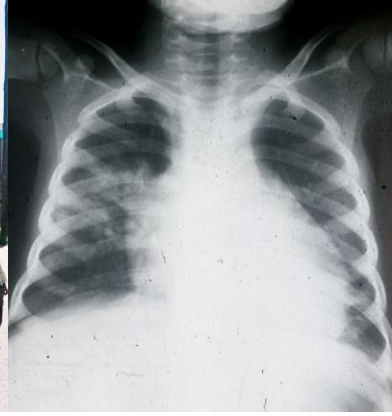
Imperial College London

Centre for Respiratory Infection

CRI



Challenges in paediatric tuberculosis and community control

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Consultant Paediatrician
NIHR Senior Research Fellow
Imperial College London, UK
and
Themeleader Vaccinology
MRC-The Gambia

Overview

- an illustrative case

- a bit of global and local epidemiology

- Diagnostic challenges:
  - Differences between adults and children
  - New Immunological Tools-how helpful are they?

- Prevention:
  for the individual patient
  for the community

- new TB vaccines on the horizon
- Contact screening approaches

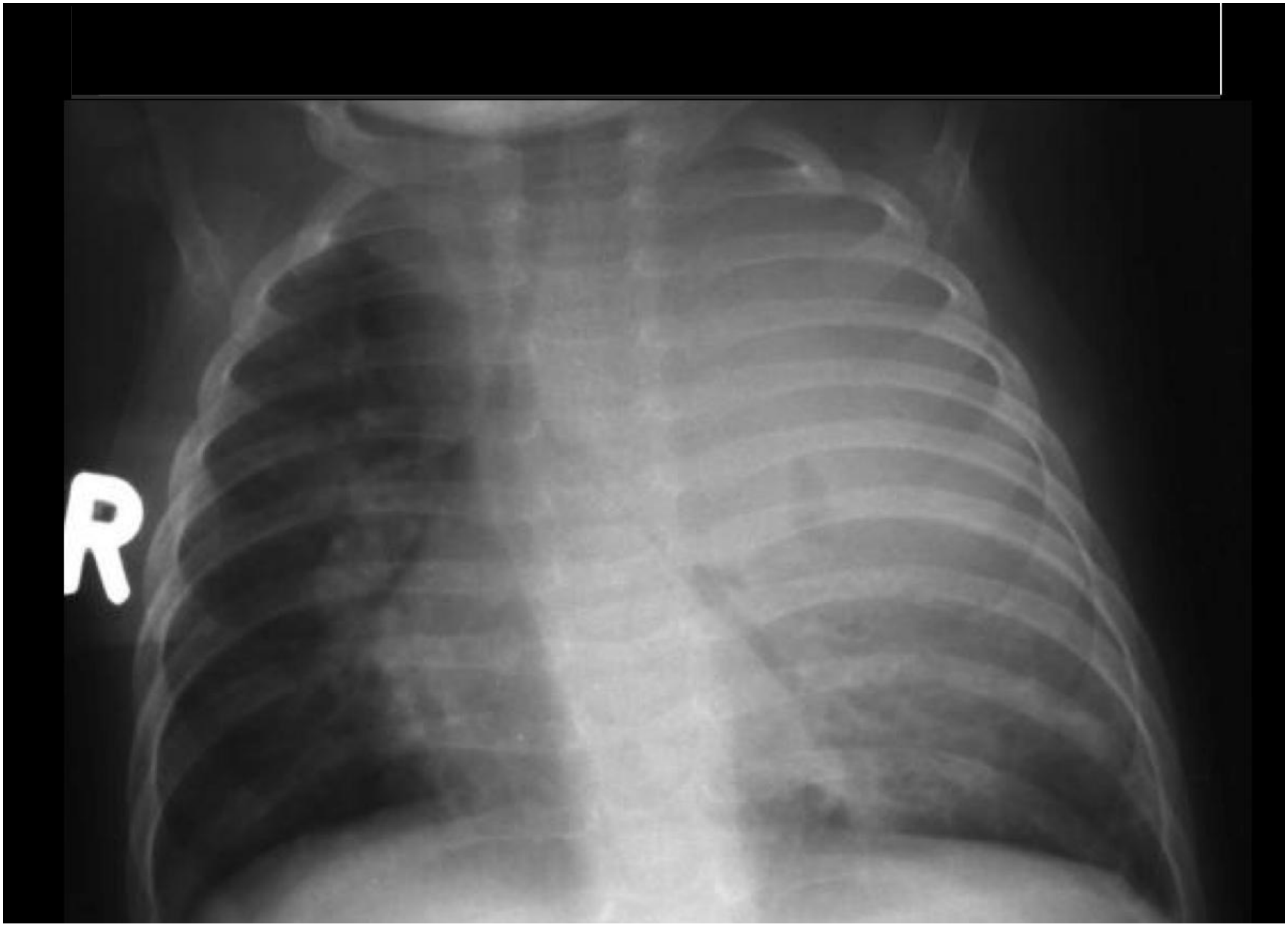
A story to start with…

Y.S.

- 3/12 old baby, BCG vaccinated at 2 months of age

  Reviewed at TB clinic since contact with Grandfather who has pulmonary TB
- Acutely unwell with cough and respiratory signs
- Failing to thrive

What are you worried about?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What’s going on?

TB exposed

TB infected

TB diseased

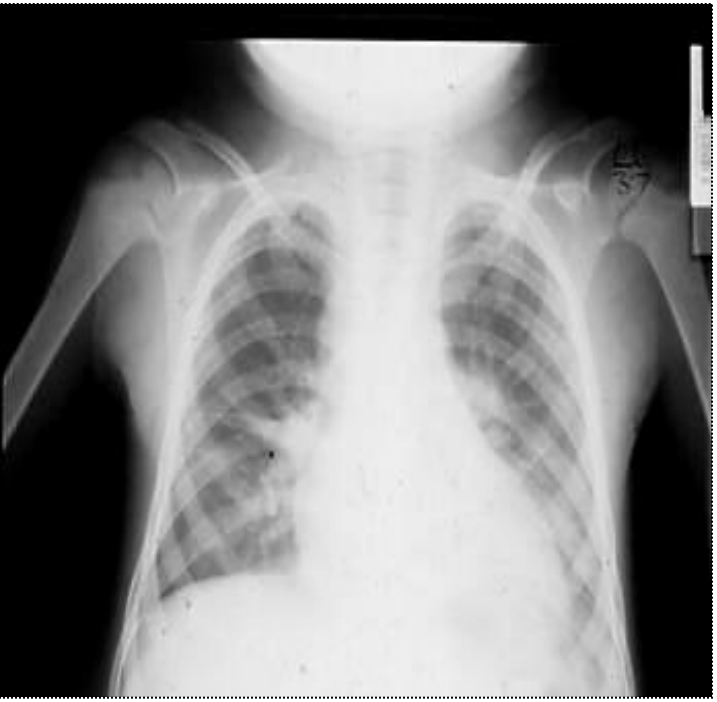
Another pulmonary disease

CHILDHOOD EXPOSURE

PRIMARY PULMONARY INFECTION

Self healing??

Inadequate immune response



PROGRESSIVE PULMONARY DISEASE

Lympho/ haematogenous spread

MILIARY TB or EXTRA-PULMONARY DISEASE

How likely is it that this child has TB?

It depends on

Age

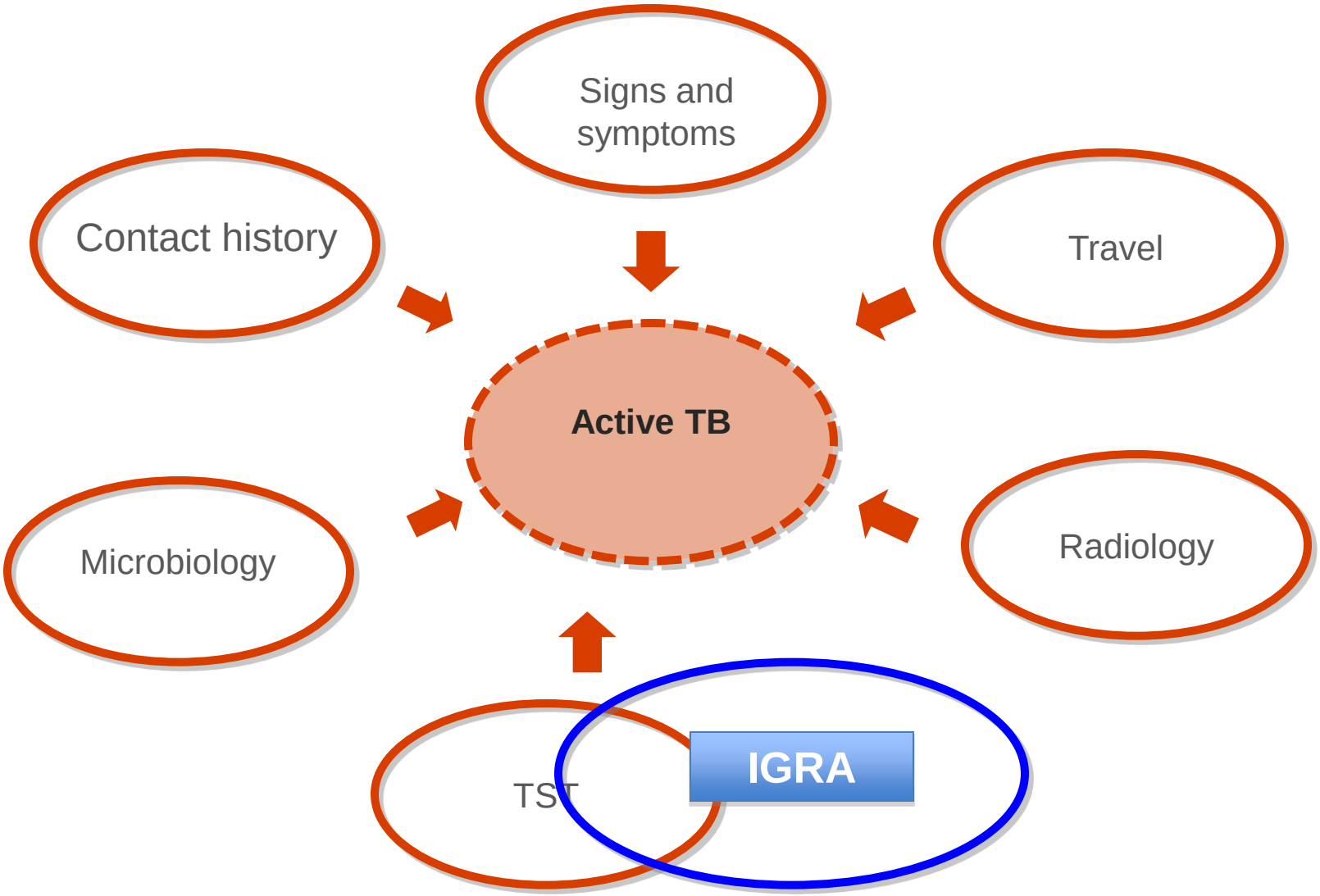
Contact history/exposure

Epidemiology

Immune status

What do we do next?

