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Isoniazid Preventive Therapy among Children Living with Tuberculosis Patients: Is It Working? A Mixed-Method Study from Bhopal, India

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ABSTRACT

Objective: We assessed uptake of isoniazid preventive therapy (IPT) among child contacts of smear-positive tuberculosis (TB) patients and its implementation challenges from healthcare providers' and parents' perspectives in Bhopal, India.

Methods: A mixed-method study design: quantitative phase (review of programme records and house-to-house survey of smear-positive TB patients) followed by qualitative phase (interviews of healthcare providers and parents).

Results: Of 59 child contacts (<6 years) of 129 index patients, 51 were contacted. Among them, 19 of 51 (37%) were screened for TB and one had TB. Only 11 of 50 (22%) children were started and 10 of 50 (20%) completed IPT. Content analysis of interviews revealed lack of awareness, risk perception among parents, cumbersome screening process, isoniazid stock-outs, inadequate knowledge among healthcare providers and poor programmatic monitoring as main barriers to IPT implementation.

Conclusion: National TB programme should counsel parents, train healthcare providers, simplify screening procedures, ensure regular drug supply and introduce an indicator to strengthen monitoring and uptake of IPT.

KEYWORDS: contact tracing, chemoprophylaxis, IPT, TB prevention

INTRODUCTION

Tuberculosis (TB) remains an important cause of childhood morbidity and mortality in high-burden settings in developing countries [1]. Worldwide, an estimated 1 million children develop TB and 136 000 die annually [2]. In India, approximately 10 million children are at risk of being infected annually because of being in contact with a sputum microscopy smear-positive for acid-fast bacilli pulmonary TB (Sp-TB) patient. Eventually, an estimated 700 000–800 000 children would develop TB over the subsequent 5 years [3].

Young children (aged <6 years) in contact with Sp-TB adults are often infected with *Mycobacterium tuberculosis* and once infected are at higher risk of progression to TB disease than adults [4, 5]. The source of infection for most children is an infectious adult living in close proximity, usually in the household [6, 7]. 'Contact screening' is an effective and simple approach that can be implemented at the primary health care setting. It is a good strategy in early identification of children eligible for isoniazid preventive therapy (IPT) and preventing susceptible children from developing the disease following recent infection from household Sp-TB patient [8, 9].

Various studies have demonstrated the efficacy of IPT to prevent TB disease in children who live with active TB patients [10–13]. A meta-analysis shows that IPT reduces the risk of TB disease by 59% among children aged <15 years [14]. India's Revised National Tuberculosis Control Programme (RNTCP) recommends that all household contacts of Sp-TB patients aged <6 years (hereafter referred as child contacts) be investigated for TB and those without TB be provided IPT for 6 months. However, there is no strategy for IPT in children beyond 6 years [15].

Globally, IPT implementation has been a challenge, including in India. At present, there is no nation-wide data in India on the screening, initiation and completion of IPT for child contacts. However, it has been evident from various studies from South India [16–19] that the implementation of IPT is deficient. Evidence regarding IPT implementation from other parts of the country, especially the urban settings of Central India is absent [20]. Also, there is limited information about the reasons for non-initiation of IPT from the perspective of parents of child contacts and healthcare providers [16]. Understanding these is crucial to address the implementation challenges and this warrants a comprehensive assessment using a mixed-method study design.

In this operational research, we aimed to assess the proportion of child contacts of registered Sp-TB cases in one Tuberculosis Unit (TU) of Bhopal district in Central India who were screened for TB, initiated and subsequently completed IPT and understand the reasons for non-initiation of IPT from healthcare providers' and parents' perspective.

METHODS

Study design

We used a mixed-method study design, wherein quantitative phase (secondary data analysis and house-to-house survey) was followed by qualitative phase (Interviews) [21].

