Pediatric TB research

Barriers and progress

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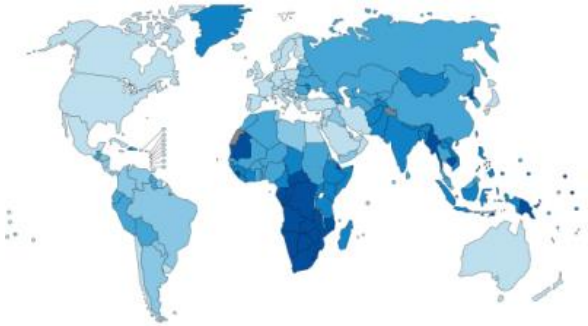
www.sydney.edu.au/mbi
www.tbcre.org.au

Global Burden of TB - 2012



	Estimated Incidence	Estimated number of deaths
All forms of TB	8.6 million (8.3–9.0 million)	940 000 (1.3–1.6 million)
HIV-associated TB	1.1 million (13%) (1.0–1.2 million)	320,000 (300,000–340,000)
Multidrug-resistant TB	450,000 (300,000-600,000)	170 000 (100 000 – 240 000)

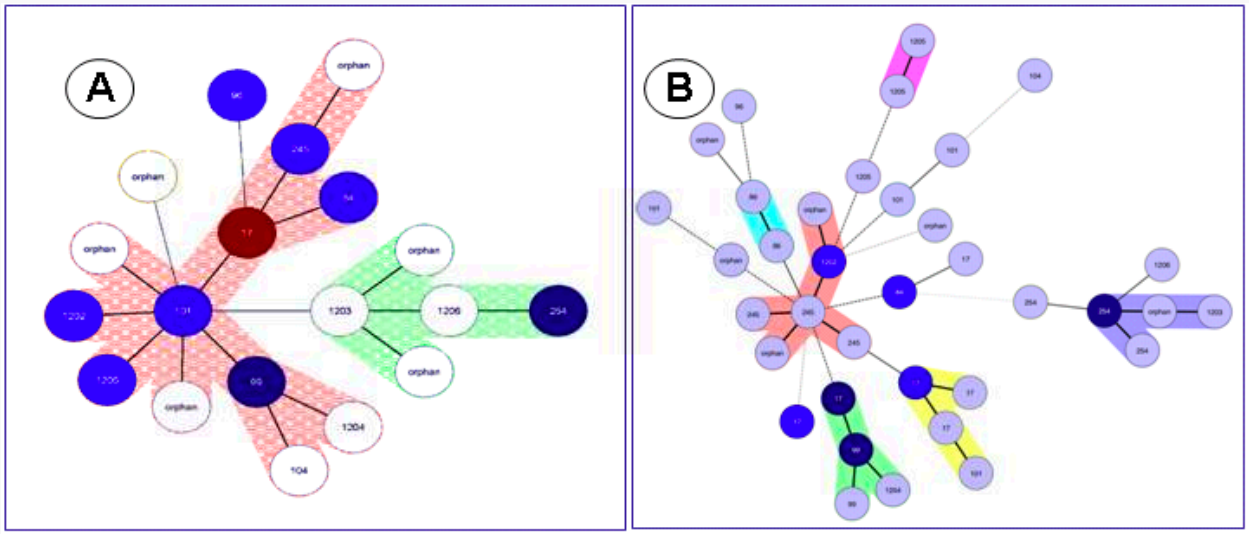
Disease burden in children

~1 million children with TB every year

Jenkins HE et.al. Lancet 2014

Epidemic spread of MDR-TB

Children are affected



Marais BJ et. al. JCM 2013; 51: 1818-25

Solid lines show a single loci-MIRU change, while dotted lines show 2 (black coloured) or more (grey colorued) changes. Circles show 12-loci MIRU international type (MIT) numbers and the color of the circles reflects the number of clinical isolates identified (N=71), illustrating unique (sky-blue) versus clustered isolates (deep blue, 2 to 5 strains; dark blue, 5 to 10 strains; brown, 10 to 20 strains; red, 20 strains and more). Additional colour groups demonstrate likely clusters with minimal strain variation.

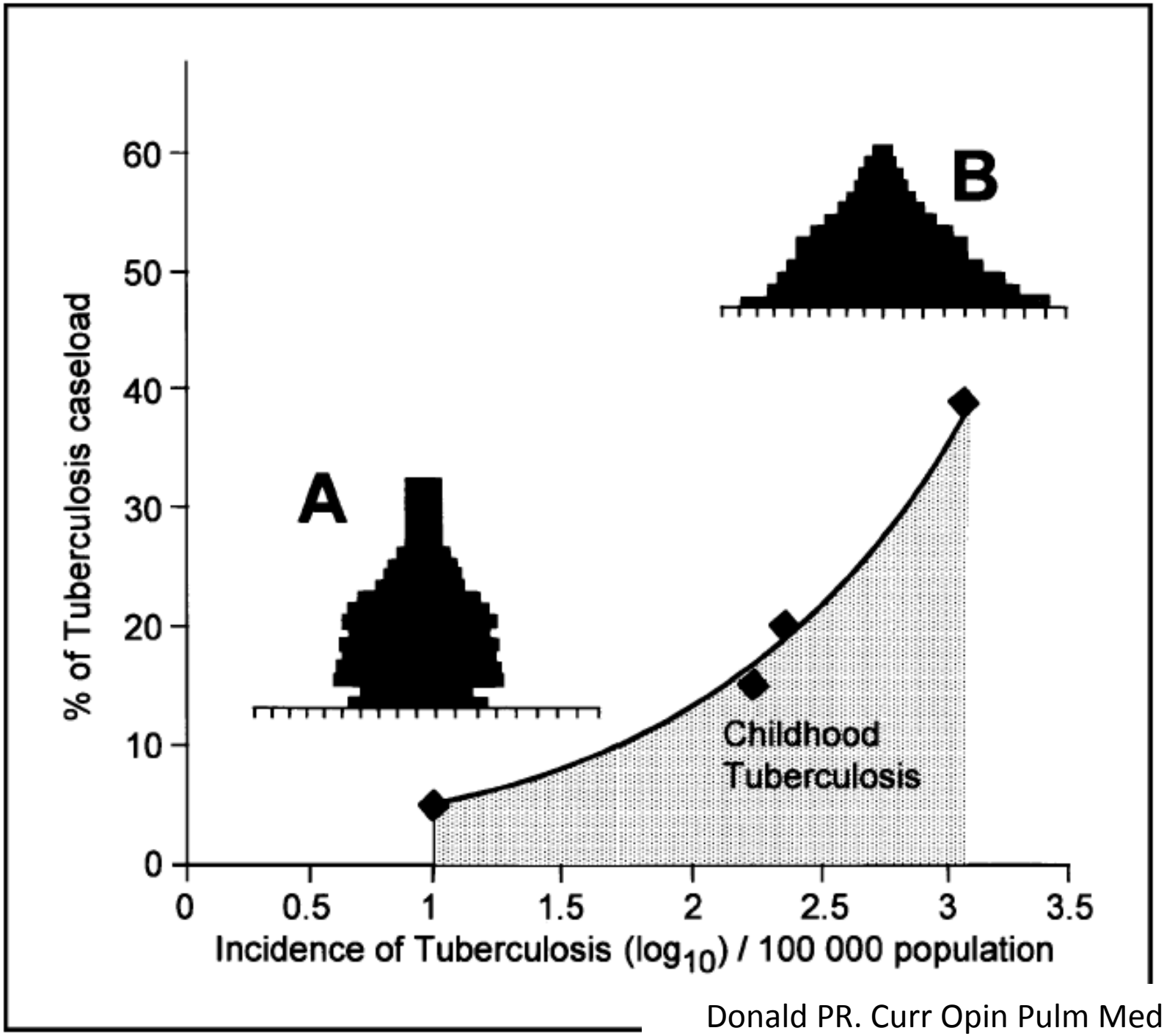
~ 32 000 children develop MDR-TB every year

