Childhood Tuberculosis

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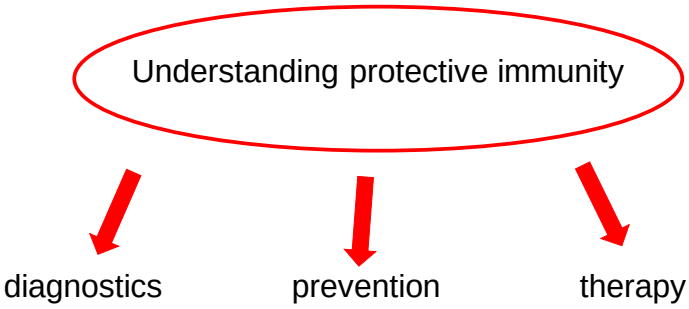
Outline of my talk

- the scale of the problem internationally
- what differs in TB between children and adults
- how do these differences impact on presentation, diagnosis and management
- particular challenges with TB in children
  - Extrapulmonary TB- example of TB meningitis
  - prevention through TB Vaccines (update and outlook)
  - MDR TB in children- gaps and an illustrative case
- Summary and research priorities

Is Tuberculosis a problem?

3 Mio estimated deaths per year, ca. 0.5 Mio cases in children

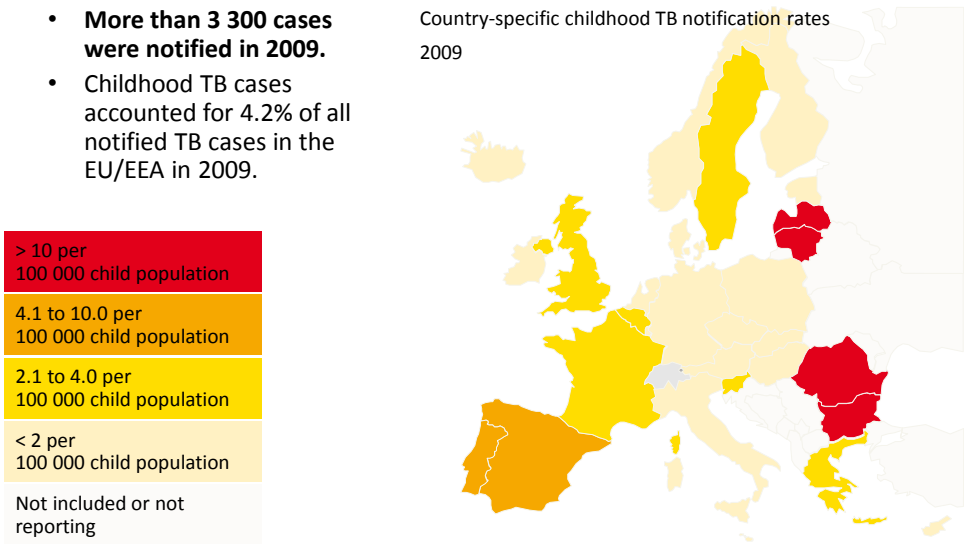
What are we missing and why do we need TB research



Europe: where do the childhood cases come from?

- **More than 3 300 cases were notified in 2009.**
- Childhood TB cases accounted for 4.2% of all notified TB cases in the EU/EEA in 2009.

Country-specific childhood TB notification rates 2009

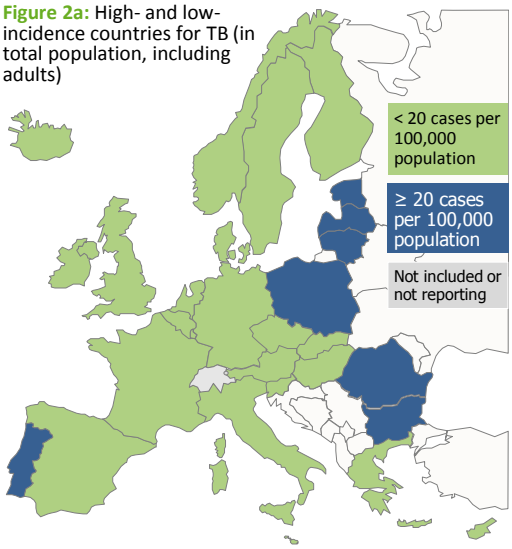


•Sandgren, ECDC, Euro Surveill. 2011 Mar 24

Childhood TB is a marker of transmission in the community

- **In certain EU settings, childhood TB is on the rise.**
- As children have a higher rate of primary progression to TB upon infection, TB in this vulnerable group is a sign of recent transmission.
- Trends in notification of childhood TB indicate that transmission to children is still occurring within the borders of the EU, particularly in low-incidence countries.
- TB is a family disease

Figure 2a: High- and low-incidence countries for TB (in total population, including adults)



•Sandgren, ECDC, Euro Surveill. 2011 Mar 24

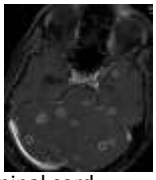
What can we do about it?

- Make an accurate diagnosis of active TB in adults and children and treat them promptly and with the appropriate drugs
- Contact-tracing in households and communities
- Screening of TB exposed individuals and treatment of LTBI in children
  - ? With what tests??
  - What is the role of the immune system?

Central Nervous system (CNS) tuberculosis

- constitutes around 13% of all cases of EPTB in children and complicates the clinical course of TB in 0.5 – 2% of cases

- Serious neurological sequelae develop in almost 50% of cases and overall mortality is about 13%.



- **Mechanism of disease:**
- Seeding of TB bacilli in the CNS
- formation of small subpial and subependymal foci in the brain and spinal cord (Rich foci)
- Rupture of Rich foci and release of bacteria into the subarachnoid space (meningitis)
- In some individuals, Rich foci enlarge to form tuberculoma

DD: bacterial meningitis, fungal (crypto in HIV), poss viral, other CNS disease

Key Ix: LP (CSF: high protein, low Glucose, lymphocytes), imaging (MRI better than CT)

What determines dissemination?

