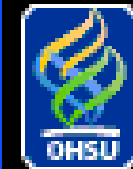


# Embracing IGRA's in Children

Deborah Lewinsohn, MD

Associate Professor

Infectious Disease, Pediatrics

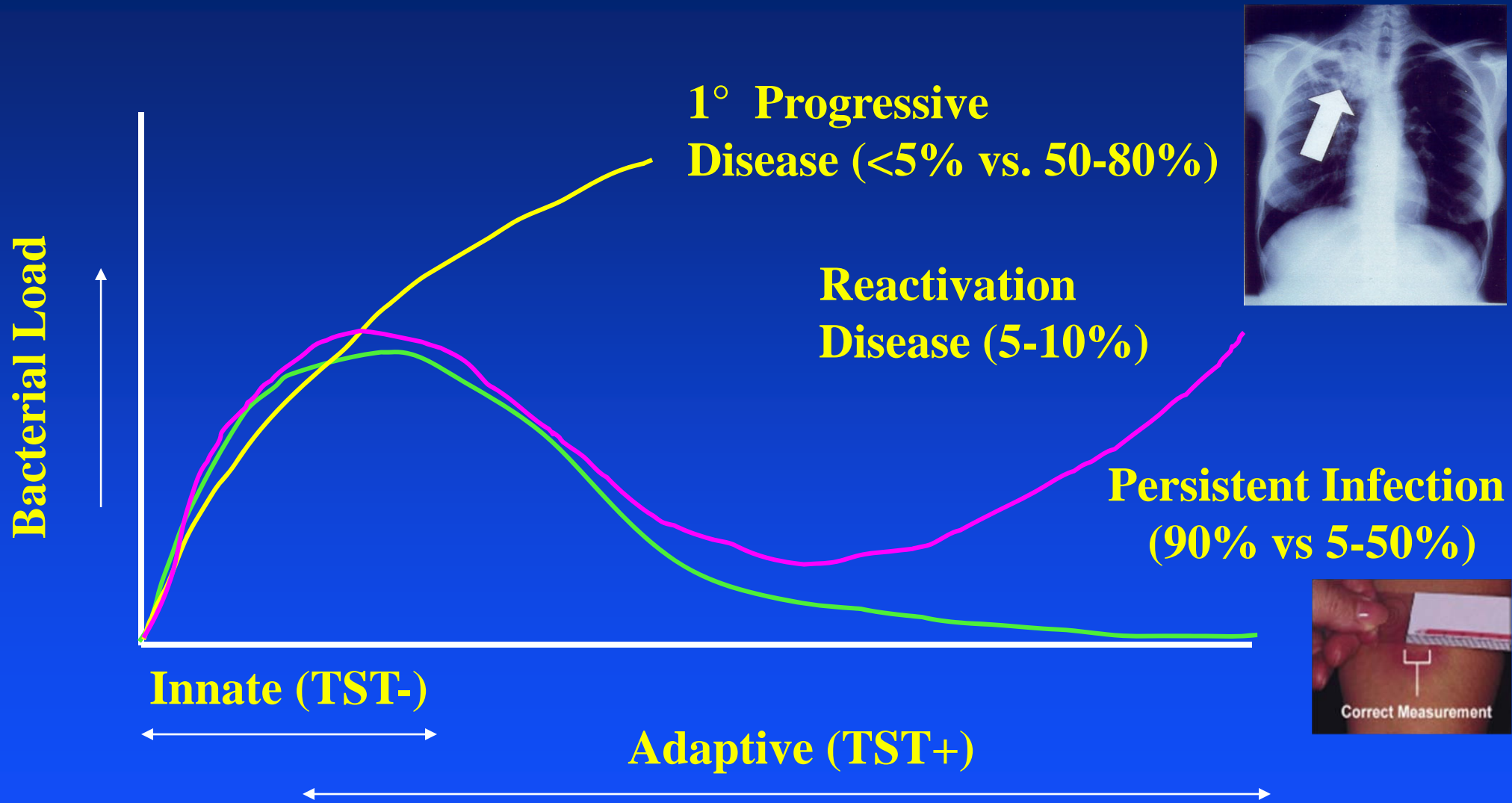


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# Disclosure Statement: Deborah Lewinsohn

- I have no significant financial interests in Cellestis or Oxford Immunotech.
- All relevant financial interests are as follows:
  - Cellestis: Honoraria for three Cellestis-sponsored meetings for role as a participant, moderator, or invited speaker.
  - Oxford Immunotech: Sponsored research contract to provide T cells to use for QC for T-spot.*TB*.

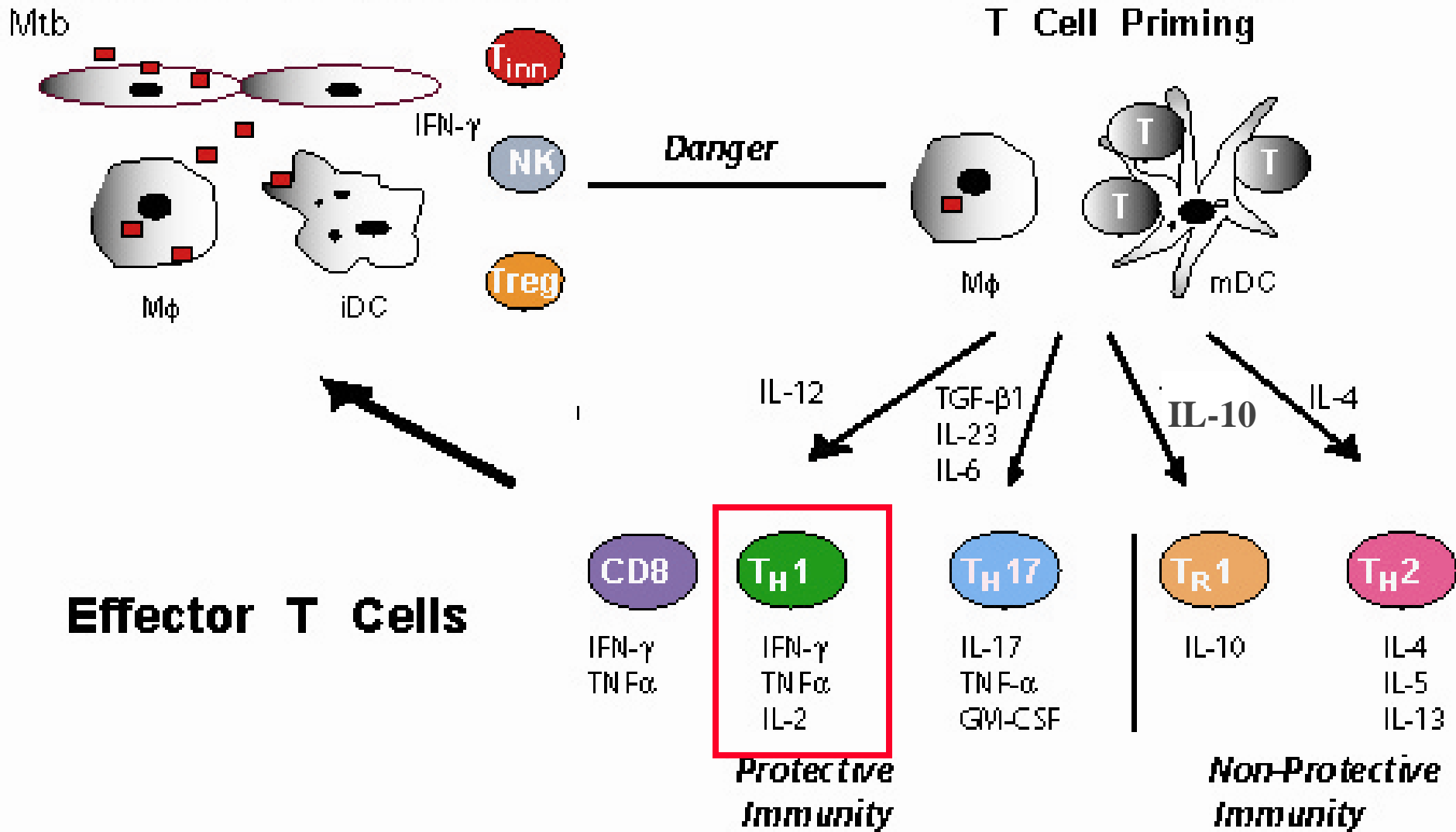
# Natural History of *M. tuberculosis* Infection



