

# The diagnosis of childhood tuberculosis in low/intermediate burden settings

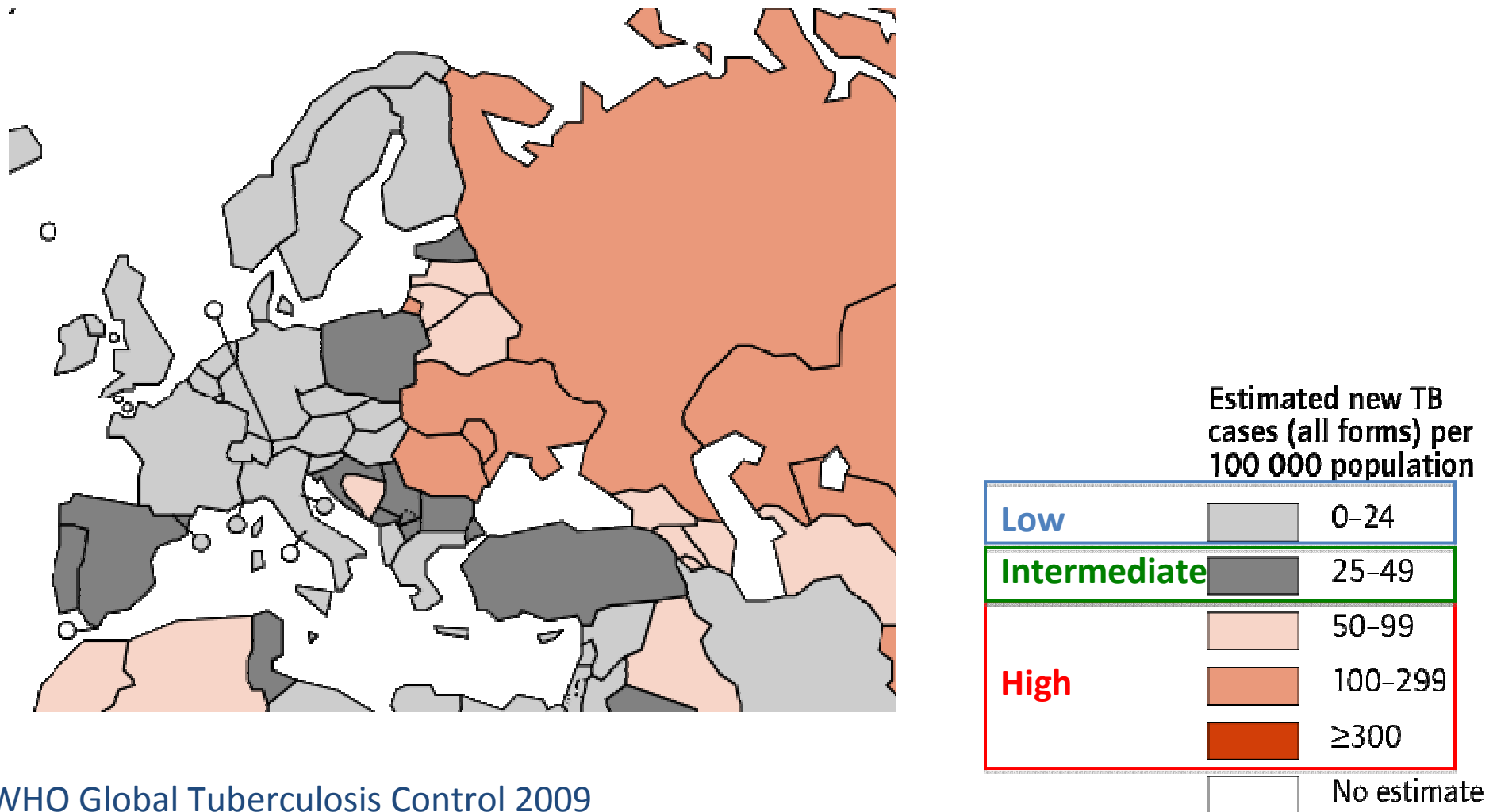
Dr. Anne Detjen

Desmond Tutu TB Centre, Cape Town

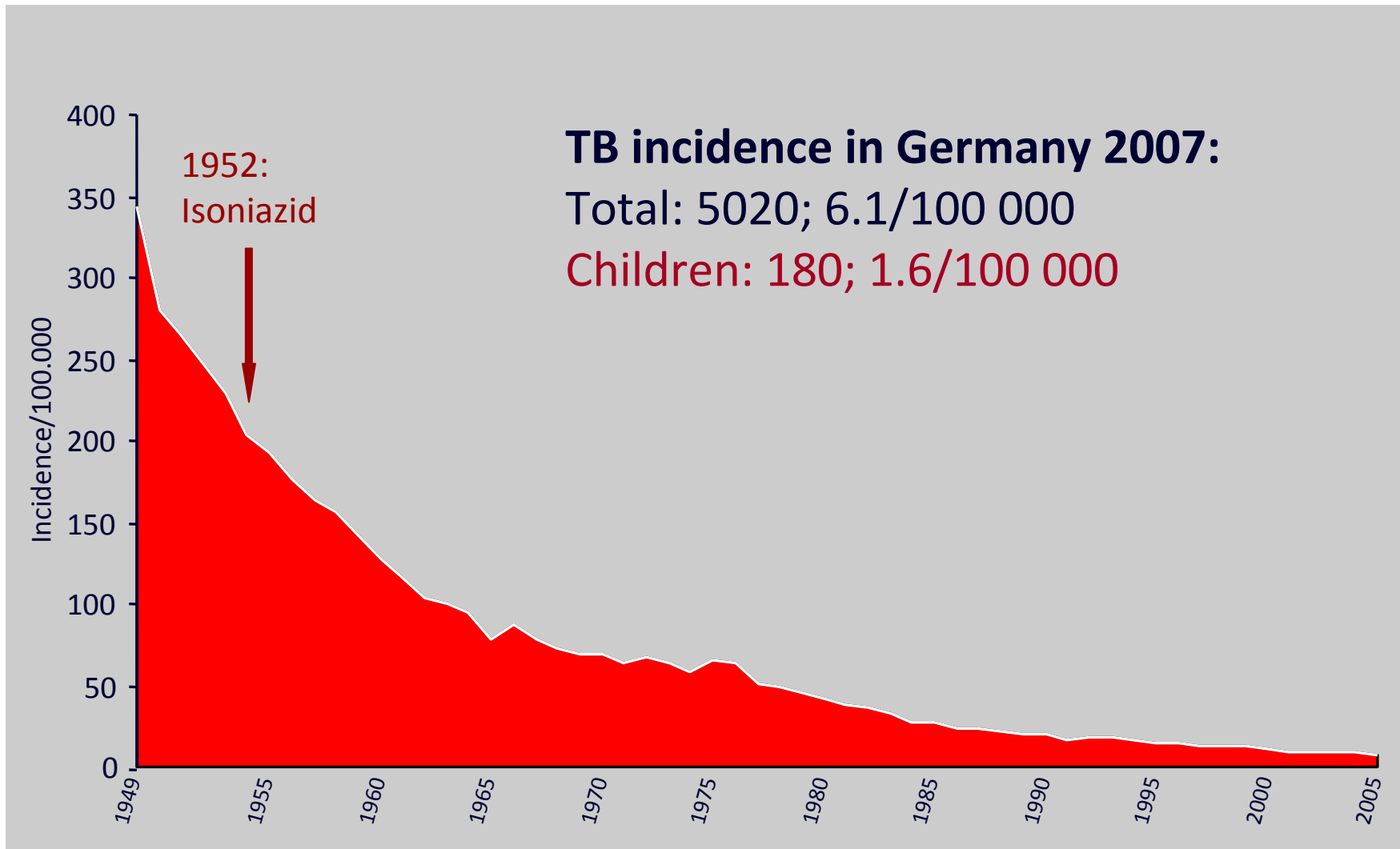
Dr. Klaus Magdorf

Charité University Hospital, Berlin

# Estimated TB incidence rates by country, 2007



# Germany: TB low-incidence setting



# Diagnosis of Childhood Tuberculosis

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**Suspicion**

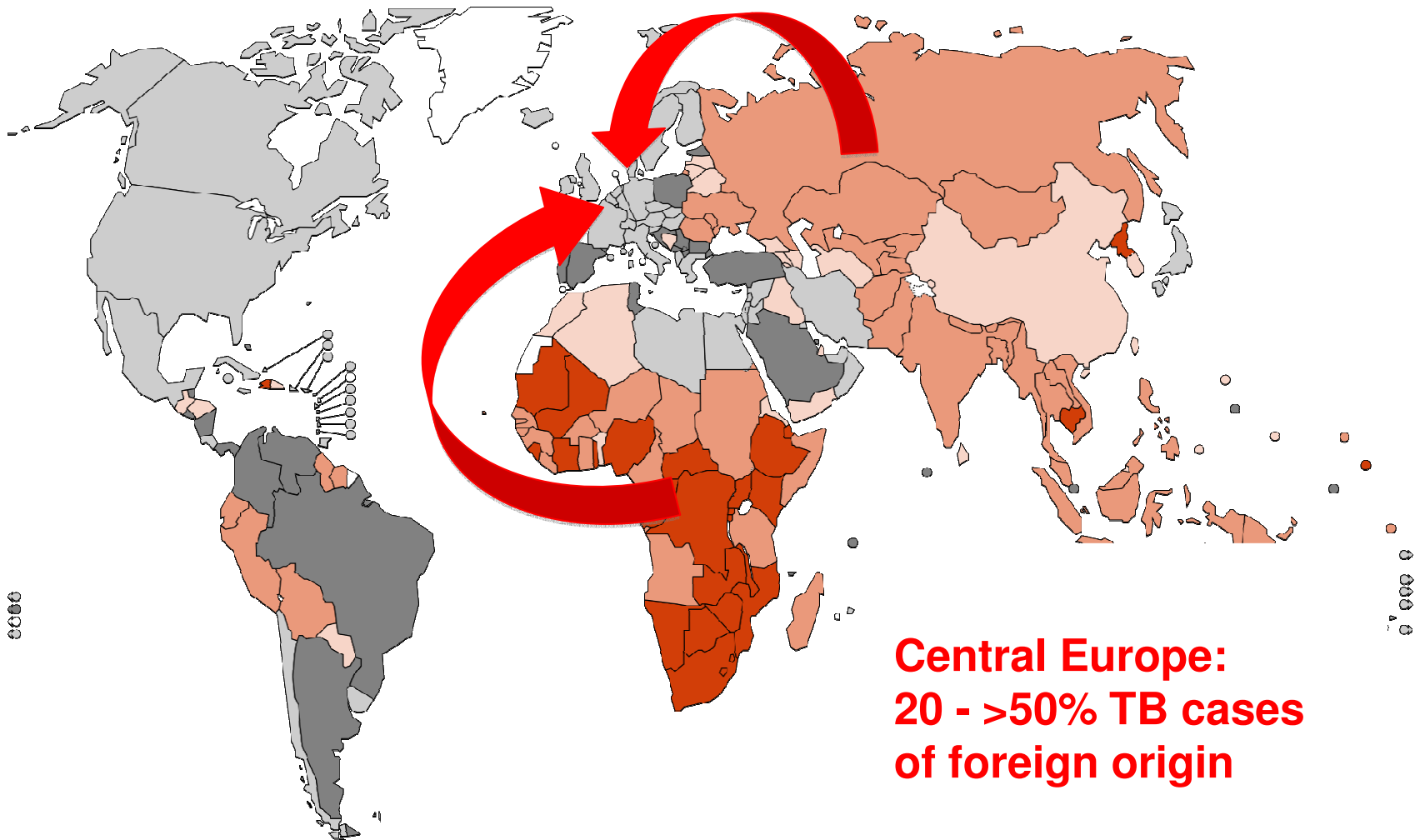


**Knowledge on**

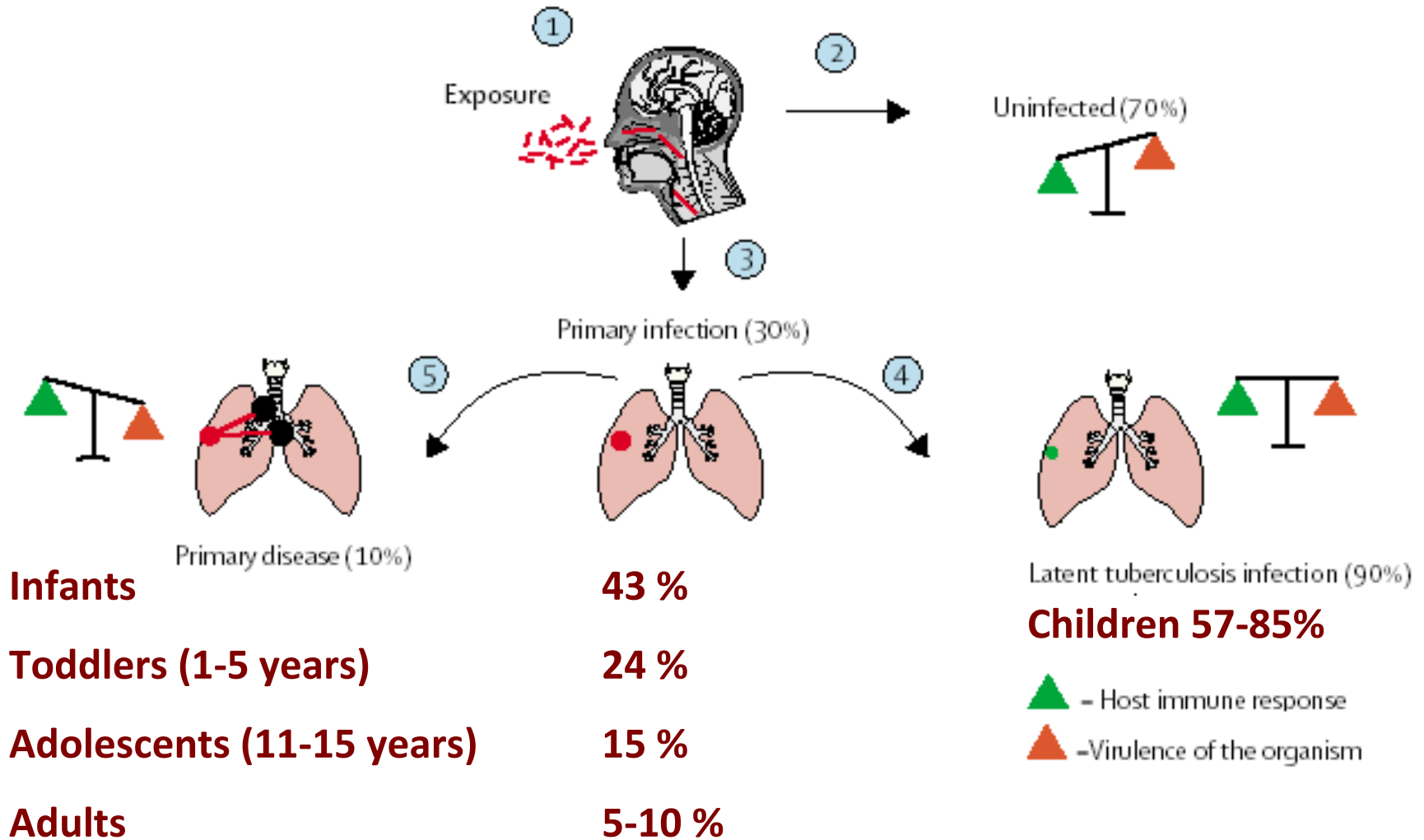
- **The local epidemiology of TB**
- **Risk groups**
- **Specific aspects of childhood TB**

# Background of Migration

Estimated TB incidence rates, by country, 2007



# Who is at risk?



# Other risk groups

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- Immune-compromised
  - HIV-infected: risk of disease progression 10%/year
  - Rheumatology patients
  - Oncology
- Poor living circumstances (asylums)
  - Homeless
  - Drug users
  - Prisoners

# Diagnosis of Childhood Tuberculosis

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# Contact?

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# Risk evaluation for TB infection in a low-burden setting

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1. Has your child had **contact** to a person with TB?
2. Was your child or another family member born in a **country with a high TB burden**? In the last two years, has your child/a family member spent a period of time in a high-burden country?
3. Is your child in **contact with adults at high risk** of TB? (e.g. drug users, people living in asylums)
4. Is your child **HIV-infected**/has your child an **immune deficiency**?

# Risk evaluation for TB infection in a low-burden setting

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## Results from New York:

- 413 children (14%) had at least one risk factor  
23 (5,6%) had positive TST
- 4 (0,16%) of 2507 children without risk factors had positive TST
- **Sensitivity : 85,2%, Specificity: 86,0%**
- **Negative predictive value: 99,8%**
- Positive predictive value: 5,4%
- OR: 35,2 (95% Konfidenz-Intervall: 12,1-102,4)

**One Question answered with yes → targeted skin testing**

# Tuberculin Skin Test (Mendel-Mantoux)

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## Comprable tuberculins:

- 2 TU RT23  
(WHO Reference-tuberculin)
- 5 TU PPD-S (USA)