The exact mechanisms that determine the clinical outcomes following infection in children are not completely understood, but include

genetic susceptibility

younger Age- Immuno-regulation in healthy children depends on age?

underlying cell-mediated immunity, i.e. **HIV, other causes of immunosuppression**
-the lower the CD4 count the higher the risk for TB and also disseminated forms

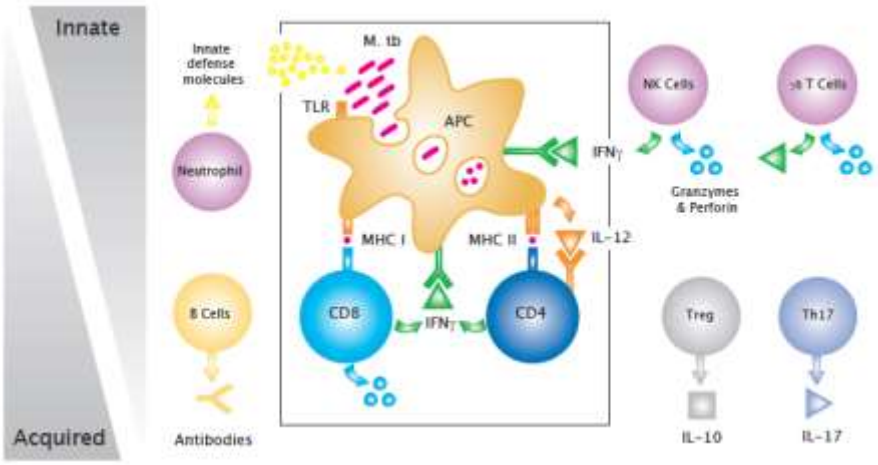
nutritional status:
studies indicate that malnutrition decreases T-cell function, cytokine production, and the ability of lymphocytes to respond appropriately to cytokines

Possibly **microbial virulence**- not all MTb strains are the same….

vaccination status- BCG vaccine adds to protection- for how long??

However, the same factors also predispose to pulmonary TB

Key immune mechanisms involved in control of *Mycobacterium tuberculosis (M.tb)*



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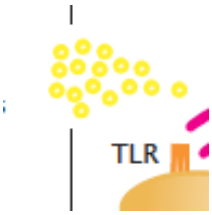
Jones et al; Review of Immunopathogenesis of childhood TB, PRR 2010

Innate responses: Differences in children

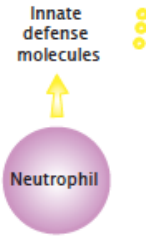
Antimicrobial peptides, proteins, TLR's
Few data in children, possibly reduced TLR-responsiveness in the very young
Caron et al, Neonatology 2010
Levy et al, Nat Immunol 2011



Collectins, Complement and complement receptor
levels differ according to age
Cosar et al, Eur. J. Clin. Microbiol. Infect. 2008

Neutrophils
Martineau et al
J Clin Invest. 2007
J Immunol. 2007

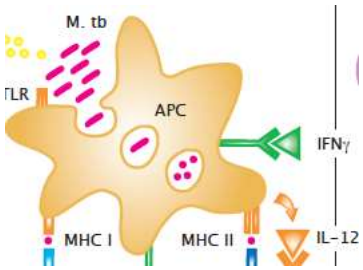
No data in TB/children yet



Antigen-presentation: differences in children

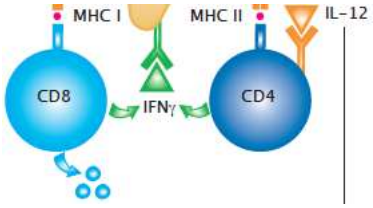
Macrophages:
deficient phagocytic function
Smith et al, J. Pediatr. 1997

Dendritic cells:
fewer circulating DC's,
reduced functional capacity
Upham et al, Infect. Immun. 2006



Adaptive responses

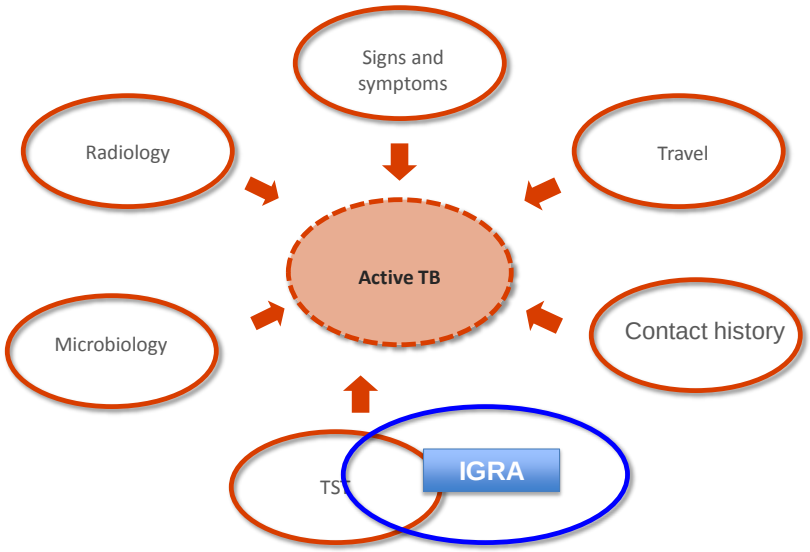
CD4 T cells:
reduced AG-specific production of Cytokines
Swaminathan S et al, Clin. Infect. Dis. 1999
Upham et al, Infect. Immun. 2002



CD8 T cells: few studies in children, but fewer CD8 responses to HIV peptides compared to adults
Luzuriaga et al, J. Immunol. 1995

Important in the context of HIV infection & vaccine responses as well as TB- diagnostics
Tena et al, JID 2003
Kampmann et al, I&I 2004
Kampmann et al, AIDS 2006, Kampmann et al ERJ 2009
Tena-Coki NG et al, AJRCCM 2010

