Update on use of IGRAs in diagnosis & management of TB

Advances in Respiratory Medicine Course 2010
National Heart & Lung Institute

Special Symposium:
What's new in the world of pulmonary infection?

Professor Ajit Lalvani

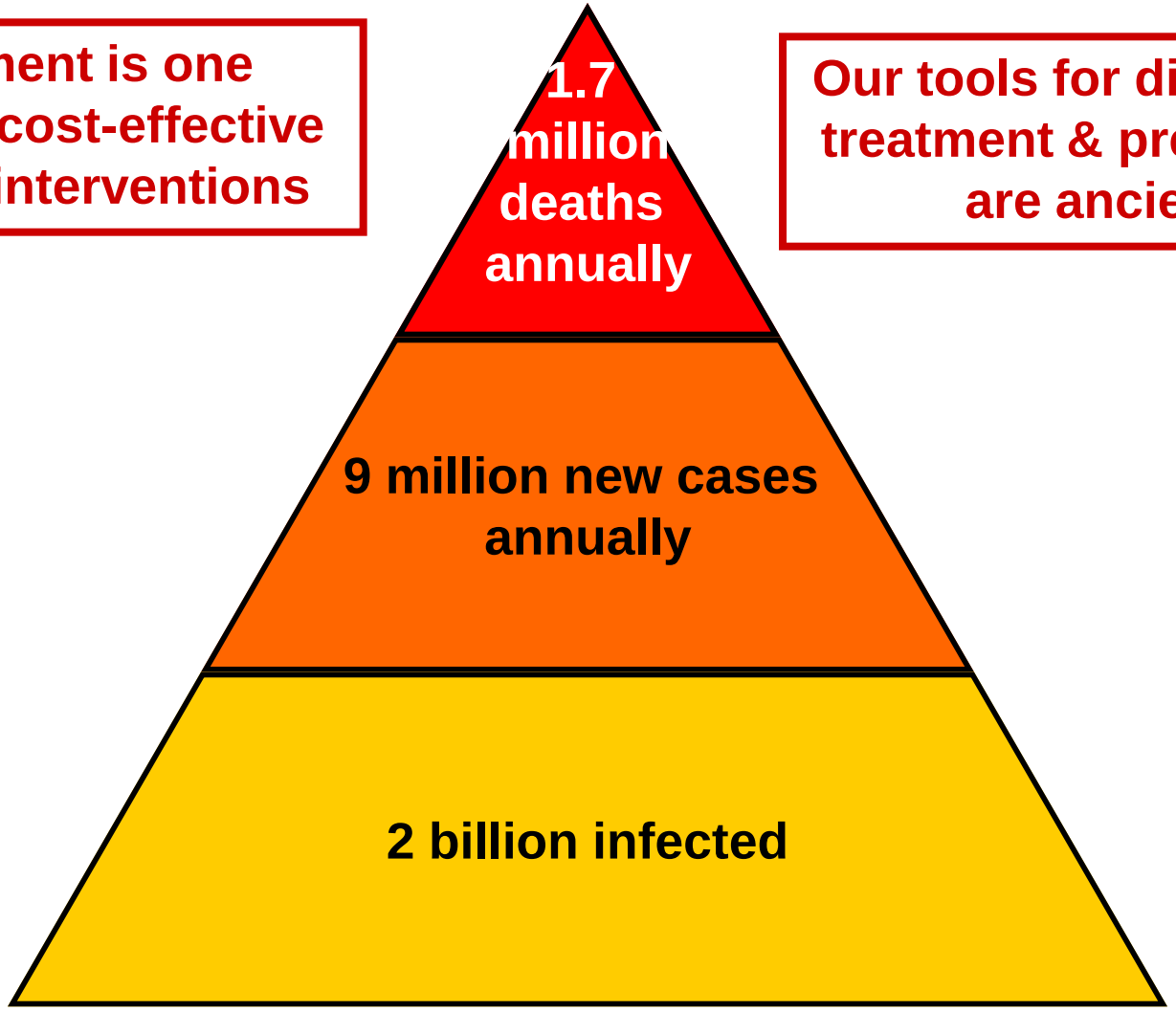
Chair of Infectious Diseases

National Heart and Lung Institute
Imperial College London

TB Service
Imperial College Healthcare NHS Trust

Global burden of TB

TB treatment is one of the most cost-effective healthcare interventions



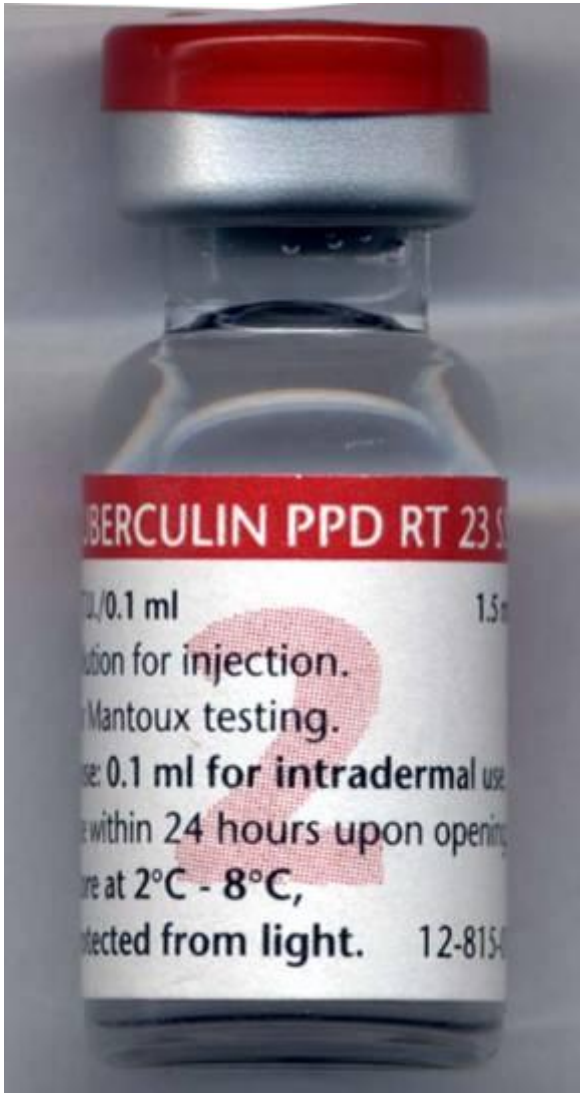
Our tools for diagnosis, treatment & prevention are ancient

We have been fighting a lethal pandemic with ancient weapons…..

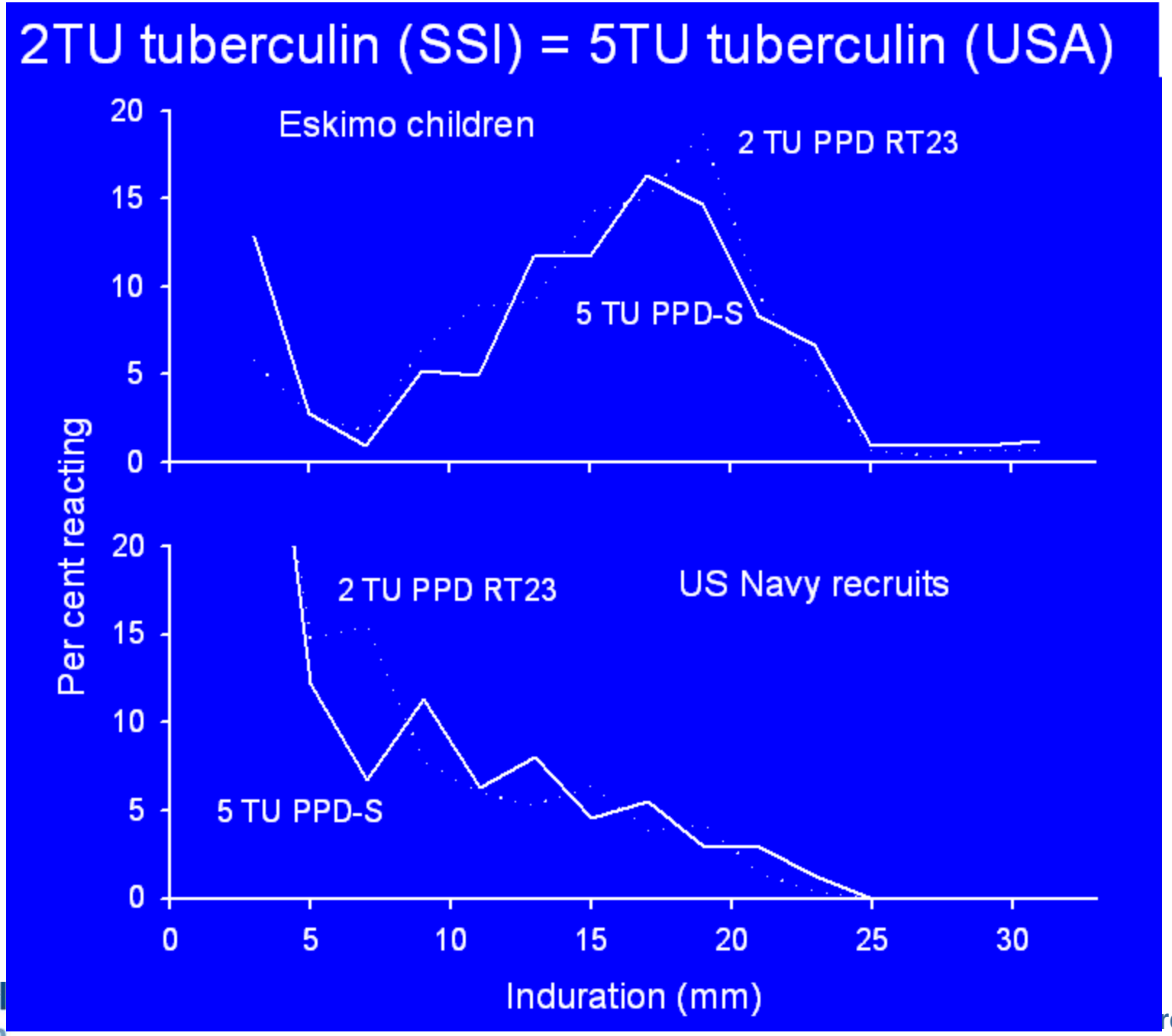
Diagnostics	Tuberculin Skin Test (TST)	1890
	Sputum microscopy	1880s
	Chest X-ray	1920
Vaccine	BCG	1921
Treatment	Streptomycin	1949
	Isoniazid	1952
	Pyrazinamide	1952
	Ethambutol	1961
	Rifampin	1966

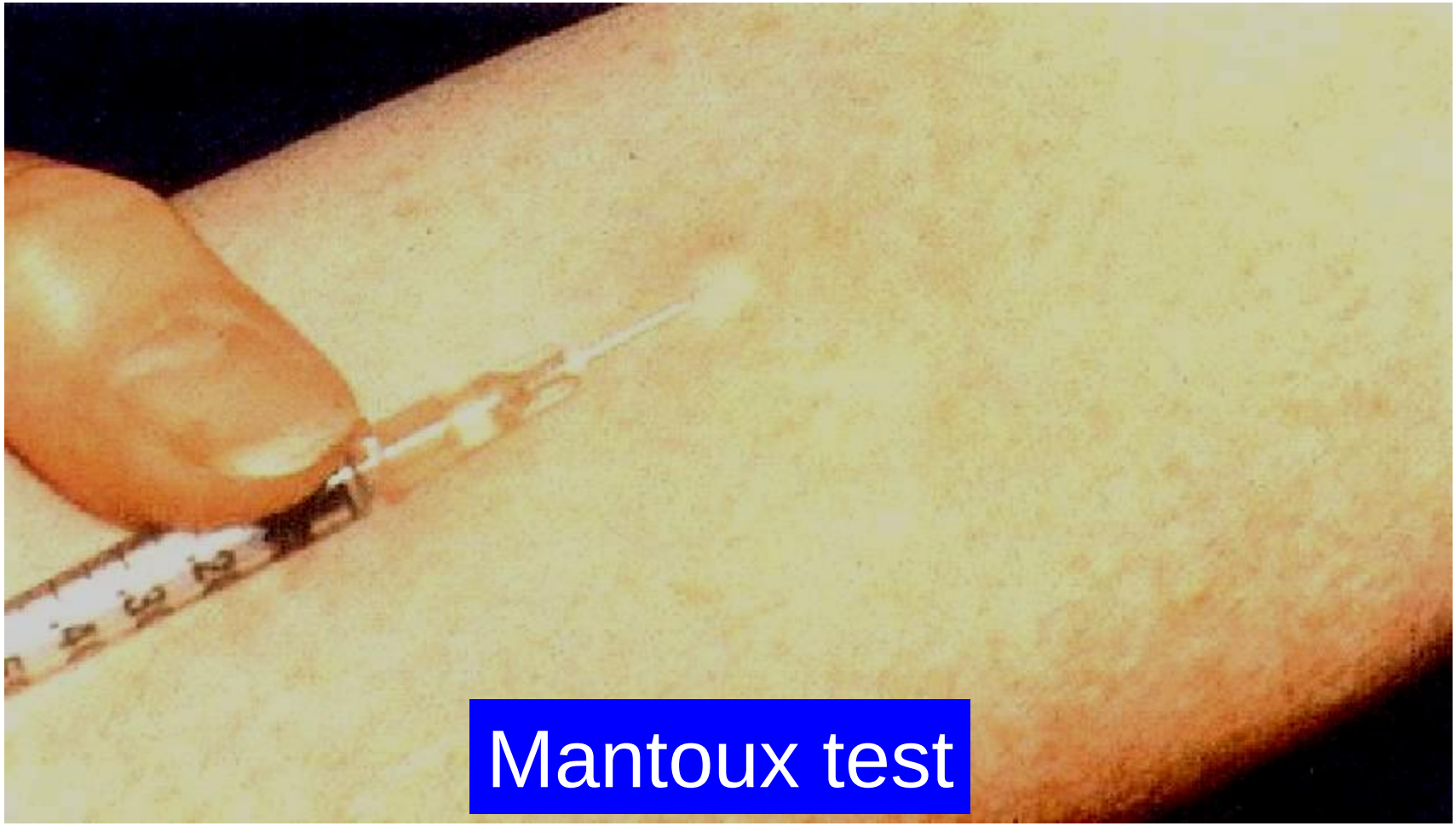
THE GLOBAL PLAN
TO STOP TB
2006-2015

2005:
tuberculin from Staten Serum Institut

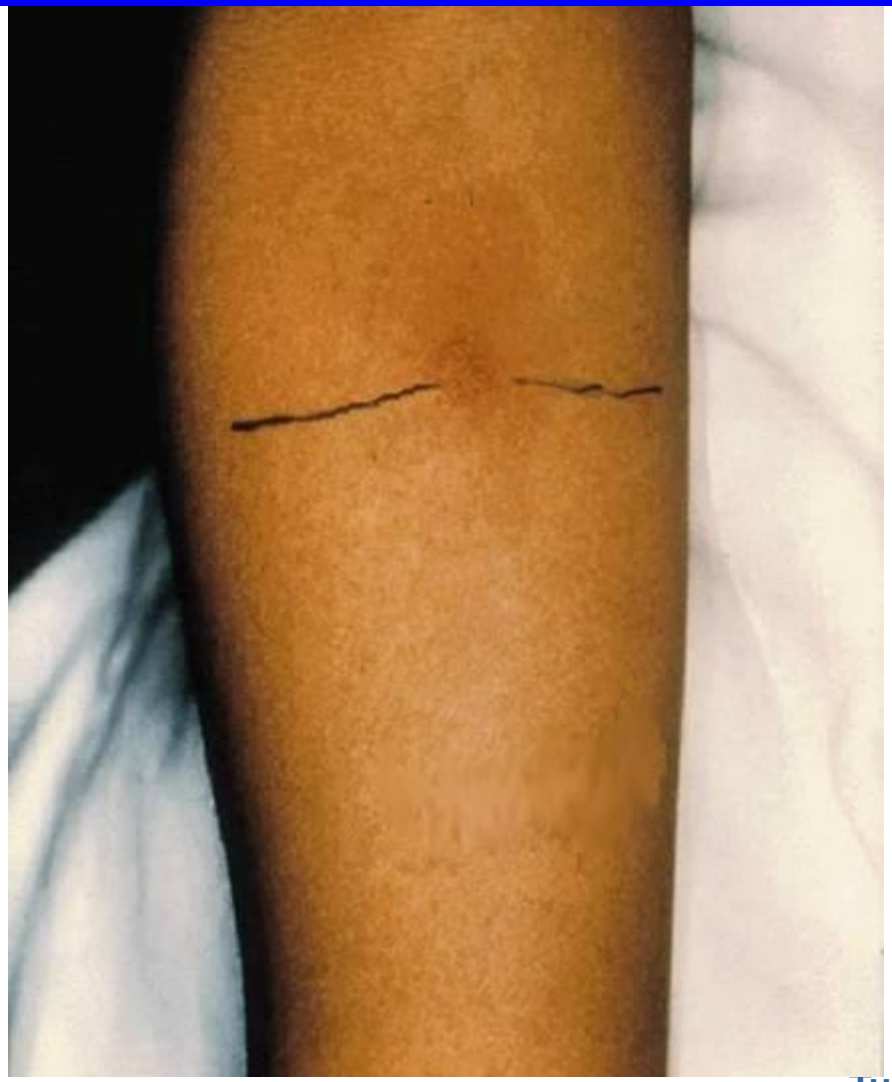


2TU tuberculin (SSI) = 5TU tuberculin (USA)

