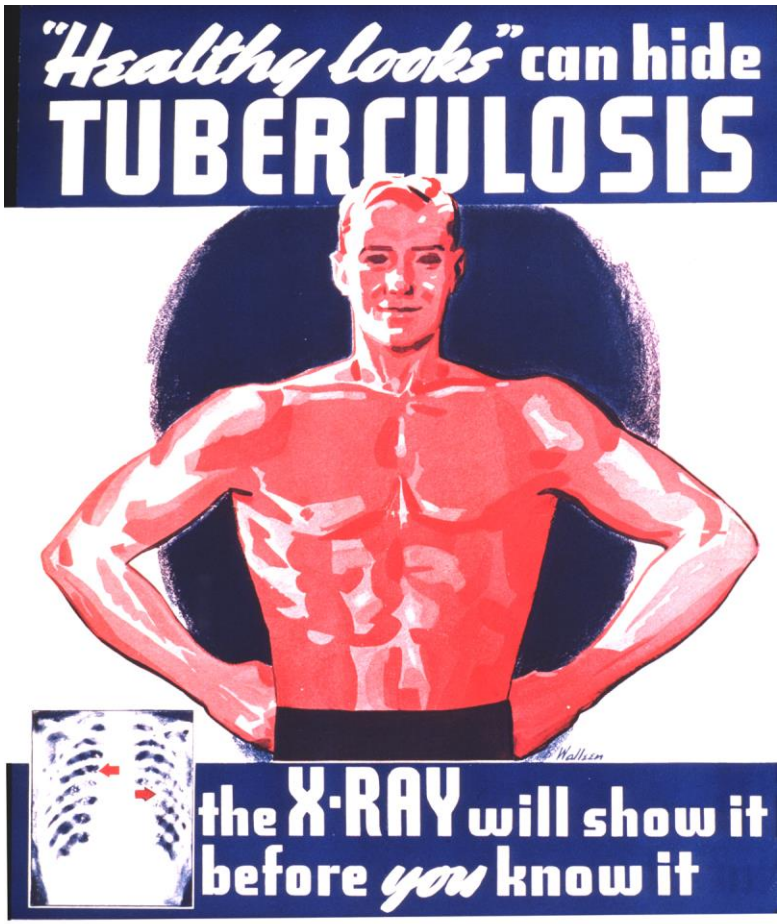


Tuberculosis in Pediatrics

13 June 2017

Tony Moody MD
Duke Pediatric Infectious Diseases

Image from the National Library of Medicine, “Profiles in Science” Collection.

Disclosures

- Advisory board member for GSK (for belimumab pregnancy registry).
- Co-founder of Grid Therapeutics (formerly Cue Biologics).
- Chief Medical Officer, DHVI.

Learning Objectives

- Choose appropriate diagnostic tests for suspected MTB disease.
- Apply proper techniques for application and reading of TSTs.
- Compare the utility of TSTs, IGRAs, and other tests.
- Use proper dosing of anti-tuberculosis drugs in pediatric patients.

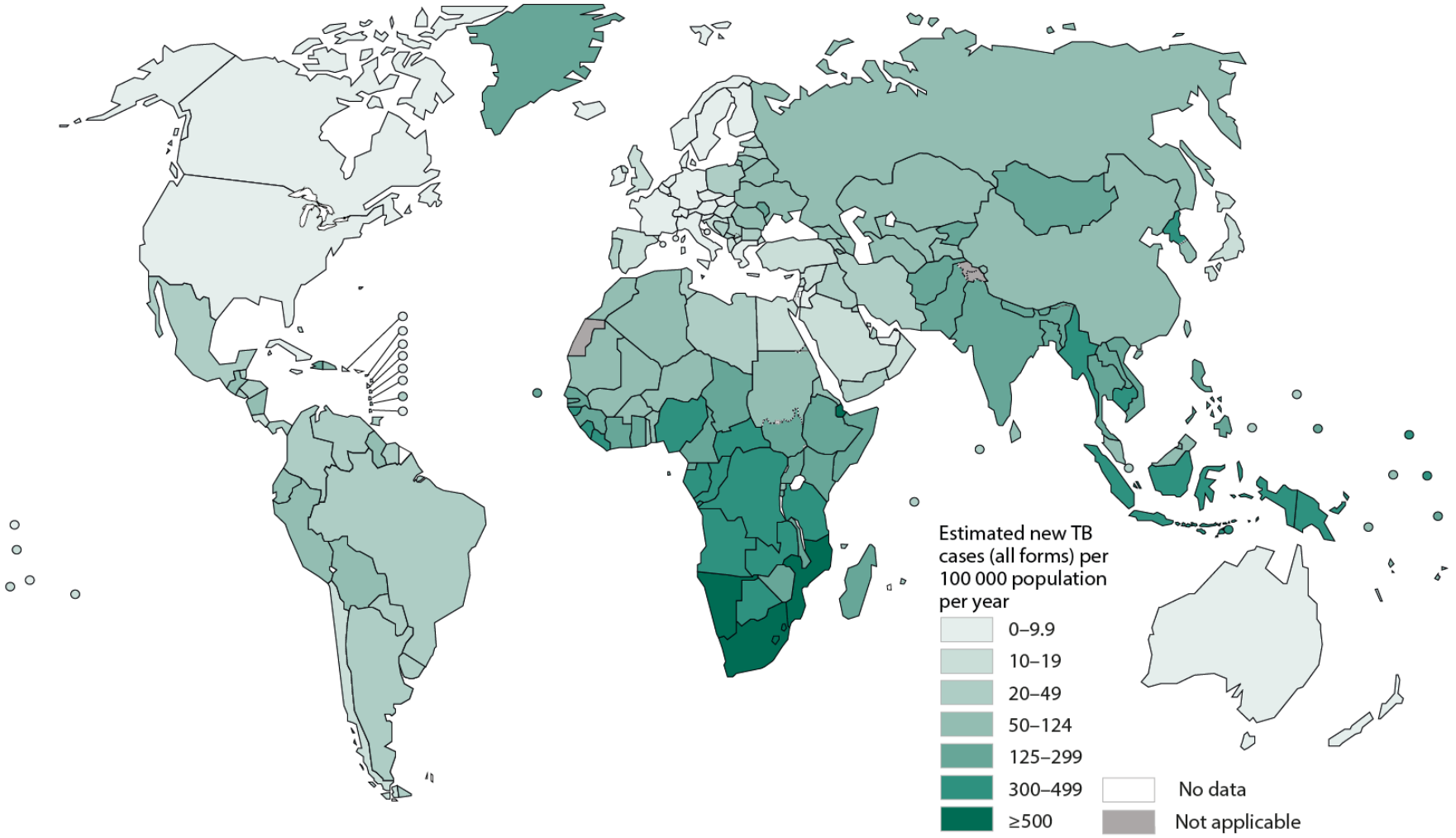
Image from the National Library of Medicine, “Profiles in Science” Collection.

Tuberculosis

first disease declared
Global Health Emergency
by WHO (1993)

estimated ⅓ of humans infected

Estimated TB incidence rates, 2014



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: *Global Tuberculosis Report 2015*. WHO, 2015.

World Health Organization

Image courtesy of the World Health Organization Global Health Observatory Map Gallery

Global distribution of estimated TB incidence by rate and absolute number, 2014. The size of each bubble is proportional to the size of the country's population. High-burden countries are shown in red.

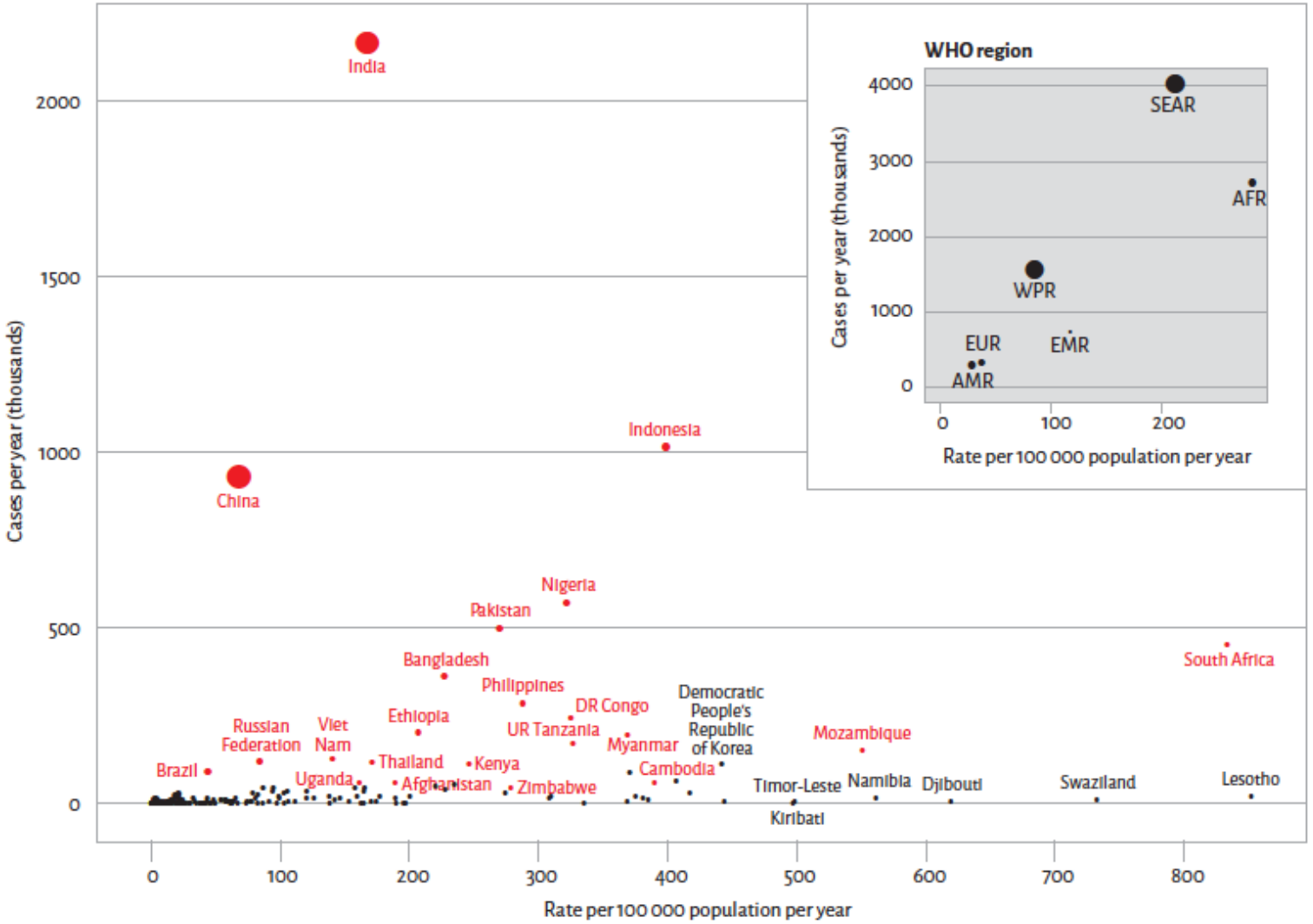
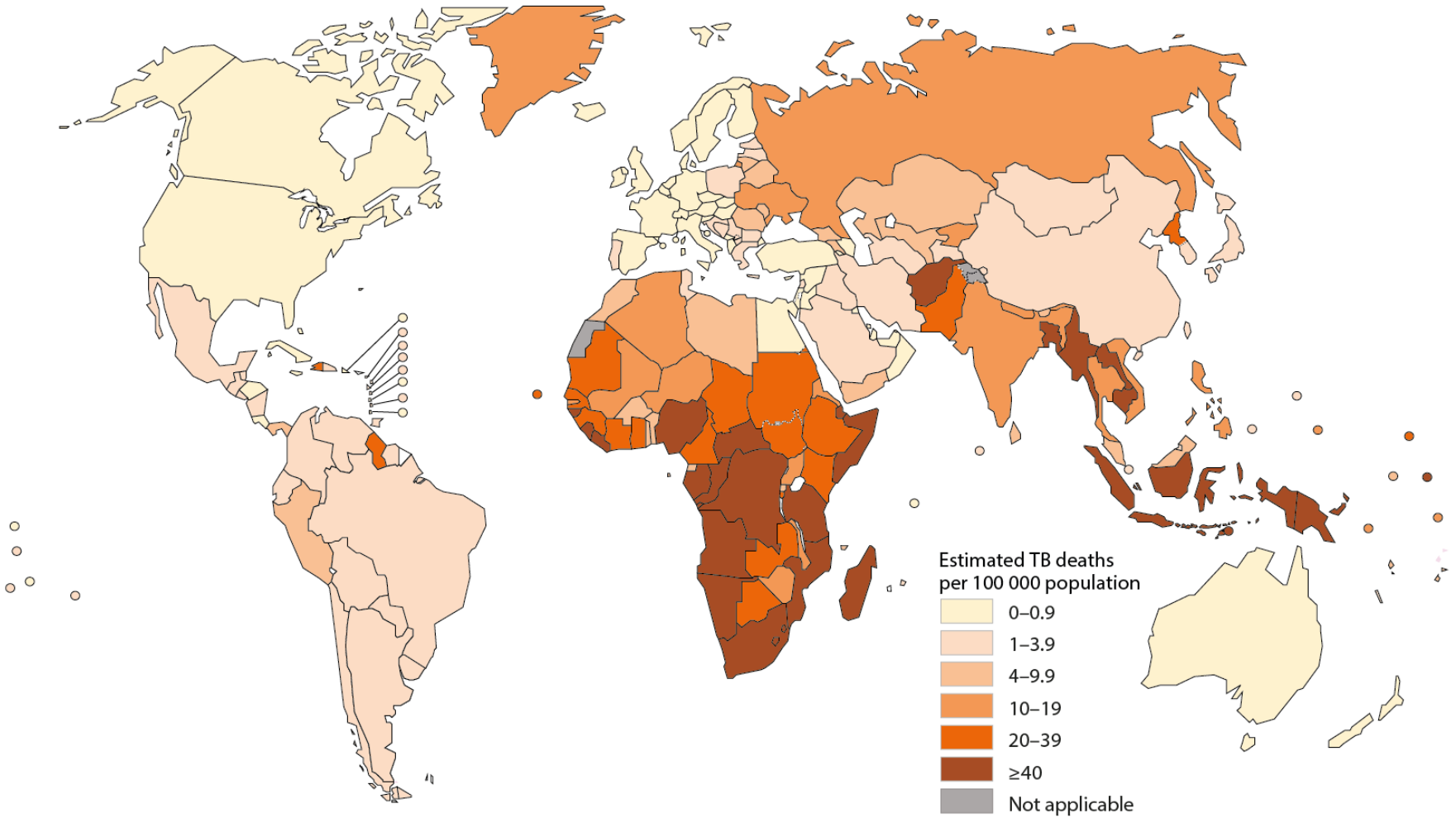