The diagnosis of active TB in children: a jigsaw



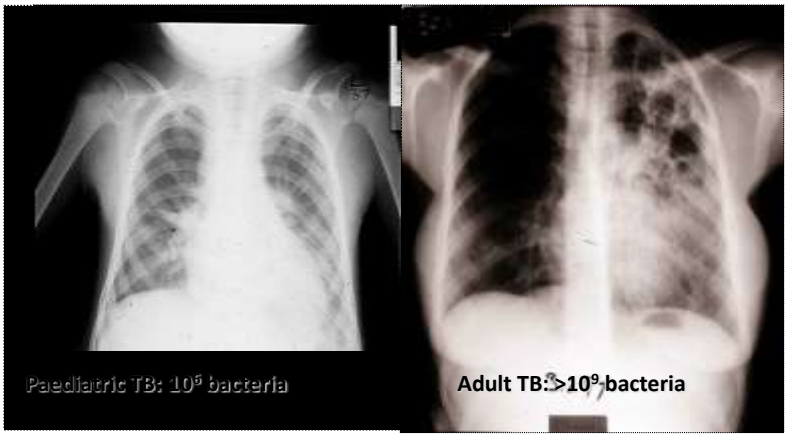
Diagnostic tests

Microbiological

Organism

smear culture molecular

PAEDIATRIC TB: Implications of bacterial load



paucibacillary, rarely culture confirmed :

Sputum smear positive in 10.3% (10-14yr), 1.8% (5-9) and 1.6% (<5)

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

- children less infectious

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

Mark P Nicol, Lesley Workman, Washiefa Isaacs, Jacinta Munro, Faye Black, Brian Eley, Catharina C Boehme, Widaad Zemanay, Heather J Zar

Results in 452 children (median age 19·4 months, IQR 11·1–46·2) 108 children (24%) had HIV infection.

27 children (6%) had a positive smear result, 70 (16%) had a positive culture and 58 (13%) had a positive MTB/RIF test result.

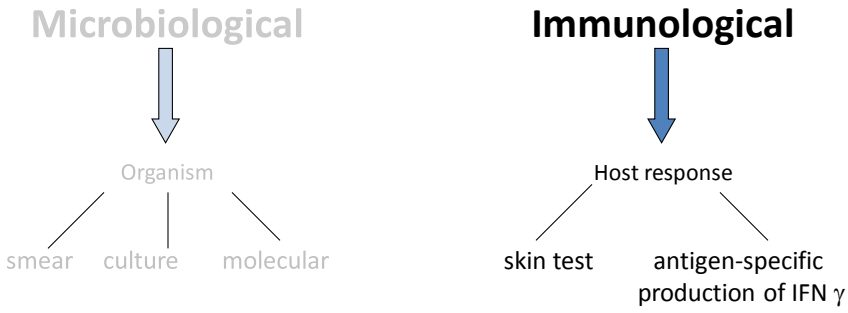
MTB/RIF tests when done **on two induced sputum samples** detected twice as many cases (75·9%, 95% CI 64·5–87·2) as did smear microscopy (37·9%, 25·1–50·8)

The specificity of MTB/RIF was 98·8% (97·6–99·9).

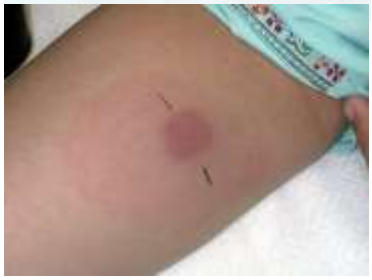
MTB/ RIF results were available in median 1 day (IQR 0–4) compared with median 12 days (9–17) for culture (p<0·0001).

But: only 16% had a positive culture!!!

Diagnostic tests

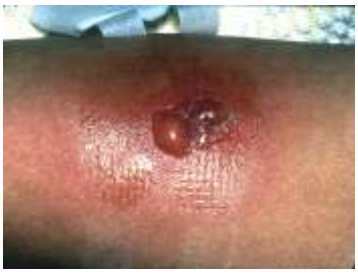


Tuberculin skin test (TST)



- 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



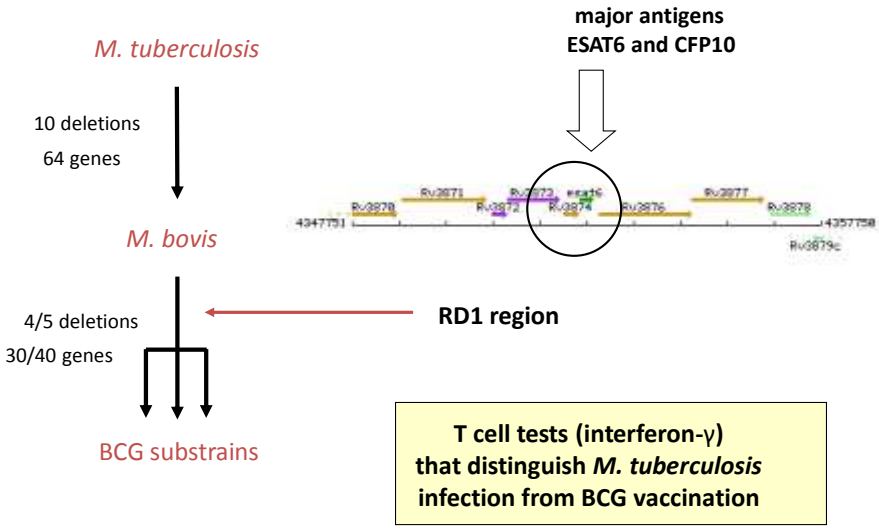
? Impact on TB diagnostics such as IGRA's?