The diagnostic jigsaw of active TB



Social History

- No siblings
- Lives with parents, paternal uncle, his wife, their 2yr old son, paternal grandparents
- No social services involvement
- Paternal grandfather with pulmonary TB- on treatment for 3 months
- The other 7 family members in the same household have been screened for TB and have a positive mantoux test, including the parents & waiting to start chemoprophylaxsis after review with respiratory team

FIGURE 1

Estimated TB incidence rates, by country, 2009

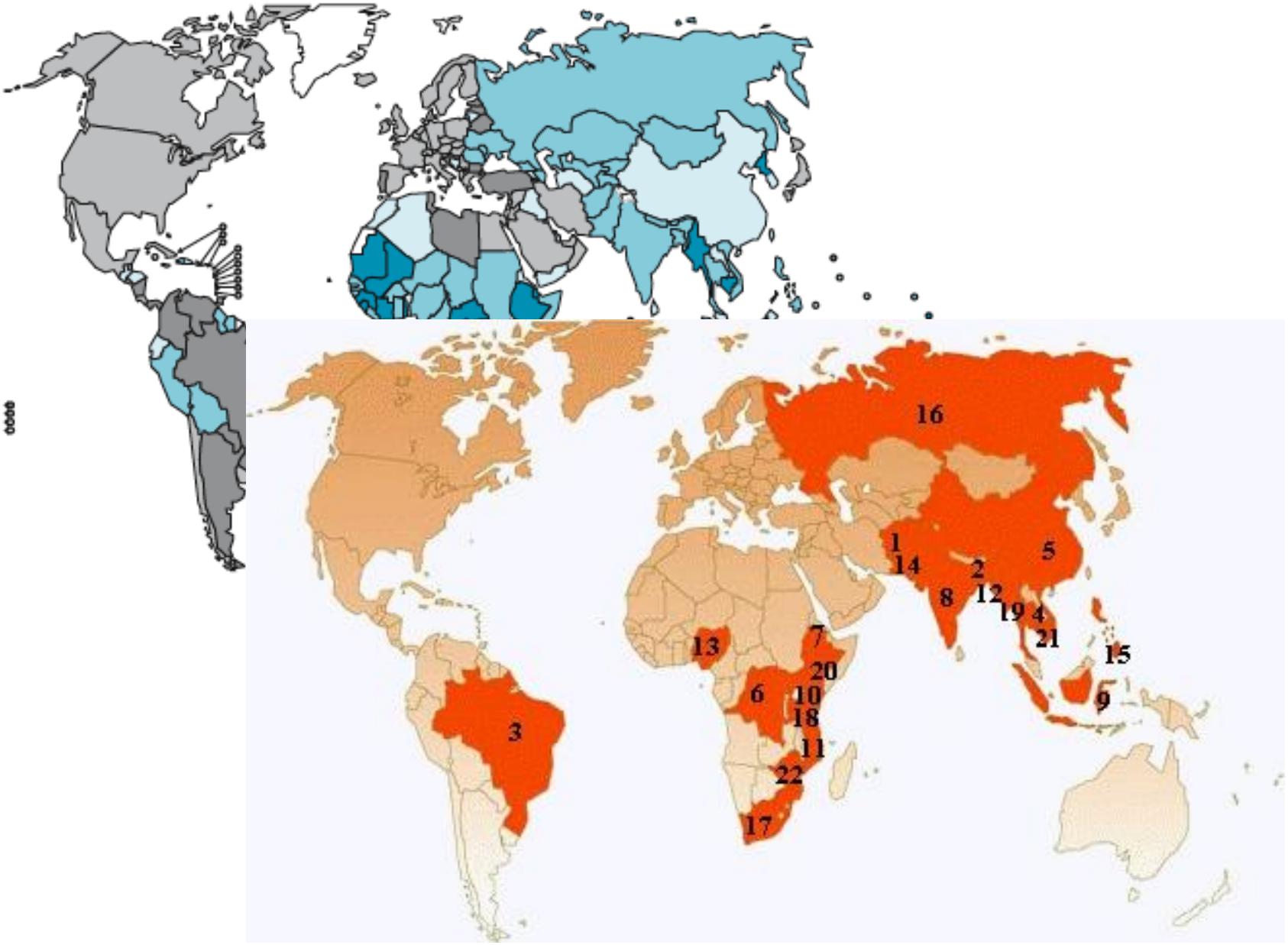
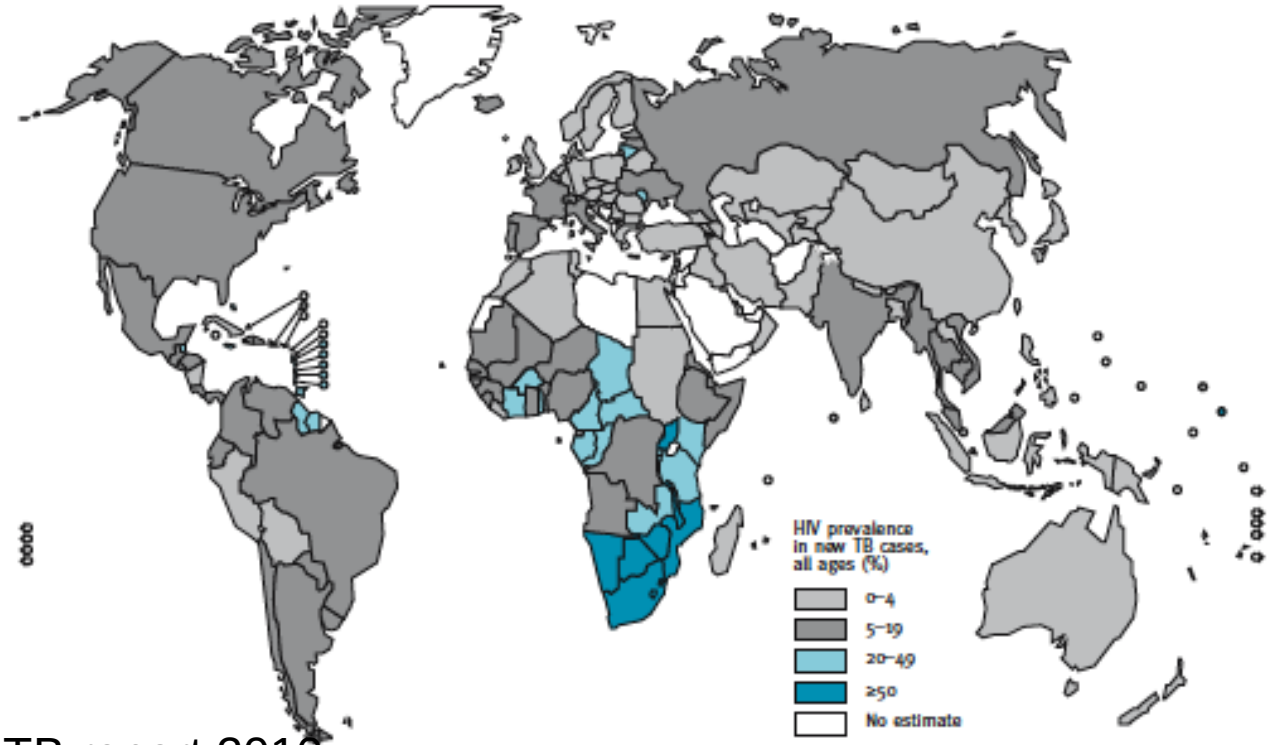


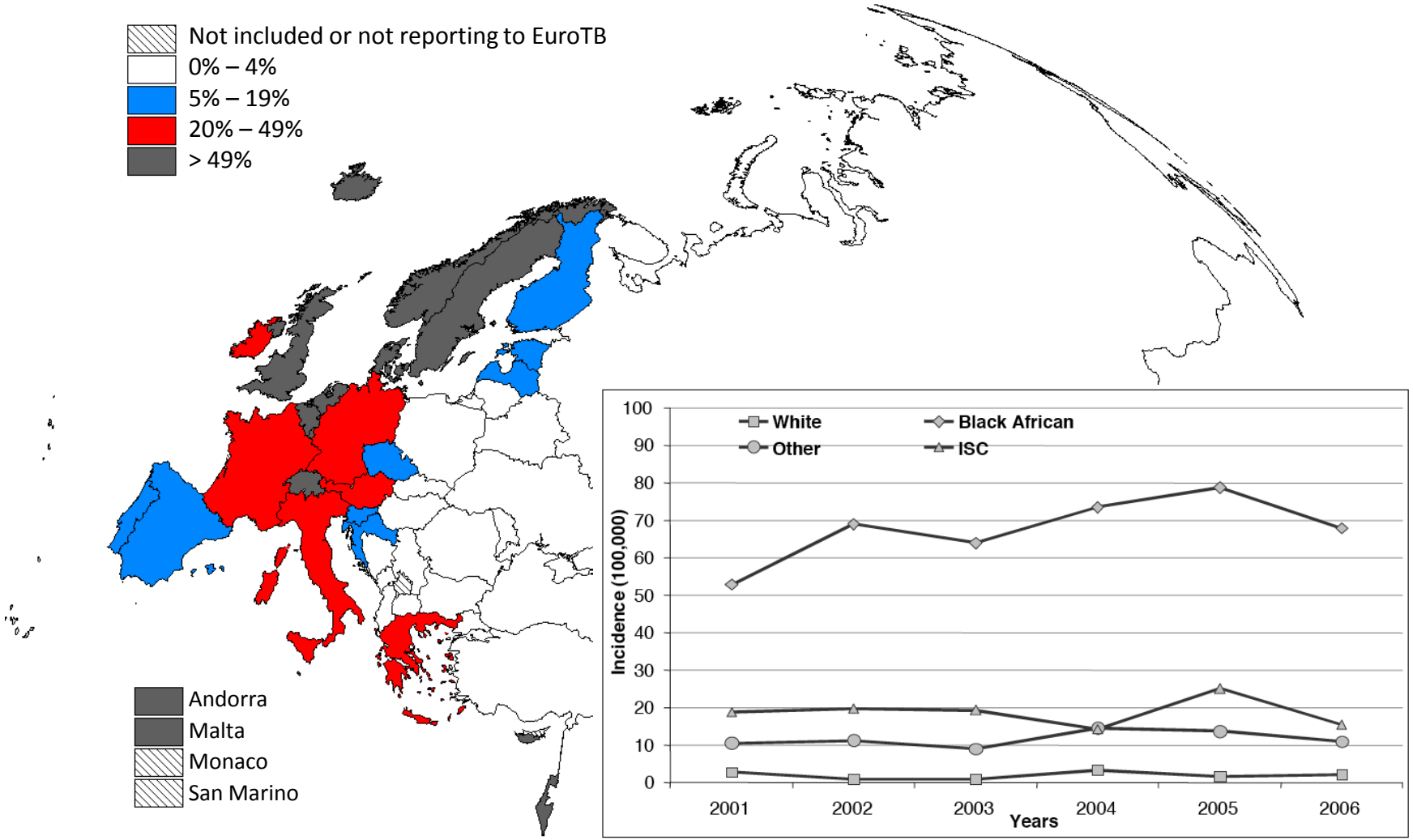
FIGURE 1
Estimated TB incidence rates, by country, 2009