Image taken from the World Health Organization Global Tuberculosis Report 2015

Estimated TB mortality rates excluding TB deaths among HIV–positive people, 2014



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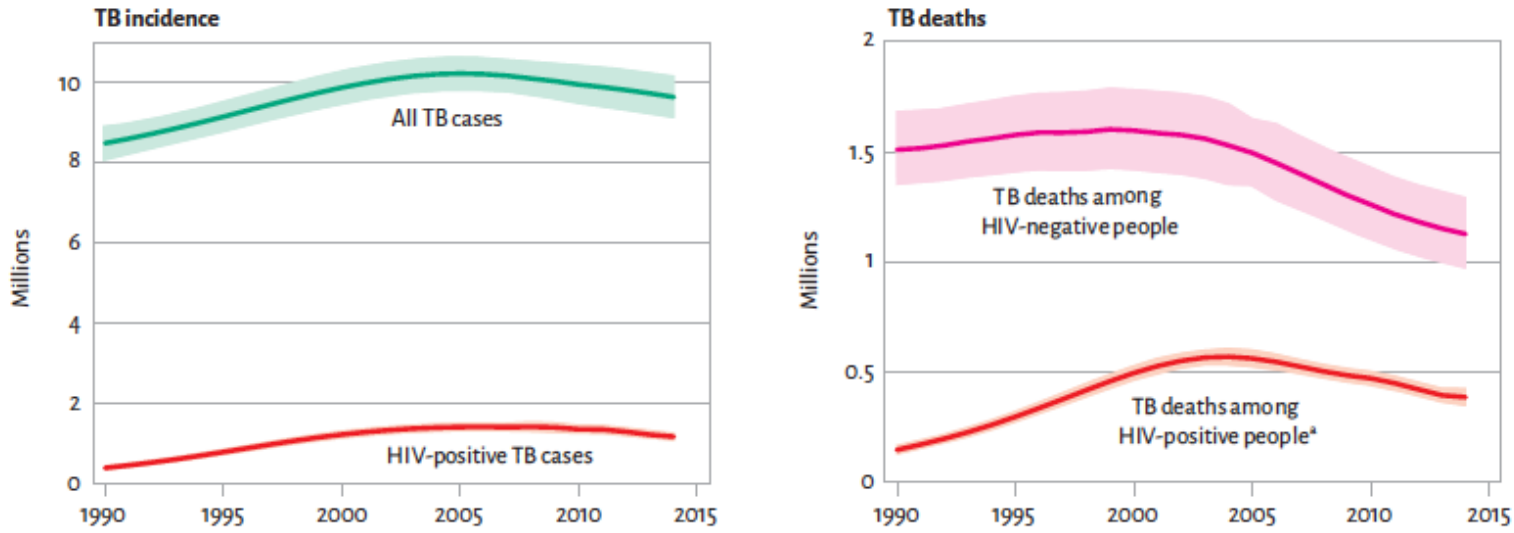
Data Source: *Global Tuberculosis Report 2015*. WHO, 2015.

World Health Organization

Image courtesy of the World Health Organization Global Health Observatory Map Gallery

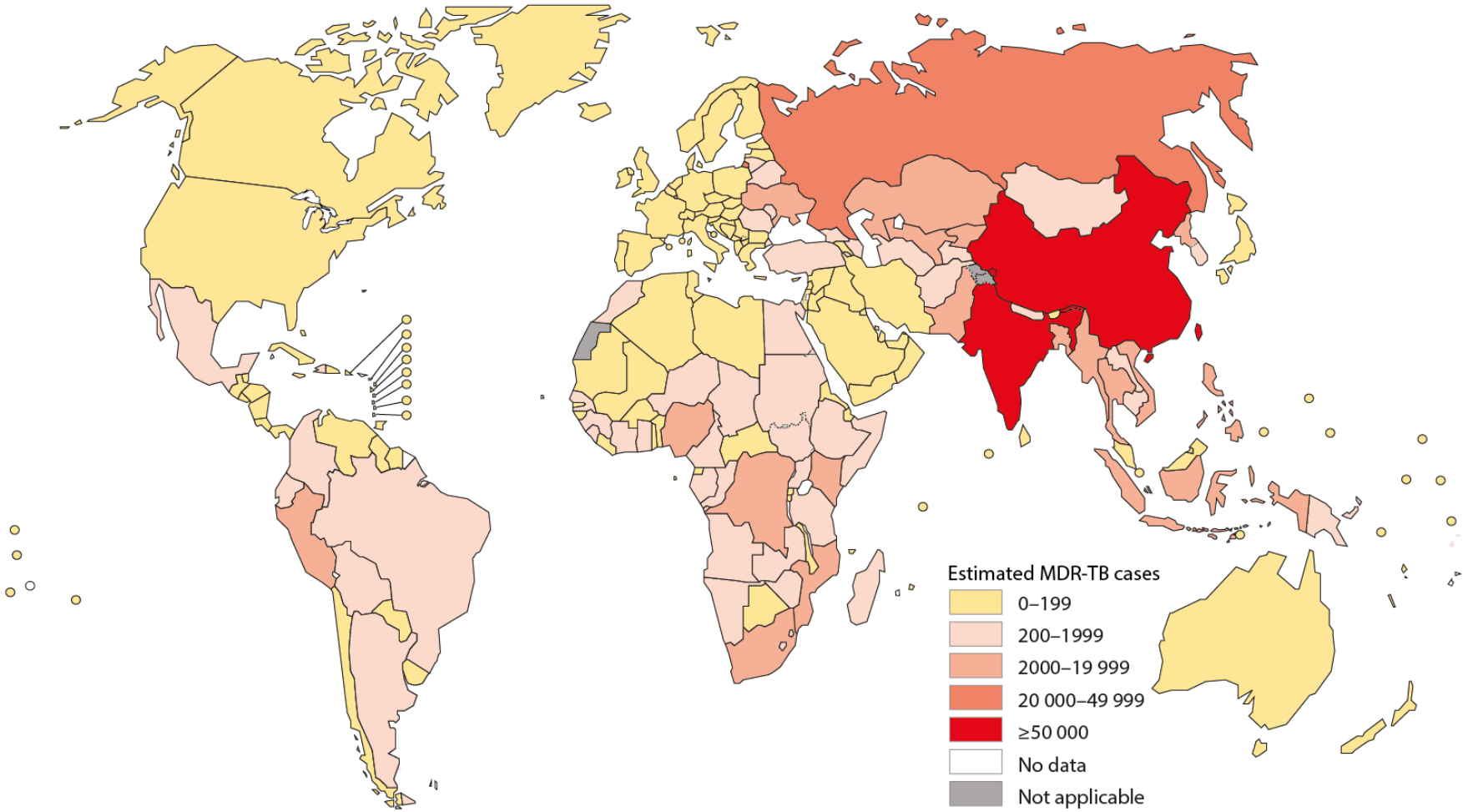
Estimated absolute numbers of TB cases and deaths (in millions per year), 1990–2014



[a] HIV-associated deaths are classified as HIV deaths according to ICD-10.

Image taken from the World Health Organization Global Tuberculosis Report 2015

Number of multidrug-resistant tuberculosis cases estimated to occur among notified pulmonary TB cases, 2014



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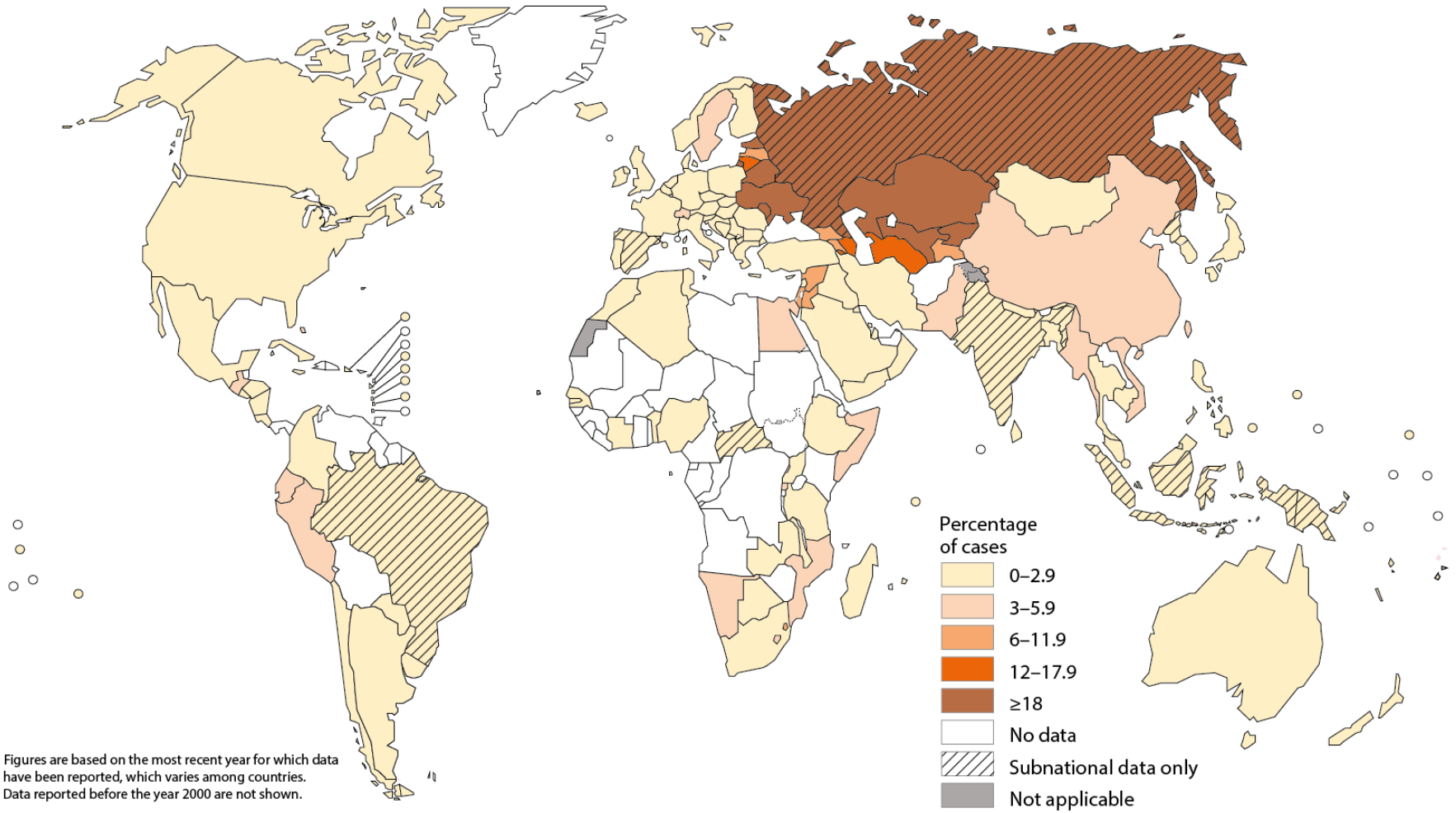
Data Source: *Global Tuberculosis Report 2015*. WHO, 2015.

World Health Organization

Image courtesy of the World Health Organization Global Health Observatory Map Gallery

Percentage of new TB cases with multidrug-resistant tuberculosis[a]



a Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before the year 2000 are not shown.

Data Source: *Global Tuberculosis Report 2015*. WHO, 2015.

World Health Organization

Image courtesy of the World Health Organization Global Health Observatory Map Gallery

Tuberculosis

tuberculosis *n*

disease caused by

MTB complex organisms

derived from

the Latin *tuberculum* (swelling) +

the Greek -*ωσις* (condition)

Image courtesy of
the Clendening History of Medicine Library,
University of Kansas Medical Center

Identification of *Mycobacterium* DNA in an Egyptian Pott's disease of 5 400 years old.

Crubézy É, Ludes B, Poveda J-D, Clayton J, Crouau-Roy B, Montagnon D.
C R Acad Sci Paris, Life Sciences **321:** 941-951 (1998).

Tuberculosis

consumption
wasting illness

Pott's disease
spinal osteomyelitis

King's evil
scrofula / lymphadenitis

By the King.

A Proclamation concerning *The Kings Euill.*

WHereas such people as repaire to His Maiestie for healing of THE KINGS EVILL, haue in former times forborne to approch or offer themselues to the former Kings of this Realme, during the Summer time, in respect of danger, and inconuenience, which order hath bene of late neglected, and such people vseth to repaire indifferently at all times: Therefore his Maiestie doeth declare and forbid, That hereafter no such person make their repaire vp for healing, betweene the Feasts of Easter and Michaelmas, for the which although it had bene enough for his Maiestie to haue signified his pleasure for recontinuing the said order vnto the Clearke of his Closet, or his Chirurgions in that behalfe; yet his Maiestie doubting that some such weake and infirme persons may come vp from remote parts, and thereby lose their trauaile, is pleased out of his goodnesse, to publish this Order by his Highnesse Proclamation.

Giuen at White-hall the xxv. day of March, in the foureteenth yeere of Our Reigne of Great Britaine, France and Ireland, And of Scotland the nine and fourtieth.

God saue the King.

Imprinted at London by Robert Barker, Printer to the Kings most Excellent Maiestie.

ANNO DOM. 1616.

