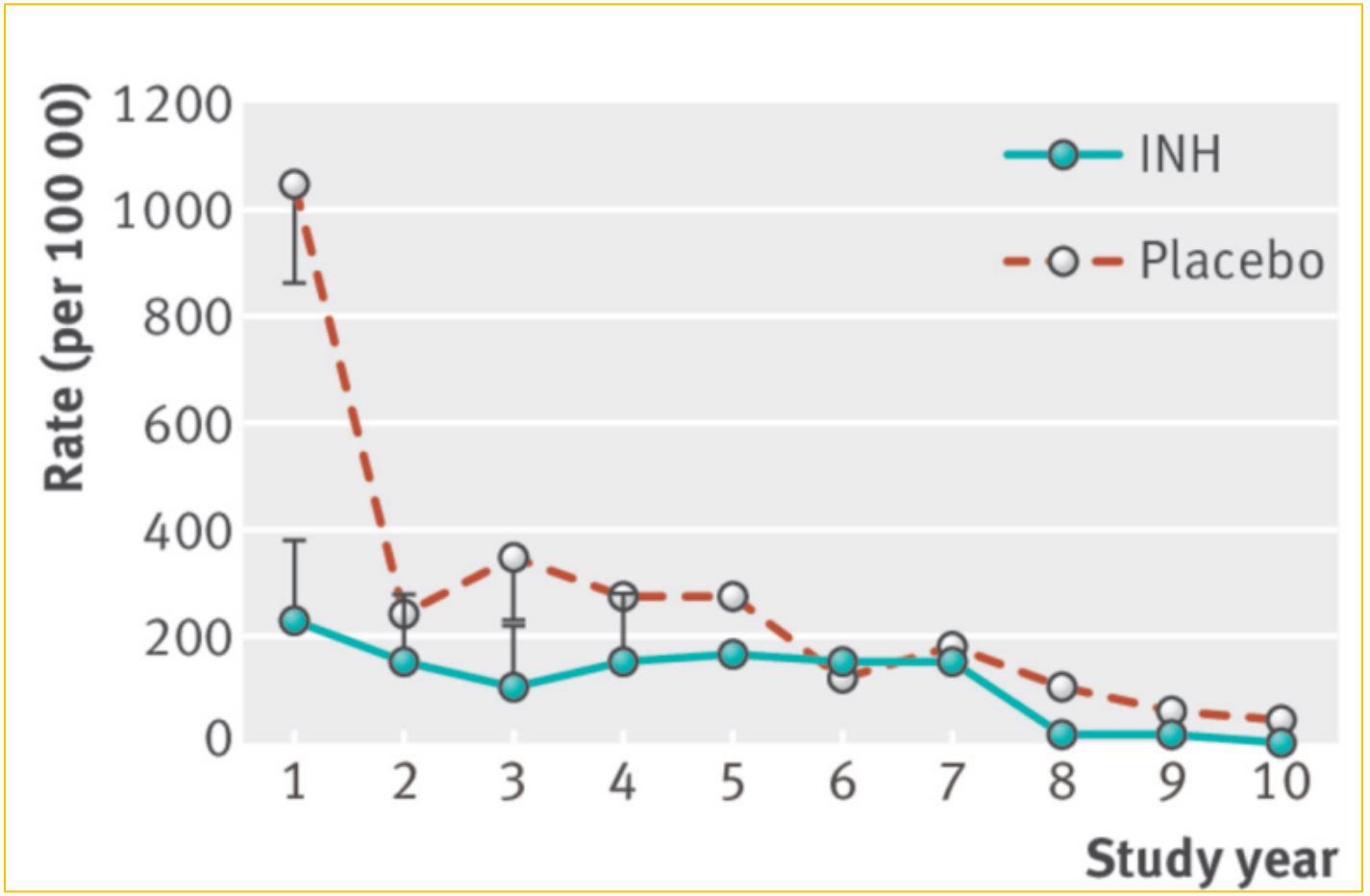
Fig 2-B. The cumulative frequency of TB development in infliximab treated patients versus the time to develop TB after starting infliximab

Behr M. BMJ 2019

Revisiting the timetable of tuberculosis

OPEN ACCESS

Tuberculosis has a much shorter incubation period than is widely thought, say **Marcel A Behr and colleagues**, and this has implications for prioritising research and public health strategies



Rates and incubation period of active TB in TST positive (induration ≥5 mm) household contacts of patients with recently diagnosed TB (Ferebee)

Behr M. BMJ 2018

¿cómo diagnosticamos la infección (latente) TB?

PT y/o IGRAs positivos sólo indican INMUNOREACCIÓN a antígenos de MTB

-**PT / IGRA positivos y sin embargo no hay infección**:

- Eliminación de MTB por la respuesta inmunitaria adquirida

- Eliminación de MTB tras tratamiento

- Infección por otras micobacterias (PT, tuberculina)

- Malos predictores de progresión a TB activa
  no distinguen " infección TB latente" de "infección TB incipiente"

- No distinguen TB inactiva de TB activa

- Informan indirectamente de infección TB.

TAG meeting outcome

1. Based on available data, **Beijing Wantai's TB-IGRA** and **QIAGEN QuantiFERON-TB Gold Plus** performance *is comparable* to that of WHO-recommended IGRAs for the detection of TB infection.
2. Based on available data, **QIAGEN** QIAreach QuantiFERON-TB, SD Biosensor Standard E TB-Feron ELISA and Oxford Immunotec T-SPOT.TB 8 with T-Cell Select *could not be adequately compared with* WHO-recommended IGRAs for detection of TB infection.
3. Current WHO recommendations for the use of IGRAs are also valid for **Beijing Wantai's TB-IGRA** and **QIAGEN QuantiFERON-TB Gold Plus**.