# Epithelium or Alveolus

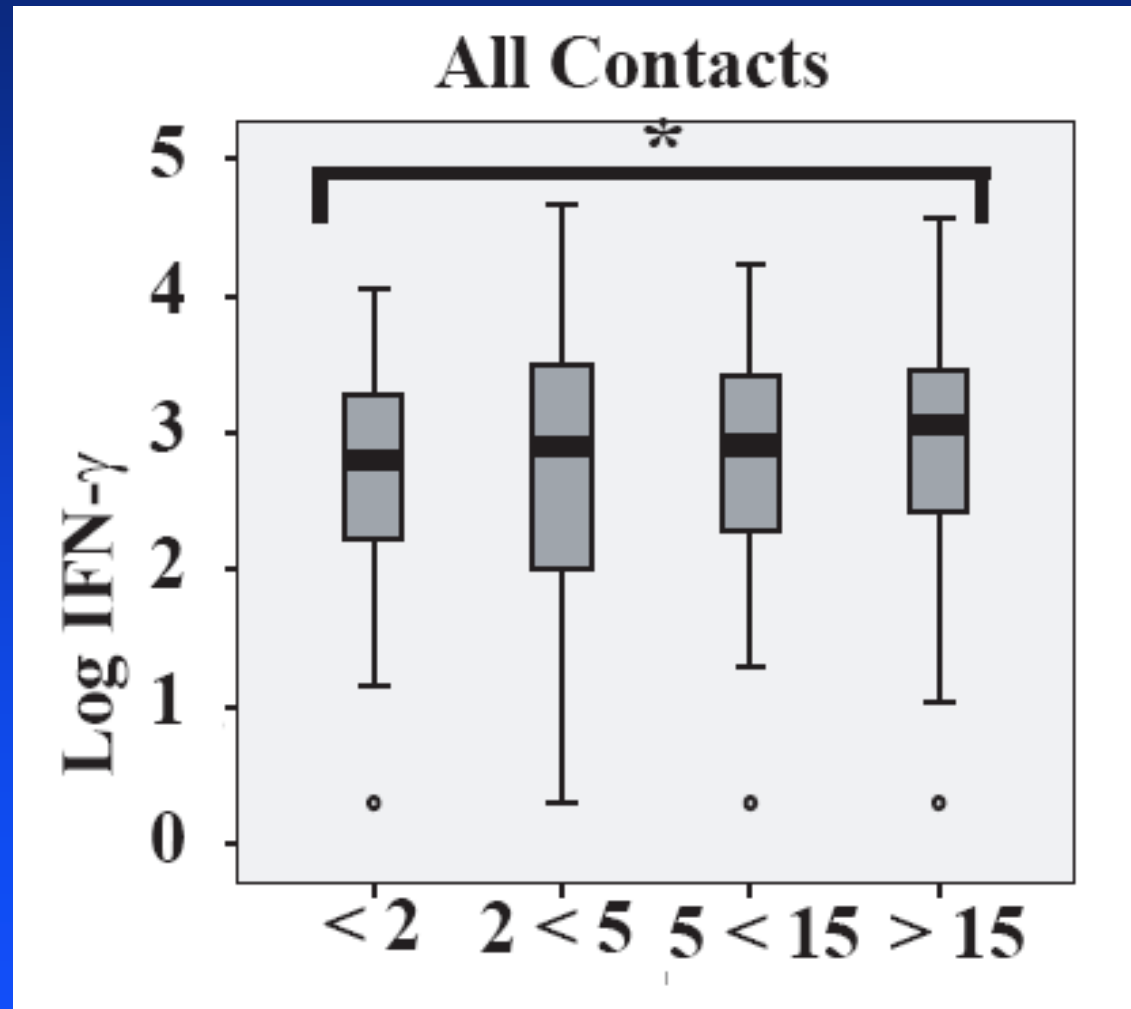
# Lymph Node

## T Cell Priming

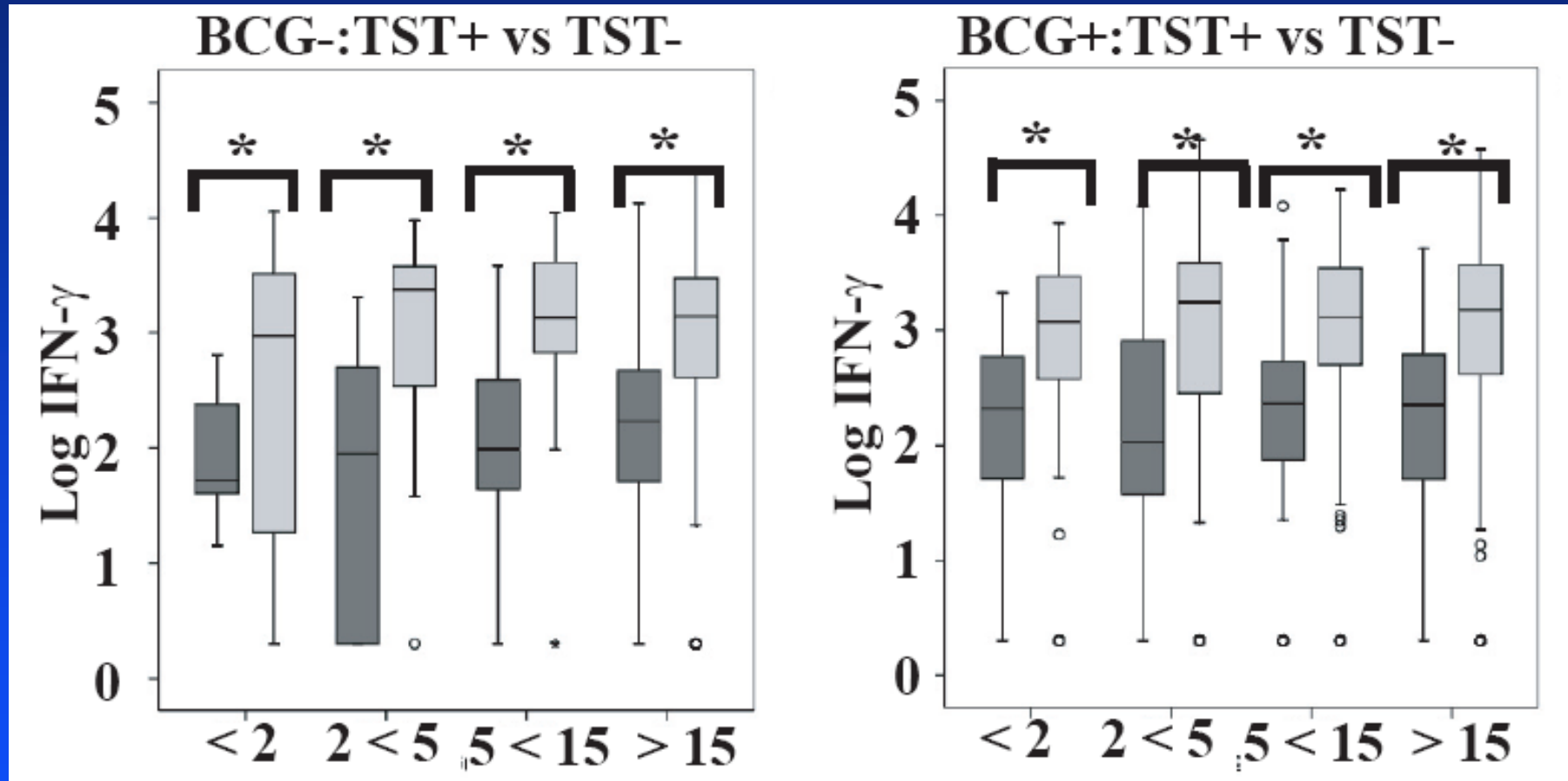


# Ugandan household contacts: IFN- $\gamma$ responses across the age span

- All HIV-, healthy contacts.
- Baseline whole blood IFN- $\gamma$  responses.