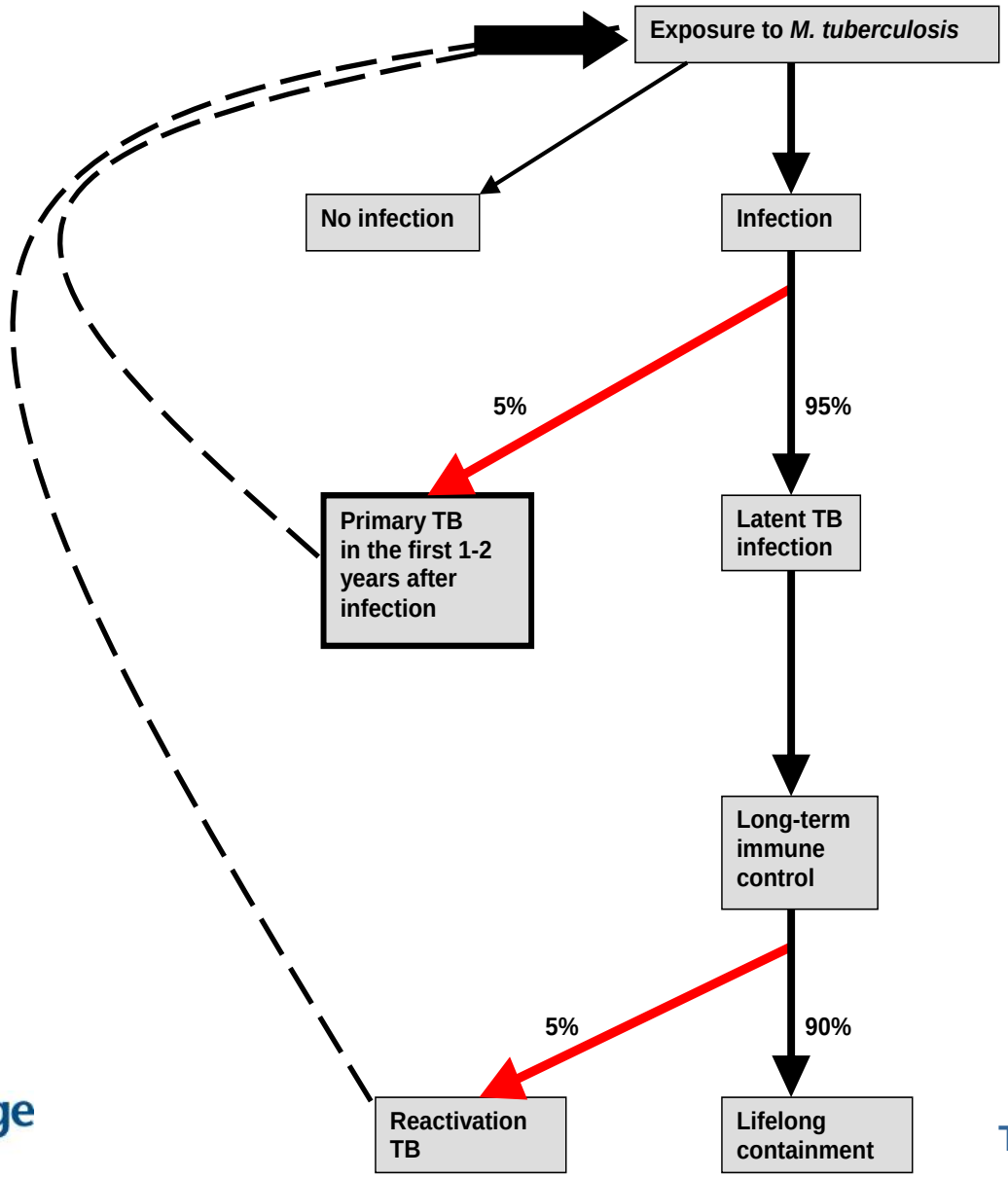



Mantoux test

Ballpoint pen method

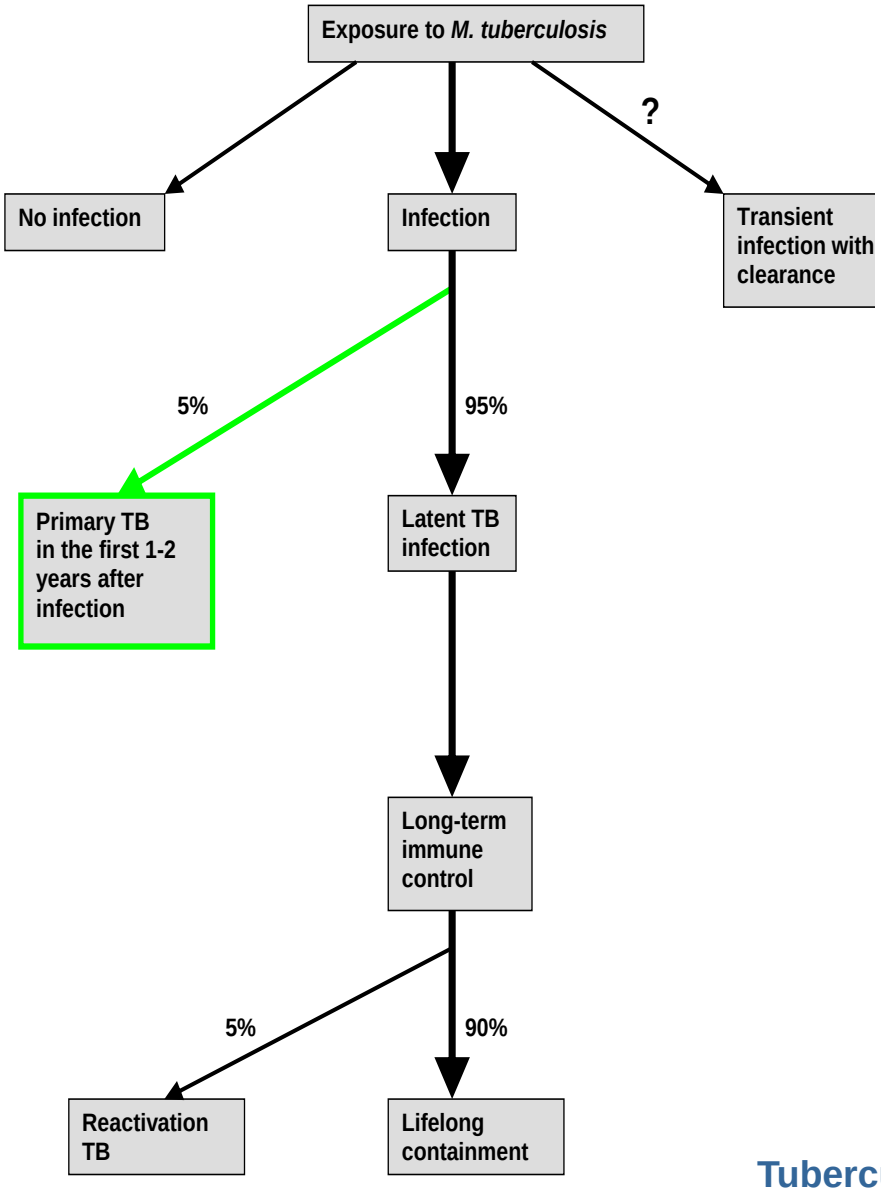


Flow Chart: The natural history of *M. tuberculosis* infection



Primary TB vs reactivation TB

Flow Chart: The natural history of *M. tuberculosis* infection



Primary lymph node TB

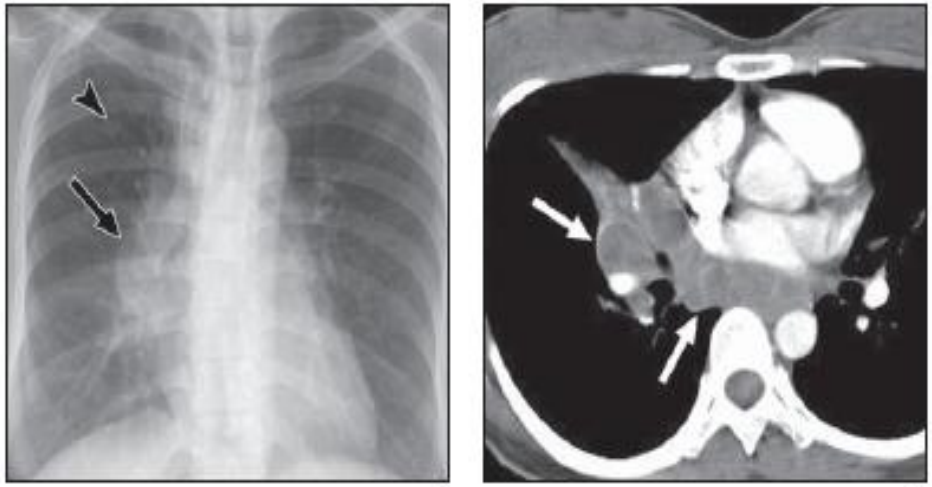


Fig. 1—Primary tuberculosis manifesting primarily as lymphadenopathy in 26-year-old woman.
A, Posteroanterior chest radiograph shows right hilar mass (*arrow*). Note smaller nodule (*arrowhead*) in right upper lung zone.
B, Contrast-enhanced transverse CT scan (5.0-mm section thickness) obtained at level of basal trunk using mediastinal window setting shows enlarged right hilar and subcarinal lymph nodes (*arrows*), central necrotic low attenuation, and peripheral rim enhancement.

Primary lymph node and pulmonary TB

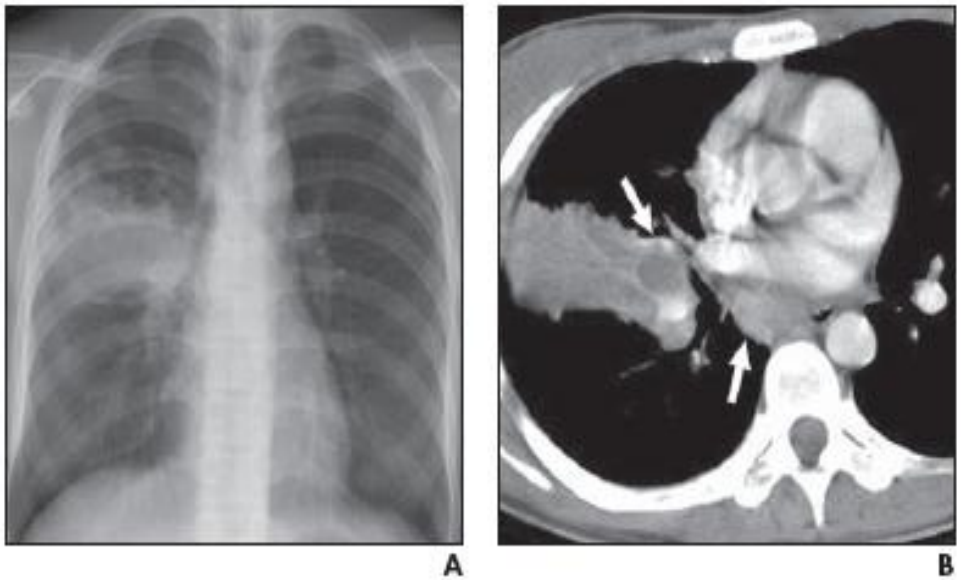


Fig. 2—Primary tuberculosis presenting with consolidation and lymphadenopathy in 21-year-old woman.
A, Posteroanterior chest radiograph shows airspace consolidation in right middle lung zone.
B, Contrast-enhanced transverse CT scan (5.0-mm section thickness) obtained at level of right middle lobar bronchus using mediastinal window setting shows airspace consolidation in right middle lobe. Note enlarged right hilar and subcarinal lymph nodes (*arrows*). Hilar node has necrotic low attenuation.

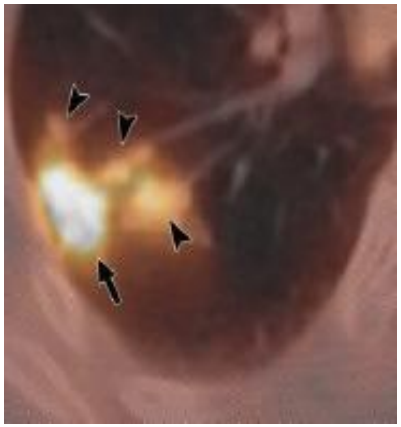
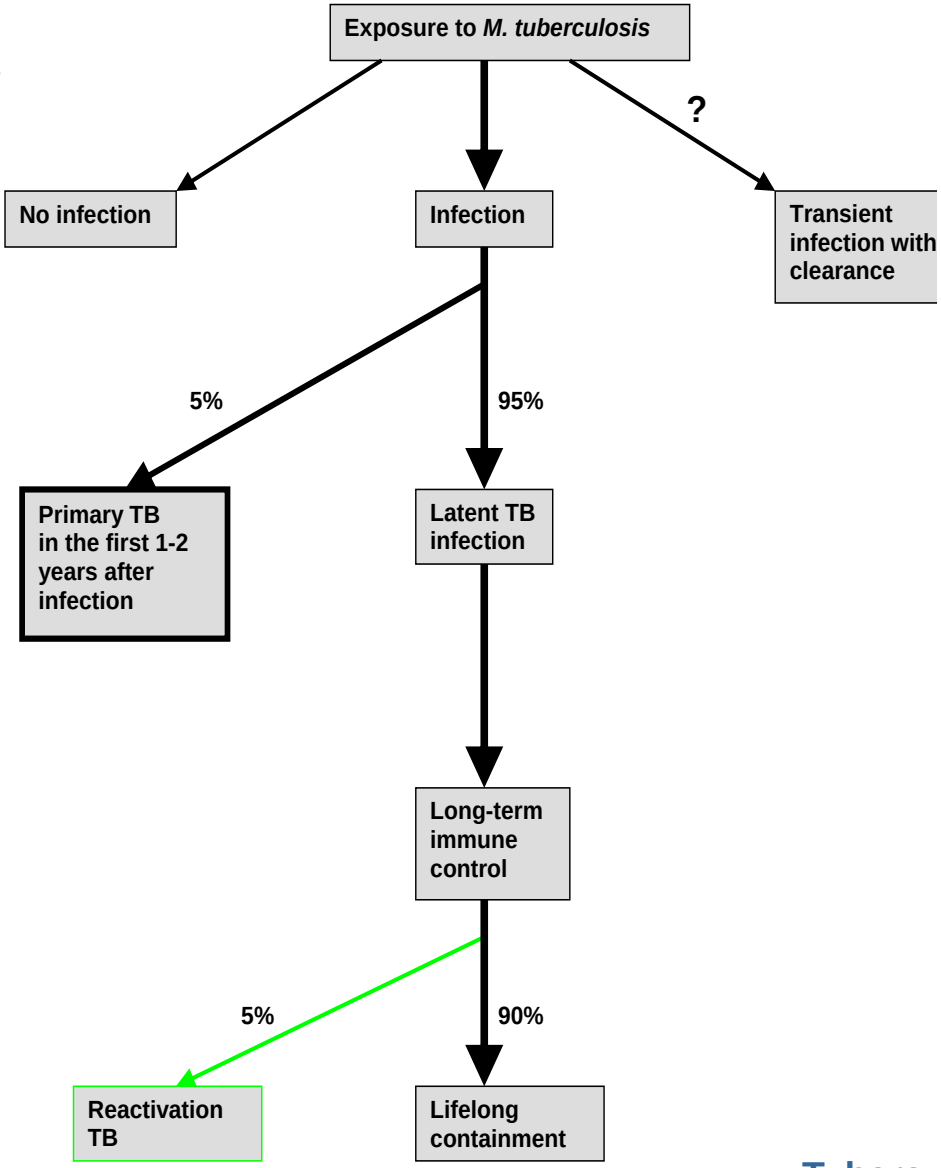


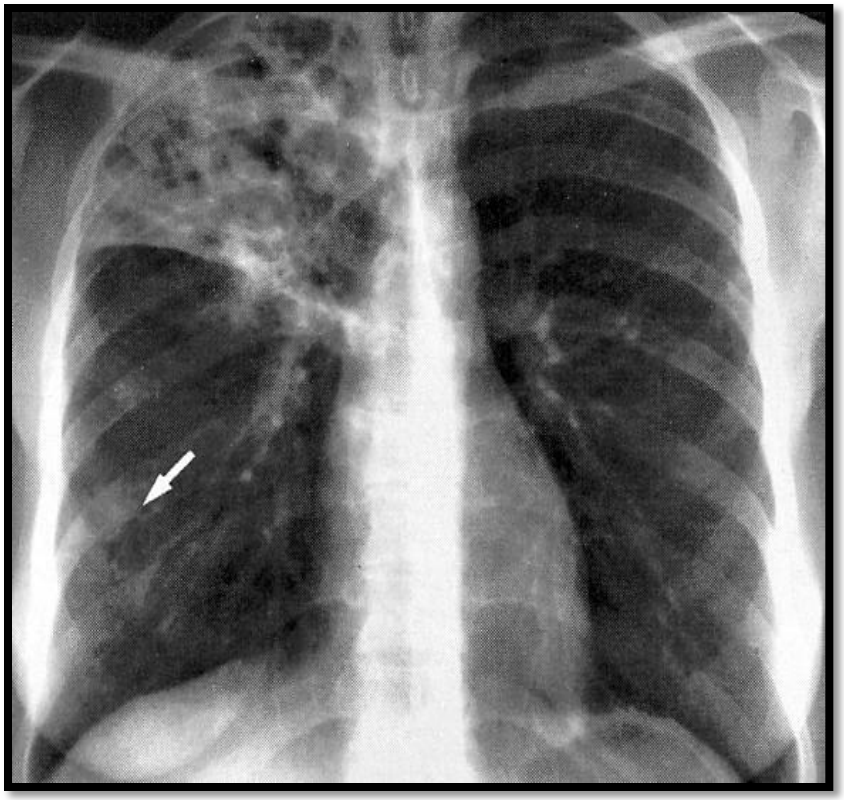
Fig. 3—Tuberculous granulomas in 58-year-old man
^{18}F-FDG PET/CT scan shows increased FDG uptake in nodules—well-defined predominant nodule (*arrow*) and surrounding smaller satellite nodules (*arrowheads*)—in right upper lobe with maximum standard uptake value of 6.1.