Images courtesy of the Clendening History of Medicine Library, University of Kansas Medical Center

Tuberculosis: Etiology?

cause

- hereditary

- punishment for sin
- bad air
- vampires

Tuberculosis: Etiology?

cause	**cure**
• hereditary	evolve / you're screwed
• punishment for sin	redemption
• bad air	move
• vampires	wooden stake

Tuberculosis Complex

Mycobacterium bovis

Mycobacterium canetti

Mycobacterium microti

Mycobacterium tuberculosis

Tuberculosis Complex

- fossils showing animal disease
- evidence of *M bovis* increase 8000-4000 BCE

Hieronymus Fracastorius (Girolamo Fracastoro) (1478-1553)

1546 treatise

De contagione et de contagiosis morbis et curatione

130 years before Leeuwenhoek first saw microorganisms

Image courtesy of the Clendening History of Medicine Library, University of Kansas Medical Center

Sylvius
(Franciscus de le Boe)

defined tubercules,
tuberculous cavities

Image courtesy of
the Clendening History of Medicine Library,
University of Kansas Medical Center

Heinrich Hermann Robert Koch (1843-1910)

1882: identified
M tuberculosis,
established MTB role in
cause of tuberculosis

Image courtesy of
the Clendening History of Medicine Library,
University of Kansas Medical Center

MTB

Aerobic

- non-spore-forming
- non-motile
- bacillus

On Gram stain, weakly GP or ghosts

MTB

Mycolic acids

very long chain fatty acids

waxy surface

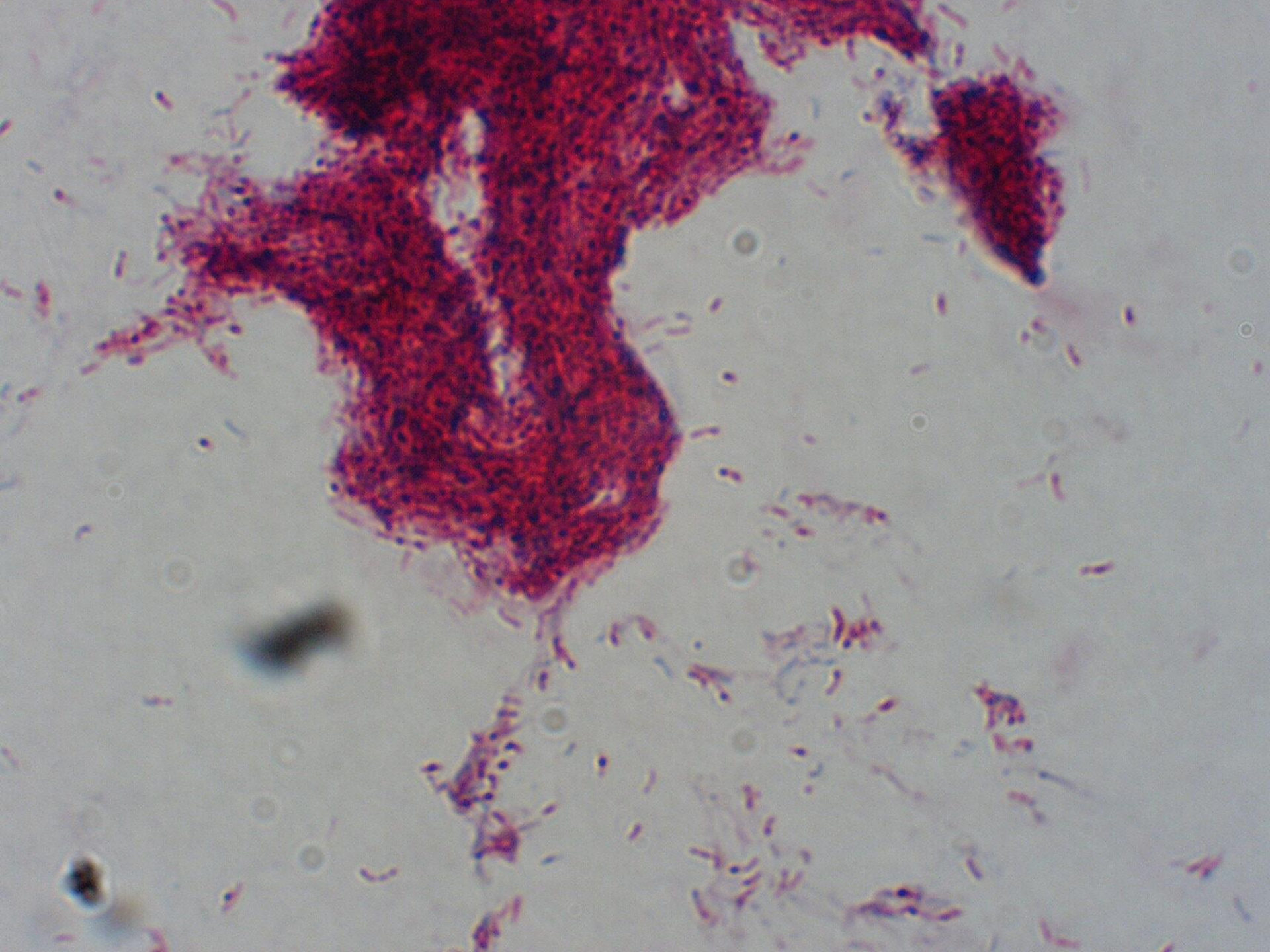
provide protection from hazards

MTB

Cording

in liquid culture TB orient parallel

MOTT orient randomly



MTB

Acid-fast

decolorization step done with acid-alcohol

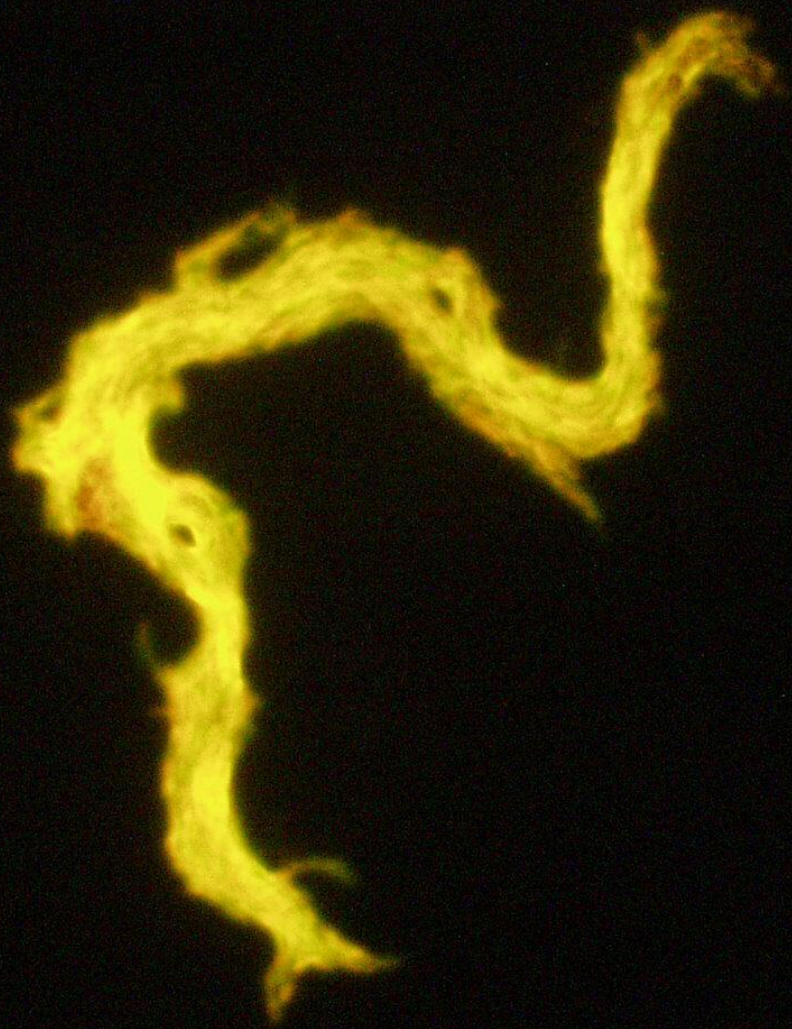
bacilli retain stain

MTB

For initial stains most labs use a fluorescent stain

auramine-rhodamine

$KMnO_4$ counterstain



MTB

Requires special media for culture

- Middlebrook 7H11
- Löwenstein-Jensen
- BACTEC
- MGIT


culosis
9/29
9-19

MTB

MTB very slow growing

average replication time

15-20 hours

E coli replicates in about 20 minutes

MTB

Starting with one bacterium in ideal conditions

	MTB	E coli
1 hour	1	4-8
1 day	2	2.3×10^{21}
1 week	1024	2.6×10^{151}

MTB—Clinical

Primary TB (childhood)

- mid lung zones
- regional lymphadenitis
- pleurisy with effusion
- persistent cough illness
- risk of hematogenous spread

MTB—Clinical

Primary TB (childhood)

can look like anything

MTB—Clinical

high risk of dissemination

miliary tuberculosis

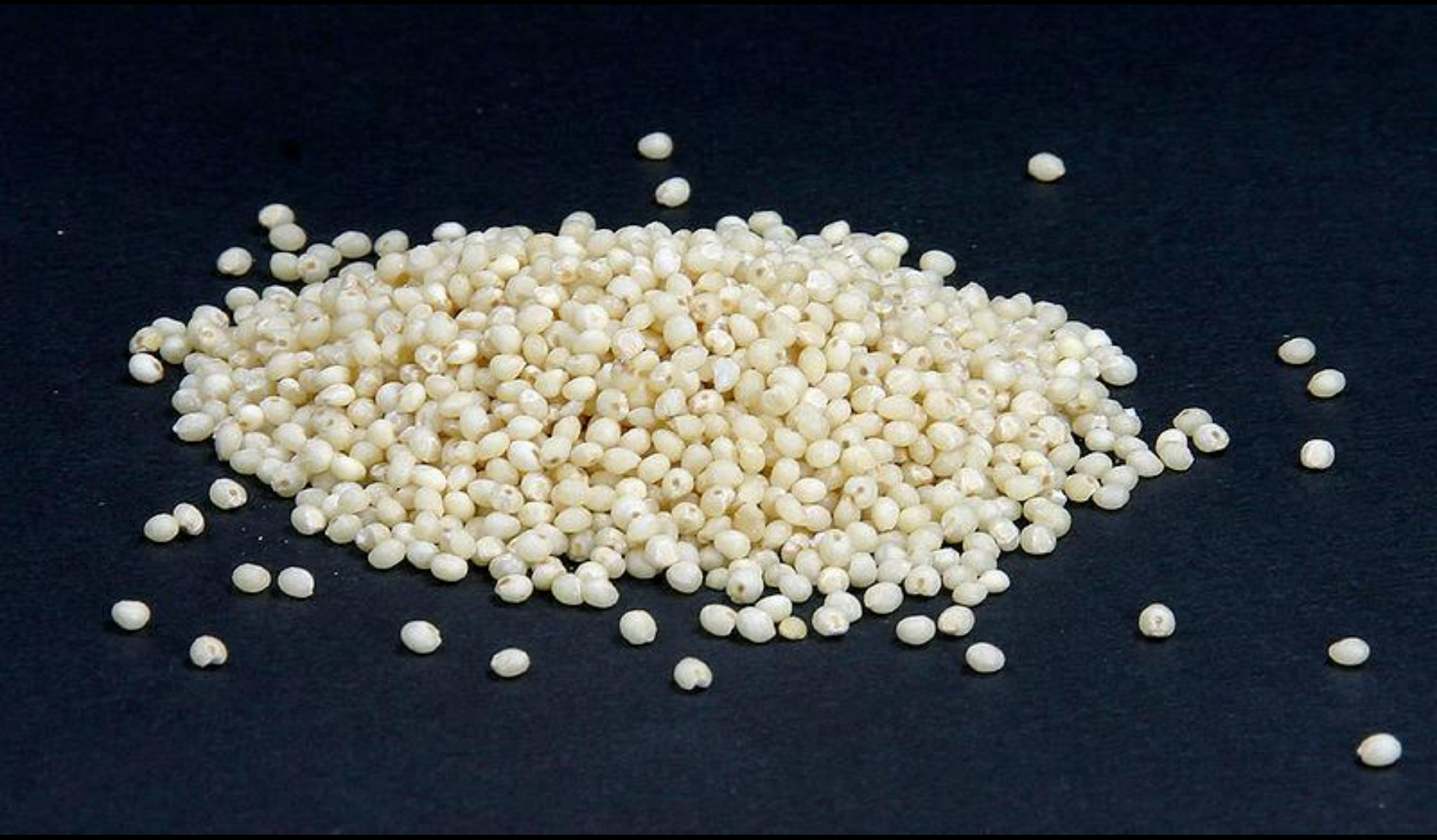


image obtained from Wikipedia

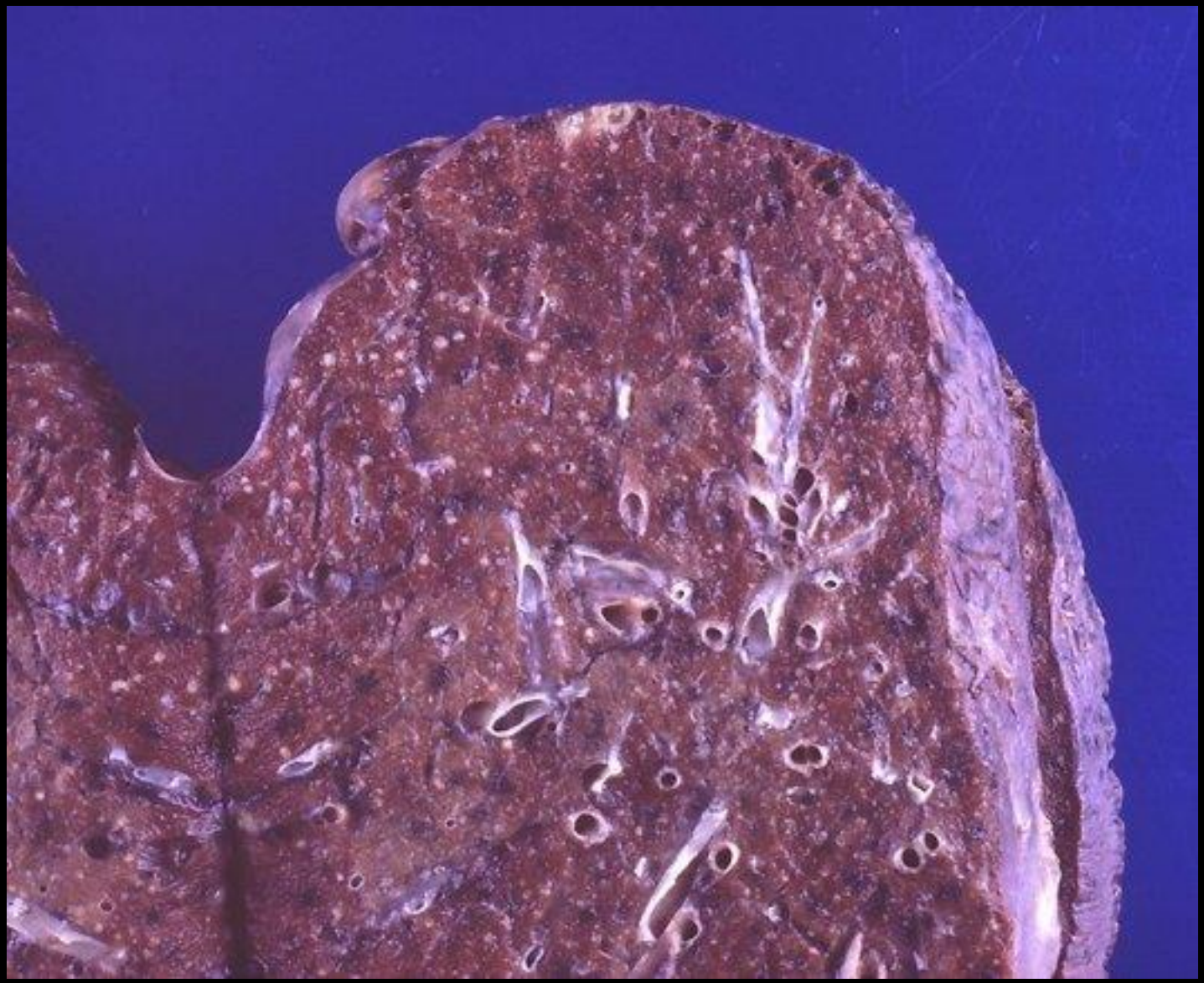


image obtained from http://www.granuloma.homestead.com/index.html

MTB—Clinical

high risk of dissemination

- cerebral tuberculosis
  - insidious
  - difficult to diagnose

MTB—Clinical

high risk of dissemination

cerebral tuberculosis

LP in any child < 3yo

LP if headache / signs

MTB—Clinical

- How often is disease recurrent vs. reinfection?
- How risky are biologics?
- Why is there a summer peak in Dx?