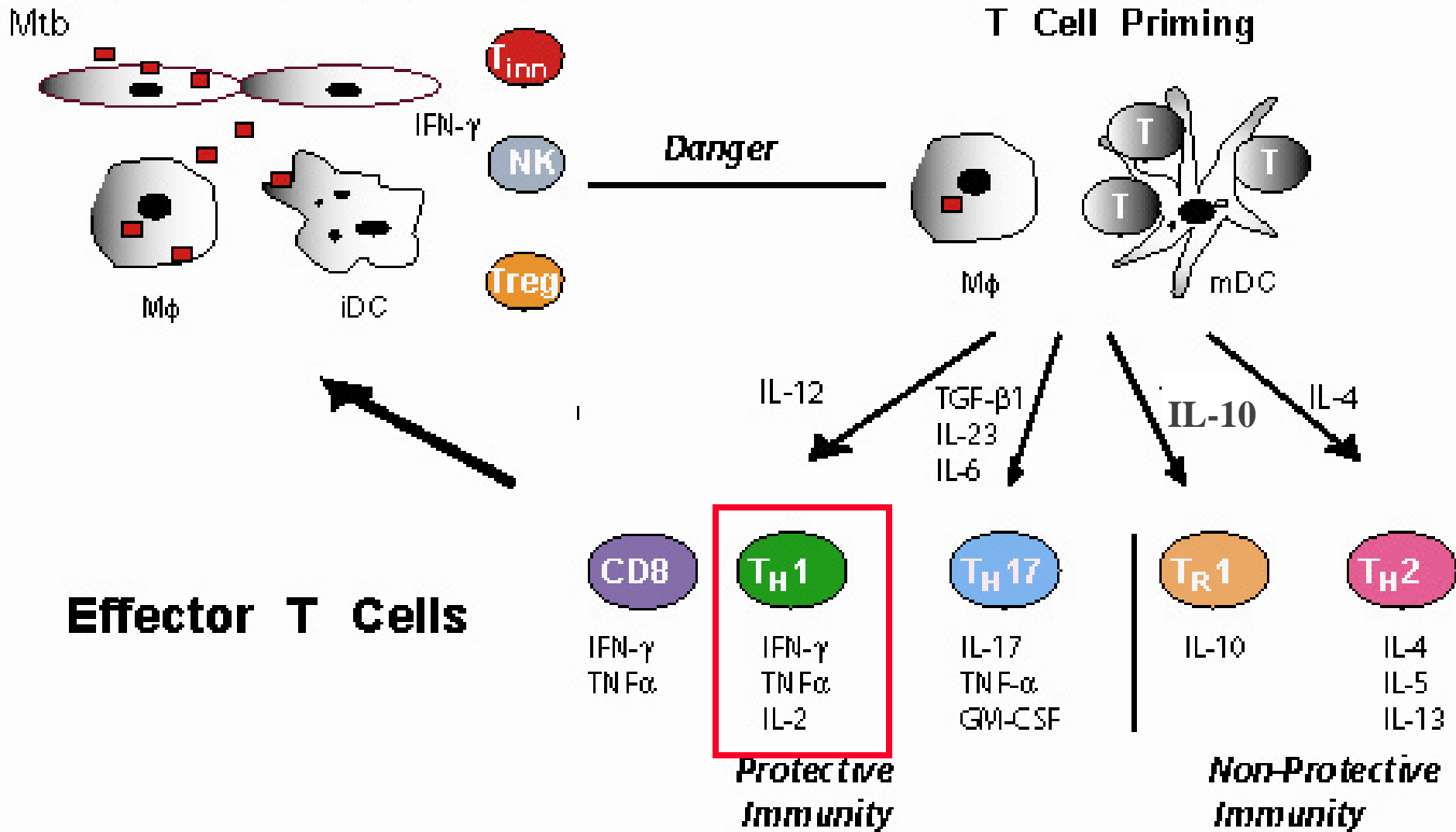
# Ugandan household contacts: IFN- $\gamma$ responses across the age span - TST & BCG



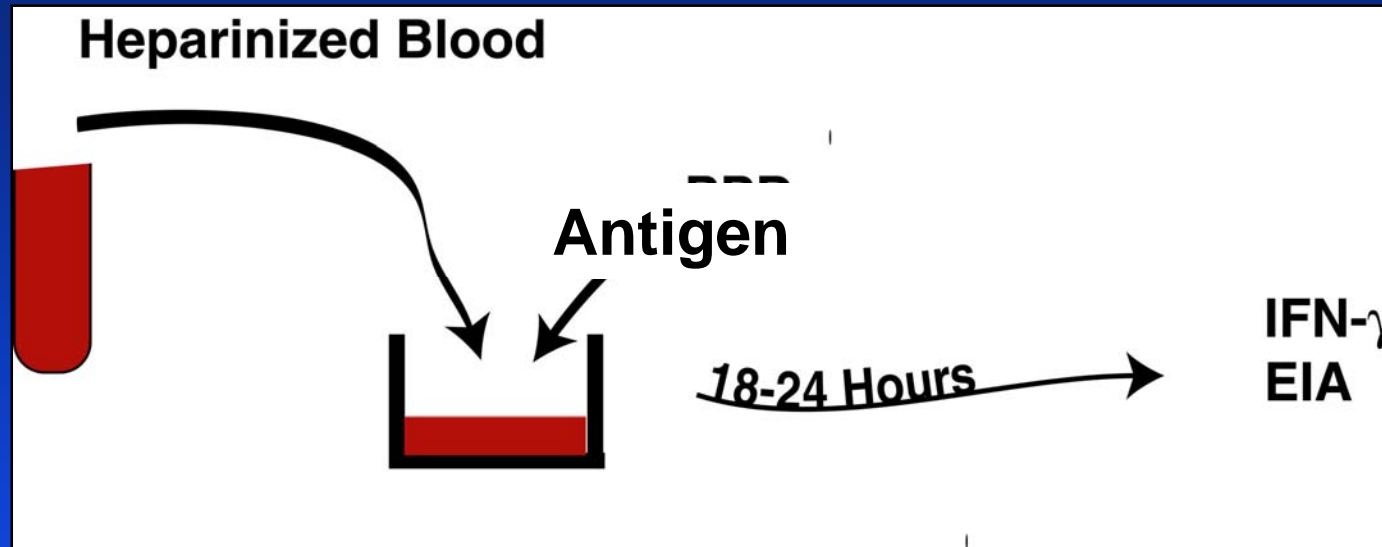
# Epithelium or Alveolus

# Lymph Node

## T Cell Priming



# QuantiFERON-TB PPD vs. QuantiFERON-TB Gold



QFT-TB PPD (1<sup>st</sup>)