All cases ever reported <2% of estimated annual burden

Jenkins HE et.al. Lancet 2014

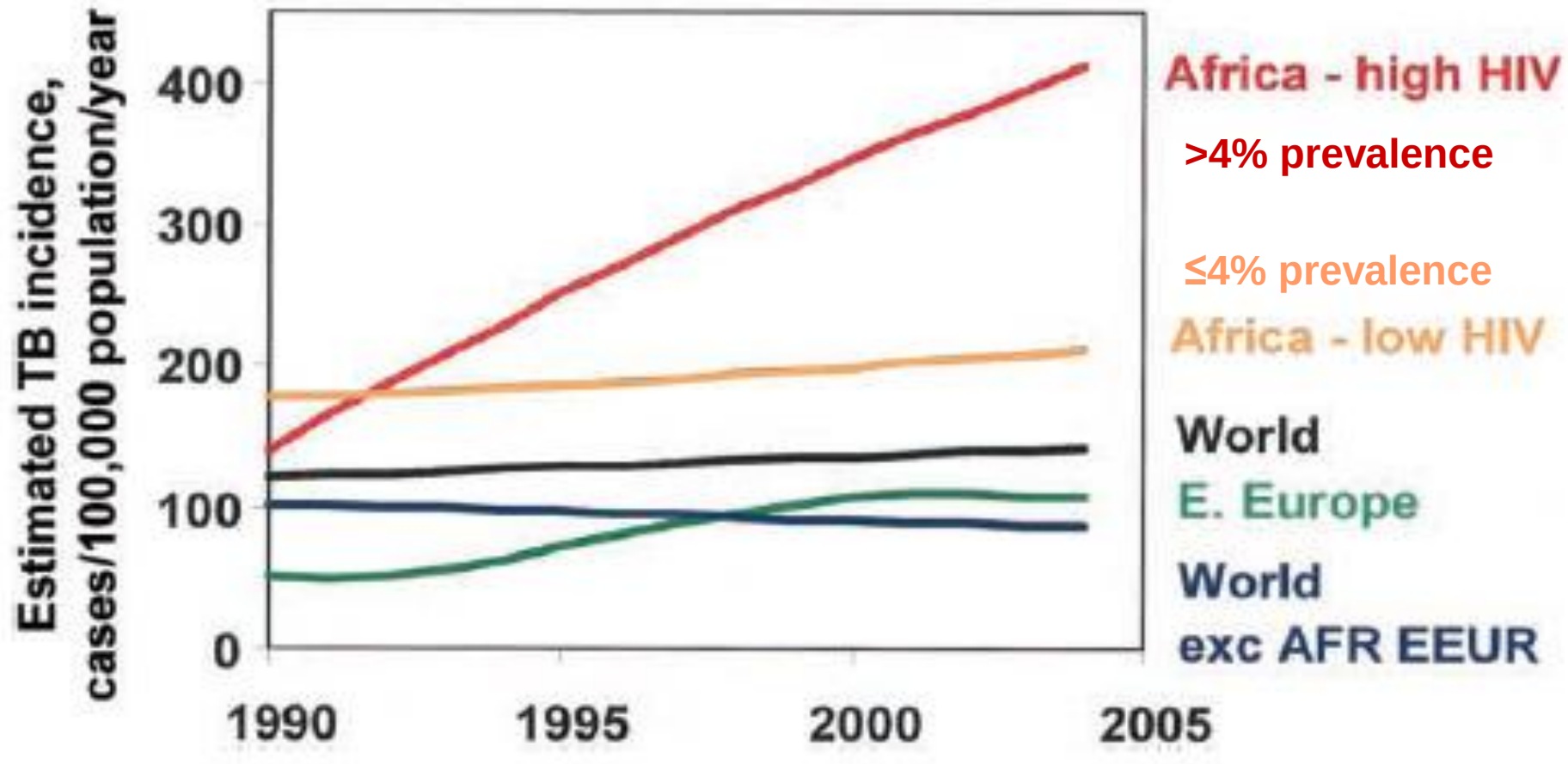
www.sentinel-project.org

www.treatmentactiongroup.org/tb/publications/2013/we-can-heal



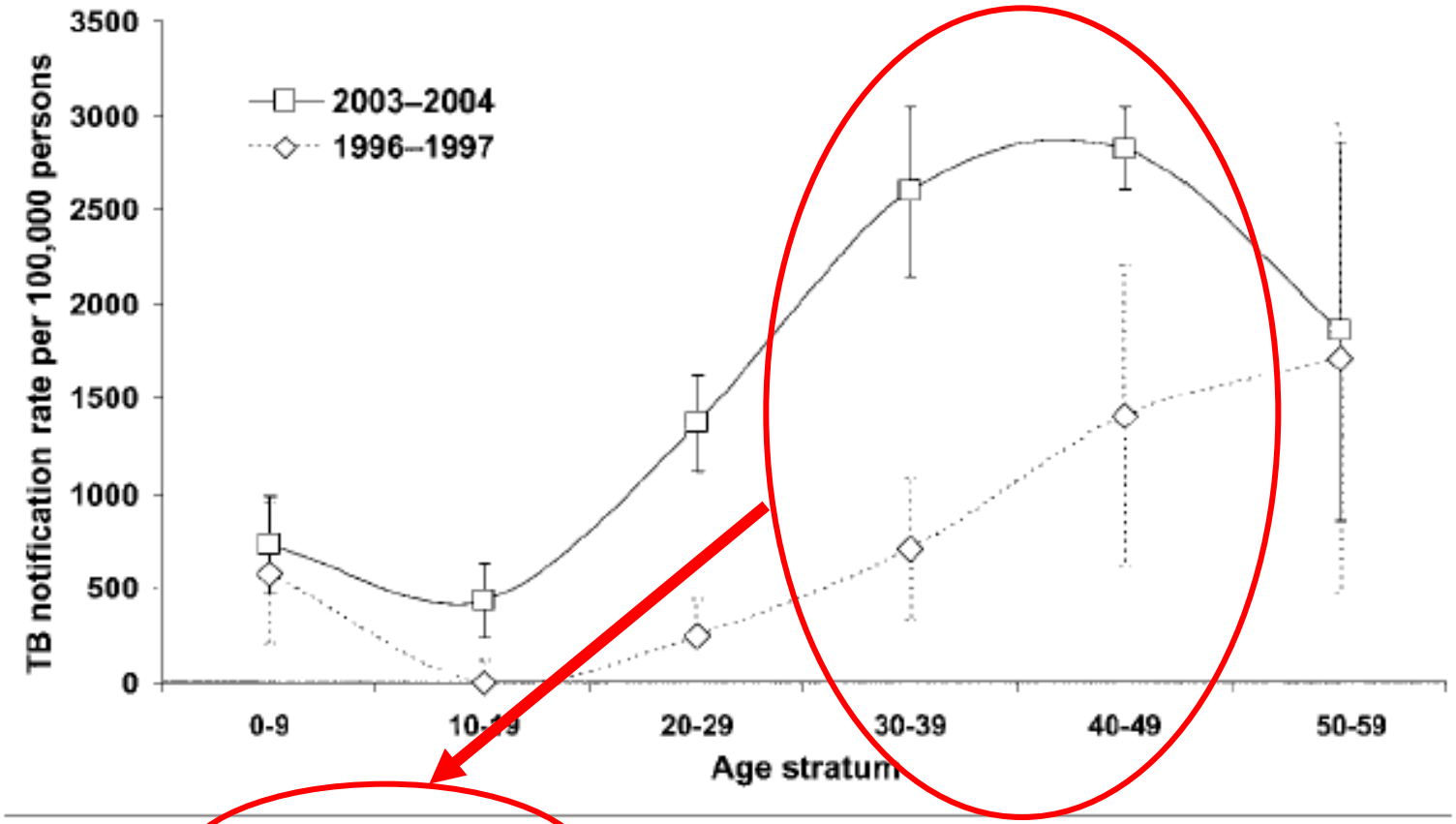
Donald PR. Curr Opin Pulm Med 2002

Incidence of All TB / 100 000 Population: 1990-2004



Nunn P et al. JID 2007; Suppl 196: S5:14

TB - Age & Gender shift



2003–2004	731	436	1369	2599	2824	1856
1996–1997	582	0	245	706	1405	1708

HIV prevalence in general population: **3-4% 0-9y** **25% 20-39y**

Lawn SD et al. CID 2006; 42: 1040-7

Child TB - Why bother?

- Morbidity / disease burden

Estimated contribution globally ~8-12% of all TB cases
~1 million children with TB every year

Jenkins HE et.al. Lancet 2014

- Mortality / cause of death

TB is a common, but unrecognized, cause of death in children from TB endemic countries

Graham S et.al. Lancet 2014

- Epidemic control

Children >10yrs of age with adult-type disease, are highly infectious and contribute to ongoing transmission

TB is treatable

TB and child survival/mortality

Grossly underestimated among deaths from

- pneumonia
- malnutrition
- meningitis
- HIV

Relative importance likely to increase

- widespread vaccine roll-out (Hib, pneumo, rota)
- rise in DR-TB

Importance of tuberculosis control to address child survival

Stephen M Graham, Charalambos Sismanidis, Heather J Menzies, Ben J Marais, Anne K Detjen, Robert E Black

Tuberculosis commonly affects young children (<5 years) in countries that have high rates of child mortality.[1] The global public health focus to control tuberculosis has traditionally aimed to reduce transmission through early

death and not contributory causes to WHO, vital registration data cannot be used to estimate the number of tuberculosis deaths in people living with HIV. Further, vital registration data are available for only 3% of global

