Tuberculosis burden in households of patients with multidrug-resistant and extensively drug-resistant tuberculosis: a retrospective cohort study

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Summary

Background Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis have emerged as major global health threats. WHO recommends contact investigation in close contacts of patients with MDR and XDR tuberculosis. We aimed to assess the burden of tuberculosis disease in household contacts of such patients.

Methods We undertook a retrospective cohort study of household contacts of patients treated for MDR or XDR tuberculosis in Lima, Peru, in 1996–2003. The primary outcome was active tuberculosis in household contacts at the time the index patient began MDR tuberculosis treatment and during the 4-year follow-up. We examined whether the occurrence of active tuberculosis in the household contacts differed by resistance pattern of the index patient: either MDR or XDR tuberculosis.

Findings 693 households of index patients with MDR tuberculosis were enrolled in the study. In 48 households, the Mycobacterium tuberculosis isolate from the index patient was XDR. Of the 4503 household contacts, 117 (2·60%) had active tuberculosis at the time the index patient began MDR tuberculosis treatment—there was no difference in prevalence between XDR and MDR tuberculosis households. During the 4-year follow-up, 242 contacts developed active tuberculosis—the frequency of active tuberculosis was nearly two times higher in contacts of patients with XDR tuberculosis than it was in contacts of patients with MDR tuberculosis (hazard ratio 1·88, 95% CI 1·10–3·21). In the 359 contacts with active tuberculosis, 142 (40%) had had isolates tested for resistance against first-line drugs, of whom 129 (90·9%, 95% CI 85·0–94·6) had MDR tuberculosis.

Interpretation In view of the high risk of disease recorded in household contacts of patients with MDR or XDR tuberculosis, tuberculosis programmes should implement systematic household contact investigations for all patients identified as having MDR or XDR tuberculosis. If shown to have active tuberculosis, these household contacts should be suspected as having MDR tuberculosis until proven otherwise.

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Introduction After treatment of patients with active tuberculosis, contact investigation—investigation of people exposed to patients with infectious tuberculosis—is the top priority for tuberculosis control programmes because close contacts of patients with known tuberculosis have a higher risk of developing active tuberculosis than do people who have not had such contact.1 The purpose of contact investigation is to promptly identify and treat individuals with active or latent tuberculosis, stop further transmission, and prevent new cases of active tuberculosis.1 However, national tuberculosis programmes are often unable to do contact investigations because of inadequate resources and staffing.

The emergence of drug-resistant Mycobacterium tuberculosis is causing tuberculosis programmes to reconsider whether contact investigation merits attention and resources. In particular, tuberculosis strains resistant to at least both isoniazid and rifampicin, defined as multidrug-resistant (MDR), pose a major problem.5 Isoniazid is a proven treatment for latent infection with isoniazid-susceptible M tuberculosis, but there is no proven preventive treatment for latent infection with MDR tuberculosis strains.5 Therefore, when patients are diagnosed with MDR tuberculosis, early detection and treatment of active tuberculosis in their close contacts is a particularly important element of prevention—an individual’s contact history should be used to inform their treatment.5 A better understanding of the risks to close contacts of patients with MDR tuberculosis has been emphasised as a priority area in one of the Stop TB Partnership research agendas, which aims to improve the scale-up of effective programmatic management of drug-resistant tuberculosis.6 International guidelines recommend that close contacts of patients with MDR tuberculosis should be carefully monitored for at least 2 years, so that prompt and appropriate treatment can be initiated if they develop active tuberculosis.5,6 The risks are unknown for
individuals exposed to MDR tuberculosis strains that are also resistant to a fluoroquinolone and a second-line injectable drug—extensively drug-resistant (XDR) strains. We aimed to estimate the occurrence of active tuberculosis in household contacts of patients with MDR tuberculosis and to examine whether the occurrence of active tuberculosis in household contacts differed according to whether an index patient had MDR or XDR tuberculosis.

