

## Treatment of childhood tuberculosis in India

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### SUMMARY

With a quarter of the global burden of tuberculosis (TB) occurring in India, children in this country are at high risk of tuberculous infection and TB disease. India's Revised National Tuberculosis Control Programme provides free diagnosis and treatment for children with TB using quality assured, weight-based individual drug boxes. Guidelines have recently been revised, updating both the diagnostic algorithm and shifting to a daily regimen with World Health Organization recommended dosages using child-friendly, fixed-dose combination

pills. Active case finding is practised in households of TB patients as well as among human immunodeficiency virus infected and malnourished children. More attention needs to be paid to the provision of preventive therapy for household contacts aged <6 years as well as to the detection of multidrug-resistant TB among children. Case notification and the use of the Standards of TB Care in India are being strengthened in the private sector.

**KEY WORDS:** India; paediatric TB; first-line treatment

ALMOST 40% of India's population is under 15 years of age. Although child tuberculosis (TB) in India is estimated to be approximately 10% of total adult incidence, only 6% of the total cases reported to the Revised National Tuberculosis Control Programme (RNTCP) are children, and this proportion has remained constant for the last 9 years (Figure 1).<sup>1</sup> A large proportion of children with TB are probably diagnosed and managed by India's vast private sector: some proof of this is now available from Nikshay, the case-based notification portal developed by the Ministry of Health and Family Welfare (Figure 2).<sup>2</sup> Data from Sitamarhi District, Bihar State, show that the proportion of children diagnosed with TB is higher in the private sector (17% vs. 8% in RNTCP). However, as most private practitioners do not notify cases to the RNTCP, the overall burden of childhood TB in the country is unknown.

Pulmonary TB remains the most common form of TB, although children suffer more from extrapulmonary forms of TB than all other age groups. Hospital records indicate that the numbers of young children with TB meningitis and disseminated TB have decreased over time, although the absolute numbers are not insignificant. This is attributed to the widespread use of the bacille Calmette-Guérin (BCG) vaccine at birth, with coverage exceeding 90% in most Indian states.

In line with global policy, the Indian government has made significant efforts to prioritise this vulnerable group in the RNTCP, with specific

guidance for children included in the 2014 Standards for TB Care in India (STCI), as well as by setting targets under the National Strategic Plan 2012–2017.<sup>2</sup>

The RNTCP has set guidelines for the diagnosis and treatment of paediatric TB since inception: it supplies quality-assured drugs in patient-wise paediatric boxes with a full course of treatment by weight band. While the RNTCP uses an intermittent (thrice-weekly) regimen, most private paediatricians use a daily regimen. The STCI recommends a daily regimen for both adults and children, and the government is in the process of procuring fixed-dose combinations (FDCs) using the World Health Organization (WHO) recommended dosing guidelines.<sup>3</sup> At least two Indian manufacturers are in the process of obtaining regulatory approvals for such products.

There are several forums addressing childhood TB involving representatives from the Indian Academy of Paediatrics (IAP; Mumbai, India), such as the National Technical Working Group (NTWG) on paediatric TB. Efforts are being made to integrate TB case finding and management into general child health activities, for example, the Integrated Management of Childhood and Neonatal Illness and Reproductive and Child Health Programmes. The RNTCP in India has a vertical structure down to the sub-district (block) level, beyond which it merges with the general health system (primary health

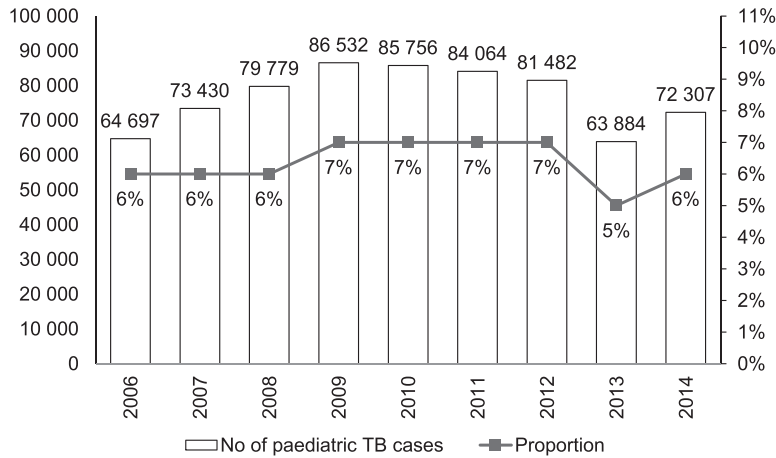


Figure 1 Number and proportion (of all TB cases) of childhood TB, 2006–2014.<sup>1</sup> TB = tuberculosis.