PPD

M. Avium control

Mitogen Control

QFT-TB Gold (2<sup>nd</sup>)

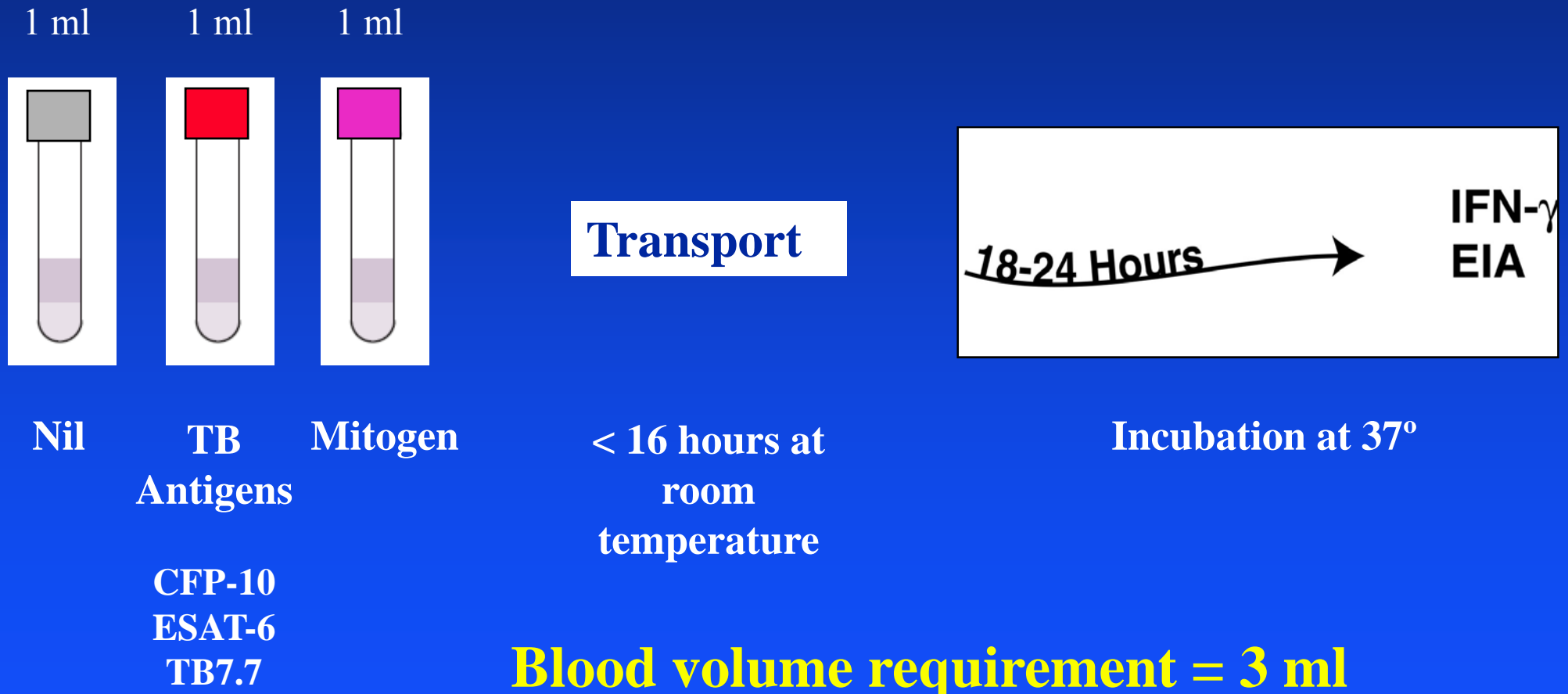
ESAT-6

CFP10

Mitogen

**Blood volume requirement = 6 ml**

# QuantiFERON®-TB Gold IT: ELISA



*Adapted from QuantiFERON®-TB Gold IT product insert*

# T-spot<sup>®</sup>.TB: ELISPOT

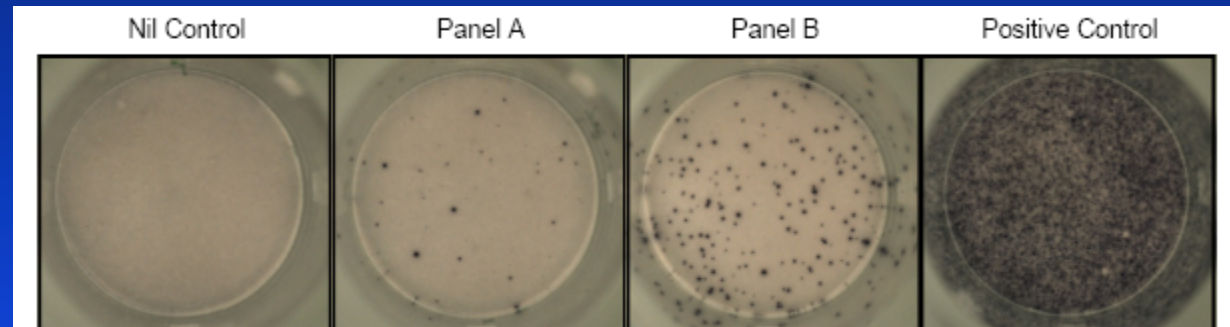


**CPT  
tubes**

**Transport <  
8 hr at room  
temperature**



**ELISPOT assay**



- Adults and children 10 years old and over: one 8mL or two 4mL tubes
- Children 2-9 years old: one 4mL tube
- Children up to 2 years old: 2mL paediatric tube

*From: T-spot<sup>®</sup>.TB Visual procedure guide*

# Evidence-based evaluation of IGRA's vs TST

Evaluation without reference to a gold standard diagnostic for LTBI:

- Sensitivity in culture positive TB.
- Relationship with exposure risk factors.
- Specificity in low risk populations.
- Prospective prognostic studies.

# Evaluation vs TST in children: Promise of IGRA's

Evaluation without reference to a gold standard diagnostic for LTBI:

- **Sensitivity in culture positive TB.**
- Relationship with exposure risk factors.
- Specificity in low risk populations.
- Prospective prognostic studies.