Study setting

Bhopal, with 2.53 million predominantly urban population, is the capital of Madhya Pradesh, the second largest state in India. The TB programme is managed by the District TB Centre (DTC) and consists of five sub-district-level programme management units. The district has 35 peripheral health institutes (PHIs), which include dispensaries, subcentres, primary health centres (PHCs), community health centres (CHCs), sub-district hospitals, district hospital and medical colleges. Under the TB control programme, district has 24 sputum microscopy centres for the diagnosis and management of TB patients; all are situated in the above-mentioned PHIs.

The present study was conducted in one TU (Bhopal TU), conveniently selected. It serves approximately 500 000 people, and has 12 PHIs. As per RNTCP guidelines, all diagnosed TB patients are to be visited at their residence by a healthcare provider before starting treatment. During this visit, the child contacts are to be identified and those with symptoms (fever, cough, loss of weight or no weight gain and sick look) are referred to a medical officer for screening and investigation. If the child is diagnosed as having active TB, a full course of anti-TB treatment is provided [22]. If the child does not

have active TB, isoniazid (INH) is recommended at the dose of 10 mg/kg daily for a duration of 6 months [22]. The guidelines for IPT in India are in line with the World Health Organization guidelines [9].

Study population

For the quantitative part, all child contacts of Sp-TB patients aged <6 years in the study TU, registered between January and March 2015 were included. For the qualitative part, we interviewed TB-related healthcare providers and parents of children. Those who were willing, vocal and knowledgeable to participate in the study were purposively selected.

Data collection and data variables

Quantitative

The secondary data related to Sp-TB patients registered between January to March 2015 were extracted out of TB treatment cards and registers and reviewed. These patients were visited at their homes and the information regarding child contacts were verified. Patients with child contacts were interviewed in Hindi (local language) using a structured, pretested questionnaire. It had questions on sociodemographic profile of the index patient and child contacts and questions related to programmatic implementation of IPT. Those who could not be contacted even after two attempts by the investigator were not interviewed and hence their child contacts if any could not be included in the study. Operational definitions used for data collection are given in Box 1, which are in line with national guidelines [17, 22, 23].

Qualitative

We interviewed 11 healthcare providers (one district TB officer, one paediatrician, one TB medical officer, three TB health visitors, one district drug store manager, one laboratory technician, two nurses of TB hospital and one community-level treatment provider) and 14 caregivers or parents of child contacts. The interview guides were prepared after analysing the quantitative data, to explore the reasons for noninitiation of IPT from healthcare providers' and parents' perspective. Participants were interviewed by the principal investigator trained in qualitative research methods. Audio recording and verbatim notes were taken during the interview. After completion, the summary of the interviews was read to the participants and validated.

Study period

Quantitative

The house-to-house survey of the index cases was conducted in the months of November and

Box 1: Operational definitions used in the study of the IPT of child contacts of TB patients in Bhopal, Madhya Pradesh, India, 2015–16

Parameter	Definition
Sp-TB	A patient with at least one positive sputum specimen for AFB of the two sputum specimens subjected for smear examination by direct microscopy.
IPT	Short course of Isoniazid monotherapy with 10 mg/kg body weight given prophylactically for all the household paediatric contacts (aged <6 years) of a sputum positive TB case. IPT is given daily for 6 months on self-administered basis.
Child contact	All the children aged ≤6 years who are in contact with smear-positive pulmonary TB case, who live or have lived (irrespective of the duration) within the household of the smear-positive PTB patient during the course of his/her disease (after the onset of symptoms)
Index TB patient	Smear-positive TB patient, perceived to be source of infection in household contact
Initiation of IPT	For the study purpose, the child contacts started on IPT within 1 month after the diagnosis of index TB case is considered initiated otherwise not.
Completion of IPT	Completion of full course of IPT within 7 months from the date of initiation.

Note. AFB, Acid-Fast Bacillus; PTB, Pulmonary Tuberculosis.

December 2015, to capture the 'completion of IPT' of the child contacts.

Qualitative

All key informant interviews were conducted from the month of January to March 2016.

Analysis and statistics

Quantitative

Quantitative data were double-entered, validated and analysed using EpiData software (EpiData version 3.1 for entry and version 2.2.2.182 for analysis EpiData Association, Odense, Denmark). The association with key analytic outputs were calculated using Relative Risk (RR) and 95% confidence intervals (CIs). The STROBE guideline was used for reporting the quantitative component of the study [24].

