TB DIAGNOSIS IN CHILDREN: EXPERIENCE WITH HIV-INFECTED CHILDREN

WHO TB/HIV 19 April 2009
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Over 2 million paediatric HIV infections in 2007

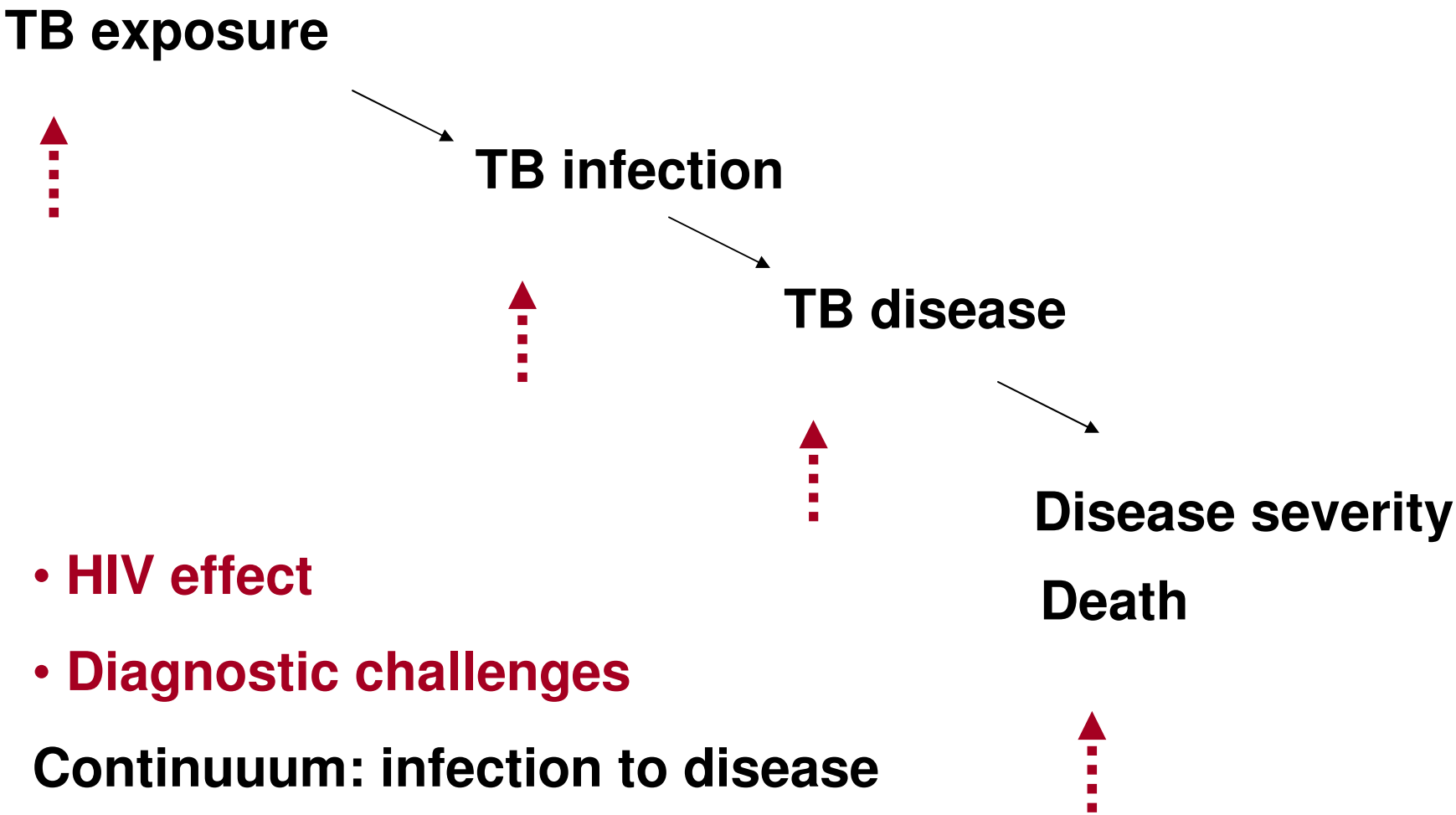
Over 1,500 new pediatric infections a day in Africa

www.who.int

WHO ESTIMATED TB CASES BY AGE, 2006

Country	Total Cases	Cases in Children < 15	% in Children
Myanmar	78,489	8,007	10.2
Nigeria	261,404	32,310	12.4
Pakistan	244,736	61,905	25.3
The Philippines	230,217	12,167	5.3
Russian Fed.	183,373	7,778	4.2
South Africa	220,486	35,449	16.1
Thailand	85,928	2,317	2.7
Uganda	75,250	12,099	16.1
Tanzania	117,489	18,890	16.1
Viet Nam	143,023	7,559	5.3
Zimbabwe	76,296	12,267	16.1
Total	6,678,188	630,722	9.4

TB DISEASE TRANSITIONS



RISK OF DISEASE PROGRESSION

- Age
  - 43% of infants (children < 1year)
  - 25% of children aged one to five years
  - 15% of adolescents
- Recent infection (1-2 years)
- Malnutrition
- HIV

Marais, 2004, Nelson, 2005

HIV: EPIDEMIOLOGICAL SHIFTS

• TB major cause of morbidity in HIV-infected children: 6-8 fold higher risk TB disease; TB in HIV+ infants: 20-25 fold higher incidence

• Incidence TB in South African HIV-infected children 9.2% (95% CI: 0.14-0.97)

• 25-60% of all hospitalized children with TB HIV+ in SA (2007)

• Mortality: tuberculosis-related deaths in 18.8% of HIV-infected Zambian children

Schaaf et al, BMC Infect Dis 2008, Bhat, J Trop Pediatr 1993, *Zar et al, BMJ 2007, Moore et al, 2007, Hesseling, 2009, Chintu Lancet 2002*

DIAGNOSTIC TOOLS AND PRINCIPLES

Presence of organism vs. host response

- Paucibacillary disease: Culture methods (Liquid), DST
- Contact history (and DST)
- CXR
- TST
- Symptoms
- Novel diagnostics (IGRAs)
- Reality: combined approaches, resource limitations (high-burden settings)

EMERGING DISEASE ENTITIES

1. Disease severity? Disseminated disease?
2. Neonatal/infant TB
3. MDR?
4. Detection of *M.tb* infection (relevant disease)
5. BCG disease and IRIS
6. NTM?
7. TB IRIS?

