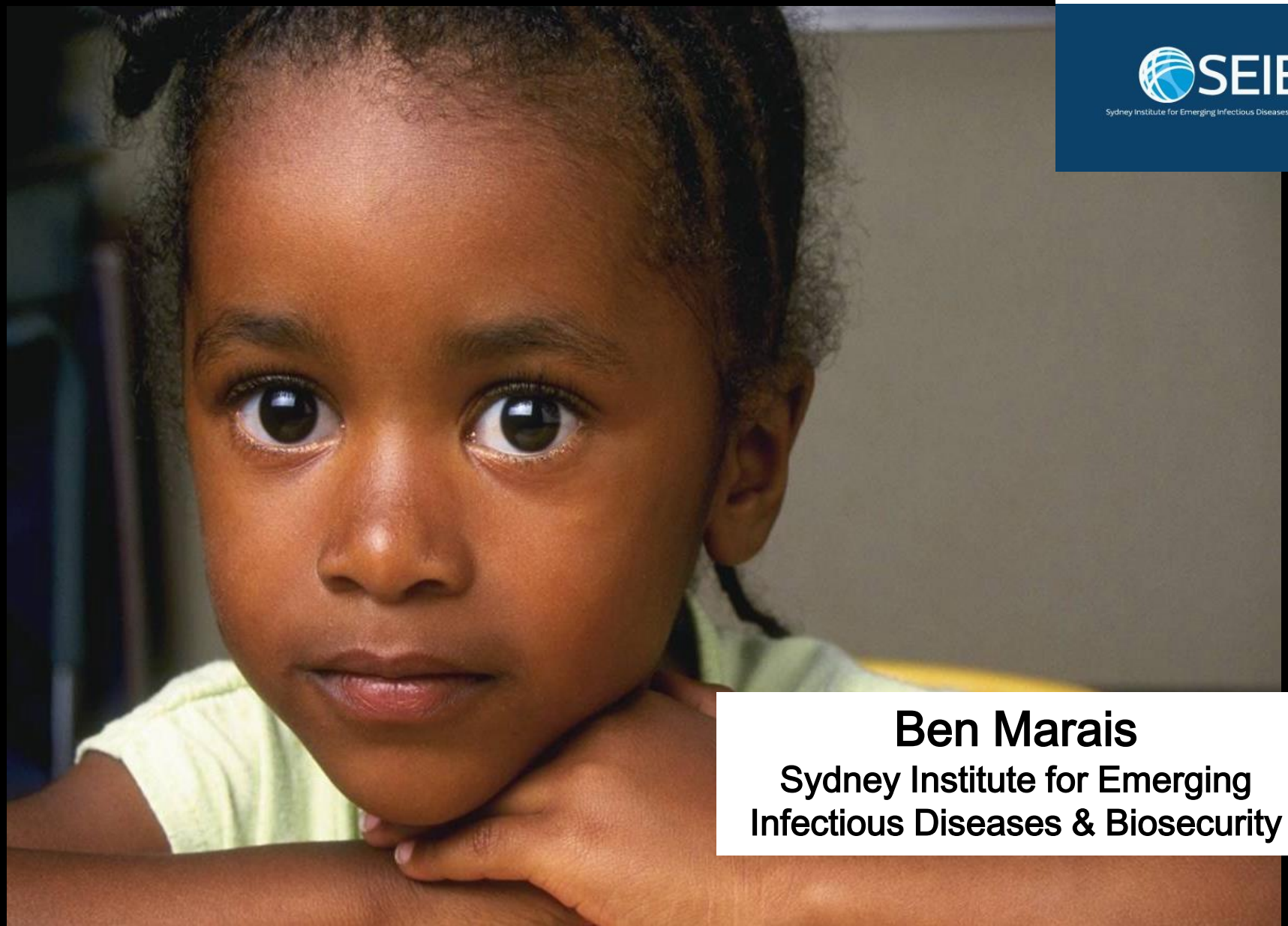
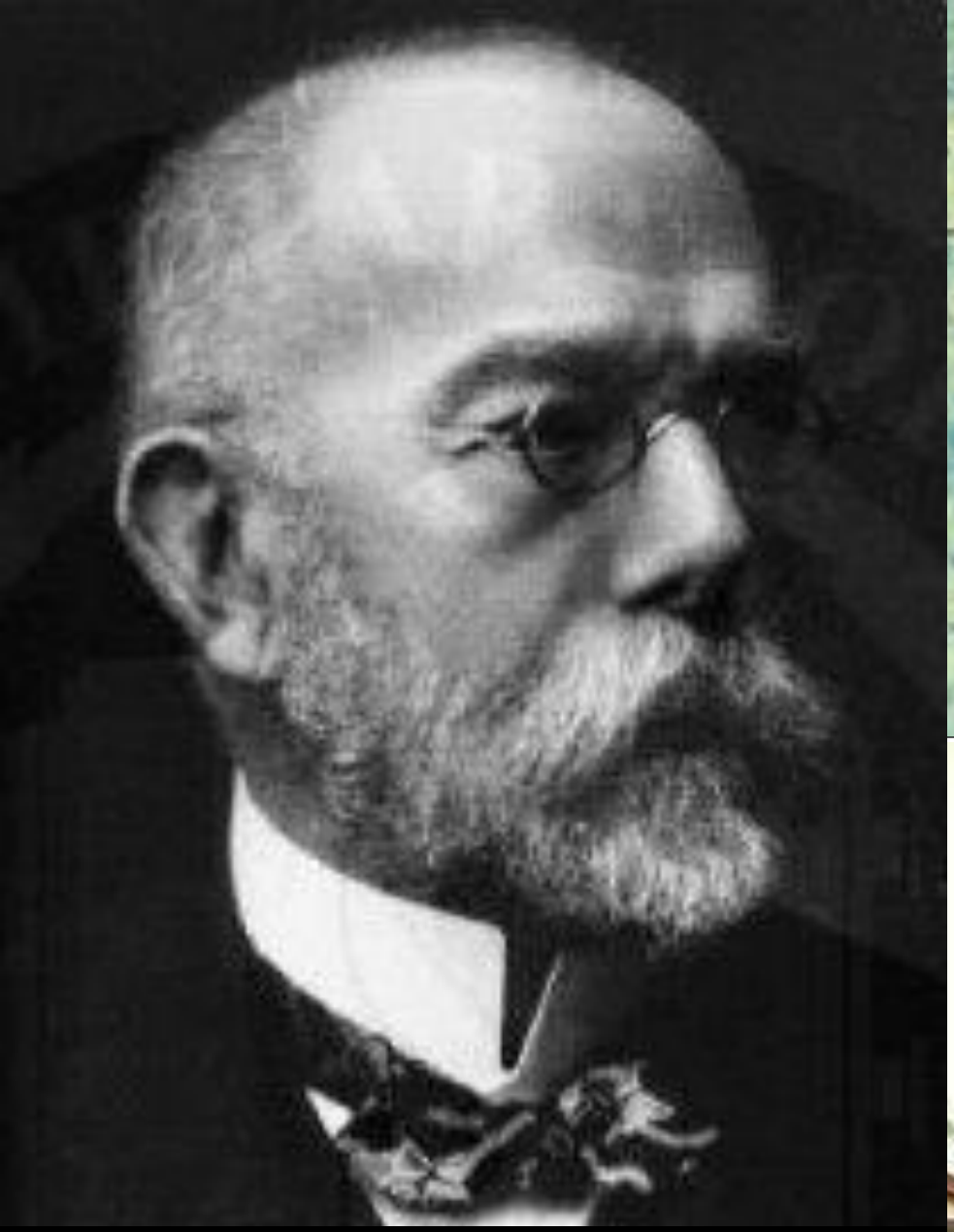
TB in children