Primary TB vs reactivation TB

Flow Chart: The natural history of *M. tuberculosis* infection



Reactivation TB: radiology, pathology and histology



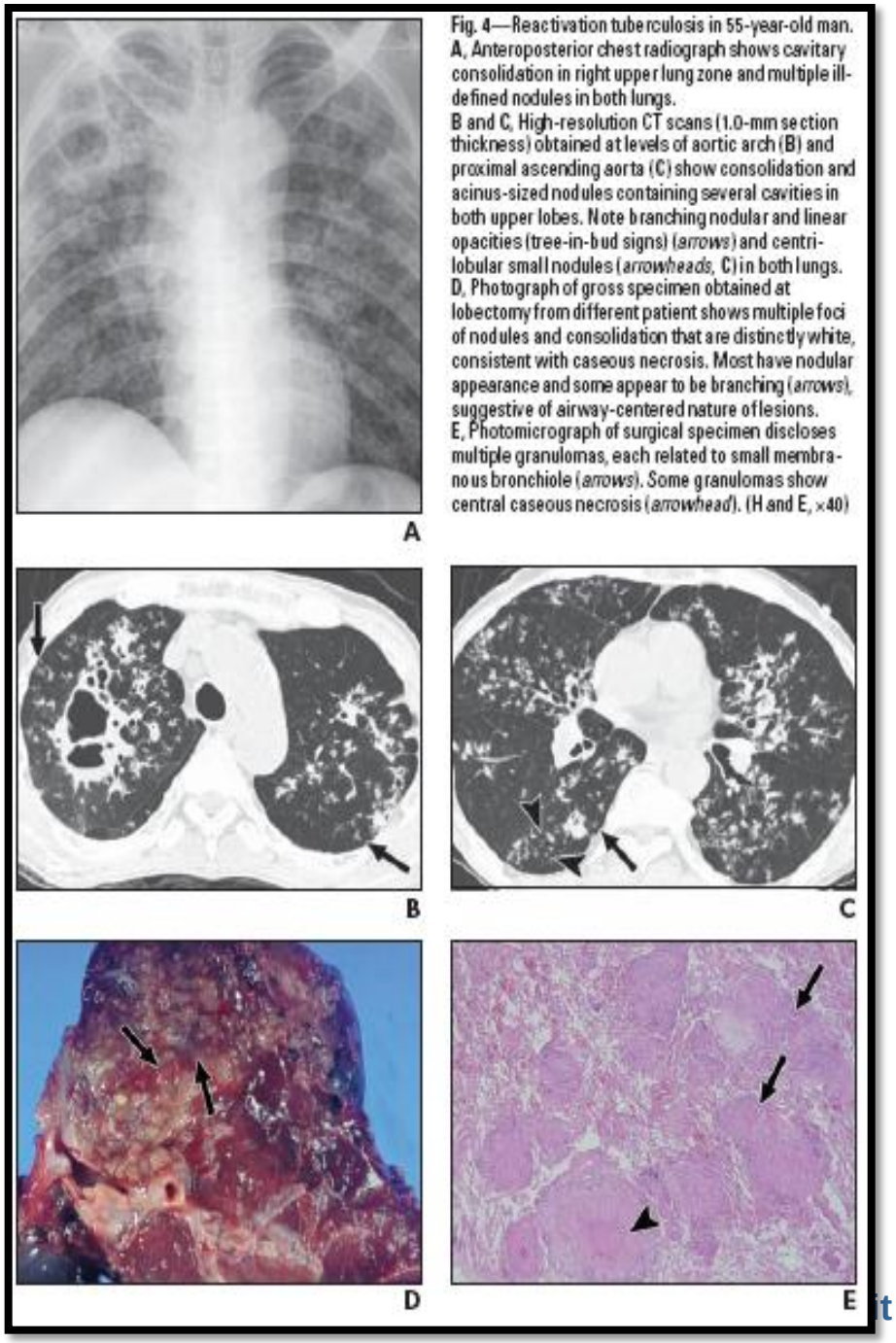
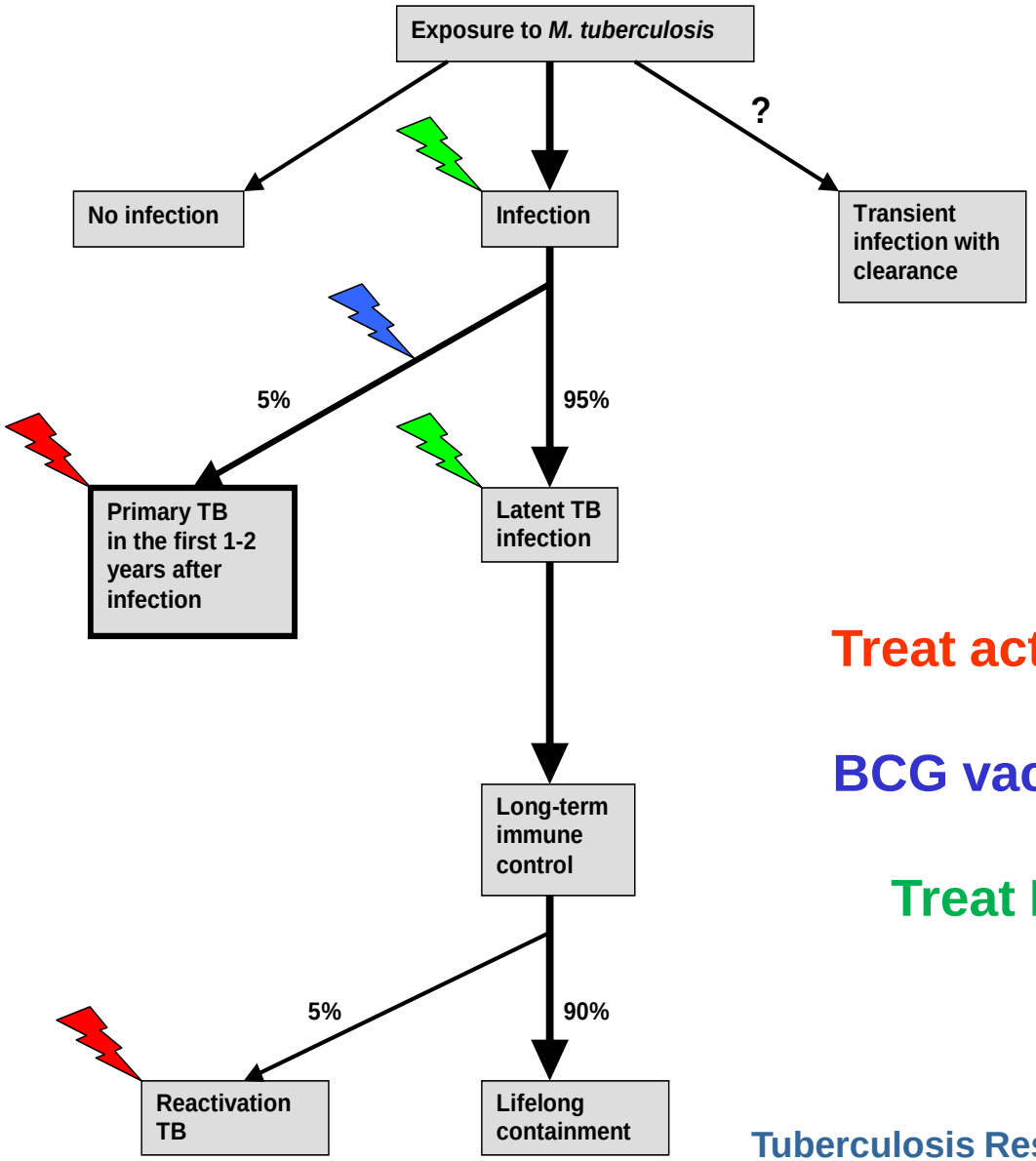


Fig. 4—Reactivation tuberculosis in 55-year-old man.
A, Anteroposterior chest radiograph shows cavitary consolidation in right upper lung zone and multiple ill-defined nodules in both lungs.
B and C, High-resolution CT scans (1.0-mm section thickness) obtained at levels of aortic arch (B) and proximal ascending aorta (C) show consolidation and acinus-sized nodules containing several cavities in both upper lobes. Note branching nodular and linear opacities (tree-in-bud signs) (*arrows*) and centrilobular small nodules (*arrowheads*, C) in both lungs.
D, Photograph of gross specimen obtained at lobectomy from different patient shows multiple foci of nodules and consolidation that are distinctly white, consistent with caseous necrosis. Most have nodular appearance and some appear to be branching (*arrows*), suggestive of airway-centered nature of lesions.
E, Photomicrograph of surgical specimen discloses multiple granulomas, each related to small membranous bronchiole (*arrows*). Some granulomas show central caseous necrosis (*arrowhead*). (H and E, ×40)

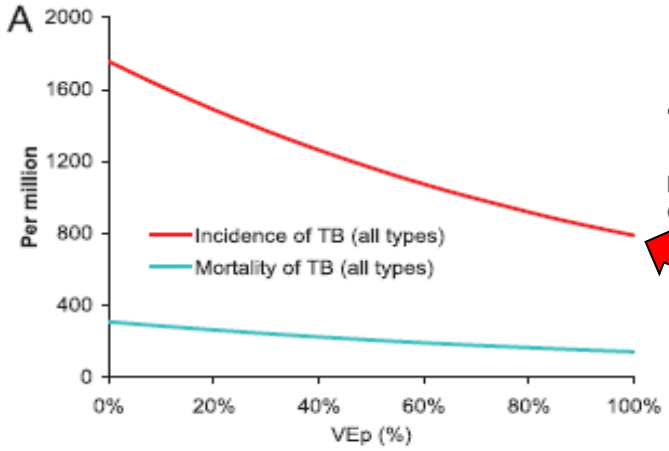
Flow Chart: The natural history of *M. tuberculosis* infection



Treat active TB

BCG vaccinate

Treat LTBI

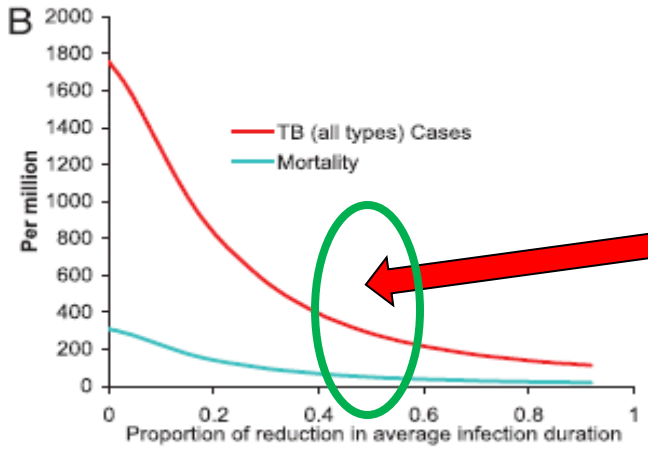


Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics

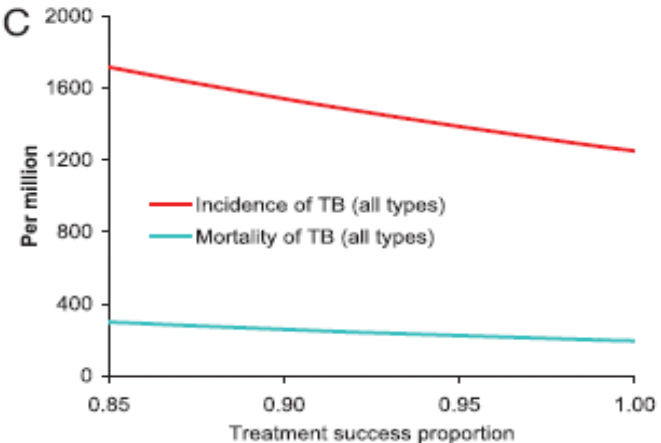
Laith J. Abu-Raddad[a,1], Lorenzo Sabatelli[a], Jerusha T. Achterberg[a,b,c], Jonathan D. Sugimoto[a,b], Ira M. Longini, Jr.[a,d], Christopher Dye[e], and M. Elizabeth Halloran[a,d,2]

PNAS 2009

Neonatal pre-exposure vaccine,
Decreasing progression from
latent to active TB



NAAT reducing average duration of
Infectiousness through earlier diagnosis



Improving proportion of
Patients cured by treatment
Of active TB

Roadblock 1

- Burden of MTB bacilli that must be present in sputum before detection is possible by sputum-smear microscopy, the only routinely and widely used same-day test for diagnosis of active TB

- Allows prolonged periods of transmission from patients with infectious smear-negative pulmonary TB before diagnosis and treatment

- DOTS is effective but only on those who are diagnosed and enter the treatment programme.....

- **We need same-day test with higher sensitivity than ZN.....and that can detect MDR and XDR-TB**

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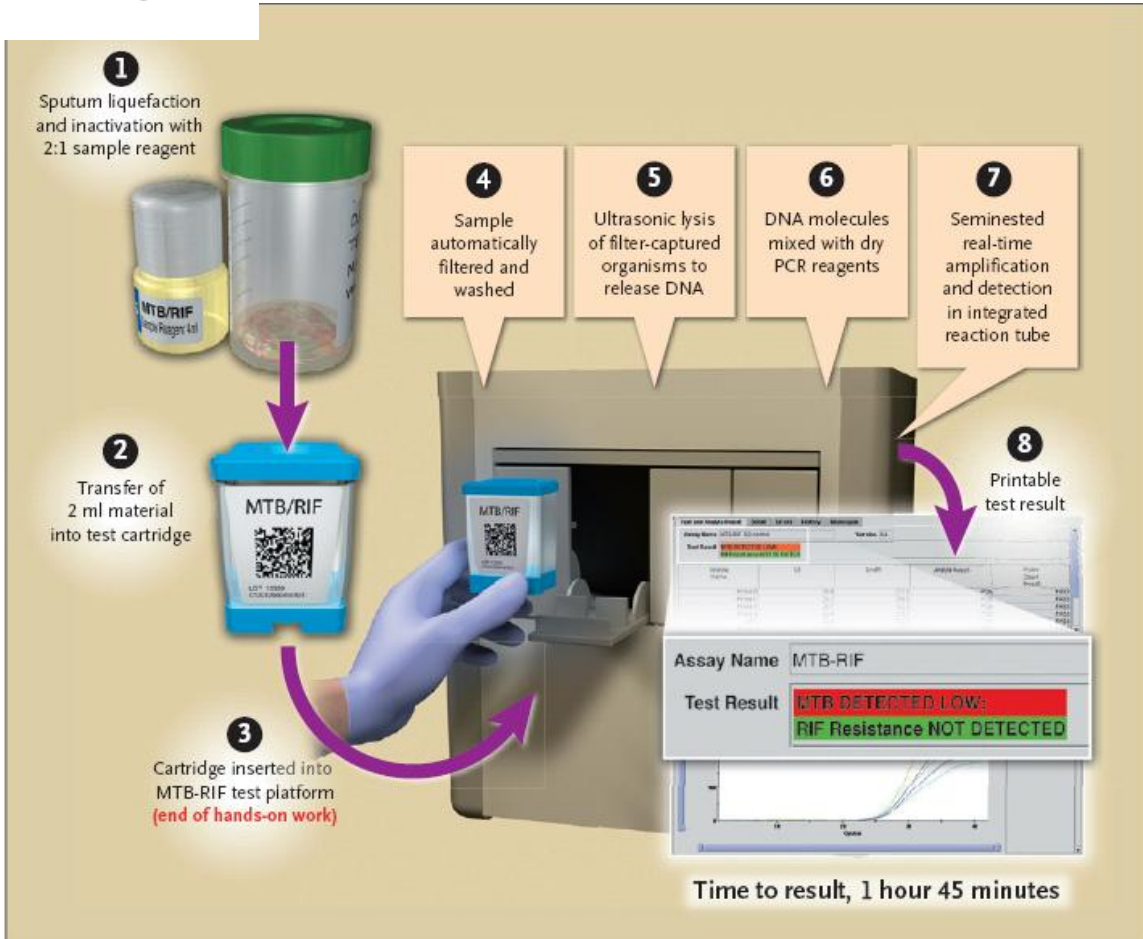
Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

Catharina C. Boehme, M.D., Pamela Nabeta, M.D., Doris Hillemann, Ph.D., Mark P. Nicol, Ph.D., Shubhada Shenai, Ph.D., Fiorella Krapp, M.D., Jenny Allen, B.Tech., Rasim Tahirli, M.D., Robert Blakemore, B.S., Roxana Rustomjee, M.D., Ph.D., Ana Milovic, M.S., Martin Jones, Ph.D., Sean M. O'Brien, Ph.D., David H. Persing, M.D., Ph.D., Sabine Ruesch-Gerdes, M.D., Eduardo Gotuzzo, M.D., Camilla Rodrigues, M.D., David Alland, M.D., and Mark D. Perkins, M.D.

Quantum leap in diagnosis
Of **active** TB

- Sensitivity of 3 samples: 98%
- May be as sensitive as culture
- Time-to-result: 90 mins
- Detects Rif resistance too
- WHO-endorsed: Dec 2010



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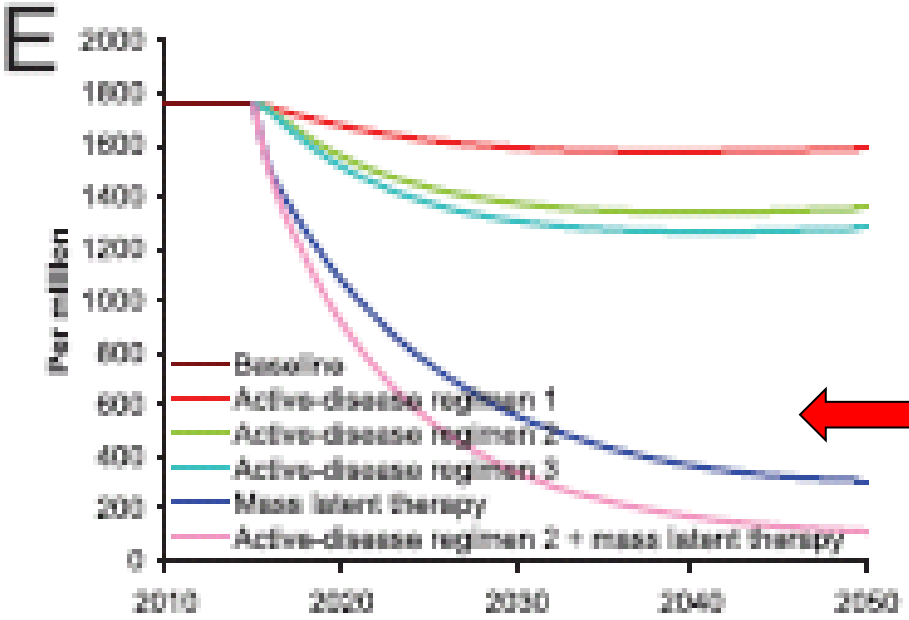
Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics

Laith J. Abu-Raddad[a,1], Lorenzo Sabatelli[a], Jerusha T. Achterberg[a,b,c], Jonathan D. Sugimoto[a,b], Ira M. Longini, Jr.[a,d], Christopher Dye[e], and M. Elizabeth Halloran[a,d,2]