1. HIV AND DISEASE SPECTRUM/SEVERITY

Incidence of culture-confirmed TB in HIV-infected and uninfected South African infants (per 100 000 infant population)

	All infants	HIV-uninfected	HIV-infected	Relative risk
All tuberculosis	**83.1** (72.9-93.7)	**65.9** (56.7-75.3)	**1595.9** (1151.3-2131.5)	**24.2** (16.9-33.6)
Pulmonary tuberculosis	**78.7** (68.6-89.0)	**62.5** (53.3-71.7)	**1505.6** (1075.2-2022.8)	**24.1** (16.7-33.7)
Extrapulmonary tuberculosis	**28.2** (22.2-34.4)	**22.9** (17.5-28.6)	**481.8** (257.0-750.8)	**21.0** (10.7-35.0)
Disseminated tuberculosis	**16.6** (11.9-21.2)	**14.1** (9.7-18.3)	**240.9** (86.6-431.7)	**17.1** (6.0-33.7)
Miliary tuberculosis	**10.9** (7.2-14.7)	**9.3** (5.8-12.7)	**150.6** (30.8-301.0)	**16.2** (3.4-37.1)
Tuberculosis meningitis	**9.2** (5.8-12.6)	**7.9** (4.7-11.1)	**120.1** (27.7-257.9)	**15.2** (2.9-38.7)

Hesseling et al, Clin Infect Dis, 2009

CRANIAL CT: HIV-INFECTED (N=34) VS. HIV-UNINFECTED (N=56) WITH TBM

	HIV-infected	HIV-uninfected	Odds ratio	Confidence Interval
Infarcts (%)	50.0	40.5	1.47	0.54 – 4.04
Granuloma (%)	0	15.0	0.11	0.01 – 2.01
Hydrocephalus (%)	72.0	97.9	0.06	0.01 – 0.49
communicating	100.0	80.0	5.49	0.29 –
non-communicating	0.0	20.0	1.00	103.46
				–
Basal exudate (%)	37.5	71.4	0.24	0.08 – 0.70
Subarachnoid space				
increased (%)	57.1	16.7	4.40	1.04 – 18.60
normal (%)	28.6	36.7	1.00	–
decreased (%)	14.3	46.6	0.39	0.80 – 1.94

van der Weert, Schoeman et al. Pediatr Infect Dis J 2006; 25: 65-9

Table 1: History, clinical characteristics and drug susceptibility test results in children with culture-confirmed TB according to HIV status (n = 596)

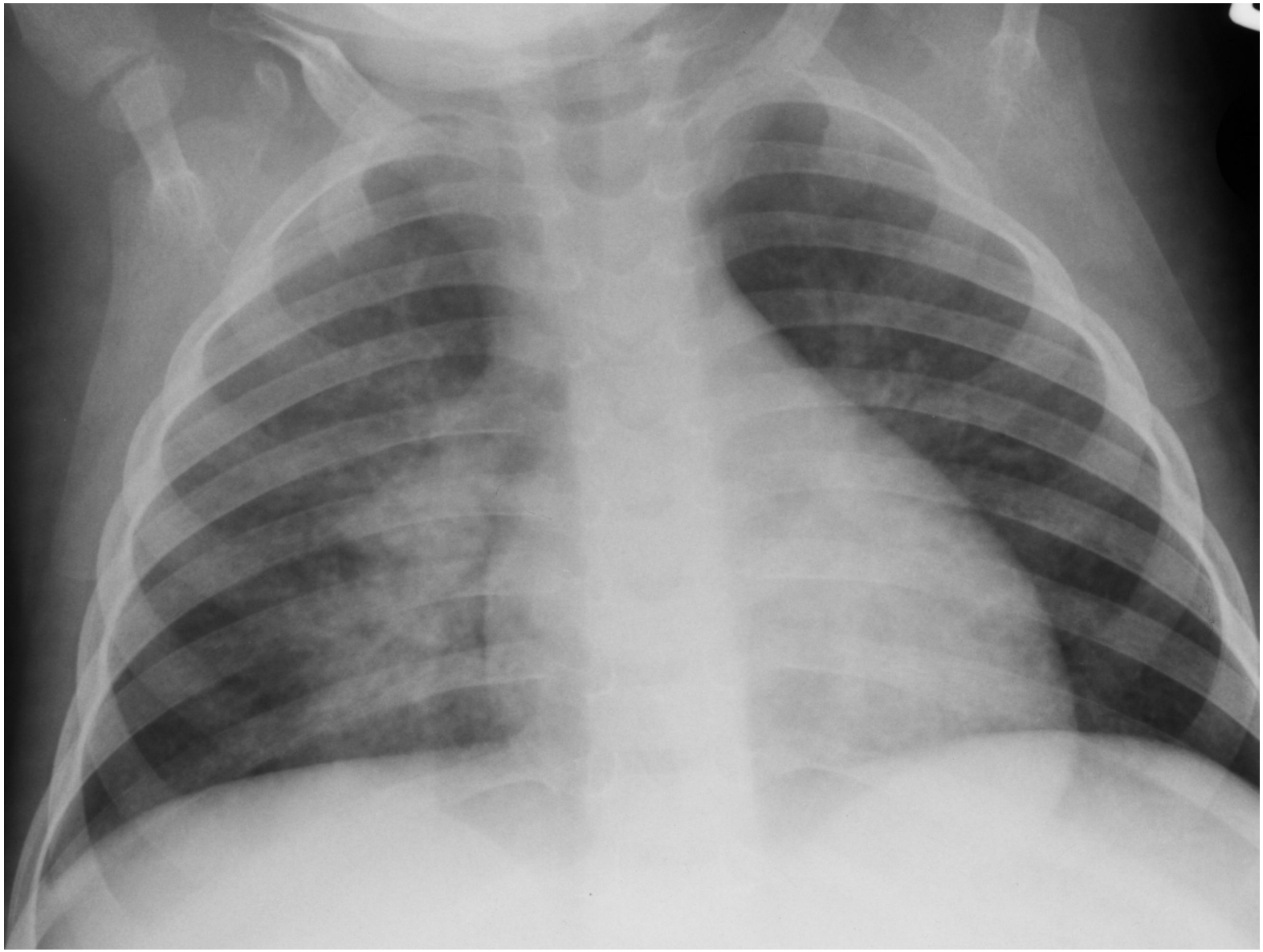
Characteristic	HIV-uninfected N = 281 (%)	HIV-infected N = 133 (%)	HIV unknown N = 182 (%)	Odds ratio (95% CI)[a]
Previous TB treatment	26 (9.3)	40 (30.1)	16 (8.8)	0.24 (0.13–0.42)
Known TB source case	152 (54.1)	73 (54.9)	70 (38.5)	NS
Nutritional status	(n = 276)	(n = 128)	(n = 173)[b]	
Severely malnourished	53 (19.2)	26 (20.3)	20 (11.6)	NS
< 3rd percentile WFA	78 (27.8)	57 (42.9)	44 (24.2)	0.49 (0.31–0.78)
Total malnourished	131 (46.6)	83 (62.4)	64 (35.2)	0.49 (0.31–0.77)
TST (Mantoux) positive	190/232 (81.9)	50/83[c] (60.2)	90/110 (81.8)	2.99 (1.66–5.38)
DST results	(n = 277)[d]			
All drug resistance	31 (11.2)	23 (17.3)	13 (7.1)	NS
INH monoresistance	21 (7.5)	12 (9.0)	10 (5.5)	NS
RMP monoresistance	0	2 (1.5)	0	
MDR	10 (3.6)	9 (6.8)	3 (1.6)	NS
TB manifestation:				
Intrathoracic TB only[e]	126 (44.8)	84 (63.2)	96 (52.7)	0.47 (0.30–0.74)
Intra- and extrathoracic TB[e]	119 (42.3)	44 (33.1)	48 (26.4)	NS
Extrathoracic TB only	37 (13.2)	5 (3.8)	37 (20.3)	3.07 (1.41–11.48)
All extrathoracic TB	156 (55.5)	49 (36.8)	85 (46.7)	2.12 (1.36–3.32)