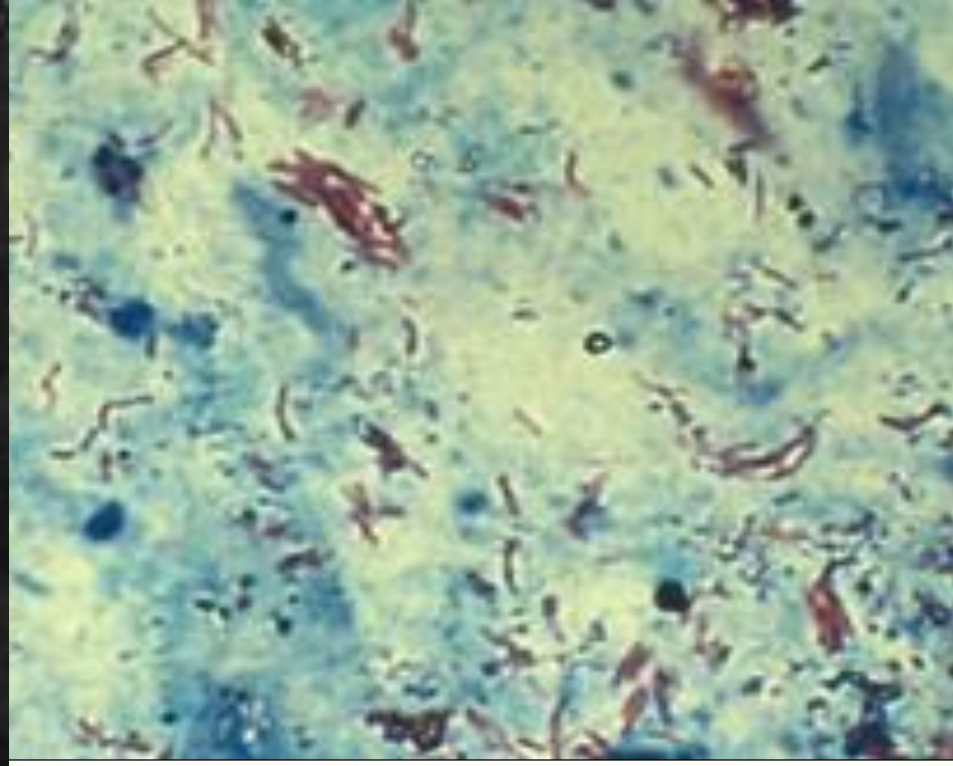
Ben Marais

Sydney Institute for Emerging Infectious Diseases & Biosecurity

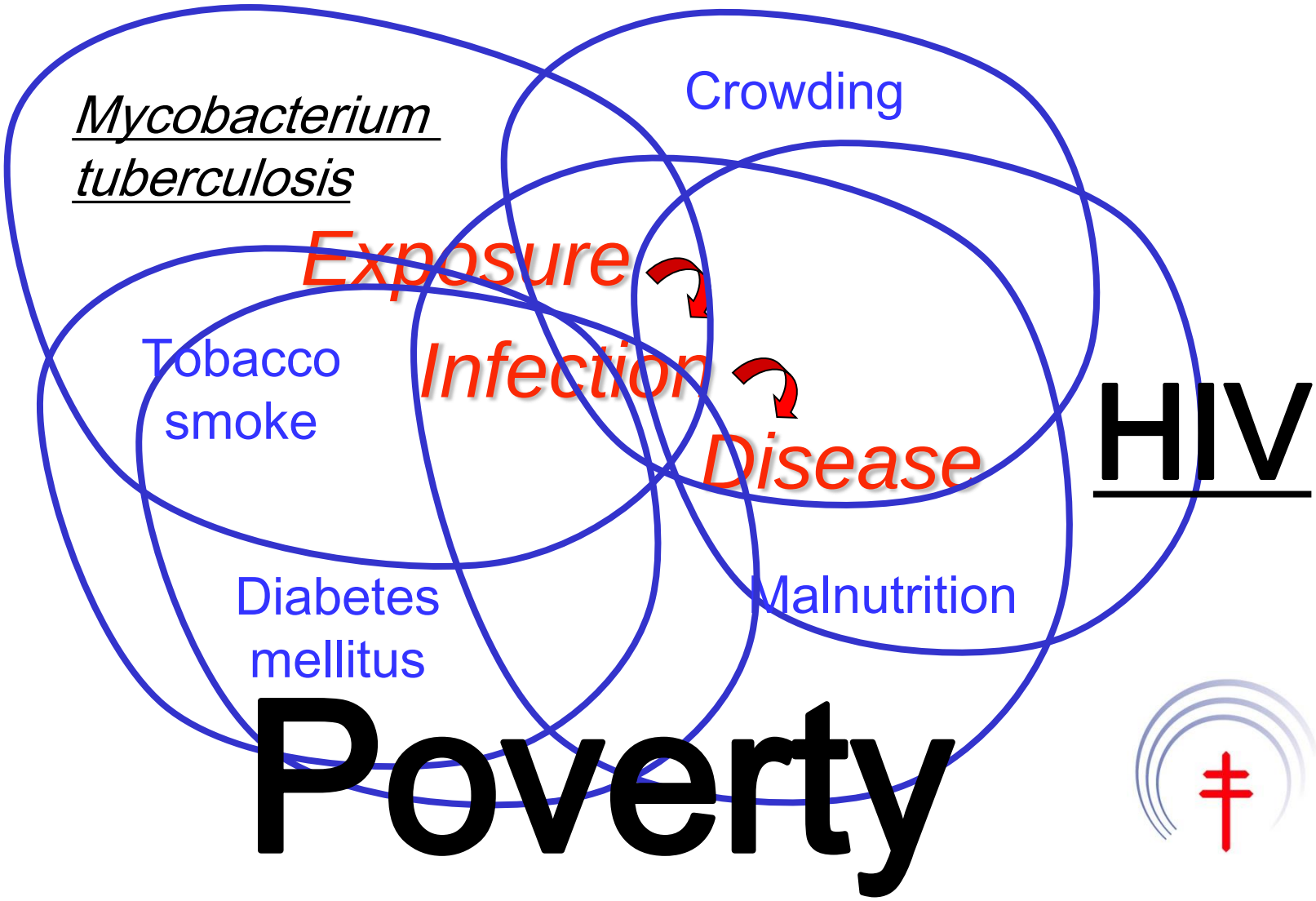


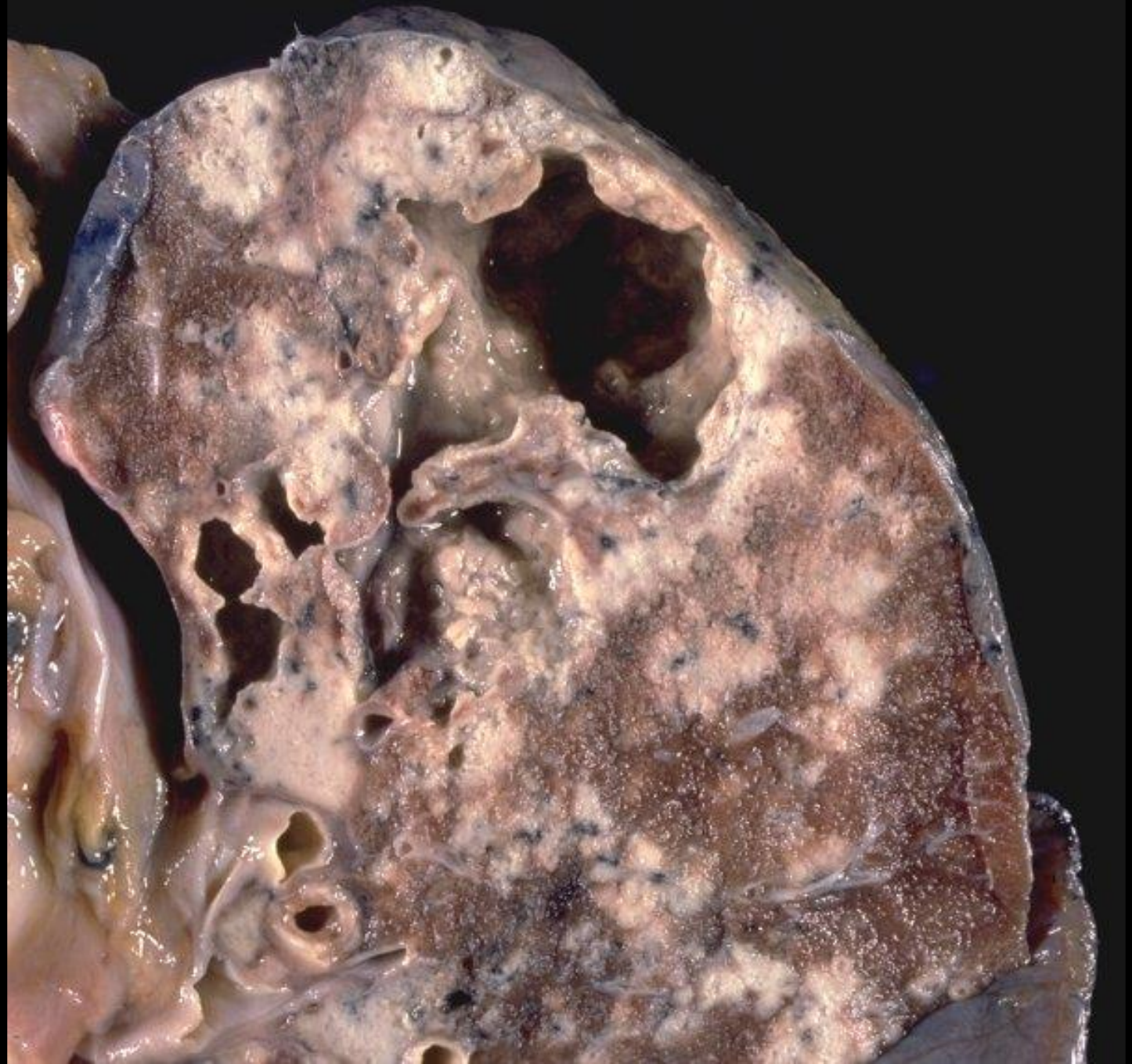
Robert Koch 1843-1910

Discovered *M. Tuberculosis* **1882**

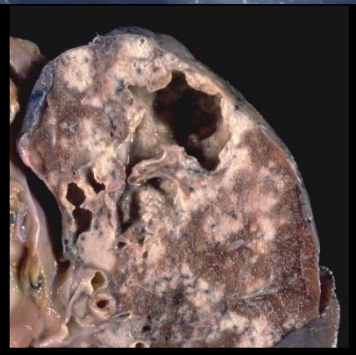


Web of causation





Child TB
"spill over" host



Adult TB
maintenance host

POVERTY / HIV

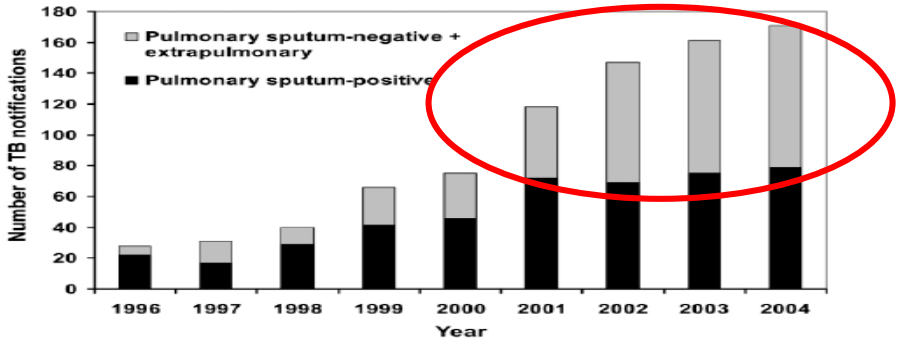
Exposure

Vulnerability


web.capetown.gov.za


Masiphumelele

Increasing TB/HIV Burden

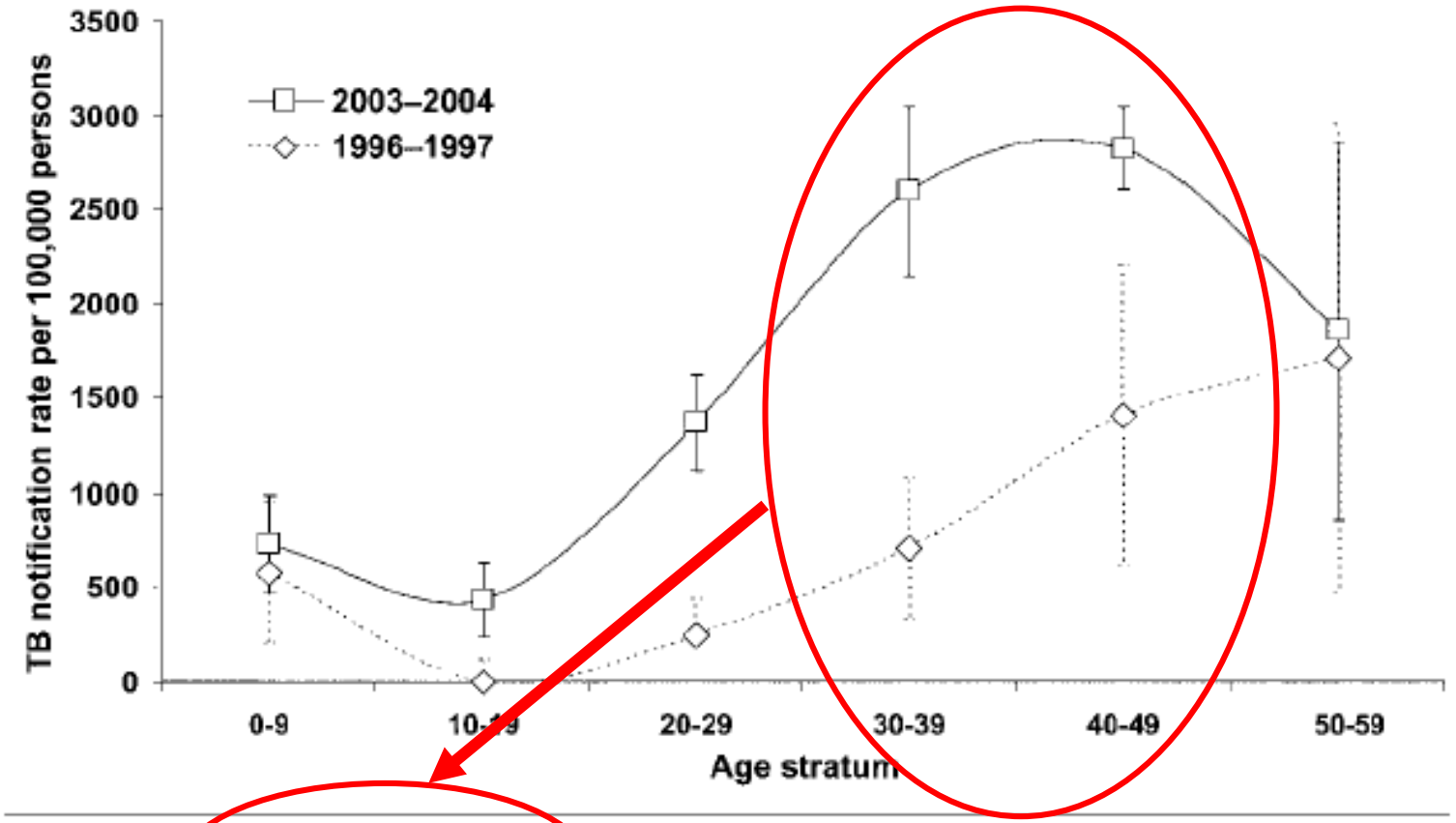


Year	No. of TB notifications	Population size	TB notification rate, cases/100,000 persons[a]	TB re-treatment rate, %[b]	Estimated prevalence of HIV infection, %
1996	32	5518	580	3	6.3
1997	42	6429	653	21	8.9
1998	67	7339	913	7	11.6
1999	74	8250	897	20	14.2
2000	90	9161	982	17	16.5
2001	142	10,071	1410	15	18.4
2002	150	10,982	1366	18	19.9
2003	175	11,892	1472	22	21.1
2004	188	12,803	1468	24	21.9

[a] $P = .007$, by test for trend.
[b] $P = .073$, by test for trend.

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

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?

- Rare (not true)

Estimated contribution globally 15-20%

Cape Town, SA

ALL TB incidence children 407/100 000/yr (adults 845)

Marais, IJTLD 2006;10:259-63

- Limited disease only (not true)

Autopsy study Zambia, as common a cause of death as acute bacterial pneumonia

Chintu, Lancet 2002; 360: 985-90

- Pose no transmission risk (not true)

Adolescents frequently as infectious as adults

Marais, PIDJ 2005; 24: 743-44

Lung Disease Identified At Necropsy In Zambian Children

Diagnosis	HIV positive N=180	HIV negative N=84	Odds ratio (95%C.I.)
Pyogenic pneumonia	41%	50%	0.7 (0.4- 1.2)
PCP	29%	7%	5.3 (2.1-15.7)
Tuberculosis	18%	26%	0.6 (0.3- 1.2)
CMV	22%	4%	7.7 (2.3-40.0)
Interstitial pneumonitis	8%	18%	0.4 (0.2-0.96)
Other	24%	16%	-

Chintu C et. al. Lancet 2002; 360: 985-90

M.tb 2nd Most Common Pathogen identified in Children with CAP who Failed Empirical Antibiotic Therapy

	Younger than 1 year				1 year or older		
	Total (n=90)	Infected (n=74)	Exposed uninfected (n=9)	Uninfected (n=7)	Total (n=20)	Infected (n=13)	Uninfected (n=7)
Pneumocystis jirovecii	29 (32%)	26 (35%)	3 (33%)	0	0	0	0
Mycobacterium tuberculosis	15 (17%)	13 (18%)	0	2 (29%)	9 (45%)	5 (39%)	4 (57%)
Cytomegalovirus	40 (45%)	37 (51%)	2 (22%)	1 (14%)	4 (20%)	3 (23%)	1 (14%)
Streptococcus pneumoniae	9 (10%)	7 (9%)	0	2 (29%)	3 (15%)	3 (23%)	0
Staphylococcus aureus	13 (14%)	11 (15%)	2 (22%)	1 (14%)	6 (30%)	4 (31%)	2 (29%)
Other gram positive	6 (7%)	5 (7%)	0	1 (14%)	3 (15%)	3 (23%)	0
Haemophilus influenzae	5 (6%)	3 (4%)	1 (11%)	1 (14%)	4 (20%)	2 (15%)	2 (29%)
Klebsiella pneumoniae	9 (10%)	8 (11%)	1 (11%)	0	0	0	0
Escherichia coli	8 (9%)	7 (9%)	1 (11%)	0	0	0	0
Salmonella spp	1 (1%)	1 (1%)	0	0	0	1 (8%)	0
Legionella spp	1 (1%)	1 (1%)	0	0	0	0	0
Other gram negative	10 (11%)	8 (11%)	1 (11%)	1 (14%)	3 (15%)	2 (15%)	1 (15%)
Adenovirus	6 (7%)	4 (5%)	0	2 (28%)	3 (15%)	2 (15%)	1 (14%)
Respiratory syncytial virus	11 (12%)	8 (11%)	3 (33%)	0	2 (10%)	0	2 (29%)

Among children who failed to respond to AB Rx:

<1yr of age: *M. tb* in 18% HIV+ / 29% HIV-

>1yr of age: *M. tb* in 39% HIV+ / 57% HIV-

Table 5: Organisms isolated from children who were investigated for failing to respond by HIV status and age

McNally L et. al. Lancet 2007; 369: 1 440-51

Under 5 mortality Kolkata, India

rate / 1000 person yrs by age grp

Cause of death	<1yr	1-4yrs	Rank
Respiratory infections	2.97	0.86	1
Tuberculosis	1.98	0.52	2
Diarrhoeal diseases	1.98	0.34	3

- Verbal autopsy study covering slum areas 29 & 30
- Death surveillance May 2003 - October 2004

Accurate baseline demographic data / numbers small

Kanungo S et. al. Bull WHO 2010; 88: 667-74

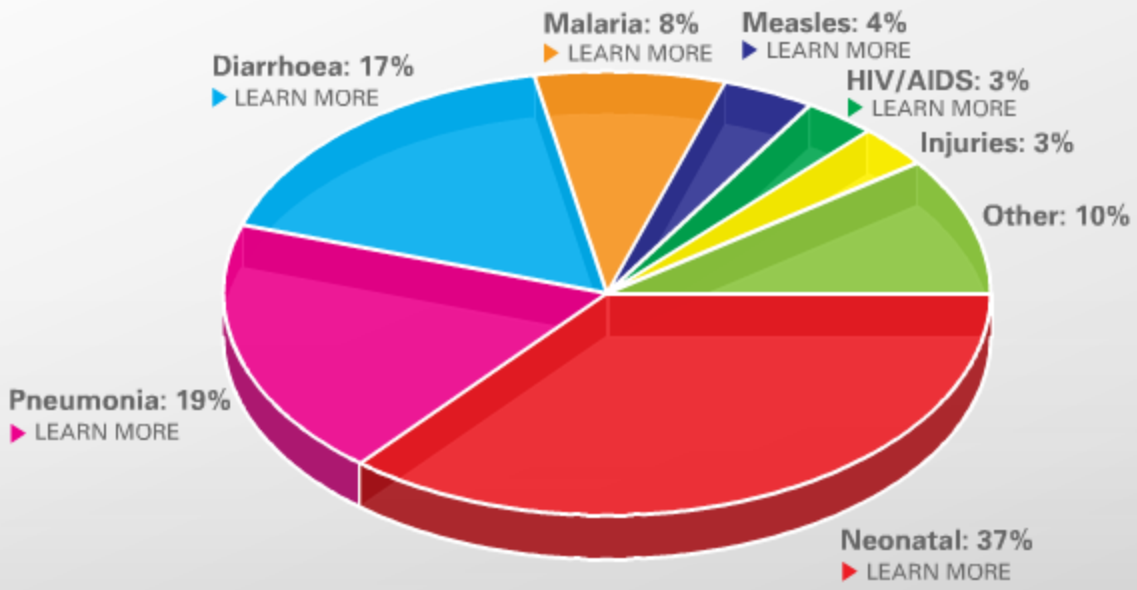
Millennium Development Goal 4

REDUCE CHILD MORTALITY

Under–Five Child Mortality
Pneumonia
Diarrhoea
Malaria
Measles
HIV/AIDS
Neonatal
Under–Nutrition

Under–Five Child Mortality

Global distribution of cause–specific mortality among children under five years of age:



Note: The global distribution of under–five deaths by cause does not sum to 100% due to rounding.

Source: CHERG estimates as presented in WHO, World Health Report 2005.