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Transitions in TB

Susceptible

Exposed

Infected

Diseased

Infectious

Sick

Accessed care

Recognized

Diagnosed

Treated

Completed

Cured

Natural History of Disease
Risk and disease profile

Major transitions

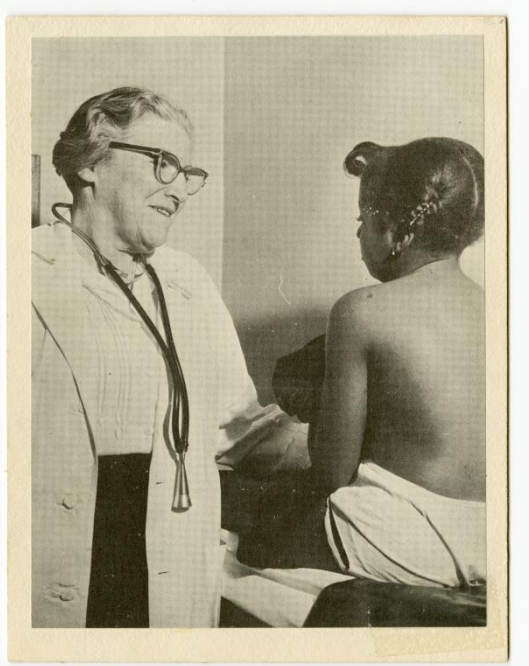
Exposure

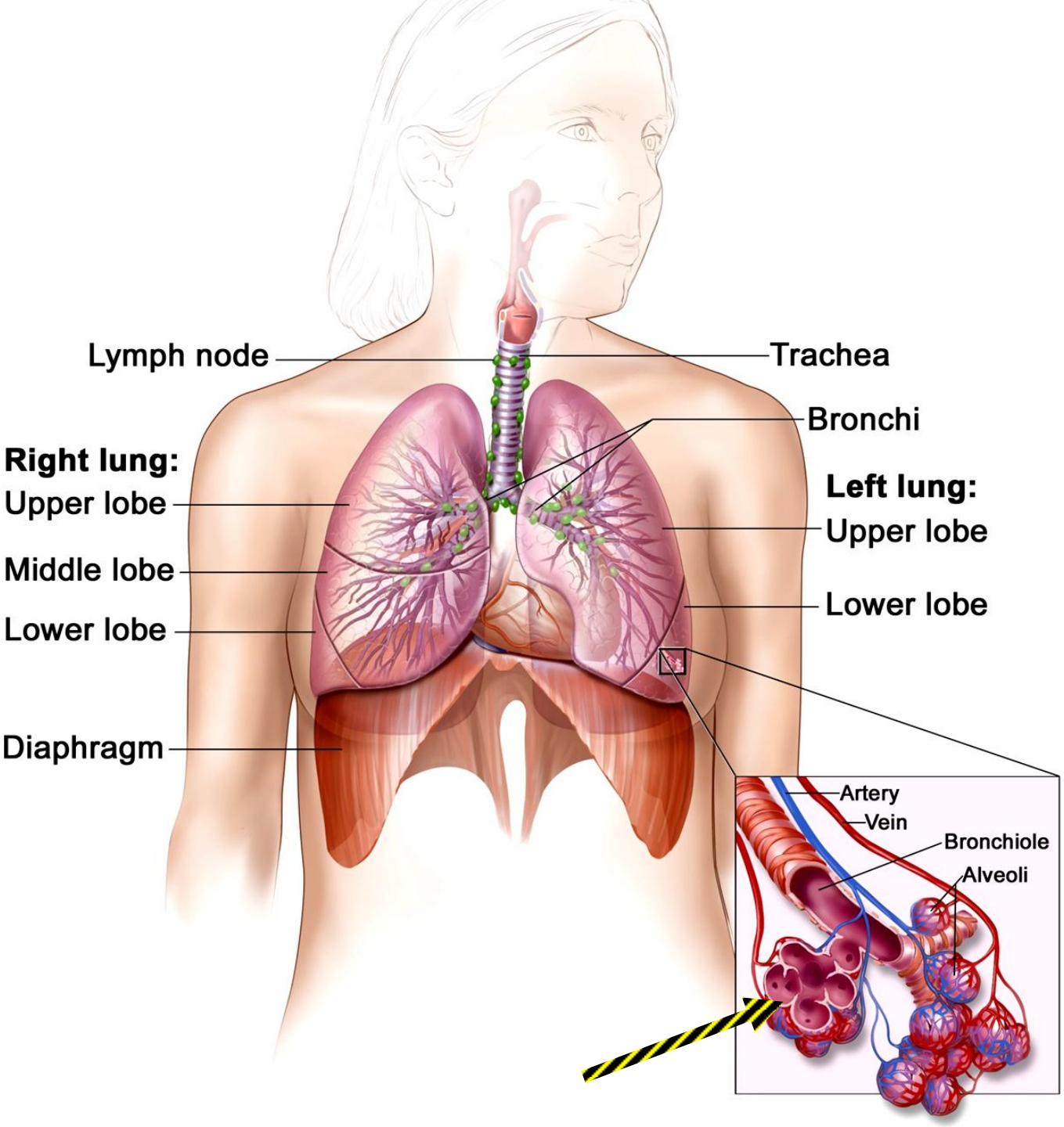
↓

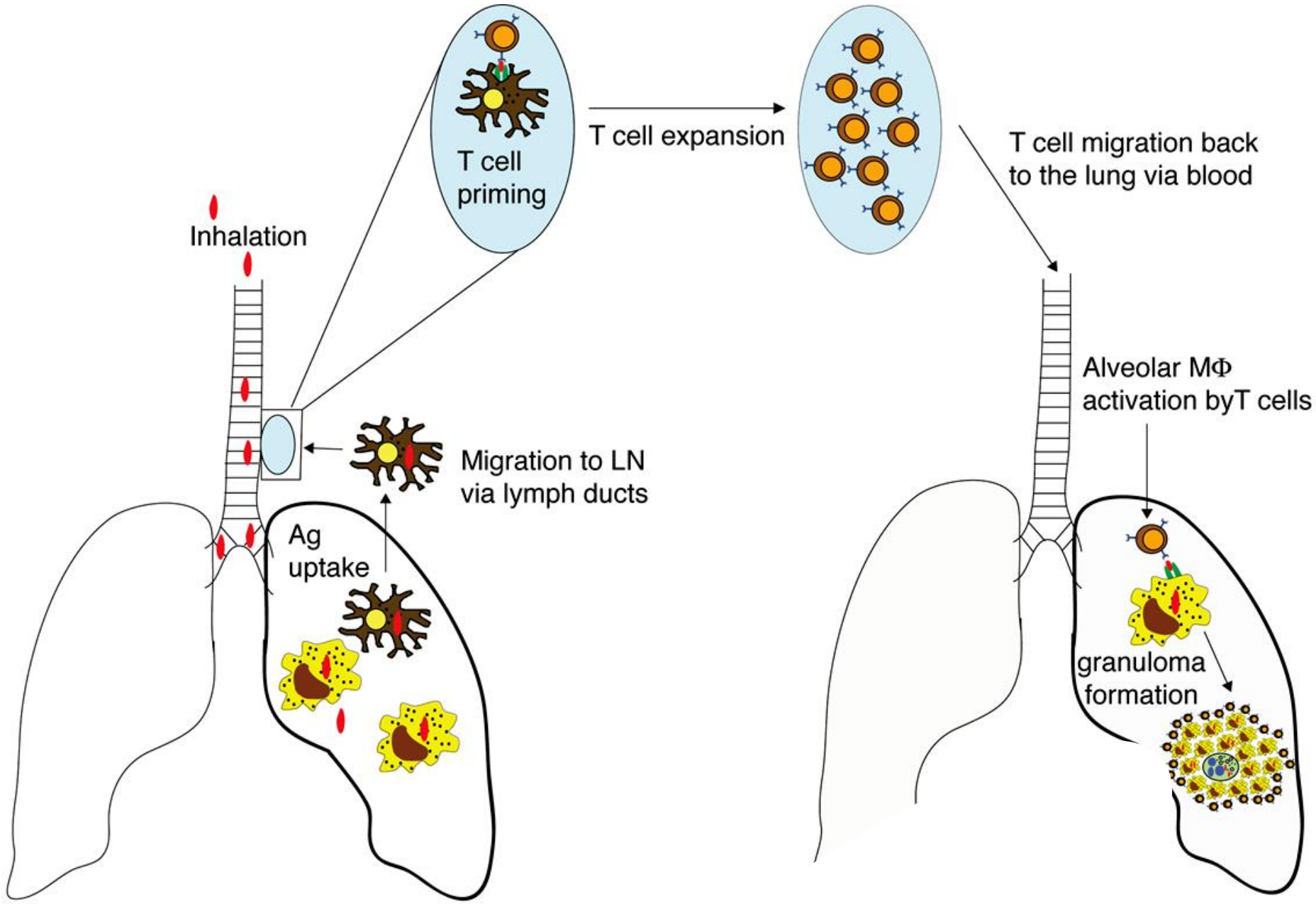
Infection

↓

Disease




Lymph node
Trachea
Bronchi
Right lung:
Upper lobe
Middle lobe
Lower lobe
Diaphragm
Left lung:
Upper lobe
Lower lobe
Artery
Vein
Bronchiole
Alveoli



