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RESOURCE UTILIZATION FOR MULTIDRUG-RESISTANT TUBERCULOSIS HOUSEHOLD CONTACT INVESTIGATIONS (A5300/I2003)

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SUMMARY

Background—Current guidelines recommend evaluation of household contacts (HHC) of individuals with multidrug-resistant tuberculosis (MDR-TB) but widespread implementation of this policy is challenging.

Objective—To describe site-level resource utilization and operational challenges encountered when identifying, recruiting, and characterizing adult MDR-TB Index Cases and their HHC.

Design—Cross-sectional study of adult MDR-TB Index Cases and HHC at 16 clinical research sites in 8 countries. Site-level resource utilization was assessed using structured surveys.

Results—Between October 2015 and April 2016, 308 Index Cases and 1018 HHC were enrolled. Of 280 Index Cases with sputum collected, 94 were smear positive (34%, 95% Confidence Interval (CI): 28–39%) and of 201 with chest x-rays, 87 had cavitary disease (43%, CI: 37–50%) after a mean duration of treatment of 8 weeks. Staff required 512 attempts to evaluate the 308 households, median time per attempt of 4 hours. 77% (CI: 73—80%) of the HHC were at increased risk for TB: 13% < 5 years; 8% >5 years. and HIV-infected; and 79% >5 years, HIV-/unknown and TST/IGRA positive. 121 previously undiagnosed TB cases were identified. Issues identified by site staff included complexity of personnel and participant transportation, infection control, personnel safety and management of stigma surrounding household visits.

Conclusion—Household contact investigations can be high yield but are labor intensive.

Keywords

MDR-TB; household contact investigation; resource utilization

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is a critical problem globally, complicated by the fact that most cases are not diagnosed and those who are, do not receive adequate treatment.(1) Household contacts (HHC) of patients with MDR-TB are at risk of infection and progression to active disease, yet evidence-based guidelines for management of contacts are lacking.(2)·(3)·(4) The World Health Organization (WHO) has identified treatment of MDR-TB contacts as a priority issue that urgently requires randomized controlled trial data to inform policy.(5)

HHC investigation is a cornerstone of TB control but is inconsistently implemented in high TB burden settings due to the human and financial resources required. Although MDR-TB contact investigations can be high yield in terms of finding prevalent cases, management of HHC without active TB is highly variable.(6) Following a Global Consultation in 2015, experts in the field recommended that all HHC of an infectious individual with MDR-TB be evaluated using visits both in the clinic and the home.(7) Symptomatic contacts should be referred for further evaluation, and those without TB disease offered preventive interventions. However, the group acknowledged the challenges presented by widespread

implementation of this recommendation in the home setting. There are published guidelines for investigating contacts of persons with infectious TB, but these also acknowledge the complex implementation issues involved.(8) HHC investigations and participation of HHC in interventional clinical trials require a variety of approaches, and multiple resources may be needed.(9)

In preparation for an interventional trial, the AIDS Clinical Trials Group (ACTG) and the International Maternal, Pediatric, Adolescent AIDS Clinical Trials Network (IMPAACT) collaborated to conduct a cross-sectional study, A5300/I2003, of adult MDR-TB index cases (IC) and their adult and child HHC.(10) This effort was undertaken in an expedited fashion, in order to inform the implementation of the interventional trial to follow, which will require significant operational and budgetary resources. The primary objectives of the study were to investigate the feasibility of identifying, recruiting, and characterizing adult MDR-TB Index Cases routinely diagnosed in a programmatic setting and their adult and child HHC. The interventional trial to follow (A5300B/I2003B, PHOENIx) will evaluate the efficacy of delamanid versus isoniazid for treatment of high risk HHC of MDR-TB cases and is will open in 2018. Here we report the site resource utilization and operational challenges encountered in the feasibility study, and some potential strategies to address the issues identified.

STUDY POPULATION AND METHODS

A cross-sectional study of adult MDR-TB Index Cases and their adult and child HHC was conducted at 16 ACTG and IMPAACT network clinical research sites. Existing international sites were invited to participate in this study if they estimated that they could enroll at least 10 MDR-TB Index Cases and their HHC from their local catchment area within a 16-week period. The protocol was distributed to the sites for local regulatory approval in July 2015 and site trainings were subsequently conducted by teleconference and webinars. A Manual of Operations was developed which included a checklist for supplies needed (Table 1).