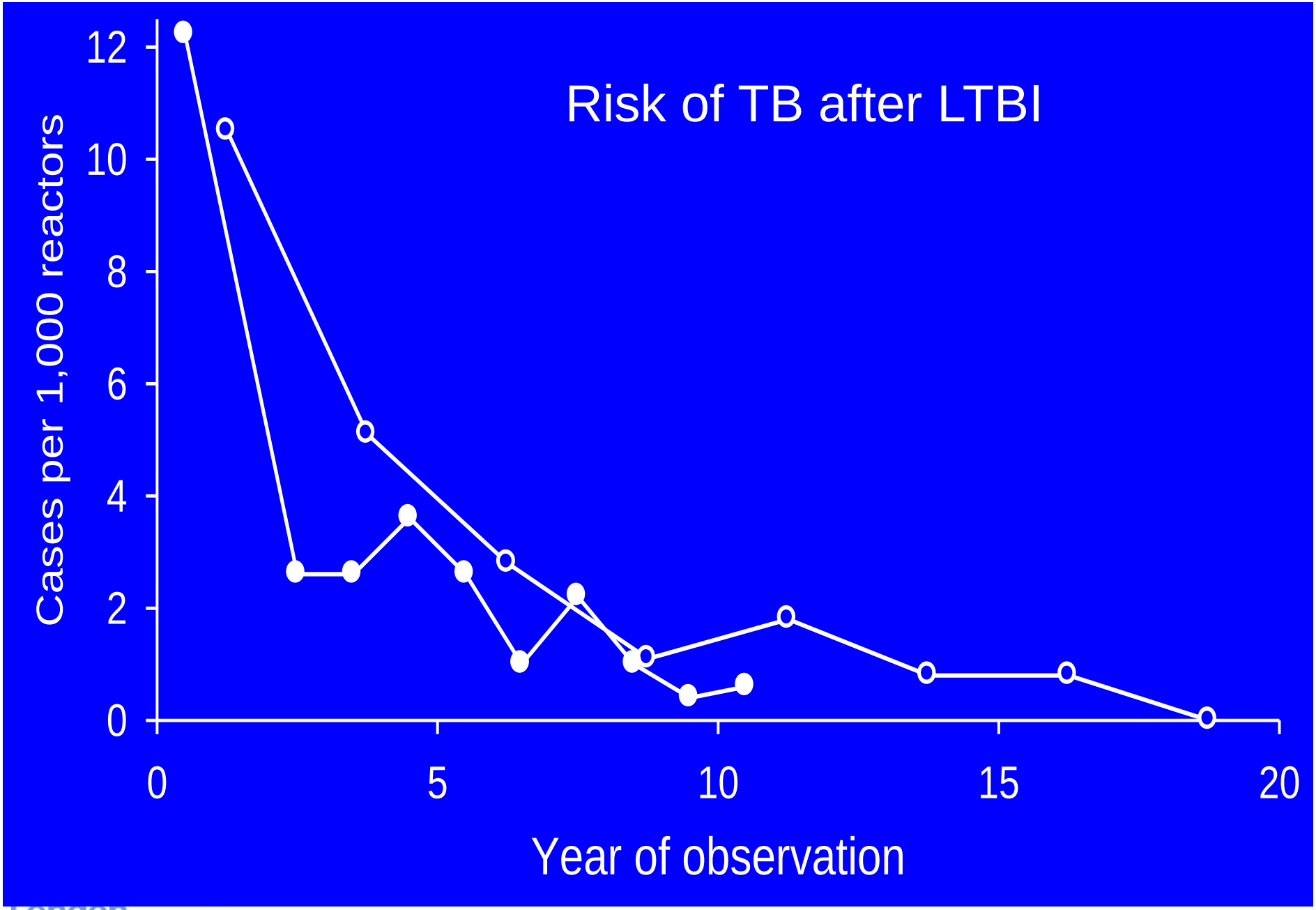
PNAS 2009



Mass latent therapy

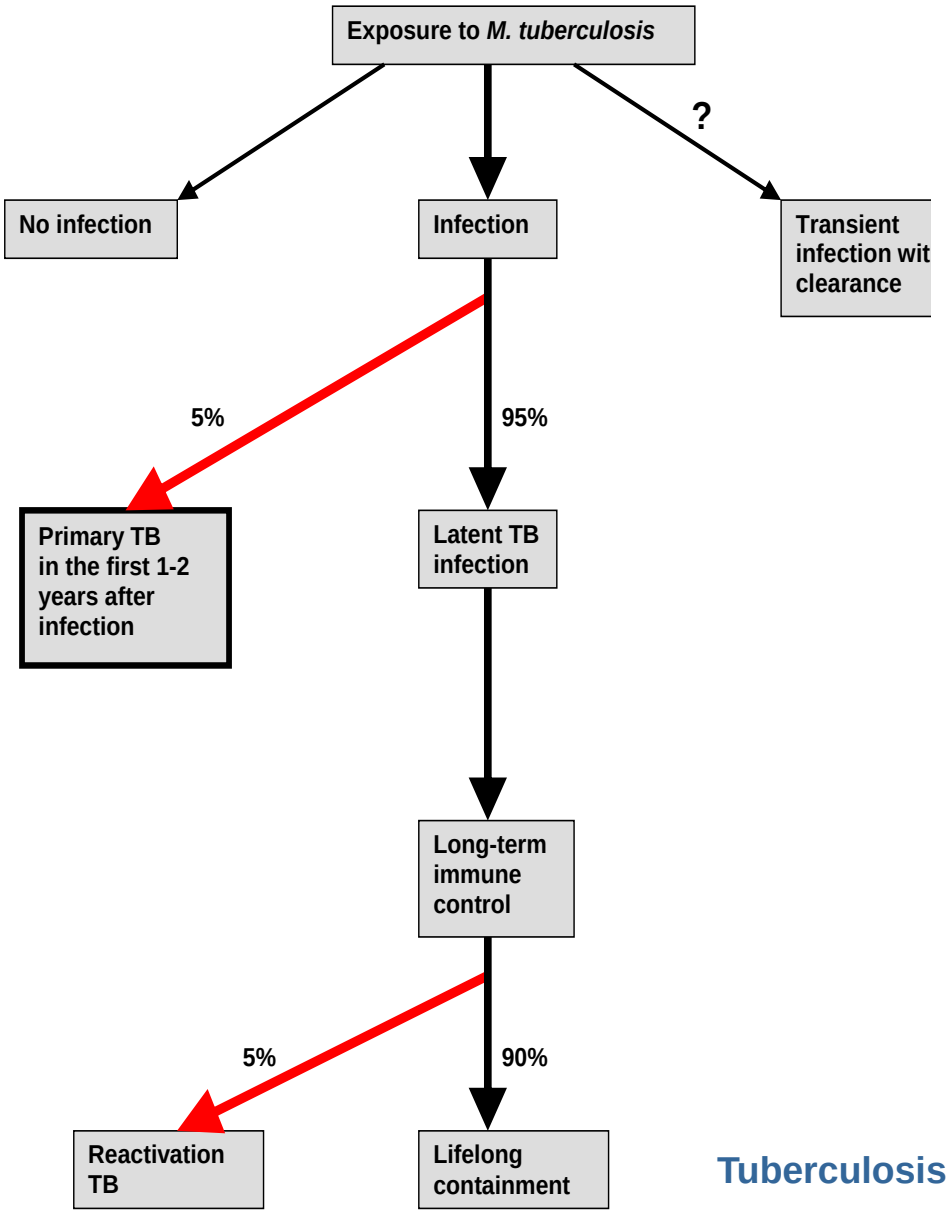
Roadblock 2

- 5% of recently-infected TB contacts - as defined by positive tuberculin skin test [TST] - progress to active TB within 2 yrs
  - Much higher for children and HIV-coinfected
- Therefore we have to treat 20 TST+ contacts to prevent a single case of active TB
- This approach is effective in low-burden nations (eg USA, EU) but is operationally impractical in regions with high TB (and HIV) burden
- **We need a test with higher prognostic power than TST**


Risk of TB after LTBI
Cases per 1,000 reactors
0
2
4
6
8
10
12
0
5
10
15
20
Year of observation

Factors promoting progression to active disease

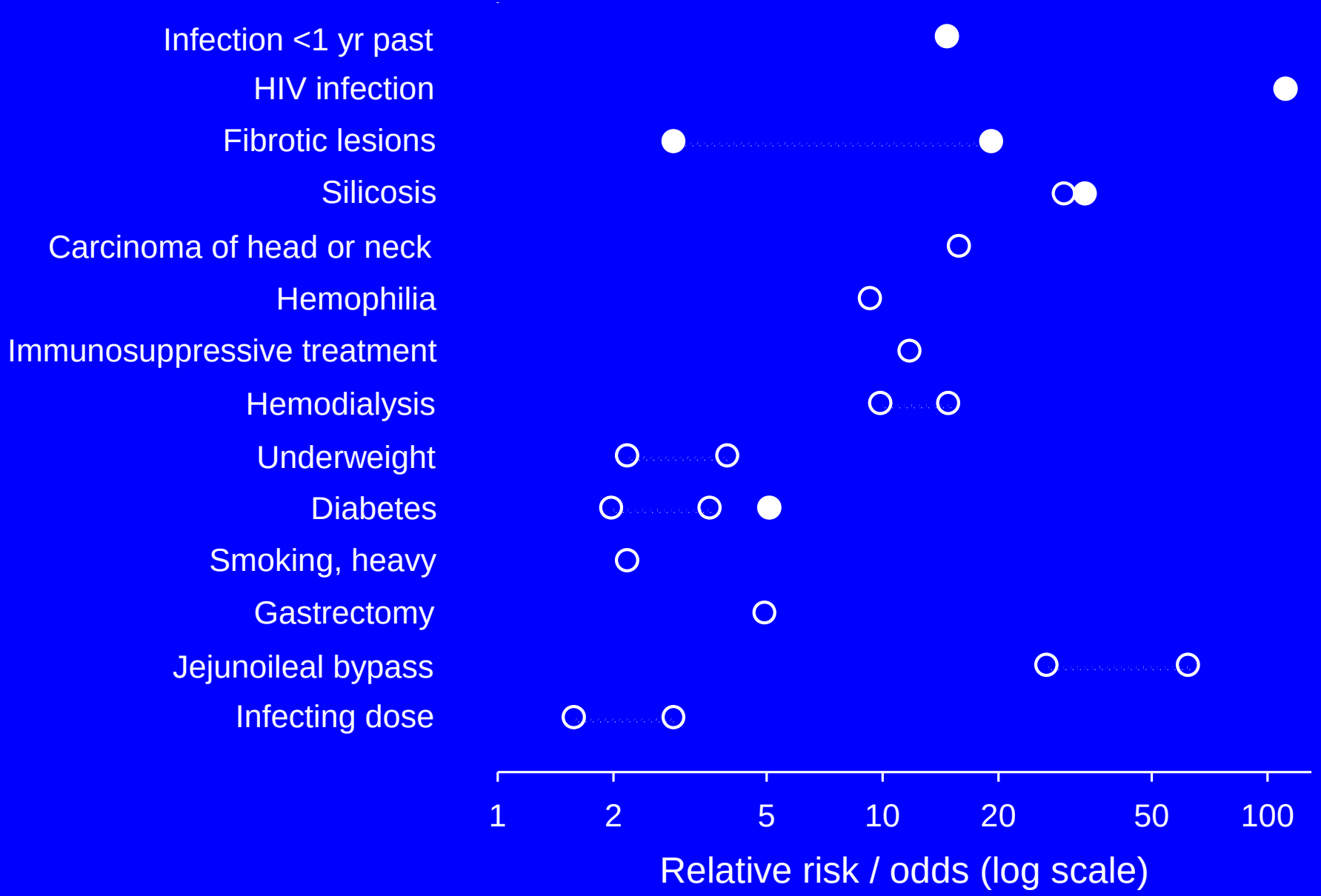
Flow Chart: The natural history of *M. tuberculosis* infection



Factors that promote progression to active disease

- HIV
  - at all CD4 counts
  - more extrapulmonary disease
- Immunosuppressive drugs:
  - High dose steroids
  - Anti-TNF alpha agents
- Age: very young; very old
- Poor nutrition
- Homelessness/ alcohol/ IVDU/ poverty

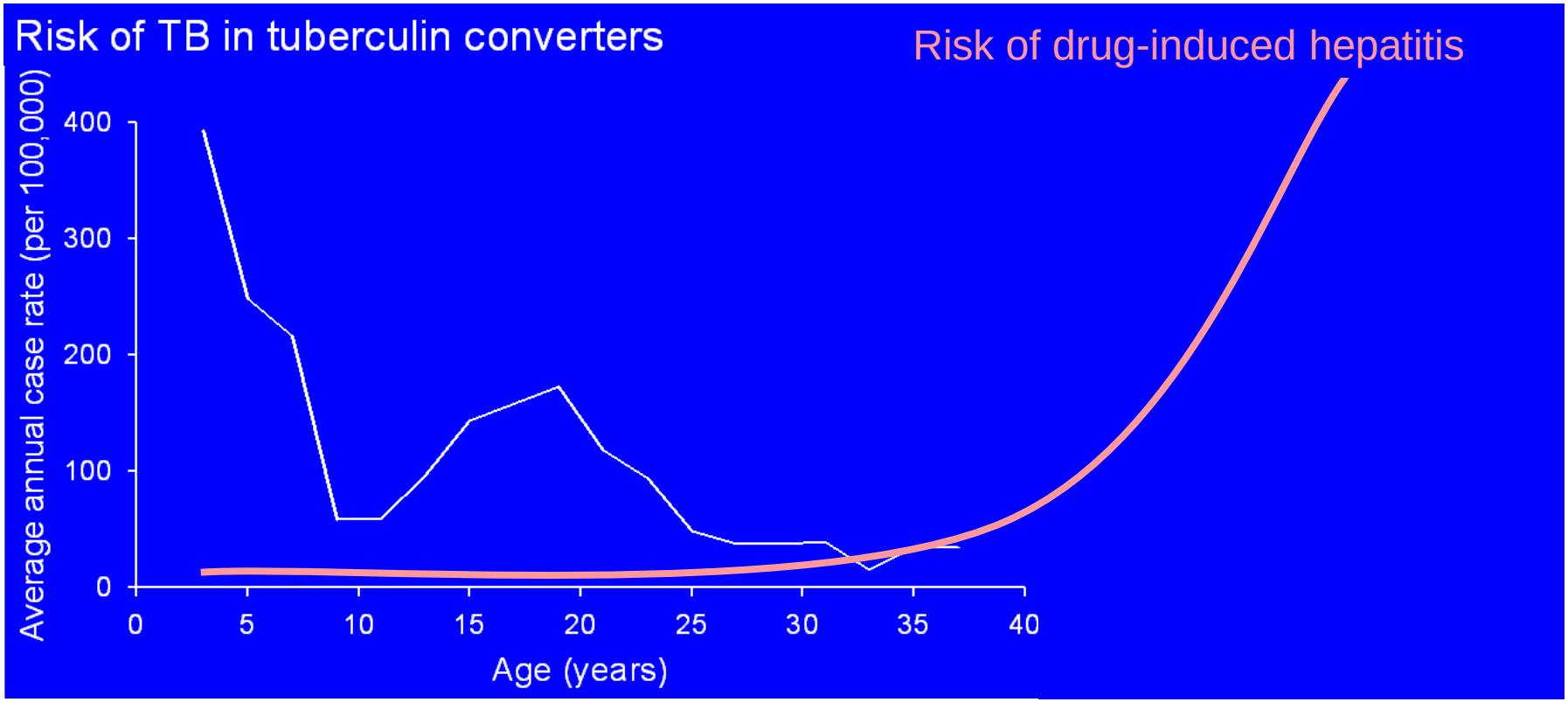
Risk factors for developing TB after LTBI



Drugs used for TLTBI

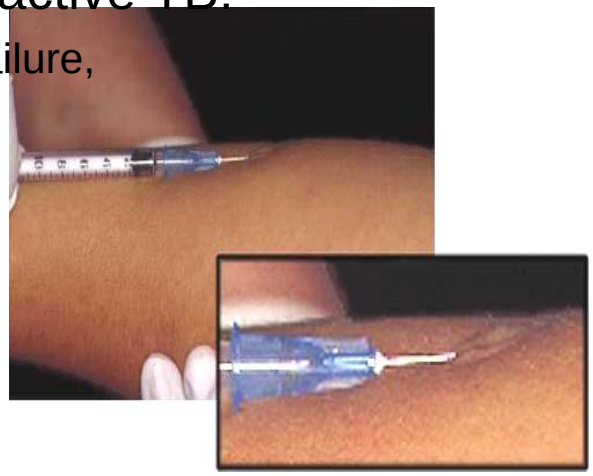
1.	Rifampicin/isoniazid	3 mo
2.	Isoniazid	6 mo
3.	Rifampicin	4 mo
4.	Rifampicin/pyrazinamide	2 mo

Is TLTBI safe?

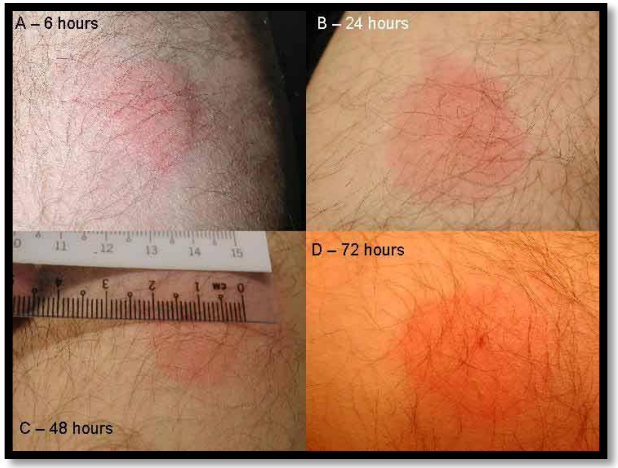


TST: inadequate tool to achieve the aims of targeted testing for LTBI

- **Targeted testing:** test and treat latently infected persons who are:
  (a) recent contacts (incl. new entrants) or
  (b) at increased risk of progression from LTBI to active TB:
    - HIV, young children, concomitant illnesses (renal failure, diabetes, etc), iatrogenic immunosuppression



- **But TST suffers from:**
- **Poor sensitivity:**
  – in the above vulnerable groups at highest risk
- **Poor specificity**:
  – Cross-reactivity with BCG vaccination
- **Problems of in vivo test**…….
  – Return visit, operator variability, inflammation



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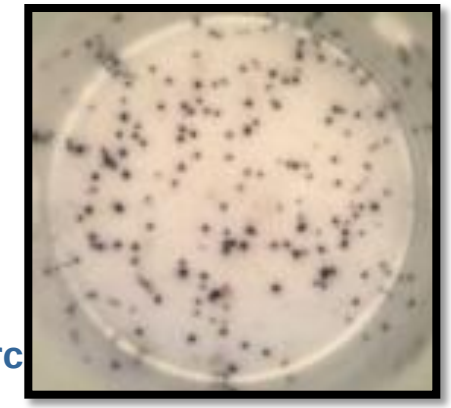
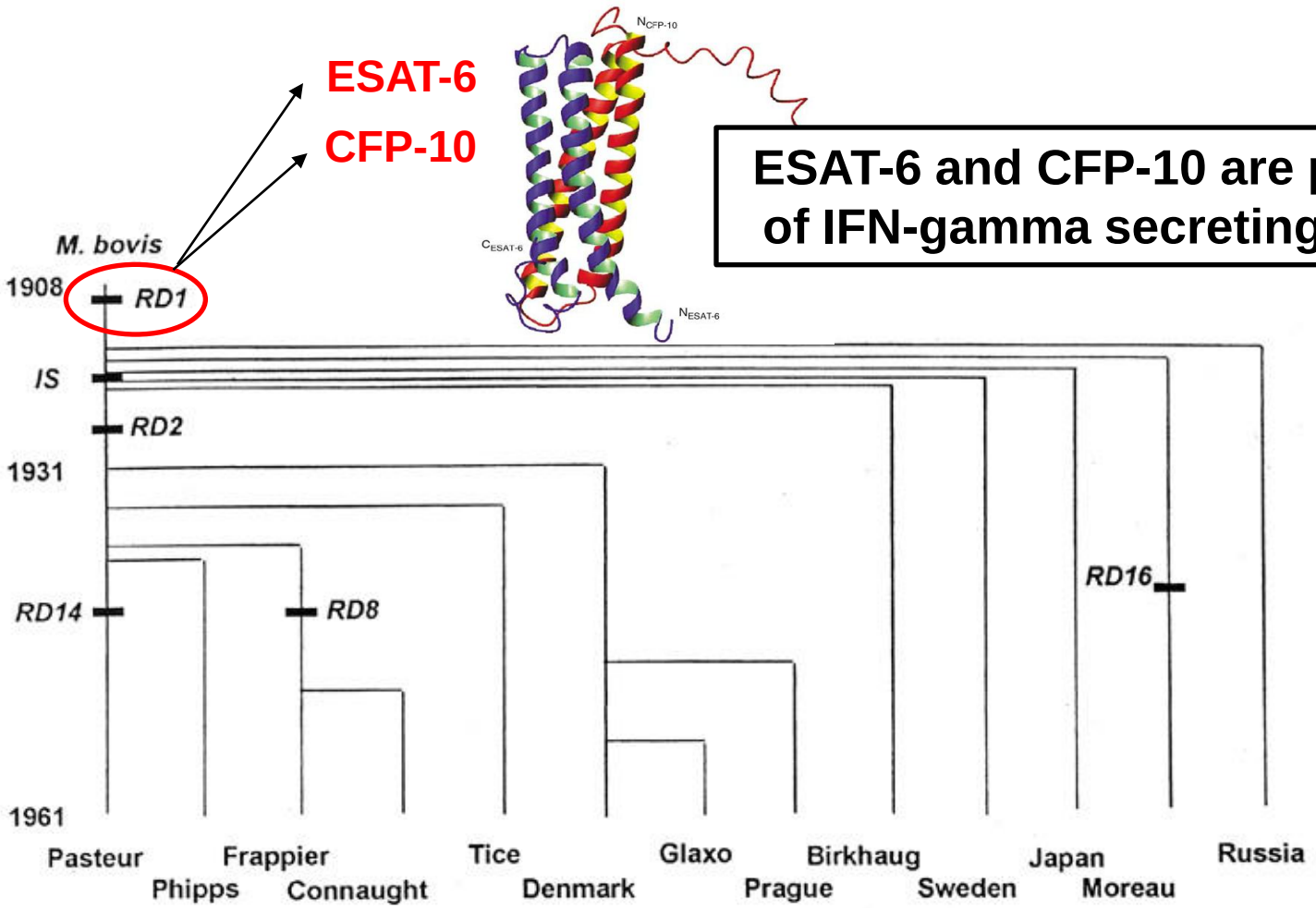
Rationale for a T cell-based approach

- *M. tuberculosis*: intracellular pathogen, difficult to recover from infected subjects
- Humoral response in *M. tuberculosis* infection is weak
- Infection evokes a strong Th1-type cell-mediated immune response (interferon-gamma CMI)
- MTB-specific interferon-gamma-secreting T cells might be an accurate marker of infection
- How can we measure them?