Courtesy Willem Hanekom

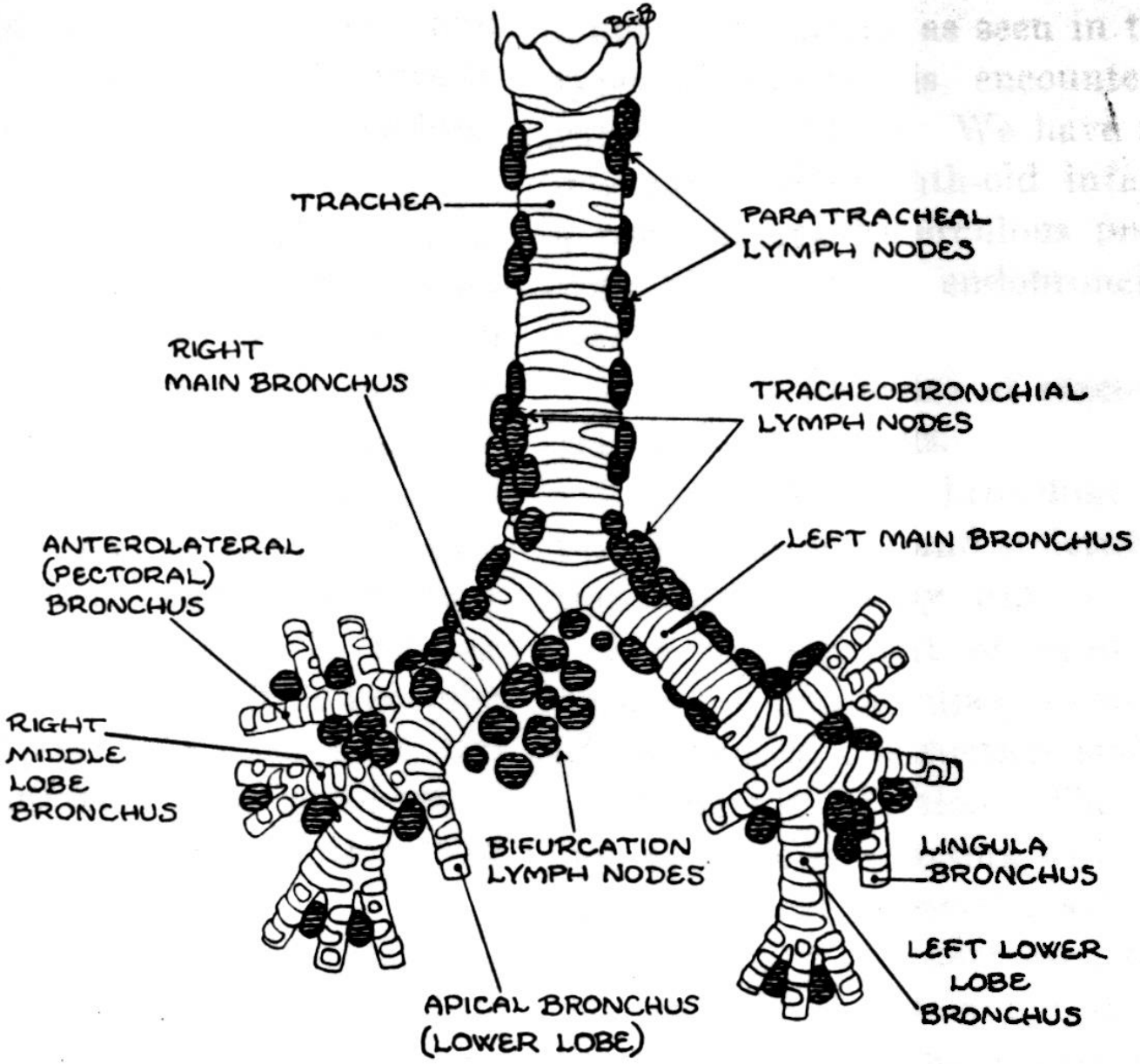
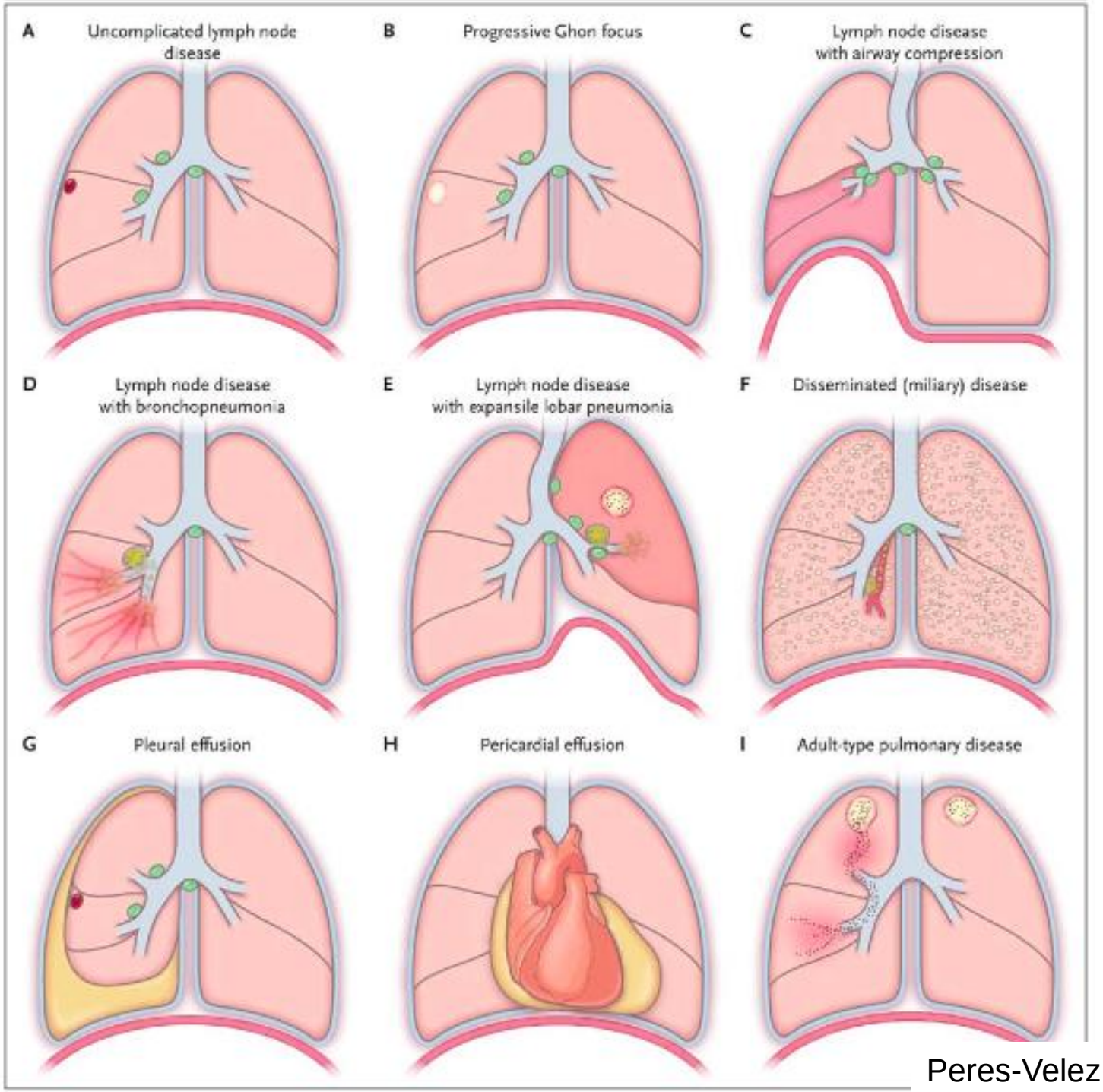


Fig. 8.—Distribution of the tracheobronchial lymph nodes. (Semidiagrammatic drawing after W. Snow Miller: *The Lung*, Springfield, Ill., 1937, Charles C Thomas.)