The Temporal Dynamics of Relapse and Reinfection Tuberculosis After Successful Treatment: A Retrospective Cohort Study

Florian M. Marx,[1,4] Rory Dunbar,[1] Donald A. Enarson,[1,5] Brian G. Williams,[3] Robin M. Warren,[2] Gian D. van der Spuy,[2] Paul D. van Helden,[2,a] and Nulda Beyers[1,a]

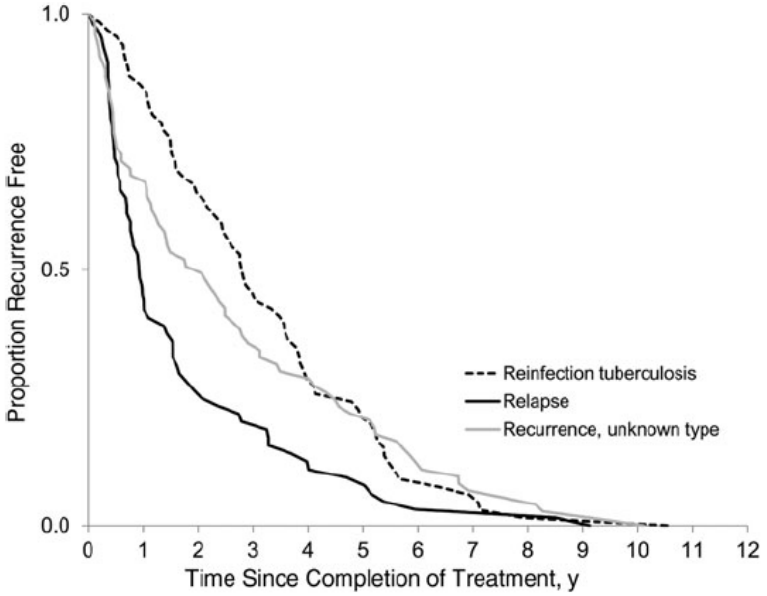


Figure 2. Kaplan-Meier survival estimates for relapse (n = 64), reinfection tuberculosis (n = 66), and unknown type of recurrence (n = 73) (Kolmogorov-Smirnov test for difference in relapse vs reinfection, $P < .001$).

Result

Recurrence most common in first year, reinfection more common thereafter.

Biologic Therapies in Rheumatoid Arthritis and the Risk of Opportunistic Infections: A Meta-analysis

Irene S. Kourbeti,[1,2] Panayiotis D. Ziakas,[1,2] and Eleftherios Mylonakis[1,2]

[1]Infectious Diseases Division, Rhode Island Hospital, and [2]Warren Alpert Medical School of Brown University, Providence, Rhode Island

Table 2. GRADE Summary of Findings on the Effects of Biologic Agents Compared With Placebo or Disease-Modifying Antirheumatic Drugs

Outcomes	Relative Effect (OR; 95% CI)	No. of Participants (No. of Studies)	Quality of Evidence (GRADE)
All OIs	1.79 (1.17–2.74)	20232 (37)	High[a,b,c,d]
Mycobacterial OIs	3.73 (1.72–8.13)	9194 (16)	High[a,b]
All viral OIs	1.91 (1.02–3.58)	6056 (16)	Moderate[a,b,c]
VZV OIs	1.51 (.71–3.22)	5515 (11)	Low[b,c]
All fungal OIs	1.31 (.46–3.72)	7507 (10)	Moderate[b]
Invasive fungal infections	2.85 (.68–11.91)	3915(7)	Moderate[b]
Pneumocystis jirovecii pneumonia	1.77 (.42–7.47)	5669 (8)	Moderate[b]
Attributed mortality	1.91 (.29–12.64)	3058 (5)	Moderate[b]

Result

Mycobacterial OIs are the most associated; fungal second.

The Seasonality of Tuberculosis, Sunlight, Vitamin D, and Household Crowding

Tom Wingfield,[1,4,5,6] Samuel G. Schumacher,[1,3] Gurjinder Sandhu,[3,4,5] Marco A. Tovar,[1,2,3] Karine Zevallos,[1,2] Matthew R. Baldwin,[3] Rosario Montoya,[1,2] Eric S. Ramos,[3] Chulanee Jongkaewwattana,[1] James J. Lewis,[1,7] Robert H. Gilman,[2,8] Jon S. Friedland,[4,5] and Carlton A. Evans[1,3,4,5]

774 • JID 2014:210 (1 September)

Cohort

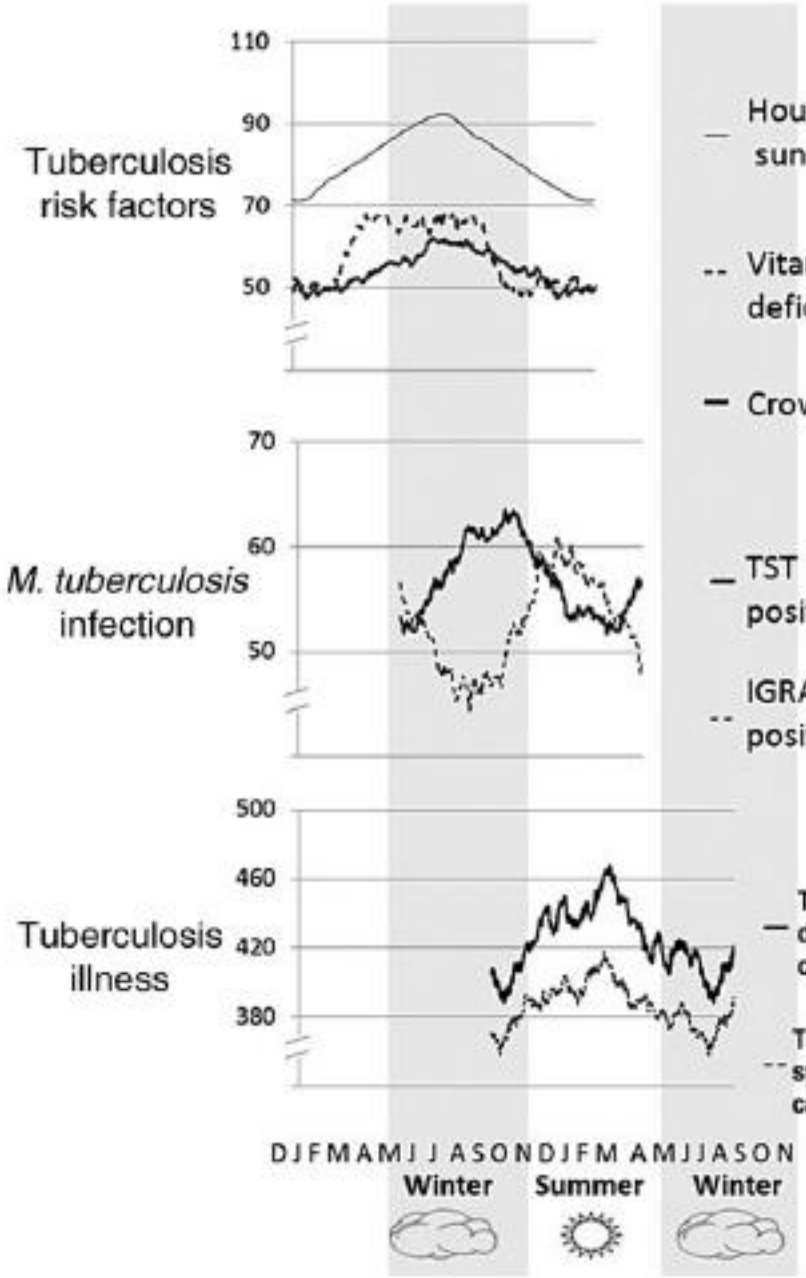
Residents of a Peruvian shantytown

Measures

Vitamin D, TST, IGRA

Results

Infections occur during winter months, but symptoms don't appear until the summer



	Peak season	Rest of year	*P* value
— Hours without sunlight (%)	87.5 (87.0 - 88.0)	76.0 (75.5 - 76.4)	<.0001
-- Vitamin D deficient (%)	63.3 (62.5 - 64.1)	53.1 (52.4 - 53.9)	<.0001
— Crowding (%)	56.4 (56.1 – 56.7)	50.9 (50.6– 51.2)	<.0001
— TST positivity (%)	60.5 (60.3 – 60.8)	54.4 (54.2 - 54.7)	<.0001
-- IGRA positivity (%)	56.2 (55.7 - 56.6)	49.1 (48.7 - 49.5)	<.0001
— Tuberculosis diagnoses, cases, no.	440 (438 - 442)	416 (414 - 418)	<.0001
-- Tuberculosis symptom onset, cases, no.	397 (396- 399)	380 (378 - 381)	<.0001

MTB—Testing

the gold standard

biopsy / specimen with culture

MTB—Testing

PPD (purified protein derivative)

Mantoux test

must be placed intradermal

Clemens Peter von Pirquet (1874-1929)

developed one of the first non-culture tests for TB

tuberculin applied to superficial abrasion on arm

Image courtesy of
the Clendening History of Medicine Library,
University of Kansas Medical Center

image courtesy of the Public Health Image Library of the CDC

Tuberculosis

Pirquet test

Der diagnostische Wert der kutanen Tuberkulinreaktion bei der Tuberkulose des Kindesalters auf Grund von 100 Sektionen.

Von Dr. C. v. Pirquet.

Moro test

Ueber eine diagnostisch verwertbare Reaktion der Haut auf Einreibung mit Tuberkulinsalbe.

Von Privatdozent Dr. Ernst Moro, Oberarzt der Klinik.

Tuberculosis

Calmette-Wolff-Eisner test

MÉDECINE. — *Sur un nouveau procédé de diagnostic de la tuberculose chez l'homme par l'ophtalmo-réaction à la tuberculine.* Note de M. A. CALMETTE.

Mendel-Mantoux test

PATHOLOGIE. — *Intradermo-réaction de la tuberculine.* Note de M. CH. MANTOUX, présentée par M. E. Roux.

Felix Mendel (1862-1925)

Zur endevenöse Applikation der Medikamente
II. Die kombinirte Arsen-Tuberkulinbehandlung

Therapeutische Monatshefte, Berlin **17:** 177-188 (1903)

Charles Mantoux (1877-1947)

PATHOLOGIE. — *Intradermo-réaction de la tuberculine.* Note de M. Ch. Mantoux, présentée par M. E. Roux.

Comptes rendus de l'Académie des Sciences, Paris
147: 355-357 (1908)

MTB—Testing

PPD (purified protein derivative)