Tuberc

The RD1 genomic segment of *M. tuberculosis* is absent from all strains of BCG vaccine



ESAT-6 and CFP-10 are potent targets of IFN-gamma secreting T cells in TB

Cole et al Nature 1998
Behr et al Science 1999

Concept validation and proof of principle

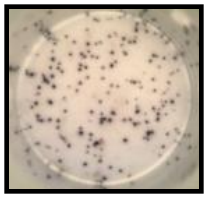
Highly *Specific* T cell antigens

Hypothesis:
ESAT-6 and CFP10-specific T cells are an accurate marker of TB infection

CONCEPT VALIDATION IN ACTIVE TB:

Cross-sectional case-control studies

Highly *Sensitive* T cell assays



Concept validation and proof of principle

Highly *Specific* T cell antigens

- **Sensitivity**: culture-confirmed (gold-standard) patients with active TB

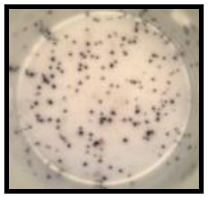
- **Specificity**:
  - unexposed BCG-vaccinated healthy controls
  - patients with non-tuberculous illnesses

Hypothesis:
ESAT-6 and CFP10-specific T cells are an accurate marker of TB infection

CONCEPT VALIDATION IN ACTIVE TB:

Cross-sectional case-control studies

Highly *Sensitive* T cell assays



Rapid Detection of *Mycobacterium tuberculosis* Infection by Enumeration of Antigen-specific T Cells

AJIT LALVANI, ANSAR A. PATHAN, HELEN McSHANE, ROBERT J. WILKINSON, MOHAMMED LATIF, CHRISTOPHER P. CONLON, GEOFFREY PASVOL, and ADRIAN V. S. HILL

Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom and Wellcome Centre for Clinical Tropical Medicine, Imperial College School of Medicine, Northwick Park Hospital, London, United Kingdom

Lalvani et al, AJRCCM 2001

Concept validation and proof of principle

- ***Lalvani et al AJRCCM 2001 (First proof-of-principle)***

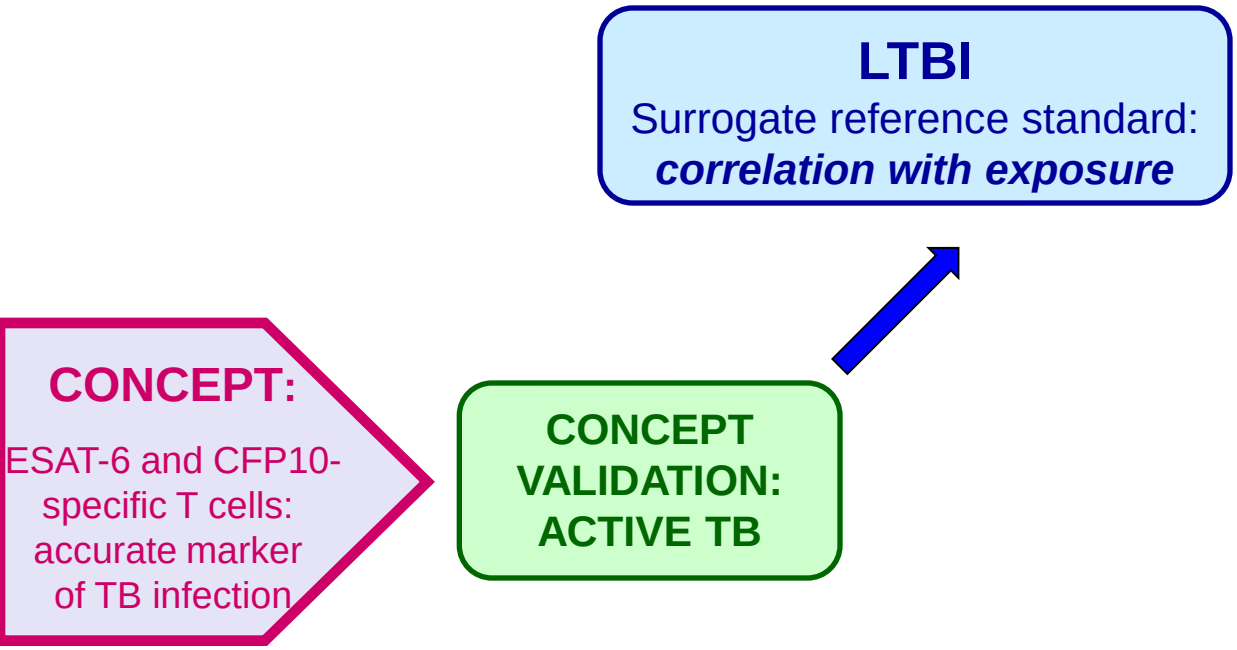
- *Pathan et al J Immunol 2001*
- ***Chapman et al AIDS 2002 (First proof-of-principle in HIV)***

- ***Mori et al AJRCCM 2004 (First proof-of-principle with QFT-Gold)***
- *Meier et al Eur J Clin Microbiol Infect Dis 2005*
- *Kang et al JAMA 2005*
- *Lee et al Eur Respir J 2006*
- *Tsiouris et al J Clin Microbiol 2006*
- *Kobashi et al CID 2006*
- *Adetifa et al BMC Infect Dis 2007*
- *Pai et al Infection 2007*
- *Wang et al EID 2007*
- *Detjen et al CID 2007*
- *Dewan et al CID 2007*
- *Dominguez et al Clin Vaccine Immunol 2008*
- *Kobashi et al Chest 2008*
- *Nishimura et al IJTLD 2008*

Conclusions

- Specificity
  - IGRAs not confounded by BCG
  - IGRAs not confounded by other illnesses
- Sensitivity
  - ELISpot > QFT > TST
  - Immunosuppressed: ELISpot > QFT >> TST

Clinical utility of IGRA: journey thru the evidence-base

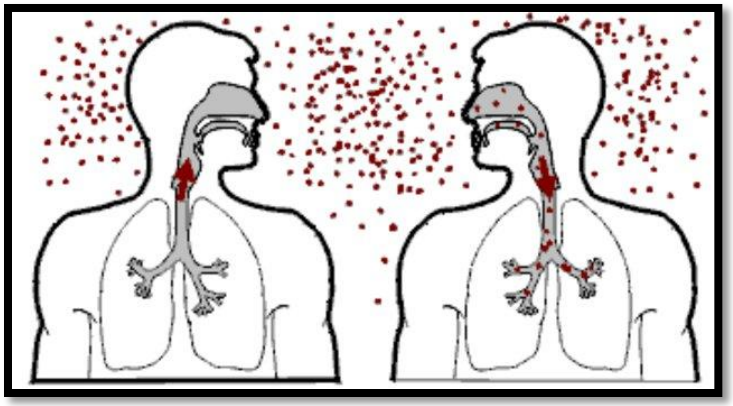


Surrogate reference standard for LTBI

MTB transmission promoted by proximity & duration of contact: key determinant of infection is amount of time spent sharing room air with source case

If IGRA are more sensitive & specific, they should correlate more closely with level of exposure to MTB than TST, but should be independent of BCG status

Cross-sectional epidemiological studies/ contact investigations comparing relationship of IGRA & TST results to intensity of TB exposure



Adults

Children

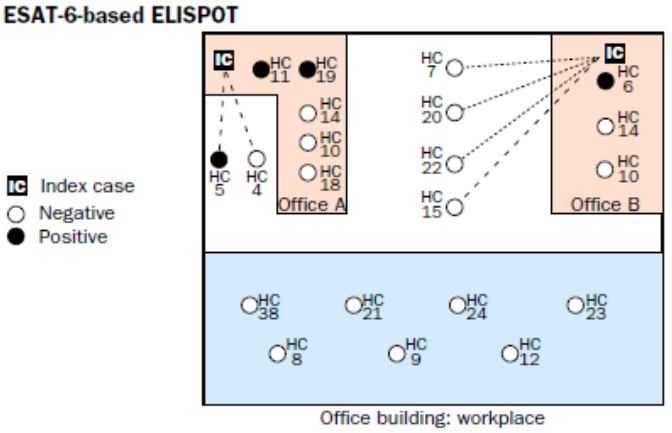
HIV+

Surrogate reference standard for LTBI: correlation with exposure

Proof-of-principle

Enhanced contact tracing and spatial tracking of *Mycobacterium tuberculosis* infection by enumeration of antigen-specific T cells

Lalvani et al Lancet 2001

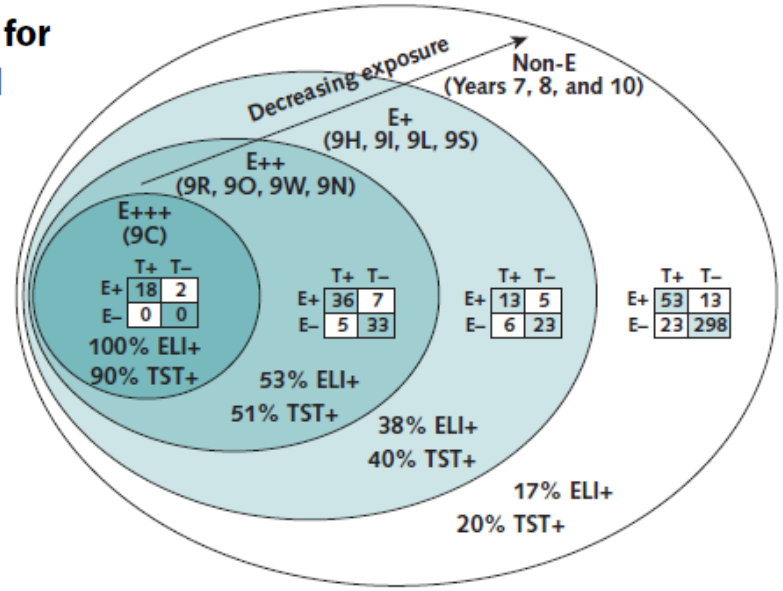


Superiority of a new test for LTBI

Comparison of T-cell-based assay with tuberculin skin test for diagnosis of *Mycobacterium tuberculosis* infection in a school tuberculosis outbreak

Ewer et al Lancet 2003

	ELISPOT	p	TST*	p	p for TST vs ELISPOT
Exposure to *M tuberculosis* in school					
Stratified exposure groups (whole school, n=535)	2·78 (2·22–3·48)	<0·0001	2·33 (1·88–2·88)	<0·0001	0·03
Direct exposure (weeks) in year 9 (n=148)	2·51 (1·58–3·99)	<0·0001	1·30 (1·10–1·54)	0·002	0·007
Indirect exposure (weeks) in years 7, 8, and 10 (n=387)	1·87 (0·87–4·04)	0·11	1·63 (0·78–3·43)	0·20	0·69



Imperial College London

Tuberculosis Research Unit

Surrogate reference standard for LTBI: correlation with exposure

- ***Lalvani et al Lancet 2001 (First proof-of-principle)***

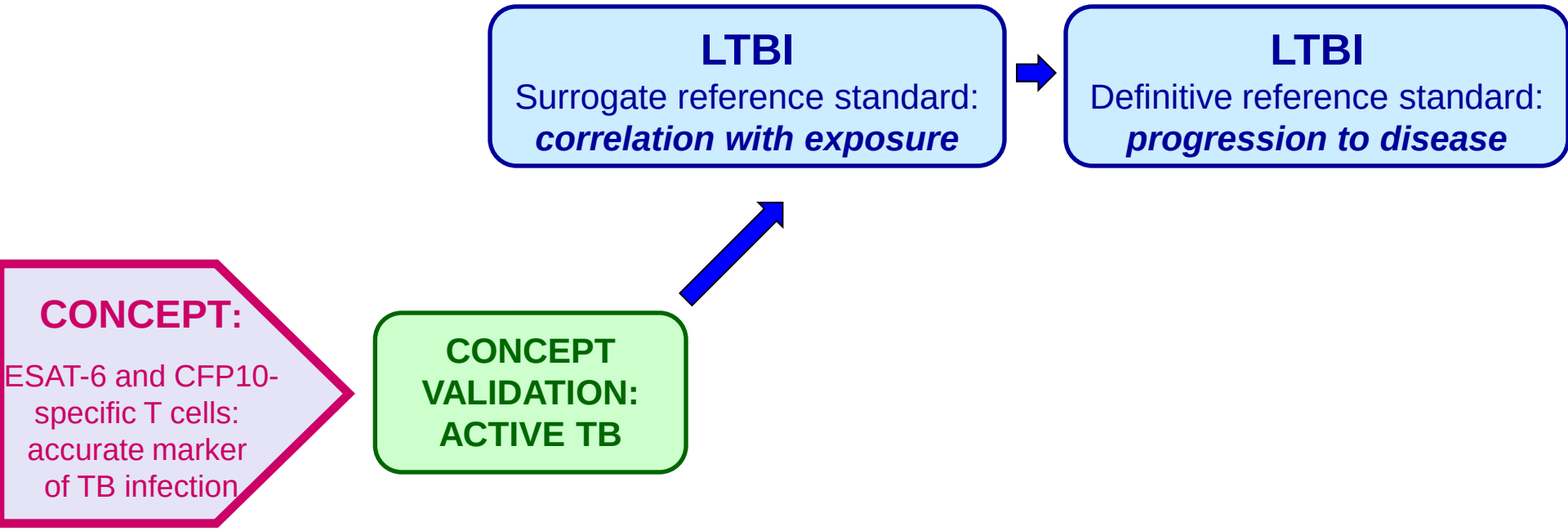
- ***Ewer et al Lancet 2003 (First to show superiority over TST)***
- *Richeldi et al AJRCCM 2004*
- *Shams et al AJRCCM 2005*
- ***Soysal et al Lancet 2005 (First in children)***

- ***Brock et al AJRCCM 2004 (First with QFT-Gold)***
- *Zellweger et al Int J Tub Lung Dis 2005*
- *Diel et al Eur Resp J 2006*
- *Kang et al JAMA 2005*
- *Hill et al Pediatrics 2006*
- ***Nakoaka et al Emerg Infect Dis 2006 (First in high-burden)***
- *Chun et al Diagn Microbiol Infect Dis 2008*
- *Okada et al Epidemiol Infect 2008*
- *Lighter et al Pediatrics 2009*

Conclusions

- IGRA correlate better with TB exposure than TST
- IGRA not confounded by TST

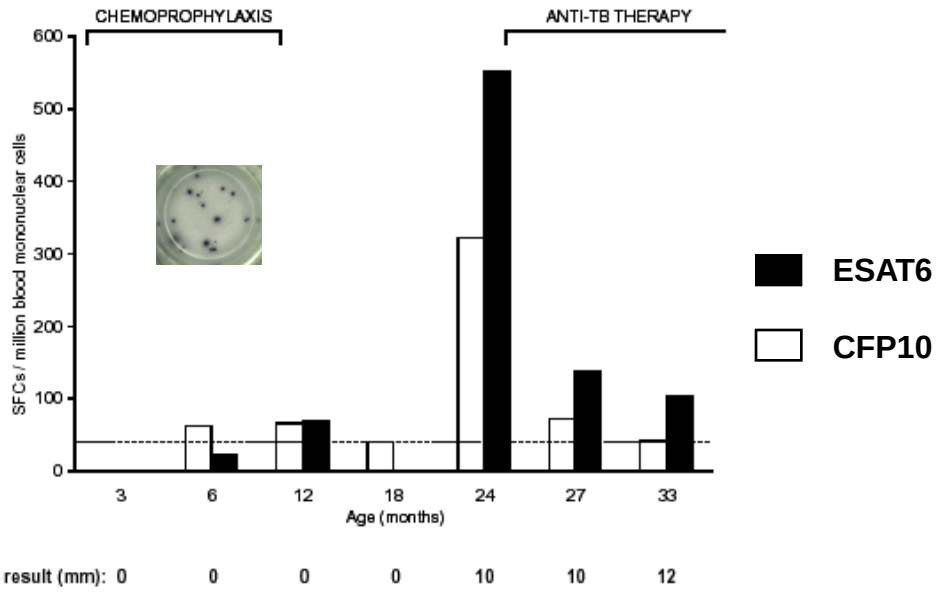
Clinical utility of IGRA: journey thru the evidence-base

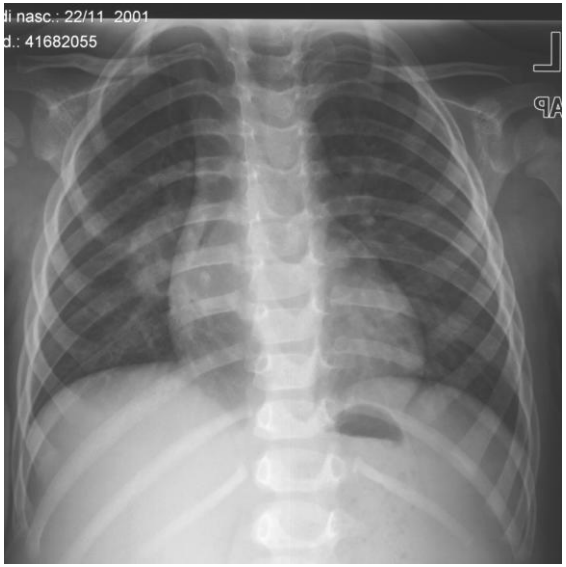


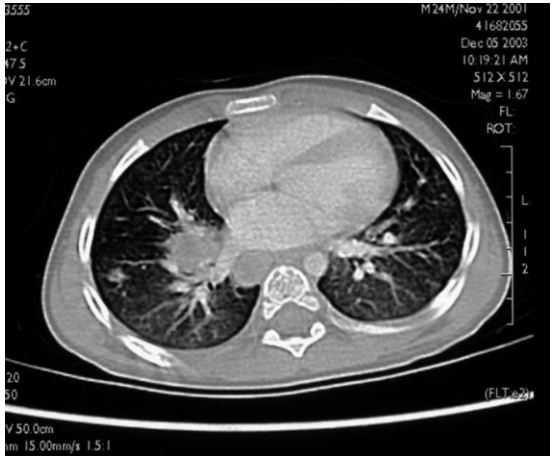
Do IGRA predict progression to active TB? The first case....