# QFT-Gold for Diagnosis of LTBI in active TB

QFT version	Study, year, country	Age range	Young/total	Sensitivity of TST in active TB n/N (%)	Sensitivity of IGRA in active TB n/N (%)
QFT Gold	Connell, 2006, Australia	0 - 18	NR/101	9/9 (100)	9/9 (100)
QFT Gold	Okada, 2007, Cambodia	0 - 5	210/210 < 6 yrs	15/19 (79)	10/19 (53)
QFT Gold IT	Connell, 2008, Australia	1 - 19	NR/100	NR	8/9 (89)
QFT Gold IT	Detjen, 2007, Germany	0 - 16	54% < 3 yrs; n = 73	28 /28 (100)	26/28 (93)
QFT Gold IT	Dogra, 2007, India	1 - 12	42/105 (40%) < 5 yrs	5/8 (52) –Cx+ 9/11 (82)-Rx	5/8 (52) – Cx+ 9/11 (82) - Rx
QFT Gold IT	Dominguez, 2007, Spain	0 - 18	15/134 (11%) < 5 yrs	9/9 (100)	6/9 (67)
QFT Gold IT	Kampmann, 2009, UK	2 - 16	26/91 < 5 years	20/24 (83) Cx+	20/25 (80) Cx+

# T-spot<sup>®</sup>.TB for Diagnosis of LTBI in active TB




Study, year, country	Age range	Young/total	Sensitivity of TST in active TB n/N (%)	Sensitivity of IGRA in active TB n/N (%)
Connell, 2008, Australia	1 - 19	NR/101	NR	9/9 (89)
Detjen, 2007, Germany	0 - 16	54% < 3 yrs; n = 73	28 /28 (100)	26/28 (93)
Dominguez, 2007, Spain	0 - 18	15/134 (11%) < 5 yrs	9/9 (100)	6/9 (67)
Kampmann, 2009, UK	2 - 16	26/91 < 5 years	20/24 (83)	14/24 (58)
Nicol, 2009, S. Africa	0 - NR	204/214 < 3 years	30/58 (52)	23/58 (40)
Warier, 2009 India	0 - 18	NR/15	NR	8/15 (53) – Cx+

# Evaluation vs TST in children: Promise of IGRA's

Evaluation without reference to a gold standard diagnostic for LTBI:

- Sensitivity in culture positive TB.
- **Relationship with exposure risk factors.**
- Specificity in low risk populations.
- Prospective prognostic studies.

# QFT-Gold for LTBI diagnosis

QFT version	Study, year, country	Age range	Young/total	TST positivity rate n/N (%)	Concordance TST/IGRA
QFT Gold	Connell, 2006, Australia	0 - 18	NR/101	42/42 (100)	11/42 (26); K = 0.30; TST+/QFT-
QFT Gold	Hesseling, 2008, S. Africa 	0 - 5	29/29	15/28 (54)	NR (88.9); K = 0.78; TST+/QFT-
QFT Gold	Mandalakas, 2008, S. Africa	NR, X = 4.4	All HIV+; NR/23	6/23 (26)	NR (75) K = .44; TST+/QFT-
QFT Gold	Okada, 2007, Cambodia 	0 - 5	210/210 : < 6 yrs	47/195 (24)	171/195 (88); K = 0.62; TST+/QFT-
QFT Gold IT	Chun, 2008, Korea 	0-13	NR: Med = 1.7 yr	26/42 (62)	24/42 (57); K = 0.19
QFT Gold IT	Connell, 2008, Australia	1 - 19	NR/100	47/97 (48)	NR; (75); K = .5
QFT Gold IT	Lighter, 2008, USA	0 - 18	67/207, < 5 yrs	116/204 (56)	112/207 (55); K = .17 TST+/QFT-
QFT Gold IT	Nakaoka, 2006, Nigeria 	0 - 14	NR/207	57/206 (28)	49/66 (74); K = .74; TST-/QFT+
QFT Gold IT	Dogra, 2007, India	1 - 12	42/105 , < 5 yrs	10/105 (9.5)	100/105; (95); K = .73
QFT Gold IT	Dominguez, 2007, Spain	0 - 18	15/134 (11%)	115/134 (86)	BCG-:23/40 (58), K=.24
QFT Gold IT	Kampmann, 2009, UK	0-16	56/118; < 5 yrs	57/114 (50)	NR (77); K = .53
QFT Gold IT	Tsiouris, 2006, South Africa	5-15	NA/NR	80/184 (44)	145/184 (79); K=.56; TST+/QFT-

# Diagnosis of LTBI/household contacts: QFT

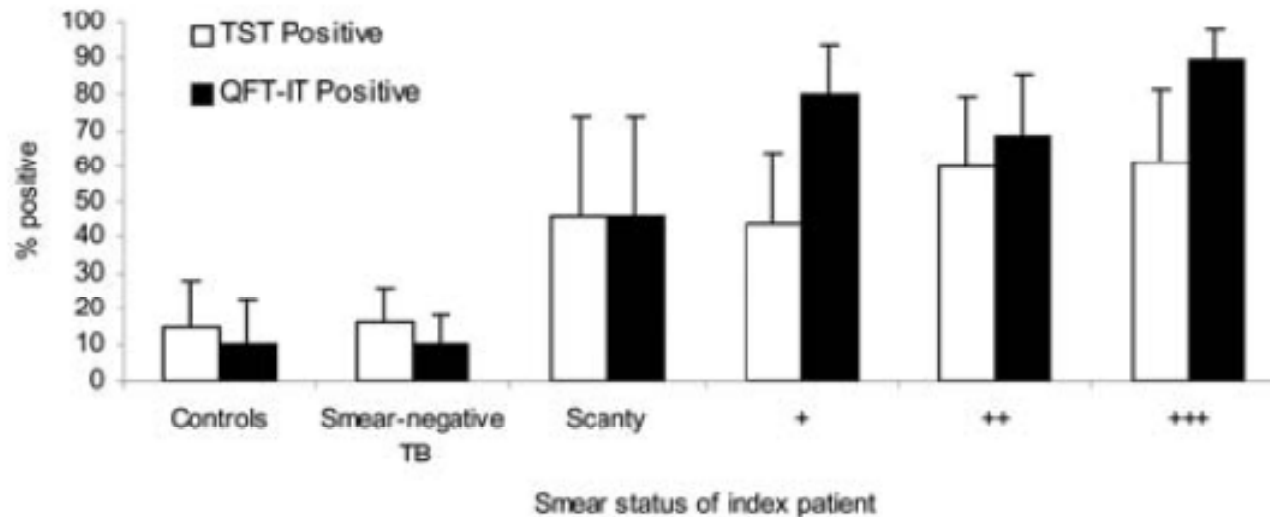



Figure 2. Proportion of children with positive tuberculin skin test (TST) (>10 mm) and QuantiFERON Gold in Tube (QFT-IT) test results, by adult smear positivity. Error bars show 95% confidence intervals.

