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Isoniazid preventive treatment in children in two districts of South India: does practice follow policy?

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SUMMARY

SETTING—Two districts of Tamil Nadu, India

OBJECTIVES—To determine the proportion of household contacts aged <6 years of patients with tuberculosis (TB) with positive sputum microscopy results who initiated and completed isoniazid preventive treatment (IPT), and to determine reasons for non-initiation and non-completion of IPT.

DESIGN—Household visits were conducted on a random sample of adult patients registered during January–June 2012 to identify household contacts aged <6 years.

RESULTS—Among 271 children living with 691 index patients, 218 (80%) were evaluated and 9 (4%) were diagnosed with TB. Of 209 remaining contacts, 70 (33%) started IPT and 16 (22.9%) completed a full course of IPT. Of 139 contacts who did not start IPT, five developed TB disease. Reasons for non-initiation of IPT included no home visit by the field staff (19%) and no education about IPT (61%). Reasons for non-completion included isoniazid not provided (52%) and long duration of treatment (28%).

CONCLUSION—This study shows that Revised National TB Programme guidance was not being followed and IPT implementation was poor. Poor IPT uptake represents a missed opportunity to prevent future TB cases. Provision of IPT may be improved through training, improved logistics and enhanced supervision and monitoring.

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Keywords

tuberculosis; contact investigation; children; isoniazid; preventive treatment

EACH YEAR, approximately 1 million new cases of tuberculosis (TB) occur in children aged <15 years worldwide, with the 22 high-burden TB countries accounting for 75% of these.¹ Young children in close contact with a smear-positive pulmonary TB case are at high risk of latent tuberculous infection (LTBI) and development of TB disease. It is estimated that up to 43% of infected children aged <12 months and 24% of those aged 1–5 years develop TB disease.² In addition, children aged <5 years are at a higher risk of developing disseminated forms of TB, including miliary TB and TB meningitis, frequently resulting in death.^{2,3}

The World Health Organization (WHO) recommends screening the household contacts of an infectious source case to identify children with TB disease and enable prompt treatment. Screening also provides an opportunity to provide isoniazid preventive treatment (IPT) for household contacts who do not have disease.⁴ Daily isoniazid (INH) for at least 6 months given as preventive therapy to young children has been shown to greatly reduce the likelihood of progression from LTBI to active TB disease.^{5–7} IPT is safe, as side effects in children are extremely rare, and its efficacy in preventing disease is as high as 90% when taken correctly.^{5–7} However, several studies have reported that adherence to IPT is generally poor, particularly in high-burden, low-resource settings.^{8–15}

India has one of the highest TB burdens in the world.¹ The Government of India's Revised National TB Control Programme (RNTCP) recommends screening of household contacts (especially children aged <6 years) of all smear-positive pulmonary TB cases.¹⁶ For children with no evidence of active TB disease, IPT at 5 mg/kg/day is recommended for 6 months.^{4,7,16} Despite these recommendations, implementation of IPT in children is suboptimal in India. Two community-based studies, conducted in Krishna District of Andhra Pradesh and the Tuberculosis Research Centre (TRC) Chennai, revealed that respectively 56% and 19% of eligible children were initiated on IPT.^{8,17} These studies, however, did not provide information on adherence to IPT after its initiation.

We undertook an operational research study in two districts of the South Indian state of Tamil Nadu, to determine the proportion of household contacts (aged <6 years) who initiated and subsequently completed IPT, and possible reasons for both non-initiation and non-completion from the patients' perspective.

METHODS

Design and setting

This cross-sectional study was conducted in the Krishnagiri and Tiruvalur districts of Tamil Nadu in South India. In 2012, these districts had a population of 1.8 and 2.8 million, respectively. The predominant occupation of people in these districts is agriculture, and people tend to live in nuclear families with an average of 4–5 persons per household. Both

districts together had nine RNTCP Tuberculosis Units (TU), each covering a population of 500 000.