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

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

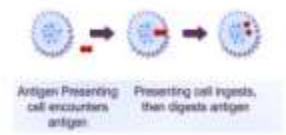
but:
Paucity of data in children
Confusion about use of IGRA

Gene deletions and the origin of BCG

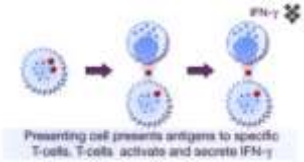


T cell tests (interferon-γ) that distinguish *M. tuberculosis* infection from BCG vaccination

Principal of Quantiferon-Gold *in tube assay*



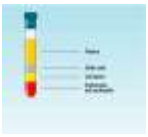
AG presentation
(ESAT-6, CFP-10, TB7.7)

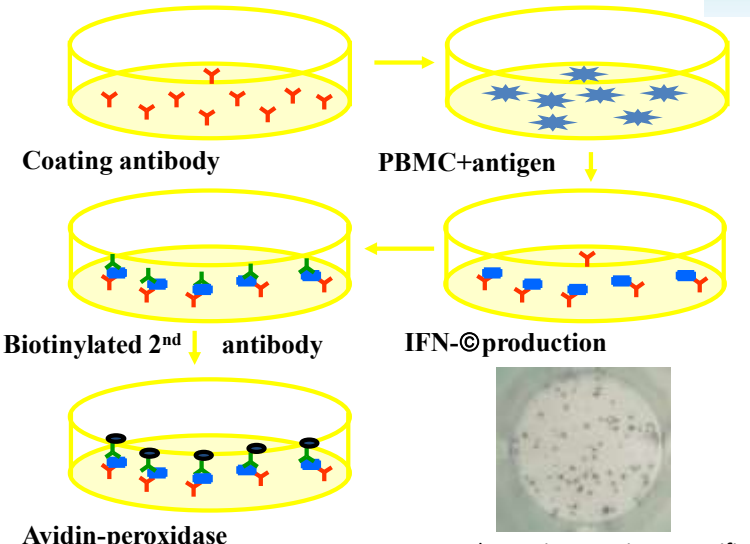


Ag-specific cytokine secretion

Cytokine quantification by ELISA

Principal of ELISPOT assay





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

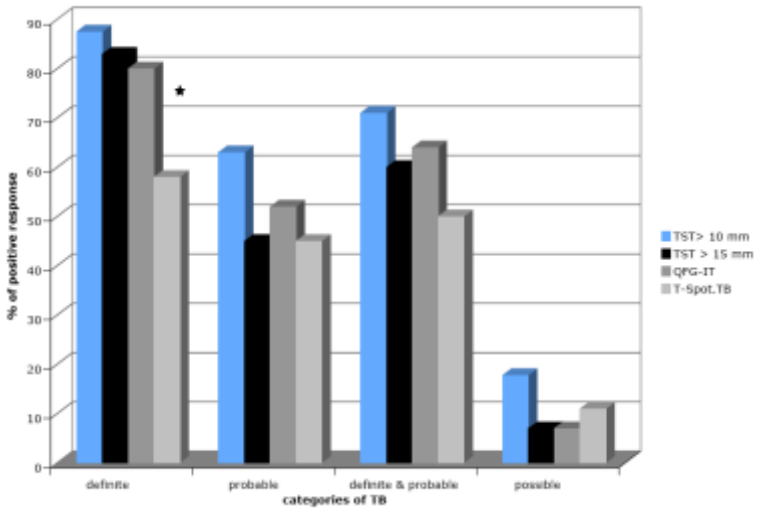
Kampmann B, Whittaker E, Williams A, Walters S, Gordon A, Martinez-Alier N, Williams B, Crook AM, Hutton AM, Anderson ST.
Interferon- gamma release assays do not identify more children with active TB than TST.
Eur Respir J. 2009 Feb 5

IGRA and 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



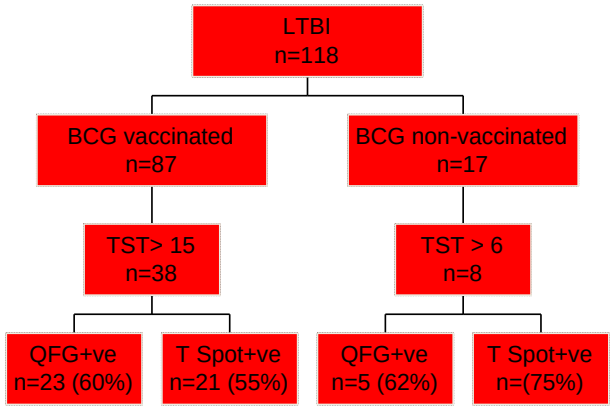
A combination of TST and IGRA increases sensitivity to above 93%

IGRA and the diagnosis of active TB

A negative IGRA does not exclude active TB

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

LTBI: BCG, TST and IGRA



More +ve TST than IGRA
Good agreement between 2 IGRAS (92%, k=0.82)

IGRA and the diagnosis of latent TB

- **No "gold standard" for LTBI**
- **Acknowledged discrepancy of TST and IGRA results**
  - due to poor specificity of TST
  (Kampmann ERJ 2009, Connell PlosOne 2008, Bianchi PIDJ 2009)
- **Which IGRA is better?**
  - Good agreement between 2 IGRAS (92%, k=0.82)
  (similar to Connell et al, PLoS One. 2008 Jul:
  agreement between QFT-IT and T-SPOT.TB 93%, k=0.83).
- **Performance in very young children- conflicting messages**
  Indeterminate results in 3.6% in <5years, 1% in >5 years
  (data from our study of > 1000 children in Europe) published in AJRCCM June 2012
- **Increased sensitivity in immuno-compromised hosts compared with TST**

Remaining questions and further research

Should we abandon the TST in screening for LTBI ?

- **How do we interpret indeterminate results**
- **Negative predictive value, i.e.**

  How many children will develop active TB if TST > 15 mm, but untreated with chemoprophylaxis as IGRA negative, according to current guidelines
- **Is the step-wise approach of TST first, IGRA second justified**?

  How many children with negative TST would have a positive IGRA at screening
- **Does the TST boost the IGRA responses**

  Current evidence suggests that boosting occurs, but not within first 72 hours
- **(Short-term) reproducibility of the commercial IGRA**

  Can IGRA be used to monitor therapy or to predict development of active TB?