All cavities: HIV-infected: 26.2% vs. 16.1%

Schaaf, BMC Infect Dis 2007

MILIARY TB

LYMPHOID INTERSTITIAL PNEUMONITIS

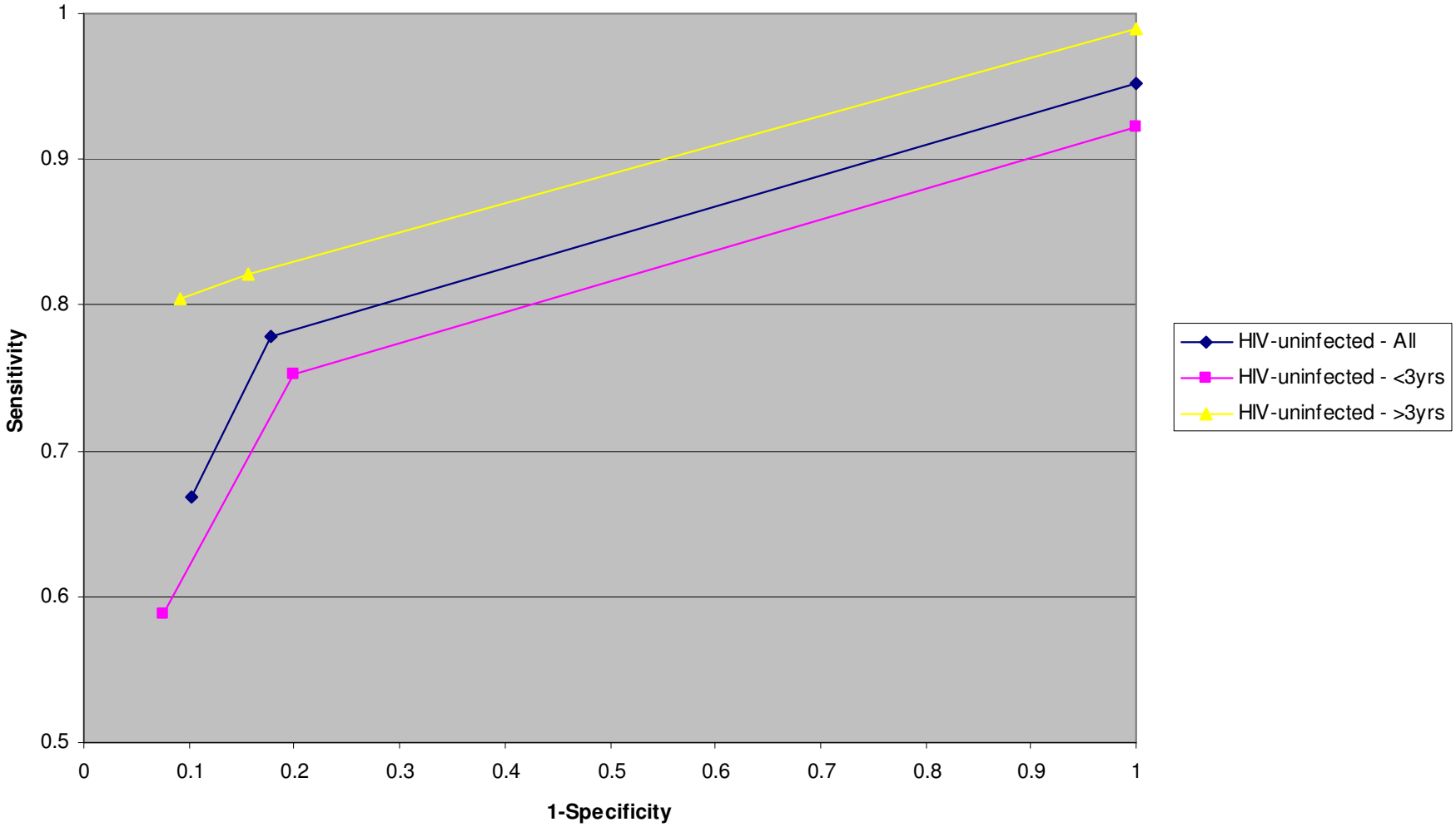


A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis.

"Sixteen systems were analysed. Comparison of systems is difficult because characteristic definitions and the ranking of characteristics are not standardised, few studies have been performed to validate these diagnostic approaches, and the gold standard of diagnosis is not practicable in most settings. The minority of systems are adapted for HIV-infected and malnourished patients. Any new diagnostic approaches developed should be relevant to developing countries with limited resources, a high burden of tuberculosis, malnutrition and HIV/AIDS and a young population."

