



Isoniazid preventive therapy in child household contacts of adults with active TB in Bamako, Mali

M. Tolofouidie,¹ A. Somboro,¹ B. Diarra,¹ Y. S. Sarro,¹ H. B. Drame,¹ A. C. G. Togo,¹ M. Sanogo,¹ A. Dembele,² T. Togun,³ E. Nkereuwem,³ B. Baya,¹ B. Konate,⁴ U. Egere,³ M. Traore,⁵ M. Maiga,⁶ K. Saliba-Shaw,⁷ B. Kampmann,³ S. Diallo,¹ S. Doumbia,¹ M. Sylla²

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BACKGROUND and OBJECTIVE: Isoniazid preventive therapy (IPT) is known to reduce the risk of developing active TB in about 59% in children aged ≤ 15 years. We assessed adherence, completion and adverse events among children who were household contacts of a newly diagnosed adult with smear-positive TB in Bamako, Mali.

METHODS: Children aged < 15 years living in the same house with an adult smear-positive index case were enrolled in the study in the Bamako Region after consent was obtained from the parent or legal guardian. Adherence was assessed based on the number of tablets consumed during 6 months.

RESULTS: A total of 260 children aged < 15 years were identified as household contacts of 207 adult patients with smear-positive TB during the study period. Among all child contacts, 130/260 (50.0%) were aged 0–4 years and were eligible for IPT; 128/130 (98.5%) were started on IPT and 83/128 (64.8%) completed with good adherence at the end of the 6 months, and without any significant adverse events.

CONCLUSION: We successfully implemented IPT with good acceptance, but low completion rate. The Mali National TB Program and partners should expand this strategy to reach more children in Bamako and the whole country and create greater awareness in the population.

TB is a major global public health challenge and represents the leading cause of death from a single infectious disease globally. According to the WHO, an estimated 10.0 million people, 12% of whom were children aged < 15 years, contracted TB in 2019 and 1.2 million died.¹

As part of the End TB Strategy, WHO recommends preventive treatment for high-risk individuals such as children under five who are contacts of positive adult cases.² One of the best strategies to increase case detection is contact screening of bacteriologically confirmed TB index cases in the population, during which eligible contacts for preventive treatment are also identified.

Young children exposed to an adult or an older child with TB, referred to as an index case,³ are at high risk of infection with *Mycobacterium tuberculosis*.^{4,5} Without any intervention, 5–10% of these infected children will develop active TB within 1 year, and the risk is higher among younger (below 2 years old) or HIV-infected children.⁴ In addition, these infants and young children are at high risk of developing severe

disseminated forms of TB such as TB meningitis, miliary TB or other TB-related mortality.^{6,7}

In preventing vulnerable individuals from disease progression, isoniazid preventive therapy (IPT) could reduce the risk of developing active TB by about 93% of children under five and in 59% of children aged ≤ 15 years.^{8,9} Active TB needs to be excluded before starting IPT. Children who are contacts of index cases should be investigated for active TB, and asymptomatic children aged < 5 years should receive IPT.¹⁰

In Mali, a resource-constrained country with a low TB detection rate, the prevalence of childhood TB was 2.0% among all TB cases diagnosed in 2018.¹¹ Despite the strong recommendation by the WHO, very few national TB programs (NTPs) in low- and middle-income countries (LMICs), including Mali, have implemented IPT.^{12,13} Collaborating with the Mali NTP, we implemented the WHO's IPT recommendations. We then assessed the adherence, completion rate and adverse events associated with IPT among child contacts living with newly diagnosed adults with smear-positive TB in Bamako, Mali.

MATERIALS AND METHODS

Study setting

Bamako, which has a population of approximately 2 million people, comprises about 14% of the population of Mali. The city is divided into six urban districts, with each district having a referral health center (*Centre de Santé de Référence*, CSREF), where TB diagnostic and treatment services are available. In 2019 alone, more than one third of the total TB patients in Mali ($n = 6,909$) were managed in Bamako.¹⁴ This longitudinal study was carried out between October 2018 and October 2019 in collaboration with Mali-NTP in CSREF-V located in district five of Bamako Region (population: $\sim 300,000$).¹⁵ CSREF-V offers outpatient and hospitalization services in pediatrics, internal medicine, surgery, obstetrics and gynecology. In addition, there is also a laboratory, surgery room, TB care unit, and HIV/AIDS counseling and care unit. The implementation of IPT was within a multi-country household child contact tracing research project ('Reach4Kids Africa') in collaboration with NTPs, and funded by the Medical Research Council-Global Challenges Research Fund.