WHO. 2022

Sensitivity of C-Tb: a novel RD-1-specific skin test for the diagnosis of tuberculosis infection

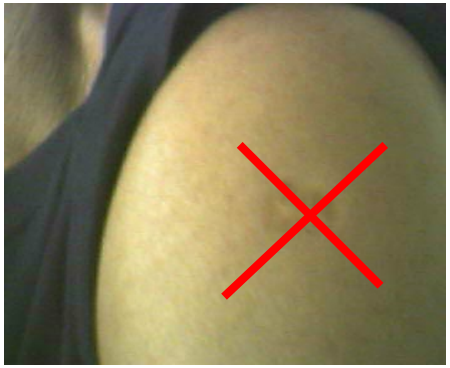
Soren T. Hoff[2], Jonathan G. Peter[1], Grant Theron[1], Mellissa Pascoe[1], Pernille N. Tingskov[3], Henrik Aggerbeck[3], Daniel Kolbus[3], Morten Ruhwald[2], Peter Andersen[2,4] and Keertan Dheda[1,4]

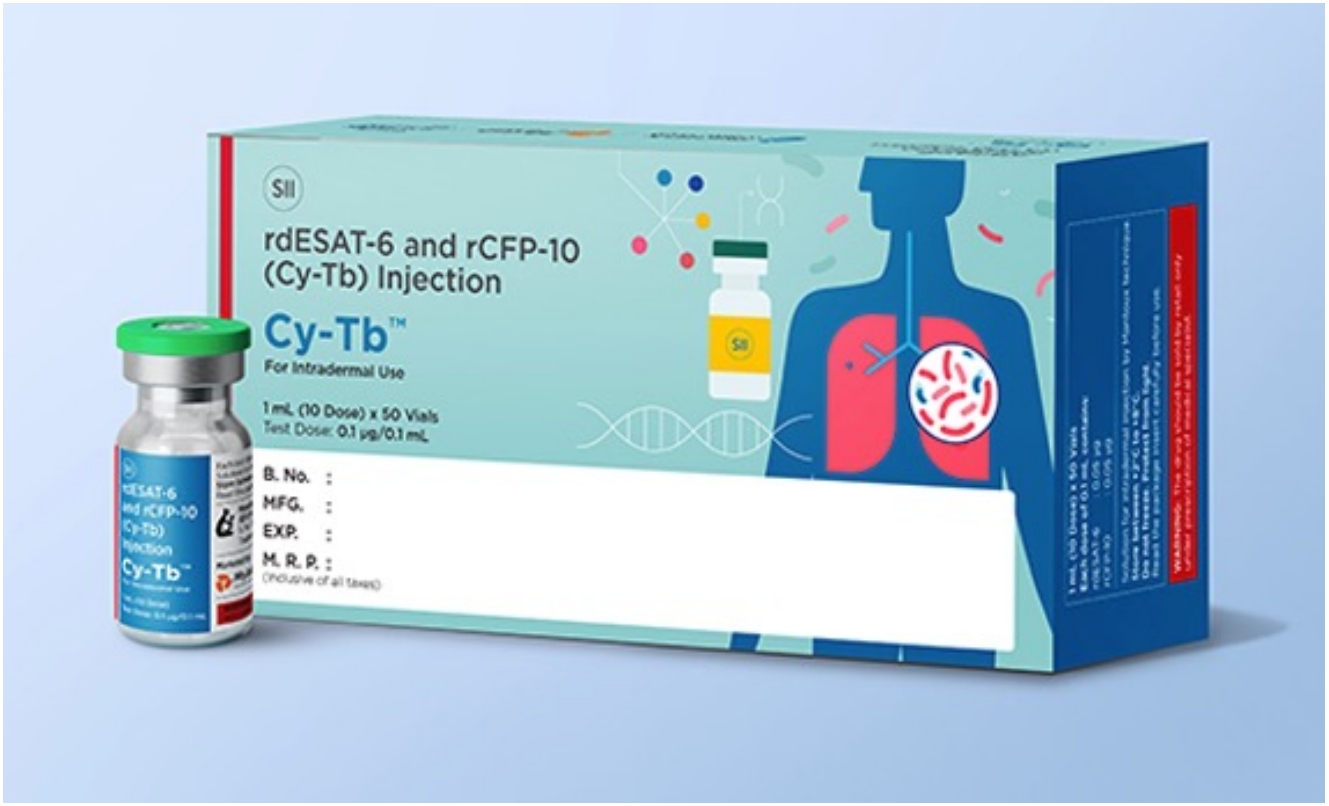
Safety and efficacy of the C-Tb skin test to diagnose *Mycobacterium tuberculosis* infection, compared with an interferon γ release assay and the tuberculin skin test: a phase 3, double-blind, randomised, controlled trial

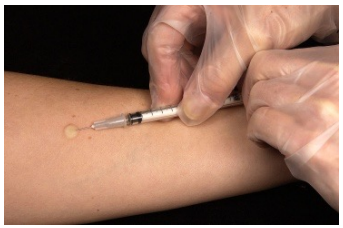
Morten Ruhwald, Henrik Aggerbeck, Rafael Vázquez Gallardo, Søren T Hoff, José I Villate, Bettine Borregaard, José A Martinez, Ingrid Kromann, Antón Penas, Luis L Anibarro, Maria Luiza de Souza-Galvão, Francisca Sánchez, Jose Ángel Rodrigo-Pendás, Antoni Noguera-Julian, Xavier Martínez-Lacasa, Maria Victoria Tuñez, Virginia Leiro Fernández, Joan P Millet, Antonio Moreno, Nazaret Cobos, José M Miró, Llanos Roldan, Angels Orcau, Peter Andersen, Joan A Caylá, the TESEC Working Group

Hoff ST. Eur Resp J 2016
Ruhwald M. Lancet Resp 2017

Cy-Tb®: tuberculina altamente específica (ags ESAT-6; CFP-10)







Hamada Y. Open Forum Infect Dis 2023

World Health Organization

Rapid communication: TB antigen-based skin tests for the diagnosis of TB infection

Overall conclusions

Overall, the new TBST class of tests were as sensitive as TST and IGRA, making them suitable alternatives. The specificity was similar to that of IGRA and better than that of TST, particularly in populations with prior BCG

· C-Tb (Serum Institute of India, India);
· C-TST (formerly known as ESAT6-CFP10 test, Anhui Zhifei Longcom, China); and
· Diaskintest (Generium, Russian Federation).