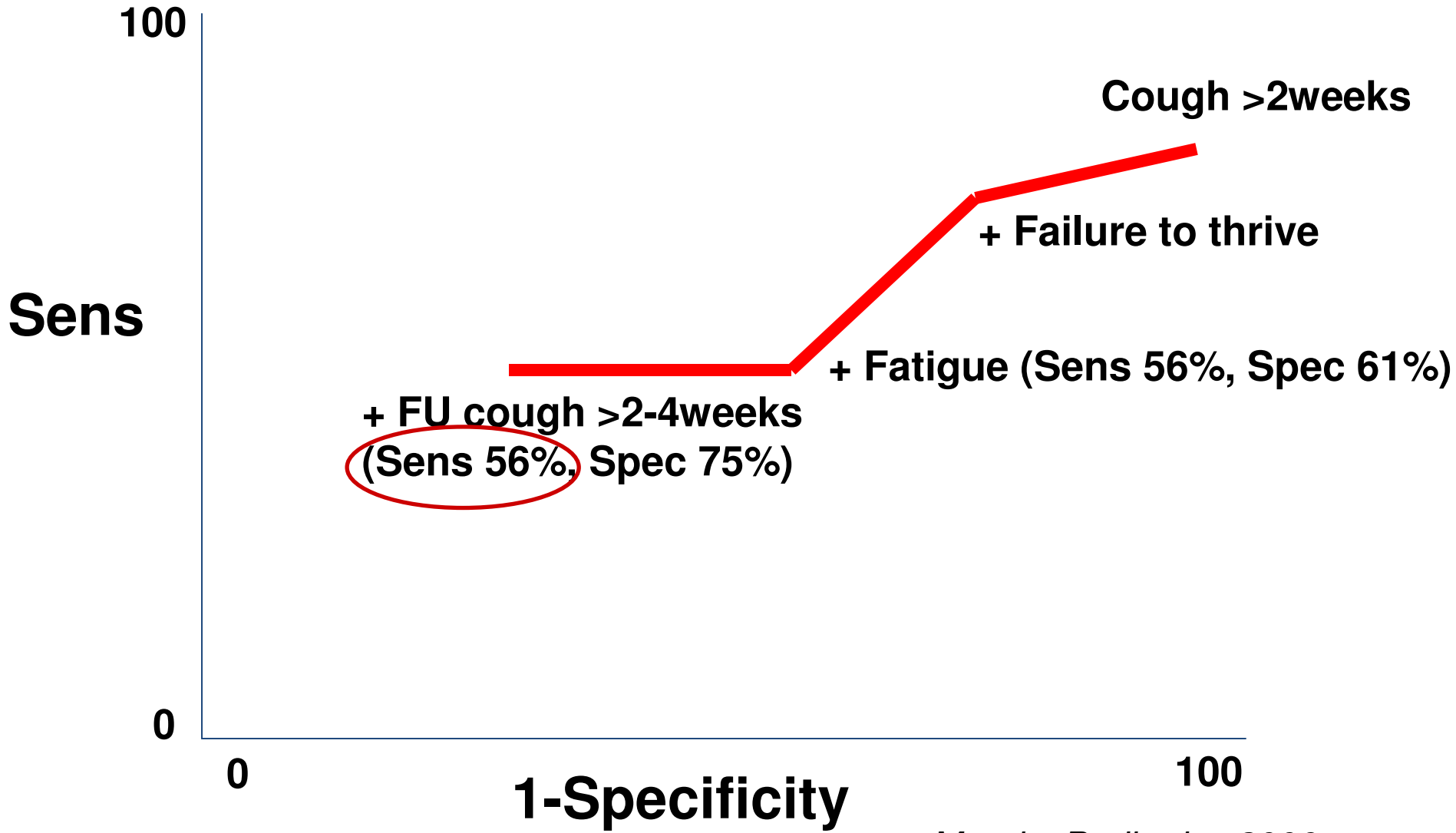
Hesseling, Int J Tuberc Lung Dis. 2002

ROC curves for symptoms documented at presentation in HIV-uninfected children diagnosed with pulmonary tuberculosis
1) Cough >2weeks, +2) documented failure to thrive, +3) reported fatigue



Marais, Pediatrics 2006

HIV INFECTION



Marais, Pediatrics 2006

Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study

	Patients	Culture positive	Smear positive	Culture or smear positive	Cumulative yield
Total	250	58 (23%)	29 (12%)	62 (25%)	100%
Induced sputum					
Total	250	51 (20%)	25 (10%)	54 (22%)	87%
First specimen	250	37 (15%)	19 (8%)	41 (16%)	66%
Second specimen	244	27 (11%)	13 (5%)	30 (12%)	79%
Third specimen	227	29 (13%)	11 (5%)	31 (14%)	87%
Gastric lavage					
Total	250	38 (15%)	17 (7%)	40 (16%)	64%
First specimen	250	19 (85%)	8 (3%)	20 (8%)	32%
Second specimen	244	22 (9%)	12 (5%)	26 (11%)	56%
Third specimen	234	18 (8%)	10 (4%)	22 (9%)	64%

Data are number or %.

Table: Cumulative yield of *M tuberculosis* from repeated induced sputum or gastric lavage specimens

Yield not by HIV status
(p=0.17, OR: 0.7 [95% CI 0.3-1.3]).

Zar et al. Lancet. 2005 Jan 8-14;365(9454):130-4.