Conclusions

- **IGRA should not currently replace the TST in children**
- **we should not forget the many additional challenging question in childhood TB**

better microbiological diagnostics
better biomarkers than IFN©
better vaccines

improved understanding of primary TB

Achievements: Therapy

Pharmacokinetic studies in children resulted in a change in dosing recommendations

Discussions re Fixed Drug Combinations (FDC's) are advancing

Growing appreciation of different metabolism of drugs in children

New anti-TB drugs entering late-phase clinical trials-
but no children included-yet

Challenges/bottlenecks: therapy

Drug regimens for children derived from adult protocols

No TB drug trials in children, or only small numbers

New drugs not tested in children

Little coherence for MDR management, incl. prophylaxis

Few pharmacokinetic studies

Age/weight-related studies needed

In the meantime….

Prevention is better than cure

Prophylactic therapy

New vaccines

We have a vaccine against TB, but is it worth giving it?

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

BCG: More than protection from disseminated disease?

Our data suggest that BCG vaccination may reduce the risk of TB infection by > 50%

Greece (491=43.5%)
Spain (459=40.7%)
UK (110=9.8%)
Italy (42=3.7%)
Bulgaria (26=2.3%)

1128
Asymptomatic
children

↓

Tuberculin Skin Test + Interferon Gamma Release Assay

↓

Multi-variate analyses: age, vaccination status and gender as predictor variables of results.

BCG vaccination associated with negative IGRA
Quantiferon Gold In-Tube: OR=0.41, p<0.001
T-SPOT.TB: OR=0.41, p<0.001

Basu Roy, Kampmann Am J Respir Crit Care Med. 2012 186(4):378-84

So,why do we need a new vaccine?

Globally, the TB mortality rate has fallen by 41% since 1990 and the world is on track to reach the global target of a 50% reduction by 2015

"Vaccines are Public Health's best buy!"

Low income countries require $ 0.2-0.3 billion per year to reach Global Plan targets

In 2011, there were an estimated 8.7 million new cases of TB (13% co-infected with HIV) and 1.4 million people died from TB, incl. 70 000 children

WHO TB report 2012

What could be achieved by a vaccine against TB?

Concepts of action of new TB vaccines

- Four main types of vaccines are currently under development:

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

(4. DNA vaccines)

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

The results of the first large scale Phase IIb trial of a new TB vaccine are now published:

Prime-boost approach: prime with BCG, then boost with MVA85A

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*

Lancet 2013; 381: 1021–28
Published Online
February 4, 2013

Study design:

Randomised

Placebo-Controlled

Double blind

BCG at birth

MVA85A or Placebo (candida AG) X 1 at 4-6/12

Follow up 3 monthly to 37 months

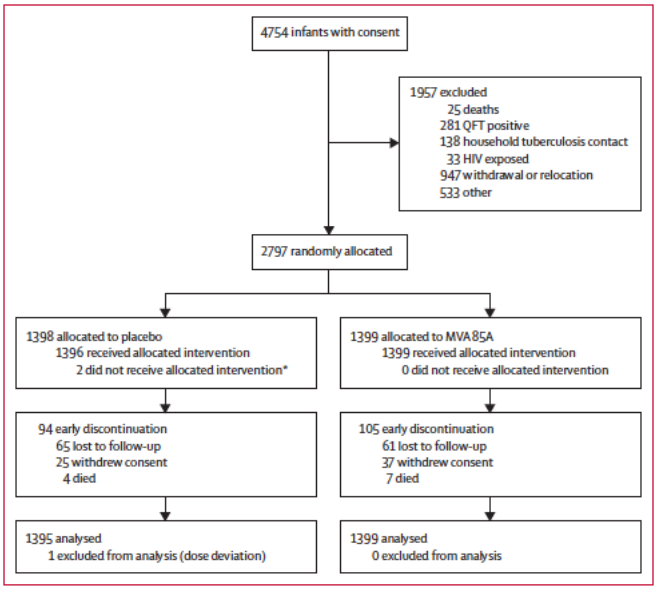


Figure 1: **Trial profile**
*One infant developed gastroenteritis that precluded inclusion and one infant became ineligible after a randomisation error. QFT=QuantiFERON-TB Gold In-tube.

Demographics

	Placebo (n=1395)	MVA85A (n=1399)	Overall (n=2794)
Age, days	145·7 (13·5)	146·6 (14·3)	146·2 (13·9)
Sex, male	714 (51%)	708 (51%)	1422 (51%)
Ethnic group			
Black	267 (19%)	287 (21%)	554 (20%)
Mixed race	1126 (81%)	1107 (79%)	2233 (80%)
Asian	1 (<1%)	3 (<1%)	4 (<1%)
White	1 (<1%)	2 (<1%)	3 (<1%)
Weight			
Infants assessed	1389 (>99%)	1394 (>99%)	2783 (>99%)
Mean, kg	6·47 (0·98)	6·45 (0·99)	6·46 (0·98)
Full-term birth (≥38 weeks)	983 (70%)	1031 (74%)	2014 (72%)

Data are mean (SD) or n (%).

Table 1: **Demographics and baseline characteristics of the per-protocol population**

Primary efficacy endpoint: incident tuberculosis

	Placebo (n=1395)	MVA85A (n=1399)	Vaccine efficacy
Endpoint 1 (primary efficacy endpoint)	39 (3%)	32 (2%)	17·3% (-31·9 to 48·2)
Endpoint 2 (exploratory efficacy endpoint)	52 (4%)	55 (4%)	-6·9% (-56·1 to 26·9)
Endpoint 3 (exploratory efficacy endpoint)	177 (13%)	196 (14%)	-12·1% (-37·4 to 8·5)

Data are n (%) or % (95% CI). Participants with more than one diagnosis were analysed in each level of diagnosis attained. Vaccine efficacy and corresponding 95% CI was estimated with the Cox regression model (1–estimated hazard ratio).