Adult MDR-TB Index Cases routinely diagnosed and initiated on treatment were identified from local TB programs, treatment centers, or laboratories, and approached for study enrollment. After obtaining written informed consent, site personnel collected basic demographic, clinical and laboratory information on the Index Cases and requested permission to approach the household. HHC were defined as any person who currently lives or has lived in the same dwelling unit or plot of land and shares or shared the same housekeeping arrangements as the index case and who reports exposure within 6 months prior to the Index Case starting MDR TB treatment. Household members could be screened and enrolled into the study at home, a mobile clinic, the research clinic, or at another setting based on their preferences and local site capacity. Potential HHC were identified and written informed consent or assent obtained. The following data were collected from the HHC: basic demographics, HIV infection status with HIV testing performed by the study if status unknown, clinical symptoms suggestive of TB, information about co-morbid medical conditions, and medications. Attempts were made to perform a chest x-ray on non-pregnant HHC, regardless of symptoms. Those without symptoms suggestive of TB underwent latent tuberculosis infection (LBTI) testing by Tuberculin Skin Testing (TST) and/or Interferon-

Gamma Release Assay (IGRA). Respiratory samples, including sputum and gastric aspirates in children, were requested for AFB smear, Xpert MTB/RIF and culture on all HHC, regardless of symptoms. HHC with symptoms or chest x-rays suggestive of TB were referred for further evaluation and management.

In order to describe site activities and resources needed, each site was also asked to complete four surveys. The first collected data about the number of adult MDR-TB cases in their catchment area. The second concerned the local TB program activities with regard to the evaluation of MDR-TB HHC and related activities at the clinical research site. The third concerned activities undertaken by the site in preparation for the feasibility study. The fourth was completed at the end of the study concerned the site resource utilization and included questions about TB infection control practices, transportation methods used for study participants, and additional resources identified by the sites in order to recruit, screen and enroll Index Cases and HHC. We also obtained informal feedback from site personnel on periodic study-related conference calls and at face-to-face network meetings.

RESULTS

MDR-TB EPIDEMIOLOGY AND TB CONTROL PROGRAM ACTIVITIES

Sites that participated in this study are in Botswana, Brazil, Haiti, India, Kenya, Peru, South Africa, Thailand. The 16 participating sites were asked about the number of adult MDR-TB cases in their catchment area who started treatment within the prior 6 months. The median number of adult MDR-TB cases (including retreatment cases) was 30, with a range from 4 to 360.

Most sites reported that their local TB Control Program did evaluate MDR-TB HHC in some manner [14/16 (88%)]. Most also reported household visits by the TB program [12/16 (75%)]. Of the 14 sites reporting that their TB control program evaluated HHC, all reported that both adults and children were evaluated. Adult evaluations almost always included symptom screening [13/14 (93%)] but only 6 of 14 (43%) included TST and none performed IGRA routinely. All but one [13/14 (93%)] site reported that their TB programs conducted sputum collection on adult contacts.

All sites reported that that when their local TB control programs evaluated child HHC, all performed symptom screening, 79% (11/14) performed TST but none performed IGRA testing. Sputum collection was done at 10/14 (71%) sites for child contacts and 7 (50%) reported collecting gastric aspirates when indicated. Ten of 16 sites reported that the TB programs performed follow-up visits with household contacts but only 6 (38%) reported that any preventive therapy was offered. Three of the six programs offered isoniazid (INH) alone, but 2 reported use of either INH alone or alternative regimens and 1 reported provision of alternative regimens only (a fluoroquinolone and ethambutol, primarily to children below 5 years of age).

SITE PREPARATION

Seven (44%) sites reported Index Cases would be evaluated at the household, with 5 of these 7 also reporting they would use the clinical site. Six sites said they would use the clinical site

alone for Index Case evaluations, and the remainder indicated other health care facilities, including the national TB program. For HHC, 5 sites indicated they would be evaluated in the household only, 4 at both the household and clinical site with or without additionally using the TB clinic, and 7 at the clinical site only. None planned to use a mobile clinic for any evaluations, and only 1 reported they would also use the workplace to evaluate HHC.