Mantoux test

must be placed intradermal

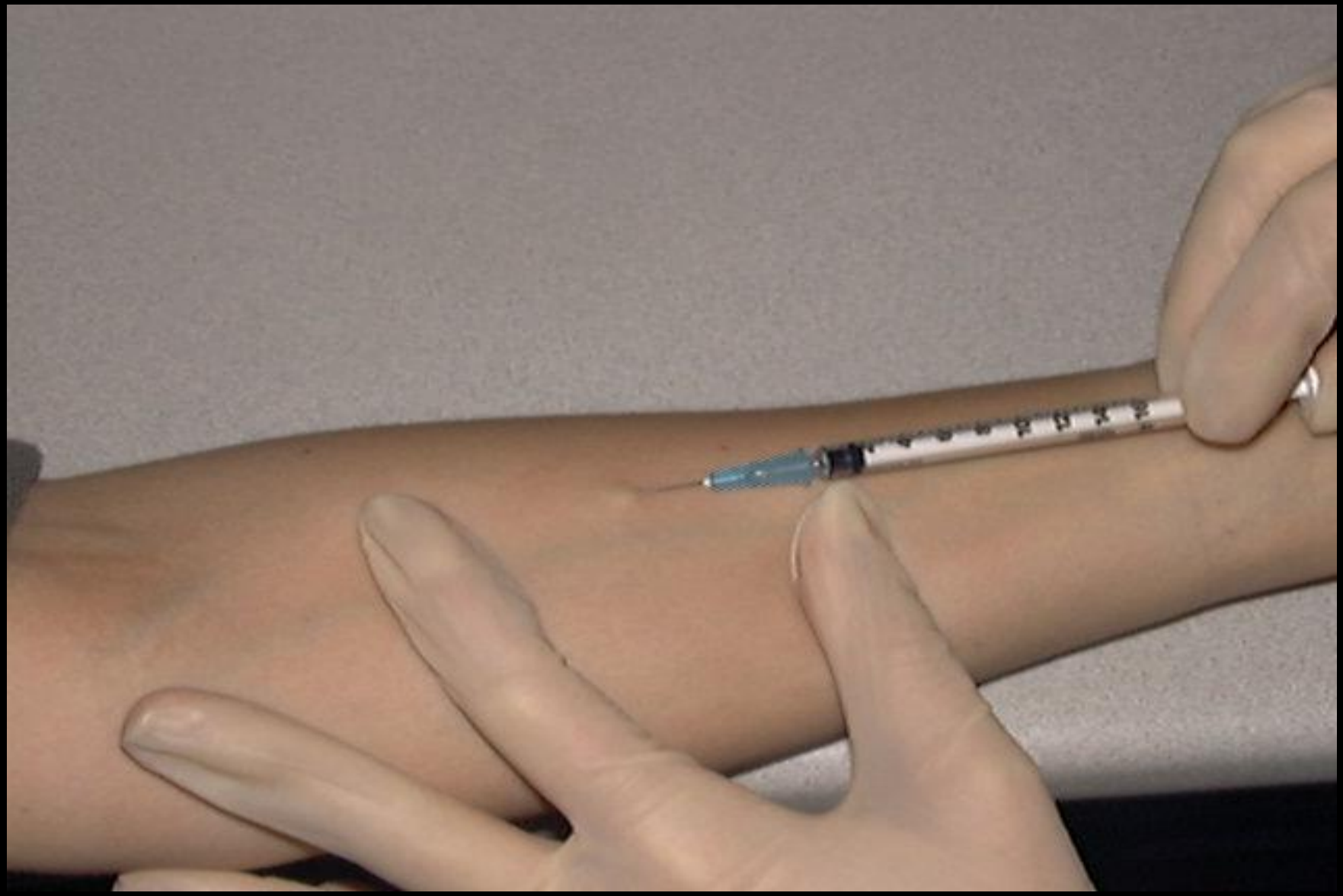


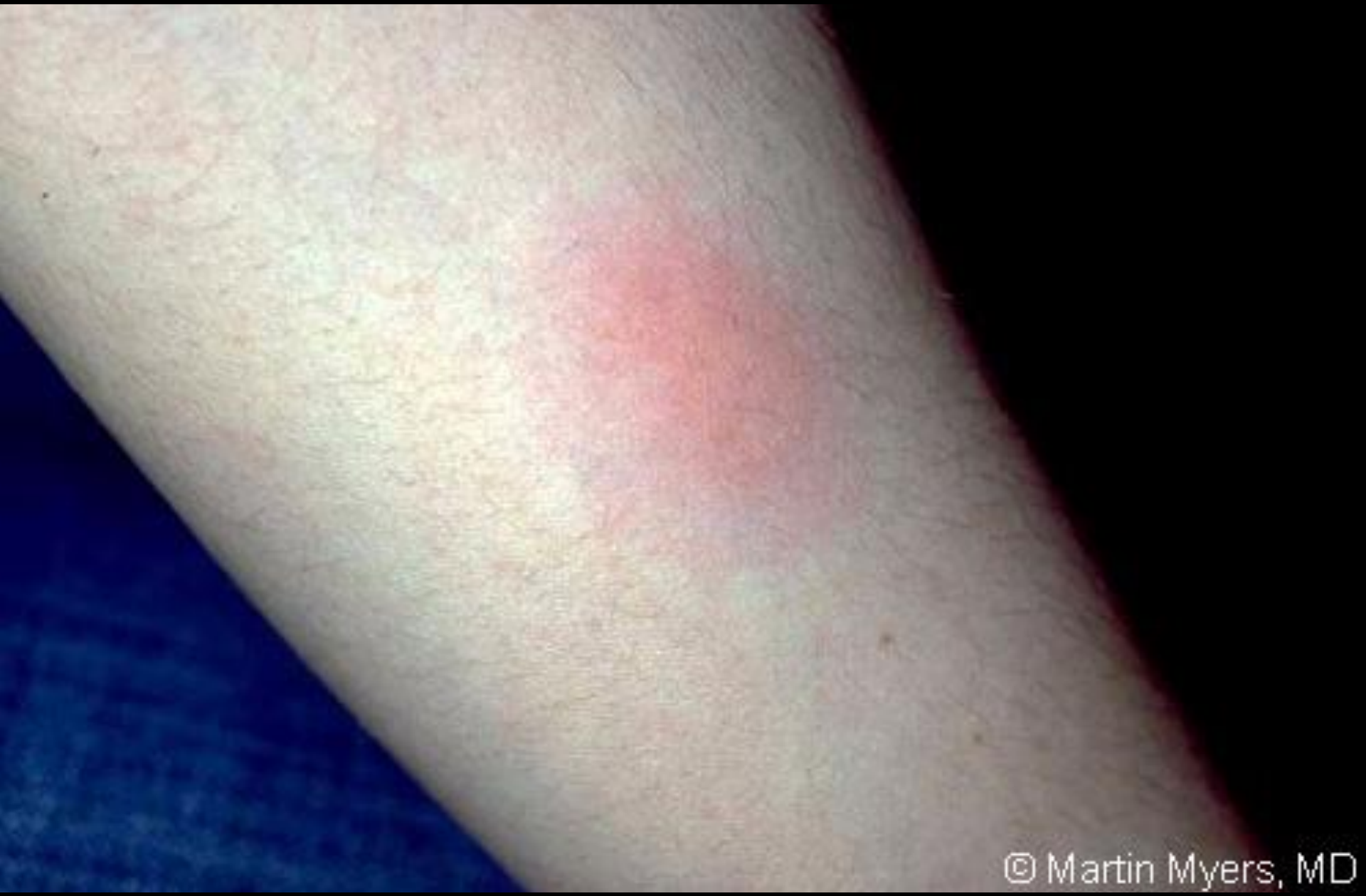
image courtesy of the CDC

MTB—Testing

PPD

read 48-72 hours after placement

can be read up to 1 week later with accuracy


© Martin Myers, MD

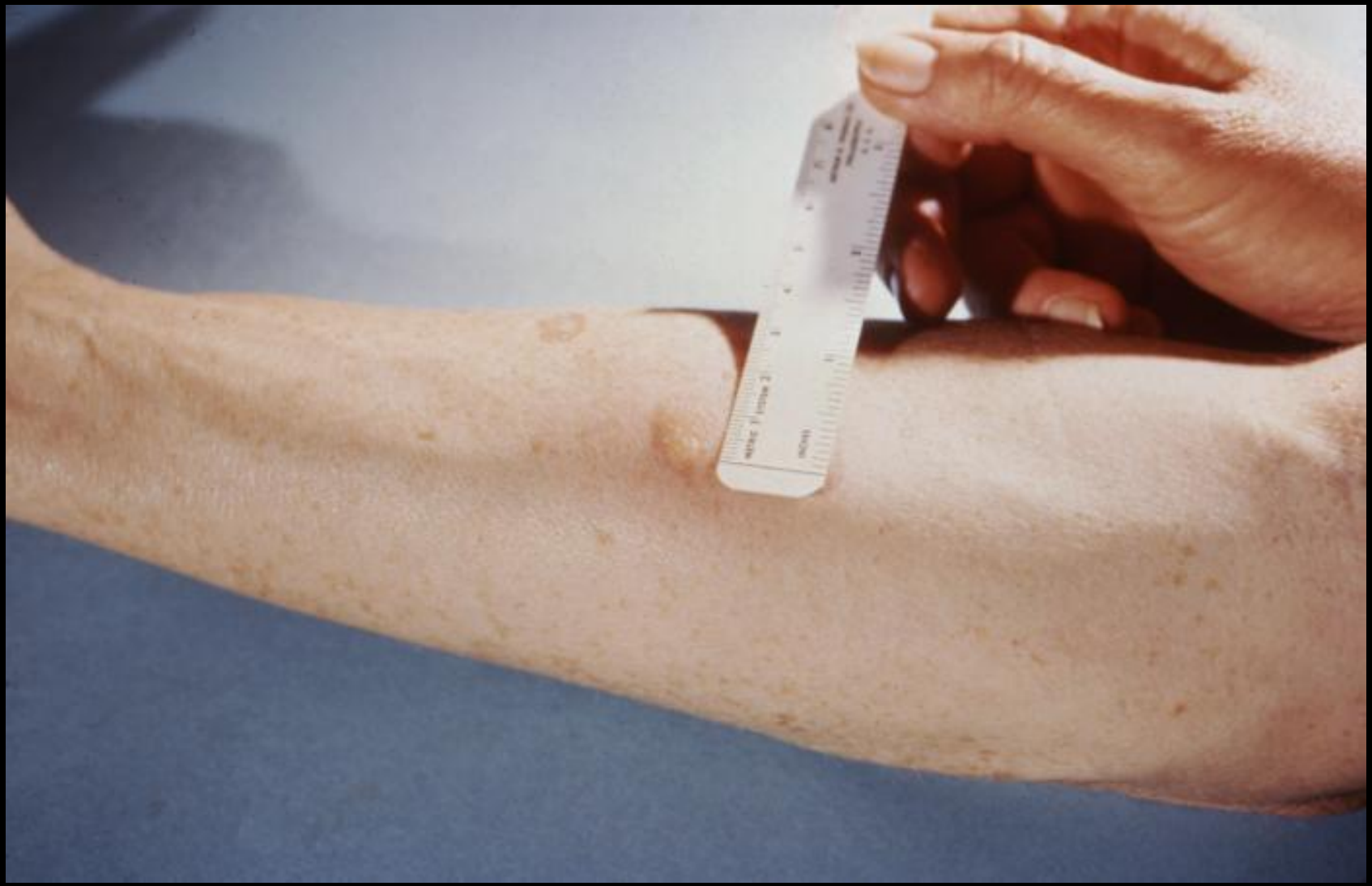


image courtesy of the Public Health Image Library of the CDC

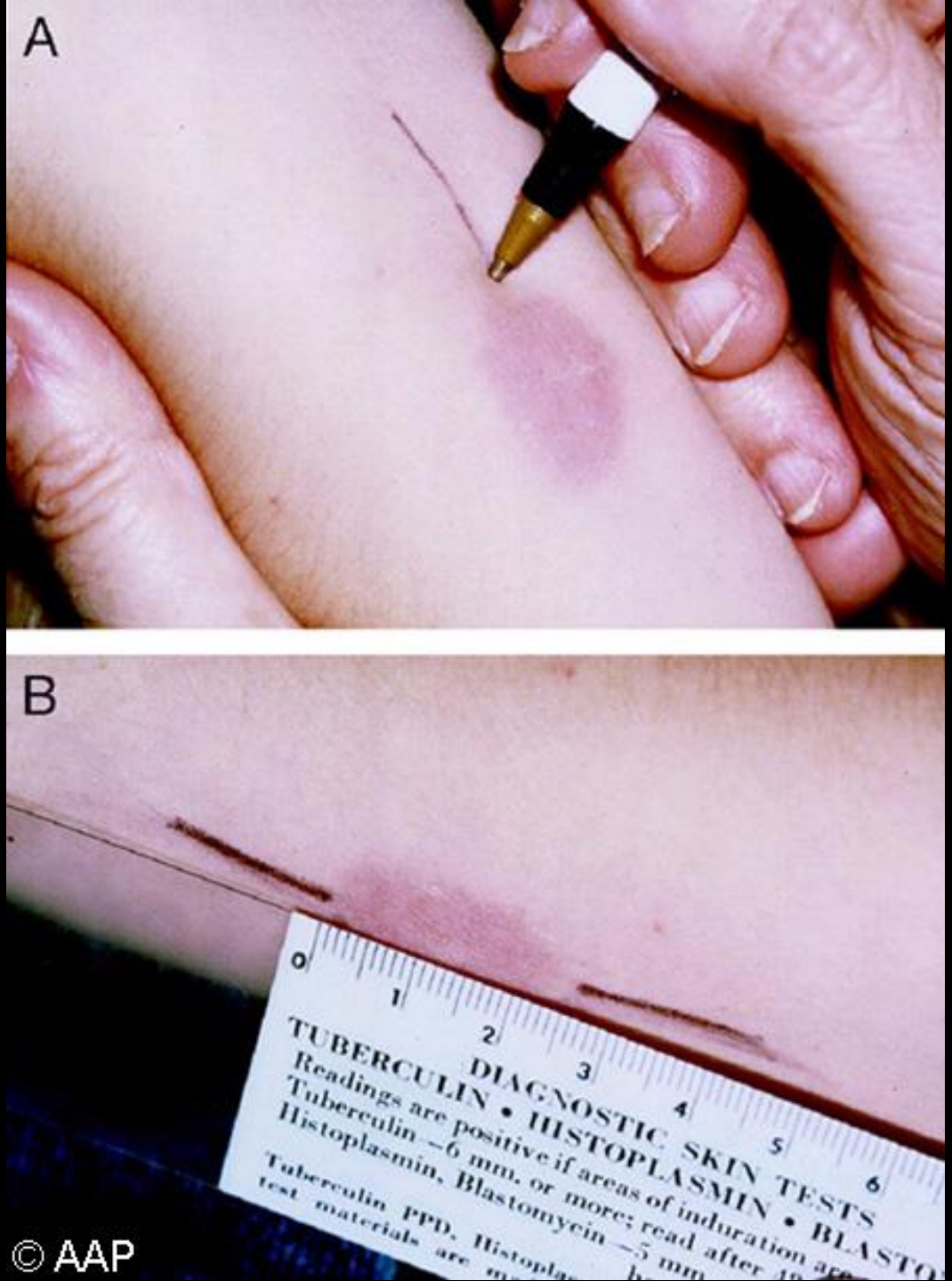
MTB—Testing

PPD

erythema is meaningless

induration is the key

Sokol method (ball-point pen)


A
B
0
1
2
3
4
5
6
DIAGNOSTIC SKIN TESTS
TUBERCULIN • HISTOPLASMIN • BLASTO
Readings are positive if areas of induration
Tuberculin—6 mm. or more; read after
Histoplasmin, Blastomycin—5 mm
Tuberculin PPD, Histopla
test materials are
© AAP

Problems with TST

- requires specialized training
  for both placement and reading
- requires two provider visits
- false positives and negatives
- vaccine confounding
- booster phenomenon

Problems with TST

- requires specialized training
  for both placement and reading
- requires two provider visits
- false positives and negatives
- vaccine confounding
- booster phenomenon

Tuberculin Skin Testing in Patients with HIV Infection: Limited Benefit of Reduced Cutoff Values.

Cobelens FG, Egwaga SM, van Ginkel T, Muwinge H, Matee MI, Borgdorff MW.
Clin Infect Dis **43:** 634-639 (2006).

result

Adult study.

Lower cutoff doesn't capture many more.

Seems to be an all or nothing phenomenon.