# T-spot<sup>®</sup>.TB for LTBI diagnosis

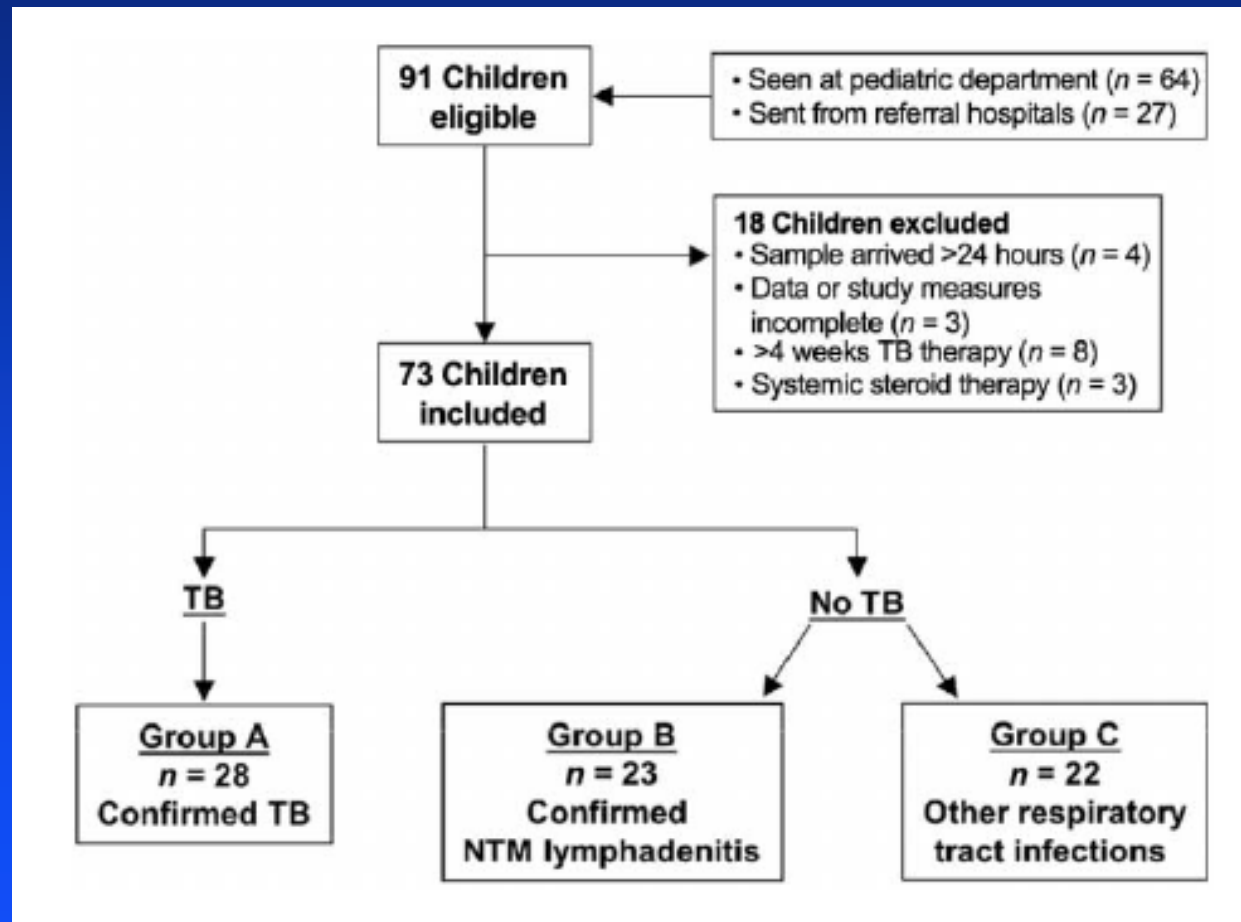
Study, year, country	Age range	Young/total	TST positivity rate n/N (%)	Concordance TST/QFT
Connell, 2008, Australia	1 - 19	NR/100	47/97 (48)	75% K = .51
Dominguez, 2007, Spain	0 - 18	15/134 (11%)	115/134 (86)	BCG-:25/40 (62), K=.33
Hesseling, 2008, South Africa 	0-5	29/29	15/28 (54)	NR (46), K=-0.15 TST-/IGRA+
Kampmann, 2009, UK	0-16	56/118; < 5 yrs	57/114 (50)	NR (75); K = .49
Mandalakas, 2008, S. Africa	NR, X = 4.4	All HIV+; NR/23	6/23 (26)	NR (67) K = .33; TST-/IGRA+

# Evaluation vs TST in children: Promise of IGRA's

Evaluation without reference to a gold standard diagnostic for LTBI:

- Sensitivity in culture positive TB.
- Relationship with exposure risk factors.
- **Specificity in low risk populations.**
- Prospective prognostic studies.

# Specificity of Diagnosis of LTBI in TB suspects: QFT-IT/ T-spot<sup>®</sup>.TB vs TST



# Specificity of Diagnosis of LTBI in TB suspects: QFT-IT/ T-spot<sup>®</sup>.TB vs TST

**Table 3. Indicators of diagnostic accuracy for the tuberculin skin test (TST), QFT-IT, T-SPOT, and the combination of QFT-IT and T-SPOT.**

Test	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	Positive PV, % (95% CI)	Negative PV, % (95% CI)
TST	100 (88–100)	58 (42–73)	2.4 (1.6–3.4)	0.1 <sup>a</sup> (0.01–0.4)	62 (47–76)	100 (85–100)
QFT-IT	93 (77–99)	100 (91–100)	37.1 <sup>b</sup> (5.3–258.0)	0.1 (0.02–0.3)	100 (87–100)	95 (84–99)
T-SPOT	93 (77–99)	98 (87–100)	37.1 (5.3–258.0)	0.1 (0.02–0.3)	96 (81–100)	95 (83–99)
QFT-IT and T-SPOT (both positive)	89 (72–98)	100 (91–100)	35.7 <sup>b</sup> (5.1–248.4)	0.1 (0.04–0.3)	100 (86–100)	93 (81–99)
QFT-IT and T-SPOT (1 positive)	96 (82–100)	98 (87–100)	38.6 (5.6–267.5)	0.04 (0.01–0.3)	96 (82–100)	98 (87–100)
Stepwise approach <sup>c</sup>	93 (77–99)	100 (91–100)	37.1 <sup>b</sup> (5.3–258.0)	0.1 (0.02–0.3)	100 (87–100)	95 (84–99)

**NOTE.** Calculations were based on 68 children, including 28 children with confirmed tuberculosis (group A) and 40 unvaccinated children without tuberculosis (19 children with confirmed nontuberculous mycobacterial lymphadenitis [group B] and 21 children with other respiratory tract infections [group C]). LR, likelihood ratio; PV, predictive value; QFT-IT, QuantiFERON-TB Gold In-Tube (Cellestis); T-SPOT, T SPOT-TB (Oxford Immunotec).

<sup>a</sup> For calculation of this LR, we classified 1 correct diagnosis in a child with tuberculosis as a false-negative result (to avoid division by 0).

<sup>b</sup> For calculation of this LR, we classified 1 correct diagnosis in a child without tuberculosis as a false-positive result (to avoid division by 0).

<sup>c</sup> We also calculated diagnostic accuracy in a stepwise approach according to recent National Institute of Health and Clinical Excellence guidelines [15]; only patients with positive TST results were tested with IFN- $\gamma$  release assays. QFT-IT and T-SPOT showed the same values for all indicators.

# Specificity of IGRA in BCG-vaccinated children

- Inclusion: No risk and TST  $\geq 5$  mm.
- 62 children age 2 months – 14 years, all BCG vaccinated.
- 0/62 QFT-IT positive

# Evaluation vs TST in children: Promise of IGRA's

Evaluation without reference to a gold standard diagnostic for LTBI:

- Sensitivity in culture positive TB.
- Relationship with exposure risk factors.
- Specificity in low risk populations.
- **Prospective prognostic studies.**

# Diagnosis of LTBI/school contacts: QFT

- 349 15-16 y/o boys, all BCG vaccinated.
- Tested with TST: 95 of 349 positive.
- 88 TST positive tested with QFT-TB Gold: 4 of 88 positive.
- 3 of 4 in high exposure group – received INH.
- Remaining TST positive students – no INH and no disease with 3+ years follow-up.