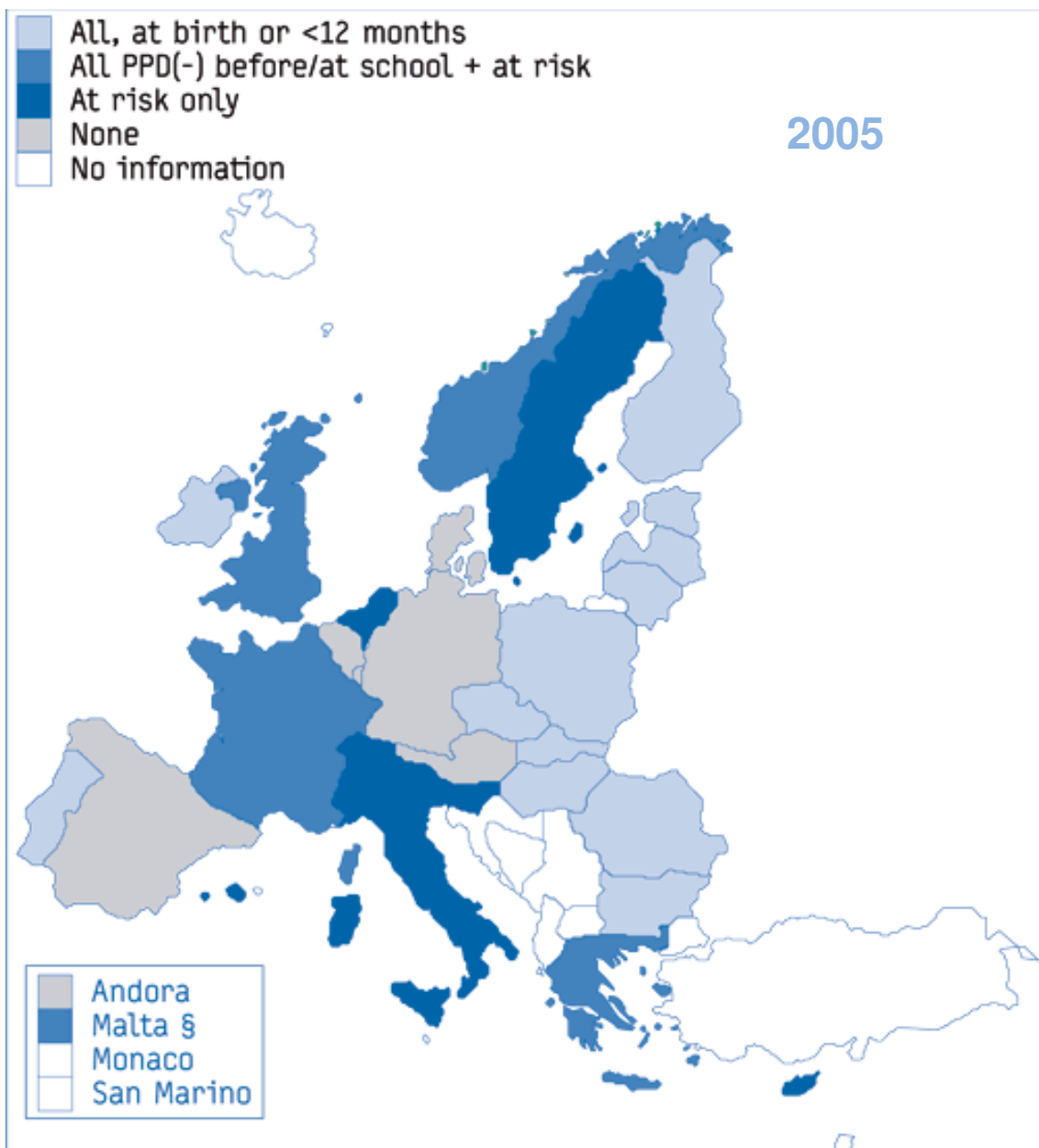
## Cut off values (ATS 2000)

> **5 mm**: Close contacts, immune suppressed

> **10 mm**: children <4, with other medical conditions, from high-burden settings, contact with risk groups

> **15 mm**: children  $\geq 4$  without risk factors

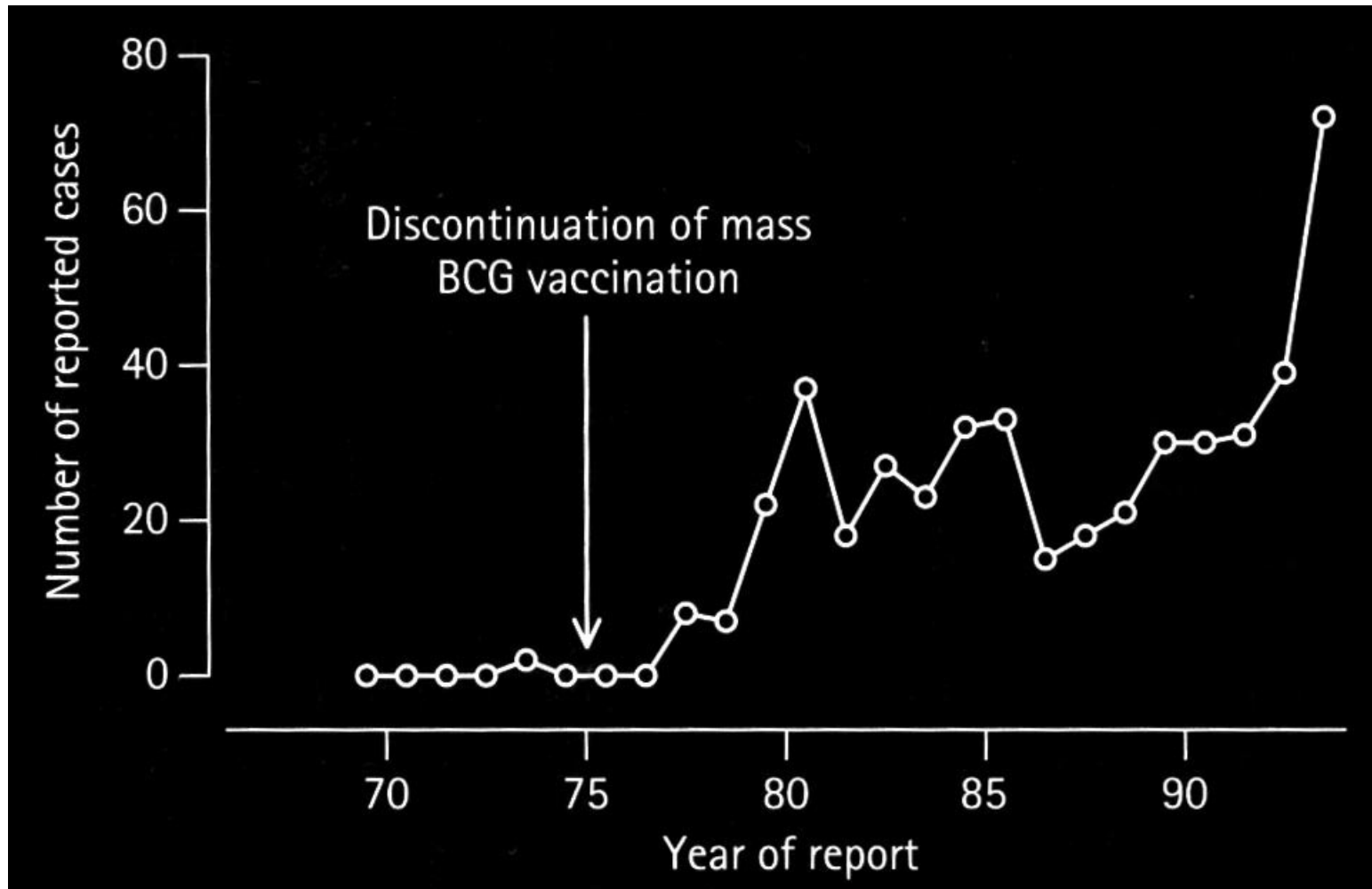
# Cross-reactivity - BCG



Left upper arm

# Cross-Reactivity - NTM

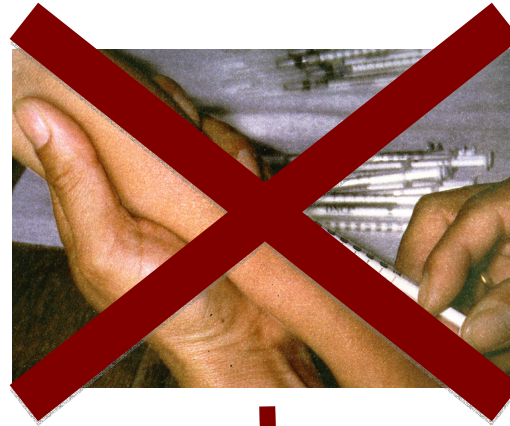
Reported cases of mycobacteriosis due to *M. avium* complex Sweden 1969-1993



# TB or NTM?



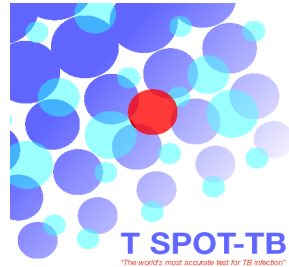
**M. tuberculosis**



**M. avium**

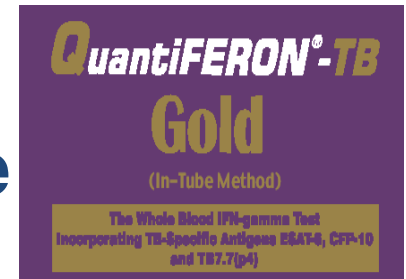
# Interferon- $\gamma$ Release Assays

T SPOT™.TB



- ELISPOT
- *In vitro* stimulation of **PBMCs** with ESAT-6 and CFP-10
- Incubation **16-20 h**
- **Specific** IFN- $\gamma$ -producing **T-cells**
- **Positive: > 5 Spots**

QuantiFERON®-Tb Gold In-Tube



- ELISA
- *In vitro* stimulation of **whole blood** with ESAT-6, CFP-10 and Tb7.7
- Incubation **16-20 h**
- **IFN- $\gamma$**
- **Positive: > 0.35 IU/l**