**Methods**

**Patients and study design**

Beginning in 1996, Partners In Health and Socios En Salud Sucursal Peru worked with Peru’s national tuberculosis programme to treat patients with active MDR tuberculosis with supervised, individualised treatment regimens delivered on an outpatient basis.7,8 Household contacts of patients initiating treatment for MDR tuberculosis were tested for active tuberculosis. For our retrospective analysis of data obtained during this period, we defined the index patient as the first patient in each household to begin an individualised MDR tuberculosis treatment regimen between Sept 9, 1996, and Sept 9, 2003. Household contacts living with the index patient on the date that the MDR tuberculosis regimen was initiated were eligible for enrolment. We identified these individuals from a list of household contacts compiled at the time that each index patient began their MDR tuberculosis regimen.

We did a retrospective cohort study of household contacts to identify the presence of active tuberculosis at the time the index patient began their treatment regimen (co-prevalent tuberculosis) and the occurrence of active tuberculosis in the subsequent 4 years (incident tuberculosis). We excluded households located outside the metropolitan Lima region and households in which the index patient was not tested for XDR tuberculosis. This study protocol was approved by the research ethics committees of the Harvard Medical School and the National Institute of Health of Peru. Written informed consent was obtained from participants before doing study interviews.

Between 2004 and 2006, a study team did household visits to gather demographic data, tuberculosis treatment history of household members, and data for the physical characteristics of the dwelling and the number of people sharing a bedroom, and to identify individuals living with the index patient at the time they began their MDR tuberculosis regimen. The study team was not aware of the index patient’s resistance status (ie, whether they had MDR or XDR tuberculosis). We defined housing conditions as substandard if the dwelling had any of the following characteristics: a dirt floor; walls or roof made of straw matting, plastic, or plywood; or no access to water in the house.

The medical records of index patients and any household contacts who reported treatment for tuberculosis were reviewed, and the dates and results of tuberculosis treatment regimens, smear and culture tests, and drug-susceptibility tests were recorded. Additionally, for index patients only, information about HIV co-infection and cavitary disease at the start of the MDR tuberculosis regimen were recorded.

MDR tuberculosis was defined as an *M tuberculosis* strain resistant to at least both isoniazid and rifampicin, and XDR tuberculosis was defined as an *M tuberculosis* strain resistant to at least isoniazid, rifampicin, a fluoroquinolone, and a second-line injectable drug (amikacin, capreomycin, or kanamycin). Drug-susceptibility test results were used to classify households according to whether or not the index patient’s strain met the XDR tuberculosis definition at the start of their treatment regimen. This classification was made retrospectively for the present analysis, with drug-susceptibility data from index patients’ medical records. Sputum specimens had been tested for resistance against at least four first-line drugs (isoniazid, rifampicin, ethambutol, and streptomycin) by Peru’s National Mycobacteriology Reference Laboratory,7 which, in 1994, began routinely testing specimens from patients in whom treatment failed. Additionally, beginning in 1996, patients who were referred to the MDR tuberculosis treatment programme7,8 had isolates routinely tested at the Massachusetts State Laboratory Institute, which also tested isolates for resistance against a wider range of drugs, including a fluoroquinolone and second-line injectable drugs. Beginning in 2001, the national tuberculosis laboratory network gradually expanded access to first-line drug-susceptibility testing for patients with tuberculosis known to be a close contact of a patient with confirmed MDR tuberculosis.

The initiation of any tuberculosis treatment regimen was used to define active tuberculosis in a household contact. Tuberculosis regimens were designed by a Ministry of Health physician according to national tuberculosis programme guidelines. Prevalent tuberculosis was defined as a case of active tuberculosis disease in a household contact in the baseline window (defined as up to 180 days before and 30 days after the date on which the index patient initiated MDR tuberculosis treatment). Incident tuberculosis was defined as a case of

<table>
<thead>
<tr>
<th>In household of index patient with XDR tuberculosis (n=312)</th>
<th>In household of index patient with MDR tuberculosis (n=4191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>24.7 (18.7)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>120 (55%)</td>
</tr>
<tr>
<td>Received tuberculosis treatment before index patient began treatment regimen</td>
<td>23 (7%)</td>
</tr>
<tr>
<td>Ever received isoniazid preventive therapy</td>
<td>25 (8%)</td>
</tr>
</tbody>
</table>

Data are median (SD) and number of patients (%). *Data are for a total 4313 individuals (303 individuals from XDR households and 4010 individuals from MDR households).