DIVERSITY OF DISEASE

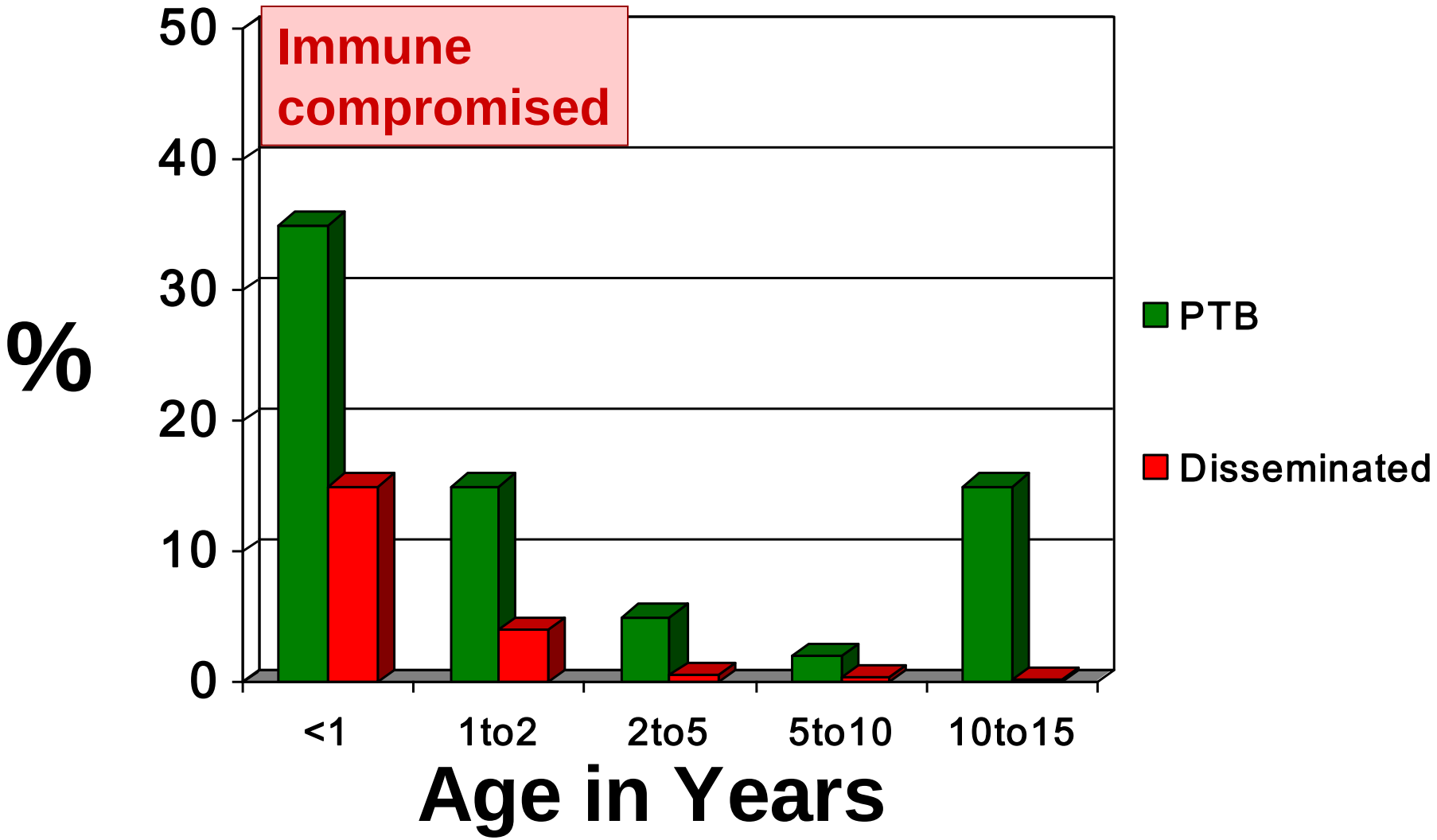
Highly variable clinical severity / relevance

Intra- & extra-thoracic



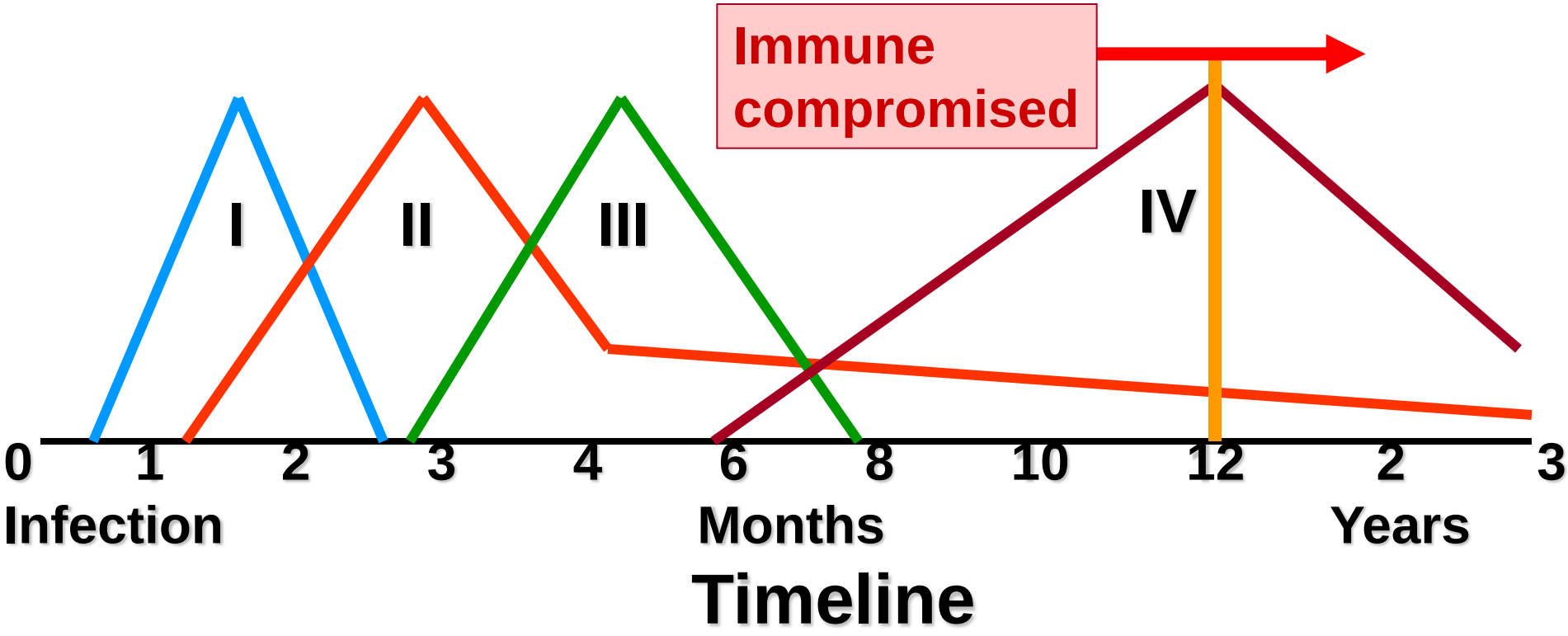
Peres-Velez NEJM 2012

Age-related risk



Marais. IJTLD 2004

Time-related risk



Phase of disease

I Hypersensitivity
II Miliary TB and TBM
III Lymph node disease / Pleural effusion
IV Adult-type disease