MAIN MENU

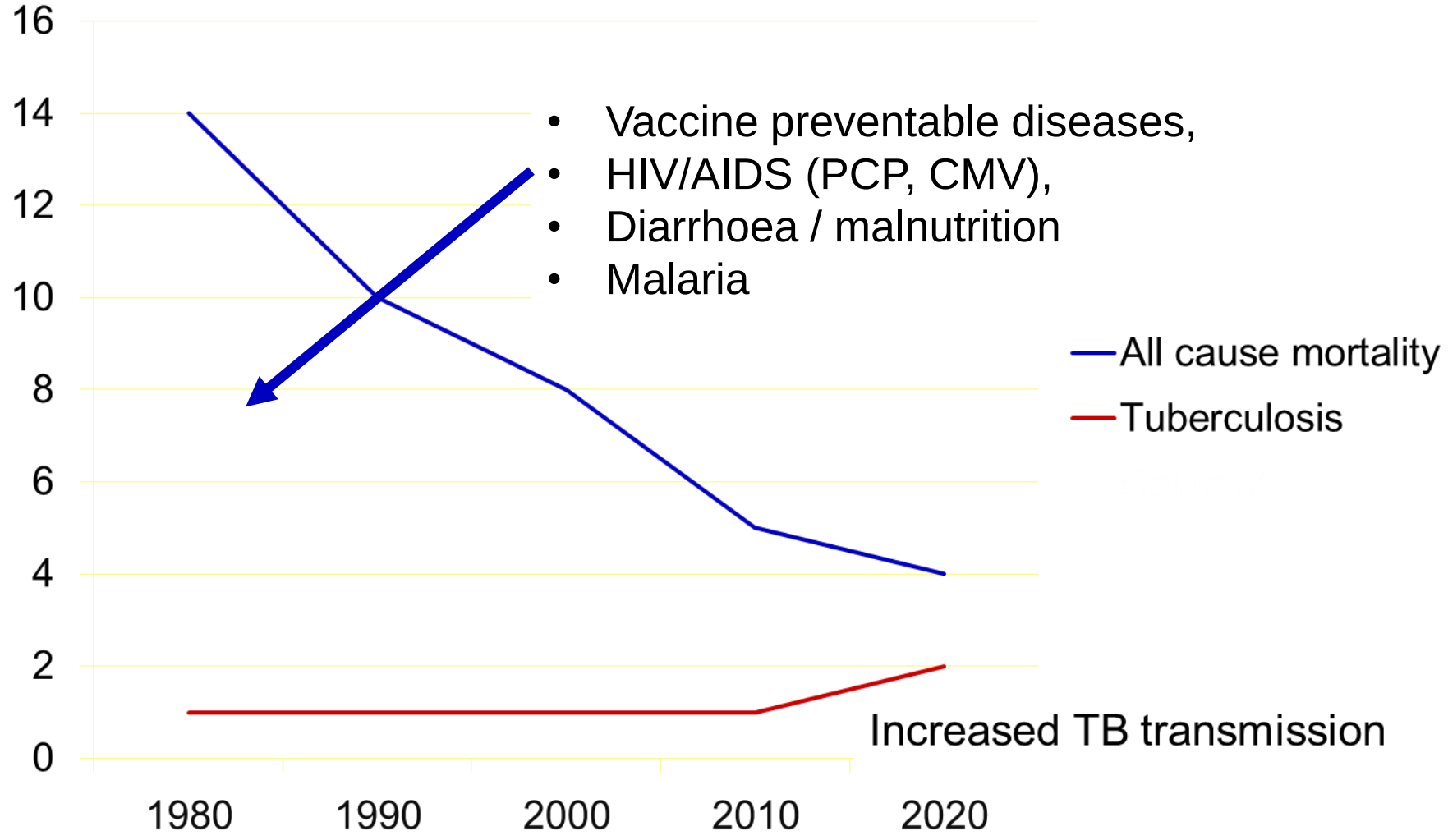
January 2007

Millennium Development Goals

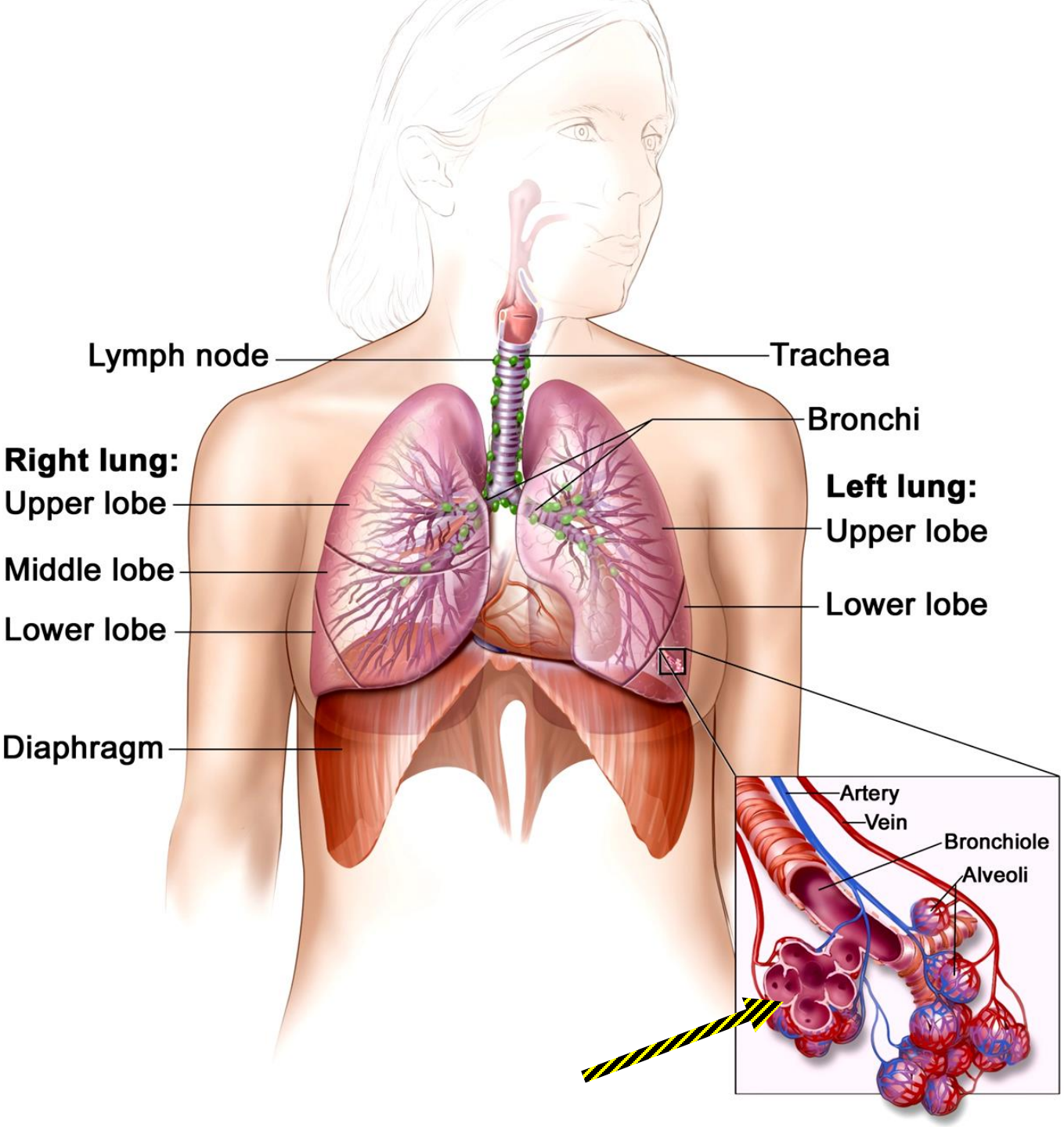
Round peg in a square hole

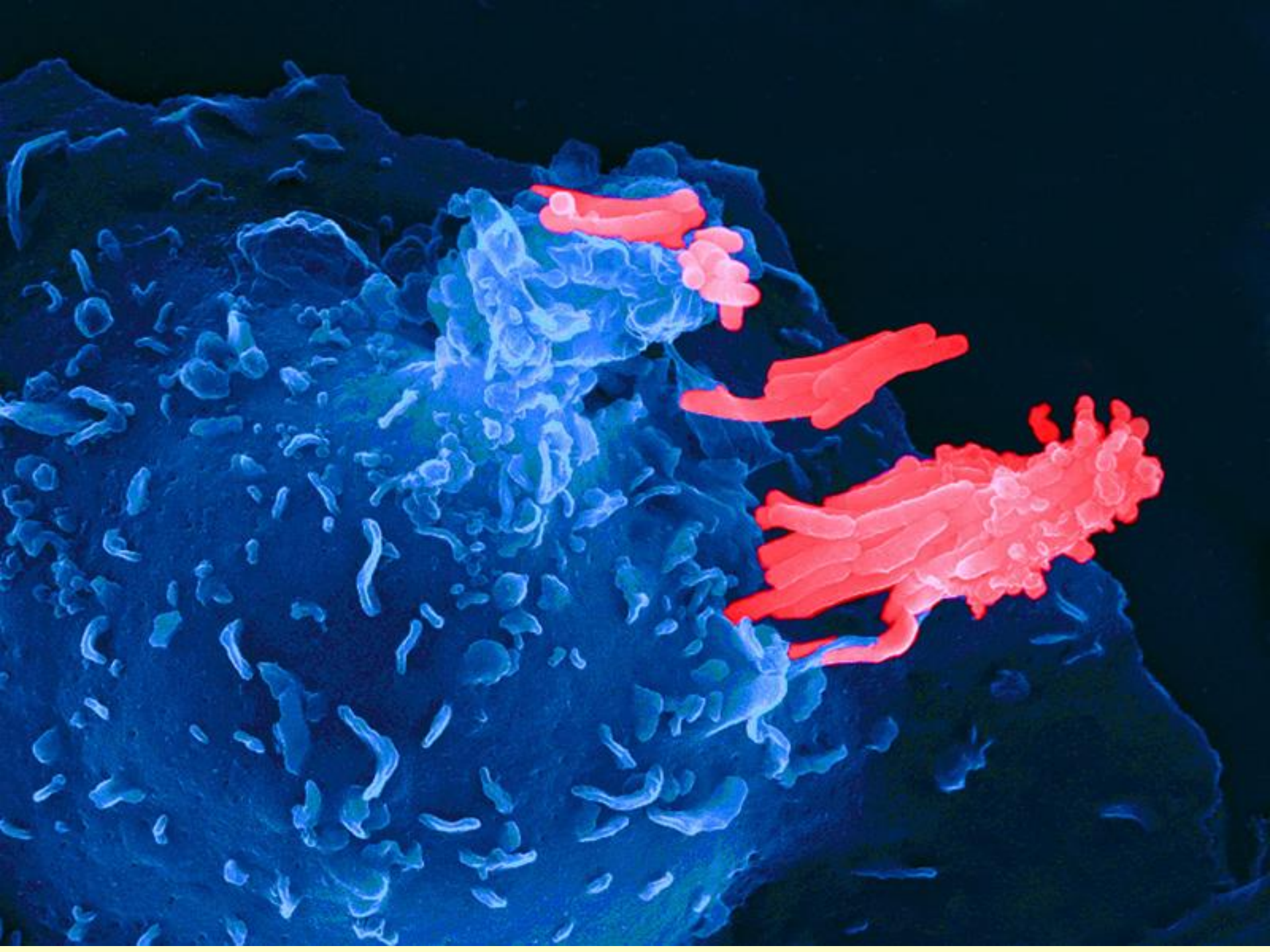
Focus mainly on epidemic control

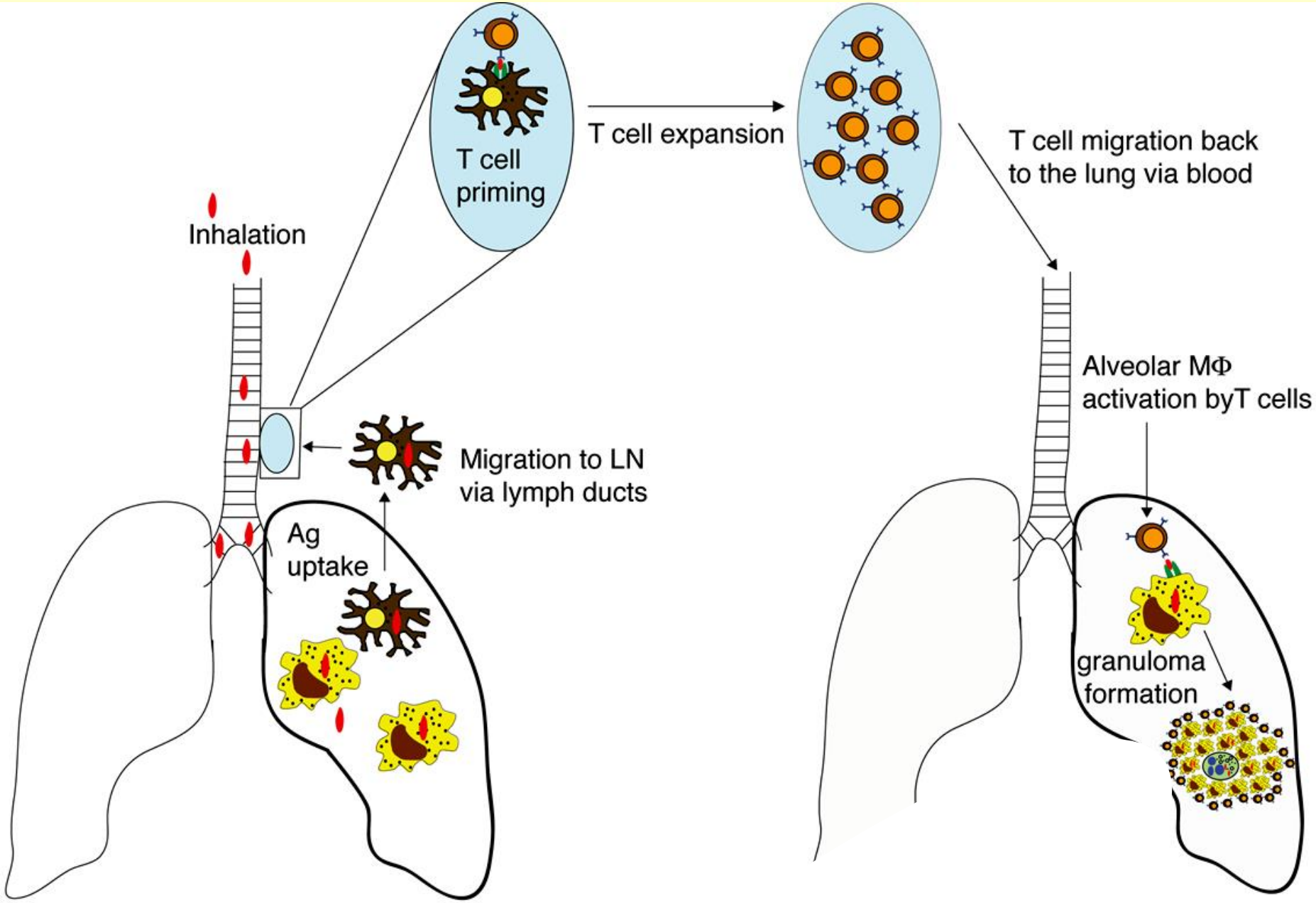
Relative contribution



Call on UNICEF and other global agencies involved in maternal & child health (MDG 4 & 5) to take child TB on board