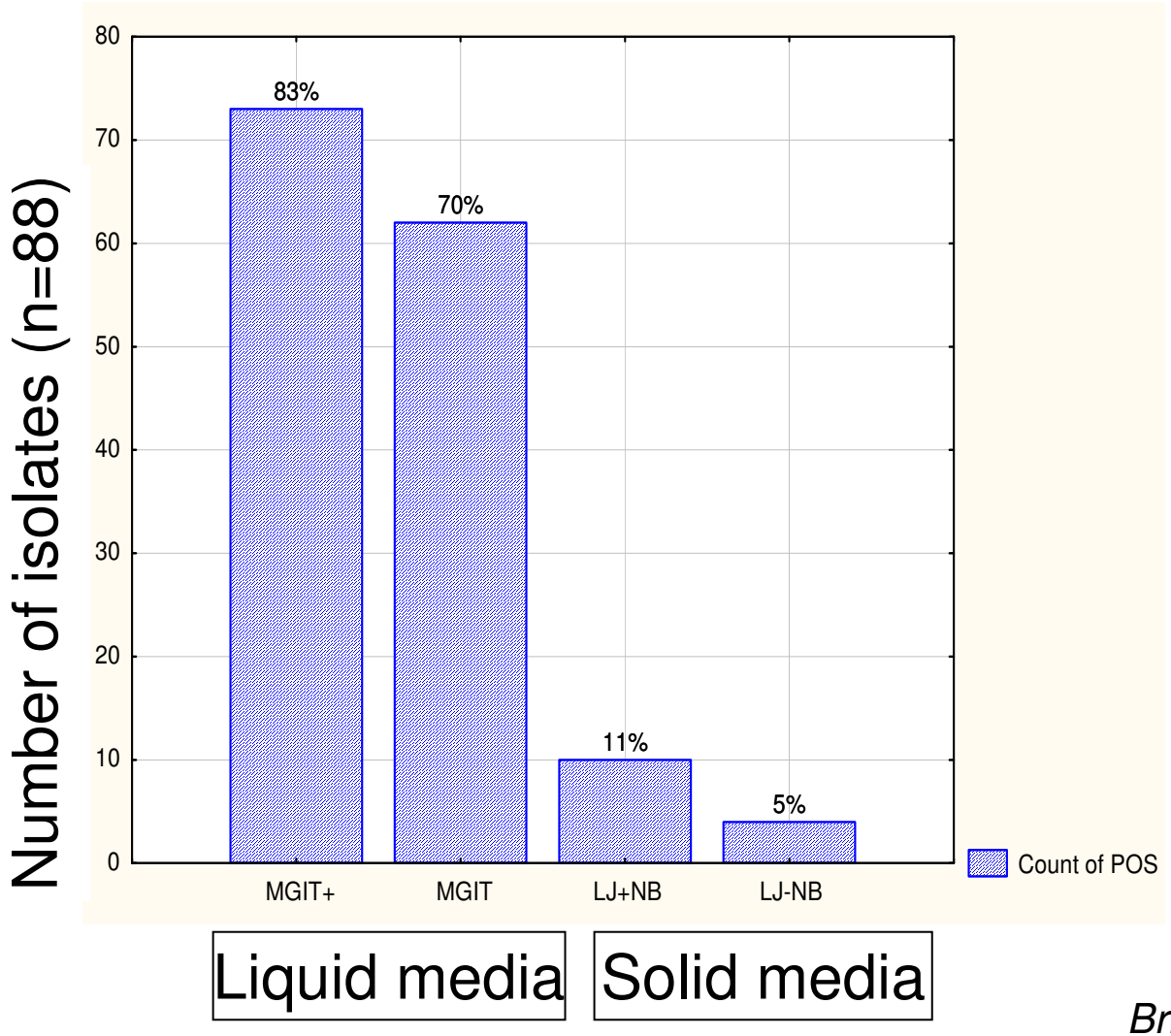
DISEASE SPECTRUM AND YIELD

Disease manifestation	Total (%) N = 439	Bacteriologic yield
Not TB	85 (19.4)	
Intra-thoracic TB	307 (69.9)	120/195 **(61.5)**
Uncomplicated LN	147 (47.9)	22/64 **(34.4)**
Complicated LN	106 (34.5)	59/80 **(73.5)**
Other	54 (17.5)	39/51 **(76.5)**
Extra-thoracic TB	72 (16.4)	31/46 **(67.4)**
Cervical lymphadenitis	35 (48.6)	27/27 **(100)**
TBM	14 (19.4)	1/10 **(10.0)**
Other	23 (31.9)	5/9 **(55.6)**
Intra+Extra	25 (5.7)	12/13 **(92.3)**

Marais, Hesseling et al. Clin Infect Dis 2007

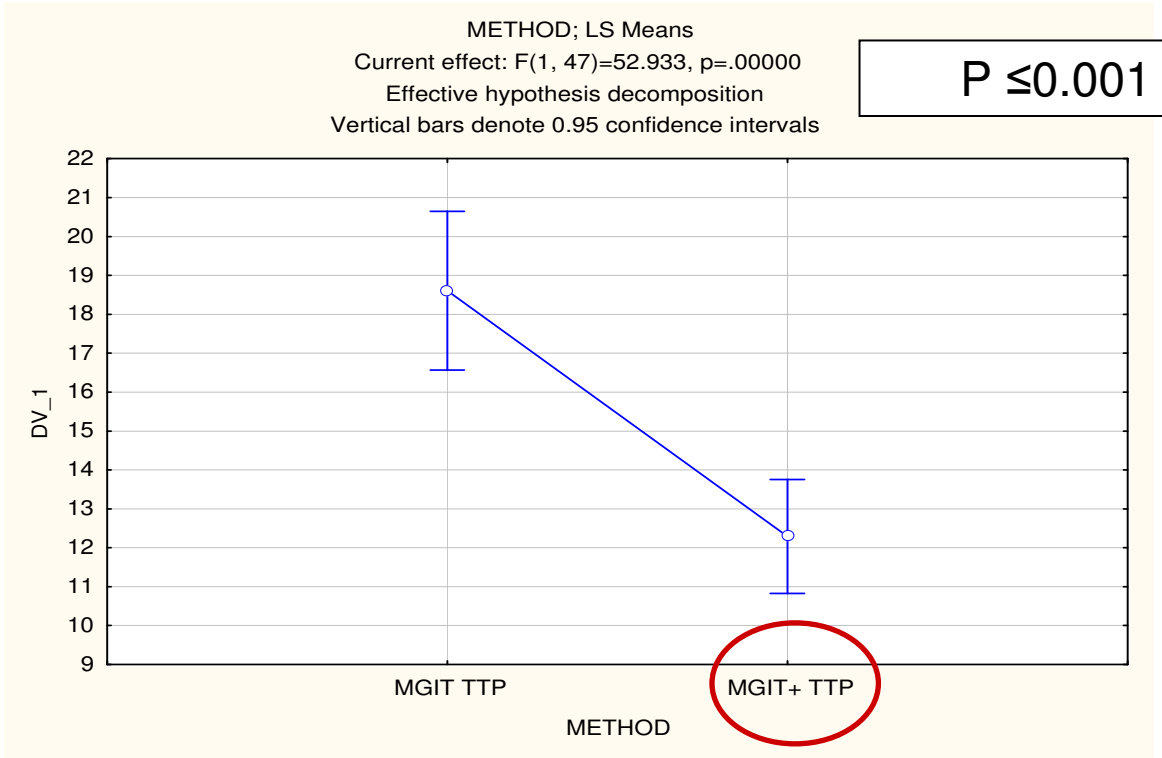
PRIMARY ISOLATION

Liquid media vs. solid media yield: role of growth supplements



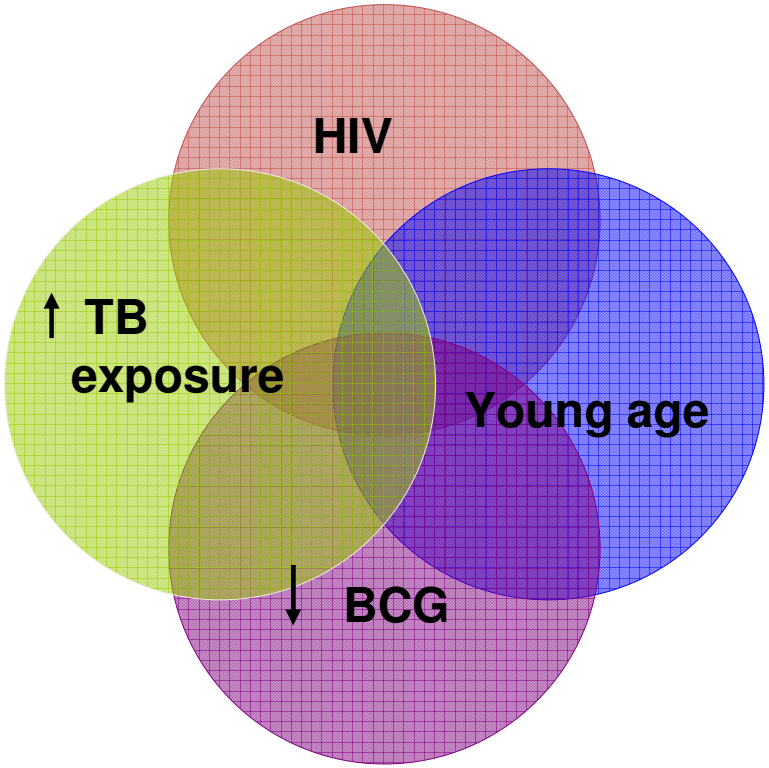
Brittle et al. JCM 2009

Mean TTD (days) for liquid media



Brittle et al. JCM 2009

2. NEONATAL/INFANT TB



- BCG-induced CD4 and CD8 T cell responses: HIV-infected (n=20), HIV-exposed uninfected (n=25), and HIV-unexposed (n=23) infants year one of life.