Qualitative

Manual descriptive content analysis was done by the principal investigator [25]. The decision on coding rules and theme generation were done by using standard procedures and in consensus. The themes and the categories were reviewed by a second investigator to reduce bias and interpretive credibility. Any disagreements were resolved in discussion with the last author. The findings were reported by using 'Consolidated Criteria for Reporting Qualitative Research' guidelines [26].

Ethics approval

Ethics approval was obtained from the institutional ethics committee of the All India Institute of Medical Sciences, Bhopal, India, and the Ethics Advisory Group of the International Union Against Tuberculosis and Lung Disease, Paris, France. Parents or caregivers of child contacts were interviewed after explaining the objectives of the study and obtaining written informed consent in local language (Hindi). For qualitative part, verbal consent was taken from all the study participants for interview and audio recording. This was accepted by the institutional ethical committees.

RESULTS

Overall, 129 index Sp-TB patients (mean age 34 years; 61% male) were registered between January and March 2015, of whom households of 117 index cases were visited (Table 1). Of 129 cases, 97 (75%) were new TB cases and 13 (10%) were dead at the time interview. There were 59 reported child contacts in the households of 129 Sp-TB patients, of whom we could obtain information of 51 child contacts (who lived in 117 index households visited). The proportions of child contacts who were screened, not screened, initiated on anti-TB treatment and IPT, their completion status and factors related to non-initiation of IPT are given in Fig. 1.

Table 1. Socio-demographic and clinical profile of smear-positive TB patients registered in Bhopal TB unit from January to March 2015

Variable	Subcategory	Number	%
Total		129	100
Age (years)	<15	4	3
	15–24	46	36
	25–34	23	18
	35–44	18	14
	45–54	22	17
	55–64	9	7
	>65	7	5
Sex	Male	78	61
	Female	51	39
Phone number documented on treatment card	Yes	123	95
	No	6	5
Patient category	New	97	75
	Retreatment	28	22
	Multidrug resistance	4	3
Number of child contacts per household			
	0	89	69
	1	25	19
	2	11	9
	3	4	3
Status of Index patient[a] at the time of visit	Live	116	90
	Dead	13	10

[a]*Note*. Index patient: smear-positive TB.