FIGURE 2
Estimated HIV prevalence in new TB cases, 2009



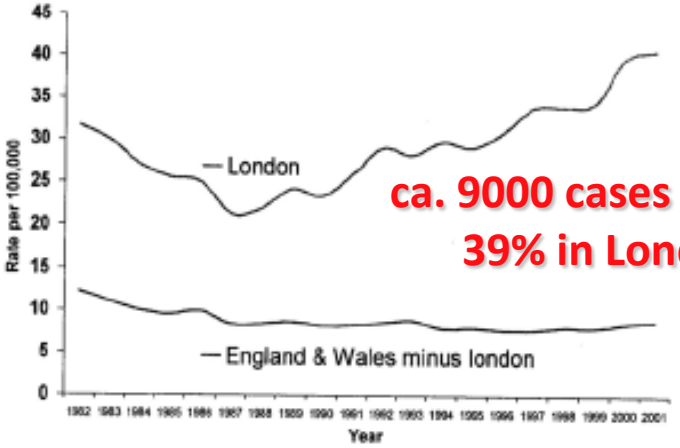
Source: WHO Global TB report 2010
http://whqlibdoc.who.int/publications/2010/9789241564069_eng.pdf

Percentage of TB cases of foreign origin, 2006



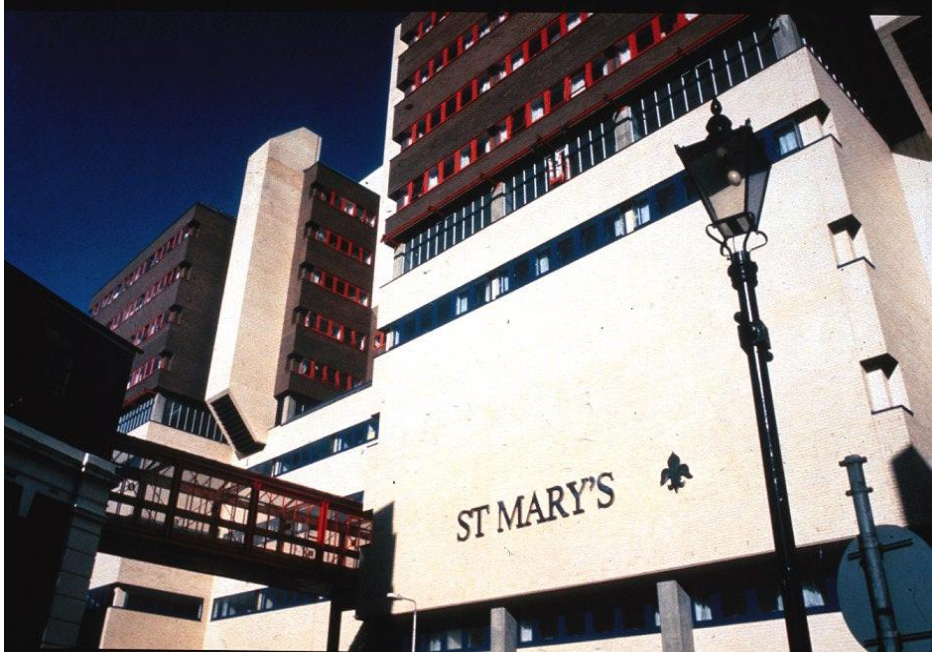
Trends in incidence of TB in children under 15 years by ethnic group in London, 2001-2006

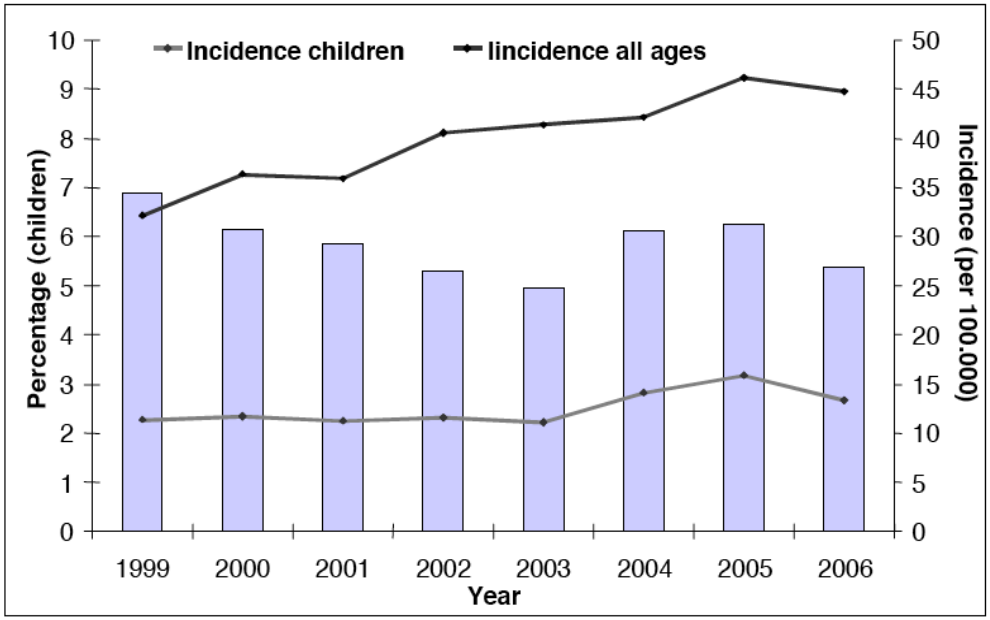
Tuberculosis in the UK:

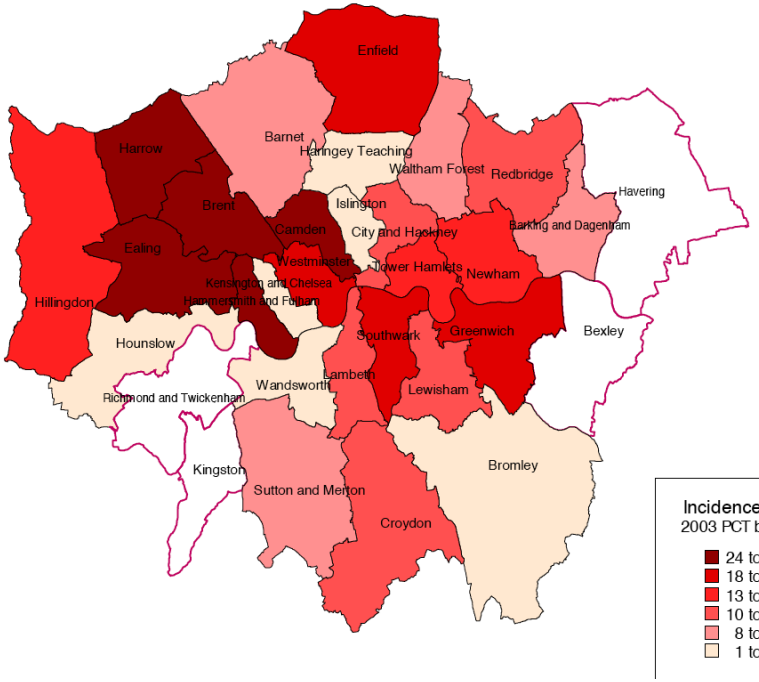


ca. 9000 cases in 2009
39% in London

Graph provided by Health Protection Agency, Communicable Disease Surveillance Centre, 2002.

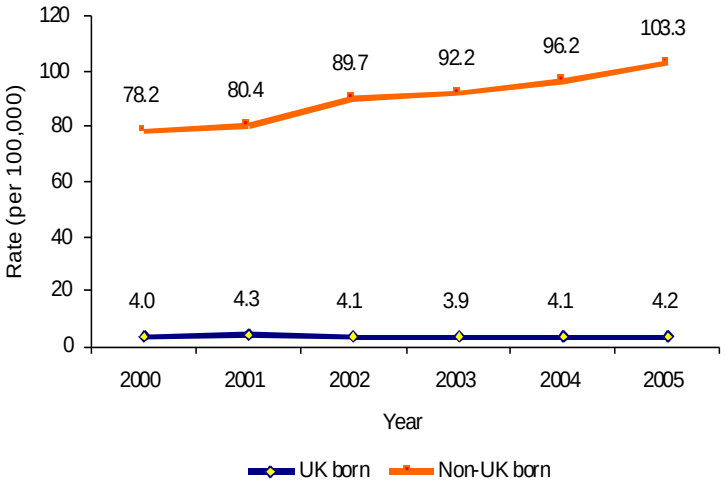






Is the general population at risk of disease from affected migrants?