Table 1: Characteristics of household contacts when index patient began treatment regimen
active tuberculosis in a household contact during the follow-up, which began 31 days after the index patient started MDR treatment, and ended on the date of the household interview or 4 years after the index patient started MDR treatment, whichever came first.

**Statistical analysis**
We compared prevalent and incident tuberculosis in household contacts according to whether the index patient had XDR or MDR tuberculosis. We calculated the prevalence of tuberculosis by dividing the number of prevalent tuberculosis cases by the number of household contacts in the study. We estimated the incidence rate of secondary tuberculosis in the 4 years after the index patient’s treatment initiation by dividing the number of incident cases by the total number of person-years of follow-up (of household contacts only). We used the Cochran’s Q test to assess whether the incidence rate of secondary tuberculosis varied by year.

To examine whether the prevalence of tuberculosis differed according to the index patients’ resistance status, we did logistic regression analyses, which adjusted for household clustering. Similarly, to investigate whether the incidence of tuberculosis differed according to the index patient’s resistance status, we did Cox proportional hazards regression analyses, right censoring at the day of follow-up and adjusting for household clustering. For both analyses we assessed potential confounding by the variables presented in Table 1. We first identified factors that were imbalanced between households of index patients with MDR tuberculosis and households of index patients with XDR tuberculosis (ie, sex of index patient, receipt of three or more previous regimens by the index patient, bilateral cavitary disease in the index patient, number of people in the household, and substandard housing conditions), then included them in analysis by use of forward selection. We retained the variables that altered the effect estimate for an index patient’s resistance status by at least 10%.

To measure the proportion of incident active tuberculosis cases who were MDR, we divided the number of household contacts with a drug susceptibility test result positive for MDR tuberculosis by the number of household contacts that were tested for resistance to at least isoniazid and rifampicin.

Data were double entered into a relational database designed in Microsoft Access 2003 and were analysed with SAS 9.1 and Stata SE 10.1. To obtain the estimates of the incidence rate ratios adjusted for household clustering, R 2.8.1 was used (R Foundation for Statistical Computing, Vienna, Austria).

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

**Results**
The figure shows the study profile. Individuals were excluded from the analysis if the index patient strain had not been tested for XDR tuberculosis. Table 1 shows characteristics of household contacts by the resistance status of index patients. Table 2 shows household characteristics including demographic and clinical characteristics of index patients by their resistance status. Compared with index patients with MDR tuberculosis, index patients with XDR tuberculosis were more likely to have already received three or more tuberculosis treatment regimens and to have cavitary disease at study baseline.

**Table 2: Household characteristics when index patient began treatment regimen**

<table>
<thead>
<tr>
<th></th>
<th>Index MDR and XDR (n=48)</th>
<th>Index MDR but not XDR (n=645)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of index patient (years)</td>
<td>28.5 (9.7)</td>
<td>28.4 (12.8)</td>
</tr>
<tr>
<td>Sex of index patient (female)</td>
<td>20 (41.7%)</td>
<td>263 (40.8%)</td>
</tr>
<tr>
<td>Index patient had 3 or more previous treatment regimens*</td>
<td>38 (80.9%)</td>
<td>400 (62.5%)</td>
</tr>
<tr>
<td>Index patient had cavitary disease at study baseline</td>
<td>37 (71.1%)</td>
<td>415 (64.3%)</td>
</tr>
<tr>
<td>Index patient had HIV at study baseline</td>
<td>0 (0%)</td>
<td>6 (0.9%)</td>
</tr>
<tr>
<td>Number of people living in the household per bedroom</td>
<td>7.5 (3.3)</td>
<td>7.0 (3.7)</td>
</tr>
<tr>
<td>Housing with sub-standard conditions†</td>
<td>12 (25.5%)</td>
<td>174 (28.5%)</td>
</tr>
</tbody>
</table>

Data are median (SD) or number of patients (%). Data are for 693 households (48 XDR households and 645 MDR households) unless stated otherwise. *Data are for 687 households (47 XDR households and 640 MDR households). †Data are for 658 households (47 XDR households and 611 MDR households).
disease at study baseline. Only six index patients (<1%) were known to have HIV infection, and none of these had XDR tuberculosis.