While 9 reported plans to evaluate HHC in the household, all 16 reported on infection control measures to be used in the household setting. All 16 sites reported that they would use open windows, 15 (94%) reported use of N95 masks for study staff, 15 (94%) surgical masks for the Index Cases, and 15 (94%) sputum collection outside, and 10 (63%) indicated that interviews would be performed outside. For infection control measures at the clinical site, 11 (69%) sites reported availability of negative pressure rooms and/or ultraviolet lights, all reported surgical masks worn by TB patients, 15 (94%) reported N95 mask worn by staff, all separate sputum collection areas, and 15 (94%) well-ventilated waiting areas.

Sites were asked to report on challenges encountered during preparation for this study. Sites that routinely care for adult patients had to make provisions for the care of children. Developing the capacity for TB infection control in the context of HHC investigations required equipment that was hard to acquire in a timely fashion. This included personal protective equipment and devices to manage air flow. Finally, one site indicated community concerns were raised because of potential stigma associated with repeat household visits by the team.

STUDY POPULATION ENROLLED

Between October 2015 and April 2016, sites approached 328 and enrolled 308 Index Cases and enumerated 305 households with 1324 HHC. 1285 HHC met the entry criterion of currently living in the same dwelling or plot of land and sharing housekeeping arrangement in the prior 6 months, and 1017 were enrolled. Index Cases were 43% female and ranged in age from 18 to 74 years (median 36). 112/308 (36%) were known HIV-infected. Results of chest x-rays were abstracted from medical records, and 87/201 (43%, 95% CI: 37—50%) had cavitary disease. 280 (91%) Index Cases had sputum collected at study entry after a median duration of TB treatment of 8.4 weeks; 74 (26%) sputum specimens were collected at the home, 92 (33%) at the research site, and the remainder at a community TB clinic or hospital. 94/280 (34%, 95% CI: 28—39%) had positive sputum smears.

Of 1017 enrolled,1016 HHC were evaluated, and 604 (59%) of the HHC were female, 16 of whom were pregnant. The median age was 25 years (interquartile range 12, 43) with 354 (35%) under 18 years old, and 103/1016 (10%) under five years old. Nine HHC had already been diagnosed with active TB prior to enrollment. Of the remaining 1007 without active TB, 39 (4%) were known to be HIV-infected. 707 (70%) of HHC underwent TST, 698 (99%) had results read and 56% (95% CI: 56—62%) were positive. 981 (97%) had IGRA testing and 965 (98%) had definitive results of which 631 (65% (95% CI: 61—69%)) were positive. The study required a chest x-ray for non-pregnant HHC and 967/991 (98%) had results available. This included 298/303 (98%) of HHC under 15 years old.

Of the 1007 HHC without active TB at entry, 775 (77% (95% CI: 73—80%)) were classified as being in one of the three mutually exclusive groups at high risk for progression to TB disease: 102 (13%) were <5 years old, 63 (8%) were ≥ 5 years old and HIV-infected, and 610 (79%) were ≥ 5 years old, HIV-uninfected/unknown, and TST and/or IGRA-positive. Only 21 (2%) HHC, including 15 among the high risk groups, were receiving TB preventive therapy. Among the 1007 HHC without active TB diagnosed prior to study entry, 121 HHC were determined by the outcome review group to have TB as a result of screening undertaken by the study, 109 who were in one of the three high risk groups. Only 17 had culture-confirmed TB, of which 4 were MDR-TB.

Information was captured on each attempt to evaluate a household. The 16 sites made 512 attempts to evaluate 308 households (up to 5 attempts were allowed to complete evaluations of a household). The median household size was 4 people in addition to the Index Cases, range 1 to 19 persons (Table 2). The median number of contacts evaluated during an attempt was 2 (range 0 to 18) and the median person-time spent by site staff per attempt was 4 hours (interquartile range 2 to 5 hours).

RESOURCE UTILIZATION

TB Infection Control & Transportation—All sites reported that staff had been trained in TB infection control measures. Nearly all sites (15/16) indicated that N95 respirators were worn by study staff and all indicated surgical masks were worn by Index Cases during study evaluations and that sputum was collected in a separate area when in the clinic (Table 3). Sputum from Index Cases was preferentially obtained at household visits (typically outside) or at the TB clinic, and unnecessary transport to the research site was avoided. 6/11 (55%) of the sites reported access to a partitioned vehicle for transportation of study participants. When reporting that Index Cases were transported, 82% made N95 respirators available for drivers and all provided surgical masks for participants. Open windows were used by all sites during transportation of participants. Specimen transport was also required with an incubator for IGRA specimens and a cold box for respiratory samples.