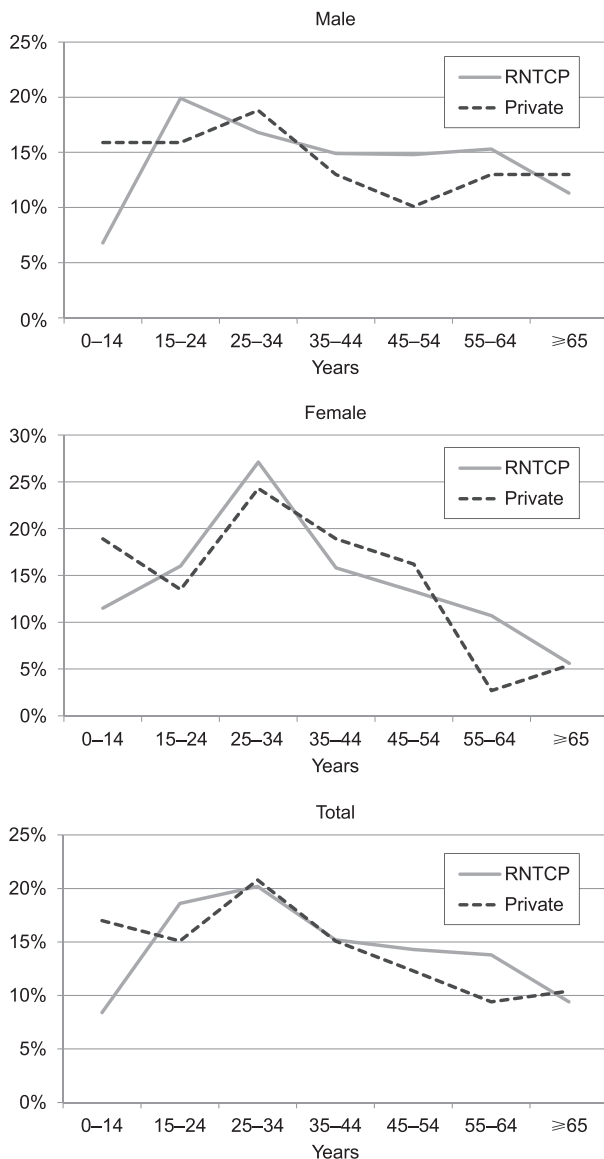


Figure 2 Tuberculosis notification in the 0–15 years age group is higher from the private sector: an example from Sitamarhi District, Bihar State (September 2012–August 2013) (Source: Nikshay Data).<sup>2</sup> RNTCP = Revised National Tuberculosis Control Programme.

centre physicians, pharmacists and village health nurses).

### ADDRESSING KEY ISSUES IN CHILDHOOD TUBERCULOSIS

- 1) Integration of TB services with the general health system: the general health system is responsible for treatment delivery, BCG immunisation and contact tracing, and refers child cases to the RNTCP. More efforts are needed to sensitise community health care providers and involve them in case finding and treatment monitoring. The government is considering a proposal to involve private paediatricians in improving diagnostic services for children in peripheral government health centres where paediatricians may not be available.
- 2) Training: the IAP and RNTCP have jointly developed training modules for paediatricians on TB management, including, but not limited to, programmatic guidelines. These modules cover all diagnostic and treatment aspects of pulmonary and extra-pulmonary TB. A comprehensive cascading training plan was initiated in early 2015 with the support of TB Alliance. A national train-the-trainers workshop was held in April 2015; this will be followed by regional and state-level workshops.
- 3) Improving diagnosis: children have been prioritised by the national policy for access to rapid diagnostics; however, implementation is still patchy. For example, a pilot to accelerate access to quality TB diagnosis for paediatric cases is being conducted in four major Indian cities—Delhi, Chennai, Kolkata and Hyderabad—with the purpose of identifying key hospitals, private clinics and paediatricians to engage and establish a referral network. This initiative has been hugely successful, testing >10 000 specimens with the Xpert<sup>®</sup> MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) in 6 months and finding >600 children with

**Table** India's response to childhood TB

Issues pertaining to childhood TB	India's response/ efforts
<b>Case finding</b>	
Improve paediatric TB case finding through better diagnostic tools	Xpert MTB/RIF currently limited to four cities, will be extended to 10 by end 2015 and entire country by 2016
Use of rapid molecular tests	Free radiography throughout the country in next 2–3 years, pilots starting now (supported by the Global Fund)
Use of existing tools: radiology and improved specimen collection	
Better engagement of private TB care providers for increased detection and notification of TB in children	With effective IAP involvement (e.g., customised training module for paediatricians), private sector participation is likely to improve Timeline 2–3 years
Intensified TB case-finding strategies to detect and treat children with TB	Major efforts required Will be scaled up over next 2–3 years
Screening vulnerable/high-risk children	
Contact screening and chemoprophylaxis	
Case definition for paediatric MDR-TB (probable MDR-TB)	Incorporated in national guidelines
<b>Treatment services</b>	
Optimal TB regimens with low pill burden and dispersible tablets	In process of manufacturing: likely availability in RNTCP at end 2016
Child-friendly treatment adherence strategy, with parents as treatment supporters	Incorporated in national guidelines
<b>Strengthening programme management</b>	
Leveraging the existing comprehensive child health services under the National Health Mission	Complete integration by 2018–2022

TB = tuberculosis; USAID = United States Agency for International Development; IAP = Indian Academy of Paediatrics; RNTCP = Revised National TB Control Programme; MDR-TB = multidrug-resistant TB.