In 4503 household contacts, we identified 117 cases (3%) of prevalent tuberculosis. In all 693 households, 86 (12%) had at least one prevalent case. The prevalence of tuberculosis in the XDR tuberculosis households was 2.56% (eight of 312 household contacts), compared with 2.60% (109 of 4191 household contacts) in the MDR tuberculosis households. Univariate analysis showed that prevalence of tuberculosis in household contacts of patients with XDR tuberculosis was not higher than it was in household contacts of patients with MDR tuberculosis (odds ratio [OR] 0.76, 95% CI 0.27–2.2). After adjustment for whether the index patient had received three or more previous tuberculosis treatment regimens, there was still no difference in tuberculosis prevalence between the two groups of household contacts (0.90, 0.32–2.5).

Study participants contributed almost 15 000 person-years of follow-up (table 3). We identified 242 cases of incident tuberculosis. Of the 693 households, 171 (24.7%) had at least one incident case. Table 3 shows the incidence rate of active tuberculosis in household contacts during the 4-year follow-up. The hazard rate of active tuberculosis in households of patients with XDR tuberculosis was nearly twice as high as it was in households of patients with MDR tuberculosis (table 3). None of the variables shown in table 1 confounded the association between the resistance status of index patients and the incidence of active tuberculosis in household contacts during the 4-year follow-up. Yearly variation in the hazard ratio during the follow-up period was not significant (p value, test for heterogeneity: 0.49).

Of the 359 household contacts with prevalent or incident tuberculosis, M tuberculosis strains from 142 (40%) had been tested for susceptibility to isoniazid, rifampicin, ethambutol, and streptomycin; none had been tested for XDR tuberculosis. Of the 142 household contacts with drug-susceptibility test results, 129 (90.9%, 95% CI 85.0–94.6) had MDR tuberculosis (41 of 44 prevalent cases and 88 of 98 incident cases). Of the 129 household contacts with confirmed MDR tuberculosis, 77 (59.7%, 51.1%–67.8%) had matching drug susceptibility test results (both ethambutol and streptomycin) with their respective index patient.

### Discussion

This study shows a very high prevalence of tuberculosis in household contacts of patients with XDR or MDR tuberculosis in metropolitan Lima, Peru. Similar prevalences have been recorded in prisons and holding centres in Siberia. Almost 40% of household contacts with active tuberculosis had drug-susceptibility test results, more than 90% of whom had MDR tuberculosis. Of those household contacts with MDR tuberculosis, almost two-thirds had drug-susceptibility test results for ethambutol and streptomycin that matched with their respective index patient. These findings lend support to international guidelines that recommend prompt assessment of close contacts of all patients with MDR tuberculosis, and to suspect a close contact presenting with active tuberculosis as having MDR tuberculosis until proven otherwise. The results provide strong motivation for systematic study of new preventive therapies in those at high risk of latent MDR tuberculosis infection.

We recorded a high tuberculosis disease burden in household contacts not only during the baseline window, but also during the 4 years of follow up. This finding suggests that guidelines, which recommend that people who have been exposed to MDR tuberculosis should be monitored for at least 2 years to detect active disease, might not be sufficient. More work is needed to establish for how long a contact should be monitored and the optimum frequency and methods with which to monitor.

MDR tuberculosis treatment regimens necessitate 2 years of daily treatment; regular household visits during this time provide an opportunity for tuberculosis programmes to continue to screen household members after the initial contact investigation. More research is needed to identify the best strategies to monitor households after an initial visit.