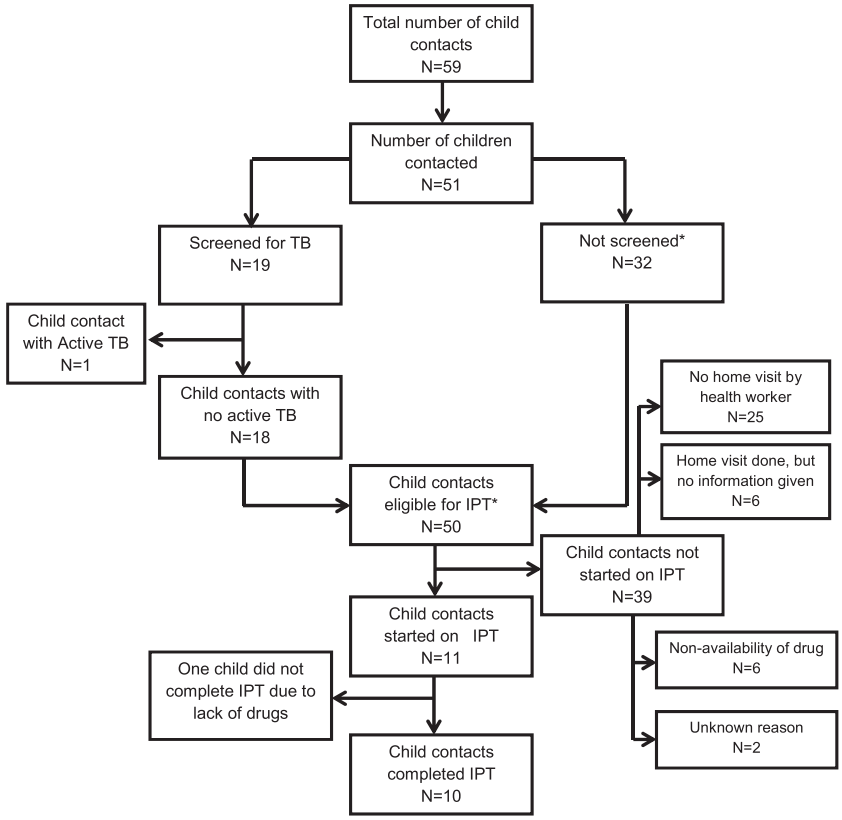

Fig. 1. IPT among child contacts of smear-positive TB patients in DTC TU Bhopal between January and March 2015, Bhopal, Madhya Pradesh, India. *Since no case of TB was identified among 'not screened child contacts' during the time of interview, we consider that these children were otherwise eligible for IPT for this analysis.
TU, Tuberculosis Unit; IPT, isoniazid preventive therapy.

TB screening, IPT initiation and completion

Of the 51 visited child contacts, 19 were screened for TB, of whom one was diagnosed with active TB and treated. While the remaining 32 child contacts were not screened for TB, the investigator did not find any of them to have suffered from active TB during field visit. Hence, for purpose of this analysis, all 50 child contacts have been considered as 'eligible for IPT' of whom, 39 (78%) children were not initiated on IPT. Of 11 initiated on IPT, 10 completed it. The reasons for non-initiation of IPT were lack of home visit by healthcare provider, lack of information on IPT and lack of drugs (Fig. 1). Children living at a distance of >5 km from the nearest PHI and living with an index patient other than parent were more likely to have not initiated on IPT (Table 2).

Barriers to IPT implementation

The barriers for initiation of IPT as perceived by the parents are summarized in Table 3. No home visit by a healthcare provider and lack of information related to IPT were the main perceived barriers for initiation of IPT from the parents' point of view. Parents opined that the health system needs to provide adequate information on IPT, which is lacking. A 35-year-old mother (a cured TB patient) of a child contact mentioned,

> Neither he [DOT provider] nor madam [TB laboratory technician] told us this. I had even asked them how to protect my child from the infection because at that time he used to even drink my milk. But since they did not tell anything, I stopped breastfeeding the child.

Table 2. Factors associated with non-initiation of IPT among child contacts of smear-positive TB patients in Bhopal, Madhya Pradesh, India 2015

Variable	Subcategory	Total	Number not initiated on IPT	% not initiated on IPT	RR	95% CI
Total		50	39	78		
Age (years)						
	<2	17	12	71	Reference	
	2-4	18	14	78	1.1	0.7–1.6
	>4	15	13	87	2.7	0.4–16.0
Gender						
	Male	27	22	82	1.1	0.8–1.5
	Female	23	17	74	Reference	
Mother's education						
	Illiterate	13	10	77	Reference	
	Literate[a]	37	29	78	0.9	0.7–1.4
Relationship with index case						
	Parent	20	13	65	Reference	
	Grandparent	11	8	73	1.1	0.7–1.8
	Others	19	18	95	1.4	**1.0–2.0**
Distance from PHI[b] where index case was initiated on treatment						
	<5 km	41	30	73	Reference	
	5–10 km	9	9	100	1.4	**1.1–1.6**
Initial home visit by healthcare provider						
	Done	13	7	54	Reference	
	Not done/Unknown	37	32	87	1.6	0.9–2.7

Note. [a]Literate: Who can read and write with understanding in any language.
[b]Public Health Institution.
The bold values signify Statistically significant risk factor for "Non-initiation on IPT" for child contacts of PTB patients.

Another 28-year-old mother (wife of Sp-TB index patient) said,

> No one has visited so far [to our house], the children have never been administered any medicine although they keep on having some or the illness like fever and 2 of them have had cough for a long time.