Tuberculosis rates by place of birth: 2000-2005



Source, Enhanced Tuberculosis Surveillance

- **Little evidence to suggest that the wider population are at significant risk**

Tuberculosis in Children…. the problem

- Significant Morbidity and Mortality

  1.4 million cases annually (95% developing countries)

  450,000 Deaths

  estimated 10-15% of global burden related to childhood TB

- Different clinical spectrum of disease

  5-10% < 2 yr meningitis

  disseminated disease more common

- Co infection with HIV- clinically very difficult to distinguish

- Remains a diagnostic challenge

  paucibacillary, rarely culture confirmed :

  Sputum smear positive in 10.3% (10-14yr), 1.8% (5-9) and1.6% (<5)

  Cultures positive 21% (10-14), 5% (5-9) and 4.2% (<5),

Tuberculosis in Children differs from adults

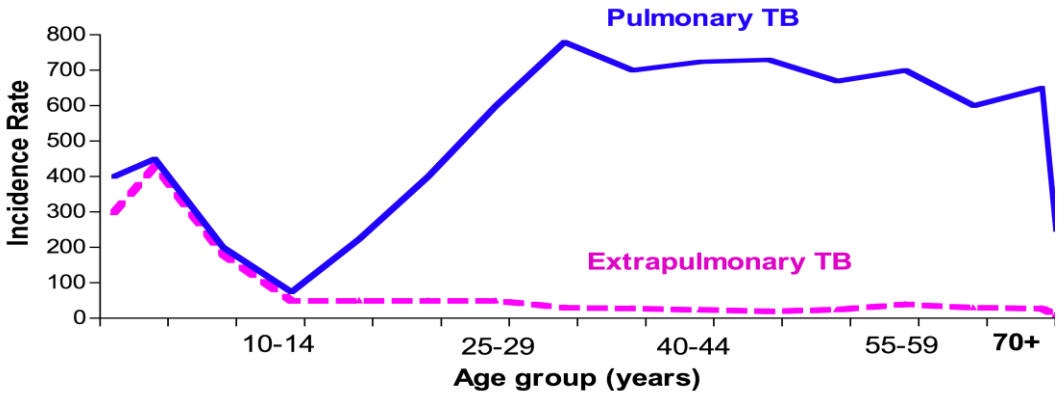
- Immune responses are

  Age-dependent: Following infection 40% < 2 yr, 25% 2-5 yr and 5-15% of older children will develop disease within 2 years

- Majority of disease results from progression of primary infection rather than reactivation

  might affect detectable immune responses

- More likely to be extrapulmonary and disseminated, particularly in infants



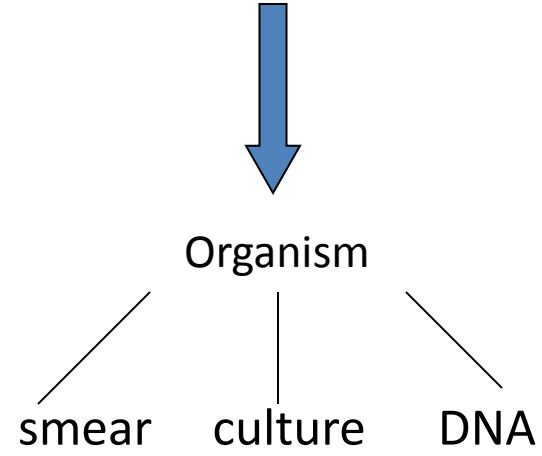
Newton, Kampmann *The Lancet Infectious Diseases*, August 2008; Vol 8: 498-510

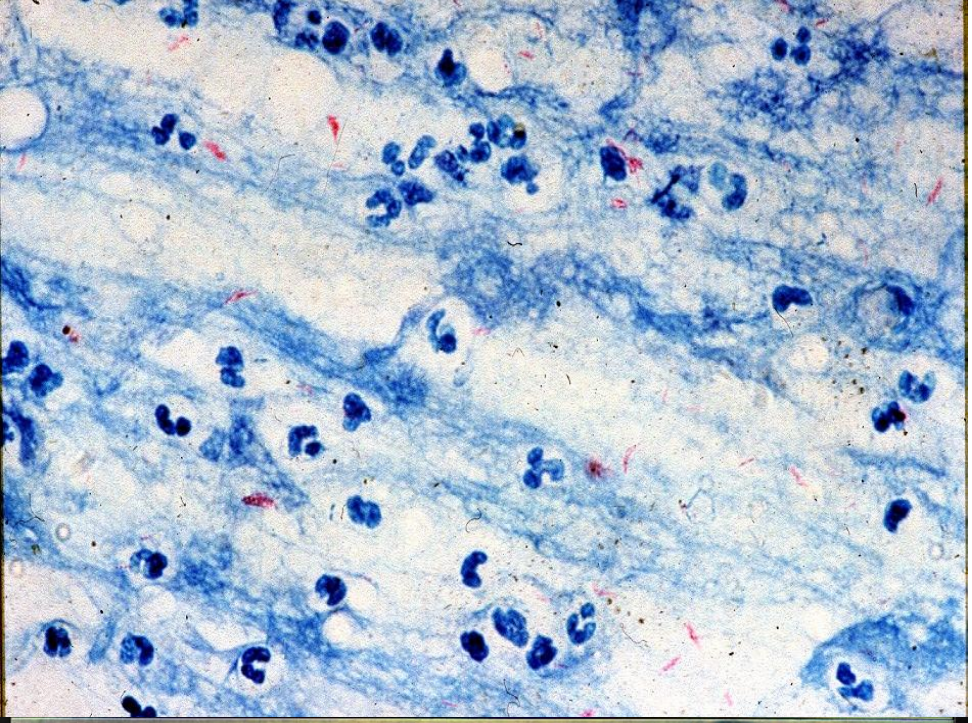
INVESTIGATIONS

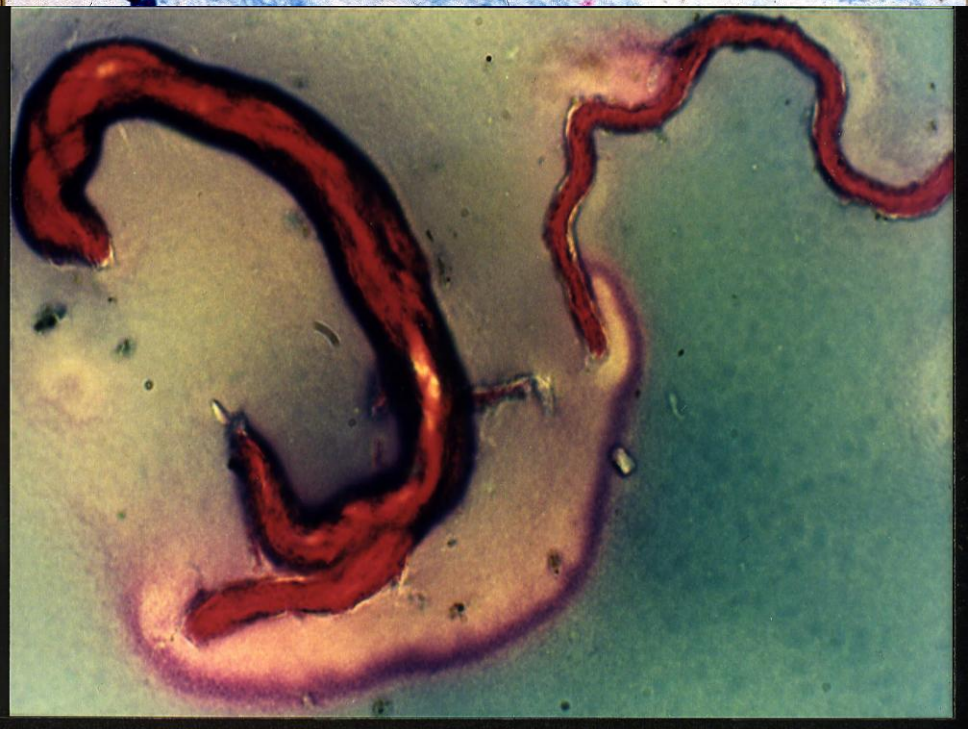
- Summary of some of his main investigations:
- Abnormal CXR with infiltrates in left lung, mediastinal widening and pleural effusion
- TST: 6 mm. IFNGRA +ve
- Gastric washouts x 3 (21-22/9/11): AFB stain negative (cultures awaited)
- Differential diagnosis?

Diagnostic tests

Microbiological





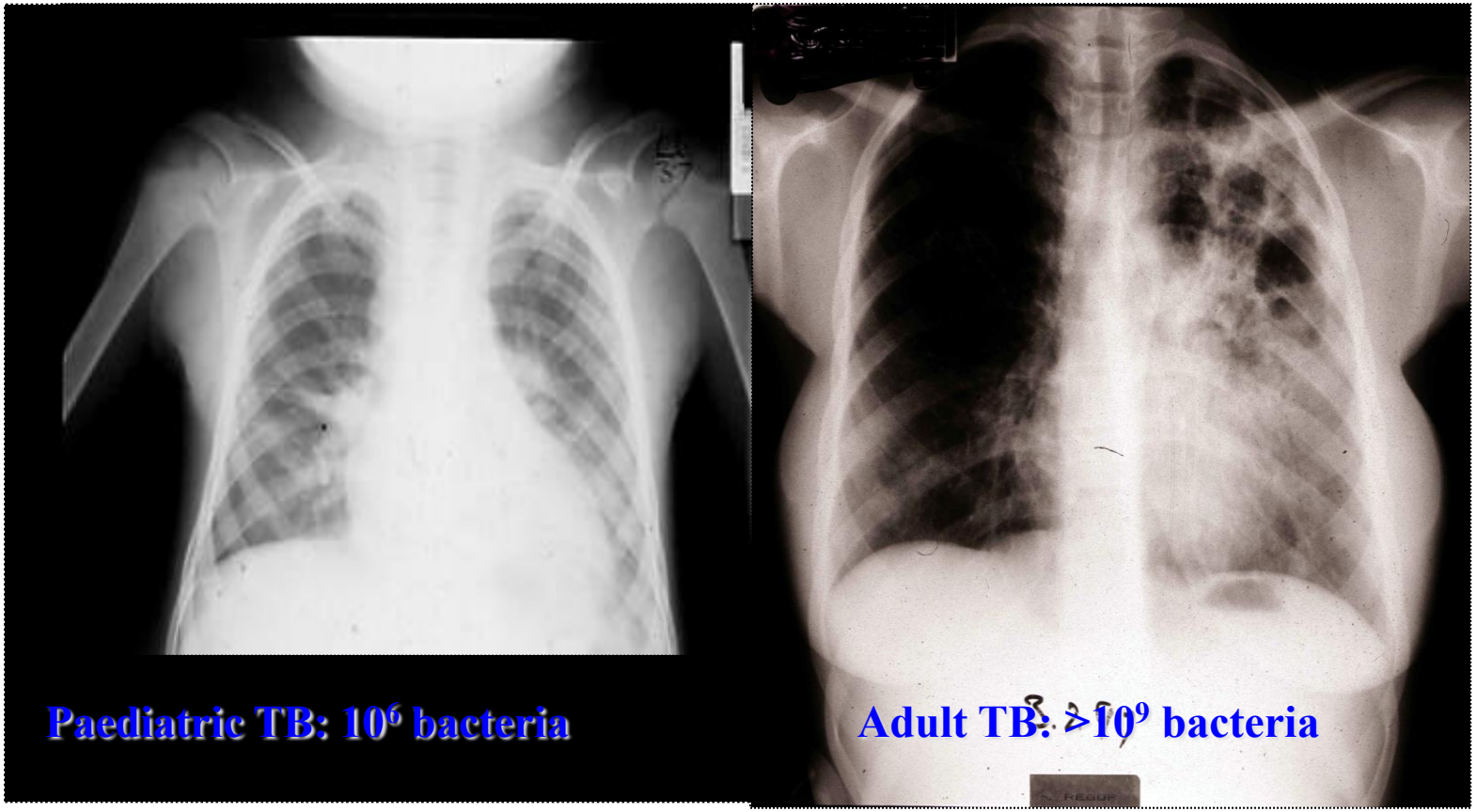


The “gold-standard”

Appearance in sputum

Appearance in culture
‘cording’