Table 2: **Primary and secondary efficacy endpoints**

Secondary endpoint: protection against infection (measured as IGRA conversion)

Bottom line: no difference in efficacy between vaccine and placebo

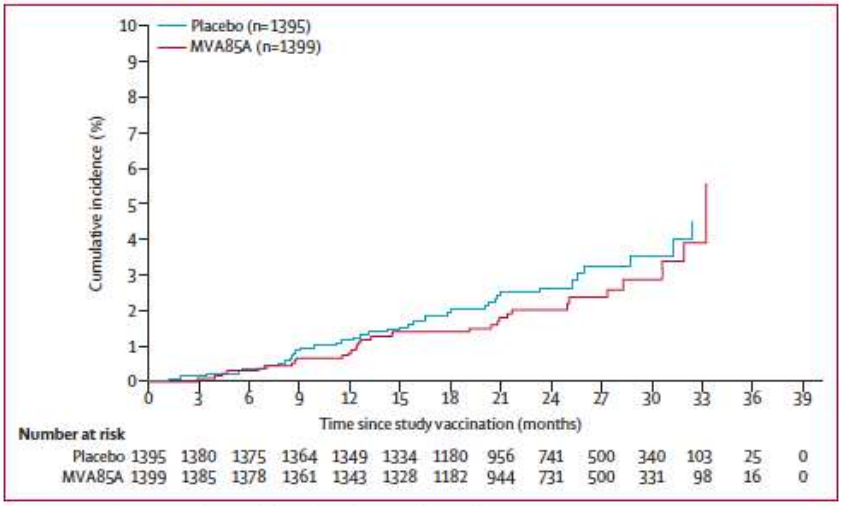


Figure 3: **Cumulative incidence of diagnosis of tuberculosis endpoint 1**

Immunogenicity data

- CD4-positive T cells induced by MVA85A did not correlate with protection against TB or M.tb infection
- Frequencies in infant were only a 10th of those observed in adults

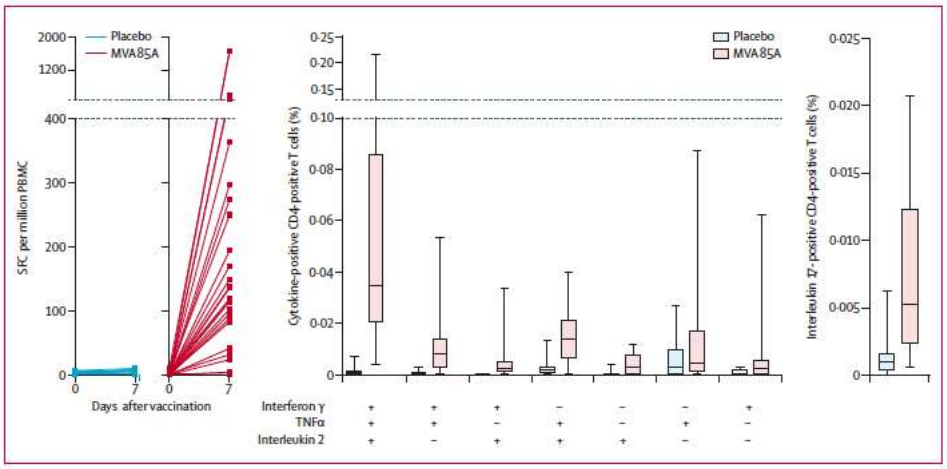


Figure 2: **Vaccine immunogenicity**
(A) Frequencies of Ag85A-specific T cells measured by interferon-γ enzyme-linked immunosorbent spot assay in infants in study group 2 (27 infants in the MVA85A group and 27 infants in the placebo group) before administration of placebo or MVA 85A (day 0) and 7 days after vaccination. (B) Frequencies of cytokine-expressing Ag85A-specific Th1 (CD4-positive T cells expressing IFN-γ, TNFα, or interleukin 2) and (C) frequencies of Ag85A-specific Th17 (CD4-positive T cells expressing interleukin 17) cells, measured by whole blood intracellular cytokine staining 28 days after administration of placebo or MVA85A to infants in study group four (17 infants in the MVA85A group and 19 infants in the placebo group). SFC=spot-forming cells. PBMC=peripheral blood mononuclear cell.

Was the writing on the wall?

Specific T Cell Frequency and Cytokine Expression Profile Do Not Correlate with Protection against Tuberculosis after Bacillus Calmette-Guérin Vaccination of Newborns

Benjamin M. N. Kagina[1], Brian Abel[1], Thomas J. Scriba[1], Elizabeth J. Hughes[1], Alana Keyser[1], Andreia Soares[1], Hoyam Gamieldien[1], Mzwandile Sidibana[1], Mark Hatherill[1], Sebastian Gelderbloem[2], Hassan Mahomed[1], Anthony Hawkridge[2], Gregory Hussey[1], Gilla Kaplan[3], Willem A. Hanekom[1], and other members of the South African Tuberculosis Vaccine Initiative[1]

[1]South African Tuberculosis Vaccine Initiative, Institute of Infectious Diseases and Molecular Medicine and School of Child and Adolescent Health, University of Cape Town, Cape Town, South Africa; [2]Aeras Global Tuberculosis Vaccine Foundation, Rockville, Maryland; and [3]Public Health Research Institute, University of Medicine and Dentistry of New Jersey, Newark, New Jersey

Am J Respir Crit Care Med Vol 182. pp 1073–1079, 2010

Conclusions: The frequency and cytokine profile of mycobacteria-specific T cells did not correlate with protection against TB. Critical components of immunity against *Mycobacterium tuberculosis*, such as CD4 T cell IFN-γ production, may not necessarily translate into immune correlates of protection against TB disease.

What is needed?

Higher magnitude of responses?

Greater breadth of responses?

A different response altogether?

Looking at other elements of the immune response/ innate responses, ? antibody

Functional growth inhibition assays??