Diagnosis and confirmation of TB disease

Pre-enrollment sputum smear microscopy using either Ziehl-Neelsen or auramine fluorescent microscopy at

AFFILIATIONS

- 1 University Clinical Research Center, University of Sciences, Techniques and Technologies of Bamako, Bamako, Mali
- 2 Department of Paediatrics, University Teaching Hospital of Gabriel Toure, Bamako, Mali
- 3 Vaccines and Immunity Theme, Medical Research Council Unit–The Gambia, Banjul, The Gambia
- 4 National Tuberculosis Control Program, Ministry of Health and Public Hygiene, Bamako, Mali
- 5 Health Referral Center Five, Ministry of Health and Social Development, Bamako, Mali
- 6 Center for Innovation in Global Health Technology, Northwestern University, Chicago, IL, USA
- 7 Collaborative Clinical Research Branch, Division of Clinical Research, National Institute of Allergy and Infectious Diseases/National Institutes of Health, Bethesda, MD, USA

CORRESPONDENCE

Correspondence to: Diarra Bassirou, University Clinical Research Center (UCRC), University of Sciences, Techniques and Technologies of Bamako (USTTB), BP 5445, Bamako, Mali. email: bdiaarra@icermali.org

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local reference centers was followed by Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) testing and culture at the University Clinical Research Center (UCRC; Bamako, Mali) Biosafety Level-3 laboratory, certified by the College of American Pathologists (CAP; Northfield, IL, USA), including external quality controls.

Symptom screening and clinical evaluation of study participants

Children aged <15 years who were household contacts with an adult smear-positive index case were eligible for inclusion in the main contact tracing project. We defined a household as a group of individuals eating from the same dish and living in the same house.

Newly diagnosed sputum smear-positive adult TB patients at the CSREF-V were asked if they had any children aged <15 years living in the same household. Where there was a child, parents or legal guardians were asked if they preferred to be visited at home or to bring the child to the clinic. A standard symptom-screening questionnaire for TB was then administered to ascertain if any child might be suffering from active TB. Following symptom screening and clinical evaluation, those without evidence of TB disease and aged <5 years were placed on daily isoniazid (INH), provided monthly at home by NTP personnel and study field workers. In addition, the drugs were provided by the NTP.

Children were eligible for IPT if they were aged <5 years and did not have any symptoms of TB disease, or were aged >5 years but HIV-positive and asymptomatic. Children of cases with suspected active TB during screening were subjected to a careful evaluation which included a complete history, clinical examination and relevant investigations, including a HIV test and chest X-ray.

Children who developed active TB while on IPT were assessed and treated according to NTP recommendations. Active screening of other household members was performed, and where symptomatic, were referred to a physician for further evaluation.

Isoniazid preventive therapy and follow-up

Before IPT initiation, parents and legal guardians of all children were shown either at home or at the clinic how to administer the appropriate daily dose of INH according to each child's weight. In addition, parents were educated on how to identify the symptoms of TB disease and the importance and possible adverse events of IPT. They were encouraged to ensure that the children took their IPT under their supervision. Each child who receive IPT had an individual register for monitoring during the follow-up period.

INH was administered to children aged <5 years at a dose of 10 mg/kg/day in tablet form. The drugs were provided every 2 weeks by a field officer either during home visits or outpatient visits, but adherence was evaluated on a monthly basis. Each child was also evaluated on a monthly basis during follow-up, which comprised monthly home visits or visits to the health center. During each visit, parents or legal guardians were asked about the presence of symptoms, adverse effects and adherence.