PAEDIATRIC TB: Implications of bacterial load



- children less infectious

- difficulty in confirming diagnosis

- difficulty in detecting resistance

New technology: GeneXpert

Lancet Infect Dis. 2011 Jul 15

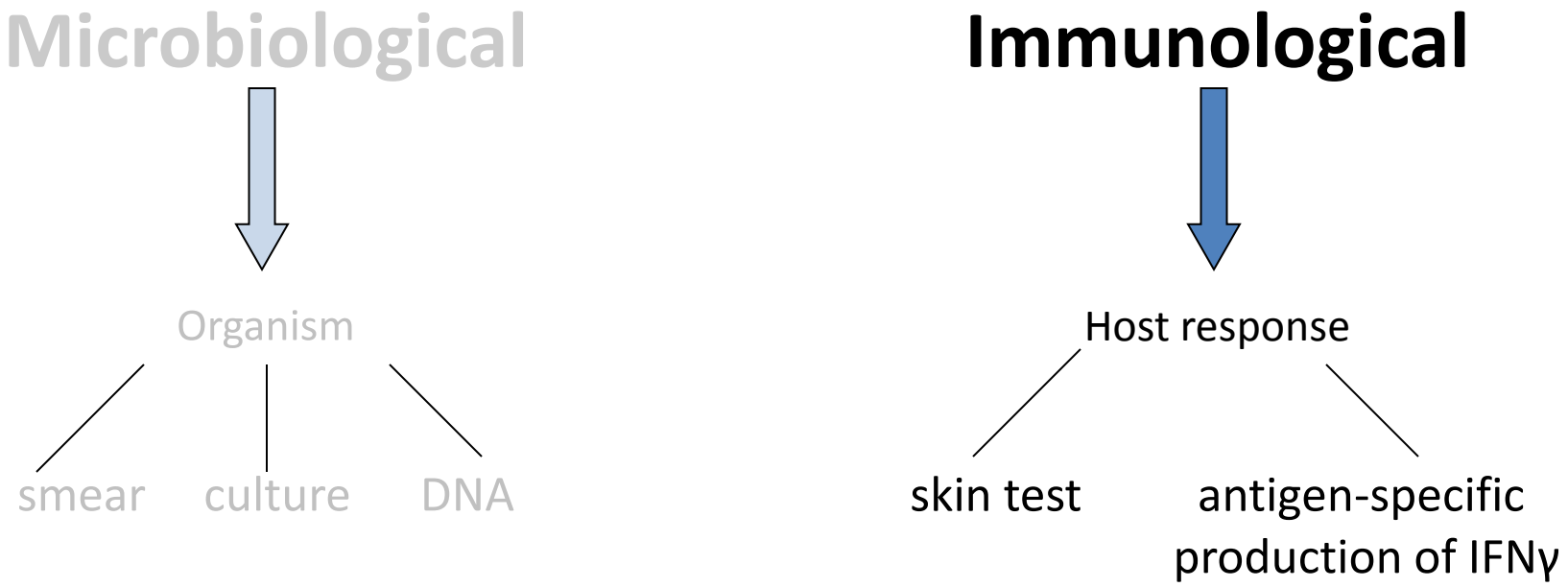
Nicol et al,

Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study

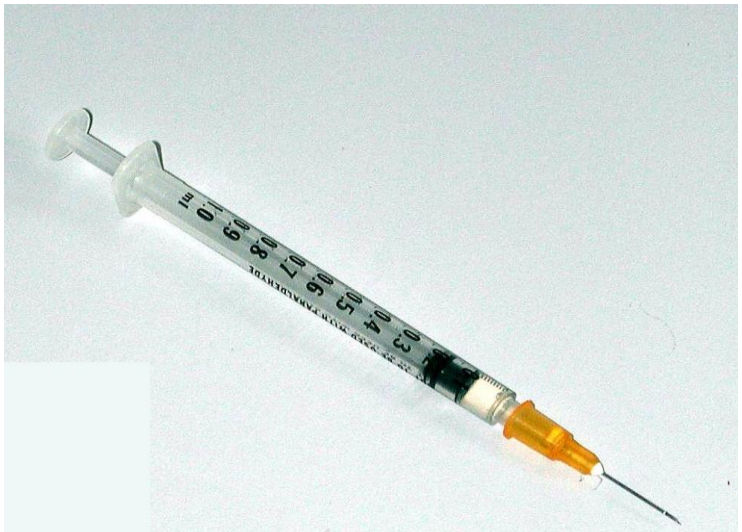
Results: “With mycobacterial culture as the reference standard, MTB/RIF tests when done on two induced sputum samples detected twice as many cases (75·9%, 95% CI 64·5–87·2) as did smear microscopy (37·9%, 25·1–50·8)”

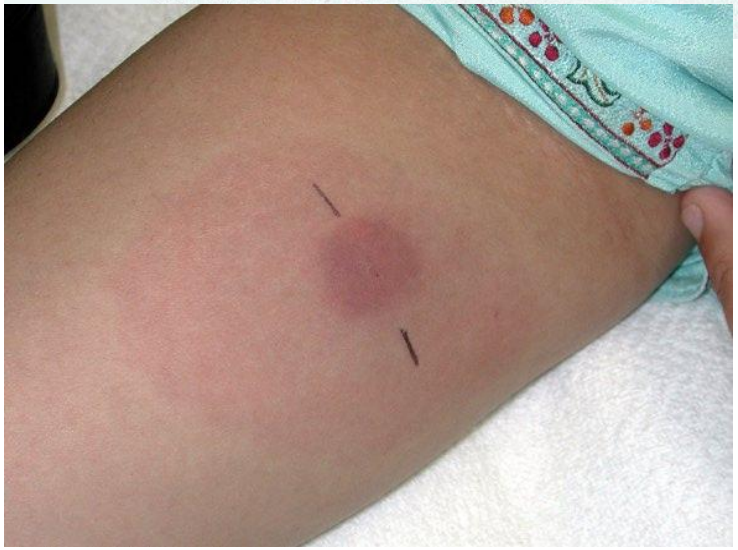
(but: culture only +ve in 16%...)

Diagnostic tests



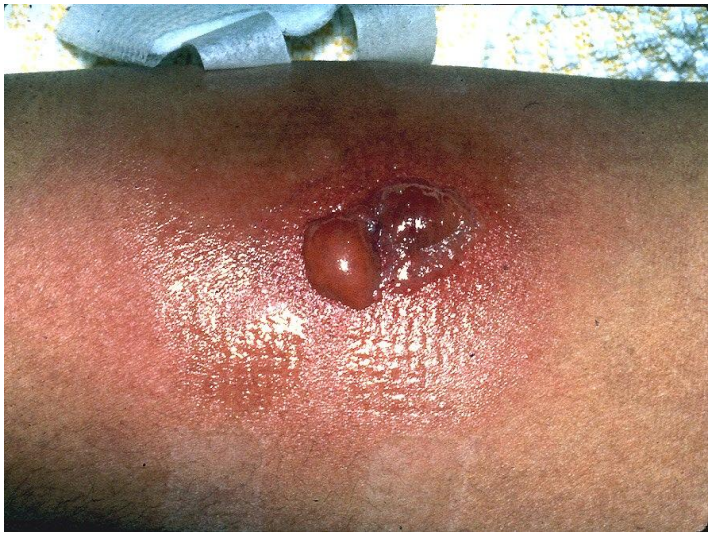
Tuberculin skin test (TST)





- technically difficult in children
- UK: 2 units of SSI tuberculin (PPD)
  > 200 antigens, incl. BCG Ag
- Read-out: degree of hypersensitivity
- **Problem:**

  lacks specificity and sensitivity

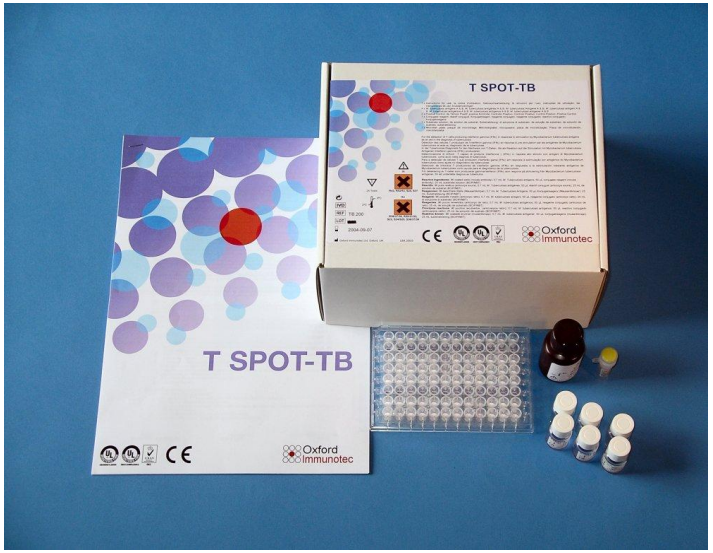


IGRA: 2 commercially available assays

Antigens used:
ESAT-6
CFP10 +/- TB7.7
mitogen
negative control

In principal: can both distinguish between BCG vaccination and *M.tuberculosis* infection

but:
Paucity of data in children
Confusion about use of IGRA



Gene deletions and the origin of BCG

M. tuberculosis

10 deletions

64 genes

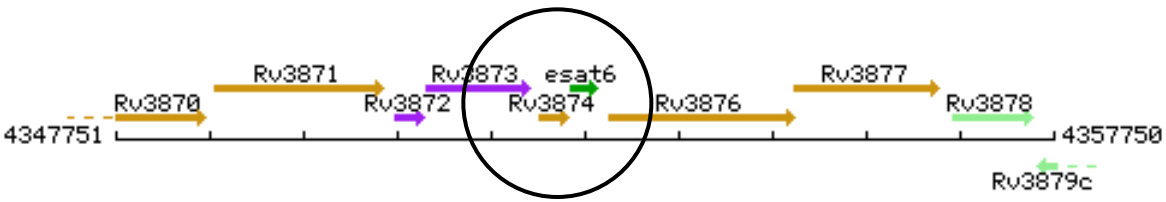
M. bovis

4/5 deletions

30/40 genes

BCG substrains

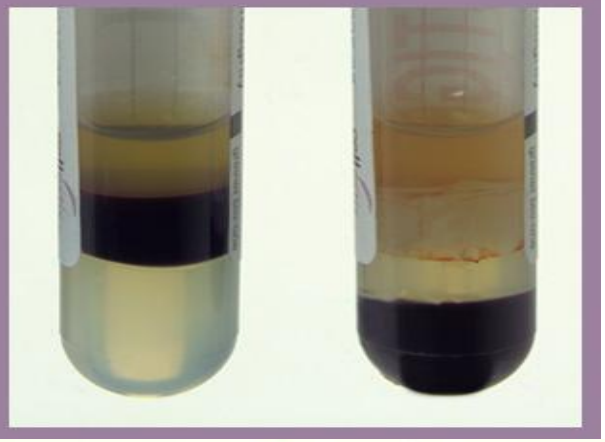
major antigens
ESAT6 and CFP10



RD1 region

T cell tests (interferon-γ)
that distinguish *M. tuberculosis*
infection from BCG vaccination