INFECTION AND IMMUNITY, Nov. 2004, p. 6401–6407
0019-9567/04/$08.00+0 DOI: 10.1128/IAI.72.11.6401–6407.2004

Novel Human In Vitro System for Evaluating Antimycobacterial Vaccines

Beate Kampmann,[1,2]* Gwen N. Tena,[3] Shumikazi Mzazi,[3] Brian Eley,[3] Douglas B. Young,[4] and Michael Levin[1,2]

Tuberculosis Vaccines: a strategic blueprint

2012, www.stoptb.org/wg/new_vaccines

Rational selection of TB vaccine candidates:
All vaccine developers need to agree to standardised selection criteria for vaccine candidates

Creativity in research and discovery:
answer the question why some people infected with M.Tb are resistant to TB disease

Correlates of immunity and biomarkers for TB vaccines

Clinical trials: harmonization and cooperation

Critical need for advocacy, community acceptance and funding

Table 1 Tuberculosis vaccine candidates in clinical trials

Clinical trial status	Vaccine name	Description	Type of vaccine	Efficacy tested in NHP and/or Bovine models	Efficacy greater than BCG in NHP/Bovine models
Phase III	DAR-901	Whole cell non-tuberculous mycobacteria	Inactivated mycobacteria	Bovine	No[10]
Phase IIb	MVA85A/ AERAS-485	Modified Vaccinia Ankara vector expressing antigen 85A	Viral vector	NHP and Bovine	No[7 8]
Phase IIb	AERAS-402/ Crucell Ad35	Adenoviral vector expressing antigen 85A, 85B, TB10.4	Viral vector	No	–
Phase II	VPM 1002	Recombinant BCG strain expressing listeriolysin and carrying a urease deletion mutation	Recombinant live attenuated mycobacteria	No	–
Phase II	RUTI	Liposomed fragments of Mtb	Whole cell vaccine	No	–
Phase II	M72	Recombinant fusion protein of Mtb antigens RV1196 and Rv0125 with AS01 adjuvant	Recombinant protein	NHP	Yes[11]
Phase II	H1-IC31	Recombinant fusion protein of Mtb antigens 85B, ESAT-6 with IC31 adjuvant	Recombinant protein	No	–
Phase I	AdAg85A	Recombinant adenoviral vector expressing antigen 85A	Viral vector	Bovine	No[5]
Phase I	AERAS-422	Recombinant BCG strain expressing mutation PhoA and Mtb antigens 85A, 85B and TB10.4	Recombinant live attenuated mycobacteria	No	–
Phase I	rBCG30	Recombinant BCG strain expressing Mtb antigen 85B	Recombinant live attenuated mycobacteria	No	–
Phase I	1269/GLA-SE	Recombinant fusion protein of Mtb antigens Rv2608, Rv3619, Rv3620 and Rv3813 with GLA-SE adjuvant	Recombinant protein	No	–
Phase I	H4-IC31	Recombinant fusion protein of Mtb antigens 85B, TB10.4 with IC31 adjuvant	Recombinant protein	No	–
Phase I	H1-CAF01	Recombinant fusion protein of Mtb antigens 85B, ESAT-6 with CAF01 adjuvant	Recombinant protein	No	–
Phase I	H56-IC31	Recombinant fusion protein of Mtb antigens 85B, ESAT-6 and Rv2660 with IC31 adjuvant	Recombinant protein	NHP	No[19]

Mtb, Mycobacterium tuberculosis; NHP, non-human primate; BCG, Bacillus Calmette-Guerin.

Lalvani A, *et al*. *Thorax* 2013;**0**:1–3

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Opportunities for human host studies to elicit the elusive correlates of protection:

- Look at naturally occurring "protected" groups:

Household cohorts with exposed, uninfected children/adults

Frequently exposed healthcare workers who remain well

- TST+ve (*long-term protected from disease?*)
- TST-ve (*resistant to infection*)

Tuberculosis Vaccines: a strategic blueprint

2012, www.stoptb.org/wg/new_vaccines

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What are we currently missing in PH?

Active TB

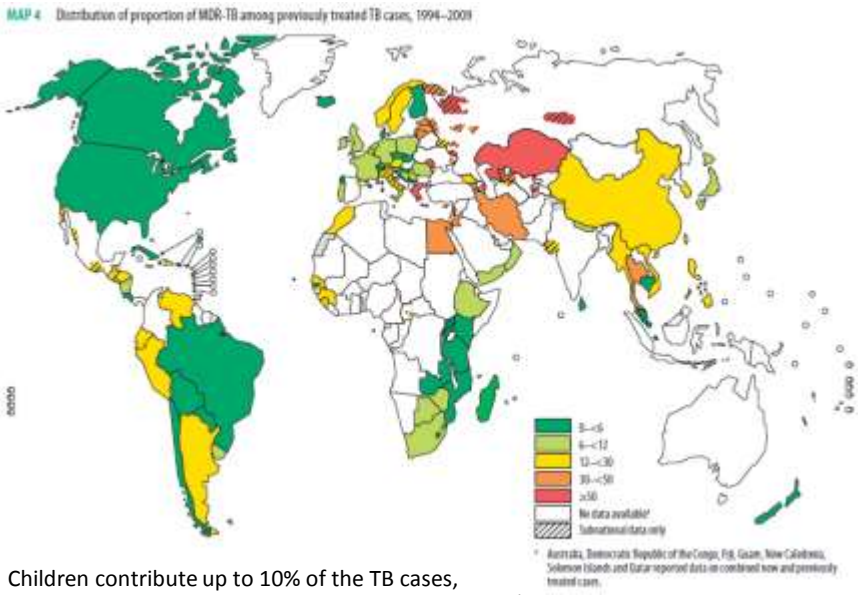
Latent TB

TB Exposure

No data that link exposure/infection to disease
This is a problem for our Mx of MDR TB

MDR TB

- 2008 - 440,000 (3.6%) cases of MDR-TB in the world
- The largest absolute numbers – China and India (50% of the World's MDR)
- 8 countries reported rates >10% (6 countries in EE and Central Asia)
- 5.4% of all the cases of MDR-TB reported were found to be XDR-TB
- The largest rates – Eastern Europe



Children contribute up to 10% of the TB cases,
There is no reason to think, this is different for MDR/XDR cases

Transmission of TB from adults to children

- Is highest in young children
- <5yrs – 50-80% exposed as household contacts get infected
- Transmissibility of MDR TB is similar to DS TB

and:

the same diagnostic challenges remain when making a diagnosis of active TB or MDR TB in children