# Specificity of ESAT-6 and CFP-10

orange = Sensitivity, red = Cross-reactivity = false positive, green = Specificity

Tuberculosis complex	Antigens		Environmental strains	Antigens	
	ESAT	CFP		ESAT	CFP
<i>M. tuberculosis</i>	+	+	<i>M. abscessus</i>	-	-
<i>M. africanum</i>	+	+	<i>M. avium</i>	-	-
<i>M. bovis</i>	+	+	<i>M. branderi</i>	-	-
<i>M. microti</i>	+	+	<i>M. celatum</i>	-	-
<i>M. canetti</i>	+	+	<i>M. chelonae</i>	-	-
BCC substrain			<i>M. flavescens</i>	+	+
gothenburg	-	-	<i>M. fortuitum</i>	-	-
moreau	-	-	<i>M. gordonae</i>	-	-
tice	-	-	<i>M. intracellulare</i>	-	-
tokyo	-	-	<i>M. kansasii</i>	+	+
danish	-	-	<i>M. malmoeense</i>	-	-
glaxo	-	-	<i>M. marinum</i>	+	+
montreal	-	-	<i>M. oenavense</i>	-	-
pasteur	-	-	<i>M. scrofulaceum</i>	-	-
			<i>M. smegmatis</i>	-	-
			<i>M. szulgai</i>	+	+
			<i>M. terrae</i>	-	-
			<i>M. vaccae</i>	-	-
			<i>M. xenopi</i>	-	-

CDC

**MMWR**<sup>TM</sup>

**Morbidity and Mortality Weekly Report**

Recommendations and Reports

December 16, 2005 / Vol. 54 / No. RR-15

**Guidelines for the Investigation of Contacts  
of Persons with Infectious Tuberculosis  
Recommendations from the National Tuberculosis  
Controllers Association and CDC**

**Guidelines for Using the QuantiFERON<sup>®</sup>-TB  
Gold Test for Detecting *Mycobacterium  
tuberculosis* Infection, United States**

## IGRA instead of TST

- Adults and children
- Contact investigations
- Evaluation of recent immigrants
- Sequential testing survey programs for infection control (Health Care Workers)

**NHS**  
National Institute for  
Health and Clinical Excellence

Issue date: March 2006

### Tuberculosis

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

Clinical Guideline 33  
Developed by the National Collaborating Centres for Chronic Conditions

**Empfehlungen für die Umgebungsuntersuchungen  
bei Tuberkulose**  
Deutsches Zentralkomitee zur Bekämpfung  
der Tuberkulose

## Stepwise testing: IGRA as confirmation of positive TST

- Active TB and LTBI
- Adults and children

# But...

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## **P.M., 1 year**

- No BCG
- Father smear positive TB 03/2006
- TST negative 03 and 10/2006
- INH Prophylaxis 3 months
- TST 07/2007 15 mm, ulcerating
- QFT negative

## **M.A., 4 years**

- No BCG
- Grandfather smear positive TB 06/2007, close contact over 2 weeks
- TST 09/2007 15 mm, ulcerating
- T SPOT negative
- No symptoms, CXR normal

# More cautious:



HAUTE AUTORITÉ DE SANTÉ

## TEST DE DÉTECTION DE LA PRODUCTION D'INTERFÉRON $\gamma$ POUR LE DIAGNOSTIC DES INFECTIONS TUBERCULEUSES

### Infection:

- **High risk contacts:** TST (and IGRA), either positive counts
- **Low risk groups:** stepwise testing

### Disease:

- IGRAs as supplementary tool

### Replacement of TST

for Dx of LTBI in **persons > 15 years**  
Contact tracing, serial testing (HCW),  
before TNF- $\alpha$  antagonists

#### National Tuberculosis Advisory Committee

#### Position Statement on Interferon- $\gamma$ Release Immunoassays in the Detection of Latent T

This document endorsed by the National Tuberculosis Advisory Committee is a general guide to appropriate the detection of latent tuberculosis infection.

Endorsed by the National Tuberculosis Advisory Committee  
Published by the Australian Government Department of Health and Ageing  
October 2007

- TST remains **preferred method** for screening for LTBI
- TST and IGRAs almost no place in diagnosis of active TB
- IGRAs may be used as **supplementary test** for LTBI for increased specificity

# Diagnosis of Childhood Tuberculosis

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## Suspicion

### Infection?

- History
- Targeted Tuberculin Skin Test
- IGRA

No

Yes

### Disease?

In case of contact:  
consider exposure  
prophylaxis for  
3 months and  
re-evaluate

75% pulmonary TB  
25% extrapulmonary TB

### Gold standard: Culture

**But** in children often combination of:

- Symptoms
- Radiologic Findings
- Microscopy/Culture/NAAT

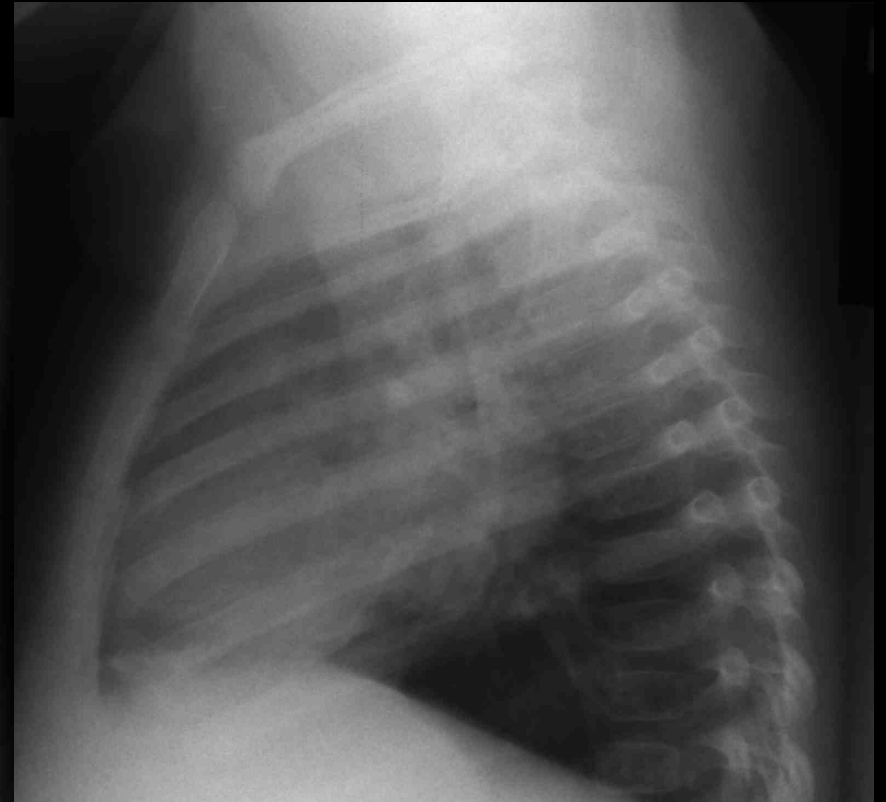
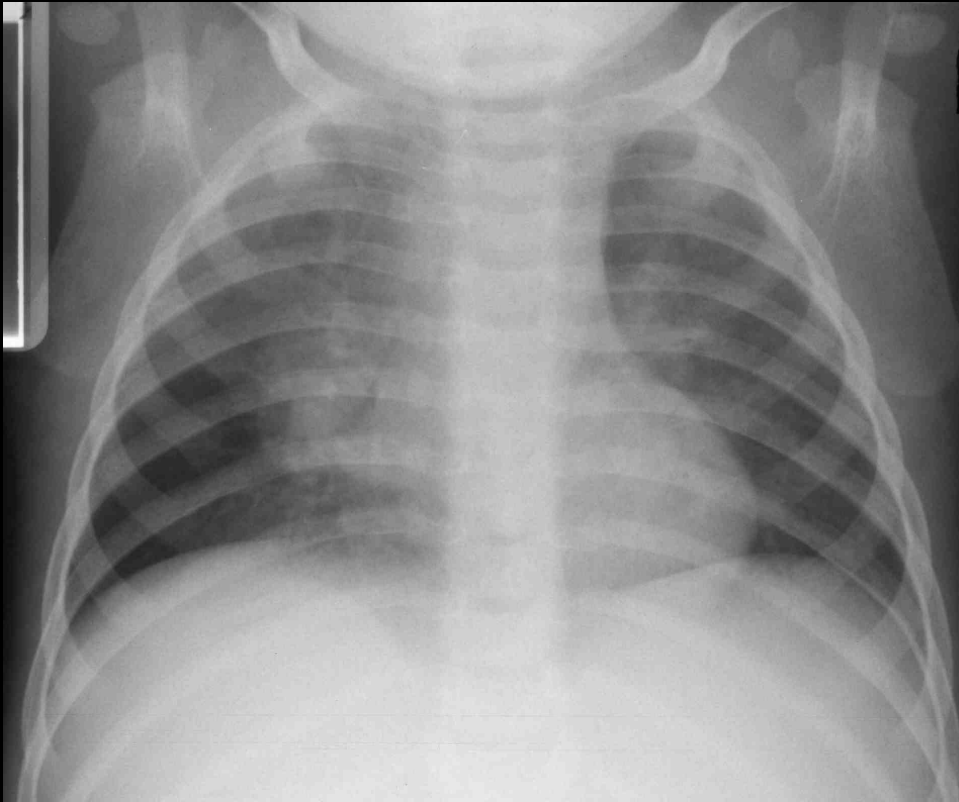
# Symptoms

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- **Early disease often asymptomatic!**
- Later:
  - Persistent cough > 2 weeks
  - Documented loss of weight
  - Reduced playfulness
  - ➔ reasonable accuracy in combination (PPV 83.6%, South Africa)
  - Organ-specific symptoms  
(Lymphadenopathy, neurologic symptoms, Gibbus etc.)