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

Understanding the Natural History of Disease & Determinants of risk

Major transitions

Exposure

↓

Infection

↓

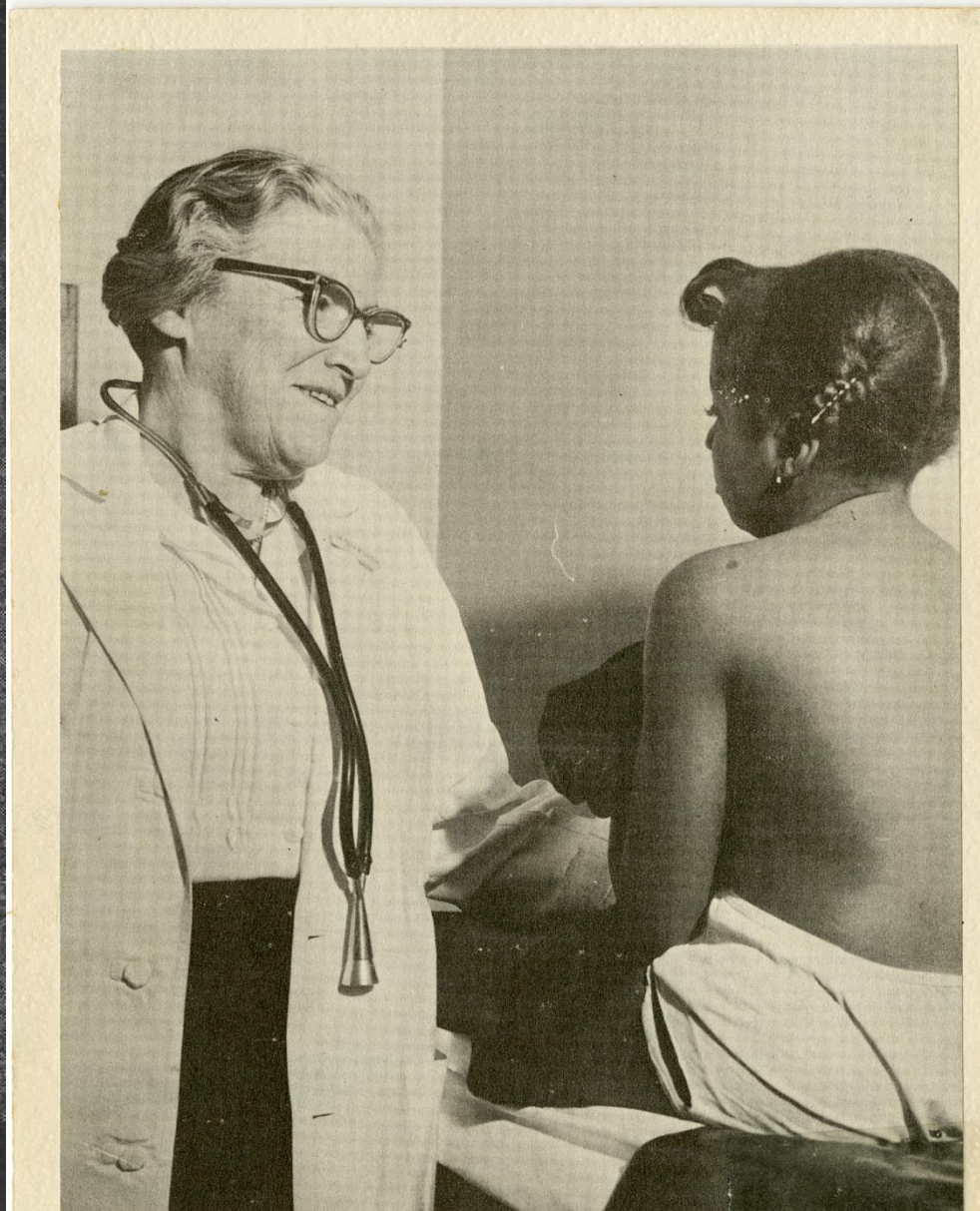
Disease

Arvid Wallgren

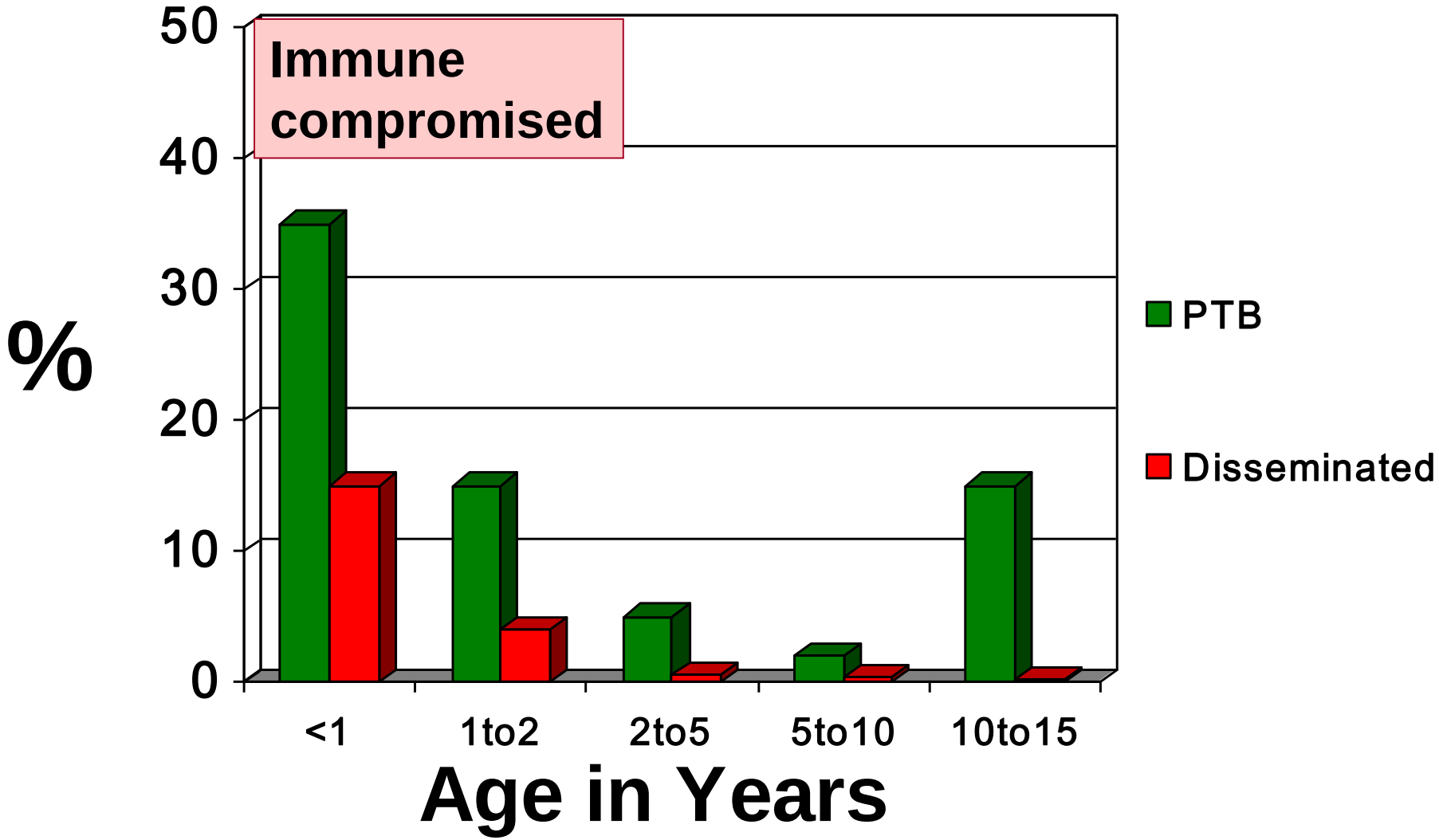
Karolinska, Stockholm

Edith Lincoln

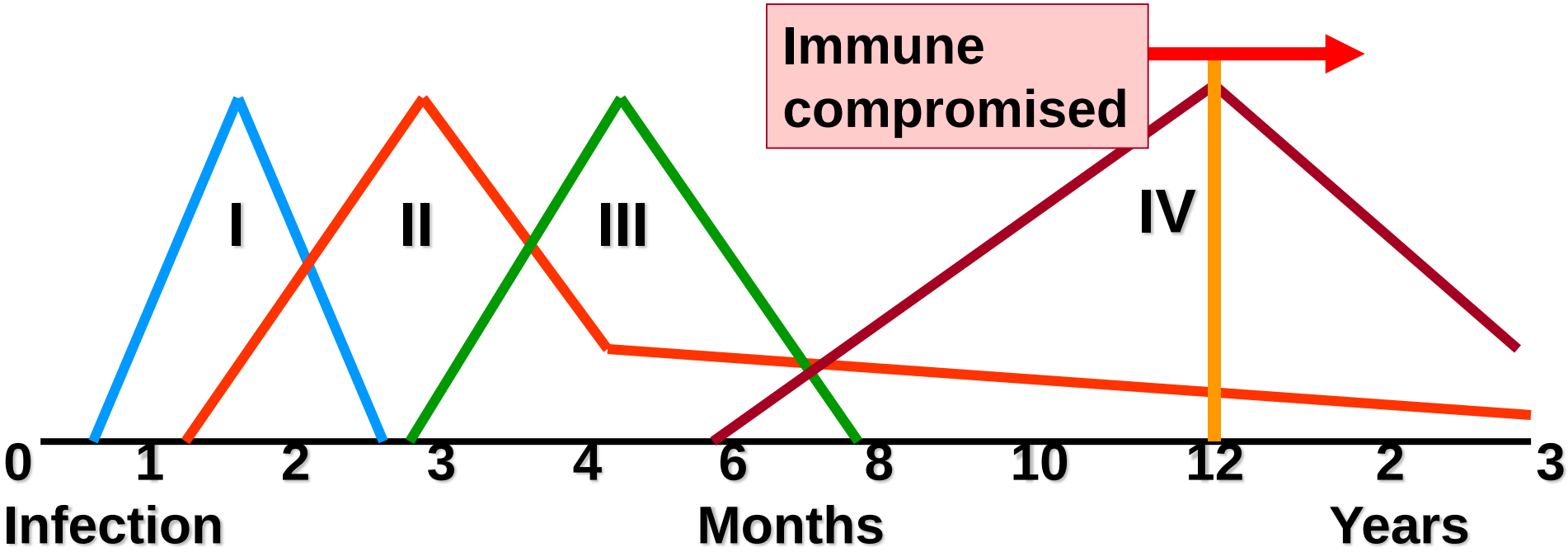
Bellevue, New York



Age-related risk



Time-related risk



Phase of disease

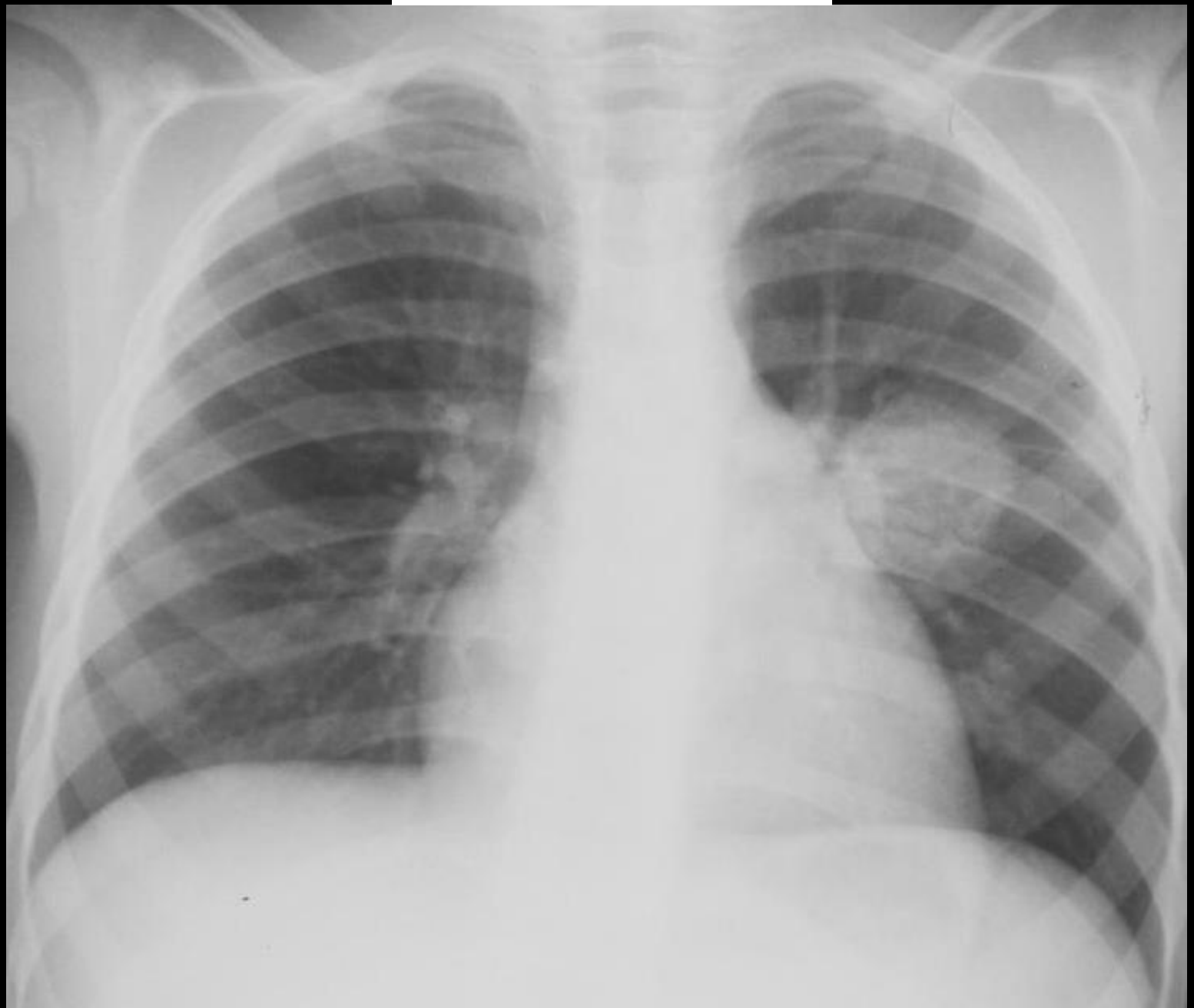
I Hypersensitivity
II Miliary TB and TBM
III Lymph node disease / Pleural effusion
IV Adult-type disease

HIV-infected - PERSISTENT RISK OF REACTIVATION DISEASE

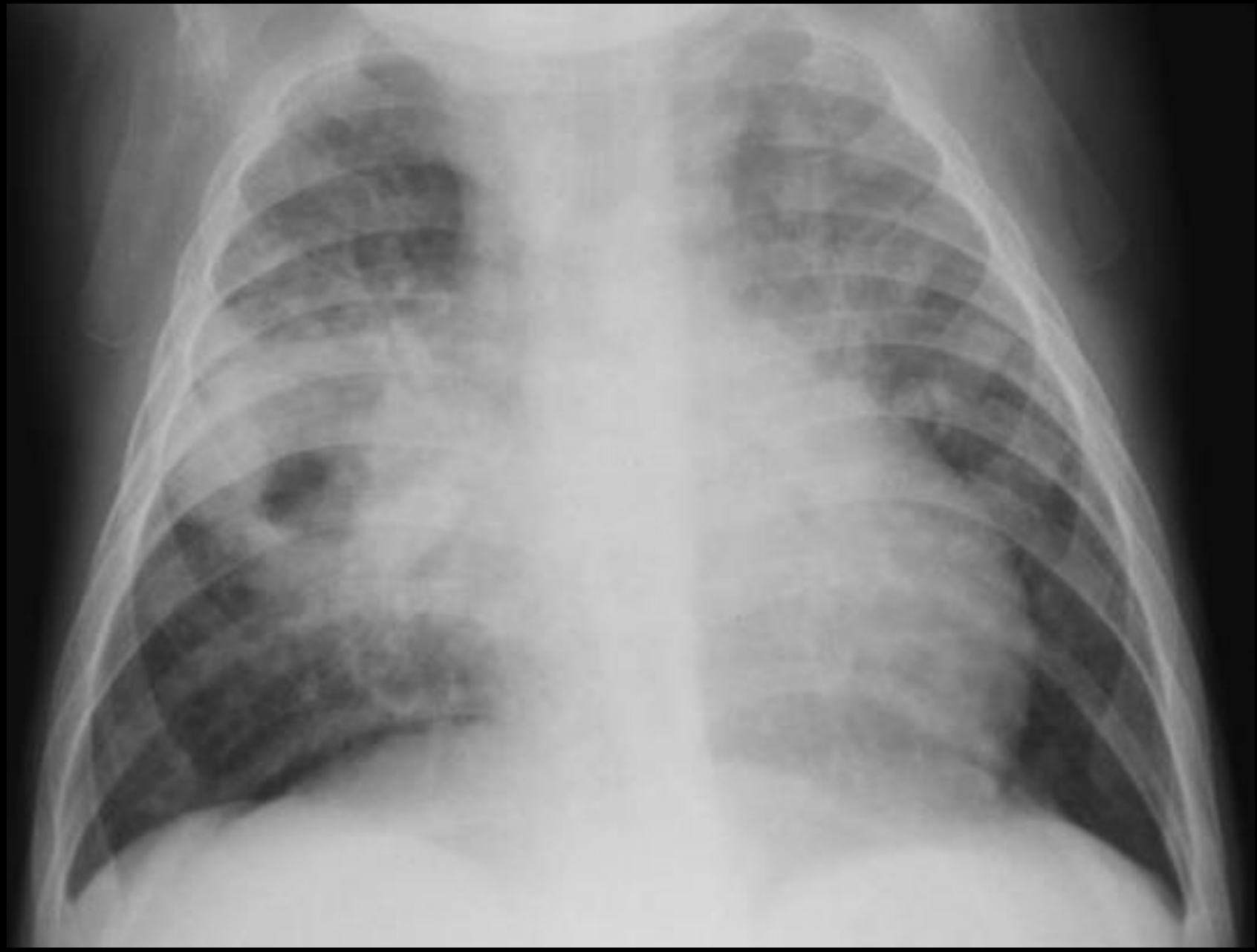
DIVERSITY OF DISEASE

Manifestations of intra-thoracic TB in children

Ghon focus



Complicated Ghon focus



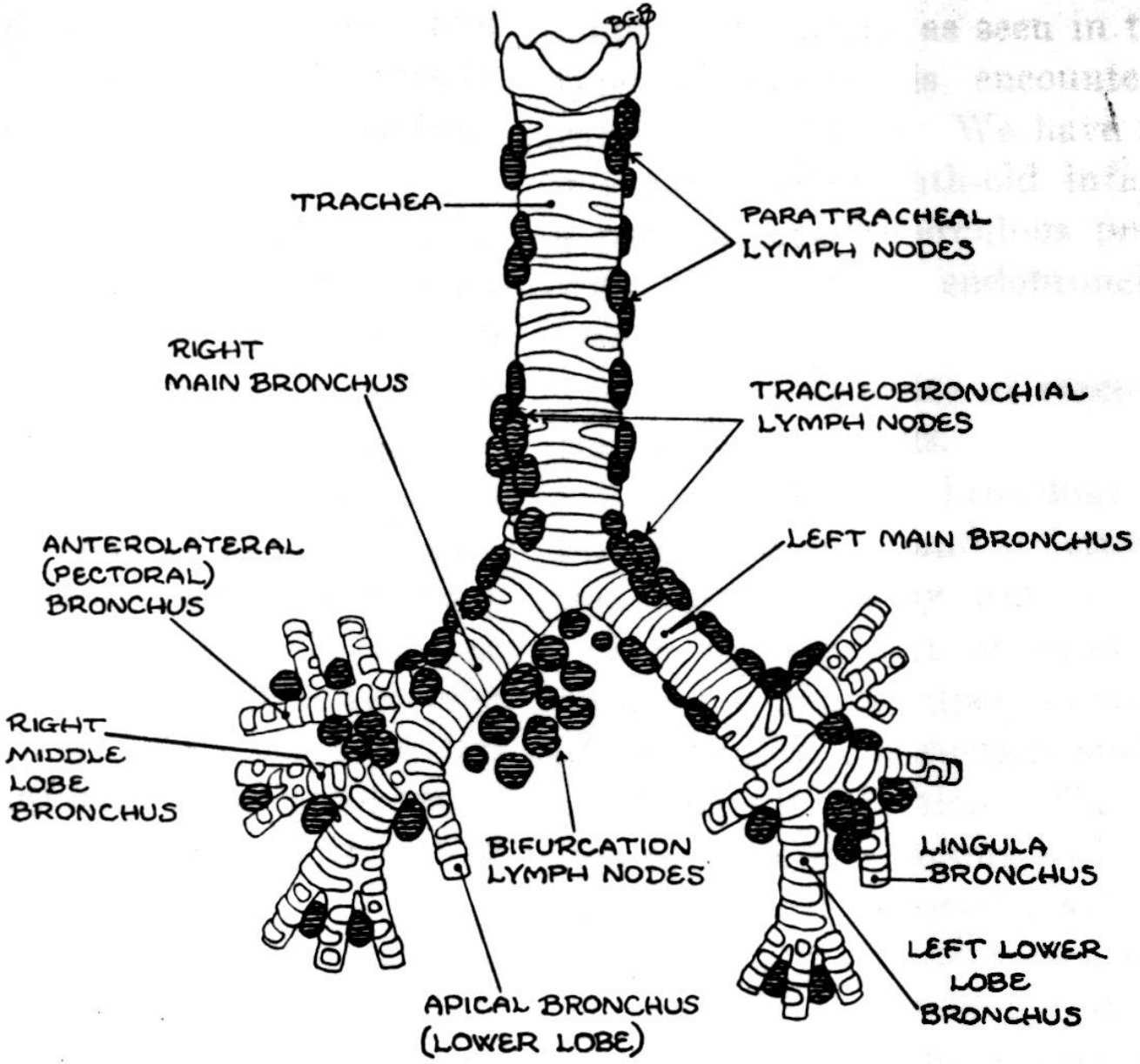
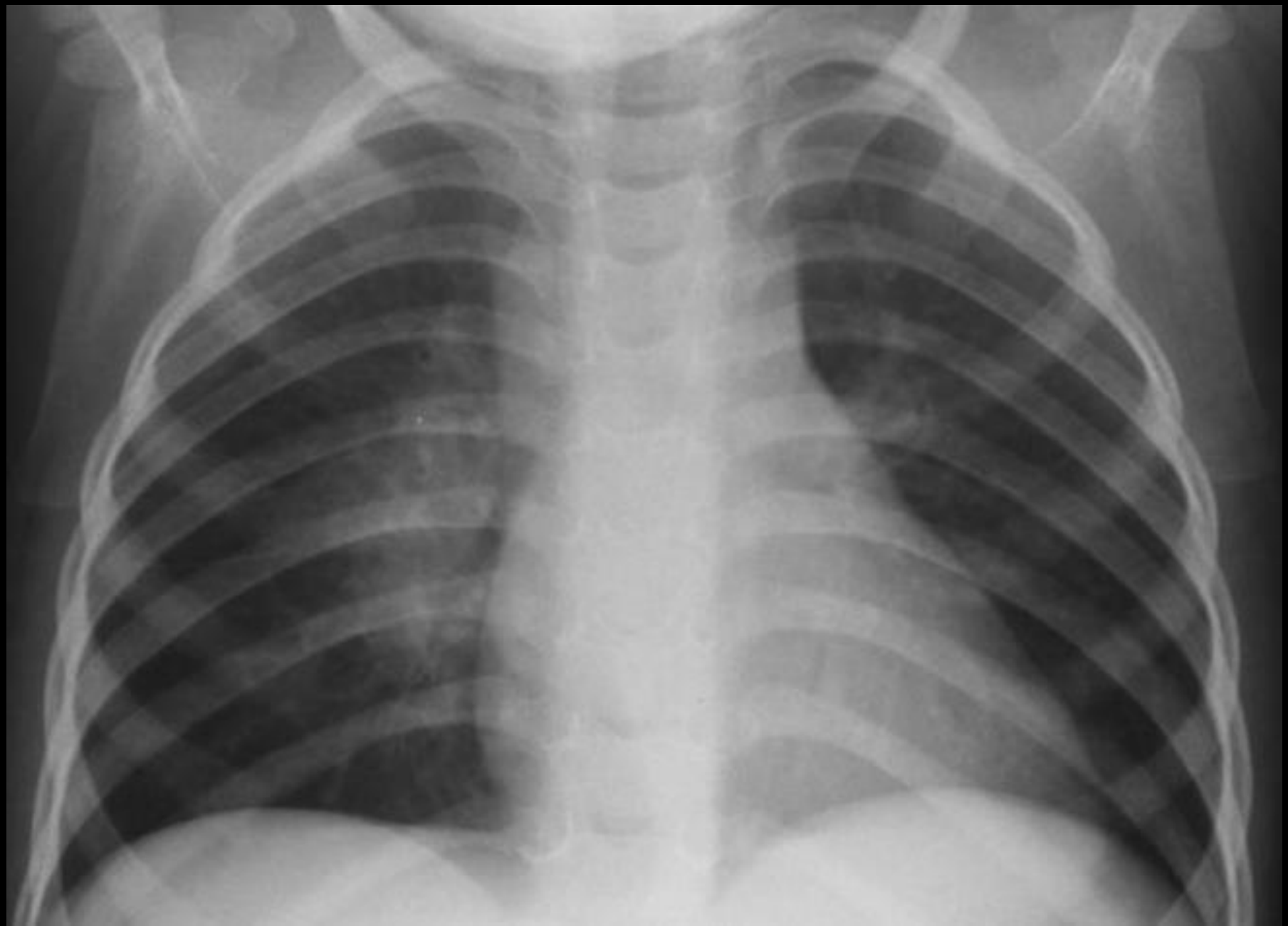
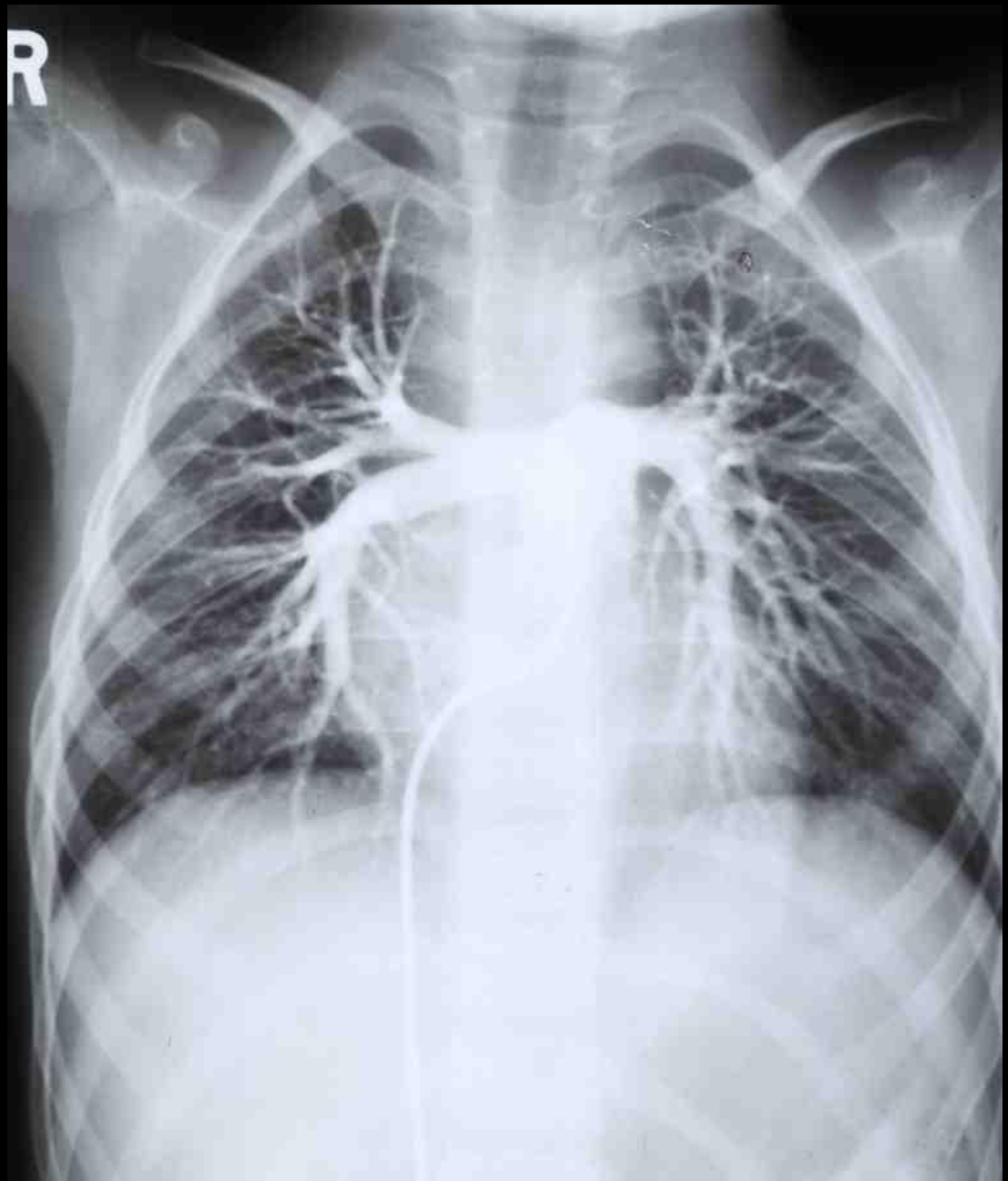


Fig. 8.—Distribution of the tracheobronchial lymph nodes. (Semidiagrammatic drawing after W. Snow Miller: *The Lung*, Springfield, Ill., 1937, Charles C Thomas.)