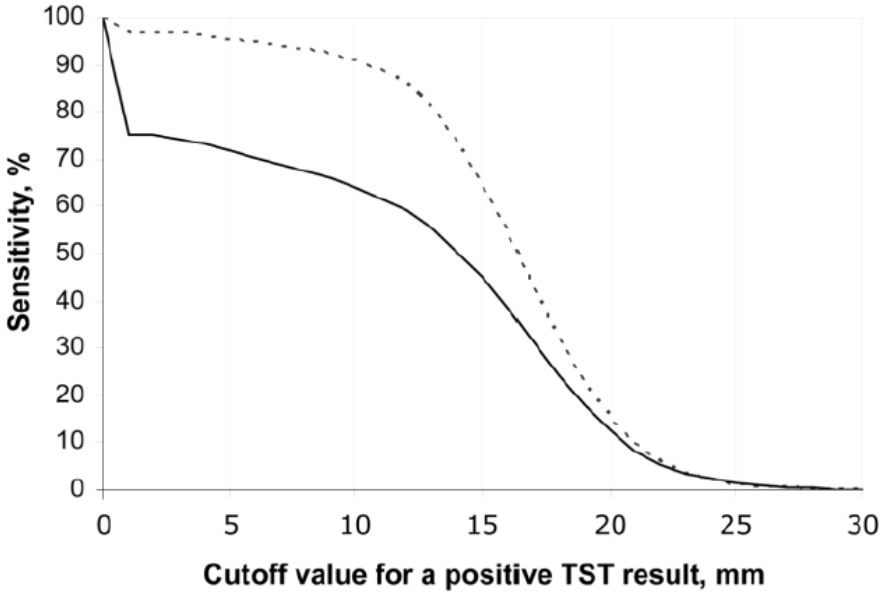


Figure 2. Sensitivity of the tuberculin skin test (TST) for detecting tuberculosis disease among HIV-infected *(solid line)* and HIV-uninfected *(dashed line)* patients at various cutoff levels. Data are based on crude reaction size distributions.

Problems with TST

- requires specialized training
  for both placement and reading
- requires two provider visits
- false positives and negatives
- vaccine confounding
- booster phenomenon

The tuberculin skin test is unreliable in school children BCG-vaccinated in infancy and at low risk of tuberculosis infection.

Jacobs S, Warman A, Richardson R, Yacoub W, Lau A, Whittaker D, Cockburn S, Verma G, Boffa J, Tyrrell G, Kunimoto D, Manfreda J, Langlois-Klassen D, Long R.

Pediatr Infect Dis J **30:** 754-758 (2011).

result

Canadian study. BCG-vaccinated children more likely to have a positive TST.

Concludes test unreliable in 6-12 yo children.

Problems with TST

- requires specialized training
  for both placement and reading
- requires two provider visits
- false positives and negatives
- vaccine confounding
- booster phenomenon

Enhancing of Tuberculin Allergy by Previous Tuberculin Testing

Narain R, Nair SS, Rao GR, Chandrasekhar P, Lal P.
Bull Wld Hlth Org **34:** 623-635 (1966).

cohort
eight villages in India

result
those with mild reactions,
8-13 mm initially, had the most increases with boosting

testing
TST using 1 TU
on upper ⅓ of L forearm

some given 20 TU tests

2 mo later
TST w/ 1 TU
on middle ⅓ of R forearm

The Booster Effect in Two-Step Tuberculin Testing among Young Adults in Montreal

Menzies R, Vissandjee B, Rocher I, St. Germain Y.
Ann Int Med **120:** 190-198 (1994).

result

boosting seen in both BCG-V +ve and –ve groups

greater effect in BCG-V gp

correlation w/ age at BCG-V

most boosters reactive to PPD-B(I)

Boosting

- CDC recommends two-step testing for HCW at first screen

Desirable Properties

- no special training
- single encounter
- reduced false positives and negatives
- distinguish between MTB and other mycobacteria

IGRA

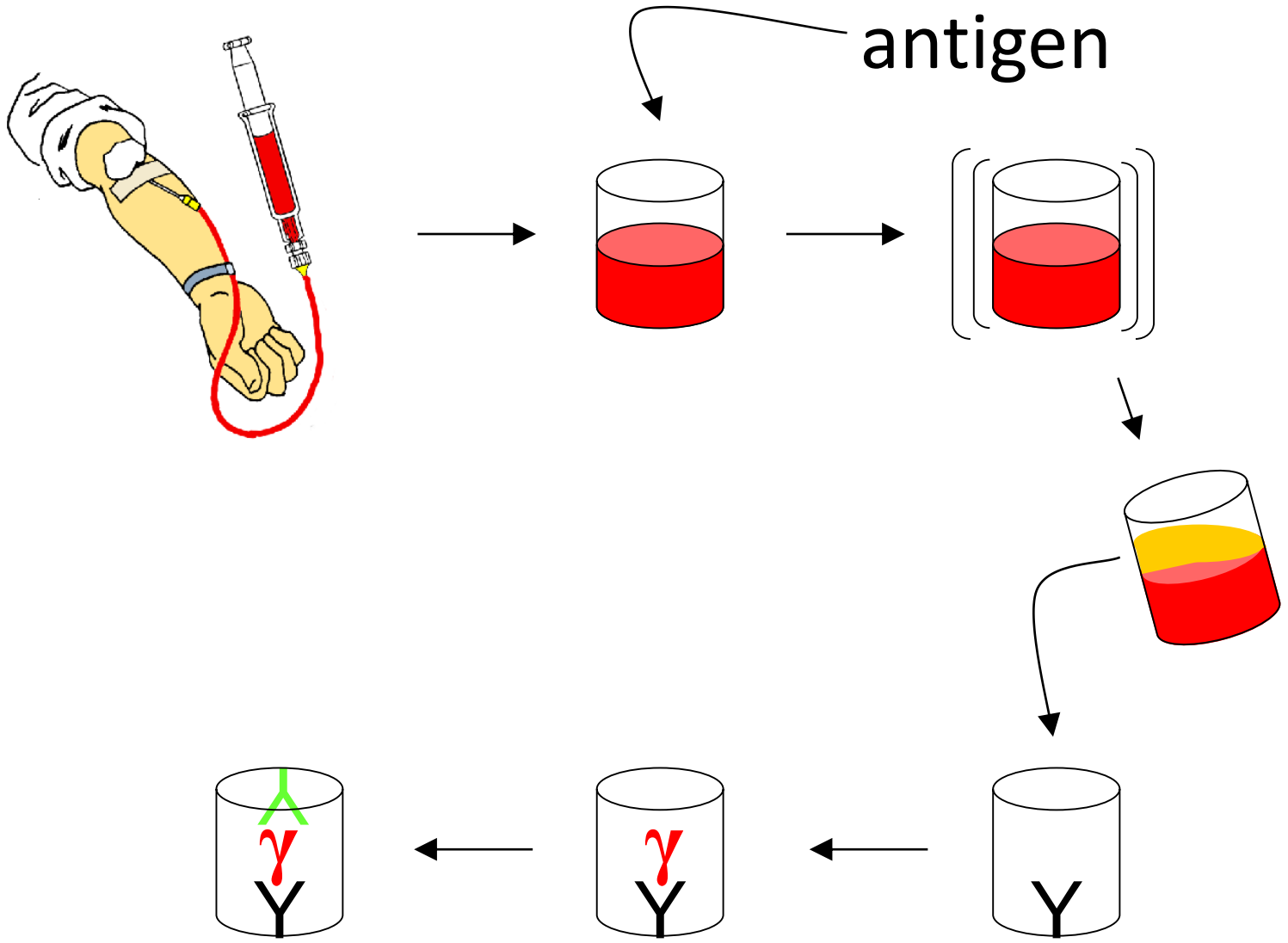
Interferon-**G**amma **R**elease **A**ssay

- reduced cross-reactivity
- lab-based test / quantitative answer
- single patient contact
- no boosting

BOVIGAM

- testing of cattle

- licensed in
  Australia & New Zealand


antigen

Evaluation of the Tuberculin Gamma Interferon Assay: Potential to Replace the Mantoux Skin Test

Pottumarthy S, Morris AJ, Harrison AC, Wells VC.
J Clin Microbiol **37:** 3229-3232 (1999).

cohort

immigrants, HCW, patients

testing

QuantiFERON using PPDs for MTB, *M bovis*, *M avium*

TST

result

64-89% concordance

71% +ve w/ smear +ve TB (Mantoux slightly better)

humans are to chimpanzees

as

M tuberculosis* is to *M bovis

>98% genetic identity

differences between
***M bovis* and BCG**

RD1 (region of difference)

encodes for ESAT-6 & CFP10

IGRA

- relies on response to RD1 antigens
- can be negative in disease
- increasing studies in pediatrics
- multiple forms (ELISA, ELISpot)

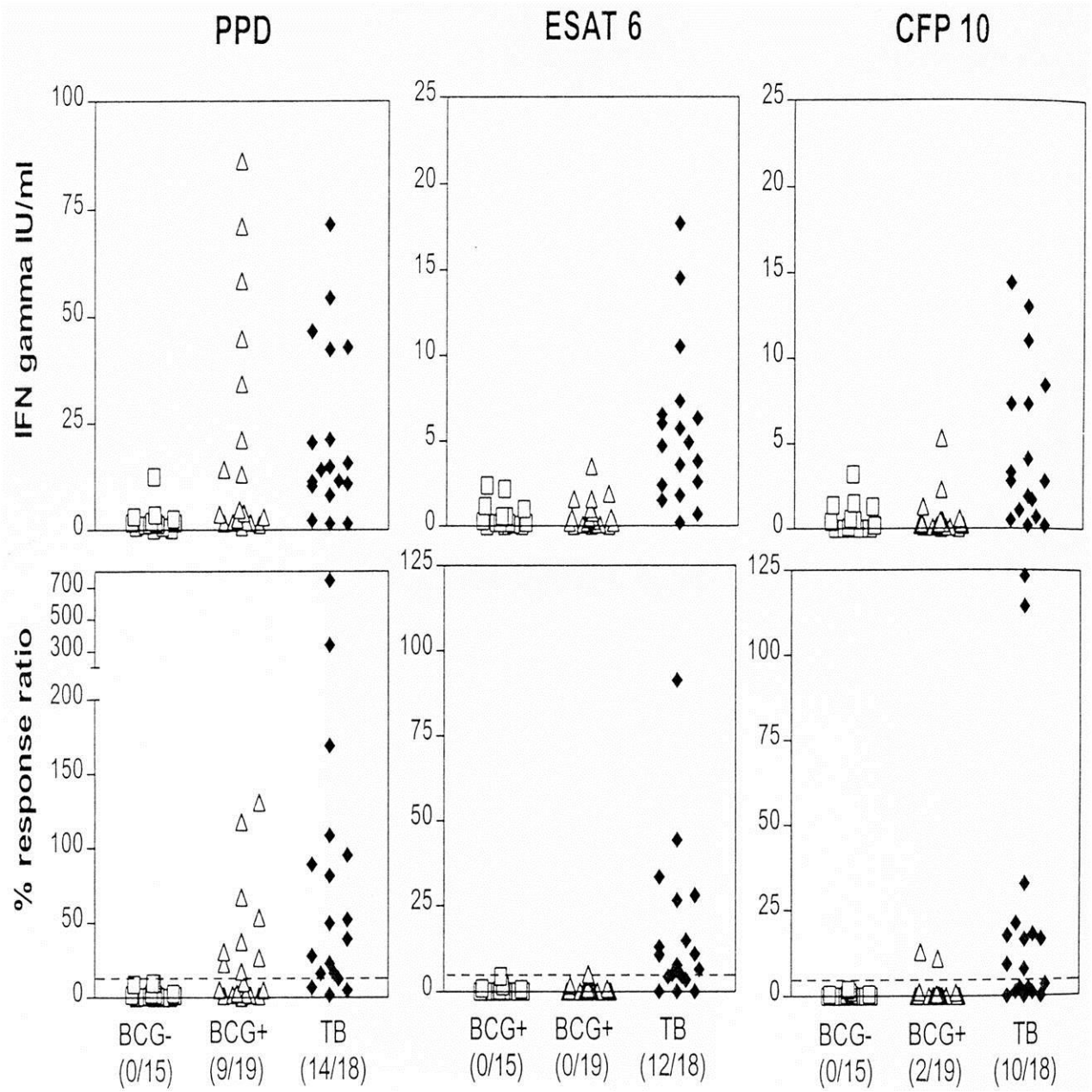
Performance of whole blood IFN-g test for tuberculosis diagnosis based on PPD or the specific antigens ESAT-6 and CFP-10

Brock I, Munk ME, Kok-Jensen A, Andersen P.
Int J Tuberc Lung Dis **5:** 462-467 (2001).

cohort
healthy volunteers
known TB +ve patients

testing
QuantiFERON using
PPDs for MTB, *M avium*,
ESAT-6, CFP-10

result
78% sensitive
100% specific in non-BCG, 89% in BCG-V


PPD
ESAT 6
CFP 10
IFN gamma IU/ml
% response ratio
BCG-
(0/15)
BCG+
(9/19)
TB
(14/18)
BCG+
(0/15)
BCG+
(0/19)
TB
(12/18)
BCG-
(0/15)
BCG+
(2/19)
TB
(10/18)

Whole blood interferon-γ release assay is a useful tool for the diagnosis of tuberculosis infection particularly among Bacille Calmette Guèrin-vaccinated children.

Tsolia MN, Mavrikou M, Critselis E, Papadopoulos NG, Makrinioti H, Spyridis NP, Metsou F, Tsagaraki M, Koulouri M, Kafetzis DA.

Pediatr Infect Dis J **29:** 1137-1140 (2010).

result

High rates of concordance between TST and IGRA in non-vaccinated children.

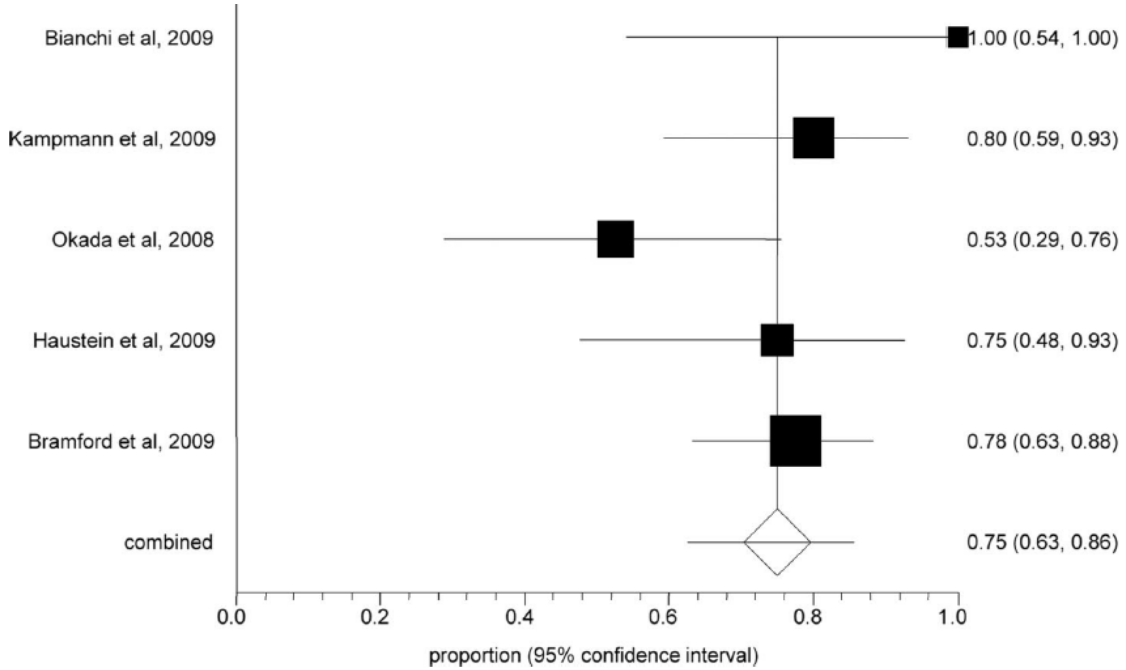
IGRA more predictive in BCG-vaccinated children.