Operational challenges encountered and some potential strategies to address

Approach to the Household and Process of Consent—The majority of the network sites are accustomed to conducting clinical research procedures at a central research clinic. Most personnel reported that they enjoyed the opportunity to go out into the community, but also reported some challenges with the conduct of the research procedures in that setting. Many households were hot, poorly ventilated and crowded. The logistics of obtaining written informed consent and performing all of the study-related procedures and survey completion for multiple household members prompted most sites to have HHC come to a more traditional location. Most used their own clinical research sites, but several also used the local TB clinic or hospital. Site staff expressed concerns about personnel safety in some community locations, and never traveled without at least two staff members in a vehicle. Study participants received a stipend for each visit, and site staff were concerned about traveling with money in the vehicle, so many adopted a cashless reimbursement system such as a reloadable debit card.

Inclusion of Children—Enrolling children presented particular challenges. ACTG and IMPAACT sites were often co-located, which facilitated enrollment of adults and children, but some adult care providers had to identify collaborators with expertise for the evaluation of children. Two adult sites were prohibited from enrolling children by their local regulators. During parental illness, children were more likely to be in the care of family members who may not have been authorized to provide consent for the children to participate in the study. In some countries, for example Peru, both parents are required to give consent to allow participation of children in clinical trials. The requirements for obtaining consent for children to participate in research exceed those for clinical care, and it is not known how much obtaining the necessary consent for treatment would hamper programmatic implementation of HHC investigations. Older children and young adults were often highly mobile and had low motivation to enroll in the study. Obtaining the necessary laboratory samples from children was often difficult. The IGRA required 4 mLs of whole blood which was difficult to obtain from small children. Also some children had to be transported to a special facility to undergo a chest x-ray or gastric aspirate.

Management of Stigma—Site personnel were acutely aware of the need to preserve confidentiality of household members and avoid the potential stigmatization of study participants associated with a team of people in personal protective equipment being seen entering the household. In balancing this need with the need for protection of study staff, most elected to put on personal protective equipment immediately after entering the household. Some also wore street clothes rather than uniforms to minimize attention from neighbors and passersby. Sites reported that community engagement prior to starting the study proved very valuable. This varied from conducting community meetings, or placing articles or advertisements in local newspapers about plans for the study and its purpose. After this, community members were less surprised to see vehicles and staff from the study sites in the neighborhoods. Some sites reported anecdotally that the presence of study vehicles was viewed as a positive service to the community.

DISCUSSION

The WHO Global End TB Strategy calls for bold, new, patient-centered, active case-finding strategies, and screening of HHC is a key component.(11) However, there is often a big gap between recommendation and implementation, and research is needed to identify barriers to and facilitators of contact investigation to better inform uptake.(12) We identified considerable diversity in local practices for evaluation and management of HHC, although higher a proportion of sites related at least some investigation of HHC than in prior reports. For example, in a survey of 25 high-MDR burden program managers in 2010, only 40% reported that they usually or always evaluated MDR-TB contacts whereas 88% of our sites reported some contact investigation.(13) Provision of preventive therapy in the 2010 survey (36%) was similar to the proportion reported by our sites of their local TB program practices (38%). With regard to children, a more recent survey in Europe found that just over half provided preventive therapy to exposed children.(14)

Several important lessons were learned from this feasibility study. Establishing collaboration is critical, the adult and pediatric networks working together made it possible for HHC of all

ages to be evaluated more or less at the same time. Participating sites built on relationships with their local TB programs, and expanded outreach to the communities where the research was conducted. Thirty-four percent of the Index Cases in our study with smear test results available had smear-positive sputum, and 43% with x-rays abstracted had cavitary lung disease, both factors which can put their HHC and healthcare workers at increased risk of transmission.(15) Therefore, TB infection control in the HHC setting and during transport of participants and samples is critical.

