Tuberculosis in Children Exposed at Home to Multidrug-resistant Tuberculosis

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Background: The tuberculosis burden in children exposed at home to multidrug-resistant tuberculosis (MDR-TB) is unquantified. With limited access to MDR-TB treatment, likely millions of children share the experience of chronic exposure to an infectious patient.

Methods: We conducted a retrospective cohort study of child and adult household contacts of patients treated for MDR-TB in Lima, Peru, in 1996 to 2003. The primary outcome was TB disease. We estimated prevalence of TB disease when the index case began MDR-TB treatment and incidence of TB disease over the subsequent 4 years.

Results: Among 1299 child contacts, 67 were treated for TB. TB prevalence was 1771 (confidence interval [CI]: 1052–2489) per 100,000 children. In 4362 child-years of follow-up, TB incidence rates per 100,000 child-years were: 2079 (CI: 1302–2855) in year 1; 315 (CI: 6–624) in year 2; 634 (CI: 195–1072) in year 3; and 530 (CI: 66–994) in year 4. TB disease rates in children aged >1 year were not significantly different from those observed in adults. Children accounted for 20% of TB cases. Seven (87.5%) of 8 children tested had MDR-TB. Child contacts had TB disease rates approximately 30 times higher than children in the general population.

Conclusions: Children were at high risk for TB disease when the index case started MDR-TB treatment and during the following year. These results highlight the need for implementing contact investigations and establishing systems for prompt referral and treatment of pediatric household contacts of MDR-TB patients, regardless of the age of the child.

Key Words: pediatric, household, contact investigation, disease burden, prevalence, incidence, follow-up, person-years, evaluation, drug resistance, multidrug-resistant tuberculosis

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Globally, the epidemic of tuberculosis (TB) in children is largely invisible.[1] Furthermore, there are no valid estimates of how many children are sick with drug-resistant TB (DR-TB). One readily identifiable population of children in whom a disease burden may be quantified is the population of children who were exposed at home to a patient with pulmonary drug-resistant disease. With effective treatment still available to only very few DR-TB patients globally,[2] millions of child contacts across high TB burden settings likely share the experience of chronic exposure to DR-TB at home.

We previously reported the prevalence and incidence of TB disease in the households of patients who were treated for multidrug-resistant TB (MDR-TB).[3] Here, we examine the disease burden specifically in children in those households and compare this with that observed in adults.

PATIENTS AND METHODS

Human Research Ethics Approvals

This study protocol was approved by the research ethics committees of the Harvard Medical School and the National Institute of Health (Instituto Nacional de Salud) of Peru. Written informed consent was obtained from each child's parent or guardian before conducting study interviews.

Study Subjects and Design

Beginning in 1996, Partners In Health worked with Peru's National Tuberculosis Program to treat patients with MDR-TB disease using supervised, individualized MDR-TB regimens delivered on an ambulatory basis.[4,5] For this analysis, the first patient in each household who started an individualized MDR-TB regimen between September 9, 1996 and September 9, 2003 was defined as the "index" case.

We conducted a retrospective cohort study among the household contacts of these index cases. We sought to identify the presence of TB disease at the time the index case initiated the MDR-TB regimen (prevalent TB) and the occurrence of TB disease in the 4 years after the index case initiated MDR-TB therapy (incident TB). A case of TB disease in a household contact was defined as any record of TB treatment in that individual's medical chart.

Household contacts who were living with the index case on the date that the index case initiated the MDR-TB regimen were eligible for study enrollment. These individuals were identified using a list of individuals living with the index case at the time the latter initiated the MDR-TB regimen. Pediatric contacts were defined as household contacts aged 14 years or younger on the date the index case initiated the MDR-TB regimen.

National TB Policy on Diagnosis and Treatment of Pediatric TB and Contact Tracing During Study Period

Peru's National Tuberculosis Program began implementing the Directly Observed Treatment, Short-course strategy in 1991.[6] The national TB guidelines during the study period indicated

initiation of TB treatment if the child was diagnosed with TB disease by a Stegen–Toledo score of 5 or more.[6] This was a clinical criteria set used in Peru and adapted from the Stegen–Kaplan criteria.[7] The Stegen–Toledo criteria are based on signs and symptoms, including abnormal findings of chest radiography and contact with a patient with TB disease. Physicians used this Stegen–Toledo clinical score for diagnosis of pediatric TB disease to classify a child into 1 of 4 categories: unlikely TB (0–2); suspected TB (3–4); probable TB (5–6); and highly probable TB (≥7). Treatment was implemented by a physician staffing a public health center or by a physician at a referral hospital. The choice of the TB regimen depended on the presence or absence of a positive culture or smear microscopy result.