Definitions

- Poly-drug resistance: Resistance to 2 or more drugs, but not to both INH and RMP
- MDR-TB: Resistance to INH & RMP +/- other
- XDR-TB: MDR & 2nd-line injectable & quinolone

- New DR (primary): No previous anti-TB Rx or less than 1 month
- Previously Rx DR (acquired): Previous anti-TB Rx >1 month

Principles of MDR-TB in children

- Is mainly new (transmitted) drug resistance – this has been confirmed with DST and DNA-fingerprinting
- Is more difficult to acquire because of the paucibacillary nature of primary disease, but is possible with cavitary pulmonary disease
- In our experience DR-TB is not less infectious and does not cause less disease than DS-TB
- Disease in children usually (>90%) develops within 12 months of infection, if it occurs

Management of active disease

Children with MDR TB should be managed following the same principles as adults:

- Use of any remaining first-line drugs to which the index strain is sensitive

- Use of at least 4 second-line drugs to which the strain is susceptible, Including an injectable and a fluoroquinolone, PZA should be continued

?? What is the evidence?

How long for the injectable drug? (adults: 6-8 months)

- Treatment should be for at least 12-18 months after the last positive culture/smear in children with minimal disease and at least 18 months In extensive disease

How long should therapy last in total ?

Source: WHO guidelines, but not specific for children,
Sentinel Field Guide, Management of MDR TB in children

An illustrative case: The father

- family from Kazakhstan
- father: weight loss, cough,..
- routine chest x-ray when crossing the border to Germany 10/2009
- smear positive, cavernous TB
- resistent to INH,RIF,EMB,PZA,SM, capreomycin, prothionamide, amikacin, rifabutin, quinolones
- susceptible only to linezolide, terizidone, PAS
- treatment since 01/2010 linezolide,terizidone,PAS, augmentin, combactam
- resection right upper lobe

Case study curteousy of Dr Folke Brinkmann, ptbnet

The children

- 4 children (3 boys, 1 girl): 9-16 years
- HIV negative
- TST and IGRA (Quantiferon) negative in 2 boys (14y, 16y)
- one boy (9 y) Quantiferon borderline 0,9 U/ml (cut off <0,35)
- No symptoms, chest x-ray normal

What would you do?

- Wait and watch (follow-up x months?)
- Treat all the children?
- Treat only the boy with the borderline IGRA?
- Which drugs? For how long?

Background: Conflicting guidelines for MDR TB contacts

- **In the UK** - screening and watchful monitoring (NICE 2011)
- The International Standards for TB Care (ISTC) and **European Union** Standards for TB Care (ESTC) (Migliori 2011,2012) - strict clinical monitoring and no preventive therapy
- **Delphi** survey supported preventive therapy but didn't reach consensus on the treatment modalities (Delphi 1994)
- **WHO** - for countries with high prevalence of TB - advises isoniazid for prevention of DS-TB (WHO 2007)
- **In South Africa**, high dose isoniazid (HD INH) in children <5 yrs (2011)
- **In the US** it is recommended to use prevention treatment with two drugs to which a source case is sensitive (CDC 1992, ATS)

Recommendations: Two options

- Preventive therapy
- Inform + close follow up

ECDC 2012:
more evidence is needed

Pros and cons

- The treatment is lengthy, expensive and associated with high toxicity
- Prevention treatment works well in DS-TB
  - 60% risk reduction in progression of TB infection to TB disease with isoniazid prophylaxis
- MDR TB - no randomised controlled trials in children or adults

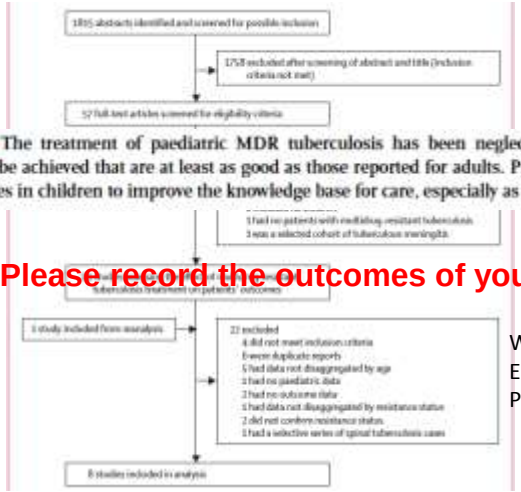
Research Questions

- Paediatric MDR guidelines- where are they?
- Do we need to treat children as long as adults, if they have pauci-bacillary disease?
- Exposure to MDR TB- what to do
- To give prophylactic treatment or not?
  On what grounds?
  Suspected versus “confirmed” latent infection
- ?? Use/role of IGRA to monitor?
- What to do if IGRA positive ?
- Issues of treatment of active TB vs chemopro vs Tx of latent TB?
  - In endemic vs non-endemic settings

Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis

Dena Ettehad, H Simon Schaaf, James A Seddon, Graham S Cooke*, Nathan Ford*

Lancet Inf Dis Feb 2012



Interpretation The treatment of paediatric MDR tuberculosis has been neglected, but when children are treated outcomes can be achieved that are at least as good as those reported for adults. Programmes should be encouraged to report outcomes in children to improve the knowledge base for care, especially as new drugs become available.

Please record the outcomes of your patients!

Williams, Kampmann et al
Eur Respir J. 2013 Jun
Pediatr Infect Dis J. 2013 Aug

Take home messages

- TB –also MDR/XDR is a family disease in children- look for the index cases
- work closely with your adult and PHTB colleagues to enhance case finding
- work closely with your microbiologists to get max info on susceptibility
- Engage with the families who have to administer the drugs
  - Compliance is key
  - social circumstances are often difficult/immigration issues
- Provide DOTS support
- Review patients regularly and adjust doses to weight/monitor weights
- Form special interest groups to share cases and expertise
- Advocate for pediatric TB studies to be undertaken as a priority

ptbnet
pediatric tuberculosis network european trials group

- founded in April 2009
- to date: 102 members from 22 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, incl. MDR cases and contacts**

Thank you for your attention

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