The Utility of an Interferon Gamma Release Assay for Diagnosis of Latent Tuberculosis Infection and Disease in Children

A Systematic Review and Meta-analysis

Shingai Machingaidze, BSc,† Charles Shey Wiysonge, MD,*† Yulieth Gonzalez-Angulo, BSc,*† Mark Hatherill, MD,*† Sizulu Moyo, MB ChB, Willem Hanekom, FCP (Paed),*† and Hassan Mahomed, MMed*†*

694 | www.pidj.com *The Pediatric Infectious Disease Journal* • Volume 30, Number 8, August 2011



Result

IGRA reasonably accurate in Dx of TB disease.

Impact of targeted testing for latent tuberculosis infection using commercially available diagnostics.

Mancuso JD, Tribble D, Mazurek GH, Li Y, Olsen C, Aronson NE, Geiter L, Goodwin D, Keep LW.

Clin Infect Dis **53:** 234-244 (2011).

result

Testing in low incidence populations gives poor results.

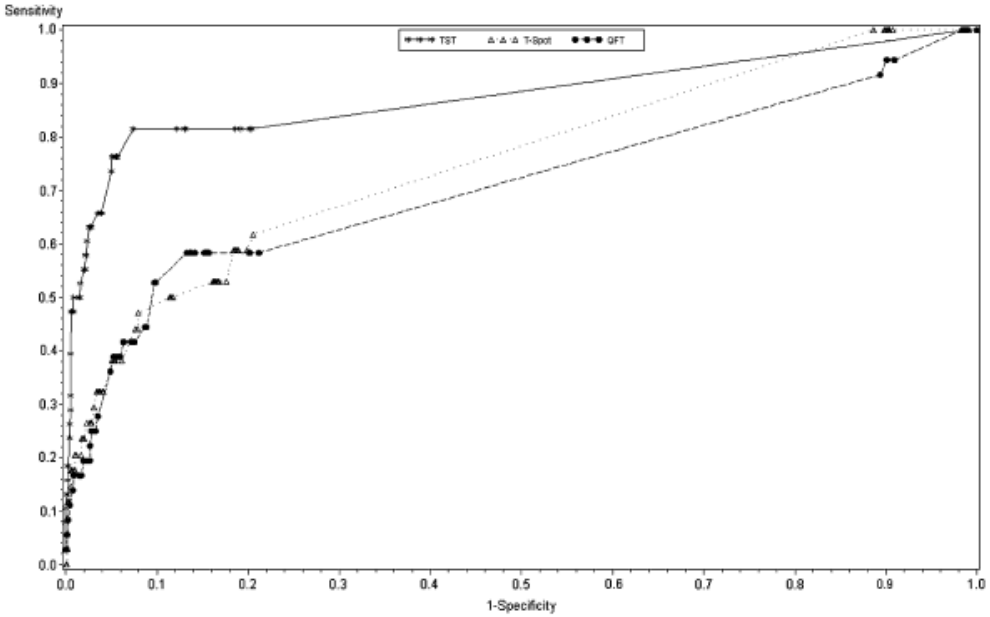


Figure 2. Receiver operator characteristics curve for predictors of latent tuberculosis infection (LTBI), as measured by the tuberculin skin test (TST), QuantiFERON® Gold In-Tube (QFT), and T-SPOT®.TB (T-Spot) among US Army Recruits. Predictors included in the logistic regression model: close contact with a tuberculosis (TB) case, casual contact with a TB case, TB prevalence in country of birth, history of living with parent born outside the US, prior positive skin test result, prior TB treatment, history of living in a congregate setting, and health care work. AUC, area under the curve.

Performance of QuantiFERON-TB Gold and Tuberculin Skin Test Relative to Subjects' Risk of Exposure to Tuberculosis

Sharon E. McMullen,[1] David A. Pegues,[2] Frances S. Shofer,[3] Alexandra C. Sheller,[4] and Evelyn B. Wiener[1]

result

In low risk college students,
TST better than IGRA;
for high risk, they are
the same.

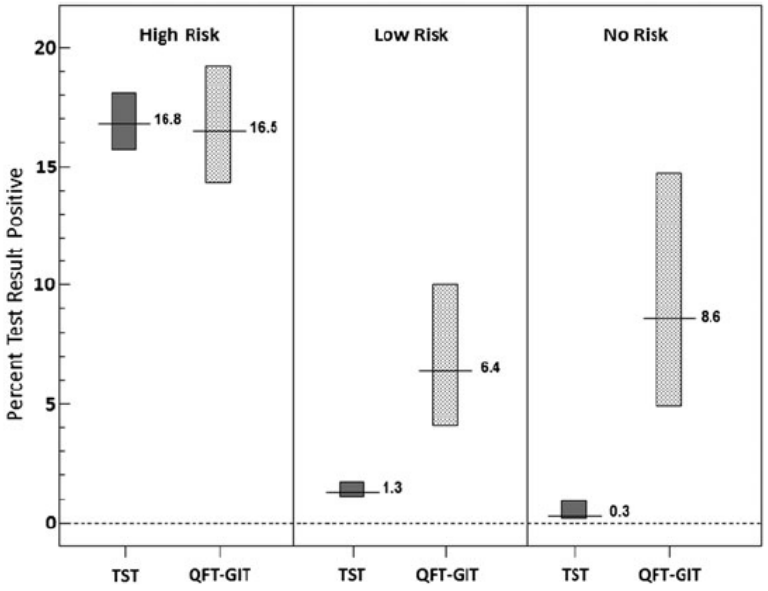


Figure 2. Results of tuberculin skin test and QuantiFERON-TB Gold In-Tube test by student risk of tuberculosis exposure. Abbreviations: QFT-GIT, QuantiFERON-TB Gold In-Tube; TST, tuberculin skin test.

Other Diagnostic Options

- In-house PCR tests
- Xpert MTB/RIF

Rapid Molecular Diagnosis of Pulmonary Tuberculosis in Children Using Nasopharyngeal Specimens

Heather J. Zar,[1,2] Lesley Workman,[1,2] Washiefa Isaacs,[1,2] Jacinta Munro,[1,2] Faye Black,[1,2] Brian Eley,[1,2] Veronica Allen,[3,4] Catharina C. Boehme,[5] Widaad Zemanay,[3,4] and Mark P. Nicol[3,4]

1088 • CID 2012:55 (15 October)

Definite TB 87 (16.3%)	Possible TB 255 (47.6%)	Not TB 193 (36.1%)
IS culture positive 84 (96.6%)	IS culture positive 0 (0%)	IS culture positive 0 (0%)
NPA culture positive 61 (70.1%)	NPA culture positive 0 (0%)	NPA culture positive 0(0%)
IS Xpert positive 64 (73.6%)	IS Xpert positive 5 (2.0%)	IS Xpert positive 0 (0%)
NPA Xpert positive 49 (56.3%)	NPA Xpert positive 7 (2.8%)	NPA Xpert positive 1 (0.5%)
Smear positive 30 (5.6%)	Smear positive 0 (0%)	Smear positive 0 (0%)

Result

TB Xpert on NP aspirates perhaps useful, esp if induced sputum impractical. (Gastric aspirates better.)

Rapid Diagnosis of Pediatric Intrathoracic Tuberculosis From Stool Samples Using the Xpert MTB/RIF Assay: A Pilot Study

Elisabetta Walters, MMed
Robert Peter Gie, MD
Anneke Catharina Hesseling, PhD
Desmond Tutu TB Centre
Stellenbosch University

Sven Olaf Friedrich, PhD
Andreas Henri Diacon, MD, PhD
Division of Medical Physiology
Department of Biomedical Sciences
Faculty of Medicine and Health Sciences
Stellenbosch University

Robert Peter Gie, MD
Paediatric Pulmonology
Tygerberg Children's Hospital
Cape Town, South Africa

The Pediatric Infectious Disease Journal • Volume 31, Number 12, December 2012

Result

Very small numbers, but results from stool and GA testing similar.

What about vaccine?

Edmond Isidore Etienne Nocard (1850-1903)

isolated virulent
M bovis strain →
'lait Nocard'

1901: transferred strain
to Institut Pasteur

Image obtained via en.wikipedia.org

Jean-Marie Camille Guérin (1872-1961)

student of Nocard

joined Institut Pasteur in 1897 under Calmette

together with Calmette attenuated *M bovis*

Image obtained via en.wikipedia.org

Léon Charles Albert Calmette (1863-1933)

1908-1919: serial passage of ‘lait Nocard’ on glycerinated bile potato medium (230 x)

continued attenuation from 1919-1929

Image courtesy of
the Clendening History of Medicine Library,
University of Kansas Medical Center

BCG Genealogy

BCG widely distributed (1924-1926)

34 nations

1927: 26 other nations given BCG

BCG Genealogy

BCG Moreau (Brazil)

BCG Tokyo (strain 172)

BCG Danish (2 transfers) (1331)

BCG Tice (BLP)

BCG Pasteur (1173P)

Mapping the global use of different BCG vaccine strains

Nicole Ritz [a,b,c], Nigel Curtis [a,b,c,*]

Tuberculosis 89 (2009) 248–251

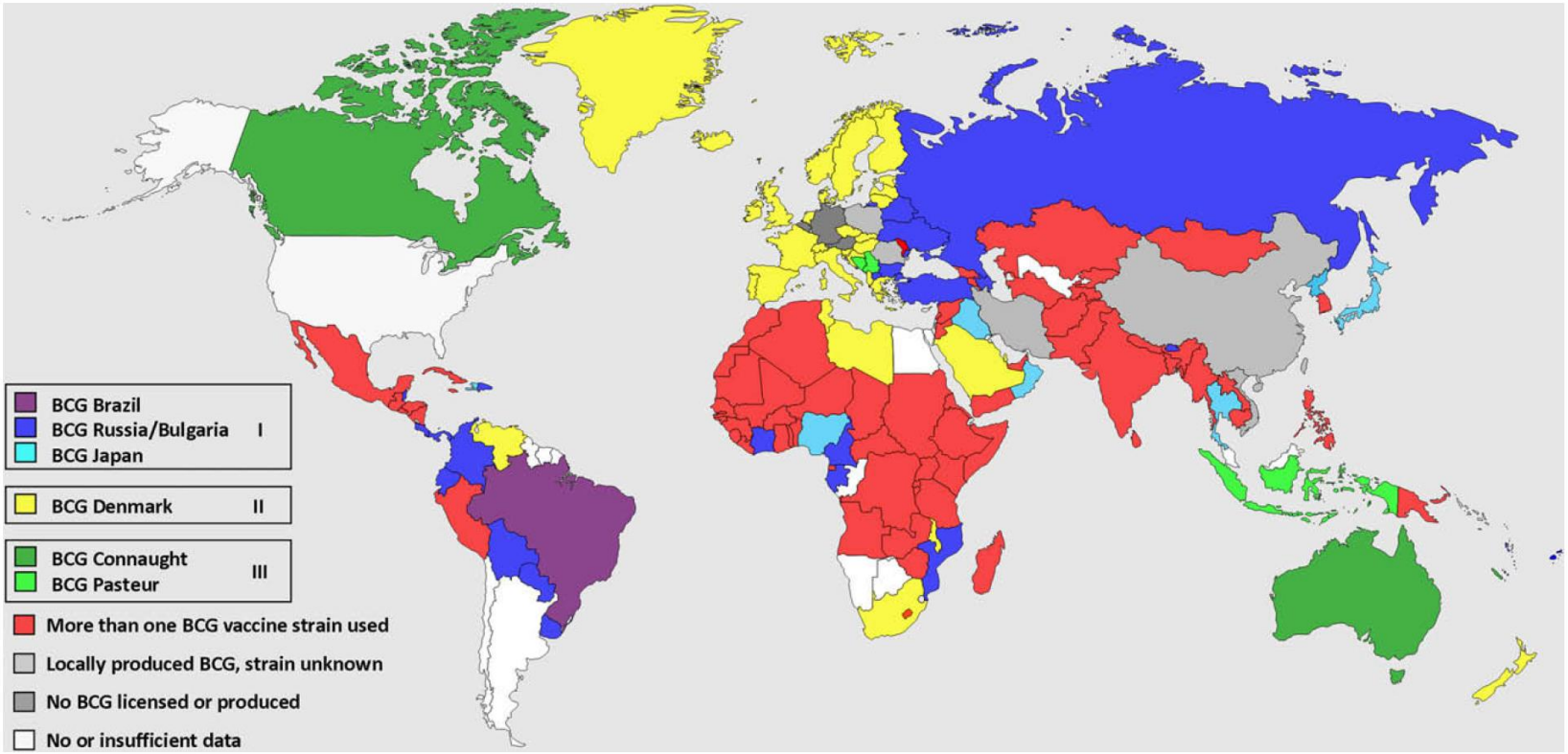


Figure 1. BCG vaccine strains used between 2003 and 2007 worldwide. Boxes surround BCG vaccines strains that are most genetically similar. Box I includes BCG vaccine strains that were obtained from the Pasteur Institute before 1926. Boxes II are III are strains obtained at later dates.

BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life

Fourth report to the Medical Research Council by its Tuberculosis Vaccines Clinical Trials Committee.
Medical Research Council. *Bull WHO* **46:** 371-385 (1972).

BCG and vole bacillus vaccines in the prevention of tuberculosis in adolescence and early adult life

Final report to the Medical Research Council.
Hart PD, Sutherland I. *Br Med J* **2:** 293-295 (1977).