After TB diagnosis and initiation of treatment, a paramedical worker from the nearest primary health centre visits each patient's home to counsel them and their families about TB disease and treatment. During this initial home visit, all the household members are screened for the presence of TB symptoms. Those with symptoms are referred to the nearest health facility for chest radiography and clinical examination. After active TB disease is ruled out, childhood household contacts should be initiated on IPT. Details on screening and IPT initiation are documented on patient TB treatment cards by paramedical workers. All patients with TB diagnosed and initiated on treatment are recorded in a TB register, which is maintained by paramedical supervisory staff at the TU level.

Definitions

Index cases were defined as all sputum smear-positive patients with TB registered for treatment during January 2012–June 2012. Household members were defined as all persons who shared food from the same kitchen as that of the index case. For this study, childhood household contacts were defined as children aged <6 years who lived with an index case during the course of their anti-tuberculosis treatment (irrespective of duration).

Study participants and study period

Study participants were household contacts of index cases. The study was conducted during November 2012–February 2013. All households were visited at least 6 months after the start of treatment of each index case, thereby reducing continued exposure and the risk of reinfection of contacts and allowing adequate time for participants to complete a full course of IPT.

Data collection procedures, data sources and variables

The District Tuberculosis Officers and Medical Officers of the TU prepared a line-list of all index cases by reviewing the tuberculosis registers and treatment cards maintained at all the TUs. Because it was not feasible to investigate all index cases during the study period, we selected approximately half ($n=740$) through simple random sampling. A line-list of all household contacts was prepared by reviewing the treatment cards. For each line-listed household contact, the respective District and Medical Officers extracted the date of IPT initiation, the number of monthly INH doses distributed and the duration of IPT (if available) from the treatment cards into a separate data collection sheet.

Trained field staff visited the homes of all 740 patients. During the home visit, a parent was informed about the study and asked to respond to a structured questionnaire. The questionnaire elicited the following information about the index case: age, sex, number of household members and contacts, residence in urban or rural area, level of education and distance (in km) to the nearest primary health centre. For household contacts of children aged <6 years, parents were also asked to provide the following information: age, sex, relationship to index case, educational level of parents, whether screened for TB, diagnosed with TB, initiated on IPT, duration of IPT intake and reasons for non-initiation and non-

completion of IPT. Principal investigators visited the homes of 10% of the index cases to cross-verify and assess the quality of the information collected by the field staff.

Data entry and analysis

Data entry operators (two from each district) entered data separately (i.e., double data entry). Both databases were compared and all discrepancies in data entry were resolved by referring to the original data collection instrument and the data were finalised. EpiData software version 3.1 (EpiData Association, Odense, Denmark) was used for data entry and analysis. Frequencies and proportions were calculated for all variables. Pearson's χ^2 test was used to compare differences in proportions between groups (e.g., IPT initiators vs. non-initiators). A *P* value of 0.05 was considered statistically significant.

Ethics issues

The study was approved by the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease (Paris, France) and the Institutional Ethics Committee of the National Tuberculosis Institute (Bangalore, India). Informed consent was obtained from the household members before interviews. Participation of the US Centers for Disease Control and Prevention (CDC) in this project did not meet the definition of engagement in human subjects' research and separate institutional review board approval was not required.

RESULTS

Of 1513 sputum smear-positive TB cases (index cases) registered during January–June 2012, 740 index cases were randomly selected. The homes of 691 (92.5%) index cases were visited, of which 188 (27%) had a childhood household contact aged ≤ 6 years (Figure 1). Of 271 childhood household contacts identified, 218 (80%) were screened for TB disease at the RNTCP district-level clinic, of which nine (4%) were diagnosed with TB disease and initiated on standard four-drug treatment as per RNTCP guidelines.¹⁶ Of the remaining 209 contacts not diagnosed with TB disease, 70 (33%) were initiated on IPT. Of these, 12 (17%) completed <1 week of treatment, 16 (23%) 1–4 weeks of treatment, 8 (11%) 1–2 months of treatment, 18 (26%) 3–4 months of treatment and 16 (23%) completed the full 6-month course. Overall, among 271 household contacts aged <6 years identified in our study, only 25 (9%) contacts (nine children in whom TB disease was diagnosed and who were linked to treatment services and 16 who completed the full course of IPT) derived all the benefits of the present policy on contact screening and IPT (i.e., screening, identification of TB disease and TB treatment initiation, or IPT initiation and IPT completion) (Figure 2).

