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Source case identification in HIV- exposed infants and Tuberculosis diagnosis in an Isoniazid prevention study

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Abstract

Background—Identifying a source case for TB-exposed children is challenging. We examined the timepoint of obtaining source case TB contact information in HIV-infected and HIV-exposed uninfected (HEU) children in a randomized, placebo-controlled trial of pre-exposure isoniazid prophylaxis.

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All authors are part of the IMPAACT study group P1041.

Methods—543 HIV-infected and 808 HEU infants without TB exposure between 3 and 4 months of age were enrolled between 2004 and 2008. At 3 monthly follow-up, infants were evaluated for TB and caregivers were asked about new TB exposures.

Results—128 cases of TB disease and 40 deaths were recorded, 19% (105/543) for HIV-infected and 8% (63/808) for HEU, 229 TB contact occasions were reported in 205/1351 (15%), (83%: 189/229) in the household. 53% of household contacts (108/189) had microbiological evaluations, 81% (87/108) were positive. HIV-infected and HEU infants had similar frequencies of TB contacts, reported in 48% with definite TB, 58% for probable TB, 43% for possible TB. Among 128 children diagnosed with TB, a TB contact was identified for 59. Of these, 29/59 (49%) were identified *at* or *after* child's TB diagnosis.

Conclusion—TB source cases are often identified at or after a child's TB diagnosis. More effort is required for earlier detection.

Keywords

Child TB diagnosis; Source case; HIV exposed

BACKGROUND

Tuberculosis (TB) is a leading infectious disease cause of morbidity and mortality. From studies preceding the HIV pandemic, 60–80% of children develop *Mycobacterium tuberculosis* (*M.tb*) infection after prolonged contact with a sputum positive household source case¹. In the first year of life, between 30 and 50% of *M.tb*-infected children without preventive therapy progress to TB disease. Most infected children below 2 years of age had contact with a household source case¹. In 22 high burden countries, over 2.6 million children below 5 years of age were infected with *M.tb* in 2010 and approximately 327 000 developed TB². Although post exposure isoniazid (INH) preventive therapy (IPT) reduces progression to TB disease, there are missed opportunities for IPT^{3,4}.

In 2008, WHO introduced the “3 I's Strategy” for HIV-infected populations comprised of intensified TB case finding, IPT and TB infection control. Intensified case finding was emphasized^{5,6}.

Active surveillance of children for *M.tb* exposure in the first few years of life is important, but can be challenging. In high prevalence settings, in approximately 50% of children with TB disease, a source case cannot be identified^{3,4} suggesting that exposure to a source case can occur outside the household³.

The randomized placebo controlled INH pre-exposure prophylaxis study IMPAACT P1041 in HIV-infected and HIV exposed uninfected (HEU) infants, showed no difference in TB-free survival between INH and placebo⁶. The cumulative incidence of TB by 96 weeks was 22.2% in HIV-infected (95% CI: 15.7, 31.0) and 11.7% (95% CI: 9.2–14.4%) in HEU infants. Here, we profile identification of TB source cases relative to the date of TB diagnosis in study participants.

The aims of this study were to describe time between TB diagnosis in study participants and identification of TB source cases and also frequency of TB contacts.

METHODS

P1041 was conducted in Chris Hani-Baragwanath Hospital, Johannesburg; Tygerberg Academic Hospital, Cape Town; King Edward VIII Hospital, Durban and Princess Marina Hospital, Gaborone from December 2004 to June 2008. HIV-infected and HEU infants given Bacille Calmette-Guérin (BCG) immunization within 30 days of birth, enrolled between 3 and 4 months of age.

Exposure to a smear or culture positive TB case pre-study entry was an exclusion criterion. At all 12 weekly study visits and unscheduled visits, the primary caregiver was asked whether the study participant was newly exposed to an adult or child with previously unreported clinical or active TB. For new exposures, source case characteristics were categorized as follows: household contact, whether or < 12 years of age or sleeping in the same room. For non-household contacts, whether the source case was a playmate 12 years of age or if contact occurred in hospital. Microbiologic data for source cases such as smear positivity and culture were noted. Treatment was documented as ongoing or completed.

All TB-exposed infants to a source case were evaluated for *M.tb* infection and TB disease. After exposure to a household source case, study drug (INH or placebo) was replaced with open-label IPT after excluding TB disease.

M.tb infection was diagnosed by intradermal tuberculin skin test using 2 units of RT23 2TU (Statens Serum Institut) giving horizontal induration 10mm for HEU and 5mm for HIV-infected children after 48 to 72 hours.

Participants were screened for TB using a clinical algorithm⁷ at study visits and post-exposure (Table 1). When pulmonary TB was suspected, two gastric washings and two induced sputa were collected for auramine staining and mycobacterial culture (Bactec) method at nationally accredited laboratories. Children were categorised as “definite”, “probable”, “possible” TB or not having TB. “Definite” TB was defined as *M.tb* cultured from any site or positive auramine staining of cerebrospinal fluid. “Probable” TB required at least two clinical criteria plus either positive auramine staining of induced-sputum or gastric fluid or suggestive histology (caseating granuloma); or with a chest radiograph suggestive of TB. “Possible” TB required an algorithm score 6 and a radiograph suggestive of TB, or a positive tuberculin skin test with chest radiograph suggestive of TB⁷. Extrapulmonary TB was included using prespecified diagnostic criteria.