Only a few observational studies of close contacts of patients with MDR tuberculosis exist. These studies recorded prevalences of active tuberculosis in household

### Table 3: Incidence of active tuberculosis in household contacts during 4-year follow-up period

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th></th>
<th>Index XDR</th>
<th></th>
<th>Index MDR</th>
<th></th>
<th>Adjusted hazard ratio (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Incidence rate per 100 000 person-years</td>
<td>Cases</td>
<td>Person-years</td>
<td>Incidence rate per 100 000 person-years</td>
<td>Cases</td>
<td>Person-years</td>
<td>Incidence rate per 100 000 person-years</td>
</tr>
<tr>
<td>Year 1</td>
<td>3165</td>
<td>140</td>
<td>4423</td>
<td>242</td>
<td>13</td>
<td>306</td>
<td>3084</td>
</tr>
<tr>
<td>Year 2</td>
<td>1992</td>
<td>47</td>
<td>4303</td>
<td>2214</td>
<td>8</td>
<td>295</td>
<td>973</td>
</tr>
<tr>
<td>Year 3</td>
<td>764</td>
<td>30</td>
<td>3927</td>
<td>1816</td>
<td>5</td>
<td>275</td>
<td>685</td>
</tr>
<tr>
<td>Year 4</td>
<td>1112</td>
<td>25</td>
<td>2247</td>
<td>2734</td>
<td>5</td>
<td>183</td>
<td>969</td>
</tr>
<tr>
<td>Overall (years 1–4)</td>
<td>1624</td>
<td>242</td>
<td>14 900</td>
<td>2928</td>
<td>31</td>
<td>1059</td>
<td>1524</td>
</tr>
</tbody>
</table>

*Adjusted for household clustering.
contacts that ranged from 1·9% in adults to 11·2% in children. The proportion of MDR tuberculosis in household contacts with active disease ranged from 62% (n=8) to 100% (n=4). In all six previous reports there were a total of 46 prevalent and 78 incident cases of tuberculosis recorded; the sum of all the follow-up periods was 3550 person-years. Our study provides unique empirical evidence afforded by a large cohort, a follow-up period of 4 years, almost 15 000 person-years of follow-up, and data for patients with both MDR and XDR tuberculosis and their household contacts.

Because most index patients had already received more than three tuberculosis treatment regimens before the study baseline, the 4-year follow-up does probably not include the initial 2-year period in which household contacts are at highest risk of disease progression. The high risk of disease for household contacts during the initial 2 years of the index patient’s illness is one of the main reasons for contact investigation when a tuberculosis case is detected. Therefore, the tuberculosis burden seen in this study should raise concerns because these findings might underestimate the burden of active and MDR tuberculosis in household contacts of patients with MDR tuberculosis.

We recorded no difference in the prevalence of tuberculosis among household contacts during the baseline window between households of index patients with MDR tuberculosis and households of index patients with XDR tuberculosis. This finding has two possible explanations. First, although more than 4000 people were included, the study was too small to have sufficient power to identify a difference in prevalence between the two groups; the number of incident tuberculosis cases in the household contact cohort was more than twice that of prevalent tuberculosis cases. Second, at study baseline, both sets of index patients had similar treatment histories (table 2) and were therefore probably similarly infectious to their household contacts. Only at study baseline, when individualised treatments were initiated, did differences between the two sets of index patients become apparent; the patients with MDR tuberculosis responded more quickly to treatment (converted to sputum culture negative) than did the patients with XDR tuberculosis, which means that once the individualised treatment regimens were initiated, the household contacts of index patients with XDR tuberculosis were at risk of infection for longer than were household contacts of index patients with MDR tuberculosis. This difference in early response to treatment is consistent with our finding that, throughout the 4-year follow-up, households of patients with XDR tuberculosis had higher rates of incident tuberculosis than did those of patients with MDR tuberculosis. Patients with MDR or XDR tuberculosis are often inadequately treated for years; an XDR tuberculosis diagnosis can mean that a patient has remained inadequately treated for even longer. In addition to the delay in response to treatment, the index patients with XDR tuberculosis had received more regimens and were more likely to have cavitary disease than were the index patients with MDR tuberculosis. All these characteristics of XDR tuberculosis suggest that close contacts of patients with XDR tuberculosis might be at increased risk compared with close contacts of patients with MDR tuberculosis.