A few parents did not start IPT although they were aware of the need to start IPT. This could either be owing to lack of drugs or lack of risk perception, which reflects lack of adequate understanding of harms of non-initiation of IPT.

> My baby was not having any infection, then why should any drug be given to the child? (21 years/female/new patient/mother of child contact)

The challenges associated with IPT implementation as perceived by the healthcare providers are summarized in Table 4. The challenges were grouped into two major themes: patient-level and healthcare providers' challenges, which were further grouped into six categories. Cumbersome screening process, unavailability of INH, lack of information and training for the healthcare providers were the striking challenges from the care providers' view point. A 36-year-old paediatrician working in a tertiary care centre said,

> Chest X-Ray is there [in district hospitals], but availability of Mantoux, we cannot say!!! May be it is not there even in District hospitals, the CHC and PHCs have nothing, 'so there is no screening at all'. The doctors of PHC and CHC are not even aware of the IPT. Nobody goes for lavage, even we don't go for that. It's

Table 3. Barriers for initiation of IPT among child contacts as perceived by caregivers in Bhopal, Madhya Pradesh, India, 2015–16

Themes	Verbatim quotes
1) No home visit by paramedical worker	'No one has visited so far [to our house]' (59 years/grandmother of child contact)
2) Lack of information provision by healthcare providers	'No, we were never been told and hence we never administered any drugs to the children' (64 years/grandmother of child contact)
	'Neither he [DOT provider] nor madam [TB LT] told us this. I had even asked them how to protect my child from the infection because at that time he used to even drink my milk. But since they did not tell anything, I stopped breastfeeding the child' (35 years/female/mother of child contact/cured case of PTB)
3) Erratic availability of INH	'It was even unavailable at the shop [private pharmacy], but somehow the shopkeeper managed to bring it for us. I am not aware of the exact cost but it was costly' (65 years/grandmother of child contact)
4) Lack of risk perception	'My baby was not having any infection, then why should any drug be given to the child?' (21 years/female/new patient/mother of child contact)
	'We didn't give the drug to the younger child because I felt that as I was taking anti TB drug and breast feeding, so the drug would automatically be going to the child's body and didn't want to give any drug additionally. Should I have given it to her also?' (26 years/mother of child contact/retreatment sputum positive patient)

> just not operationally feasible. We go only for Mantoux and Chest X-Ray; we diagnose most of the patients on the basis of these two tests only.

Healthcare providers mentioned that owing to cumbersome screening process, they tended to initiate IPT bypassing the screening process, as illustrated by the following quote:

> I am not sure to whom it should be started & to whom it shouldn't be so I used to start all the children <6 years who is contact of Sputum Smear positive patient.

Non-availability of INH for long periods was another major challenge and this discouraged them from doing home visits and initiating TB screening among child contacts, as they did not have anything to offer after screening. A healthcare provider managing drug stores at DTC mentioned,

> Non-availability of INH is the biggest problem. Being a store manager myself, I can tell you exactly that it ran out of stock from the store (DTC) from 1-4-15 to 15-3-16.

Another healthcare provider opined that there were challenges related to dosage form of INH and felt a syrup form is better suited for consumption by young children.

DISCUSSION

This is one of the few studies from Central India revealing unsatisfactory TB screening and IPT initiation among child contacts of Sp-TB cases in programme setting. Only one-third of child contacts underwent screening for TB in our study, while other studies from South India reported much higher screening rates (75–80%) [18, 19]. Only one-fifth of child contacts started IPT in our study, although most of those who started, completed it. Other studies from India have reported varying IPT initiation (19–84%) and completion (23–55%) rates [16–20]. Khaparde *et al.* reported screening of 65% child contacts and 63% initiation of IPT even after an active intervention in Rajnandgaon district of central India [20]. A community-based study from South Africa

Table 4. Challenges associated with implementation of IPT among the child contacts as perceived by the healthcare providers in Bhopal, Madhya Pradesh, India, 2015–16