WHO. 2022

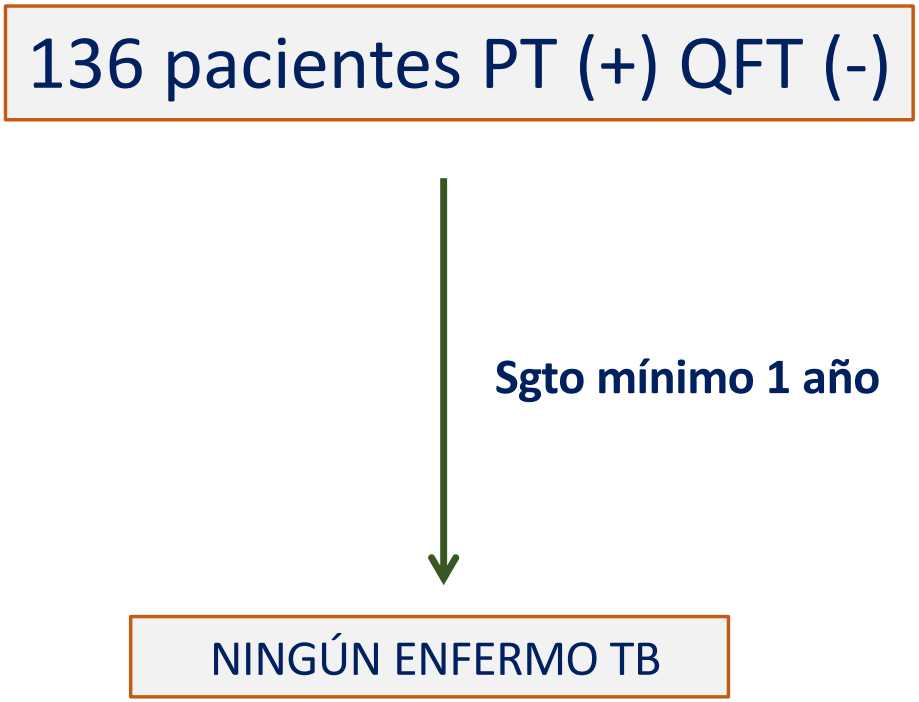
Interferon-γ release assays or tuberculin skin test for detection and management of latent tuberculosis infection: a systematic review and meta-analysis

Guozhong Zhou, Qingyi Luo, Shiqi Luo, Zhaowei Teng, Zhenhua Ji, Jiaru Yang, Feng Wang, Shiyuan Wen, Zhe Ding, Lianbao Li, Taigui Chen, Manzama-Esso Abi, Miaomiao Jian, Lisha Luo, Aihua Liu, Fukai Bao

	All studies (n=40)			
	Cohorts	Individuals	Result (95% CI)	I^2
NPV				
IFN-γ release assay	40	23 607	99·7% (99·5–99·8)	68%
Tuberculin skin test	28	19 638	99·3% (99·0–99·5)	65%
QFT	24	17 973	99·6% (99·4–99·8)	66%
T-SPOT.TB	16	10 825	99·8% (99·6–100)	69%
TST-10	18	17 459	99·2% (98·9–99·4)	51%
TST-5	15	6022	99·4% (98·7–99·8)	75%

Zhou G. Lancet Inf Dis 2020

¿Qué VPN tiene un IGRA negativo en antiTNF?



Muñoz L. Clin Infect Dis 2015

Table 5. Tuberculosis Incidence Among Participants According to Baseline QuantiFERON and Tuberculin Skin Test Status

	Events, n	Observation Time, Person-years[a]	Rate Per 100 Thousand Person-years	95% Confidence Interval
All Participants	13	32 430	40.1	22.3–66.8
QuantiFERON Gold In-Tube				
Negative QFT	4	25 806	15.5	4.9–37.4
Positive QFT	9	6624	135.9	66.3–249.3
Tuberculin skin tests				
Negative TST	5	20 172	24.8	9.1–54.9
Positive TST	8	12 258	65.3	30.3–123.9
Combination of both tests				
QFT and TST negative	4	18 438	21.7	6.9–52.3
TST positive, QFT negative	0	7368	0	
TST negative, QFT positive	1	1734	57.7	28.9–284.4
QFT and TST positive	8	4890	163.6	76.0–310.7

Seguimiento: 7386 personas /año

QFT was substantially more predictive of progression to active TB than the TST

Lu P. Clin Infect Dis 2021

Interferon-γ release assays or tuberculin skin test for detection and management of latent tuberculosis infection: a systematic review and meta-analysis

Guozhong Zhou, Qingyi Luo, Shiqi Luo, Zhaowei Teng, Zhenhua Ji, Jiaru Yang, Feng Wang, Shiyuan Wen, Zhe Ding, Lianbao Li, Taigui Chen, Manzama-Esso Abi, Miaomiao Jian, Lisha Luo, Aihua Liu, Fukai Bao

Pooled RR for rates of disease progression (untreated)