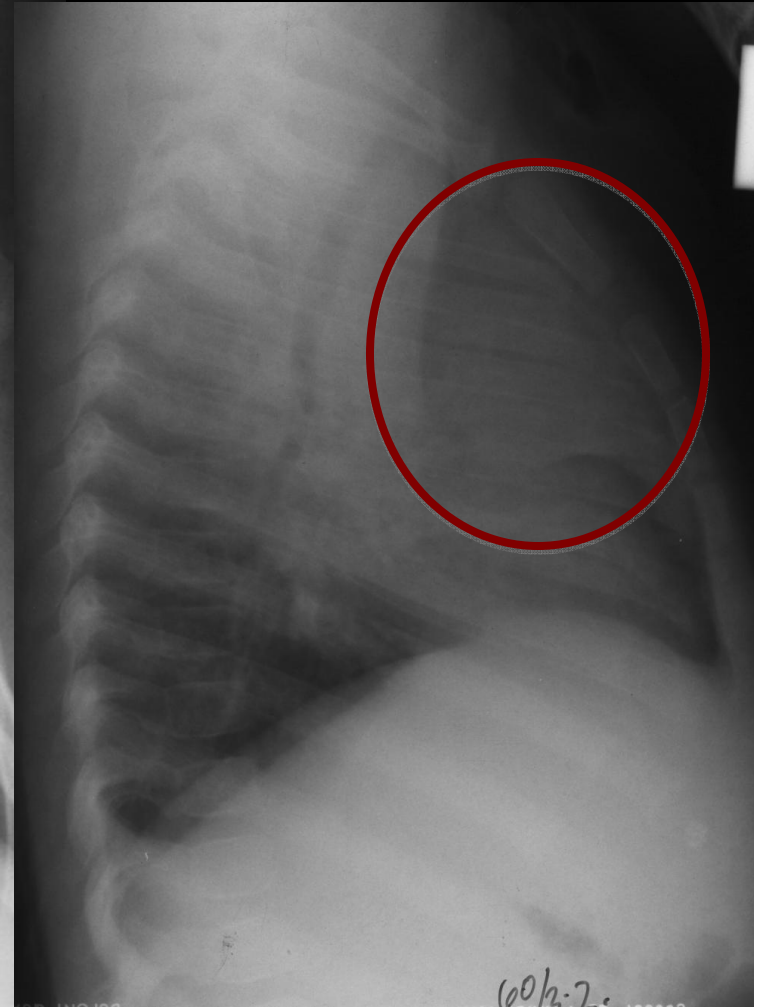
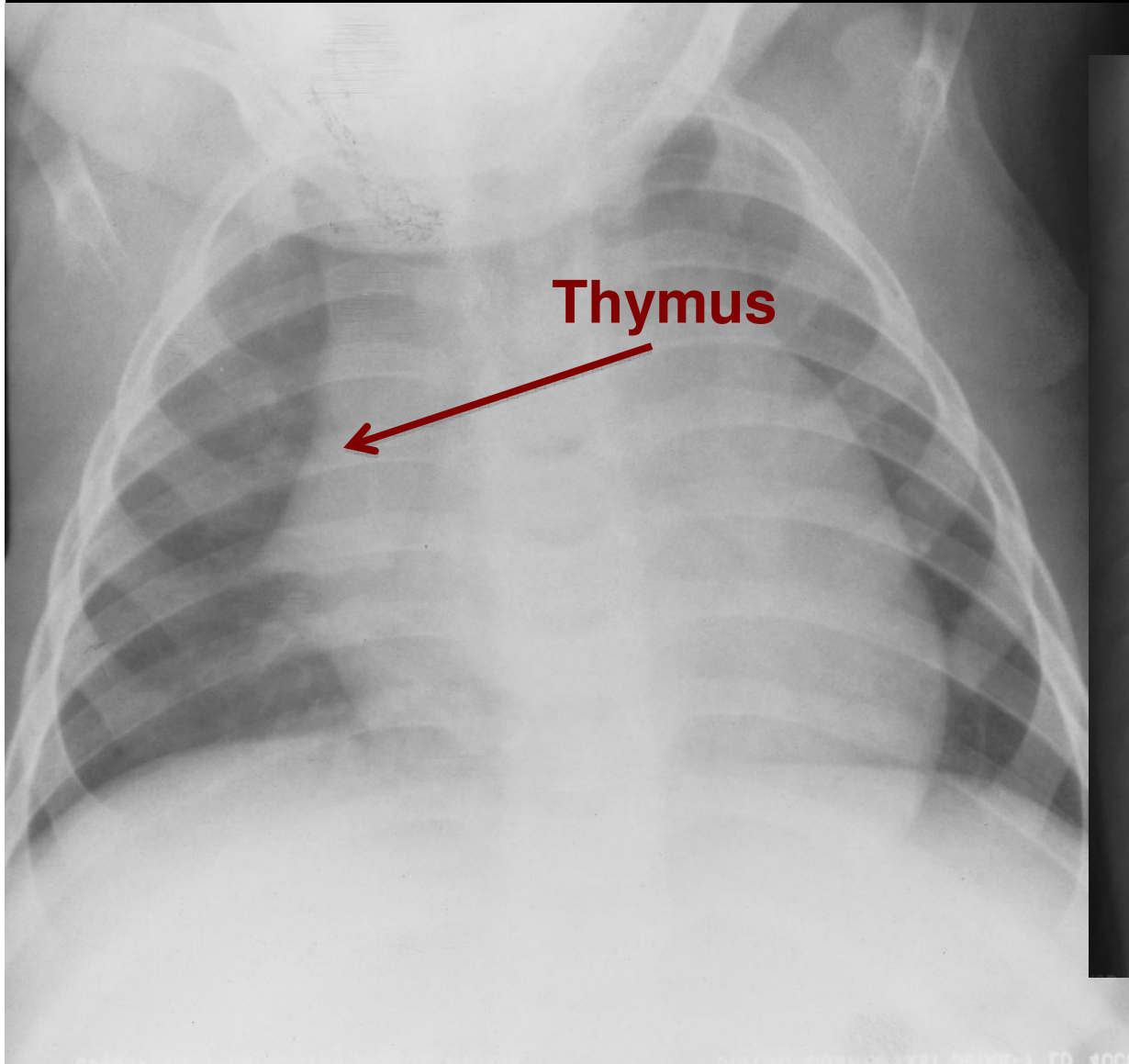
# Most common - Lymphnode disease

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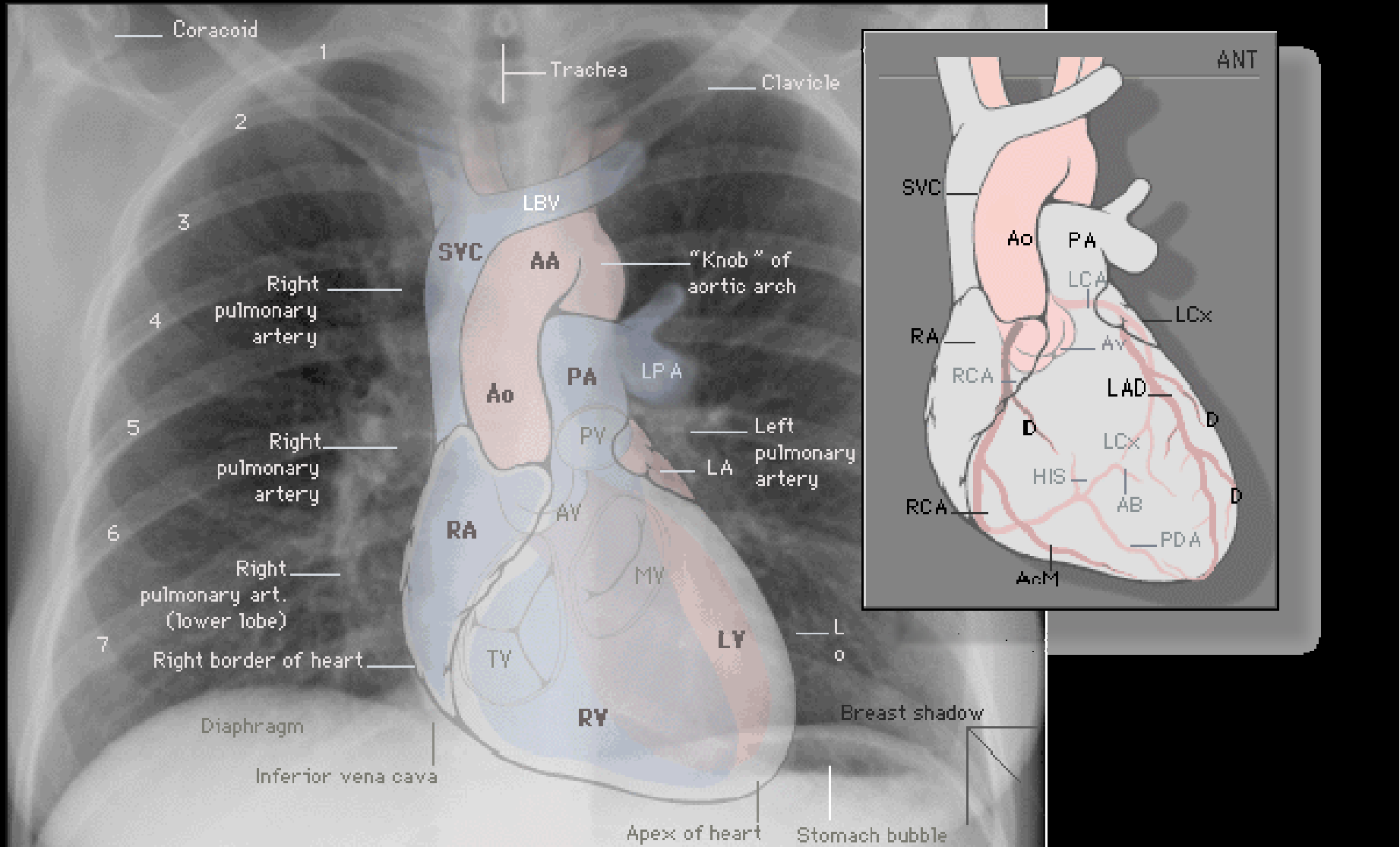
# The value of lateral CRXs