Parents or legal guardians of children with minor adverse events (such as vomiting) were advised to continue IPT and to immediately report any changes. Children with more serious adverse events such as hepatitis, high transaminase levels, jaundice, or TB symptoms were told to discontinue IPT and were referred to the hospital, where they were investigated and monitored. The children were followed up monthly until completion of IPT, and then at 18 months after IPT completion by phone to check their status.

Ethics

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Pharmacy and Dentistry of the University of Sciences, Techniques and Technologies of Bamako (*Faculté de Médecine et d'Odontostomatologie/Faculté de Pharmacie*), Bamako, Mali. The content of the information sheet was explained to the parents or legal guardians in their own language, after which they were invited to sign the consent form before the child was enrolled in the study.

Data analysis

We used the symptom screening questionnaire among child household contacts to collect data related to diagnosis for active TB and IPT outcomes. Additionally, information about tablet taking and the number of consecutive months completed was collected on individual follow-up register. Treatment completion was defined as the intake of $\geq 80\%$ of all pills prescribed during the 6 months of prophylaxis.¹⁶ We defined good, reasonable and poor adherence, if $>80\%$, $60\text{--}80\%$ and $<60\%$ respectively of the monthly quota of pills were taken.¹⁷ All variables are presented as frequencies and percentage, or as medians with interquartile ranges for age. All data were double-entered by a data officer into a MS Excel spreadsheet (Microsoft, Redmond, WA, USA).

RESULTS

Characteristics of study participants who accepted IPT

We identified 260 children aged <15 years as household contacts of 207 newly diagnosed adult TB patients interviewed. Of the household contacts, 130/260 (50%) were ineligible for IPT because they were aged >5 years and not HIV-positive ($n = 127$) or had confirmed TB ($n = 3$). Of the 130 children eligible, 128 (98.5%), including 1 who was HIV-positive were started on IPT and 2 refused (Figure 1). The Table shows the demographic characteristics of the children who were started on IPT.

Adherence and completion of IPT

The total number of children who completed with good adherence at the end of the 6-month period was 83 (64.8%) (Figure 2). Respectively 37 (28.9%) and 8 (6.3%) had poor and reasonable adherence. During the 13 months of observation, none of the patients had any of the more severe adverse events of interest described above that could have required discontinuation of IPT.

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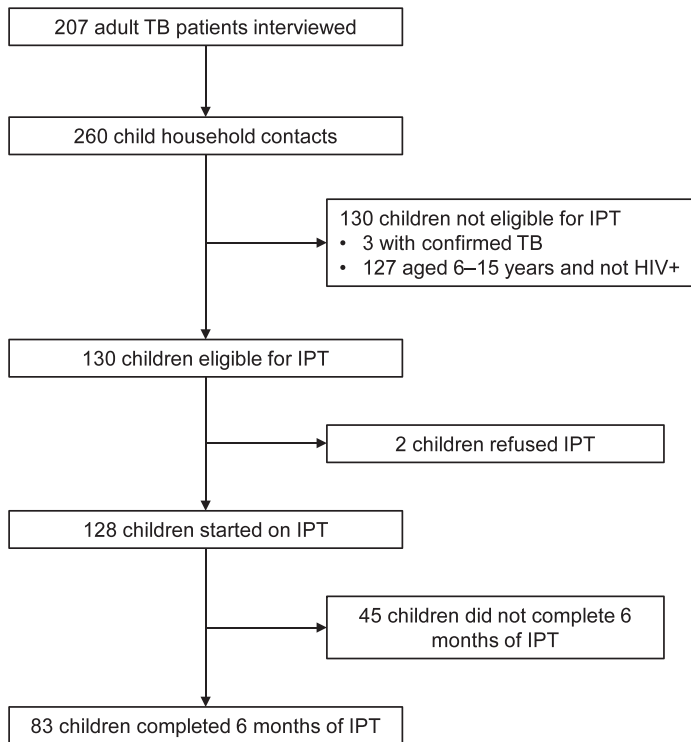


FIGURE 1 Flow chart of the study participants. IPT = isoniazid preventive therapy; HIV+ = HIV-positive.