· IGRA (pos vs neg): 9,35

· TST: (pos vs neg): 4,24

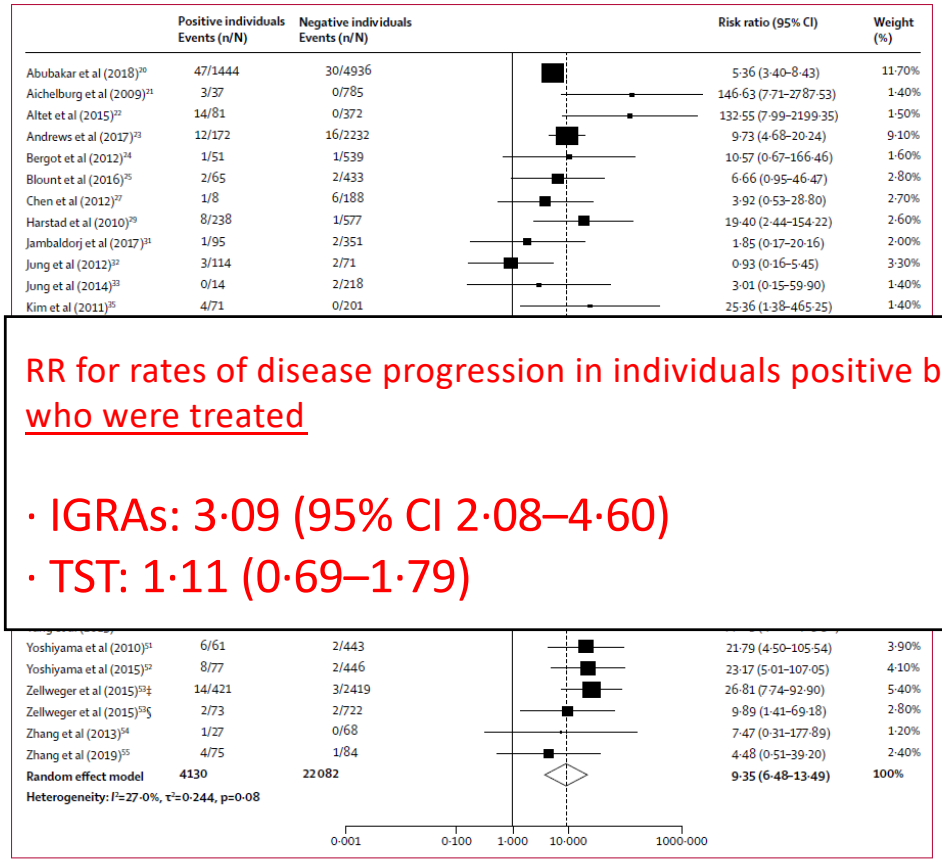


Figure 2: Forest plot of the risk ratio for rates of disease progression in untreated individuals who were positive versus negative by IFN-γ release assay

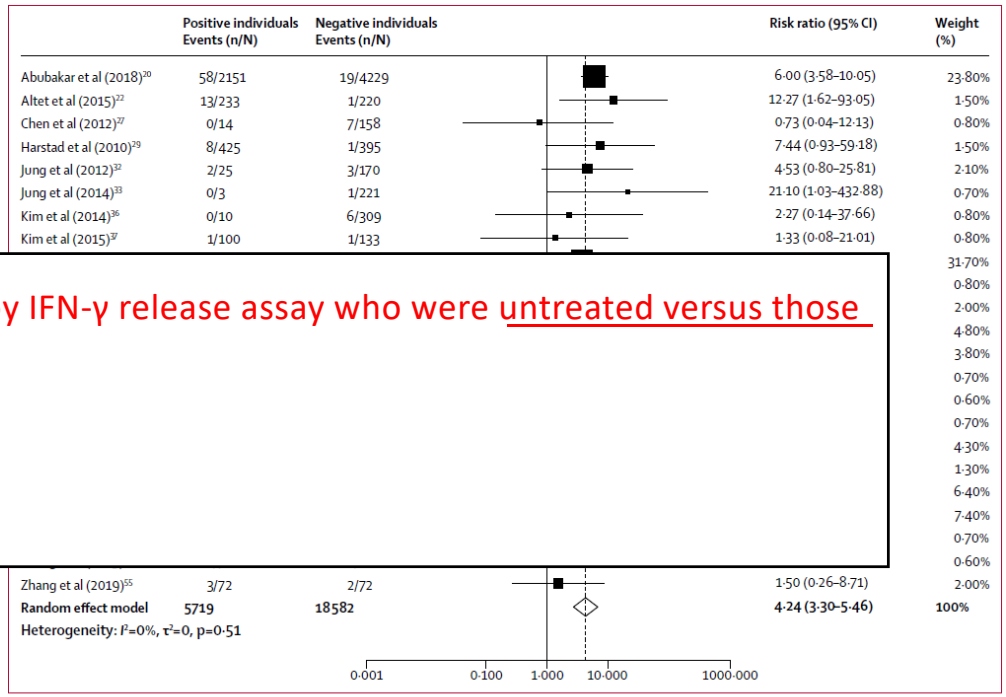


Figure 3: Forest plot of the risk ratio for rates of disease progression in untreated individuals who were positive versus negative by tuberculin skin test

RR for rates of disease progression in individuals positive by IFN-γ release assay who were untreated versus those who were treated

· IGRAs: 3·09 (95% CI 2·08–4·60)

· TST: 1·11 (0·69–1·79)

Interpretation: IFN-γ release assays have a better predictive ability than tuberculin skin tests. Individuals who are positive by IFN-γ release assay might benefit from preventive treatment, but those who are positive by tuberculin skin test probably will not.

Zhou G. Lancet Inf Dis 2020

Enfermedades Infecciosas y Microbiología Clínica
www.elsevier.es/eimc

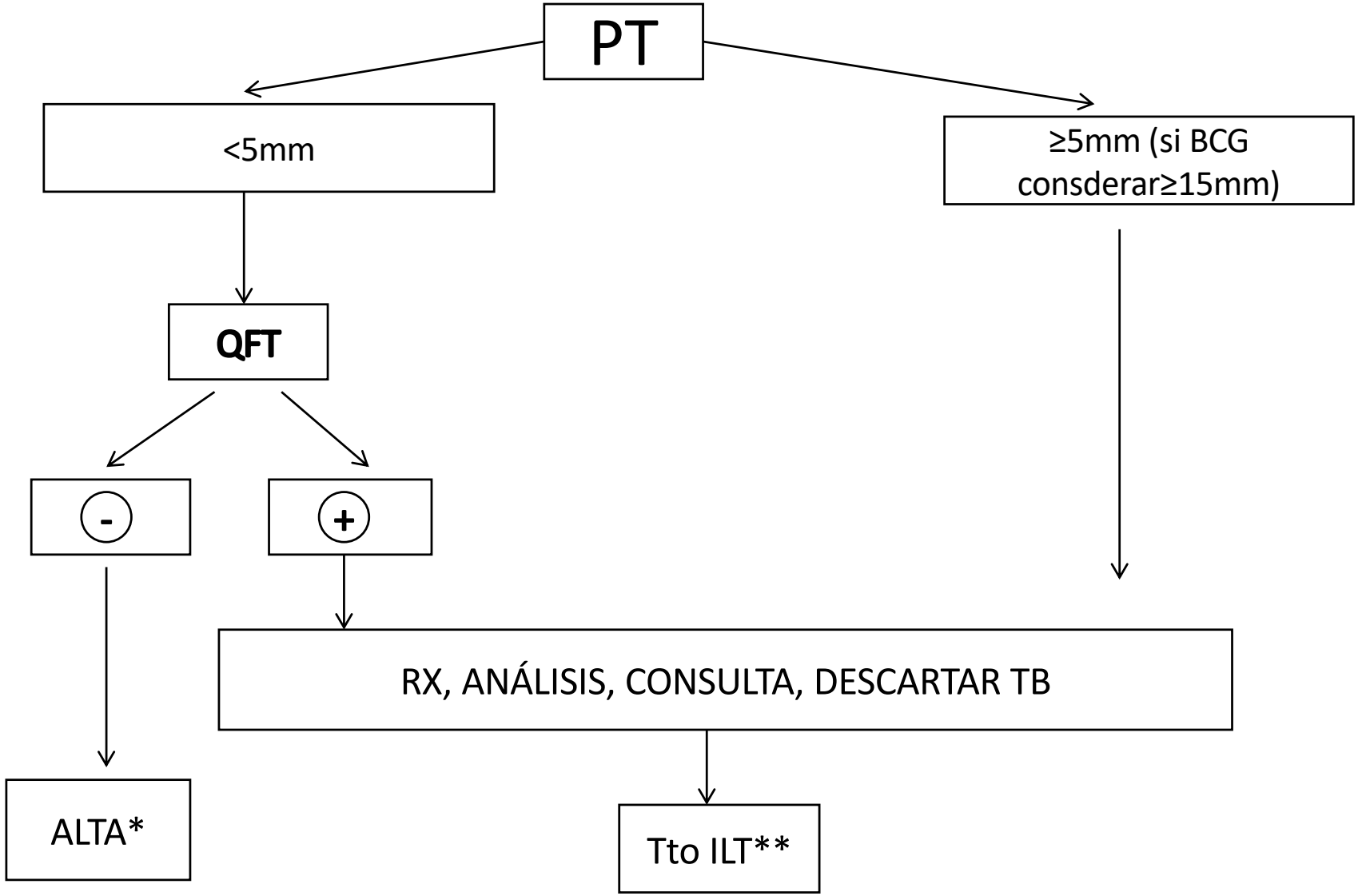
Sociedad Española de Neumología y Cirugía Torácica SEPAR
ARCHIVOS DE Bronconeumología
www.archbronconeumol.org