HIV-infected - PERSISTENT RISK OF REACTIVATION DISEASE

Bacteriologic yield is variable

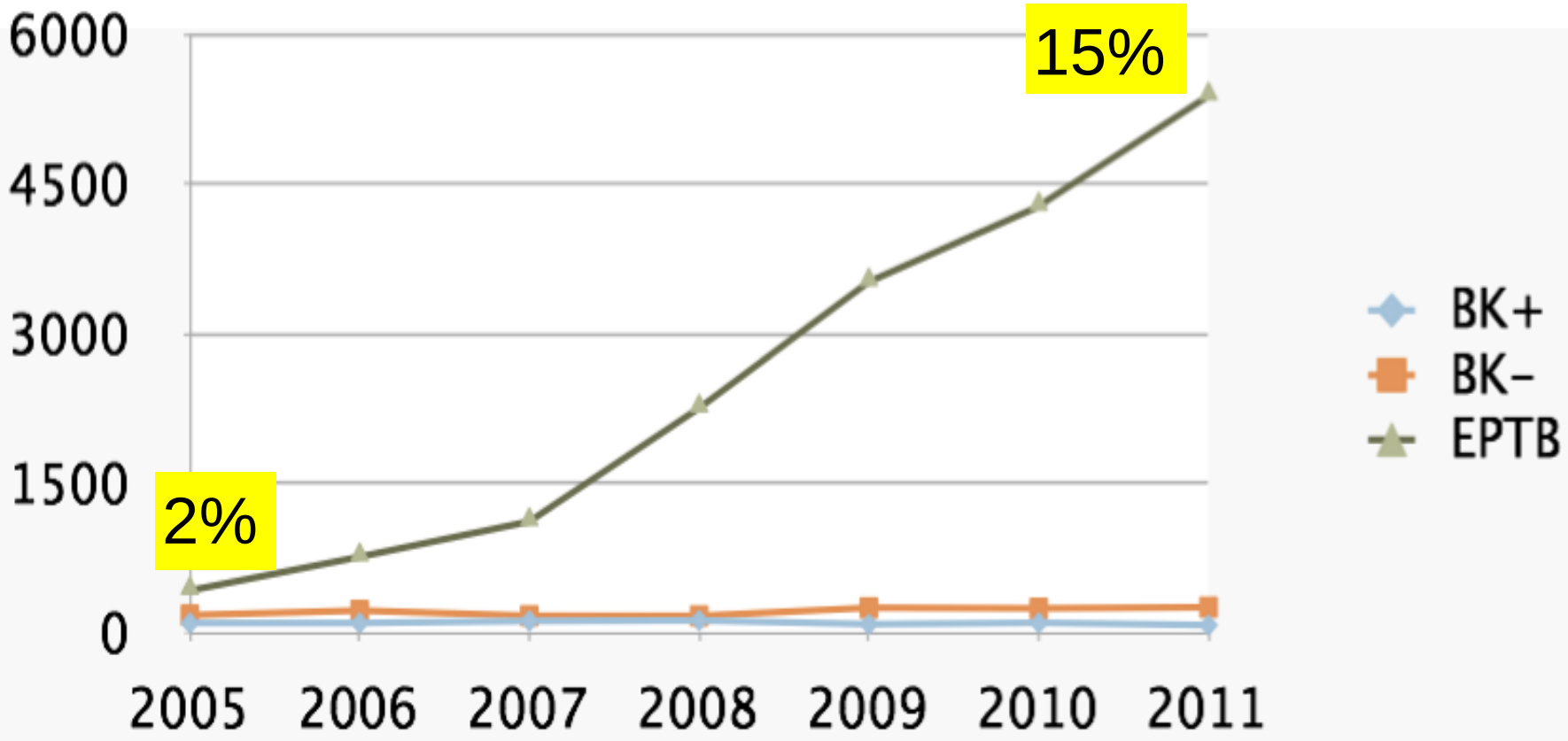
Disease manifestation	Total (%) N = 439	Bacteriologic yield
Not TB	85 (19.4)	
Intra-thoracic TB	307 (69.9)	120/195 (61.5)
Uncomplicated LN	147 (47.9)	22/64 (34.4)
ALL other	160 (52.1)	98/131 (74.5)
Extra-thoracic TB	72 (16.4)	31/46 (67.4)
Cervical adenitis	35 (48.6)	27/27 (100)
TBM	14 (19.4)	1/10 (10.0)
Other	23 (31.9)	5/9 (55.6)

Marais et.al. IJTLD 2006;10:732-738

EXPECTED

1) Disease burden
2) Geographic spread
3) Age spectrum
4) Case mix

Child TB Notifications since 2005

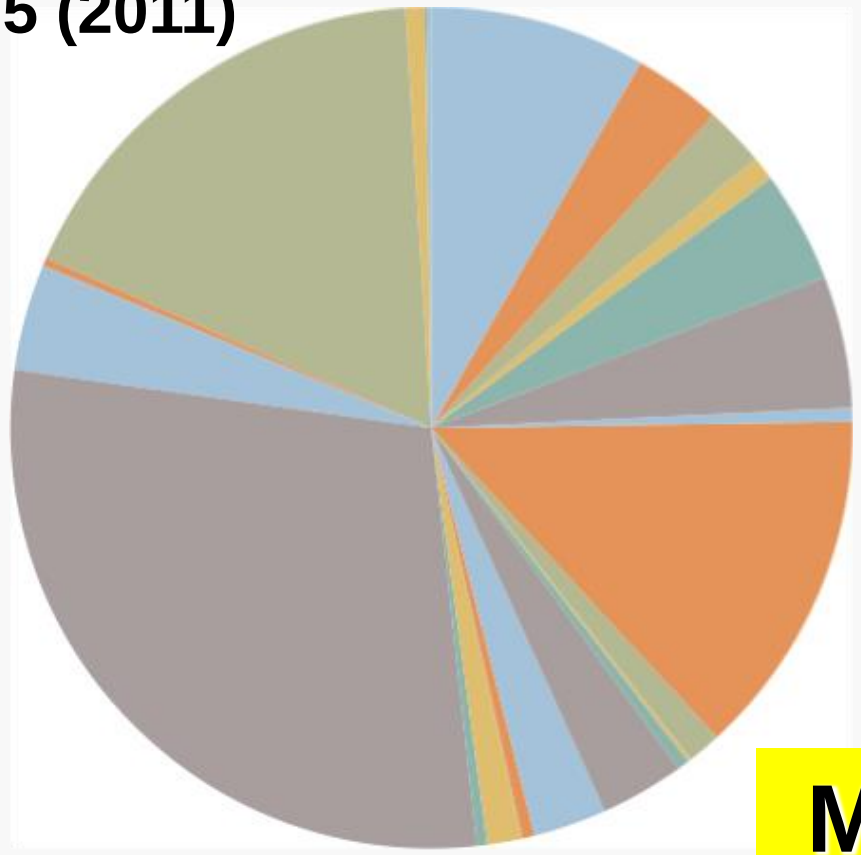


>75% cases clinically Dx cervical adenitis

Kindly provided by the Cambodian NTP

Geographic clustering
Provincial Breakdown of child TB cases

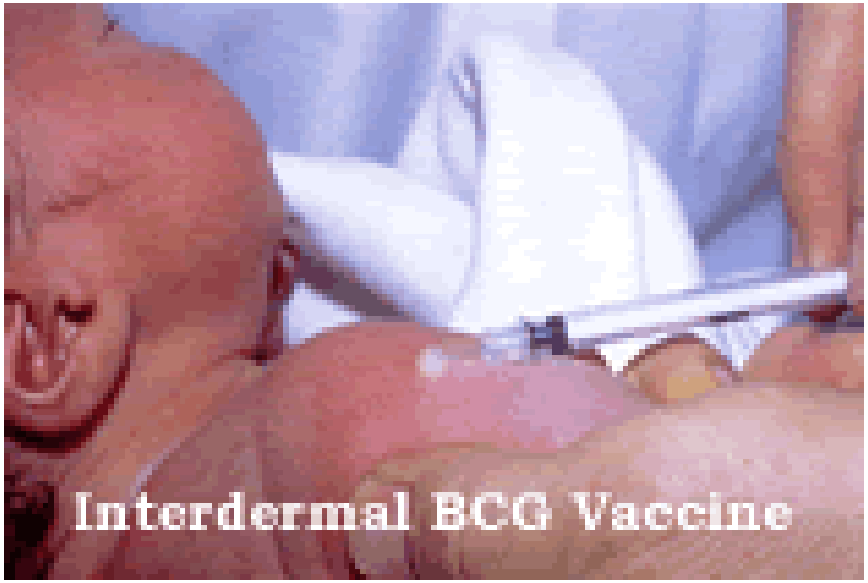
N = 5 375 (2011)