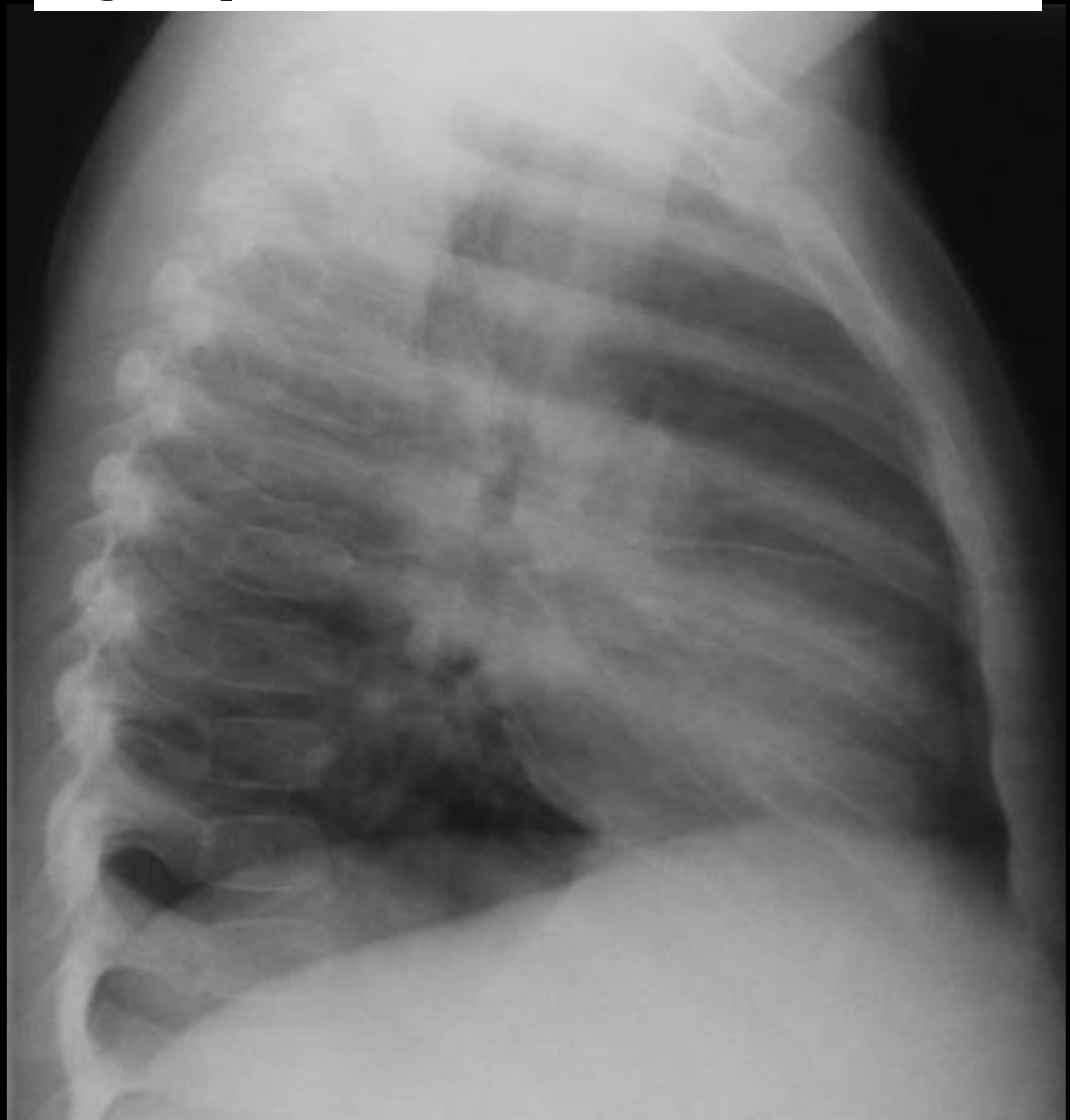
Lymph node disease AP



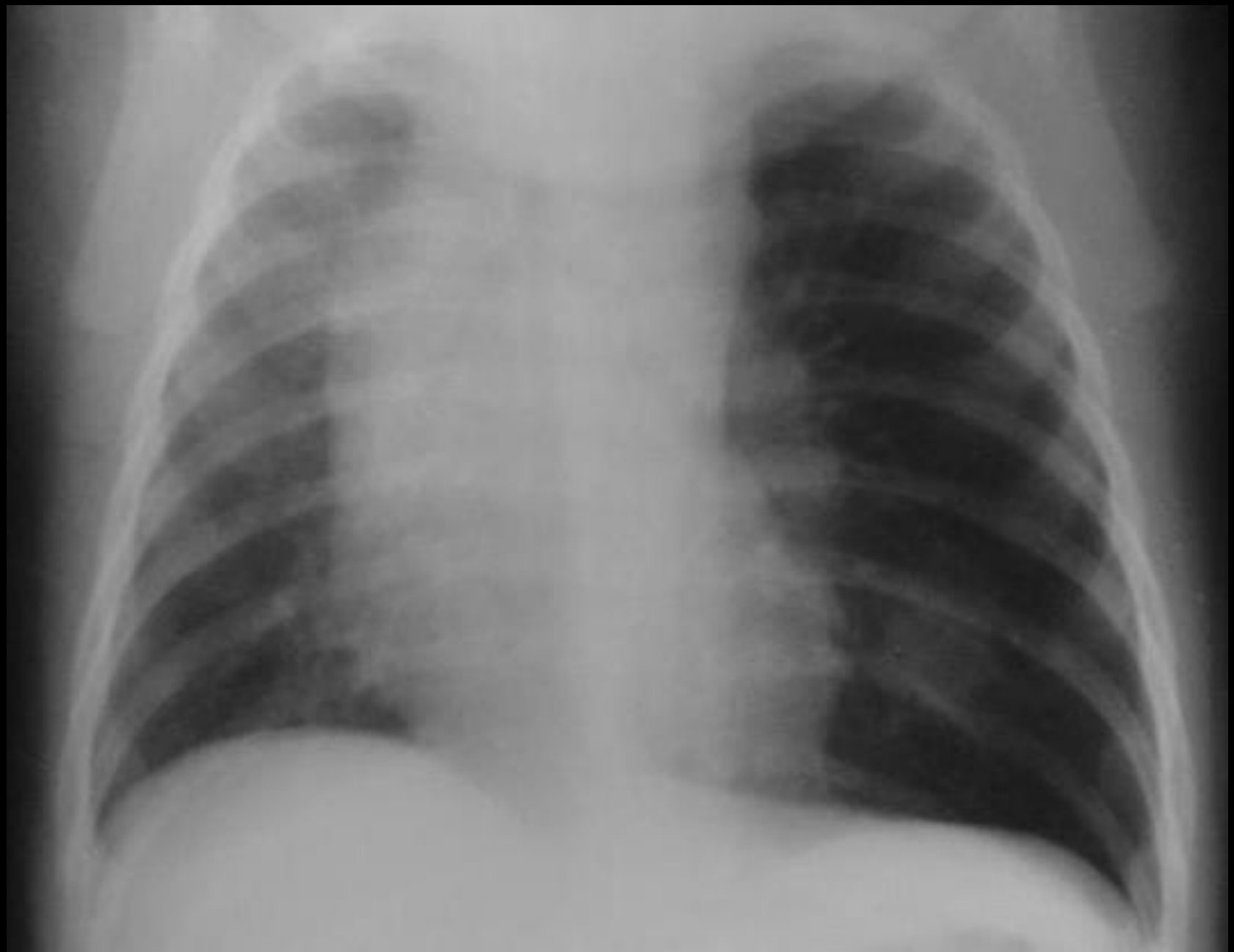
Cardiac Catheterization



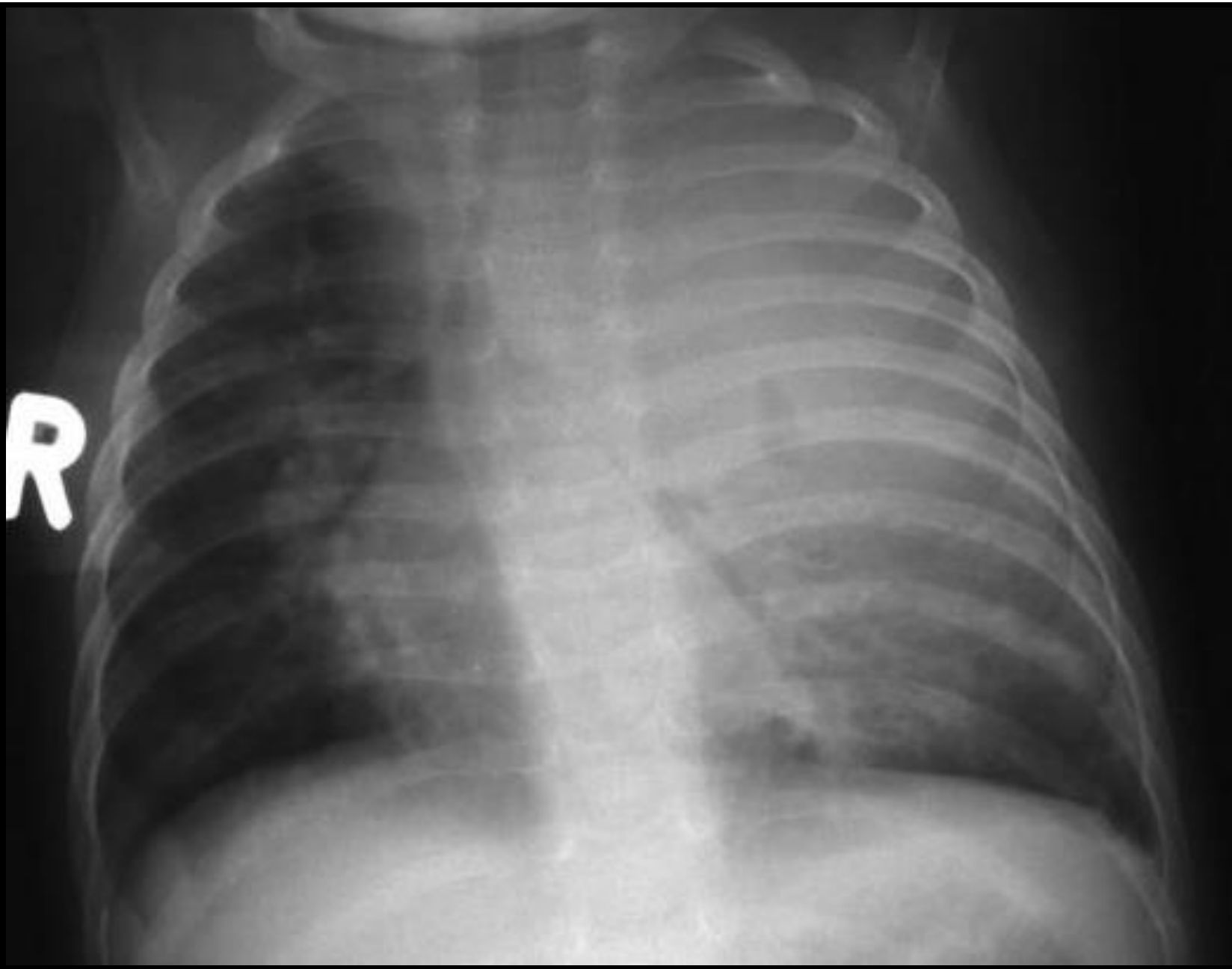
Lymph node disease Lat



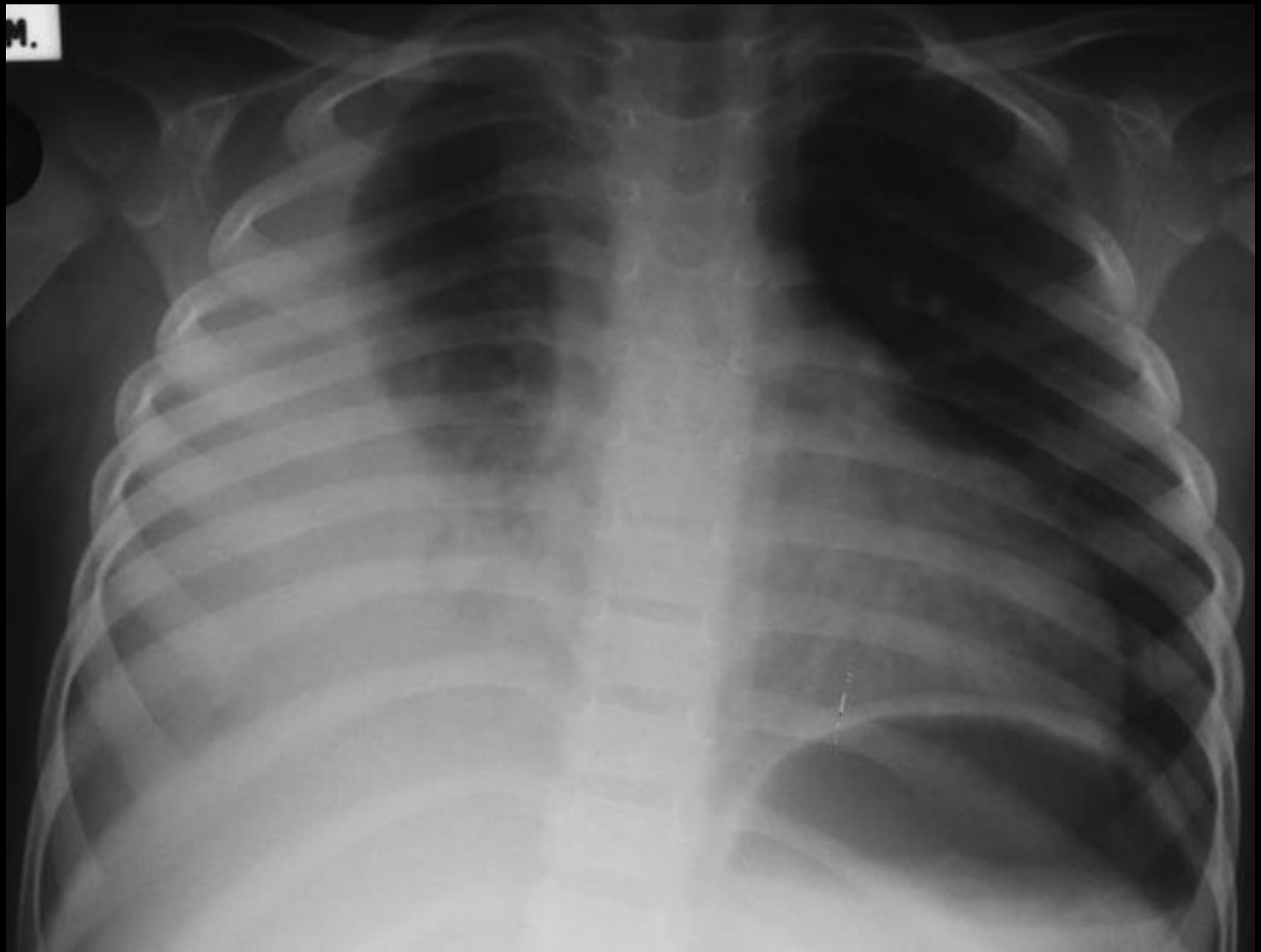
Complicated lymph node disease



TB caseating / expansile pneumonia

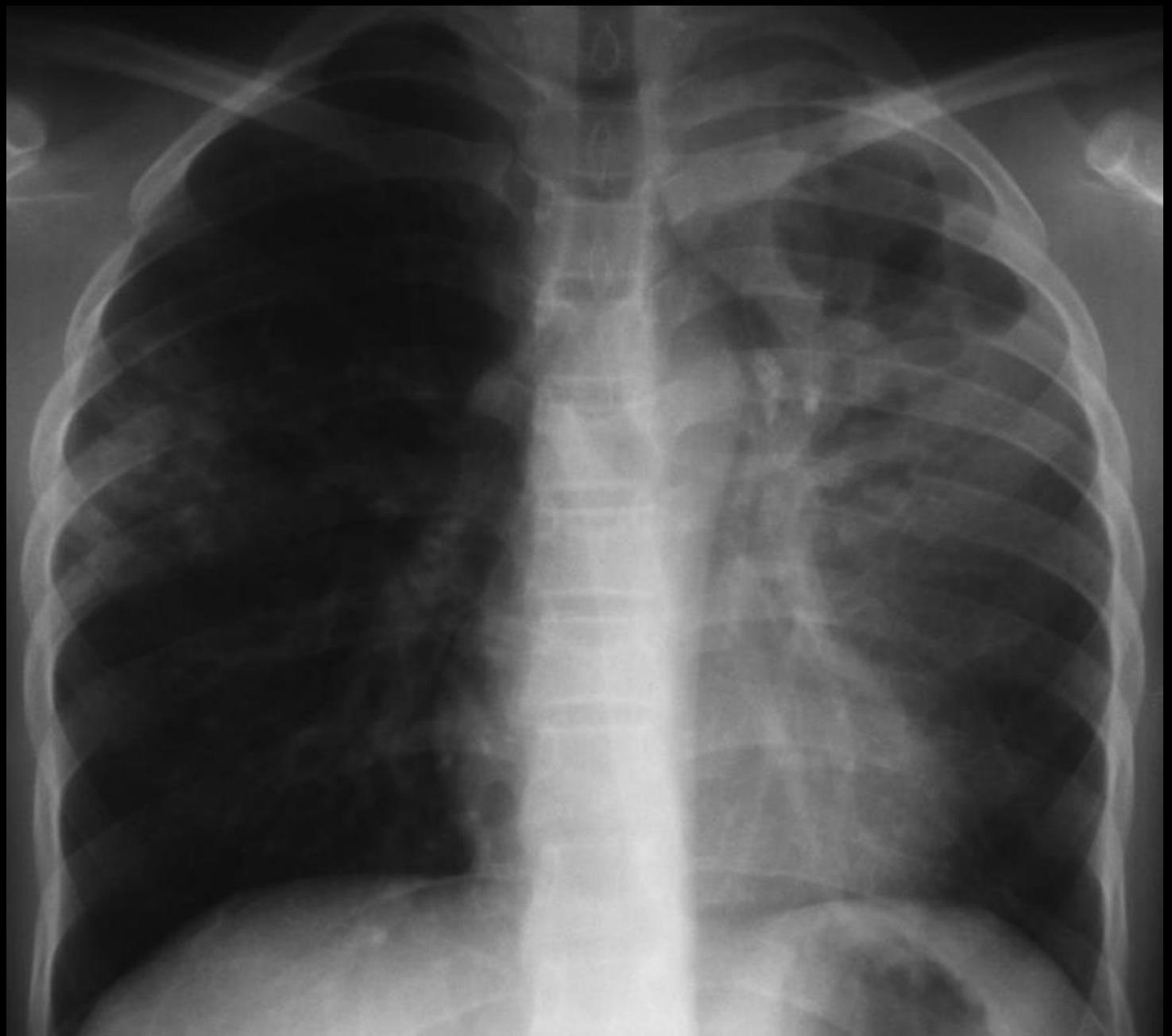


Pleural effusion

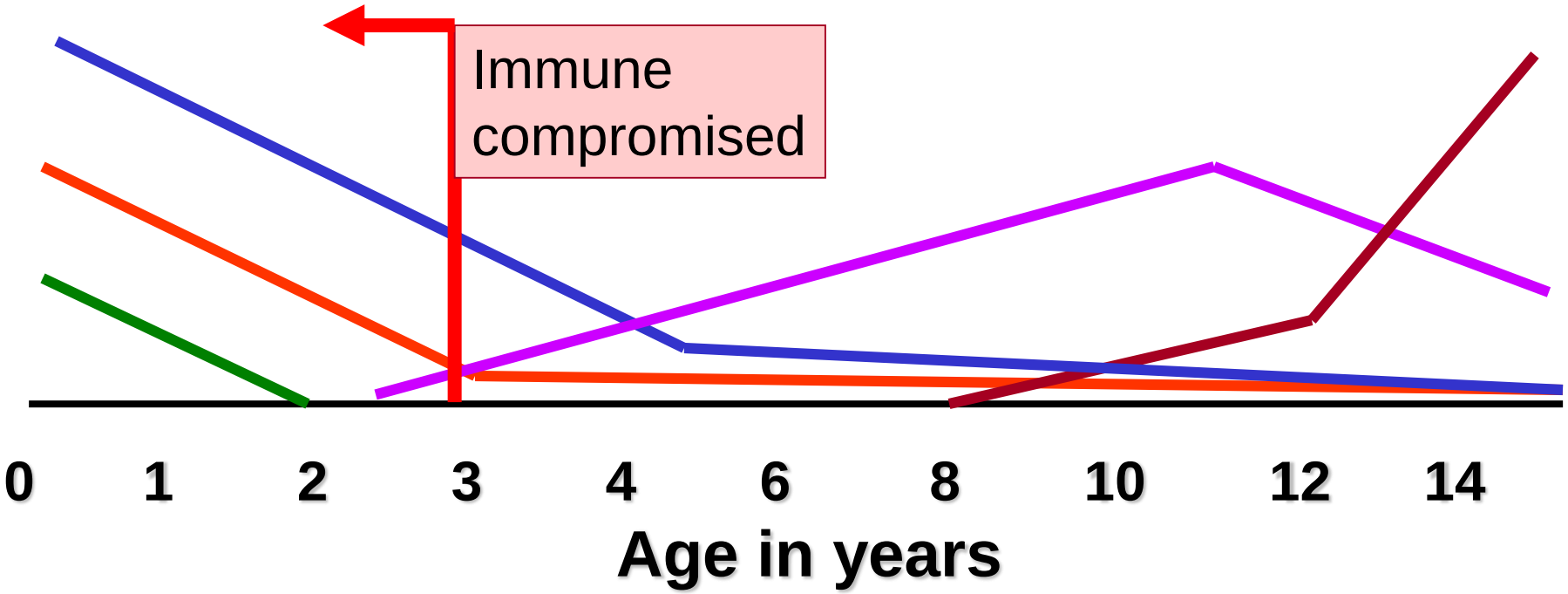


Disseminated (miliary) disease

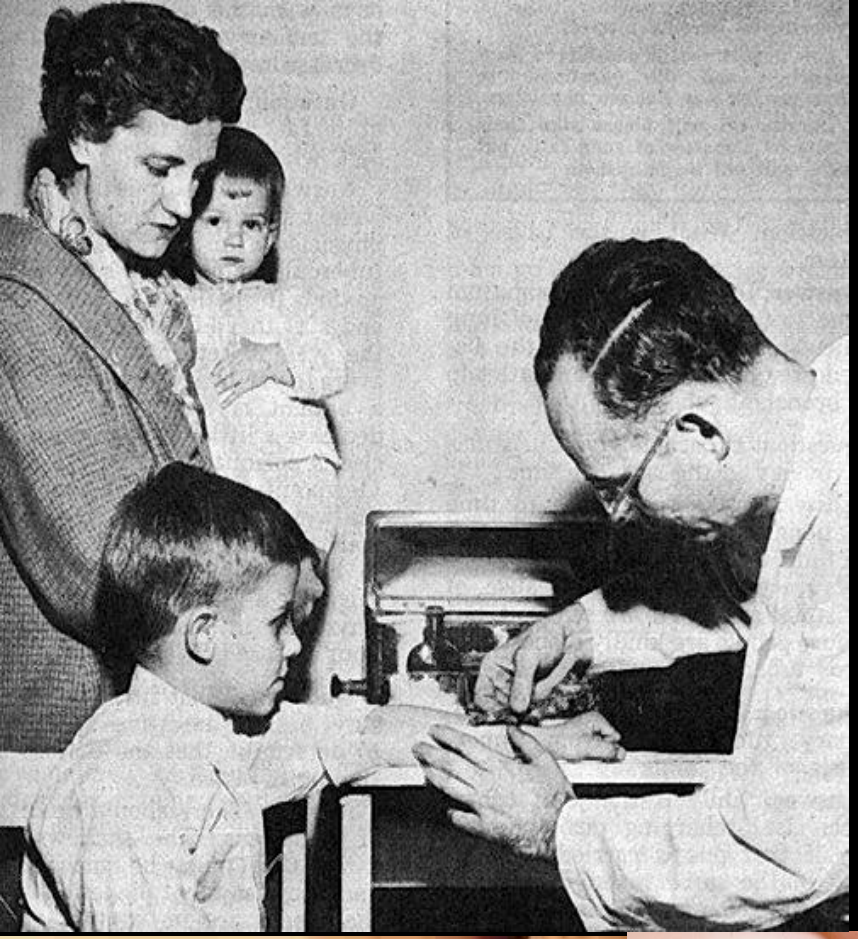
Adult-type disease



Different age-related patterns



Complicated Ghon focus
Miliary TB
Lymph node disease
Pleural effusion
Adult-type disease



INH preventive Rx

It works