- HIV-infected infants demonstrated a markedly lower immune response characterized by CD4 T cells expressing interferon IFN-γ, TNF-alpha, and/or IL-2 and significantly reduced numbers of polyfunctional CD4 T cells co-expressing IFN-gamma, TNF-alpha, and IL-2

Mansoor, J Infect Dis. 2009

• 715 HIV-infected women: TB incidence: 5.0 per 100 person-years (95% CI 3.2–7.4 cases per 100 person-years).

• Women with incident TB and their infants had a 2.2- and 3.4-fold increased probability of death, respectively, compared with women without active TB and their infants

• Rates of TB in HIV-infected pregnant women are high, and screening for TB during routine antenatal care should be implemented in high HIV-prevalence settings.

Gupta, Clin infect Dis 2007; Kali et al, J Acquir Immune Defic Syndr. 2006

DIAGNOSIS NEONATAL TB

- HIV increases likelihood of maternal EPTB - more genital/placental TB?
- High index suspicion required
- Contact history: mother often undiagnosed (mother and infant; HIV)
- TST: limited SENS
- CXR:
  - Often non-specific
  - Miliary (bronchopneumonic?) 26%
  - Hilary (52%) and paratracheal (37%) LN
  - large airway compression (56%)
- Culture and microscopy: GW, BA, LN biopsy, BM, Bct
- Placenta + endometrial culture/histology

Schaaf HS. Arch Dis Child 1993
Cantwell. NEJM 1993;330:1051

3. HIV AND EMERGENT DR?

DST results	1994-98	2003-05	2005-2007
All culture+ cases	338 (%)	323 (%)	291 (%)
DST available*	306 (90.5)	320 (99.1)	285 (97.9)
Drug susceptible	285 (93.1)	279 (87.2)	239 (84.5)
Drug resistant (All)	21 (6.9)	41 (12.8)	43 (15.1)
INH mono-R	14 (4.6)	22 (6.9)	22 (7.7)
RMP mono-R	0	0	2 (0.7)
Multidrug resistant	7 (2.3)	19 (5.9)	19 (6.7)

- **Significant increase in All DR and MDR TB between 1st and 3rd surveys; no association HIV and DR**
- **Contact data, culture, DST essential** **MOPEB019**

Schaaf, Int J Epid 2008

4. TB EXPOSURE AND INFECTION

• Exposure of young children often at household level (60%); missed opportunities IPT

• HIV proxy for TB exposure: 77 of 766 (10.1%; 95% CI 8.0–12.4) HIV-exposed South African infants had TB contact at 3 months; HIV-exposed infants 2 fold higher risk of TB exposure

• TB infection in HIV+ children="relevant disease"?

• TST limitations (SENS, SPE, standardization)

• No gold standard for *M. tb* infection: advances (IGRA)

• Determined by exposure to an infectious case, mediated by duration of infectiousness, infectivity, proximity*:* may be used as measure of likelihood of infection: impact of HIV?

Schaaf, PIDJ, 2006, Shams, 2006, Hesseling Thorax 2008, Cotton IJTLD 2008, Hesseling Infect Dis 2009

T- CELL INTEFERON-γ RELEASE ASSAYS (IGRAs)

• **QuantiFERON-TB-in-tube assay**: Whole-blood ELISA measuring IFN-γ production (ESAT-6, CFP-10 and TB7.7)

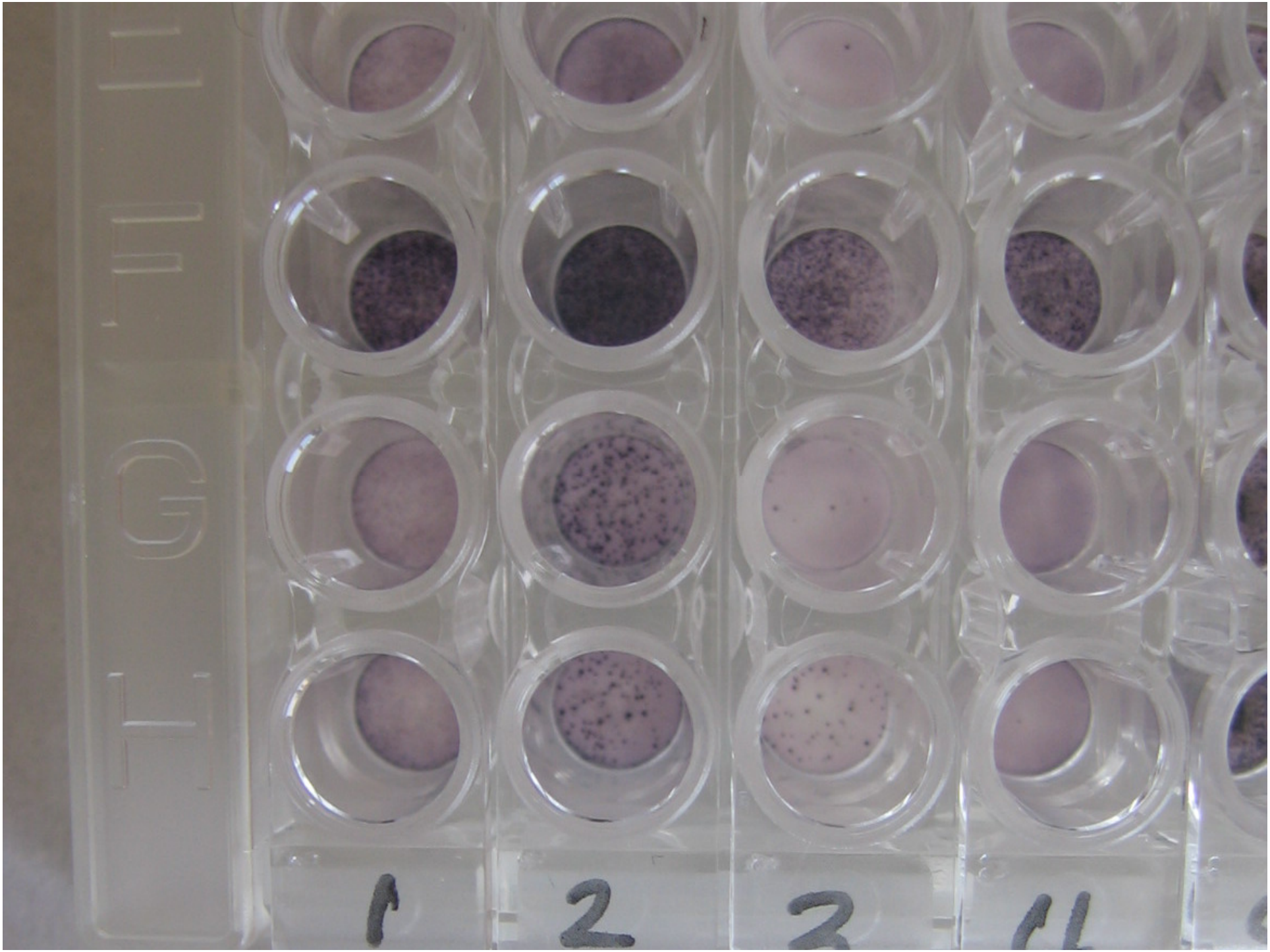
• **T.SPOT.*TB***: Enzyme-linked immunospot (ELISPOT) assay peripheral mononuclear cells (PBMC) to detect number of IFN-γ-producing T cells (ESAT-6 and CFP-10)