A third of household contacts with MDR tuberculosis had a different drug-susceptibility profile from their respective index patient. This finding draws attention to a central dilemma in the management of close contacts of patients with MDR tuberculosis: just how informative are drug-susceptibility results of a purported source patient? We argue that such data should be used cautiously to inform conclusions about whether or not a case of tuberculosis in a household contact is caused by the same strain of M. tuberculosis that caused the index patient’s infection. We have previously reported that index–contact pairs with MDR tuberculosis often had different resistance profiles when all drug tests were compared. One explanation could be that susceptibility tests to ethambutol, streptomycin, and most second-line drugs are not reliable. Another explanation could be the repeated inadequate treatment regimens received by many patients with drug-resistant tuberculosis. Household contacts could have initially been infected with the index patient’s MDR tuberculosis strain, but inadequate treatment selected strains that were resistant to different drugs so that the final resistance profiles no longer matched. Until genotyping can confirm that MDR tuberculosis strains with different resistance profiles are actually different strains, this unfortunate effect of inadequate treatment policies cannot be ruled out.

Had this been a study that aimed to measure transmission of MDR or XDR tuberculosis strains, genotyping results would have been essential. The objective, however, was to describe tuberculosis risk in households of patients with MDR tuberculosis, to inform tuberculosis programmes that are considering contact investigation as one component of a systematic response to MDR and XDR tuberculosis. The absence of genotyping data means that we cannot be sure that the household contact cases were caused by the index patient’s strain. Nevertheless, once the index patient was appropriately treated, disease rates continued to be very high—even 4 years after treatment. Whether or not the household contact’s infection came from the index patient becomes a moot point. Our findings suggest a worrisome hypothesis: household members face a common and persistent exposure to MDR tuberculosis in the community. Therefore, these results lend support to the rationale for focusing intensive contact investigation resources on a high-risk group that can be readily identified—the household of any patient diagnosed with MDR tuberculosis. Further work, including genotyping studies, will be needed to understand the
various sources of tuberculosis infection to which household contacts of patients with MDR tuberculosis are exposed.

Another limitation of the study is the absence of HIV testing for the household members. Notably, the HIV seroprevalence in Peru’s adult population is estimated to be 0–5%, and, in one study, in patients with tuberculosis to be 6–7%. The prevalence of HIV infection in this cohort of household contacts is probably not higher than it is in the index patients (<1%). This low prevalence limits the ability of HIV co-infection to be a confounder of the association between XDR tuberculosis in the index patient and tuberculosis disease in the household members, and, if anything, it would bias association towards the null.

Thus, our results lend support to the prioritisation of prompt and systematic assessment of close contacts of patients with MDR or XDR tuberculosis. Household contacts are the most readily identified group of close contacts; if presenting with active disease, they should be treated as patients with MDR tuberculosis until proven otherwise.1 We believe the results of this study are generalisable to other impoverished settings with a low HIV prevalence in which patients receive repeated tuberculosis treatments before initiating an MDR tuberculosis regimen. An urgent need exists to better understand the amount of untreated disease and prevalent deaths that occur in household contacts who also have HIV co-infection. Tuberculosis programmes should implement systematic contact investigations for all patients identified as having MDR or XDR tuberculosis.

References
18 Medical Research Council. BCG and vole bacillus in the prevention of tuberculosis in childhood. Academic Studies at Harvard University, and the Bill & Melinda Gates Foundation funded this study. The authors also acknowledge the support of career development awards from the National Heart, Lung, and Blood Institute (K01 HL080939, to MCB) and the National Institute of Allergy and Infectious Diseases (K01 AI065836, to CDM).

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Articles