T-Cell–Based Diagnosis of Neonatal Multidrug-Resistant Latent Tuberculosis Infection

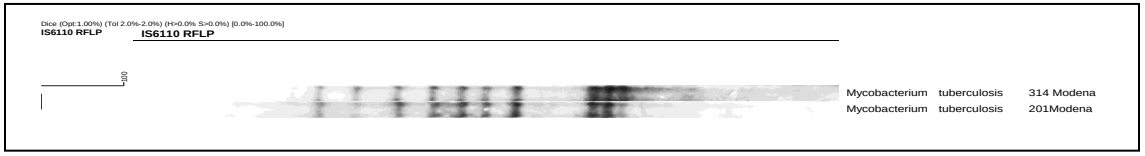
Luca Richeldi, MD, PhD[a], Katie Ewer, PhD[b], Monica Losi, PhD[a], Barbara M. Bergamini, MD[a], Kerry Millington, BSc[b,c], Leonardo M. Fabbri, MD[a], Ajit Lalvani, FRCP, DM[b,c]







RFLP analysis of MTB isolate from bronchoalveolar lavage: identical strain to that of the mother



Richeldi et al Pediatrics 2007

Imperial College London

Tuberculosis Research Unit

LTBI: prognostic power for progression to disease

Prospective longitudinal cohort study in community-based contact investigations

443 index patients with sputum smear-positive pulmonary tuberculosis

1024 child contacts enrolled at central study clinic

965 child contacts with complete baseline data

N=57 Never attended follow-up

908 child contacts

15 incident cases active TB over 2 years follow-up

337 ELISpot-positive TST-positive 317 (94%) received IPT **10**	**44 ELISpot-positive TST-negative** 18 (41%) received IPT **1**	**213 ELISpot-negative TST-positive** 140 (66%) received IPT **2**	**314 ELISpot-negative TST-negative** 146 (47%) received IPT **2**

Annals of Internal Medicine | ARTICLE

Prognostic Value of a T-Cell–Based, Interferon-γ Biomarker in Children with Tuberculosis Contact

Mustafa Bakir, MD; Kerry A. Millington, DPhil; Ahmet Soysal, MD; Jonathan J. Deeks, PhD; Serpil Efee; Yasemin Aslan, SRN; Davinder P.S. Dosanjh, DPhil; and Ajit Lalvani, DM

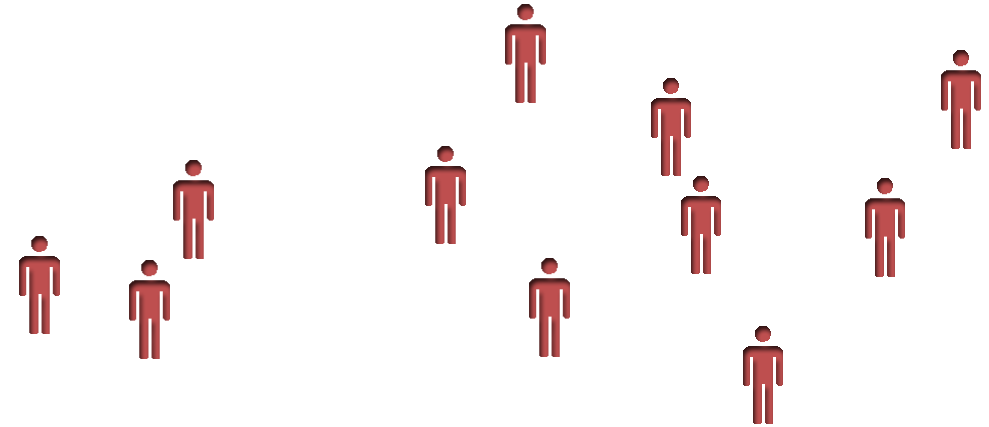
Imperial College London

LTBI: prognostic power for progression to disease

	ELISpot		TST	
Test	ESAT-6/CFP-10		5 mm threshold	
Test result	**positive**	**negative**	**positive**	**negative**
N	381	527	550	358
TB incident cases, n	11	4	12	3
Person years at risk	536	664	722	478
Unadjusted analysis				
Incidence rate per 1000 person years (95% CI)	**20.5** (10.2, 36.7)	6.0 (1.6, 15.4)	**16.6** (8.6, 29.0)	6.3 (1.3, 18.3)
Incidence rate ratio (95% CI)	**3.41** (1.08, 10.70)		2.65 (0.75, 9.39)	
P value	0.036		0.13	
Adjusted analysis				
Incidence rate ratio (95% CI)	**3.86** (1.19, 12.5)		3.28 (0.87, 12.4)	
P value	0.024		0.08	

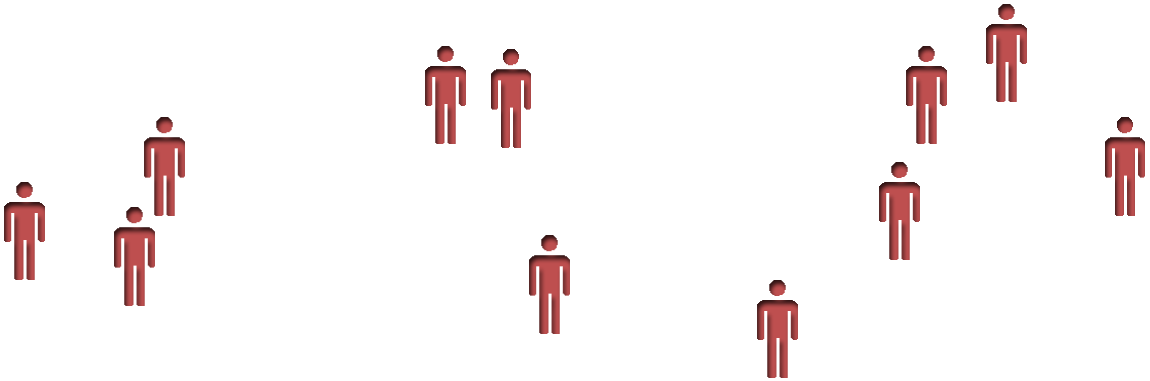
- **ELISpot-positive contacts 3-4-fold more likely to progress than negative contacts**
- **A positive ELISpot result is a useful and valid biomarker of LTBI**

Clinical implication: more focussed targeting of preventive therapy to fewer contacts



IGRA

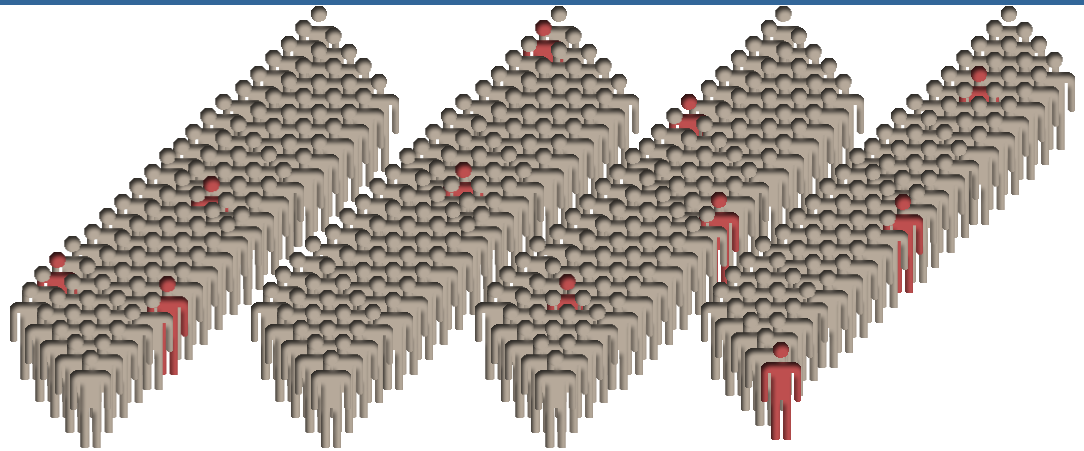
11 ELISpot-positive contacts progressed to active TB



TST

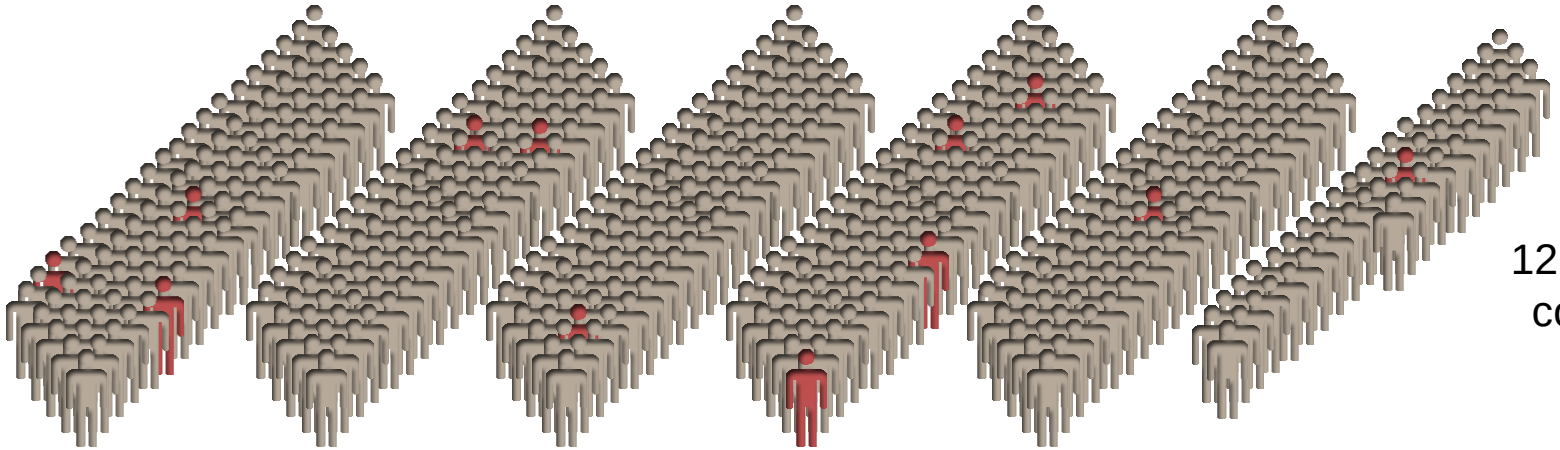
12 TST-positive contacts progressed to active TB

Clinical implication: more focussed targeting of preventive therapy to fewer contacts



IGRA

11 of 381 ELISpot-positive contacts progressed to active TB



TST

12 of 550 TST-positiv contacts progressed to active TB

If test-positive contacts are targeted with preventive treatment, more TST-positive contacts compared to IGRA-positive contacts would need to be treated to prevent a similar number of TB cases

Prognostic power of positive IGRA results now proven in low and high burden settings, and in most risk groups

Author, Year	Study population	Country	Follow up (years)	IGRA(s) used	Number of incident cases	IGRA Prognostic	
						ELISA	ELISPOT
Aichelburg, 2009	HIV+ Adults	Austria	1.6	QFT-G in-tube	3	**Yes**	
Diel, 2008, 2010	Household contacts: Adults	Germany	4	QFT-G in-tube	19	**Yes**	
Bakir, 2008	Household contacts: Children	Turkey	1.3	ELISpot	15		**Yes**
Hill, 2008	Household contacts: Children & Adults	Gambia	2	ELISpot	26		**No**
Doherty, 2002	Household contacts: adults	Ethiopia	2	ELISA (ESAT6 only)	7	**Yes**	
Kik, 2010	Immigrant close contacts: adults	Holland	2	ELISA and ELISpot	9	**Yes**	**Yes**
del Corral, 2010	Household contacts: adults and children	Colombia	2-3 years	ELISA (CFP-10)	33	**No**	
Lienhart,2010	Household contacts: Children & Adults	Senegal	2	ELISpot	52		**Yes**
Leung, 2010	Male silicosis patients	Hong Kong	2.45 years	ELISpot	17		**Yes**
Yoshiyama, 2010	Household contacts: Children & Adults	Japan	2	ELISA (QFT-G)	39	**Yes**	
Mahomed, 2009a	Adolescents 12-18	South Africa	2	ELISA (QFT-G in-tube)	84 (but only 50 reported)	**Yes**	
Haldar, 2009a	Household contacts: Children & Adults	UK	1.2	ELISA (QFT-G in-tube)	39 (but only 20 in the ELISA screened group)	**Yes**	

LTBI: prognostic power for progression to disease

- *Diel et al AJRCCM 2008 (First prognostic evidence for QFT)*
- *Bakir et al Ann Intern Med 2008 (First prognostic evidence for ELISpot)*
- *Hill et al PLoS ONE 2008 (neither TST nor IGRA predictive – high transmission setting)*
- *Aichelburg et al Clin Infect Dis 2009 (First prognostic evidence of IGRA in HIV)*

Conclusions

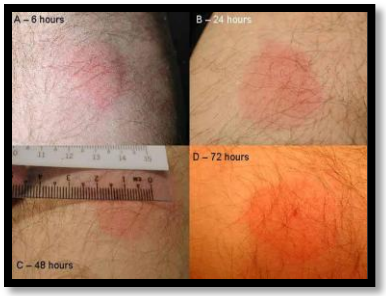
- IGRA are prognostic of subsequent TB

Remaining questions

- Comparative studies not yet conducted: need very large sample size (approx 10,000 contacts and 100 incident cases)
- Can we rely on IGRA alone in immunosuppressed persons with LTBI?
- Does treatment on the basis of IGRA results reduce the risk of active TB?

New tests for latent TB infection: IGRAs

1907 **Tuberculin skin test** – oldest biomarker in medicine



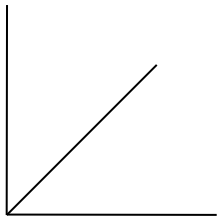
2004 **Interferon-gamma release assays** – new biomarkers of LTBI

ELISpot
quantification IFN-γ-releasing cells

T-SPOT.TB

Oxford Immunotec
Harnessing the power of T cell measurement

Based on Lalvani ELISpot 2002

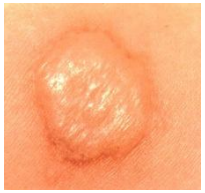


ELISA
quantification released IFN-γ

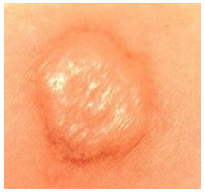
QuantiFERON-TB Gold (In-Tube Method)

cellestis

1907



2000



2006

Issue date: March 2006

NHS
National Institute for Health and Clinical Excellence

Tuberculosis

Clinical diagnosis and management of tuberculosis, and measures for its prevention and control

Use blood tests (IGRA), if available, in:

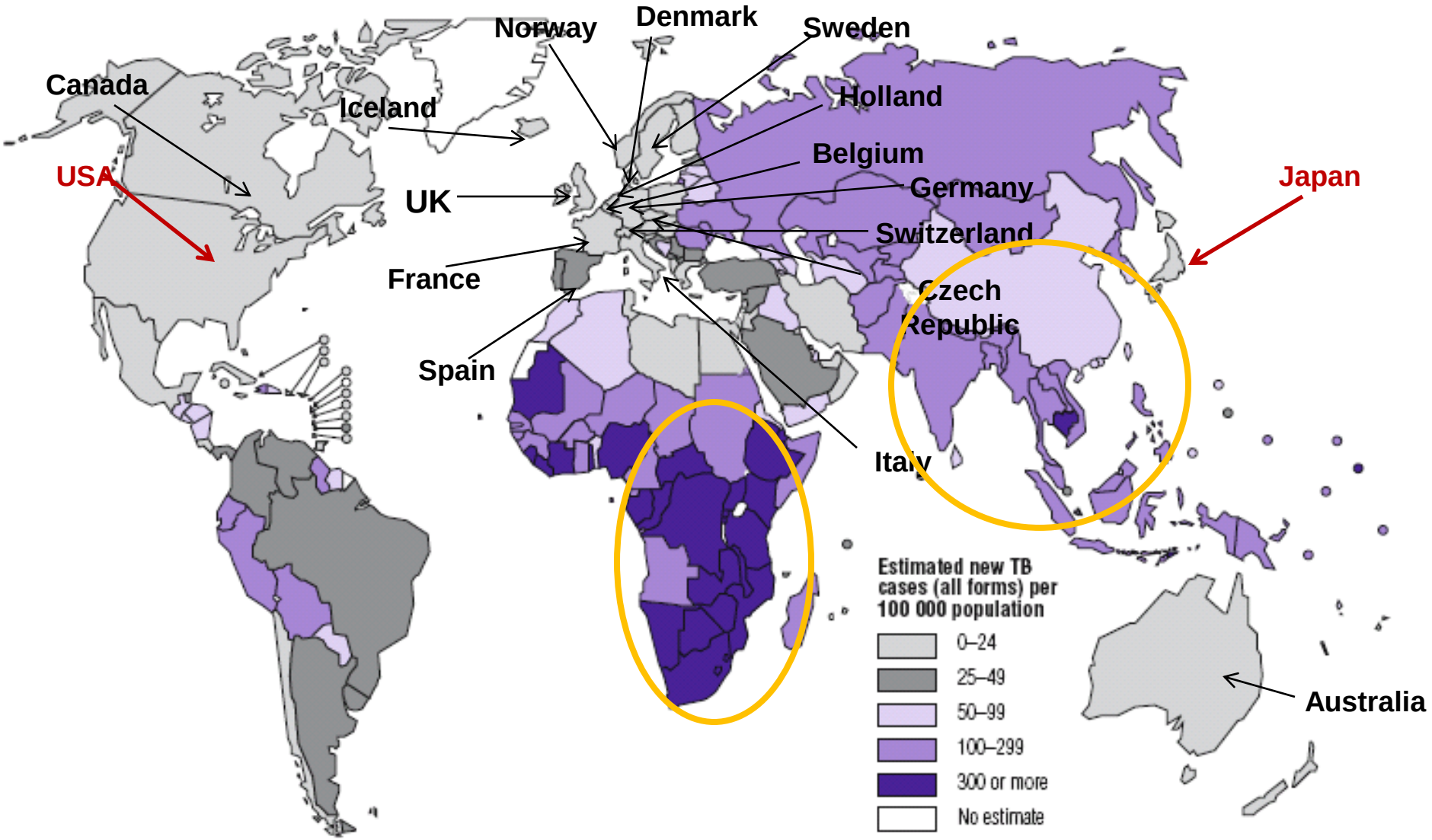
- Individuals who have tested positive by TST

- Individuals in whom TST is unreliable

NICE reviewed 11 studies published before July 2005:

Recent HPA guidelines very similar

Impact on global policy: TB guidelines endorsing IGRA, 2008



TST: inadequate tool to achieve the aims of targeted testing for LTBI

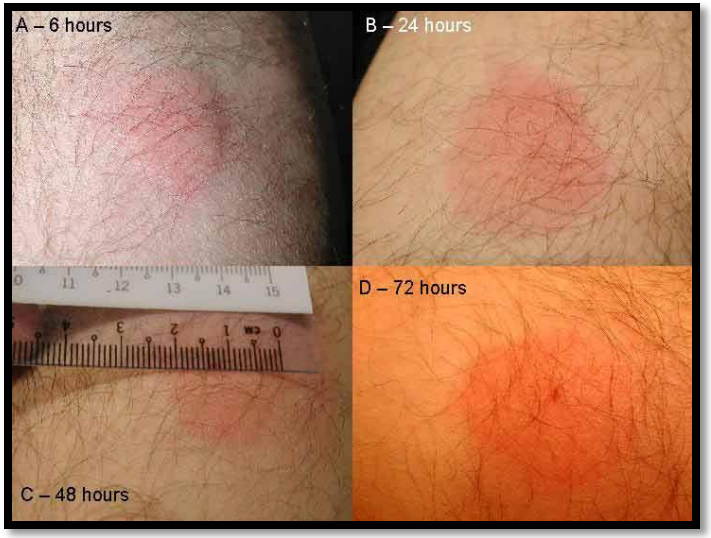
- **Targeted testing:** test and treat latently infected persons who are:
  (a) recent contacts or
  (b) at increased risk of progression from LTBI to active TB:
    - HIV, young children, concomitant illnesses (renal failure, diabetes, etc), iatrogenic immunosuppression