The national TB guidelines also included instructions that public health center staff were to conduct household contact evaluations for all TB patients.[6] These guidelines specified the use of isoniazid preventive therapy in household contacts aged less than 15 years in whom active disease was ruled out. The guidelines did not specify the timing of the first or any subsequent visits to evaluate these contacts.

Data Collection

Clinical data about the index cases were abstracted from their medical charts. In 2004 to 2006, a study team conducted household visits to collect demographic data about the other individuals in the household and information about any TB treatments they received, as well as data about the physical characteristics of the dwelling. We defined housing conditions as substandard if the dwelling demonstrated any of the following characteristics: (1) dirty floor; (2) walls or roof made of straw matting, plastic and/or plywood; or (3) no running water.

For the index cases and for the household contacts who reported any TB treatment, study workers reviewed their medical charts to abstract the dates and results of TB regimens, smear and culture testing and drug-susceptibility testing. In addition, for index cases only, HIV coinfection status and lung cavitation at the start of the MDR-TB regimen was abstracted.

We compared TB isolates available from the child contacts and the index cases using the methods we described elsewhere.[8] For this analysis, we classified paired isolates as a match if the 2 isolates had exactly the same spoligotype and 24-loci mycobacterial interspersed repetitive units containing variable number of tandem repeats profiles.

Definitions

MDR-TB was defined as a *Mycobacterium tuberculosis* strain resistant to at least isoniazid and rifampicin, and extensively drug-resistant TB (XDR-TB) was defined as an *M. tuberculosis* strain resistant to at least isoniazid, rifampicin, a fluoroquinolone, and a second-line injectable agent (amikacin, capreomycin, kanamycin). Isolates were tested for resistance to at least 4 first-line drugs (isoniazid, rifampicin, ethambutol and streptomycin) at either the National Mycobacteriology Reference Laboratory in Peru[9] or at the Massachusetts Supranational TB Reference Laboratory (Jamaica Plain, MA).[4] The latter also routinely conducted testing to a larger drug panel, including a fluoroquinolone and second-line injectables.

Documentation in the medical chart of the initiation of any TB treatment regimen in a household contact was used to define a case of TB disease. Prevalent TB was defined as a case of TB disease in the baseline window (defined as up to 180 days before and 30 days after the date that the index case initiated MDR-TB treatment). Incident TB was defined as a case of TB disease in the follow-up period. The follow-up period began 31 days after the index case started the MDR-TB regimen. The end of the follow-up period was the date of the household interview or 4 years after the index case's MDR-TB regimen start date, whichever came first. If a household contact was treated for TB in the baseline window, a new treatment episode during the follow-up period was not considered as a new event.

Analysis

Each child was classified in 1 of 5 age cohorts, according to the age of the child on the date that the index case in the household initiated the MDR-TB treatment: (1) under 1 year old, (2) 1 or 2 years old, (3) 3 or 4 years old, (4) 5–10 years old, and (5) 11–14 years old. For this analysis, all contacts greater than 14 years of age are classified as adults.

For each age cohort, we calculated the prevalence of TB. For each of the 4 years after the index case's MDR-TB treatment initiation, we estimated the 1-year TB incidence for each age cohort by dividing the number of incident pediatric cases by the total number of person-years (child-years) of follow-up accrued by the children in that age cohort in that year.

We accounted for household clustering, for both prevalence and incidence, by using delete-one jackknifing to estimate 95% confidence intervals [CIs].[10] In addition, in strata with no prevalent cases, we estimated an upper 95% confidence limit for the proportion by using a numerator of n = 3.[11] In strata with no incident cases, we estimated an exact upper 95% confidence limit for the rate by using a numerator of n = 3.689.[12]

Data were double entered into a relational database designed in Microsoft Access 2003 (Microsoft Corporation, Seattle, WA) and analyzed with SAS 9.1 (SAS Institute Inc., Cary, NC) and Stata SE 10.1 (Statacorp, College Station, TX).

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The sponsors had no role in the study design, data collection, data analysis, data interpretation or writing of this report. The corresponding author had full access to all data and final responsibility to submit for publication.