• IGRAs include internal positive and negative controls

• More sensitive in HIV? More specific (TST, NTM)

• Limited data on direct comparison of 2 IGRAs in high-burden settings in children, HIV: distinction between infection vs. disease?

Pai et al, Lancet ID 2007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Clinical characteristics and measures of *M. tb* infection in HIV-negative adults and children in household contact with a TB index case

	All subjects N=82 % (number)	Children (N=29) % (number)	Adults (N=53) % (number)
Age mean in years (SD) †	22.8 (18.1)	2.9 (2.6)	33.8 (12.8)
% with documented BCG vaccination	75.6 (62/82)	100 (29/29)	62.2 (33/53)
TST†%			
% Positive*†	69.2 (54/78)	53.6 (15/28)	78.0 (39/50)
% Not read	4.9 (4/82)	3.5 (1/29)	5.7 (3/53)
T SPOT.*TB*			
% Positive†	75.0 (60/80)	92.6 (25/27)	66.0 (35/53)
% Indeterminate	1.2 (1/81)	3.6 (1/28)	0 (0/53)
QTF			
% Positive	40.9 (29/71)	44.4 (8/18)	39.6 (21/53)
% Indeterminate	4.1 (3/74)	14.3 (3/21)	0 (0/53)
Mean *M. tb* contact score (SD) †	6.4 (5.6)	10.2 (SD 3.5)	4.3 (SD 5.4)
Proportion with high *M. tb* contact score (>4) ‡ †	59.8 (49/82)	93.1 (27/29)	41.5 (22/53)

Hesseling et al, Thorax, 2008

Logistic regression of *M. tb* infection in relation to exposure and age in adults and children in recent household contact with TB

	Measures of *M. tb* infection					
	TST positive		**T SPOT.*TB* positive**		**QTF positive**	
	Unadjusted	Age adjusted	Unadjusted	Age adjusted	Unadjusted	Age adjusted
Covariates	OR (95% CI) *	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
***M. tb* contact score ≥ 4**	1.56 (0.59 – 4.15)	3.83 (1.05-14.03)	62.42 (7.67 – 508.69)	38.40 (7.59- 616.11)	9.60 (3.02 – 30.54)	14.94 (4.02-55.58)
Age in years	-	1.07 (1.02 – 1.11)	-	1.01 (0.96 – 1.06)	-	1.04 (1.01-1.08)

Hesseling, Thorax, 2008

Table 1. Clinical characteristics and measures of *M. tb* infection in HIV-infected adults and children

	All subjects N=43 % (number)	Children (N=23) % (number)	Adults (N=20) % (number)
Age mean in years (SD) †	18.7 (16.6)	4.4 (3.3)	35.2 (7.7)
% with BCG vaccine documented or scar present (number)	81.4 (35/43)	91.3 (21/23)	70.0 (14/20)
TST			
% positive¥†	41.0 (16/39)[1]	26.1(6/23)	62.5 (10/16)[2]
% not read	9.3 (4/43)	0	20.0 (4/20)
T SPOT.*TB*			
% positive	61.0 (25/41)[3]	52.2 (12/23)[4]	72.2 (13/18)[5]
% indeterminate	4.7 (2/43)	0	10.0 (2/20)
% failed phlebotomy**	0	0	0
QTF Gold			
% positive	27.6 (8/29)[1,3]	16.7 (2/12)[4]	35.3 (6/17)[2,5]
% indeterminate	9.4 (3/32)	0	15.0 (3/20)
% failed phlebotomy	25.6 (11/43)	47.8 (11/23)	0
Proportion with known TB contact	23.3 (10/43)	26.1 (6/23)	20.0 (4/20)
Mean CD4 count (SD) †	787.7 (635.1)	1162.3 (602.8)	334.3 (280.0)
Mean CD4 percentage (SD) †	22.7 (11.6)	27.7 (9.5)	16.7 (11.3)
Number on ARV	25.6 (11/43)	48.0 (11/23)	0.0 (0/20)

Mandalakas, Hesseling et al, IJTLD 2008

Diagnosis of tuberculosis in South African children with a T-cell-based assay: a prospective cohort study

ELISPOT assay for the diagnosis of active TB disease in children: effect of HIV, nutritional status and age

	ELISPOT positive/ total tested by ELISPOT	Sensitivity of ELISPOT* (95% CI)	TST positive/total tested by TST	Sensitivity of TST* (95% CI)
Age				
>36 months	64/79	81% (71 to 89)	46/63	73% (60 to 83)
<36 months	46/54	85% (73 to 93)	27/53	51% (37 to 65)
p†		0·53		0·01
HIV				
Negative or not tested	88/103	85% (77 to 92)	64/91	70% (60 to 80)
Positive	22/30	73% (54 to 88)	9/25	36 % (18 to 58)
p†		0·12		0·002
Z score				
>−2	61/71	86% (76 to 93)	48/63	76% (64 to 86)
<−2	46/59	78% (65 to 88)	22/50	44 % (30 to 59)
p†		0·24		0·0003

*p values for difference between sensitivity of ELISPOT and sensitivity of TST in children who were aged <36 months, HIV positive, or very malnourished (Z<−2) were 0·001, 0·005, and 0·002, respectively. †p for difference in sensitivity of each test in children who were aged less than 36 months, HIV positive, or malnourished, versus children without these features (χ^2 test).