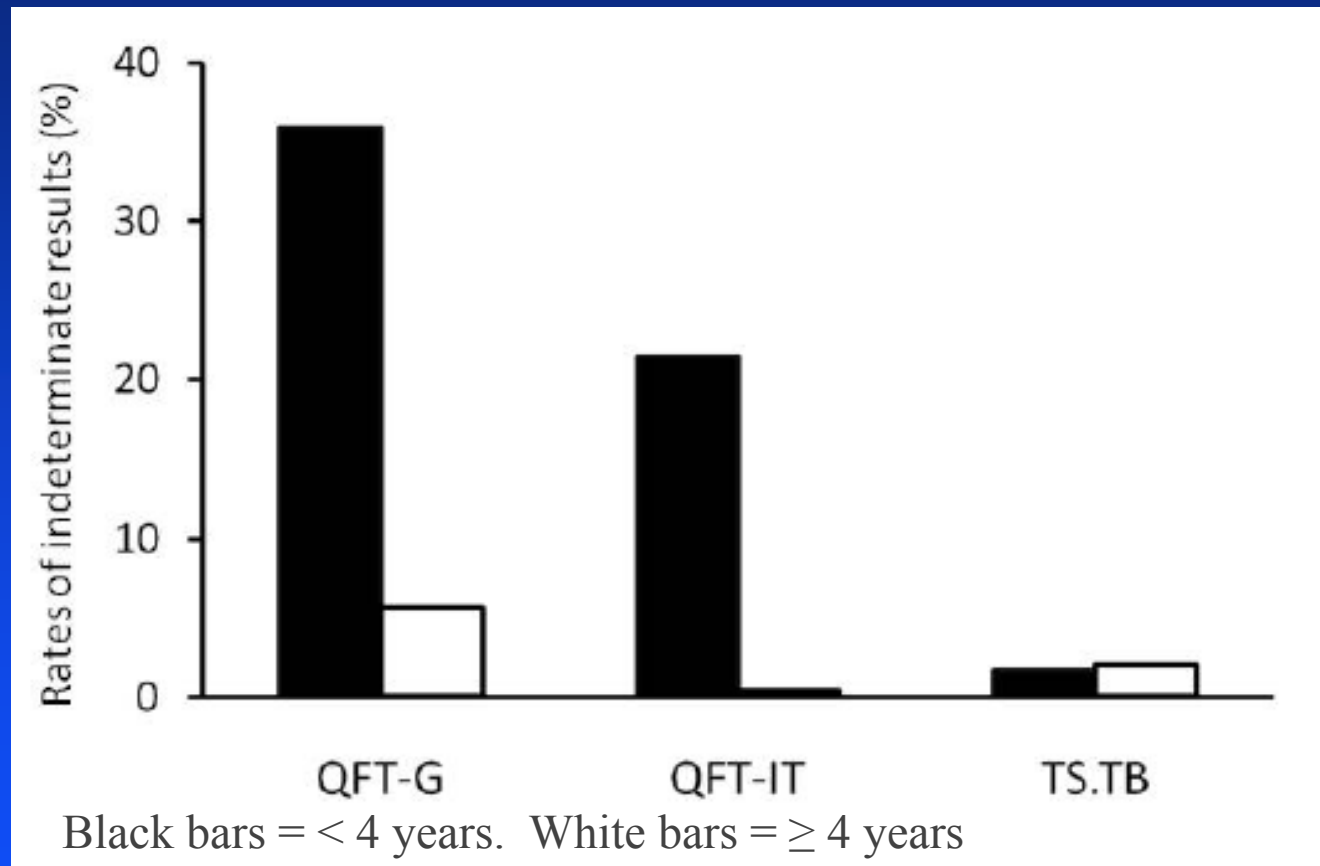
# Limitations of IGRA's in Children

- Paucity of data in children < 5 years.
- Increased frequency of indeterminate assays in children < 5 years.
- Required blood volumes.
- Lack of longitudinal data.

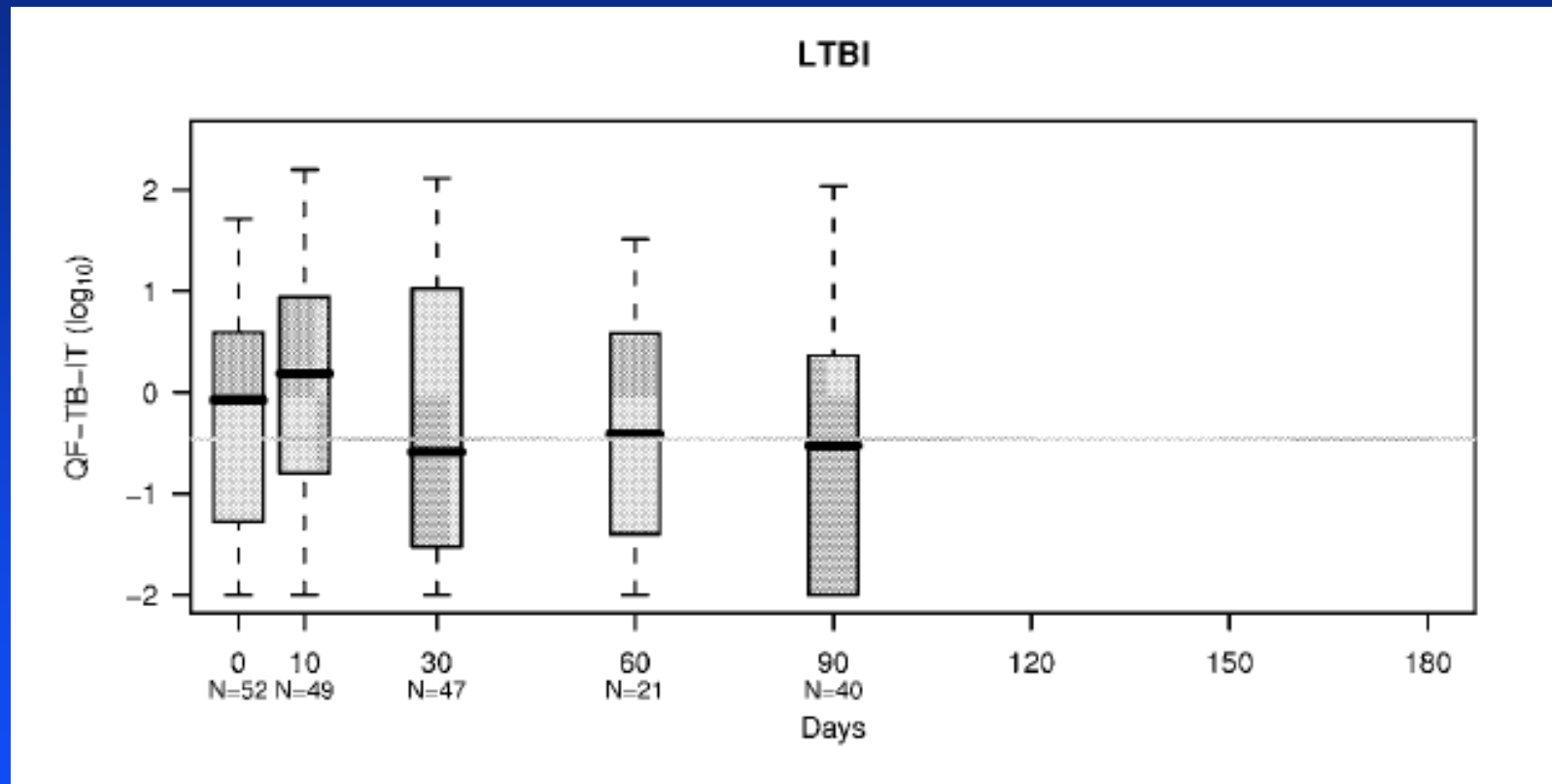
# Limitations of IGRA's in young children