Only data until 108 weeks post-entry, when data collection was uniform were used in this analysis. Clopper-Pearson exact tests were performed to compare proportions between two groups. SAS 9.2. in UNIX was used for descriptive statistics and p-values.

Institutional review boards of participating centers, the Medicines Control Council of South Africa and the Division of AIDS at the NIAID approved P1041. Legal guardians of study participants gave written informed consent prior to randomization.

RESULTS

After confirming HIV status, 543 HIV-infected and 808 HEU infants were enrolled. At baseline, the median age was 96 days (range: 91–120) with 97% being black-African. There were fewer HIV-infected than HEU males (43% vs 51%, $p=0.007$). The biological mother was the main primary guardian, albeit being slightly lower among the HIV-infected cohort (92% vs 99%, $p<0.001$). Sixty percent of participants lived in formal (brick) housing. The median household size was 4 (Interquartile range (IQR): 3–6) and the median number of sleeping rooms was 2 (IQR: 1–2). The HIV-infected cohort had fewer instances where > 3 people slept in a room compared to HEU (34% vs 41%, $p=0.01$).

By week 108, 128 TB cases (possible, probable or definite) and 40 deaths occurred. The rates of loss to follow-up were 12% and 31% in the HIV-infected and HEU cohorts, respectively. Overall, 12.4% (168/1351) either had TB disease or had died; 19% (105/543) HIV-infected and 8% (63/808) in HEU children. The total follow-up period 568 person-years for HIV-infected cohort and 1461 for HEU participants, the incidence rate of TB disease or death being 18.5 and 4.3 per 100 person-years, respectively.

Exposure to a source case occurred in 205/1351 (15%) of participants but was more common among those with TB disease (59/128: 46%) than those remaining TB-free (143/1183: 12%). Exposure to a TB source case was reported in 3/40 (8%) of deaths without a TB diagnosis (Table 2).

The majority of source cases were household members above 12 years old (189/229, 79%). Of the 127 (55%) having microbiologic evaluations, 105 had either positive smears or cultures (Table 3).

The timing of reported TB exposure relative to date of TB diagnosis in participants is in Table 4. TB exposure was reported either at or after TB diagnosis in 29 (49%) of the 59 children with exposure to a TB source case, with 10 reported more than 6 months later.

The proportion of participants with exposure to a TB source case was similar in HIV-infected and HEU participants (14% vs 16%, $p=0.19$). Incidence of reporting a TB contact was 13 per 100 person-years for HIV-infected and 9 per 100 person-years for HEU. In 105 HIV-infected participants with protocol-defined TB, 30 (29%) had exposure to a TB source case versus 44 (10%) among the 438 HIV-infected participants without exposure ($p<0.001$). Similarly, for HEU, documented TB exposure was higher among the 63 participants with TB compared to the 745 without TB [32 (51%) vs 99 (13%), $p<0.001$]. There was a significant association in both HIV-infected and HEU participants, between reported TB exposure and TB disease or death.

DISCUSSION

Identifying a source case is not a simple process. In this study, we demonstrated that a source case was identified only after TB was diagnosed in 17% and at TB diagnosis in 32% of participants. These observations support our previous experience during screening infants for the trial. After counselors had excluded 52 infants because of exposure to a TB source

case, an additional 25 TB-exposed infants were identified by a medical doctor⁸. A limitation of the present and earlier screening studies is that P1041 was not designed to evaluate detailed information on TB exposure. The TB exposure questionnaire requested limited information. One question addressed TB source case infectivity (whether smear or culture positive, whether adolescent/adult or child) and one question on the intensity of a child's exposure to the TB source case (whether within the household). More detailed questioning may identify TB source cases. For example, Mandalakas et al developed a contact score using a 10-item questionnaire to collect child-specific information about TB exposure (ranging from "1" for the lowest to "10" for the highest exposure)⁹. The score demonstrated a strong correlation between the intensity of TB exposure and TB infection. In children aged 3 months to 6 years with household TB exposure, the odds for *M.tb* infection increased by 74% with each 1-point increase in the contact score⁹. Nevertheless, using only a binary indicator of TB exposure (whether or not TB exposure was reported), we demonstrated an association between reported TB exposure and TB disease or death in P1041. Had we collected more detailed information, we may have been able to determine how intensity of exposure to a source case influenced our classification of TB disease into definite, probable or possible.

For many children with TB in our study, source cases were not identified, as previously reported by Schaaf et al, in a study of hospitalized children with culture-confirmed TB from a high TB prevalence setting.^{3,10} A limitation of our study is that it does not reflect low TB prevalence settings where there is often active identification of source cases.