bacteriologically confirmed TB, ~10% of whom had rifampicin resistance.<sup>4</sup>

- 4) Screening vulnerable/high-risk children: in some states nutritional rehabilitation centres (NRCs) are used to screen malnourished children for TB.<sup>5</sup> Human immunodeficiency virus (HIV) infected children attending government antiretroviral therapy centres are regularly screened for TB. Coordination mechanisms and service linkages exist, with upfront molecular diagnosis offered to children in a limited number of facilities. Most children diagnosed with TB undergo HIV testing.
- 5) Contact screening and chemoprophylaxis: contact screening to identify additional cases within the household has been implemented by the RNTCP since its inception. All children aged <6 years who are contacts of a family member with active TB are to be screened for TB, and are given isoniazid chemoprophylaxis after active TB has been ruled out. However, coverage is less than satisfactory. Internal evaluations conducted between 2012 and 2014 noted that 35–70% of children aged <6 years did not receive chemoprophylaxis, highlighting the need to prioritise this activity.
- 6) Treatment: patient-wise treatment boxes for different paediatric weight categories have been used for the past 15 years, with overall good treatment success rates. However, there were concerns that dosages were not optimal in terms of bioavailability and blood levels.<sup>6</sup> To implement the updated guidelines for paediatric treatment in the STCI, which follow the current WHO dosing guidelines, the government is planning to introduce a daily

dosing regimen using child-friendly FDCs. Discussions have been held with the RNTCP, the Drugs Controller General of India (New Delhi, India), and manufacturers to fast-track the approval of appropriate formulations for use in the programme. An option for family members to provide directly observed treatment to paediatric patients has been incorporated in the guidelines.

- 7) Drug-resistant TB: the RNTCP has expanded the Programmatic Management of Drug-resistant TB (PMDT) to cover the entire country: children and HIV-infected individuals have been prioritised for testing with molecular diagnostics (cartridge based nucleic acid amplification test or line-probe assay), in addition to patients with a history of previous treatment, treatment failures or contacts of multidrug-resistant TB (MDR-TB) cases. A definition of 'probable MDR-TB' has been accepted in situations where bacteriological confirmation is not possible. Treatment with second-line drugs (Category IV and V for MDR- and extensively drug-resistant TB [XDR-TB], respectively) is available for all age and weight ranges. However, the identification of children with MDR-TB continues to lag behind that of adults, and further training and sensitisation of paediatricians and health care workers will be required to improve access to diagnostic and treatment services.

In conclusion, while policy prescription and willingness to address this group on a priority basis is in place, mainstreaming of resources to implement these changes is likely to take another 2–4 years. Momen-

tum on the issue has been generated and the process of strengthening this component must be seen as an irreversible process.

*Conflicts of interest:* none declared.

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**R E S U M E**

L'Inde représente un quart du fardeau de la tuberculose (TB) et les enfants ont donc un risque élevé d'infection et de maladie tuberculeuse. Le Programme national contre la TB offre un diagnostic et un traitement gratuits pour les enfants atteints de TB, et recourt à des boîtes de médicaments individuelles, en fonction du poids, et dont la qualité est vérifiée. Les directives ont été révisées récemment avec une mise à jour de l'algorithme de diagnostic et le passage à un protocole quotidien avec les doses recommandées par l'Organisation Mondiale de la

Santé de comprimés combinés à dose fixe, acceptables par les enfants. La recherche active des cas est pratiquée dans les foyers de patients TB ainsi que parmi les enfants infectés par le virus de l'immunodéficience humaine et malnutris. Il faut accorder davantage d'attention à l'offre de traitement préventif pour les contacts domiciliaires d'âge <6 ans et aussi à la détection de la TB multirésistante chez l'enfant. La déclaration des cas et l'utilisation des normes de soins TB en Inde dans le secteur privé est en voie de renforcement.

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**R E S U M E N**

La India representa un cuarto de la carga de morbilidad total por tuberculosis (TB) y los niños son sumamente vulnerables a la infección y la enfermedad tuberculosa. El Programa nacional contra la TB ofrece diagnóstico y tratamiento sin costo alguno a los niños y provee cajas individuales de medicamentos adaptados al peso, con garantía de la calidad. Recientemente se llevó a cabo una revisión de las directrices que consistió en actualizar el algoritmo diagnóstico y adoptar un régimen de tratamiento diario según las posologías recomendadas por la Organización Mundial de la Salud, usando comprimidos con asociaciones en dosis fijas adaptadas

al uso pediátrico. Se practica una búsqueda activa de casos en los hogares de los pacientes con diagnóstico de TB, en los niños infectados por el virus de la inmunodeficiencia humana y los niños desnutridos. Es preciso prestar mayor atención al suministro del tratamiento preventivo a los contactos domiciliarios de edad <6 años y a la detección de la TB multidrogorresistente en los niños. En la actualidad se está fortaleciendo la notificación de casos y el uso de las normas de tratamiento de la TB en el sector privado en la India.

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