QFT version	Study, year, country	Age range	Young/total	Indeterminate n/N (%)	QNS Blood n/N (%)
QFT Gold	Connell, 2006, Australia	0 - 18	NR/101	17/101 (17)	3/101 (3)
QFT Gold	Hesseling, 2008, S. Africa	0 - 5	29/29	3/21 (14)	7/29 (24)
QFT Gold	Mandalakas, 2008, S. Africa	NR, X = 4.4	All HIV+; NR/23	0/12 (0)	11/23 (47)
QFT Gold	Okada, 2007, Cambodia	0 - 5	210/210 : < 6 yrs	9/208 (6)	13/217 (6)
QFT Gold IT	Chun, 2008, Korea	0-13	NR: Med = 1.7 yr	17/227 (7.5)	NR
QFT Gold IT	Connell, 2008, Australia	1 - 19	NR/100	0/38 (0)	5/101 (5)
QFT Gold IT	Lighter, 2008, USA	0 - 18	67/207, < 5 yrs	3/207 (1)	0/207 (0)
QFT Gold IT	Nakaoka, 2006, Nigeria	0 - 14	NR/207	33/207 (16)	NR
QFT Gold IT	Dogra, 2007, India	1 - 12	42/105 , < 5 yrs	0/105 (0)	0/105 (0)
QFT Gold IT	Dominguez, 2007, Spain	0 - 18	15/134 (11%)	3/134 (2)	NR
QFT Gold IT	Kampmann, 2009, UK	0-16	56/118; < 5 yrs	14/209 (7)	0/209 (0)
QFT Gold IT	Tsiouris, 2006, South Africa	5-15	NA/NR	NR	37/221 (17)

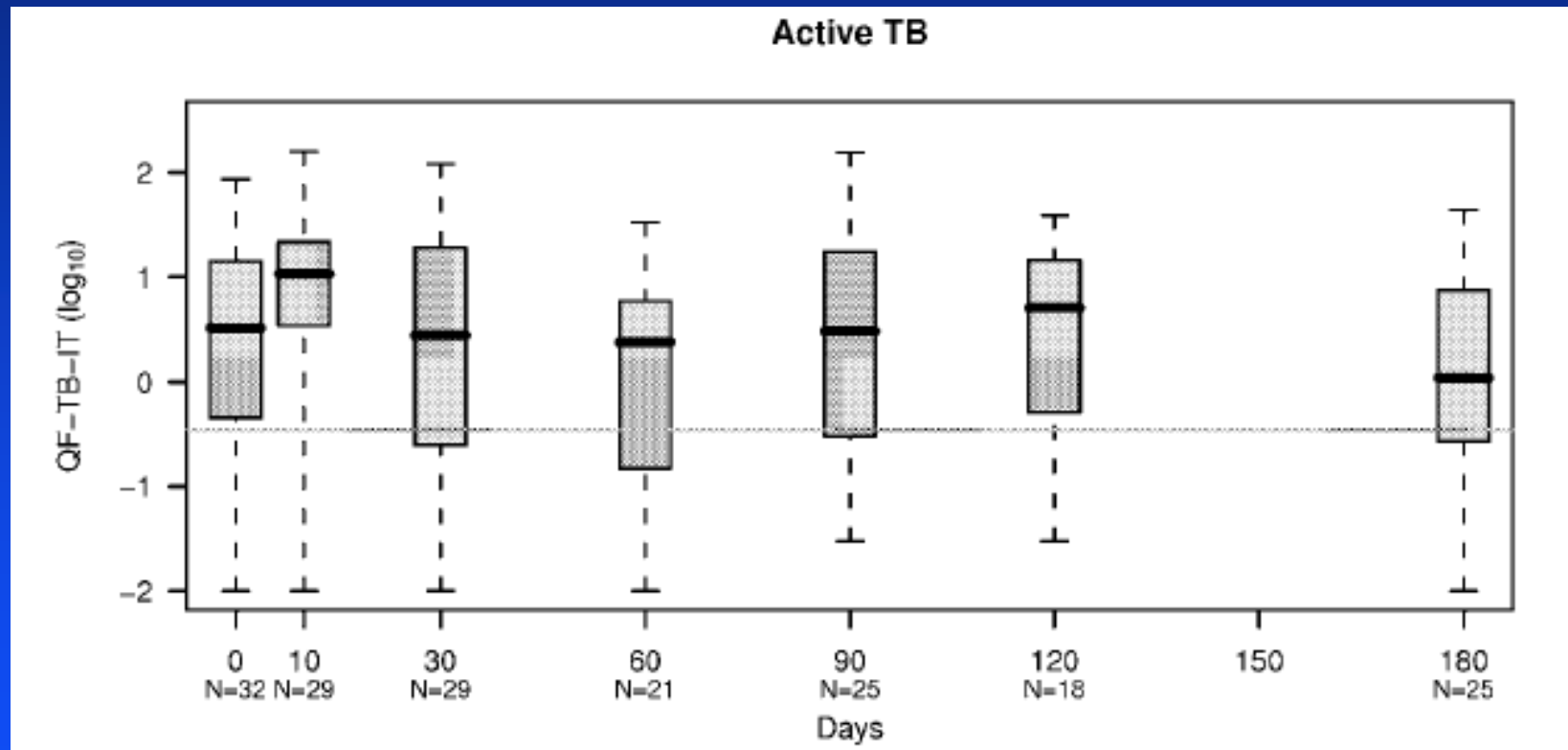
# Indeterminate rates of IGRA's



# Longitudinal IGRA data in children



# Longitudinal IGRA data in children



# QFT vs T-SPOT.TB



Specificity: QFT

- BCG-vaccinees



Sensitivity: T-SPOT.TB

- Immunocompromised
- Young children

What would we like in a test?

Specificity and Sensitivity: The DiCaprinator



*With permission: Photoshop by David Lewinsohn*

## QFT vs T-SPOT.*TB* in children

- QFT more available than T-SPOT.*TB*
- More published data in children for QFT than for T-SPOT.*TB*.
- Less indeterminate results for T-SPOT.*TB* compared to QFT.
- Less blood required for T-SPOT.*TB* than for QFT.
- Specificity equivalent in one study.
- More positive tests with T-SPOT.*TB* than QFT-IT.
- Sensitivity of T-SPOT.*TB* increased, equal, decreased when compared with QFT-IT.

# Indications for IGRA's and TST in children (My opinion)

- IGRA preferred to TST in children  $\geq 5$  years.
- TST preferred to IGRA in children  $< 5$  years.
  - Close contacts of active TB cases
  - Immigrants from endemic countries
  - Significant travel history

# Indications for IGRA's and TST in children (My opinion - continued)

- Consider both IGRA and TST and take either positive as evidence of infection.
  - TB suspects
  - HIV infection
  - Increased risk of progression of LTBI

# Upcoming recommendations

- ATS/CDC/IDSA (AAP) guidelines:
- CDC guidelines – updated for QFT-Gold-IT and T-SPOT.*TB*.
- AAP – 2009 RedBook

## Future research needs for IGRA's in children

- High risk young children in low incidence setting (Household contact study in young children).
- Longitudinal data in young children (Data to inform “window prophylaxis”).
- Young immunosuppressed and HIV-infected children.
- Commercial tests with decreased blood volume requirements.

## New assays for LTBI/TB diagnosis in children

- IP-10 assays (ELISA/CD4)
- IFN- $\gamma$  , IL-2, TNF- $\alpha$  (Flow cytometry)
- CD8+ T cells (ELISPOT)
- Antibodies in lymphocyte supernatant (ALS)

Slides Credits:

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Chuck Daley

David Lewinsohn

Madhu Pai

Lewinsohn Labs

Laura Byrd

Megan Null

Melissa Nyendak

Lynne Swarbrick

David Lewinsohn

**PROTECT**

*them from*

**TUBERCULOSIS**

**Keep them away from sick people**  
**Insist on plenty of rest**  
**Train them in health habits**  
**Consult the doctor regularly**

This campaign made possible through the sale of ChristmasSeals

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