- **But TST suffers from:**

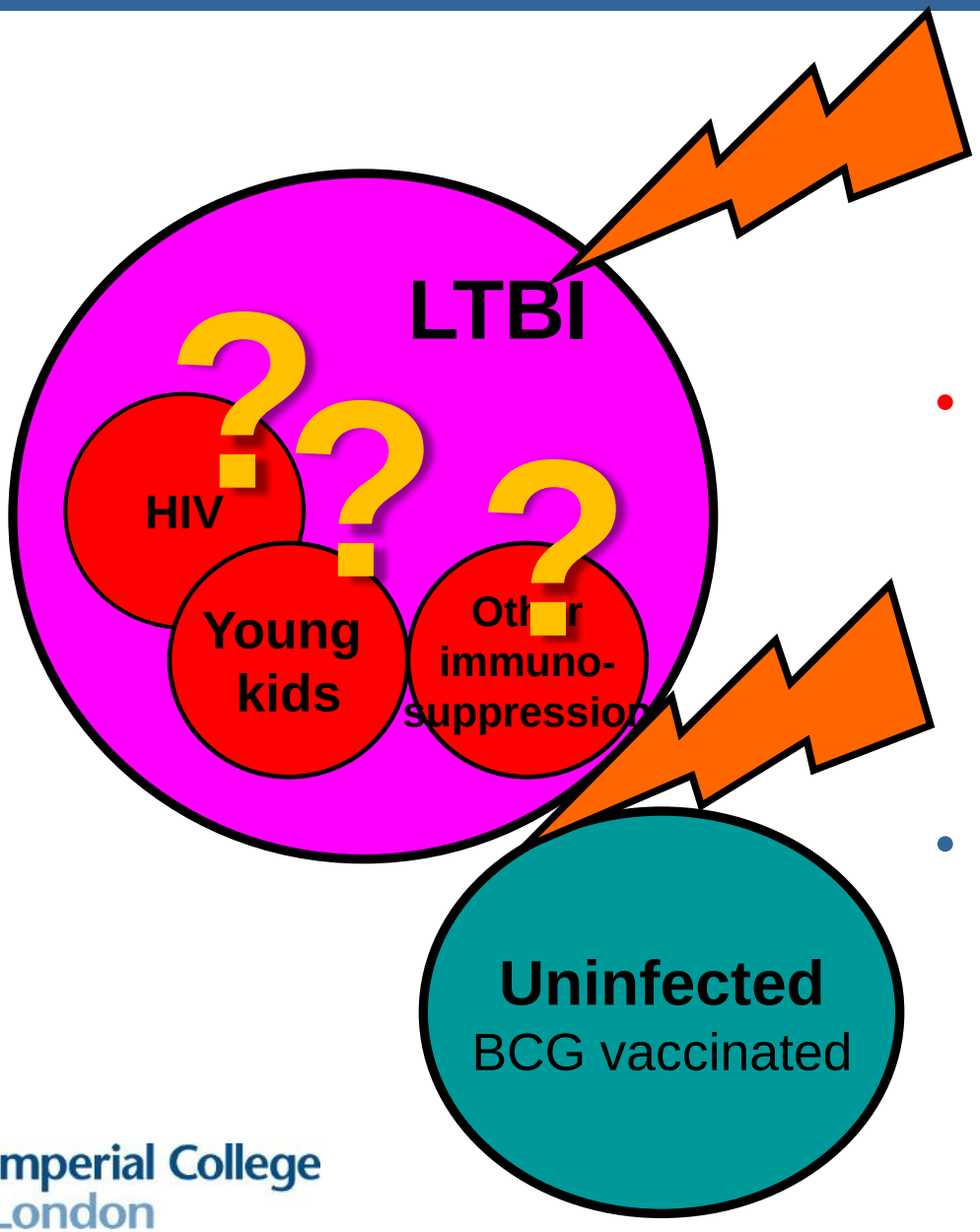
- **Poor sensitivity:**
  - in the above vulnerable groups at highest risk

- **Poor specificity**:
  - Cross-reactivity with BCG vaccination

- **Problems of in vivo test**…….
  - Return visit, operator variability, inflammation

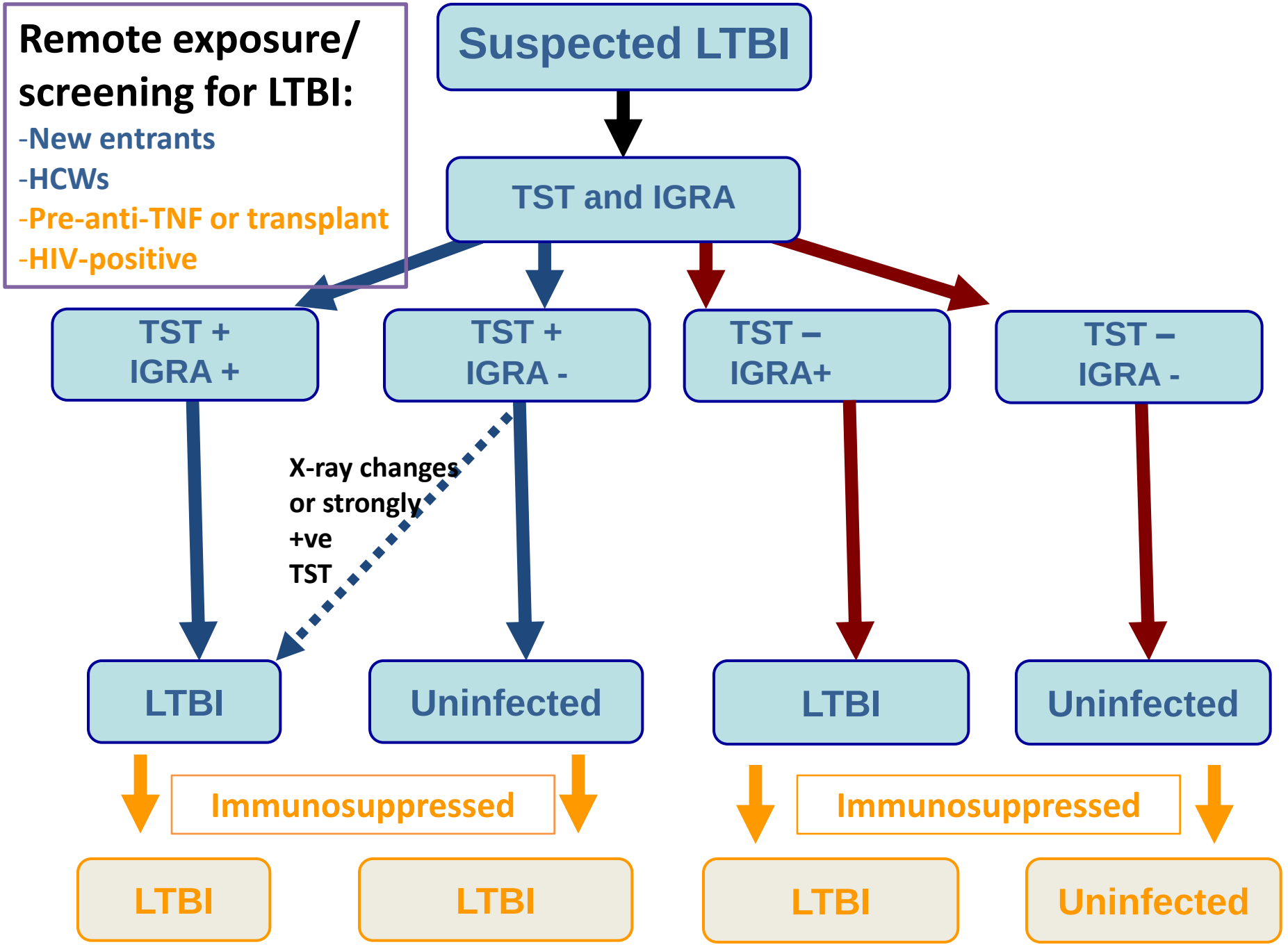


Clinical utility in LTBI

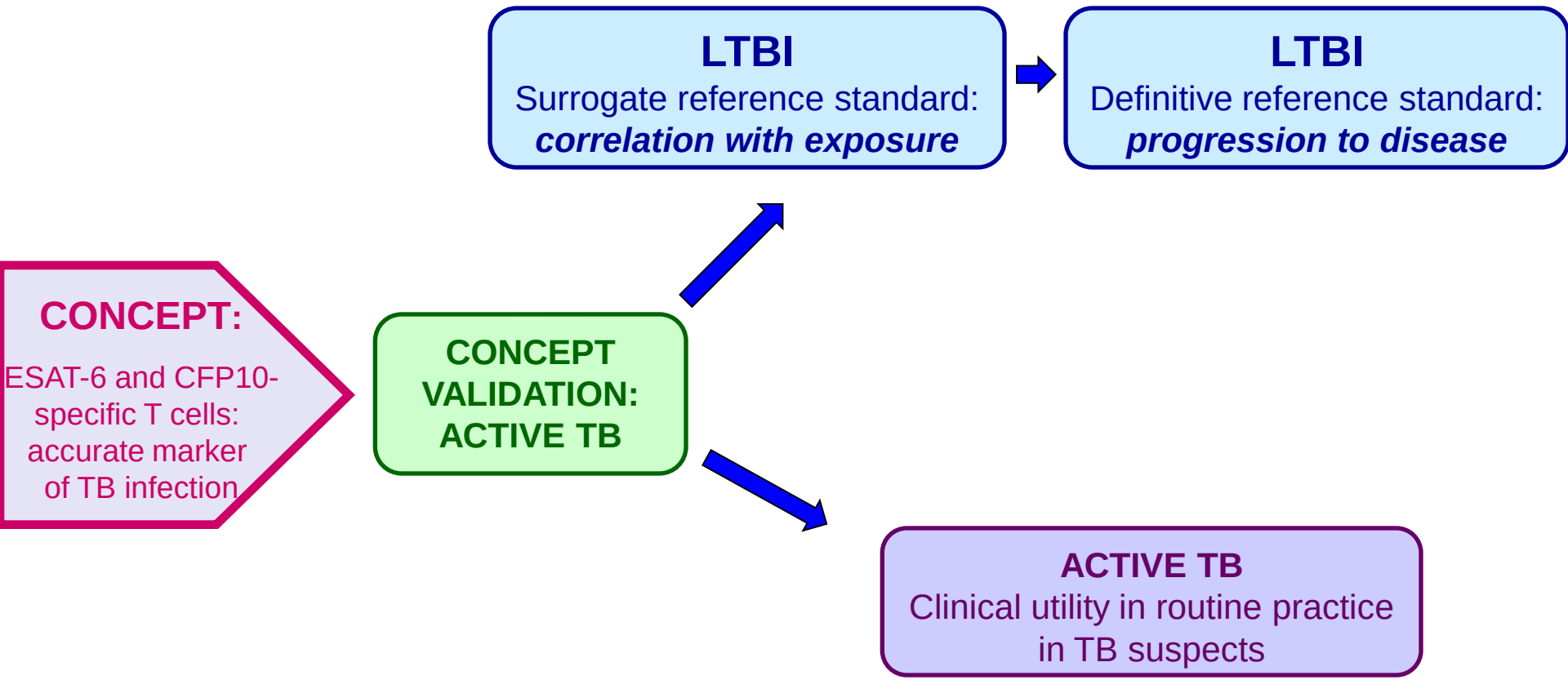


'Rule-in' as well as 'rule-out' test

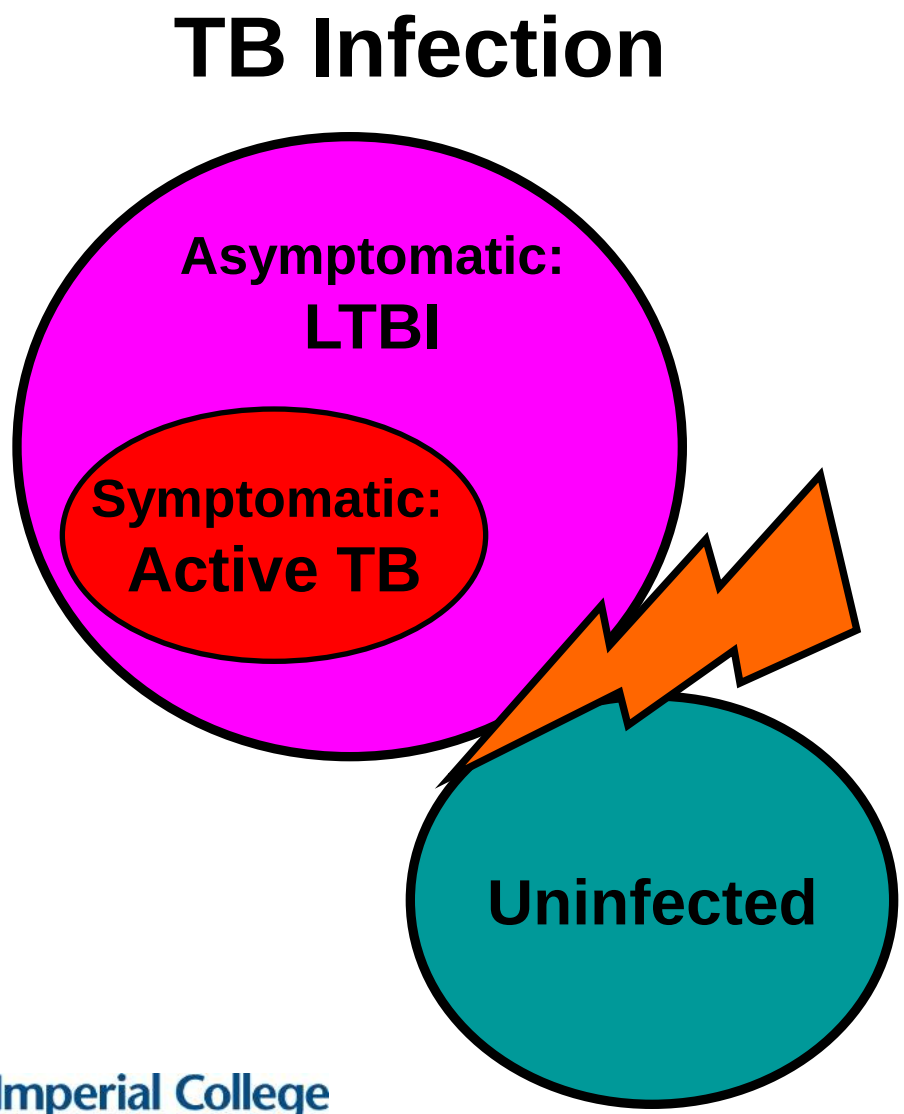
- Sensitivity in young children and immunosuppressed populations is better than TST but **we do not know the false-negative rates in these subgroups**
- **High specificity lessens the number of people inappropriately treated on the basis of false-positive TST**


Remote exposure/ screening for LTBI:
-New entrants
-HCWs
-Pre-anti-TNF or transplant
-HIV-positive
Suspected LTBI
TST and IGRA
TST + IGRA +
TST + IGRA -
TST – IGRA+
TST – IGRA -
X-ray changes or strongly +ve TST
LTBI
Uninfected
LTBI
Uninfected
Immunosuppressed
Immunosuppressed
LTBI
LTBI
LTBI
Uninfected

Clinical utility of IGRA: journey thru the evidence-base



Clinical utility in active TB



- Immune-based tests are tests of **infection**, not active disease: **cannot distinguish between the two**
- TB infection is a prerequisite for TB disease
- But by ruling out infection, you can 'rule-out' active TB
- **Requires test of very high diagnostic sensitivity: higher than either of the current IGRAs**
- **Sensitivity in real-life routine practice is only around: 75%(QFT) to 85%(T-SPOT)**

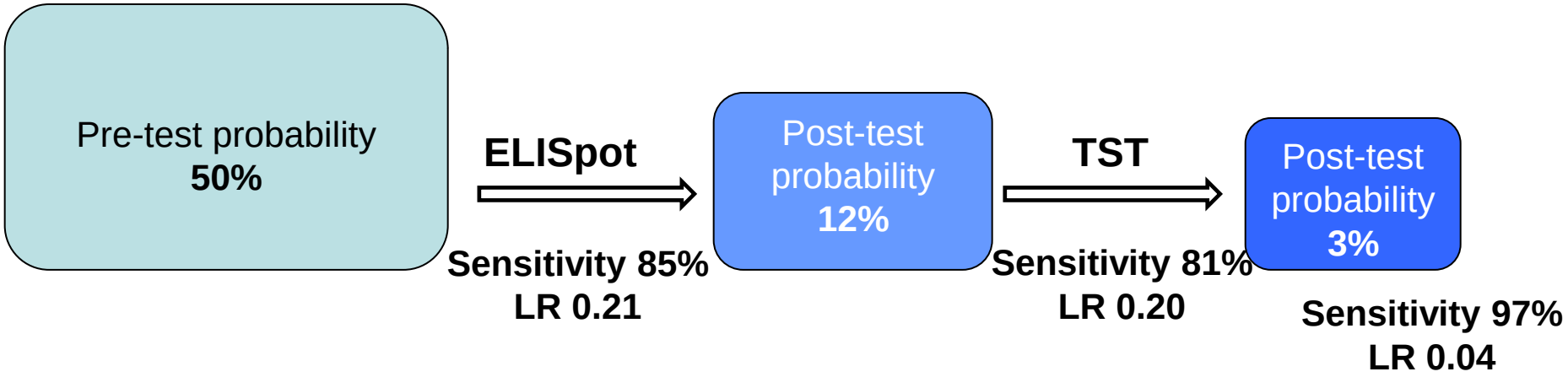
Clinical utility for evaluation of TB suspects

Large prospective blinded studies of IGRA vs TST in TB suspects

Neither IGRA is a reliable rule-out

Maximum sensitivity: IGRA &TST in combination

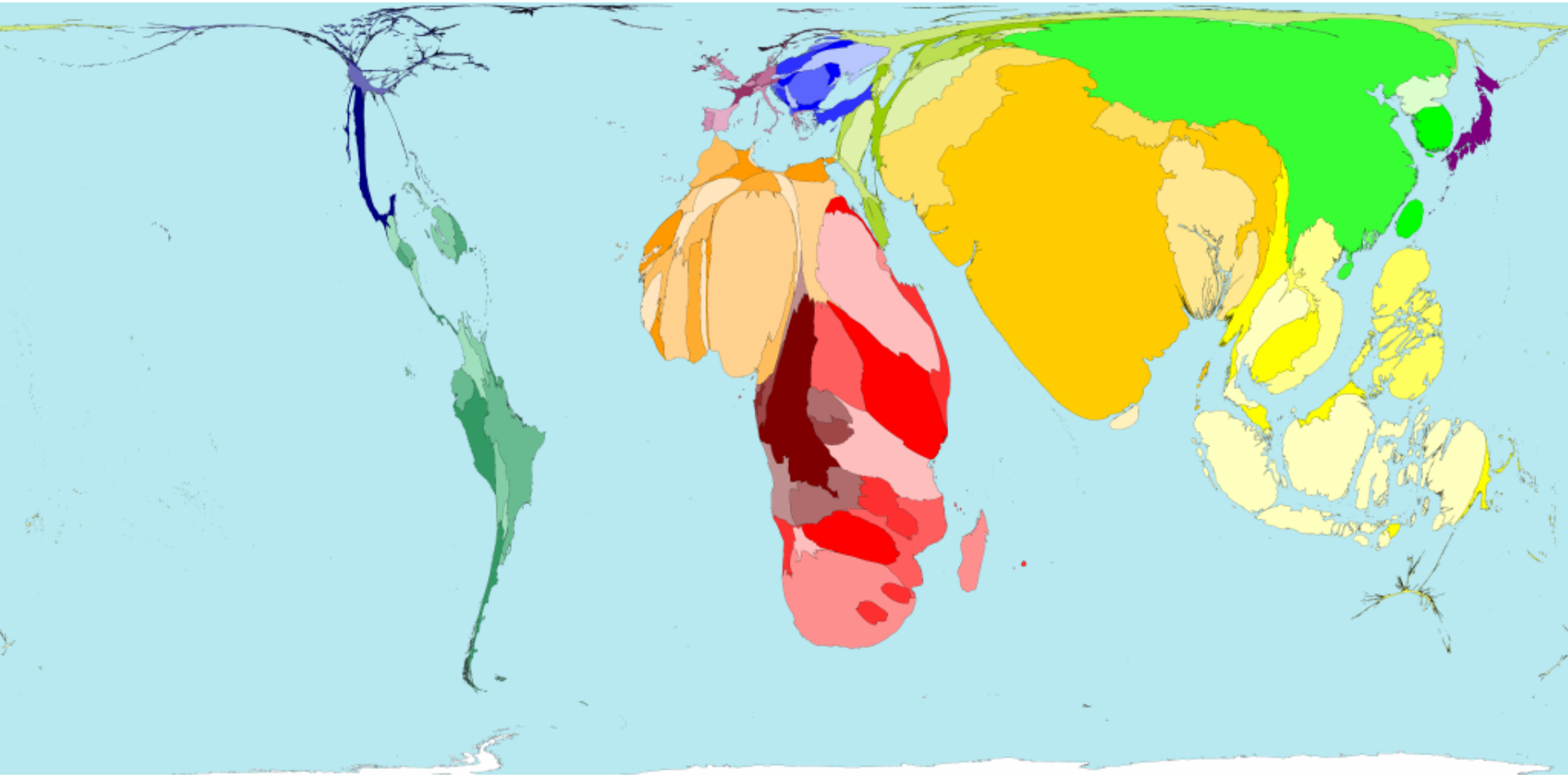
	Sensitivity IGRA	Sensitivity IGRA and TST
Liebeschuetz et al Lancet 2004 (Children, HIV, malnutrition)	83% (ELISpot)	91%
Dosanjh et al Ann Intern Med 2008	85% (ELISpot)	97%
Golletti et al PLoS ONE 2008	85% (T-SPOT) 78% (QFT)	97%