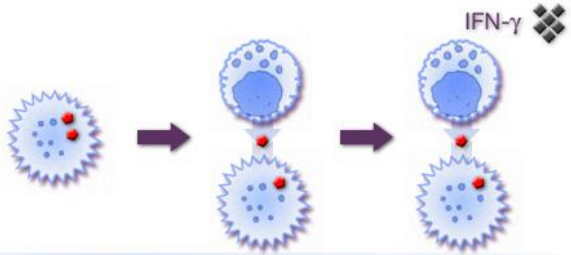
Principal of Quantiferon-Gold *in tube assay*



Antigen Presenting cell encounters antigen

Presenting cell ingests, then digests antigen

AG presentation
(ESAT-6, CFP-10, TB7.7)



Presenting cell presents antigens to specific T-cells. T-cells activate and secrete IFN-γ

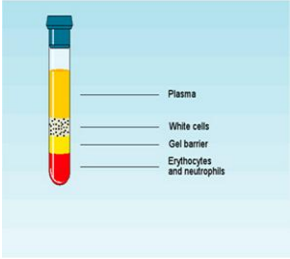
Ag-specific cytokine secretion

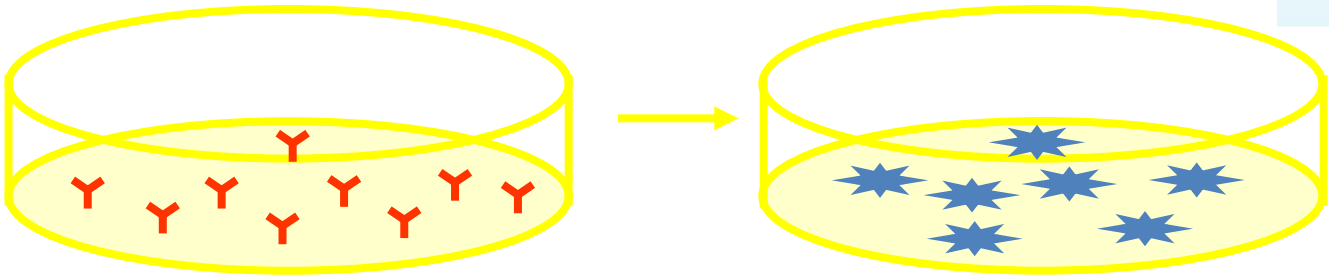
If the antigen is TB-specific, only TB specific T-cells will activate and secrete IFN-γ

TB-specific peptide antigens

Cytokine quantification by ELISA

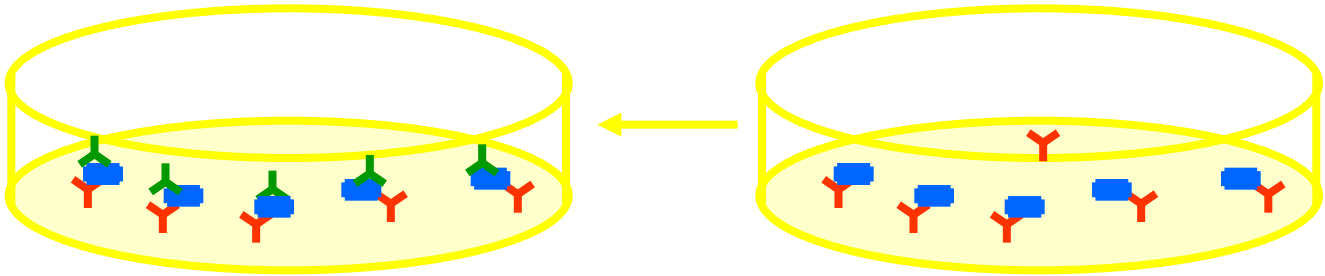
Principal of ELISPOT assay





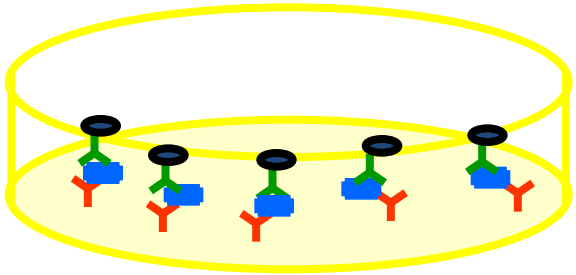
Coating antibody

PBMC+antigen

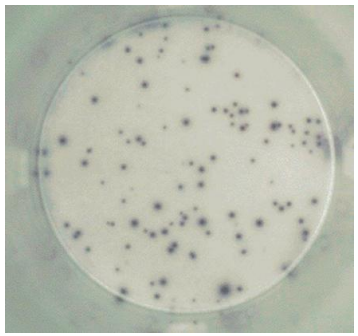


Biotinylated 2nd antibody

IFN-© production



Avidin-peroxidase



each spot is an antigen-specific T cell that has released IFN©

Spot the Difference

Interferon-© release assays (IGRA) in paediatric active and latent tuberculosis in London - a side-by-side comparison with TST

Kampmann B, Whittaker E, Williams A, Walters S, Gordon A, Martinez-Alier N, Williams B, Crook AM, Hutton AM, Anderson ST.

Interferon- gamma release assays do not identify more children with active TB than TST.

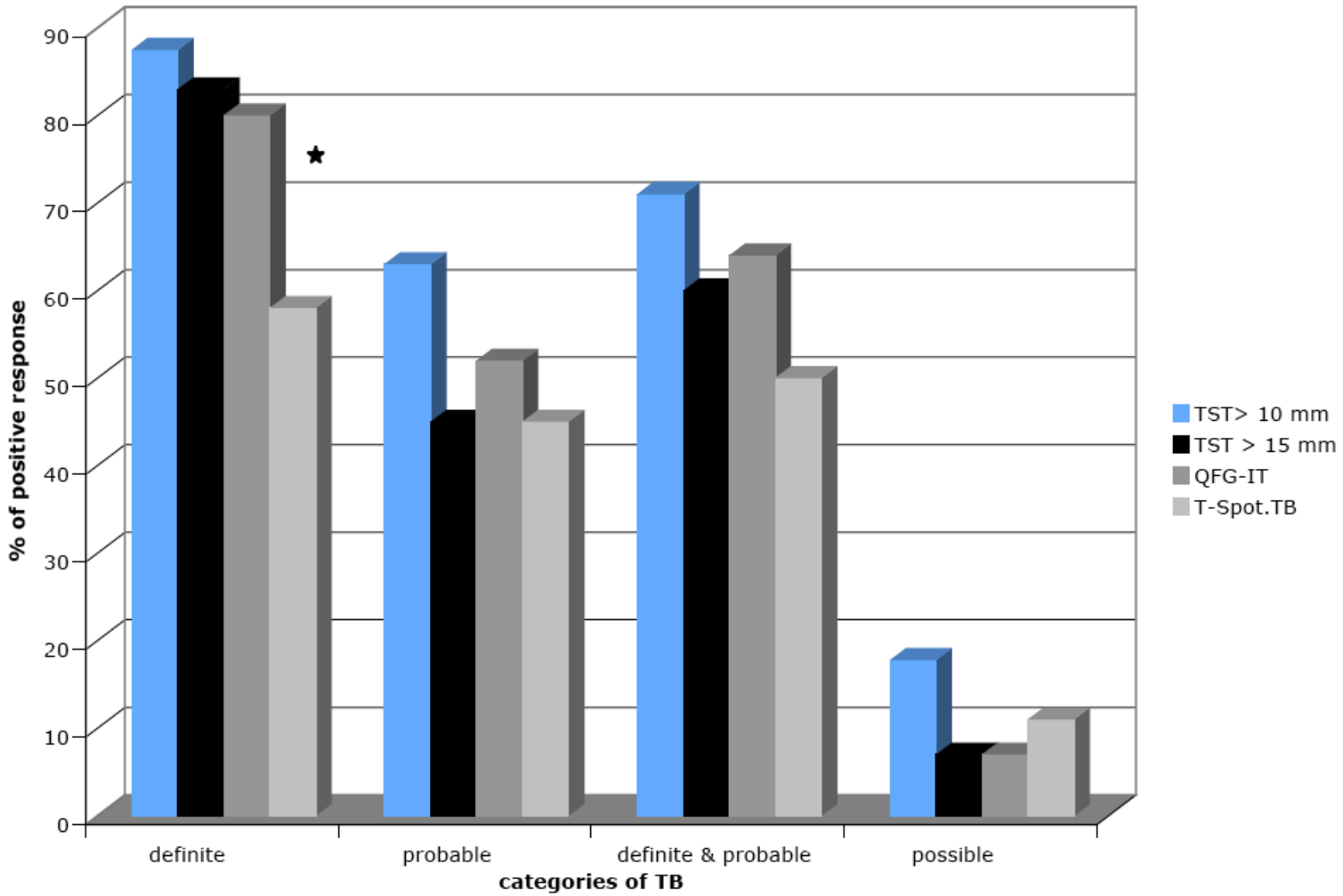
Eur Respir J. 2009 Jun;33(6):1374-8

IGRA and the diagnosis of active TB

	Results (%) of all three test in the different sub-groups of Active TB								
	TST			QFG -IT			Tspot.TB		
	>15	6-15	<6	+	-	Ind	+	-	TF
All active TB (N=91)	43	19	38	46	45	9	38	53	9
Definite (N=25)	83	8	8	80	12	8	58	38	4
Probable (N=38)	45	30	26	52	42	5	45	45	10
Definite & Probable (N=63)	60	21	19	64	29	6	50	42	8
Possible (N=28)	7	14	79	7	79	14	11	79	11

IGRA missed between 20-40% of definite active TB

Combining IGRA and TST in the diagnosis of active TB



A combination of TST and IGRA increases sensitivity to above 93%

A negative IGRA does not exclude active TB

IGRA is not a rule-out test,
but can add value to additional investigations

Diagnosis of TB in children

- Poor microbiology
- Suspicion rather than confirmation
- Treatment dilemma

History of signs and symptoms incl. weight chart
Contact history, incl previous TB treatment in carers, as this could be a reason for drug-resistant strains!
Travel history
BCG status
CXR/(CT chest)
Other radiological investigations, depending of presumed site of infection
Sputum/gastric washings/induced sputum
Mycobacterial blood culture (BacTec) with routine investigations of constitutional symptoms
Mantoux test
Exclusion of active (viral/bacterial) infections **Consider HIV-coinfection**
Interferon-gamma-release assays such as T Spot, Quantiferon where available
Close link with Tb services re contact tracing and any results of drug sensitivities/resistance patterns of strains in members likely to have been the index case **TB is a family disease**