RESULTS

Of the 758 households of patients treated for MDR-TB in the study period, 556 (73.4%) included at least 1 child, for a total of 1299 child household contacts. Characteristics of the children are summarized in Table 1, whereas characteristics of the index cases and households are summarized in Table 2. The median age of the children was 7.1 years (interquartile range 3.7–10.3). Less than a third had ever initiated a regimen of isoniazid preventive therapy. At the start of follow-up, most index cases had received at least 3 prior TB regimens and had lung cavitation.

Age-specific Prevalence

Table 3 shows the age-specific prevalence of treated TB in the contacts. Among children, it was highest in the cohort of 1–2 year olds, with prevalence of 2513 per 100,000 children (CI: 319–4706 per 100,000). This can be compared with a prevalence of 2257 per 100,000 (CI: 1759–2756 per 100,000) in the adults. No statistically significant difference in prevalence was detected among pediatric age groups or between the children and the adults.

Age-specific Incidence Rate

The incidence rate of treated TB during the 4 years of follow-up for the 5 age strata of children, as well as the adults, is reported in the Table, Supplemental Digital Content 1, http://links.lww.com/INF/B316. There were 4362 child-years of follow-up. The highest rates of TB disease were seen in the first year of follow-up,

TABLE 1. Characteristics of Children (Aged 14 Years and Younger) Living in the Household at the Time of Initiation of the MDR-TB Regimen in the Index Case (n = 1299)

Variable	N (%)
Age (yr), median (IQR)	7.1 (3.7–10.3)
Female sex	646 (49.7)
Ever initiated isoniazid therapy for TB prevention	380/1299 (29.3)
0–4 years old	139/448 (31.0)
5–14 years old	241/851 (28.3)
Ever received treatment for TB disease	32 (2.5)
Relationship to index patient	
Nephew or niece	454 (35.0)
Son or daughter	400 (30.8)
Sibling	250 (19.3)
Grandchild	111 (8.6)

Data are proportion of child household contacts (percentage), unless otherwise indicated.

IQR indicates interquartile range.

TABLE 2. Index Patient and Household Characteristics at the Time of Initiation of the MDR-TB Regimen in the Index Case (n = 556 Households With At Least 1 Child)

Characteristic	N (%) or median (IQR)
Index's age (yr), median (IQR)	28.3 (22.9–35.8)
Index, female sex	236/556 (42.5)
Index patient had 3 or more treatment episodes (vs. fewer than 3)	343/551 (62.3)
Index, baseline lung cavitation	351/556 (63.1)
Index, baseline HIV infection	6/556 (1.1)
Index, baseline XDR-TB	39/506 (7.7)
Number of children living in household (median, IQR)	2 (1–3)
Number of adults living in household, excluding index patient (median, IQR)	4 (2–6)
Dwelling of substandard conditions*	157/528 (29.7)

Data are proportion of index patients or households (percentage), unless otherwise indicated. Data are for 556 households, unless otherwise indicated.

*We defined housing conditions as substandard if the dwelling demonstrated any of the following characteristics: (1) dirty floor; (2) walls or roof made of straw matting, plastic and/or plywood; or (3) no access to water in the home.

IQR indicates interquartile range; XDR-TB, extensively drug-resistant tuberculosis.

TABLE 3. Age-specific Prevalence of Treated TB in Child and Adult Contacts (Cases per 100,000 Population)

Age Group	Number in Cohort at Risk	Number Treated for TB	Prevalence (per 100,000 Population)	Lower 95% CI, Upper 95% CI*
<1 yr	72	0	0	0, 4167
1–2 yr	199	5	2513	319, 4706
3–4 yr	177	1	565	0, 1680
5–10 yr	500	10	2000	769, 3231
11–14 yr	351	7	1994	525, 3464
All children	1299	23	1771	1052, 2489
All adults (≥ 15 yr)	3411	77	2257	1759, 2756

*CIs are adjusted for household clustering.

exceeding 2000 per 100,000 child-years in the 1–2 year olds, the 3–4 year olds and the 5–10 year olds. This can be compared with 3255 (CI: 2659–3851 per 100,000 person-years) in adults.