Our findings support those of Puryear et al whose household investigation was triggered by children with TB in Gaborone, Botswana. Here 31% of households had at least 1 additional previously undiagnosed person with either latent or active TB disease¹³.

Although household contact is the main driver of childhood TB, the definition of what comprises a household is often not considered as separate families may live in close proximity on the same plot of land and develop TB asynchronously¹¹. The definition of "household" should be sufficiently broad to include structures on the same plot of land, where facilities are frequently shared¹².

Despite the active surveillance and trained research personnel to identify potential exposure to TB and to collect TB contact data, the process missed timely identification of many source cases. This is likely more pronounced when healthcare professionals incorporate active surveillance into their daily work at busy clinics (community health centres) and hospitals¹⁴. Caregivers may be unaware of TB source cases in close vicinity until TB treatment begins. Also, household visitors might not disclose their TB status either due to stigma or lack of awareness. Although it is commonly accepted that children, especially those <5 years of age are most likely infected by a household contact, transmission can occur in the community^{10,14,15}.

P1041 facilitated prospective evaluation of children for TB and to identify source cases. We suspect that knowledge of TB disease in children increased awareness in the caregivers for identifying source cases. Late identification of source cases, eliminated an opportunity for

either IPT (for those on placebo) or earlier TB diagnosis. More attention should be given to sensitizing carers to identify active TB disease in the household and community. Routine IPT for HIV-infected adults was only implemented in 2011 which should reduce risks for children.

There was a high loss to follow up (LTFU) in the HEU cohort; young maternal age being a risk factor. Household support was important for participant retention, particularly for HEU. Maternal history of TB reduced the risk of LTFU by nearly 70%¹⁶. TB cases among HEU might have been missed due to LTFU, another limitation of the study.

CONCLUSION

Exposure to TB occurs frequently in a high prevalence setting. Identification of a source case often occurs simultaneously or after TB diagnosis in children and represents a missed opportunity for prevention or earlier diagnosis. More emphasis is needed to sensitize caregivers to identify signs and symptoms of TB and to improve health care worker skills to identify TB source cases sooner.

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Table 1

Algorithm for screening and diagnosis of clinical tuberculosis

Feature	Score				
	0	1	2	3	4
Weeks of illness (including cough)	<2	2-4		>4	
Nutrition (% weight for age)/malnutrition	>80%	60-80%	<60%/drop 2 lines		
Family history of TB	None	Reported by family		Sputum proven	
<u>Tuberculin skin test</u>				Reactive 5mm for HIV-infected or 10 mm for HEU)	
Fever not responding to rx for >2 weeks			X		
Confirmed or suspected EPTB					X

Table 2

TB outcomes in participants with reported TB Exposure by Event

		Event Observed on Participant					Total (N=1351)
		Definite TB (N=25)	Probable TB (N=19)	Possible TB (N=84)	Death (N=40)	No TB or death (N=1183)	
Reported TB Exposure							
Yes	12 (48%)	11 (58%)	36 (43%)	3 (8%)	143 (12%)	205 (15%)	
	No	13 (52%)	8 (42%)	48 (57%)	37 (93%)	1,040 (88%)	1,146 (85%)

Table 3

Information on potential TB Source Cases

Description of potential source case	TB Source Case Evaluated	Frequency N	If Microbiological Evaluation was done on Source Case			
			Frequency N	Type	Positive	Negative
			AFB Smear	Culture		Result *
Household 12 years old	189	108	86 (80%)	22 (20%)	87 (80%)	21 (20%)
Household < 12 years old	10	5	4 (80%)	1 (20%)	4 (80%)	1 (20%)
Playmate	1	0	0	0	0	0
Non-household 12 years old	29	14	11 (79%)	3 (21%)	14 (100%)	0 (0%)
Total	229	127	101 (80%)	26 (20%)	105 (83%)	22 (17%)

NOTE: Percentages are over those with microbiological evaluations

No potential source cases from 'hospital' or 'other'.

* Combined smear and/or culture

Table 4

Timing of Reporting of TB Exposure among Children with TB Diagnosis (N=59)

Timing of Report	Definite TB (N=12)	Probable TB (N=11)	Possible TB (N=36)	Total (N=59)
Reported before TB diagnosis	5 (42%)	6 (55%)	19 (53%)	30 (51%)
Reported after TB diagnosis	6 (50%)	3 (27%)	10 (28%)	19 (32%)
Reported same time as TB diagnosis	1 (8%)	2 (18%)	7 (19%)	10 (17%)

Definitions:

Definite TB: *Mycobacterium tuberculosis* cultured from any site, or positive auramine staining of a cerebro- spinal fluid specimen

Probable TB: The presence of at least two clinical criteria, plus either positive auramine staining of an induced-sputum or gastric-washing smear or suggestive histologic findings (caseating granuloma); or positive auramine staining of a gastric- washing or induced-sputum smear and a chest radiograph suggestive of tuberculosis*

Possible TB: An algorithm score 3 – 6 and a radiograph suggestive of tuberculosis, or a positive tuberculin skin test (induration 5 mm in horizontal diameter) and a chest radiograph suggestive of tuberculosis.