Major themes	Categories	Verbatim quotes
Patient level	1) Fear of drug and its side effects	'Some patients do not even tell that they have small children at home. People hide this fact to avoid their child from being given the medication.' (32 years/male/TB HV/experience, 2 years)
		'mother of the child prefers to keep the child away from the patient rather than taking the drugs for 6 months' (42 years/male/TB HV/experience, 10 years)
		'main concern of the patient is how the little child will consume the tablets' (42 years/male/TB HV/experience, 10 years)
	2) Lack of awareness and risk perception	'Even though their child does not suffer from any illness, why he is being treated is a question of all parents' (38 years/male/DOT provider/NGO/experience, 4 Years)
		'Every mother believe that my child cannot suffer from TB, so why should I give h/o related to trivial symptoms like neck swelling, cough, fever etc' (42 years/male/TB HV/experience, 10 years)
		'because parents feel that this drug is meant to be given only for Tb affected children' (38 years/male/DOT provider/NGO/experience, 4 Years)
Programme level	3) Inadequate knowledge among healthcare providers	'Its (INH chemoprophylaxis) schedule is similar to that of DOTS, i.e. thrice-a-week' (32 years/male/TB HV/experience, 2 Years)
		'We give INH as a dose of 5 mg/kg body weight' (42 years/male/TB HV/experience, 10 years)
		'I am not sure to whom it should be started & to whom it shouldn't be so I used to start all the children <6 years who is HH contact of SS positive patient' (42 years/male/TB HV/experience, 10 Years)
		'Our MOs are not aware of the RNTCP guidelines. Most of the times, screening of the contacts of positive patients is not done simultaneously. Also there are other MOs who even screen the children of sputum negative patients and those who start chemoprophylaxis for them' (39 years/male/store manager previously TB HV/experience, 15 years)
	4) Inadequate facilities for and cumbersome screening process	'About INH, it is usually not spoken about in LT training' (51 years/female/nurse in TB hospital/experience, 25 years)
		'Chest X-Ray is there (in district hospitals), but availability of Monteux, we cannot say. Every district hospital has X-ray facility but its interpretation might be a problem especially by MOs, but yes they advise it and see it also. Nobody goes for lavage, even we don't go for that. It's just not operationally feasible. We go only for Mantoux and Chest X-Ray; we diagnose most of the patients on the basis of these two tests only.' (36 years/male/paediatrician/experience, 3 years)
		'The problem [In screening of child-contacts] would be only for Medical Officers because in children, x-ray findings are not that absolute and clear-cut and also it is difficult to get sputum. So the results come positive rarely. If it comes positive they start the treatment.' (50 years/male/DTO)

(continued)

Table 4. Continued

Major themes	Categories	Verbatim quotes
	5) Unavailability of drugs and appropriate dosage forms	'Non-availability of INH is the biggest problem. Being a store manager myself, I can tell you exactly that it ran out of stock from the store (DTC) from 1-4-15 to 15-3-16.' (39 years/male/store manager previously TB HV/experience, 15 years)
		'most important difficulty now is that the medicines are not available' (38 years/male/DOT provider/NGO/experience, 4 years)
		'The INH 100 mg availability is in shortage for quite some time' (50 years/male/DTO)
		'We do inform those patients who are positive and has severe illness that the medicines (INH) are available in the market and they could purchase it. Still, patients from the slum areas and all never take them' (38 years/male/DOT provider/NGO/experience, 4 years)
		(a) 'we feel that if it is provided in syrup form it will be easy for parent to administer it, it will be much better' (42 years/male/TB HV/experience, 10 years)
	6) Poor monitoring	(b) 'Proper monitoring is not being done in the case of chemoprophylaxis. This cause slight difficulty and delay' (32 years/male/TB HV/experience, 2 years)

Note. INH, isoniazid; TB HV, TB health visitor; DOT, directly observed treatment; IPT, isoniazid preventive therapy; LT, laboratory technician; DTO, district TB officer, Bhopal, MP; HH, House-hold; SS, Sputum smear; MO, Medical Officer.

reported that 244 of 525 eligible child contacts were screened, 141 initiated and only 19 completed the IPT. Inadequate and incomplete recording and suboptimal identification of child contacts were the main reasons identified [27].