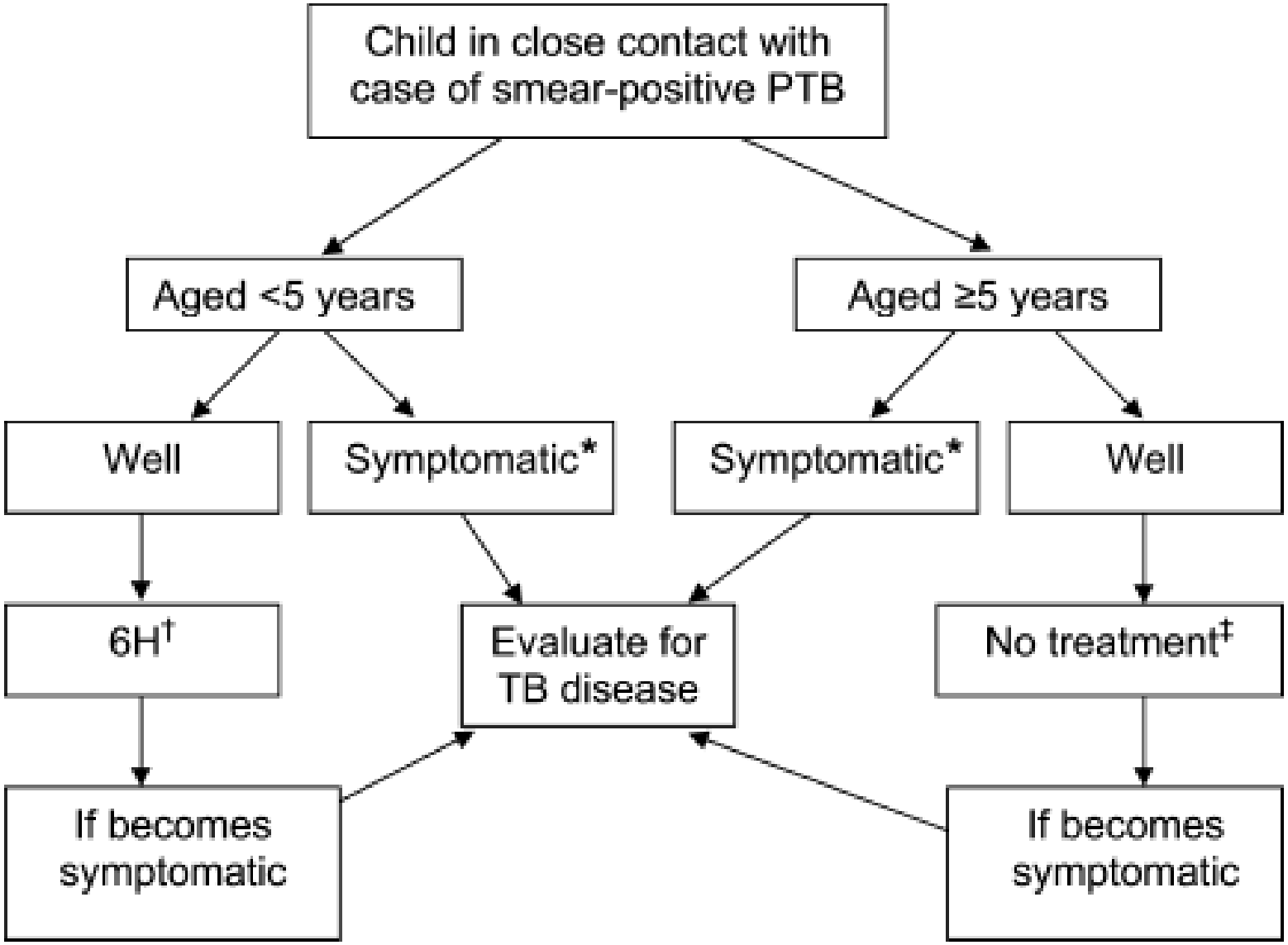
- **Up to 90% TB reduction *with good adherence***
- **Focus on the most vulnerable children with documented close exposure**

WHO – IPT in children

- **Close contact with an infectious TB source case (pulmonary TB)**
  - **All children <5 years of age**
  - **All HIV-infected children**
    - **Likelihood of TB infection is high**
    - **Risk of TB disease progression is high**

Asymptomatic for TB – provide IPT

No TST or CXR required prior to commencing

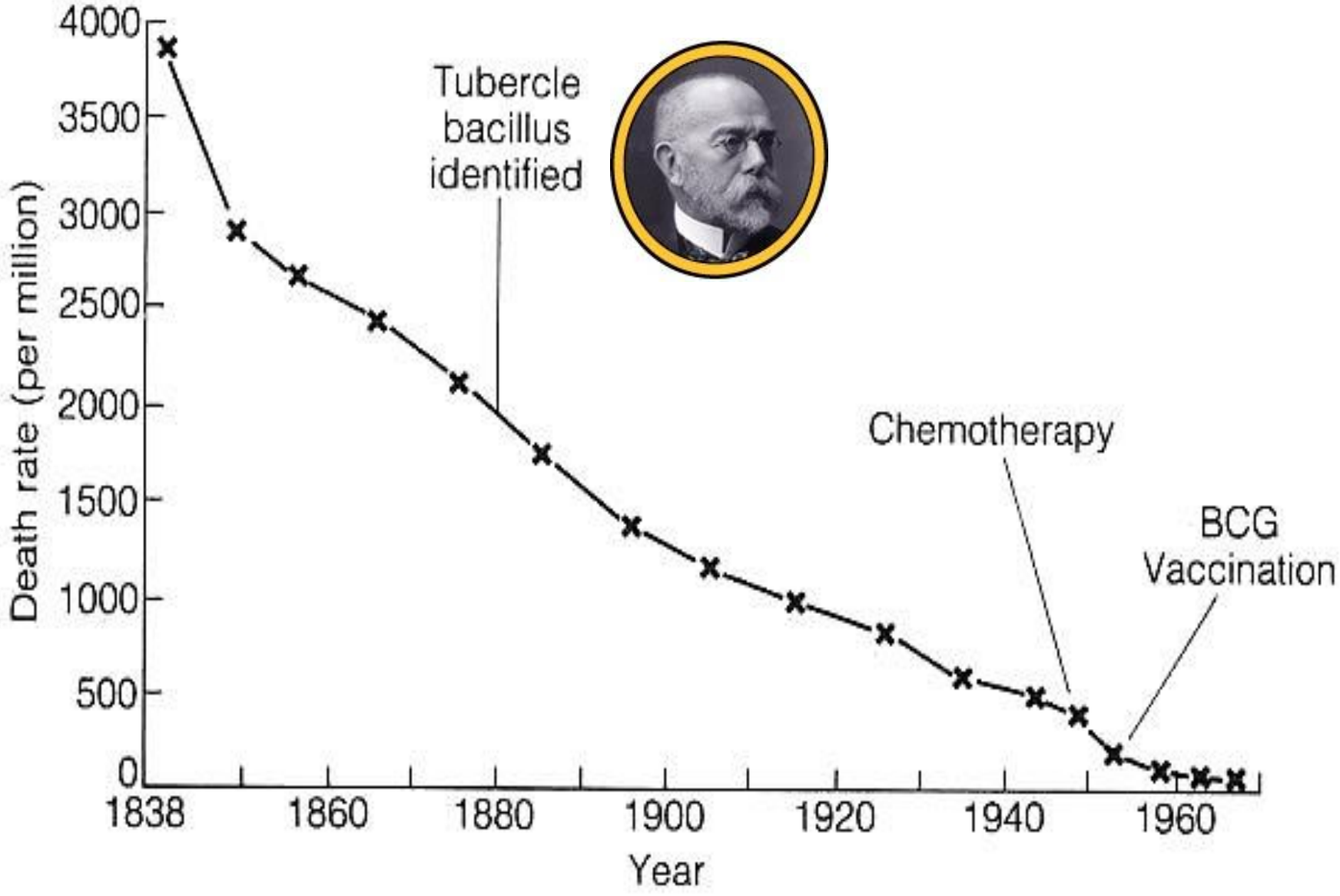


*If TB is suspected, investigate as per guidelines

‡ unless the child is HIV-infected (in which case INH 6/12)