HHC contact investigations are resource intensive; our site staff spent several hours for each outreach attempt but we did find that completion of the necessary testing was feasible: 97% of HHC in our study underwent latent tuberculosis infection (LTBI) testing and 98% had chest x-rays performed. Other published reports describing HHC investigations do not include details of the resources required but several have shown that active case finding is cost effective, with salary and transportation costs are included in the calculations.(16, 17) Costs may vary from country to country and according to local practices.

Transport of Index Cases and household contacts presented further challenges. Some sites had a partitioned vehicle available, although the efficacy of the partitions used has not been tested in preventing transmission of airborne disease. Using smoke as a proxy, the partition effectively separates the front and rear compartments of the vehicle.(18)

Finally, acknowledging that our findings were dominated by data from South Africa where prevalence of both HIV and TB infection is high, these efforts proved high yield as we found 121 HHC who met criteria for undiagnosed TB and 26 with undiagnosed HIV infection. Three quarters of the HHC had risk factors for development of TB disease, because they were small children, had HIV infection or LTBI.

CONCLUSIONS

HHC outreach is feasible but significant resources are required. This effort is time intensive and careful planning is needed to ensure proper evaluation of HHC and avoid problems of inadequate infection control and/or stigmatization. Nonetheless, return on this investment of time and resources is high in terms of case finding and opportunity to provide preventive treatment. In concert with other studies, we found a high yield for our investigations.(19) An interventional study comparing delamanid to isoniazid for the prevention of TB in HHC of patients with MDR-TB is in development, building on the important lessons learned from this feasibility study.

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Table 1:

Checklist for Site Outreach Personnel

General	Bags with multiple compartments
Testing	Consent forms, HIV test kits, lancets, buffer, small plastic testing surface
Supplies	Cotton wool, alcohol wipes, tissues
	Portable sharps container
	N95 respirators, masks, gowns, gloves
	Biohazard waste bag
	Sputum containers for TB testing, lab forms for TB testing
	Information, Education, and Communication material on TB
Data	Electronic mobile device
Transport	Map of index case locations
	Diary for appointments
	Referral letters
	Incubator for IGRA samples
	Cold box for respirator samples
Safety	Mobile phones, airtime sufficient for work in the field, identity cards, lockbox for participant stipends
Personal	Rain gear, water bottles, hand sanitizer, torches, gum boots, umbrellas/caps, sunblock

Table 2:

Number of Households According to Number of Potentially Eligible Contacts in Household and Number of Contacts in Household Enrolled and Evaluated*

Number of potentially eligible contacts	Number of contacts in household enrolled and evaluated																				Total eligible households	Total contacts eligible (n=1285)
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19		
1	2	31																			33	33
2	6	10	40																		56	112
3	5	7	11	35																	58	174
4	3	4	6	8	38																59	236
5	3	1	1	3	4	21															33	165
6		2	2	1	1	4	8														18	108
7	2	1		2	1	3	3	5													17	119
8				1	3		2	3	4												13	104
9								1	1	2											4	36
10									1		1										2	20
11										1	1	1									3	33
12				1							1										2	24
13														1							1	13
14																					0	0
15																					0	0
16																					0	0
17										1								1			2	34
18														1					1		2	36
19														1						1	2	38
Total enrolled households	21	56	60	51	47	28	13	9	6	4	3	1	0	3	0	0	0	1	1	1	305	
Total contacts enrolled and evaluated (n=1016)	0	56	120	153	188	140	78	63	48	36	30	11	0	39	0	0	0	17	18	19		

* Of 1,324 enumerated contacts, 1,285 in the table above were potentially eligible based on exposure criteria and 1,017 enrolled, and 1,016 were evaluated.

Table 3:

Use of TB Infection Control Measures by Participating Sites When Evaluating Participants in the Research Clinic and in the Household

Location/Measure	Number (percentage) reporting use of measure (n=16 sites)
Research Clinic:	
Use of negative pressure	7 (44%)
Use of ultraviolet light	7 (44%)
Surgical mask worn by patient with TB	16 (100%)
N95 respirator worn by staff	15 (94%)
Availability of a separate sputum collection area	16 (100%)
Access to a partitioned transport vehicle	8 (50%)
Staff training	16 (100%)
Separate ventilated waiting area	15 (94%)
Household:	
Surgical mask worn by patient with TB	15 (94%)
N95 respirator worn by staff	15 (94%)
Open windows	16 (100%)
Interview outside	10 (63%)
Sputum collected outside	15 (94%)