Consensus statement

Executive summary of the guidelines for the use of interferon-γ release assays in the diagnosis of tuberculosis infection☆,☆☆

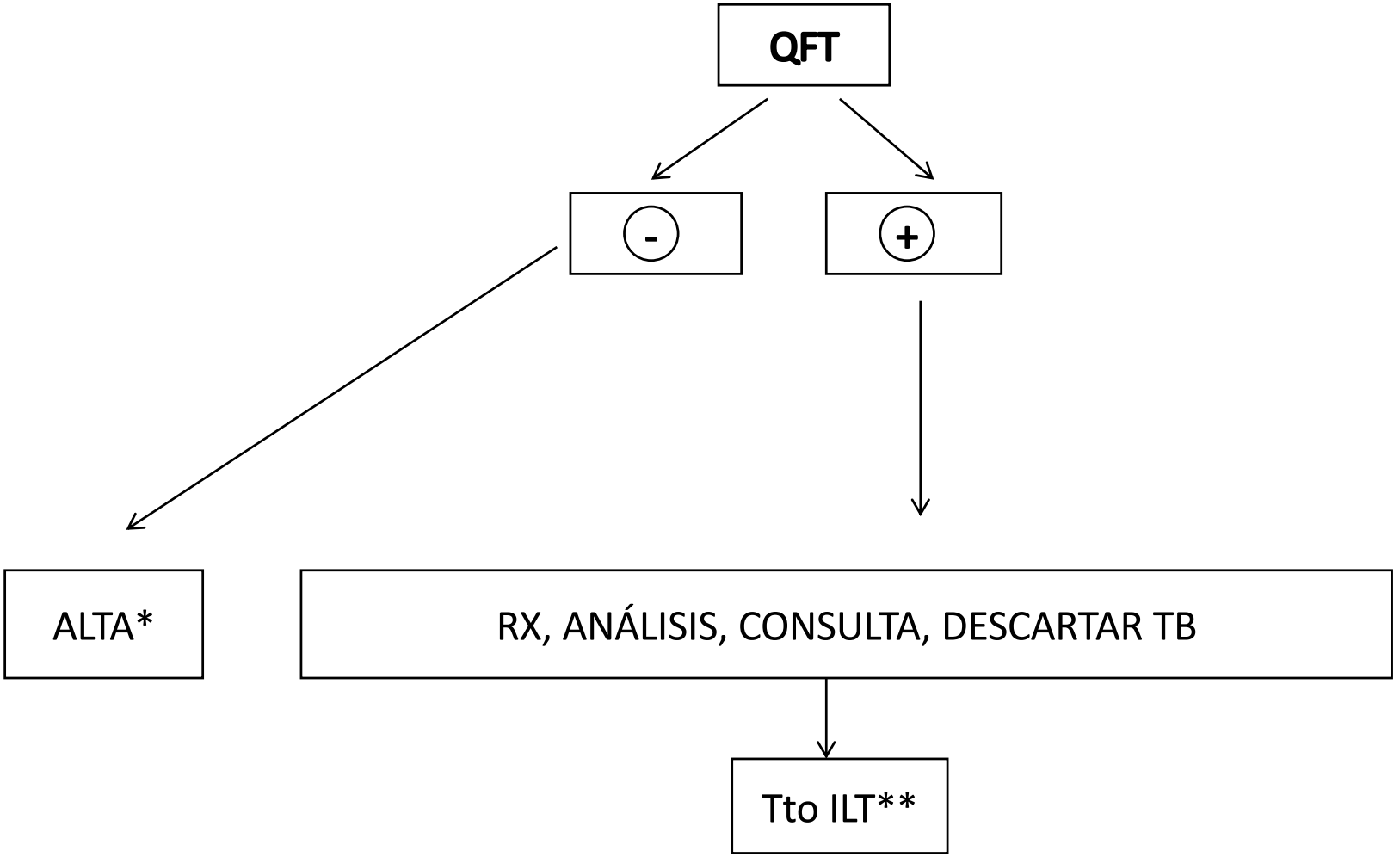
Miguel Santin,[a,b] José-María García-García,[c] David Rigau,[d] Neus Altet,[e] Luis Anibarro,[f] Irma Casas,[g,h] Nuria Díez,[i] Mercedes García-Gasalla,[j] Xavier Martínez-Lacasa,[k] Antón Penas,[l] Elvira Pérez-Escolano,[m] Francisca Sánchez,[n] José Domínguez[o,*], Panel of experts from the Mycobacteria Study Group (GEIM) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) and the Spanish Society of Respiratory Diseases and Thoracic Surgery (SEPAR)

Documento de Consenso SEPAR- SEIMC.
Enf Infecc Microbiol Clin /Arch Bronconeumol 2016



*Repetir procedimiento en caso de exposición a TB o decisión definitiva de inicio de tratamiento antiTNF y haya transcurrido más de 1 año.