BCG: World Experience

- > 2.5 billion immunizations
- given routinely to infants
- can be given PO
- quite heat stable

The Impact of a Change in Bacille Calmette-Guérin Vaccine Policy on Tuberculosis Incidence in Children in Cape Town, South Africa

Hassan Mahomed, MMed,† Maurice Kibel, FCP,*† Tony Hawkridge, FCPHM,*† H. Simon Schaaf, PhD,‡ Willem A. Hanekom, FCP,*† Karen Iloni, MBBCh, MSc,† Desiré Michaels, MPhil,† Lesley Workman, RN,*† Suzanne Verver, PhD,§ Lawrence Geiter, PhD,‖ and Gregory D. Hussey, FCCH*†*

The Pediatric Infectious Disease Journal • Volume 25, Number 12, December 2006

TABLE 3. Disseminated Tuberculosis by Type and Route of BCG Administration

Disseminated TB by Type	BCG by Route of Administration		
	Percutaneous (n = 1369)	Intradermal (n = 1397)	No BCG (n = 48)
Miliary TB	61 (4.5%)	36 (2.6%)	9 (18.8%)
Tuberculous meningitis (TBM)	51 (3.7%)	27 (1.9%)	5 (10.4%)
Miliary and TBM	6 (0.4%)	2 (0.1%)	0
Total disseminated	118 (8.6%)	65 (4.7%)	14 (29.2%)
95% confidence interval	7.2–10.2%	3.6–5.9%	17.0–44.1%

BCG indicates bacille Calmette-Guerin vaccine; TB, tuberculosis.

Result

Overall case number not changed, disseminated cases reduced.

Randomized Trial of BCG Vaccination at Birth to Low-Birth-Weight Children: Beneficial Nonspecific Effects in the Neonatal Period?

Peter Aaby,[1,2] Adam Roth,[3,6] Henrik Ravn,[3] Bitiguida Mutna Napirna,[2,a] Amabelia Rodrigues,[1] Ida Maria Lisse,[4] Lone Stensballe,[3] Birgitte Rode Diness,[1] Karen Rokkedal Lausch,[1] Najaaraq Lund,[1] Sofie Biering-Sørensen,[1] Hilton Whittle,[5] and Christine Stabell Benn[1,3]

JID 2011:204 (15 July) • 245

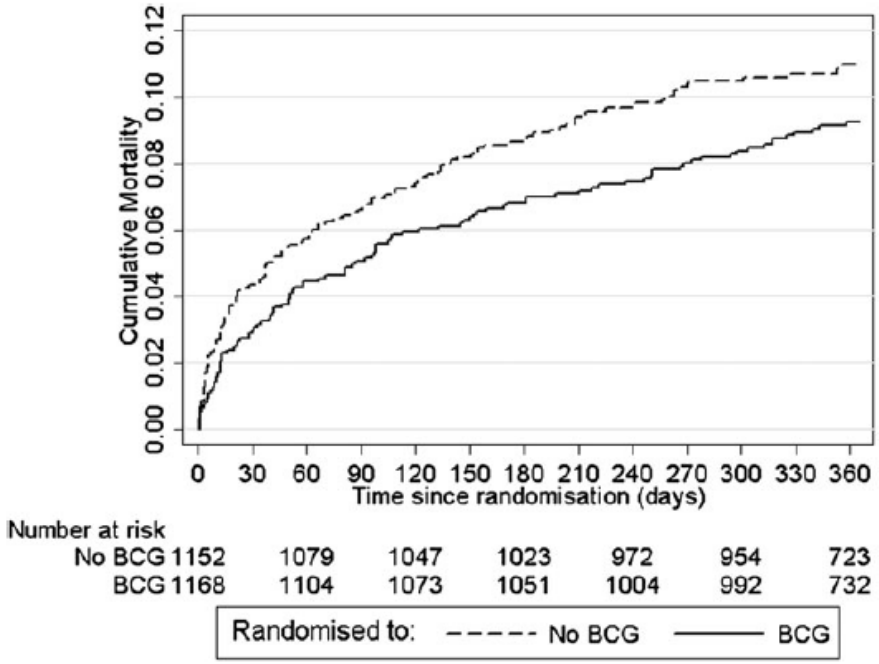


Figure 2. Cumulative mortality curves during the first year of life according to randomization group.

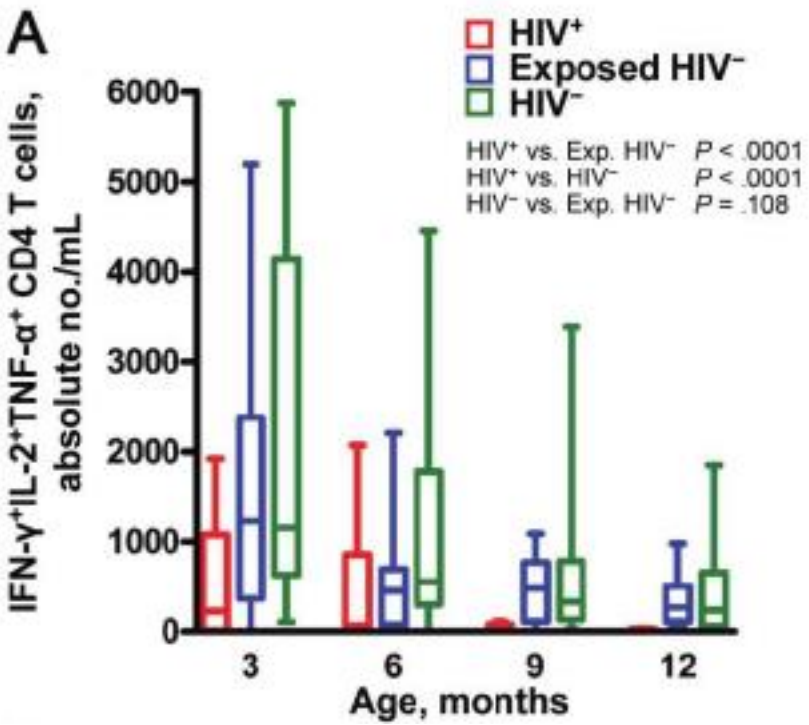
Result

BCG given to LBW infants reduced all-cause mortality.

HIV-1 Infection in Infants Severely Impairs the Immune Response Induced by Bacille Calmette-Guérin Vaccine

Nazma Mansoor,[1,a] Thomas J. Scriba,[1,a] Marwou de Kock,[1] Michele Tameris,[1] Brian Abel,[1] Alana Keyser,[1] Francesca Little,[3] Andreia Soares,[1] Sebastian Gelderbloem,[1] Silvia Mlenjeni,[1] Lea Denation,[1] Anthony Hawkridge,[1,2] W. Henry Boom,[4] Gilla Kaplan,[5] Gregory D. Hussey,[1] and Willem A. Hanekom[1]

982 • JID 2009:199 (1 April)



Result

BCG responses reduced in both HIV infection and HIV exposure.

Image from the National Library of Medicine, “Profiles in Science” Collection.

MTB—Treatment

Isolation

- MTB aerosolized into fine droplets
- light enough to be suspended
- air in room is infectious
- 1 cough = 5 min talking

MTB—Treatment

Isolation

- negative pressure room
- N95 masks / PAPRs

Family should be isolated until tested

- must wear masks outside of room

MTB—Treatment

Isolation and drugs

- streptomycin
- isoniazid
- pyrazinamide
- rifampin
- ethambutol
- amikacin
- quinolones

MTB—Treatment

isoniazid

- nicotinamide analog
- primarily active against MTB
- hepatic toxicity
- neurotoxicity (slow-acetylators)
  - prevented by giving pyridoxine

MTB—Treatment

pyrazinamide

- nicotinamide analog
- good CNS penetration
- hepatic toxicity
  (compounded by INH)
- reduces uric acid excretion

MTB—Treatment

rifampin

- inhibits DNA-dependent RNA polymerase
- dye
- enhances metabolism of some drugs

MTB—Treatment

ethambutol

- bacteriostatic
- affects mycobacterial cell wall
- optic neuritis
  - (needs careful monitoring in children)

MTB—Treatment

streptomycin

- still an excellent drug

- only available as an IM preparation

MTB—Treatment

Drug	Pediatric Dose	Adult Dose	Daily Maximum
Isoniazid	10 mg/kg (10-15)	5 mg/kg (4-6)	300 mg
Rifampin	15 mg/kg (10-20)	10 mg/kg (8-12)	600 mg
Pyrazinamide	35 mg/kg (30-40)	25 mg/kg (20-30)	—
Ethambutol	20 mg/kg (15-25)	15 mg/kg (15-20)	—
Streptomycin	—	15 mg/kg (12-18)	1000 mg

Recommendations from the World Health Organization.

Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis

Payam Nahid,[1] Susan E. Dorman,[2] Narges Alipanah,[1] Pennan M. Barry,[3] Jan L. Brozek,[4] Adithya Cattamanchi,[1] Lelia H. Chaisson,[1] Richard E. Chaisson,[2] Charles L. Daley,[5] Malgosia Grzemska,[6] Julie M. Higashi,[7] Christine S. Ho,[8] Philip C. Hopewell,[1] Salmaan A. Keshavjee,[9] Christian Lienhardt,[6] Richard Menzies,[10] Cynthia Merrifield,[1] Masahiro Narita,[12] Rick O'Brien,[13] Charles A. Peloquin,[14] Ann Raftery,[1] Jussi Saukkonen,[15] H. Simon Schaaf,[16] Giovanni Sotgiu,[17] Jeffrey R. Starke,[18] Giovanni Battista Migliori,[11] and Andrew Vernon[8]

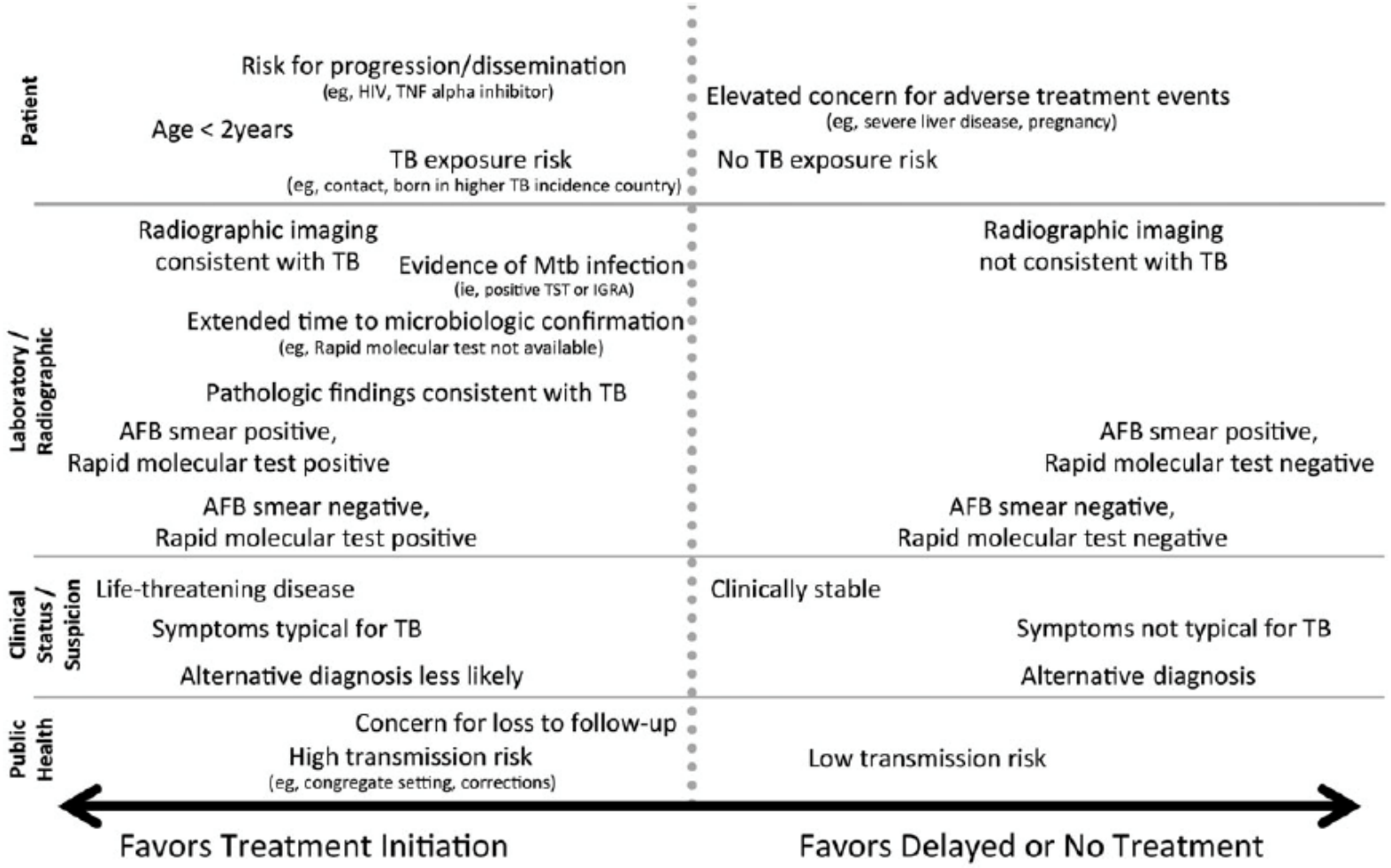


Figure 1. Factors to be considered in deciding to initiate treatment empirically for active tuberculosis (TB) (prior to microbiologic confirmation). Abbreviations: AFB, acid-fast bacilli; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; Mtb, *Mycobacterium tuberculosis*; TNF, tumor necrosis factor; TST, tuberculin skin test.

Table 2. Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.	Lesser

Increasing adherence for latent tuberculosis infection therapy with health department–administered therapy.

Cruz AT, Starke JR.
Pediatr Infect Dis J **31:** 193-195 (2012).

result

Looked at multiple variables related to therapy completion.

Only variable associated was health department DOT
(>90% completed vs. 50% for self administered; OR 7.7).

Unexplained deterioration during antituberculous therapy in children and adolescents: clinical presentation and risk factors.

Thampi N, Stephens D, Rea E, Kitai I.
Pediatr Infect Dis J **31:** 129-133 (2012).

result

Canadian case series.

Some children deteriorated during therapy; hard to distinguish from clinical failure.

Corticosteroids seemed to help a subset.

Time to Symptom Resolution in Young Children Treated for Pulmonary Tuberculosis

Nkosilesisa Mpofu, MPH,† Sizulu Moyo, PhD,*† Humphrey Mulenga, MPH,*† Kany Kany A. Luabeya, MBBS,*† Michele Tameris, MBChB,*† Hennie Geldenhuys, MFamMed,*† Gregory Hussey, FFCH,† Thomas Scriba, PhD,*† Willem Hanekom, FCPaed,*† Hassan Mahomed, PhD,‡ and Mark Hatherill, MD*†*

1226 | www.pidj.com *The Pediatric Infectious Disease Journal* • Volume 33, Number 12, December 2014

result

In children with Sx referable to TB (cough, wheeze, FTT) symptoms took ≥60 days to resolve on appropriate Tx.

Do not use response to Tx as proof of Dx.

Image from the Library of Congress, WPA Posters Collection.