The demographic characteristics of the household contacts and those who were initiated on IPT are given in Table 1. Household contacts whose parents were index cases and those whose homes were visited by paramedical workers were more likely to be initiated on IPT.

The most common reasons for non-initiation and non-completion of IPT are given in Table 2. Eighty-five (61%) contacts received no information about IPT at the time of the initial home visit and 27 (19%) received no initial home visit at all. Among persons who initiated IPT but did not complete treatment, 28 (52%) had not received INH tablets, and 15 (28%) contacts did not complete IPT due to the lengthy duration of treatment (i.e., 6 months).

During the study, when field investigators visited the households to collect data, they enquired about the current status of the household contacts (Table 3). Three contacts who had not completed IPT had died; none had been previously diagnosed with TB disease. Forty-five contacts were found to have symptoms suggestive of TB; all were investigated for active TB disease at the nearest health facility and five children who had not received IPT were diagnosed with TB disease and were started on the standard four-drug TB treatment regimen.

DISCUSSION

In this study, 27% of the sputum smear-positive patients with TB registered for treatment under the RNTCP in two districts of Tamil Nadu, India, had a household contact aged <6 years. One fifth of these household contacts were not screened for TB. Of those screened, more than 95% did not have TB disease and were eligible for IPT, but only a third of these were initiated on IPT. Furthermore, among those starting IPT, approximately 75% did not complete the full course of IPT. Overall, of the 271 household contacts aged <6 years, only 25 (9%) received all the benefits of the present policy on contact screening and IPT. This included only 2 of 18 (11%) children aged <2 years, the group at highest risk of developing active TB disease.

This study had several strengths. First, in addition to reviewing the programme records, we validated this information by visiting the households of more than 90% of patients with TB and ascertained the status of screening, IPT initiation, duration of intake and completion, an investigation that had not previously been reported in India. Second, the study assessed the implementation of national guidelines for contact tracing and IPT under routine programmatic conditions. The active engagement of the programme staff throughout the study enhanced the quality and validity of the data reported in this article. This study thus reflects realities at field level.

The study findings have several policy and programmatic implications. First, household contact screening and IPT in households of patients with sputum smear-positive TB was poorly implemented despite national and international guidelines.⁴ This is consistent with earlier studies conducted in other parts of the country^{8,17} and across the world.^{3,9}

Second, our study revealed several important concerns of the care givers of household contacts. Most care givers stated that they had not received adequate education about the benefits of IPT to make an informed decision about whether to initiate treatment. While not systematically evaluated in this study, these results imply that more education and monitoring of paramedical workers are needed in this setting. Even among those who received this information, no drugs were offered to more than half (52%) of them. These shortcomings might be explained, in part, by the programme staff themselves not fully understanding the benefits of IPT in preventing disease among children, and thus a lack of urgency, and also to some degree by the challenges of procuring and delivering IPT drugs to patients on a monthly basis.⁸ This difficulty might also be due to the absence of systems to monitor implementation. Our findings thus highlight an urgent need to develop and implement monitoring and evaluation tools to assess IPT initiation and completion in India.

Third, about 10% of all non-initiators and 30% of the parents of non-completers stated that the long duration of IPT (daily for 6 months) influenced non-compliance. Reducing the frequency or duration of drug intake may thus enhance initiation and completion of IPT. In adults, a new combination regimen of INH and rifapentine (RPT) administered once weekly for 12 weeks as directly observed treatment (DOT) has been shown to be as effective in preventing TB as other regimens.¹⁸ However, the safety and efficacy of INH-RPT in children has not been demonstrated and it is thus not currently recommended for this age group.¹⁸ If clinical trials establish the safety, efficacy and tolerability of this combination in preventing TB among children, it may be a viable option in reducing treatment duration in this high-risk population, particularly in high TB burden settings. Other potential treatment options have been studied to reduce the duration of treatment. A high-dose INH regimen (i.e., 20–30 kg/bodyweight twice weekly)¹⁹ and 4 months of daily rifampicin²⁰ have shown higher completion rates and lower rates of hepatotoxicity than 9 months of daily INH.^{21–23}

Finally, this study also provides information about the status of household contacts 6–9 months after the index case was diagnosed and initiated on treatment. Some contacts had died, and about 17% had symptoms suggestive of TB, of which some TB cases were detected. This represents a missed opportunity for TB control and prevention; regular screening and IPT could have led to early TB detection or have prevented the disease.