** En pacientes con indicación definitiva de tratamiento antiTNF. En el resto, valoración individualizada.



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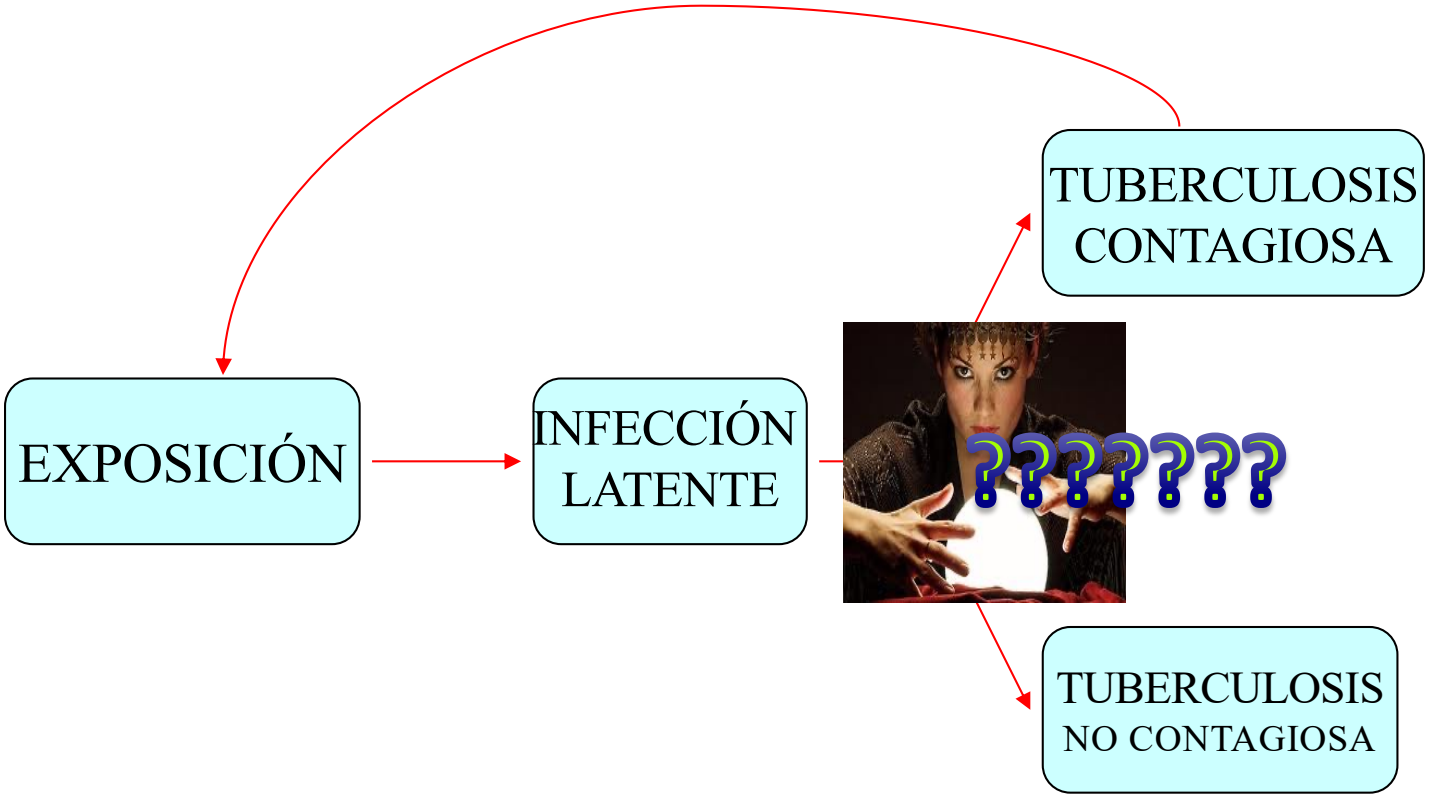
** En pacientes con indicación definitiva de tratamiento antiTNF. En el resto, valoración individualizada.

¿a quién recomendamos tto de la infección (latente) TB?

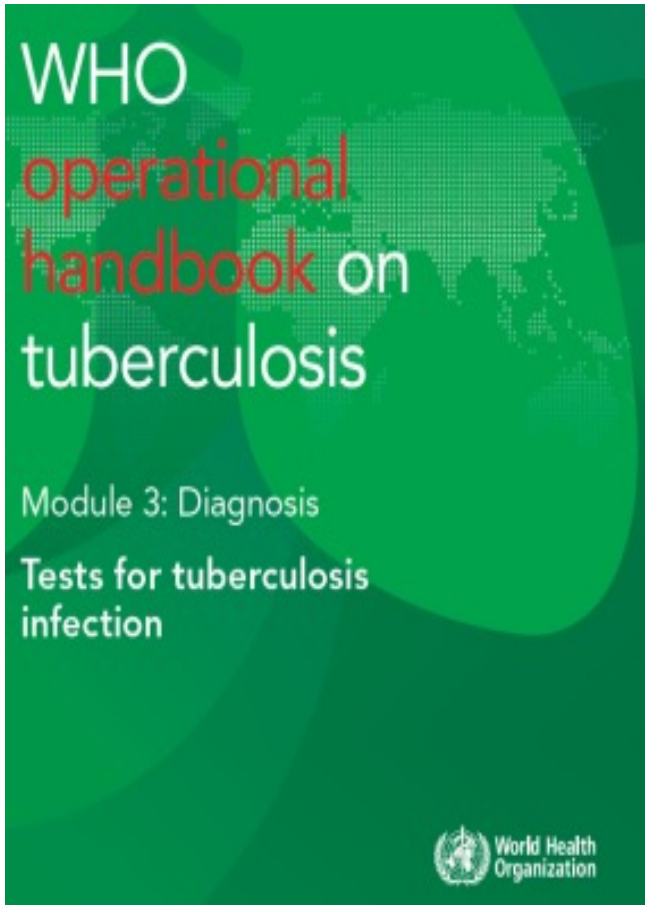
CADENA DE TRANSMISIÓN DE LA TB



Quién desarrollará TUBERCULOSIS??????