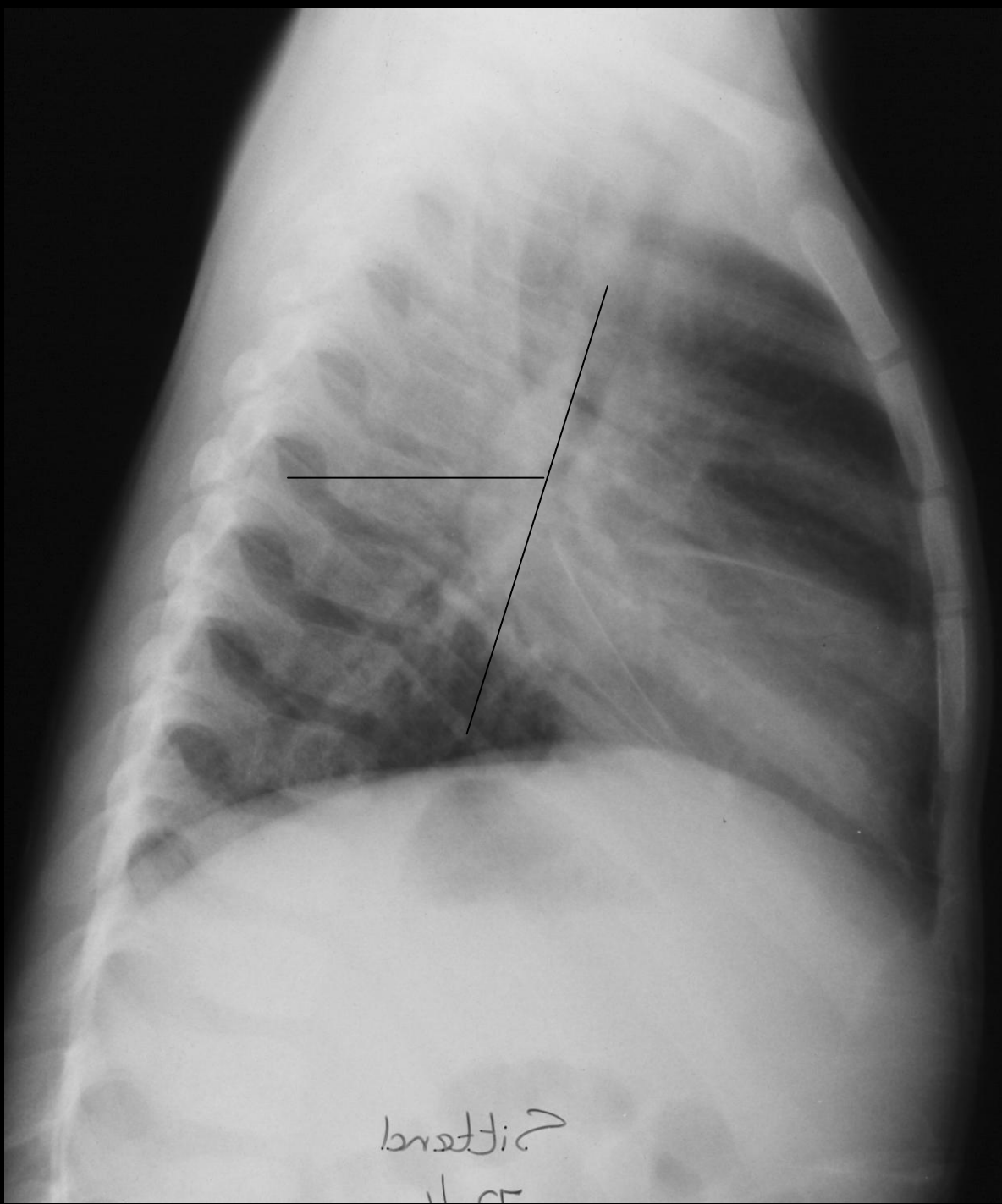
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# Additional structures