TABLE Demographic characteristics of children who were started on IPT

	Frequency (<i>n</i> = 128) <i>n</i> (%)
Age, months, median [IQR]	25.5 [13–48]
Age group, months	
1–12	27 (21.1)
13–24	35 (27.4)
25–36	25 (19.5)
37–48	36 (28.1)
49–60	5 (3.9)
Sex	
Male	63 (49.2)
Female	65 (50.8)
Relationship of child to index case	
Mother	28 (21.9)
Father	40 (31.2)
Brother/sister	8 (6.3)
Grandparents	23 (18.0)
Uncle/aunt	25 (19.5)
Others	4 (3.1)
Proximity to index cases	
Same bed	15 (11.7)
Same bedroom	52 (40.6)
Same house	60 (46.9)
Separate apartment	1 (0.8)

IPT = isoniazid preventive therapy; IQR = interquartile range.

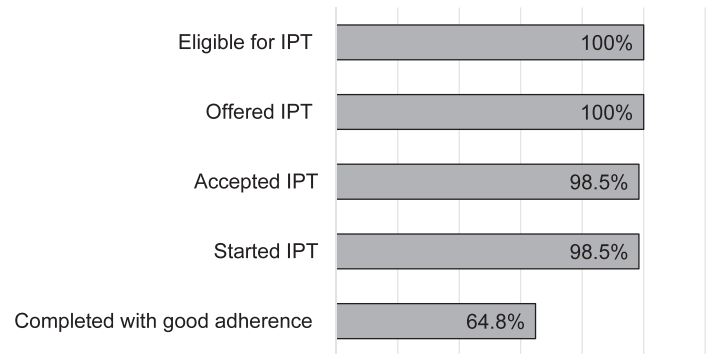


FIGURE 2 Cascade of care of child contacts eligible for IPT. IPT = isoniazid preventive therapy.

Eighteen-month follow-up

Of the 83 who completed IPT, 59/83 (71.1%) were alive and well at the 18-month follow-up, and 23/83 (27.7%) were lost to follow-up. There was one case of sudden death due to unknown cause 11 months after treatment completion.

Relationship between child and index cases

In 40 cases (31.3%), the father was the index case, while 60 children (46.9%) were living in the same house as their index cases (Table).

Frequency of TB disease among household contacts

During initial clinical screening of the 260 eligible child contacts, 29 (11.2%) were symptomatic and were referred for further investigation. Thereafter, three (1.2%) children (two males and one female, aged 2, 4 and 6 years, respectively) had bacteriologically confirmed TB and were started on standard treatment.

DISCUSSION

We implemented IPT in CSREF-V of Bamako Region in collaboration with NTP in line with the WHO Stop TB by 2035 Strategy. To the best of our knowledge, this is the first report of IPT implementation in children who are household contacts of adult TB cases in Mali. We found that 98.5% of eligible children were started on IPT, and more encouragingly, two-thirds of the children initiated on IPT completed the 6-month course with good adherence. Given that the overall first-line treatment success in Mali of 77% is far from the DOTS target of 85%, and the high rate of loss to follow-up observed in Mali since 1994, we were initially concerned that acceptancy and adherence would be low due to the perception of ‘administering drugs in healthy persons’.^{18–20}

Fifty percent of our study population were eligible and 98.5% of eligible contacts started IPT in our study, which is a very high rate of acceptancy compared to other studies in LMICs: acceptancy in India was respectively 63% and 22%;²¹ and in the Gambia this was reported to be 81.2%.²² In Ethiopia, IPT uptake was reported to be 58%.²³

Parents or legal guardians were required to monitor children for completion of IPT over the 6-month period. In order to monitor compliance, children were evaluated each month to verify the number of tablets taken. We found an IPT completion rate of 64.8% at 6 months’ follow-up. This rate is less than the one reported in Rwanda (88%),²⁴ while two neighboring countries in West Africa (Benin and Gambia) reported completion rates of respectively 86% and 77%.^{22,25} In contrast to our unique urban site

(which may be the reason for the relatively low completion rate), the Gambian study included both urban and rural areas, and in Benin, two sites, Cotonou and Porto-Novo, were involved. Moreover, some parents or legal guardians were wondering about the long-term duration of ‘taking medication without disease’, and this may have impacted the completion rate. Another explanation of the low completion rate compared to the Gambian study was the mechanism of tablet delivery. The tablets were exclusively delivered at home in the Gambia, whereas in this study we combined clinic and home delivery, and some parents or legal guardians may not have had adequate access to the clinic. More investigations, especially qualitative studies, of group focus discussions with parents or legal guardians need to be conducted.