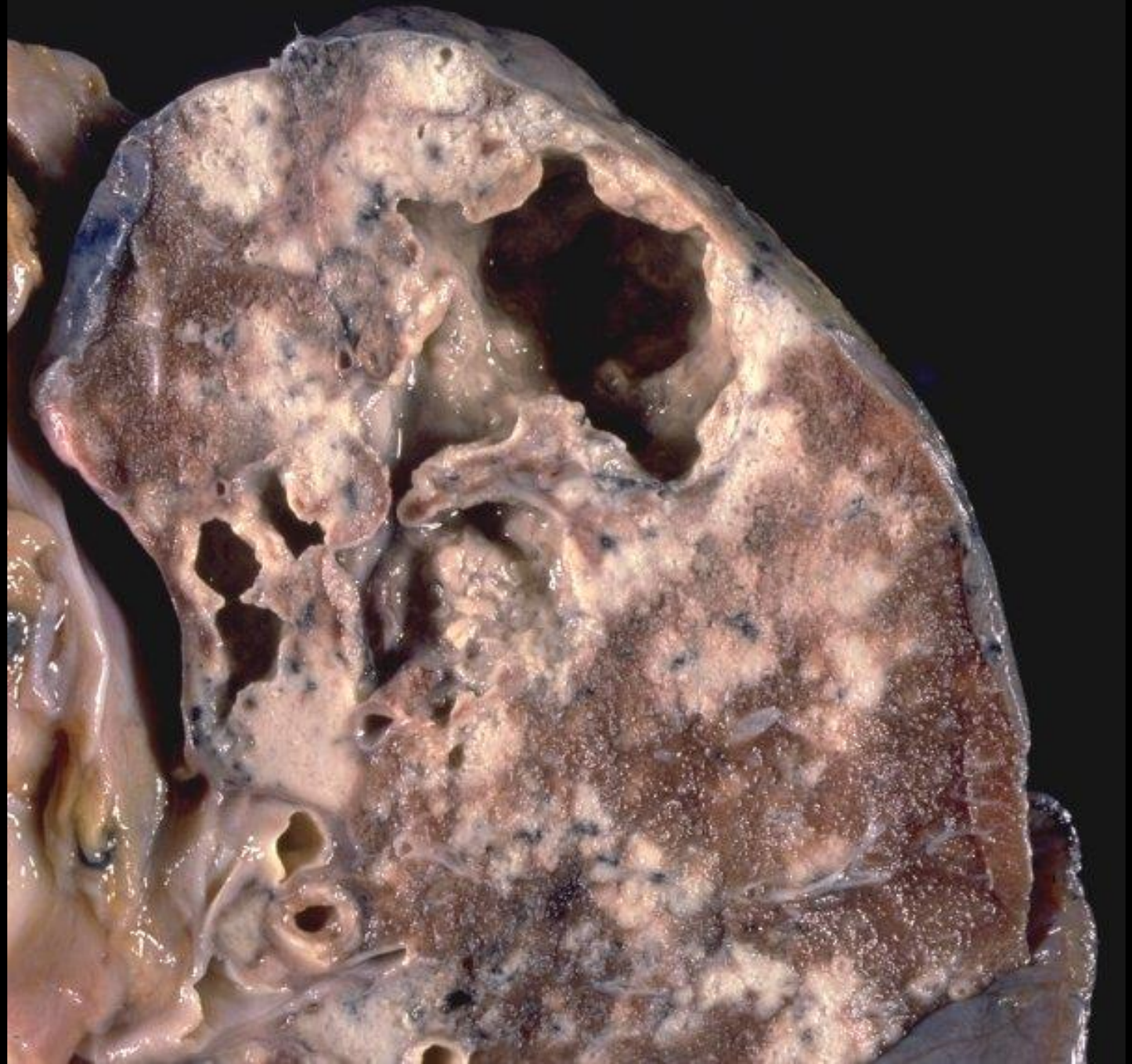
TB treatment

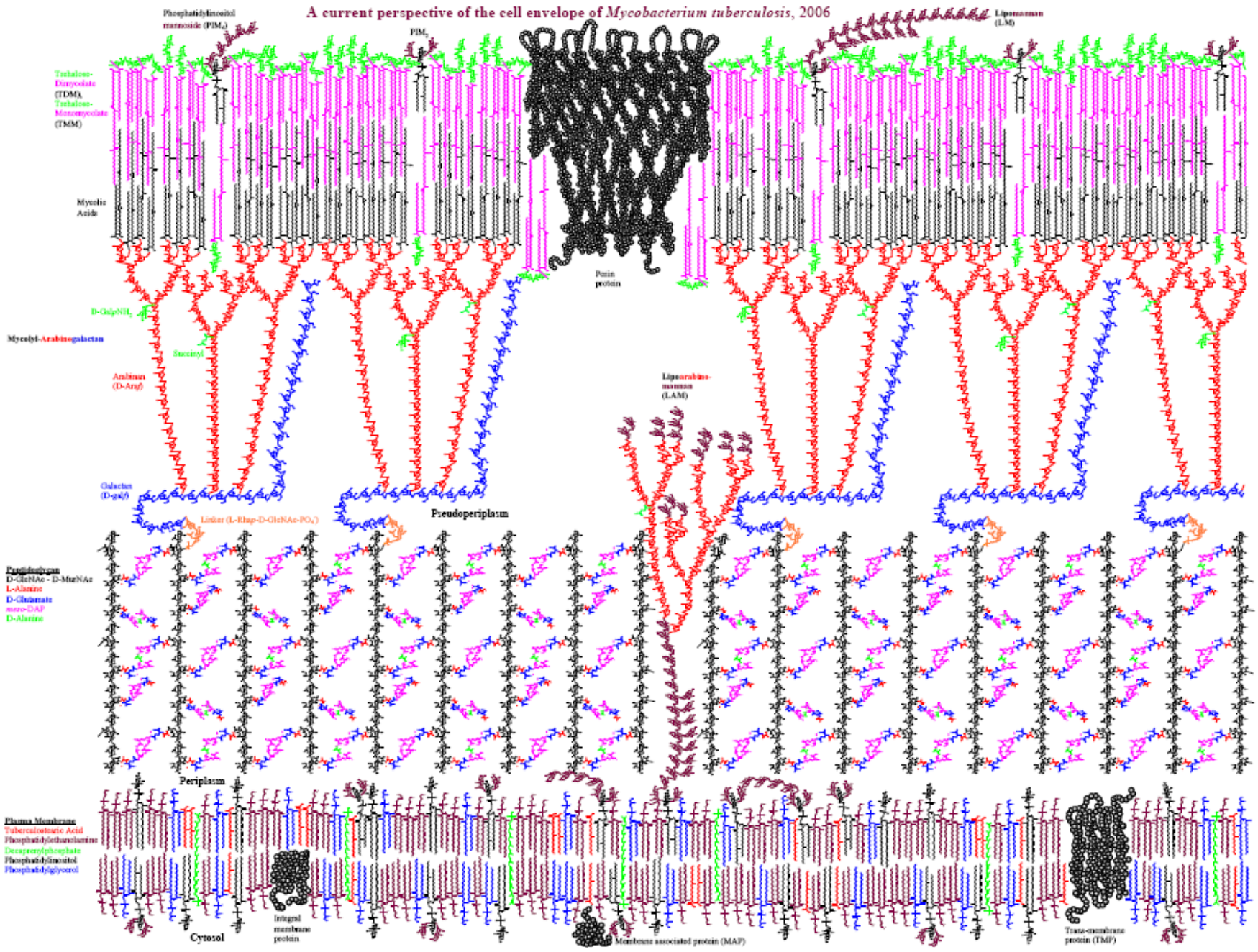
TB deaths in England and Wales



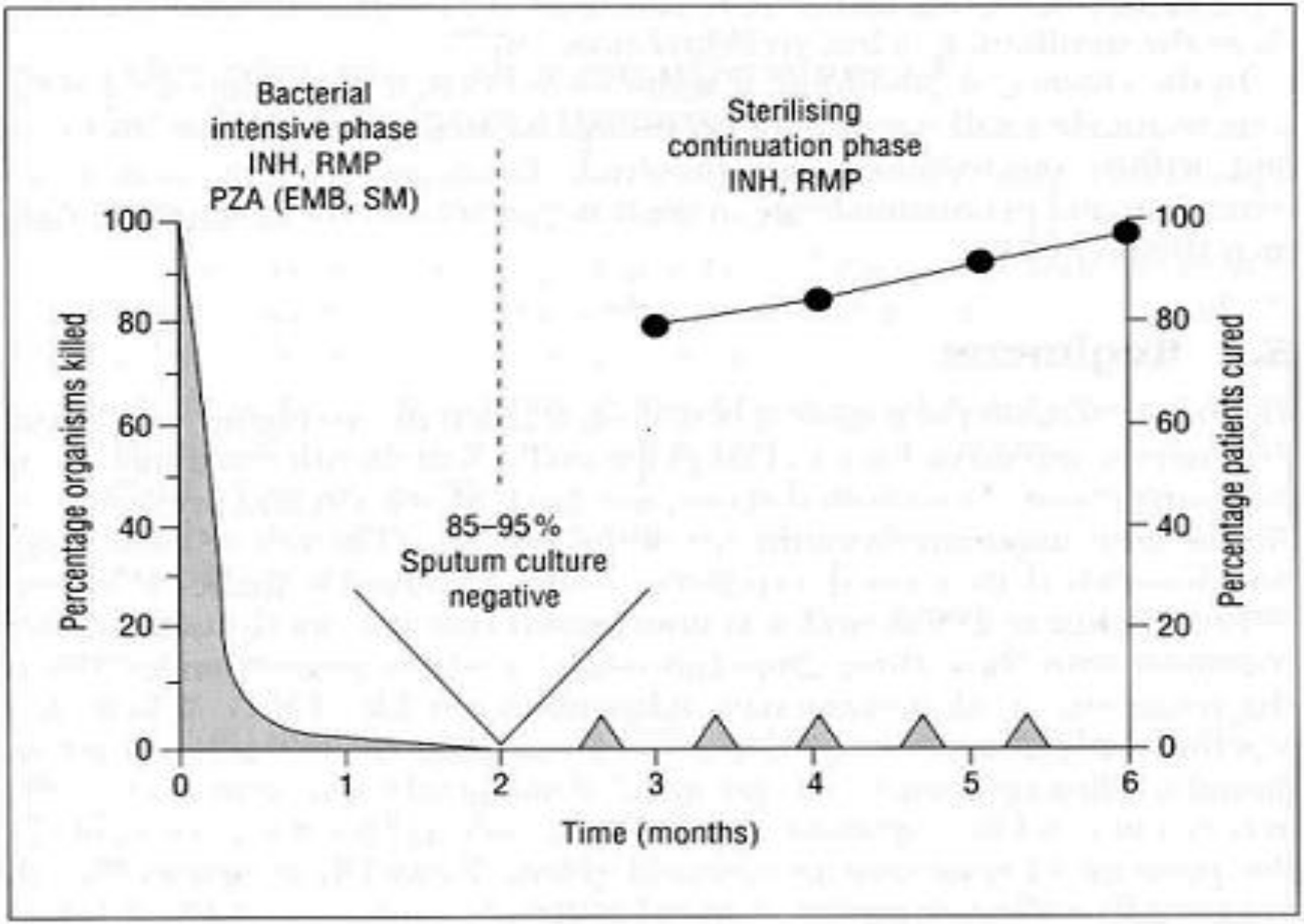
Main objectives in TB Rx

- Rapidly kill most bacilli
  - stop disease progression
  - terminate ongoing transmission
- Effect cure and prevent relapse (eliminate dormant bacilli)
- Minimal adverse events
- Prevent emergence of drug-resistance




A current perspective of the cell envelope of *Mycobacterium tuberculosis*, 2006
Phosphatidylinositol mannoside (PIM_6)
PIM_2
Lipomannan (LM)
Trehalose-Dimycolate (TDM), Trehalose-Monomycolate (TMM)
Mycolic Acids
Porin protein
D-GalpNH$_2$
Mycolyl-Arabinogalactan
Succinyl
Arabinan (D-Araf)
Lipoarabino-mannan (LAM)
Galactan (D-galf)
Linker (L-Rhap-D-GlcNAc-PO$_4$)
Pseudoperiplasm
Peptidoglycan
D-GlcNAc - D-MurNAc
L-Alanine
D-Glutamate
meso-DAP
D-Alanine
Periplasm
Plasma Membrane
Tuberculostearic Acid
Phosphatidylethanolamine
Decaprenylphosphate
Phosphatidylinositol
Phosphatidylglycerol
Cytosol
Integral membrane protein
Membrane associated protein (MAP)
Trans-membrane protein (TMP)

Current First-Line Regimen



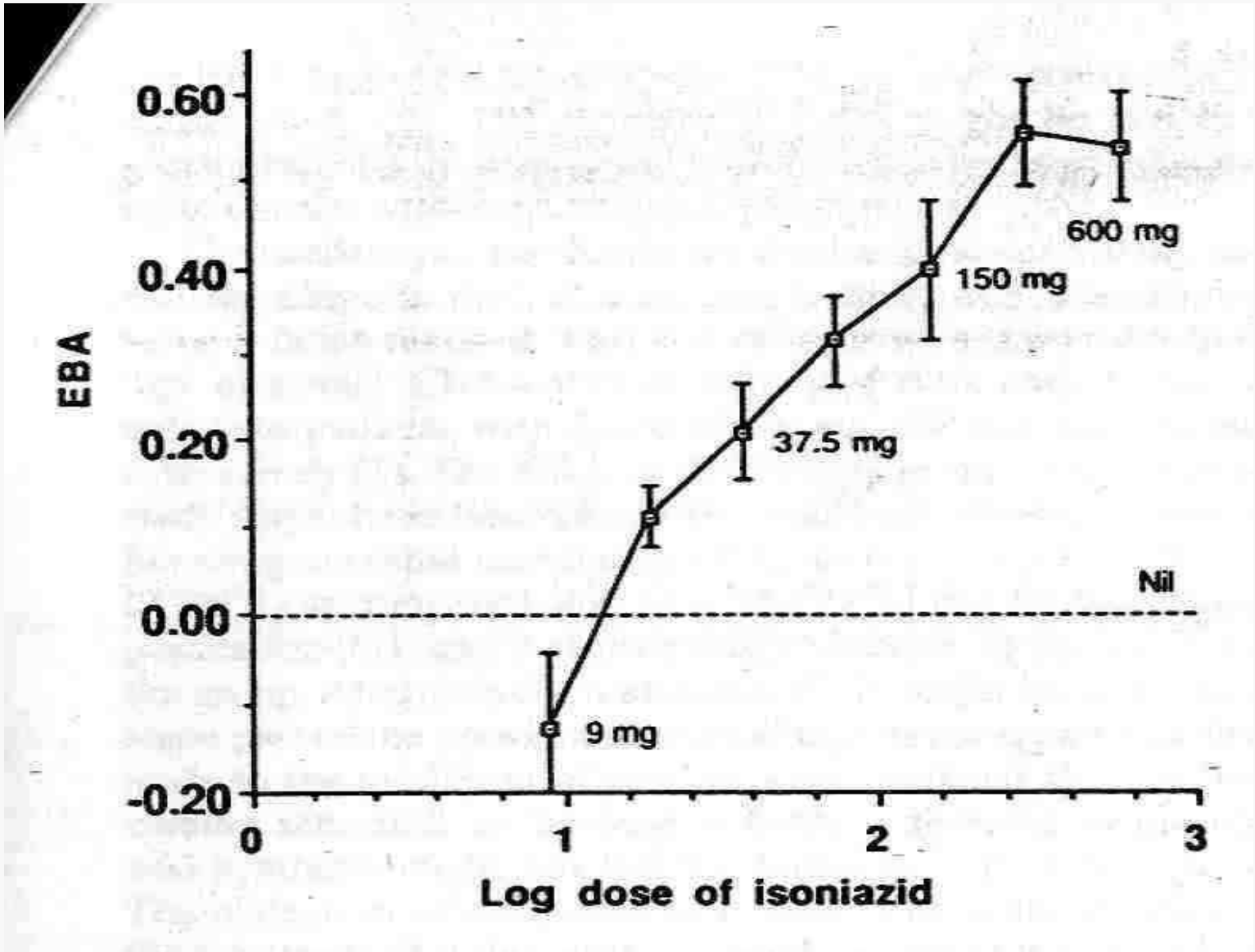
Early Bactericidal Activity

Drug	EBA
Isoniazid	0.5-0.6
Rifampicin	0.2
Ethambutol	0.2
Streptomycin	0.04
Pyrazinamide	0.004

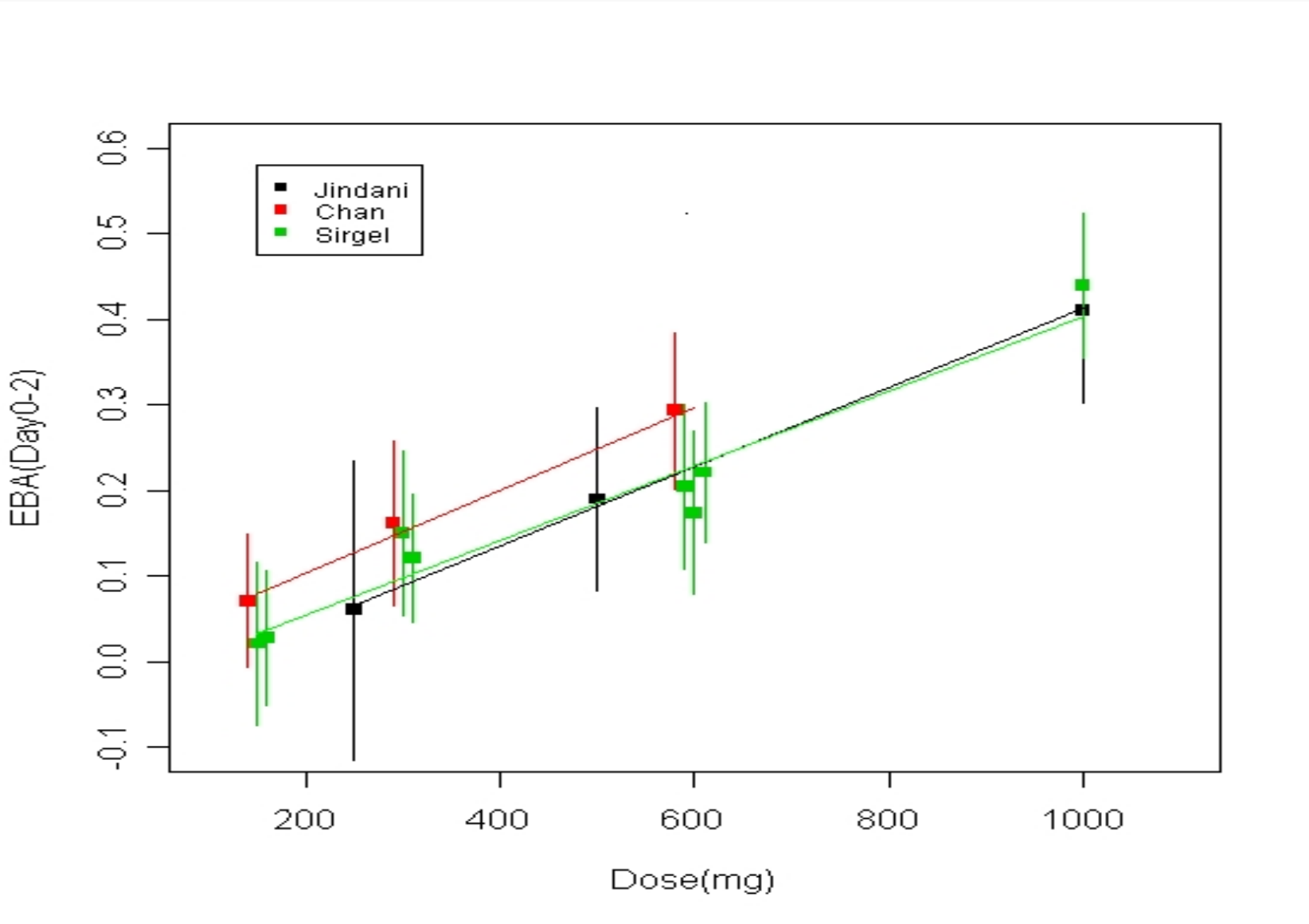
Peter Donald

Dose related response of INH

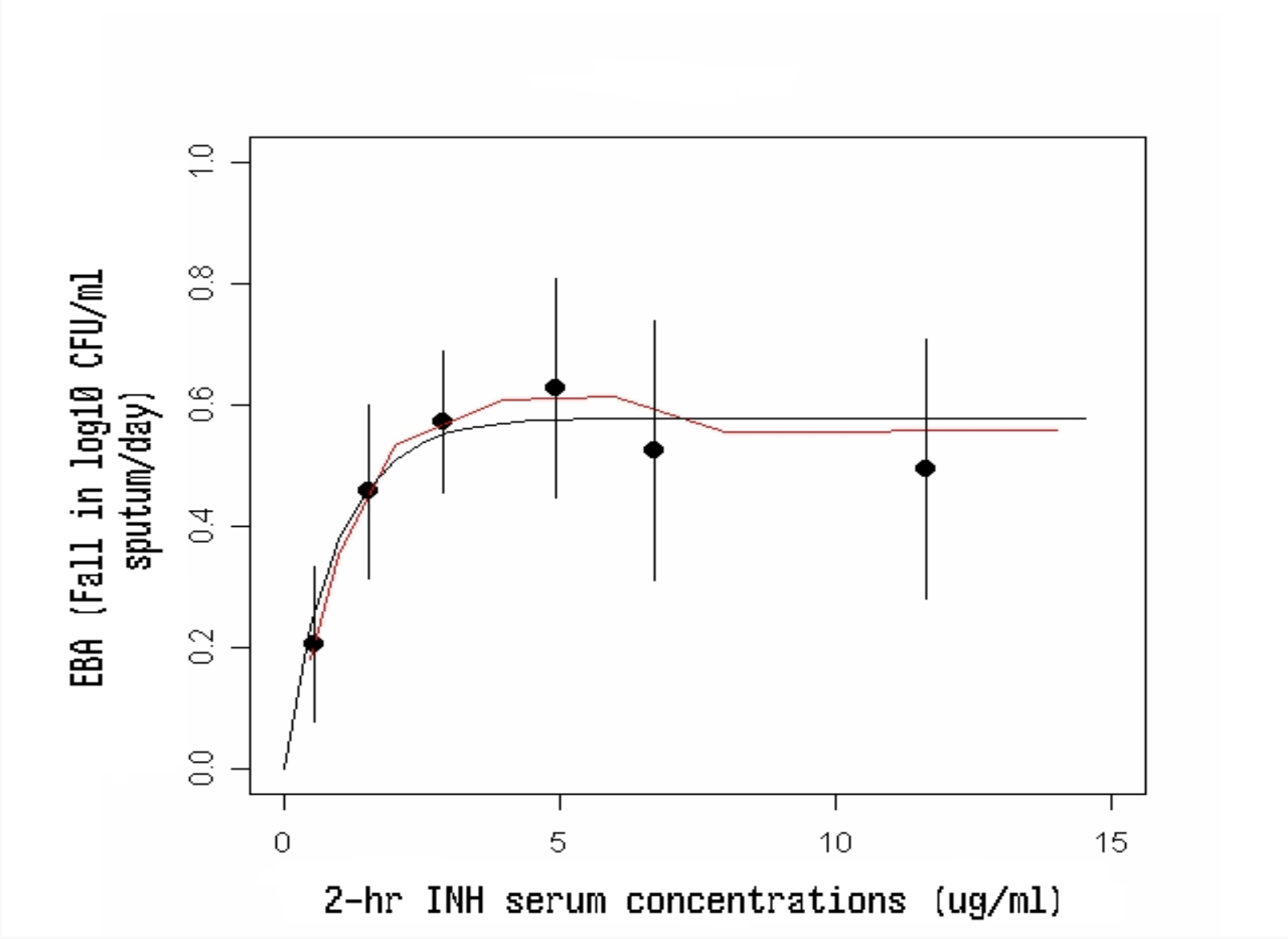
Donald PR et al. Am J Respir Crit Care Med 1997; 156: 895-900