¿Quién está en mayor riesgo de desarrollar TUBERCULOSIS?

- Infección VIH
- Silicosis
- Insuficiencia Renal (diálisis)
- Desnutrición, bajo peso
- Gastrectomía
- Cáncer de cabeza y cuello
- Cáncer pulmón
- Neoplasias hematológicas
- Enfermedad celiaca
- Tratamiento con corticoides
- Tratamientos antiTNF
- Alcoholismo
- Diabetes
- Tabaquismo
- Edades extremas de la vida
- Trasplantes órganos sólidos / hematológicos
- Otros tratamientos inmunusupresores
- Contacto con TB pulmonar
- Lesiones cicatriciales Rx
- Trabajadores sanitarios
- Presos
- Inmigrantes de países de alta prevalencia
- UDVP
- Sin techo



World Health Organization 2022

INDICACIONES DE TTO DE ILT

- VIH
- Contactos con TB pulmonar
- anti-TNF
- Insuficiencia Renal terminal
- Candidatos a trasplante
- Silicosis

Indicaciones condicionadas de tto de ILT

- Sanitarios
- Inmigrantes (países alta prevalencia)
- Presos
- Sin techo
- Usuarios de drogas

¿Quién está en mayor riesgo de desarrollar TUBERCULOSIS?

- **Infección VIH**
- **Silicosis**
- **Insuficiencia Renal (diálisis)**
- Desnutrición, bajo peso
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- Trabajadores sanitarios
- Presos
- Inmigrantes de países de alta prevalencia
- UDVP
- Sin techo

Clinical Infectious Diseases
MAJOR ARTICLE

Joint Associations of Multiple Lifestyle Factors With Risk of Active Tuberculosis in the Population: The Singapore Chinese Health Study

Huiqi Li,[1] Cynthia B. E. Chee,[2] Tingting Geng,[1] An Pan,[1,3,a] and Woon-Puay Koh[4,5,a]

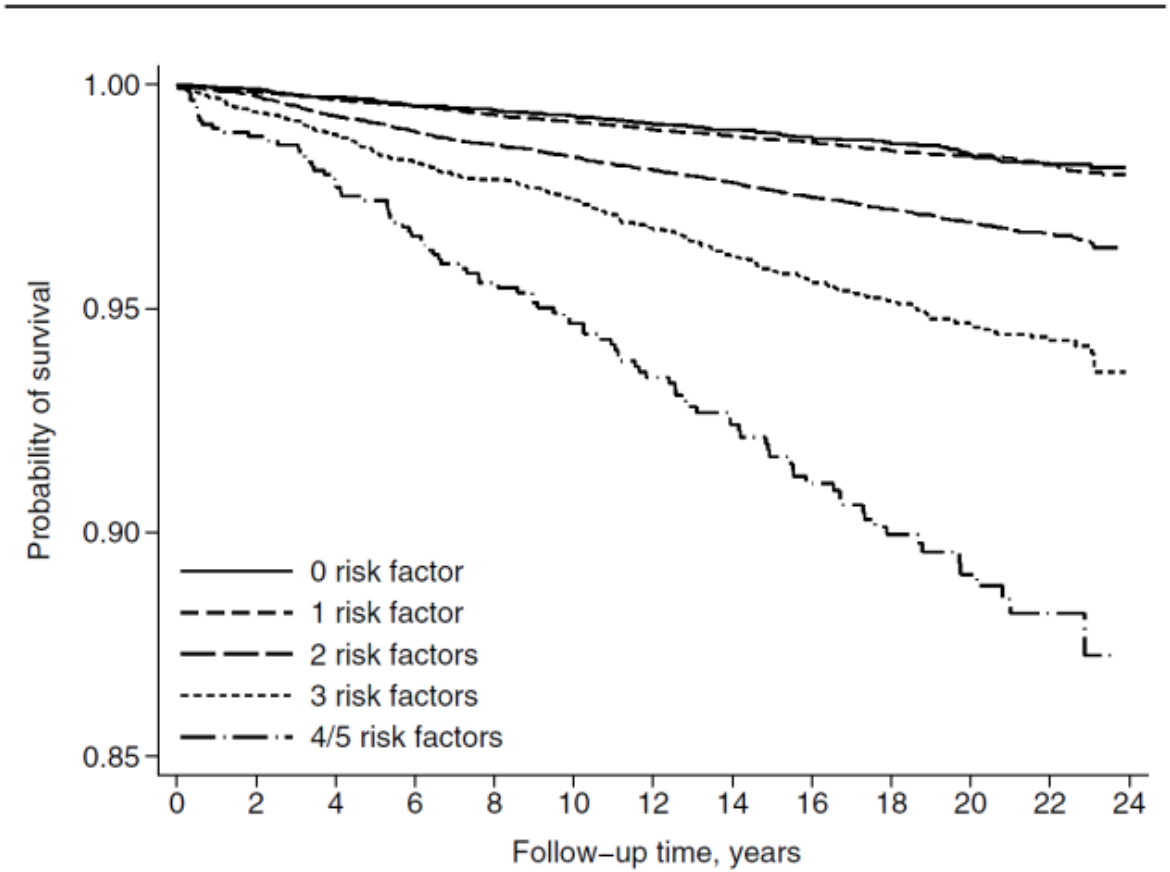


Figure 1. Kaplan-Meier survival curves for active tuberculosis stratified by the number of risk factors at baseline.