- 60% of cases diagnosed in 3 provinces
- Almost 30% in 1 province alone

Majority of cases 5-10yrs of age

Kindly provided by the Cambodian NTP


Interdermal BCG Vaccine


27-May-08 10:36 am

Calculated risk of distant/disseminated BCG disease in HIV-infected children

Risk scenarios of disseminated BCG disease	**Cases/year 2002**	**Cases/year 2003**	**Cases/year 2004**
Actual cases/year	2	2	3
Risk of disseminated BCG disease Case scenario 1, assuming 5% total vertical HIV infection	2/571= **350/100 000/year**	2/608= **329/100 000**/year	3/719= **417/100 000**/year
Case scenario 2, assuming 10% total vertical HIV infection	2/1142= **175/100 000/year**	2/1217= **164/100 000**/year	3/1439= **208/100 000**/year
Case scenario 3, assuming 15% total vertical HIV infection	2/1713= **117/100 000/year**	2/1825= **110/100 000**/year	3/2158= **139/100 000**/year

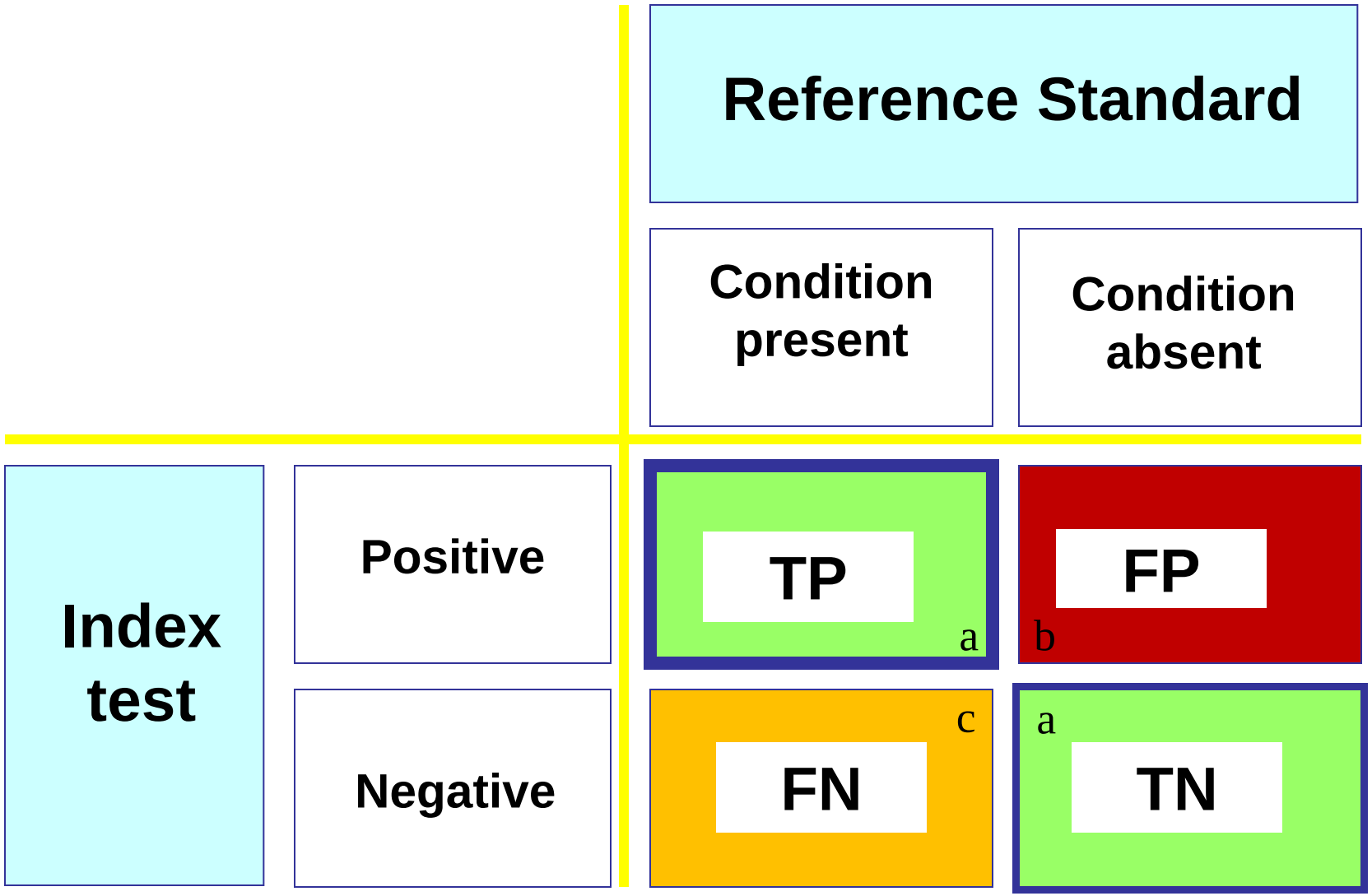
Hesseling et al, Vaccine 2007

New vaccines

Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameris, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team*

Interpretation MVA85A was well tolerated and induced modest cell-mediated immune responses. Reasons for the absence of MVA85A efficacy against tuberculosis or *M tuberculosis* infection in infants need exploration.



The culture conundrum

Dodd LE et.al. Lancet 2012

Xpert MTB/Rif in children

Study	Sample	Sm+	Xpert +
Nicol (2011) Cape Town	**2x Induced sputa**	39% (21/87)	74% (52/70)
Zar (2012) Cape Town	**1x NPA** **1x IS**	24% (21/87) 32% (28/87)	56% (49/87) 74% (64/87)
Rachow (2012) Tanzania	**2-3x sputa or IS**	25% (7/28)	75% (21/28)
Bates (2012) Zambia	**1x sputum** **1x GA**	30% (3/10) 25% (12/48)	90% (9/10) 69% (33/48)

SUPPLEMENT ARTICLE

Evaluation of Tuberculosis Diagnostics in Children: 1. Proposed Clinical Case Definitions for Classification of Intrathoracic Tuberculosis Disease. Consensus From an Expert Panel

SUPPLEMENT ARTICLE

Evaluation of Tuberculosis Diagnostics in Children: 2. Methodological Issues for Conducting and Reporting Research Evaluations of Tuberculosis Diagnostics for Intrathoracic Tuberculosis in Children. Consensus From an Expert Panel[a]

Tuberculous meningitis: a uniform case definition for use in clinical research

Suzaan Marais, Guy Thwaites, Johan F Schoeman, M Estée Török, Usha K Misra, Kameshwar Prasad, Peter R Donald, Robert J Wilkinson, Ben J Marais

Treatment

Old drugs

- No pharmakokinetic (Pk) data in children
- Extrapolated pediatric doses from adult mg/kg dosages

New drugs

- Development cost / ethical barriers / small market
- Nearly impossible to establish efficacy
- Major risk / Minimal potential benefit

Need to separate the issues

1) No reason why efficacy cannot be inferred from adult data
2) Safety and Pk profile must be established seperately

Accepted in principle by FDA/EMA

- NIH workshop consensus document in press