Management of our case:

- Admitted to the ward, started on quadruple anti-TB medications plus ceftriaxone
- Progressive respiratory deterioration- intubated and transferred to St.Marys PICU on 23/09/11

TB treatment in children

- Treatment regimens are adopted from adult schemes
- Children respond very well to treatment, incl DOTS
- Dosages need to be adjusted for weight
- Pharmakokinetics in children differ from adults
  - INH 10-15 mg/kg, rapid acetylators (1)
  - Ethambutol 15-25 mg/kg (2)
  - Rifampicin 10-15 mg/kg
  - Pyrazinamide 30-35 mg/kg

1: Schaaf et al, Arch Dis Child 2005; 90:614
2: Donald et al, Int J Tuberc Lung Dis 2006; 10:1318

Drugs and ADHERENCE

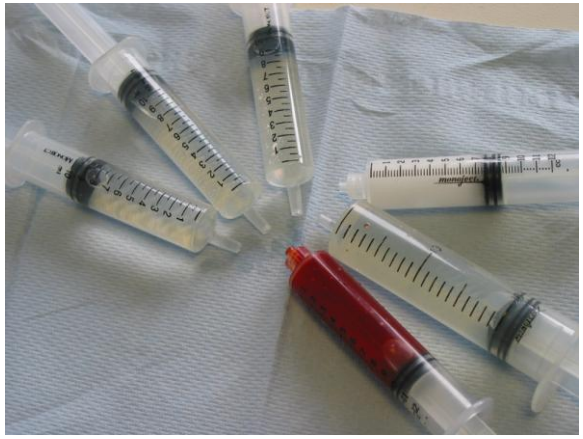
IF YOU DON'T TAKE THE DRUGS, THEY WON'T WORK

PAEDIATRIC TB

POOR ADHERENCE

Support

- -hospital TB clinic
- -community
  - -health care workers
  - -social services
- -DOT (Directly Observed Therapy)
  - -accurate record of treatment
  - -successful treatment
  - -prevention of resistance
  - -different adult
  - -different location



PROGRESS

- Intubated and ventilated, air entry-better, lungs improving
- CVS-stable
- Low grade temperature
- NGT + IV Fluids
- Medications- HRZE, Pyridoxine

- Now: off ITU, doing well, chest much improved

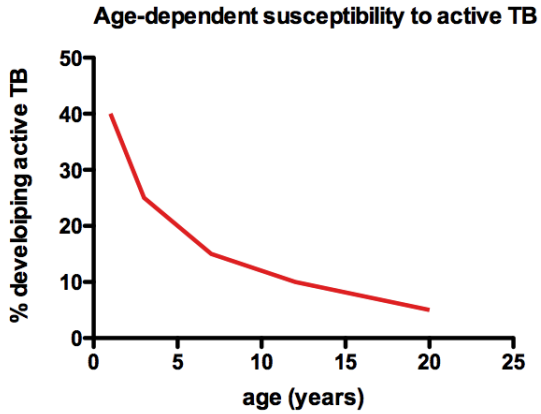
Any issues with this case??

Missed opportunity for the patient and the community?

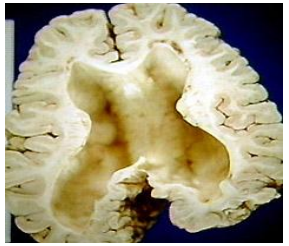
Tuberculosis in children

is transmitted from adult contacts

susceptibility is age dependent



can have severe manifestations



can be prevented by chemoprophylaxis

Who needs chemoprophylaxis?

Children with evidence of infection following exposure

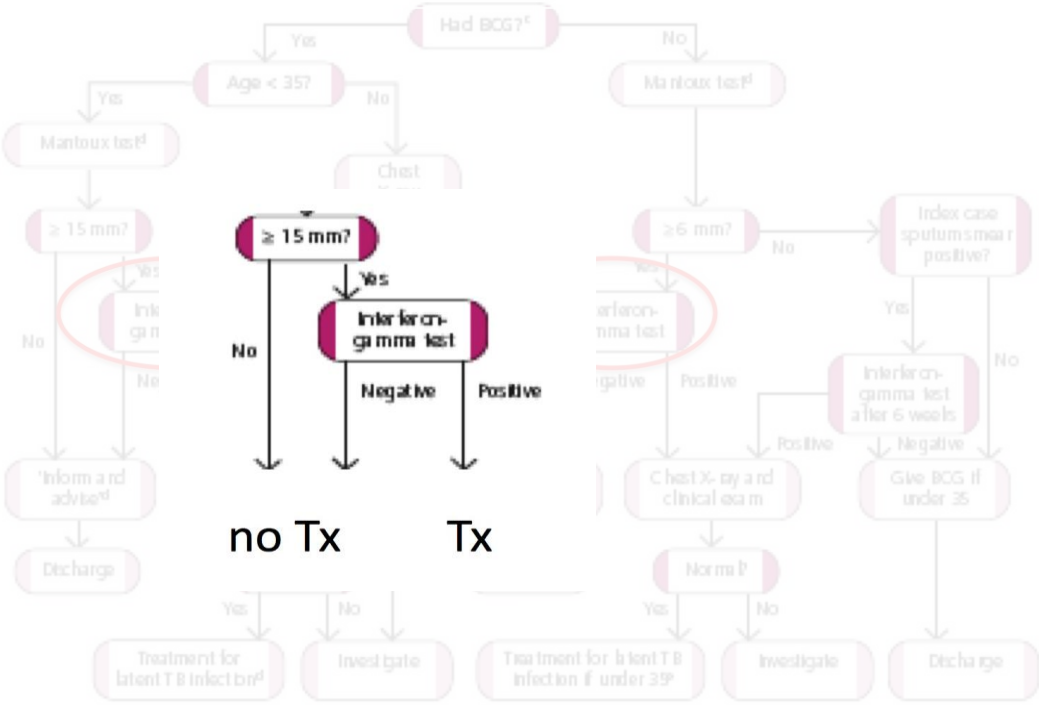
Infection with mycobacteria

TST

IGRA

Infection with *M.tuberculosis*

NICE 2006



Major change in policy

avoids unnecessary drug exposure

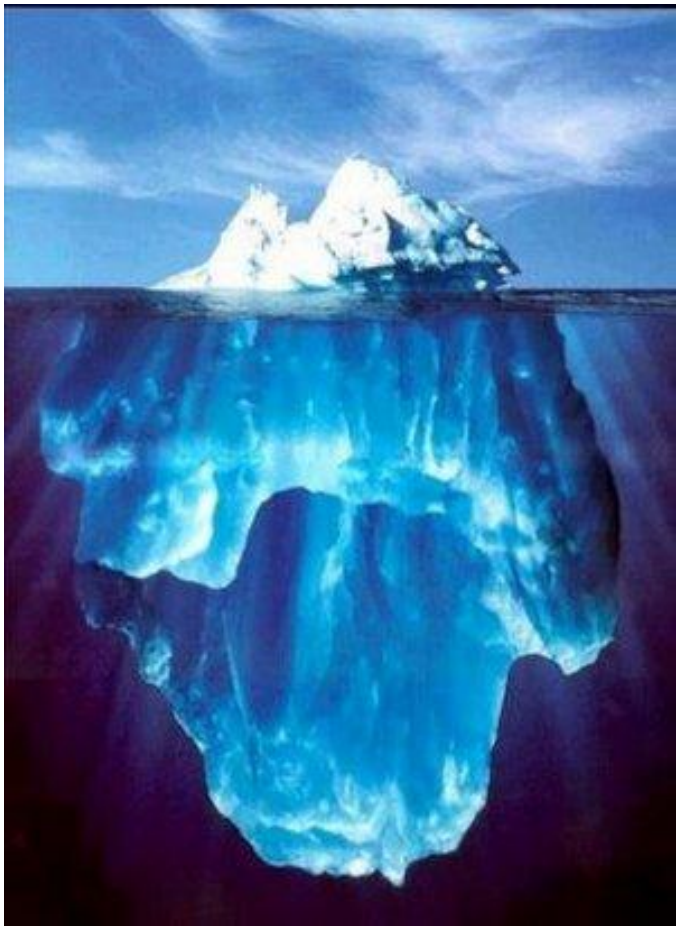
limited experience with IGRA negative predictive value?

London pilot data (n=200)

6% of all children:	TST-/IGRA+
60 % of children under 2:	TST+/IGRA-
16% of children over 2:	TST+/IGRA-

Is this approach safe for children?

What are we currently missing?



Active TB

Latent TB

TB Exposure

No data that link exposure/infection to disease

CHILDHOOD EXPOSURE

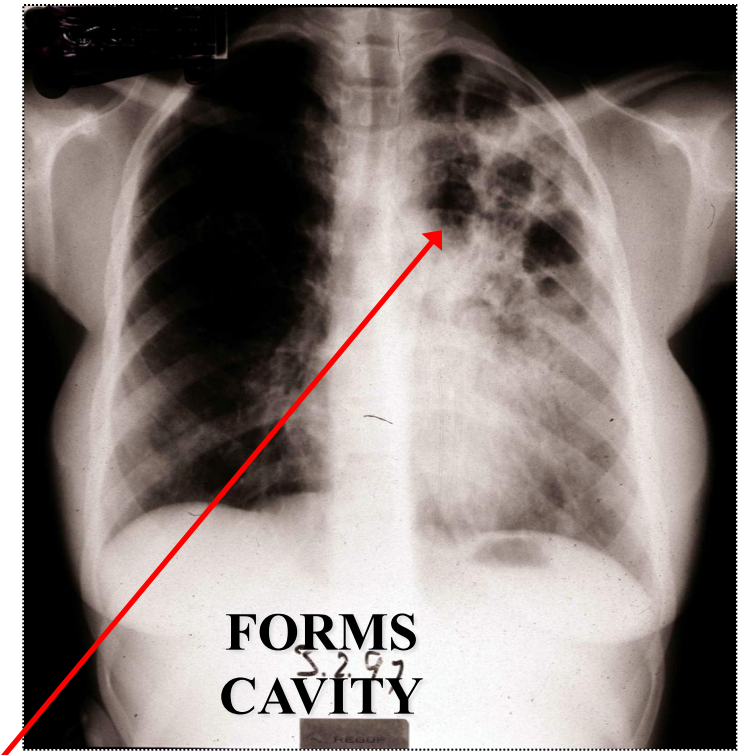
PRIMARY PULMONARY INFECTION

Successful immune response

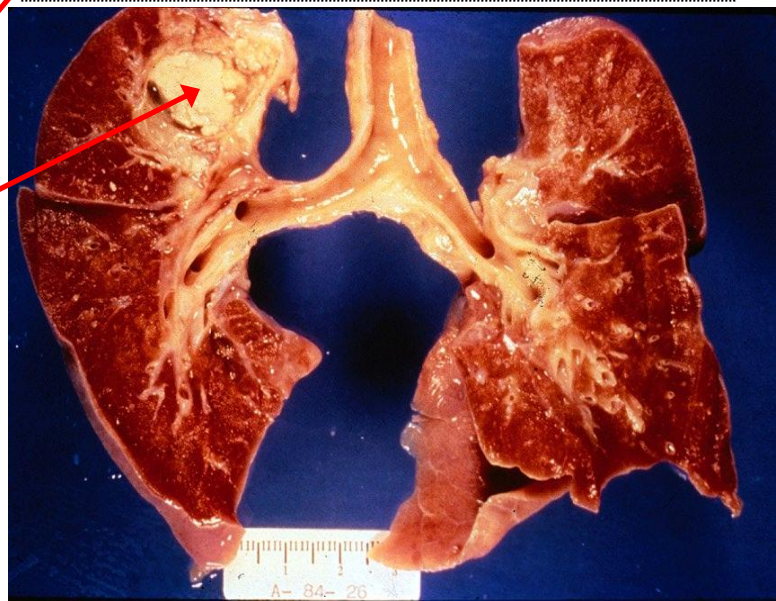
WELL ADULT

IMMUNITY (live MTB)

LATE REACTIVATION OF PULMONARY DISEASE



FORMS CAVITY



Does contact tracing work?