It is important to conduct a thorough clinical evaluation before IPT initiation to exclude active TB. Symptom screening was found useful in our setting, and we were able to identify 3 (1.2%) children with bacteriologically confirmed TB. Others have reported similar rates of co-prevalent TB: in India, 1.6% of active TB cases were found in child contacts living with an adult index.²¹ The frequency of co-prevalent TB was high in Benin, reaching 16.9% of active TB in children aged <5 years.²⁵

In our study, only children under 5 years without TB disease were initiated on IPT, in line with the WHO recommendations at the time. These have since been updated by the WHO; it is now recommended that treatment of latent TB infection also include those older than 5 years without TB disease.²⁶ Given the implementation challenges already encountered, this might be difficult to achieve, and further studies to address acceptability and completion rates are now needed.

There were no severe IPT-related adverse events during our study. We recommend increased sensitization of the population about symptoms of TB such as cough and/or weight loss that should prompt care-seeking for the timely diagnosis of TB and clinical evaluation for IPT initiation. In comparison, six deaths were reported among children during IPT follow-up in Benin, probably due to the greater number of children involved in the study.²⁵

We found that 46.9% of household contacts were living in the same house with the index cases; in Benin, this proportion was 40.3%.²⁵ NTP should continue sensitization of the population to ensure that all children eligible for the IPT program are enrolled. Our study was limited by the relatively low number of children included, as well as the low completion rate at the end of the 6-month period compared to neighboring countries.

Despite the relatively low completion rate, our study was innovative in implementing monitored IPT in children in Mali without major challenges. Moreover, the acceptance rate of 98.5% by parents or legal guardians is a good indicator for successful nationwide implementation of IPT in future.

CONCLUSION

We successfully implemented IPT in the CSREF-V in the Bamako Region, with a good acceptance rate. Although the IPT completion rate compared to neighboring countries was low, those who completed had good adherence at the end of 6 months, and no significant adverse events. The Mali NTP and partners should ex-

pand this strategy to more centers and hospitals to reach more children in Bamako and the country.

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CADRE et OBJECTIF : Le traitement préventif par isoniazide (IPT) réduit le risque de développer une TB active chez environ 59% des enfants ≤ 15 ans. Nous avons évalué l'observance, l'achèvement du traitement et les événements indésirables chez des enfants qui étaient contacts domestiques d'un adulte ayant récemment reçu un diagnostic de TB à microscopie positive à Bamako, Mali.

MÉTHODES : Les enfants âgés < 15 ans vivant sous le même toit qu'un cas index adulte de TB à microscopie positive ont été inclus dans l'étude dans la région de Bamako, après obtention du consentement des parents ou du tuteur légal. L'observance a été évaluée en fonction du nombre de comprimés consommés au cours d'une période de 6 mois.

RÉSULTATS : Au total, 260 enfants âgés < 15 ans ont été identifiés

comme contacts domestiques de 207 patients adultes atteints de TB à microscopie positive pendant la période d'étude. Parmi tous les contacts pédiatriques, 130/260 (50,0%) étaient âgés de 0–4 ans et étaient éligibles à l'IPT ; 128/130 (98,5%) ont été mis sous IPT et 83/128 (64,8%) ont achevé leur traitement avec une bonne observance à la fin de la période de 6 mois, sans événement indésirable significatif.

CONCLUSION : Nous avons mis en place l'IPT avec succès. L'acceptation était bonne mais le taux d'achèvement du traitement était faible. Le programme national de lutte contre la TB du Mali et ses partenaires devraient élargir cette stratégie afin d'inclure davantage d'enfants de Bamako et du pays, et d'accroître la sensibilisation de la population.