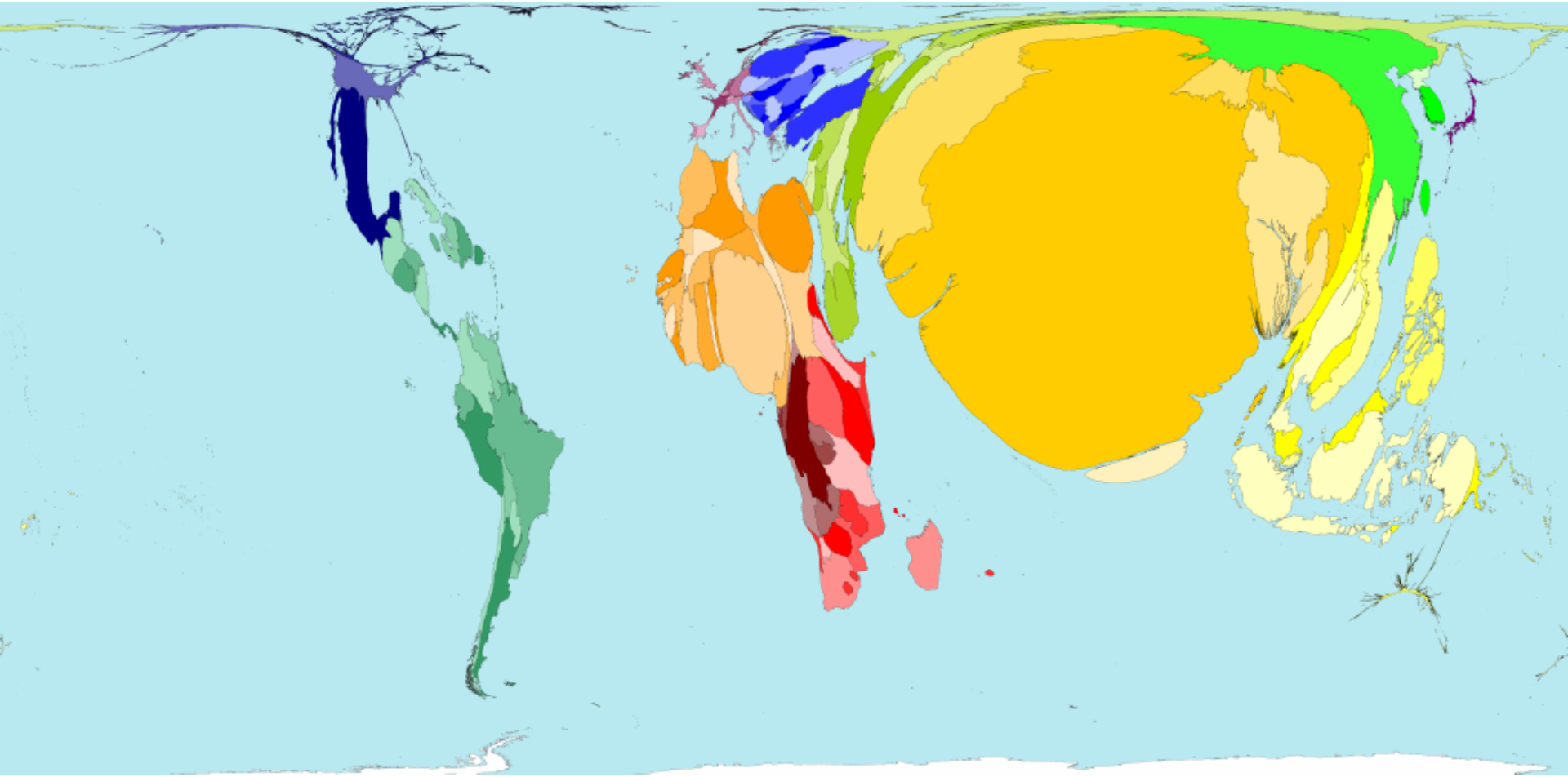
Dosanjh et al Ann Intern Med 2008

Also: Ravn et al Clin Diagn Lab Immunol 05; Ferrara et al Lancet 06; Kang et al Chest 07

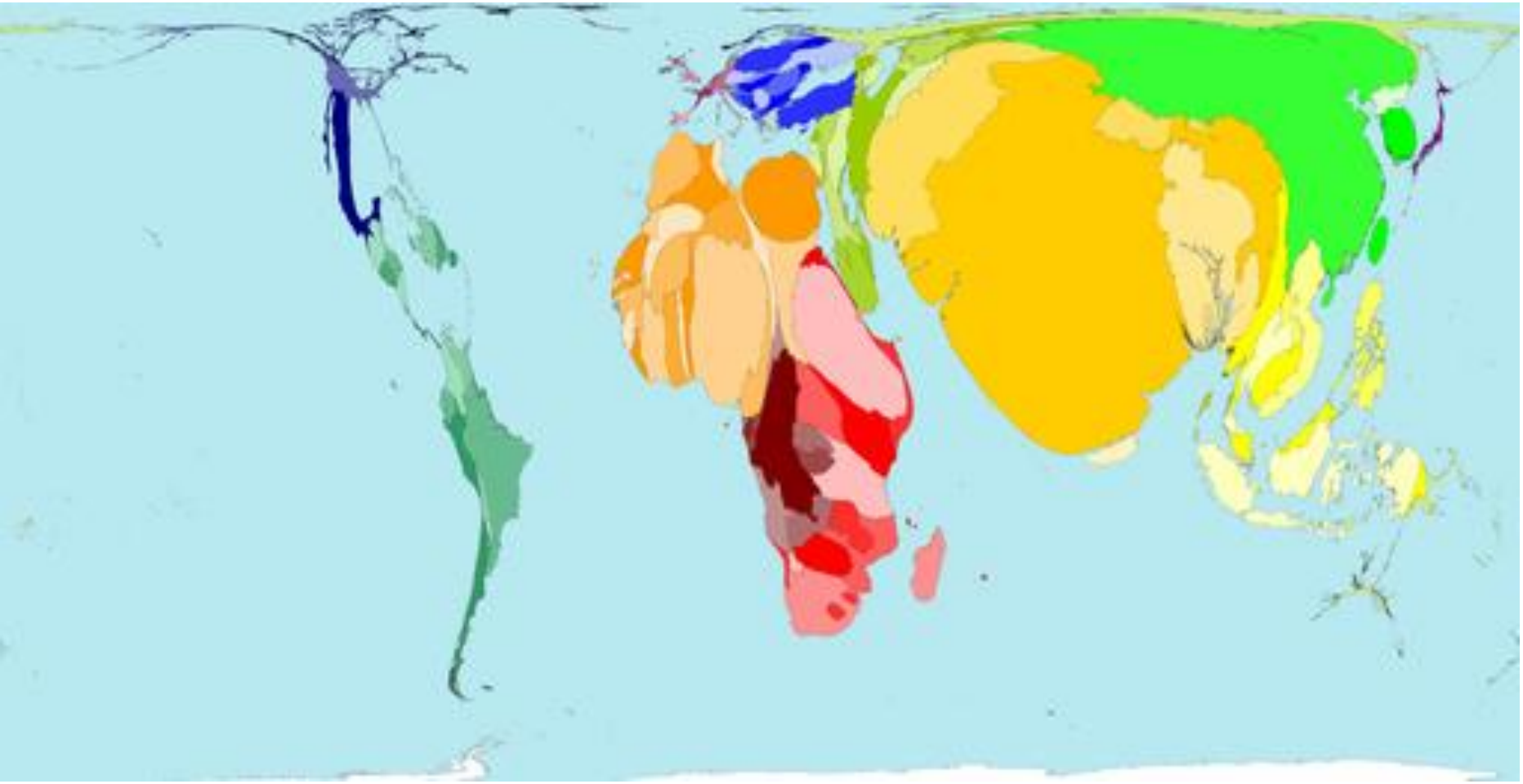
TB



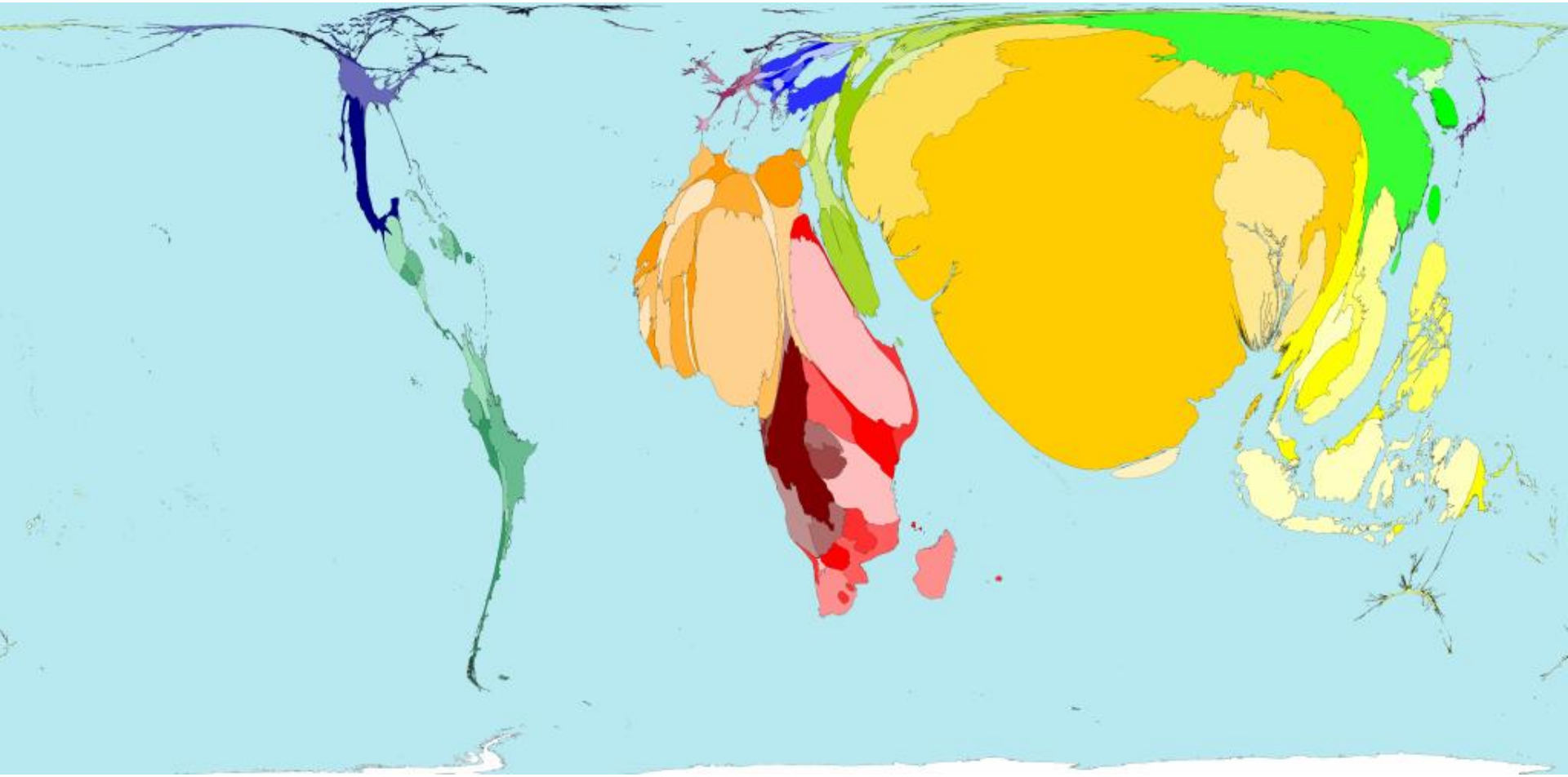
OVERCROWDING



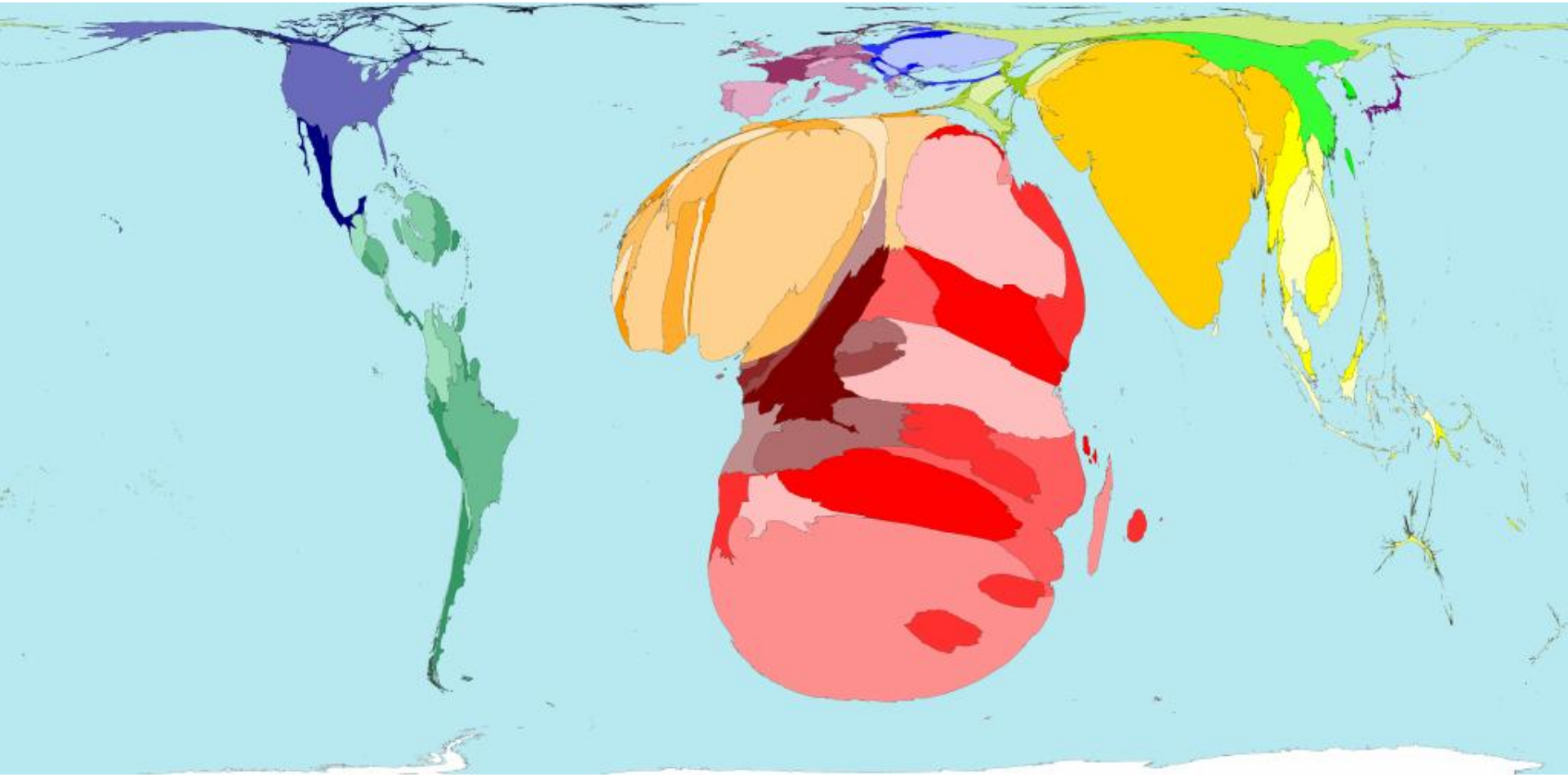
POVERTY



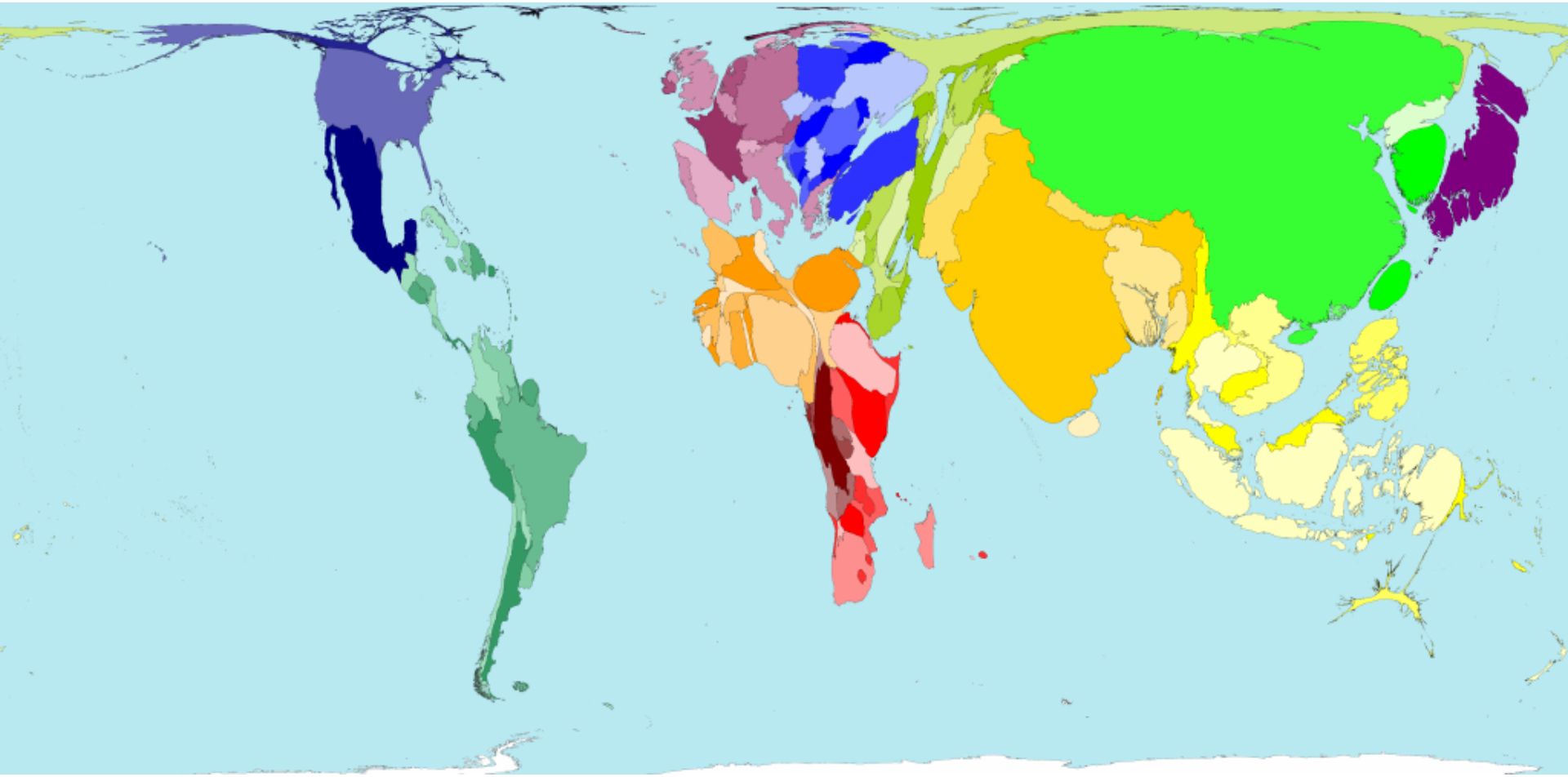
UNDERWEIGHT CHILDREN



HIV



SMOKING



DIABETES