Q1.2

How can the contacts at greatest risk of tuberculosis be identified?

- LTBI initial yield by contact factors
- In all contacts, by age and HIV status

	Included studies	Contacts investigated	Cases found	Prevalence (%) [95% CI]
All contacts	82	74,358	40,521	45.9% (41.3-50.6)
Child contacts <5y	35	13,784	5,256	30.0% (23.4-37.5)
Contacts 5-14y	23	12,673	6,595	44.0% (30.8-58.0)
HIV+ contacts	4	108	41	41.2% (23.9-61.1)

Q1.2

How can the contacts at greatest risk of tuberculosis be identified?

- TB initial yield by contact factors
- In all contacts, by age and HIV status

	Included studies	Contacts investigated	Cases found	Prevalence (%) [95% CI]
All contacts	78	898,619	38,209	3.5% (2.3-5.4)
Child contacts <5y	21	6,617	856	9.6% (5.5-16.0)
Contacts 5-14y	11	5,366	300	4.5% (1.6-12.3)
HIV+ contacts	5	282	79	28.4% (9.8-59.2)

NIKS
NIHR IGRA Kids Study

NHS
National Institute for Health Research

Aims of the project

1. To determine if it is safe to withhold chemoprophylaxis from children exposed to TB with negative IGRA but positive TST

Prospective cohort study

2. To link TB exposure, infection and outcome in children by adapting the existing data collection tool

Contact module

mcrn
Medicines for Children Research Network

Health Protection Agency

Design

TB exposed children (n=600)

↓

TST and IGRA at screening/3 months

↓

TST+ve/IGRA-ve followed for 2 years

↓

Primary endpoint: Development of active TB
(Nice: how safe are the guidelines?)

Secondary endpoint: how concordant are TST and IGRA
(Nice: is the step-wise screening approach justified?)

Patient benefit

- Evidence- base for NICE recommendations
- Contact module that allows linking of exposure, infection and disease
- Improved clinical and epidemiological framework for the care for children with TB

PTB-NET (UK)

Clinical **R**esearch **N**etwork

- microbiological and immunological sample collections
- future studies of immunopathogenesis, novel TB diagnostics and therapeutics, incl. MDR TB

3/12 old baby,
BCG vaccinated at 2 months of age

What do you know about this vaccine?

What do you think of the timing of the vaccination?

Why didn’t the BCG vaccine protect this infant?

Is it worth giving BCG?

Lancet. 2006 Apr 8;367(9517):1173-80.

Trunz BB, Fine P, Dye C.

Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness.

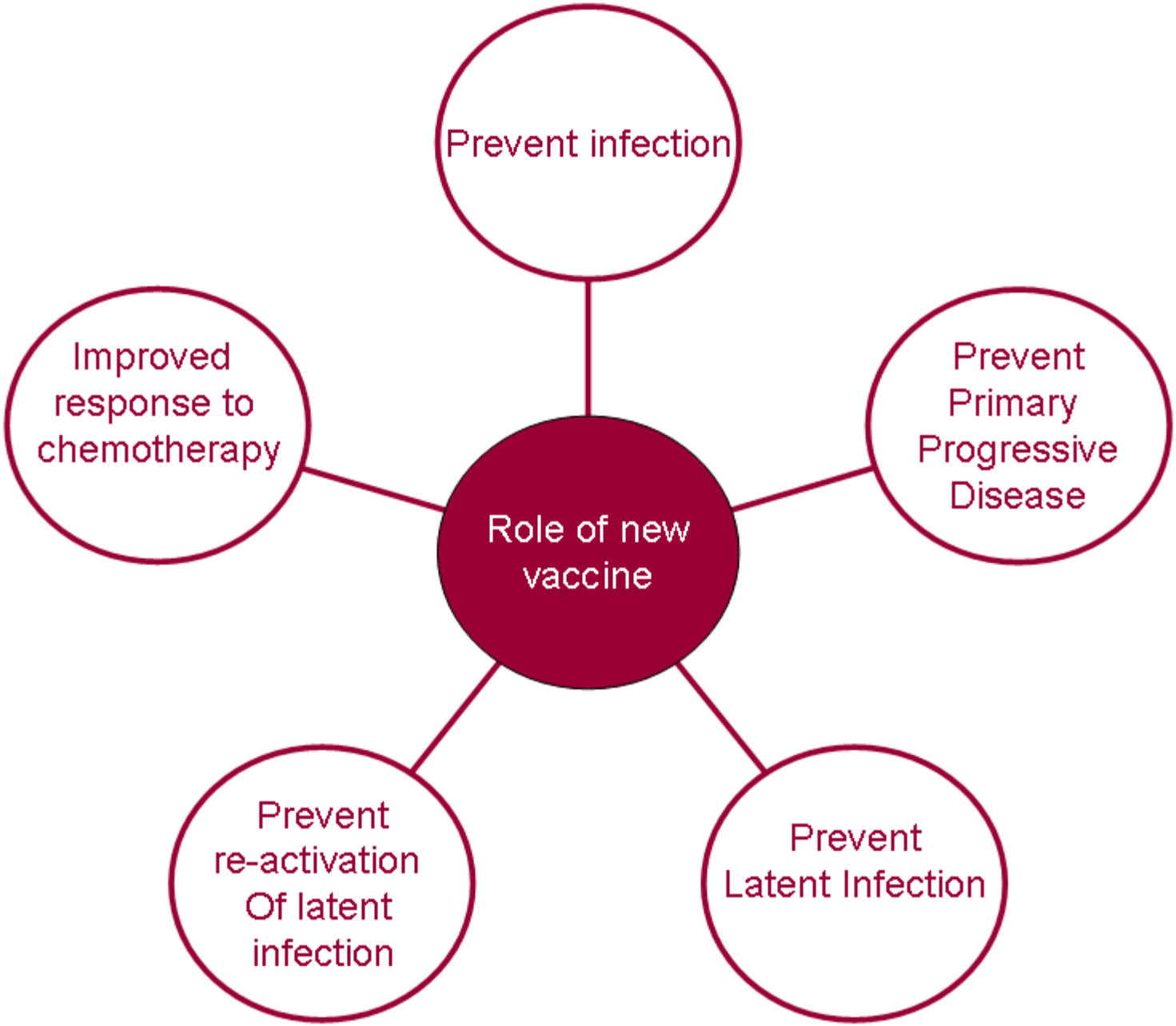
Interpretation:

BCG vaccination is a highly cost-effective intervention against severe childhood tuberculosis; it should be retained in high-incidence countries as a strategy to supplement the chemotherapy of active tuberculosis.

	Publication date	Efficacy (%, 95% CI)	Reference
Tuberculous meningitis			
Buenos Aires, Argentina	1988	98% (70 to 100)	48
Bahia, Brazil	1991	91% (78 to 97)	49
São Paulo, Brazil	1990/93	87% (72 to 94)	50,51
São Paulo, Brazil	1990/93	92% (65 to 98)	50,51
Belo Horizonte, Brazil	1988	81% (47 to 93)	52
Belo Horizonte, Brazil	1988	65% (17 to 86)	52
Yangon, Burma	1987	52% (13 to 73)	53
Nagpur, India	1996	87% (70 to 94)	54
Chennai, India	1996	77% (63 to 86)	55
Delhi, India	1996	64% (30 to 81)	56
Delhi, India	1989	84% (69 to 97)	57
Lucknow, India	1999	47% (–6 to 74)	58
Papua New Guinea*	1980	58% (–36 to 87)	59
Delhi, India	1993	56% (–49 to 87)	60
Summary efficacy		73% (67 to 79)	
Miliary tuberculosis			
Buenos Aires, Argentina	1988	78% (28 to 93)	48
Yangon, Burma	1987	80% (45 to 92)	53
Papua New Guinea*	1980	70% (0 to 91)	59
Djakarta, Indonesia	1983	75% (5 to 94)	61
Summary efficacy		77% (58 to 87)	

*Not designed as a case-control study.

Table 3: Meta-analysis of BCG efficacy against tuberculous meningitis and miliary tuberculosis from case-control studies


Prevent infection
Improved response to chemotherapy
Role of new vaccine
Prevent Primary Progressive Disease
Prevent re-activation Of latent infection
Prevent Latent Infection

New vaccines on the horizon

- Four main types of vaccines are currently under development:

1. **Vaccines based on BCG**
2. **Subunit (protein and peptide) vaccines**
3. **DNA vaccines**
4. **Live attenuated and inactivated whole cell vaccines**

E.Whittaker & B.Kampmann, Vaccines in Practice, 2011

Take Home messages:

- Think of the diagnosis, especially in the epidemiological context

- TB is a family disease

- The diagnosis of active TB in children is based on a jigsaw of findings

- IGRA can be an additional piece in the jigsaw, but a negative IGRA does not exclude active TB

- TB therapy needs a lot of support

- Contact screening is important

Comprehensive review of childhood TB in Paediatric Resp Rev 2010

ptbnet
pediatric tuberculosis network european trials group

- founded in April 2009
- to date: 60 members from 16 European countries, incl. Eastern Europe
- includes clinicians, epidemiologists and laboratory scientists

www.ptbnet.org

Aims

- enhance the understanding of the **pediatric aspects** of tuberculosis
- facilitate **collaborative research studies** for childhood TB in Europe
- provide **expert opinion** through excellence in science and teaching
- establish a better **evidence base** for diagnosis and treatment of TB in children

Thank you

Any questions?

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