RMP: Dose-ranging EBA

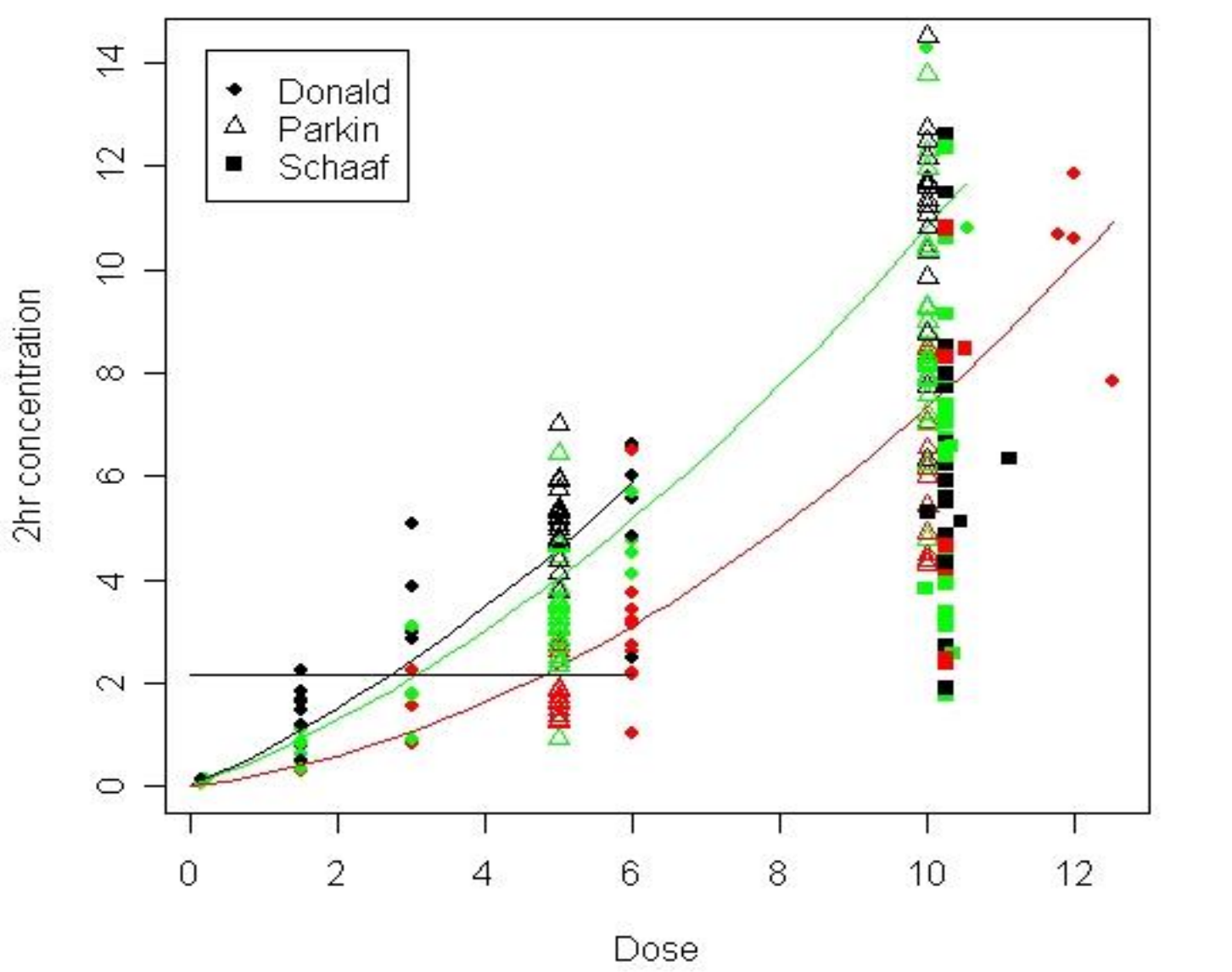


Isoniazid PK vs EBA



2-hr INH concentration vs. dose.

concentration associated with the EBA90 is 2.2 µg/ml



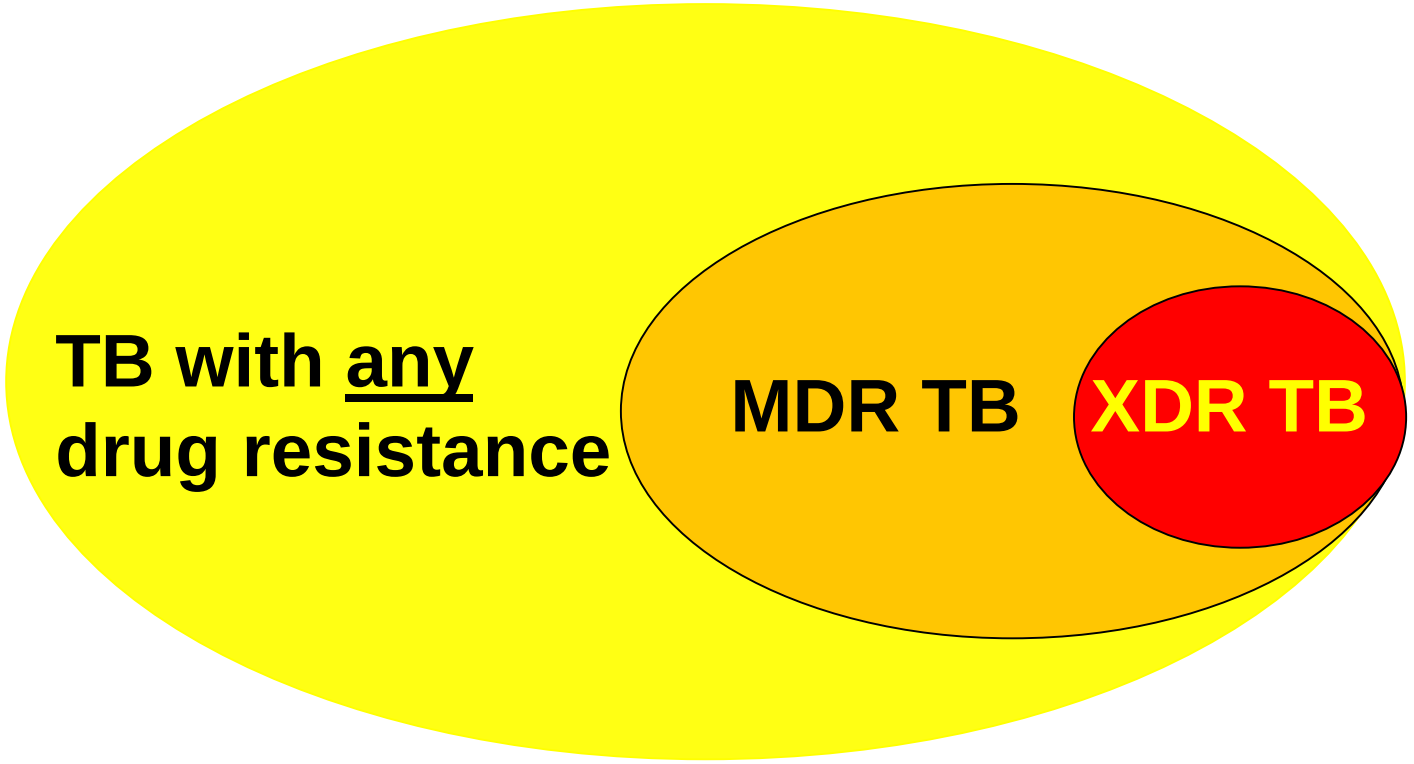
Doses of 1st-line TB drugs

Drug	Recommended daily dose in mg/kg	
	Previous	*New*
Isoniazid (H)	5 (4-6)	10 (5-15)
Rifampicin (R)	10 (8-12)	15 (10-20)
Pyrazinamide (Z)	25 (20-30)	35 (30-40)
Ethambutol (E)	not given	20 (15-25)
Streptomycin (S)	15 (12-18)	15 (12-18)?

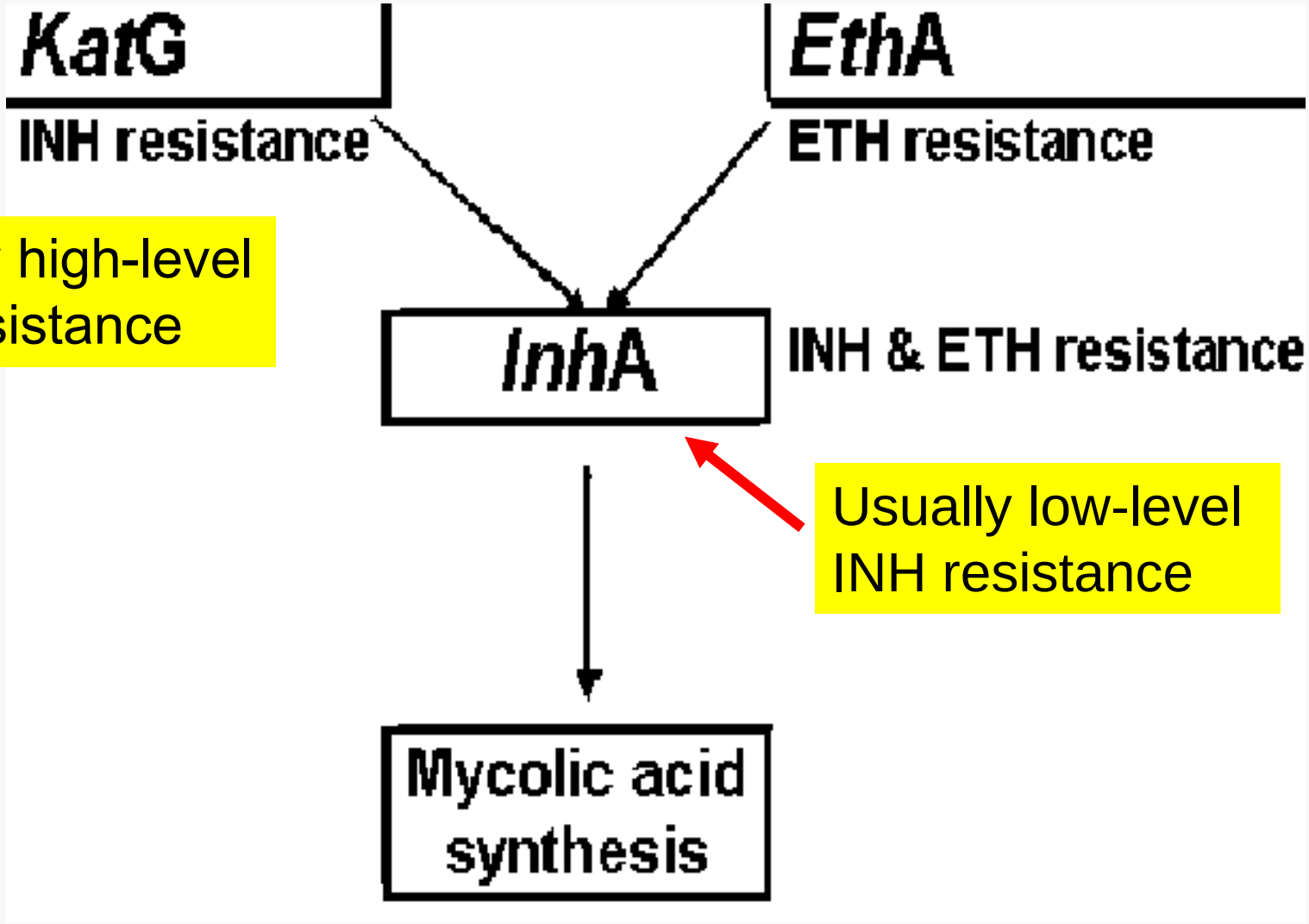
Drug resistant TB

MDR TB - resistant to at least INH and RMP

XDR TB – MDR with additional resistance to any fluoroquinolone AND any second-line injectable (amikacin, kanamycin, capreomycin)



ETH & INH cross resistance

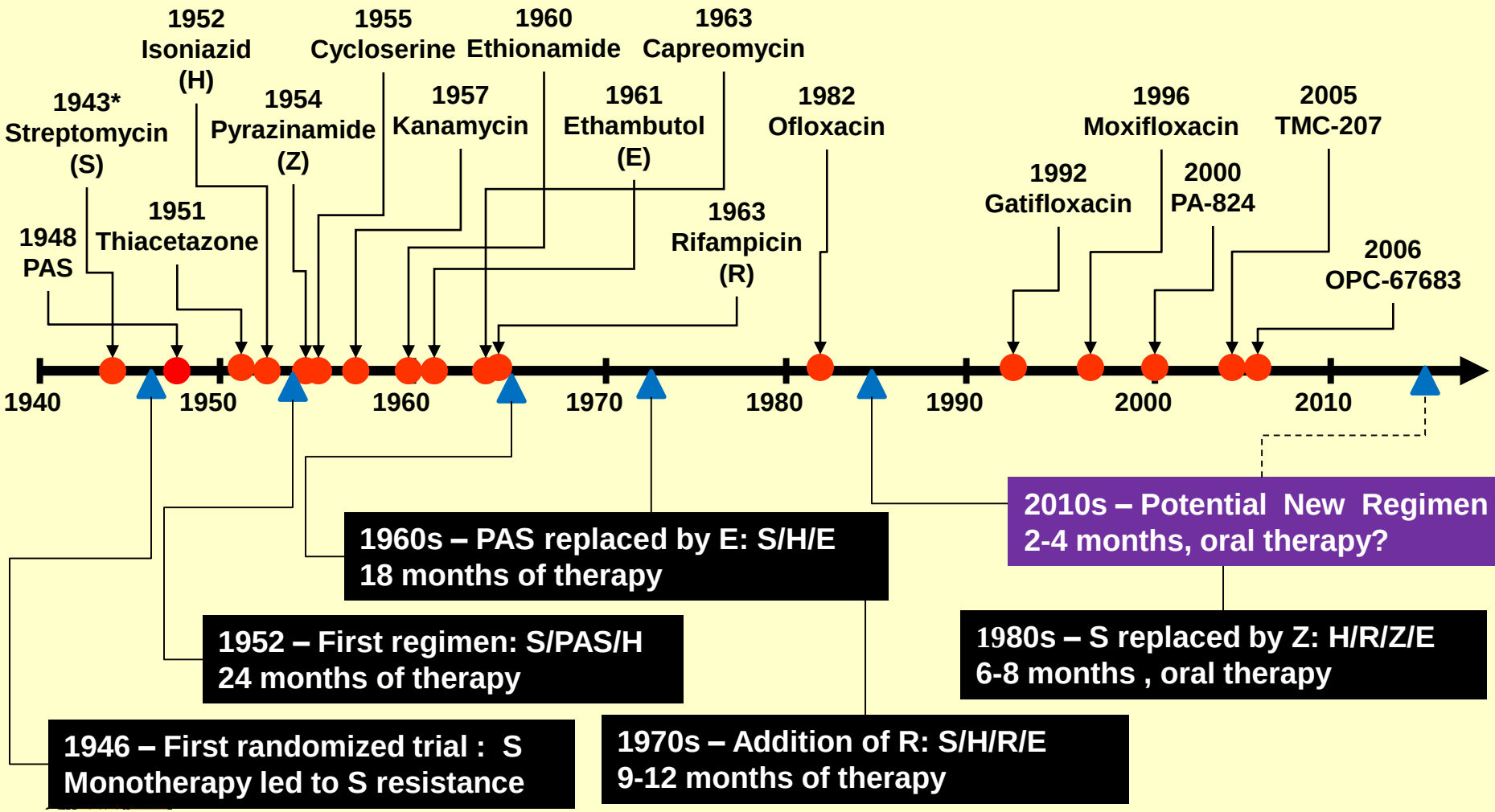


Usually high-level INH resistance

Usually low-level INH resistance

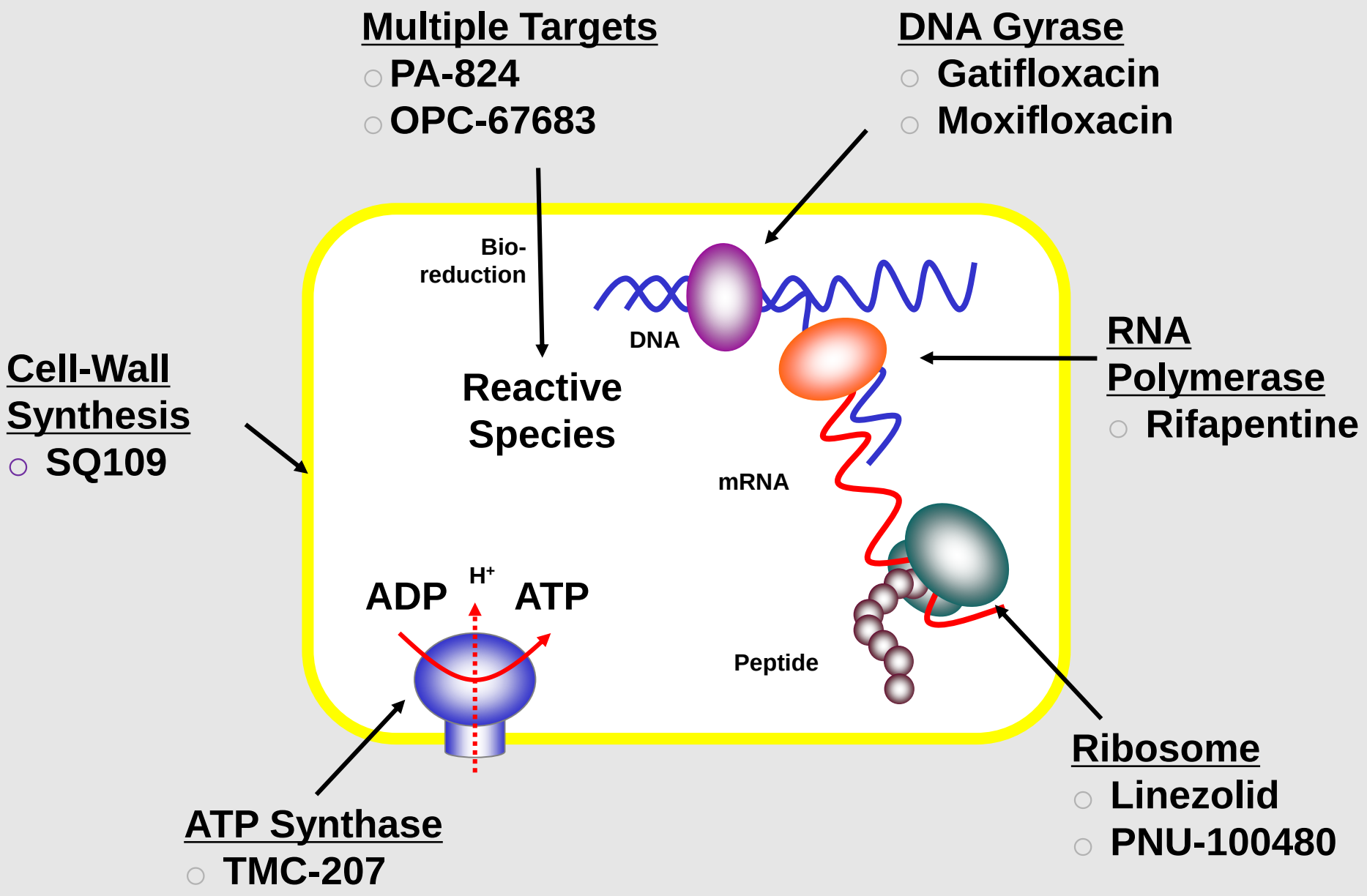
Schaaf HS et. al. IJTLD 2009

Discovery of TB Drugs



Development of Regimens

Ma Z et al. Lancet TB series 2010



Ma Z et al. Lancet TB series 2010

Questions?

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