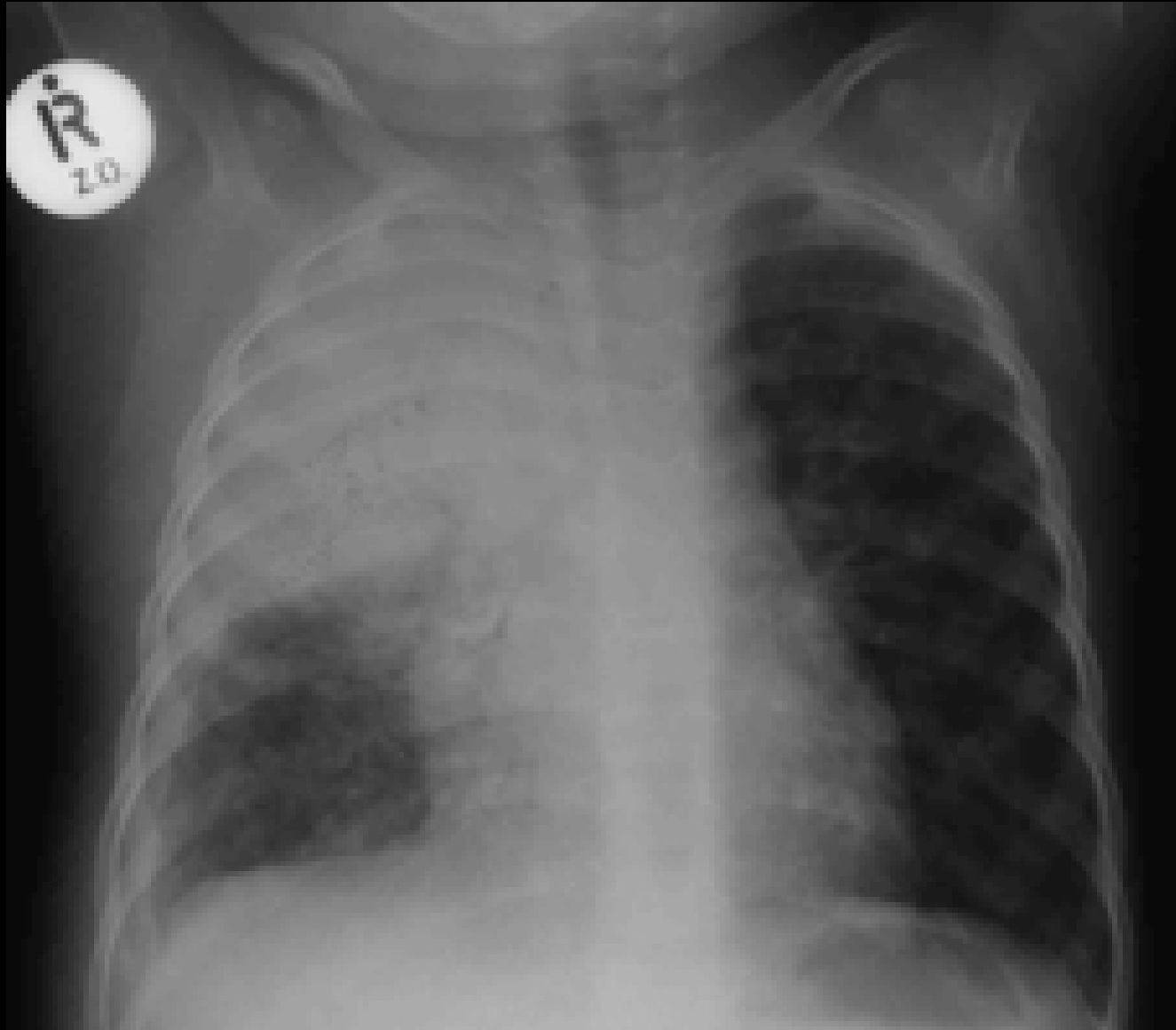




brettic →  
1/05

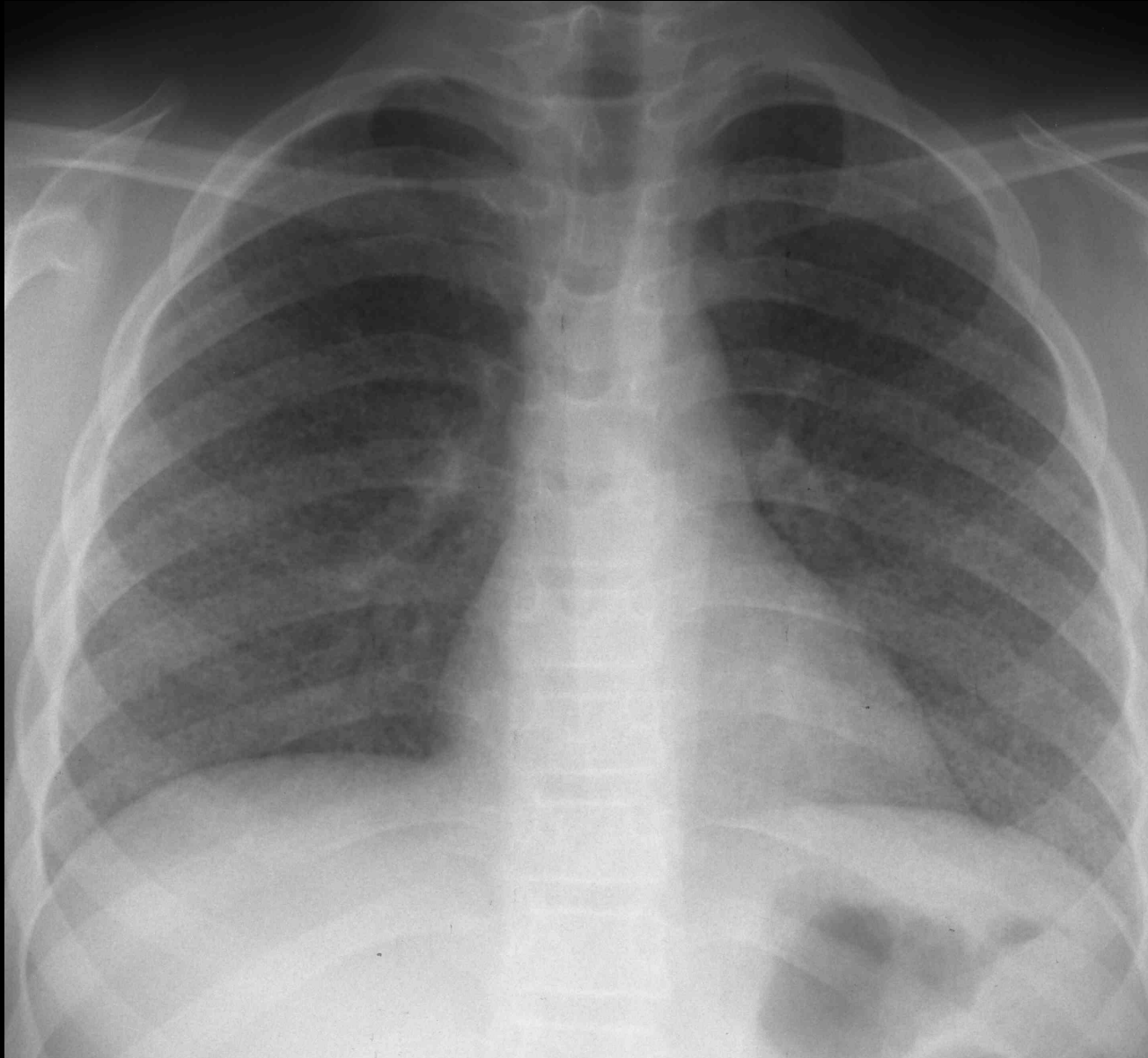
# Bronchogenic spread - Expansile pneumonia

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# Most specific - Miliary TB

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# Adult-type disease

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# CT and MRI

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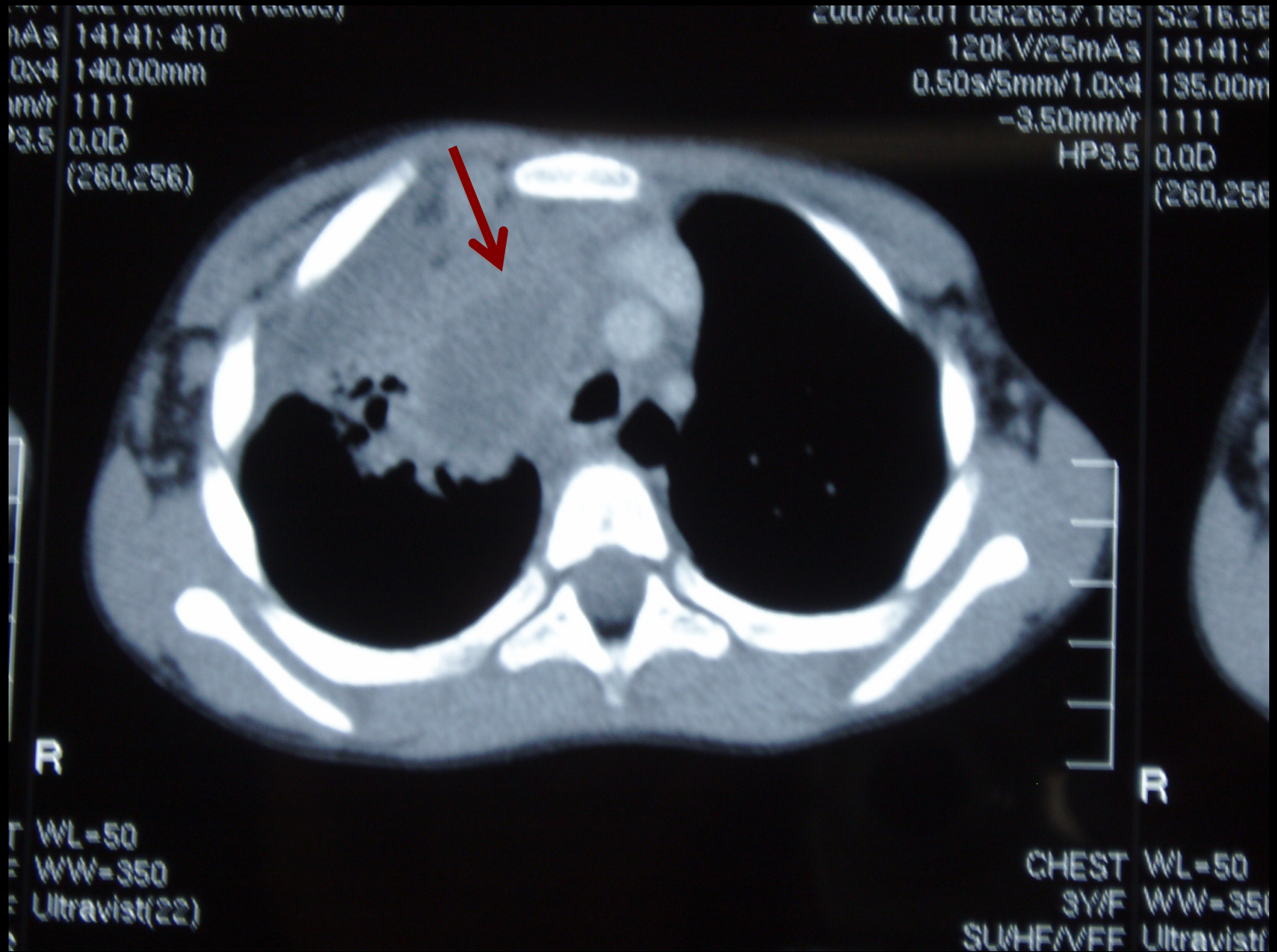
## CT indication

- Pulmonary TB:
  - Small lymphnodes (value?)
  - Endobronchial involvement
  - Bronchiectasis
  - Early cavities
- Pleural/Pericardial disease
- TB Meningitis:
  - Basal enhancement
  - Hydrocephalus
  - Tuberculomas
  - Focal lesions

## MRI indication

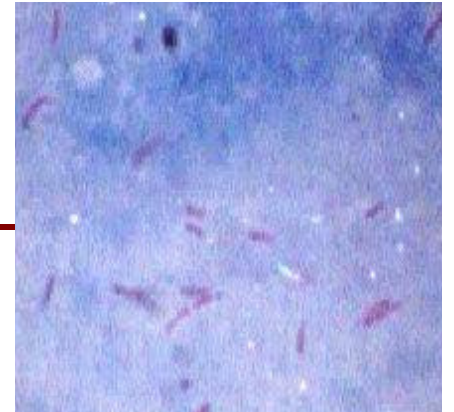
- Brain/spinal cord involvement
- Chronic Osteomyelitis
  - Early marrow involvement
  - Soft tissue extension
- Spinal TB
  - Cold abscess formation

