Is the prevalence of *M. tuberculosis* infection higher in HIV-exposed children?

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Introduction

- The effect of HIV exposure on the risk of *Mycobacterium tuberculosis (M.tb)* infection and tuberculosis (TB) in children is not well understood [1]
- HIV-exposed uninfected children have an increased risk of morbidity and mortality in sub-Saharan Africa compared to HIV-unexposed children [2]
- In high HIV/TB burden settings increased susceptibility and/or exposure to *M.tb* in children born to HIV-positive mothers may contribute to ill health despite PMTCT

Study hypothesis: Prevalence of *M.tb* infection is higher in HIV-exposed children compared to HIV-unexposed children

Methods

Study setting: **Karonga Demographic Surveillance Site (DSS), Malawi**

- Total population ~ 36,000; adult HIV prevalence ~ 8%
- Annual incidence of new smear-positive TB ~ 87 per 100,000 adults per year
- Bacille Calmette-Guérin (BCG) vaccination is administered at birth

Design, procedures and analysis:

- Cross-sectional tuberculin skin test survey in children aged 2 to 4 years resident in DSS (January 2012 to December 2014)
- 2TU of purified protein derivative RT23; read at 48-72 hours
- Maternal HIV sero-status, BCG vaccination, household socioeconomic status (SES), household TB contact and smear-positive notification data were available from related studies within the DSS
- A positive TST was defined as induration≥15mm. Children under 2 years were excluded to minimise misclassification due to BCG-attributable induration. Children whose mothers were known to be HIV-positive at the time of delivery were defined as HIV-exposed
- Random effects logistic regression model, taking into account clustering within households was used

Ethics:

- Study approved by the Malawi National Health Sciences Research Committee and the London School of Hygiene and Tropical Medicine Ethics committee
- Written informed consent was obtained from the parent or guardian of all the children who participated in the study

Results

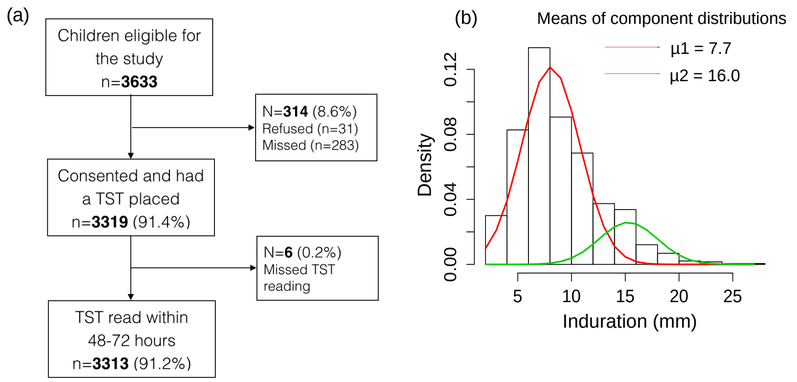


Figure 1. (a) Study flowchart (b) Observed and mixture distributions of non-zero TST induration (n=273)

36/3313 (1.1%) children had TST≥15mm; 92/3313 (2.8%) were HIV-exposed.

The crude odds ratio of prevalent *M.tb* infection in HIV-exposed children compared to HIV-unexposed children was 3.7 (95% CI 1.1 – 12.6). See table. Adjustment for age, sex and time since BCG did not alter the effect estimate.

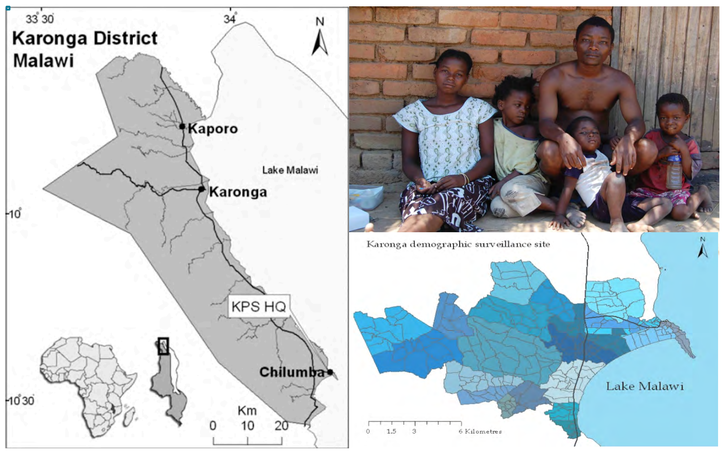


Figure 2. Study setting: Karonga demographic surveillance site (DSS), northern Malawi. DSS composed of 21 geographically-defined residential areas.

Risk factor	TST≥15mm n/N (row%)	Crude OR (95% CI)	p-value	Adjusted OR* (95% CI)	p-value
Maternal HIV status at birth					
Negative	26/2908 (0.9%)	1	0.004	1	0.04
Positive	3/92 (3.2%)	3.7 (1.1 – 12.6)		4.0 (1.2 – 13.8)	
Unknown	7/313 (2.2%)	2.5 (1.1 – 5.9)		2.5 (1.1 – 5.8)	
Known household contact with TB (during child's lifetime)					
No	34/3279 (1.0%)	1	0.009	1	0.09
Yes	2/34 (5.9%)	6.0 (1.4 – 25.9)		4.6 (1.1 – 20.5)	
Community *M.tb* exposure (av. smear-positive TB notification rate per 100,00 population per residential area)^					
<30	15/2033 (0.7%)	1	0.02	1	0.01
≥30	21/1280 (1.6%)	2.2 (1.2 – 4.4)		2.3 (1.2 – 4.5)	
Household SES					
Very 'poor'	5/873 (0.6%)	1	0.07	1	0.02
Less 'poor'	31/2440 (1.3%)	2.2 (0.9 – 5.8)		2.7 (1.0 – 7.1)	

Table. Univariable and multivariable analysis of risk factors associated with TST≥15mm among children aged 2 to 4 years. * Adjusted for all risk factors shown.

Conclusions

- Children aged 2 to 4 years born to HIV-positive mothers have a 4-fold increased risk of *M.tb* infection compared to HIV-unexposed children, after adjusting for known household TB contact, community *M.tb* exposure and household SES.
- This increased risk may be higher than measured as HIV-infected children (a subset of those whose mothers are HIV-positive) may not react to TST
- Further research is required to investigate whether the observed increased risk in HIV-exposed children is due to increased susceptibility to *M.tb* and/or increased *M.tb* exposure
- These findings add to the evidence base for the implementation of a family-centred approach to HIV and TB prevention, treatment and care in high-burden settings.

References

1. Cotton MF, Schaaf HS, Lottering G, et al. Tuberculosis exposure in HIV-exposed infants in a high-prevalence setting. *Int J Tuberc Lung Dis.* Feb 2008;12(2):225-227.
2. Afran L, Garcia Knight M, Nduati E, Urban BC, Heyderman RS, Rowland-Jones SL. HIV-exposed uninfected children: a growing population with a vulnerable immune system? *Clin Exp Immunol.* Apr 2014;176(1):11-22.

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