A major limitation of this study is that information on screening for TB disease, IPT initiation and completion was ascertained through a questionnaire administered to care givers of household contacts. If there were any deficiencies in information recall or in understanding the questions, then the results may be biased. To address this possibility, we also reviewed the information recorded in the programme records to cross-verify the consistency of information. The magnitude of errors as a result of deficiencies in recall are therefore likely to be minimal.

CONCLUSIONS

This study shows that in the two districts of Tamil Nadu, RNTP guidance was not being followed and IPT implementation was poor. Failure to routinely provide IPT for childhood contacts represents missed opportunities to prevent future TB cases. Major gaps in non-initiation may be corrected by training, improved logistics and enhanced supervision and monitoring. Moreover, as daily pill intake for 6 months was noted as a barrier, shorter regimens, when available, may improve both initiation and completion of preventive treatment. The decision to use alternative preventive regimens as a means to improve adherence should be balanced against the potentially high cost of delivering these regimens under direct observation as recommended.

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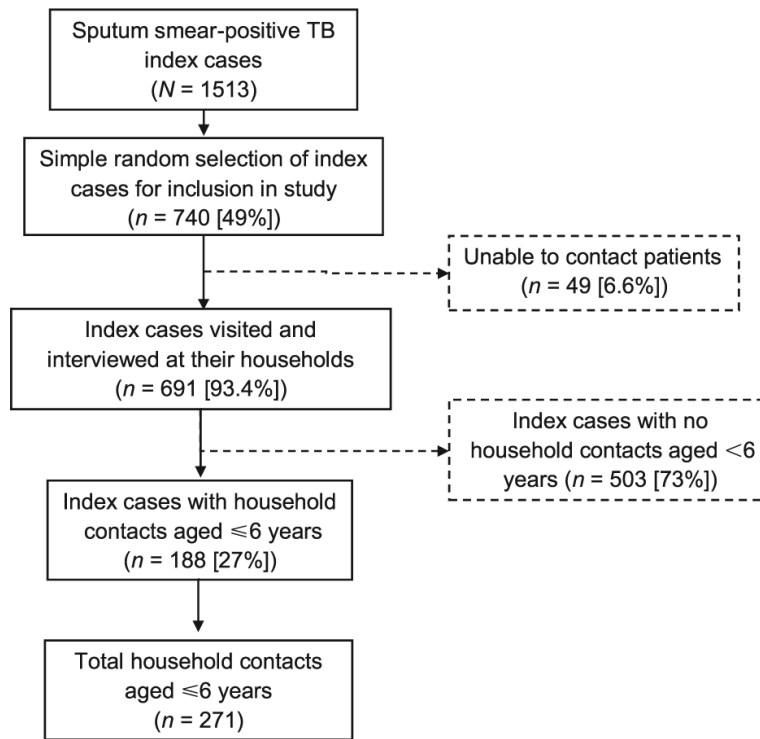


Figure 1. Children aged ≤ 6 years identified through household contact investigation of patients with sputum smear-positive tuberculosis (TB) in Krishnagiri and Tiruvalur districts, India, 2012.