# CT with Contrast: Ring enhancement



# Bacteriology

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## Culture = gold standard

- Challenge: paucibacillary disease in children
  - But:** Sensitivity ↑ with severity of disease
- Bacteriological prove must be tried
  - ➔ **Rigorous** and **standardized** sample collection
    - 3x Gastric washing/sputum
    - Suspected site of infection



# Gastric washing vs. induced Sputum

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## Gastric washing

- Fasting for 8 hours
- Up to 50% yield if performed in a standardized manner<sup>1</sup>
- Stain and culture yield from 3 GW higher than BAL<sup>2</sup>

## Induced sputum

- Inhalation of 3-5% hypertonic saline
- Possible side effect: bronchospasm
- Yield of one induced sputum equivalent to 3 GW<sup>3</sup>
- Physiotherapy to support sputum production

<sup>1</sup> Pomputius Pediatr Inf Dis J1997 <sup>2</sup> Lighter Curr Probl Pediatr Adolesc Health Care 2009, <sup>3</sup> Zar Lancet 2005

# Drug resistance

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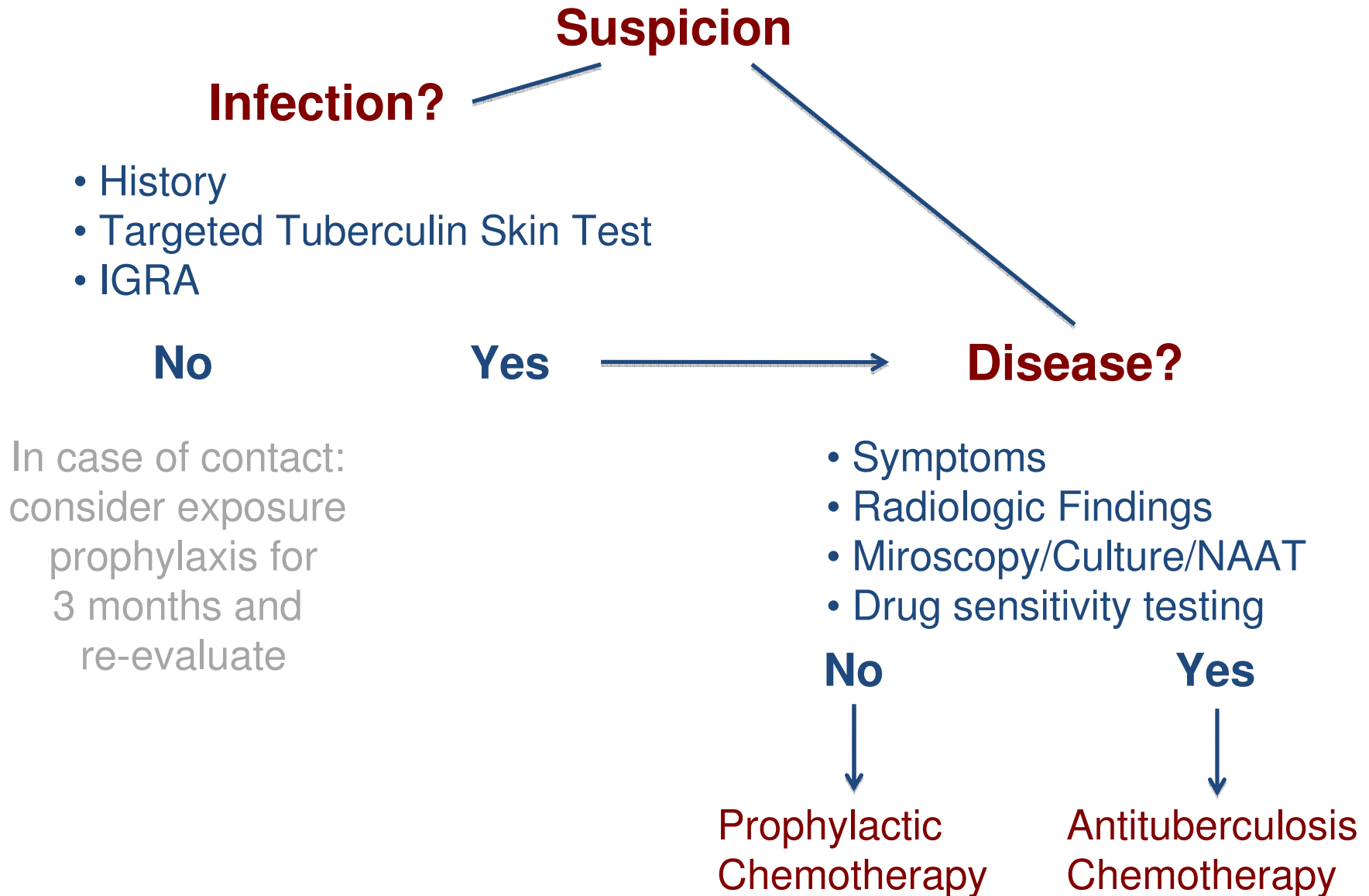
**Drug susceptibility testing has to be performed  
on the first positive culture**

In the case of negative culture:

- History!!!!
- Drug susceptibility results or regimen of the index case

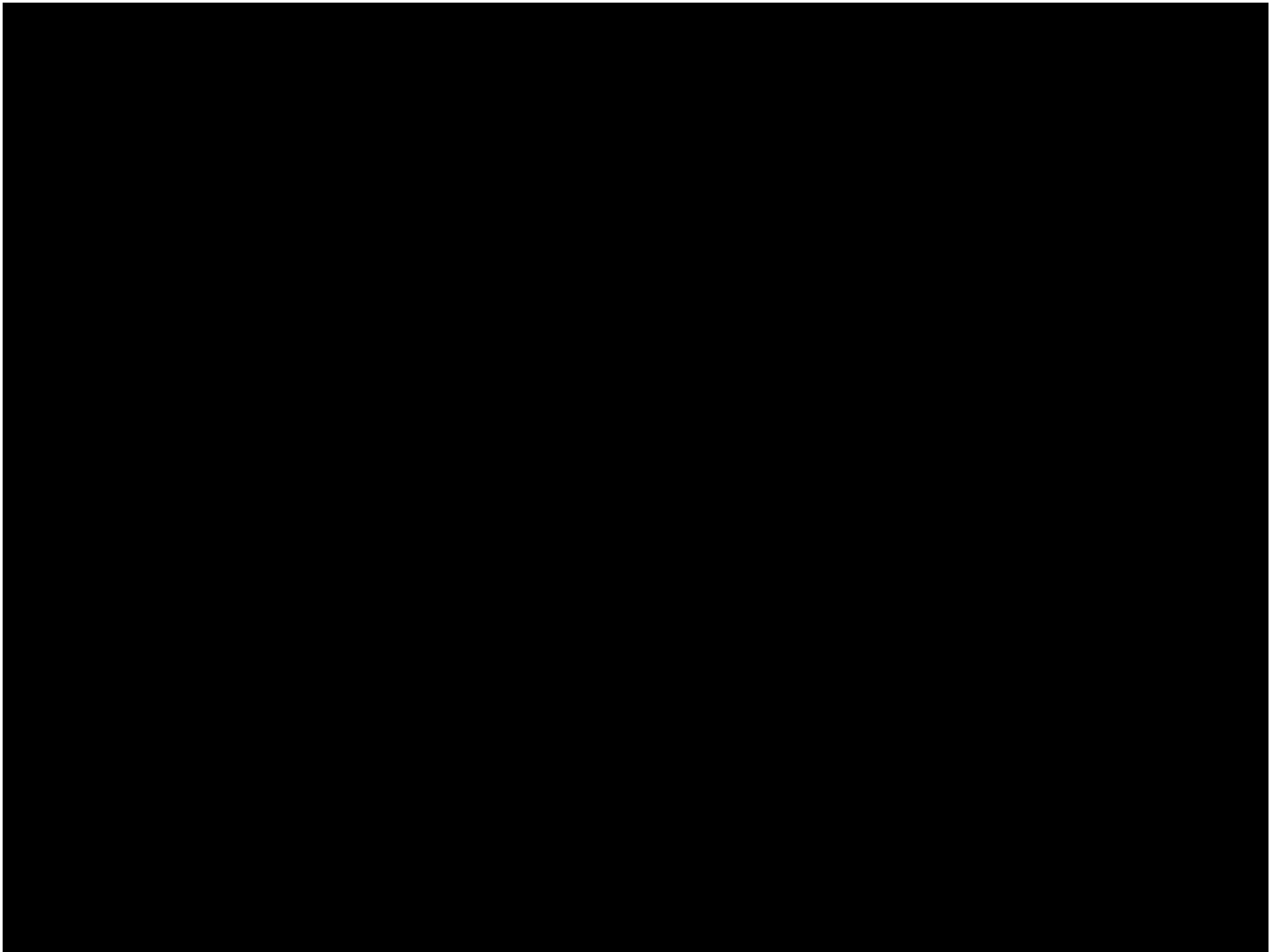
# Diagnosis of Childhood Tuberculosis

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Thank you!





# TB cases of foreign origin

## WHO European Region 2006