In quantitative analysis, non-initiation of IPT was more likely among child contacts where index case is other than parent. This is coherent with the study findings from Timor-Leste [28]. Lack of adequate information among the caregivers of child contacts and lack of risk perception were the key patient-related challenges. Healthcare providers' interviews revealed several programmatic challenges including irregular supply of INH, inadequate screening facilities (owing to unavailability of chest radiography and Tuberculin Skin Test (TST) at all peripheral health institutions), inadequate knowledge and training of healthcare providers and poor monitoring mechanism in the programme. These reasons have also been reported in other studies from India and elsewhere [19]. Some healthcare providers mentioned that they tended to bypass screening and start IPT, without even asking for symptoms. This practice is dangerous and must be discouraged, as it might lead to missed 'active TB' in the child [2].

Our study findings with respect to barriers in IPT provision are similar to other studies. A previous study from South India reported that irregular supply of drugs and 'social stigma' were the main barriers [16]. Lester *et al.* reported lack of knowledge as a key barrier [29]. Study from Timor-Leste reported difficult terrain as main barrier for IPT [28]. A community-based study from Malawi reported the transport cost for getting chest radiography done was the main reason for low uptake of IPT [30]. Another study from an urban area of Malawi has reported that hospital-based contact screening was poorly used because either chest radiography and Mantoux test were not available in the hospitals or it required repeated visits to the hospitals. It also reported that most of the healthcare providers were not aware of the rationale of contact tracing [31].

Our study had several strengths. First, we used a mixed-method study design, which not only quantified the magnitude of the problem, but also provided insights into the reasons for the problem, thus providing holistic overview. Secondly, we conducted the study in programmatic settings of central India, thus reflects the realities on the ground. Thirdly, we used internationally accepted guidelines for reporting the quantitative and qualitative parts of the study [24, 26]. There were a few limitations, which relates to the small sample size (reflects in wide CIs of effect estimates) and challenges related to recall of information during interviews of caregivers of child contacts. While the social status of the child contacts may potentially impact the uptake of IPT, we could not collect the same during our survey. Duration of IPT, for example, was assessed based on interview alone and could not be validated through documents.

The study has several programmatic implications and we make the following recommendations to the RNTCP. First, the screening of child contacts should be simplified and there should be a clear guidance to conduct 'symptom screening' by healthcare providers and to start IPT in an asymptomatic child with no signs of TB. Secondly, healthcare providers need to be trained and regularly sensitized on the job about need for dose and frequency of IPT. Thirdly, there should be an uninterrupted supply of INH, as without this, healthcare providers do not feel motivated to even initiate the process of contact screening. Fourthly, there should be better patient and programmatic monitoring of IPT. The recent RNTCP operational guidelines have expanded on the data captured in the treatment card to include crucial details of child contacts, IPT initiation and completion [32]. This should be supplemented by an indicator in the quarterly report, which captures INH initiation and completion rates. Fifthly, steps must be taken to simplify IPT regimen. The current 6-month regimen is challenging to adhere to, especially by asymptomatic, healthy children with potential side effects. And, as suggested by a healthcare provider, child-friendly dosage forms need to be provided by RNTCP. One possibility is to try a more patient-friendly regimen with less number of doses. A study has shown that the 12-dose, once-a-week regimen containing INH and Rifapentine is efficacious in adults and older children (>2 years old) but needs to be tested urgently for its efficacy and safety in younger children (especially <2 years of age), as they are at highest risk of TB after infection [33].

CONCLUSION

The study reveals unsatisfactory screening and IPT initiation among child contacts of Sp-TB cases in Bhopal, Central India. The key barriers were lack of information to patients about the need for IPT, inadequate screening facilities, unavailability of INH, inadequate knowledge and training of healthcare providers and poor monitoring of IPT in the programme. The study recommends RNTCP to optimize screening procedure, ensure drug supply and streamline monitoring of IPT in child contacts to enhance its uptake.

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