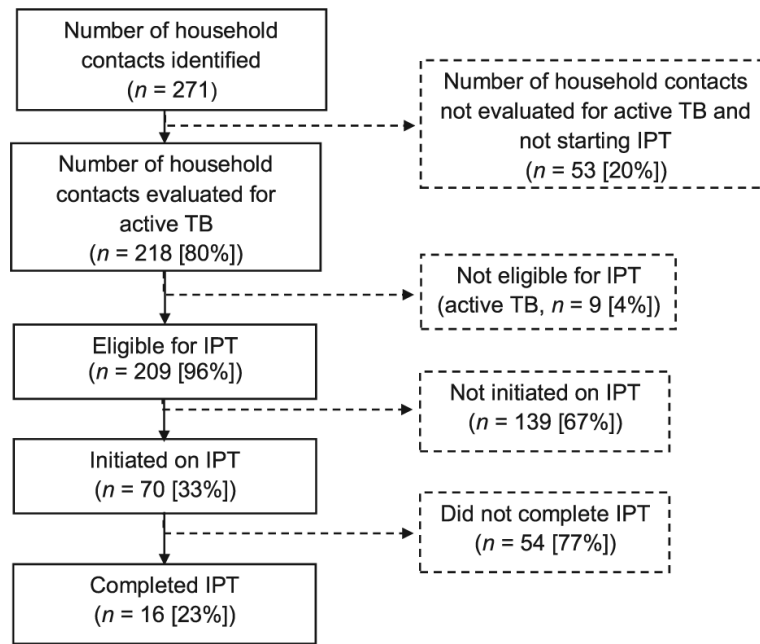


Figure 2. Paediatric tuberculosis contacts identified, screened, initiated and completing isoniazid preventive treatment (IPT) in Krishnagiri and Tiruvalur districts, India, 2012.

Table 1

Characteristics of household contacts who started IPT in Krishnagiri and Tiruvalur Districts, India, 2012

Characteristic	Total <i>N</i>	Initiated on IPT		<i>P</i> value
		<i>n</i>	(%)	
Total	209	70	(33)	
Sex				
Male	97	36	(37)	0.61
Female	112	34	(30)	
Age, years				
0–1	18	2	(11)	0.07
1–2	39	15	(38)	
2–3	38	14	(37)	
3–4	36	13	(36)	
4–5	46	17	(37)	
5–6	32	9	(28)	
Mother's education				
Illiterate	49	12	(25)	0.27
Literate	160	58	(36)	
Distance from nearest healthy facility, km				
3	107	42	(39)	0.25
>3 to 5	44	12	(27)	
>5	58	16	(27)	
Relationship between index case and child				
Parent	111	51	(46)	0.001
Other	98	19	(19)	
Initial home visit by paramedical worker				
Yes	140	58	(41)	0.004
No	69	12	(17)	

IPT = isoniazid preventive therapy.

Table 2

Reasons reported by child care givers for non-initiation and non-completion of IPT among household contacts in Krishnagiri and Tiruvalur districts, India, 2012

	<i>n</i>	(%)
Reasons for non-initiation of IPT (<i>n</i> = 139)		
Home visits done but no information about IPT	85	(61)
No initial home visit by the field staff	27	(19)
Informed about IPT but drugs not provided	15	(11)
Drugs provided but not initiated due to pill burden	12	(9)
Reasons for non-completion of IPT (<i>n</i> = 54)		
INH tablets not provided	28	(52)
Long treatment duration	15	(28)
Due to side effects	6	(11)
Migration/death of the contact	5	(9)

INH = isoniazid, IPT = isoniazid preventive therapy.

Table 3

Status of household contacts at time of visit by field investigators to collect data on IPT initiation and completion in Krishnagiri and Tiruvalur Districts, India, 2012

Category of household contact	Had already died <i>n</i> (%)	Already diagnosed with TB disease <i>n</i> (%)	Had symptoms suggestive of TB disease <i>n</i> (%)	Of those with TB symptoms, diagnosed with TB <i>n</i> (%)
Screened but not eligible for IPT (<i>n</i> = 53)	0	0	9 (17)	0
Screened and found eligible, but not initiated on IPT (<i>n</i> = 139)	0	0	28 (20)	5 (4)
Initiated on IPT but had not completed the full course of IPT (<i>n</i> = 54)	3 (6)	0	7 (13)	0
Who had completed the full course of IPT (<i>n</i> = 16)	0	0	1 (6)	0

IPT = isoniazid preventive therapy; TB = tuberculosis.