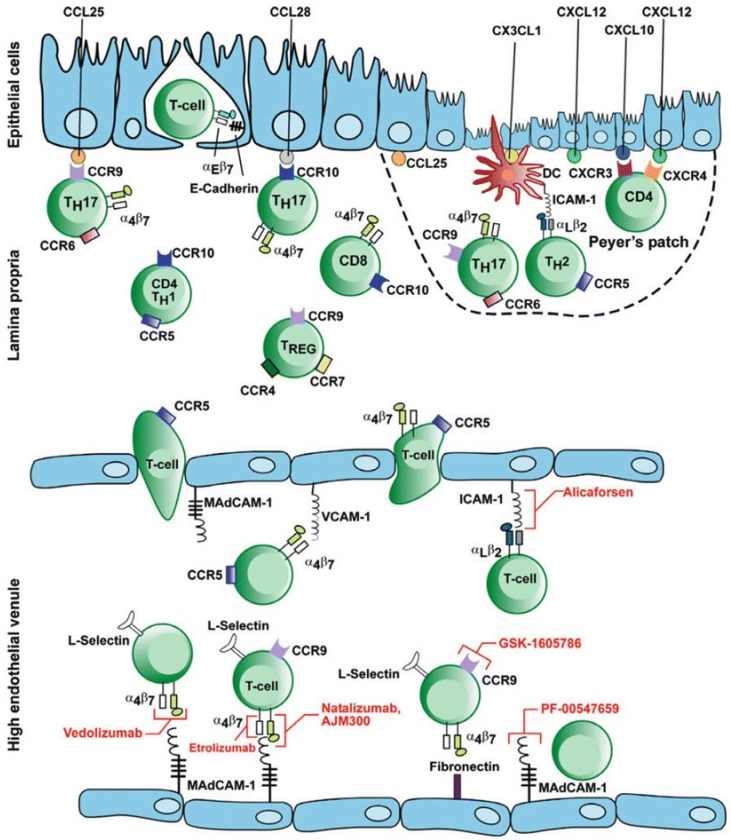
- Tabaquismo
- IMC bajo
- Sedentarimso
- Enolismo
- Dieta no saludable

Li H. Clin Infect Dis 2022

¿recomendamos tto de la infección (latente) TB en biológicos no-antiTNF?

VEDOLIZUMAB

- **Inhibe migración linfocitaria. Anti-alpha-4-beta-7 integrina.**
- **Alta afinidad en el sistema digestivo**



Litchtenstein GR. Medical Therapy of Ulcerative Colitis. Springer Ed.

¿qué nos dicen las fichas técnicas?

USTEKINUMAB, Sterala®

STELARA no debe ser administrado a pacientes con tuberculosis activa (ver sección 4.3). Se iniciará el tratamiento de la tuberculosis latente antes de administrar STELARA. También se debe considerar

VEDOLIZUMAB, Entyvio®

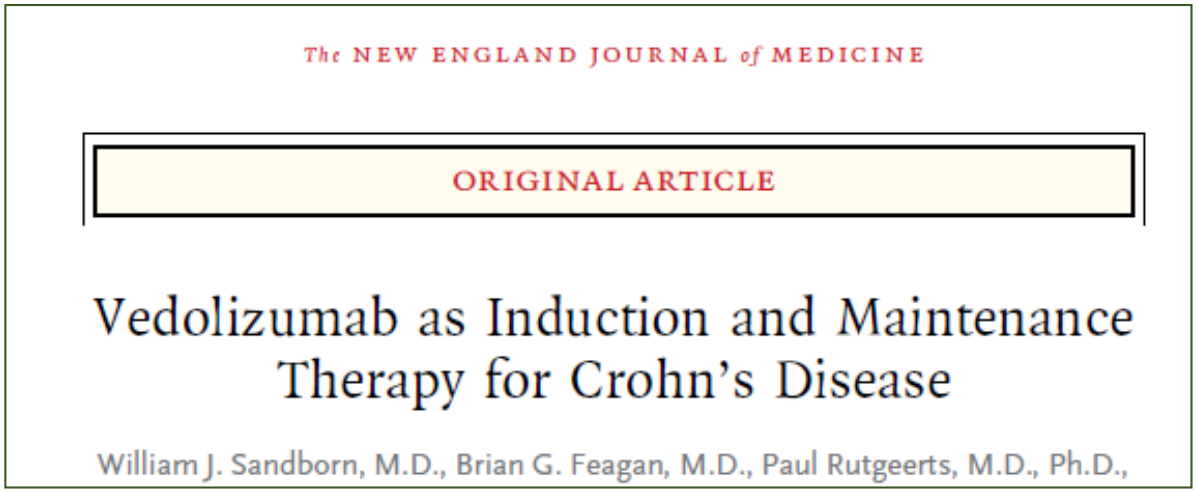
contraindicado en pacientes con tuberculosis activa (ver sección 4.3). Antes de iniciar el tratamiento con vedolizumab, se deben realizar pruebas de tuberculosis en los pacientes de acuerdo con la práctica local. Si se diagnostica una tuberculosis latente, se debe iniciar un tratamiento antituberculoso

TOFACITINIB, Xeljanz®

Se debe tratar a los pacientes con tuberculosis latente, con análisis positivo, con un tratamiento antimicobacteriano estándar antes de administrar tofacitinib.

VEDOLIZUMAB

- Inhibe migración linfocitaria. Anti-alpha-4-beta-7 integrina.
- Alta afinidad en el sistema digestivo



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease

William J. Sandborn, M.D., Brian G. Feagan, M.D., Paul Rutgeerts, M.D., Ph.D.,

tion, intestinal stricture, abdominal abscess, active or latent tuberculosis, or cancer were excluded.

Sandborn WJ, NEJM, 2013

Conclusiones

✓ **La infección TB es un espectro continuo que abarca desde la infección latente con muy escaso riesgo de progresión, hasta la enfermedad activa. Son situaciones reversibles y nunca definitivos sin tto.**

✓ **En la práctica diaria, todavía debemos considerar la "dictomía" infección latente vs TB activa**

✓ **El diagnóstico de infección latente es siempre de presunción. No distingue infección de enfermedad y su valor predictivo de desarrollo de enfermedad es muy bajo. Sin embargo, el valor predictivo negativo es próximo al 100% en situaciones de inmunidad preservada.**

✓**Existen 6 situaciones de indicación de tratamiento de infección tuberculosa. En otras situaciones también de riesgo de progresión a TB activa, debe haber valoración individualizada**

¡Muchas gracias!

SERVIZO GALEGO de SAÚDE | Xestión Integrada Pontevedra e O Salnés

Fundación Biomédica Galicia Sur

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