Table 4: Effect of age, HIV infection, and malnutrition on test sensitivity in children with confirmed or highly probable tuberculosis (n=133)

Liebeschuetz, Lancet 2006

- 188 children, 139 (74%) were HIV-infected
- Significantly higher proportion of HIV-infected children with TB had a positive ELISPOT compared with a positive TST [25/39 (64%) vs. 10/34 (29%), P = 0.005].
- In contrast to TST, ELISPOT not affected by young age or severe immunosuppression.
- Although more sensitive than TST current ELISPOT assays not sufficiently high to be used as a rule out test for TB.
- Infection vs. disease?
- Prognostic utility?

Davies MS, Connell, T et al. AIDS. 2009 May 15;23(8):961-9.

Multi-centre population estimates of incidence rate of disseminated BCG disease in HIV-infected children, Western Cape Province, South Africa

Year	2004	2005	2006
Annual number of dBCG disease cases in HIV-infected infants	12	12	8
Total estimated number of infants ≤ 1 year of age	98 236	98 339	98 137
Provincial maternal HIV prevalence (95% CI)	15.4% (12.5-18.2)	15.7% (11.3-20.1)	15.2% (11.6-0.18.7)
Reported provincial vertical HIV transmission rate (total number estimated HIV-infected infants)	0.1004 (1573)	0.061 (942)	0.054 (806)
Estimated incidence of dBCG disease per 100 000; (95% CI), given 98% BCG coverage	778 (361-1319)	1300 (587-2290)	1013 (377-1895)

- **Pooled estimate of dBCG incidence: 992 per 100 000 (95% CI: 567-1495 per 100 000)**
- **No HAART, mortality >75%**
- **High index suspicion, GA, Bct, BM, PCR**

Hesseling et al, Bull WHO, 2009

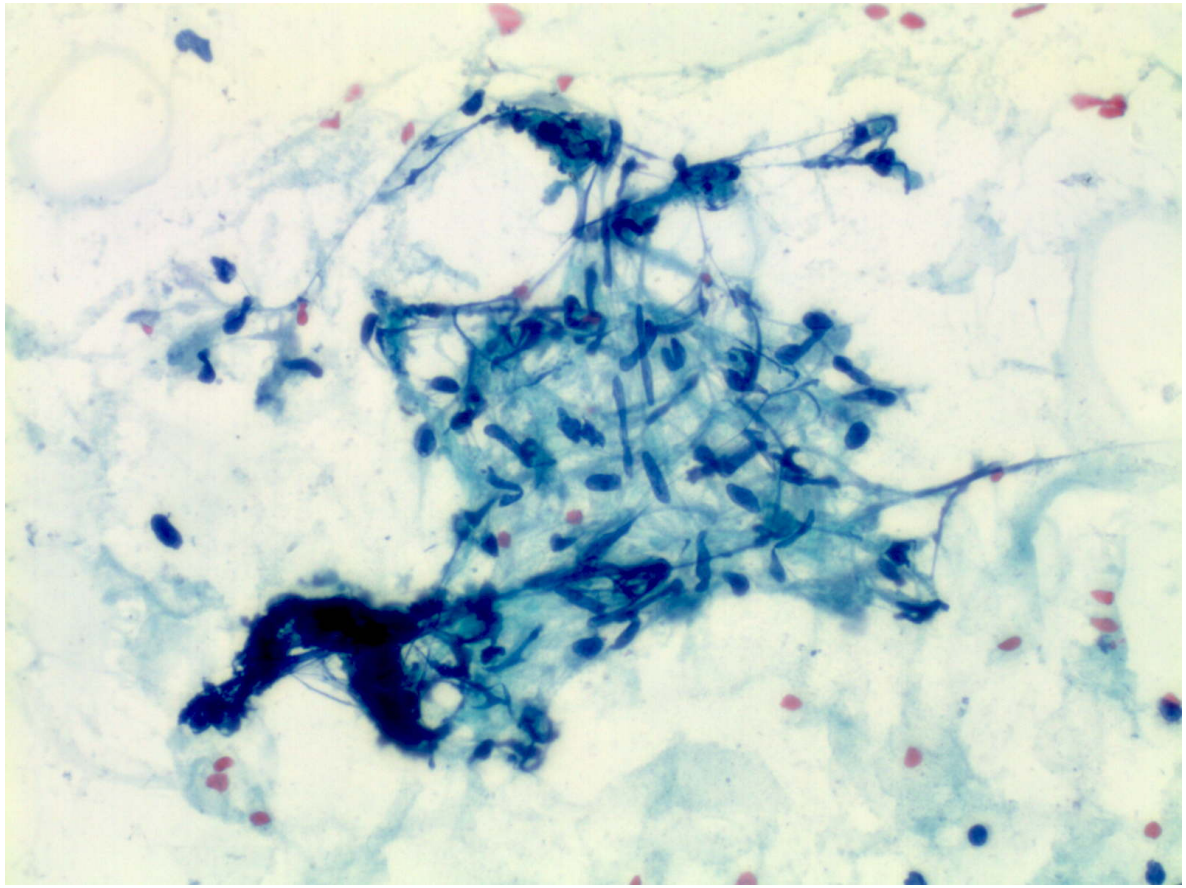
Effect of HAART on BCG adverse events?

BCG IRIS in infants with baseline CD4≥25%: Early vs. Deferred HAART (CHER study)

	Deferred Arm (n=83)	Early Treatment Arm (n=250)	P-value / Odds Ratio
Cases of IRIS(CI)	13/83: 15.7% (8.6% - 25.3%)	13/250: 5.20% (2.8% - 8.7%)	P=0.004 OR= 3.4 (1.5 - 7.7)
Incidence	27.9 Events per 100 person years	6.4 Events per 100 person years	

CHER study, Rabie, Cotton et al, CROI, 2008

FNA AND MYCOBACTERIAL INFECTION



Well formed granuloma

Michelow, Cytopathology. 2008

CHILDHOOD TB: COMING OF AGE?

- WHO guidelines: reporting age-brackets
- WHO Paediatric Guidelines
- Diagnosis: paucibacillary disease (gold standard), clinical co-morbidity
- Childhood TB diagnostics agenda driven by HIV?
- WHO Diagnostics Group DEWG: Childhood TB Sub Group

WHO 2006

CONCLUSIONS

1. High risk of TB infection and disease in HIV-infected children
2. Diagnostic challenges due to co-morbidities, immune suppression requires combined approach
3. Bacteriological confirmation: sensitive, inexpensive methods required (novel collection methods)
4. Bacteriological yield not affected
5. Emerging disease entities
6. Infection vs. active disease
7. Novel diagnostic tools needed relevant to paucibacillary disease and immune suppression

Anna Mandalakas, Gerhard Walzl, Harleen Grewal, Simon Schaaf, Nulda Beyers, Rob Gie, Anne Detjen, Peter Godfrey-Faussett, Mark Cotton, Gill Black, Nonhlanhla Nene, Willem Hanekom, Greg Hussey, Ben Marais, Simon Schaaf

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