Proportion of Cases of TB Disease That Were Among Children

Children accounted for 23.0% (CI: 15.9–32.2%) of the 100 prevalent cases in the households (Table 3). Among the 217 incident cases, children accounted for 20.3% (CI: 15.5–26.1%): 23.3% in year 1, 8.5% in year 2, 25.8% in year 3 and 21.7% in year 4 (Table, Supplemental Digital Content 1, http://links.lww.com/INF/B316).

Proportion of Children With TB Disease Who Had MDR-TB

Overall, 67 child contacts were treated for TB disease, of whom 8 (11.9%) had drug susceptibility testing results. Three of these were prevalent cases, and the other 5 were treated only in the follow-up period. Seven of the 8 (87.5% [CI: 51.8–97.2%]) had an isolate resistant to at least isoniazid and rifampicin. Among 150 adults with DST results, 137 (91.3% [CI: 85.7%-94.8%]) had an isolate resistant to at least isoniazid and rifampicin.

Drug-susceptibility Profiles and Genotyping in Child-index Pairs

For the 8 children with drug-susceptibility test results, we compared these results with the drug-susceptibility test results of the index case (Table, Supplemental Digital Content 2, http://links.lww.com/INF/B317). Six of the children had an isolate available for genotyping. All 6 of these isolates were identical to the index case's isolate by spoligotyping and 24-loci mycobacterial interspersed repetitive unit-variable-number tandem repeat typing.

DISCUSSION

We found a high burden of TB disease in children living with MDR-TB patients both at the time that the patient began MDR-TB treatment and during the first year thereafter. This finding is not surprising because the index MDR-TB patients were sick, and likely infectious, for prolonged periods before receiving a regimen designed to treat MDR-TB. This is supported by the observation that nearly two thirds of index patients had received more than 3 TB regimens before receiving an individualized regimen for MDR-TB.

Notably, we observed a TB disease prevalence of over 2000 cases per 100,000 children in the 1–2 year olds, the 5–10 year olds and the 11–14 year olds. This was comparable with TB disease prevalence among the adult contacts. Also, similar to adult rates was the incidence of TB disease in the first year after the MDR-TB patient started treatment, which exceeded 2000 per 100,000 child-years in the 1–2 year olds, the 3–4 year olds and the 5–10 year olds. The incidence rates among children during the first year were 5–10 times those observed in later years.

Household contacts of TB patients are known to have an elevated risk of developing TB disease.[13,14] The TB disease burden observed in our study can first be compared with Peru's national TB case notification rate in children, which declined from 61 per 100,000 in 1994 to 43 per 100,000 in 2000.[15] Our study found that children exposed to MDR-TB at home had TB disease rates approximately 30 times higher than case notification rates for children in the general population.

The pediatric disease burden we observed is consistent with only 2 cohort studies describing the occurrence of TB disease among young children exposed to MDR-TB at home, both conducted in Cape Town, South Africa.[16,17] The first described an even higher prevalence (>10% or 10,000 per 100,000 children) of TB disease among the 125 child contacts aged 0–4 years of MDR-TB patients. Our results are also consistent with the second of these

studies, which followed these children over time and found that most cases of TB disease occurred in the first 12 months after the baseline evaluation.[17] In contrast to both of these reports, however, in Peru, we were also able to include children aged 5–14 years, in whom both prevalence and incidence rates in the first year were as high as those observed in the younger children. Our observations in this age group contrast with studies of the natural history of TB, which showed that children aged 5–14 years are generally at much lower risk of developing TB disease than the children aged 0–4 years.[18] We attribute these unexpectedly high TB disease rates in the older children to their close and chronic exposure to infectious MDR-TB patients, most of whom had been sick and inadequately treated for years.

Another finding of our study is that, among the children with isolates tested for drug-susceptibility, almost all had MDR-TB. This is consistent with what was observed in the adult contacts. And all the children's isolates available for genotyping had identical patterns to those of the index case, confirming that one had transmitted to the other or that both were part of the same transmission chain.[8] Furthermore, the strains' drug-susceptibility profiles were almost identical to that of the purported source case. These observations are also consistent with other reports among child contacts of MDR-TB patients.[16,17,19–21]

Confirmation of MDR-TB in children is very difficult, because viable sputum samples are often not available for testing.[22,23] Therefore, it is not surprising that we found few children with documented drug-susceptibility test results. It should be noted that the children who did have documentation of DST results were in the oldest pediatric age group. Again this is consistent with existing knowledge, because older children are better able to produce adequate sputum samples. With current tests, the great majority of children with MDR-TB disease cannot be confirmed to have this form of the disease.[22,23] Urgently needed are new tests, which do not rely on sputum samples, to promptly and accurately detect both TB and drug resistance in children.

Our results are subject to several limitations. The first is related to the diagnostic limitations noted above: the high frequency of MDR-TB found in the small number of children tested, as well as the similarity to the index case, may not be generalizable. The children who had DST results were older and may have been more likely to be referred for testing for unknown reasons.

The absence of treated TB cases in the infant population and the lack of difference among age groups may reflect the large sampling variability due to the small number of children in most of the age strata. This is captured in the (overlapping) CIs we report. It is also possible that some infants died with undiagnosed TB disease and, therefore, were not counted as secondary cases in this study; however, we lacked the mortality data needed to explore this hypothesis. Alternatively, the low TB disease rate findings in infants may be also due to the universal Bacillus Calmette–Guérin vaccination in Peru or the extreme difficulties of diagnosing TB disease in this group.

The TB disease rates observed may be overestimates, or underestimates, of the true risk in the child contacts. All children who were treated for TB disease were defined as cases, and it is possible that public health center providers were "over diagnosing" children with nonspecific TB symptoms. Until diagnostic methods for children are improved, however, programs must continue to rely on clinical criteria and contact history to guide TB treatment in children.[24] At the same time, it is possible that the long period about which some respondents were questioned regarding their TB history resulted in some treatment episodes being missed. Moreover, it is in fact more likely that TB disease rates are underestimated due to the aforementioned challenges of diagnosing TB disease in infants and small children.

The final limitation is that data were not available about HIV infection status for children. Notably, the HIV seroprevalence in Peru's adult population is estimated at 0.5%,[25] and among TB patients in 1 study at 7%.[26] It is unlikely that the prevalence of HIV infection in this cohort of child contacts is higher than that in the index cases (<1%).[5] In settings where HIV prevalence in the general pediatric population is much higher, the true TB rates in child contacts of MDR-TB patients can be expected to be higher. There the importance of early detection and treatment would be even more critical.[27] Certainly, in a setting with HIV coinfection, the lack of HIV testing data among the child contacts would make it difficult to rule out HIV as a source of elevated TB risk. Given the very low expected prevalence of HIV infection in this cohort of children, however, it is unlikely that HIV explains the high rates of TB disease observed.

Conclusions

This cohort is the largest reported group of children with known household exposure to MDR-TB, and follow-up time extends to 4 years after the index MDR-TB patient initiated treatment for MDR-TB. The results reveal that children living with MDR-TB patients in Lima had alarmingly high TB disease rates, in the range observed in prisons and holding centers in Siberia.[28] Our results highlight the need for performing contact investigations and establishing systems for prompt referral and treatment of pediatric household contacts of MDR-TB patients, regardless of the age of the child. This contrasts with the traditional approach of giving priority to child contacts under 5 years of age.[13] International recommendations point to the importance of prompt and effective treatment of drug-resistant disease in children,[29,30] but few TB programs even have written guidelines for the management of persons exposed to drug-resistant strains.[31] Needed now are systematic assessments of strategies for follow-up observation in children and adults exposed at home to DR-TB, including the timing of repeat evaluations.

Our results also provide empirical data to inform future research to improve the care of child contacts of MDR-TB patients. Presently, there is a crucial knowledge gap about what to do for child contacts in whom TB disease can be ruled out. Data are scant about preventive therapy in persons exposed to MDR-TB.[32] An important case series from South Africa showed that isoniazid was inadequate to prevent TB disease in children exposed to MDR-TB.[33] This study also revealed favorable outcomes in other case series of children treated with chemoprophylaxis regimens based on the index patients' drug-susceptibility data.[17,34] But the safety and efficacy of specific drugs or regimens to treat suspected latent infection with MDR-TB have not been studied systematically.[31] This knowledge gap has been identified as a research priority in multiple reviews.[23,35,36] Observational cohort data like ours will be invaluable for estimating the required sample sizes of new randomized trials for the treatment of latent infection in children and adults with known exposure to drug-resistant TB strains.

In summary, our results provide strong evidence to support the prompt, systematic evaluation of pediatric household contacts of DR-TB patients, regardless of the child's age. Children living with DR-TB patients are a high-yield population not only for contact investigations but also for evaluating new tests that can detect both TB disease and drug resistance.

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